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Unusual heterochiral crystallization tendency of 3-arylphthalide compounds in non-racemic solution: reinvestigation on asymmetric Ni-catalyzed tandem reaction of substituted *o*-halobenzaldehydes

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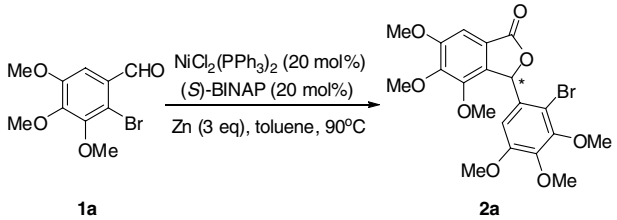
Abstract—The phenomenon of unusual heterochiral crystallization tendency of several 3-arylphthalide compounds in non-racemic solution was observed. With this finding, a range of highly enantiomerically enriched 3-arylphthalides were easily accessed through heterochiral crystallization. In addition, the previously reported nickel-catalyzed tandem reaction to asymmetric synthesis of chiral phthalides was reinvestigated and partial data were corrected.

Phthalides represent a large class of naturally occurring and biologically active compounds.[1] They are important pharmacological molecules as well as useful building blocks.[2] Enantiopure compounds substituted at *C*-3 are particularly valuable. The asymmetric synthesis of chiral 3-substituted phthalides have thus attracted much attention from organic chemists.[3] However, examples of highly efficient enantioselective synthesis remain few. Previously, we reported a nickel-catalyzed tandem reaction for the asymmetric synthesis of chiral 3-arylphthalides.[4] The products were obtained with moderate to high enantiomeric excesses. In our continuous work to further improve the reaction enantioselectivity, we observed a unique and interesting crystallization behavior of chiral 3-arylphthalide products. A range of highly enantiomerically enriched 3-arylphthalides could be easily accessed through unusual heterochiral crystallization method. Herein, we wish to describe these findings and at the same time present a correction of our former work.

In the previous work,[4] we reported that phthalide **2a** was produced by Ni–BINAP catalyzed tandem reaction of *o*-bromobenzaldehyde **1a** in good yield and with 43% ee (Scheme 1). During the further investigation, we noticed a very strange phenomenon that the reaction result, particularly the enantioselectivity, varied upon the same reaction conditions. The ee value of the same reaction product **2a** tested at different times by chiral HPLC even differentiated with each other most of the time. After a more careful examination, we assumed the possible reason of solubility factor of **2a** in HPLC eluent. Solid **2a** has relatively poor solubility in the mixed HPLC solvent of hexane and 2-propanol. By adding very small amount of CH_2Cl_2 to the HPLC solution, **2a** could be entirely dissolved, the ees remeasured then are reproducible. These results suggest that the ee determination from a completely dissolved **2a** solution is very important. To obtain the accurate enantioselectivity, all product **2a** isolated from the reaction was dissolved in



1a **2a**

Scheme 1.

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CH_2Cl_2, and a small part of this **2a** solution was used for HPLC analysis. After several attempts, a reproducible 71% ee was observed instead of 43% ee reported previously.

With the above unique experience, we realized that the enantiomeric composition of the solid and solution may be different. To further confirm this, we did crystallization (one time) of phthalide **2a** (71% ee) and measured the ees of both crystal and mother liquor. Surprisingly, the HPLC showed that the crystal was almost racemic (<5% ee), while in mother liquor a 97% ee was obtained! This is different with the common situation of recrystallization that enantiomerically enriched crystals are usually formed. The X-ray crystallographic analysis demonstrated that the crystal is a heterochiral one that contains both (*R*) and (*S*)-enantiomers with symmetric space group $P2_1/c$.[5] In this particular case, it turns out that the formation of a heterochiral crystal is much more preferential than that of a homochiral crystal.[6] As a result, enantiomerically enriched **2a** (97% ee) in mother liquor was thus afforded through rapid crystallization (Fig. 1).

To gain some insight into this unusual heterochiral crystallization tendency, the structural X-ray investigation of homochiral **2a** was also proceeded. Phthalide **2a** with high enantiomeric excess of 97% was carefully crystallized in EtOH to give homochiral crystal (Fig. 2). Unlike heterochiral **2a**, homochiral **2a** was found crystallized in a nonsymmetric $P2_1$ space group.[7] In the structure of heterochiral **2a** (Fig. 3, the top one), two opposite enantiomers each forms homochiral chains, and such chains form layers stacked with each other possibly by van der Waals forces such as weak hydrogen bondings between oxygen and C–H. For example, C(15)–H(15B)···O(3), C(15)–H(15A)···O(2), C(8)–H(8)···O(4), and C(20)–H(20C)···O(7), et al. In contrast, in the structure of homochiral crystal **2a** (Fig. 3, the bottom one), a single chiral packing arrangement was observed. Although the exact understanding of homochiral and heterochiral organizations is difficult at this time,[8] the preferred formation of heterochiral over homochiral crystal suggests lower packing discrimination energy and better packing efficiency of racemic forms compared with chiral conglomerates.

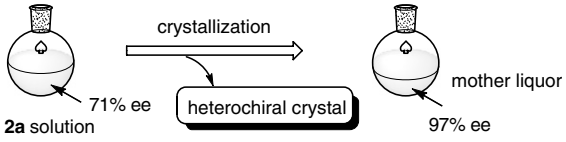


Figure 1. Heterochiral crystallization process of phthalide **2a**.

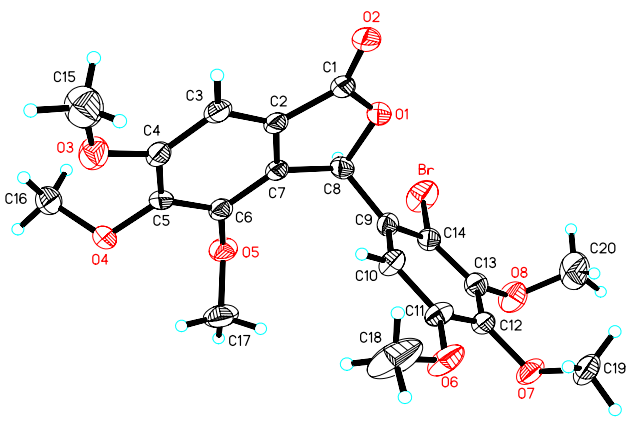


Figure 2. X-ray crystal structure of homochiral **2a**.

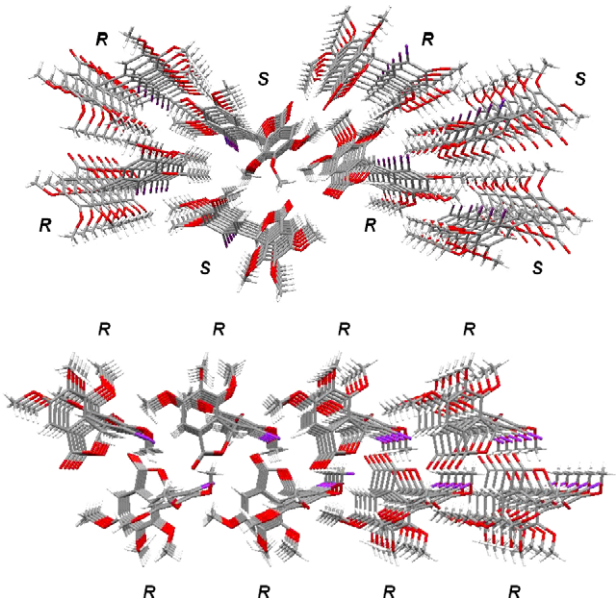
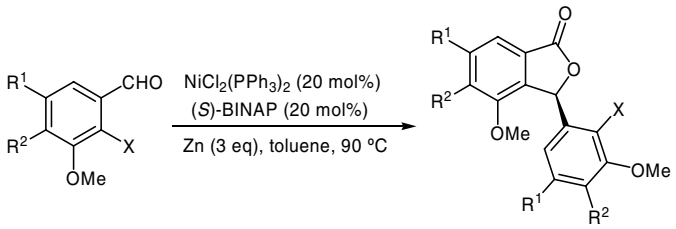


Figure 3. The 3-D crystalline packing arrangement of heterochiral **2a** (top) and homochiral **2a** (bottom).

In our previous report,[4] the stereochemistry of the obtained reaction product was not clear. With X-ray crystal structure of homochiral **2a**, illustrated in Figure 2, the absolute configuration of the newly formed carbon center was determined to be (*R*)[7] when (*S*)-BINAP was chosen as a ligand in the reaction.

Having observed the phenomenon of unusual heterochiral crystallization tendency of **2a**, we decided to reinvestigate the Ni-catalyzed tandem reaction to check the validity of other previously reported data, and meanwhile to see the crystallization behavior of other phthalide products. As shown in Table 1, the reactions of various *o*-halobenzaldehydes **1b–e** were carried out at 90 °C using (*S*)-BINAP as ligand, and chiral phthalide products **2b–e** were accordingly produced.[9] Although the reactions were carefully proceeded, the yields were found not to be as high as those reported previously due to the inevitable formation of dehalophthalides (usually in 20–30% isolated yield).[10] The new results are provided in Table 1. For the reaction enantioselectivities, the same ee values were detected in the cases of products **2b** and **2c** (entries 2 and 3). The difference of ee in the case of **2d** was corrected after repeated measurement (entry 4). A new substrate **1e** was also employed in the reaction to give phthalide **2e** (entry 5).[12] In all the cases, solid products with moderate reaction enantioselectivities (63–71%) were obtained.

Table 1. Reinvestigation of nickel-catalyzed reaction of iodo-and bromo-substituted aromatic aldehydes[a]



1a-e **2a-e**

Entry	Sub **1**	X	R^1	R^2	*T* (h)	Yield[b,d] (%)	ee[c,d] (%)
1	**1a**	Br	OMe	OMe	1.5	75 (85)	71 (43)
2	**1b**	I	OMe	OMe	0.5	45 (92)	71 (71)
3	**1c**	I	H	OMe	3.5	35 (48)	70 (71)
4	**1d**	Br	OMe	H	2	49 (97)	63 (81)
5	**1e**	Br	H	OMe	3	52	64

[a] The reactions were carried out with aldehydes **1a–e** (0.8–1 mmol), $NiCl_2(PPh_3)_2$ (20 mol %), (*S*)-BINAP (20 mol %) and Zn (3 equiv) in freshly distilled dry toluene at 90 °C under argon for several hours as indicated in Table 1.
[b] Isolated yield.
[c] Determined by chiral HPLC, see Ref. 11.
[d] The data in parenthesis are inaccurate data reported before.

With various solid phthalide products in hand, we attempted their recrystallization to see the potential of ee improvement as in the case of **2a**.[13] They were consequently subjected to one time recrystallization. Interestingly, similar heterochiral crystallization tendency was found in the cases of **2c–e**, phthalide in the mother liquor was collected in very high optical purity after crystallization process. In all examples, only phthalide **2b** that bears an iodo group and six methoxy groups favors the homochiral type of crystallization. Fortunately, as indicated in Table 2, all excellent enantioselectivities up to 98% ee were achieved. Thus, starting from a solution containing a moderate enantiomeric excess, a dramatic ee increase of the final phthalide can be reached after rapid one time crystallization.

We have also investigated the physical property such as melting point difference between racemic forms (heterochiral) and enantiomeric forms (homochiral). In all heterochiral preferential crystallization cases, racemic crystals have a higher melting point. These results may suggest that the heterochiral crystals are thermodynamically more stable than the homochiral ones due to the more tighter crystal packing[8b,14] (**2a**, **2c–e**). However, for the enantiomorphous crystal **2b**, the melting point was observed to be 31 °C higher than its racemate, indicating a better crystal structure stability of homochiral forms (see Table 3).

In summary, we have described an unusual heterochiral crystallization phenomenon of a series of 3-arylphthalide compounds. In these cases, the heterochiral crystal (racemic) formed highly preferentially to the homochiral crystal (enantiomorphous). The X-ray crystal structures of both heterochiral and homochiral **2a** were investigated. These findings provide interesting examples of chiral discrimination in molecular crystals and can be expected to be useful in understanding chiral organization. In addition, we have reinvestigated the previously reported nickel-catalyzed tandem reaction to asymmetric synthesis of chiral 3-arylphthalides and made a correction on some results. Using heterochiral crystallization process, a range of highly enantioenriched 3-arylphthalides (91–98% ee) were easily accessed.

Table 2. Heterochiral/homochiral crystallization for improving the enantiomeric excesses of chiral phthalides

Entry	Product **2**	ee before[a] (%)	ee after[b] (%)	Yield[c] (%)
1	**2a**	71	97	64
2	**2b**[d]	71	98[e]	64
3	**2c**	70	96	65
4	**2d**	63	91	50
5	**2e**	64	97	62

[a] The ee measured before recrystallization as indicated in Table 1.
[b] The ee of mother liquor after heterochiral crystallization, unless otherwise noted.
[c] The isolated yield of enantiomerically enriched phthalide after recrystallization.
[d] The compound is subjected to homochiral crystallization.
[e] The ee of chiral crystals.

Table 3. The Melting points of racemic forms and enantiomeric forms of phthalide **2**

Entry	**2**	Melting point (°C)	
		Racemic forms[a]	Enantiomeric forms[b] (ee)
1	**2a**	130–131	121–122 (97% ee)
2	**2b**[c]	129–131	160–162 (98% ee)
3	**2c**	146–148	132–134 (96% ee)
4	**2d**	194–195	133–134 (91% ee)
5	**2e**	161–163	124–126 (97% ee)

[a] Heterochiral crystals except **2b**, ee <5%.
[b] (*R*)-Enantiomers that were obtained from mother liquor after heterochiral crystallization except **2b**.
[c] The compound is subjected to homochiral crystallization.

Acknowledgments

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5. The crystallographic data for heterochiral **2a** have been deposited at CCDC under the registry number 639744. They can be obtained free of charge at 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 336033; e-mail: deposit@ccdc.cam.ac.uk]. Empirical formula: $C_{20}H_{21}BrO_8$; Formula weight: 469.28; Temperature: 293 (2) K; Wavelength: 0.71073 Å; Crystal system: Monoclinic, space group: $P2_1/c$; Unit cell dimensions: $a = 6.7707(7)$ Å, $\alpha = 90°$, $b = 38.382(4)$ Å, $\beta = 98.159$ (2)°, $c = 7.6178(8)$ Å, $\gamma = 90°$; Volume = 1959.6(4) Å^3; $Z = 4$; $\rho_{calc} = 1.591$ Mg/m^3; $F(000) = 960$; final R indices $[I > 2\sigma(I)]$: $R_1 = 0.0507$, $wR_2 = 0.1250$; R indices (all data), $R_1 = 0.0679$, $wR_2 = 0.1301$.
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9. General procedure: Under argon, to a 25 mL Schlenk flask were added substrate **1** (0.8–1 mmol), $NiCl_2(PPh_3)_2$ (20 mol %), (*S*)-BINAP (20 mol %), Zn (3 equiv) and 8–10 mL of fresh distilled dry toluene. The mixture was stirred at 90 °C and monitored by TLC. After the completion of the reaction, the mixture was cooled to room temperature. CH_2Cl_2 was added, and insoluble matters were filtrated through Celite. The solution was concentrated under vacuum. The obtained residue was purified by silica gel column chromatography to afford the corresponding phthalide product **2** as a solid.
10. In general, the phthalide and dehalophthalide products are very close on the TLC plate. For the previously reported high yield, we assumed that the authors missed the formation of dehalophthalides during the former experiments.
11. For optical rotation and HPLC conditions: **2a**. $[\alpha]_D^{20}$ −4.6 (0.25, $CHCl_3$) for 97% ee; HPLC: Chiralcel AD-H, hexane/ ^{i}PrOH = 80:20, flow rate = 0.7 mL/min, detected at 254 nm, $t_{R1} = 12.7$ min (minor), $t_{R2} = 14.6$ min (major). **2b**. $[\alpha]_D^{20}$ 13.0 (0.50, $CHCl_3$) for 98% ee; HPLC: Chiralcel AD-H, hexane/^{i}PrOH = 90:10, flow rate = 0.7 mL/min, detected at 254 nm, $t_{R1} = 27.4$ min (minor), $t_{R2} = 32.9$ min (major). **2c**. $[\alpha]_D^{20}$ −34.9 (0.9, $CHCl_3$) for 96% ee; HPLC: Chiralcel OD-H, hexane/^{i}PrOH = 90:10, flow rate = 0.7 mL/min, detected at 254 nm, $t_{R1} = 52.2$ min (minor), $t_{R2} = 61.6$ min (major). **2d**. $[\alpha]_D^{20}$ −9.78 (0.3, $CHCl_3$) for 91% ee; HPLC: Chiralcel OD-H, hexane/^{i}PrOH = 70:30, flow rate = 1.0 mL/min, detected at 220 nm, $t_{R1} = 8.7$ min (major), $t_{R2} = 21.2$ min (minor). **2e**. $[\alpha]_D^{20}$ −67.8 (1.45, $CHCl_3$) for 97% ee; HPLC: Chiralcel AD-H, hexane/^{i}PrOH = 70:30, flow rate = 0.5 mL/min, detected at 254 nm, $t_{R1} = 18.6$ min (minor), $t_{R2} = 20.7$ min (major).
12. **2e.** ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 3.54 (s, 3H, OMe), 3.85(s, 3H, OMe), 3.89 (s, 3H, OMe), 3.96 (s, 3H, OMe), 6.63 (d, $J = 8.7$ Hz, 1H, Ph), 6.78 (d, $J = 9.0$ Hz, 1H, Ph), 6.90 (s, 1H, CH), 7.13 (d, $J = 8.4$ Hz, 1H, Ph), 7.69 (d, $J = 8.4$ Hz, 1H, Ph); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 169.96, 157.37, 154.17, 146.50, 143.11, 141.39, 127.94, 124.22, 121.80, 120.69, 119.43, 114.21, 111.11, 79.88, 60.54, 60.16, 56.35, 56.00; ESIMS (m/z, %): 409.0 (M^++H), 431.1 (M^++Na); FT-IR (KBr) ν 2941, 2838, 1771, 1612, 1492, 1347, 1286, 1097, 813, 734 cm^{-1}; Anal. Calcd for $C_{18}H_{17}BrO_6$: C, 52.83; H, 4.19. Found: C, 52.82; H, 4.49.
13. A typical procedure of recrystallization for **2a**: 100 mg of compound **2a** with 71% ee was dissolved in about 10 mL of absolute ethanol under heating. The clear solution was allowed to cool to room temperature naturally. It was then kept in refrigerator at −20 °C for 2 h. The white precipitate formed was filtrated to give 31 mg of racemic **2a** (~4% ee), while the mother liquor was evaporated to afford 64 mg of enantiomerically enriched chiral **2a** (97% ee). The yield of chiral **2a** after recrystallization was calculated as 64%.
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