

Reactivity, Chemoselectivity, and Diastereoselectivity of the Oxyfunctionalization of Chiral Allylic Alcohols and Derivatives in Microemulsions: Comparison of the Chemical Oxidation by the Hydrogen Peroxide/Sodium Molybdate System with the Photooxygenation

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Abstract: The chiral allylic alcohols **1a–d** and their acetate (**1e**) and silyl ether (**1f**) derivatives have been oxidized by the H₂O₂/MoO₄²⁻ system, a convenient and efficient chemical source of singlet oxygen. This chemical peroxidation (formation of the allylic hydroperoxides **2**) has been conducted in various media, which include aqueous solutions, organic solvents, and microemulsions. The reactivity, chemoselectivity, and diastereoselectivity of this chemical oxidation are compared to those of the sensitized photooxygenation, with the emphasis on preparative applications in microemulsion media. While a similar *threo* diastereoselectivity is observed for both modes of peroxidation, the chemoselectivity differs significantly, since in the chemical oxidation with the H₂O₂/MoO₄²⁻ system the undesirable epoxidation by the intermediary peroxomolybdate competes efficiently with the desirable peroxidation by the in situ generated singlet oxygen. A proper choice of the type of microemulsion and the reaction conditions furnishes a high chemoselectivity (up to 97%) in favor of *threo*-diastereoselective (up to 92%) peroxidation.

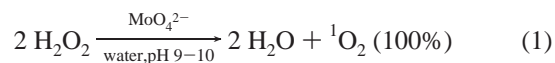
Introduction

Singlet molecular oxygen, ¹O₂ (¹Δ_g), is a highly reactive but yet selective oxidant. Most commonly, it is generated by photosensitization of triplet molecular oxygen.^{1,2} This versatile and convenient method may be conducted in a large variety of nonpolar and polar solvents and a wide range of temperature (−100 to +100 °C); the low temperatures are particularly advantageous when labile oxidation products have to be prepared.

¹O₂ may also be generated in high yields in a number of chemical reactions.^{3–5} These have been employed mainly in mechanistic studies but scarcely used in organic synthesis. The reasons are that they involve either highly oxidizing inorganic reagents (ClO[−], BrO[−]), which may cause side reactions, or

organic sources such as phosphite ozonide⁶ or polycyclic aromatic endoperoxides;⁷ the latter require previous preparation. A more serious disadvantage is the fact that they are used in stoichiometric amounts and large quantities of organic byproducts are generated, which encumber the isolation of the wanted oxidation product.

More recently, a catalytic chemical source has been developed, in which the ¹O₂ is quantitatively generated in a mild and convenient method, namely the disproportionation of hydrogen peroxide, effected catalytically by sodium molybdate (eq 1).^{8,9a–d}



On mixing of these commercially available reagents, a high flux of ¹O₂ may be produced in situ at room temperature without the need of light and photochemical equipment. The reaction

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proceeds efficiently in alkaline aqueous solutions^{8,9a-d} or in highly polar organic solvents such as methanol;^{9e} hydrophilic, low-molecular-weight organic substrates may be effectively oxidized on the preparative scale under these conditions.¹⁰ The use of microemulsions (submicronic biphasic systems), however, allows us to extend the scope to any organic substrate without loss of efficiency, neither in the chemical yield nor in the trapping efficiency of ¹O₂.¹¹

A microemulsion consists of water, an organic solvent (oil), a surfactant, and in most cases a cosurfactant (alcohol). It forms a transparent or translucent, thermodynamically stable, isotropic dispersion of two immiscible liquids, with microdomains of one or both liquids stabilized by an interfacial film of surface-active molecules.¹² Although more complex in composition than traditional reaction media, microemulsions present definite advantages: (i) they are particularly well-suited for the chemical peroxidation of highly hydrophobic substrates on the preparative scale;¹¹ (ii) they protect substrates and products sensitive to alkaline conditions; and (iii) they limit the direct contact of the oxidant source with the substrate and the product. In particular, the chemical ¹O₂ source under consideration herein, namely the H₂O₂/MoO₄²⁻ system, which generates efficiently ¹O₂ in alkaline medium, actually also acts as an efficient epoxidizing agent under acidic and neutral conditions.^{10a} Consequently, the chemoselectivity may be of concern for substrates with electron-rich double bonds, which may be readily epoxidized under normal conditions, instead of being oxidized to the desired peroxides by the in situ generated ¹O₂.

One of the prominent peroxidations by ¹O₂ is its ene reaction with alkenes, the so-called Schenck reaction.^{1,2} It constitutes a convenient preparation of allylic hydroperoxides; the latter have proven to be synthetically useful building blocks.^{1,2,13} Much work has been devoted to the elucidation of the mechanistic aspects of the ene reaction of allylic alcohols by photochemically generated ¹O₂, notably the regiochemistry and stereoselectivity.¹⁴⁻¹⁶ Expectedly, for substrates with several allylic hydrogen atoms, abstraction may be expected to take place at all possible sites to result in complex mixtures of isomeric allylic hydroperoxides.¹⁷ Nevertheless, significant regioselectivity may be achieved in the ene reaction through the choice of appropriate structural features within the allylic substrate, namely the so-

called *cis*, the *gem*-directing, and the “nonbonding-large-group” effects.¹⁸⁻²¹ The stereochemistry, specifically the diastereoselectivity, is subject to the recently recognized “hydroxy-group directivity”,¹⁸ in which the synergism between conformational and electronic factors may dictate a high degree of stereochemical control.

The incentive of the present work was to assess the chemoselectivity and the diastereoselectivity in the ene reaction of a series of chiral allylic alcohols and derivatives **1** with ¹O₂, chemically generated by the H₂O₂/MoO₄²⁻ source in microemulsion media. Our unprecedented results are to be compared with conventional methods, namely photooxygenation and chemical oxidation by H₂O₂/MoO₄²⁻ in homogeneous solvent systems. The purpose was to develop a convenient and selective chemical peroxidation process under catalytic conditions for the preparation of allylic hydroperoxides through the ene reaction with ¹O₂, but without the use of light and photochemical equipment. For this purpose, the allylic alcohol **1a** (mesitylol) was chosen as model substrate, since its diastereoselectivity has been well studied for photochemically produced ¹O₂, which should enable a detailed comparison with the data to be acquired herein.^{16,22} These chemical oxidations were to be carried out in various reaction media, which encompass organic solvents, water, and especially water-in-oil (W/O) microemulsions. Such microemulsions, which consist of water microdroplets dispersed in a continuous organic phase, should limit the direct interaction between the substrate and the peroxomolybdate intermediates (precursors to the chemically generated ¹O₂), to minimize thereby the substrate epoxidation and guarantee a high chemoselectivity. The W/O microemulsions to be used for the present study were to be made up of sodium dodecyl sulfate (SDS) as the surfactant, ethanol or butanol as cosurfactant, and CH₂Cl₂ or CCl₄ as continuous organic phase. The reactivity, chemoselectivity, and diastereoselectivity of the chemically generated ¹O₂ in the microemulsion medium were to be determined by varying the substrate structure in terms of the degree and pattern of the methyl substitution on the double bond in the allylic alcohols. Herein, we report our findings, which unequivocally demonstrate the preparative feasibility and synthetic advantages of the present concept.

Results

Substituent Effects on the Reactivity. To assess the reactivity of the chiral allylic alcohols **1** toward singlet oxygen as a function of the degree and pattern of methyl substitution of the double bond, the so-called “Foote reactivity index” (β value²³) was determined for these substrates. The β value corresponds to the minimum concentration of the required substrate, such that the overall interaction of ¹O₂ with the substrate surpasses

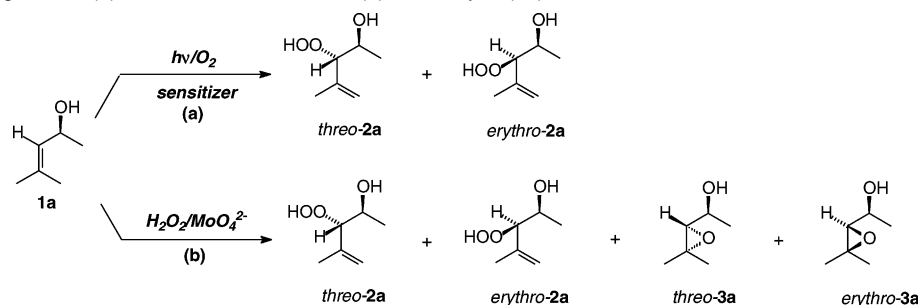
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Table 1. Overall Rate Constants ($k_r + k_q$) and β Values for the Photooxygenation of the Chiral Allylic Alcohols **1a–d**, as Determined by Laser Flash Photolysis^a

				$k_r + k_q$ ($10^4 \text{ M}^{-1} \cdot \text{s}^{-1}$) ^a	β (M) ^b
	R ¹	R ²	R ³		
1a	CH ₃	CH ₃	H	2.4	0.43
1b	H	CH ₃	CH ₃	14	0.074
1c	CH ₃	H	CH ₃	18	0.058
1d	CH ₃	CH ₃	CH ₃	320	0.0032

^a In CD₃OD with sodium tetraphenylporphine sulfonate (TPPS) as sensitizer; error is $\pm 5\%$ of the stated value. ^b In CH₂Cl₂; error is $\pm 5\%$ of the stated value.

Scheme 1. Photooxygenation (a) and Chemical Oxidation (b) of Mesityl (1a)

the physical deactivation (quenching) by the solvent. For this purpose, laser flash photolysis was employed to measure the overall rate constants ($k_r + k_q$) in CD₃OD, in which k_q and k_r represent the physical quenching and the chemical reaction of ¹O₂ by the substrate.^{23,24}

The kinetic data are given in Table 1 for the alcohols **1a–d**. Clearly, the results indicate that both the degree (substrates **1a–c** versus **1d**) and the pattern (substrates **1a** versus **1b** and **1c**), but not the *cis–trans* geometry (substrates **1b** versus **1c**) of the methyl substitution, affect the chemical reactivity of ¹O₂ toward these allylic alcohols. As shall become evident, in view of the quite low reactivity of the allylic alcohols **1a–c** toward ¹O₂, a large excess of hydrogen peroxide will be needed to peroxidize them by the H₂O₂/MoO₄^{2–} system in the microemulsion.

Substituent Effects on the Chemoselectivity. In the photooxygenation, only the expected allylic hydroperoxides **2a–d** were produced, as illustrated for mesityl as model substrate in Scheme 1a.

In contrast, in the chemical peroxidation, (H₂O₂/MoO₄^{2–}) of the allylic alcohols **1a–d**, solubilized in a microemulsion made up of CH₂Cl₂ as the solvent, SDS as the surfactant, and EtOH as the cosurfactant, also the corresponding epoxides **3a–d** are formed in appreciable amounts (Scheme 1b). The formulation of the microemulsions was chosen in order to permit the solubilization of a large amount of hydrogen peroxide without demixing, such that the oxidation of the substrate **1** could be conducted on the preparative scale (0.50 mol kg^{–1}) within a reasonable time (for the actual conditions, see Table S3 in the Supporting Information section). Thus, the microemulsions made of CH₂Cl₂ (or CCl₄)/EtOH (or BuOH)/SDS/H₂O (or D₂O) in the proportions 74.8/9.5/9.5/6.2 (wt %) and 49.0 mmol kg^{–1} of sodium molybdate were found to solubilize up to 20% (by

Table 2. Substituent Effects on the Chemoselectivity for the Chemical Oxidation^a of the Allylic Alcohols **1a–d** by the H₂O₂/MoO₄^{2–} Oxidant, Solubilized in Microemulsions^b

				2 : 3 ^c
	R ¹	R ²	R ³	
1a	CH ₃	CH ₃	H	83 : 17
1b	H	CH ₃	CH ₃	89 : 11
1c	CH ₃	H	CH ₃	95 : 05
1d	CH ₃	CH ₃	CH ₃	> 95 : 05

^a The conditions are given in Table S3 (see Supporting Information).

^b The microemulsion is composed of CH₂Cl₂, D₂O, EtOH and SDS (sodium dodecyl sulfate) in the proportions 74.8:6.2:9.5:9.5 (wt %). ^c Product ratios were determined by ¹H NMR spectroscopy on the isolated reaction mixture for > 95% conversion; error is $\pm 5\%$ of the stated value.

volume) of aqueous H₂O₂. Furthermore, the presence of the allylic alcohol **1** increased the water content without demixing up to 35% in the BuOH-based microemulsion and up to 25% in the EtOH-based one. This may be rationalized in terms of the amphiphilic nature of the allylic alcohol **1**, which plays the role of a cosurfactant. For preparative purposes which were advantageous, the use of EtOH instead of BuOH considerably facilitates the isolation of the oxidation products by simple evaporation of the solvent at reduced pressure.^{11a}

The hydroperoxide (**2**)/epoxide (**3**) ratios are presented in Table 2. It is noteworthy that, in the CH₂Cl₂/EtOH/SDS/D₂O microemulsion, mesityl (**1a**) showed the lowest chemoselectivity (**2**:**3** ratio is 83:17). Furthermore, no epoxide was obtained with the allylic alcohol **1d** under these conditions.

Substituent Effects on the Diastereoselectivity. The photooxygenation as well as the chemical oxidation of the allylic substrates **1** afforded the *threo* and the *erythro* diastereomers

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Table 3. Dependence of the Diastereoselectivity on the Substrate Structure in the Peroxidation of the Allylic Alcohols **1a–d**, Acetate **1e**, and Silyl Ether **1f** by Photochemically (CDCl₃ Solution) and Chemically (CH₂Cl₂ Microemulsion) Generated ¹O₂

					O ₂ /sens./hv ^{a,b}		H ₂ O ₂ /MoO ₄ ²⁻ ac	
	R ¹	R ²	R ³	X	<i>threo</i> - 2	<i>erythro</i> - 2	<i>threo</i> - 2	<i>erythro</i> - 2
1a	CH ₃	CH ₃	H	OH	94	6	85	15
1b	H	CH ₃	CH ₃	OH	88	12	86	14
1c	CH ₃	H	CH ₃	OH	61	39	50	50
1d	CH ₃	CH ₃	CH ₃	OH	94	6	78	22
1d^d	CH ₃	CH ₃	CH ₃	OH	80	20	-	-
1d^e	CH ₃	CH ₃	CH ₃	OH	79	21	-	-
1e	CH ₃	CH ₃	H	OAc	35	65	12	88
1f	CH ₃	CH ₃	H	OSiMe ₂ - <i>t</i> Bu	82	18	78	22

^a Product ratios were determined by ¹H NMR spectroscopy on the isolated reaction mixture; error is ±5% of the stated value. ^b CDCl₃, tetraphenylporphine (TPP). ^c The microemulsion is composed of CH₂Cl₂, D₂O, EtOH, and SDS in the proportions 74.8:6.2:9.5:9.5 (wt %). ^d Photooxygenation in the microemulsion with TPP as sensitizer. ^e Photooxygenation in the microemulsion with sodium tetraphenylporphine sulfonate (TPPS) as sensitizer. Conversion > 95%, and the yield of isolated products ranged between 65 and 93%.

Table 4. Solvent Effects on the Diastereoselectivity in the Photooxygenation of Mesitylyl (**1a**)

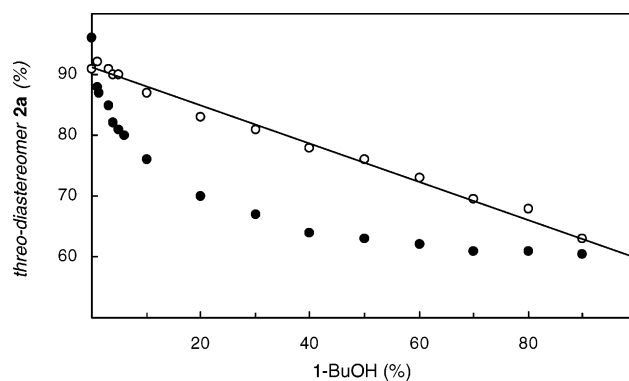
entry	solvent ^a		
		<i>threo</i> - 2a ^b	<i>erythro</i> - 2a ^b
1	CCl ₄ ^c	96	4
2	CDCl ₃ ^c	94	6
3	CH ₂ Cl ₂ ^c	91	9
4	EtOH ^d	59	41
5	PrOH ^d	59	41
6	BuOH ^d	59	41
7	H ₂ O ^d	80	20
8	D ₂ O ^d	78	22
9	CCl ₄ /H ₂ O (90/10) ^{c,e}	90	10
10	microemulsion ^{f,c}	78	22
11	microemulsion ^{f,g}	78	22

^a The conditions are given in Table S2 (see Supporting Information). ^b Determined by ¹H NMR spectroscopy on the isolated reaction mixture; error is ±5% of the stated value. ^c Tetraphenylporphine as sensitizer. ^d Methylene blue as sensitizer. ^e With and without sodium molybdate. ^f The microemulsion consisted of CH₂Cl₂, D₂O, EtOH, and SDS in the proportions 74.8:6.2:9.5:9.5 (wt %). ^g TPPS as sensitizer. Conversion > 95%.

of the allylic hydroperoxides **2**, as illustrated for mesitylyl (**1a**) in Scheme 1a. The observed *threo/erythro* ratios are given in Table 3 for both modes of peroxidation.

The photooxygenation of allylic alcohols **1a**, **1b**, and **1d**, which all bear a methyl substituent *cis* to the hydroxyethyl group, proceeded in high *threo* diastereoselectivity, whereas the allylic alcohol **1c** showed only a moderate *threo* preference. Compared to the chiral allylic alcohol **1a**, the corresponding silyl ether **1f** gave a lower diastereoselectivity in favor of the *threo*-configured hydroperoxide **2f**. In contrast, the opposite sense of stereocontrol was observed in the ene reaction of the allylic acetate **1e**, for which the *erythro*-configured hydroperoxide **2e** dominates.

The *threo/erythro* diastereoselectivities of the hydroperoxides **2a–f**, generated from the allylic substrates on chemical oxidation (Table 3), are similar for the substrates **1b** and **1f** (within

**Figure 1.** Dependence of the *threo* diastereoselectivity on the solvent composition in the photooxygenation of mesitylyl (**1a**) in CCl₄/*n*-BuOH (●) and CH₂Cl₂/*n*-BuOH (○) mixtures.

experimental error) to those observed in the photooxygenation, whereas for the allylic alcohols **1a**, **1c**, and **1d** the *threo*-configured hydroperoxides are produced in a lower diastereoselectivity. In the ene reaction of the allylic acetate **1e**, the opposite sense of stereochemical control is observed and the *erythro* selectivity is even more pronounced than that found in the photooxygenation.

Medium Effects on the Chemoselectivity and Diastereoselectivity. The photooxygenation of mesitylyl (**1a**) in various solvents afforded the corresponding allylic hydroperoxides **2a**, for which the *threo/erythro* ratio depends markedly on the solvent nature (Table 4).

In nonprotic solvents (entries 1–3), significantly higher *threo* selectivities were observed compared to protic ones (entries 4–8). Mechanistically significant, the diminution of the *threo* selectivity is more pronounced in the alcohols (entries 4–6) than in H₂O and D₂O (entries 7 and 8), although water is the most “protic” solvent of all. Clearly, the diastereoselectivity is not sensitive to the alkyl chain of the alcohol (entries 4–6), nor does it matter whether regular or deuterated water is used (entries 7 and 8).

The photooxygenation of mesitylyl (**1a**) in the solvent mixtures CCl₄/BuOH and CH₂Cl₂/BuOH gave *threo/erythro* ratios which are a sensitive function of the solvent composition, as displayed in Figure 1.

Table 5. Medium Effects on the Chemoselectivity and Diastereoselectivity in the Chemical Oxidation of Mesityl (1a) by the H₂O₂/MoO₄²⁻ Oxidant

entry	medium ^b	[1a] mol·kg ⁻¹	selectivity ^a		
			chemo 2:3	diastereo	
				threo-2:erythro-2	threo-3:erythro-3
1	D ₂ O	0.50	07:93	^c	85:15
2	CH ₃ OH	0.05	39:61	^c	^c
3	CCl ₄ /H ₂ O (90:10) ^d	0.05	07:93	^c	90:10
4	CCl ₄ /D ₂ O/EtOH/SDS	0.50	68:32	72:28	89:11
5	CCl ₄ /H ₂ O/BuOH/SDS	0.10	55:45	91:09	89:11
6	CH ₂ Cl ₂ /D ₂ O/EtOH/SDS	0.50	83:17	85:15	83:17
7	CH ₂ Cl ₂ /D ₂ O/EtOH/SDS	0.05	91:09	85:15	^c
8	CH ₂ Cl ₂ /D ₂ O/BuOH/SDS	0.50	79:21	83:17	91:09
9	CH ₂ Cl ₂ /D ₂ O/BuOH/SDS	0.05	97:03	87:13	^c
10	CH ₂ Cl ₂ /H ₂ O/BuOH/SDS	0.05	97:03	84:16	^c
11	CH ₂ Cl ₂ /D ₂ O/BuOH/SDS	0.10	92:08	92:08	^c

^a Product ratios determined by ¹H NMR spectroscopy on the isolated reaction mixture; error is ±5% of the stated value. ^b The microemulsion (entries 4–11) is composed of organic solvent, water, alcohol, and SDS in the proportions 74.8:6.2:9.5:9.5 (wt %). ^c The diastereoselectivity was not determined because an insufficient amount of product was isolated. ^d Vigorously stirred at 500 turns/min.

Table 6. Changes of the Chemoselectivity and Diastereoselectivity in the Photooxygenation (*hν*/O₂/Sensitizer) and Chemical Oxidation (H₂O₂/MoO₄²⁻) in Various Reaction Media

experimental parameter	chemoselectivity		diastereoselectivity ^a	
	2:3	table (entry)	threo/erythro	table (entry)
<i>hν</i> /O ₂ /sens → H ₂ O ₂ /MoO ₄ ²⁻	decrease	2 (1–4)	no effect	3 (4–6)
hydrophobicity of 1	increase	2 (1–4)	complex effect	3 (1–4)
concentration of 1	decrease	5 (8,9)	no effect	5 (8,9)
protic and polar environment	large decrease	5 (1,2,6)	large decrease	4 (1,8)
biphasic medium → microemulsion	large increase	5 (3,5)	^b	^b
H ₂ O → D ₂ O (microemulsion)	no effect	5 (9,10)	no effect	5 (9,10)
CCl ₄ → CH ₂ Cl ₂ (microemulsion)	large increase	5 (4,6)	increase	5 (4,6)
EtOH → BuOH (microemulsion)	no effect	5 (6,8 and 7,9)	no effect	5 (6,8 and 7,9)

^a For the hydroperoxides. ^b The diastereoselectivity of the hydroperoxides in the biphasic medium could not be determined because an insufficient amount of product was isolated.

In both pure CCl₄ and CH₂Cl₂, mainly the *threo*-configured hydroperoxide of mesityl (1a) is produced, but increasing the amounts of butanol lowers the diastereoselectivity significantly. Moreover, a high (*threo/erythro* ratio of 90:10) diastereoselectivity is observed for the photooxygenation of substrate **1a** in a stirred biphasic 90:10 CCl₄/H₂O (entry 9) mixture with or without sodium molybdate.

The chemical oxidation of mesityl (1a) by H₂O₂/MoO₄²⁻ in various reaction media afforded a mixture of the hydroperoxy allylic alcohol **2a** and the epoxide **3a** (Scheme 1b). The observed product ratios are given in Table 5.

In neat D₂O, in methanol, or in the biphasic CCl₄/H₂O (90:10) medium (entries 1–3), mesityl (1a) leads mainly to the undesirable epoxide **3a** in a high *threo* diastereoselectivity. On the contrary, in the CH₂Cl₂ microemulsion (entries 6–11), the allylic alcohols **1a** gave mainly the desirable hydroperoxide **2a**, but also in high *threo* selectivity. Yet, in the CCl₄ microemulsion (entries 4 and 5), epoxide formation competed more significantly with the hydroperoxidation; both products were obtained preferably in *threo* diastereoselectivity. It is also noteworthy that BuOH and EtOH provided similar results in terms of chemoselectivity and diastereoselectivity (entries 6 and 8). This was also observed when H₂O was replaced by D₂O (entries 9 and 10); however, an increase of the substrate concentration led to a lower chemoselectivity but similar diastereoselectivity (entries 6 versus 7, 8 versus 9).

For convenience, an overview of the mechanistically and preparatively important effects on the chemoselectivities and the diastereoselectivities are summarized in Table 6. These have

been caused by changing a variety of experimental reaction parameters during the oxidation of the model allylic alcohol **1**.

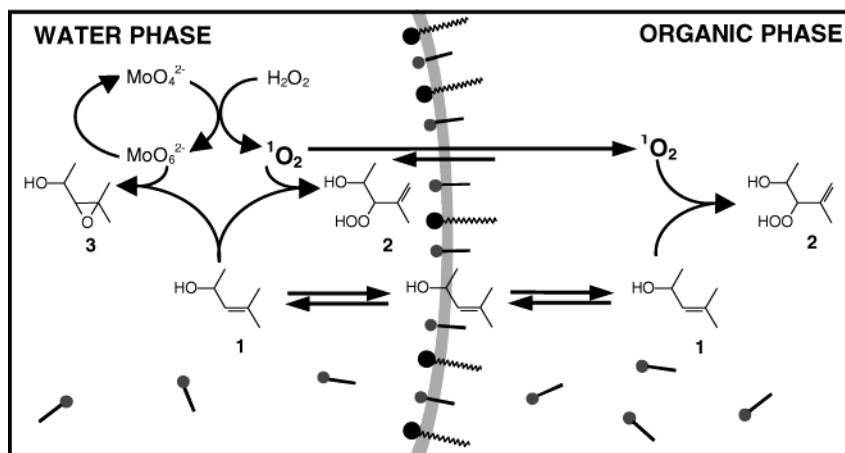
Discussion

The aspects we shall address and compare for the photo-sensitized and chemical oxidation of the chiral allylic alcohols **1** (Scheme 1) concern *reactivity*, *chemoselectivity*, and *diastereoselectivity*. In particular, we shall examine *substituent* and *medium* effects and point out advantages and disadvantages of these two modes of singlet-oxygen generation in regard to preparative-scale applications.

Before entering into the mechanistic rationalization of the present data on the reactivity, chemoselectivity, and diastereoselectivity, it is instructive to emphasize the complexities of the composition and dynamics that a microemulsion presents (Scheme 2).

For this purpose, the various constituents of the microemulsion in the three possible *locales*, namely the aqueous phase, the interfacial boundary, and the organic phase may be viewed in the form of a cartoon. As may be appreciated from this scheme, the hydrophilic species (H₂O₂, MoO₄²⁻, and the peroxomolybdates) are confined in the aqueous droplets, whereas the amphiphilic components (SDS, *n*-BuOH or EtOH, the allylic alcohol **1**, the hydroperoxide product **2**, and the epoxide product **3**) are distributed in the interfacial boundary between the aqueous and organic phases and in the latter phases. The interfacial boundary may be considered as a pseudo-phase, constituted of amphiphilic compounds in equilibrium between the aqueous and the organic phases.

Scheme 2. Localization of Reactants, Substrates, and Oxidation Products in the Aqueous Microdomain, in the Organic Continuous Phase, and at the Interface of the Microemulsion; for Sakes of Clarity, the Configurations of the Two Diastereoisomers Are Not Shown



The relative amount of these materials in these distinct locales depends, of course, on their hydrophobicities and amphiphilicities. For sakes of clarity, in Scheme 2 only the transport of the substrate **1** and $^1\text{O}_2$ across the interfacial boundary into the water and organic phases is portrayed in the form of equilibrium arrows because evidently the whereabouts of these two reacting components of the microemulsion will be relevant for the mechanistic rationalization of the results.

As becomes conspicuous from Scheme 2, the allylic alcohol **1** is distributed over all three possible locales, namely the water phase, the interfacial boundary, and the organic phase. In contrast, like ordinary molecular oxygen ($^3\text{O}_2$), $^1\text{O}_2$ is both hydrophilic and lipophilic but not amphiphilic; consequently, this small and uncharged molecule diffuses freely through the charged interfacial boundary and mainly resides in the water and organic regions. Since the typical size of a microdroplet (ca. 10 nm) is much smaller than the mean travel distance of $^1\text{O}_2$ in water (ca. 200 nm), a snapshot will show $^1\text{O}_2$ to be concentrated in the water and organic phases. Moreover, previous flash-photolysis studies have disclosed that an equilibrium is established for $^1\text{O}_2$ between the water and organic phases of a CH_2Cl_2 -based microemulsion; the local $^1\text{O}_2$ concentration in the organic phase was determined to be about 4.2 times higher than that in the aqueous droplets.^{11a}

Substituent Effects. In concordance with the general paradigm of substituent effects in electrophilic oxidations, the reactivity of the allylic alcohols **1a–d** toward $^1\text{O}_2$ increases as the number of electron-releasing methyl groups on the allylic double bond increases, as confirmed by the rate data in Table 1 for the photooxygenation. Qualitatively, this trend applies irrespective of whether the singlet oxygen is generated by photosensitization in solvents or by chemical generation ($\text{H}_2\text{O}_2/\text{MoO}_4^{2-}$) in microemulsions.

The chemical oxidation of the allylic alcohols **1** by the $\text{H}_2\text{O}_2/\text{MoO}_4^{2-}$ system was found to be more intricate than the photochemical one: Besides the desirable peroxidation through the ene reaction with $^1\text{O}_2$ (the major process), in the chemical mode the undesirable epoxidation also takes place, as indicated in Scheme 1b for mesityllole (**1a**). This chemoselectivity, measured in terms of the hydroperoxide **2**/epoxide **3** ratio, also varies with the degree and pattern of methyl substitution on the double bond (Table 2), but to a lesser extent than the reactivity data in Table 1. The observed trend in the **2**:**3** ratio,

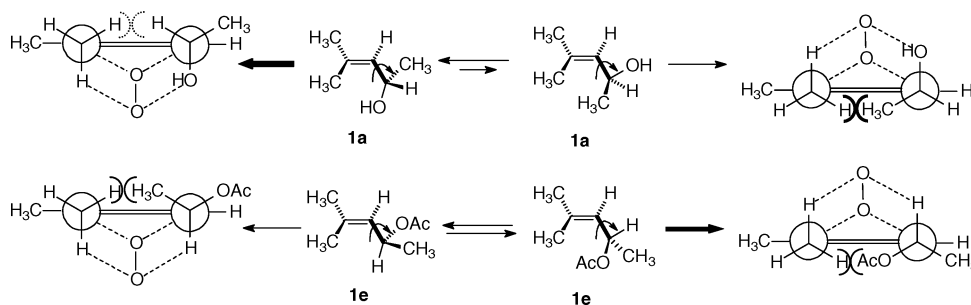
i.e., **1a** < **1b,c** < **1d**, may be accounted for by the synergistic interplay between the reactivity of the substrate **1** toward $^1\text{O}_2$ and its hydrophobicity. Actually, the allylic alcohols **1** are small lipophilic molecules with only a moderate hydrophilicity due to the hydroxy functionality; hence, these quite hydrophobic substrates are mainly located in the organic phase of the microemulsion, but appreciable amounts are also present in the aqueous phase as well as at the interfacial boundary. Consequently, when their hydrophobicity is enhanced by increasing the number of methyl groups on the allylic double bond, the amount of the substrate **1** in the aqueous phase will also decrease, which favors peroxidation by $^1\text{O}_2$, i.e., **1d** > **1a–c** (Table 6, entry 2).

In regard to the substituent effects on the diastereoselectivity in the oxidation of allylic alcohols **1**, it is the pattern rather than the extent of methylation of the double bond that is decisive. Both in the peroxidation as well as epoxidation, a relatively high *threo* diastereoselectivity is observed for the chiral substrates **1** (Tables 3 and 5). The preferred formation of the *threo* oxidation products is the consequence of the *hydroxy-group directivity*,^{18–21,25a,25b} in which the two diastereotopic faces in the chiral allylic alcohol **1** are differentiated on account of the 1,3-allylic ($A^{1,3}$) strain during the attack of the oxidant. Conformational effects in the substrate are responsible, as portrayed for the reaction of $^1\text{O}_2$ with mesityllole (**1a**) in Scheme 3.

Analogously, the photooxygenation of the allylic alcohols **1b** and **1d** with a methyl group *cis* to the hydroxy functionality proceeds with *threo* selectivity on account of $A^{1,3}$ strain.^{16,22} The absence of a methyl group *cis* to the hydroxy-bearing substituent in the derivative **1c** signifies little $A^{1,3}$ strain and, consequently, a substantially lower diastereoselectivity is observed (Table 3, entry 3). Furthermore, the presence of an additional methyl group next to the hydroxy-bearing substituent, which exerts 1,2-allylic ($A^{1,2}$) strain, causes only a minor effect on the *threo* diastereoselectivity (Table 3, entry 4).

Protection of the hydroxy functionality by an electron donor (silyl ether **1f**) leads to a substantial drop in the π -facial *threo* selectivity compared to the parent allylic alcohol **1a** (Table 3, entries 1 and 6). This derivative lacks the efficacy of hydrogen bonding between the allylic hydroxy functionality and the oxidant; nevertheless, the preference for the *threo* diastereomer implies some, but less effective, association of the $^1\text{O}_2$ with the

Scheme 3. Diastereoselective Control in the Photooxygenation of the Allylic Alcohol **1a** [Hydroxy-Group Directivity (ref 25a,b)] and Its Acetate **1e** [*cis* Effect (ref 25c)]



oxygenophilic silyl functionality.^{16,25} Additionally, probably steric hindrance by the silyl group impedes the approach of the $^1\text{O}_2$ so that the *cis* effect^{16,25} competes and reduces the *threo* selectivity. In the case of the acetate **1e** with an electron acceptor (Table 3, entry 5), despite the fact that this substrate possesses an $\text{A}^{1,3}$ strain, a low preference for the *erythro* product is expressed in its photooxygenation. This may be rationalized in terms of combined steric and electrostatic repulsion by the OAc functionality on the incoming dioxygen molecule; hence, the peroxidation is governed by the *cis* effect.

In regard to substituent effects on the diastereoselectivity of the peroxidation by the chemically generated $^1\text{O}_2$ in microemulsions (Table 3), we observe the same sense, namely *threo* stereoselectivity, but a systematic drop in the efficacy of control. Evidently, this difference between the photooxygenation (Table 4) and chemical peroxidation (Table 5) arises from medium effects, as shall be divulged in the following subsection.

Medium Effects. For a meaningful comparison of the medium effects on the selectivity of the photooxygenation and the chemical oxidation, the model substrate, namely mesitylrol (**1a**), was photooxygenated (Table 4) as well as chemically oxidized (Table 5) in a variety of corresponding media. The solvents for the photooxygenation were selected to take proper account of the constituents in the microemulsions used for the chemical oxidation, i.e., CCl_4 versus CH_2Cl_2 , EtOH versus BuOH, and H_2O versus D_2O .

The fact that the allylic hydroxy functionality of the substrate **1a** is directly involved in the control of the diastereoselectivity is inferred from its solvent dependence (Table 4). In aprotic solvents (CCl_4 , CDCl_3 , CH_2Cl_2), the photooxygenation proceeds in a high *threo* diastereoselectivity, whereas a significant drop is found in alcohols (EtOH, PrOH, BuOH). The reason for this is the competitive hydrogen bonding of the allylic hydroxy functionality with the alcoholic solvent, rather than with the attacking singlet oxygen, which results in the observed decrease of the *threo* diastereoselectivity. Surprisingly, the diastereoselectivity is higher in water than in alcohols despite the strong hydrogen-bonding ability of this solvent. This unexpected result may be rationalized in terms of the amphiphilic nature of the allylic alcohol **1a** on account of its hydrophobic C_5 chain. The hydrophobic portion of the substrate molecule minimizes its contact with water, which induces aggregation or possibly even micelle formation.²⁶ Although the $^1\text{O}_2$ is generated in the aqueous phase, it diffuses into the hydrophobic core of the O/W

micelles to react with the double bond; such unpolar environment favors *threo* selectivity.

When mesitylrol (**1a**) is photooxygenated in mixtures of CCl_4 /BuOH or CH_2Cl_2 /BuOH of varying proportions, the increase of the amount of butanol leads to a significant decrease in *threo* diastereoselectivity (Figure 1). In the case of CH_2Cl_2 , a smooth linear variation is observed, whereas, in CCl_4 , the diastereoselectivity diminishes first sharply and then remains almost constant. Thus, when 10% of BuOH is added to these chlorinated solvents, a 4% and a 20% decrease of the diastereoselectivity is observed for CH_2Cl_2 and CCl_4 . This differing behavior may be explained in terms of the Hildebrand solubility parameter δ_{H} ,²⁷ which is $20.3 \text{ MPa}^{0.5}$ for CH_2Cl_2 and $23.1 \text{ MPa}^{0.5}$ for BuOH. We suggest that for the substrate **1a** this parameter must be close to that of hexanol ($\delta_{\text{H}} \approx 21.5 \text{ MPa}^{0.5}$).^{27b} Consequently, the similar δ_{H} values of the three components CH_2Cl_2 , BuOH, and **1a** in the microemulsion suggest a strong affinity for each other, such that their molecules are effectively randomly distributed as a nearly ideal mixture. In contrast, the δ_{H} value of CCl_4 is only $17.8 \text{ MPa}^{0.5}$ and, therefore, quite different from that of BuOH and the substrate **1a**. On the macroscopic scale, a mixture of **1a** in CCl_4 /BuOH appears perfectly homogeneous, but on the microscopic scale, the substrate **1a** is preferentially surrounded by BuOH rather than by CCl_4 molecules; thus, a proportionally lower *threo* selectivity is expected for such a BuOH environment, as verified by the data in Figure 1.

The nature of the medium is a key factor in the type of chemoselectivity observed for the $\text{H}_2\text{O}_2/\text{MoO}_4^{2-}$ system, as illustrated for mesitylrol (**1a**) in Table 5. In water (entry 1), mesitylrol (**1a**) affords mainly the epoxide **3a**. Also in methanol, a solvent particularly well-suited for the preparative oxidation of the allylic alcohols **1**, since large amounts of the substrate may be solubilized, the epoxidation mode dominates (entry 2). This chemoselectivity is quite unexpected, since it has been recently shown that even hydrophilic organic substrates may be efficiently peroxidized in methanol by the $\text{H}_2\text{O}_2/\text{MoO}_4^{2-}$ system, provided that the $\text{H}_2\text{O}_2/\text{Mo}$ ratio is about 3.5.^{9e} To rationalize this unusual result, it should be recalled that the $\text{H}_2\text{O}_2/\text{MoO}_4^{2-}$ system is well-known to be also an efficient epoxidizing agent.^{28–37} In view of the fact that sodium tiglolate (no allylic

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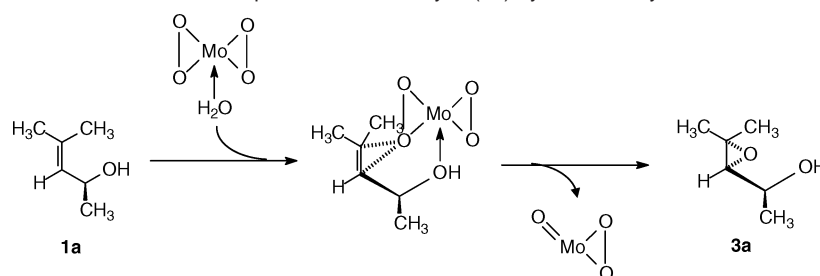
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Scheme 4. Template Effect in the *Threo*-Selective Epoxidation of Mesitylyl (**1a**) by Peroxomolybdates

hydroxy functionality) is not epoxidized under these conditions,^{10a} we speculate that a direct interaction between the hydroxy group of the allylic alcohols **1** and the peroxomolybdates occurs. Presumably, the substrate **1a** binds through its hydroxy functionality to the molybdenum center and experiences subsequently epoxidation (Scheme 4).

Indeed, in such an aggregate, the double bond of the allylic substrate **1** is quite close to one of the peroxo bridges of the molybdate and expected to be readily epoxidized. Such a template effect would also account for the preferred *threo* selectivity (dominance of A^{1,3} strain) in this epoxidation.

In a heterogeneous aqueous medium, however, the allylic alcohols **1** should be efficiently peroxidized rather than epoxidized by the H₂O₂/MoO₄²⁻ system, since these moderately hydrophilic substrates mainly populate the organic phase. Contrary to this expectation, predominantly the epoxide **3a** is formed in the oxidation of mesitylyl (**1a**) under biphasic aqueous conditions (Table 5, entry 3). This may be rationalized by the fact that in the aqueous phase, the intermediary peroxomolybdate may either epoxidize the substrate or decompose into singlet oxygen. Since most of the generated ¹O₂ is wasted in the aqueous phase through quenching by water molecules (the mean travel distance of ¹O₂ in water is only about 200 nm), epoxidation prevails in the aqueous phase (Table 6, entry 5).

Consequently, microemulsions are the more appropriate reaction media to carry out the peroxidation of the allylic alcohols **1** by the ¹O₂, chemically generated from H₂O₂/MoO₄²⁻, irrespective of the degree and pattern of the double-bond methylation (Table 2). The reason for this is that the substrate and the oxidant are compartmentalized in such a microheterogeneous medium (Φ_{aq} ca. 10 nm) and cannot directly react with one another; hence, the intermediary peroxomolybdate may freely decompose into ¹O₂ to perform peroxidation rather than engage in epoxidation of the substrate.

The **2a:3a** ratio of the oxidation in the microemulsion depends not only on the nature of the medium but also on the concentration of the allylic alcohol **1a**; both experimental variables play a decisive role in the control of chemoselectivity, as displayed by the data in Table 5. The observed trend may be

readily explained by examining the substrate amount in the aqueous phase, where the ionic epoxidizing peroxomolybdates are located. Thus, the concentration of **1a** is maximal in pure water, whereas, in the CCl₄ and CH₂Cl₂ microemulsions, the proportion of substrate **1a** in the aqueous phase is lower; the amount may be estimated from the independently determined equilibrium constant $K = [\mathbf{1a}]_{\text{org}}/[\mathbf{1a}]_{\text{aq}}$ {K(CCl₄) = 2.4 and K(CH₂Cl₂) = 6.4} to be 7% and 2%. Expectedly, the extent of peroxidation increases in the order D₂O < CCl₄ (microemulsion) < CH₂Cl₂ (microemulsion), as confirmed by the chemoselectivity ratio **2a:3a** in Table 5 (entries 1, 4, and 6). In the same manner, an increase of the amount of substrate **1a** causes its concentration in the aqueous phase to be larger, which favors epoxidation (Table 5, entries 6 and 7).

Furthermore, when the H₂O is replaced by D₂O in the CH₂Cl₂ microemulsion (Table 5, entries 10 and 11), the **2a:3a** ratio stays constant within the experimental error. Clearly, since the lifetime of ¹O₂ is ca. 15 times longer in D₂O than in H₂O, the quenching of ¹O₂ by water is not the kinetically determining step under our experimental conditions (Table 5). The reason for this is, of course, that ¹O₂ habitates mainly in the organic phase; the distribution constant $K_{\text{dis}} = [^1\text{O}_2]_{\text{aq}}/[^1\text{O}_2]_{\text{org}}$ is 0.24.^{11a}

Finally, to account for no epoxidation in the chemical oxidation of substrate **1d** (Table 2, entry 4), we propose that the combined high hydrophobicity of the allylic alcohol **1d** and its high reactivity toward ¹O₂ are responsible, since a low amount of this substrate will be located in the aqueous phase for epoxidation by the peroxomolybdate, such that peroxidation in the interfacial boundary and in the organic phase prevail (Scheme 2).

In regard to the diastereoselectivity of the two oxidation modes of the model substrate **1a** in the microemulsion, we notice that in the peroxidation as well as in the epoxidation the *threo* selectivity dominates (Table 5). As already stated above, the peroxidation of the substrate by ¹O₂ occurs in the organic phase (CCl₄ or CH₂Cl₂), and thus, a similar diastereoselectivity is expected for the chemical oxidation in the microemulsion as that for the photooxygenation in the corresponding neat solvents (Table 4). Evidently, the *threo/erythro* ratio depends on the medium; thus, it is about 95:5 for CCl₄ and 90:10 for CH₂Cl₂, but only about 60:40 for ROH and 80:20 for H₂O. In contrast, in the microemulsion, the diastereoselectivity is always lower than in the neat organic solvent because of the presence of some butanol (or ethanol) in all three locales (water and organic phases, and interfacial boundary) of the microemulsion (see Table 4 and Figure 1), which reduces the efficacy of the hydroxy-group directivity. Consequently, the *threo* preference should be intermediate between that obtained in the organic and aqueous media. Indeed, as Figure 1 shows, a small amount of

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BuOH in CH_2Cl_2 or in CCl_4 decreases notably the diastereoselectivity of the $^1\text{O}_2$ ene reaction. This behavior was additionally confirmed by photooxygenating the substrates **1a** (Table 4 entries 10 and 11) and **1d** (Table 3) directly in the microemulsion. As anticipated, in both cases we observe a decrease in the *threo* diastereoselectivity.

The high chemoselectivity of **1d** is explained by its hydrophobicity on account of which the derivative **1d** is virtually absent from the aqueous phase. As a consequence, no epoxide is observed, since the epoxidation takes place only in the water microdroplets. In contrast, substrate **1d**, like the other allylic alcohols **1a–c**, is an amphiphilic molecule and, thus, will be located as a cosurfactant in the organic phase as well as at the interfacial boundary (see Scheme 2). In the latter locale, the *threo* diastereoselectivity should decrease, since the interfacial boundary is a highly polar environment (constituted of SDS and alcohol) and should reduce the efficacy of the hydroxy-group directivity. Indeed, as experimentally confirmed in Table 4, such media lead to the lowest *threo* diastereoselectivities in the photooxygenation.

Finally, compared to the other derivative **1a–c**, the allylic alcohol **1d** has the lowest *threo* diastereoselectivity, which may be explained in terms of its higher $^1\text{O}_2$ reactivity (see Table 1). Since the **1d** derivative is about 100 times more reactive toward $^1\text{O}_2$ than the model substrate **1a**, the former scavenges almost all of the available $^1\text{O}_2$ molecules, when they cross the interfacial boundary; nearly all the peroxidation of **1d** takes place at the interfacial boundary. In contrast, for the less reactive substrates **1a–c**, most of the $^1\text{O}_2$ molecules reach the less polar organic phase and react in a higher *threo* diastereoselectivity.

Conclusion

The present results demonstrate that the $\text{H}_2\text{O}_2/\text{MoO}_4^{2-}$ system in suitably formulated microemulsions constitutes a convenient

alternative to the usually employed method of generating $^1\text{O}_2$, namely photosensitization. This chemical mode of singlet-oxygen generation may be readily conducted at the preparative scale and the oxidation performed in short reaction times, without the need of photochemical equipment. The use of EtOH instead of BuOH as cosurfactant facilitates the workup and isolation of the oxidation product. When applied to the labile chiral allylic alcohols **1** as substrates, a high chemoselectivity (up to 97%) and diastereoselectivity (up to 92% *threo* preference) may be achieved. In regard to the latter, the *threo* π -facial control is subject to the *hydroxy-group* directivity,²⁵ in which the $A^{1,3}$ strain of the allylic substrate and hydrogen bonding between the allylic hydroxy functionality and the attacking singlet oxygen play the decisive role. A chemoselectivity in favor of the desirable peroxidation by singlet oxygen versus the undesirable epoxidation by the intermediary peroxomolybdate may be obtained through the proper choice of the microemulsion to attain the necessary hydrophobic conditions for the oxidation. This is acquired by selecting an organic solvent which is not miscible with water but possesses a strong affinity for organic substances (CH_2Cl_2 is particularly well suited) and by employing BuOH as cosurfactant, which minimizes the substrate concentration in the aqueous phase.

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Supporting Information Available: Experimental procedures and Tables S1–S3 (4 pages, print/PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>. JA048589F