Remarkable Change of the Diastereoselection in the Dye-Sensitized Ene Hydroperoxidation of Chiral Alkenes by Zeolite Confinement
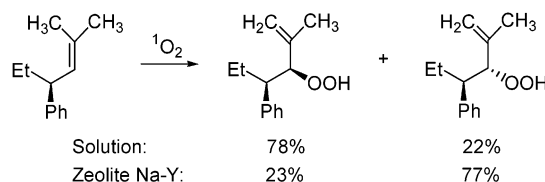
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ABSTRACT

| | Solution: | 78% | 22% |
| Zeolite Na-Y: | 23% | 77% |

The ene reaction of singlet oxygen with chiral trisubstituted alkenes bearing an alkyl and a phenyl group at the stereogenic center is *erythro* diastereoselective in solution and *threo* diastereoselective if carried out within zeolite Na−Y. The change of the diastereoselection trend by zeolite confinement is attributed to a synergism of steric effects and cation−π interactions.

Dye-exchanged zeolite Na−Y is a unique medium for carrying out large-scale singlet oxygen ($^1O_2$) ene reactions,[1] with significant enhancement of product regioselectivity[2] and chemoselectivity.[3] The diastereoselectivity for the intrazeolite photooxygenation of chiral alkenes has received little attention so far. We have reported that 2-methyl-5-phenyl-2-hexene,[4] a chiral alkene that bears a stereogenic center at the β-position with respect to the double bond, gives enhanced regioselectivity and diastereoselectivity, for the secondary allylic hydroperoxides, by zeolite confinement. In addition, intrazeolite photooxygenation of (R)-(−)-α-phellandrene[5] affords enhanced regioselectivity and diastereoselectivity among the ene products, with predominant formation of (1S,5R)-5-(1-methylethyl)-2-methylidene-3-

cyclohexen-1-yl hydroperoxide, a precursor of the naturally occurring *trans*-yabunikkeol.

The reaction of $^1O_2$ with chiral alkenes, bearing a sterogenic center at the α-position with respect to the double bond, has been extensively studied in solution.[6] For the majority of the chiral alkenes, the reaction is *erythro* diastereoselective. This trend was attributed to steric and electronic repulsions between the incoming oxygen and the substituents on the stereogenic carbon atom and to a preferable conformational arrangement to minimize the 1,3-allylic strain as well. Only the photooxygenation of chiral allylic alcohols and amines[6] is *threo* diastereoselective due to an oxygen−hydroxy/amine steering effect.

In this paper, we present our results on the regioselectivity and diastereoselectivity in the photooxygenation of chiral alkenes **1**−**3**, in solution and by confinement within zeolite Na−Y. Alkenes **1**−**3** possess a phenyl group and an alkyl group that may vary in size on the stereogenic carbon atom

(1) Pace, A.; Clennan, E. L. *J. Am. Chem. Soc.* **2002**, *124*, 11236−11237.

(2) (a) Ramamurthy, V.; Lakshminarasimhan, P.; Grey, C. P.; Johnston, L. J. *J. Chem. Soc., Chem. Commun.* **1998**, 2411−2418. (b) Stratakis, M.; Nencka, R.; Rabalakos, C.; Adam, W.; Krebs, O. *J. Org. Chem.* **2002**, *67*, 8758−8763. (c) Clennan, E. L.; Sram, J. P. *Tetrahedron* **2000**, *56*, 6945−6950.

(3) Stratakis, M.; Rabalakos, C.; Mpourmpakis, G.; Froudakis, G. E. *J. Org. Chem.* **2003**, *68*, 2839−43.

(4) Stratakis, M.; Kosmas, G. *Tetrahedron Lett.* **2001**, *42*, 6007−6009.

(5) Stratakis, M.; Sofikiti, N. *J. Chem. Res., Synop.* **2002**, 374−375.

(6) (a) Adam, W.; Brünker, H.-G.; Kumar, A. S.; Peters, E.-M.; Peters, K.; Schneider, U.; von Schnering, H. G. *J. Am. Chem. Soc.* **1996**, *118*, 1899−1905. (b) Prein, M.; Adam, W. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 519−538.

(methyl, **1**; ethyl, **2**; and cyclohexyl, **3**). The reaction of $^1O_2$ with **1**–**3**[7] in dichloromethane (methylene blue as a sensitizer) is regioselective with preferential formation of the secondary allylic hydroperoxides. Among the secondary hydroperoxides, the *erythro* isomer prevails (Scheme 1).

Scheme 1. Photooxygenation of Chiral Alkenes **1**–**3** in Solution
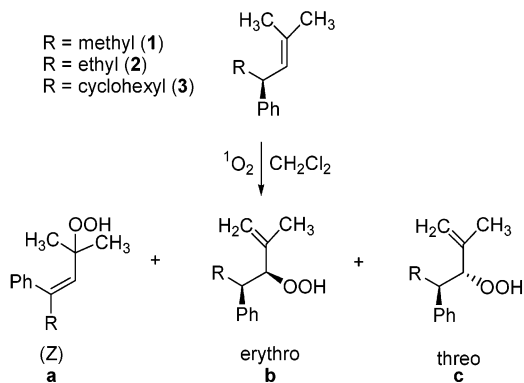

Alkene	a (%)	b (%)	c (%)
1[ref 7]	6	72	22
2	10	70	20
3	14	71	15

The (*Z*)-stereochemistry for the minor tertiary allylic hydroperoxides **1a**–**3a** was established by NOE experiments. Upon irradiation of the olefinic hydrogen absorption, the allylic hydrogen(s) of the R chain exhibited signal enhancement, indicative of a cis arrangement between the olefinic H and the R group. The predominant formation of the *erythro* isomers among the secondary allylic hydroperoxides (**b** > **c**) was confirmed as follows. The hydroperoxides were reduced in situ to the corresponding allylic alcohols by PPh$_3$, and their ^1H NMR spectra were compared to the diastereomeric addition products from the reaction of 2-propenyl-magnesium bromide with the chiral α-alkyl-substituted phenylacetaldehydes. It is well-known[8] that the addition of organolithium or Grignard reagents to α-alkyl-substituted phenylacetaldehydes is *erythro* diastereoselective. For example, in our case, reaction of 2-propenylmagnesium bromide with 2-phenylpropionaldehyde gave 2-methyl-4-phenyl-pent-1-en-3-ol in a ratio of *erythro/threo* = 4.6/1, while in the addition of the same Grignard reagent to α-cyclohexyl phenylacetaldehyde, 2-methyl-4-cyclohexyl-4-phenyl-but-1-en-3-ol was formed in a ratio of *erythro/threo* = 1.4/1.

The preferential formation of the *erythro* isomer in the photooxygenation of **1**–**3** in solution can be explained

considering the approach of singlet oxygen to the double bond as shown in transition state **TS**$_1$ of Scheme 2.[9] The

Scheme 2. Possible Transition States for the Photooxygenation of Alkenes **1**–**3** in Solution
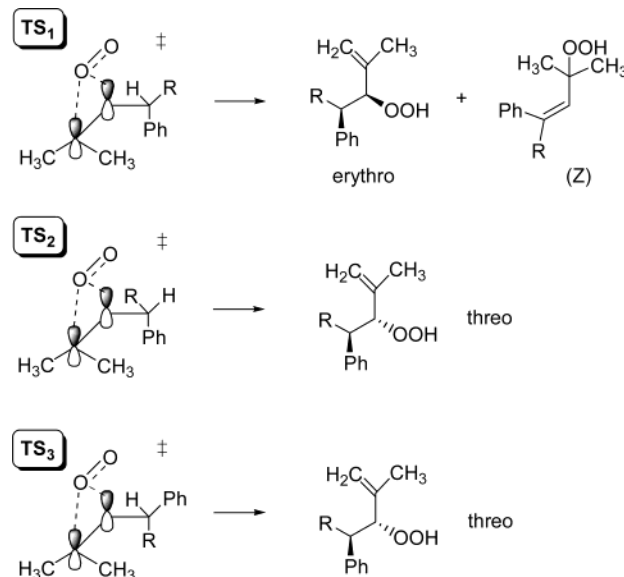
phenyl group is placed to the opposite plane of the double bond with respect to the attacking oxygen, due to unfavorable oxygen−arene electronic repulsions. In addition, for **TS**$_1$, a minimum 1,3-allylic strain between the tertiary allylic hydrogen and the *twix* allylic methyl group is in operation. For this conformation, singlet oxygen interacts to the tertiary allylic hydrogen, whose abstraction can lead to the formation of the (*Z*)-allylic hydroperoxides **1a**–**3a**. Transition state **TS**$_1$ can also nicely explain the high degree of *erythro* diastereoselection in the photooxygenation of alkene **3** (*erythro/threo* = 82/18), where the substituents on the stereogenic carbon atom (phenyl and cyclohexyl) have similar steric demands. It is worth mentioning here that for the case of 2,4,5,5-tetramethyl-2-hexene,[6a] where the diastereoselection in the $^1O_2$ ene reaction arises from the size difference between a methyl and a *tert*-butyl group, the selectivity is lower (*erythro/threo* = 71/29). Transition states **TS**$_2$ and **TS**$_3$ (Scheme 2) which lead to the *threo* diastereomer are expected to be less stable compared to **TS**$_1$, due to substantial 1,3-allylic strain between the R group and the *twix* allylic methyl group for **TS**$_2$ and to unfavorable oxygen−phenyl electronic repulsion for the case of **TS**$_3$.
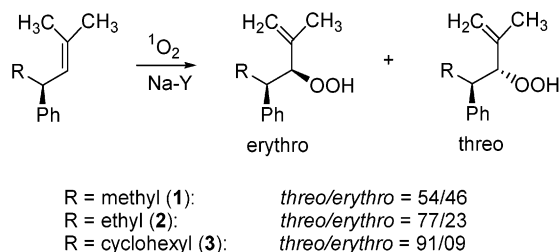
The thionin-sensitized photooxygenation of **1**–**3** adsorbed within zeolite Na−Y is highly regioselective, since only the secondary allylic hydroperoxides are formed, however, with an inverse diastereoselection trend (Scheme 3). The *threo*

(7) Photooxygenation of **1** in solution gave results similar to those reported in the literature: (a) Adam, W.; Nestler, B. *Liebigs Ann. Chem.* **1990**, 1051−1053. (b) Kropf, H.; Reichwaldt, R. *J. Chem. Res., Synop.* **1987**, 412−413.

(8) Karabatsos, G. J. *J. Am. Chem. Soc.* **1967**, *89*, 1367−1371 and references therein.

(9) For the singlet oxygen ene reactions, apart from the classical stepwise mechanism involving formation of a perepoxide intermediate,[13] Singleton and co-workers recently proposed a two-step no-intermediate mechanism (Singleton, D. A.; Hang, C.; Szymanski, M. J.; Meyer, M. P.; Leach, A. G.; Kuwata, K. T.; Chen, J. S.; Greer, A.; Foote, C. S.; Houk, K. N. *J. Am. Chem. Soc.* **2003**, *125*, 1319−1328). For both mechanisms, however, a rate-limiting transition state such as **TS**$_1$−**TS**$_3$ is in operation.

Scheme 3. Diastereoselectivity for the Intrazeolite Photooxygenation of **1−3**

R = methyl (**1**):   *threo/erythro* = 54/46
R = ethyl (**2**):   *threo/erythro* = 77/23
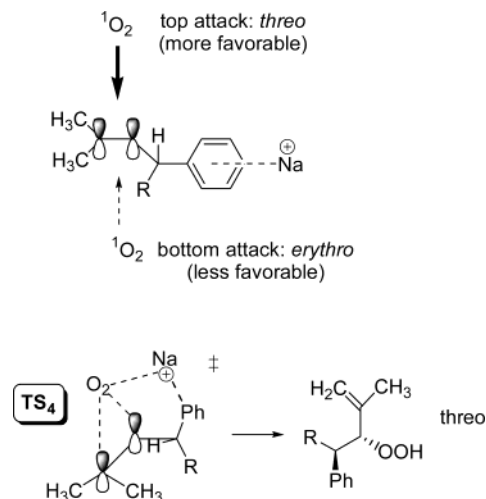R = cyclohexyl (**3**):   *threo/erythro* = 91/09

diastereomer is now predominant, and the ratio of *threo/erythro* increases by increasing the size of the R group. For example, while the photooxygenation of **3** in solution gives a ratio of *erythro/threo* = 82/18, by zeolite confinement, the ratio of *erythro/threo* = 09/91. The intrazeolite photooxygenation experiments were accomplished as described in ref 2b. Control experiments revealed that the phenyl-substituted alkenes were completely adsorbed within Na−Y after 2−3 min of mixing, in accordance with the observation of Ramamurthy and co-workers[10] for the higher adsorption ability of arylalkenes relative to simple alkenes. The ratio of the ene products was very reproducible (the error of three measurements for each substrate was ±3%), and the mass balance for all reactions was always higher than 80%. To ensure the accuracy of our intrazeolite results, the mixtures of the allylic hydroperoxides obtained from the photooxygenation of each alkene **1−3** in solution were adsorbed within the thionin/Na−Y and then irradiated under a constant flow of O_2 gas for 3 min. After extraction with moistened tetrahydrofuran, it was found that the ratio of the hydroperoxides was almost the same (before and after the zeolite treatment).

The remarkable change of the diastereoselection on going from the solution to the confined environment of the zeolite can be explained by considering the electrostatic interaction of the phenyl ring to the Na^+ present within the supercages.[11] Most probably, due to the strong cation−phenyl interaction,[12] the alkene adopts the conformation shown in Scheme 4. In that conformation, preferential attack of singlet oxygen from the less hindered top phase leads to the formation of the *threo* allylic hydroperoxide as the major adduct. As the size of the R group increases, the energy difference between the *threo*- and *erythro*-forming transition states is expected to increase, in favor of the *threo* isomer. A possible singlet oxygen−cation coordination leading preferably to the *threo* allylic hydroperoxide, as shown in **TS₄**, which has a minimum 1,3-allylic strain, cannot be excluded.

To determine the ratio of the *threo/erythro* diastereoselection induced by abstraction of an allylic hydrogen atom

(10) Kaanumalle, L. S.; Shailaja, J.; Robbins, R. J.; Ramamurthy, V. *J. Photochem. Photobiol., A: Chem.* **2002**, *153*, 55−65.
(11) For a recent review on the role of cation−π interactions in intrazeolite reactions, see: Sivaguru, J.; Natarajan, A.; Kaanumalle, L. S.; Shailaja, J.; Uppili, S.; Joy, A.; Ramamurthy, V. *Acc. Chem. Res.* **2003**, *36*, 509−521.
(12) Interaction of Na^+ to benzene in the gas phase is exothermic by ~25 kcal/mol. Feller, D. *Chem. Phys. Lett.* **2000**, *322*, 543−548.

Scheme 4. Possible Phenyl−Na^+ Coordination within Na−Y Directing $^1O_2$ Attack

either from the more (*twix* CH_3) or the less (*twin* CH_3) substituted side of the double bond, we prepared stereoselectively the chiral alkenes **1d₃−3d₃** labeled with deuterium at the *twin* position. The synthesis of the labeled alkenes was accomplished in >95% geometrical purity for the (*E*)-isomer following a procedure reported[2b] earlier by our group (see Supporting Information). The ratio of *H-threo/H-erythro* allylic hydroperoxides (Scheme 5) formed by abstraction of

Scheme 5. Products from the Photooxygenation of **1d₃−3d₃** within Zeolite Na−Y
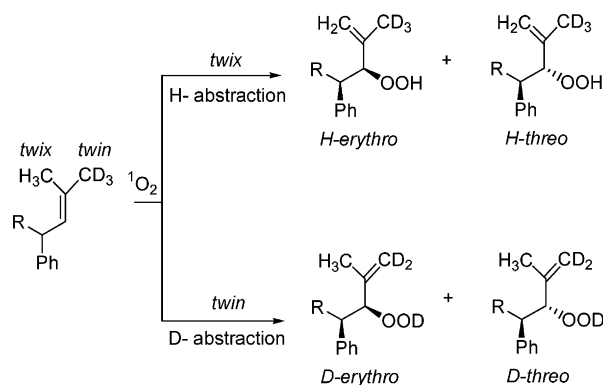
Alkene	*twin/twix* (%)	H-threo/H-erythro	D-threo/D-erythro
1d₃	62/38	48/52	56/44
2d₃	60/40	77/23	78/22
3d₃	55/45	89/11	92/08

an allylic hydrogen atom from the *twix* methyl group can be assessed by integration the terminal olefinic hydrogen atoms in the region of 5 ppm. On the other hand, the *D-threo/D-erythro* ratio formed by abstraction of an allylic deuterium atom from the *twin* methyl group (CD_3 in our case) can be assessed by integration of the diastereotopic allylic methyls

or extrapolated, taking into account the total ratio of *threo/erythro* hydroperoxides and the ratio *H-threo/H-erythro* as well.

While photooxygenation of $1d_3-3d_3$ in solution gave the typical *twin/twix* ratio of approximately 5/95 ("cis effect" selectivity[13]), by zeolite confinement, the *twin/twix* regioselectivity changes to approximately 60/40. The substantial increase in the reactivity of the *twin* methyl group is in accordance with earlier observations in the intrazeolite photooxygenation of trisubstituted alkenes.[2b,c] Also, the *threo/erythro* ratio either from H or from D abstraction is very similar within experimental error. This result indicates that within Na−Y, $^1O_2$ forms preferentially a *threo*-perepoxide intermediate oriented either toward the more or the less substituted side of the double bond.

In conclusion, we have shown that the *erythro* diastereoselectivity trend in the photooxygenation of chiral alkenes bearing a phenyl and an alkyl group at the stereogenic center can be reversed to *threo* by confinement within zeolite Na−Y. A similar change in the π facial photoreduction of steroids[14] has been observed on going from a homogeneous environment to the zeolite Na−Y confinement and has been postulated to be the result of $Na^+-\pi$ interactions. Intrazeolite photooxygenation studies of other chiral alkenes are in progress to explore novel and selective oxyfunctionalization pathways.

Supporting Information Available: Full experimental details for the synthesis of $1d_3-3d_3$ and ^1H NMR spectra of $1d_3-3d_3$ and their photooxygenation reactions in solution or within Na−Y. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0352660

(13) Stratakis, M.; Orfanopoulos, M. *Tetrahedron* **2000**, *56*, 1595−1615.

(14) Rao, V. J.; Uppili, S. R.; Corbin, D. R.; Schwarz, S.; Lustig, S. R.; Ramamurthy, V. *J. Am. Chem. Soc.* **1998**, *120*, 2480−2481.