An asymmetric $S_\mathrm{N}Ar$ reaction using the molecular chirality in a crystal†

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An asymmetric $S_\mathrm{N}Ar$ reaction was performed by using molecular chirality generated and amplified by the spontaneous crystallization of achiral naphthamides; the chirality was retained in a cold solution, caused by slow racemization, and was transferred to stable axially chiral materials with high enantiomeric excesses.

Asymmetric generation influenced by a chiral crystalline environment is considered an attractive methodology for obtaining optically active compounds from achiral compounds.[1,2] In recent years, solid-state reactions using chiral crystals in a variety of new systems has progressed to such an extent that it can now be regarded as an important branch of organic chemistry.[3] Furthermore, recently, a new methodology using molecular chirality in a crystal as a source of chiral memory in solution was explored (Fig. 1). The chirality can be effectively transferred to optically active products by asymmetric reactions involving nucleophilic carbonyl addition[4] and intermolecular photochemical[5,6] reactions. Asymmetric synthesis becomes possible with two requirements; one is spontaneous crystallization of achiral materials and the other is slow racemization at a controlled temperature. We have now found that the apparent molecular chirality in a crystal could be fixed by an $S_\mathrm{N}Ar$ reaction, leading to stable axial chirality with a high enantiomeric excess. This reaction provides the first example of an asymmetric $S_\mathrm{N}Ar$ reaction using chirality generated by the spontaneous crystallization of achiral materials.

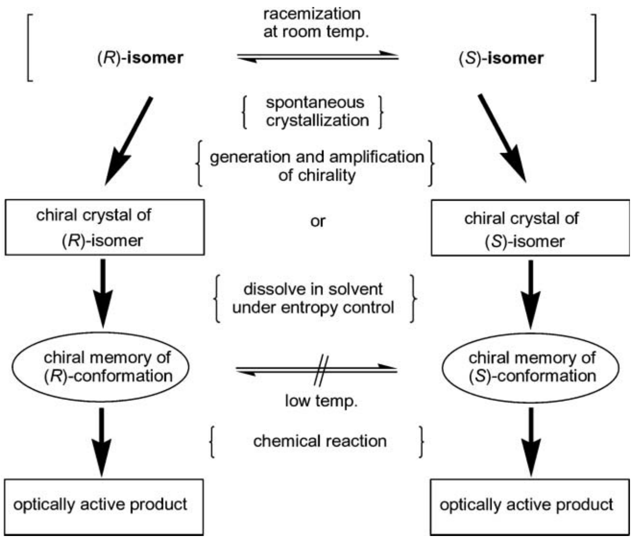

Fig. 1 Chiral crystallization and asymmetric synthesis using chiral memory.

Previously, we reported that achiral naphthamide **1b**, prepared from 2-methoxy-1-naphthalenecarboxylic acid and piperidine, crystallized in a chiral space group, $P2_12_12_1$ (Fig. 2).[5] We also found that **1a** crystallized in a chiral fashion in space group $P2_12_12_1$, and X-ray crystallographic analyses of the crystals revealed that both amides **1a** and **1b** have almost the same molecular conformation; remarkably, each carbonyl group twists almost orthogonally to the naphthalene plane.[7]

The rate of racemization was measured according to changes in the circular dichroism (CD) spectra using a cryostat apparatus, and the activation free energy ($\Delta G^\ddagger$) and half-life ($t_{1/2}$) were calculated. When the crystals of **1a** were dissolved in THF at 15 °C, the $t_{1/2}$ of enantiomerization was 973 s. The $t_{1/2}$ increased as the temperature was lowered; $t_{1/2}$ was 1546 and 2445 s at temperatures of 10 and 5 °C, respectively. $\Delta G^\ddagger$ was calculated as a temperature dependence of the kinetic rate constant (5 °C: 1.42×10^{-4} s^{-1}, 10 °C: 2.24×10^{-4} s^{-1}, 15 °C: 3.56×10^{-4} s^{-1}) to be 21.2 ± 0.2 kcal mol^{-1}. In the case of **1b**, derived from piperidine, the racemization showed a slightly lower activation free energy and exhibited a $t_{1/2}$ of 707 s at 15 °C.[5] These facts indicate that the racemization of both amides **1a** and **1b** is too fast to be resolved in the usual manner; however, it can be controlled by lowering the temperature, and the lifetime becomes long enough for utilization in asymmetric synthesis.

Next, we tried to lock the bond rotation that affects the racemization of amides **1** by an $S_\mathrm{N}Ar$ reaction.[8] The racemization should be suppressed by substitution of the methoxy group at the 2-position of the naphthalene ring with a more bulky group. Chiral crystals of **1a** were added to a toluene solution containing 3.0 equiv. of *n*-BuLi at −80 °C. After the reaction mixture had been stirred for 1 h at the same temperature, a saturated aqueous solution of ammonium chloride was added to quench the reaction, and the organic layer was washed with brine and dried over

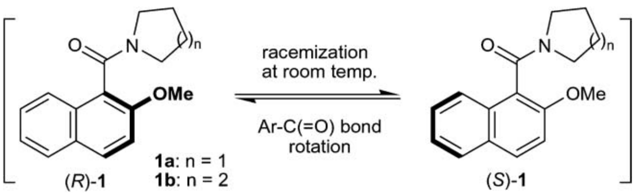

Fig. 2 Racemization of 2-methoxy-1-naphthamides.

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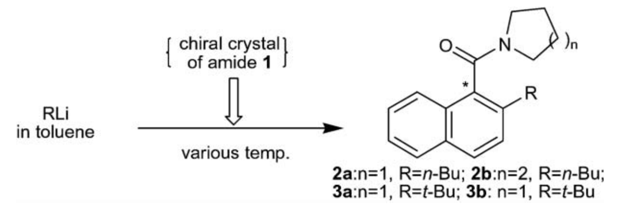
Table 1 S_NAr reaction of amides **1a** and **1b** with *n*-BuLi and *t*-BuLi[a]



2a:n=1, R=*n*-Bu; **2b**:n=2, R=*n*-Bu; **3a**:n=1, R=*t*-Bu; **3b**: n=1, R=*t*-Bu

Entry	Amide	RLi	Temperature/ °C	Conversion (%)	Yield of **2** or **3** (%)	ee of **2** or **3** (%)[b]
1	**1a**	*n*-BuLi	−80	32	28[c]	36[e]
2	**1b**	*n*-BuLi	−80	35	65[c]	0[e]
3	**1a**	*t*-BuLi	20	92	43[d]	43[f]
4	**1a**	*t*-BuLi	0	92	68[d]	58[f]
5	**1a**	*t*-BuLi	−40	92	71[d]	81[f]
6	**1a**	*t*-BuLi	−80	94	72[d]	85[f]
7	**1b**	*t*-BuLi	20	97	52[d]	12[f]
8	**1b**	*t*-BuLi	0	82	87[d]	31[f]
9	**1b**	*t*-BuLi	−40	99	98[d]	79[f]
10	**1b**	*t*-BuLi	−80	85	97[d]	85[f]

[a] Powdered crystals of **1** (0.5 mmol) were added to a cooled toluene solution (5.0 mL) containing butyllithium (1.5 mmol), and the reaction mixture was stirred for 1 h at the same temperature under an argon atmosphere. [b] The ee was determined by HPLC using a CHIRALCEL-IA column. [c] Isolated yield of **2**. [d] Isolated yield of **3**. [e] ee of **2**. [f] ee of **3**.

magnesium sulfate. The organic solvent was removed *in vacuo* and the residual mixture was subjected to chromatography on silica gel. Analysis of the reaction product showed the formation of 2-*n*-butyl derivatives **2a** and **2b**, as shown in Table 1, entries 1–2. The S_NAr product **2a** was obtained in an optically active form with 36% ee; on the other hand, in the case of the reaction of **1b**, racemic **2b** was isolated. Furthermore, it was observed that the ee value of **2a** decreased gradually as time passed. Even if an optically active product was yielded, these results show that racemization had occurred in the work-up process.

The *n*-butyl group was not bulky enough to lock the bond rotation along Ar–C(=O). Therefore, a reaction with *t*-BuLi was tried. A toluene solution containing 3.0 equiv. of *t*-BuLi was cooled to −80 °C and was followed by the addition of chiral crystals of **1a**. After reaction for 1 h at the same temperature, the mixture was treated in the same way as the reaction with *n*-BuLi. Analysis of the reaction product showed the formation of 2-*tert*-butyl derivatives **3a** in 72% yield and in an optically active form with 85% ee (Table 1, entry 6). With rises in temperature, ee values decreased (Table 1, entries 4–6); however, even at 20 °C, a 43% ee of the product was obtained (Table 1, entry 3). When chiral crystals of **1b** were used for the S_NAr reaction, similar results were obtained. The reaction at 20 °C gave a 12% ee of product **3b** (Table 1, entry 7), and a high ee product (85%) was obtained in a reaction at −80 °C (Table 1, entry 10). When crystals of (+)-**1a**/**1b** were used for the S_NAr reaction, (+)-**2** and (+)-**3** were obtained; however, their absolute configurations could not be determined.

The rate of racemization of all amides **2a**/**2b** and **3a**/**3b** were measured on the basis of changes to their $[\alpha]_D$ value in *n*-nonane, and their $\Delta G^\ddagger$ and $t_{1/2}$ were calculated (Table 2). The $t_{1/2}$ of racemization of **2a** was about 5585 s (93.1 min) at 40 °C; however, that of **2b** was rather shorter than that of **2a**, and was 1057 s (17.6 min) at 40 °C.[9] These results clearly show the reason why the ee values of **2a** and **2b** were low (Table 1, entries 1 and 2). On the other hand, both amides **3a** and **3b** have stable axial chirality and did not racemize at room temperature for several months. The $t_{1/2}$ of **3a** racemization was about 11184 s (186 min) at 100 °C, and that of **3b** was 3182 s (53.0 min).

Table 2 Kinetic parameters for the racemization of amides **2** and **3** in *n*-nonane[a]

Amide	Temperature/ °C	$t_{1/2}$/s	$\Delta G^\ddagger$/ kcal mol^{-1}	$\Delta H^\ddagger$/ kcal mol^{-1}	$\Delta S^\ddagger$/cal mol^{-1} K^{-1}
2a	40	5585	24.39	21.72	−8.53
2b	40	1057	23.35	20.01	−10.69
3a	100	11184	29.71	28.91	−2.13
3b	100	3182	28.78	24.34	−11.90

[a] The Arrhenius parameters (*E* values) were 22.34, 20.63, 29.65 and 25.08 kcal mol^{-1} for **2a**, **2b**, **3a** and **3b**, respectively.

Bulk crystals of naphthamides **1a** and **1b** used for the asymmetric reaction were prepared by stirred crystallization from the melt.[10] The samples melted completely at 120 °C, well over their melting points (mp: **1a**, 103–105 °C; **1b**, 110–112 °C), and were cooled and solidified by lowering the temperature with stirring to 95 °C for **1a** and 100 °C for **1b**. In five crystallization experiments of **1a** followed by an S_NAr reaction, product **3a** showed optical activities of 90, 85, 84, 89 and 85% ee, respectively. High reproducibility of both chiral crystallization and asymmetric reaction were achieved by this method; however, the direction of the optical rotation of the photoproduct was inconsistent and appeared random. This is because the first-generated enantiomorphic crystal acts as a seed in the crystallization step, and all the crystals in the batch turn out with the same absolute configuration; three experiments yielded (−)-**3a** and two gave (+)-**3a**. As a matter of course, a large quantity of the desired crystals can be prepared by seeding the desired crystal through crystallization.

In conclusion, we have provided an example of the generation of chirality by the spontaneous crystallization and hitherto unknown absolute asymmetric synthesis of axially chiral compounds by locking the apparent molecular chiral conformation *via* an S_NAr reaction.

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