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Diastereoselective Epoxidation of Oxazolidine-Substituted Alkenes by Dimethyldioxirane and *m*-Chloroperbenzoic Acid: π-Facial Control through Hydrogen Bonding by the Urea Functionality

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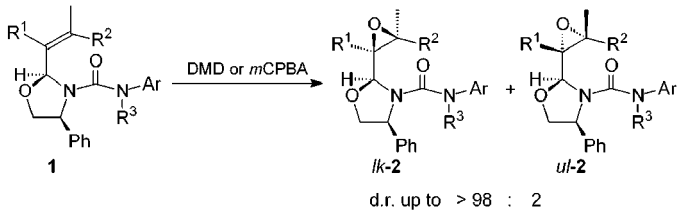
ABSTRACT



A high diastereoselectivity (up to >98:2) is found for the DMD and *m*-CPBA epoxidations of chiral oxazolidine-substituted olefins with a urea group. The selectivity is explained in terms of hydrogen bonding between the remote NH group of the urea functionality and the epoxidizing reagent. Methylation of the NH group prohibits hydrogen bonding, and a reversed selectivity is observed due to steric repulsion between the reagent and the urea functionality.

Epoxidations are among the most useful oxidation reactions in organic synthesis, since the epoxy functionality may be transformed by ring opening stereoselectively into a large number of highly functionalized products.[1] For this purpose, peracids[2] and, more recently, dioxiranes[3] have been used extensively as effective and mild epoxidants. These versatile reagents become particularly valuable when their epoxidations are controlled stereoselectively; that is, the attack of the epoxidant prefers one of the π faces of the olefinic substrate.[4] Besides reagent-controlled diastereoselectivity, the influence of the olefin structure and especially directing groups in controlling the attack of the oxygen-transferring agent, both in experimental[5] and theoretical[6] studies, has received much attention. In this context, the directing propensity of allylic substituents is well documented,[4b−d,7] but only relatively few examples are known for which the

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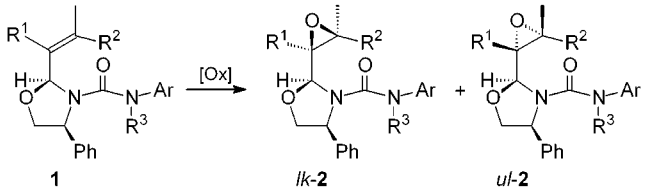
directing group is located further away from the double bond.[7] The observed stereoselectivity is significantly lower than for allylic substituents due to less efficient alignment of the substrate by the directing entity for a selective π-face attack. Nonetheless, recently we discovered the directing propensity of the remote urea NH functionality of chiral oxazolidines in the singlet-oxygen ene reaction.[8] As the factors controlling singlet-oxygen reactions are often also valid for DMD and *m*-CPBA epoxidations, these substrates appeared to be promising for remote-functionality controlled diastereoselective epoxidations. Herein we report that chiral oxazolidine-substituted olefins undergo highly diastereoselective (up to >98:2) epoxidation with DMD and *m*-CPBA. The diastereoselectivity is induced by a remote urea NH group.

The synthesis of oxazolidine-substituted olefins **1a**−**c** was described previously,[8] and derivative **1d** was prepared by condensation of tiglic aldehyde and *S*-phenylglycinol, followed by acylation with phenylisocyanate (cf. the Supporting Information). The substrates **1** were epoxidized with dimethyldioxirane in acetone and *m*-chloroperbenzoic acid in chloroform to yield the corresponding epoxides **2** (Table 1).

Table 1. Diastereoselective Epoxidation of Oxazolidine-Substituted Olefins **1** by DMD and *m*-CPBA

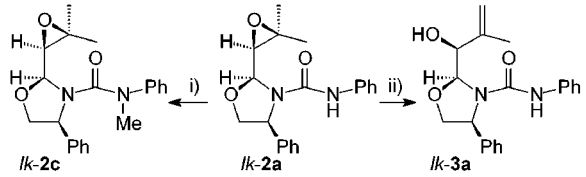


entry		Ar	R^1	R^2	R^3	oxidant[b]	convn (%)[a]	dr[a] *lk*-**2**:*ul*-**2**
1	**1a**	C_6H_5	H	Me	H	DMD	>95	>98:2[c]
2	**1b**	*p*-NO_2-C_6H_4	H	Me	H	DMD	>95	>98:2[c]
3	**1c**	C_6H_5	H	Me	Me	DMD	94	26:74
4	**1d**	C_6H_5	Me	H	H	DMD	78	74:26
5	**1a**	C_6H_5	H	Me	H	*m*-CPBA	94	81:19
6	**1b**	*p*-NO_2-C_6H_4	H	Me	H	*m*-CPBA	>95	87:13
7	**1c**	C_6H_5	H	Me	Me	*m*-CPBA[d]	52	40:60
8	**1d**	C_6H_5	Me	H	H	*m*-CPBA	>95	74:26

[a] Determined by ^{1}H NMR spectroscopy, error ±5% of the stated values; the mass balance was >90% in all cases. [b] DMD: acetone, 20 °C, 5 h; *m*-CPBA: $CDCl_3$, 20 °C, 2 h. [c] Not even traces of the corresponding *unlike* epoxides were detected. [d] CH_2Cl_2/aqueous $NaHCO_3$ buffer, 20 °C, 4 h (see text).

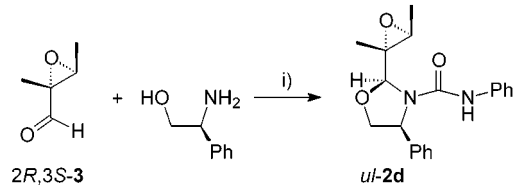
The epoxidation of **1c** with peracid was done in a buffered two-phase system to avoid acid-catalyzed decomposition of the product that was observed under standard reaction conditions. For the substrates **1a**,**b** (entries 1 and 2), the *like* product is formed exclusively with DMD (not even traces of the *unlike* diastereomer could be detected), but for the derivative **1d** (entry 4) a significantly lower *like* selectivity is observed; in contrast, with the *N*-methylated urea **1c** (entry 3) even the *unlike* epoxide is preferred. The stereochemical assignment was made by base-catalyzed rearrangement of the epoxide *lk*-**2a** to the known allylic alcohol *lk*-**3a**,[8,9] which establishes the *like* configuration. Furthermore, the *lk*-**2a** epoxide was converted to its *lk*-**2c** derivative through methylation, which allowed us to assign the relative configuration of the *lk*- and *ul*-**2c** epoxides (Scheme 1). The *ul*-**2d** epoxide was synthesized independently from the optically active aldehyde 2*R*,3*S*-**3**[10] (Scheme 2).

Scheme 1[a]



[a] Key: (i) NaH, MeI, DMSO, 20 °C, 15 h; (ii) activated Al_2O_3, *n*-hexane, 20 °C, 16 h.

Scheme 2[a]



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

The exclusive *like* diastereoselectivity in the DMD epoxidation of the **1a**,**b** derivatives (entries 1 and 2) may be explained in terms of the highly effective hydrogen bonding

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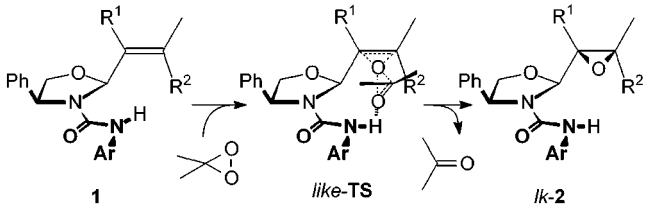
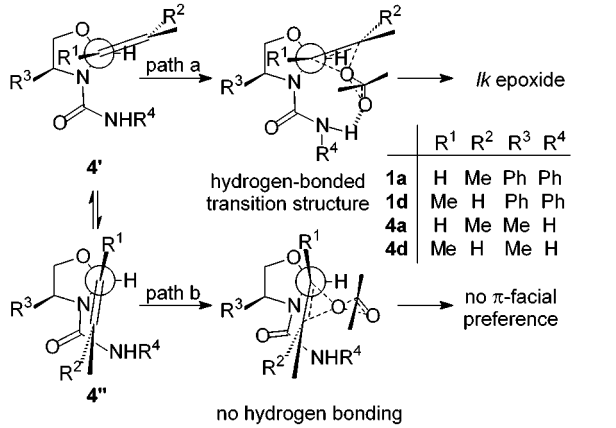
between the urea NH functionality of the olefinic substrate and the oxygen atom of the DMD oxidant in the lower-energy transition structure *like*-**TS** (Scheme 3). The importance of the free NH functionality for the *like* diastereoselectivity is emphasized by the reversal of selectivity upon capping of this group by methylation (entry 3). For substrate **1c**, hydrogen bonding is not possible and steric repulsion between the urea functionality and DMD disfavors the *like* attack and, therefore, a reversal of the diastereoselectivity is observed to favor the *unlike* epoxide *ul*-**2c**.

Scheme 3



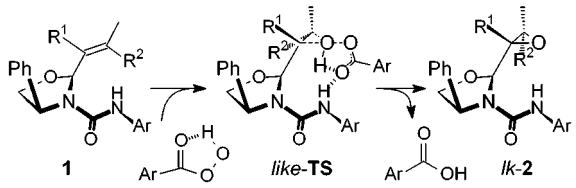
The importance of proper conformational alignment of the double-bond functionality in the substrate is demonstrated in the epoxidation of *cis*-dimethyl derivative **1d** (entry 4). Although this substrate bears a urea NH group, the *like* selectivity for the DMD epoxidation is significantly lower than that of the oxazolidines **1a**,**b**. The reason for the reduced *like* diastereoselectivity is to be sought in the steric interactions between the additional α-methyl group of the double bond and the oxazolidine. To assess this, DFT calculations (B3LYP/6-31G*) of the model substrates **4a** and **4d** were carried out, in which the aryl group of the urea moiety was replaced by a hydrogen atom and the phenyl substituent of the oxazolidine ring by a methyl group. Two conformational energy minima were found for the derivatives **4a** and **4d** (Scheme 4). In the conformers **4a′** and **4d′**, the π system is oriented favorably for hydrogen bonding with the urea NH functionality, whereas in the conformers **4a″** and **4d″**, the double bond is located directly above the NH_2 group and hydrogen bonding is obstructed. The hydrogen-bonding conformer **4a′** is favored by 3.2 kcal/mol over **4a″**; thus, this conformer is preferentially populated and epoxidation by assistance through hydrogen bonding leads to the observed high *like* diastereoselectivity (path a in Scheme 4). In contrast, the conformers **4d′** and **4d″** are nearly equal in energy (the conformer **4d″** is even favored by 0.36 kcal/mol over **4d′**) and both conformers will be essentially equally populated. Since for the conformer **4d″** effective hydrogen bonding is difficult, the epoxidation along this reaction channel (path b in Scheme 4) is expected to be unselective. Thus, the moderate selectivity (74:26) for the substrate **1d** results from the 50:50 superposition of the exclusively *like*-selective epoxidation of the conformer **1d′** and the totally unselective epoxidation of conformer **1d″**. Application of the computational results for **4a**,**d** on the experimental cases **1a**,**b**,**d** (Scheme 4), the overall diastereoselectivity for **1d** should be lower than for **1a** and **1b**, as manifested by the data in Table 1 (entries 1, 2 and 4).

Scheme 4



For *m*-chloroperbenzoic acid a similar trend is observed. Thus, the oxazolidines with a free NH group and a properly aligned olefin conformation as in the substrates **1a**,**b** predominantly afford the corresponding *like* epoxides (entries 5 and 6). N methylation as in substrate **1c** (entry 7) expresses a slight preference for the *unlike* epoxide (control by steric effects), while for the tiglyl derivative **1d** (entry 8) a slightly reduced *like* diastereoselectivity is observed. As in the DMD epoxidations, hydrogen bonding between the oxidant and the NH functionality lowers the energy of the *like* transition state and, thus, this attack is preferred (Scheme 5).

Scheme 5

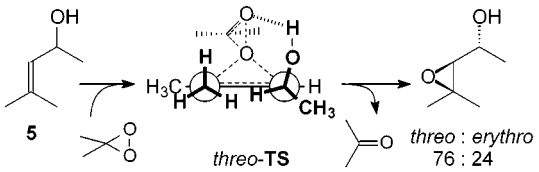


Usually hydrogen bonding is more effective for *m*-CPBA compared to DMD epoxidations[7c] and, therefore, it was unexpected, that the diastereoselectivity for *m*-CPBA was lower than for DMD, especially since the reaction medium is less polar for the peracid (chloroform) than for dioxirane (acetone) and stronger hydrogen bonding should operate for *m*-CPBA. Inspection of molecular models suggests that the lower diastereoselectivity of the peracid compared to the dioxirane may be explained in terms of the higher steric constraints for a proper alignment of the hydrogen bonding between the urea NH functionality and the carbonyl group of the peracid in the *spiro* transition structure of the peracid epoxidation (Scheme 5).

It is instructive to compare the present results with the DMD epoxidation of chiral allylic alcohols.[11] In the reaction of mesitylol (**5**) with DMD, a preference of the threo attack

is observed (threo/erythro = 76:24), which was explained by beneficial hydrogen bonding between the oxygen atom of the oxidant and the allylic hydroxy functionality, the latter properly aligned by 1,3-allylic strain (Scheme 6). This

Scheme 6



diastereoselectivity is substantially lower than for the urea derivative **1a** (>98:2), although both possess structurally the same double-bond functionality. This impressive difference in the diastereoselectivity between the allylic alcohol and the substrates demands an explanation. For a high diastereoselectivity, two prerequisites must be fulfilled: First, the directing group must be fixed sufficiently on one side of the double bond; second, there must be an efficient interaction between the directing group and the reagent. For the allylic alcohol and the urea substrates the alignment of the directing functionality is similar in energy (1,3-allylic strain favors one conformer by 3−4 kcal/mol[12]) since both possess the same π system and, thus, the difference in the diastereoselectivity must arise from more effective hydrogen bonding in the urea case. Since the ability to act as hydrogen donor correlates with the acidity of a molecule, the stronger acid should form the stronger hydrogen bond. From a comparison of the acidities of 2-propanol (pK_a = 30.3)[13] and *N*,*N*-dimethyl-*N*′-phenylurea (pK_a = 21.2)[14] in DMSO it becomes clear that the urea moiety is more acidic and, therefore, the better hydrogen donor.[15] Additionally, the hydrogen-donating NH functionality of the urea substrate is located directly opposite of the double bond, in optimal juxtaposition for interaction with the oxygen atom of the epoxidant. Thus, the urea-substituted olefin hydrogen bonds more strongly with the dioxirane and exhibits a much higher diastereoselectivity than the allylic alcohol.

In summary, the present results show that a favorably disposed urea NH functionality not only induces a very high diastereoselectivity in the epoxidation by DMD (>98:2), but it surpasses in efficacy that for *m*-CPBA (up to 87:13), which is remarkable in view of the fact that peracids are generally more effective than dioxiranes.[7c] Although the directing group is located four bonds away from the reacting site, namely the π bond to be attacked, the perfect stereoselectivity is caused by the optimal conformational alignment of the olefin functionality for beneficial hydrogen bonding between the urea NH group of the substrate and the oxygen atom of the reagent. The directing ability of the urea NH group should find valuable applications in the control of stereoselectivity.

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Supporting Information Available: Experimental Section with the details for the preparation of **1d**, the epoxidation of oxazolidines **1a**−**d**, and the calculations for the preferred conformations of the oxazolidines **4a** and **4d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) DMSO rather than water was chosen for comparison of the acidities, because like the actual reaction medium (acetone), it is an aprotic polar solvent.