Asymmetric induction during photocyclization of chiral and achiral α-oxoamides within achiral zeolites†

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The photochemistry of 31 α-oxoamides capable of undergoing γ-hydrogen transfer has been examined within zeolites. These molecules, upon excitation, yield two products—a β-lactam and oxazolidinone—in solution, both resulting from γ-hydrogen transfer. While in benzene the major product is oxazolidinone, within an MY zeolite, the main product is a β-lactam. In this investigation, we have focused our attention on asymmetric induction in the formation of the β-lactam product. Two approaches—using a chiral inductor and chiral auxiliary—have been employed. While in solution, in the presence of chiral inductors, achiral α-oxoamides yield β-lactams with zero enantioselectivity; within zeolites, an ee of up to 44% has been achieved. α-Oxoamides appended with a chiral auxiliary gave β-lactams with less than 5% diastereoselectivity in solution while within zeolites, the same α-oxoamides gave the products with de's of up to 83%. Such a remarkable influence of zeolites is attributed to an alkali ion interaction with the reactant α-oxoamides and to the confined environment of the zeolite interior. At this stage, we have not been able to provide a model with predictive power and further work is needed to understand this valuable asymmetric induction strategy.

Introduction

A number of elegant and efficient chiral induction strategies have evolved for thermal reactions in the past few decades. The short lifetimes of excited states have hampered the development of an effective interaction between an excited reactant and a chiral perturber thus slowing down similar progress with photoreactions. Despite the stumbling blocks, due to the persistent efforts of various groups notably of Bach,[1,2] Inoue,[3,4] Pete,[5] Scharf,[6] Scheffer,[7,8] Toda,[9,10] Turro[11] and ours,[12–14] advances have been made during the last decade. In 1965, Hammond and Cole established that chiral induction could be obtained in solution through sensitization of an achiral molecule with a chiral sensitizer.[15] A few years later, the groups of Kagan[16,17] and Calvin[18] obtained chiral induction in solution by irradiation of helicenes with circularly polarized light. Schmidt and Penzien[19] established in 1969 that global chirality due to crystallization of achiral molecules into a chiral space group could be transformed into local chirality by irradiation of the crystal. The efforts of Scharf[6] and Pete[5,20] and their co-workers have established the value of chiral auxiliaries in solution. Following the initial observation by Hammond and Cole, Inoue and co-workers have extensively explored the chiral sensitization technique using cyclooctene photoisomerization as the model.

The elegant technique of transformation of chiral crystals of achiral molecules into chiral products has been slow to develop.[21,22] Using an ionic chiral auxiliary approach, Scheffer and co-workers,[7,8,23] who introduced this new methodology, have repeatedly crystallized achiral molecules in a chiral space group to subsequently transform to chiral products.

During the last two decades supramolecular approaches towards chiral photochemistry have attracted considerable attention. Lahav, Leiserowitz and their co-workers[24] and Toda and co-workers[9,10] employed optically pure hosts to form solid host–guest complexes with achiral guest molecules. The use of chiral hosts such as cyclodextrins, proteins and DNA to complex achiral reactant molecules in aqueous solution has resulted in low chiral induction in photoproducts.[4,25–31] In this context, a novel method being developed by Bach and co-workers is particularly noteworthy.[1,2] In this approach, upon complexation an optically pure template distinguishes the two pro-chiral faces of an achiral molecule allowing chiral selectivity in the photoproducts. However, to obtain significant chiral induction, the irradiations had to be conducted at low temperatures as the association constants for host to guest with toluene as solvent were low. Thus chiral photochemistry, clearly still in its infancy, needs development of more general methods.

Towards this need our contribution to chiral photochemistry has been the introduction of zeolite as a medium for photoreactions. We proposed that the confining cavities of zeolites studded with alkali ions would force a stronger interaction between the reactant and a chiral inductor which would result in chiral induction higher than that encountered in solution. During the last decade, we have provided several examples in which enantio- and diastereoselectivities were obtained in zeolites but not in solution.[32–39] Recognizing the lack of availability of chiral zeolites, we have modified the interior of an achiral zeolite by adsorbing optically pure chiral inductors. In another approach, we employed covalently linked chiral auxiliaries to bring about chiral induction in photoreactions. By this technique, we were able to achieve chiral induction (de) over 85% with a few examples that gave less than 5% de in solution. These examples revealed the importance of a cation–π interaction in the chiral induction process within zeolites.[40] Beyond discovering more and newer examples, a clear

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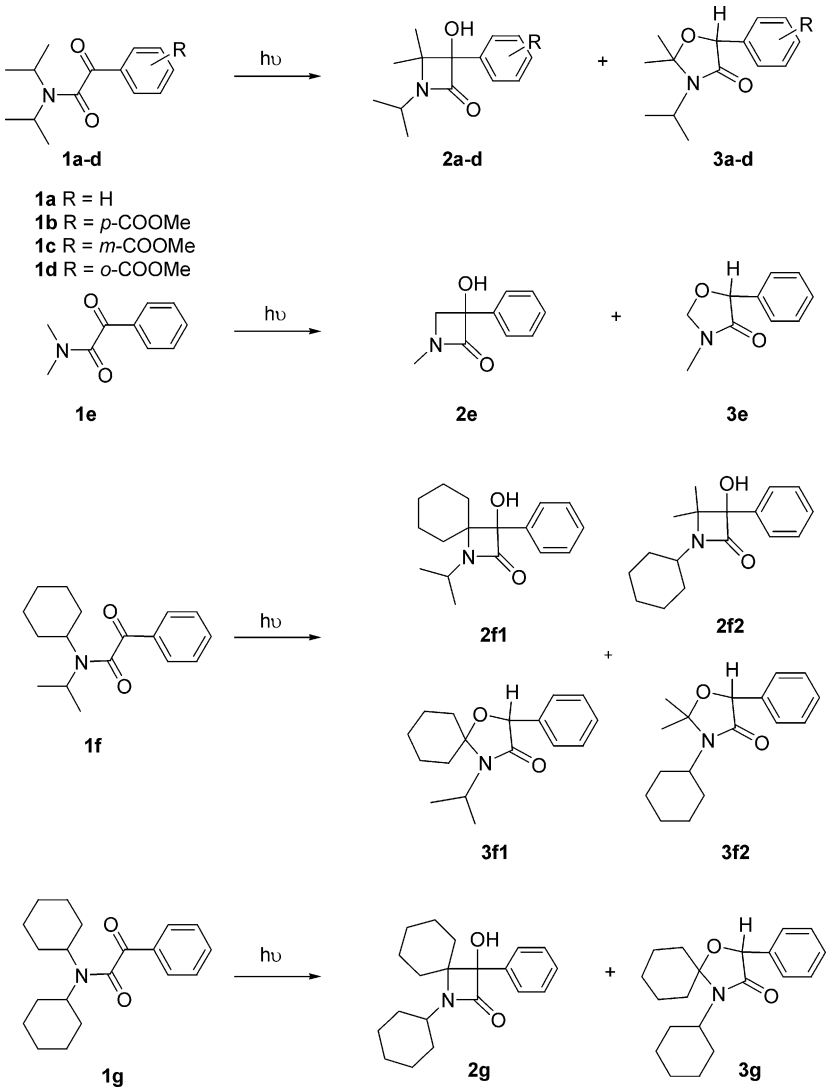
understanding of how the cation–π interaction and confinement provided by a zeolite bring about chiral induction remains elusive to us. In this report, admitting that we have yet to develop a general model for chiral induction within zeolites, we present our results on chiral induction during the photocyclization of α-oxoamides to β-lactams. There have been a considerable amount of studies related to chiral induction during photocyclization of oxoamides in crystals and in solid inclusion complexes. We believed that the photobehavior of the same molecules in crystals would help us understand the chiral induction process within zeolites. Examples provided in this report further confirm the usefulness of zeolites as media in performing chiral photochemistry.[41]

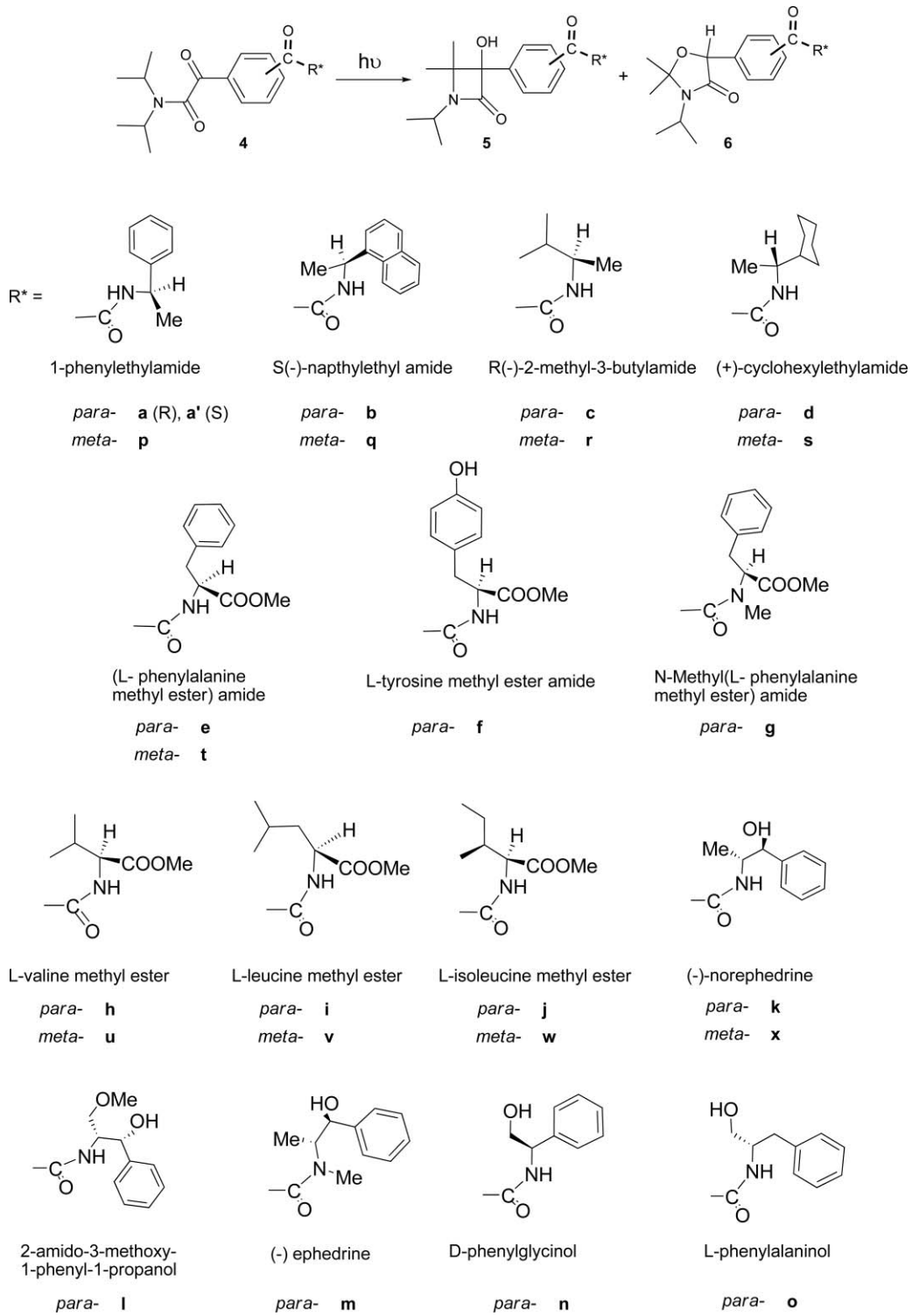
Results

In order to establish the value of zeolites as media for achieving enantio- and diastereoselectivities during a photoreaction, we have investigated thirty one α-oxoamide derivatives (**1a–g**, **4a–x**; Schemes 1 and 2). β-Lactams and oxazolidinones are the main products of γ-hydrogen transfer on excitation of α-oxoamides (Scheme 1).[42,43] The γ-hydrogen transfer, depending upon the medium in which the photochemical reaction is conducted, can occur either *via* direct transfer or through two steps—electron transfer followed by proton transfer (Scheme 3).[44–46] β-Lactam was the major product (60–88%) from all α-oxoamide derivatives investigated in this study although oxazolidinone was obtained as the major product (>85%) in benzene solution (Table 1). Despite the fact that the mechanism of hydrogen transfer has yet to be resolved, we believe that the chiral induction could be understood by either one of these two primary processes—electron or hydrogen atom transfer. We focused our attention on the β-lactam product and the enantiomeric/diastereomeric excess in this product was monitored through HPLC. Since the oxazolidinone product was formed in smaller amounts, no enantiomeric excess (ee) or diastereomeric excess (de) measurements of this product were made.

In this article we show that reactions conducted within zeolites are more selective both in terms of product distribution and chiral induction, than those in solution. Two independent approaches we have been exploring were utilized:[13] (a) the 'chiral inductor approach' where a chiral inductor adsorbed onto the zeolite interior provides an asymmetric environment; (b) the 'chiral

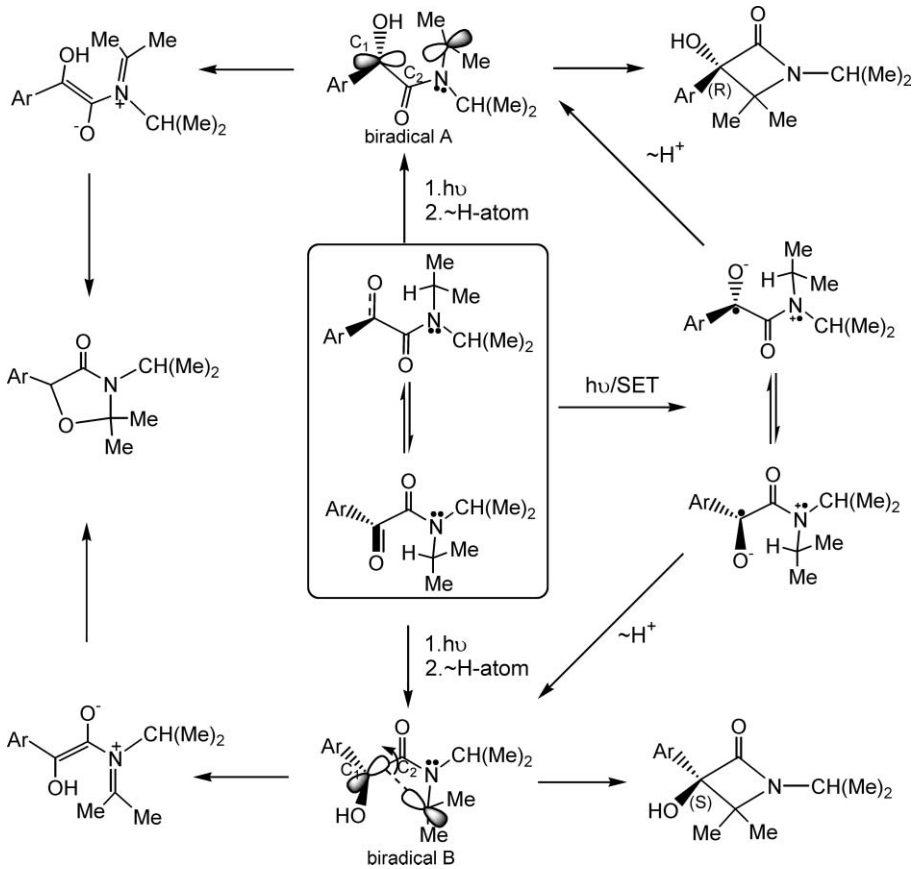


Scheme 1 Photochemical reaction of α-oxoamide derivatives **1a–1g**.



Scheme 2 Diastereoselective studies on covalent chiral auxiliary derivatives **4a–x**.

auxiliary approach' where the chiral information is covalently attached to the reactant molecule. The absolute configurations of the photoproducts except **5a** were not determined due to the relatively difficult conversion of the β-lactam products to compounds with known absolute configuration. In the absence of this information, we denote the two enantiomeric or diasteromeric product peaks in GC and HPLC as A and B. The isomer that eluted first was always assigned as A. Our main goal of establishing the utility of zeolites as useful media for achieving asymmetric induction in photochemical reactions was achievable even without the absolute configurations of the enantiomeric and diastereomeric products. However, our recent studies in the



Scheme 3 Mechanism of photocyclization of α-oxoamides.

Table 1 Photoreaction of **1a–g** in solution and within NaY: percentages of the two photoproducts, β-lactam (**2**) and α-oxazolidinone (**3**)[a]

	Benzene		NaY	
Substrates[b]	**2**	**3**	**2**	**3**
1a	11	89	88	12
1b	9	91	85	15
1c	7	93	87	13
1d	6	94	80	20
1e	5	95	60	40
1f	2 (**f1**)	45 (**f1**)	48 (**f1**)	10 (**f1**)
	3 (**f2**)	50 (**f2**))	37 (**f2**)	4 (**f2**)
1g	11	89	78	22

[a] Based on GC analysis, the relative ratios of the product peaks are presented; the reported values represent averages of three independent runs. [b] All irradiations were conducted at room temperature.

crystalline state of one of the systems enabled us to assign the absolute configuration of the newly formed chiral center in the photoproduct **5a**.[47]

Chiral inductor approach

The major products upon irradiation of zeolite included α-oxoamides **1a–g** were the β-lactams **2a–g** (Scheme 1). Among the various chiral inductors explored, ephedrine, norephedrine and pseudoephedrine gave better results (Table 2). Alkali ion exchanged Y type zeolites rendered chiral by adsorption of the above chiral inductors on their internal surfaces were used as reaction media. The experimental section provides details for the inclusion of the reactants and the chiral inductors within a zeolite, irradiation procedure, extraction and analysis. The loading level (represented as ⟨S⟩ and defined as the average number of molecules per supercage) of 1 and 0.01 of the chiral inductor and the substrate, respectively, were maintained. A higher ratio of the chiral inductor was employed to maximize the chances of the substrate molecule being adjacent to the chiral inductor within the supercage. Sample handling was carried out under laboratory conditions (temperature, 20 °C; humidity, 50%). Since the external surface of the NaY zeolites constitutes less than 1% of the total surface area, in the absence of any specific interactions, adsorption of molecules would be expected to be on the internal surface thereby leading to photoreaction within and not on the external surface of a zeolite.

Photoreaction of **1a** in solution in the presence of a chiral inductor and within NaY in the absence of a chiral perturber resulted only in racemic **2a**. Photoreaction of **1a** within chirally modified NaY using (−)norephedrine as a chiral inductor gave the β-lactam **2a** with 44% ee (Table 2). Moderate enantioselectivities ranging between 10–23% (maximum) depending upon the chiral inductor used were obtained with substrates **1b–d** (Table 2). Irradiations of **1a–d** included within Li^+, Na^+, K^+, Rb^+ and Cs^+ exchanged Y zeolites were conducted to investigate the role of alkali ions in asymmetric induction showed enantioselectivities varying with the alkali ion with all substrates proving their importance (Table 2).

Table 2 Enantioselective studies on β-lactam photoproducts[a]

Medium/chiral inductor[a,b]	**2a** ee (%)	**2b** ee (%)	**2c** ee (%)	**2d** ee (%)	**2e** ee (%)	**2f1** ee (%)	**2g** ee (%)
Benzene	0	0	0	0	0	0	0
Benzene/(−)ephedrine	0	0	0	0	0	0	0
NaY	0	0	0	0	0	0	0
LiY/(−)-ephedrine	3A	6A	1A	4A	1A	1A	4A
NaY/(−)-ephedrine	18B	27A	13A	10A	5A	4A	10A
KY/(−)-ephedrine	3A	7A	3A	13A	2A	3A	13A
RbY/(−)-ephedrine	3B	3A	0	5A	0	0	5A
NaY/(−)-ephedrine/50° C	18B	27A	7A	11A	—	—	11A
NaY/(−)-ephedrine/−60 °C	17B	27A	25B	8A	—	—	8A
NaY/(+)-ephedrine	20B	23B	12B	11B	5B	5B	11B
NaY/(−)-norephedrine	44B	4A	6A	5A	3B	20B	5A
NaY/(+)-norephedrine	40A	6B	5B	7B	2A	19A	7B
NaY/(−)-pseudoephedrine	10B	10A	—	—	10A	5B	—
NaY/(−)-phenylethylamine	10B	10A	—	—	3B	23A	15A

[a] All irradiations unless stated were conducted at room temperature. [b] The A's and B's refer to the first and second peak that elute from the HPLC column.

The isopropyl groups of the amide moiety of the substrate **1a** were replaced with two methyl, one isopropyl and one cyclohexyl, and two cyclohexyl groups (**1e–g** respectively) to determine the influence of the structure of the substrate on enantioselectivity. The best ee obtained within an MY zeolite for the photoproducts (**2e–2g**) using a specific chiral inductor is presented in Table 2.

Examination of the effect of temperature on systems **1a–d** showed it had no effect on the enantioselectivity of β-lactam products **2a**, **2b**, and **2d** (Table 2). Product **2c** showed variation in ee with temperature (RT to −60 °C; Table 2) and a switching of enantiomer was observed from 13% (A) at 23° to 25% (B) at −60 °C.

Chiral auxiliary approach

It is evident from the presentation above that photoreaction of α-oxoamides **1a–g** within chirally modified zeolites produced only low to moderate enantioselectivity. Hence we explored a strategy in which the chiral influence on the reactant is brought forth by a chiral substituent covalently linked to the reactant at a location remote to the reaction site. A variety of chiral auxiliaries such as amines, amino acid methyl esters and amino alcohols were examined by covalently linking them *via* the carboxyl group at the *para* or *meta* position of the phenyl unit of the α-oxoamide (Scheme 2). Attempts to synthesize *ortho* substituted α-oxoamides were unsuccessful.

Excitation of the chiral auxiliary coupled oxoamides **4a–x** within zeolites gave β-lactams **5a–x** as major products (Scheme 2). The oxazolidine product **6a–x** was formed only in 15–20% within zeolites. The percentage de's obtained on the β-lactam photoproduct with various covalently linked chiral amines, amino acids, and amino alcohols as chiral auxiliaries at *para* (**4a–o**) and *meta* (**4p–x**) positions of the phenyl moiety of *N*,*N*-diisopropylglyoxylamides are presented in Table 3. In all cases, higher de's were obtained within a zeolite than in solution. Examples **4e** and **4v** are particularly noteworthy. Both **4e** and **4v** photolyzed in NaY zeolite resulted in a maximum 83% de of **5e** and **5v**. It is important to note that the same compounds in solution (CH_3CN) gave 2% and 7% de. Additionally, the diastereoselectivity in all examples (Table 3) varied with the alkali ion in the zeolite. For example, the de obtained on compound **5e** within MY zeolites were: LiY, 2%; NaY, 83%; KY, 54%; and RbY, 16%. Apart from the alkali ion dependent de, in some cases, the diastereomer formed in excess was dependent on the alkali ion present in zeolites. For example, compounds **4e** and **4l** gave 83% and 74% B respectively within NaY and 54% and 68% respectively of A within KY. Unlike the *para* substituted derivatives, most *meta* substituted oxoamides did not show an alkali ion dependent diastereomer switch on the β-lactam products. Our desire to investigate the asymmetric induction with the chiral auxiliaries appended at the *ortho* position of the *N*,*N*-diisopropylglyoxylamide could not be realized owing to the difficulties in their synthesis.

Table 3 Influence of *para*- and *meta*-amide, amino alcohol and amino acid derivatives on % de of the β-lactam photoproducts (**5a–5x**)[a,b]

Substrates	Solution	LiY	NaY	KY	RbY	CsY
4a	2A	5A	62A	25A	16A	—
4p	0	13A	45A	19A	5A	—
4b	2A	30A	54A	16A	15A	—
4q	7A	14A	38A	1A	1A	—
4c	2A	19A	22A	30A	12A	5A
4r	0	5A	25A	1A	40B	33B
4d	6B	17A	30B	19B	14B	3B
4s	2A	3A	40A	19A	1A	44B
4e	2B	2B	83B	54A	16A	—
4t	6B	10B	35B	9B	5B	—
4f	3B	6A	40A	47B	12B	10B
4g	5B	8B	43B	12B	20A	5A
4h	6A	9A	22A	17B	20B	25B
4u	0	12A	49A	40A	35A	16A
4i	1B	12B	60B	11A	40A	47A
4v	7A	1A	83A	42A	3A	0
4j	1A	29A	20A	5B	30B	—
4w	2A	0	45A	19A	10A	5A
4k	5A	5A	20A	60B	25B	—
4x	3A	9B	25B	24B	8A	5A
4l	5A	40A	68A	74B	30B	5B
4m	5B	41B	50B	9A	30A	10A
4n	5B	2B	9B	10B	8A	—
4o	15B	20A	9B	16B	5B	4B

[a] All irradiations unless stated were conducted at room temperature. [b] The A's and B's refer to the first and second peak that elute from the HPLC column.

The dependency of diastereoselectivity on the nature of the alkali ion when various alkali ion exchanged zeolites were used as listed in Table 3 clearly points out that no single alkali ion is in general more effective than others and that it varies with

the different compounds. There was a drastic reduction in de to 2% when irradiation of silica gel-adsorbed **4a** was conducted (no alkali ion and no supercage). Furthermore, even when irradiation was conducted in NaY with increases in the silicon content (with a corresponding adjustment of the alkali ion content), the de decreased. For example an increase in Si–Al ratio from 2.4 to 40 resulted in the de of product **5a** changing from 62% to 7% respectively. Similarly, changes in moisture content of the zeolite that would alter alkali ion concentration were reflected in changes in de. For example, **4a** within dry and wet (alkali ion exposed to normal laboratory humidity) NaY resulted in 62% and 18% de respectively in the product **5a**. All these observations emphasize the importance of the alkali ion in the chiral induction process. In addition to the effect observed due to the absence of both alkali ion and supercage when silica gel was used the importance of the confined space became apparent when irradiation of **4a** in $LiClO_4$ or $NaClO_4$ saturated acetonitrile produced **5a** with 5% de. Thus the above observations lead us to conclude that both the alkali ion and the confined space of zeolites are crucial to chiral induction during γ-hydrogen transfer in α-oxoamides.

Discussion

As presented above, we have experimented with two approaches to achieve chiral induction during the photocyclization of α-oxoamides to β-lactams within zeolites. We discuss the 'chiral inductor approach' first. The ideal approach to achieve chiral induction within zeolites would be the use of 'chiral zeolites' as reaction media. In the absence of stable chiral zeolites, we have resorted to modifying an achiral zeolite to a chiral one by physical adsorption of optically pure organic molecules (chiral inductors) within zeolites. The chiral inductors were selected based on their availability, size, functionality and inertness to irradiation conditions. Recently we succeeded in achieving moderate enantioselectivity by this approach in diverse reactions including (1) photocyclization of tropolone and pyridone derivatives,[32] (2) light initiated geometric isomerization of 1,2-diphenylcyclopropanes and 2,3-diphenyl-1-benzoyl cyclopropanes,[35,36] (3) Norrish type II reaction of phenyl adamantyl ketones, phenyl norbornyl ketones and phenyl cyclohexyl ketones[34,38] and (4) oxa-di-π-methane rearrangement of naphthalenones and cyclohexenones.[48,49] Despite the extensive list, we are unable to formulate rules that would allow prediction of the chiral outcome of a photoreaction within a zeolite. Nevertheless we have established, unequivocally, the usefulness of zeolites as reaction media to bring about chiral induction in photochemical reactions. In the following paragraphs a brief discussion of the observations on the photocyclization of α-oxoamides is presented.

Photoreaction of α-oxoamides **1a–g** using the chiral inductor approach gave enantioselectivities ranging between 4–44% on β-lactam products within zeolites (Table 2). It is important to note that in solution, even in the presence of chiral inductors, only a racemic product mixture was obtained. The best results were obtained with **1a**. Photoreaction of **1a** within NaY using (−)-norephedrine as a chiral inductor gave ee (44%, B) on the β-lactam photoproduct. As expected, the enhanced isomer switched when (+)-norephedrine was used confirming the observed chiral induction to be no artifact. Unfortunately, this observation could not be extended to **1b–g** where the same chiral inductor gave the β-lactams with very low ee (3–20%). As indicated in Table 2, the chiral inductor that gave the best ee in each case was different. Based on our experience with α-oxoamides as well as the systems investigated earlier, we conclude that the best chiral induction is usually obtained with ephedrine, norephedrine and/or pseudoephedrine. In our hands, depending on the system, one of these compounds works best though the exact one can't be predicted.

We visualize chiral induction to be the result of close interaction between the reactant and the chiral inductor enforced by the alkali ion present within a zeolite. Our computational and solid-state NMR results in the case of phenyl cyclohexyl ketones were recently presented.[33] In this example, we showed that the alkali ion enforces an interaction between the chiral inductor and the ketone. We believe that the same phenomenon plays a role in α-oxoamides as well. If this was true one would expect that any variation of the structure of the ternary supramolecular complex made up of an alkali ion, chiral inductor and α-oxoamide would have a consequence on the ee within a zeolite. This was found to be the case. As seen in Table 2, the ee was dependent on the nature of the alkali ion, and the structures of the α-oxoamide and the chiral inductor. Even though prediction of the structure of the ternary complex and its chiral outcome might be possible, we at this time are unable to do so. Since the flexibility of the ternary complex would depend on the temperature, one would expect the ee also to depend on the temperature of irradiation. This was found to be so in the case of **1c** where a difference in ee was observed when irradiations were conducted at different temperatures (Fig. 1). Not only was there a variation in ee but also the isomer being enhanced switched between high and

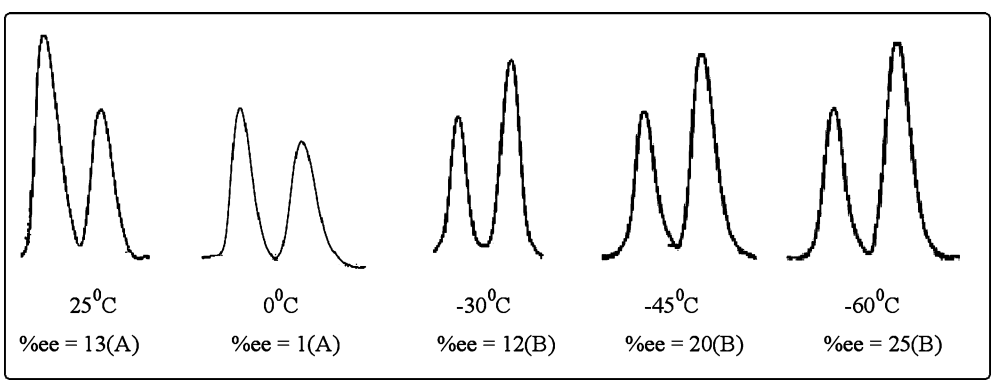


Fig. 1 HPLC traces showing the temperature effect on enantioselectivity of β-lactam (**2c**) within NaY; reactant: **1c**, chiral inductor: (−)-ephedrine.

low temperatures. Such a temperature dependent enantiomer switch has been noted during the geometric isomerization of *cis*-cyclooctene in solution.[50] We anticipate that the temperature dependent enantioselectivity might be due to the rigidity of the substrate–cation–CI complex on lowering the temperature. This rigidity results in better interaction between the CI and the substrate. The above mentioned argument is supported by the observation that during the high temperature (50° C) photolysis of substrate **1c** within NaY/(−)-ephedrine, the % ee reduced to 7(A) owing to an increase in the mobility of the substrate and the chiral inductor. Whereas at RT or higher, the molecule is still flexible and therefore favors a different conformation from which hydrogen abstraction might result in enantiomeric excess of the opposite isomer A. Since the temperature effect was not uniform with other substrates, it was not pursued in detail. We do not have a clear explanation why only **1c** showed the temperature dependence but not the others.

Having obtained partial success with chiral inductor methodology, we decided to explore the chiral auxiliary approach. In this approach with an achiral Y zeolite as the reaction medium, the chiral influence is provided by an optically pure substituent covalently linked to the reactant molecule. In the case of α-oxoamides, to examine the influence of the location as well as the nature of the chiral auxiliary on the extent of chiral induction, we covalently linked various chiral auxiliaries at the *para* and *meta* positions of the aryl ring of the α-oxoamide (Table 3).

The greater efficiency of chiral auxiliaries containing aromatic or carbonyl groups as noted in our earlier studies proved true in this study as well.[13] For example S(−)-phenyl ethyl amide as the chiral auxiliary (**4a**) gave the product with a de of 55% while cyclohexyl ethyl amide as the chiral auxiliary (**4d**) gave only 30%. Similar differences were observed between **4e** containing an aryl substituent and **4h**, **4i** and **4j** that contain alkyl substituents. Perusal of Table 3 reveals that **4e** yields a maximum de of 83% in NaY while **4h**, **4i** and **4j** gave the products in 22%, 60% and 20% de respectively in NaY.

In order to gain an insight into the role of the cation during the chiral induction process, structures of the cation–reactant supramolecular complexes were computed at HF/3–21G* level.[51] We find gas phase computational data useful as a guide in formulating a preliminary working model for the chemical behavior of molecules within a zeolite. We recognize that the above computations refer to a naked cation whereas the chemistry relates to the cation bound to the walls of the zeolite. Therefore, conclusions drawn using the computational results are expected to be only approximate. The substrates chosen for the study were *para* substituted S(−)-phenyl ethyl amide and S(−)-cyclohexylethylamide of *N*,*N*-diisopropylglyxylamide. Geometry optimization of the above structures in the presence of Na^+ gave four cation–reactant bound complexes for (S(−)-**4a** and S(−)-**4d**). The most stable structure (−74.8 kcal mol^{-1}) obtained for S(−)-**4a** is the one where Na^+ is bound to the carbonyl and the phenyl moiety of the chiral auxiliary through cation-dipolar and cation-π interactions (Fig. 2a). In such a structure, the chiral auxiliary has very little conformational flexibility. On the other hand, in the case of S(−)-**4d**, the structure with the cation-dipolar (with the carbonyl group) interaction with energy of only −58 kcal mol^{-1} (Fig. 2b) that would allow free rotational mobility of the chiral auxiliary was obtained. Based on the above results, we believe that 'rigidification' of the chiral auxiliary through a cation–chromophore interaction plays a role in the chiral induction process within a zeolite. One should note that the zeolite supercage contains several cations and even though visualization of structures with more than one alkali ion interacting with the reactant molecule within a zeolite is possible, we did not perform computation in the presence of multiple cations. From our above computational data, we wish to draw attention only to the fact that an interaction between the alkali ion and the chiral auxiliary, depending on the chromophores present, could restrict the conformational flexibility of the chiral auxiliary that would influence the extent of chiral induction.

We observed, in the case of 2,3-diphenyl-1-benzoyl cyclopropane derivatives, that the chiral auxiliary functions better at

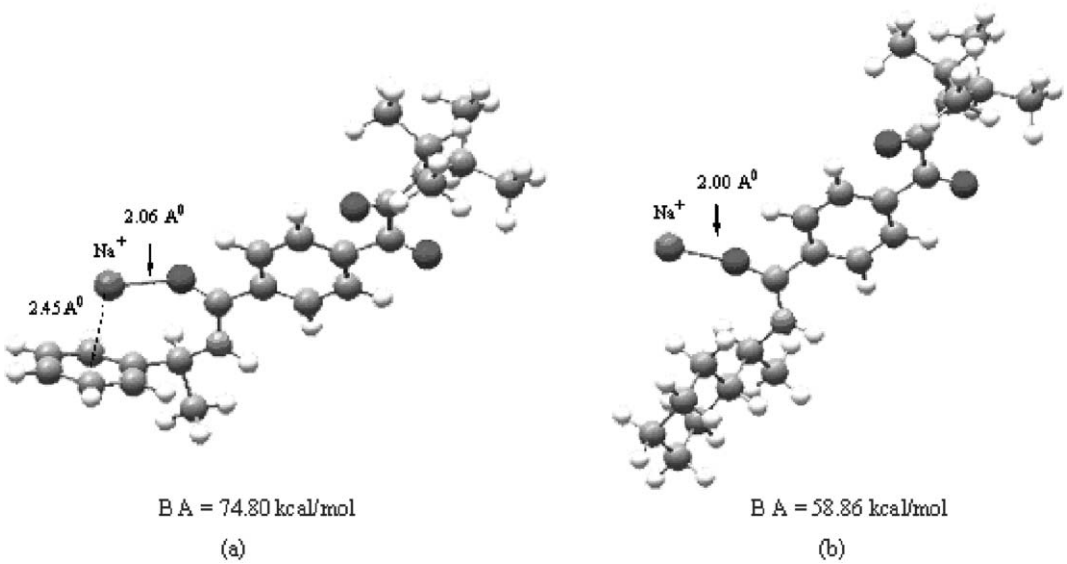
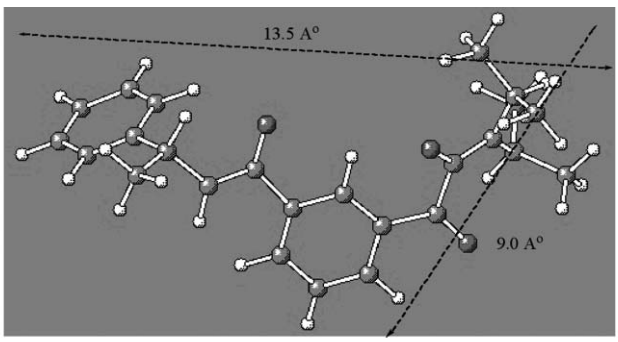


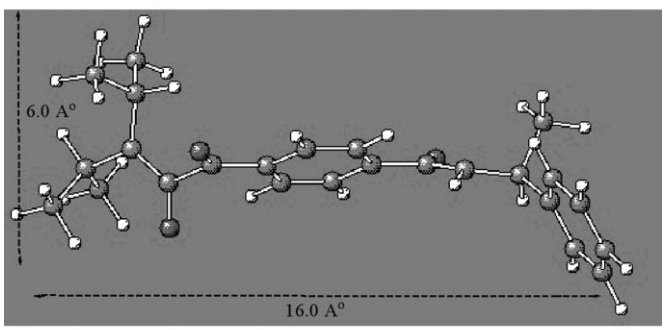
Fig. 2 Binding affinity of Na^+ with (a) S (−)-phenyl ethyl amide of *N*,*N*-diisopropyl-α-oxoamide (**4a**) and (b) S(+)-cyclo hexyl ethyl amide of *N*,*N*-diisopropyl-α-oxoamide (**4d**), optimized using Gaussian-98 software [HF, 3–21G*].

the *meta* than at the *para* position.[35] We ascribe this effect to the proximity of the chiral auxiliary to the reaction site. The results of examination of the influence of a chiral auxiliary linked at the *para* and *meta* positions of the aryl ring of an α-oxoamide as shown in Table 3 are not clear-cut with the chiral auxiliary functioning better at the *para* position in some cases and at the *meta* position in others. For example, bulkier chiral auxiliaries such as phenyl ethyl amide, naphthyl ethyl amide and phenyl alanine methyl ester functioned better at the *para* position while slightly smaller chiral auxiliaries such as 3-methyl-2-butyl amide, valine methyl ester, leucine methyl ester and isolecuine methyl ester functioned better at the *meta* position. Results with α-oxoamides suggest that the conclusion drawn based on 2,3-diphenyl-1-benzoyl cyclopropane derivatives, namely that a chiral auxiliary works better when it is closer to the reaction site, is not general and that the mechanism by which a chiral auxiliary functions within a zeolite is yet to be understood.

The geometry optimized structures (HF/3–21G*) of the *para* and *meta* substituted phenyl ethyl amide of *N*,*N*-diisopropylglyoxylamide (**4a** and **4p**) shown in Fig. 3 are larger than the dimensions of the supercage (dia 13 Å).[51] We believe that it is quite likely that the reactant molecule is stationed between the two supercages through the window (~8 Å dia). Under such a condition, it is possible that two cations are holding the reactant molecule in two different cages by interacting with the chiral auxiliary in one cage and with the reactant chromophore, diketone, in the other cage. Although we are confident that the chiral induction within a zeolite is far more effective than in an organic



a)



b)

Fig. 3 a) Geometry optimized *meta*-substituted phenyl ethyl amide of α-oxoamide (**4a**); b) geometry optimized *para*-substituted phenyl ethyl amide of α-oxoamide (**4d**), optimized using Gaussian-98 software [HF, 3–21G*].

solvent and the cation present within a zeolite plays an important role in the process, at this stage we do not have an insight into how the cation within the supercage influences the chiral outcome.

Among the 24 *para* and *meta* substituted compounds studied within zeolites, 15 compounds (**4d–o**, **4r**, **4s**, and **4x**) showed an alkali ion dependent diastereomer switch on the β-lactam products upon variation of cations occupying the zeolite framework. Among the 15 compounds, 13 of them are *para* substituted derivatives and 2 are *meta* substituted derivatives. It is particularly revealing in the case of product **4e** which gave 83% of the B isomer with NaY but switched to the 54% of A diastereomer in KY. Though the exact reason for this behavior has not been understood we believe that the probable reason for the switch could be the difference in site to which the two alkali metal ions (Na or K) bind. This suggestion, although in our case has no experimental support, has literature precedence.[52–55] Based on density functional calculations and low energy collisionally activated and thermal radiative dissociation experiments, a difference in binding pattern between Li^+ and K^+ ions with valine and glycine has been proposed. For example, Li^+ binds to these molecules through N, O coordination (oxygen on the carboxyl group and nitrogen on the amino group), whereas K^+ binds through O, O coordination (oxygens on the carboxyl moiety). A similar switch in the binding site has also been reported during the interaction of Li^+ and Cs^+ to arginine. Such a phenomenon could be involved within a zeolite and responsible for the observed cation controlled diastereomer switch within a zeolite. It is important to recognize that it is not only the cation size that controls the extent and direction of diastereoselectivity but also the binding ability and charge density of cations play an important role. Overall, too many factors control the chiral induction process within a zeolite making prediction a bit risky.

The final part of the presentation deals with the identification of the absolute configuration of the β-lactam product from **4a**. Knowledge of the absolute configuration of the newly formed chiral center allows us to speculate the mechanism of chiral induction within zeolite Y. Using the data obtained from our recent studies on single crystal to single crystal transformation of **4a** to **5a**, we were able to identify the β-lactam **5a** that is enhanced within NaY to have the *R* configuration at the newly formed chiral center. As illustrated in Scheme 3 upon excitation of α-oxoamide either an electron transfer (followed by proton transfer) or a hydrogen abstraction (the exact nature of it being dependent on the medium and the substituents attached to the amide nitrogen) is believed to be the primary process. Independent of the primary step, the 1,4-biradical intermediate is involved in the formation of β-lactam and 1,3-zwitterion in the formation of oxazolidinone products (Scheme 3). In general, the absolute configuration of the newly formed chiral center in the β-lactam product is decided at the stage of the ring closure of the 1,4-biradical intermediate (Scheme 3), *i.e.*, to which face of the prochiral benzylic radical center the γ-carbon radical adds. In media where the equilibrium between the two rotomers of the biradical (biradicals A and B in Scheme 3) is not established, the chirality would be decided at the hydrogen abstraction (or proton transfer) stage. Both crystal structure determination[47] on **4a** and computation of **4a**′ suggest that the dicarbonyl part of **4a** and **4a**′ is twisted with respect to the aryl ring. As illustrated in Fig. 4 the torsion angle O=C–C_α–N_β in **4a** could be either positive or negative, *i.e.*, the carbonyl

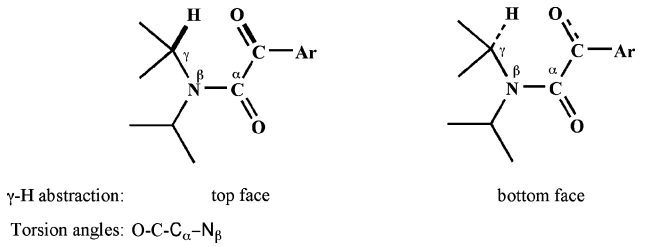


Fig. 4 Positive or negative torsion angles based on carbonyl group facing above or below the aromatic π-plane.

could be above or below the aryl π-plane. Under these conditions the hydrogen abstraction could occur from either the top or the bottom prochiral face of the carbonyl group leading to two biradical rotomers A and B (Scheme 3).

In the isotropic media, the chiral auxiliary has little or no influence on the reactant α-oxoamide and therefore there is no preference for either of the rotomers leading to very low diastereoselectivity on the β-lactam (Table 3). Clearly within a zeolite this is not the case and enhanced formation of an *RR* diastereomer (**5a**)[15] during photoreaction of **4a** suggests that the hydrogen abstraction occurs preferentially from one rotomer of the reactant α-oxoamide. Based on formation of the *R* isomer, the same one formed during crystal irradiation, we believe that **4a** adopts a structure similar to that in a crystal where the torsion angle O=C–C_α–N_β is positive. In this structure, of the two γ-hydrogens present in two isopropyl groups, one is expected to be closer to the carbonyl chromophore. Based on comparing the isomer (A or B) enhanced during irradiation of eight oxoamide molecules included within zeolites or as crystals we believe that the majority of molecules have a conformation in which the reactive carbonyl chromophore has a positive tilt with respect to the aryl π-plane within zeolites (Fig. 5). The comparative study presented in Table 4 reveals six out of eight molecules (except **4c** and **4p**) adopt a positive tilt within the NaY zeolite with respect to the aryl π-plane. Understanding how the chiral auxiliary controls the torsion angle O=C–C_α–N_β of the diketoamide part might get us closer to uncovering the mechanism of chiral induction within a zeolite.

Experimental

Loading and photoreaction of α-oxoamides

All photoreactions were performed by using a 450 W medium pressure mercury lamp placed in a water-cooled Pyrex immersion well (transmits $\lambda > 290$ nm). For solution photolysis, the sample

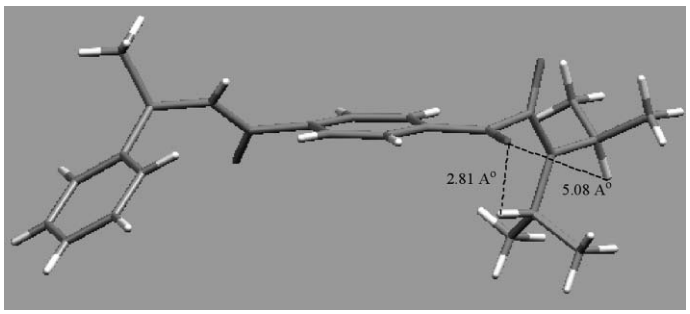


Fig. 5 X-Ray crystal structure of oxoamide derivative **4c**; note the two γ-hydrogens are placed at different distances from the carbonyl chromophore.

was taken in a Pyrex test tube and dissolved in methanol or ethyl acetate solution.

Loading and photolysis of achiral α-oxoamides (1a–g) in the presence of chiral inductors in MY zeolites

In order to activate the zeolite, commercially available NaY (300 mg) was kept in a furnace maintained at 500 °C for 12 h prior to use. The activated NaY was added to the hexane–dichloromethane (4 : 1) solution of the substrate, being careful not to add it too fast which would result in charring of the sample, and not too slow as the moisture in the atmosphere would hydrate the zeolite. α-Oxoamides (~4 mg) and the chiral inductor (25 mg) were stirred with activated NaY (300 mg) in 5 mL of dichloromethane–hexane (1 : 4) for 12 h at room temperature. The loading level of the chiral inductor was maintained at one molecule in every supercage, while the loading level of the substrate was kept at one molecule in every ten supercages. A higher ratio of the chiral inductor is employed to maximize the chances of the substrate molecule being adjacent to the chiral inductor within a supercage. The zeolite containing both the reactant and the chiral inductor was collected by filtration, washed with hexane and irradiated (450 W medium pressure Hg lamp, Pyrex filter) as a hexane slurry for 1–3 h. Sample handling was carried out under laboratory conditions (temperature = 20 °C, humidity 55%). The product was extracted with dichloromethane and analyzed by GC or HPLC.

Loading and irradiation of α-oxoamide derivatives (4a–x)

The α-oxoamide derivative (4 mg), was dissolved in a mixture of dry methylene chloride–hexane (1 : 4). NaY (300 mg), dried at 500 °C was added to the above. The slurry was stirred for 12 h, filtered and washed with hexane (3 × 5 ml). The supernatant hexane layer was tested for complete loading by removing hexane

Table 4 Comparison of isomers enhanced within the NaY zeolite and in the crystalline state

Substrate	Torsion angle in crystalline state/deg	% de (in crystals)	% de (within NaY)
4a	90.36	>99A	60A
4c	89.55	96B	54A
4e	−89.51	82A	83B
4f	−86.99	99B	40A
4m	86.48	91B	50B
4n	88.12	95B	9B
4p	−69.12	80A	45A
4q	−100	99B	45A

under a positive pressure of nitrogen. The zeolite complexed with the guest was dried under vacuum (3×10^{-3} Torr) at 65 °C for 6 h and irradiated (450 W medium pressure Hg lamp) in dry hexane (5 ml) for 45 min. The products were extracted from the zeolite by stirring with 5 mL of acetonirile.

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