10664 *J. Am. Chem. Soc.* **1996,** *118,* 10664−10665

Crystal-to-Crystal Solid-State Photochemistry: Absolute Asymmetric *β*-Thiolactam Synthesis from an Achiral α,*β*-Unsaturated Thioamide

Masami Sakamoto,*[†] Masaki Takahashi,[‡] Kenji Kamiya,[†]
Kentaro Yamaguchi,[§] Tsutomu Fujita,[†] and Shoji Watanabe[†]

Department of Applied Chemistry
Faculty of Engineering
Graduate School of Science and Technology
Chemical Analysis Center, Chiba University
Yayoi-cho, Inage-ku, Chiba 263, Japan

Received June 4, 1996

Absolute asymmetric induction studies in the crystalline state are of wide interest since they occur spontaneously in the absence of any outside chiral influence and are relevant to theories concerning the prebiotic origin of natural chirality.[1] The development of photochemical reactions using chiral crystals has potential for the synthesis of optically active compounds that are difficult to prepare in other ways from the viewpoint of chemo-, regio-, and enantioselectivity.[2−4] In most cases, solid-state photochemical reactions involve transformation of achiral molecules into racemic products because of the absence of a chiral environment for reaction through crystallization in a racemic space group. For the special cases of achiral molecules which could adopt a chiral conformation in the crystal lattice, the molecular environment may be chiral and present an opportunity for the induction of asymmetry into photoproducts, and several successful "absolute" asymmetric syntheses involving unimolecular reaction have been reported.[5−14] Here we report a striking example of an absolute *β*-thiolactam synthesis through a solid-state unimolecular photochemical reaction of achiral *N*,*N*-dibenzyl-1-cyclohexenecarbothioamide **1** which occurs in a crystal-to-crystal manner.

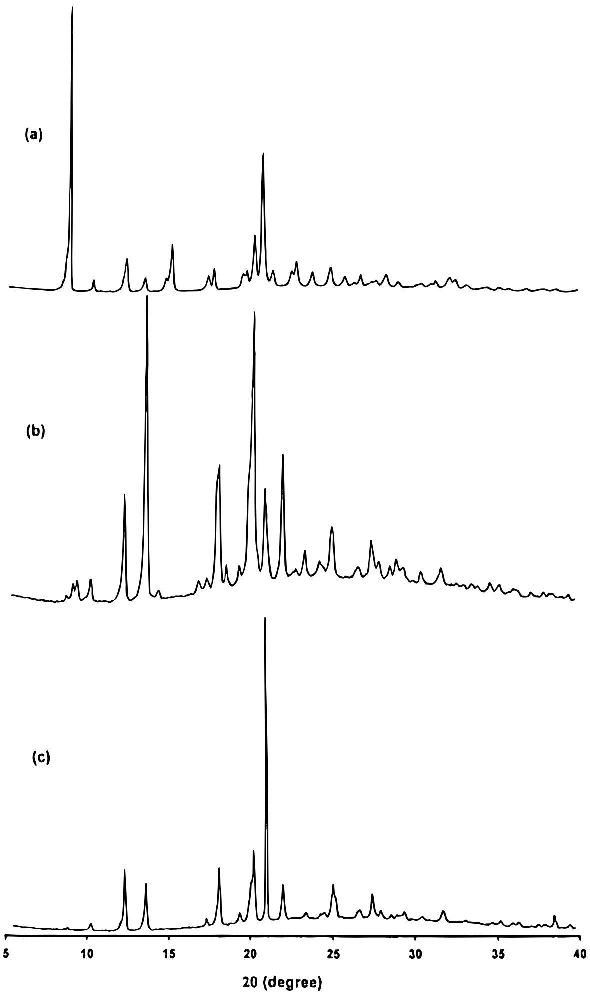
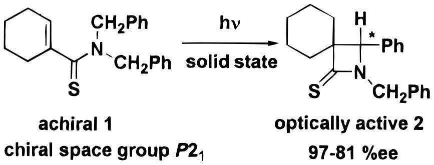


Figure 1. X-ray diffraction patterns of photochemical transformation of crystals of **1**: (a) crystals of **1**; (b) irradiated for 8 h (100% conversion); and (c) recrystallized **2**.

Scheme 1



The crystalline substrate **1** was conveniently prepared by thionation of *N*,*N*-dibenzyl-1-cyclohexenecarboamide with Lawesson's reagent.[15] Recrystallization from chloroform−hexane solution gave slightly yellow prismatic crystals, mp 73−74 °C. X-ray crystallographic analysis indicated the chiral space group $P2_1$, $a = 8.760$ (2) Å, $b = 10.262$ (3) Å, $c = 10.238$ (3) Å, $\beta = 100.15$ (2)°, $V = 905.9$ (4) Å^3, $Z = 2$, $\rho = 1.178$ g/cm^3, and $\mu(\text{Cu}-\text{K}_\alpha) = 15.55$ cm^{-1}. Powdered crystals of **1**, well ground and sandwiched by Pyrex glass plates, were irradiated with 500 W Hg lamp at 0 °C for 2 h, which led to the exclusive production of optically active *β*-thiolactam, 1-benzyl-4-phenylazetidine-2-thione-3-spiro-1′-cyclohexane **2**, in 96% yield at 58% conversion (Scheme 1). This material was purified by column chromatography, and the structure was determined by spectroscopy. As expected, the thiolactam **2** showed optical activity ($[\alpha]^{20}_{D}$ +109°, 94% ee), which was determined by comparison of the $[\alpha]_D$ value with enantiomerically pure *β*-thiolactam **2**.[16] This reaction exhibited good enantioselectivity throughout the whole conversion range, where small differences were detected in the ee value from 97 to 81% ee with increasing conversion from 20 to 100%. It is worth noting that the solid-

---

[†] Department of Chemistry, Faculty of Engineering.
[‡] Graduate School of Science and Technology.
[§] Chemical Analysis Center.

(1) Addadi, L.; Lahav, M. *Origin of Optical Activity in Nature*; Walker, D. C., Ed.; Elsevier: New York, 1979; Chapter 14.

(2) Green, B. S.; Lahav, M.; Rabinovich, D. *Acc. Chem. Res.* **1979**, *69*, 191−197.

(3) Scheffer, J. R.; Garcia-Garibay, M.; Nalamasu, O. *Organic Photochemistry*; Padwa, A., Ed., Marcel Dekker: New York and Basel, 1987; Vol. 8, pp 249−338.

(4) Ramamurthy, V.; Weiss, R. G.; Hammond, G. S. *Advances in Photochemistry*; Volman, D. H., Hammond, G. S., Neckers, D. C., Ed.; John Wiley & Sons: New York, 1993; Vol. 18, pp 67−234.

(5) Evans, S. V.; Garcia-Garibay, M.; Omkaram, N.; Scheffer, J. R.; Trotter, J.; Wireko, F. *J. Am. Chem. Soc.* **1986**, *108*, 5648−5649.

(6) Roughton, A. L.; Muneer, M.; Demuth, M. *J. Am. Chem. Soc.* **1993**, *115*, 2085−2086.

(7) Sekine, A.; Hori, K.; Ohashi, Y.; Yagi, M.; Toda, F. *J. Am. Chem. Soc.* **1989**, *111*, 697−680.

(8) Sakamoto, M.; Hokari, N.; Takahashi, M.; Fujita, T.; Watanabe, S.; Iida, I.; Nishio, T. *J. Am. Chem. Soc.* **1993**, *115*, 818.

(9) Sakamoto, M.; Takahashi, M.; Fujita, T.; Watanabe, S.; Iida, I.; Nishio, T. *J. Org. Chem.* **1995**, *60*, 3476−3477.

(10) Sakamoto, M.; Takahashi, M.; Shimizu, M.; Fujita, T.; Nishio, T.; Iida, I.; Yamaguchi, K.; Watanabe, S. *J. Org. Chem.* **1995**, *60*, 7088−7089.

(11) Sakamoto, M.; Takahashi, M.; Moriizumi, S.; Yamaguchi, K.; Fujita, T.; Watanabe, S. *J. Am. Chem. Soc.* **1996**, *118*, 8138−8139.

(12) Garcia-Garibay, M.; Scheffer, J. R.; Trotter, J.; Wireko, F. *J. Am. Chem. Soc.* **1989**, *111*, 4985−4986.

(13) Fu, T. Y.; Liu, Z.; Scheffer, J. R. *J. Am. Chem. Soc.* **1993**, *115*, 12202−12203.

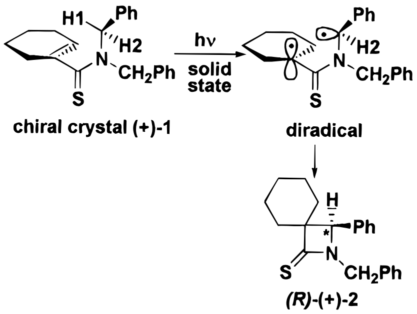
(14) Hashizume, D.; Kogo, H.; Sekine, A.; Ohashi, Y.; Miyamoto, H.; Toda, F. *J. Chem. Soc., Perkin Trans. 2* **1996**, 61−66.

(15) We reported the solution photochemistry of the relevant *N*,*N*-dialkyl-α,*β*-unsaturated thioamides leading to the *β*-thiolactams and the debenzylated thioamides. Sakamoto, M.; Kimura, M.; Shimoto, T.; Fujita, T.; Watanabe, S. *J. Chem. Soc., Chem. Commun.* **1990**, 1214−1215.

(16) Enantiomerically pure **2** was obtained by recrystallization from chloroform−hexane, and the optical rotation was $[\alpha]^{20}_{D}$ +116° in $CHCl_3$ at *c* 1.0.

S0002-7863(96)01878-1 CCC: $12.00

Scheme 2



state photoreaction proceeded without phase separation even after 100% reaction conversion. The crystal-to-crystal nature of the transformation was confirmed by X-ray diffraction spectroscopy as shown in Figure 1. The diffraction patterns of the crystals after completion of the photochemical transformation are markedly inconsistent with those obtained after recrystallization (Figure 1b,c), which implies that the photolyzed crystals are in a metastable state.[17] Optically active β-thiolactam that shows reversed optical rotation was also obtained with similar ee value by photolysis of enantiomorphous crystals of **1** obtained from another batch; each enantiomorph could be obtained selectively and in bulk by seeding.[8]

Absolute asymmetric syntheses involving absolute-to-absolute configuration correlation studies are of mechanistic interest since they have much relevance to stereochemical features of the reaction.[10−13] Accordingly, the absolute configurations of both prochiral substrate (+)-**1**, where the (+) symbol designates the possibility of favoring (+)-**2** by its irradiation, and enantiomerically pure recrystallized (+)-**2** were established by the Bijvoet X-ray method. The Bijvoet measurements assigned the helical configuration of (+)-**1** demonstrated in Figure 2a.[18,20] The stereochemistry of the chiral center in (+)-**2** was determined as (*R*)-configuration.[19,20] The stereochemical relationship before and after the photoreaction is clearly consistent with a mechanism that involves the intermediacy of a diradical generated by H1-atom abstraction, followed by cyclization with a minimum amount of molecular movement affected by steric repulsion of neighboring molecules (Scheme 2). As shown in Figure 2a, the cyclohexenyl moiety is aimed properly at one of the benzyl hydrogen atoms (H1). The distance of C1=C2···H1 is 2.68 Å, less than the sum of the van der Waals radii for carbon and hydrogen (2.90 Å), whereas that of C1=C2···H2 is 4.06 Å, which indicates that solid-state photoreaction of **1** leading to β-thiolactam **2** is topochemically allowed.[3]

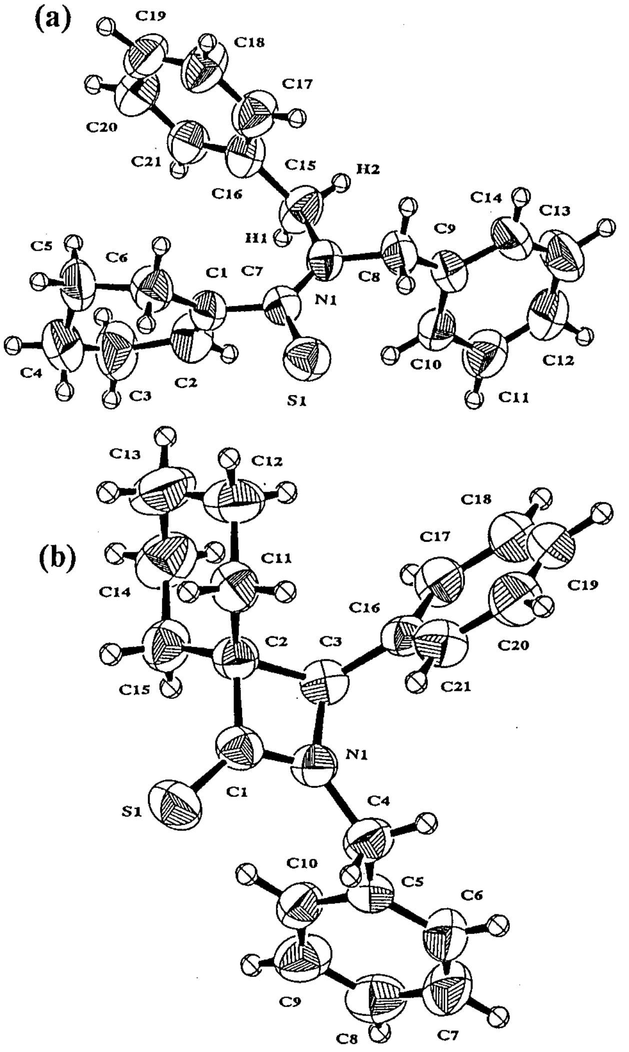


Figure 2. The ORTEP drawing of the absolute configuration of (a) thioamide **1** and (b) β-thiolactam **2**.

In conclusion, this solid state photoreaction provides an ideal example of absolute asymmetric induction since it leads to a single product in high enantiomeric excess via a crystal-to-crystal process. This photoreaction is the first example of an absolute asymmetric synthesis involving hydrogen abstraction by an alkenyl carbon atom and also provides a useful synthesis of an optically active β-thiolactam.

JA961878M

---

[17] Suzuki, T.; Fukushima, T.; Yamashita, Y.; Miyashi, T. *J. Am. Chem. Soc.* **1994**, *116*, 2793−2803.

[18] The absolute structure of (+)-**1** was solved by the Bijvoet difference method. A total of 962 Friedel pairs with F_c differing significantly at the end of the refinement were measured with great care. For these, 669 agreement and 293 disagreement between the observed and calculated ΔF for the structure with a configuration for the helix as shown in Figure 2a gives clear evidence that this structure has the correct absolute configuration, where the final R and R_w were 0.063 and 0.057.

[19] The X-ray crystal data of (+)-**2**: recrystallized from hexane−chloroform, mp 109−110 °C, chiral space group $P4_1$, $a = 10.366$ (1) Å, $c = 17.133$ (3) Å, $V = 1841.0$ (4) Å^3, $Z = 4$, $\rho = 1.160$ g/cm^3, and μ(Cu−K$_\alpha$) = 15.30 cm^{-1}. The structure was solved by the direct method and refined by the method of full-matrix least-squares. The absolute configuration was solved by the Bijvoet difference method. For 1026 Friedel pairs, 675 agreement with 351 disagreement between observed and calculated ΔF for the structure of **2** with the (*R*)-configuration clearly showed that this structure is that with the correct absolute configuration, where the final R and R_w were 0.052 and 0.071.

[20] The author has deposited atomic coordinates for both structures **1** and (*R*)-(+)-**2** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB 1EZ, UK.