Angewandte Chemie

Asymmetric Synthesis

DOI: 10.1002/ange.200501156

Asymmetric Photocycloaddition in Solution of a Chiral Crystallized Naphthamide**

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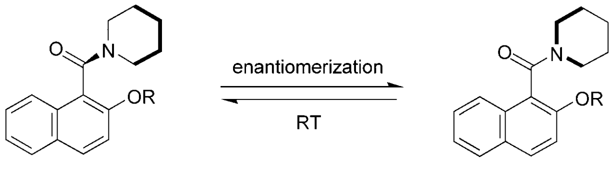
Asymmetric synthesis starting from an achiral material and in the absence of any external chiral agent has long been an intriguing challenge to chemists[1] and is also central to the origin of optical activity in Nature.[2] Stereospecific solid-state chemical reactions of chiral crystals formed by spontaneous crystallization of achiral materials are defined as “absolute” asymmetric synthesis, and most of the successful examples of such transformations involve photochemical reactions.[1,3] If the molecular chirality generated by chiral crystallization is retained even after the crystals are dissolved in a solvent, the “frozen” chirality is effectively transferred to the optically active products by various types of asymmetric reactions, besides the solid-state photochemical reaction.[4,5] Herein, we provide the first example of an asymmetric intermolecular photochemical reaction in solution through transfer of the chirality generated by chiral crystallization of an achiral naphthamide.

2-Alkoxy-1-naphthamides **1** were chosen to perform this asymmetric synthesis because the bond rotation between the naphthalene ring and the C=O(NR^{1}R^2) group corresponds to enantiomerization of **1**, and the rate is considerably affected by the substituents on both the naphthalene ring and the amide group (Scheme 1).[6] Naphthamides comprising a bulky



1a: R = CH_3
1b: R = C_2H_5

Scheme 1. Enantiomerization of naphthamides **1a**, **b** upon rotation about the naphthalene–C(=O) bond.

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[**] This work was supported by a Grant-in-Aid for Scientific Research on Priority Area 417 from the Ministry of Education, Culture, Sports, Science, and Technology (MEXT) of the Japanese Government.

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group such as *N,N*-diisopropylamide have stable axial chirality, which is used to advantage in many asymmetric synthesis methods.[7] Therefore, achiral naphthamides **1a** and **1b** that contain a relatively compact amide group derived from piperidine were prepared. X-ray crystallographic analysis of single crystals of **1a** and **1b** revealed that both amides adopt similar molecular conformations and, remarkably, that the carbonyl group in each is twisted such that it lies almost orthogonal to the naphthalene plane.

It was important that the achiral materials crystallized to yield chiral precursors for the proposed asymmetric synthesis. Fortunately, **1a** crystallized in a chiral space group, $P2_12_12_1$, and the constituent molecules adopted a chiral and helical conformation in the crystal lattice. On the other hand, ethoxy derivative **1b** formed a racemic crystalline system, $P2_1/c$.[8]

Recrystallization of **1a** from a mixed solvent system of hexane/chloroform gave colorless cubic crystals. X-ray analysis revealed that each single crystal was chiral and composed of one enantiomer. Circular dichroism (CD) spectra were measured to ascertain whether the chiral conformation was retained after the crystals were dissolved in an organic solvent. When a single crystal selected randomly was dissolved in THF at 5 °C using a cryostat apparatus, a strong Cotton effect was observed at below $\lambda = 350$ nm (Figure 1).

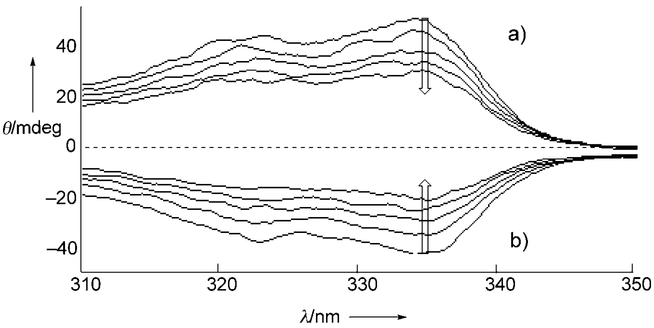


Figure 1. CD spectra of enantiomorphic crystals of **1a** in THF recorded at 5 °C using a cryostat apparatus: a) CD spectra of a solution of crystal (+)-**1a** measured every 10 minutes; b) CD spectra of a solution of a crystal (−)-**1a** measured every 12 minutes.

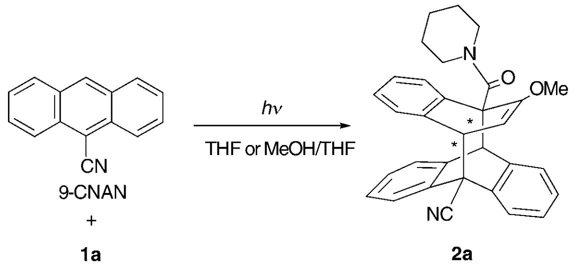
As expected, crystals of both enantiomers, which showed mirror-image CD curves, were easily obtained by crystallization from the solvent. One showed a positive Cotton effect (Figure 1 a), and the other showed a negative Cotton effect at the same wavelengths (Figure 1 b). Furthermore, the Cotton effect gradually decreased with racemization as a result of the rotation about the naphthalene–C(=O) bond.

To study how long naphthamide **1a** retained its molecular chirality after dissolving the crystals in a solvent, we measured the rate of racemization according to the changes in the CD spectra and calculated both the Gibbs free energy of activation ($\Delta G^{\neq}$) and the half-life of enantiomerization ($t_{1/2}$). The half-life was 11.8 minutes when the crystals were dissolved in THF at 15 °C, and the value increased upon lowering the temperature; $t_{1/2}$ values of 19.4 and 36.7 min were determined at 10 °C and 5 °C, respectively (Table 1). The free energy of activation was calculated as $\Delta G^{\neq} = 21.1–21.2$ kcal mol^{-1} from the temperature dependence of the kinetic constant, k (5 °C: $k = 4.90 \times 10^{-4}$; 10 °C: $k = 2.98 \times 10^{-4}$; 15 °C: $k = 1.58 \times 10^{-4}$). The rate of enantiomerization slowed considerably in a mixed solvent system of MeOH/THF. The half-life was 128.3 min at 15 °C and 21.2 min at 25 °C. In MeOH, naphthamide **1a** freezes its molecular conformation and maintains the molecular chirality derived from the crystal over a long period as result of the hydrogen-bonding interaction between the carbonyl group and methanol and also through the rather strong zwitterionic character of the amide group in a polar solvent. These facts indicate that achiral amide **1a** can retain the axial chirality induced in the crystal lattice after the crystallinity is lost and that the lifetime is long enough for application of **1a** in asymmetric synthesis.

Table 1: Kinetic parameters for enantiomerization of naphthamide **1a**.

Solvent	T [°C]	$t_{1/2}$ [min]	$\Delta G^{\neq}$ [kcal mol^{-1}]	$\Delta H^{\neq}$ [kcal mol^{-1}]	$\Delta S^{\neq}$ [cal mol^{-1} K^{-1}]
THF	5	36.7	21.08	17.53	−12.77
	10	19.4	21.11	17.52	−12.69
	15	11.8	21.21	17.51	−12.84
MeOH/	15	128.3	22.58	30.13	26.19
THF	20	62.6	22.46	30.12	26.11
(1:1)	25	21.2	22.32	30.11	26.13

To the best of our knowledge, there are no examples of photocycloaddition reactions of naphthamides with anthracene derivatives, [9,10] so the photocycloaddition of **1a** with 9-cyanoanthracene (9-CNAN) was first examined at room temperature. When a solution of naphthamide **1a** and 9-CNAN (0.05 M each) in THF was irradiated with a high-pressure mercury lamp under argon at room temperature, photocycloaddition occurred effectively and the [4+4] cycloadduct **2a** was obtained in quantitative yield (Scheme 2). The structure of the adduct **2a** was unequivocally established by X-ray crystallographic analysis.[11]



Scheme 2. Photochemical cycloaddition reaction of **1a** in the presence of 9-cyanoanthracene (9-CNAN).

Next, we attempted the asymmetric photocycloaddition using the frozen chirality. A number of chiral crystals of (+)-**1a** were dissolved in a cooled solution of 9-CNAN in THF (−20 °C), and the solution was irradiated with an ultrahigh-pressure mercury lamp for 30 minutes. Only one cycloadduct, (+)-**2a**, was obtained in 100 % yield with 95 % *ee* (Table 2,

Table 2: Asymmetric photochemical cycloaddition reaction of (+)-**1a** with 9-cyanoanthracene (9-CNAN) using the frozen axial chirality.

Entry	Solvent	T [°C][a]	Conc. [M][b]	Conv. [%][c]	*ee* of (+)-**2a** [%][d]
1	THF	−20	0.05	52	95
2	THF	20	0.05	45	29
3	MeOH/THF[e]	−20	0.025	54	94
4	MeOH/THF[e]	20	0.025	40	88

[a] A solution of 9-CNAN was cooled to the cited temperature, and then powdered chiral crystals of (+)-**1a** were added. [b] Concentration of both **1a** and 9-cyanoanthracene. [c] Determined on the basis of the amount of **1a**. [d] *ee* value was determined by HPLC using a CHIRALCEL-ADH column. [e] A 1:1 mixture of MeOH/THF was used.

entry 1). When a mixed solvent system of MeOH and THF was used, a similar enantioselectivity was obtained (94% *ee*; entry 3). Even at 20 °C, at which temperature the enantiomerization of **1a** occurs competitively with the photocycloaddition, the adduct from the reaction in THF was obtained with 29% *ee* (entry 2). The rate of enantiomerization is suppressed in MeOH/THF ($t_{1/2} = 62.6$ min at 20 °C; Table 1) relative to pure THF, and, surprisingly, the cycloaddition product from the mixed solvent system was obtained with 88% *ee* at 20 °C (Table 2, entry 4).

As the rate of racemization of naphthamide **1a** is slow, a high enantiomeric excess of the bulk crystals could not be obtained by recrystallization from a mixed solvent of hexane/chloroform. Therefore, crystals of **1a** used for the asymmetric photoreaction were prepared by stirred crystallization at high temperature,[12] by which the completely melted sample of **1a** at 120 °C (m.p.: 110–112 °C) was cooled and solidified by lowering the temperature to 100 °C with stirring. Five independent crystallization experiments followed by photocycloaddition reactions with 9-CNAN were performed, and the photoadduct **2a** was obtained with enantioselectivities of 92, 97, 96, 94, and 97% *ee*. A high level of reproducibility of both chiral crystallization and asymmetric photoreaction was achieved by this method.

In many cases, the initially generated enantiomorphic crystal works in situ as a seed in the crystallization step such that all the subsequent crystals in the batch have the same absolute configuration.[12] The use of crystals generated in this fashion in the photocycloaddition reaction can lead to isolation of either of the enantiomers of the cycloadduct. For instance, from three independent experiments, (+)-**2a** was obtained on one occasion while (−)-**2a** was afforded in the other two reactions. Of course, the desired crystals of **1a** could be selectively prepared in large quantities by the addition of a corresponding seed crystal during the crystallization process.[13]

In conclusion, we have demonstrated asymmetric intermolecular photocycloadditions with high enantiomeric excess using the "frozen chirality" generated by spontaneous crystallization. The crystallization of achiral molecules in chiral space groups, while rare and unpredictable, is well documented.[1] Extension of spontaneous chiral crystallization to a variety of new systems is possible, and we believe that this methodology can be applied to the development of new absolute asymmetric syntheses.

Received: April 1, 2005
Revised: May 16, 2005

Keywords: asymmetric synthesis · chirality · cycloaddition · enantioselectivity · photochemistry

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[8] Crystal data for **1a**: Orthorhombic, space group $P2_12_12_1$, $a = 7.963(3)$ Å, $b = 11.713(3)$ Å, $c = 15.708(4)$ Å, $V = 1465.2(8)$ Å^3, $Z = 4$, $\rho = 1.221$ Mg m^{-3}; in the final least-squares refinement cycles on F^2, the model converged at $R_1 = 0.0499$, $wR_2 = 0.1316$, and GOF = 1.125 for 1611 reflections. Crystal data for **1b**: Monoclinic, space group $P2_1/n$, $a = 9.762(4)$ Å, $b = 12.702(4)$ Å, $c = 12.534(5)$ Å, $\beta = 99.84(3)$, $V = 1531.3(10)$ Å^3, $Z = 4$, $\rho = 1.229$ Mg m^{-3}; in the final least-squares refinement cycles on F^2, the model converged at $R_1 = 0.0683$, $wR_2 = 0.2369$, and GOF = 1.149 for 2903 reflections.

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[11] Crystal data for **2a**: Monoclinic, space group $P2_1/c$, $a = 20.198(6)$ Å, $b = 9.073(3)$ Å, $c = 16.056(4)$ Å, $\beta = 96.08(2)$, $V = 2925.7(16)$ Å^3, $Z = 4$, $\rho = 1.237$ Mg m^{-3}; in the final least-squares refinement cycles on F^2, the model converged at $R_1 = 0.0894$, $wR_2 = 0.2242$, and GOF = 1.149 for 2903 reflections. CCDC 267437 (**1a**), 267438 (**1b**), and 267439 (**2a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[13] Seeding was carried out as follows: the melted sample of **1a** at 120 °C was gradually cooled, and a powdered single crystal (about 0.5 mm size) was added at below the melting point of 110–112 °C. The presence of the seed crystal induces the same conformation in the subsequent crystallization such that all the crystals in the batch have the same optical rotation.