

Absolute asymmetric synthesis by nucleophilic carbonyl addition using chiral crystals of achiral amides†

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Reaction of the chiral crystals of the achiral amides with *n*-butyllithium in toluene at $-80\text{ }^{\circ}\text{C}$ gave optically active alcohols in 17–84% ee.

Spontaneous crystallization is a most attractive phenomenon because achiral molecules are doped in molecular chirality or chiral arrangement in the crystals without any outside chiral source. A number of apparent achiral organic compounds have been obtained as chiral crystals, and many successful absolute asymmetric syntheses have been achieved using the chiral crystals.¹ Most of them were limited to photochemical reactions. Exceptionally, a few fine examples are reported for gas–solid heterogeneous reactions; however, regrettably, the ee values were not so high.² Now, we are able to achieve absolute asymmetric synthesis *via* nucleophilic carbonyl addition using *n*-butyllithium with chiral crystals of achiral amides in high optical yields.³

The rotational barrier of *N,N*-disubstituted aromatic amides has considerably high activation energy for Ar–(C=O) bond rotation, which corresponds to the enantiomerization of the atropisomerism (Fig. 1).⁴ Clayden *et al.* reported that some axially chiral amides with bulky substituents on its ortho-position have been isolated in optically active form, and used to further asymmetric synthesis.⁵

Here we studied the chiral crystallization of achiral aromatic amide with one substituent on the *ortho*-position and further application to asymmetric synthesis without any outside chiral source.

2-Benzoylbenzamide derivatives **1a–d** were conveniently prepared by a condensation reaction from commercially available amine and benzoylbenzoic acid (Fig. 2). Recrystallization of these amides from a chloroform–hexane solution afforded colorless prisms in all cases. All crystals were subjected to X-ray crystallographic analysis to obtain details of the molecular conformation and the architecture in the crystals.^{6–9}

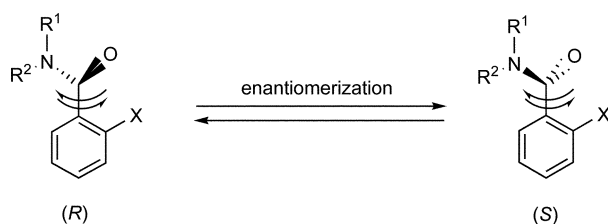


Fig. 1 Enantiomerization of aryl amides.

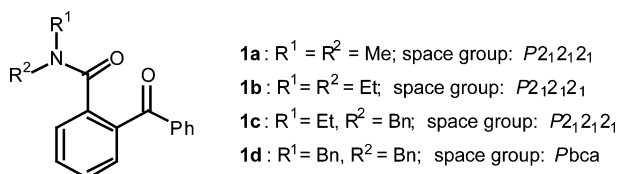


Fig. 2

To achieve the proposed absolute asymmetric synthesis, it was requisite that the achiral materials crystallize in a chiral space group.¹ Whereas **1d** forms racemic crystals (space group: $Pbca$), fortunately the other three amides **1a–c** afforded a chiral crystal system $P2_12_12_1$, and the constituent molecules adopted a chiral and helical conformation in the crystal lattice. Each single crystal is chiral, and all molecules in one crystal are optically active, offering the same chiral configuration. Generally, the selection of either enantiomeric form of molecular configuration is equally probable. Once enantiomeric crystals are formed, a large amount of chiral crystals with the same optical rotation can be selectively prepared through recrystallization by seeding the desired crystals.

The X-ray structural analysis also revealed that all amides tend to have almost the same molecular conformation. The twist angle defined by the benzoyl and the amide groups against the central phenyl ring may be the most important factor for the formation of the helical and chiral structure. Remarkably, both carbonyl groups are considerably inclined to opposite sides of each other, and the twist angle formed by the amide group ($55.8\text{--}82.1^\circ$) is relatively bigger than that of the benzoyl group ($31.8\text{--}43.0^\circ$). The asymmetrically substituted amide **1c** exists as a mixture of *syn*- and *anti*-isomers (*anti/syn* = 1.13) in solution; however, in the crystal, it takes on *anti*-form. The X-ray analyses did not establish the absolute stereochemistry of the compounds **1a**, **1b**, and **1c**.

Can the amides **1a–c** retain the molecular chirality after dissolving the crystals into a cold solution? Activation free energies for racemization of **1b** were studied by the use of VT NMR spectroscopy,^{10,11} and the barrier to interconversion of the enantiomers in toluene- d_6 was found to be 42.6 kJ mol^{-1} , corresponding to a half-life for racemization of 0.002 s at $-60\text{ }^{\circ}\text{C}$. If the subsequent chemical reaction can occur on the surface of the crystals or proceed faster than the enantiomerization, chiral conformation in the chiral crystal will be transferred effectively to optically active products.

Nucleophilic addition with *n*-butyllithium was examined to achieve absolute asymmetric synthesis. The powdered crystals of **1** (0.5 mmol) were added to a toluene solution (10 ml) containing *n*-butyllithium (commercially available hexane solution 2.5 mmol) at $-80\text{ }^{\circ}\text{C}$. After the mixture was stirred for 2.0 h at the same temperature, aq. NH_4Cl was added to quench the reaction, and was followed by the usual work-up. The products were separated by chromatography on silica gel. When chiral crystals of *N,N*-dimethyl derivatives **1a** were used, nucleophilic addition to the benzoyl carbonyl group occurred effectively and the adduct **2a** was obtained; however, **2a** was not stable and gradually changed to phthalide **3a**. Then, the crude reaction mixture in toluene was heated at $80\text{ }^{\circ}\text{C}$ for 2 h in the presence of AcOH. Phthalide **3a** was isolated in 82% yield, which showed optical activity of 17% ee, determined by HPLC using a chiral cel OD column (Table 1, entry 1). The cyclization to **3** from **2** should involve substitution reaction at C=O.

In the case of *N,N*-diethyl derivative **1b**, the corresponding alcohol **2b** was obtained in 82% yield, surprisingly in the highly optically active form of 84% ee (entry 2). The reaction with chiral crystals of **1c** also gave alcohol **2c** which was also unstable and then changed to phthalide **3** as in the case of the reaction of **1a**. Phthalide **3c** also showed optical activity of 80% ee (entry 3). The reaction with racemic crystals of **1d** gave the corresponding phthalide **3d** in

† Electronic supplementary information (ESI) available: crystal data for **1a–1d**; determination of ee. See <http://www.rsc.org/suppdata/cc/b3/15729f/>

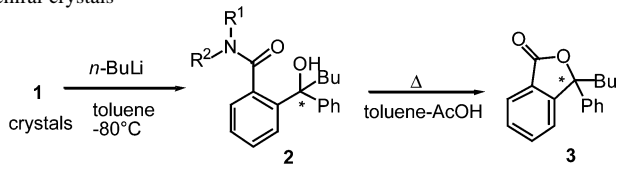
87%, and naturally in racemic form (entry 4). Whereas the optical rotations of the products were dependent on the configuration of the starting amides, they were inconsistent in the case of auto-seeding. However, the desired crystals could be easily prepared by the seeding method.

Table 2 shows the results of the reaction of the chiral crystals of **1b** with *n*-butyllithium under various conditions. When a hexane solution of *n*-butyllithium was added to a toluene solution of **1b** at $-80\text{ }^{\circ}\text{C}$, which was prepared by dissolving the crystals in toluene at room temperature and cooling to $-80\text{ }^{\circ}\text{C}$, racemic **2b** was obtained. As a matter of course, the molecules immediately lost chirality on dissolving the chiral crystals in a solvent at room temperature (entry 1). As the reaction temperature was raised, the ee's of the product decreased (entries 2–6); however, it is noteworthy that optically active products were isolated from the reaction even at $0\text{ }^{\circ}\text{C}$ (entry 6).

Addition of TMEDA or THF, both of which are effective in coordination to the lithium ion, resulted in low enantioselectivity (entries 7 and 8). When hexane was used as a solvent, the crystals did not dissolve at the early stage; however, the crystals dissolved according to the progress of the reaction and gave 64% chemical and 74% optical yields (entry 9). It is concluded that toluene is the most appropriate solvent for this asymmetric nucleophilic reaction.

In conclusion, we have provided a new example of absolute asymmetric synthesis *via* nucleophilic reaction by the use of molecular chirality generated by chiral crystallization of achiral

Table 1 Absolute asymmetric synthesis *via* nucleophilic reaction using chiral crystals



Entry	Amide	Yield (%) of 2 or 3	ee (%) ^b
1	1a	82 ^a	17 ^c
2	1b	82	84
3	1c	83 ^a	80 ^c
4	1d	87 ^a	0 ^c

^a These alcohols **2** were unstable, and then the reaction mixture was heated in toluene in the presence of acetic acid leading to phthalide **3**. ^b Directions of optical rotations were dependent on the configuration of the starting amides in the chiral crystals, and were inconsistent in the case of auto-seeding. ^c Enantiomeric yields of phthalide **3**.

Table 2 Asymmetric synthesis using chiral crystals of **1b** with *n*-butyllithium in various conditions

Entry	Solvent	<i>T</i> /°C	Yield (%)	ee (%)
1 ^a	toluene	-80	82	0
2 ^b	toluene	-80	82	84
3 ^b	toluene	-60	60	70
4 ^b	toluene	-40	58	59
5 ^b	toluene	-20	55	35
6 ^b	toluene	0	55	16
7 ^c	toluene, TMEDA	-80	77	18
8 ^b	THF	-80	83	17
9 ^b	hexane	-80	64	74

^a A commercially available hexane solution of *n*-butyllithium (2.5 mmol) was added to a toluene solution (10 ml) of **1b** (0.5 mmol) at $-80\text{ }^{\circ}\text{C}$, which was prepared by dissolving **1b** at room temperature. ^b Powdered crystals of **1b** were added to a cooled solution of *n*-butyllithium and cited solvent. ^c Powdered crystals (0.5 mmol) were added to a cooled toluene solution including *n*-butyllithium (2.5 mmol) and TMEDA (2.5 mmol).

amides. The absolute configuration of the starting amides in chiral crystals and the products has not been determined yet. Whereas a mechanistic approach for the asymmetric synthesis can not be determined without correlation of the absolute configuration of both the starting amides **1** and the products **2**, we believe that this methodology can be applied to the development of new absolute asymmetric syntheses.

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- Crystal data of **1a**: $\text{C}_{16}\text{H}_{15}\text{NO}_2$, $M = 253.301$, orthorhombic, $a = 10.420(2)\text{ \AA}$, $b = 17.208(4)\text{ \AA}$, $c = 7.519(2)\text{ \AA}$, $U = 1348.3(6)\text{ \AA}^3$, $T = 293\text{ K}$, space group $P2_12_12_1$ (no. 19), $Z = 4$, $\mu(\text{Cu-K}\alpha) = 0.66\text{ mm}^{-1}$, 1511 reflections measured, 1326 unique ($R_{\text{int}} = 0.046$) which were used in all calculations. The final $wR(F^2)$ was 0.151 (all data). CCDC 215658.
- Crystal data of **1b**: $\text{C}_{18}\text{H}_{19}\text{NO}_2$, $M = 281.355$, orthorhombic, $a = 10.937(5)\text{ \AA}$, $b = 13.987(5)\text{ \AA}$, $c = 9.896(4)\text{ \AA}$, $U = 1513.8(10)\text{ \AA}^3$, $T = 293\text{ K}$, space group $P2_12_12_1$ (no. 19), $Z = 4$, $\mu(\text{Cu-K}\alpha) = 0.64\text{ mm}^{-1}$, 1655 reflections measured, 1616 unique ($R_{\text{int}} = 0.059$) which were used in all calculations. The final $wR(F^2)$ was 0.346 (all data). CCDC 215659.
- Crystal data of **1c**: $\text{C}_{23}\text{H}_{21}\text{NO}_2$, $M = 343.426$, orthorhombic, $a = 14.384(4)\text{ \AA}$, $b = 16.234(5)\text{ \AA}$, $c = 8.049(4)\text{ \AA}$, $U = 1879.6(12)\text{ \AA}^3$, $T = 293\text{ K}$, space group $P2_12_12_1$ (no. 19), $Z = 4$, $\mu(\text{Cu-K}\alpha) = 0.61\text{ mm}^{-1}$, 2086 reflections measured, 1810 unique ($R_{\text{int}} = 0.037$) which were used in all calculations. The final $wR(F^2)$ was 0.094 (all data). CCDC 215660.
- Crystal data of **1d**: $\text{C}_{28}\text{H}_{23}\text{NO}_2$, $M = 405.497$, orthorhombic, $a = 19.753(5)\text{ \AA}$, $b = 22.214(7)\text{ \AA}$, $c = 9.936(3)\text{ \AA}$, $U = 1513.8(10)\text{ \AA}^3$, $T = 293\text{ K}$, space group $P2_12_12_1$ (no. 61), $Z = 8$, $\mu(\text{Cu-K}\alpha) = 0.61\text{ mm}^{-1}$, 4437 reflections measured, 2926 unique ($R_{\text{int}} = 0.050$) which were used in all calculations. The final $wR(F^2)$ was 0.217 (all data). CCDC 215661. See <http://www.rsc.org/suppdata/cc/b3/b315729f/> for crystallographic data in CIF or other electronic format.
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