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Asymmetric induction in the solid state photochemistry of an α-mesitylacetophenone derivative through the use of ionic chiral auxiliaries

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Abstract

Irradiation in the crystalline state of salts formed between α-mesitylacetophenone-*p*-carboxylic acid and a variety of optically pure amines — the so-called 'ionic chiral auxiliary' approach to asymmetric synthesis — leads to the corresponding 2-indanol in excellent yield and in high enantiomeric excess. X-Ray crystallography reveals the source of the enantioselectivity. © 1999 Elsevier Science Ltd. All rights reserved.

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An ionic chiral auxiliary is defined as an optically pure ion that controls the enantioselectivity of a chemical reaction of its achiral counterion. Research from our laboratory has shown that the use of ionic chiral auxiliaries is an excellent method of preparing enantiomerically enriched carboxylic acids and organic amines, and that it works best in the crystalline state where the role of the auxiliary is to guarantee the presence of a chiral space group.[1] The fact that the ionic chiral auxiliary can be far from the reaction site implies that direct steric interactions between the reactant and chiral auxiliary are not the primary source of the enantioselectivity; rather it is the overall asymmetric nature of the solid state reaction cavity (whose walls may be composed in part of one or more adjacent chiral auxiliaries) that is responsible. In the present communication we report the use of ionic chiral auxiliaries to control enantioselectivity in the solid state photochemistry of an α-mesitylacetophenone derivative.

The photochemistry of the achiral ketone α-mesitylacetophenone (**1a**) has been thoroughly studied by Wagner and co-workers and shown to consist of δ-hydrogen atom abstraction from an *ortho* methyl group followed by closure of the resulting 1,5-hydroxybiradical to form a chiral, racemic 2-indanol derivative **2a** (Scheme 1).[2] In order to apply our asymmetric induction strategy to this reaction, a starting material was required that contained a carboxylic acid or amine functionality to which an ionic chiral auxiliary could be attached through salt formation. For this purpose we selected carboxylic acid derivative **1b**, which proved to be readily available through standard synthetic methods.[3] As expected from the work of

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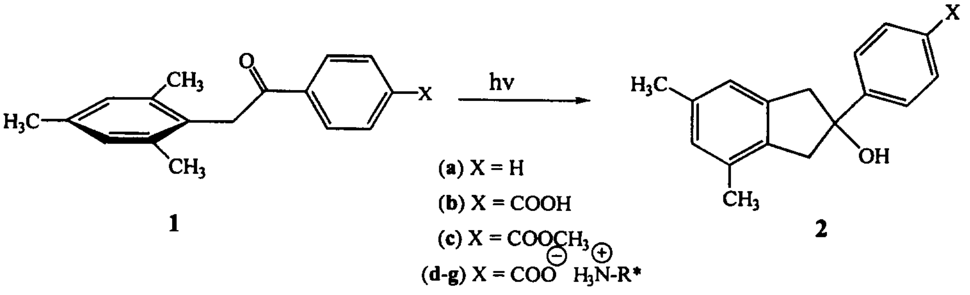
Wagner et al.,[2] irradiation of keto-acid **1b** and its methyl ester **1c** in acetonitrile solution or the solid state led to racemic indanols **2b** and **2c** as the only products (>98%) observable by GC.



Scheme 1. Photochemistry of α-mesitylacetophenone derivatives

Salts **1d–g**, formed between carboxylic acid **1b** and four commercially available, enantiomerically pure amines, were prepared and crystallized (Table 1). X-Ray crystal structures were successfully obtained for three of the salts — **1e**, **1f** and **1g**.[4] Solid state irradiations were conducted under nitrogen at different temperatures and to various conversions on 5–10 mg crystalline samples sandwiched between Pyrex plates. The extent of conversion was estimated by gas chromatography following workup with diazomethane, and the enantiomeric excess in which the resulting photoproduct **2c** was formed in each case was determined using chiral HPLC. The results of the photochemical studies in the solid state are compiled in Table 1.

With enantiomeric excesses over 80% at 80–90% conversions, the ionic chiral auxiliary method is once again shown to be synthetically viable, and either enantiomer of photoproduct **2c** can be prepared as desired by simply using the optical antipode of the auxiliary. As observed previously,[1] increasing conversion leads to decreasing ee values due to loss of topochemical control resulting from breakdown of the ordered crystal lattice as starting material converts into photoproduct. As shown for some salts in Table 1, low temperature photolysis can be used to compensate this effect. Irradiation of the salts in solution gave only racemic product.

Table 1
Solid state photolysis results for chiral salts of keto-acid **1b**

Salt	Chiral Auxiliary	Temp (°C)	Conversion (%)[a]	ee of **2c** (%)[b]	HPLC Peak[c]
1d	(S)-(-)-α-methylbenzylamine	room temp	16	94	1
		room temp	69	69	
		-20	61	83	
1e	(R)-(+)-α,4-dimethylbenzylamine	room temp	32	92	1
		room temp	89	83	
1f	(1S,2R)-(+)-norephedrine	room temp	12	90	2
		room temp	80	80	
		-19	30	98	
1g	(R)-(+)-N,α-dimethylbenzylamine	room temp	14	0	

[a] Percentage of total GC integral due to compound **1c**. Remaining integral due >98% to photoproduct **2c**. [b] Enantiomeric excesses measured by chiral HPLC (Chiralcel OD column). [c] Peak 1 indicates major enantiomer is first peak eluted from chiral HPLC. In the case of α-methylbenzylamine and norephedrine, use of the enantiomeric chiral auxiliary leads to similar ee favoring the optical antipode of **2c**.

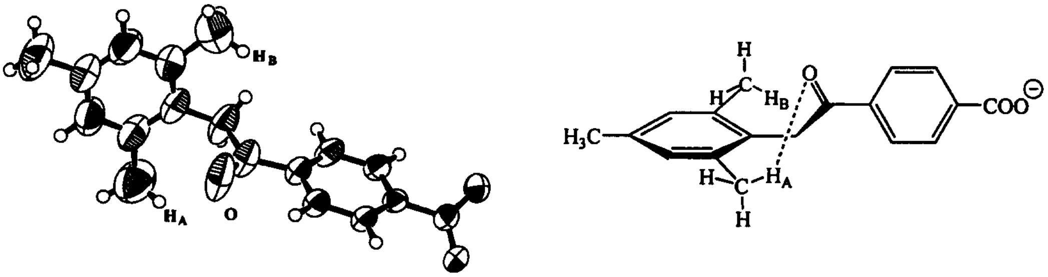


Figure 1. Absolute conformation of salt **1e** in the crystalline state

Turning now to the crystallographic results, the absolute conformation of the α-mesitylacetophenone moiety of salt **1e** in the solid state is shown in Fig. 1.[5] This indicates that the molecule crystallizes in a conformation that situates the carbonyl oxygen closer to one *ortho* methyl group than the other. If we label the methyl group proximal to the *Re* face of the carbonyl group as A and the methyl group proximal to the *Si* face as B as shown in Fig. 1, the $C{=}O\cdots H_A$ distance is 2.60 Å and the $C{=}O\cdots H_B$ distance is 3.66 Å. This difference in abstraction geometry clearly predicts preferential abstraction of H_A,[6] and least motion closure of the resulting 1,5-biradical is predicted to lead to the (*S*)-enantiomer of photoproduct **2c**.[7]

Support for the picture presented above comes from the crystal structure of salt **1f**. In this case, the absolute conformation of the reacting molecule is such that abstraction of H_B (2.69 Å) rather than H_A (3.68 Å) is favored, and this predicts that the (*R*)-enantiomer of photoproduct **2c** should be formed in excess. The experimental finding that irradiation of salts **1e** and **1f** leads to opposite enantiomers of photoproduct **2c** is consistent with this prediction.

Finally, the crystal structure of salt **1g** explains why photolysis of this material in the solid state gives racemic **2c**. Crystals of salt **1g** contain equal amounts of two independent conformers of the mesitylacetophenone moiety in the asymmetric unit. In one conformer, abstraction of H_A is very slightly favored (3.05 Å vs 3.11 Å), while in the other abstraction of H_B has a slight edge (3.07 Å vs 3.14 Å). With abstraction of H_A and H_B equally probable, it is not surprising that racemic photoproduct is formed.[8] It is also interesting to note that salt **1g** reacted slowest of the four salts studied, a result that can be attributed to the relatively long hydrogen abstraction distances involved in this case.

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3. Carboxylic acid **1b** was prepared from reaction of α-mesitylacetyl chloride with *p*-fluorophenylmagnesium bromide followed by treatment with sodium cyanide and hydrolysis. All new compounds described in the present paper gave spectroscopic data and elemental analyses completely in accord with their assigned structures. Details will be provided in a subsequent full paper.
4. Salt **1e**: $P2_1$; a=7.182(1) Å, b=6.048(1) Å, c=27.779(2) Å; β=97.094(9)°; Z=2; R=4.4%. Salt **1f**: $C2$; a=17.732(5) Å, b=5.612(2) Å, c=25.720(4) Å; β=109.18(2)°; Z=4; R=4.5%. Salt **1g**: $P1$; a=10.519(3) Å, b=13.927(5) Å, c=9.501(3) Å; α=99.57(3)°, β=114.97(2)°, γ=101.68(3)°; Z=2; R=6.3%; two independent molecules in the asymmetric unit.
5. Since the absolute configuration of the chiral auxiliary of salt **1e** is known, the absolute conformation of the α-mesitylacetophenone moiety is established unequivocally.
6. For a discussion of the distance and angular requirements in Norrish/Yang type II hydrogen atom abstraction reactions, see: Ihmels, H.; Scheffer, J. R. *Tetrahedron* **1999**, *55*, 885 and references cited therein.
7. Absolute configuration studies aimed at verifying this prediction are planned. Formation of the (*R*)-enantiomer would require an approximately 180° rotation of the acyl group, which is topochemically unlikely in the crystalline state.
8. For additional examples of salts that give low ees owing to the presence of independent, mirror-image related conformers in the asymmetric unit, see the preceding paper in this issue as well as: (a) Jones, R.; Scheffer, J. R.; Trotter, J.; Yang, J. *Tetrahedron Lett.* **1992**, *33*, 5481; (b) Jones, R.; Scheffer, J. R.; Trotter, J.; Yang, J. *Acta Crystallogr.* **1994**, *B50*, 601.