Diastereoselective and Regioselective Singlet-Oxygen Ene Reaction of Oxazolidine-Substituted Alkenes: Control through Hydrogen Bonding Mediated by the Urea Functionality of Chiral Auxiliaries

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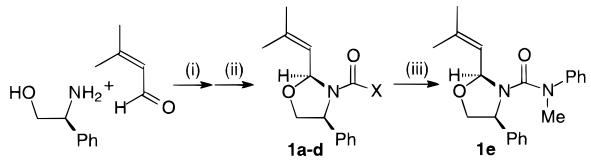
The ene reaction between singlet oxygen ($^1O_2$) and alkenes with allylic hydrogen atoms has attracted much attention in the last years both from the synthetic[1] and mechanistic[2] points of view. Most attention has been directed toward the stereochemical control of the new stereogenic center that is formed in this process.[3] Although much data has by now been accumulated to define the prerequisites for high diastereoselectivity in this reaction, all attempts hitherto to achieve chiral-auxiliary-induced diastereomeric control in the singlet-oxygen ene reaction led only to low or at best moderate (dr ≤ 82:18) selectivities.[3,4] Nevertheless, chiral auxiliaries have been successfully employed in directing effectively the stereochemical course of a great variety of reaction types,[5] also that of singlet oxygen ([4 + 2] cycloaddition).[6] The facts at hand accentuate that singlet oxygen, the smallest possible enophile, is not sensitive enough to the steric repulsion usually exerted by the chiral auxiliaries and that such an approach seems futile. Clearly, a completely different strategy must be used for achieving efficient diastereoselectivity mediated by chiral auxiliaries in the singlet-oxygen ene reaction.

The recently established *hydroxy-group directivity*[3b] in the photooxygenation of chiral allylic alcohols with 1,3-allylic strain has focused on the efficacy of electronic interactions through hydrogen bonding between the substrate and singlet oxygen. Herein we report that, indeed, a high chiral-auxiliary-controlled diastereoselectivity may be realized by providing beneficial hydrogen bonding in the ene reaction between singlet oxygen and an urea functionality. As chiral auxiliaries, we chose optically active *N*-acetylated oxazolidines,[7,8] which are readily removed after the key diastereoselective step,[8] and are structurally related to those introduced by Kanemasa and Porter.[11]

The oxazolidines **1a**−**d** were synthesized by condensing *S*-phenylglycinol with 3-methyl-2-butenal in analogy with the reported procedure,[8] followed by acylation (Scheme 1). The

Scheme 1[a]

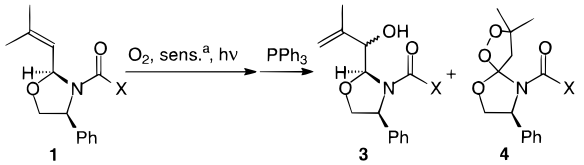


[a] (i) molecular sieves (4 Å), CH_2Cl_2, 20 °C, 3 h. (ii) **1a** (X = O^{t}Bu): Boc_2O, EtOAc, 77 °C, 15 h; **1b** (X = Ph): PhCOCl, *N*-methylmorpholine, CH_2Cl_2, 20 °C, 10 h; **1c**/**1d** (X = ArNH, see Table 1): ArNCO, Et_2O/CH_2Cl_2, 20 °C, 16 h. (iii) CH_3I, KOH, DMSO, 20 °C, 16 h.

N-methylated oxazolidine **1e** was prepared by methylation of *N*-phenyl derivative **1c**. The *like* relative configuration of the stereogenic centers in the oxazolidine ring was assessed by NOE spectroscopy for all cases.

The oxazolidines **1** were photooxygenated at low temperature (−5 °C or below) by using 5,10,15,20-tetrakis(pentafluorophenyl)-porphine (TPFPP) as sensitizer, followed by in situ reduction of the resulting hydroperoxides with triphenylphosphine. The allylic alcohols **3** were obtained as main regioisomers, along with some of the *spiro*-dioxolanes **4** (Table 1) that arise from hydrogen

Table 1. Regio- and Diastereoselectivities in the Photooxygenation of the Optically Active Oxazolidines **1**



			conditions				selectivity[b]	
entry	substrate	X	solvent	*T* [°C]	*t*[d] [h]	mb[b,c] [%]	regio (**3**:**4**)	diastereo (***lk*-3**:***ul*-3**)
1	**1a**	O^{t}Bu	CCl_4	−5	20	92	75:25	25:75
2	**1b**	Ph	$CDCl_3$	−5	23	86	86:14	45:55
3	**1c**	NHPh	$CDCl_3$	−5	4	>95	93: 7	94: 6
4	**1c**	NHPh	d_6-acetone	−10	40	72	96: 4	85:15
5	**1d**	NHAr[e]	$CDCl_3$	−10	28	85	96: 4	>95: 5
6	**1e**	NMePh[f]	$CDCl_3$	−10	48	90	70:30	41:59

[a] Sensitizer was 5,10,15,20-tetrakis(pentafluorophenyl)porphine (TPFPP). [b] Determined by ^{1}H NMR spectroscopy with 1,2-diphenylethane as internal standard, error ±5% of the stated value. [c] Mass balance. [d] Time needed for full conversion (>95%). [e] *p*-Nitrophenyl. [f] Dimethyl isophthalate as internal standard.

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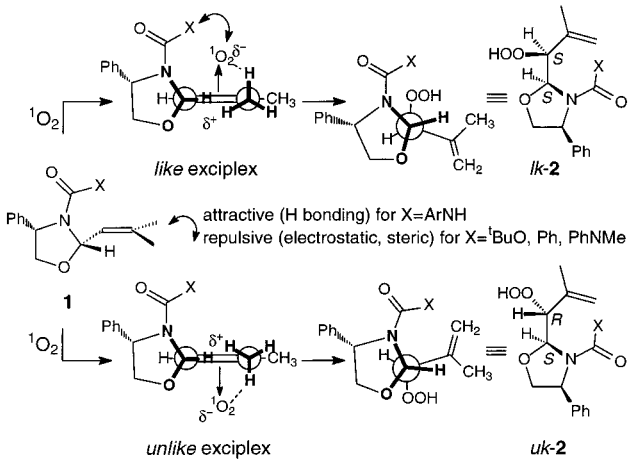
abstraction at the aminal position in the substrates **1**, followed by cyclization of the resulting hydroperoxides. The relative configuration of the predominantly formed allylic alcohol **3c** was determined by X-ray analysis.[10] Comparison of the NMR data did not allow a definitive assignment of the configurations for the other derivatives; however, for the reported bromination of similar oxazolidine-substituted olefins, the usually observed *unlike* selectivity was established[8] and by chemical correlation assessed for **3a**, **3b**, and **3e**.

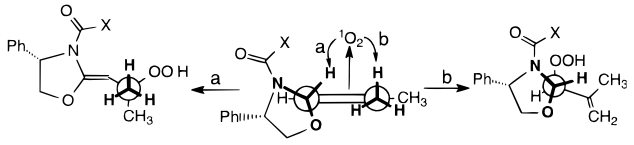
The ene reaction of the oxazolidines **1a** and **1b** with $^1O_2$ (entries 1 and 2 in Table 1) displays the moderate or even low diastereoselectivity that is usually found in attempted chiral-auxiliary-controlled singlet-oxygen ene reactions.[4] The observed slight preference for the *unlike* attack of singlet oxygen, that is, opposite to the urethane (**1a**, X = O^{t}Bu) and amide (**1b**, X = Ph) functionalities, may be understood in terms of the repulsive (electrostatic, steric) interactions between the incoming singlet oxygen and the carbonyl substituent on the nitrogen atom that shields the *like* face of the double bond (Scheme 2). This

Scheme 2



interaction may derive from a weak electrostatic repulsion between the partially negatively charged carbonyl oxygen[11] and the negatively polarized singlet oxygen or a weak steric interaction between singlet oxygen and the substituent of the carbonyl moiety (^{t}BuO or Ph in **1a** or **1b**). Furthermore, the appreciable (up to 25%) amounts of the 1,2-dioxolanes **4**, formed by cyclization of the minor regioisomer (path a in Scheme 3), reflect the moderate regioselectivity of the reaction.

Scheme 3



In contrast to the low selectivities in the above ene reactions, the photooxygenation of the ureas **1c** and **1d** in $CDCl_3$ (Table 1, entries 3 and 5) yielded, after in situ reduction, the corresponding *like* allylic alcohols *lk*-**3c** and *lk*-**3d** nearly exclusively. Not only does this oxyfunctionalization proceed highly diastereo- and regioselectively, but also *the sense of the preferred attack is reversed*! This impressive selectivity cannot be explained in terms of steric or electrostatic interactions, as proposed for the urethane (**1a**) and amide (**1b**) substrates. Instead, electronic attraction through hydrogen bonding between the negatively charged terminal oxygen atom and the favorably oriented NH donor of the urea functionality in the *like* exciplex (Scheme 2) manifests itself, which lowers the barrier of the exciplex formation. Since such coordination is prohibited in the *unlike* exciplex, the *like* product is formed predominately, in compliance with the observed high diastereoselectivity. In addition, an excellent regioselectivity accompanies the photooxygenation of the derivatives **1c** and **1d**; presumably in the preferred *like* exciplex, the hydrogen bonding of the singlet oxygen to the NH group impedes the abstraction of the aminal hydrogen atom (see Scheme 2). The high regioselectivity coupled with the excellent diastereoselectivity (cf. Table 1) is fortunate and speaks unequivocally for the efficacy of hydrogen bonding in oxygen-transfer processes.[3b] That hydrogen bonding operates as controlling factor is further emphasized by the fact that in the more polar solvent acetone, the diastereoselectivity of the ene reaction drops significantly (cf. Table 1, entry 4). The beneficial intra-exciplex hydrogen bonding is disturbed through competing intermolecular associations of the substrate to acetone molecules. Similar to the ene reaction of allylic alcohols and derivatives with singlet oxygen,[12] no appreciable effect has been detected on the regioselectivity. The dioxolanes **4c** and **4d** stem from the *unlike* exciplex (Scheme 2), which constitutes a minor pathway and the expected change in the regioselectivity in acetone versus chloroform is too small to be sensed within experimental error. However, capping of the NH functionality by methylation, as in the derivative **1e**, not only completely erases the control of diastereoselectivity, it significantly reduces also the regioselectivity (cf. Table 1, entry 6).

In summary, the present results show convincingly that the diastereoselectivity as well as the regioselectivity in the ene mode of singlet oxygen may be effectively steered by chiral oxazolidine auxiliaries through hydrogen bonding between the NH group of the urea functionality and the attacking singlet oxygen. Although the directing propensity of hydroxy[12] and amino[13] groups to act as efficient hydrogen donors in the singlet-oxygen ene reaction is well documented, it is unprecedented for the NH hydrogen-bonding donor of an urea functionality, especially, since it is attached to the chiral auxiliary. Subsequent removal of the chiral auxiliary opens up promising prospects in the preparation of optically active building blocks for asymmetric synthesis.

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

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