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Chiral-Auxiliary-Controlled Diastereoselectivity in the Epoxidation of Enecarbamates with DMD and *m*CPBA

Waldemar Adam, Sara G. Bosio,* and Barbara T. Wolff

Institut für Organische Chemie, Universität Würzburg, Am Hubland, D-97074 Würzburg, Germany

adam@chemie.uni-wuerzburg.de

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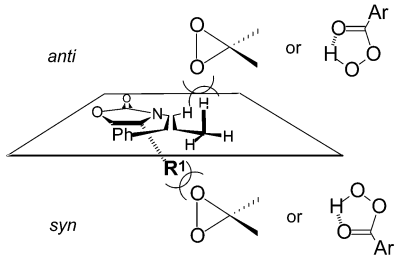
ABSTRACT



Chiral oxazolidinone-substituted enecarbamates 1 are epoxidized in a diastereoselectivity up to 93:7 for both DMD and *m*CPBA. The diastereofacial differentiation depends on the steric interaction between the R^1 substituent on the oxazolidinone ring and the incoming electrophile. The stereochemical course of epoxidation was assessed by chemical correlation with the known optically active diols.

Besides the well-established stereoselective oxidations based on the steric,[1] electronic,[1b−e] stereoelectronic,[2] and conformational[3] effects exerted by the functional group present in the substrate or reagent, an alternative approach utilizes chiral auxiliaries to control the stereochemical course of the oxygen-transfer process.

Such diastereoselective control has become an important strategy in asymmetric synthesis,[4] because the configuration of the new stereogenic centers may be specified at will and the desired enantiomerically enriched oxidation product may be readily released by removal of the chiral inductor under mild conditions. In favorable cases, the chiral auxiliary may be recovered in high yield, which makes this methodology economically feasible and preparatively attractive. In this context, auxiliary-controlled epoxidations should be of general synthetic interest, because the epoxy functionality may be transformed into a great number of target molecules.

High diastereoselectivity may be achieved in the asymmetric epoxidation of chiral oxazolidine-substituted olefins,[5] in which hydrogen bonding of the remote urea functionality with the oxidizing reagent directs the stereochemical course of the oxygen transfer (Figure 1, transition structure **A**). A remarkable competition was observed for related chiral oxazolidine auxiliaries,[6] in which steric repulsions dominated for dimethyldioxirane (DMD) and hydrogen bonding for

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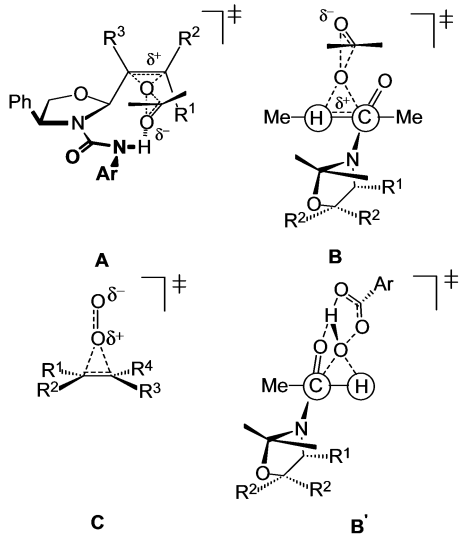


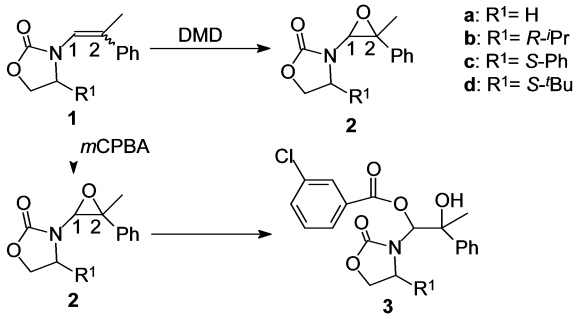
Figure 1. Transition structures for the addition of DMD and *m*CPBA to oxazolidine-substituted olefins and perepoxide-like transition structure for the addition of singlet oxygen to olefins.

m-chloroperbenzoic acid (*m*CPBA) to give diastereoselectivities of opposite senses for these two oxygen-transferring agents (Figure 1, structures **B** and **B′**).

Recently, we discovered the directing propensity of chiral oxazolidinone-substituted ene-carbamates **1** in the [2 + 2] cycloaddition[7] and ene reaction[8] of singlet oxygen, which gave very high (up to >95:5) diastereoselectivities. In this case, the chiral auxiliary is directly connected to the reacting double bond, and the π-facial attack of the oxidant[9] may be expected to be guided by steric blocking caused through conformational effects. In view of the perepoxide-like transition structure (Figure 1, structure **C**),[10] the factors that control singlet oxygen reactions may also operate in the DMD and *m*CPBA epoxidation.[11] That this is, indeed, the case for the oxazolidinone-substituted enecarbamates **1** is demonstrated herein in their highly diastereoselective epoxidation by DMD and *m*CPBA, provided that the appropriate geometrical isomer, namely, the (*Z*)-enecarbamate, is employed.

The enecarbamates **1** were synthesized according to the literature pocedure[8] and epoxidized with DMD in acetone and *m*CPBA acid in chloroform (Table 1). The epoxidation of the achiral (*Z*)-**1a** (R^1 = H) with DMD gave, as expected, a racemic mixture of the epoxides (**1*S***,2*S*)-**2a** and (**1*R***,2*R*)-**2a** (entry 1). In the epoxidation of the chiral (*Z*)-**1b** (R^1=^{i}Pr) at ca. 20 °C, the epoxide **2b** was formed in a 1*S*:1*R* diastereomeric ratio (dr) of only 60:40 (entry 3a);[12] at −25 °C, no significant increase in the dr value was observed (entry 3b). An increase in the size of the R^1 substituent on the oxazolidinone ring caused a significant increase in the diastereoselectivity of the epoxidation. For

Table 1. Diastereoselectivity in the Epoxidation of Enecarbamate **1** by DMD and *m*CPBA



			diastereoselectivity of epoxide **2**[b,c]
entry[a]	reagent	substrate	1*S*:1*R*
1	DMD	(*Z*)-**1a**	50:50
2	*m*CPBA	(*Z*)-**1a**	50:50
3a	DMD	(*Z*)-**1b**	60:40
3b	DMD[d]	(*Z*)-**1b**	63:37
4	*m*CPBA	(*Z*)-**1b**	70:30
5	DMD	(*Z*)-**1c**	8 (10):92 (90)
6	*m*CPBA	(*Z*)-**1c**	8 (10):92 (90)
7	DMD	(*Z*)-**1d**	7 (6):93 (94)
8	*m*CPBA	(*Z*)-**1d**	7:93
9	DMD	(*E*)-**1a**	50:50
10	*m*CPBA	(*E*)-**1a**	50:50
11	DMD	(*E*)-**1b**	53:47
12	*m*CPBA	(*E*)-**1b**	50:50
13	DMD	(*E*)-**1c**	40 (42):60 (58)
14	*m*CPBA	(*E*)-**1c**	48:52[e]
15	DMD	(*E*)-**1d**	25 (25):75 (75)
16	*m*CPBA	(*E*)-**1d**	21:79

[a] DMD epoxidation was run in acetone at ca. 20 °C, with *m*CPBA in $CHCl_3$ at ca. 20 °C, which gave the ester **3** by acid-catalyzed ring opening of the intermediary epoxides **2**; the diastereomeric ratio is given for the epoxides **2**; conversion > 95%, material balance > 95%. [b] Only the configuration at the C1 position of the epoxides **2** is specified, because it does not depend on the double-bond configuration of the starting material; in the text, these descriptors are marked in bold. [c] Diastereoselectivity determined by ^{1}H NMR spectroscopy (5% error of the stated value) directly on the reaction mixture and by HPLC analysis (2% error, numbers in parentheses) of the diol **5**, prepared from epoxide **2** (DMD) and from the ester **3** (*m*CPBA). [d] Run at −25 °C. [e] Also 50% epoxide (**1*S***,2*R*)-**2c** and 2% ester (**1*R***,2*R*)-**3c**.

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(12) In Table 1, only the configuration at the C1 position is given for the two diastereomers, namely, the stereochemical descriptors 1*S* and 1*R*, because this position does not depend on the initial double-bond configurations of the enecarbamates (*Z*)-**1** and (*E*)-**1**; for clarity and convenience, the 1*S* and 1*R* desriptors are marked in bold in the text when in combination with the C2 position.

the enecarbamates (*Z*)-**1c** (R^1 = Ph) and (*Z*)-**1d** (R^1 = ^{t}Bu), high dr values (92:8) were obtained with DMD, the major epoxide isomers being (**1*R***,2*R*)-**2c** (entry 5) and (**1*R***,2*R*)-**2d** (entry 7).

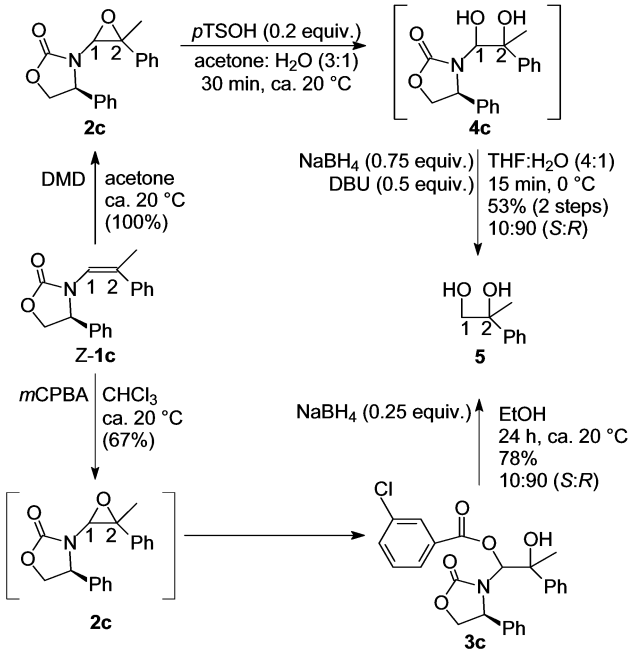
The epoxidation of the (*E*)-**1** isomers by DMD shows the same trend: for the achiral (*E*)-**1a** (R^1 = H), no selectivity is observed (entry 9), whereas the diastereofacial differentiation increases with the size of the R^1 substituent. The 1*S*:1*R* ratios range from 53:47 for (*E*)-**1b** (R^1 = ^{i}Pr, entry 11) to 40:60 for (*E*)-**1c** (R^1 = Ph, entry 13) and to 25:75 for (*E*)-**1d** (R^1 = ^{t}Bu, entry 15). Notable, and mechanistically pertinent, are the much lower dr values for the DMD epoxidation of the (*E*)-configured chiral enecarbamates **1** (entries 11, 13, and 15) compared to the (*Z*)-**1** diastereomers (entries 3, 5, and 7).

In the epoxidations with *m*CPBA, the epoxide was observed directly in the ^{1}H NMR spectrum of the reaction mixture at low (only ca. 10%) conversion of the enecarbamates **1**. In all cases, the major diastereomer epoxide is the same as in the DMD reaction; however, the epoxide was opened exclusively at the C1 position to the ester **3** by the acid generated from *m*CPBA. When the *m*CPBA epoxidation of the (*E*)-**1a** enecarbamate was conducted in a $NaHCO_3$-buffered two-phase system to avoid the acid-catalyzed ring opening of the epoxide product, the formation of the ester (1*R**,2*S**)-**3a** could not be avoided (not shown in Table 1) under these conditions either.

As in case of DMD, the achiral (*Z*)-**1a** (R^1 = H, entry 9) is epoxidized also unselectively by *m*CPBA in the unbuffered reaction, whereas the diastereomeric ratios of the chiral enecarbamates (*Z*)-**1b**−**d** increase as the size of the R^1 substituents on the oxazolidinone ring is increased. Thus, for the isopropyl-substituted enecarbamate (*Z*)-**1b** (entry 4), the diastereomeric ratio is substantially lower than for the phenyl-substituted derivative (*Z*)-**1c** (entry 6) and the *tert*-butyl one (*Z*)-**1d** (93:7, entry 8). Again, the (*E*)-configured enecarbamates are epoxidized by *m*CPBA in lower diastereoselectivity than the (*Z*)-configured counterparts (entries 12, 14, and 16), as was the case for DMD (entries 11, 13, and 15). In fact, for the substrate with the large *tert*-butyl substituent (*E*)-**1d**, an appreciable dr value of 71:29 was observed, in favor of the (**1*S***,2*S*)-**3d** isomer (entry 16). An exceptional case is the *m*CPBA epoxidation of the (*E*)-**1c** (R^1 = Ph) enecarbamate. This substrate also affords a mixture of the two diastereomeric epoxides, but only the (**1*R***,2*S*)-**2c** diastereomer is converted to the ester (**1*S***,2*S*)-**3c**, while the (**1*S***,2*R*)-**2c** epoxide resists esterification. Presumably, nucleophilic attack on the C1 position is sterically hindered.

The absolute configurations of the epoxides **2** and esters **3** were determined by their transformation to the common diol **5** (Scheme 1). For this purpose, the hydrolysis of the epoxide **2c** derived from the enecarbamate (*Z*)-**1c** was catalyzed by *p*-toluensulfonic acid (*p*-TsOH) in an acetone/water mixture, followed by reductive cleavage of the chiral auxiliary with $NaBH_4$/DBU. The chiral auxiliary could be recovered in amounts up to 67%. Similarly, the mixture of the ester **3c** derived from the *m*CPBA epoxidation of the enecarbamate (*Z*)-**1c** was readily reduced in one step to the diol **5** by $NaBH_4$. The chiral HPLC analysis of the resulting

Scheme 1. Transformation of Epoxide **2c** and Ester **3c** to Common Diol **5**



common diol **5** gave the same enantiomeric ratio as the diastereomeric ratios of the epoxide **2c** and the ester **3c** (within the experimental error). Moreover, the absolute configuration of the major enantiomer was found to be *R* by comparison with an authentic reference sample of enantiomerically enriched diol **5**, prepared independently according to the literature.[13] From the (*R*)-configuration of the major enantiomer of diol **5**, the configuration at the C2 position in the major isomer of the epoxide **2c** and the ester **3c**, both derived from encarbamate (*Z*)-**1c**, may also be assigned as *R*, provided that the C2 site is not involved in the ring-opening hydrolysis **2c** → **4c** and esterification **2c** → **3c**. That this is so could be unequivocally established for the latter process, because NMR analysis of the reaction mixture revealed that exclusively the regioisomer with nucleophilic attack on the C1 position had been formed. Consequently, the absolute configuration of the ester **3c** is **1*S***,2*R* and, hence, that of the epoxide **2c** is **1*R***,2*R*.

With the absolute configuration of epoxides **2** assessed, the stereochemical course of the oxygen-transfer process may be now scrutinized. The diastereoselectivity is controlled by the R^1 substituent in the oxazolidinone ring, because for the parent enecarbamate **1a** (R^1 = H) an unselective epoxidation occurs and the dr ratio depends on the size of R^1. Moreover, the configuration of stereogenic center in the oxazolidinone ring determines the absolute configuration of the epoxide product; that is, the (*R*)-configuration in the enecarbamate (*Z*)-**1b** (entries 3 and 4) leads mainly to the (**1*S***,2*R*)-**2b**, whereas the (*S*)-configuration in substrates (*Z*)-**1c** (entries 5

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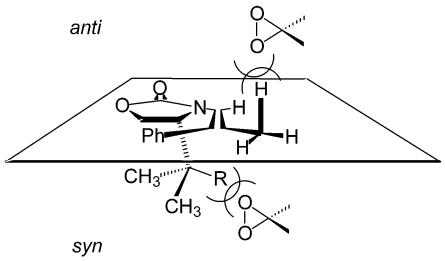

Figure 2. Preferred π-facial attack of the DMD epoxidation as a function of the substituent R size in the enecarbamates (*Z*)-**1b**,**c** (R = H, CH_3).

and 6) and (*Z*)-**1d** (entries 7 und 8) affords mainly the corresponding (**1*R***,2*R*)-epoxides. To account for the fact that the size and the location of the R^1 substituent dictate the extent and the sense of the diastereoselectivity, we propose the mechanism in Figure 2 for the oxygen transfer.

When the R^1 substituent is below the plane of the enecarbamate double bond, as shown in Figure 2, steric hindrance obstructs the syn attack (syn with respect to the R^1 substituent of the oxazolidinone auxiliary) and the anti attack is favored. For R^1 a *tert*-butyl group (R = CH_3 in Figure 1), as in the enecarbamate (*Z*)-**1d** (entries 7 and 8), the highest anti diastereoselectivity (dr 7:93) is obtained, such that the (**1*R***,2*R*)-**2d** epoxide is formed almost exclusively for both oxidants DMD and *m*CPBA.

The preferred π-face that is attacked remains the same for the (*Z*)- or (*E*)-configured enecarbamates; however, the extent of the diastereofacial differentiation depends decisively on the double-bond configuration, because the epoxidation of the (*Z*)-isomer is more selective than that of the (*E*)-isomer. This difference is due to conformational effects in the (*Z*)- and (*E*)-isomers, which express the efficacy of shielding of one side of the double bond in the enecarbamate (Figure 3).

As can be seen from the DFT-calculated lowest-energy conformations for the (*E*)-**1d** and (*Z*)-**1d** isomers in Figure 3, the shielding of the syn face of the double bond by the ^{t}Bu group is more effective for the (*Z*)- than for the (*E*)-diastereomer, such that anti attack should be facilitated for the former, as is documented by the higher dr values for these substrates (entries 7 and 8 for (*Z*)-**1d** versus entries 15 and 16 for (*E*)-**1d**). Thus, only the large steric demand of a *tert*-butyl group is sufficient to shield the double bond effectively in the (*E*)-configured enecarbamate **1d** and then induce an appreciable diastereoselectivity. In the case of enecarbamate (*E*)-**1c**, the phenyl group is smaller than the *tert*-butyl group and is not effective in shielding the double bond.

In contrast with previous findings,[6] the same π-facial selectivity is observed for *m*CPBA and DMD in the present

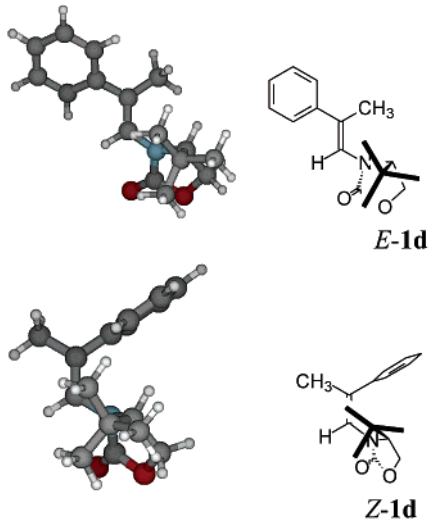

Figure 3. DFT-calculated (B3LYP-3-21G*) preferred conformations for the diastereomeric pair of *tert*-butyl enecarbamates (*E*)-**1d** and (*Z*)-**1d** as a function of the double-bond configuration.

epoxidation. In this case, the same steric interactions operate for both DMD and *m*CPBA because hydrogen-bonding effects are not involved for the latter. If hydrogen bonding between the carbonyl group in the oxazolidinone and the proton of the *m*CPBA were taking place, a higher diastereoselectivity would be expected for *m*CPBA, because the steric repulsion with the substituent R^1 should be enhanced.

In summary, we have shown that the chiral encarbamate **1** may be epoxidized in a diastereoselectivity up to 93:7 for both DMD and *m*CPBA. The diastereofacial differentiation has been rationalized in terms of the steric interaction between the R^1 substituent on the oxazolidinone ring and the incoming electrophile on account of conformational effects, such that anti attack (opposite to the R^1 substituent) is favored. Chemical correlation of epoxides **2** and esters **3** to the known optically active common diol **5** established the π-facial stereochemical course of this unprecedented oxygen-transfer process.

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Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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