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Control of the Mode Selectivity (Ene Reaction versus [2 + 2] Cycloaddition) in the Photooxygenation of Ene Carbamates: Directing Effect of an Alkenylic Nitrogen Functionality

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The control of the mode selectivity (ene reaction, [2 + 2] and [4 + 2] cycloaddition) in the reaction of singlet oxygen with olefins persist to be a formidable challenge to this day.[1] For example, in the photooxygenation of electron-rich olefins with allylic hydrogen atoms, ene reaction and [2 + 2] cycloaddition may occur concurrently, and usually ene reactivity dominates.[2] Nevertheless, the [2 + 2] cycloaddition becomes the preferred reaction mode when the allylic C−H bond is conformationally not properly aligned (coplanar with the π bond)[3] or when the incoming singlet oxygen is steered to the side of the double bond without an abstractable allylic hydrogen atom.[3,4] Such a steering effect is exercized by allylic nitrogen[4] or oxygen[5] functionalities, which promote [2 + 2] cycloaddition.

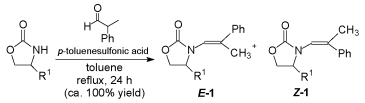
No examples appear to have been reported in which an alkenyl nitrogen functionality controls the mode selectivity in the competition between ene reaction and [2 + 2] cycloaddition of singlet oxygen. For this purpose, we have chosen the *E* and *Z* diastereomers of the ene carbamates **1** (Table 1), equipped with an oxazolidinone chiral auxiliary to assess also the π-facial selectivity for the competing reaction modes, a novel concept that merits mechanistic examination. The ene carbamates **1** are well suited substrates to test the mode selectivity because all three reaction modes may take place, namely the ene reaction (allylic proton), [2 + 2] cycloaddition (activated double bond), and [4 + 2] cycloaddition (styrene functionality).

The ene carbamates **1** were obtained by condensing Evans' chiral oxazolidinones[6] with the 2-phenylpropanal (Table 1). The *E*/*Z* ratio depended on the size of the substituent in the oxazolidinone ring. While the unsubstituted ene carbamate **1a** and the phenyl derivative **1d** were formed nondiastereoselectively (ca. 50:50 mixture of the two double-bond isomers), the methyl and the isopropyl substituent gave appreciable amounts of *E* diastereomers. As expected, the *tert*-butyl substituent displayed the highest *E* selectivity since the steric repulsion with the phenyl group on the double bond is the most effective.

After chromatographic separation of the double-bond isomers, the individual *E* and *Z* diastereomers of the optically active ene carbamates **1** were photooxygenated at −32 °C with 5,10,15,20-tetrakis(pentafluorophenyl)porphine (TPFPP) as sensitizer and an 800-W sodium lamp as light source (Table 2).

As a general trend, a substantial difference in the mode selectivity is displayed by the product data in Table 2: Whereas the photooxygenation of the ene carbamates ***E*-1** leads preferably to the hydroperoxides **3** (entries 1 and 3−6), the reaction of the ***Z*-1** diastereomer yields mainly the [2 + 2]-cycloadducts **2** (entries 2 and 7−10).

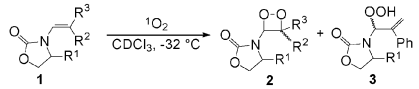
Table 1. Diastereomeric Ratios of the Ene Carbamates ***E,Z*-1** in the Condensation of Oxazolidinones and 2-Phenylpropanal



substrate	R^1	***E*-1**	***Z*-1**
1a	H	53	47
1b	Me	73	27
1c	*i*Pr	71	29
1d	Ph	50	50
1e	*t*Bu	83	17

[a] Determined from the area under the characteristic signals in the ^{1}H NMR spectrum directly on the crude product (error ±5% of the stated value).

Table 2. Photooxygenation of the Enecarbamates **1a**−**e**



					selectivity[a]		
					mode	diastereo	
entry[b]	substrate	R^1	R^2	R^3	[2 + 2]:ene **2**:**3**	ene	[2 + 2]
1	***E*-1a**	H	Me	Ph	15:85	−	−
2	***Z*-1a**	H	Ph	Me	80:20	−	−
3	***E*-1b**	(*R*)-Me	Me	Ph	16:84	88:12	n.d.
4	***E*-1c**	(*R*)-*i*Pr	Me	Ph	36:64	83:17	n.d.
5	***E*-1d**	(*S*)-Ph	Me	Ph	8:92	71:29	n.d.
6	***E*-1e**	(*S*)-*t*Bu	Me	Ph	23:77	91:9	n.d.
7	***Z*-1b**	(*R*)-Me	Ph	Me	80:20	53:47	>95:5
8	***Z*-1c**	(*R*)-*i*Pr	Ph	Me	75:25	56:44	>95:5
9	***Z*-1d**	(*S*)-Ph	Ph	Me	87:13	85:15	>95:5
10	***Z*-1e**	(*S*)-*t*Bu	Ph	Me	60:19[c]	>95:5	>95:5

[a] Determined from the area under the characteristic signals in the ^{1}H NMR spectrum directly on the photooxygenate (error ±5% of the stated value) at the very beginning (5−10% conversion) of the photooxygenation, at which point the decomposition products are still absent. [b] Run in $CDCl_3$ at −32 °C with TPFPP as sensitizer; 100% conversion of the enecarbamate. [c] Also 21% of the endoperoxide **4e** was obtained (see Supporting Information).

This diastereomer-dependent dichotomy in the mode selectivity may be understood in terms of an orbital-directing effect of the enamine-type functionality. The orbital interaction between the HOMO (Figure 1, for ***Z*-1d**) of the ene carbamate and the LUMO of the incoming singlet oxygen directs the attack onto the side that bears the nitrogen atom. Since for the ene carbamates ***Z*-1** no allylic hydrogen atom is present on this side of the double bond, [2 + 2] cycloaddition takes place preferably (entries 2 and 7−10). The [4 + 2] and the [2 + 2] cycloadditions may compete, when the double-bond and the phenyl substituent are essentially coplanar, as is presumably the case for substrate ***Z*-1e** (Table 2, entry 10).

In contrast, in the case of enecarbamates ***E*-1,** the nitrogen atom and the methyl group are located on the same side of the double

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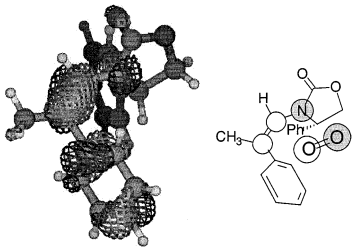


Figure 1. HOMO of the ***Z*-1d** ene carbamate (calculated by the B3LYP method) and its orbital-directing effect of the singlet oxygen attack.

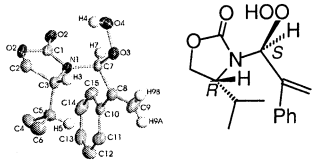


Figure 2. X-ray crystal structure of the hydroperoxide **3c**.

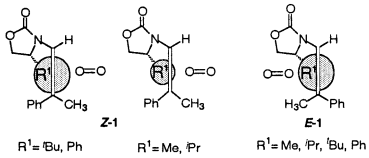


Figure 3. Steric shielding for the ene reaction of singlet oxygen with ***Z*-1** and ***E*-1** substrates.

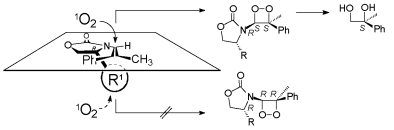
bond. Thus, the incoming singlet oxygen abstracts an allylic hydrogen atom from the methyl group and a high mode selectivity in favor of the ene reaction is expressed (entries 1 and 3−6). A similar effect (*cis*-methoxy effect[7]) was found for the addition of singlet oxygen to methoxy styrenes,[8] but in that case the competition occurs between the ene reaction and [4 + 2] cycloaddition.

The diastereoselectivity of the ene reaction for the ene carbamates ***E*-1** ranges from 71:29 to 91:9 (Table 2), except for the encarbamates ***E*-1a** and ***Z*-1a** without a substituent at the oxazolidinone ring, for which no diastereomers are possible (entries 1 and 2, Table 2). The absolute configuration for the major diastereomer of the hydroperoxide **3c** (entry 5) was determined to be 1*S*,4′*R* by means of X-ray analysis (Figure 2). The ene reaction of the ***Z*-1** isomer gave diastereomeric ratios that ranged from 53:47 to >95:5. For both sets of *E*/*Z* ene products, the increasing trend in the dr values (Table 2) follows the steric demand of the R^1 substituent in the oxazolidinone ring, but for the *Z* isomers (entries 7−10) the differentiation is more pronounced than for the *E* isomers (entries 3−6).

To obtain ene products, the attack of singlet oxygen must occur on the side of the methyl group (Figure 3). As expected, for the smaller methyl and isopropyl substituents (Table 2, entries 7 and 8), the steric shielding is not as effective as for the larger phenyl and *tert*-butyl groups (entries 9 and 10). The latter R^1 substituents are sufficiently spacious to cover up the double bond from below and block sterically hydrogen abstraction from the methyl group in the ***Z*-1** substrates. Not only does the $^1O_2$ attack occur preferentially from above (Figure 3), but also the ene reactivity is suppressed in favor of [2 + 2] cycloaddition compared to that in the ***E*-1** isomers. In the case of the ***E*-1** substrates, the oxazolidinone ring is on the same side of the double bond as the methyl group. Such proximity of the latter to the nitrogen functionality favors ene reactivity (orbital steering in Figure 1). The more severe steric interactions of the substituents of the ***E*-1** substrates with singlet oxygen are responsible for the increased but less differentiated attack from above compared to that in the ***Z*-1** diastereomers.

In regard to the diastereoselectivity of the [2 + 2] cycloaddition, the photooxygenation of the ene carbamates ***Z*-1** proceeds exclusively from above for all R^1 substituents (Table 2, entries 7−10), except R^1 = H (Table 2, entry 2). The absolute configuration of the dioxetanes was determined by their conversion to the corresponding diols[9] and HPLC analysis, with the enantiomerically pure diol as reference (see Supporting Information). In the case of the ene carbamates ***E*-1**, the diastereoselectivity could not be determined because the dioxetanes were too labile and only the decomposition products were detected. The high diastereoselectivity in the dioxetane formation from the ***Z*-1** ene carbamates may be explained in terms of complete steric hindrance[10] (Scheme 1) of the $^1O_2$ attack on the lower side of the double bond by the R^1 oxazolidinone substituent.

Scheme 1. Steric Shielding in the [2 + 2] Cycloaddition of Singlet Oxygen to the ***Z*-1** Substrates



The present study demonstrates that the choice of the diastereomeric ene carbamates ***E*-1** and ***Z*-1** has been most fortunate in assessing the control of the mode selectivity of singlet oxygen, namely the ene reaction versus [2 + 2] cycloaddition. For the first time, the usually preferred ene reactivity may be supressed in favor of [2 + 2] cycloaddition by manipulating the double-bond geometry in the ene carbamate. Additionally, the oxazolidinone chiral auxiliary provides high π-facial selectivity through purely steric shielding by its R^1 substituent for both the ene reaction and the [2 + 2] cycloaddition. Thus, through the judicious combination of the double-bond geometry and the chiral auxiliary in olefinic substrates, mode-selective photooxygenations with high diastereoselectivity may be developed, an unprecedented concept in singlet-oxygen chemistry.

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

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