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Control of Enantioselectivity in the Photochemical Conversion of α-Oxoamides into β-Lactam Derivatives

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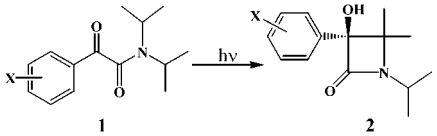
ABSTRACT



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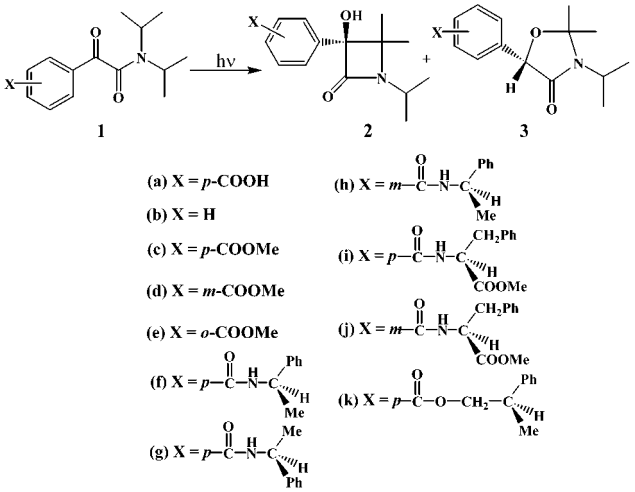
Several approaches to asymmetric induction in the α-oxoamide (1) to β-lactam (2) photorearrangement are described. Best results are obtained via irradiation of ionic and covalent chiral auxiliary-containing reactants in the crystalline state and in the interior supercages of zeolites.

Photochemical rearrangements that convert achiral reactants into chiral products provide ideal vehicles to test new strategies of asymmetric induction.[1] The reaction with which we shall be concerned in this Letter is the well-known and synthetically attractive conversion of α-oxoamides (**1**) into β-lactams (**2**) (Scheme 1).[2] There have been two previous approaches to achieving enantioselectivity in this photorearrangement, the first involving the "absolute" asymmetric photochemistry of chiral single crystals[3] and the second consisting of irradiating crystalline host−guest complexes in which the α-oxoamides are the guests and the hosts are optically pure clathrate-forming compounds.[3c,4]

Although the above two methods lead to β-lactams in respectable ee, each suffers from certain limitations that render it less than general. The drawback of absolute asymmetric synthesis is that it relies on rare and unpredictable crystallization of the reactants in chiral space groups, while the clathrate method is limited to host−guest combinations that form well-defined crystalline complexes. This Letter deals with our attempts to overcome these limitations through the following approaches: (1) irradiation of achiral α-oxoa-

Scheme 1



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(2) (a) Akermark, B.; Johanson, N. G.; Sjoberg, B. *Tetrahedron Lett.* **1969**, 371. (b) Aoyama, H.; Hasegawa, T.; Omote, Y. *J. Am. Chem. Soc.* **1979**, *101*, 5343. (c) Aoyama, H.; Sakamoto, M.; Kuwabara, K.; Yoshida, K.; Omote, Y. *J. Am. Chem. Soc.* **1983**, *105*, 1958. (d) Chesta, C. A.; Whitten, D. G. *J. Am. Chem. Soc.* **1992**, *114*, 2188. Oxazolidinones (**3**) are also formed in the photolysis of α-oxoamides, but in the present study, products of this type were formed in minor amounts and were not analyzed for ee.

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mides in "chirally modified" zeolites[5] and as crystalline complexes with β- and γ-cyclodextrin, (2) photolysis of covalent chiral auxiliary-containing α-oxoamides in conventional zeolites[6] and in α-, β-, and γ-cyclodextrin and the pure crystalline state. Also, experiments employing ionic chiral auxiliaries in the pure crystalline state are described.[7] We begin our presentation on this last topic.

The ionic chiral auxiliary approach requires that the reactant be equipped with an acidic (or basic) functional group to which an optically pure amine (or carboxylic acid) can be attached through salt formation. Accordingly, the carboxylic acid-containing α-oxoamide **1a**[8] was treated with a variety of optically pure amines to form the corresponding salts (Table 1). Irradiation of the crystalline salts was carried out under nitrogen on 5 mg samples sandwiched between Pyrex microscope slides. Table 1 summarizes the results of these experiments. L-Prolinamide proved to be the best chiral auxiliary, giving essentially optically pure photoproduct **2c** at nearly 100% conversion. In a dramatic demonstration of the synthetic potential of the ionic chiral auxiliary approach, a hexane suspension of 500 mg of the prolinamide salt was irradiated to 99% conversion to afford a 91% isolated yield of photoproduct **2c** with an ee of >99%. Equally noteworthy is the extremely low ee observed in the case of the 1-phenylethylamine salt. We shall have more to say about this result later in the paper. As a final point that emphasizes the importance of the crystalline state to these results, photolysis of the salts in methanol gave negligible enantiomeric excesses, e.g., 5% ee in the case of the L-prolinamide salt.

Table 1. Ionic Chiral Auxiliary-Induced Asymmetric Induction in Solid-State Photolysis of Salts of Keto Acid **1a**[a]

amine	convn (%)	**2c**[b] (%)	**3c** (%)	ee of **2c** (%)	$[\alpha]_D$[c]
L-prolinamide[b]	99	94	2	99	(+)
(*S*)-(−)-1-phenylethylamine[b]	99	79	10	3	(−)
(1*R*,2*S*)-(+)-1-amino-2-indanol[b]	23	15	1	91	(+)
	58	44	7	71	(+)
	75	59	9	58	(+)
	98	75	10	45	(+)
(*R*)-(+)-bornylamine	100	92	7	96	(−)
(*R*)-(−)-1-cyclohexylethylamine[b]	60	38	15	83	(−)
(*S*)-(+)-1-aminoindan	100	94	5	89	(+)

[a] All photolyses were conducted at room temperature followed by diazomethane workup to form the corresponding methyl esters. Enantiomeric excesses (ee) were determined by HPLC on a Chiralcel OD column. [b] X-ray crystal structure determined. [c] Sign of rotation of predominant enantiomer; absolute configuration unknown.

We next turn to the use of covalent chiral auxiliaries in the crystalline state. The compounds studied were the amides **1f**−**i** and ester **1k** shown in Scheme 1. The results of photolyzing crystalline samples of these compounds are summarized in Table 2. It is evident from Tables 1 and 2 that both ionic and covalent chiral auxiliaries lead to high levels of asymmetric induction in the crystalline state.

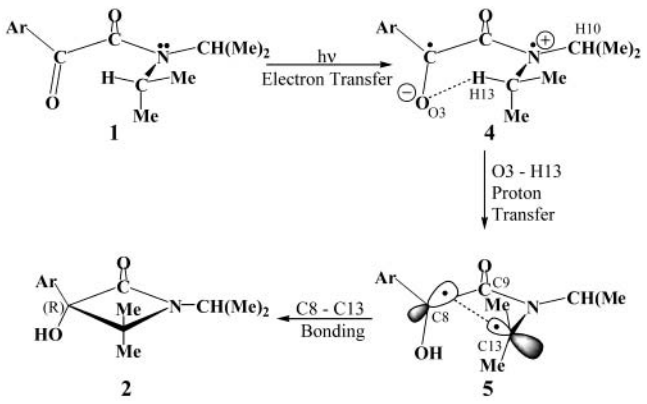
Table 2. Covalent Chiral Auxiliary-Induced Asymmetric Induction in Solid-State Photolysis of Amides **1f**−**i** and Ester **1k**[a]

compound photolyzed	convn (%)	de of **2** (%)	peak
1f[b]	98	>99	A
1g	97	>99	A
1h[b]	17	80	A
1i	80	76	A
1k[b]	98	84[c]	B
	94	95[d]	B

[a] All photolyses were conducted at room temperature. Diastereomeric excess (de) values represent the average of three runs and were determined by HPLC on a Chiralcel OD column. Peak A refers to the first peak eluted from the chiral column and peak B to the second; the absolute configuration of the photoproducts is unknown. [b] X-ray crystal structure determined. [c] Photolysis carried out on neat polycrystalline samples. [d] Photolysis carried out on crystals suspended in water.

What features in the crystalline environment favor the formation of one enantiomer or diastereomer over the other? To answer this question, a basic understanding of the reaction mechanism is required. As depicted in Scheme 2, β-lactam

Scheme 2



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(8) For the method of synthesis of compound **1a** and a preliminary account of the solid-state photochemistry of its L-prolinamide salt, see: Scheffer, J. R.; Wang, K. *Synthesis* **2001**, 1253.

formation is thought to involve photoinduced electron transfer from nitrogen to the benzoyl group followed by transfer of a tertiary γ-proton from one of the isopropyl groups to the carbonyl oxygen. This generates 1,4-hydroxybiradical **5**, which closes to cyclobutanol **2**.[2d] The chirality of the photoproduct is determined not only by which of the two γ-protons (H13 or H10) is abstracted but by the stereochemistry of biradical closure as well. As discussed below, both of these factors depend in turn on the conformation of the reactant in the crystal as well as on the unforgiving nature of the crystal lattice medium, which permits only minimum atomic and molecular motions.

For the purposes of illustration, consider the X-ray crystal structure of the (*R*)-(−)-1-cyclohexylethylamine salt shown in Figure 1. From this conformation (also depicted in Scheme 2) it is apparent that γ-hydrogen H13, which lies at a distance of 2.71 Å from O3, is much more favorably disposed for proton transfer than is γ-hydrogen H10 (C═O···H distance 4.99 Å), and there can be little doubt that H13 is preferentially abstracted in the solid state.[9]

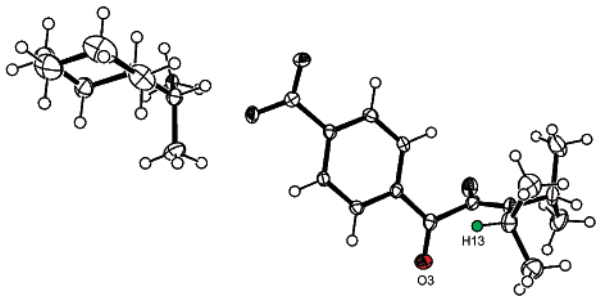

Figure 1. Solid-state conformation of (*R*)-(−)-1-cyclohexylethylamine salt of α-oxoamide **1a**. Abstraction of H13 (green) by O3 (red) is favored.

The stereochemistry of biradical closure can also be reasonably interpreted in terms of molecular conformation. Assuming that biradical **5** has a conformation similar to that of its α-oxoamide precursor, it can be seen from Scheme 2 that least motion closure of this species should lead to the (*R*) absolute configuration at the newly generated chiral center (retention). Formation of the (*S*) enantiomer (inversion) would require rotation about the C8—C9 bond so as to bring the back lobe of the p-orbital on C8 into proximity with C9. Such a process, with its concomitant large amplitude motions of the pendant aryl and hydroxyl groups, is expected to be topochemically forbidden in the rigid, close-packed environment of the crystal.

All of the compounds in Tables 1 and 2 whose crystal structures were determined (7 in total) have conformations compatible with the above mechanistic interpretation. In each case, one γ-hydrogen was much closer ($d = 2.72 \pm 0.05$ Å) to the benzoyl oxygen than the other ($d = 5.03 \pm 0.08$ Å), and biradical closure with retention of configuration at the carbonyl carbon was topochemically favored.[10]

To date we have been unable to determine the absolute configuration of β-lactam **2c** to verify the structure−reactivity correlation outlined above. There is, however, indirect evidence that supports this picture. This comes from the very low ee (3%) observed in the solid-state photolysis of the (*S*)-(−)-1-phenylethylamine salt. The X-ray crystal structure of this salt shows that it contains equal amounts of two independent and *mirror image related* α-oxoamide moieties in the asymmetric unit, while the phenylethylammonium ions retain their original absolute configuration. The near-perfect enantiomeric relationship between the carboxylate ions is shown by computationally inverting one and overlapping it with the other, which leads to a root-mean-square error (RMSE) of 0.06 Å.[11] Half of the molecules in the crystal have conformations that lead to the (*R*)-β-lactam, while the other half are conformationally poised to give (*S*). The fact that the two sets of conformers are not perfect mirror images of one another, plus the fact that they are diastereomerically related when the presence of the (*R*)-ammonium ion is considered, accounts for the fact that they react at slightly different rates, thus leading to a low but measurable ee. Similar conformational effects have been reported by Scheffer and co-workers and termed "conformational enantiomerism".[12]

The remainder of this Letter deals with our investigation of the α-oxoamide to β-lactam photorearrangement in zeolites and cyclodextrins. Our initial studies were on achiral oxoamides **1b**−**e** in "chirally modified" zeolites, i.e., zeolites that had been preloaded with an external, optically pure chiral inductor such as ephedrine. Table 3 lists the zeolites and chiral inductors used along with the ee's in which the

Table 3. Chiral Inductor-Mediated ee of Photoproducts **2b**−**e** from Photolysis of Achiral α-Oxoamides **1b**−**e** in MY Zeolites[a]

zeolite/chiral inductor	**2b** ee (%)	**2c** ee (%)	**2d** ee (%)	**2e** ee (%)
LiY/(−)-ephedrine	3A	6A	1A	4A
NaY/(−)-ephedrine[b]	18B	27A	13A	10A
KY/(−)-ephedrine	3B	7A	3A	13A
RbY/(−)-ephedrine	3B	3A	0	5A
NaY/(−)-ephedrine, −65 °C	17B	27A	25B	10A
NaY/(−)-norephedrine[b]	44B	4A	6A	5A
NaY/(−)-pseudoephedrine[b]	10B	10A		
NaY/(−)-menthol	12B	12A		
NaY/(−)-1-phenylethylamine[b]	24B			
β-cyclodextrin	11A	7A		
γ-cyclodextrin	8B			

[a] Unless otherwise indicated, all photolyses were conducted at room temperature. Enantiomeric excess (ee) values represent the average of three runs and were determined by HPLC on Chiralcel OC or OD columns. Peak A refers to the first peak eluted from the chiral column and peak B to the second; the absolute configuration of the photoproducts was not determined. See the Supporting Information for more details on the experimental procedures employed. [b] The optical antipode of the chiral inductor gave comparable ee (±3%) favoring the opposite enantiomer.

(9) For studies relating to the selectivity of hydrogen atom abstraction as a function of abstraction distance and geometry, see: Ihmels, H.; Scheffer, J. R. *Tetrahedron* **1999**, *55*, 885.

corresponding β-lactams **2b**−**e** were formed. Also included are the results of photolyzing oxoamides **1b** and **1c** as crystalline 1:1 complexes with β- and γ-cyclodextrin.

To complete the presentation of the experimental results, we turn to our studies of photolyzing covalent chiral auxiliary-containing α-oxoamides **1f**−**j** in the interior cavities of conventional zeolites, i.e., those that had not been preloaded with chiral inductors. The de's in which photoproducts **2f**−**j** were formed are given in Table 4. This table also includes the results of irradiating oxoamides **1f**,**g**,**i** as crystalline 1:1 complexes with α-, β-, and γ-cyclodextrin.

Table 4. Covalent Chiral Auxiliary-Mediated de of Photoproducts **2f**−**j** from Photolysis of α-Oxoamides **1f**−**j** in Various Media[a]

medium	2f	2g	2h	2i	2j
MeOH	2A	2A	0	2B	6B
benzene	28A	0	0	5B	6B
LiY	5A	7A	13A	5B	10B
NaY	62A	55A	45A	82B	35B
KY	25A	25A	19A	54A	9B
RbY	16A	13A	5A	16A	5B
α-CD	20A				
β-CD	87A	75A		12A	
γ-CD	35A			7B	

[a] All photolyses were conducted at room temperature. Diastereomeric excess (de) values represent the average of three runs and were determined by HPLC on a Chiralcel OD columns (**2f**, **2g**, **2i**, **2j)** or GC on an SE-30 column (**2h**). Peak A refers to the first peak eluted from the column and peak B to the second; the absolute configuration of the photoproducts was not determined. See the Supporting Information for more details on the experimental procedures employed.

From the data presented in Tables 3 and 4, it is clear that, for certain substrates, the use of zeolites and cyclodextrins as restricted media can lead to remarkably high levels of asymmetric induction. Particularly noteworthy is the outstanding 82% de obtained in the case of photolysis of α-oxoamide **1i** in zeolite NaY, as well as the excellent 75−87% de obtained by irradiating compounds **1f**,**g** in β-cyclodextrin.[13] On average, however, the degree of asymmetric induction in zeolites is well below that observed in the pure crystalline state (Tables 1 and 2). This undoubtedly reflects a greater level of organization, regularity, and rigidity in crystals compared to the interior supercages of zeolites. In the latter, the fit of the α-oxoamide guest in the zeolite host differs from compound to compound, as does the strength and nature of the binding interaction between the zeolite cations and the functional group(s) of the guest. As a result, it is not surprising that variable ees and des are observed.

In comparing the use of external chiral inductors to covalently bound chiral auxiliaries in zeolites, it is interesting to note that NaY gives the best results in both cases, but that asymmetric induction is generally higher in the latter. On this last point, the overall difference in ee/de can be attributed to the fact that, when the reactant and chiral inductor are separate entities, there will inevitably be a certain fraction of zeolite supercages that contain only one or the other but not both, as is required for asymmetric induction.

The results summarized in Tables 3 and 4 also demonstrate that the nature of the zeolite cation profoundly affects the extent of ee and de, and in some cases leads to a complete reversal of enantio- or diastereoselectivity. For example, in the case of β-lactam **2i**, diastereomer B predominates in zeolite NaY (82% de), whereas diastereomer A is favored in KY (54% de). While we can only speculate on possible reasons for this remarkable result, it is relevant to note that recent computational and experimental studies have shown that the nature of alkali metal cation binding to amino acids is cation-dependent in solution[14] and such an effect may well be operating with the α-oxoamides in zeolites as well.

The importance of the zeolite medium for asymmetric induction is highlighted by the low de's observed in the case of oxoamides **1f**−**j** in solution (Table 4). Similar "confinement" effects have been noted previously[6] and may be related to differences in the conformation of the reactant in the two media. Recent computational studies have shown that phenylalanine adopts different conformations in its Na^+ bound and free states.[15] β-Lactam **2f** (28% de in benzene) is a notable exception to the general rule of vanishingly low de's in solution. This may be due to aggregation of oxoamide **1f** in the nonpolar solvent, since the effect disappears in methanol. Studies of de dependence on concentration support this interpretation. The de in which photoproduct **2f** is formed in benzene increases more or less linearly from 28% at 1.1 mM to nearly twice that (54%) at 6.6 mM (saturated). Diastereomer A is favored in both benzene and the solid state, which is reasonable, since aggregation may be considered as the initial stage of crystallization.

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Supporting Information Available: Photolysis methods and analytical techniques used in asymmetric induction studies. This material is available free of charge via the Internet at http://pubs.acs.org.

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