Efficient Control of the Diastereoselectivity and Regioselectivity in the Singlet-Oxygen Ene Reaction of Chiral Oxazolidine-Substituted Alkenes by a Remote Urea NH Functionality: Comparison with Dimethyldioxirane and *m*-Chloroperbenzoic Acid Epoxidations

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Abstract: The singlet-oxygen ene reaction and the epoxidation by DMD of chiral oxazolidine-substituted alkenes, equipped with a free urea NH functionality and a conformationally fixed double bond, proceed in high *like* diastereoselectivity (up to >95:5); also a high regioselectivity was found for the $^1O_2$ ene reaction. Capping of the free NH functionality by methylation erases this *like* selectivity for both oxidants and significantly reduces the regioselectivity in the ene reaction. These data demonstrate effective hydrogen bonding between the remote urea NH functionality and the oxidant that favors the *like* attack on the C−C double bond. For $^1O_2$, the hydrogen bonding in the exciplex results in preferred hydrogen abstraction from the alkyl group cis to the directing urea functionality.

Introduction

The ene reaction of singlet oxygen ($^1O_2$) with alkenes constitutes a convenient route to allylic hydroperoxides and, after reduction, allylic alcohols; the latter are versatile building blocks with synthetic utility.[1] Much effort has been expended to achieve control of the regio- as well as the diastereoselectivity for such oxyfunctionalizations.[2]

The regioselectivity of the $^1O_2$ ene reaction, that is, the site of hydrogen abstraction, is governed by several empirical facts: The so-called *cis effect*[3] predicts that hydrogen abstraction occurs predominantly from the higher substituted side of the double bond. In contrast, the *gem effect*[4] and *large-group nonbonding effect*[5] entail predominant abstraction at the *geminal* position, promoted by electron-withdrawing and bulky substituents.

In regard to the diastereoselectivity, singlet oxygen as a linear two-atomic molecule cannot itself transmit steric effects, so that diastereoselection may only arise through substrate control. In this context, the directing propensity of allylic hydroxy[6] and amino[7] groups has recently received much attention, and high stereocontrol was achieved through the advent of beneficial hydrogen bonding between the conformationally aligned allylic functionality and the singlet-oxygen enophile. However, as indicated by the low diastereoselectivities obtained in the photooxygenations of chiral homoallylic alcohols,[8] it is essential that the directing hydrogen-bonding functionality is positioned in the proximate neighborhood of the double bond and fixed on one π face of the C−C double bond by conformational constraint.

Similar directing effects were also found to operate in the epoxidations of olefins by dimethyldioxirane (DMD)[9] and *m*-chloroperbenzoic acid (*m*CPBA).[10] Thus, allylic hydrogen-bonding donors such as the hydroxy and amino groups, which are favorably aligned by allylic strain, may steer the incoming

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Table 1: Diastereo- and Regioselectivity in the Photooxygenation[a] of Oxazolidine-Substituted Olefins **1** (cf. Scheme 2)

								regioselectivity[b]				diastereoselectivities[b]								
entry		R^1	R^2	R^3	R^4	Ar	solvent	**2**		**2′**	**2″**	**3**	*lk*-**2**:	:	*ul*-**2**	*lk*-**2′**	:	*ul*-**2′**	*lk*-**2″**	:	*ul*-**2″**
1	**1a**	Me	Me	H	H	Ph	$CDCl_3$		93[c]		–	7				94:6[c]					–	
2[d]	**1a**	Me	Me	H	H	Ph	$CDCOCD_3$		96[c]		–	4				85:15[c]					–	
3	**1b**	Me	Me	H	H	*p*-NO_2[e]	$CDCl_3$		>95[c]		–	<5				>95:5[c]					–	
4	**1c**	Me	Me	H	Me	Ph	$CDCl_3$		70[c]		–	30				41:59[c]					–	
5[f]	**1d**	Et	H	H	H	Ph	$CDCl_3$	>95		–	–	<5	>95[g]	:	5						–	
6	**1e**	H	Me	Me	H	Ph	$CDCl_3$	–		31	69	<5		–		53	:	47	52	:	48	
7	*E*-**1f**	Me	Et	H	H	Ph	$CDCl_3$	92		8	–	<5	>95	:	5		*h*				–	
8	*Z*-**1f**	Et	Me	H	H	Ph	$CDCl_3$	12		76	–	12		*h*		>95[i]	:	5			–	

[a] Sensitizer was 5,10,15,20-tetrakis(pentafluorophenyl)porphine (TPFPP), the reactions were conducted at −10 °C; unless otherwise stated, conversion and mass balance were >90%. [b] Determined by ^1H NMR spectroscopy, error ±5% of the stated values. [c] Differentiation between the products **2** and **2′** is not possible when $R^1 = R^2$=Me, because these products are identical. [d] Mass balance was only 74%. [e] *p*-Nitrophenyl. [f] Conversion was 47%. [g] The newly formed double bond is *E*-configured. [h] Not determined due to small amounts. [i] The *E*/*Z* ratio of the newly formed double bond was 86:14.

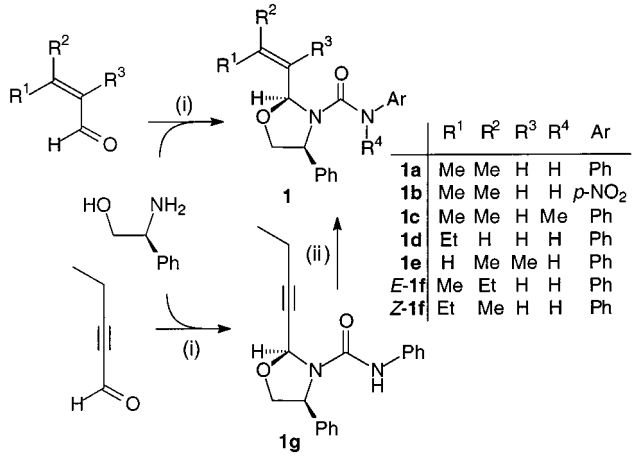
oxidant through hydrogen bonding. Nevertheless, only a few examples of the remote directing group are known for selective epoxidations. The observed diastereoselectivity for homoallylic alcohols is significantly lower than for allylic substituents due to the less efficient alignment of the directing hydrogen-bonding entity.[7c,8a,10h,11]

Recently, we reported that alkenyl-substituted oxazolidines, similar to those that have been used as chiral auxiliaries,[12,13] undergo highly diastereoselective singlet-oxygen ene reaction[14] as well as epoxidations by *m*CPBA and DMD.[15] The controlling feature derives from a remotely positioned urea NH functionality, which provides beneficial hydrogen bonding with the oxidant. In the present contribution, we supply the full synthetic and mechanistic details on this new remotely directed diastereocontrol and demonstrate that the regioselectivity of the $^1O_2$ ene reaction is also governed by the hydrogen-bonding directing group of the oxazolidine.

Results

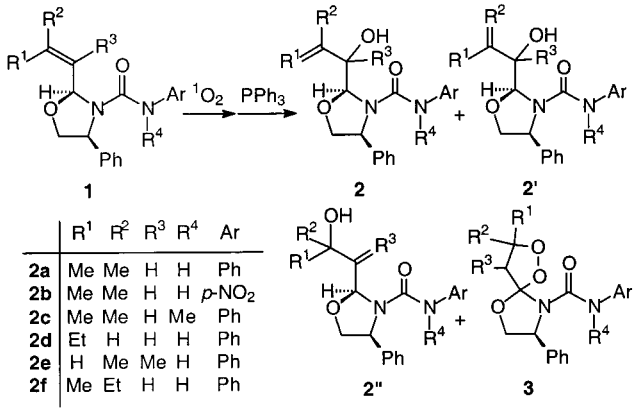
The oxazolidine-substituted alkenes **1a**, **b**, **e**, **f** were synthesized by the condensation of the corresponding aldehyde with *S*-phenylglycinol in analogy to the reported procedure,[12g] followed by reaction with the appropriate aryl isocyanate (Scheme 1).[16] The *cis*-disubstituted olefin **1d** was obtained by partial catalytic hydrogenation of the alkyne **1g**, which was synthesized from 2-pentynal, *S*-phenylglycinol, and phenylisocyanate (Scheme 1). Methylation of the urea functionality in the oxazolidine **1a** yielded the *N*-methylated derivative **1c**. The *like* relative configuration of the stereogenic centers of the oxazolidine ring was assessed for all cases by NOE measurements.

Scheme 1[a]



[a] (i) 1. Molecular sieves (4 Å), CH_2Cl_2, 20 °C, 3 h. 2. ArNCO (see Table 1), CH_2Cl_2, 20 °C, 16 h. (ii) H_2, Lindlar catalyst, MeOH, 20 °C, 3 h.

Scheme 2



The oxazolidines **1** were photooxygenated at low temperature, and the resulting hydroperoxides **6** were reduced in situ, usually after complete conversion of the starting material. The reaction sequence afforded the corresponding regioisomeric allylic alcohols **2**, **2′**, and **2″** and, in some cases, the *spiro*-dioxolanes **3** (Scheme 2). The product distribution and the diastereomeric ratios of the allylic alcohols were determined from the crude reaction mixture by ^1H NMR spectroscopy and are given in Table 1. In the case of the substrates **1a**, **b**, **d** and *E*-and *Z*-**1f**, the allylic alcohols **2** were formed in high *like* diastereoselectivity and good yields in the nonpolar chloroform (entries 1, 3, 5, 7, 8). The diastereoselectivity depends strongly on the reaction medium, as demonstrated by the significantly lower selectivity

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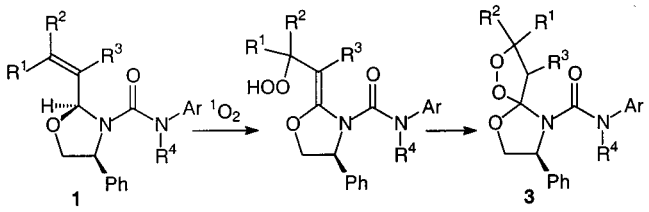
Scheme 3



Scheme 4

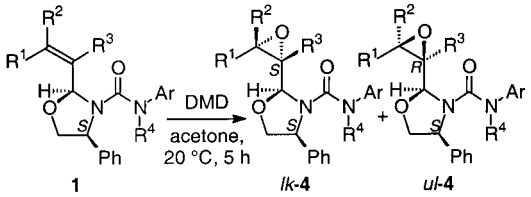


Table 2: Diastereoselectivities in the DMD Epoxidation of Oxazolidine-Substituted Olefins **1** (cf. Scheme 4)[a]

							diastereoselectivity[b]		
entry		R^1	R^2	R^3	R^4	Ar	*lk*-**4**	:	*ul*-**4**
1	**1a**	Me	Me	H	H	Ph	>95	:	5
2	**1b**	Me	Me	H	H	*p*-NO_2[c]	>95	:	5
3	**1c**	Me	Me	H	Me	Ph	26	:	74
4	**1d**	Et	H	H	H	Ph	>95	:	5
5	**1e**	H	Me	Me	H	Ph	74	:	26
6	*E*-**1f**	Me	Et	H	H	Ph	>95	:	5
7	*Z*-**1f**	Et	Me	H	H	Ph	>95	:	5

[a] Conversion and mass balance were >90%. [b] Determined by ^{1}H NMR spectroscopy, error ±5% of the stated values. [c] *p*-Nitrophenyl.

of the photooxygenation of the olefin **1a** in the polar acetone. Furthermore, the diastereoselectivity is dramatically reduced for the olefin **1e** that bears no abstractable allylic hydrogen atom positioned cis to the oxazolidine moiety (entry 6). A slight *unlike* preference was found for the *N*-methylated olefin **1c**.

Besides the high diastereoselectivity in the photooxygenation of olefins **1**, the site of hydrogen abstraction (regioselectivity) is also usually well defined. In the ene reaction of olefins **1a**, **b**, **d**, **e** and *E*- and *Z*-**1f**, hydrogen abstraction occurs predominantly from one of the methyl groups and only a small amount from the aminal position. The hydroperoxides derived from the latter H abstraction mode cyclize in situ to the dioxolanes **3** (Scheme 3). Here, the *N*-methylated derivative **1c** exhibits again a lower selectivity; as much as 30% of the dioxolanes **3c** was found in the reaction mixture (entry 4). For the isomeric olefins *E*- and *Z*-**1f**, the ene reactivity of the two geminal alkyl groups of the double bond (*twix* versus *twin* reactivity[17]) differs; the abstraction occurs in both cases predominantly at the *twix* alkyl group, that is, the one located cis to the *lone* oxazolidine substituent (entries 7 and 8).

The olefins **1** were epoxidized with dimethyldioxirane (DMD) to yield the corresponding epoxides **4** (Scheme 4). The diastereomeric ratios of the epoxides were determined by ^{1}H NMR spectroscopy from the crude product mixture and are given in Table 2. The epoxidations of the olefins **1a**, **b**, **d**, and *E*- and *Z*-**1f** proceeded highly *like* diastereoselectively; not even traces of the *unlike* diastereomer could be detected in the spectra (entries 1, 2, 4, 6, 7). The reaction of the *cis*-dimethyl-substituted olefin **1e** is less selective, but still a significant *like* preference was observed (entry 5). In contrast, the epoxidation

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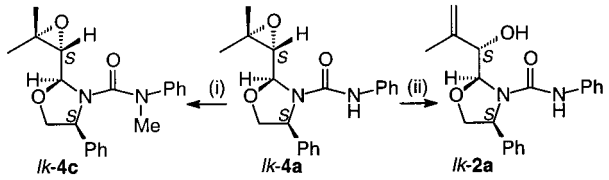
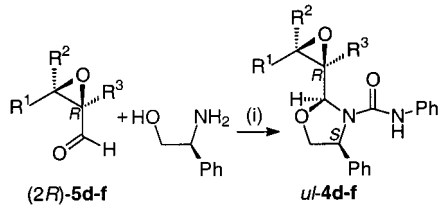
Scheme 5[a]



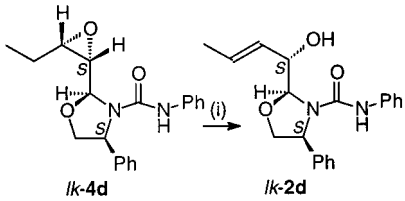
[a] (i) MeI, KOH, DMSO, 20 °C, 16 h. (ii) Activated Al_2O_3, *n*-hexane, 20 °C, 16 h.

Scheme 6[a]



[a] (i) 1. K_2CO_3, $CDCl_3$, 20 °C, 2 h. 2. PhNCO, $CDCl_3$, 20 °C, 3 h.

Scheme 7[a]



[a] (i) Activated Al_2O_3, *n*-hexane, 20 °C, 16 h.

of the *N*-methylated derivative **1c** afforded mainly the *unlike* epoxide *ul*-**4c**.

Also the epoxidation of the olefins **1a**−**c**, **e** by *m*-chloroperbenzoic acid (*m*CPBA) shows the same trend in diastereoselectivity as DMD. Thus, *like* selectivity for **1a**, **b**, **e** and *unlike* for **1c** are observed, but these diastereoselectivities are lower than the ones found for the corresponding DMD epoxidations. These results[15] are given in the Supporting Information section.

Configurational Assignments

To assess the relative configuration of the allylic alcohol *lk*-**2a**, single crystals were grown and submitted to X-ray analysis (cf. Figure 1 in the Supporting Information).[18] The *like* configuration of the corresponding epoxide *lk*-**4a** was established by base-catalyzed rearrangement to *lk*-**2a** (Scheme 5).[19] Furthermore, epoxide *lk*-**4a** was methylated to yield the epoxide *lk*-**4c** (Scheme 5), and thus, also its relative *like* configuration was established. The epoxides **4d**, **e**, and *E*-**4f** were synthesized independently as epimeric mixtures from the corresponding racemic epoxy aldehydes **5**, and their absolute configuration was assigned by independent synthesis of the *unlike* isomers from the optically active epoxy aldehydes (2*R*)-**5d**−**f** (Scheme 6). The *like* configuration of the allylic alcohol *lk*-**2d** was determined by base-catalyzed rearrangement of epoxide *lk*-**4d** (Scheme 7).

Discussion

The present results provide compelling evidence for an attractive hydrogen-bonded interaction between the attacking

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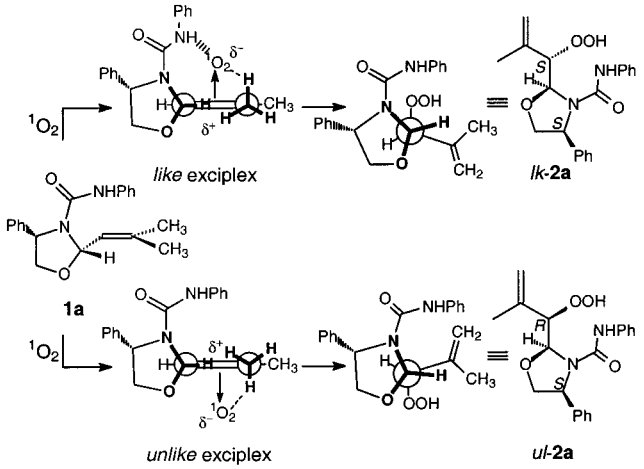
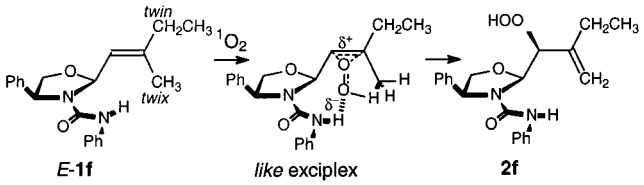
Scheme 8



Scheme 9



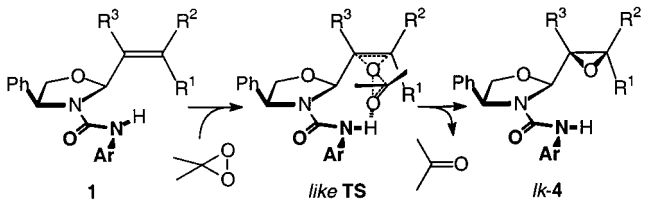
singlet-oxygen enophile and the NH group of the urea functionality in the photooxygenation of the oxazolidines **1a**, **b**, **d**, **f** (entries 1, 3, 5, 7, and 8 in Table 1). Hydrogen bonding is only feasible in the transition state for the *like* exciplex, whereas such interaction is prevented for the *unlike* attack (Scheme 8). The hydrogen bonding between the urea-NH moiety and the negatively polarized, terminal oxygen atom of singlet oxygen lowers the energy of the corresponding *like* transition state, and therefore, the attack on this π face of the double bond is favored.

That hydrogen bonding plays an important role in the transition state of the *like* exciplex is confirmed by the dependence of the diastereoselectivity on the reaction medium, which is exemplified for oxazolidine **1a**. In acetone, a hydrogen-bonding acceptor itself, the hydrogen bonding between the oxazolidine substrate and the singlet-oxygen enophile is less effective, and consequently, the diastereoselectivity of the ene reaction in this solvent is significantly lower than in the nonpolar chloroform (entry 1 and 2 in Table 1). Furthermore, methylation of the NH functionality as in oxazolidine **1c** prevents hydrogen bonding, and hence, a poor diastereoselectivity is found; in fact, the opposite (*unlike*) diastereomer is slightly favored (entry 4).

The urea hydrogen bonding not only controls the diastereoselectivity of the singlet-oxygen attack but also promotes a high regioselectivity as demonstrated in the hydrogen abstraction of the diastereomeric olefins *E*- and *Z*-**1f**. As exemplified for the *E*-**1f** diastereomer (Scheme 9), due to the hydrogen bonding, along this *like* trajectory the terminal oxygen atom of $^1O_2$ points toward the urea functionality. Clearly, hydrogen abstraction from the *twin* ethyl group is prohibited, and instead, removal from the *twix* and *lone* positions is expected. Thus, the geometrical fixation in the *like* exciplex due to hydrogen bonding promotes abstraction predominantly from the allylic substituent located *cis* to the oxazolidine (*twix* position); thus, the *twix*-methyl group in substrate *E*-**1f** and the *twix*-ethyl group for the olefin *Z*-**1f** are ene-active (Scheme 9).

Furthermore, the hydrogen bonding in the exciplex hinders effectively the possible abstraction of the aminal (*lone*) hydrogen atom, as witnessed by the minor amounts of the dioxolanes **3** (cf. Scheme 3), which are formed in the ene reaction of the

Scheme 10



olefins **1a**, **b**, **d**−**f** by such *lone* abstraction (entries 1−3 and 5−7 in Table 1). The unfavorable *lone* abstraction is due to fixation of the oxazolidine moiety by the hydrogen bonding in the energy-favored *like* exciplex, in which the C−H bond of the aminal (*lone*) hydrogen atom is in the nodal plane of the C−C double bond (cf. Scheme 8). Since a perpendicular arrangement of this C−H bond is necessary for hydrogen abstraction,[20] the aminal hydrogen atom at the *lone* site is not available for abstraction.

For the methylated derivative **1c** (entry 4 in Table 1), hydrogen bonding is prevented, and the oxazolidine moiety rotates quite freely; consequently, the dioxolane **3c** is formed to a significant extent (30%). It is important to emphasize that the observed regioselectivity does not arise from the so-called cis *effect*, which predicts that hydrogen abstraction takes place from the higher substituted side of the double bond.[3] If this were the case, a similar regioselectivity would be expected for the olefin **1a** with a nonmethylated urea functionality and its methylated derivative **1c**, which is not the case (entries 1 and 4 in Table 1).

Since the singlet-oxygen ene reaction involves a perepoxide-like geometry (Schemes 8 and 9), it was of mechanistic interest to compare the photooxygenation results of the oxazolidines **1** with those of the DMD epoxidations. Indeed, both oxyfunctionalizations display strikingly similar trends, in that the high diastereoselectivity observed in the singlet-oxygen reaction of substrates **1a**, **b**, **d**, **f** is found also for the DMD epoxidations (entries 1, 2, 4, 6, and 7 in Table 2). Here again, hydrogen bonding between the urea NH functionality and the DMD oxidant operates in the *like* transition state (Scheme 10). This favorable bonding reduces the energy of the transition state, which leads to the high (>95:5) diastereoselectivities given in Table 2. Methylation of the NH group as in olefin **1c** (entry 3) prevents such hydrogen bonding, and instead, the urea group imposes a steric constraint such that a moderate (26:74) *unlike* selectivity is observed.

The reason for the relatively low selectivity observed in the case of the *cis*-dimethyl-substituted olefin **1e** (entry 5) may be explained in terms of less effective fixation of the double bond. Calculations (B3LYP/6-31G*) reveal two possible ground-state conformers for the model compounds **7a** and **7e** (Scheme 11), of which conformer **A** forms a hydrogen bond to the dioxirane but conformer **B** does not. In the case of the olefin **7a**, conformer **A** is nearly exclusively populated (structure **A** is favored by 3.2 kcal/mol), and expectedly, only the *like* epoxide should result. In contrast, for the substrate **7e** both conformers are nearly equally populated (structure **B** is favored by 0.36 kcal/mol), and both may react with the oxidant equally likely. Applied to the experimental results (entries 1 and 5 in Table 2), the lower selectivity in the epoxidation of oxazolidine **1e** compared to **1a** arises from the superposition of the *like*-selective attack on conformer **A** and a completely unselective attack on conformer **B** (Scheme 11). Despite this less effective fixation of the double

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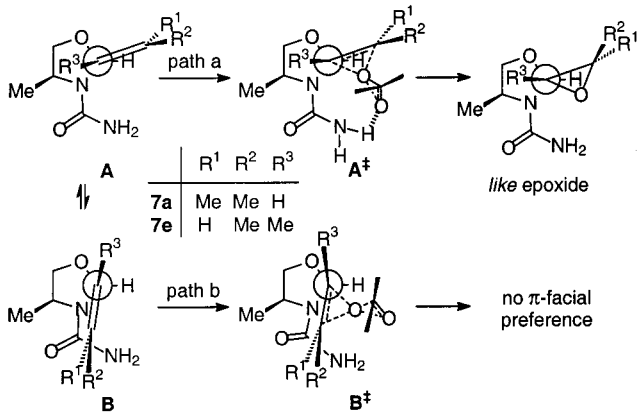
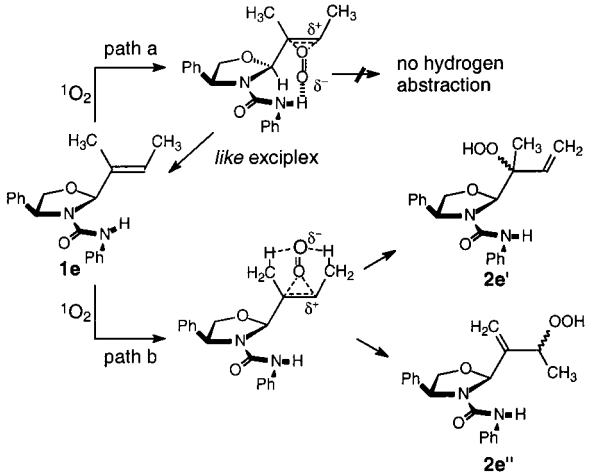
Scheme 11



Scheme 12



bond in oxazolidine **1e**, the moderate (74:26) *like* diastereoselectivity in its epoxidation clearly shows that hydrogen bonding also operates for this substrate.

This is mechanistically significant in view of the completely unselective ene reaction of the substrate **1e** with singlet oxygen (entry 6 in Table 1). Thus, the two possible regioisomeric allylic alcohols **2e′** and **2e″** were formed each as ca. 1:1 diastereomeric mixture (entry 6 in Table 1), although the substrate bears a free NH functionality available for hydrogen bonding. This remarkable lack of selectivity may be accounted for in terms of two different singlet-oxygen attacks. When the $^1O_2$ approaches the double bond with the terminal oxygen located on the side of the urea functionality (path a in Scheme 12), good hydrogen bonding is expected; however, hydrogen abstraction from the allylic methyl groups is not possible, because they point away from the abstracting terminal oxygen atom of $^1O_2$ in this *like* exciplex. The only allylic hydrogen on the same side of the terminal oxygen atom is the one at the aminal position. Nevertheless, no abstraction occurs from this site due to fixation of the oxazolidine ring by hydrogen bonding, which places the aminal hydrogen atom in the nodal plane of the π system. Instead, the exciplex dissociates, and no ene reaction occurs.

When the $^1O_2$ attacks along the approach in path b (Scheme 12), that is, the terminal oxygen atom points toward the two allylic methyl groups, the NH functionality is too far away for hydrogen bonding with the singlet oxygen, and there is no π-facial selection; therefore, low if any diastereoselectivity is observed. The slight (69:31) preference in regioselectivity for the formation of the allylic alcohol **2e″** over its regioisomer **2e′** (entry 6 in Table 1) is caused by the *large-group-nonbonding effect*, which favors *geminal* abstraction to a bulky substituent.[2,5]

Unexpected is the fact that the diastereoselectivities for the *m*CPBA epoxidations[15] (cf. the Supporting Information) show the same trend as DMD (Table 2), but are generally lower. Usually *m*CPBA is more diastereoselective than DMD, for example, in the epoxidations of chiral allylic alcohols.[8a] This has been explained in terms of less efficient hydrogen bonding in the DMD case, especially because the reaction medium is more polar for this reagent (acetone versus chloroform). In the peracid epoxidation of the oxazolidines **1**, hydrogen bonding also favors the *like* transition state (Scheme 10), but for the peracid the distance between the hydrogen-bond acceptor (the carbonyl oxygen atom)[21] and the transferred oxygen atom (2.4 Å)[22] is significantly larger than for the dioxirane (1.5 Å)[23] and for the singlet oxygen (1.2 Å).[24] Since the distance between the C−C double bond and the hydrogen atom of the NH group is only 2.6 Å (calculated for the model compound **7a**), presumably the peracid does not fit as well into the cavity formed by the alkenyl group and the urea functionality. Therefore, the hydrogen bonding is less effective for *m*CPBA than for DMD or $^1O_2$, and consequently, a lower diastereoselectivity is found for the peracid oxidant.

In summary, the present results clearly demonstrate that the remotely located urea-NH functionality of chiral carbamoyl-substituted oxazolidines is highly effective in controlling the diastereoselectivity, as well as the regioselectivity, of the singlet-oxygen ene reaction. The controlling feature is the efficient hydrogen bonding between the urea functionality and the oxidant, which besides singlet oxygen also operates well in the epoxidation by dimethyldioxirane and *m*-chloroperbenzoic acid. The control of diastereoselectivity through hydrogen bonding is well established in the oxyfunctionalization by these oxidants;[6,7,9,10] however, such high directivity has hitherto not been observed by a hydrogen-bonding functionality that far away from the C−C double bond of the substrate. Furthermore, it should be emphasized that the present oxazolidine chiral auxiliary exerts better diastereoselectivity control for DMD than *m*CPBA epoxidation reactions, an unprecedented fact. Since the oxazolidine ring system is usually readily cleaved by hydrolysis,[12f,g,25] the present methodology offers promising prospects in the preparation of optically active building blocks for asymmetric synthesis.

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Supporting Information Available: Complete experimental procedures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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