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A Supramolecular “Ship in Bottle” Strategy for Enantiomeric Selectivity in Geminate Radical Pair Recombination

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ABSTRACT

Reactions in which zeolites are modified with chiral inductors to serve as media for chiral induction are often limited by the propensity of both substrate and inductor to occupy the same supercage. Herein, we report a “ship in bottle” strategy utilizing the thermal decomposition of dioxetanes obtained from oxazolidinone-substituted enecarbamates for the enantioselective generation of methyl desoxybenzoin (MDB). Photoexcitation of the supramolecular geminate molecular pair results in enrichment of the opposite enantiomer of MDB.

The past several decades have seen tremendous advances in molecular stereochemistry, in particular with respect to enantiomerically selective synthesis.[1] In this report we consider strategies for enantiomerically selective synthesis involving reactive supramolecular geminate stereochemically isomeric radical pairs.[2] Control of stereochemistry in the recombination reactions of reactive geminate radical pairs is a challenge because of the inherently high reactivity of the pair.

We have demonstrated that the confinement of a geminate triplet radical pair to a zeolite supercage can lead to a small degree of enantiomeric selectivity upon recombination of the pair when a supramolecular chiral auxiliary is present in the same supercage with the radical pair.[3] However, available strategies for creating a supercage that is occupied by both a precursor to the radical pair and a chiral inductor involve the random addition of both the chiral inductor and radical pair precursor (i.e., a ketone) so that there is no control over the initial supramolecular composition and stereochemistry of the inductor/inductee pair or even any guarantee that the inductor/inductee pair will occupy the same supercage.[4] As a result of this lack of control of the supramolecular

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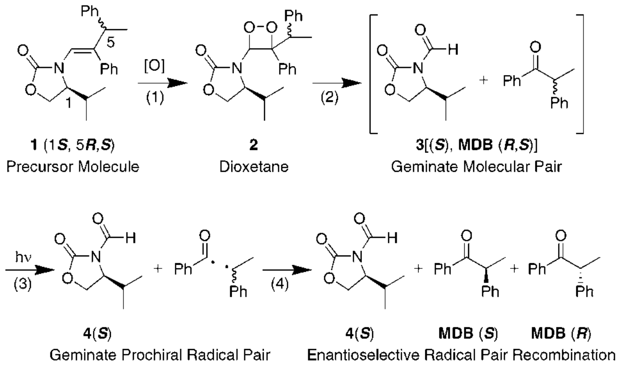
constitution and stereochemistry, we have devised a novel strategy through which both the initial supramolecular constitution and stereochemistry can be controlled.

The strategy involves (1) application of a variation of the "ship in bottle" method that has been used for selective reactivity of guests in zeolite supercages[5] and (2) the stereoselective formation of supramolecular stereoisomers as the result of geminate molecular pair formation in a supercage. A specific example of this strategy is shown in Scheme 1 for the supramolecular enantiomeric selectivity of a radical pair produced by the photolysis of methyl desoxybenzoin (MDB) in the presence of a non-covalently attached chiral oxazolidinone inductor, **3**.

Scheme 1



1 (1***S***, 5***R***,***S***)
Precursor Molecule

2
Dioxetane

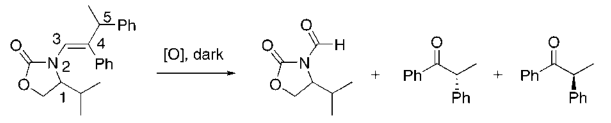
3[(***S***), **MDB** (***R***,***S***)]
Geminate Molecular Pair

4(***S***)
Geminate Prochiral Radical Pair

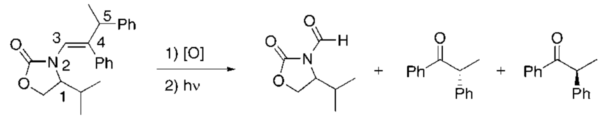
4(***S***) **MDB** (***S***) **MDB** (***R***)
Enantioselective Radical Pair Recombination

The enecarbamates **1a** and **1b** (Scheme 2) were designed to provide an example of the proposed "ship in bottle" strategy. Compound **1a** is a mixture of molecular diastereomers that is enantiomerically pure (R configuration) at position 1 and racemic (R,S) at position 5; **1b** is a mixture of molecular diastereomers that is enantiomerically pure (S configuration) at position 1 and racemic (R,S) at position 5. The strategy involves a diasteromer-differentiating oxidation of the double bond of **1** to produce a supramolecular geminate molecular pair **3**. In the case of singlet oxygen oxidation of **1**, the formation of **3** probably occurs through the intermediacy of a diastereomeric mixture of dioxetanes, **2**.[6] Decomposition of **2** results in the formation of a supramolecular geminate pair of diastereomers, **3**. The photoexcitation of the MDB partner of the diastereomeric geminate pair **3** will produce a prochiral radical pair as the result of α-cleavage of the MDB molecule (Scheme 1). Recombination of the prochiral geminate diastereomeric pair **4** occurs under the influence of the neighboring supramolecular chiral inductor isopropyl oxazolidinone carbaldehyde. The hypothesis behind the strategy is that geminate radical pairs will be produced by photolysis of MDB, and because the recombination of the geminate radical pair will occur in a supercage under the influence of a supramolecular chiral auxiliary, the supramolecular recombination will occur with a degree of enantiomeric selectivity higher than that achieved through the random addition of MDB and **3** to a host. The supercage of the NaY zeolite was selected to test the experimental feasibility of the strategy for supramolecular enantiomeric selectivity outlined in Scheme 1.

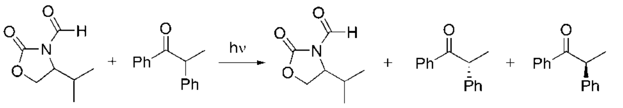
Scheme 2



1a (1***R***, 5***S***,***R***)@ **NaY**	**4**(***R***)	**MDB** (***R***) **75%**	**MDB** (***S***) **25%**
1b (1***S***, 5***S***,***R***)@ **NaY**	**4**(***S***)	**MDB** (***R***) **25%**	**MDB** (***S***) **75%**



1a (1***R***, 5***S***,***R***)@ **NaY**	**4**(***R***)	**MDB** (***R***) **30%**	**MDB** (***S***) **70%**
1b (1***S***, 5***S***,***R***)@ **NaY**	**4**(***S***)	**MDB** (***R***) **70%**	**MDB** (***S***) **30%**



[**3** (***R***) + **MDB** (***S***,***R***)]@ **NaY**	**4**(***R***)	**MDB** (***R***) **52%**	**MDB** (***S***) **48%**
[**3** (***S***) + **MDB** (***S***,***R***)]@ **NaY**	**4**(***S***)	**MDB** (***R***) **48%**	**MDB** (***S***) **52%**

We have shown[6] that the reaction of **1** with singlet oxygen in solution is highly diastereoselective with respect to producing dioxetanes (Scheme 1) from attack upon the less hindered face of the enecarbamate **1**. The thermal oxidation of **1** was achieved by simply allowing a sample of **1** loaded on NaY to stand in the dark. For example, the enecarbamate **1** (ca. 3 mg) was dissolved in isooctane and loaded on freshly calcined NaY (ca. 300 mg). This loading corresponds to an occupancy of ca. 1 molecule of **1** for 10 supercages of NaY. Samples were washed 4× with fresh isooctane, and UV spectroscopy confirmed that there was no **1** remaining in the supernatant. Samples were immediately covered with Al foil to maximize dark reaction and to minimize photochemical reaction of **1** resulting from room light. The samples were allowed to stand at room temperature for 1−21 h and then washed with isooctane and subjected to micro-Soxhlet extraction with acetonitrile for 24 h. The products were analyzed by both conventional GLC to determine the conversion and by chiral GC to determine the ee. MDB was identified as a product by both methods, and stereochemical assignment was made by comparison with an authentic sample of (*S*)-MDB.[7]

The values of the enantiomeric excess of MDB produced by dark oxidation of **1a** and **1b** are given in Scheme 2. Starting with **1a** an ee of 50 ± 7% of (*R*)-MDB is formed, and starting with **1b** an ee of ca. 47 ± 8% of (*S*)-MDB is formed. A control was performed in which the isopropyl group was absent from the oxazolidinone ring. This yielded ca. 0% ee and supports the role of the oxazolidinone moiety

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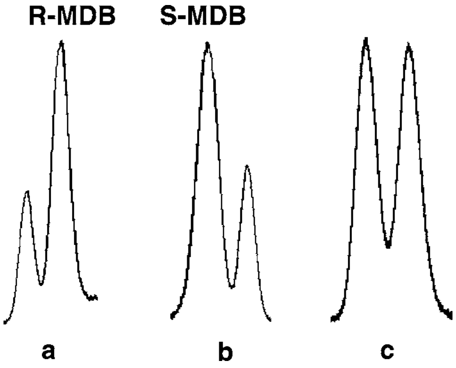

Figure 1. Representative chiral GC traces for the enantiomeric pair of MDB recovered from the dark oxidation of **1@**NaY. Products from the oxidation of **1a@**NaY and **1b@**NaY, are shown in traces a and b, respectively. Trace c is the MDB product from the dark oxidation of the enecarbamate lacking a stereocenter at position 1.

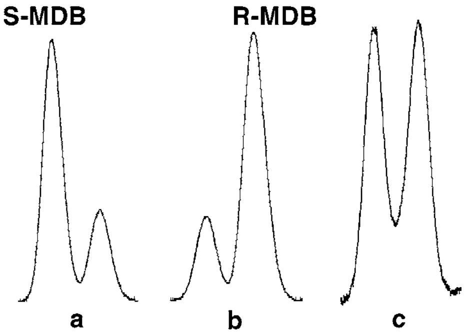

Figure 2. Representative chiral GC traces for the enantiomeric pair of MDB recovered from the irradiation of **3@**NaY formed from the thermal oxidation of **1@**NaY. Products from the irradiation of **3a@**NaY and **3b@**NaY, are shown in traces a and b, respectively. Trace c is the MDB product from irradiation of the enecarbamate lacking a stereocenter at position 1.

as a chiral inductor in the reaction (Figure 1). The yields of MDB are low (less than 1%) and quickly build up to a maximum and then do not change with time. These results indicate that there is a limiting amount of an oxidizing agent (e.g., molecular oxygen included in the zeolite or a fixed number of oxidizing defects in the zeolite framework) contained by the zeolite that is not replenished. Since the oxygen available for the oxidation is small and the conversion of the enecarbamate will run to only a few percent conversion, only the more reactive diastereomer will react, leading to an ee:diastereomer-differentiating reaction.

The next issue to be explored was the effect of photolysis on the enantiomerically enriched supramolecular geminate pairs **3a@**NaY and **3b@**NaY produced by oxidation of **1a@**NaY and **1b@**NaY. It has been shown previously[3a] that low ee's of the order of ca. 5−10% are achieved in the photolysis of racemic MDB@NaY that is coloaded with ephedrin (or diethyl tartrate) as a random supramolecular chiral auxiliary. In the case of an enriched sample of **3**[3(*R*)/MDB(*R*)]@NaY an hour of photolysis produces **3**[3(*R*)/MDB(*S*)]@NaY in ca. 35−40% ee of (*S*)-MDB. The photolysis of **3**[3(*S*)/MDB(*S*)]@NaY produces **3**[3(*S*)/MDB-(*R*)]@NaY in ca. 35−40% ee of (*R*-)MDB. The control in which the isopropyl group is absent, producing racemic MDB upon thermal oxidation, yields racemic MDB after photolysis (Figure 2).

Remarkably, an initial ee of ca. 50% of (*R*)-MDB (or (*S*)-MDB) is converted to an ee of ca. 40% of (*S*)-MDB (or (*R*)-MDB), corresponding to a reversal of the ee of nearly 100%! The values of the ee are among the highest reported for enantiomerically selective recombination of geminate radical pairs under any conditions.[8] This result indicates the potential power of the strategy to produce enantiomeric excesses of either enantiomer of MDB depending on the reaction conditions.

A comparison of the results of the geminate supramolecular chiral inductor/inductee pairs, $\mathbf{3}_{\text{gem}}$**@**NaY (Scheme 2), with those for random supramolecular chiral-inductor/inductee pairs, $\mathbf{3}_{\text{ran}}$**@**NaY (Scheme 2) was examined. Samples of racemic MDB(*R*,*S*) and enantiomerically pure **4**(*R*) or **4**(*S*) were loaded on NaY to produce samples of $\mathbf{3}_{\text{ran}}$[**4**(*R*)/MDB-(*R*,*S*)]@NaY and $\mathbf{3}_{\text{ran}}$[**4**(*S*)/MDB(*R*,*S*)]@NaY, respectively. Photolysis of these samples resulted in the conversion of a racemic mixture of [**4**(*R*) + MDB(*R*,*S*)]@NaY to a mixture that was enantiomerically enriched in either MDB(*R*) or MDB(*S*) by only a few %, a value close to the experimental uncertainty in the evaluation of the ee. However, since the enantiomerically favored MDB "flipped" in going from **4**(*R*)- to **4**(*S*) as a random chiral auxiliary, the small selectivity is outside of the experimental error.

The products of **1** with singlet oxygen have been investigated in solution.[6] It was found that a dioxetane is formed with essentially complete diastereoselectivity; the singlet oxygen reacting from the least hindered face of the molecule (Scheme 3) to diastereoselectively form a dioxetane, which then decomposes to form MDB. Although the source of the oxygenation in the thermal reaction (Scheme 1) of **1@**NaY is not known, the high ee of the process is consistent with molecular oxygen (either ground state or singlet oxygen) being the reagent responsible for the oxidation. Another possibility is that oxygen atoms from the zeolite framework add to a radical cation formed from loss of an electron from **1** to the zeolite,[9] followed by a framework oxygen atom transfer.

The photolyses of ketones that undergo reversible α-cleavage have been extensively investigated.[10] When a racemic ketone such as MDB undergoes α-cleavage to form a geminate radical pair in the presence of a chiral auxiliary in a zeolite supercage, the geminate pair undergoes enantio-

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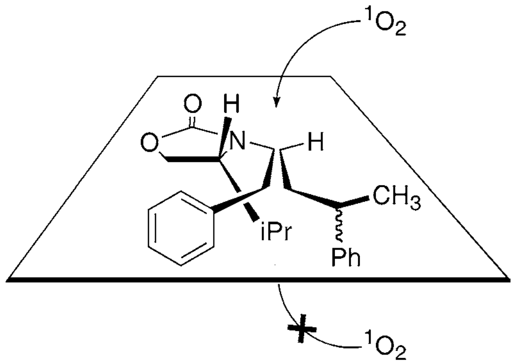
Scheme 3



selective recombination. However, in the reactions in which the probability of a chiral inductor and a geminate radical pair being in the same supercage is not controlled, the limiting enantiomeric excesses are typically low (<10%). According to Scheme 1, enantiomerically pure **3** is produced along with MDB as a geminate molecular pair. This guarantees that the prochiral radical pair produced in the photolysis of MDB will be produced in a supercage with a chiral inductor.

In conclusion, we have demonstrated that the recombination reactions of supramolecular geminate inductor/inductee radical pairs in zeolite photochemical reactions produce significant enantiomeric excesses through a "ship in bottle" strategy. The recombination reactions of random supramolecular inductor/inductee radical pairs in zeolite photochemical reactions produce only minor enantiomeric excesses of the recombination products, although significant de's have been observed.[2] The nature of the thermal oxidation of **1@**NaY is not clear and warrants further study. Whatever the mechanism, the enantiomeric selectivity is one of the highest achieved today with a noncovalent supramolecular inductor/inductee pair in a zeolite supercage.[11] Remarkably, the enantioselectivity produced in the creation of a geminate supramolecular pair can be reversed by photolysis of an enriched geminate noncovalent supramolecular inductor/inductee pair in a zeolite supercage. These initial studies demonstrate the potential power of generating supramolecular geminate chiral inductor/inductee pairs. It is to be noted that the precursor structure **1** can exist as eight completely independent stereoisomers, each of which can be stereoselectively oxidized to four completely independent supramolecular geminate isomeric inductor/inductee pairs, which upon photolysis will, in principle, produce different enantiomeric selectivity. The investigation and correlation of the initial supramolecular stereochemistry with the final photochemically induced enantioselectivity opens the door to a novel field for the investigation of supramolecular stereochemical issues.

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