ORGANIC LETTERS

2000
Vol. 2, No. 8
1019−1022

Opposite π-Face Selectivity for the DMD and *m*-CPBA Epoxidations of Chiral 2,2-Dimethyloxazolidine Derivatives of Tiglic Amides: Control by Steric Interactions versus Hydrogen Bonding

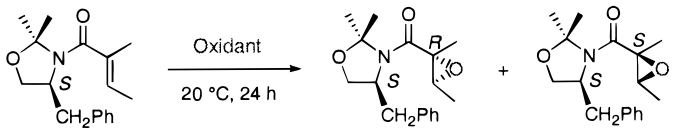
Waldemar Adam,[†,‡] Aurelia Pastor,*[,†] Karl Peters,[§,||] and Eva-Maria Peters[§]

Institut für Organische Chemie, Universität Würzburg, Am Hubland, D-97074 Würzburg, Germany, and Max-Planck-Institut für Festkörperforschung, Heisenbergstrasse 1, D-70506 Stuttgart, Germany

adam@chemie.uni-wuerzburg.de

Received December 20, 1999

ABSTRACT



	ul-2a		*lk*-2a
DMD	91	:	09
***m*-CPBA**	15	:	85

A high extent but opposite sense in the diastereoselectivity has been observed for the DMD and *m*-CPBA epoxidations of the optically active tiglic amides (*S*)-1 with 2,2-dimethyloxazolidines as chiral auxiliaries. This unprecedented reversed π-facial differentiation for these two peroxidic oxidants is rationalized in terms of *like* (*lk*) and *unlike* (*ul*) transition structures: For DMD, steric interactions dominate, such that the *unlike* transition structure is favored, while for *m*-CPBA, hydrogen-bonding effects overcome these steric repulsions and the *like* one is preferred.

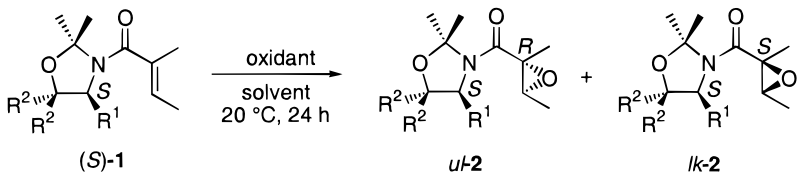
Optically active epoxides are key building blocks in organic synthesis.[1] These versatile functionalities are readily and stereoselectively introduced[2] and then further transformed by ring opening into a plethora of oxyfunctionalized derivatives.[3] Despite much progress in recent years, efficient reagents for the regio- and diastereoselective epoxidations are still in great demand. Popular oxidants for epoxidations are dioxiranes[4] and peracids,[2a,5] which have received much attention from both the preparative and mechanistic point of view. These extensively used oxidants are mild (isolated dioxiranes epoxidize under strictly neutral conditions) and react selectively at the site of higher nucleophilicity.[6] Attractive opportunities for preparative purposes offer the

[†] Universität Würzburg.
[‡] FAX: +49 931/888 4756. Internet: http://www-organik.chemie.uni-wuerzburg.de.
[§] Max-Planck-Institut für Festkörperforschung.
[||] FAX: +49 711/689 1503. E-mail: karpet@vsibm1.mpi-stuttgart-.mpg.de.

(1) (a) Harvey, R. G. *Synthesis* **1986**, 605−619. (b) Jørgensen, K. A. *Chem. Rev.* **1989**, *89*, 431−458.
(2) (a) Rao, A. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 7, Chapter 3.1, pp 357−387. (b) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307−1370.
(3) (a) Fukuyama, T.; Wang, C.-L. J.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 260−262. (b) Marino, J. P.; Fernández de la Pradilla, R.; Laborde, E. *J. Org. Chem.* **1984**, *49*, 5279−5280.
(4) Adam, W.; Smerz, A. *Bull. Soc. Chim. Belg.* **1996**, *105*, 581−599.
(5) (a) Rebek, J., Jr.; Marshall, L.; McManis, J.; Wolak, R. *J. Org. Chem.* **1986**, *51*, 1649−1653. (b) Koerner, T.; Slebocka-Tilk, H.; Brown, R. S. *J. Org. Chem.* **1999**, *64*, 196−201.
(6) (a) Bovicelli, P.; Lupattelli, P. *J. Org. Chem.* **1994**, *59*, 4304−4307. (b) Adam, W.; Smerz, A. K. *J. Org. Chem.* **1996**, *61*, 3506−3510. (c) Camps, F.; Messeguer, A.; Sánchez, F.-J. *Tetrahedron* **1988**, *44*, 5161−5167.

10.1021/ol990405s CCC: $19.00 © 2000 American Chemical Society
Published on Web 03/23/2000

Scheme 1



control of their diastereoselectivity by steric,[7] electronic,[7b−e] hydrogen-bonding,[7b−c,8] solvent,[7b−e] and torsional effects.[9]

Although the diastereoselective epoxidation of electron-rich alkenes by these two oxidants is well documented,[4,5] the use of electron-poor substrates has to date not been much explored.[10] For example, an attractive and synthetically valuable application would be the diastereoselective DMD or *m*-CPBA oxyfunctionalization of tiglic acid derivatives with 2,2-dimethyloxazolidines as chiral auxiliaries, which would afford optically active epoxides after removal of the chiral auxiliary.[11] Subsequent ring opening with the appropriate nitrogen nucleophile would readily lead to optically active α-amino acids with α-methyl and *β*-hydroxy groups. Such conformationally constrained, oxyfunctionalized α-amino acids have hitherto been synthesized from tiglic acid as starting material.[12] They possess important utility as an effective probe to understand the local conformations responsible for the bioactivity of peptides.[13]

In view of these facts, we have examined the diastereoselectivity in the DMD and *m*-CPBA epoxidation of the optically active tiglic amides (*S*)-**1**, in which the amide functionality is connected to optically active 4-substituted 2,2-dimethyloxazolidines. Indeed, high (dr > 90:10) diastereoselectivities have been achieved for both oxidants; mechanistically more significant, the sense of the *π*-facial selectivity is opposite, i.e., *unlike* for DMD and *like* for *m*-CPBA.[14] These unprecedented results and their mechanistic rationalization are reported presently.

The optically active amides (*S*)-**1a**−**c** were obtained in good yields from the appropriate amino alcohols by following standard published procedures (cf. Supplementary Information). Subsequent epoxidation of the tiglic acid amides (*S*)-**1a**−**c** at 20 °C for 24 h (3-fold excess of DMD) led to a diastereomeric mixture of epoxides *ul*-***2*****a**−**c** and *lk*-***2*****a**−**c**, with the *ul* diastereomers as the major ones (Scheme 1).

High conversions (up to 95%) and diastereoselectivities (up to 91:9) were obtained for the three tested auxiliaries (Table 1; entries 1−3). For comparison, the *m*-CPBA (2-fold excess) epoxidation of the tiglic amides (*S*)-**1a**−**c** was performed at 20 °C for 24 h; the conversions and diastereoselectivities are given in Table 1 (entries 4−6). These high conversions under such mild conditions are impressive, especially since electron-poor olefins possess a rather low reactivity toward electrophilic oxidants such as DMD and *m*-CPBA.[4] Also significant is the fact, as depicted in Table 1, that the substituents in the oxazolidine ring have only a minor influence on the diastereoselectivity of the epoxidation for DMD (entries 1−3) as well as *m*-CPBA (4−6). Still more surprising is the reversed diastereoselectivity between *m*-CPBA and DMD, since for *m*-CPBA the major diastereomer is the *lk* one, but for DMD it is *ul*. The configurational assignment is based on the X-ray structure of the *lk*-***2*****c** derivative (cf. Supplementary Information). To test the influence of the medium polarity and hydrogen bonding on the diastereoselectivity, the *m*-CPBA epoxidation of the substrate (*S*)-**1c** was conducted in several solvents. Although only a small effect was found on the diastereoselectivity (entries 6−9), a dramatic drop was observed for the conversion in MeOH.

To rationalize the opposite sense in the diastereoselectivity observed herein for the epoxidation of the tiglic amides (*S*)-**1** by DMD and *m*-CPBA (no other examples appear to be known for this pair of oxidants), it is necessary to know the preferred conformation of the starting amides. Although the

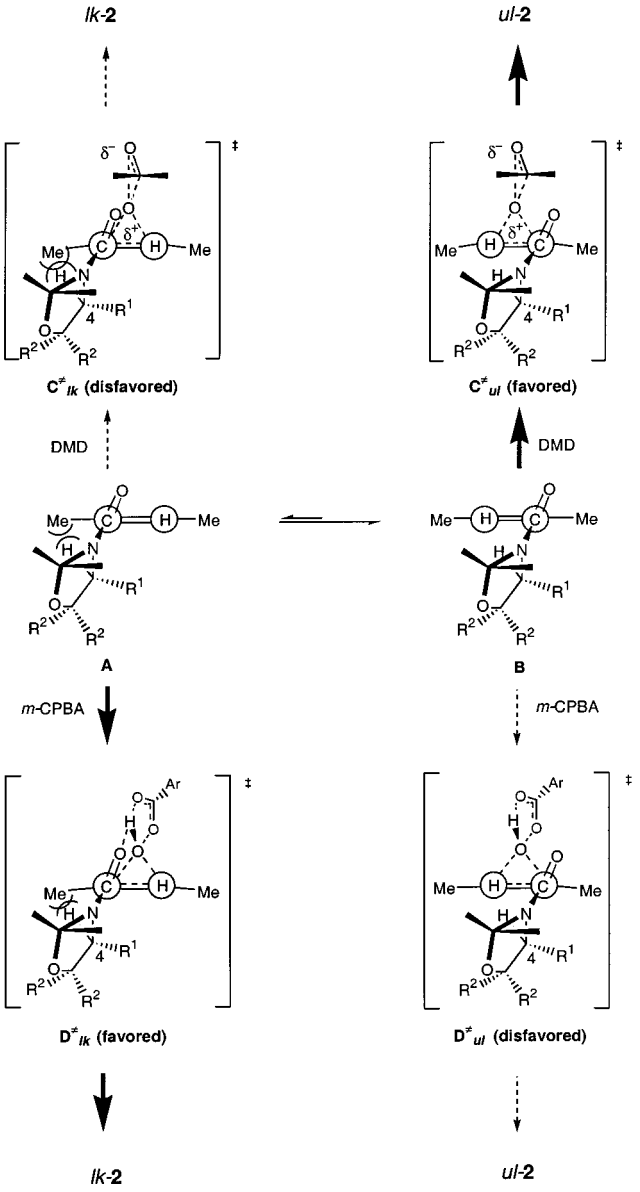
Table 1. Diastereoselectivities for the Epoxidation of Amides (*S*)-**1** by DMD and *m*-CPBA

entry	amide	R^1	R^2	oxidant	solvent	mb (%)[a]	convn (%)[a,b]	epoxides **2** *ul*:*lk*[a]
1	(*S*)-**1a**	CH_2Ph	H	DMD	CH_3COCH_3	89	88	91:09
2	(*S*)-**1b**	CH_2Ph	Me	DMD	CH_3COCH_3	>95	95	90:10
3	(*S*)-**1c**	Ph	H	DMD	CH_3COCH_3	91	>95	83:17
4	(*S*)-**1a**	CH_2Ph	H	*m*-CPBA	CH_2Cl_2	86	>95	15:85
5	(*S*)-**1b**	CH_2Ph	Me	*m*-CPBA	CH_2Cl_2	89	>95	07:93
6	(*S*)-**1c**	Ph	H	*m*-CPBA	CH_2Cl_2	87	>95	15:85
7	(*S*)-**1c**	Ph	H	*m*-CPBA	CH_3CN	82	>95	24:76
8	(*S*)-**1c**	Ph	H	*m*-CPBA	*t*-BuOH	88	>95	22:78
9	(*S*)-**1c**	Ph	H	*m*-CPBA	MeOH	83	7	34:66

[a] Determined by ^{1}H NMR analysis of characteristic signals directly on the crude product (error ± 5 of the stated value); durene was used as internal standard. The mass balances (mb) for entries 4−9 were determined gravimetrically. [b] All experiments were run for 24 h.

favored conformation of the *N*-tigloyl fragment is *syn* with respect to the oxazolidine ring, analogous to the *N*-acryloyl-oxazolidines described by Kanemasa and Porter,[15] the double bond is twisted with respect to the carbonyl group to avoid steric interactions with the substituent at the 4 position in the oxazolidine ring (Scheme 2). This conformational

Scheme 2



orientation of the double bond with respect to the carbonyl group is general for methacrylate and tiglate derivatives of imides and amides since the planar rotamers (*s-trans* and *s-cis* cannot be accommodated with the auxiliary for steric reasons.[16] Semiempirical calculations (cf. Supplementary Information) confirm this expectation for the tiglic amides (*S*)-**1** and give values of 56° (conformer **A** in Scheme 2) and 249° (conformer **B** in Scheme 2) for the dihedral angle between the double bond and the carbonyl group in their lowest energy conformations. The energy difference amounts to only ca. 1.4 kcal/mol in favor of conformer **B** due to the destabilization of **A** with respect to **B** on account of the steric interaction between the H-4 atom in the oxazolidine ring and the α-methyl group of the tigloyl moiety. On the basis of the Curtin−Hammett principle,[17] from this relatively low energy difference in the ground-state conformations, no significant diastereoselective control would be expected. Moreover, both π faces of the double bond are equally well shielded by the chiral auxiliary toward the attack of the oxidant in these two conformers; thus, the *Si* face is shielded in conformer **B** and the *Re* face in conformer **A**.

The opposite and high diastereoselectivities observed for DMD and *m*-CPBA may be rationalized in terms of the energy differences between the *unlike* and *like* transition structures for these oxygen-transfer processes, i.e., $\mathbf{C}^{\ddagger}_{lk}$ versus $\mathbf{C}^{\ddagger}_{ul}$ for DMD and $\mathbf{D}^{\ddagger}_{lk}$ versus $\mathbf{D}^{\ddagger}_{ul}$ for *m*-CPBA, as depicted in Scheme 2. The $\mathbf{C}^{\ddagger}_{lk}$ transition structure suggests that the DMD attack on the olefin is disfavored by the steric interactions between the H-4 atom in the oxazolidine ring and the α-methyl group of the tiglate moiety. These steric repulsions are absent in the $\mathbf{C}^{\ddagger}_{ul}$ transition structure, which would implicate a pronounced *unlike* diastereoselectivity, as is observed experimantally (Table 1, entries 1−3). In fact, these steric interactions should become more important in the transition structure $\mathbf{C}^{\ddagger}_{lk}$ compared to the ground-state conformer **A** of the amide (*S*)-**1** due to the partial rehybridization of the olefinic carbon atoms during the epoxidation trajectory. That the H-4/α-Me steric interaction appears to be decisive is suggested by the experimental fact that the

(7) (a) Bovicelli, P.; Lupattelli, P.; Mincione, E.; Prencipe, T.; Curci, R. *J. Org. Chem.* **1992**, *57*, 2182−2184. (b) Adam, W.; Brünker, H.-G.; Kumar, A. S.; Peters, E.-M.; Peters, K.; Schneider, U.; Schnering, H. G. *J. Am. Chem. Soc.* **1996**, *118*, 1899−1905. (c) Murray, R. W.; Singh, M.; Williams, B. L.; Moncrieff, H. M. *J. Org. Chem.* **1996**, *61*, 1830−1841. (d) Adam, W.; Paredes, R.; Smerz, A. K.; Veloza, L. A. *Liebigs Ann./Recueil* **1997**, 547−551. (e) Yang, D.; Jiao, G.-S.; Yip, Y.-C.; Wong, M.-K. *J. Org. Chem.* **1999**, *64*, 1635−1639.

(8) (a) Henbest, H. B.; Wilson, R. A. L. *J. Chem. Soc.* **1957**, 1958−1965. (b) Narula, A. S. *Tetrahedron Lett.* **1981**, *22*, 2017−2020. (c) Adam, W.; Smerz, A. K. *Tetrahedron* **1995**, *51*, 13039−13044. (d) Adam, W.; Paredes, R.; Smerz, A. K.; Veloza, L. A. *Eur. J. Org. Chem.* **1998**, 349−354.

(9) Lucero, M. J.; Houk, K. N. *J. Org. Chem.* **1998**, *63*, 6973−6977.

(10) Adam, W.; Hadjiarapoglou, L. In *Topics of Current Chemistry*; Herrmann, W. A., Ed.; Springer-Verlag: Berlin, Heidelberg, 1993; Vol. 164, pp 45−62.

(11) Adam, W.; Wirth, T.; Pastor, A.; Peters, K. *Eur. J. Org. Chem.* **1998**, *501*, 1−506.

(12) Shao, H.; Rueter, J. K.; Goodman, M. *J. Org. Chem.* **1998**, *63*, 5240−5244.

(13) (a) Huang, Z.; He, Y.-B.; Raynor, K.; Tallent, M.; Reisine, T.; Goodman, M. *J. Am. Chem. Soc.* **1992**, *114*, 9390−9401. (b) He, Y.-B.; Huang, Z.; Raynor, K.; Reisine, T.; Goodman, M. *J. Am. Chem. Soc.* **1993**, *115*, 8066−8072.

(14) The *like* and *unlike* stereochemical descriptors are defined in Seebach and Prelog (Seebach, D.; Prelog, V. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 654−660) and have been applied to the transition structures.

(15) (a) Kanemasa, S.; Onimura, K. *Tetrahedron* **1992**, *48*, 8631−8644. (b) Porter, N. A.; Rosenstein, I. J.; Breyer, R. A.; Bruhnke, J. D.; Wu, W.-X.; McPhail, A. T. *J. Am. Chem. Soc.* **1992**, *114*, 7664−7676.

(16) (a) Oppolzer, W.; Mills, R. J.; Réglier, M. *Tetrahedron Lett.* **1986**, *27*, 183−186. (b) Oppolzer, W.; Barras, J.-P. *Helv. Chim. Acta* **1987**, *70*, 1666−1675. (c) Curran, D. P.; Heffner, T. A. *J. Org. Chem.* **1990**, *55*, 4585−4595. (d) Kim, B. H.; Curran, D. P. *Tetrahedron* **1993**, *49*, 293−318.

(17) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Commpounds*; John Wiley & Sons: New York, 1994; Chapter 10, pp 647−655.

substitution pattern in the oxazolidine ring exerts only a small effect on the diastereomeric ratios (entries 1−3) and, thus, on the energy difference of the two transition structures $\mathbf{C}^{\ddagger}_{lk}$ and $\mathbf{C}^{\ddagger}_{ul}$.

The opposite sense in the stereoselectivity for *m*-CPBA implies that the *like* transition structure $\mathbf{D}^{\ddagger}_{lk}$ is favored over the *unlike* one $\mathbf{D}^{\ddagger}_{ul}$; consequently, factors other than the steric ones for DMD appear to operate in the case of *m*-CPBA. Indeed, sufficiently strong hydrogen-bonding interactions have been previously postulated between the peracid hydrogen atom and the carbonyl group of cyclic allylic carbamates and amides to rationalize the preferred *syn* diastereoselectivity in the *m*-CPBA epoxidation of 3-cyclohexenyl derivatives.[18] We propose similar hydrogen bonding to be also responsible in our acyclic tiglic substrates, which outweigh the steric effects implicated for the DMD oxidant. Thus, the $\mathbf{D}^{\ddagger}_{lk}$ transition structure would be favored over the $\mathbf{D}^{\ddagger}_{ul}$ one because hydrogen bonding between the amide carbonyl oxygen and the *m*-CPBA hydrogen atom is presumably sufficiently strong to override the H-4/α-Me steric repulsions in the $\mathbf{D}^{\ddagger}_{lk}$ geometry. This stabilization is not expected in the *unlike* transition structure $\mathbf{D}^{\ddagger}_{ul}$ because the carbonyl group and the peracid hydrogen atom are too far apart for effective hydrogen bonding. For the first time such unique hydrogen-bonding effects have been now uncovered for acyclic, electron-poor olefins such as the tiglic substrates. Mechanistically more significant, the opposite sense in the diastereoselectivity observed for *m*-CPBA and DMD may be rationalized by hydrogen bonding in the transition structure. While state-of-the-art computational chemistry might corroborate these unusual directing effects, the synthetic utility of these novel findings should be imperative: The mere choice of DMD versus *m*-CPBA permits us now to select the desired epoxide diastereomer for such tiglic substrates.

A dramatic drop in the *m*-CPBA reactivity was found when the epoxidation of the tiglic amide (*S*)-**1c** was conducted in MeOH (entry 9). That this decreased reactivity for this electron-poor olefin relates to the hydrogen-bonding efficiency of the solvent was confirmed when the reaction was conducted in *t*-BuOH, also a protic solvent but of lower acidity[19] and hence less effective for hydrogen bonding (entry 8). This reduced reactivity, which has also been observed in the *m*-CPBA epoxidation of the *N*,*N*-diethyltiglic amide **3** (cf. Supplementary Information), agrees well with the previously reported epoxidation of ethyl crotonate[20] and may be explained in terms of competitive hydrogen bonding between the solvent and the peracid. Therefore, for the less reactive electron-poor olefins (*S*)-**1** and the *N*,*N*-diethyltiglic amide **3**, assistance through hydrogen bonding is critical in the peracid epoxidation process.

In conclusion, a highly diastereoselective epoxidation of the (*S*)-**1a**−**c** tiglic acid amides by DMD and *m*-CPBA has been discovered which displays the reversed sense in the diastereoselectivity. For DMD, steric interactions dominate to afford the *unlike* diastereoselectivity, while hydrogen-bonding effects are responsible for the *like* diastereoselectivity in the case of *m*-CPBA.

Acknowledgment. We are grateful to the Deutsche Forschungsgemeinschaft (Schwerpunktprogramm: Sauerstofftransfer/Peroxidchemie), the European Comission (postdoctoral fellowship for A.P.), and the Fonds der Chemischen Industrie for financial support. Prof. Dr. K.-H. Drauz and Dr. M. Schwarm (Degussa-Hüls AG) are thanked for a generous gift of the optically active amino alcohols.

Supporting Information Available: Experimental Section with the synthetic details and characteristic spectral data of the α,β-unsaturated ammides (S)-**1a**−**c**, the optically active epoxides *ul*-**2a**−**c** and *lk*-**2a**−**c**, the *N*,*N*-diethyltiglic amide **3**, and the *N*,*N*-diethyldimethyloxiranecarboxamide **4**, the configurational assignment of *ul*-**2a**−**c** and *lk*-**2a**−**c** amides, and the semiempirical calculations for the preferred conformation of the amides (S)-**1a**−**c**. This material is available free of charge on the Internet at http://pubs.acs.org.

OL990405S

(18) Kocovský, P.; Starý, I. *J. Org. Chem.* **1990**, *55*, 3236−3243.

(19) Taft, R. W.; Kamlet, M. J. *J. Am. Chem. Soc.* **1976**, *98*, 2886−2894.

(20) Schwartz, N. N.; Blumbergs, J. H. *J. Org. Chem.* **1964**, *29*, 1976−1979.