J|A|C|S
COMMUNICATIONS

Published on Web 07/09/2002

Highly Diastereoselective Dioxetane Formation in the Photooxygenation of Enecarbamates with an Oxazolidinone Chiral Auxiliary: Steric Control in the [2 + 2] Cycloaddition of Singlet Oxygen through Conformational Alignment

Waldemar Adam,[†] Sara G. Bosio,*[,†] and Nicholas J. Turro[‡]

Institut für Organische Chemie, Universität Würzburg, Am Hubland, D-97074 Würzburg, Germany, and Department of Chemistry, Columbia University, 3000 Broadway, New York, New York 10027

Received May 7, 2002

Chiral auxiliaries have been successfully employed in controlling the diastereoselectivity of numerous reactions.[1] A notoriously difficult problem is the manipulation of the stereochemical course of singlet oxygen ($^1O_2$), the smallest possible cyclophile. In the past few years, we have shown that through the appropriate choice of the chiral inductor it is possible to control the stereoselectivity of the [4 + 2] cycloaddition of $^1O_2$.[2] For this purpose, optically active 2,2-dimethyloxazolidines proved to be highly effective chiral auxiliaries when attached to sorbic acid in the form of an amide linkage. Recently we have also discovered the diastereoselective ene reaction of $^1O_2$ with optically active oxazolidines, which have been equipped with an urea functionality.[3] The diastereoselective control was achieved in this ene reaction through remote hydrogen bonding between the urea NH bond and $^1O_2$, whereas steric factors were held responsible in the [4 + 2] cycloaddition. Similar efficacious hydrogen-bonding effects have been documented[4] for the [2 + 2] cycloadditions of $^1O_2$ with chiral allylic alcohols. To date, no cases appear to be known in which steric interactions efficiently guide the π-facial attack of $^1O_2$ in the dioxetane formation; however, the stereoselective dioxetane formation in the ozonolysis of vinylsilanes has been reported.[5] Herein we report the first example of a chiral-auxiliary-induced [2 + 2] cycloaddition between $^1O_2$ and oxazolidinone-functionalized enecarbamates, which proceeds with complete diastereoselectivity as a result of steric repulsions.

Evans' chiral auxiliary[6] was introduced into the enecarbamate substrate **2** by condensing the 4-alkyl-substituted oxazolidinones with the aldehyde **1**, which was prepared in three steps from methyl phenylacetate (Scheme 1). The 1-phenylethyl substituent at the C3 position of the double bond was chosen to minimize the ene reaction since the required coplanar alignment of the only allylic hydrogen atom is encumbered.[7] The optically active enecarbamates **2** were photooxygenated at −35 °C with 5,10,15,20-tetrakis(pentafluorophenyl)porphine (TPFPP) as sensitizer and a 800-W sodium lamp as light source. The dioxetanes **3** (Table 1) were obtained exclusively, but they readily decomposed at room temperature (ca. 20 °C) to the expected carbonyl products because of their thermally labile nature.

The [2 + 2] cycloaddition between the unsubstituted enecarbamate **2a** and $^1O_2$ displayed no diastereoselectivity (Table 1, entry 1), whereas the methyl derivative **2b**(3*S*) (Table 1, entry 2) and the isopropyl derivative **2c** (entries 3 and 4) afforded the diastereomerically pure dioxetanes [1*S*,2*S*]-**3c**(3*R*) and [1*S*,2*S*]-**3c**(3*S*). Within the experimental error of 5%, the other possible diastereomer could not be observed in the 600-MHz ^{1}H NMR spectra of the photooxygenate. When the configuration of the oxazolidinone stereogenic center was changed from *R* to *S*, the inverse configuration at the new stereogenic centers was obtained (entries 4 and 5). Also, in the polar solvent mixtures CD_3OD:$CDCl_3$ (4.1:1) and CD_3COCD_3:$CDCl_3$ (2.4:1), the diastereomerically pure dioxetane [1*S*,2*S*]-**3c**(3*R*) was formed in the photooxygenation of enecarbamate **2c**(3*R*).

Scheme 1. Synthesis of Enecarbamate **2** with Oxazolidinones as Chiral Auxiliary

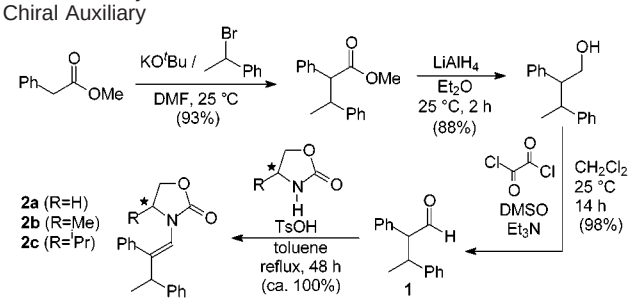
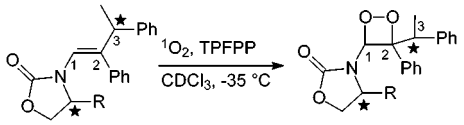


Table 1. Diastereoselective Dioxetane Formation in the Photooxygenation of Enecarbamate **2**



2a-d **3a-d**

entry[a]	enecarbamate	R	dr[b]
1	**2a**	H	50:50
2	**2b**(3*S*)	(*R*)-Me	>95:05 [1*S*,2*S*]
3	**2c**(3*R*)	(*R*)-^{i}Pr	>95:05 [1*S*,2*S*]
4	**2c**(3*S*)	(*R*)-^{i}Pr	>95:05 [1*S*,2*S*]
5	**2d**(3*S*)	(*S*)-^{i}Pr	>95:05 [1*R*,2*R*]
6[c]	**2c**(3*R*)	(*R*)-^{i}Pr	>95:05 [1*S*,2*S*]
7[d]	**2c**(3*R*)	(*R*)-^{i}Pr	>95:05 [1*S*,2*S*]

[a] The mass balance was ≥95% at complete conversion in all cases; determined by ^{1}H NMR spectroscopy with dimethyl isophthalate as internal standard. [b] Determined by the area under the characteristic signals in the ^{1}H NMR spectrum directly on the photooxygenate (error ±5% of the stated value); in brackets are given the configurations of the dioxetane at the two new stereogenic centers. [c] CD_3OD:$CDCl_3$ (4.1:1). [d] CD_3COCD_3:$CDCl_3$ (2.4:1).

The absolute configuration of the dioxetanes **3** was established by reduction to the diol **4** with L-methionine[8] (Scheme 2). From the diol **4**, the chiral auxiliary was removed by treatment with $NaBH_4$/DBU[9] to afford the diol **5**, as shown exemplarily for dioxetane **3c** (see Supporting Information).

The *R* configuration at the C3 position is known (Scheme 2) from an X-ray diffraction analysis of the (*S*)-configured enecar-

* To whom correspondence should be addressed. E-mail: adam@chemie.uni-wuerzburg.de.
† Universität Würzburg.
‡ Columbia University.

10.1021/ja026815k CCC: $22.00

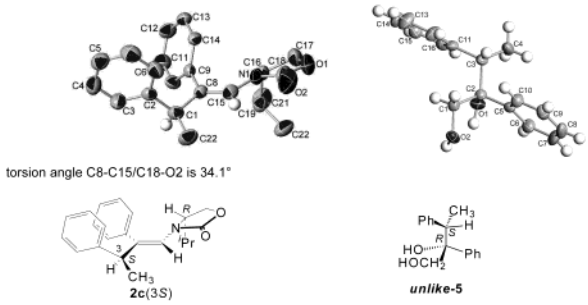
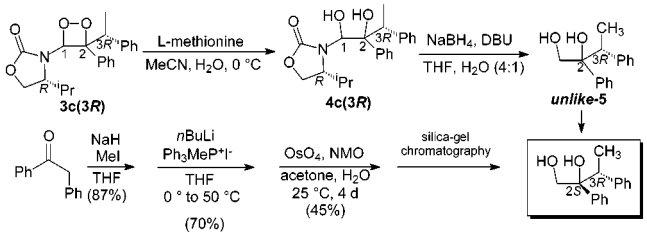
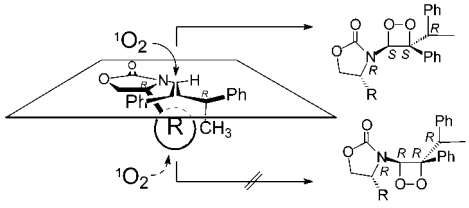


Figure 1. Crystal structures of the enecarbamate **2c** and diol **5**.

Scheme 2. Chemical Correlation for the Configurational Assignment of the Dioxetane **3c**



Scheme 3. Preferred π-Facial Attack of $^1O_2$, Controlled by Steric Shielding of the R Substituent in the Enecarbamate **2**



bamate diastereomer **2c(**3*S***)** (Figure 1). The diol **5** was prepared independently in three steps from desoxybenzoin (Scheme 2). The two diastereomers of the diol **5** were separated by silica gel chromatography and the NMR spectra of the *unlike* diastereomer [the configuration was determined by X-ray analysis (Figure 1)] were identical with those of the diol **5**, obtained from dioxetane **3c(**3*R***)** with dr > 95:5. Since in the 2,3-diphenyl-1,2-butanediol (**5**) derived from the dioxetane **2c(**3*R***)**, the C3 stereogenic center is already known to possess the *R* configuration, it follows that the C2 site possesses the *S* configuration. Thus, since the oxazolidinone stereogenic center is *R*-configured, the (1*S*,2*S*)-dioxetane was obtained in the photooxygenation (entry 3, Table 1), which establishes that $^1O_2$ attacks exclusively from above (see Scheme 3) in the [2 + 2] cycloaddition to the enecarbamate **2c**, and that with complete π-facial control.

The exclusive diastereoselectivity of the $^1O_2$ reaction is already expressed in the case of the (*R*)-4-methyl-substituted enecarbamate **2b(**3*S***)**, since the other possible diastereomer could not be observed within the experimental uncertainty of 5%; thus, even a methyl group in the oxazolidinone suffices for perfect π-facial control (entry 2, Table 1). It should be emphasized that the configuration at the C3 position of the enecarbamate does not influence the diastereoselectivity, since the same diastereomer is obtained irrespective of whether the (3*R*)- or (3*S*)-configured encarbamates **2c(**3*R***)** and **2c(**3*S***)** (entries 3 and 4, Table 1) are employed. Furthermore, the photooxygenation of enecarbamate **2c(**3*R***)** in CD_3OD:$CDCl_3$ (4.1:1) and in CD_3COCD_3:$CDCl_3$ (2.4:1) solvent mixtures (entries 6 and 7, Table 1) resulted in the same selectivity as in $CDCl_3$. Therefore, the diastereomeric ratio also does not depend on the solvent polarity, which suggests that the carbonyl group plays no significant role in the stereochemical outcome of this [2 + 2] cycloaddition. Substantiating this inference is the X-ray structure of the enecarbamate **2c(**3*S***)**, which shows a dihedral angle of only 34° between the CO double bond in the oxazolidinone and the CC double bond of the enecarbamate (Figure 1). This is due to the conjugation of the nitrogen atom with both the carbonyl group and the CC double bond. Consequently, the carbonyl group may be distorted only moderately from the planar arrangement and cannot engage in steric or electronic or both effects with the attacking $^1O_2$.

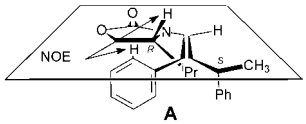


Figure 2. Conformer **A** of the enecarbamate **2c**(3*S*) assigned by NOE.

Mechanistically significant are the NOE effects of the enecarbamate **2c(**3*S***)**, which show that the conformer **A** is preferred in solution (Figure 2). In this conformer, the lower face of the enecarbamate double bond is shielded by the isopropyl substituent of the oxazolidinone ring. Consequently, $^1O_2$ attack occurs from the upper face [see Scheme 3, shown for **3c(**3*R***)**],[10] as is observed experimentally.

Our unprecedented results for the reaction of oxazolidinone-substituted enecarbamates with $^1O_2$ demonstrate that an appropriate choice of the chiral auxiliary enables complete diastereofacial control in the [2 + 2] cycloaddition even for $^1O_2$, the smallest of all cyclophiles. This high diastereoselectivity is rationalized in terms of effective π-facial control through steric shielding by the substituent at the chirality center of the oxazolidinone auxiliary. Two new stereogenic centers are introduced with complete control of diastereoselectivity; the resulting dioxetane may be derivatized to synthetically useful, enantiomerically pure hydroxylated products.

Acknowledgment. The work at Würzburg was generously supported by the Deutsche Forschungs-Gemeinschaft (Schwerpunktprogramm "Peroxidchemie") and the Fonds der Chemischen Industrie; the work at New York was financed by the National Science Foundation through Grant CHE-01-10655. We thank Dr. M. Schwarm (Degussa-Hüls AG) for a generous gift of the oxazolidinones and alaninol.

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

References

(1) (1) Jones, S. J. *Chem. Soc., Perkin Trans. 1* **2002**, *95*, 1−21.
(2) Adam, W.; Güthlein, M.; Peters, E.-M.; Peters, K.; Wirth, T. *J. Am. Chem. Soc.* **1998**, *120*, 4091−4093.
(3) Adam, W.; Peters, K.; Peters, E.-M.; Schambony, S. B. *J. Am. Chem. Soc.* **2000**, *122*, 7610−7611.
(4) Adam, W.; Saha-Möller, C. R.; Schambony, S. B. *J. Am. Chem. Soc.* **1999**, *121*, 1834−1838.
(5) Avery, M. A.; Jennings-White, C.; Chong, W. K. M. *J. Org. Chem.* **1989**, *54*, 1789−1792.
(6) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238−1256. (b) Evans, D. A.; Urpi, F.; Somers, T. C.; Clark, J. S.; Bilodeau, M. T. *J. Am. Chem. Soc.* **1990**, *112*, 8215−8216. (c) Evans, D. A.; Chapman, K. T.; Bisaha, J. *J. Am. Chem. Soc.* **1988**, *110*, 1238−1256. (d) Ager, D. J.; Prakash I.; Schaad, D. R. *Aldrichimica Acta* **1997**, *30*, 3−12.
(7) Gollnick, K.; Hartmann, H.; Paur, H. In *Oxygen and Oxy-Radicals in Chemistry and Biology*; Rodgers, M. A. J., Powers, E. L., Eds.; Academic Press: New York, 1981; pp 379−395.
(8) Adam, W.; Hadjiarapoglou, L.; Mosandl, T.; Saha-Möller, C. R. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 200−202.
(9) Gaul, C.; Schärer, K.; Seebach, D. *J. Org. Chem.* **2001**, *66*, 3059−3073.
(10) Note that in the chemical correlation (Scheme 2), the **3c**(3*R*) dioxetane was used, whereas the NOE effects (Figure 2) were determined on the **2c**(3*S*) enecarbamate; fortunately, the stereogenic center at the C3 position does not influence the π-facial attack (Scheme 3).

JA026815K