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Temperature and Solvent Control of the Stereoselectivity in the Reactions of Singlet Oxygen with Oxazolidinone-Substituted Enecarbamates

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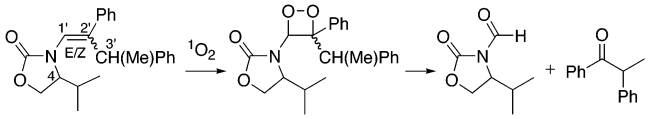
Oxazolidinone-substituted chiral enecarbamates **1** are mechanistically versatile systems for the study of conformational, electronic, stereoelectronic, and steric effects on the stereoselectivity of oxidation reactions at the alkene functionality.[1] The photooxygenation of the *Z*-isomers of **1** leads to diastereomerically pure dioxetanes **2**, which result from the attack of $^1O_2$ exclusively on the face *anti* to the isopropyl substituent of the oxazolidinone stereogenic center at the C-4 position (Table 1).[1e] The rate of addition is further governed by the configuration of the chirality center at the C-3′ position of the alkenyl side chain, such that partial conversion of **1** affords nonracemic methyldesoxybenzoin (MDB), the decomposition product of **2**.[1b] Thus, the enantiomeric excess (ee) of MDB serves as a chemical probe for the reactivity of the substrate diastereomers as a function of structure and environment.

We now report that the *E*-isomers **1c**,**d** yield higher ee values for MDB than their *Z* counterparts **1a**,**b**. Thus, by simple modification of the geometry of the alkene functionality, the directing influence of the allylic chirality center is approximately doubled. For example, a ca. 50:50 mixture of (3′*R*)-**1c** and (3′*S*)-**1c** reacts with $^1O_2$ to give 55±5% ee of *R*-MDB, i.e., about twice as high as the corresponding *Z* substrate pair **1a**. The reaction of the diastereomeric pair (3′*R*,*S*)-**1d**, the enantiomeric complement to **1c**, gives similar ee values, but the opposite enantiomer of MDB is favored. Furthermore, as we show in Table 2, the ee values for the *E*-isomers **1c** and **1d** are remarkably sensitive to temperature and solvent; i.e. we demonstrate control of enantioselectivity as has been achieved in the enantiodifferentiating *Z*/*E* photoisomerization of cyclooctene.[2] The latter provides an exemplar for the solvent and temperature dependence of the stereocontrol in the systems reported here.

The enantioselectivity of MDB is based on a critical balance of the enthalpy and entropy terms, and the large contribution of the entropy factor (Table 2, Figures S1 and S2 of the Supporting Information) suggests that the conformational flexibility/rigidity of the substrates/transition states and their solvation/desolvation behavior are crucial in the stereodifferentiating component of the mechanism for dioxetane (and MDB) formation. In such a case, the ee value is directly related to the differential activation parameters $\Delta\Delta H^{\ddagger}$ and $\Delta\Delta S^{\ddagger}$ through eqs 1 and 2.[3] Enthalpic control applies when the stereoselectivity is enhanced upon decreasing the reaction temperature, a phenomenon common to many thermal asymmetric reactions.[4] In CD_3CN, CD_2Cl_2, and $CDCl_3$, however, the sense in the selectivity switches as the reaction temperature is changed at the equipodal temperature, T_0 (at T_0, the % ee is zero). These results suggest the formation of a reversible exciplex intermediate in the stereodifferentiating step[3a] with the conformational mobility more pronounced in the *E*- than in the *Z*-isomer;

Table 1. Stereoselectivity of the MDB Formation in the Photooxygenation[a] of the Enecarbamates **1** in $CDCl_3$



1 **2** **3** **MDB**

entry	substrate	convn (%)[b]	**MDB** (% ee)[b]
1	(*Z*,4*R*,3′*R*)-**1a** + (*Z*,4*R*,3′*S*)-**1a**	49 ± 12	27 ± 4 (*R*)
2	(*Z*,4*S*,3′*S*)-**1b** + (*Z*,4*S*,3′*R*)-**1b**	47 ± 10	11 ± 2 (*S*)
3	(*E*,4*R*,3′*R*)-**1c** + (*E*,4*R*,3′*S*)-**1c**	47 ± 3	55 ± 5 (*R*)
4	(*E*,4*S*,3′*S*)-**1d** + (*E*,4*S*,3′*R*)-**1d**	50 ± 3	40 ± 8 (*S*)

[a] Photooxygenations were performed using methylene blue as sensitizer. [b] Values are an average of three determinations, and ranges are taken at the 95% confidence level.

Table 2. Activation Parameters and Stereoselectivity Factors (**s**) for the MDB Formation in the Oxidation of **1** by $^1O_2$ as a Function of Solvent and Temperature

substrate[a]	solvent	temp (°C)	MDB[b] (% ee)	convn[c] (%)	s[d]	$\Delta\Delta H^{\ddagger}$ (kcal mol^{-1})	$\Delta\Delta S^{\ddagger}$ (cal mol^{-1} K^{-1})
(3′*R*,*S*)-**1c**	CD_3CN	50	64 (*S*)	23	5.5	−4.5	−17
		18	30 (*S*)	34	2.1		
		−15	0	28	1.0		
		−40	58 (*R*)	37	5.2		
(3′*R*,*S*)-**1c**	CD_3OD	50	70 (*R*)	30	7.6	−2.8	−4.9
		18	85 (*R*)	34	19		
		−15	90 (*R*)	17	23		
		−40	94 (*R*)	12	37		
(3′*R*,*S*)-**1c**	CD_2Cl_2	20	34 (*S*)	25	2.3	−4.0	−15
		−20	27 (*R*)	65	2.7		
		−60	74 (*R*)	31	9.2		
(3′*R*,*S*)-**1d**	CD_2Cl_2	18	28 (*R*)	29	2.0	5.3	19
		−20	36 (*S*)	59	3.4		
		−60	88 (*S*)	56	45		
(3′*R*,*S*)-**1c**	$CDCl_3$	50	8 (*S*)	5	1.2	−4.5	−14
		18	63 (*R*)	17	5.0		
		−15	78 (*R*)	37	13		
		−40	88 (*R*)	43	31		

[a] A ca. 50/50 mixture of diastereomers (total concentration = 3.0×10^{-3} M) in an NMR tube under O_2 pressure was used, with methylene blue (3.7×10^{-4} M) as sensitizer. [b] Determined by GC using a Varian Chirasil-Dex CB 25 m × 0.25 mm column. [c] Determined by ^{1}H NMR analysis. [d] Calculated from the equation[6] $\mathbf{s} = \ln[1 - C(1 + ee_{MDB})]/\ln[1 - C(1 - ee_{MDB})]$, where C = conversion.

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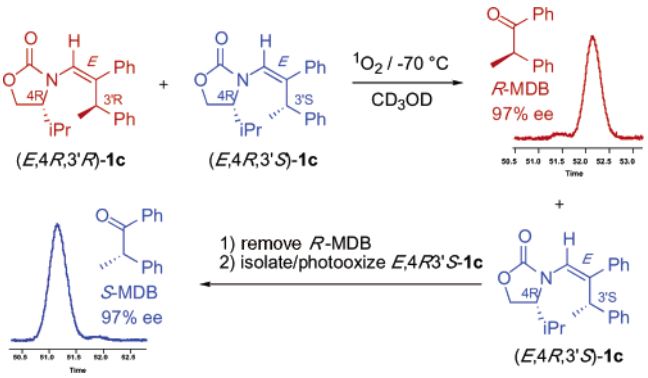
Scheme 1. Preparation and Kinetic Resolution of *R*-MDB and *S*-MDB by the Photooxidation of a 50/50 Diastereomeric Mixture of the Enecarbamates (*E*,4*R*,3′*R*,*S*)-**1c**



the latter is quite insensitive to temperature-based switching.

$$\ln(k_R/k_S) = \ln[(100 + \%\ \text{ee})/(100 - \%\ \text{ee})] \qquad (1)$$

$$\ln(k_R/k_S) = \Delta\Delta S^{\ddagger}_{R-S}/R - \Delta\Delta H^{\ddagger}_{R-S}/RT \qquad (2)$$

The reactions of *E*-**1c** with $^1O_2$ were performed in four different solvents at various temperatures.[5] The values that were extracted from the data in Table 2 reveal these striking features: (1) A significant solvent effect on the ee values is observed for comparable temperatures, (2) the sense of the enantioselectivity is switched within the temperature range in CD_3CN, CD_2Cl_2, and $CDCl_3$, of which CD_3CN shows the widest range in the ee values, and (3) the reaction in CD_3OD at −40 °C gives an ee value of 94%, the highest enantioselective formation of MDB that has been reported to date.[6] In contrast, the reaction of the *Z*-**1a** diastereomer with $^1O_2$ in various solvents resulted in a minimal effect and no switching of enantioselectivity sense. The conformational features of the *Z*-isomers and their role in the mechanism of the $^1O_2$ reaction have been previously reported,[1] but similar studies (2D and variable temperature NMR) on the *E*-isomers are silent on the mechanistic details (computational data are forthcoming).

The stereoselectivity factor (**s**) is the ratio of the rates of formation of the enantiomeric products ($\mathbf{s} = k_R/k_S$).[7] The photooxidation of **1c** in CD_3OD at −40 °C has an **s** value of 37, which predicts that an ee value as high as 97% is possible below −70 °C. To validate this prediction, the photooxidation of (3′*R*,*S*)-**1c** was run at −70 °C in CD_3OD, and indeed, an ee value of 97±0.7% for *R*-MDB was obtained, which corresponds to $\mathbf{s} = 72$ at an average of 8% conversion (Scheme 1).

By taking advantage of the high **s**-factor, the photooxidation of (3′*R*,*S*)-**1c** was run to nearly 50% conversion. The *R*-MDB product was removed from the reaction mixture by silica-gel chromatography and analyzed on a chiral stationary phase (ee = 97±0.7%).[8] The CD spectrum of the *R*-MDB obtained in Scheme 1 possesses an opposite configurational sense to that of the independently synthesized *S*-MDB,[9] as expected (Figure S2, Supporting Information). The remaining reaction mixture was again photooxidized to consume the unreacted (3′*R*)-**1c**, the pure (3′*S*)-**1c** isomer was isolated by chromatography and then quantitatively photooxidized at room temperature to give the *S*-MDB product with an ee value of 97% (Scheme 1).

The *Z*-diastereomers, which from molecular models and quantum-chemical computations appear to be conformationally more rigid than the *E*-isomers of **1**, do not show a significant solvent or temperature sensitivity on the ee values. One factor that may contribute to the enhanced selectivity in the *E*-isomers is greater $A^{1,3}$ strain[10] between the oxazolidinone auxiliary and the 3′-vinyl substituent, which would magnify the conformational energy difference between the diastereomers with opposite configurations at the C-3′ position. Since previous studies[1b] have shown that for each $^1O_2$ molecule that is quenched, only about 1 in 10 substrate molecules react, physical quenching of $^1O_2$ to $^3O_2$ is the major event. The remarkable stereoselectivity of this photooxidation may be due to the relatively small number of $^1O_2$ trajectories that are available for chemical reaction with the alkene compared to those for physical quenching. This postulate implies a remarkable selective vibrational control in the $^1O_2$ reactivity, a novel concept that merits further investigation.

We have shown that the chiral-auxiliary functionalized enecarbamates **1** react in high diastereoselectivity to give the enantiomeric *R*-MDB and *S*-MDB in ee values of up to 97% (isolated products). The stereochemical control depends on the *E*/*Z* substrate geometry, temperature, and solvent as internal and external variables. Through the optimization of these variables, we demonstrate that a "photochemical" Pasteur-type kinetic resolution is achieved, with a high degree of stereoselectivity.

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Supporting Information Available: Experimental procedures, NMR spectra of **1**, and figures. This material is available free of charge via the Internet at http://pubs.acs.org.

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