



Asymmetric induction through the use of remote covalent and ionic chiral auxiliaries in the solid state photochemistry of 2-benzoyladamantane-2-carboxylic acid derivatives[†]

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Abstract

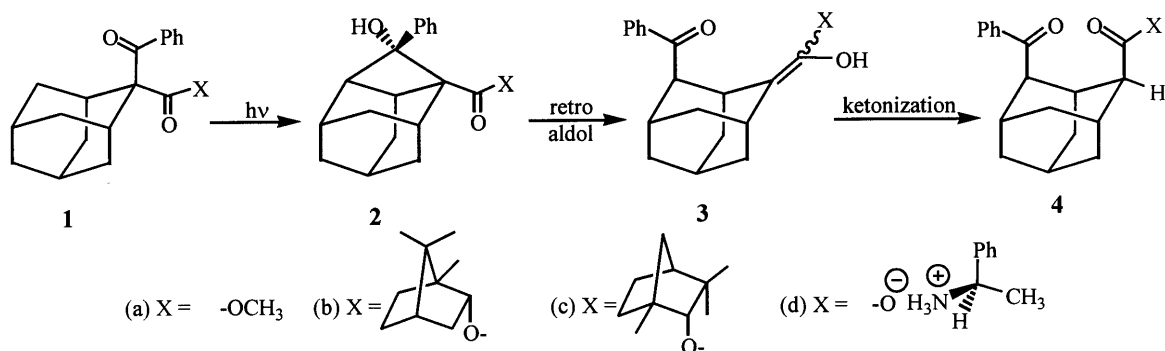
Attachment of chiral auxiliaries to 2-benzoyladamantane-2-carboxylic acid, either covalently through ester formation with optically pure alcohols, or ionically via salt formation with optically pure amines, leads to substrates whose irradiation in the crystalline state affords chiral rearranged photoproducts in $\geq 96\%$ diastereo- and enantiomeric excess. © 2000 Elsevier Science Ltd. All rights reserved.

In solution, remote chiral auxiliaries, i.e. those located distantly from the site of reaction, generally lead to insignificant levels of asymmetric induction. In the crystalline state, however, remote chiral auxiliaries can have a profound asymmetric influence through (1) ensuring the presence of a chiral reaction medium (chiral space group) and (2) causing the molecules in the crystal to adopt uniform, homochiral conformations that predispose them to react diastereoselectively.¹ To date, our use of remote chiral auxiliaries in the crystalline state has dealt nearly exclusively with *ionic* chiral auxiliaries, i.e. those attached to the reactant through salt bridges.² *Covalently* attached chiral auxiliaries should be equally effective, however, and in the present communication we report the results of a study comparing the efficacy of remote ionic and covalent chiral auxiliaries on the same solid state organic photorearrangement.

The compound chosen for study was methyl 2-benzoyladamantane-2-carboxylate (**1a**, Scheme 1).³ Based on ample literature precedent,^{1e,4} it was expected that photolysis of this substance would lead to Yang cyclization⁵ followed by spontaneous retro-aldol ring opening to afford δ -keto ester **4a**. In the event, the reaction proceeded as anticipated, and compound **4a** was formed in $\geq 85\%$ yield in both the solid state and solution.⁶ The stereochemistry of photoproduct **4a** is presumably the result of protonation of the enol intermediate **3a** from the less hindered side.

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[†] Dedicated to Professor Harry H. Wasserman on the occasion of his 80th birthday.



Scheme 1.

In order to explore asymmetric induction in this reaction by covalent chiral auxiliaries, the (1*S*)-bornyl ester **1b** and the (1*R*)-fenchyl ester **1c** of 2-benzoyladamantane-2-carboxylic acid were prepared. Both were crystalline substances with melting points of 139–141 and 111–112°C, respectively. Each compound was photolyzed in acetonitrile solution as well as the crystalline state. Once again the reactions proceeded efficiently to afford $\geq 90\%$ yields of photoproducts **4b** and **4c**. The diastereomeric excess (de) obtained in each photolysis is shown in Table 1. Interestingly, the de was much higher in the solid state for bornyl ester **4b** (96%) than for fenchyl ester **4c** (18%).

Table 1
Conditions and product distributions for photolysis of keto-esters **1b** and **1c**

Compound	Conditions ^a	Conversion (%)	de (%) ^b
1b	CH ₃ CN, 2.5 h	100	14 (1)
1b	Crystalline state, 40 min	100	96 (2)
1c	CH ₃ CN, 1 h	98	26 (1)
1c	Crystalline state, 1 h	76	18 (1)

^a Irradiations were conducted with a Hanovia 450 W medium pressure mercury lamp through a Pyrex filter. Solid state irradiations were conducted on 5–10 mg samples crushed between two Pyrex plates.

^b The number in parenthesis indicates whether the predominant diastereomer is the first or second peak off the GC column.

In order to understand why bornyl is a better covalent chiral auxiliary than fenchyl, the X-ray crystal structures of esters **1b** and **1c** were determined.⁷ These showed that bornyl ester **1b** crystallizes with all the molecules having the same conformation (Fig. 1(a)) in which the carbonyl oxygen atom is much closer to γ -hydrogen atom H_X (2.50 Å) than H_Y (3.38 Å). In contrast, fenchyl ester **1c** crystallizes with four independent molecules in the asymmetric unit. In two of these, the C=O \cdots H_X contacts (2.38 and 2.34 Å) are much shorter than the C=O \cdots H_Y contacts (3.16 and 3.23 Å), while in the other two conformers, the reverse is true (C=O \cdots H_X = 3.24 and 3.32 Å; C=O \cdots H_Y = 2.39 and 2.42 Å). In effect, crystals of compound **1c** are made up of two pairs of conformational diastereomers.⁸ Fig. 1(b) depicts the solid state conformation of the independent molecule of ester **1c** for which C=O \cdots H_Y = 2.39 Å.

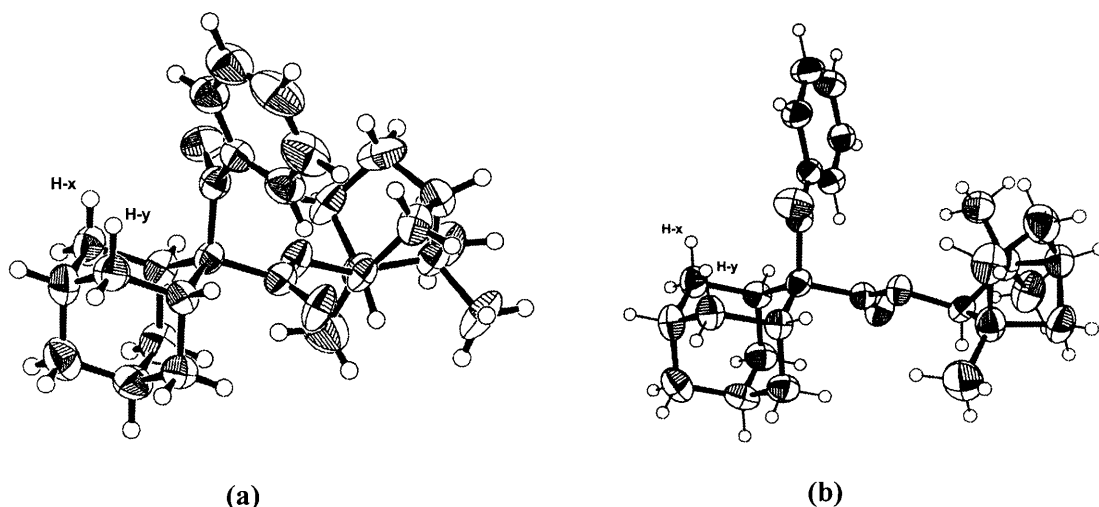
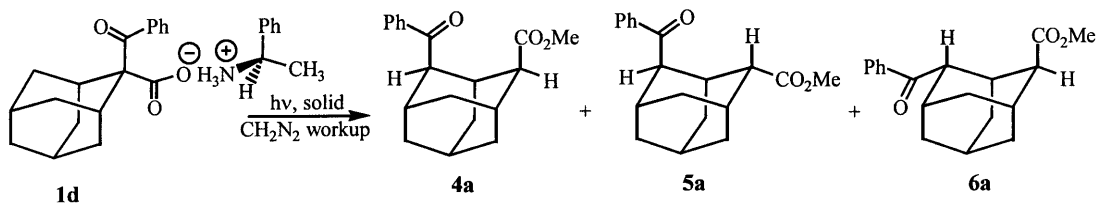


Figure 1. (a) Solid state conformation of bornyl ester **1b**. (b) Solid state conformation of one of four independent molecules in the asymmetric unit of fenchyl ester **1c**

With this information, the explanation of the de results is clear-cut. Photolysis of bornyl ester **1b** in the solid state involves selective abstraction of the closer hydrogen H_x , leading ultimately to a single diastereomer of photoproduct **4b**.⁹ In contrast, crystals of fenchyl ester **1c** are composed of equal amounts of two types of molecules: those that favor abstraction of H_x and those that favor abstraction of H_y . If conformation were the sole controlling factor, the de in this case should be 0%. The finding that the de is 18% can be taken as a measure of the extent to which the photoreaction is governed by environmental effects due to the chiral crystal lattice.¹⁰

In order to test the ionic chiral auxiliary approach to asymmetric synthesis in the 2-benzoyladamantane-2-carboxylate system, it was first necessary to prepare the parent β -ketoacid **1** ($X=OH$). This was accomplished through synthesis of the corresponding *tert*-butyl ester (**1**, $X=-O^tBu$) followed by hydrolysis using trifluoroacetic acid at 0°C.¹¹ After removal of the trifluoroacetic acid under reduced pressure at 0°C, the β -ketoacid was treated immediately with (*R*)-(+)-1-phenylethylamine to produce crystalline salt **1d**, mp 99–100°C.

Irradiation of salt **1d** in the solid state at room temperature for 1 hour (100% conversion), followed by diazomethane workup to afford the corresponding methyl esters, gave a mixture of photoproducts **4a** (60%), **5a** (33%) and **6a** (7%) (Scheme 2).¹² These same three photoproducts were formed by photolysis of methyl ester **1a** in acetonitrile, but in this case, the **4a**:**5a**:**6a** product ratio was found to be 86:3:11. The reason for this difference between the solid state and



Scheme 2.

solution results is unclear at the present time. After considerable effort, chiral GC conditions were found that allowed the determination of the optical purity of product **4a** from these photoreactions. As expected, compound **4a** from the solution phase photolysis of ester **1a** proved to be racemic, but the same material isolated from the solid state photolysis of salt **1d** was essentially optically pure (ee >99%). Unfortunately, we were unable to find HPLC or GC conditions that permitted analysis of the optical purity of photoproducts **5a** or **6a**.

In summary, the results of the present study demonstrate that both covalent and ionic remote chiral auxiliaries are capable of leading to excellent diastereomeric and enantiomeric excesses when employed in the crystalline state. The crystallographic results with the substrates containing covalent chiral auxiliaries indicate that the source of the asymmetric induction is primarily conformational in nature, i.e. the compounds crystallize in conformations in which the ketone oxygen is directed more toward one γ -hydrogen atom than the other, and abstraction of this stereoelectronically favored hydrogen is the diastereodifferentiating step of the reaction. In comparing the use of covalent and ionic chiral auxiliaries, our experience has been that the ionic materials are easier to work with owing to ease of introduction and removal of the auxiliary, but that purely covalent substrates are more likely to give crystals suitable for X-ray crystallography. We are extending our work in this area to the study of remote covalent and ionic chiral auxiliaries capable of energy and electron transfer.

Acknowledgements

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6. Small amounts of epimeric ketones **5a** and **6a** (Scheme 2) were also formed in this photolysis (see later discussion). The intermediacy of cyclobutanol **2a** was established by ^{13}C NMR following irradiation of ketone **1a** in CD_3CN at 0°C . The stereochemistry of compounds **2a-d** is assumed to be identical to that observed in analogous systems.^{1c}
7. Compound **1b**: $P2_12_12_1$; $a=10.709(5)$, $b=30.209(6)$, $c=7.258(1)$ Å; $Z=4$; $R=0.042$. Compound **1c**: $P\bar{1}$; $a=13.432(2)$, $b=15.523(4)$, $c=12.140(6)$ Å; $\alpha=110.7(2)$, $\beta=94.16(2)$, $\gamma=79.69(2)^\circ$; $Z=4$; $R=0.062$.

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