Diastereoselective photocycloaddition using memory effect of molecular chirality controlled by crystallization†

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Naphthamides derived from L-proline, which exist as a mixture of several diastereomers in solution, converged to single diastereomer by crystallization, and the conformational transformation was controlled after the crystals were dissolved in the solvent at low temperature, where the frozen conformation was retained long enough for subsequent asymmetric reaction.

Recently we have reported a new methodology of asymmetric synthesis under homogeneous conditions by using a frozen molecular conformation derived from spontaneous crystallization of achiral materials.[1,2] We have now investigated a wide application of this methodology to diastereoselective reactions.

Two stereogenic units in one molecule lead to diastereoisomerism, and a valuable method of getting one pure diastereomer is achieved when these units can be epimerized during crystallization.[3,4] We explored the idea and undertook the separation of diastereomers of naphthamides possessing a chiral center and axial chirality by crystallization. Furthermore, a highly controlled stereoselective reaction was also performed using the frozen molecular conformation after dissolving the crystals at low temperature.

2-Alkoxy-1-naphthamides, **1a,b**, possessing proline methyl ester as the chiral handle were chosen to perform this reaction (Fig. 1). These amides were easily prepared from L-proline methyl ester and 2-alkoxy-1-naphthoyl chloride. The ^{1}H NMR spectrum showed that **1a** existed as a mixture of three diastereomers owing to the bond rotation between naphthalene and carbonyl and the *E*,*Z*-isomerization of the amide group at room temperature as shown in Fig. 1 and Fig. 2(a). The amide **1b** also existed as a mixture of diastereomers. The energy barrier for the bond rotation was low; therefore, diastereomers were not separable.

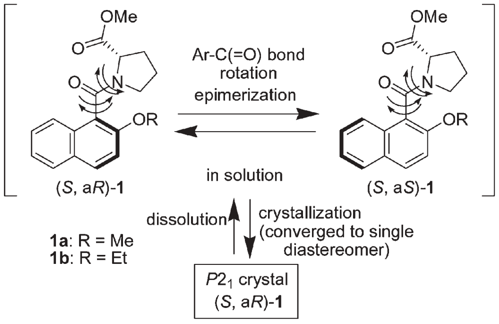

Fig. 1 Epimerization in solution of the amides **1** and convergence by crystallization.

When the naphthamides were recrystallized from a mixed solvent of $CHCl_3$–hexane they gave single crystals. These were subjected to X-ray crystallographic analysis, and the crystal structure and molecular conformation were revealed on the basis of the configuration of the (*S*)-proline group. By the effect of a chiral proline group, amides **1a** and **1b** clearly crystallized in a chiral space group $P2_1$ and formed the (*S*,*aR*)-conformation in the crystals.[5]

Next, we studied whether the chiral molecular conformation in the crystals can be retained in solution after the single crystals were dissolved in a solvent. The ^{1}H NMR spectrum of amide **1a** immediately after dissolving the crystals into $CDCl_3$ at room temperature clearly showed that the crystals were composed of a single diastereomer as shown in Fig. 2(b). The diastereotopic signals derived from several diastereomers gradually formed and increased with time. Finally, the same spectrum before crystallization was obtained. The same phenomena were observed in the case of **1b**.

The convergence of diastereomers to a single isomer by crystallization was also performed by stirred crystallization at high temperature,[3] by which the completely melted sample of **1a** in the absence of solvent at 120 °C (mp 109–110 °C) was cooled and solidified by lowering the temperature to 100 °C with stirring. In the case of **1b** (mp 133–135 °C), the solid was melted over 140 °C at once, then solidified at 120 °C with stirring. The bulk crystals obtained from the melt were also composed of a single diastereomer and showed the same behavior for NMR measurement as in the case of the single crystals described above.

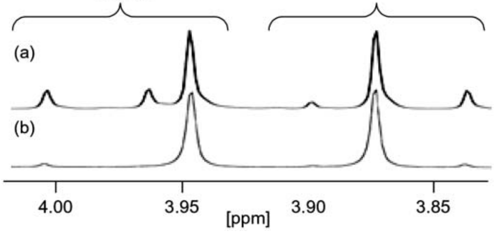

Fig. 2 ^{1}H NMR spectra of **1a** in $CDCl_3$. (a) Before crystallization; (b) measured immediately after dissolving the crystals in $CDCl_3$ at room temperature.

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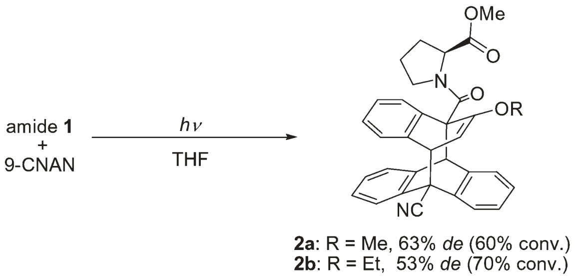
Then the crystals were used for subsequent diastereoselective reactions.

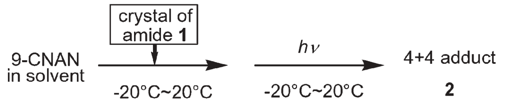
Photocycloaddition reaction of amides **1a,b** with 9-cyanoanthracene was examined. An argon-purged THF solution containing 0.05 M of amide **1a** and 0.05 M 9-cyanoanthracene (9-CNAN), which was prepared at room temperature, was irradiated with a high-pressure mercury lamp for 30 min at −20 °C.[1,6] The photocycloaddition reaction occurred effectively and 4 + 4 cycloadduct **2a** was obtained in 100% chemical yield where the diastereomeric excess (de) of **2a** was 63% (Scheme 1 and Table 1, entry 1). When **1b** was irradiated under the same conditions, 53% de of **2b** was isolated in 100% chemical yield (Table 1, entry 6). Since the epimerization did not occur at −20 °C, it seems that the de value of the photoproducts should be attributed to the ratio of diastereomers in solution.

To study the energy barriers of the conformational transformation owing to the axial chirality, we measured the changes in ^{1}H NMR and calculated both the activation free energy ($\Delta G^{\neq}$) and the half-life of epimerization ($t_{1/2}$). The half-life of **1a** was 11.0 min when the crystals were dissolved in CD_3OD–$CDCl_3$ (1 : 1) at 30 °C, and the value increased upon lowering the temperature; $t_{1/2}$ values of 18.0 and 32.3 min were determined at 25 and 20 °C. The free energy of activation was calculated as $\Delta G^{\neq}$ = 22.2–22.3 kcal mol^{-1} from the temperature dependence of the kinetic constant.[7,8] The activation free energy for epimerization of **1b** was slightly larger than that of **1a**, because of an increase of the steric factor by the change from the methoxy to an ethoxy group. The half-life of **1b** in CD_3OD–$CDCl_3$ (1 : 1) was 40.3, 25.2 and 16.6 min at 30, 35 and 40 °C. These facts indicate that both amides **1a** and **1b** can retain the molecular conformation long enough for a subsequent stereoselective reaction after dissolving the crystals in the solvent.



Scheme 1 Photocycloaddition reaction of amide **1a** with 9-CNAN.

Table 1 Photocycloaddition reaction of amides **1a,b** with 9-CNAN using the frozen molecular conformation



Entry[a]	Amide	Temp./°C	Solv.	Conv. (%) of **1**[d]	de (%) of **2**[e]
1[b]	**1a**	−20	THF	60	63
2		−20	THF	62	96
3		20	THF	56	78
4		−20	MeOH[c]	50	100
5		20	MeOH[c]	58	84
6[b]	**1b**	−20	THF	70	53
7		−20	THF	70	100
8		20	THF	71	75
9		−20	MeOH[c]	49	100
10		20	MeOH[c]	61	90

[a] A 0.05 M solution of 9-cyanoanthracene was cooled to the stated temperature, and then powdered crystals of **1** (1.0 eq.) were added. [b] Naphthamides **1** before crystallization were used. [c] A 1 : 1 mixture of MeOH–THF was used. [d] Determined on the basis of the consumed amount of the amide **1**. [e] De value was determined by ^{1}H NMR spectroscopy.

Next, we tried a diastereoselective photocycloaddition reaction using the molecular conformation converged by crystallization. The crystals were composed of a single diastereomer of (*S*,*aR*)-conformation, and the epimerization in solution caused by the bond rotation between naphthalene and the carbonyl group can be highly controlled by the temperature. In other words, the conformation in the crystals may be retained as frozen after dissolving the crystals in the solvent at low temperature, and the molecular chirality can be effectively transferred to the products. Crystals of **1a** (1.0 eq.) were dissolved in a cooled 0.05 M solution containing 9-cyanoanthracene, and was irradiated with a high-pressure mercury lamp for 30 min. When the reaction was performed at −20 °C using THF as a solvent (Table 1, entry 2), 100% yield of the 4 + 4 adduct **2a** was obtained. As expected, epimerization was strongly controlled at this temperature, and a high de of 96% was achieved. Surprisingly, the reaction in a 1 : 1 mixed solvent of MeOH–THF gave 100% de (entry 4), because the energy barrier for epimerization in a protic solvent is greater than that in an aprotic solvent, which is explainable by the effect of the hydrogen bond between the carbonyl oxygen and methanol.[3] Even at 20 °C, high de values were still obtained (entries 3 and 5). When the photoreaction was carried out using crystals of **1b**, photoadduct **2b** was obtained in 100% de in both THF and MeOH–THF at −20 °C (entries 7, 9). The diastereoselectivity slightly decreased to 75% de (in THF) and 90% de (in MeOH–THF) in the reaction at 20 °C (entries 8 and 10), because competitive epimerization occurred at this temperature.

Though the 4 + 4 adduct **2a** did not afford single crystals for X-ray crystallographic analysis, the crystal structure of the photoadduct **2b** could be analyzed, and the absolute configuration was determined on the basis of the configuration of the (*S*)-proline group.[5] By comparing the absolute structure of both **1b** and **2b**, the reaction course became clear in that the excited 9-cyanoanthracene approached naphthamide **1** from the side of the carbonyl group to avoid the bulky proline group.

In conclusion, naphthamides **1** derived from L-proline methyl ester, which exists as a mixture of several diastereomers in solution, converged to a single diastereomer by crystallization with epimerization. The epimerization was controlled after the crystals were dissolved in solvent at low temperature, and the frozen conformation was retained long enough for a subsequent chemical reaction. The axial chirality evoked by crystallization directed the course of approach of the reacting molecules, and a fully controlled diastereoselective intermolecular photocycloaddition reaction was performed.[9] This reaction provides a new methodology for highly controlled stereoselective reaction using the property of a process of crystallization and the memory effect of molecular chirality.

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Notes and references

1 M. Sakamoto, A. Unosawa, S. Kobaru, A. Saito, T. Mino and T. Fujita, *Angew. Chem., Int. Ed.*, 2005, **44**, 5523–5526.

2 M. Sakamoto, T. Iwamoto, N. Nono, M. Ando, W. Arai, T. Mino and T. Fujita, *J. Org. Chem.*, 2003, **68**, 942–946; M. Sakamoto, S. Kobaru, T. Mino and T. Fujita, *Chem. Commun.*, 2004, 1002–1003.

3 J. Jacques, A. Collet and S. H. Wilen, in *Enantiomers, Racemates, and Resolutions*, Krieger Publishing, Malabar, FL, 1994, 369–377; H. Nohira and K. Sakai, in *Enantiomer Separation*, ed. F. Toda, Kluwer Academic Publishers, Netherlands, 2004, pp. 165–191; K. M. J. Brands and A. J. Davies, *Chem. Rev.*, 2006, **106**, 2711–2733.

4 R. E. Pincock, R. R. Perkins, A. S. Ma and K. R. Wilson, *Science*, 1971, **174**, 1018–1020; D. K. Kondepudi, J. Laudadio and K. Asakura, *J. Am. Chem. Soc.*, 1999, **121**, 1448–1449; M. Sakamoto, T. Utsumi, M. Ando, M. Saeki, T. Mino, T. Fujita, A. Katoh, T. Nishio and C. Kashima, *Angew. Chem., Int. Ed.*, 2003, **42**, 4360–4363.

5 *Crystal data*: for (*S*,*aR*)-**1a** (recrystallized from $CHCl_3$–hexane): monoclinic, space group $P2_1$, a = 11.0267(17), b = 6.9804(11), c = 11.2114(17) Å, β = 116.392(2)°, V = 773.0(2) Å^3, Z = 2, D_c = 1.346 Mg m^{-3}; in the final least-square refinement cycles on F^2, the model converged to R_1 = 0.0352, wR_2 = 0.0884 for 4315 reflections, CCDC 630580. *Crystal data* for (*S*,*aR*)-**1b** (recrystallized from $CHCl_3$–hexane): monoclinic, space group $P2_1$, a = 7.6617(7), b = 12.7932(12), c = 9.0838(8) Å, β = 99.4840(10)°, V = 878.20(14) Å^3, Z = 2, D_c = 1.238 Mg m^{-3}; in the final least-square refinement cycles on F^2, the model converged to R_1 = 0.0462, wR_2 = 0.0834 for 3567 reflections, CCDC 630581. *Crystal data* for **2b** (recrystallized from $CHCl_3$–hexane): orthorhombic, space group $P2_12_12_1$, a = 10.1985(5), b = 12.5024(6), c = 21.8216(10) Å, V = 2782.4(2) Å^3, Z = 4, D_c = 1.267 Mg m^{-3}; in the final least-square refinement cycles on F^2, the model converged to R_1 = 0.0443, wR_2 = 0.1204 for 6395 reflections, CCDC 630582. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b617888j.

6 Photochemical cycloaddition of 9-cyanoanthracene and naphthalene has been reported: A. Albini, E. Fasani and D. Faiardi, *J. Org. Chem.*, 1987, **52**, 155–157.

7 We reported the rate of enantiomerization of axially chiral 1-naphthamide, which was suppressed in a protic solvent rather than an aprotic solvent, and was explainable in terms of hydrogen bonding, see ref. 1.

8 A. Ahmed, R. A. Bragg, J. Clayden, L. W. Lai, C. McCarthy, J. H. Pink, N. Westlund and S. A. Yasin, *Tetrahedron*, 1998, **54**, 13277–13294.

9 For recent reviews for stereoselective photoreactions, see: S. S. L. Everritt and Y. Inoue, in *Organic Molecular Photochemistry*, ed. V. Ramamurthy, K. S. Schanze, Marcel Dekker, New York, 1999, vol. 3, pp. 71–130; Y. Inoue, in *Chiral Photochemistry*, ed. Y. Inoue and V. Ramamurthy, Marcel Dekker, New York, 2004, pp. 129–177; N. Hoffmann and J.-P. Pete, in *Chiral Photochemistry*, ed. Y. Inoue and V. Ramamurthy, Marcel Dekker, New York, 2004, pp. 179–233; B. L. Feringa and R. Van Delden, *Angew. Chem., Int. Ed.*, 1999, **38**, 3419–3438; M. Sakamoto, in *Chiral Photochemistry*, ed. Y. Inoue and V. Ramamurthy, Marcel Dekker, New York, 2004, pp. 415–461; A. G. Griesbeck and U. J. Meierhenrich, *Angew. Chem., Int. Ed.*, 2002, **41**, 3147–3154.