Solid state asymmetric synthesis of chiral crystals of 5- and 7-membered ring ketones

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The results of absolute asymmetric photochemical studies on 5- and 7-membered spiroketones in the solid state are described. Photolysis of 7-membered spiroketone undergoing a Norrish type II cyclisation reaction gives enantioselectivity excesses up to 93%. Irradiation of 5-membered spiroketone afforded a racemic product. The results are rationalised by the X-ray crystallographic method.

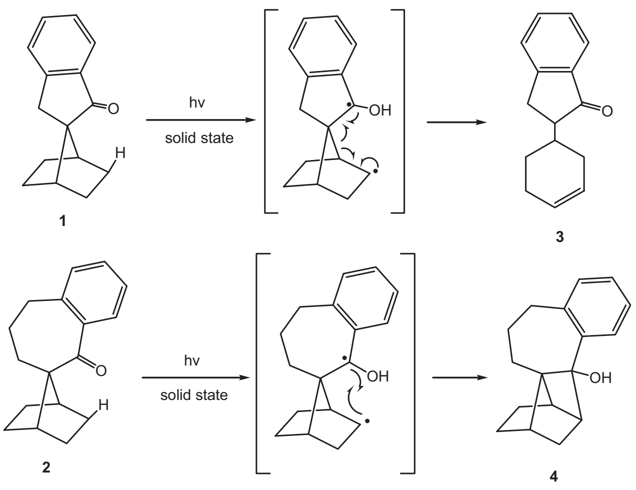
Keywords: absolute asymmetric, spiroketones, Norrish type II, solid state, enantioselectivity

Absolute asymmetric synthesis refers to the situation in which an asymmetric induction occurs in the absence of an externally imposed source of chirality.[1] Such reactions are invariably carried out in the crystalline state, where the asymmetric influence governing the enantioselectivity derives from the spontaneous crystallisation of an achiral compound in a chiral space group (*i.e.* $P2_12_12_1$).[2-4]

During the course of our investigation on the correlation between the crystal structure and solid-state reactivity,[5] we found 5-, 7-membered ketones (Scheme 1, **1** and **2**) were crystallised in a chiral space group, $P2_12_12_1$. Furthermore, the photochemical procedure is the conversion of an achiral reactant to a chiral product, which is suitable for asymmetric studies. We now present the results of our investigations.

The ketones **1** and **2** chosen for studies were synthesised from commercially available compound norbornene.[5] Irradiation of the above ketones in acetonitrile through Pyrex using a 450 W medium-pressure mercury lamp successfully afforded the Norrish type II cleavage product **3** and cyclisation product **4**, respectively.[6,7] Solid-state photolysis of ketone **1** afforded a racemic product **3**. Shortening photolytic time and lowering reaction temperature have no effects on improving the enantiomeric excess (ee) values of the product **3**. To rationalise the results obtained in the solid state, the single crystal structure of ketone **1** was determined and is presented in Fig. 1, **1**. For photochemical reactions involving intramolecular hydrogen atom abstraction, it requires a conformation in which the carbonyl oxygen is within approximately 2.7 ±0.2 Å of a γ-hydrogen atom. As it can be seen, the distance of C=O····Ha (2.478 Å) is very similar to the distance of C=O····Hb (2.533 Å),[8] leading to an equal probability in abstraction of Ha and Hb. As a result, there is no surprise obtaining racemic photoproduct **3** when the reactant **1** was photolysed in the solid state. The other possibility for racemic product (**3**) is that the racemisation occurred in the course of ketonisation.

Now we turn to the asymmetric studies on ketone **2**. A single crystal of **2** was crushed between two Pyrex microscope slides, sealed in polyethylene bags under nitrogen, and irradiated with a 450 W medium-pressure mercury lamp. Following photolysis, the photoproducts were analysed by chiral HPLC to obtain the enantiomeric excess (*ee*) values and GC for the conversions. The results of the enantiomeric excess determinations are summarised in Table 1. As can been seen, the enantiomeric excesses vary from 23% to 93%. The reaction at room temperature led to low *ee* (23%), which is presumably due to the breakdown in the crystal lattice when the photoproduct replaces the reactant. Fortunately, this could be compensated by lowering the reaction temperature or decreasing the conversion. At temperatures much below –40°C, the solid-state photoreaction became sluggish (*e.g.* the reaction was conducted at –40°C for one week, only trace amount of photoproduct was obtained).



Scheme 1

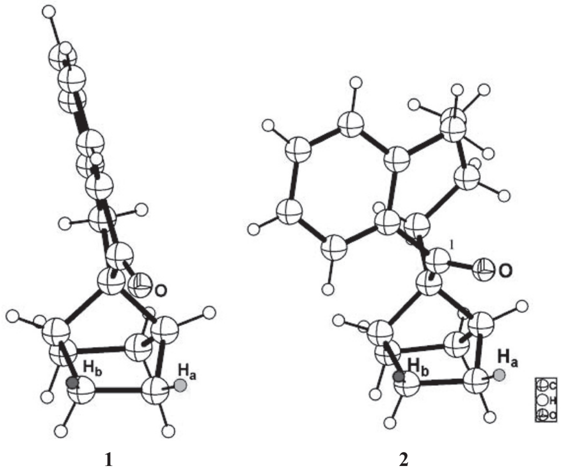


Fig. 1 ORTEP representation of the X-ray crystal structure of compound **1** and **2** with 50% probability thermal ellipsoids.[a]

As shown in Fig. (**1**), **2**, the distance of C=O····Ha (2.659Å) is much closer than the distance of C=O····Hb (3.289Å). As a result, bond formation between C1 and Ca is favoured, affording one enantiomer of photoproduct **4**. In contrast, formation of the optical antipode of the photoproduct obtained by abstraction of Hb and bonding between C1 and Cb is, not only unlikely on distance grounds, but following abstraction, also requires a large amplitude rotation of the aryl group, which is topochemically forbidden in the solid state.

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Table 1 Absolute asymmetric studies on ketone **2**[a]

Temperature/°C	Time/h	Conversion/%[b]	*ee*%[c]	[α][d]
–5	72	21	93	–
–20	160	25	92	+
–7	68	79	79	+
r.t.	21.5	53	23	+
r.t.	3.5	23	70	–

[a]Samples were irradiated through Pyrex using a 450-W Hanovia medium-pressure mercury lamp.
[b]Conversion% based on GC.
[c]Determined by a Chiralpak® AS® HPLC column with hexane/isopropanol (99:1) as eluting solvent.
[d]Sign of rotation of major enantiomer of photoproduct (**4**) at the sodium D-line.

Current efforts in asymmetric studies on ketones **1** and **2** using the chiral auxiliary method[10-15] are ongoing in our group.

Experimental

General

Commercial spectral grade solvents were used for photochemical experiments unless otherwise stated. All reactions were performed under a nitrogen atmosphere unless otherwise noted. Preparative chromatography was performed using either the flash column method with silica gel (particle size 230–400 mesh). IR spectra were recorded on a Perkin-Elmer 1710 Fourier transform spectrometer. High-resolution mass spectra were obtained from a Kratos MS 50 instrument using electron impact (EI) ionisation at 70 eV. Elemental analyses were performed on a Carlo Erba CHN Model 1106 analyser. ^{1}H NMR spectra were obtained at either 300 or 400 MHz on Bruker AV-300 or Bruker AV-400 instruments. ^{13}C NMR spectra were recorded at either 75 or 100 MHz.

Photolysis of spiroketone (**1**): A solution of ketone **1** (310 mg, 1.46 mmol) in 2:1 *tert*-butanol/benzene (40 ml) containing anhydrous barium oxide (15 mg) was irradiated (Pyrex filter, 450 W Hanovia lamp) for 6 h at room temperature. Removal of solvent followed by silica gel chromatography (5% Et_2O in petroleum ether) gave ketone **3** (19 mg, 6%) as a colourless oil. Also isolated was indan-1-one (14 mg, 7%) resulting from secondary photocleavage of ketone **3**. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 1.41 (m, 4H), 1.82 (m, 3H), 2.13 (m, 9H), 2.71 (septet, J = 4.2 Hz, 2H), 2.95 (m, 2H), 3.21(m, 2H), 5.60 (m, 1H), 5.68 (m, 3H), 7.36 (t, J = 7.0 Hz, 2H), 7.49 (d, J = 7.5 Hz, 2H),7.58 (m, 2H), 7.69 (d, J = 7.3 Hz, 2H) ppm; ^{13}C NMR ($CDCl_3$, 75 MHz): δ 24.36, 25.29, 25.41, 26.54, 26.57, 29.12, 29.17, 29.71, 35.19, 35.45, 51.74, 51.85, 123.08, 125.95, 126.25, 126.42, 126.48, 126.72, 126.79, 127.06, 134.37, 137.52, 137.54, 154.06, 154.09, 207.92, 208.15 ppm; IR (neat): 3021, 2917, 1708, 1280, 1205, 753, 660 cm^{-1}; HRMS (EI) Calcd for $C_{15}H_{16}O$: 212.1201, found: 212.1205. Anal. Calcd for $C_{15}H_{16}O$: C, 84.87; H, 7.60. Found: C, 84.60; H, 7.81.

Photolysis of spiroketone (**2**): A solution of ketone **2** (39 mg, 0.16 mmol) in acetonitrile (10 ml) was irradiated (Pyrex filter, 450 W Hanovia) for 47 h. Removal of solvent *in vacuo* and silica gel chromatography (10% Et_2O in petroleum ether) afforded starting material **2** (17 mg, 44%) and cyclobutanol **4** (12 mg, 31%; 55% based on recovered starting material) as a colourless oil. ^{1}H NMR (CD_2Cl_2, 400 MHz): δ 1.68 (br, 11H), 1.99 (dt, J = 3.4, 3.2 Hz, 1H), 2.73 (m, 3H), 3.01 (m, 1H), 6.97 (m, 1H), 7.12 (m, 3H) ppm; ^{13}C NMR (CD_2Cl_2, 75 MHz): δ 22.42, 24.94, 27.27, 27.52, 33.58, 37.02, 38.61, 46.67, 48.47, 61.17, 85.74, 125.81, 127.36, 127.42, 131.53, 141.54, 143.71 ppm; IR (neat): 3445, 2948, 2931, 2863, 1448, 1077, 1030, 893 cm^{-1}; HRMS (EI) Calcd for $C_{17}H_{20}O$: 240.1514, found: 240.1516; Anal. Calcd for $C_{17}H_{20}O$: C, 84.96; H, 8.39. Found: C, 84.60; H, 8.55.

General procedure for solid-state photolyses: One single crystal of the samples was ground and sandwiched between two microscopic slides. The sample plates were then fixed to one another with tape and placed in a polyethylene bag, and heat-sealed under a positive pressure of nitrogen. Following irradiation, the samples were quantitatively washed from the plates with an appropriate solvent and concentrated *in vacuo*. The samples were analysed directly by GC for yields and conversions and/or HPLC for *ee*s.

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References

1 L. Caswell, M. Garcia-Garibay, J.R. Scheffer and J. Trotter, *J. Chem. Ed*., 1993, 70, 785.
2 S.V. Evans, M. Garcia-Garibay, N. Omkaram, J.R. Scheffer, J. Trotter and F. Wireko, *J Am. Chem. Soc.,* 1986, **108**, 5648.
3 M. Sakamoto, *Chem. Eur. J.* 1997, **3**, 684.
4 M. Sakamoto, In: Y. Inoue and V. Ramamurthy, (eds) *Chiral photochemistry*, Marcel Dekker, New York, (2004) chap 11.
5 D. Braga, S. Chen, H. Filson, L. Maini, M.R. Netherton, B.O. Patrick, J.R. Scheffer, C. Scott and W. Xia, *J. Am. Chem. Soc*., 2004, **126**, 3511.
6 P. Wagner and B.S. Park, In *Organic Photochemistry*, Ed., A. Padwa, Marcel Dekker: New York, 1991; Vol. 11, Chap. 4.
7 N.C. Yang and D.H. Yang, *J. Am. Chem. Soc.,* 1958, **80**, 2913.
8 W. Xia, J.R. Scheffer, M. Botoshansky, M. Kaftory, *Org. Lett*., 2005, **7**, 1315 and references therein.
9 D. Braga, S. Chen, H. Filson, L. Maini, M.R. Netherton, B.O. Patrick, J.R. Scheffer, C. Scott and W. Xia, *J. Am. Chem. Soc.*, 2004, **126**, 3511.
10 C. Yang, W. Xia and J.R. Scheffer, *Tetrahedron*, 2007, **63**, 6791.
11 W. Xia, C. Yang, B.O. Patrick, J.R. Scheffer and C. Scott, *J. Am. Chem. Soc*., 2005, **127**, 2725.
12 J.R. Scheffer and W. Xia, *Top. Curr. Chem.,* 2005, **254**, 233.
13 C. Yang, W. Xia, J.R. Scheffer, M. Botoshansky and M. Kaftory, *Angew. Chem. Int. Ed.,* 2005, **44**, 5087.
14 W. Xia, J.R. Scheffer and B.O. Patrick, *Cryst. Eng. Comm.*, 2005, **7**, 728.
15 W. Xia, C. Yang, J.R. Scheffer and B.O. Patrick, *Cryst. Eng. Commun.,* 2006, **8**, 388.