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An ionic chiral auxiliary-induced regioselective and enantioselective Yang photocyclization reaction in the crystalline state

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Abstract

cis-9-Decalyl aryl ketones undergo Yang photocyclization in solution to afford an approximately 1:1 mixture of two regioisomeric racemic cyclobutanols. In contrast, irradiation in the crystalline state in the presence of various ionic chiral auxiliaries leads to a single cyclobutanol in >98% enantiomeric excess. X-Ray crystallography reveals the source of the regio-, diastereo- and enantioselectivity. © 1999 Elsevier Science Ltd. All rights reserved.

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As outlined in the paper immediately preceding this one, a major objective of recent work from our laboratory has been to develop a general method of asymmetric synthesis for photochemical reactions, a relatively unexplored subject compared to similar studies in the ground state.[1] Our strategy has been to use the chiral crystalline state as the asymmetric influence in these processes, since this medium can be engineered by tethering a chiral auxiliary to the substrate being photolyzed.[2] Such chiral auxiliaries can be introduced covalently (e.g., ester formation between a carboxylic acid and an optically pure alcohol) or ionically (salt formation with an optically pure amine), and for a variety of reasons — chief among them being ease of introduction/removal of the auxiliary and increased likelihood of crystallinity — we have concentrated on the latter method, the so-called 'ionic chiral auxiliary' approach to asymmetric synthesis.[3] In this paper we report the application of this method to the control of both the enantioselectivity and the regioselectivity of a new Yang photocyclization reaction.[4]

cis-9-Decalyl ketones of general structure 1 (Scheme 1) are intriguing substrates for photochemical study. Owing to their C_s-symmetry, they offer the possibility of investigating not only regioselectivity in the Norrish/Yang type II reaction (abstraction of H2 vs H4 or H7 vs H5) but enantioselectivity as well (H2 vs H7 or H4 vs H5). In addition, since each Yang photocyclization (cyclobutanol) product can be produced with two different configurations at the hydroxyl-bearing carbon atom, diastereoselectivity can

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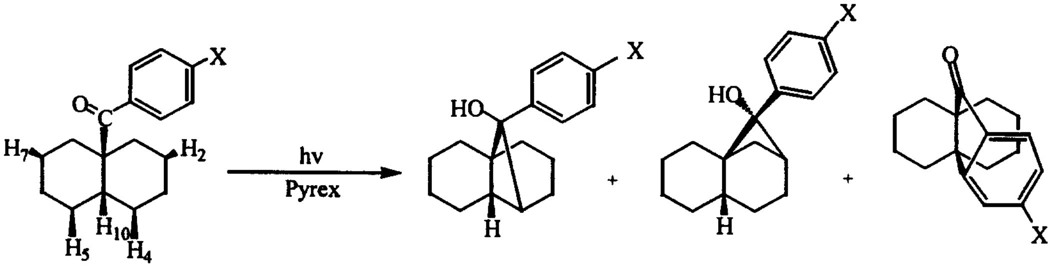
also be investigated. With this in mind we synthesized ketones **1a–c** and studied their photochemistry in solution as well as the crystalline state.[5]



1 2 3 4

(a) X = CN (b) X = COOMe (c) $X = COO^{\ominus}\ H_3\overset{\oplus}{N}R^*$

Scheme 1. Yang photocyclization of ketones **1a–c**

Irradiation of ketones **1a** and **1b** in acetonitrile solution afforded three products: racemic cyclobutanols **2a** (51%) and **2b** (47%) from abstraction of H4/H5, racemic cyclobutanols **3a** (39%) and **3b** (47%) from abstraction of H2/H7 and the novel achiral ketones **4a** (7%) and **4b** (6%) from abstraction of H10. The structure and stereochemistry of each photoproduct was deduced from detailed NOE difference and 2D NMR studies, and in the case of ketone **4a** the structure was verified by a single crystal X-ray diffraction study.[6] Hydrolysis of nitrile **1a** afforded the corresponding carboxylic acid, and a series of salts of general structure **1c** were prepared by treating this acid with various optically pure amines (Table 1). Crystals of these salts were crushed, sandwiched between two Pyrex plates and irradiated under an argon atmosphere at room temperature. Following photolysis the samples were treated with excess ethereal diazomethane, which converted the acids present to the corresponding methyl esters. The reaction mixtures were subjected to silica gel chromatography to remove the chiral auxiliaries and then analyzed for percent conversion by gas chromatography and for enantiomeric excess by chiral HPLC. For every salt investigated, cyclobutanol **2b** was by far the major product; only traces of cyclobutanol **3b** could be detected in some instances and no **4b** was formed. Table 1 summarizes the solid state results.

Molecular mechanics calculations[7] indicate that aryl ketones of general structure **1** have two minimum energy conformations that differ by only around 0.1 kcal/mole (Fig. 1). In the lower energy conformer, **A**, the ketone oxygen atom is poised to abstract either H4 (C=O···H distance=2.4 Å) or H10 (2.4 Å) and improperly oriented to abstract H2 (3.2 Å).[8] Conversely, in conformer **B** abstraction of H2 at 2.4 Å is favored over abstraction of H4 (3.2 Å) or H10 (>3.5 Å). Thus in solution, where conformers **A** and **B** and their enantiomers are in rapid equilibrium, it is not surprising that a mixture of cyclobutanols **2** and **3** (both racemic) is obtained. With regard to the formation of photoproduct **4**, this undoubtedly arises via abstraction of H10 (five-membered transition state) in conformer **A** followed by radical recombination at the *ortho* position of the aryl ring, tautomerization and oxidation.[9] Photochemical β-hydrogen atom abstraction in the presence of suitably oriented γ-hydrogens is, to the best of our knowledge, unprecedented.[10]

The results with salts **1c** in the crystalline state (nearly exclusive formation of photoproduct **2b**) are strongly suggestive of reaction through conformer **A**. This was verified in the case of the (–)-norephedrine salt by an X-ray crystal structure determination. Interestingly, this salt crystallizes with two independent molecules of conformer **A** in the asymmetric unit, and these independent molecules have a near, but not exact, mirror image relationship (Fig. 1). This finding very nicely explains why cyclobutanol **2b** is formed in only 20–30% ee in this case: half the molecules in the crystal have a conformation that favors formation of one enantiomer of **2b**, while the other half are predisposed toward formation of its optical antipode.

Table 1

Results of photolyzing salts **1c** in the crystalline state[a]

Amine	Conversion (%)[b]	Yield of **2b** (%)[c]	ee (%)[d]
(R)-(+)-bornyl amine	9	>99	>98 (-)
	18	>99	>98
	78	>99	>98
(S)-(-)-methyl benzyl amine	17	74[e]	>98 (+)
	35	69	>98
	56	67	>98
	85	63	98
(-)-norephedrine	10	94	30 (-)
	24	93	23
	55	95	30

[a]Typical data for three amines; other amines investigated include ephedrine, pseudoephedrine, *cis*-1-amino-2-indanol, β-methyl phenethyl amine and prolinol. [b]Percentage of total GC integral due to compound **1b**. [c]Percentage of total GC integral due to compound **2b**. [d]Measured on Chiralcel OD column; sign of rotation of major enantiomer at 675 nm given in parenthesis. Use of the enantiomeric chiral auxiliary leads to identical ee of opposite rotation. [e]Yield reduced owing to presence of several small unidentified GC peaks.

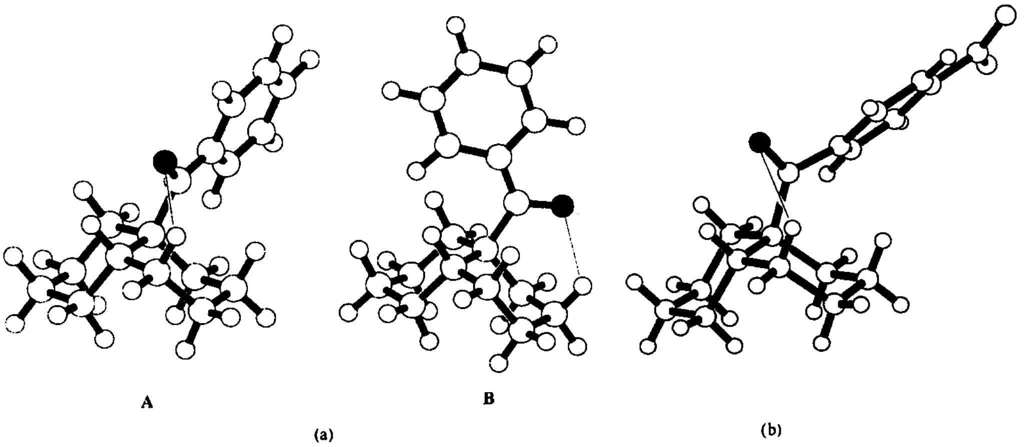


Figure 1. (a) Molecular mechanics-derived conformers **A** and **B**; (b) one of two independent, mirror image related forms of conformer **A** present in (–)-norephedrine salt **1c**. The stereoelectronically favored γ-hydrogen atoms are indicated by the light solid lines

Since these processes occur in a chiral environment caused by the presence of (–)-norephedrine, the competing reactions occur at different rates through diastereomeric transition states of unequal energy, thus accounting for the nonracemic nature of the photoproduct.[11]

Given the >98% ee in which photoproduct **2b** is formed in the case of the (*R*)-(+)-bornyl amine and (*S*)-(–)-methyl benzyl amine salts, it is virtually certain that these materials crystallize with a single enantiomer of conformer **A** in the asymmetric unit. To date, efforts to confirm this point by X-ray crystallography have not been successful. Reaction via conformer **A** also accounts for the diastereoselectivity observed in the formation of photoproduct **2b**. Following abstraction of H4, least motion coupling of the resulting radical center at C4 to the *Re* face of the acyl carbon[12] leads to the experimentally observed diastereomer; formation of the alternative diastereomer requires a nearly 180° rotation of the acyl group, which is topochemically forbidden in the crystalline state and evidently slow relative to radical coupling in solution as well.

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