Chiral Resolution

Breaking the Symmetry of Axially Chiral *N*-Aryl-2(1*H*)-pyrimidinones by Spontaneous Crystallization**

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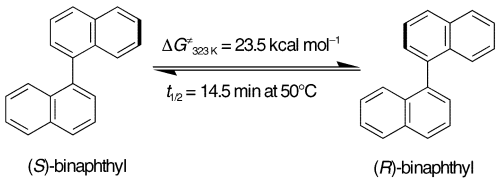
The atropisomerism of biaryl molecules has been studied extensively from both theoretical and synthetic perspectives.[1] When rotation about the pivotal 1,1′-bond is slowed, these molecules can be resolved as optically active enantiomers. Many axially chiral biaryls such as BINAP (1,1′-binaphthalene-2,2′-diyl)bisdiphenylphosphane) or BINOL (2,2′-dihydroxy-1,1′-biphenyl) serve as ligands in transition-metal complexes used in catalytic asymmetric synthesis.[2,3]

In 1971 Pincock et al. discovered that racemic binaphthyl undergoes spontaneous resolution to generate the optically active *R* or *S* enantiomer when crystallized from the melt.[4] The racemization kinetics of optically active 1,1′-binaphthyl was studied by Cooke and Harris,[5] who found that its racemization half-life is 14.5 min at 50 °C ($\Delta G^{\ddagger} = 23.5$ kcal mol^{-1}, Scheme 1). Furthermore, Kondepudi et al. have reported that each enantiomer of binaphthyl can be resolved with higher enantiomeric purity by stirred crystallization.[6] This is a unique example of asymmetric disequilibration of atropisomers by crystallization, and no other examples have been reported in the past three decades.



Scheme 1. Racemization of 1,1′-binaphthyl.

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Now we have found that the chiral pyrimidinones with C–N axial chirality can be resolved by crystallization without any outside chiral source. Absolute asymmetric transformations 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.[7,8] To resolve the racemate, axially chiral materials must crystallize as conglomerates, in other words, in a chiral space group.[9] Four pyrimidin-2(1*H*)-ones (**1a–d**, Figure 1) were synthesized which have a variety of aryl groups with substituents at the *ortho* and/or other positions.[10,11]

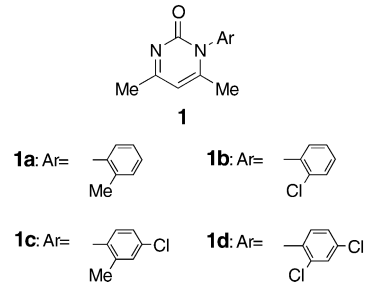
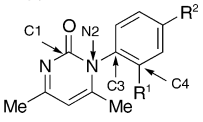


Figure 1. Pyrimidin-2(1*H*)-ones examined in this work.

To determine whether each pyrimidinone affords conglomerate or racemic crystals, each single crystal was analyzed by HPLC employing Chiral Cell OJ and OD columns (Daicel Chemical Industry). In the HPLC analysis of single crystals of pyrimidinone **1b** two peaks arise from the two enantiomers in the ratio of 1:1. This indicates that the crystals of **1b** are not conglomerate crystals but racemic crystals. On the other hand, three other pyrimidinones (**1a**, **1c**, **1d**) afforded conglomerates. They were analyzed by single-crystal X-ray diffraction.[12–15] Table 1 shows the results;

Table 1: The crystal systems obtained by X-ray structural analysis and the molecular conformation of pyrimidinones **1a**, **1c**, and **1d**.



1	R^1	R^2	Space group	Torsion angle C1-N2-C3-C4 [°]
1a	Me	H	$P2_1$	83.4
1a·H_2O	Me	H	$I4_1/a$	88.1
1c	Me	Cl	$P2_1$	80.9
1d	Cl	Cl	$P2_1$	81.2

the three pyrimidinones crystallize in the $P2_1$ space group. Figure 2 shows the ORTEP diagram of the absolute configuration of (*S*)-(+)-**1d** in the crystal, which was determined by an anomalous X-ray scattering method. In the case of **1a**, recrystallization from ethanol gave two types of crystals, one yellow and the other reddish. X-ray crystallographic analysis revealed that the yellow crystal has a $P2_1$ crystal system.[12]

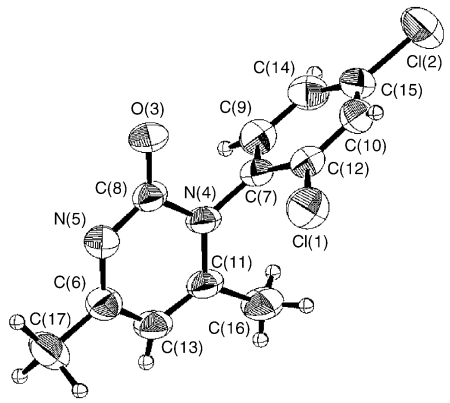


Figure 2. Absolute configuration of (*S*)-(+)-**1d** in the crystal (ORTEP).

The other crystal includes an equimolar amount of water molecules, and the crystal system is achiral, $I4_1/a$.[13] X-ray analyses also revealed the molecular conformation of the pyrimidinones. The two arene planes are almost perpendicular to each other (torsional angle $\theta = 80.9$–$88.1°$) in all cases.

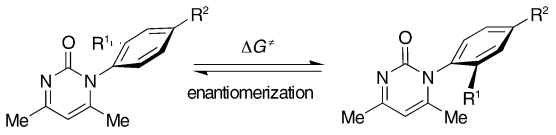
To achieve the disequilibration by crystallization, fast enantiomerization should occur at the temperature of crystallization. In order to estimate the conformational stability of **1**, the rate constants (k_{rot}) and activation parameters for the enantiomerization in these compounds have been studied. Kashima et al. obtained optically active **1a** (5% *ee*) by making its salt with optically active camphorsulfonic acid.[10] Furthermore, they measured the racemization kinetics arising from C–N bond rotation to be 30.3 kcal mol^{-1} at 359.6 K in diglyme. Roussel et al. also studied similar pyrimidinone derivatives independently and proposed a different mechanism for racemization via an open form.[11]

The rate of enantiomerization of the chiral pyrimidinones **1a**, **1c**, and **1d** was studied in three kinds of solvents: xylene (nonpolar and aprotic), dimethylformamide (DMF; polar and aprotic), and 1-propanol (polar and protic). Each enantiomorphic crystal obtained from usual crystallization was dissolved in the solvent, and the rate of enantiomerization at three temperatures (70, 80, and 90°C) was followed by HPLC with the Chiral Cell OD columun. The Arrhenius and Eyring plots have excellent linear relationships. The activation parameters obtained from the plots are listed in Table 2.

The rate of racemization was considerably influenced by the solvents. The half-life ($t_{1/2}$) of **1a** at 90°C in xylene was 46 min but 254 min in DMF and 1160 min in 1-propanol. In all cases, the free energy of activation in a polar solvent is higher than that in a nonpolar solvent. Furthermore, a protic solvent like 1-propanol restricts the enantiomerization; polarity, hydrogen bonding, or solvation by alcohol seem to be important factors influencing the interconversion. A nonpolar solvent lowers the $\Delta G^{\neq}$ value by about 2 kcal mol^{-1} relative to the value in a polar or a protic solvent. The results also indicate the effect of the substituents on the phenyl group. Methyl and chloro groups at the *ortho* position show little difference in the energy barrier for enantiomerization.

None of the pyrimidinones **1** racemized at room temperature even after several days in a nonpolar solvent; however, they racemize immediately at temperatures above 170°C in

Table 2: Activation parameters for enantiomerization of pyrimidin-2(1*H*)-ones **1** under various conditions.



Cmpd.	Solvent	$t_{1/2}$ [min] at 90 °C[a]	$\Delta G^{\neq}_{363}$ [kcal mol^{-1}]	$\Delta H^{\neq}$ [kcal mol^{-1}]	$\Delta S^{\neq}$ [cal mol^{-1} K^{-1}]
1a[b]	xylene	46	27.9	27.8	−0.32
	DMF	254	29.1	27.9	−3.35
	1-propanol	1160	30.2	28.8	−3.78
1c	xylene	31	27.6	28.2	1.57
	DMF	176	28.8	28.9	0.09
	1-propanol	875	30.0	29.8	−0.71
1d	xylene	24	27.4	31.2	10.56
	DMF	109	28.5	30.9	6.61
	1-propanol	579	29.7	31.4	4.78

[a] Half-life. [b] Kinetics of racemization of **1a** have been studied in diglyme at 359.6 K. $\Delta G^{\neq}$ value was reported as 28.3 kcal mol^{-1} (ref. [10]) and 30.3 kcal mol^{-1} (ref. [11]).

1,2,3,4-tetramethylbenzene. We tried to force the asymmetric disequilibration of atropisomeric pyrimidinones by crystallization at high temperature. The crystallization was examined in a solvent or without a solvent. Table 3 shows the melting points of pyrimidinones **1**, the chemical yields, and optical purity of the crystals obtained.

In the case of **1a**, the melting point was low (**1a**: 126–129 °C); therefore, **1a** was crystallized with stirring at 125 °C after the crystals were melted at 140 °C. The resulting solid was a 1:1 mixture of enantiomers. When the seed crystal, which was obtained as a conglomerate by usual recrystallization from ethanol, was added to the crystallization, the same results were obtained and, regrettably, asymmetric disequilibration could not be observed. We conclude that the rate of racemization is not as high as the rate of crystallization at that temperature.

On the other hand, the other pyrimidinones exhibited high melting points above 200 °C. All pyrimidinones gradually decompose at above the melting point and could not be left for more than one hour at that temperature. The melting point of **1c** is 224–225 °C, which is too high for crystallization without a solvent because of decomposition. Therefore, TMB (1,2,3,4-tetramethylbenzene, b.p. 203–204 °C) was used as a solvent for crystallization. After pyrimidinone **1c** (50 mg) was dissolved in TMB (180 mg) at 200 °C, the solution was gradually cooled to 150 °C (at the rate of 1.5 °C min^{-1}) with stirring; crystals formed at around 180 °C and multiplied as the temperature was lowered to 150 °C. A homogeneous solution was prepared by adding THF without filtration at room temperature. The chemical yield and enantiomeric purity of the recovered pyrimidinones were determined by HPLC with the Chiral Cell OD column using benzyl phenyl ether as a standard. The *ee* values varied and optical rotations were inconstant; however, **1c** was obtained in 25–68 % *ee* by autoseeding (Table 3, entry 2).[17] When the seeding method was used in the crystallization (the seed crystal was added at 180 °C), consistent *ee* values were obtained (70–72 % *ee*) and the optical rotation was the same as that of the seed crystal (entry 3). Disequilibration (68–70 % *ee*) could also be effected in a crystallization on a ten-times larger scale (entry 4).

For the dichlorophenyl derivative **1d**, TMB was also used as a solvent. Pyrimidinone **1d** (50 mg) was dissolved in TMB (100 mg) at 200 °C, and the solution was cooled to 150 °C (at the rate of 1.5 °C min^{-1}) under stirring and with or without seeding. Enantiomeric purity ranging from 13 to 66 % *ee* and indecisive optical rotation were obtained from autoseeding (entry 5).[19] On the other hand, crystals with constant enantiopurity (72–73 % *ee*) and the desired optical rotation were obtained when the seeding method was used in the crystallization (entry 6). The larger-scale experiment also gave optically active **1d** between 63 and 65 % *ee* (entry 7).

Furthermore, when the crystals of **1c** and **1d** obtained in entries 4 and 7, respectively, were recrystallized once from ethanol or a mixture of chloroform and hexane, the pyrimidinones were easily obtained with 100 % *ee*. That is, enantiomeri-

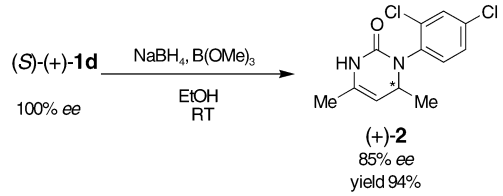
Table 3: Asymmetric disequilibration of racemic pyrimidinones **1a**, **1c**, and **1d** by crystallization.

Entry	**1**	M.p. [°C][a]	Solvent	Seeding	Cryst. temp. [°C]	*ee* [%]	Recov. [%]
1	**1a**	126–129	none	yes[f]	125	0–1	90–93[l]
2	**1c**[b]	224–225	TMB	no[g]	180–150[h]	25–68[j]	90–92[l]
3	**1c**[b]		TMB	yes[f]	180–150[h]	70–72[k]	89–99[l]
4	**1c**[c]		TMB	yes[f]	180–150[h]	67–70[k]	90–93[m]
5	**1d**[d]	210–211	TMB	no[g]	175–150[i]	13–66[j]	84–89[l]
6	**1d**[d]		TMB	yes[f]	175–150[i]	72–73[k]	82–85[l]
7	**1d**[e]		TMB	yes[f]	175–150[i]	63–65[k]	92–94[m]

[a] All pyrimidinones gradually decomposed above the melting point. [b] A solution of **1c** (50 mg) and TMB (180 mg) was used for crystallization. Each crystallization was tried five times. [c] Ten-times larger scale (500 mg **1c** and 1.8 g TMB) was used for crystallization. [d] A solution of the pyrimidinone (50 mg) and TMB (100 mg) was used for crystallization. Each crystallization was tried five times. [e] Ten-times larger scale (500 mg **1d** and 1.0 g TMB) was used for crystallization. [f] Small amount of enantiomerically pure pyrimidines (100 % *ee*) was added as seeds. [g] Crystallization by autoseeding. [h] Crystals were dissolved at 200 °C, and the seed crystal was added at 180 °C; the solution was then cooled to 150 °C. [i] Crystals were dissolved at 200 °C, and the seed crystal was added at 175 °C; the solution was then cooled to 150 °C. [j] The direction of optical rotation of the obtained crystals was inconstant in the case of autoseeding. [k] By the seeding method, crystals were obtained with the same direction of optical rotation as the seed crystal. [l] Yields were determined by HPLC with benzyl phenyl ether as a standard. [m] Yield of product isolated by column chromatography.

cally pure, axially chiral pyrimidinones could be easily obtained without any chiral source. If seed crystals are used in the crystallization, the bulk of the desired enantiomorphic crystals can be prepared selectively.

Pyrimidinones can be transformed into other heterocycles by various reactions including photochemical reactions, nucleophilic reactions, and reduction.[19] We demonstrated one example, the enantioselective reduction of axially chiral pyrimidinone **1d** with $NaBH_4$. When enantiomerically pure (100% *ee*) (*S*)-(+)-**1d** prepared by the above method was treated with $NaBH_4$ in the presence of trimethylborate at room temperature, the attack of hydride was highly controlled by the chlorine atom at the *ortho* position of the aryl group, and optically active product (+)-**2** was obtained in 94% yield and 85% *ee* (Scheme 2). In compound **2**, the rotation about the N–C bond occurs slowly at room temperature, and the *ee* value was determined by HPLC with the Chiral Cell OD column at 50°C. A distortion of the methyl group from the amide plane removes restrictions for the N–C bond rotation.



Scheme 2. Enantioselective reduction of **1d**.

In conclusion, we have provided the first example of breaking the symmetry of N–C axially chiral atropisomers by spontaneous crystallization. Furthermore, the resulting optically active atropisomer was converted to other heterocycles with high enantioselectivity. We believe that this method can be applied to resolve many axially chiral compounds, and may also have important implications as a mechanism for the amplification of optical activity that led to the homochirality of life.

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Keywords: asymmetric synthesis · atropisomerism · chiral resolution · chirality · heterocycles

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[12] X-ray crystallographic analysis of **1a**: monoclinic, space group $P2_1$, $a = 7.162(3)$ Å, $b = 14.480(6)$ Å, $c = 6.084(3)$ Å, $\beta = 111.77(4)$, $V = 585.9(5)$ Å^3, $Z = 2$, $\rho = 1.21$ g cm^{-3}, $\mu(Cu_{K\alpha}) = 0.62$ cm^{-1}; $R = 0.039$, $Rw2 = 0.125$ for 964 reflections. The structure was solved by direct methods and refined by the method of full-matrix least-squares.[16]
[13] X-ray crystallographic analysis of **1a**·H_2O: tetragonal, space group $I4_1/a$, $a = 26.80(1)$ Å, $b = 26.80(1)$ Å, $c = 7.149(5)$ Å, $V = 5134.(4)$ Å^3, $Z = 16$, $\rho = 1.11$ g cm^{-3}, $\mu(Cu_{K\alpha}) = 0.57$ cm^{-1}; $R = 0.053$, $Rw2 = 0.158$ for 1660 reflections. The structure was solved by the direct method and refined by the method of full-matrix least-squares.[16]
[14] X-ray crystallographic analysis of **1c**: monoclinic, space group $P2_1$, $a = 7.229(3)$ Å, $b = 13.826(6)$ Å, $c = 6.548(3)$ Å, $\beta = 108.06(4)$, $V = 622.2(5)$ Å^3, $Z = 2$, $\rho = 1.33$ g cm^{-3}, $\mu(Cu_{K\alpha}) = 2.59$ cm^{-1}; $R = 0.040$, $Rw2 = 0.113$ for 1038 reflections. The structure was solved by direct methods and refined by the method of full-matrix least-squares.[16]
[15] X-ray crystallographic analysis of **1d**: monoclinic, space group $P2_1$, $a = 7.228(4)$ Å, $b = 14.110(7)$ Å, $c = 6.349(4)$ Å, $\beta = 107.21(4)$, $V = 618.5(6)$ Å^3, $Z = 2$, $\rho = 1.32$ g cm^{-3}, $\mu(Cu_{K\alpha}) = 4.54$ cm^{-1}; $R = 0.039$, $Rw2 = 0.104$ for 1071 reflections. The structure was solved by direct methods and refined by the method of full-matrix least-squares.[16]
[16] CCDC 208362–208365 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
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