CONCEPTS

Absolute Asymmetric Synthesis from Achiral Molecules in the Chiral Crystalline Environment

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Abstract: The current status of absolute asymmetric synthesis in a chiral crystalline environment has been reviewed. A number of topochemically controlled four-center type photocycloadditions are described for a series of unsymmetrically substituted diolefin crystals and CT crystals. This concept has been applied to intramolecular photoreactions, and several successful absolute asymmetric syntheses have been achieved, involving Norrish Type II reaction, di-π-methane rearrangement, electrocyclization, thietane formation, oxetane formation, hydrogen abstraction by thiocarbonyl and alkenyl groups, and radical-pair intermediates.

Keywords
absolute asymmetric synthesis · asymmetric synthesis · chirality · photochemistry · solid-state chemistry

Chirality is a concept well known to organic chemists and to all chemists concerned in any way with structure. The geometric property that is responsible for the nonidentity of an object with its mirror image is called chirality. A chiral object may exist in two enantiomorphic forms, which are mirror images of one another. Such forms lack inverse symmetry elements, that is, a center, a plane, or an improper axis of symmetry. Objects that possess one or more of these inverse symmetry elements are superimposable on their mirror images, that is, they are achiral. All objects belong to one of these categories.

Asymmetric synthesis starting from an achiral reagent and in the absence of any external chiral agent has long been an intriguing challenge to chemists[1] and is also central to the problem of the origin of optically activity in nature.[2] Stereospecific solid-state chemical reactions of chiral crystals formed from achiral materials are defined as absolute asymmetric syntheses.[3] There are two aspects to this type of process: the generation of chiral crystals and the topochemically controlled solid-state reaction, which yields a chiral product.

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There are 230 unique space groups, which may be divided into two categories: a) the chiral space groups, 65 in number, have only symmetry elements of the first kind, that is, translations, rotations, and combinations of these; b) the achiral space groups, such as mirror planes, glide planes, or centers of inversion. Thus the unit cell of a compound belonging to an achiral space group will contain both the object and its mirror image.

To achieve asymmetric synthesis we should begin with a compound crystallizing in any one of the 65 chiral space groups. Crystal engineering is not so advanced that any desired crystal environment can be prepared to order. Of the 230 distinct space groups, the most common are $P2_1/c$, $P\bar{1}$, $P2_12_12_1$, $P2_1$, $C2/c$, and $Pbca$, of which $P2_12_12_1$ and $P2_1$ are chiral (Table 1).[4] In these instances, the chiral environment of the crystal forces the molecule to adopt a chiral conformation (e.g. benzophenone, binaphthyl, benzil).

Table 1. The most common space groups of organic crystalline compounds based upon a survey of 29 059 crystal structure determinations.

Order	Space group	No.	Frequency/%
1	$P2_1/c$	10450	36.0
2	$P\bar{1}$	3986	13.7
3	$P2_12_12_1$ [a]	3359	11.6
4	$P2_1$ [a]	1957	6.7
5	$C2/c$	1930	6.6
6	$Pbca$	1261	4.3
7	$Pnma$	548	1.9
8	$Pna2_1$	513	1.8
9	$Pbcn$	341	1.2
10	$P1$ [a]	305	1.1

[a] Chiral space group.

It is clear that the chirality in solid-state asymmetric synthesis is in fact introduced in the crystallization step; the chemical reaction then transforms the chirality of the crystal into that of the product. Chiral crystals, like any other asymmetric object, exist in two enantiomorphic equienergetic forms, but careful crystallization of the material can induce the entire ensemble of molecules to aggregate into one crystal, of one handedness, presumably starting from a single nucleus. The photochemical process then transforms the conformational chirality frozen in the crystals into stable molecular chirality.

Pedone and Benedetti have indicated that the crystal structure of an optically active compound frequently may be deduced

from that of the racemic compound, and vice versa.[5] In general, the structure of the two forms have in common homochiral layers or columns of molecules arranged in a compact way. The repetition of the layers or columns allows either the enantiomeric structure or that of the racemic compound to be built up, due account being taken of the different symmetry elements possible. This process may be envisaged as follows (Figure 1): With columns of homochiral molecules one can construct a layer and then a three-dimensional structure, either through the application of direct symmetry elements (e.g., a binary axis; labeled *direct* in Figure 1) or through the application of inverse symmetry elements (e.g., a center of symmetry; labeled *inverse* in Figure 1).
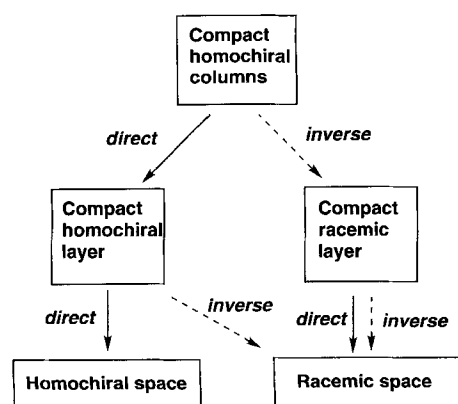

Figure 1. Construction of homochiral and racemic crystal structures.

There are three alternative ways of building up the crystal to form the three-dimensional "racemic space", whereas for construction of the "homochiral space" the route is unique. Depending on the route by which the racemate is obtained, the two forms (enantiomer and racemate) possess in common either a linear packing (columns) or a molecular plane (layers).

A systematic solid-state approach to asymmetric synthesis demands the design of chiral crystal structures having specific intermolecular or intramolecular features. Owing to the strict requirements, the discovery of new systems appropriate for such syntheses has been slow.[6] Since the concept of a topochemically controlled reaction was established by Schmidt in 1964,[1a] various approaches to asymmetric synthesis using solid-state

Abstract in Japanese:

Abstract: 外的な不斉源を全く用いずアキラルな化合物から光学活性物質を合成する絶対不斉合成は単なる不斉合成の領域を越え, 絶対起源の問題にまで発展してくる。不斉結晶環境下での不斉合成も絶対不斉合成に属し, ジオレフィン類のシクロブタン生成反応に於いて優れた成果が得られ, 分子内反応でも近年多くの成功例が報告された。NorrishType II 反応, di-π-methane 転位反応, 電子環状反応, チエタン形成反応, オキセタン形成反応, ラジカル対を経由する反応, チオカルボニル基やアルケニル基による水素引き抜き反応, フェニル基の転位を伴う環化反応により絶対不斉合成が達成されている。

reaction have been attempted, most actively by the research group at the Weizmann Institute. They have been concerned with the bimolecular reactions in chiral crystals. In these studies absolute asymmetric synthesis was achieved by using topochemically controlled four-center type photodimerizations of a series of unsymmetrically substituted diolefin crystals. The strategy and the main results were reported by these investigators for the mixed crystal of 2,6-dichlorophenyl-4-phenyl-*trans,trans*-1,3-butadiene with the 4-thienyl analogue (Scheme 1).[7] These two

Ar = 2,6-C$_6$H$_3$Cl$_2$
Th = 2-Thienyl

Space group: *P*2$_1$2$_1$2$_1$
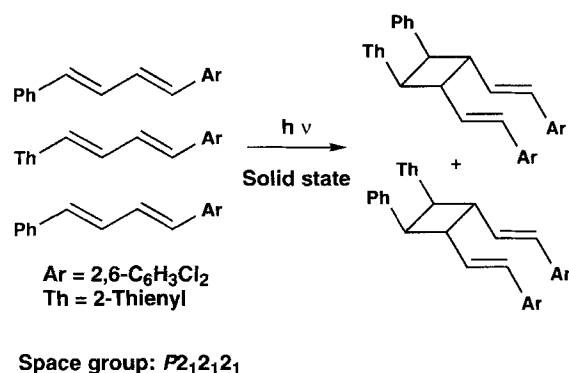
Scheme 1. Asymmetric synthesis with mixed crystals.

materials crystallized in two isostructural arrangements in the chiral space group $P2_12_12_1$. Large mixed crystals of the phenyl material containing approximately 15% of the thienyl derivative as guest were prepared. The latter absorbs light at a longer wavelength. As a result of this selective excitation, the thienyl reacted with a phenyl neighbor to form a mixed cyclobutane dimer, which was isolated with an enantiomeric excess of around 70%.

Hasegawa et al. reported another example of a $2\pi-2\pi$ asymmetric transformation in a chiral crystal (Scheme 2).[8] Ethyl 4-[2-(pyridyl)ethenyl]cinnamate crystallized in a chiral space group $P2_12_12_1$ and yielded a chiral dimer with 92% *ee* upon irradiation.

Suzuki et al. reported the photochemical reaction of charge-transfer (CT) crystals. The cycloaddition reaction of 2-divinylstylene (electron donor) and bis[1,2,5]thiadiazolotetracyanoquinodimethane (electron acceptor) was efficiently induced (Scheme 3).[9] The inclusion lattice of the CT crystal is asymmetric, because of the adoption of a chiral space group ($P2_1$). The [2 + 2] photoadduct was formed, accompanied by a transformation from single crystal to single crystal, and the optically pure product was obtained with 95% *ee*.

Recently, Scheffer et al. reported two elegant unimolecular "absolute" asymmetric transformations (Scheme 4).[10] This group demonstrated that the extensively studied di-π-methane solution-phase photorearrangement can also occur in the solid state. The compounds investigated included dibenzobarrene-11,12-diester derivatives. The corresponding diisopropylester is dimorphic and one of the forms grown from the melt is chiral (space group $P2_12_12_1$). Irradiation of the crystals gave rearranged product exhibiting average specific rotation of 24.2 ± 2.9 (sodium D line). The products were obtained in 100% *ee*, as was established by ^{1}H NMR studies using optically active shift reagent.
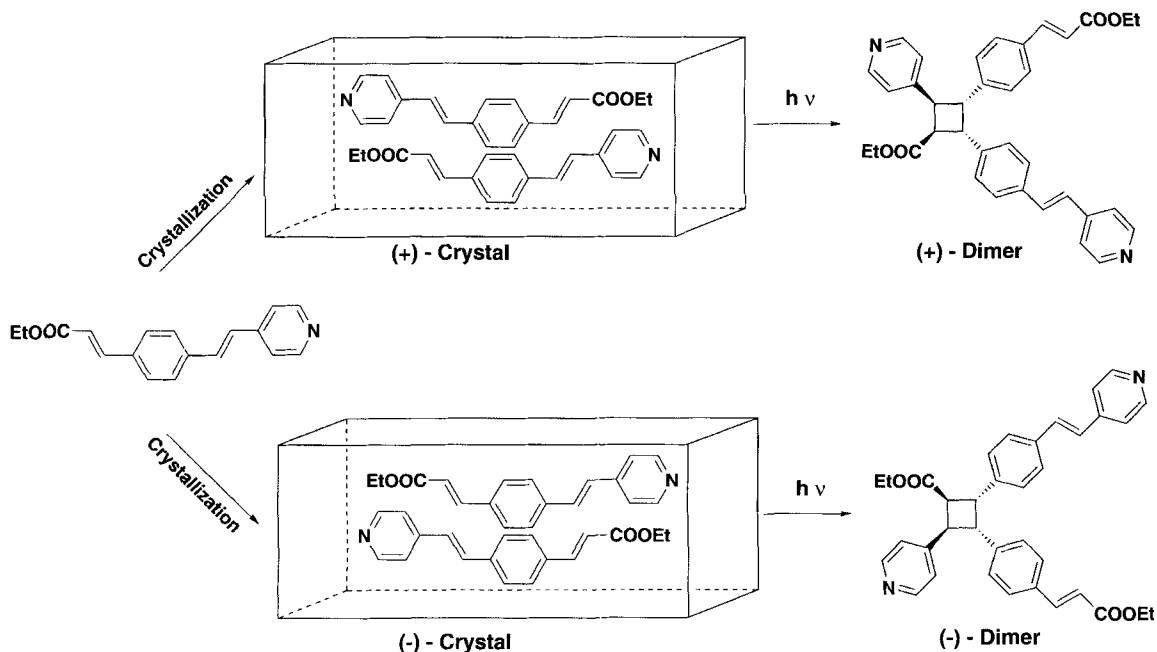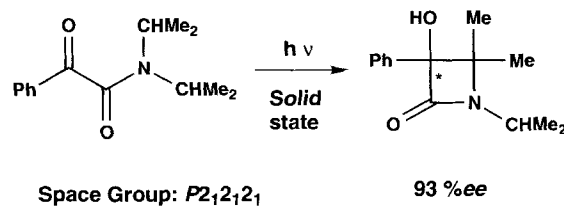
Scheme 2. The signs of optical rotations are arbitrary.
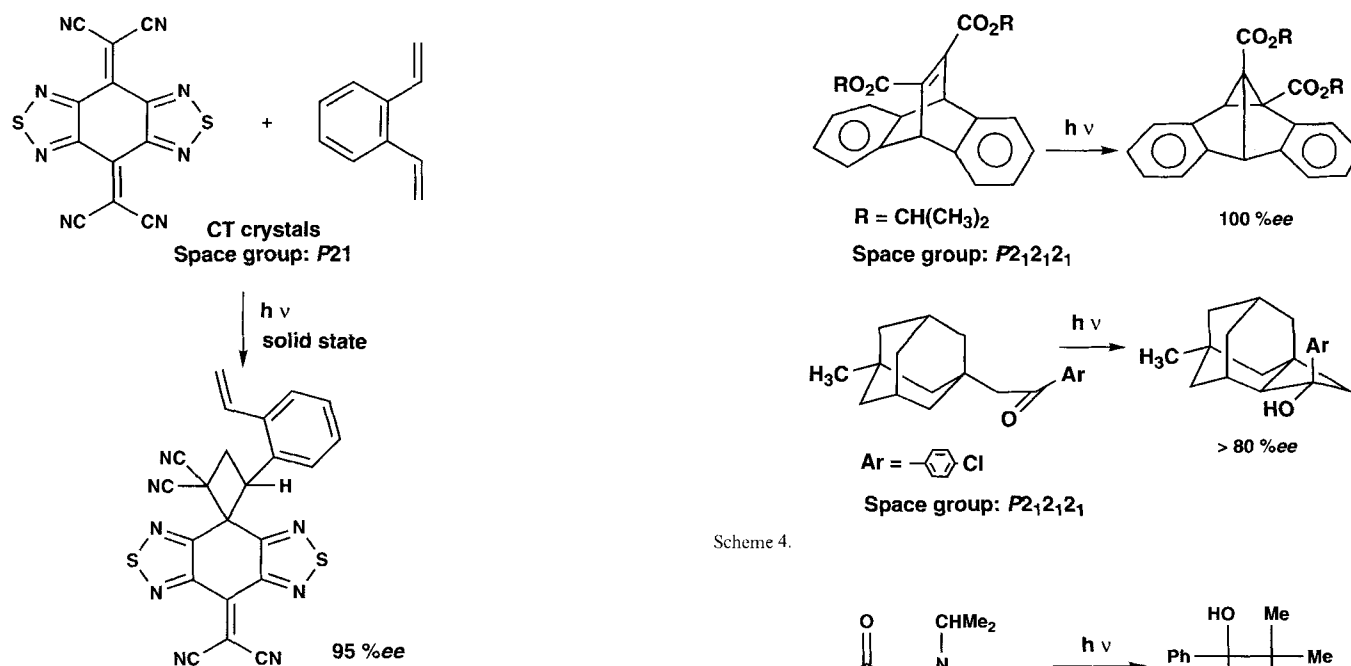
Scheme 3. Asymmetric synthesis with CT crystals.

Scheme 4.

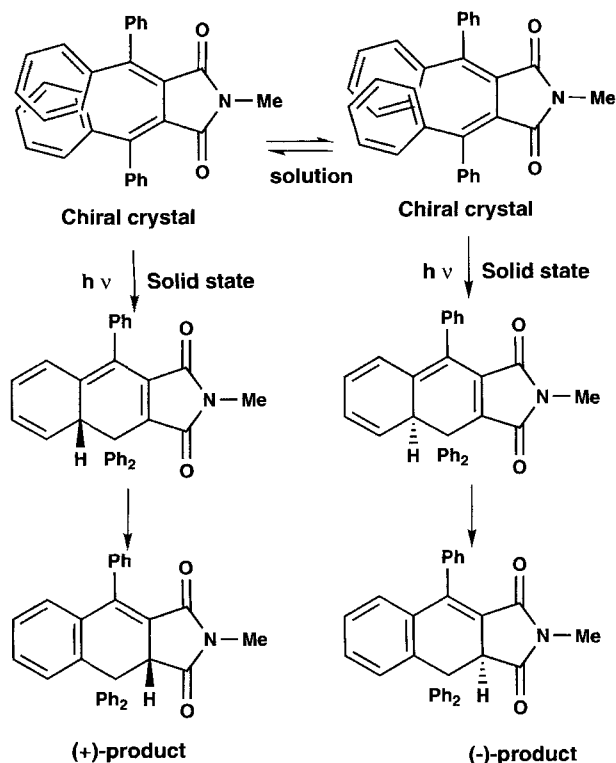Scheme 5. Asymmetric synthesis involving a Norrish Type II reaction.

Another unimolecular asymmetric transformation is the Norrish type II reaction.[10a] An adamantyl ketone derivative crystallized in the chiral space group $P2_12_12_1$. Upon irradiation of single crystals of this ketone, a 1,4-diradical was formed, which underwent exclusive closure to a cyclobutanol derivative. The product cyclobutanol was obtained in 80% *ee*, while in solution racemic product resulted.

Toda and co-workers demonstrated two examples. In the first system, N,N'-diisopropylphenylglyoxylamide, previously studied by Aoyama et al.,[11] crystallized in the chiral space group $P2_12_12_1$ (Scheme 5).[12] Irradiation of single homochiral crys-

tals resulted in the formation of an optically active β-lactam (75%) with 93% *ee* by the Norrish type II reaction. By using methods of seeding during recrystallization, both enantiomers could be obtained, and the structure of the reacting crystal was elucidated.
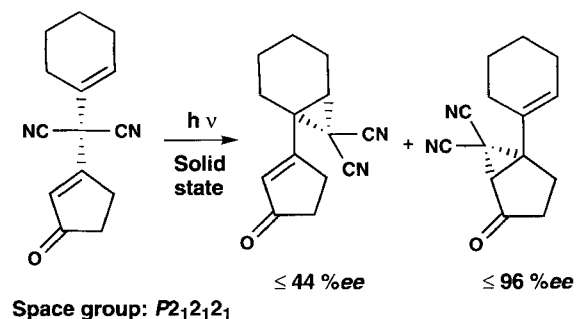
In the second system, the crystallization of 3,4-bis(phenylmethylene)-N-methylsuccinimide gave chiral crystals as orange

hexagonal plates and two racemic crystals as orange rectangular plates and yellow rectangular plates (Scheme 6).[13] Irradiation of powdered enantiomeric crystals gave an optically active photocyclization product in 64% ee. The photolysis of eight other derivatives led to racemic cyclization products in quantitative yield. Deeper understanding of the reaction pathway of this system must await a crystallographic study akin to that carried out with the electrocyclization.

a chiral packing arrangement, space group $P2_12_12_1$, and a helical molecular conformation. The rearrangement products were obtained in respective enantiomeric excesses of ≤ 44 and $\leq 96\%$, and the ee's decreased proportionately with conversion.

Recently, we have reported six examples of absolute asymmetric synthesis involving intramolecular reaction. The first example is the intramolecular [2 + 2] thietane formation in the solid state (Scheme 8).[15] N-(Thiobenzoyl)methacrylamide

Scheme 6. Asymmetric synthesis involving electrocyclization.
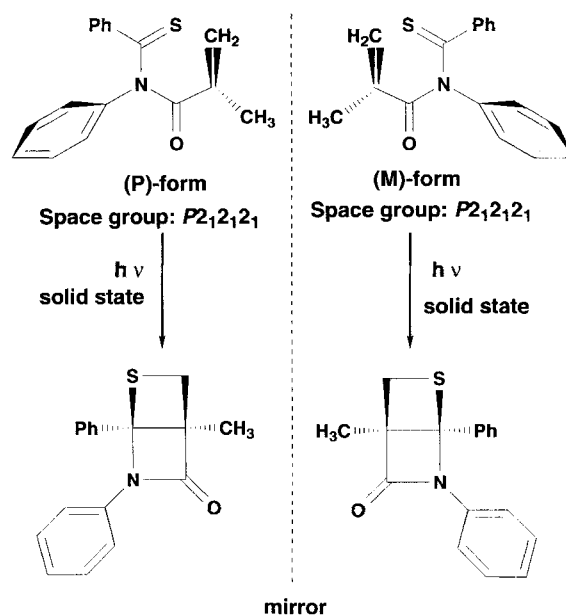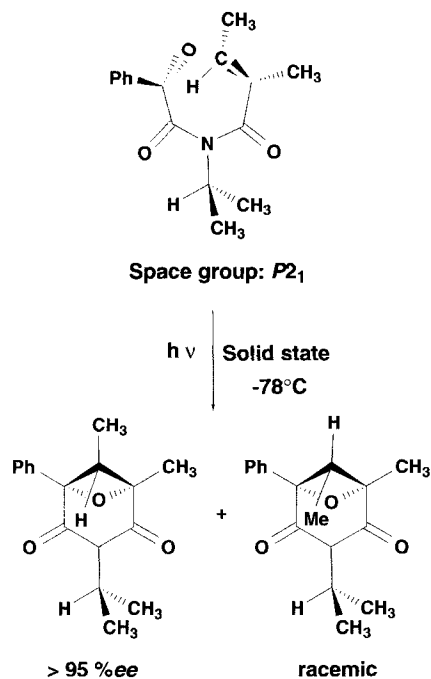

Scheme 8. Absolute asymmetric synthesis of a thietane.

Demuth et al. have also reported the photochemical solid-state di-π-methane type rearrangement of seemingly homochirally crystallized starting material to give preparative quantities of two rearranged products (Scheme 7).[14] A considerable change in product selectivity was observed for the rearrangement in the solid state compared to that in homogeneous solution. The differences are explained in terms of the packing constraints in the crystal, leading to a frozen geometry and a proximity of the reacting sites. The starting material adopts

crystallized in a chiral space group $P2_12_12_1$, and the photolysis of single homochiral crystals at room temperature resulted in the formation of an optically active thietane-fused β-lactam (75%) with 10% ee. The solid-state photoreaction proceeded at temperatures as low as −45 °C and then gave a higher ee value of 40% ee (conv. 30%, yield 70%). By using methods of seeding during recrystallization, both enantiomers could be obtained selectively and in bulk.

The absolute oxetane synthesis has also been demonstrated in the solid-state photolysis of an acyclic imide (Scheme 9).[16] N-Isopropyl-N-tiglylbenzoylformamide formed colorless needle crystals, and an X-ray crystal structure analysis indicated the presence of the chiral space group $P2_1$. Irradiation of the enantiomeric crystals of the imide at 0 °C gave a bicyclic oxetane in 84% yield, with a syn/anti ratio of 3.7. The major syn isomer showed optically activity of 35% ee, whereas the minor anti isomer was obtained as racemate. The solid-state photoreaction proceeded at temperatures as low as −78 °C, and the optically active syn isomer was then obtained with a higher ee value of over 95%. The fact that racemic anti isomer is obtained in the solid-state photoreaction is explained in terms of the defects in the crystal lattice, in which racemization of the reactant already takes place prior to reaction.

The next example involves two different types of reaction, which occur concurrently and exhibit almost the same ee values

Space group: $P2_12_12_1$

Scheme 7. Asymmetric synthesis involving a di-π-methane rearrangement.

Scheme 9. Absolute asymmetric synthesis of an oxetane.

(Scheme 10). The solid-state photolysis of the enantiomorphic crystals of *S*-phenyl *N*-(benzoylformyl)thiocarbamate, which crystallized in the chiral space group $P2_1$, gave optically active oxazolidine-2,4-dione and β-lactam.[17] The amount of conver-
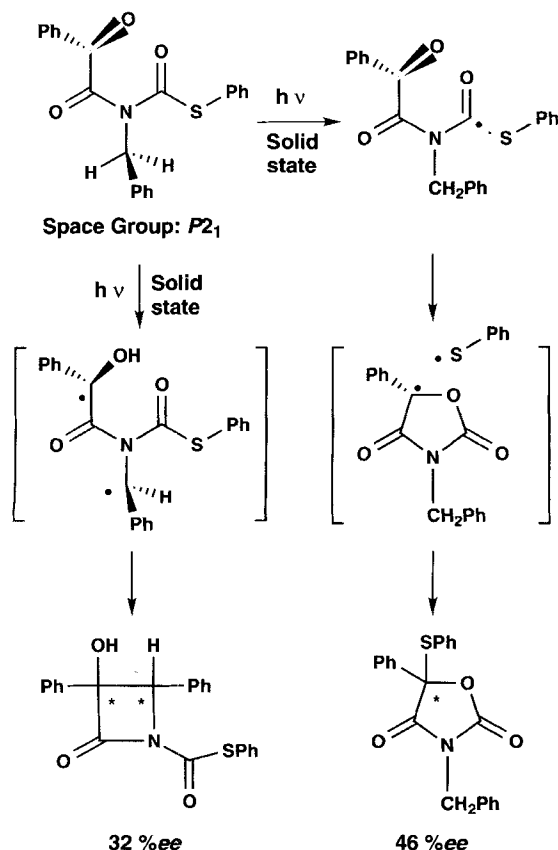
Scheme 10. Absolute asymmetric synthesis involving a Norrish Type II reaction (left) and a radical-pair intermediate (right).

sion of the reactant is important in determining the enantiomeric excess. Better optical purity was obtained at lower conversion. At 17% conversion the oxazolidine-2,4-dione was isolated with 46% *ee* and the β-lactam with 32% *ee*. The formation of a radical-pair intermediate initiated by homolytic C–S bond cleavage leads to the oxazolidine-2,4-dione; hydrogen abstraction by carbonyl oxygen induces β-lactam formation.

Hydrogen abstraction by thiocarbonyl sulfur also occurs in the solid state with retention of the chirality of the crystal lattice (Scheme 11).[18] *N*-Diphenylacetyl-*N*-isopropylthiobenzamide
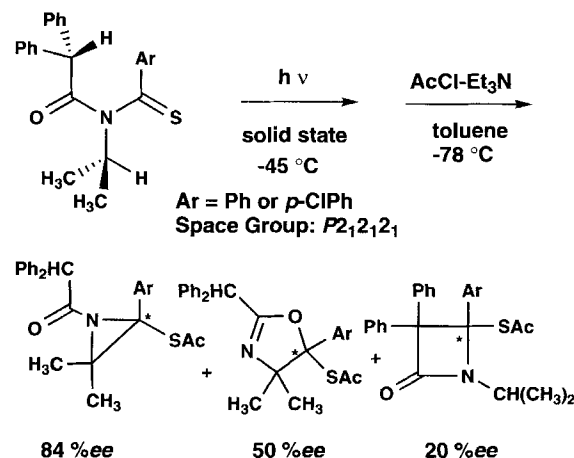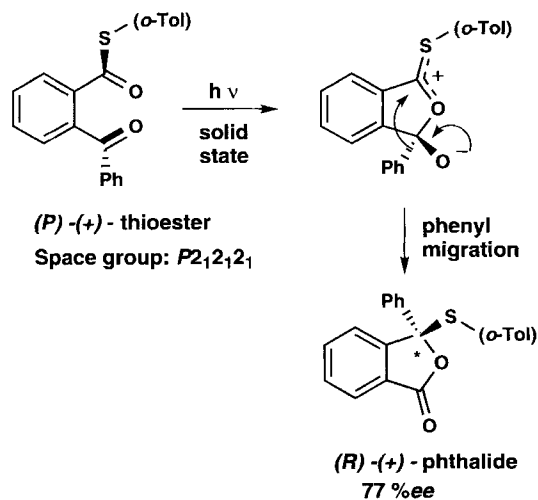
Scheme 11. Asymmetric synthesis involving hydrogen abstraction by thiocarbonyl sulfur.
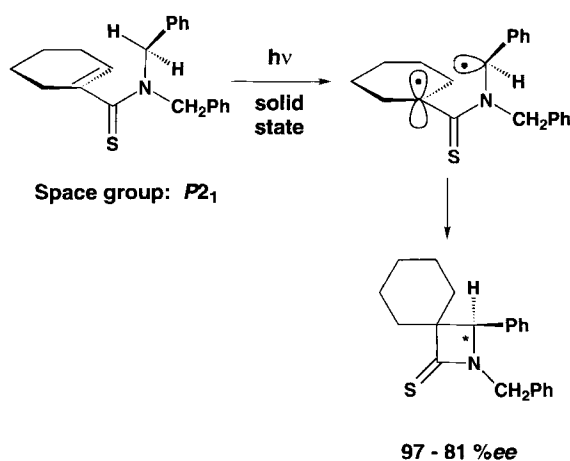
crystallized in chiral space group $P2_12_12_1$. This thioimide showed a preference for the (*E,E*) geometry in the crystalline state, which is favorable for photochemical β-hydrogen transfer mediated by the thiocarbonyl sulfur. Irradiation of powdered enantiomorphic crystals at $-45\,°C$ followed by acetylation gave three optically active products. β-Hydrogen transfer led to aziridine and oxazoline formation, in 84% *ee* and 50% *ee*, respectively. Hydrogen transfer from γ-position also took place as a minor process leading to the β-lactam in 20% *ee*. The (*p*-chloro)phenyl derivative also crystallized in the chiral space group $P2_12_12_1$, and the solid-state photolysis followed by acetylation gave very similar results.

Recently we demonstrated that the stereocontrolled photochemical phenyl migration can also occur in the solid state (Scheme 12).[19] Thioester prepared from *o*-benzoylbenzoylchloride and *o*-methylthiophenol crystallized in a chiral space group $P2_12_12_1$. The circular dichroism (CD) spectra of the two enantiomorphs in KBr were investigated. When the enantiomorphic crystals of the thioester were irradiated as white powders, an optically active phthalide was obtained in 30% *ee* at 100% conversion. Better optical purity (77% *ee*) was exhibited at low conversion (5%). The formation of phthalide could be explained in terms of arylthio- or phenyl-migration processes. The phenyl-migration mechanism was confirmed on the basis of studies correlating the absolute configurations of the product and of the achiral molecule influenced by the chiral crystal lattice.

The latest example involves the hydrogen abstraction by an alkenyl carbon atom (Scheme 13).[20] The *N,N*-dibenzyl-1-cy-

(P) -(+) - **thioester**

Space group: $P2_12_12_1$

phenyl migration

(R) -(+) - **phthalide**

77 %ee

Scheme 12. Asymmetric synthesis involving aryl migration.

Space group: $P2_1$

97 - 81 %ee

Scheme 13. Asymmetric synthesis involving hydrogen abstraction by an alkenyl carbon.

clohexenecarbothioamide crystallized in a chiral space group $P2_1$, and was irradiated at 0 °C, which led to the exclusive production of optically active β-thiolactam. 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 %. The crystal-to-crystal nature of the transformation was confirmed by X-ray diffraction spectroscopy.

The current status of organic transformations using solid-state photoreactions proceeding in chiral crystals have been

summarized. The future of this field is intimately connected with progress in the general area of organic solid-state chemistry as well as with a deeper understanding of the molecular packing modes of crystals. If crystals can be made to order, solid-state asymmetric synthesis will be extended to a variety of new systems, and this field will then be established as an important branch of organic chemistry.

[1] a) M. D. Cohen, G. M. J. Schmidt, *J. Chem. Soc.* **1964**, 1969. b) G. M. J. Schmidt, *Pure Appl. Chem.* **1971**, *27*, 647. c) B. S. Green, M. Lahav, D. Rabinovich, *Acc. Chem. Res.* **1979**, *12*, 191. d) G. Kaupp, M. Haak, *Angew. Chem.* **1993**, *105*, 727; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 694.

[2] a) L. Addadi, M. Lahav, *Origin of Optical Activity in Nature* (Ed.: D. C. Walker), Elsevier, Amsterdam, **1979**, Chapt. 14. b) S. F. Mason, *Nature (London)*, **1984**, *311*, 19.

[3] For reviews see, see a) M. Hasegawa, *Chem. Rev.* **1983**, *83*, 507. b) V. Ramamurthy, *Tetrahedron*, **1986**, *42*, 5753. c) J. R. Scheffer, M. Garcia-Garibay, O. Nalamasu, *Organic Photochemistry* (Ed.: A. Padwa), Marcel Dekker, New York and Basel, **1987**, Vol. 8, pp. 249–338. d) V. Ramamurthy, K. Venkatesan, *Chem. Rev.* **1987**, *87*, 433.

[4] V. K. Blasky, P. M. Zolkii, *Acta Crystallogr. Sect. A*, **1977**, *33A*, 1004.

[5] a) C. Pedon, E. Benedetti, *Acta Crystallogr.* **1972**, *B28*, 1970. b) J. Jacque, A. Collet, S. H. Wilen, *Enantiomers, Racemates, and Resolutions*, Kreiger, Malabar and Florida, **1991**, Chapt. 1, pp. 3–31.

[6] a) L. Addadi, M. D. Cohen, M. Lahav, *J. Chem. Soc.* Chem. Commun. **1975**, 471. b) L. Addadi, M. Lahav, *J. Am. Chem. Soc.* **1978**, *100*, 2838. c) L. Addadi, M. Lahav, *ibid.* **1979**, *101*, 2152. d) J. van Mil, L. Addadi, M. Lahav, L. Leiserovitz, *J. Chem. Soc.* Chem. Commun. **1982**, 584. e) L. Addadi, J. van Mil, M. Lahav, *J. Am. Chem. Soc.* **1982**, *104*, 3422. f) J. van Mil, L. Addadi, E. Gati, M. Lahav, *ibid.* **1982**, *104*, 3429.

[7] A. Elgavi, B. S. Green, G. M. J. Schmidt, *J. Am. Chem. Soc.* **1973**, *95*, 2058.

[8] a) M. Hasegawa, C.-M. Chung, N. Murro, Y. Maekawa, *J. Am. Chem. Soc.* **1990**, *112*, 5676. b) C.-M. Chung, M. Hasegawa, *ibid.* **1991**, *113*, 7311.

[9] T. Suzuki, T. Fukushima, Y. Yamashita, T. Miyashi, *J. Am. Chem. Soc.* **1994**, *116*, 2793.

[10] a) S. V. Evans, M. Garcia-Garibay, N. Omkaram, J. R. Scheffer, J. Trotter, F. Wireko, *J. Am. Chem. Soc.* **1986**, *108*, 5648. b) J. Chen, M. Garcia-Garibay, J. R. Scheffer, *Tetrahedron Lett.* **1989**, *30*, 6125. c) A. D. Gudmundsdottir, J. R. Scheffer, *ibid.* **1990**, *31*, 6807. d) T. Y. Fu, Z. Liu, J. R. Scheffer, J. Trotter, *J. Am. Chem. Soc.* **1993**, *115*, 12202. e) T. Y. Fu, J. R. Scheffer, J. Trotter, *Tetrahedron Lett.* **1994**, *35*, 3235.

[11] H. Aoyama, T. Hasegawa, Y. Omote, *J. Am. Chem. Soc.* **1979**, *101*, 5343.

[12] a) F. Toda, S. Soda, *J. Chem. Soc. Chem. Commun.* **1987**, 1413. b) A. Sekine, K. Hori, Y. Ohashi, M. Yagi, F. Toda, *J. Am. Chem. Soc.* **1989**, *111*, 697. c) F. Toda, H. Miyamoto, *J. Chem. Soc. Perkin Trans. 1* **1993**, 1129.

[13] F. Toda, K. Tanaka, *Supramol. Chem.* **1994**, *3*, 87.

[14] A. L. Roughton, M. Muneer, M. Demuth, *J. Am. Chem. Soc.* **1993**, *115*, 2085.

[15] a) M. Sakamoto, N. Hokari, M. Takahashi, T. Fujita, S. Watanabe, I. Iida, I. T. Nishio, *J. Am. Chem. Soc.* **1993**, *115*, 818. b) M. Sakamoto, M. Takahashi, N. Hokari, T. Fujita, S. Watanabe, *J. Org. Chem.* **1994**, *59*, 3131.

[16] M. Sakamoto, M. Takahashi, T. Fujita, S. Watanabe, I. Iida, T. Nishio, N. H. Aoyama, *J. Org. Chem.* **1993**, *58*, 3476.

[17] M. Sakamoto, M. Takahashi, T. Fujita, S. Watanabe, I. Iida, T. Nishio, *J. Org. Chem.* **1995**, *60*, 3476.

[18] M. Sakamoto, M. Takahashi, M. Shimizu, T. Fujita, T. Nishio, I. Iida, K. Yamaguchi, S. Watanabe, *J. Org. Chem.* **1995**, *60*, 7088.

[19] M. Sakamoto, M. Takahashi, S. Moriizumi, K. Yamaguchi, T. Fujita, S. Watanabe, *J. Am. Chem. Soc.* **1996**, *116*, 8138.

[20] M. Sakamoto, M. Takahashi, K. Kamiya, K. Yamaguchi, T. Fujita, S. Watanabe, *J. Am. Chem. Soc.* **1996**, *116*, 10664.