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Enantio- and Diastereodifferentiating *cis,trans*-Photoisomerization of 2β,3β-Diphenylcyclopropane-1α-carboxylic Acid Derivatives in Organized Media

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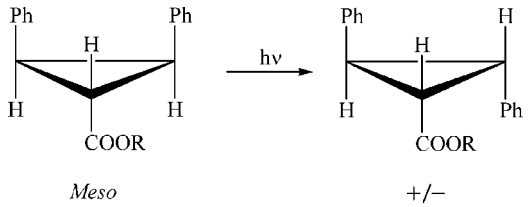
ABSTRACT



Four methods of asymmetric induction in the *cis,trans*-photoisomerization of 2β,3β-diphenylcyclopropane-1α-carboxylic acid derivatives were studied. Best results (ca. 80% de) were obtained by irradiation of chiral esters, amides, and salts in NaY and LiY zeolites and in the pure crystalline state.

1,2-Diphenylcyclopropane has played a central role in the quest for new methods of asymmetric induction in organic photochemistry. *cis*-1,2-Diphenylcyclopropane, which is achiral, can be transformed into its chiral *trans* isomer by both singlet- and triplet-photosensitized irradiation. The first attempt to carry out this reaction enantioselectively was reported by Hammond and Cole in 1965.[1] These authors demonstrated that using an optically pure naphthalene derivative as a singlet sensitizer led to enantiomeric excesses (ees) of 6.7%; subsequent work by Ouannès et al. using an optically active triplet energy sensitizer gave even lower ees (3%).[2] Additional attempts by Ueno et al.[3] (optically active polypeptide) and Faljoni et al.[4] (optically active solvents) likewise gave very low ees (0% and <2.3%, respectively). The best results so far, although still with ees of less than 10%, were obtained by Inoue et al.,[5] who used optically active alkyl arenecarboxylates as electron-accepting photosensitizers.

In attempting to improve upon these results, it occurred to us that using an *intramolecular* chiral auxiliary might lead to better ees. This required the introduction of a third substituent on the cyclopropane ring to which the chiral

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(1) (a) Hammond, G. S.; Cole, R. S. *J. Am. Chem. Soc.* **1965**, *87*, 3256. (b) Aratani, T.; Nakanisi, Y.; Nozaki, H. *Tetrahedron* **1970**, *26*, 1675.
(2) Ouannès, C.; Beugelmans, R.; Roussi, G. *J. Am. Chem. Soc.* **1973**, *95*, 8472.
(3) Ueno, A.; Toda, F.; Iwakura, Y. *J. Polym. Sci., Polym. Chem. Ed.* **1974**, *12*, 1841.
(4) Faljoni, A.; Zinner, K.; Weiss, R. G. *Tetrahedron Lett.* **1974**, 1127.
(5) Inoue, Y.; Yamasaki, N.; Shimoyama, H.; Tai, A. *J. Org. Chem.* **1993**, *58*, 1785.
(6) Blatchford, J. K.; Orchin, M. *J. Org. Chem.* **1964**, *29*, 839.
(7) Absolute asymmetric synthesis refers to the formation of enantiomerically enriched products from achiral precursors without the intervention of a preexisting source of optical activity. For a discussion, see: Caswell, L.; Garcia-Garibay, M. A.; Scheffer, J. R.; Trotter, J. *J. Chem. Educ.* **1993**, *70*, 785.
(8) The unknown photoproduct was initially assigned the structure methyl 3,4:5,6-dibenzo-1,3,5-cycloheptatriene-1-carboxylate, but independent synthesis of this material by the method of Ford and Newcomb (Ford, W. T.; Newcomb, M. *J. Am. Chem. Soc.* **1973**, *95*, 6277) did not give a match. Efforts are ongoing to establish the structure of this compound.

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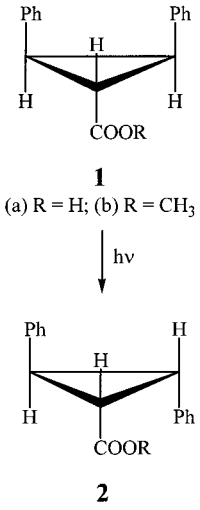
auxiliary could be attached, and for this purpose we chose the readily available[6] 2β,3β-diphenylcyclopropane-1α-carboxylic acid **1a** (Scheme 1). In this Letter we report that

Scheme 1



irradiation of chiral salts, esters, and amides of compound **1a** in the crystalline state and zeolitic media leads to the corresponding chiral *cis,trans*-isomer in much higher stereoselectivity than observed in the case of 1,2-diphenylcyclopropane. In addition, the methyl ester of acid **1a** was found to crystallize in a chiral space group, which gave us the opportunity to study its absolute asymmetric photoisomerization in the solid state.[7]

Direct irradiation of methyl ester **1b** in acetonitrile using the unfiltered output of a 450 W medium-pressure mercury lamp led to *cis,trans*-photoisomerization (**1b**:**2b** = 2:1) as well as formation of traces of a second photoproduct of unknown structure and origin.[8] Photolysis of acetone solutions of ester **1b** through Pyrex, on the other hand, gave a substantially different **1b**:**2b** photostationary state ratio of 1:2.3, with no detectable amount of photoproduct **3** being formed.

Crystals of ester **1b** were found to be dimorphic. Recrystallization of this substance from ethyl acetate led to prisms, mp 74−75 °C, space group *Pbca*.[9] From methanol, both prisms and fine needles were deposited, which showed significantly different solid state IR spectra. Because of their small size, the hair-like needles were not suitable for X-ray crystallography. Vacuum sublimation as well as crystallization from the melt reproducibly afforded the needle dimorph of **1b** rather than prisms. Differential scanning calorimetry of the needles showed melting at 65−66 °C followed by exothermic crystallization and remelting at 74−75 °C (Figure 1a). Prolonged irradiation of the prisms gave trace amounts (<5%) of racemic *trans*-isomer **2b** and no detectable second photoproduct. Racemic **2b** is expected in this case because

(9) Ester **1b**: *Pbca*; a = 17.648(5) Å, b = 16.540(5) Å, c = 9.679(5) Å; $\alpha = \beta = \gamma = 90°$; Z = 8; R = 5.1%.

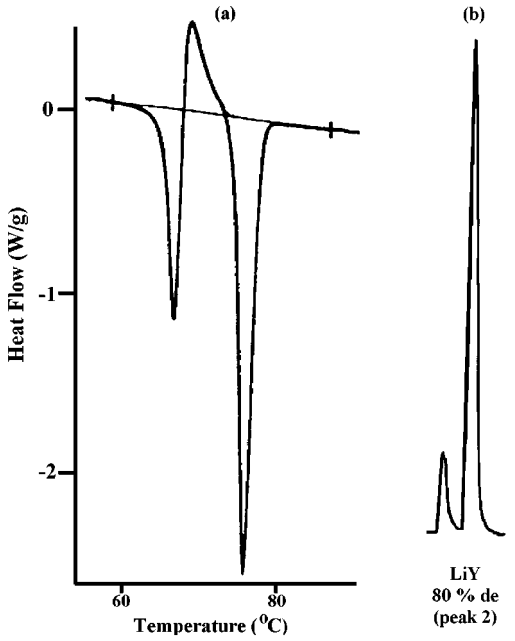


Figure 1. (a) DSC thermogram of needle dimorph of ester **1b**. (b) GC trace of product resulting from photolysis of 1-phenylethylamide of acid **1a** in zeolite LiY.

the prisms are in an achiral space group. In contrast, photolysis of the needles led to enantiomerically enriched **2b**. The reaction was more efficient in this case, and once again, no second photoproduct was formed. Samples taken from different recrystallization batches led to different results. In some photolyses the first enantiomer eluted from the chiral GC column was the major enantiomer; in others, the second peak predominated. Furthermore, the enantiomeric excesses varied from run to run, ranging from a low of 0% to a high of 60%. These results are what one would expect from photolysis of a mixture of enantiomorphous chiral crystals that are formed randomly in varying proportions during the crystallization process, with one enantiomorph forming one enantiomer of **2b**, and the other enantiomorph affording its mirror image.[7] We cannot state with certainty that this is the case in the present instance, since the very small size of the needles prevented attempts to determine the ee resulting from photolysis of an enantiomorphously pure single crystal. For the same reason it was not possible to determine whether seeding techniques were successful in preparing enantiomorphously homogeneous polycrystalline samples.

Seeking a more reliable and reproducible method of asymmetric induction in the photochemistry of the *meso*-2,3-diphenyl-1-carboxylate system, we turned to the use of chirally modified zeolites. In this approach the zeolite is first loaded with a chiral inductor and the compound to be photolyzed is then added in a second, separate adsorption step. Asymmetric induction ensues as a result of the close proximity enforced between reactant and chiral inductor in the confined space of the zeolite supercage.[10] Accordingly, the ethyl ester of acid **1a** was adsorbed onto zeolite NaY and irradiated in the presence of a variety of optically active

coadsorbates, including ephedrine, pseudoephedrine, norephedrine, diethyl tartrate, alaninol, phenylalaninol, valinol, menthol, and bornylamine. Disappointingly low ees were obtained in these experiments. Diethyl tartrate proved to be the best chiral inductor (12% ee); all the rest gave ees of 5% or lower.

Our next attempt was to try to induce *diastereoselectivity* in the photoisomerization through the use of covalently attached chiral esters. In these experiments both the zeolites (LiY, NaY, KY, RbY, CsY) and the ester substituents (menthyl, neomenthyl, isomenthyl, fenchyl, isopinocamphyl, 2-methyl-1-butyl) were varied. No external chiral inductors were used. The chiral esters of acid **1a** were first photolyzed in the absence of the zeolites (dichloromethane/hexane solution), which showed slight diastereomeric excesses (des) of 3−5% (0% de for 2-methyl-1-butyl). In the zeolite runs, best results were obtained with the menthyl ester in zeolite NaY, which led to a diastereomeric excess of 55%. LiY gave a de of 50%, KY 30%, RbY 22%, and CsY 5%.[11] Identical results were obtained with the (−)-menthyl ester, the (+)-menthyl ester, and the (±)-menthyl ester. In each case peak 2 predominated, which is what one would expect from the use of an achiral GC column.[12] The (*S*)-(−)-2-methyl-1-butyl ester of acid **1a** was also photolyzed in NaY in the presence of various chiral inductors (norephedrine, pseudoephedrine, ephedrine, menthol, diethyl tartrate, phenylalinol, borneol), but these additives failed to boost the de above the 19% observed in their absence.

Two chiral amides of acid **1a** (1-cyclohexylethyl, 1-phenylethyl) were also prepared and photolyzed in solution (2% de favoring peak 2 in both cases) and in the MY zeolites without any added chiral inductors. In LiY, the 1-phenylethyl amide led to the highest de (80%, peak 2) observed in any of the current zeolite studies (Figure 1b). Interestingly, in the other zeolites peak 1 predominated, but the des were much lower (NaY 28%, KY 14%, RbY 5%, and CsY 5%). In the case of the 1-cyclohexylethyl amide, the des were all below 40%, and here too, LiY gave an excess of peak 2 (29%), while the other zeolites afforded peak 1 with des ranging from 24 to 37%.

As a final approach to bringing about asymmetric induction in the 2,3-diphenyl-1-carboxylate system, we turned to the solid state ionic chiral auxiliary method.[13] In this approach an achiral, carboxylic acid-containing photoreactant is treated with an optically pure amine and the resulting salt is irradiated in the crystalline state. As in the covalent chiral auxiliary method, asymmetric induction occurs as a result of the kinetic preference for the diastereomeric transition state of lower energy. Accordingly, salts were formed between *meso*-acid **1a** and a randomly selected group of 10 different optically pure amines.[14] Solid state irradiations were conducted under nitrogen at room temperature to various conversions on 5−10 mg crystalline samples of the salts sandwiched between quartz plates. The extent of conversion was estimated by gas chromatography following workup with diazomethane (to form the corresponding methyl esters), and the ee in which the resulting photoproduct **2b** was formed in each case was determined using chiral GC. Of the 10 salts studied, 5 gave ees above 40% (Table 1). Best results were obtained with L-proline, which gave an ee of 79% at low conversion.

Table 1. Enantiomeric Excesses Obtained through Solid State Photolysis of Chiral Salts of Acid **1a**

amine	convn (%)	ee (%)	peak
(*R*)-(+)-1-phenylethylamine	10	44	2
	17	33	2
(*S*)-(−)-1-*p*-tolyl ethylamine	10	58	1
	27	48	1
L-proline[a]	4	79	2
	15	69	2
	20	66	2
(*R*)-(+)-*N*-benzyl-1-phenylethylamine	10	60	1
(*S*)-(−)-2-(diphenylmethyl)pyrrolidine	6	60	2
	12	55	2

[a] Most likely a hydrogen-bonded complex rather than a salt.

The present study provides a unique opportunity to compare four different methods of asymmetric induction applied to the same reaction. Each of the four methods—absolute asymmetric synthesis, the use of chirally modified zeolites, the use of covalent chiral auxiliaries in zeolites, and the solid state ionic chiral auxiliary method—has certain advantages and drawbacks. Absolute asymmetric synthesis, while giving reasonable ees in some runs, is severely limited in the present instance by small crystal size and erratic and unpredictable ees. Similarly, while giving moderate to good ees in other photoreactions,[10] the use of chirally modified zeolites led to poor results in the present study for reasons that we do not understand. Best results (80% de and 79% ee, respectively) were obtained by irradiation of covalently

(10) (a) Joy, A.; Uppili, S.; Netherton, M. R.; Scheffer, J. R.; Ramamurthy, V. *J. Am. Chem. Soc.* **2000**, *122*, 728. (b) Joy, A.; Scheffer, J. R.; Ramamurthy, V. *Org. Lett.* **2000**, *2*, 119. (c) Joy, A.; Ramamurthy, V. *Chem. Eur. J.* **2000**, *6*, 1287.

(11) The experimental procedure consisted of adding the activated (500 °C) MY zeolite to the compound to be photolyzed in a mixture of anhydrous methylene chloride/hexane. After stirring for 8 h, the zeolite was filtered and washed thoroughly with fresh hexane and the supernatant analyzed for the presence of substrate. The zeolite was then dried in vacuo (2×10^{-3} Torr) at 65 °C for 8−12 h and transferred to a quartz tube inside a drybox. Freshly distilled anhydrous hexane was added, the tube sealed, and the resulting slurry irradiated for 1 h (30−40% conversion) using the unfiltered output of a 450 W hanovia medium-pressure mercury lamp. The de was found to be independent of the extent of conversion. After photolysis, the zeolite was filtered, washed again with fresh hexane, and then stirred with acetonitrile for 6−8 h to extract the product(s). The extracts were then concentrated and analyzed using capillary gas chromatography. The extent of de depends on the dryness of the zeolite. For example, in the case of the 1-phenylethyl amide of **1a**, wet LiY gave an 8% de of peak 1, whereas dry LiY zeolite afforded peak 2 in 80% de.

(12) The ratio of the two enantiomers in peak 2 was not determined.

(13) Gamlin, J. N.; Jones, R.; Leibovitch, M.; Patrick, B.; Scheffer, J. R.; Trotter, J. *Acc. Chem. Res.* **1996**, *29*, 203.

(14) The amines used were (*R*)-(+)-1-phenylethylamine, (*S*)-(−)-1-*p*-tolylethylamine, (*S*)-(−)-1-*p*-bromophenylethylamine, (*R*)-(+)-1-*p*-chlorophenylethylamine, L-proline, (*S*)-(−)-α,α-diphenyl-2-pyrrolidinemethanol, (R)-(+)-*N*-benzyl-1-phenylethylamine, (*S*)-(−)-2-(diphenylmethyl)pyrrolidine, (*S*)-(+)-2-methoxymethylpyrrolidine, and (*R*)-(−)-2-methyl-2-phenylethylamine.

and ionically modified chiral substrates in zeolites and the pure crystalline state. The zeolite method has the advantage that it can be carried out on neutral (nonionic) substrates, but a disadvantage is that the size of the substrate is limited by the pore size of the zeolite being used. While there are no size limitations involved in the ionic chiral auxiliary method, it is restricted to substrates containing acidic or basic functional groups.

Current efforts in both laboratories are aimed at determining exactly what combination of conformational and environmental factors is responsible for determining ee and de in these reactions.

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