

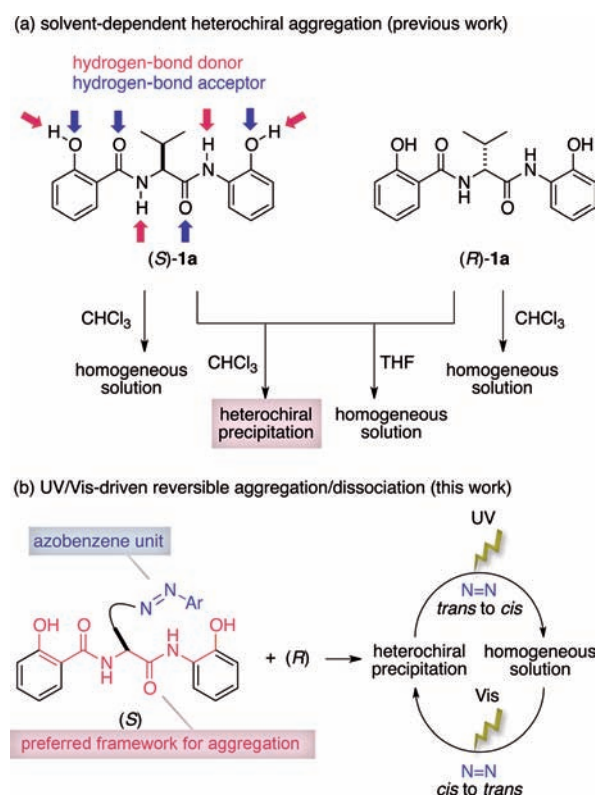
Reversible Heterochiral Aggregation/Dissociation of Bis(2-hydroxyphenyl)diamides Driven by UV/Vis Irradiation**

Akihiro Nojiri, Naoya Kumagai,* and Masakatsu Shibasaki*

The dynamic self-assembly of molecules into supramolecular ensembles is the basis for a vast array of living systems and has inspired chemists to design and construct molecular architectures with dynamic and responsive properties.^[1] Because molecular assembly is often exerted by the integration of various noncovalent interactions, such as hydrogen bonding, π - π interactions, and solvophobic effects, programmed perturbation of these interactions with external stimuli gives rise to a dynamic supramolecular system.^[2] For example, a hydrogen-bonding pattern can be modified by temperature,^[3] pH value,^[4] metal cations,^[5] and light,^[6] leading to stimuli- and environment- responsive materials. Among these external stimuli, light offers a particularly effective noncontact method for perturbation, because wavelength and intensity can be finely tuned and the response is both rapid and reversible.^[7] Indeed, considerable efforts have been devoted to the development of smart molecular materials exhibiting a photoresponsive dynamic assembly.^[6,7] Chirality is an additional factor used to control molecular assembly.^[8] Heterochiral assembly is ubiquitous in nature, as exemplified by proteinogenic amino acids,^[9] and has attracted particular attention as a possible rationale for the evolution of homochirality in a prebiotic environment.^[10] Remarkable differences in the assembly properties of homochiral and heterochiral samples have been observed in some cases and exploited for significant enantiomeric amplification.^[11] The heterochiral assembly is a viable target for perturbation with external stimuli, producing a new dynamic self-assembly system. Herein, we report low-molecular-weight bis(2-hydroxyphenyl)diamides armed with a light-responsive azobenzene unit that exhibit a reversible heterochiral aggregation/dissociation capability driven by irradiation with ultraviolet (UV) and

visible light (Vis). Multiple alignments of hydrogen-bond donors and acceptors allowed for efficient aggregation and dissociation with high fidelity. X-ray crystallographic analysis of the heterochiral aggregate provides clues to the molecular basis of the aggregation and dissociation properties.

Recently, we reported a solvent-dependent heterochiral aggregation of low-molecular-weight bis(2-hydroxyphenyl)diamide **1a**.^[12,13] (*R*)-**1a** forms insoluble heterochiral aggregates in halogenated solvents upon the addition of (*S*)-**1a**, and the aggregation is highly dependent on the arrangements of the hydrogen-bond donor and acceptor (Scheme 1a). Based on these studies, we hypothesized that the arrangement of phenol and amide functionalities in **1a** is essential for the aggregation properties of low-molecular-weight compounds so that they exhibit significant solubility differences between the homochiral and racemic samples. We envisioned that this unique aggregation property could be applied to a dynamic system, allowing for arbitrary control of aggregation and dissociation by light as a non-accumulative and noncontact external trigger.^[7] Exploitation of the *trans*-*cis* isomerism of



Scheme 1. a) A static heterochiral aggregation system and b) a dynamic heterochiral aggregation system.

[*] A. Nojiri, Dr. N. Kumagai, Prof. Dr. M. Shibasaki
Institute of Microbial Chemistry, Tokyo
3-14-23 Kamiosaki, Shinagawa-ku, Tokyo 141-0021 (Japan)
E-mail: nkumagai@bikaken.or.jp
mshibasaki@bikaken.or.jp
Homepage: http://www.bikaken.or.jp/research/group/shibasaki/shibasaki-lab/index_e.html

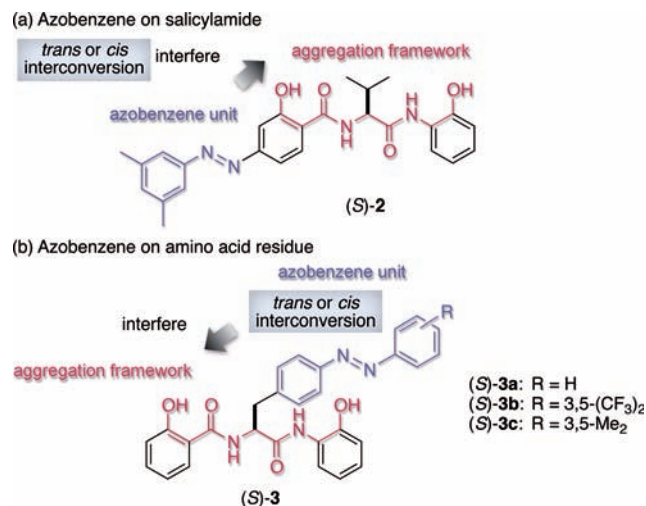
A. Nojiri
Graduate School of Pharmaceutical Sciences
The University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033 (Japan)

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azobenzenes for perturbing intermolecular hydrogen-bond interactions was anticipated to offer an effective method for regulating aggregation properties (Scheme 1 b).

The design of bis(2-hydroxyphenyl)diamides bearing the azobenzene unit is depicted in Scheme 2. Initially, preserving the isopropyl group derived from valine as well as the preferred hydrogen-bond donor/acceptor arrangement



Scheme 2. Design of bis(2-hydroxyphenyl)diamides **2** and **3** bearing an azobenzene unit.

(shown in red), we attached the azobenzene unit (shown in blue) of diamide **2** to the salicylic acid moiety (Scheme 2 a). We anticipated that the *trans* and *cis* configurations of azobenzene, which are interconverted by UV and Vis irradiation, would have an impact on the aggregation capability, thus allowing us to control aggregation and dissociation by external light irradiation. Unexpectedly, **2** afforded few insoluble heterochiral aggregates and photoisomerism of **2** was not efficient.^[14,15] This finding led us to focus on the amino acid residue in the diamide framework, to which the azobenzene unit is installed. As a preliminary study, “cross” heterochiral aggregation was examined, where heterochiral diamides bearing different amino acid residues were mixed to test the precipitation capability. Whereas the mixture of [(S)-**1a** + (R)-**1a**] derived from valine or the mixture of [(S)-**1b** + (R)-**1b**] derived from phenylalanine underwent heterochiral precipitation in CHCl₃,^[16] the “cross” mixture of [(S)-**1a** + (R)-**1b**] did not produce insoluble heterochiral aggregate, and the resulting mixture remained homogeneous even after 24 h (Figure 1 a). For the ensemble of three molecules of [(S)-**1a** + (R)-**1a** + (R)-**1b**], no formation of a heterochiral aggregate with a “cross” pair was observed, but the insoluble heterochiral aggregate of [(S)-**1a** + (R)-**1a**] was formed exclusively, and (R)-**1b** was not recognized and remained in the solution phase (Figure 1 b). These results indicated that the amino acid residue had a significant impact on the aggregation to form precipitates, and the uniformity of the residue is essential to the precipitation.^[17] Therefore, we anticipated that the installation of the azobenzene unit at the residue part would be

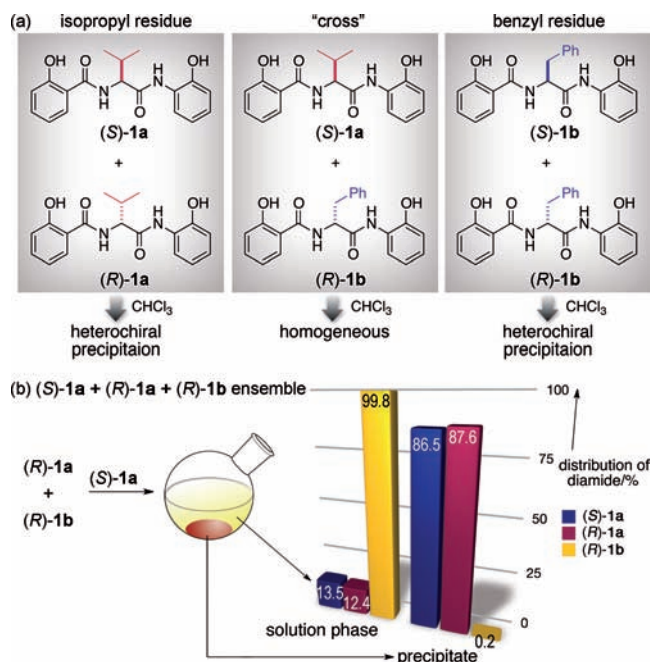
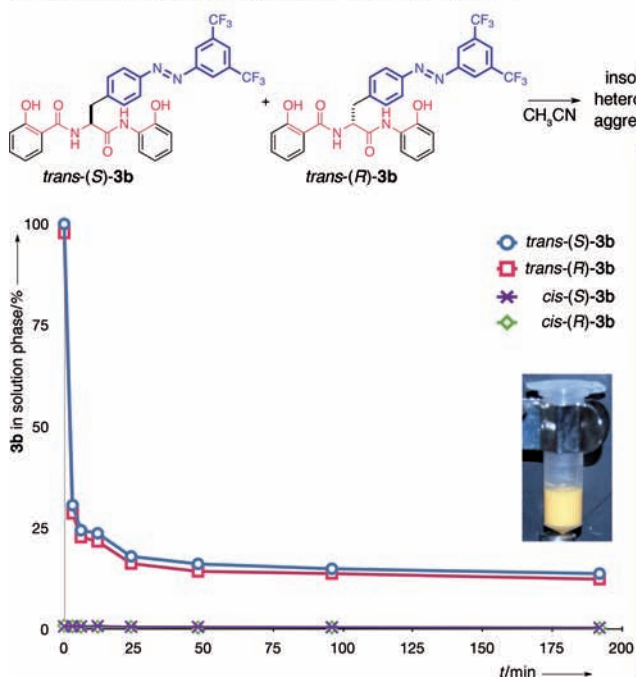


Figure 1. a) Impact of the amino acid residue on heterochiral precipitation. b) High fidelity in the formation of insoluble heterochiral aggregates from the ensemble of three diamides bearing different amino acid residues.

suitable for perturbing the intermolecular interaction by *trans*–*cis* photoisomerization and induce reversible heterochiral precipitation and dissolution.

Based on the above assumption, we next designed diamides **3** bearing a pendant azobenzene unit at the residue part (Scheme 2 b).^[18] Although the solubility of diamide (S)-**3a** was too low in most of the common organic solvents to conduct further studies, (S)-**3b** and (S)-**3c** exhibited suitable solubility to allow for the preparation of a homochiral solution in CHCl₃ or CH₃CN. (S)-**3b** was easy to handle and the heterochiral aggregation of **3b** was examined next. When 0.05 M solutions of *trans*-(S)-**3b** and *trans*-(R)-**3b** in CH₃CN were mixed, an insoluble heterochiral aggregate was produced immediately; approximately 70 % of **3b** was precipitated within three minutes (Figure 2 a).^[19] Aggregation reached completion after approximately three hours, and 87 % of **3b** was precipitated.^[20] Subsequently, the resulting suspension was irradiated with UV light at 365 nm for six hours with stirring to isomerize the pendant *trans*- to the *cis*-azobenzene unit. The isomerization resulted in the gradual disappearance of precipitates to increase the concentration of **3b** in the solution phase (Figure 2 b). Eventually, a clear homogeneous solution of **3b** developed, and over 95 % of **3b** went back into solution, probably because the bent *cis* configuration of the azobenzene moiety disturbed the efficiency of the intermolecular hydrogen-bond interactions between the preferred framework of (S)-**3b** and (R)-**3b**.^[21,22]

To dissect the origin of the heterochiral precipitation, we performed an X-ray crystallographic analysis of a single crystal obtained from the heterochiral aggregate of **3b** (Figure 3).^[23] Similar to the heterochiral aggregate of **1a**,^[12,24] we observed a zig-zag tight packing of (S)-**3b** and

(a) Formation of insoluble heterochiral aggregate of *trans*-**3b**


(b) Dissolution of insoluble heterochiral aggregate

by UV (365 nm) irradiation

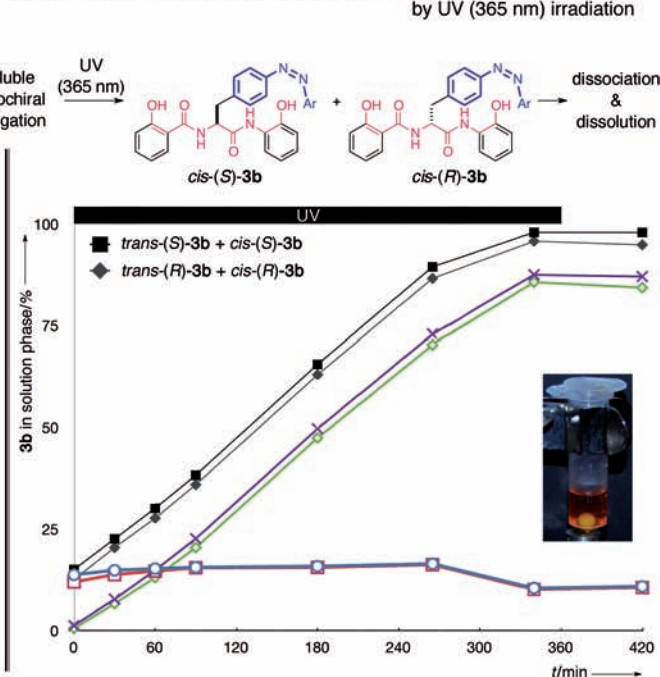


Figure 2. a) Formation of insoluble heterochiral aggregates of *trans*-**3b**. CH_3CN solutions of *trans*-(*S*)-**3b** and *trans*-(*R*)-**3b** (both 0.05 M) were mixed and the content of the solution phase was analyzed by HPLC. b) Dissolution of insoluble heterochiral aggregates by UV irradiation (365 nm). As the fraction of *cis*-(*S*)-**3b** and *cis*-(*R*)-**3b** increased, the concentration of diamides (*S*)-**3b** and (*R*)-**3b** in the solution phase increased to form a clear orange solution after six hours. The white object in the photograph is a teflon-coated magnetic stir bar. $\text{Ar} = 3,5\text{-(CF}_3)_2\text{C}_6\text{H}_3$.

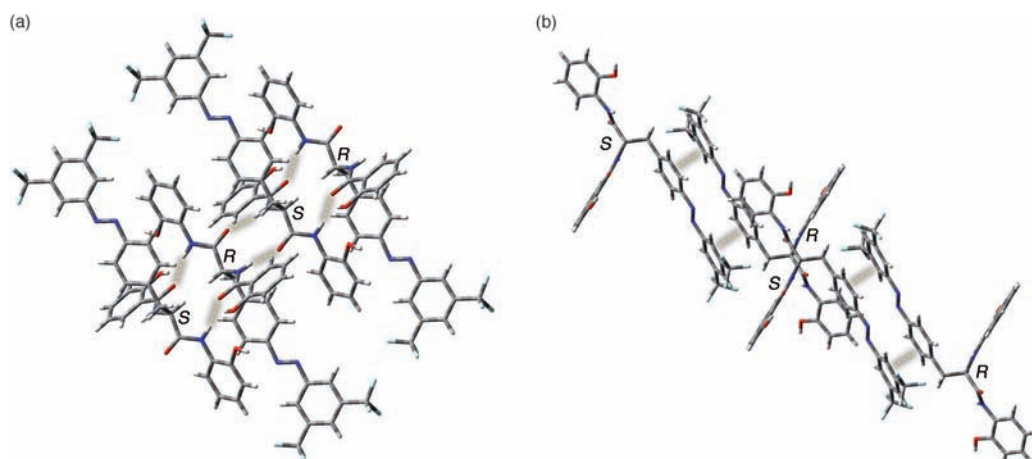


Figure 3. X-ray crystal structure of the heterochiral aggregate of **3b** represented in a tube model. a) Tight hydrogen-bond packing in an *R/S* alternating array along the amide functionalities of *trans*-(*S*)-**3b** and *trans*-(*R*)-**3b**. b) A close offset π - π contact (3.58 Å) was observed between azobenzene units. The electron-deficient $(\text{CF}_3)_2\text{C}_6\text{H}_3$ group and C_6H_4 group were paired. H white, C gray, N blue, O red, F light blue.

(*R*)-**3b** through hydrogen bonding between amide functions (Figure 3a). Furthermore, azobenzene units lined up in parallel and offset π - π stacking was operative as a secondary interaction (Figure 3b). Although the crystal structure could not directly reflect the packing pattern of the insoluble heterochiral aggregate, isomerization of the *trans*-azobenzene unit to *cis*-azobenzene might attenuate the heterochiral association through the preferred hydrogen-bond framework,

leading to dissociation and dissolution of the insoluble heterochiral aggregate.

The reversible nature of *trans*-*cis* photoisomerism can be exploited to produce reversible heterochiral precipitation and dissolution in the present diamide system (Figure 4). After the initial formation of the insoluble heterochiral aggregate (point (A) in Figure 4), UV irradiation at 365 nm was used to produce a clear solution (point (B) in Figure 4). The thus-formed homogeneous heterochiral so-

lution of *cis*-configured **3b** was irradiated with visible light at a wavelength above 422 nm for three hours to re-isomerize to *trans*-azobenzene, and subsequent stirring again resulted in the formation of insoluble heterochiral aggregate (point (C) in Figure 4). When the mixture was left in the dark, the *trans*/*cis* ratio of **3b** remained stable, and the precipitation persisted (point (D) in Figure 4). This precipitation/dissolution process can be repeated at least five times.^[25] Furthermore, in contrast to the [(*S*)-**1a** + (*R*)-**1b**] mixture, for which no “cross”

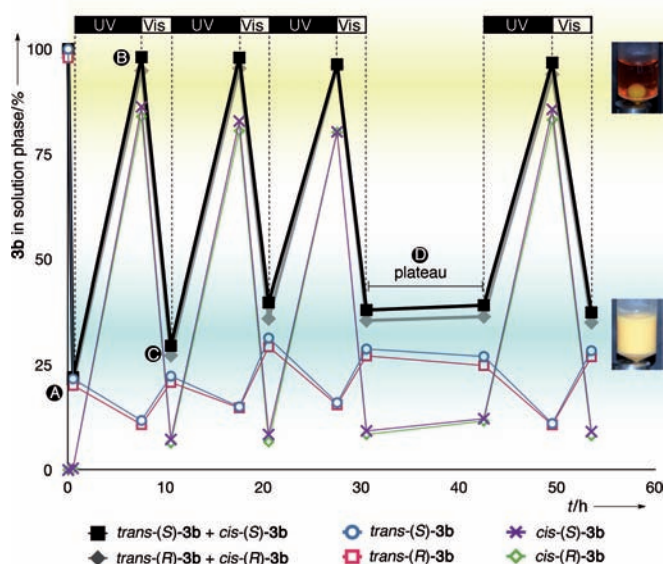


Figure 4. Iterative formation of an insoluble heterochiral aggregate of diamide **3b** driven by UV/Vis irradiation. CH₃CN solutions of *trans*-(S)-**3b** and *trans*-(R)-**3b** (both 0.04 M) were mixed and the content of the solution phase was monitored by HPLC analysis.

aggregation occurred (Figure 1), the “cross” aggregation proceeded with a [(R)-**3b** + (S)-**3c**] combination to form heterochiral precipitate (Figure 5), presumably because the positions of distinct substituents were sufficiently far apart

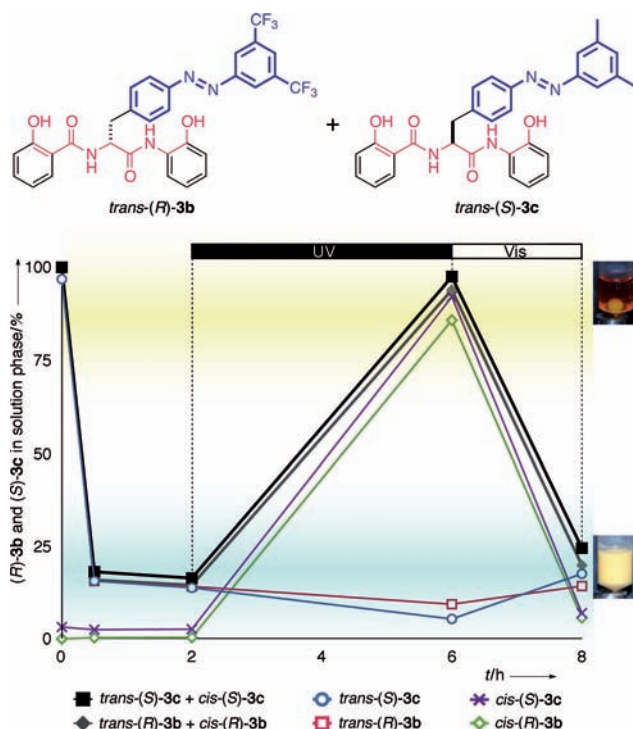


Figure 5. Reversible formation of “cross” insoluble heterochiral aggregate of (R)-**3b** and (S)-**3c**. CH₃CN solutions of *trans*-(R)-**3b** and *trans*-(S)-**3c** (both 0.05 M) were mixed and the content of the solution phase was analyzed by HPLC.

from the preferred hydrogen-bonding framework and favorable π - π interaction and hydrogen bonding were achieved without attenuating each other. Introduction of a functional group to endow a specific catalytic function to these dynamic precipitation/dissolution systems would be possible and will be examined in future studies.^[26,27]

In conclusion, we demonstrated the reversible formation of insoluble heterochiral aggregate of low-molecular-weight diamides bearing an azobenzene unit. *Trans*-*cis* isomerism of the azobenzene unit had a significant impact on the precipitation properties, allowing us to control precipitation and dissolution of the diamides by UV/Vis irradiation, which can be repeated reproducibly. The concentration of the diamides in the solution phase can be manipulated by this reversible precipitation/dissolution, and the introduction of catalytic functional groups to the diamides would foster the development of a smart catalyst, the catalytic efficiency of which is controlled by an external signal.^[26] Further exploration of diamides to exploit this aggregation/dissociation property in molecular catalysis is underway.

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- [14] Synthesis of diamide **2** is described in the Supporting Information.
- [15] *Trans* to *cis* isomerism of **2** was not efficient and a sample with a *trans/cis* ratio of 44:56 was used for the experiment of the heterochiral precipitation of *cis*-(*R*)-**2**. The reluctant isomerism of **2** was also a negative property for the present study.
- [16] Quantitative analysis of the heterochiral precipitation of [(*S*)-**1a** + (*R*)-**1a**] and [(*S*)-**1b** + (*R*)-**1b**] is described in the Supporting Information.
- [17] As described in the last section, diamides **3** exhibited “cross” heterochiral precipitation.
- [18] Synthesis of diamide (*S*)-**3a-c** is described in the Supporting Information.
- [19] The mixture was stirred with a magnetic stirrer. At each point, the mixture was centrifuged and a small aliquot of the resultant supernatant was subjected to HPLC analysis to determine the content in the solution phase. Salicylamide was used as an internal standard for HPLC analysis. See the Supporting Information for details.
- [20] 13% of *trans*-**3b** would give a saturated solution in CH₃CN.
- [21] At concentrations lower than 0.02 M, the formation of insoluble heterochiral aggregate was not efficient. Because of the inherent solubility limit of homochiral *trans*-**3b**, concentrations higher than approximately 0.06 M were not suitable.
- [22] At the photostationary state by UV irradiation (365 nm) in CD₃CN, the *cis/trans* ratio of **3b** was 89:11.
- [23] CH₃CN solutions of (*R*)-*trans*-**3b** and (*S*)-*trans*-**3b** (both 0.021 M) were mixed and the resulting heterochiral solution of *trans*-**3b** was left standing at room temperature to grow a single crystal of the heterochiral aggregate of *trans*-**3b**. Only the concentration and stirring were different from the conditions for Figure 2, in which immediate precipitation was observed. CCDC 843843 (*trans*-**3b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. A summary of the crystallographic analysis of heterochiral *trans*-**3b** is provided in the Supporting Information.
- [24] In the X-ray crystal structure of the heterochiral aggregate of **1a**, the phenol moiety was involved in the *R/S* array. In contrast, face-to-face hydrogen bonding between two amide groups was observed for the insoluble heterochiral aggregate of *trans*-**3b**, presumably because maximum π - π interaction was achieved in this orientation.
- [25] The thermal return of the azobenzene unit was very slow. Re-precipitation of the dissolved heterochiral mixture was not observed when the mixture was left in the dark over one week.
- [26] The present reversible heterochiral precipitation/dissolution system is applicable to switchable catalysis. The dissolved state (high concentration in solution) can catalyze a specific reaction by the installation of a catalytic functional group to the diamide molecule. On the other hand, the precipitated state (low concentration in solution) would fail in the catalysis.
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