Chiral Resolution

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Total Spontaneous Resolution by Deracemization of Isoindolinones**

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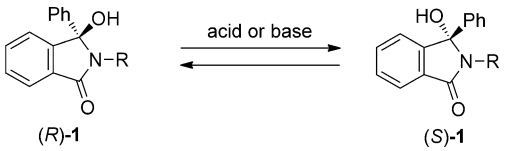
Preferential crystallization is a powerful tool to obtain optically active materials from racemic mixtures without any chiral source, and has been utilized widely for optical resolution on large scales for example in industrial processes.[1] To resolve optically active materials by crystallization efficiently, dynamic preferential crystallization involving a racemization process, a so-called total spontaneous resolution, has been developed.[2] Many efforts have been invested in new variations of this method, and the racemization processes can be classified into three groups: 1) involving an intermediate enolate anion or enol at the α-position of a carbonyl group,[3] 2) involving atropisomerism of axially chiral materials,[4] and 3) involving an equilibrium reaction via an achiral intermediate.[5–7] We have now developed a new example of total spontaneous resolution of isoindolinones that involves a combination of an intramolecular equilibrium reaction via an achiral intermediate and preferential crystallization.

Various heterocyclic compounds containing the isoindolinone skeleton have important biological activities, and many of these have been prepared and examined as pharmaceutical agents.[8] Much effort has also been focused on the asymmetric synthesis of the isoindolinone structure,[9] which is widely used as a building block for the synthesis of natural products.[10] Therefore, development of a new methodology to obtain optically active heterocycles such as isoindolinones is eagerly anticipated.

We found that 3-hydroxy-3-phenylisoindolin-1-ones **1** afforded conglomerates by spontaneous crystallization and were racemized under acidic or basic conditions (Scheme 1). The dynamic preferential crystallization resulted in total spontaneous resolution in high *ee* values.

N-Alkylated 3-hydroxy-3-phenylisoindolin-1-ones **1a–f** were synthesized from 2-benzoylbenzoic acid and the corresponding primary amines (Table 1).[11] To perform preferential crystallization, it is a requirement that the materials crystallize as a conglomerate. The crystal structure of **1c** was reported with the chiral space group $P2_12_12_1$.[12] Recrystallization of the other isoindolinones in a chloroform–hexane solution afforded prismatic crystals except in the case of **1b**. These crystals were subjected to X-ray crystallographic analysis to determine the crystal structure. Fortunately, X-ray analyses indicated that isoindolin-1-ones **1d** and **1f** also crystallized in a chiral fashion with the orthorhombic chiral space group $P2_12_12_1$. Isoindolinones **1a** and **1e** crystallized in the racemic space groups $C2/c$ and $P\bar{1}$, respectively. The space group of **1b** could not be determined; however, a racemic crystal system was suggested from the results of dynamic preferential crystallization described below.



(*R*)-**1** (*S*)-**1**

Scheme 1. Racemization of 3-hydroxyisoindolinones under acidic or basic conditions.

Table 1: Space groups of 3-hydroxy-3-phenylisoindolin-1-ones **1a–f**.

Isoindolinone	R	Space group
1a	Me	$C2/c$
1b	Et	racemic
1c	Pr	$P2_12_12_1$
1d	*i*Pr	$P2_12_12_1$
1e	$PhCH_2$	$P\bar{1}$
1f	$PhCH_2CH_2$	$P2_12_12_1$

Racemization must proceed much faster than crystallization to achieve total resolution by dynamic preferential crystallization. All 3-hydroxy-3-phenylisoindolin-1-ones **1** were not easily racemized under neutral conditions or in the solid state; however, they were racemized in solution under both acidic and basic conditions. The rates of racemization using trifluoroacetic acid (TFA) as an acid and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a base were measured according to the change of optical rotation at 20 °C, and the activation free energy and the half-life were calculated (Table 2).

When optically active isoindolinone **1c** was dissolved in a chloroform solution (2.0×10^{-2} mol L^{-1}) containing TFA (1.0×10^{-2} mol L^{-1}), the half-life of racemization was 478 min and the $\Delta G^{\ddagger}$ value was 23.8 kcal mol^{-1}. DBU was more effective than TFA; the half-life of racemization was 347 min and the $\Delta G^{\ddagger}$ value was 23.6 kcal mol^{-1}, even if diluted DBU (1.0×10^{-4} mol L^{-1}) was used as a catalyst. The same tendency was observed in the cases of **1d** and **1f**. Therefore, we selected DBU as a catalyst for racemization to perform total sponta-

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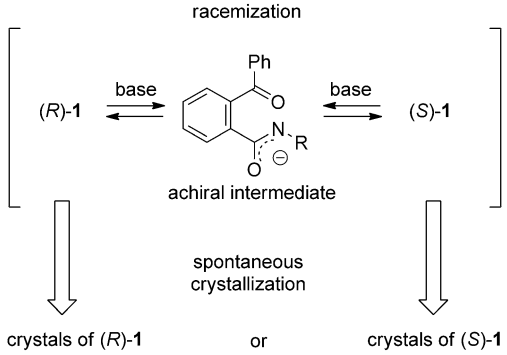
Table 2: Kinetic parameters for racemization of 3-hydroxy-3-phenylisoindolin-1-ones **1c**, **1d**, **1f**.[a]

Isoindolinone	Catalyst	$t_{1/2}$ [min]	$\Delta G^{\neq}$ [kcal mol^{-1}]
1c	TFA[b]	478	23.8
1c	DBU[c]	347	23.6
1d	TFA[b]	146	23.1
1d	DBU[c]	15	21.7
1f	TFA[b]	2066	24.6
1f	DBU[c]	228	23.3

[a] Measurement conditions: 2.0×10^{-2} mol L^{-1} of each isoindolinone in $CHCl_3$ at 20 °C. [b] 1.0×10^{-2} mol L^{-1}. [c] 1.0×10^{-4} mol L^{-1}.

neous resolution of **1** by dynamic preferential crystallization (Scheme 2).



Scheme 2. Total spontaneous resolution by dynamic preferential crystallization involving an intramolecular equilibrium reaction.

From the X-ray results, **1c**, **1d**, and **1f** afforded conglomerates and have the possibility for total resolution by crystallization. When a mixed solution of chloroform and hexane containing **1c** and DBU (0.5 mol %) in a test tube was stirred at room temperature until all the solvent evaporated completely, crystals of **1c** were generated at the bottom of the test tube (Table 3, method A). After DBU was removed through a short silica gel column using ethyl acetate as an eluent, the enantiomeric excess of **1c** was analyzed by HPLC using a chiral stationary phase (Daicel Ind. CHIRALPAK AD-H). As a result, **1c** was recovered quantitatively without loss by decomposition or side reactions, and obtained in optically active form at 15 % *ee* (Table 3, entry 1). Optically active **1c** was obtained from all crystallizations with random signs of optical rotation. However, enantiomerically pure **1c** could not be obtained by using this method, because racemization did not proceed faster than crystallization. Thus, the crystallization temperature and the DBU concentration were increased to obtain better *ee* values by accelerating the rate of racemization (Table 3, method B). The use of toluene as a solvent and crystallization at 100 °C gave 97 % *ee* as expected (Table 3, entry 2). In both methods A and B given in Table 3, the compounds were dissolved in solution and then the solvent was allowed to evaporate to achieve supersaturation and slow crystallization.

Table 3: Dynamic preferential crystallization of racemic isoindolinones.

Entry	1	Method	T [°C]	Recovered 1 [%]	*ee* [%][a]
1	**1c**	A[b]	RT	99	15
2	**1c**	B[c]	100	96	97
3	**1d**	A[b]	RT	98	71
4	**1d**	A[b,d]	RT	100	84
5	**1d**	B[c]	100	100	97
6	**1f**	A[b]	RT	91	13
7	**1f**	B[c]	100	100	94

[a] Determined by HPLC using a chiral stationary phase (Daicel Ind. CHIRALPAK AD-H). [b] Method A: $CHCl_3$/hexane as a solvent, DBU (0.50 mol %) as a base, room temperature. [c] Method B: $CHCl_3$/toluene as a solvent, DBU (50 mol %) as a base, 100 °C. [d] Seeding.

In the case of **1d**, the rate of racemization was much greater than in that of **1c** (Table 2), and an optical resolution of 71 % *ee* was obtained by crystallization at room temperature (Table 3, entry 3). Seeding with the powdered single crystal obtained by the normal recrystallization method from a $CHCl_3$–hexane solution gave a better *ee* value of 84 % (Table 3, entry 4). In this case, crystals with the same chirality as the seed crystal were obtained as a matter of course.[4] Crystallization at 100 °C using toluene instead of hexane gave excellent results of 97 % *ee* (Table 3, entry 5).[13]

In the case of **1f**, crystallization from a mixture of $CHCl_3$ and hexane at room temperature resulted in the low resolution of 13 % *ee* (Table 3, entry 6); however, crystallization at 100 °C from toluene using 50 mol % of DBU gave an excellent *ee* value of 94 % (Table 3,entry 7). All crystallizations at high temperatures using increased amounts of DBU (Table 3, entries 2, 5, 7) resulted in high *ee* values with good reproducibility. Deracemization could be controlled by the use of seed crystals during crystallization.

The stereogenic center of **1** did not racemize under neutral conditions; therefore, optically pure materials were easily obtained by recrystallization from a THF–hexane solution of the solid obtained by dynamic crystallization (Table 3, entries 2, 5, 7).

Recently, attrition-enhanced deracemization and resolution of chiral conglomerate solids were performed.[5] We also tried the attrition-enhanced deracemization using glass beads; unfortunately, the deracemization could not be achieved with our substrates.[14]

In conclusion, we succeeded in the total spontaneous resolution of three 3-hydroxy-3-phenylisoindolin-1-ones by dynamic preferential crystallization. Each compound was efficiently racemized in the presence of DBU, and the enantiomer was obtained in quantitative recovery rates and with excellent *ee* values. Three of the six 3-hydroxy-3-phenylisoindolin-1-ones yielded conglomerate crystals by spontaneous crystallization. An incidence of 50 % conglomerates is striking, because the typical incidence is only around 20 %.[15] We are continuing to explore the high incidence by synthesizing many derivatives by changing the phenyl group. This research provided not only a new example of the total spontaneous resolution process involving racemization through ring-opening and ring-closing reactions, but also a fine preparative method of optically active heterocycles without an external chiral source.

Experimental Section

Dynamic preferential crystallization (method A): A mixed solution of chloroform and hexane containing **1** (5–50 mg) and DBU (0.50 mol%) was stirred in a test tube or a vial at room temperature until all solvent evaporated. After DBU was removed through a short silica gel column using ethyl acetate as an eluent, the enantiomeric excess of **1** was analyzed by HPLC using a chiral stationary phase (Daicel Ind. CHIRALPAK AD-H).

Dynamic preferential crystallization (method B): A mixed solution of chloroform and toluene containing **1** (5–50 mg) and DBU (50 mol%) was stirred in a test tube at 100 °C until all solvent evaporated. After DBU was removed through a short silica gel column using ethyl acetate as an eluent, the enantiomeric excess of **1** was analyzed by HPLC using a chiral stationary phase.

Determination of activation free energy and half-life: The time course of optical rotation of a solution of optically active **1** (4.0×10^{-2} mol L^{-1}) containing trifluoroacetic acid (1.0×10^{-3} mol L^{-1}) or DBU (1.0×10^{-4} mol L^{-1}) was measured by using a DIP 370 polarimeter (JASCO) at 20 °C.

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[1] a) J. Jacques, A. Collet, S. H. Wilen in *Enantiomers, Racemates and Resolutions*, Wiley, New York, **1981**; b) K. M. J. Brands, A. J. Davies, *Chem. Rev.* **2006**, *106*, 2711 – 2733.

[2] a) L. Addadi, Z. Berkovitch-Yellin, N. Domb, E. Gati, M. Lahav, L. Leiserowitz, *Nature* **1982**, *296*, 21 – 26; b) L. Addadi, S. Weinstein, E. Gati, I. Weissbuch, M. Lahav, *J. Am. Chem. Soc.* **1982**, *104*, 4610 – 4617; c) C. Viedma, *Phys. Rev. Lett.* **2005**, *94*, 065504; d) C. Viedma, *Cryst. Growth Des.* **2007**, *7*, 553 – 556; e) G. Coquerel, *Top. Curr. Chem.* **2007**, *269*, 1 – 51; f) R. Yoshioka, *Top. Curr. Chem.* **2007**, *269*, 83 – 132.

[3] a) W. J. Boyle, Jr., S. Sifniades, J. F. Van Peppen, *J. Org. Chem.* **1979**, *44*, 4841 – 4847; b) S. Yamada, C. Hongo, R. Yoshioka, I. Chibata, *J. Org. Chem.* **1983**, *48*, 843 – 846; c) B. Kaptein, W. L. Noorduin, H. Meekes, W. J. P. van Enckevort, R. M. Kellogg, E. Vlieg, *Angew. Chem.* **2008**, *120*, 7336 – 7339; *Angew. Chem. Int. Ed.* **2008**, *47*, 7226 – 7229.

[4] a) R. E. Pincock, R. R. Perkins, A. S. Ma, K. R. Wilson, *Science* **1971**, *174*, 1018 – 1020; b) D. K. Kondepudi, J. Laudadio, K. Asakura, *J. Am. Chem. Soc.* **1999**, *121*, 1448 – 1451; c) M. Sakamoto, N. Utsumi, M. Ando, M. Saeki, T. Mino, T. Fujita, A. Katoh, T. Nishio, C. Kashima, *Angew. Chem.* **2003**, *115*, 4496 – 4499; *Angew. Chem. Int. Ed.* **2003**, *42*, 4360 – 4363; d) M. Sakamoto, F. Yaghishita, M. Ando, Y. Sasahara, N. Kamataki, M. Ohta, T. Mino, Y. Kasashima, T. Fujtia, *Org. Biomol. Chem.* **2010**, *8*, 5418 – 5422.

[5] For intermolecular reaction, see a) W. L. Noorduin, A. A. C. Bode, M. van der Meiden, H. Meekes, A. F. van Etteger, W. J. P. van Enckevort, P. C. M. Christianen, B. Kaptein, R. M. Kellogg, T. Rasing, E. Vlieg, *Nat. Chem.* **2009**, *1*, 729732; b) W. L. Noorduin, P. Van DerAsdonk, H. Meekes, W. J. P. van Enckevort, B. Kaptein, M. Leeman, R. M. Kellogg, E. Vlieg, *Angew. Chem.* **2009**, *121*, 3328 – 3330; *Angew. Chem. Int. Ed.* **2009**, *48*, 3278 – 3280; c) W. L. Noorduin, B. Kaptein, H. Meekes, W. J. P. van Enckevort, R. M. Kellogg, E. Vlieg, *Angew. Chem.* **2009**, *121*, 4651 – 4653; *Angew. Chem. Int. Ed.* **2009**, *48*, 4581 – 4583.

[6] Catalytic asymmetric synthesis coupled with in situ deracemization. S. B. Tsogoeva, S. Wei, M. Freund, M. Mauksch, *Angew. Chem.* **2009**, *121*, 598 – 602; *Angew. Chem. Int. Ed.* **2009**, *48*, 590 – 594.

[7] Intramolecular equilibrium reaction is very rare. J. Siegwarth, J. Bornhoft, C. Nather, R. Herges, *Org. Lett.* **2009**, *11*, 3450 – 3452.

[8] a) K. Smith, G. A. Ei-Hiti, A. S. Hegazy, B. Kariuki, *Beilstein J. Org. Chem.* **2011**, *7*, 1219 – 1227; b) P. Pigeon, B. Decroix, *Tetrahedron Lett.* **1997**, *38*, 2985 – 2988; c) I. Osante, E. Lete, N. Sotomayor, *Tetrahedron Lett.* **2004**, *45*, 1253 – 1256; d) R. A. Abramovitch, I. Shinkai, B. J. Mavunkel, K. M. More, S. O'Connor, G. H. Ooi, W. T. Pennington, P. C. Srinivason, J. R. Stowers, *Tetrahedron* **1996**, *52*, 3339 – 3354; e) J.-M. Ferland, C. A. Demerson, L. G. Humber, *Can. J. Chem.* **1985**, *63*, 361 – 365; f) Z.-P. Zhuang, M.-P. Kung, M. Mu, H. F. Kung, *J. Med. Chem.* **1998**, *41*, 157 – 166.

[9] a) S. Yamada, K. Yamashita, *Tetrahedron Lett.* **2008**, *49*, 32 – 35; b) V. Agouridas, F. Capet, A. Couture, E. Deniau, P. Grandclaudon, *Tetrahedron: Asymmetry* **2011**, *22*, 1441 – 1447; c) V. More, R. Rohlmann, O. G. Mancheno, C. Petronzi, L. Palombi, A. D. Rosa, A. D. Mola, A. Massa, *RSC Adv.* **2012**, *2*, 3592 – 3595.

[10] a) D. L. Comins, S. Schilling, Y. Zhang, *Org. Lett.* **2005**, *7*, 95 – 98; b) H. Heaney, K. F. Shuhaibar, *Synlett* **1995**, 47 – 48; c) D. L. Boger, J. K. Lee, J. Goldberg, Q. Jin, *J. Org. Chem.* **2000**, *65*, 1467 – 1474.

[11] K. Bowden, S. P. Hiscocks, A. Perjéssy, *J. Chem. Soc. Perkin Trans. 2* **1998**, 291 – 295.

[12] E. J. Valente, S. B. Martin, L. D. Sullivan, *Acta. Crystallogr. Sect. B* **1998**, *54*, 264 – 276.

[13] Gram scale crystallization was also examined. A toluene solution (50 mL) containing **1c** (5.0 g) and DBU (20 mol%) was stirred in a flask at 100 °C until **1c** was gradually crystallized and all solvent evaporated. After DBU was removed, the enantiomeric excess of **1c** was analyzed by HPLC, and was shown to be 93% *ee*. It was revealed that the total spontaneous resolution could be applied for large scale crystallization.

[14] Optically active solid of **1d** (10% *ee* or 20% *ee*, 0.50 g, 1.98 mmol) was suspended in hexane (10.0 mL) with 1.0 g of glass beads (2 mm) and was stirred in the presence of DBU (0.06 g, 0.40 mmol) for 12 h. The enantiomeric excess of the crystalline solid was measured and found to be racemic in both cases.

[15] M. Sakamoto, *J. Photochem. Photobiol. C* **2007**, *7*, 183 – 196.