Photochemical Asymmetric Synthesis

Preorganization of Achiral Molecules for Asymmetric Synthesis through Crystallization-Induced Immobilization in Homochiral Conformations**

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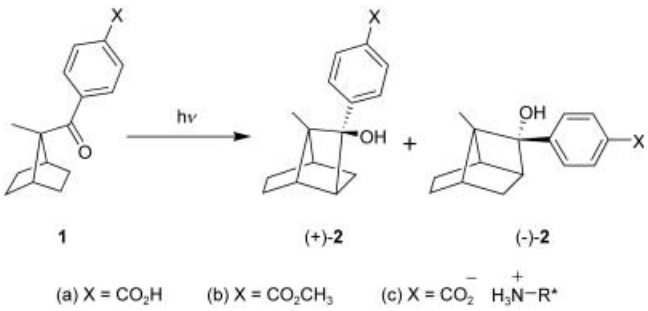
The work described in this article represents the latest installment from our laboratory in a long-term program aimed at developing new methods of asymmetric synthesis in organic photochemistry,[1] a relatively unexplored field that has recently attracted widespread attention and interest.[2] By way of introduction, consider the common situation of a conformationally mobile molecule that is achiral in solution as a result of rapid equilibration between enantiomeric conformers. If such conformers could be immobilized and caused to react in enantiomerically pure form, this could be used to great advantage in asymmetric synthesis. The prevention of conformational equilibration is relatively straightforward and can be achieved through crystallization. Selective crystallization in an enantiomerically pure form, however, is more problematic, as the great majority of achiral, conformationally mobile molecules crystallize as racemic compounds containing equal amounts of both conformational enantiomers.[3]

Our approach to this problem has been to introduce a second element of chirality to the system in the form of an easily removed, enantiomerically pure chiral auxiliary. In this situation the conformers become diastereomers rather than enantiomers, and one diastereomer will generally crystallize out in a process known as a "crystallization-induced asymmetric transformation."[3,4] The crystals are then subjected to a chemical reaction that fixes the evanescent conformational chirality in the form of permanent molecular chirality; removal of the temporary chiral auxiliary completes the process, leaving the reaction product in enantiomerically enriched form.

Specifically, we consider here enantio- and diastereoselection in the photochemical conversion of 7-benzoylnorbornane derivatives initiated by hydrogen atom abstraction (**1**, Scheme 1) into the corresponding cyclobutanols (**2**), a new example of the well known Yang photocyclization reaction.[5] The application of the conformational preorganization technique described above leads to near-quantitative *de* and *ee* values in the crystalline state, even at very high conversions. A bonus was the finding that one of the reactions was a single crystal-to-single crystal process.[6] This allowed crystal structures to be obtained at the beginning, mid-point and end of the reaction and absolute configuration correlations to be established between reactant and product.[7]



Scheme 1. Photochemical conversion of 7-benzoylnorbornane derivatives into the corresponding cyclobutanols.

The key starting material, 7-methyl-7-benzoylnorbornane-*p*-carboxylic acid (**1a**) was synthesized in a straightforward fashion from 7-methyl-7-carboxynorbornane[8] by a) acid chloride formation ($(COCl)_2$, CH_2Cl_2, catalyst DMF), b) nucleophilic acyl substitution (*p*-FPhMgBr, THF, 0°, 43% overall for steps a and b), c) nucleophilic aromatic substitution (KCN, DMSO, △, 93%) and d) hydrolysis of the nitrile (KOH, aq. EtOH, 98%).

Prior to the asymmetric induction studies, the photochemistry of methyl ester **1b** was investigated in solution and the solid state. In both instances the reaction was remarkably clean, affording racemic cyclobutanol **2b** as the exclusive product; according to GC, no other photoproducts were formed in amounts greater than 0.5%. The structure and relative stereochemistry of cyclobutanol **2b** were established by detailed spectroscopic analysis and confirmed by an X-ray crystal structure of one of the corresponding ammonium salts, **2c** (see below).

For the asymmetric induction studies, chiral auxiliaries were introduced by the treatment of carboxylic acid **1a** with a series of optically pure amines to form the corresponding 1:1 ammonium salts (**1c**); Table 1 lists the amines used. Polycrystalline samples of the salts (1–2 mg) were sandwiched between pyrex microscope slides and irradiated to varying degrees of conversion under nitrogen. The chiral auxiliaries

Table 1: Asymmetric induction in the solid state photochemistry of salts **1c**.[a]

Entry	Amine	Conversion [%]	*ee* values of **2b** [%]	[α][b]
1	(*R*)-(+)-1-phenylethylamine	100	98	(−)
2	(*S*)-(−)-1-phenylethylamine	100	97	(+)
3	(1*S*,2*R*)-(−)-1-amino-2-indanol	94	96	(+)
4	(1*S*,2*S*)-(+)-2-amino-3-methoxy-1-phenyl-1-propanol	88	95	(−)
5	(*R*)-(−)-2-amino-1-butanol	100	84	(−)

[a] All photolyses were conducted at room temperature. Irradiation of the salts in solution invariably led to racemic **2b**. [b] Sign of rotation of predominant enantiomer of **2b** at the sodium D line.

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were removed by treatment of the photolysis mixtures with ethereal diazomethane, and the resulting methyl esters were analyzed to obtain the *ee* values by chiral HPLC and for the extent of conversion by GC. As before, cyclobutanol **2b** was the sole GC-detectable photoproduct. The results are summarized in Table 1.

The data in Table 1 reveal that the *ee* values obtained for photoproduct **2b** in the solid state were excellent (84–98%), even at very high conversions. As expected for a well-behaved system, the use of (*R*)-(+)- and (*S*)-(−)-1-phenylethylamine as chiral auxiliaries (entries 1 and 2) led to the optical antipodes of cyclobutanol **2b** in equal *ee*. In contrast to the results in the solid state, photolysis of the salts in solution led to racemic **2b**, a result that highlights the critical role played by the reaction medium in controlling enantioselectivity.

To gain a greater understanding of the solid-state photochemistry, X-ray crystal-structure studies were undertaken. To date only the 1-phenylethylamine salt has given crystals suitable for X-ray analysis, but fortuitously, the solid state photoreaction in this case proved to be of the rare single crystal-to-single crystal variety,[6] which permitted the structure of both reactant and product to be obtained at various stages of reaction. Figure 1a shows the crystal structure of the (*S*)-(−)-1-phenylethylamine salt prior to photolysis, and Figure 1b and 1c depict the structure of the mixed crystal following 70% and 93% conversion to the corresponding cyclobutanol. The final ORTEP drawing (Figure 1d) shows the structure of the cyclobutanol photoproduct following its recrystallization from methanol.

The crystal structures reveal the source of the high enantio- and diastereoselectivity. Under the influence of the ionic chiral auxiliary, the reactant crystallizes in a homochiral conformation in which the carbonyl oxygen (red) is much closer to γ-hydrogen atom H_X (green, 2.70 Å) than to γ-hydrogen H_Y (purple, 3.43 Å). As a result, only H_X is abstracted,[9] leading to a 1,4-hydroxybiradical that undergoes least motion closure with "retention of configuration" at the carbonyl carbon. Closure of the biradical with inversion would require rotation of the aryl and hydroxyl groups about the C7-carbonyl carbon bond, a large amplitude motion that is topochemically forbidden in the crystalline state.[10] Enantioselectivity and diastereoselectivity are thus a direct consequence of conformational preorganization of the reactant in a rigid matrix that severely limits the range of motions available along the reaction coordinate.[11]

Figure 1b and 1c prove that H_X is, in fact, the hydrogen abstracted. Because the absolute configuration of the ionic chiral auxiliary is known, the absolute configuration of both reactant and product is established, which in turn allows us to state with certainty that abstraction of H_X leads to the experimentally observed photoproduct. We note that the reactant and product have nearly identical geometries, except for an upward movement of the γ-carbon to allow for cyclobutane ring formation and a change in orientation of the C–O bond accompanying the change in hybridization at the carbonyl carbon from sp^2 to sp^3. Presumably it is this close resemblance in size and shape between reactant and product that makes the single crystal-to-single crystal transformation possible.

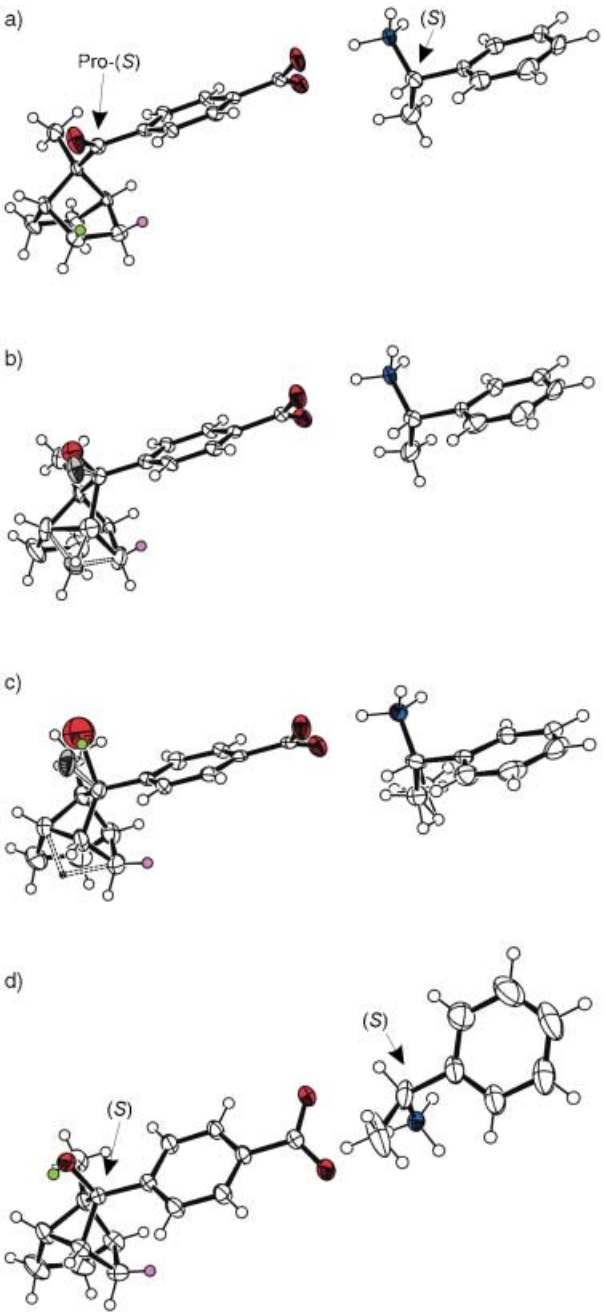

Figure 1. ORTEP representations of a) (*S*)-(−)-1-phenylethylamine salt **1c**; b) mixed crystal containing 70% **2c** and 30% **1c**; c) mixed crystal containing 93% **2c** and 7% **1c**; d) salt **2c** after recrystallization from methanol. The oxygen atoms are red, nitrogen blue, γ-H_X (most favored for abstraction) green and γ-H_Y purple. In (b) and (c) portions of salt **1c** are represented by dashed bonds and gray atoms. Ellipsoids are set at the 50% probability level.

An interesting question associated with single crystal-to-single-crystal transformations is whether the crystal structure of the "as formed" product is the same as that of the recrystallized material. Figure 1d shows that, in the present instance, it is not. Recrystallization has brought about not only a substantial change in molecular conformation (reorientation of the aromatic ring and its associated ionic auxiliary), but also a complete change in packing arrange-

ment (from orthorhombic to monoclinic). Based on a very limited number of examples, such changes appear to be the rule rather than the exception when the products of single crystal-to-single crystal reactions are recrystallized.[12]

In summary, the use of ionic chiral auxiliaries to preorganize achiral organic molecules for asymmetric synthesis through crystallization-induced immobilization in homochiral conformations works well for the Yang photocyclization of 7-methyl-7-benzoylnorbornane derivatives. Related studies from our research group have shown the technique to give high *ee* values in a wide variety of excited state processes,[1] and it is clear that this approach represents one of the most powerful methods of asymmetric synthesis available in the field of organic photochemistry. Finally we point out that optically pure photoproducts, such as those formed in the present study, have potential as chiral synthons, and current efforts in our laboratory are directed along these lines. In addition, we are currently working toward extending the solid-state ionic chiral-auxiliary method to ground state as well as excited state processes.

Experimental Section

See the Supporting Information for the cell constants and related crystallographic data as well as the details of the synthesis of keto-acid **1a**, its conversion into an ionic chiral auxiliary-containing salt, the photolysis of the salt in the crystalline state, the diazomethane workup procedure and the characterization of cyclobutanol photoproduct **2b**.

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[9] There is now a large body of crystallographic evidence indicating that γ-hydrogen atom abstraction in the solid state occurs preferentially over distances near the sum of the van der Waals radii of oxygen and hydrogen (2.72 Å). See H. Ihmels, J. R. Scheffer, *Tetrahedron* **1999**, *55*, 885.
[10] 1,4-Hydroxybiradical ring closure involving retention of configuration at the hydroxyl-bearing carbon has been noted previously and appears to be a general feature of Yang photocyclization reactions conducted in the crystalline state. See for example A. D. Gudmundsdottir, T. J. Lewis, L. H. Randall, S. J. Rettig, J. R. Scheffer, J. Trotter, C.-H. Wu, *J. Am. Chem. Soc.* **1996**, *118*, 6167; M. Leibovitch, G. Olovsson, J. R. Scheffer, J. Trotter, *J. Am. Chem. Soc.* **1998**, *120*, 12755.
[11] Interestingly, the diastereoselectivity of the solution phase photoreaction is identical to that observed in the crystalline state. One explanation of this result is that, even in solution, rotation about the C7-carbonyl carbon bond in the initially formed biradical is slow relative to closure owing to unfavorable steric interactions developed between the aryl and methyl groups. In addition, the biradical (a triplet) may be formed in a conformation in which intersystem crossing to the singlet and closure is faster than rotation. For examples in which geometry-dependent intersystem crossing is thought to control the stereochemistry of 1,4-biradical closure, see A. G. Griesbeck, H. Heckroth, *J. Am. Chem. Soc.* **2002**, *124*, 396, and references therein.
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