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Enantioselective Photoreduction of Arylalkyl Ketones via Restricting the Reaction to Chirally Modified Zeolite Cages

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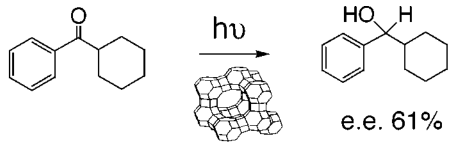
ABSTRACT



Obtaining a high enantiomeric excess during a photoreaction within a zeolite is hampered by the statistical distribution of reactant and chiral inductor molecules within the cages of a zeolite. By restricting the photoreactions to only those cages that contain both the reactant and a chiral inductor, one should be able to avoid reactions that yield racemic products. This approach is illustrated with the photoreduction of an arylalkyl ketone by a chiral inductor with an amino group.

The strategy of employing chirally modified zeolites as a reaction media requires inclusion of two different molecules, C (a chiral inductor) and R (a reactant), within the interior space of an achiral zeolite.[1] By its very nature this strategy does not allow quantitative chiral induction. When two different molecules, C and R, are included within a zeolite, the distribution is expected to follow the pattern shown in Figure 1. The six possible distributions of guest molecules are cages containing single C (type I), two C (type II), single R (type III), two R (type IV), one C and one R molecule (type V), and none at all (type VI). The products obtained from the photoreaction of R represent the sum of reactions that occur in cages of types III, IV, and V. Of these, only V should lead to asymmetric induction. Obtaining high chiral induction requires a strategy that permits placement of every reactant molecule (R) next to a chiral inductor molecule (C), i.e., enhancement of the ratio of type V cages to the sum of types III and IV. Recognizing the current lack of knowledge concerning the distribution of guest molecules within a zeolite and the highly unlikely probability of placing every chiral inductor molecule next to a reactant molecule in the absence of any specific interaction between them, we have devised a strategy which would limit the photoreaction of interest to reactant molecules next to a chiral inductor. Such a condition eliminates the possibility of formation of the product of interest in cages of types III and IV. The photoreaction we have investigated in this context is the well-known electron-transfer-initiated intermolecular hydrogen abstraction reaction of carbonyl compounds.[2] Under the

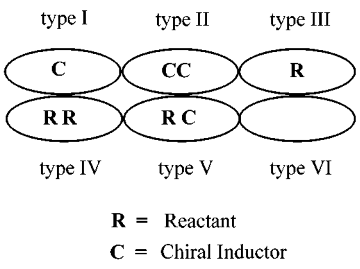


Figure 1. Six possible modes of distribution of two different molecules within zeolite supercages.

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[1] Joy, A.; Ramamurthy, V. *Chem. Euro. J.* In press.

[2] Cohen, S. G.; Parola, A.; Parsons, G. H., Jr. *Chem. Rev.* **1973**, *73*, 141.

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conditions we have employed, one of the guest molecules (e.g., ephedrine, norephedrine, and pseudoephedrine, etc., Table 1) assumes the dual role of chiral inductor and electron donor.

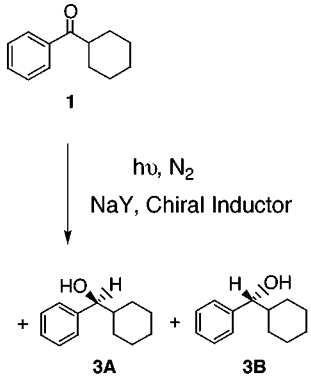
Table 1. Enantiomeric Excesses Obtained with Various Chiral Inductors Included in NaY

chiral inductor	% ee in **3**	chiral inductor	% ee in **3**[a]
(−)-norephedrine	63 − B	(−)-ephedrine	8 − B
(+)-norephedrine	61 − A	(+)-ephedrine	10 − A
(−)-pseudoephedrine	25 − B	D-valinol	10 − A
(+)-pseudoephedrine	27 − A	L -valinol	9 − B
(1*S*,2*S*)-(+)-2-amino-3-methoxy-1-phenyl-1-propanol	30 − B	L-α-methyl benzylamine	8 − B
(1*S*,2*S*)-(+)-2-amino-1-phenyl-1,3-propanediol	54 − B	L-phenylalaninol	13 − A
(1*R*,2*R*)-(−)-diaminocyclohexane	28 − A	L-phenylglycinol	11 − B

[a] The first of the two enantiomeric peaks on the GC is marked as A.

We have investigated the photochemistry of phenyl cyclohexyl ketone **1**[3] to establish the above concept (Scheme 1). As expected on the basis of solution behavior, irradiation as a hexane slurry of **1** included within zeolite NaY gave **2** as the only product. On the other hand, irradiation of **1** included within ephedrine-, pseudoephedrine-, or norephedrine-modified NaY gave intermolecular hydrogen abstraction product **3**, in addition to the expected product of intramolecular hydrogen abstraction, **2**.[4] We believe alcohol **3** to be the product of electron transfer from the amino group of the chiral inductors since it was not formed in their absence. The absence of alcohol **3** when ephedrine hydrochloride was used as the chiral inductor supports this view. Further, **3** was not formed when the chiral inductor was (−)-diethyl tartrate, which does not contain an amino group. If the role of the amine is to serve as an electron donor, the ratio of inter- vs intramolecular hydrogen abstraction products (**3** to **2**) should depend on the electron-donating ability of the chiral inductor. One would expect the **3**/**2** ratio to be higher when secondary amine chiral inductors such as ephedrine and pseudoephedrine are the donors than when they are primary as in the case of norephedrine. The results presented in Figure 2 show this to be the case.

Scheme 1



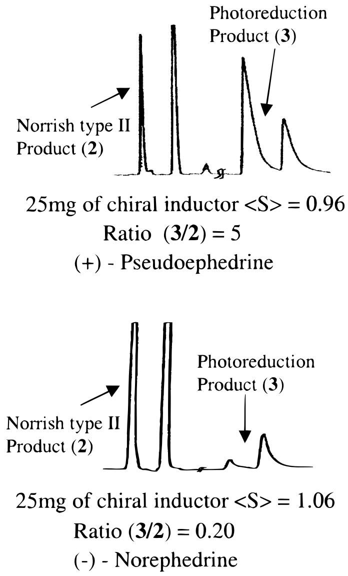


Figure 2. GC traces of the product mixtures (Supelco *β*-dex 350/1701 custom-made column). The ratio of the intermolecular to intramolecular hydrogen abstraction products from **1** within NaY depends on the nature of the electron donor. $\langle S \rangle$ indicates the number of chiral inductor molecules per cage.

The expected photochemical behavior of ketone **1** included within a chirally modified NaY zeolite can be summarized as follows: Ketone **1** present in cages of types III and IV (Figure 1) should give only **2**, whereas those molecules of **1** present in cages of type V are expected to yield both **2** and **3**. This generalization predicts that the ratio of inter- vs intramolecular hydrogen abstraction should depend on the ratio of the cages that contain the chiral inductor and those that do not, which in turn depends on the loading level of the chiral inductor. The GC traces of the product distribution upon irradiation of **1** included within NaY at two loading levels of pseudoephedrine are presented in Figure 3. Clearly, the amount of intermolecular reduction product increases with the loading level of pseudoephedrine. An additional important point noticeable from Figure 3 is that although the amount of alcohol product **3** (with respect to **2**) is dependent on the loading level of the chiral inductor, the ratio of the optical isomers of **3** (enantiomeric excess, ee) is independent of the loading level of the chiral inductor. This

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(3) (a) Lewis, F. D.; Johnson, R. W.; Johnson, D. E. *J. Am. Chem. Soc.* **1974**, *96*, 6090. (b) Stocker, J. H.; Kern, D. H. *J. Chem. Soc., Chem. Commun.* **1969**, 204.

(4) To a solution of 7 mg (3.87 × 10^{-5} mol) of **1** were added 26 mg of chiral inductor, 20 mL of hexanes, and 250 mg of activated NaY zeolite while stirring. The mixture was allowed to stir under nitrogen for 2−3 h and then irradiated for 3 h. The conversions in most experiments were in the range of 20 to 35% as monitored by GC. The zeolite was filtered, and the organic contents were extracted using acetonitrile. The chiral inductor was removed from the solution by column chromatography (silica gel/hexanes−ethyl acetate). The solution was concentrated and analyzed on Supelco *β*-dex 350/1701 custom-made column. The enantiomeric excesses were measured both electronically and manually.

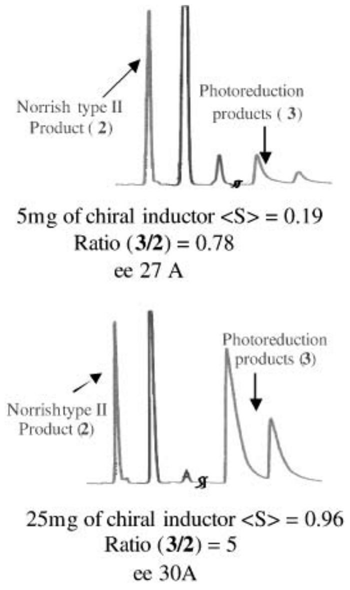


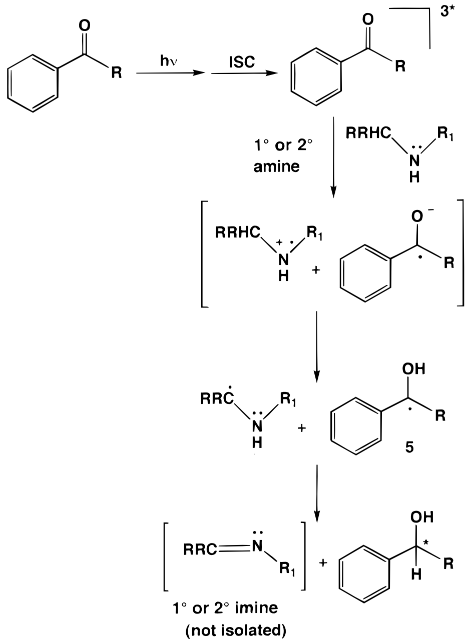
Figure 3. GC traces of the product mixtures (Supelco β-dex 350/1701 custom-made column). The dependence of the inter- and intramolecular hydrogen abstraction products from **1** on the loading level of the chiral inductor, pseudoephedrine, within NaY. The ee remains the same under the two conditions. $\langle S \rangle$ indicates the number of chiral inductor molecules per cage. The first of the two enantiomeric peaks on the GC is marked as A.

observation supports the view that reduction occurs only in cages containing the chiral inductor. The ee would have increased with increased loading levels of the chiral inductor had there been intermolecular reduction (to yield racemic products) in cages that do not contain pseudoephedrine.

The ability to restrict the reduction reaction to the cages containing both the reactant and the chiral inductor allows one to examine, for the first time, chiral induction within a zeolite without any interference from reactions that occur in cages lacking the chiral inductors. Thus far, chiral induction within a zeolite has been complicated by racemic reactions within cages that do not contain the chiral inductor.[5] By restricting the photoreaction to cages containing the chiral inductor, we have achieved moderate chiral induction during the photoreduction of **1**. The ee obtained in this study is noteworthy, as earlier attempts to achieve chiral induction during photoreduction of aryl alkyl ketones by chiral amines resulted in ee values of less than 8% (at room temperature).[6] Furthermore, the major products in earlier studies were pinacols (diols) and not the ketone-derived alcohols. The results obtained with various chiral inductors are summarized in Table 1. Of the various chiral inductors tested, the best results were obtained with norephedrine (ee 61%). The use of (+)-norephedrine afforded the optical antipode of the photoproduct produced by the use of (−)-norephedrine, indicating that the system is well behaved. Similar to our observations with other systems, the ee obtained was dependent on the water content of the zeolite.[7] When the above-prepared zeolite complex was intentionally made "wet" by adsorption of water, the ee was low relative to the ee obtained under dry conditions (dry, 61%; wet, <2%).[8]

While the ee obtained in this study is the highest thus far reported for the photoreduction of any achiral ketone, we do not fully understand the mechanism of chiral induction. The following observations (Table 1) are noteworthy: (a) despite the entire reaction occurring within chirally modified cages, the ee is not quantitative; (b) there is a significant variation in ee between the two diastereomers (compare ephedrine and pseudoephedrine) and (c) among the two closely related chiral inductors ephedrine and norephedrine. The less than quantitative ee obtained in this study is most likely related to the multistep nature of the reaction, which involves at least two distinct intermediates (Scheme 2).[2,9]

Scheme 2



Both the starting ketone and the intermediate radical **5** (Scheme 2) possess pro-chiral faces. In solution, the equally likely addition of hydrogen to both faces of **5** results in racemic product. In the absence of a chiral inductor, ketone **1** is unlikely to show preference for adsorption from either face onto the zeolite surface.[10]

On the other hand, the presence of a chiral inductor might allow the reactant ketone to differentiate between the two

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(5) The chiral auxiliary approach has been employed to keep the reactant and the chiral inductor together within a cage, and this has yielded high de. (a) Joy, A.; Uppili, S.; Netherton, M. R.; Scheffer, J. R.; Ramamurthy, V. *J. Am. Chem. Soc.* **2000**, *122*, 728.

(6) (a) Cohen, S. G.; Laufer, D. A.; Sherman, W. V. *J. Am. Chem. Soc.* **1964**, *86*, 3060. (b) Pitts, J. N., Jr.; Letsinger, R. L.; Taylor, R. P.; Patterson, J. M.; Recktenwald, G.; Martin, R. B. *J. Am. Chem. Soc.* **1959**, *81*, 1068. (c) Seebach, D.; Daum, H.*J. Am. Chem. Soc*. **1971**, *93*, 2795. (d) Seebach, D.; Oei, H.-A.; Daum, H. *Chem. Ber*. **1977**, *110*, 2316. (e) Horner, L.; Klaus, J. *Liebigs. Ann. Chem*. **1979**, 1232.

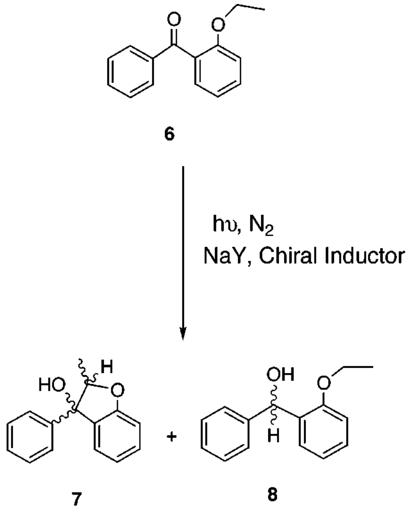
(7) Joy, A.; Scheffer, J. R.; Ramamurthy, V. *Org. Lett.* **2000**, *2*, 119.

(8) The extent of ee depends on the water content of the zeolite. The ee will be in the range between 0 and 61% if the sample is not dried properly.

pro-chiral faces for adsorption. Asymmetric induction is likely if this preference is retained until the completion of the reaction. We believe that the cations present within the zeolite help to anchor the ketone/radical during the course of the reaction. The absence of chiral induction within a “wet” zeolite, where the cations are expected to be complexed to water, is consistent with this model. The magnitude of the chiral induction depends on the ability of the chiral inductor to allow the ketone to adsorb from a single enantiotopic face and on the ability of the cation to keep it anchored from the same face. This admittedly primitive model can serve as a starting point for further understanding the process of chiral induction within chirally modified zeolites.

By adopting the above strategy, we have achieved moderate chiral induction during the photoreduction of *o*-ethoxybenzophenone **6**[11] (Scheme 3). Like ketone **1**, this molecule gives intramolecular cyclization product **7** as the only product in solution as well as within NaY. However, in chirally modified NaY zeolite (amine based chiral inductor), intermolecular reduction product **8**, in addition to **7**, was obtained. More importantly, with pseudoephedrine and (1*R*,2*R*)-diaminocyclohexane as chiral inductors, moderate ee was obtained on the product **8** (39 and 51%, respectively). Presently we are unable to predict which chiral inductor will work best with a given ketone.

Scheme 3



In this report we have disclosed a new and novel approach that has allowed us to eliminate reactions within a zeolite which by their very nature would give only racemic products. Achieving high chiral induction should be possible by restricting reactions to those cages that contain the reactant and a chiral inductor. Work along these lines is underway in our laboratory.

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(10) As pointed out by a referee, it is likely that the radical **5** is sufficiently long-lived for it to diffuse away from the cage in which it was generated. Such a process can result in a decreased ee.

(11) Wagner, P. J.; Meador, M. A.; Giri, B. P.; Scaiano, J. C. *J. Am. Chem. Soc*. **1985**, *107*, 1087. (b) Wagner, P. J.; Meador, M. A.; Park, B.-S. *J. Am. Chem. Soc*. **1990**, *112*, 5199.