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Photochemical studies on *exo*-bicyclo[2.1.1]hexyl and bicyclo[3.1.0]hexyl aryl ketones: two approaches for synthesis of enantiomerically enriched cyclopentene derivatives

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ABSTRACT

Two approaches for the photochemical synthesis of cyclopentene derivatives through the Norrish type II cleavage reaction were described. Asymmetric studies using ionic chiral auxiliaries afforded enantiomeric excesses of up to 98% at the conversion of 85%. The results were rationalized by single X-ray crystal structures.

1. Introduction

Enantiomerically enriched cyclopentene derivatives have been found to be crucial building blocks in the synthesis of naturally occurring products, which are widely distributed throughout the animal, bacterial, and plant kingdoms. Consequently, the syntheses of such compounds have attracted the interest from organic chemists.[1] The general efficient methods involve intramolecular carbon–hydrogen insertions of alkylidenecarbenes[2], organocatalytic [3+2] cyclizations,[3] RCM reaction of the acyclic precursors[4] and carbonyl allylation with cyclic allyl halide.[5] Among them stoichiometric amounts of metal catalysts should be first prepared in multiple synthetic steps and/or halides were employed in the reaction. For example, in the [3+2] annulation reaction, the planar chiral 2-phospha[3]ferrocenophanes were synthesized in five steps and expensive reagents were involved. Therefore, room exists for developing environmentally friendly approaches for synthesis of enantiomerically enriched cyclopentenes, a feature that has been embodied in the synthesis of natural products.[6] As part of research interest in solid-state organic photochemistry,[7] we found that such a goal can be achieved through a typical Norrish type II cleavage process using the ionic chiral auxiliary method. The ionic chiral auxiliary concept, developed by Scheffer and coworkers, has proven to be a reliable method of asymmetric studies on 1,4-hydroxybiradical behavior.[8] We extended this method to the asymmetric synthesis of cyclopentene derivatives owing to its features that make this particular method attractive in terms of general applicability: 1) it makes use of a large pool of commercially available, inexpensive, optically pure amines; 2) the auxiliary is easily attached and removed through acid–base chemistry; 3) ionic solids are generally high melting, giving robust crystals (essential for studying reactions in the solid state). In this paper, we present what we have achieved in asymmetric photochemical studies on *exo*-bicyclo[2.1.1]hexyl and bicyclo[3.1.0]hexyl aryl ketones.

2. Results and discussion

Our strategy for synthesis of the above ketones **2** and **9** was started from norbornene **1** and bicyclo[2.2.1]heptadiene **6**, respectively. As shown in Schemes 1 and 2, according to the reported procedures[7c,9], norbornene **1** was converted to the ketone **2** through a straightforward pathway. Irradiation of **2a** in acetonitrile solution with a 450 W medium mercury pressure lamp under N_2 for 24 h gave the cyclization product **5** in 30% yield and the cleavage product **4** in 66% yield.[10] In this reaction, compound **5** containing a plane of symmetry is an achiral molecule, which is not suitable for

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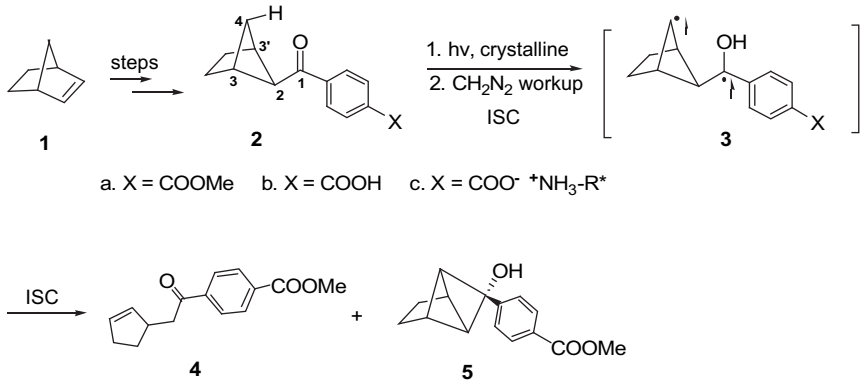
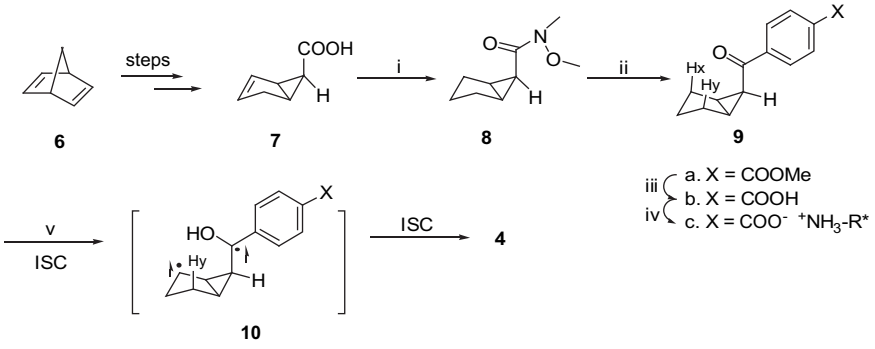


Scheme 1.



Scheme 2. (i) PtO_2, H_2, ethyl acetate; CDI, MeO(Me)NH.HCl, CH_2Cl_2; (ii) $IC_6H_4CO_2CH_3$, ^iPrMgBr, THF; (iii) Na_2CO_3, THF/H_2O (1:5); 10% HCl; (iv) R^*NH_2, Et_2O; (v) *hv*, solid state; CH_2N_2 workup.

asymmetric studies, whereas the formation of cyclopentene **4** is the conversion of achiral reactants to chiral products, which is ideal for asymmetric photochemical studies. Therefore, the carboxylic ester **2a** was hydrolyzed with LiOH in THF/H_2O followed by conc. HCl workup to give the carboxylic acid **2b** in quantitative yield. The compound **2b** was then treated with a variety of optically pure amines to form the corresponding ammonium carboxylate salts **2c**. Such salts are required to crystallize in chiral space groups, which provide the asymmetric environment responsible for chiral induction. Crystals of the salts **2c** (3–5 mg) were crushed between two microscope slides and sealed in a polyethylene bag under nitrogen, and irradiated with a 450 W medium mercury pressure lamp. After irradiation, the photoproduct was treated with ethereal diazomethane to give the methyl esters, which were then analyzed by chiral HPLC to obtain enantiomeric excess values and by GC to give the conversions. The results are summarized in Table 1.

As it can be seen in Table 1, the enantiomeric excess (*ee*) as high as 98% was obtained in the solid state. To rationalize the results observed, the X-ray single crystal structure of the (*S*)-(-)-1-phenylethyl amine salt of the keto acid **2b** was determined and presented in

Table 1
Asymmetric studies on the irradiation of salts **2c** and **9c** in the solid state[a]

Amine	**2c**					**9c**[f]			
	T (°C)	conv[b] (%)	ee[c] (%)	[α][d]	5:4[e]	*T* (°C)	conv[b] (%)	ee[c] (%)	[α][d]
(*S*)-(-)-1-phenylethylamine	−20	85	98	−	23:74	−20	59	76	+
	rt	21	>98	−	20:79	rt	70	66	+
	rt	53	98	−	21:77	rt	96	43	+
(*R*)-(+)-1-phenylethylamine	−20	27	92	+	20:79	−20	41	90	−
	rt	74	77	+	22:75	rt	79	67	−
	rt	51	81	+	21:77	rt	95	55	−
(*R*)-(-)-1-Cyclohexylethylamine	rt	97	91	−	23:75	−20	32	60	+
	−20	53	93	−	22:77	rt	25	55	+
	rt	31	92	−	21:77	rt	57	25	+
(1*S*,2*R*)-(-)-*cis*-1-amino-2-indanol	−20	48	72	+	21:77	−20	67	74	+
	rt	67	60	+	20:79	rt	89	67	+
	rt	91	53	+	22:76	rt	95	64	+

[a] Samples were irradiated through Pyrex using a 300-W hanovia medium-pressure mercury lamp.
[b] Conversion % based on GC.
[c] Ee % analyzed on chiral OD-H column with hexane:isopropanol=99.5:0.5 as the eluting solvent.
[d] Sign of rotation at the sodium D-line.
[e] Based on GC analysis.
[f] **9c** was the sole photoproduct if no prolonged time was employed.

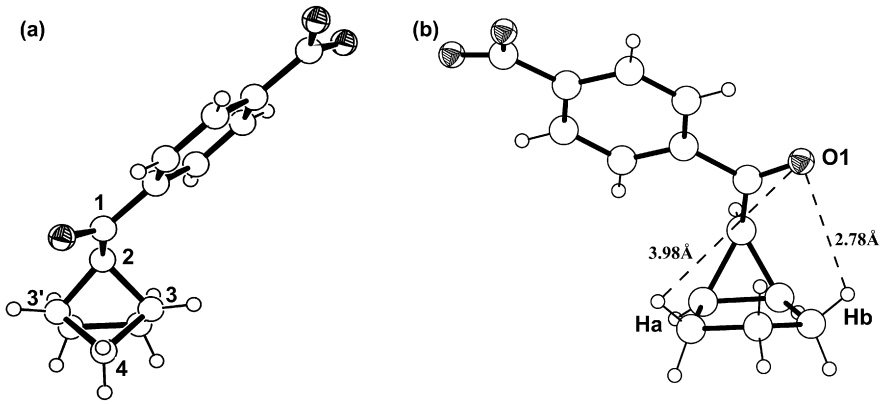


Figure 1. X-ray crystal structures of (*S*)-(-)-1-phenylethylamine salts of keto acids (a) **2b** and (b) **9b**. (The chiral auxiliary was omitted for clarity).

Figure 1. It is of interest to point out that, for the aryl ketone **2**, there is only one γ-hydrogen could be abstracted in the first step of Norrish type II reaction. As a result, the factor of distance between oxygen and H_4 for the determination of *ee* could be excluded. Therefore, the enantioselectivity is controlled by the geometric parameters φ_1 and φ_4.[11] Under the influence of the chiral auxiliary, (*S*)-(-)-1-phenylethyl amine, the keto acid **2b** recrystallized in a homochiral conformation, in which C2–C3 bond was preferentially cleaved than C2–C3′ (φ_1=16°, φ_1'=78°, φ_4=φ_4'=35°), affording one enantiomer of photoproduct **4**.[12] In contrast, formation of the optical antipode of the photoproduct 4 obtained by rupture of C2–C3′ requires a large amplitude rotation of the aryl group, which is topochemically forbidden in the solid state. Therefore, high *ee* (>98%) of the (*S*)-(-)-1-phenylethyl amine salt of the keto acid **2b** was obtained.

Next we turn to the asymmetric studies on bicyclo[3.1.0]hexyl aryl ketones **9**. The synthesis of compound **9a** was started from bicyclo[2.2.1]heptadiene **6**, which was first converted to the carboxylic acid **7** according to the literatures.[13] Hydrogenation of **7** with PtO_2 followed by the treatment with 1,1′-carbonyldiimidazole and *N*,*O*-dimethyl hydroxyl amine hydrochloride afforded the amide **8** in 63% yield (two steps), which was then reacted with Grinard reagent at −40 °C to give the target compound **9** in 37% yield. Irradiation of compound **9a** in acetonitrile with a 300 W medium-pressure mercury lamp for 2 h at room temperature afforded cyclopentene **4** in 53% yield. For the asymmetric studies, compound **9a** was hydrolyzed with Na_2CO_3 in THF/H_2O (1:5) and acidified with 10% HCl to give the carboxylic acid **9b** in 75% yield, which was then treated with a variety of optically pure amines to form the corresponding ammonium carboxylate salts **9c**. Irradiation of **9c** in the solid state according to the procedures as mentioned above afforded the enantiomerically enriched cyclopentene **4**, the results are listed in Table 1.

As shown in Table 1, the enantiomeric excess of up to 90% was obtained. For the salts studied, there was a decline in photoproduct *ee* with increasing conversion, which is presumably due to the breakdown in order of the crystal lattice as product replaces starting material. To rationalize the enantioselectivity observed in the solid state, the X-ray crystal structure of the (*S*)-(-)-1-phenylethylamine salt was determined and is presented in Figure 1b. As shown in Figure 1b, the enantioselectivity of the asymmetric studies on compound **9c** in the crystalline state was attributed to conformational factors. Under the influence of the ionic chiral auxiliary, the carboxylate reactant crystallizes in a homochiral conformation in which the carbonyl oxygen is significantly closer to Hb (2.78 Å) than to Ha (3.98 Å). As a result, the Hb is abstracted preferentially, affording a 1,4-biradical that leads to one enantiomer of the final cleavage photoproduct. The optical antipode of the photoproduct results from Ha abstraction, which requires a large amplitude rotation of the pendant aryl group that is topochemically and geometrically disfavored in the crystalline state. Finally, a control experiment was conducted by irradiation of the salts **9c** in methanol, which led to racemic product **4**. This is typical and highlights the critical importance of carrying out the reactions in the solid state and avoiding conditions that could lead to crystal softening or melting. Therefore, the enantioselectivity is the result of preorganization of the reactant in a homochiral conformation favorable for the formation of a single enantiomer of the product.

3. Conclusion

In summary, the present study reports two convenient approaches for synthesis of the enantiomerically enriched cyclopentene derivative via a Norrish type II photoreaction. Remarkably, it should be pointed out either optical isomer of the cyclopentene derivative could be produced through the photochemical synthesis pathway by simply switching the chirality of the auxiliary. The work on the asymmetric syntheses of other key intermediates for bioactive natural products is ongoing in our group.

Crystallographic data for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 265555, 735645.Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44 (0)1223 336033 or e-mail:deposit@ccdc.cam.ac.uk).

4. Experimental

4.1. General methods

Commercial spectral grade solvents were used for photochemical experiments unless otherwise stated. Infrared spectra were recorded on a Perkin–Elmer 1710 Fourier transform spectrometer. Melting points were determined on a Fisher-Johns apparatus. Low-resolution mass spectra were obtained from a Kratos MS 50 instrument using electron impact (EI) ionization at 70 eV. ^{1}H NMR spectra were obtained at 400 MHz on Bruker AV-400 instrument. ^{13}C NMR spectra were recorded at 100 MHz.

4.2. Bicyclo[3.1.0]hex-6-endo-carboxylic acid-*N*-methoxy-*N*-methyl amide (8)

The known compound 7 was synthesized from a procedure modified from that of Meinwald et al. was used.[13]

Platinum oxide catalyst (264 mg, 1.16 mmol) was suspended in 88 mL of ethyl acetate and reduced with hydrogen gas at 2 atm. Pressure in a hydrogen bomb for about 12 h. The acid **7** (1.5 g, 12 mmol) was dissolved in 20 mL of ethyl acetate and was then

added to the prereduced catalyst. The hydrogenation was continued overnight. The solution was filter through a pad of Celite and washed with ethyl acetate. The solvent was removed in vacuo, crystallized from petroleum ether to yield 1.1 g of hydrogen reduced acid.

A solution of the above acid (600 mg, 4.76 mmol) in 20 mL of anhydrous dichloromethane was cooled to 0 °C, treated with 1,1′-carbonyldiimidazole (932 mg, 5.76 mmol) and stirred for 30 min. *N,O*-Dimethyl hydroxyl amine hydrochloride (1172 mg, 12 mmol) was then added, and the resultant suspension was warmed to room temperature, stirred for 24 h, and filtered. The precipitate was washed with diethyl ether and the filtrate was washed with water, brine, and dried over anhydrous sodium sulfate. The solvent was concentrated in vacuo to yield 720 mg (90%) of Weinreb amide. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.72 (s, 3H), 3.24 (s, 3H), 2.01 (m, 2H), 1.84 (m, 2H), 1.66 (m, 4H), 1.25 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 173.25, 60.84, 26.27, 24.7, 23.08, 22.08. IR (NaCl) ν_{max}: 3044, 2979, 2937, 2869, 1655, 574 cm^{-1}. LRMS (EI): 169 (M^+), 154, 138, 109, 81, 53. Anal. Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.93; N, 8.28. Found: C, 63.34; H, 8.97; N, 8.23.

4.3. Bicyclo[3.1.0]hex-6-endo-1-(4-carbomethoxyphenyl) methanone (9a)

A solution 393 mg (1.5 mmol) of methyl 4-iodobenzoate in 15 mL of anhydrous THF was cooled to −40 °C and 0.75 mL (2 M, 1.5 mmol) of ^{i}PrMgBr was added. The reaction mixture was stirred for 1 h at −40 °C whereupon 127 mg (0.75 mmol) of compound **8** in 4 mL of anhydrous THF was added. The solution was warmed slowly to room temperature and stirred overnight. The reaction was quenched with excess of 10% HCl solution and extracted with diethyl ether. The combined extracts were washed with water and dried over anhydrous sodium sulfate. The solvent was removed in vacuo and the residue purified by chromatography on silica gel with pet ether–ethyl acetate (30:1) to afford a methyl ester **9a** as a colorless solid (68 mg, 37%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.13 (s, 4H), 3.95 (s, 3H), 2.03–1.85 (m, 7H), 1.61–1.57 (m, 1H), 0.95–0.87 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.8, 166.4, 141.2, 133.7, 129.7, 128.4, 52.4, 27.3, 26.1, 26.0, 22.7. IR (KBr) ν_{max}: 2952, 1723, 1670, 1574, 1503, 1440, 1411, 1278, 1211, 1108, 1015 cm^{-1}. LRMS (EI): 244 (M^+), 213, 178, 163, 147, 135, 120, 103, 91, 76, 67, 50. Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.62; H, 6.81.

4.4. Irradiation of compound 9a in acetonitrile

The solution of **9a** (40 mg, 0.164 mmol), in acetonitrile (20 mL) was purged with N_2 for 15 min and irradiated with 300 W medium-pressure mercury lamp for 2 h. After irradiation, the solvent was removed in vacuo and the residue was purified by chromatography with pet ether–ethyl acetate (30:1) to afford photoproduct **4** (21 mg, 53%). Mp 97–97.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.10 (d, J=8.8 Hz, 2H), 7.97 (d, J=8.8 Hz, 2H), 5.77 (m, 1H), 5.69 (m, 1H), 3.93 (s, 3H), 3.25 (m, 1H), 3.10 (m, 1H), 2.98 (m, 1H), 2.35 (m, 2H), 2.19 (m, 1H), 1.46 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.0, 166.3, 140.4, 133.9, 133.7, 131.5, 129.8, 128.0, 52.4, 45.1, 41.2, 31.8, 30.0. IR (KBr) ν_{max}: 2953, 2927, 1727, 1279, 1108, 769, 711 cm^{-1}. LRMS (EI): 244 (M^+), 229, 179, 163, 147, 104, 76, 50. Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.81; H, 6.57.

4.5. Synthesis of carboxylic acid (9b)

Methyl ester **9a** (350 mg, 1.43 mmol) was suspended in a water (100 mL) and THF (20 mL) solution containing 3.04 g (28.7 mmol) of sodium carbonate. The solution was stirred for 30 h at room temperature and acidified with 10% HCl. The white precipitate formed upon acidification was removed by extraction with ether. The combined organic fractions were washed with water and dried over magnesium sulfate. Removal of the solvent in vacuo gave a white solid, which was recrystallized from methanol to afford **9b** (230 mg, 75.4%) as a white solid.

4.6. General procedure for synthesis of salts (9c)

To a solution of acid 9b (70 mg, 0.3 mmol) in diethyl ether (10 mL) was added an equivalent of optically pure amide. Upon the addition, the precipitate formed immediately. The resulting suspension was filtered by suction to give the salt, which was then recrystallized from methanol.

4.7. General procedure for the irradiation of salts in the solid state

The salt crystals (2–5 mg) were crushed between two Pyrex microscope slides and sealed in a polyethylene bag under a positive pressure of nitrogen. The sample was irradiated from both sides with a 450 W medium-pressure mercury lamp. After irradiation, the salt crystals were suspended in an excess of ethereal diazomethane solution and allowed to stand until dissolution was complete. Ether and excess diazomethane were removed in vacuo and the residue was taken up in methylene chloride and passed through a short plug of silica gel to remove the chiral auxiliary. The residue was then submitted to HPLC analysis to give the enantiomeric excesses and GC analysis to give the conversions.

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11. φ_1 presents the angle between the p orbital on atoms C1 and the C2–C3 or/and C2–C3′ bonds. φ_4 presents the angle between the p orbital on atoms C4 and the C2–C3 or/and C2–C3′ bonds. The ideal value for both parameters is 0°.
12. The (*R*)-1-phenylethylamine salt and the (*S*)-1-phenylethylamine salt are conformational enantiomers and afford the enantiotropic products in the solid-state photoreaction. All attempts to get the same conversions of these two salts in the reaction to compare the enatioselectivity were failed.
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