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ASYMMETRIC INDUCTION IN THE SOLID STATE PHOTOCHEMISTRY OF SALTS OF CARBOXYLIC ACIDS WITH OPTICALLY ACTIVE AMINES

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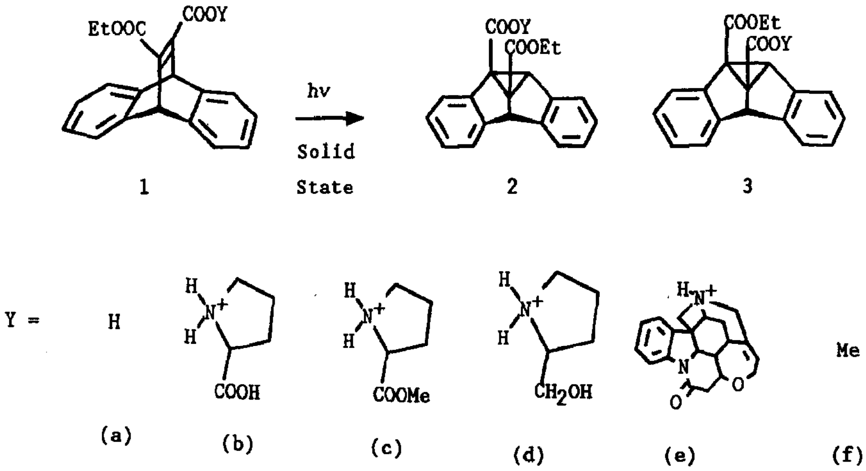
Abstract. A general approach to using crystal chirality in asymmetric synthesis is described. It consists of the preparation of crystalline salts of prochiral carboxylic acids with optically active amines followed by photolysis of the salts in the solid state. Conversion of the photoproducts to the corresponding methyl esters by using diazomethane followed by chiral shift reagent NMR analysis revealed enantiomeric excesses ranging from 14-80% depending on the optically active amine employed. In contrast to the solid state results, photolysis of the salts in solution gave only racemic products.

Achiral organic molecules are capable of crystallizing in chiral space groups ("spontaneous resolution")[1], and this crystal chirality can be utilized as a source of asymmetry to induce optical activity in the products of chemical reactions carried out in the solid state.[2] An example taken from our own work is to be found in the communication immediately preceding this one.[3] Only a few such processes are known, however, because spontaneous resolution coupled with solid state reactivity is extremely rare.[2] In contrast, chiral space groups are obligatory for optically active compounds, and in seeking a more general approach to utilizing crystal chirality in asymmetric synthesis, it occurred to us that achiral compounds containing carboxylic acid groups could be forced into chiral space groups by formation of salts with optically active amines (e.g., brucine, strychnine and other classical resolving agents). Provided that the carboxylate-containing portions of such salts undergo chemical processes that generate at least one new chiral center, reaction (in our case, photolysis) of the salts in the solid state followed by esterification of the products would lead to mixtures whose enantiomeric excesses provide a measure of the extent of asymmetric induction by the crystalline medium. Such an approach has the added advantages that (1) liquid carboxylic acids can be investigated owing to the fact that their salts will almost certainly be solid, and (2) the strong lattice forces present in ionic crystals may help to enforce topotactic (single crystal-to-single crystal) behavior. In the present communication we describe our initial results in this area.

As in the preceding paper,[3] the compound chosen for study was a dibenzobarrelene derivative, namely the mixed acid-ester 1a (Y = H, Scheme 1), synthesized by treatment of the corresponding anhydride[4] with ethanol. It was expected that salts of 1a would undergo the well known di-π-methane photorearrangement in the solid state to afford chiral dibenzosemibullvalene derivatives, and in this case, two regioisomers (2 and 3) are possible. Salts of acid/ester 1a with various optically active amines were prepared by mixing equimolar quantities of acid and base in ethanol or ether and filtering the resulting precipitate. The solids were shown to be simple 1:1 salts by infrared and nmr spectroscopy, mass spectrometry and elemental analysis.

Scheme 1



The salts (*ca*, 100 mg) were irradiated (450 W Hanovia medium pressure mercury lamp) as white powders sandwiched between two Pyrex microscope slides and sealed in polyethylene bags; best results were obtained at temperatures of -40 °C, and conversions were kept below 20%. The reaction mixtures were acidified, treated with excess diazomethane to produce the corresponding methyl/ethyl diesters, and then subjected to silica gel column chromatography. This afforded the known[5] photoproducts 2f and 3f as a mixture whose regioisomeric and enantiomeric composition was determined by 400 MHz NMR spectroscopy. For the enantiomeric excess determinations, use was made of the chiral shift reagent (+)-Eu(hfc)$_3$ (Aldrich). The results of these experiments are summarized in Table 1.

Table 1. Solid State Photoproduct Mixture Composition as a Function of Amine Structure and Configuration.

	Photoproduct 2f		Photoproduct 3f	
Optically Active Amine	Yield (%)[a]	ee[b]	Yield (%)[a]	ee[b]
(R)-(+)-Proline (b)	96	(-)-80	4	0
(S)-(-)-Proline (b)	94	(+)-76	6	0
(R,S)-(±)-Proline (b)	84	0	16	0
(S)-(-)Proline Methyl Ester (c)	93	(+)-58	7	0
(S)-(+)-2-Pyrrolidene Methanol (d)	100	(-)-37	-	-
(-)-Strychnine (e)	65	(+)-14	35	0

[a]As determined by capillary gas chromatography after correcting for unreacted starting material; [b]The estimated accuracy in these values is ± 3%; the sign of rotation of predominant enantiomer is shown in parenthesis.

The regioselectivities of the solid state photoreactions reported in Table 1 are in the same direction as those observed previously for a related sodium carboxylate salt in aqueous solution.[6] In all cases, initial benzo-vinyl bridging is favored at the carboxylate salt-bearing vinyl carbon atom, a result that can be attributed to preferential radical formation at the ester-bearing vinyl carbon atom.[6] With regard to the enantioselectivities, it is interesting to note (Table 1) that only one of the two regioisomeric photoproducts (2) is produced in optically active form. Owing to a lack of crystal structure data (the salts are white powders, and attempted recrystallization results in deposition of the parent acid), we can only speculate at the present time on the factors responsible for this outcome. It may be, for example, that a proximity effect is operative. The benzo-vinyl bridging leading to major photoproduct 2 occurs at the vinyl position that is closer to the chiral center (assuming close association between the ammonium and carboxylate ions). A similar asymmetric proximity effect has been postulated recently in some non-ionic solid state photochemistry from our group.[7]

Overall, the results are encouraging, and we are currently screening additional optically active amines in the hope of improving the optical yields. We are also extending the procedure in the opposite sense, that is, to salts of prochiral, photoreactive amines with optically active carboxylic acids.

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