ORGANIC LETTERS

2008
Vol. 10, No. 18
4085−4088

Enantioselective Synthesis Utilizing Enantiomorphous Organic Crystal of Achiral Benzils as a Source of Chirality in Asymmetric Autocatalysis

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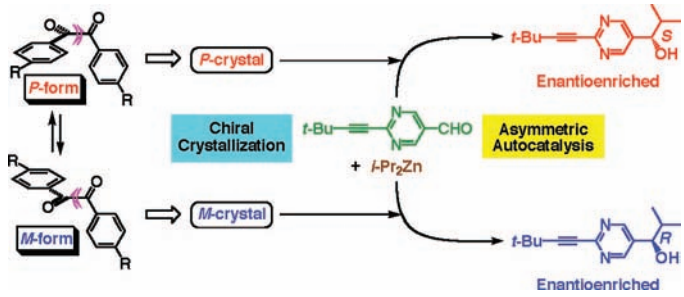
Received July 14, 2008

ABSTRACT



Chiral crystals of achiral benzils act as efficient chiral initiators of asymmetric autocatalysis to afford highly enantioenriched pyrimidyl alkanols whose absolute configurations depend upon the enantiomorph of the crystal used in conjunction with asymmetric autocatalysis with amplification of enantiomeric excess.

The homochirality of biomolecules such as L-amino acids and D-sugars is one of the essential features of life and has been a puzzle for the chemical origin of life.[1] In addition, chiral crystallization of achiral organic compounds has been one of the important candidates for the origin of chirality. Enantiomorphous organic crystals stereospecifically react in the solid state to form enantioenriched organic compounds.[2]

On the other hand, we have continued studying asymmetric autocatalysis with amplification of enantiomeric excess (ee).[3−5] In the reaction between pyrimidine-5-carbaldehyde and diisopropylzinc (*i*-Pr_2Zn), the produced 5-pyrimidyl alkanol acts as an asymmetric autocatalyst to catalyze the enantiomeric amplification of its own production. In this reaction, the chiral initiator[6−9] controls the absolute configuration of the produced 5-pyrimidyl alkanols and the ee's of the produced alkanols are increased in conjunction with asymmetric autocatalysis.

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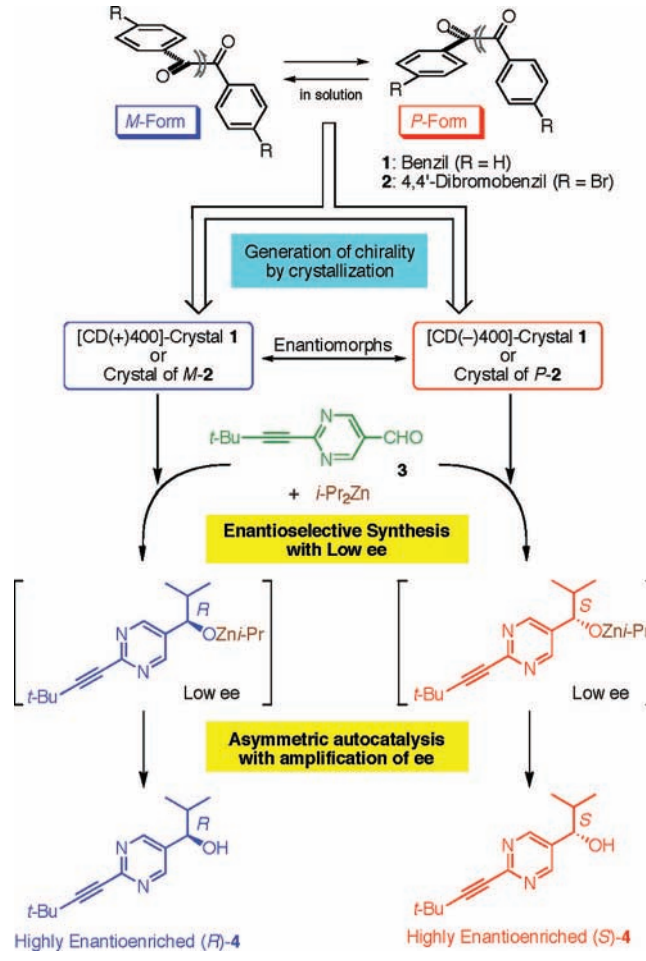
10.1021/ol801600y CCC: $40.75
Published on Web 08/23/2008

We previously reported the asymmetric autocatalysis induced by inorganic chiral crystals of quartz[10a] and sodium chlorate.[10b,c] In addition, chiral organic crystals formed from achiral organic compounds also act as sources of chirality[11] in asymmetric autocatalysis. In this process, after the generation of chirality by crystallization of achiral molecules, tiny enantiomeric imbalance is induced in the external organic compound, i.e., 5-pyrimidyl alkanol, and then the autocatalytic amplification increases the chirality to afford an increased amount of enantioenriched organic compound. We have reported that the chiral two-component molecular crystal of achiral tryptamine and *p*-chlorobenzoic acid acted as a chiral inducer to control the enantioselectivity in asymmetric autocatalytic reactions.[11a] In addition, we showed that crystals of a biologically related achiral organic compound, i.e., hippuric acid (*N*-benzoylglycine)[11b] and the nucleobase, cytosine,[11c] can act as the origin of chirality in asymmetric autocatalysis with amplification of ee.

We herein report the highly enantioselective asymmetric autocatalysis mediated by a chiral crystal of achiral benzil **1** and its dibromo derivative, 4,4′-dibromobenzil **2** (Scheme 1). The enantiomorphous one-component single crystals of achiral benzil **1** and 4,4′-dibromobenzil **2** induce enantioselective addition of *i*-Pr_2Zn to pyrimidine-5-carbaldehyde **3** to afford, in cooperation with asymmetric autocatalysis, 5-pyrimidyl alkanol **4** with significantly increased ee. The absolute configuration of the corresponding 5-pyrimidyl alkanol **4** was controlled efficiently by the solid-state crystalline chirality of these single crystals of benzils. To the best of our knowledge, this is the first example of highly enantioselective synthesis[12] using a chiral organic crystal of achiral benzil and its derivative.

Scheme 1. Enantioselective Synthesis of Enantioenriched 5-Pyrimidyl Alkanol **4** Induced by Chiral Crystals of *P* or *M*-Benzil **1** and 4,4′-Dibromobenzil **2**



Benzil **1** is one of the best-known examples of achiral compounds that exhibit optical activity only in the crystalline

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state,[13] and the crystal of benzil is often called "organic quartz" because it has the same space group ($P3_121$ or $P3_221$)[14] as quartz. The benzil molecules in a specific crystal lattice are fixed into a chiral conformation; i.e., two benzoyl groups in the molecule are torsionally arranged to point in the same *P* or *M* direction so that crystalline chirality is generated. However, in the solution or melt states, free rotation of the twisted bond leads to racemization causing the optical activity to disappear. The enantiomorphous single crystal of benzil **1** can be obtained by recrystallization from a saturated xylene solution at room temperature by slow evaporation of xylene. The enantiomorph of the benzil crystal can be determined by solid-state circular dichroism (CD) analysis with KBr disks. One crystal **1** exhibits a positive Cotton effect at approximately 400 nm ([CD(+)400]), while the other crystal **1** shows a negative Cotton effect ([CD(−)400]) (Figure 1).

In addition, we found that the dibromo derivative of benzil, i.e., 4,4′-dibromobenzil **2**, crystallizes in a chiral form (enantiomorphous space group: $P2_12_12$). The CD spectra of compound **2** and the X-ray single-crystal structure of **2** are shown in Figure 1. The single crystals of 4,4′-dibromobenzil **2** were grown from saturated chloroform solutions by slow evaporation at room temperature under atmospheric pressure. The absolute configuration of the helicity around the 1,2-diketone moieties was determined by X-ray single-crystal analysis. The crystal of the molecules with *M* helicity shows a positive Cotton effect at ca. 320 nm ([CD(+)320]), and the crystal with *P* helicity shows a negative Cotton effect ([CD(−)320]).

The results of the asymmetric autocatalysis mediated by the chiral crystals of benzil **1** and 4,4′-dibromobenzil **2** are summarized in Table 1. Because the absolute configuration of the single crystal of benzil **1**[15] cannot be completely determined, the enantiomorphs of benzil crystals are depicted using the sign of the Cotton effect at 400 nm. The (*S*)-pyrimidyl alkanol **4** with 94% ee was obtained in 86% yield (series A, entry 1) when the autocatalytic reaction was performed in the presence of the powder of [CD(−)400]-crystal of benzil **1** as the chiral inducer. On the other hand, when pyrimidine-5-carbaldehyde **3** was treated with *i*-Pr_2Zn in the presence of powdered single crystal [CD(+)400]-1, the formation of (*R*)-5-pyrimidyl alkanol **4** was observed in 89% yield with 96% ee (entry 2). The correlation between the crystal chirality of benzil **1** and the produced chiral 5-pyrimidyl alkanol **3** was reproducible; i.e., a single crystal of [CD(−)400]-**1** induces the formation of alkanol **4** with the *S* configuration and the opposite [CD(+)400]-**1** controlled the production of the *R* enantiomer **4** (entries 3−6). To exclude any chiral factor other than the chirality of the subjected crystals, the reactions were run using the same apparatus but only changing the crystal enantiomers. The results were found to be reproducible; i.e., [CD(−)400]- and [CD(+)400]-**1** afforded (*S*)- and (*R*)-**4**, respectively (entries 7 and 8).

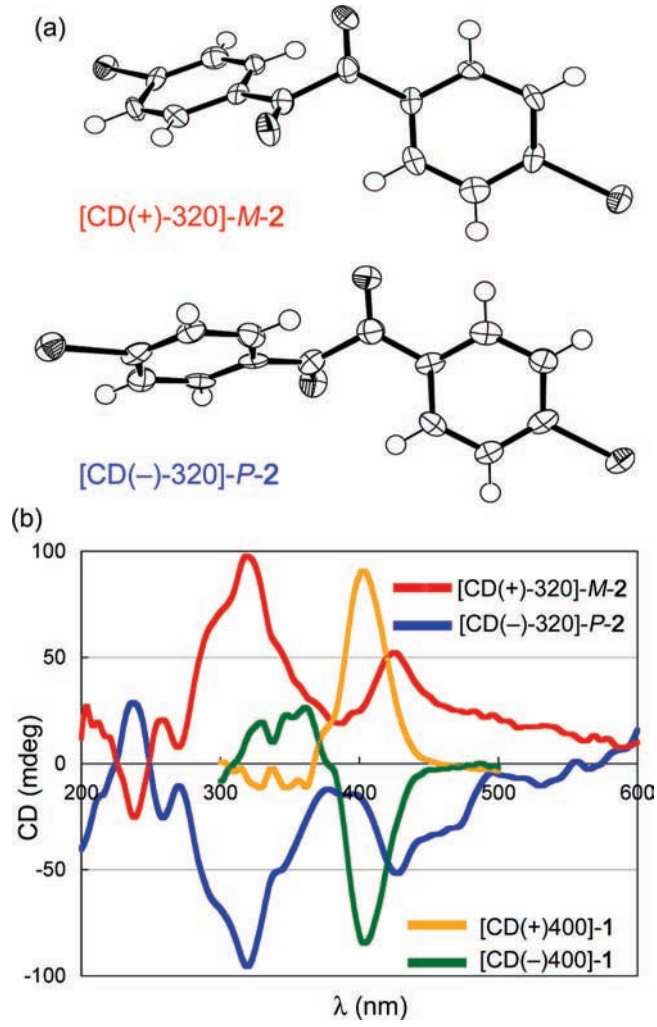

Figure 1. (a) X-ray single-crystal analysis of *P*- and *M*-4,4′-dibromobenzil **2** with skew structure (80% thermal elipsoid). (b) Solid-state CD spectra of the both enantiomorphous crystals of benzil **1** and 4,4′-dibromobenzil **2**, taken in KBr disks.

Next, we examined the addition of *i*-Pr_2Zn to aldehyde **3** under the same conditions using a chiral crystal of 4,4′-dibromobenzil **2** (Scheme 1).[16] In the X-ray single-crystal analysis, the absolute sense of the helicity around the skewed 1,2-dicarbonyl moieties can be determined (Figure 1). Therefore, the chirality of the crystalline form is depicted using the *P* or *M* helicity of the component molecules in the single crystal. In entry 9 (Table 1), the enantioselective formation of (*R*)-5-pyrimidyl alkanol **4** was induced in the presence of a powdered crystal of *M*-**2** and was obtained with 96% ee in 87% yield. On the other hand, when the enantiomorphous crystal of *P*-**2** was subjected to the reaction, the production of enantiomerically amplified (*R*)-**4** with 94%

(12) Although the possibility of the solid-state stereospecific reaction using the chiral crystal of benzil **1** as a reactant has been envisaged, to the best of our knowledge, there has not been the report of the observation of the asymmetric induction in the solid-state reaction. See also ref 2b and references cited therein.

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Table 1. Correlation between the Enantiomorphs of the Crystal of Benzils **1** and **2** Used as Chiral Inducer and Chiral Pyrimidyl Alkanol **4** by Asymmetric Autocatalysis

	chiral source		pyrimidyl alkanol **4**		
entry[a]	chirality	compd	yield (%)	ee[b] (%)	config
series A[c]					
1	[CD(−)400]	**1**	86	94	*S*
2	[CD(+)400]	**1**	89	96	*R*
3	[CD(−)400]	**1**	90	93	*S*
4	[CD(+)400]	**1**	92	96	*R*
5	[CD(−)400]	**1**	89	95	*S*
6	[CD(+)400]	**1**	86	93	*R*
7[d]	[CD(−)400]	**1**	85	88	*S*
8[d]	[CD(+)400]	**1**	87	92	*R*
series B[e]					
9	*M*	**2**	87	96	*S*
10	*P*	**2**	92	94	*R*
11	*M*	**2**	89	97	*S*
12	*P*	**2**	93	95	*R*
13	*M*	**2**	98	96	*S*
14	*P*	**2**	90	96	*R*
15	*M*	**2**	87	96	*S*
16	*P*	**2**	89	97	*R*

[a] General procedure of asymmetric autocatalysis was described in ref 17. [b] The ee value was determined by HPLC on a chiral stationary phase. The ee can be amplified to almost enantiomerically pure >99.5% ee by the consecutive asymmetric autocatalysis (see ref 5c). [c] The molar ratio of powdered single crystal of benzil **1**/pyrimidine-5-carbaldehyde **3**/*i*-Pr_2Zn = 0.15:1.45:3.3. The powder (particle size: 5−10 μm) of enantiomorphous crystal **1** used as chiral initiator of asymmetric autocatalysis was prepared from the single crystal of benzil **1** by grinding using a pestle and mortar after the discrimination of the chirality by CD analysis. [d] To exclude any asymmetric effect other than that of the chiral crystal of benzil, the reactions were performed using the same apparatus, and the enantioface selectivity induced by the crystal chirality was checked. [e] The molar ratio of powdered crystal of **2**/**3**/*i*-Pr_2Zn = 0.15:0.65:1.7.

ee was obtained in 92% yield (entry 10). The correlation between the helicity of the twisted 1,2-diketone unit and the absolute configuration of the formed **4** was reproducible, that is, the crystals of *M*- and *P*-**2** act as the chiral source of asymmetric autocatalysis to afford the enantiomerically enriched *S*- and *R*-**4**, respectively (entries 11−16). In this system, after the crystal chirality induced a tiny ee in the produced asymmetric autocatalyst **4**, the subsequent asymmetric autocatalysis with amplification of ee gave an increased amount of enantiomerically enhanced product.

The enantioselectivity observed in this asymmetric reaction may be explained as follows: the powdered chiral crystals of **1** and **2** form the chiral reaction field, which mediate the small face-selection in the addition reaction of *i*-Pr_2Zn to pyrimidine-5-carbaldehyde **3**, so that a tiny ee was induced in the initially forming autocatalyst **4** (as isopropylzinc alkoxide). Then, subsequent asymmetric autocatalysis afforded alkanol **4** (as zinc alkoxide) in a high ee and with the absolute configuration corresponding to the chirality of the submitted crystals. We assume the possibility of asymmetric $\pi-\pi$ interactions between the benzene rings of the benzils and pyrimidine ring in the aldehyde **3** and/or initially formed isopropylzinc alkoxide of alkanol **4**. The coordination of zinc atom with the benzoyl oxygen of benzils may form the chiral complex. These chiral influences would induce the initial asymmetry in the autocatalyst that was amplified to a significant enantiomeric enrichment during the asymmetric autocatalytic reaction. In addition, there is the possibility that the coordination of *i*-Pr_2Zn on the chiral surface of the benzil crystal should form the chiral zinc species to generate the enantioselectivity of alkylzinc addition.

In summary, the highly enantioselective addition of *i*-Pr_2Zn to pyrimidine-5-carbaldehyde **3** was achieved by utilizing the crystal chirality of benzil **1** and 4,4′-dibromobenzil **2**. These results clearly demonstrate that the chirality of "organic quartz", a representative chiral organic crystal of achiral benzils, is responsible for the enantioselective addition of *i*-Pr_2Zn to aldehyde **3**. This is the first realization of an asymmetric reaction using a chiral crystal of achiral benzils as the origin of chirality in conjunction with asymmetric autocatalysis. Further mechanistic details are now under investigation.

Acknowledgment. This work was supported by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology. N.F. acknowledges the exchange program between University of Modena and Reggio Emilia and Tokyo University of Science.

Supporting Information Available: Methods to prepare the single and powder-like crystals of 4,4′-dibromobenzil **2** and X-ray crystallographic data (CIF) of **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) The single crystal with enough size to perform the asymmetric autocatalysis using as the chiral initiator could not be obtained in the present stage. Thus, the powder (particle size: 10−20 μm) of 4,4′-dibromobenzil crystals used as chiral source of asymmetric autocatalysis was prepared by grinding the powder-like crystals of **2**, which were grown by a seeding method under stirring conditions using the fragment of native single crystals whose absolute configuration was known by X-ray analysis (The details on the preparation of single and powder-like crystals of **2** are presented in the Supporting Information).

(17) General procedure for asymmetric autocatalysis (Table 1, entry 9): An enantiomorphous powder-like crystal of 4,4′-dibromobenzil **2** was ground into a fine powder using a pestle and mortar (particle size: 10−20 μm). *i*-Pr_2Zn (0.03 mmol, 0.3 mL, 1.0 M hexane solution) was added dropwise to a finely powdered crystal of M-**2** (55.2 mg, 0.15 mmol) and aldehyde **3** (9.4 mg, 0.05 mmol) over a period of 1 h at 0 °C. After the mixture was stirred for 12 h, toluene (2.0 mL) and *i*-Pr_2Zn (0.6 mmol, 0.6 mL, 1.0 M toluene solution) were added at 0 °C. Then, a solution of **3** (37.4 mg, 0.2 mmol) in toluene (1.0 mL) was added over a period of 1 h at 0 °C and the reaction mixture stirred at 0 °C for 2 h. Once again, after toluene (5.0 mL) and *i*-Pr_2Zn (0.8 mmol, 0.8 mL, 1.0 M toluene solution) were added, a solution of **3** (75.3 mg, 0.4 mmol) in toluene (2.0 mL) was added dropwise over a period of 50 min at 0 °C. After the mixture was stirred for 2 h, the reaction was quenched with a mixture of 30% aqueous ammonia and saturated aqueous ammonium chloride (2:1, v/v) solution (10 mL). The mixture extracted using ethyl acetate three times. The combined organic layers were dried over anhydrous sodium sulfate and evaporated in vacuo. Purification of the residue by silica gel column chromatography (hexane/ethyl acetate, 3:1 to 2:1, v/v) gave the (*R*)-alkanol **4** (131.4 mg, 0.566 mmol, 96% ee) in 87% yield.