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# *In situ* manipulation of catalyst performance *via* the photocontrolled aggregation/dissociation state of the catalyst†

Akihiro Nojiri,[ab] Naoya Kumagai*[a] and Masakatsu Shibasaki*[ac]

**A diamide armed with a photochromic azobenzene unit and a nucleophilic pyridyl group varied its aggregation/dissociation state depending on the *trans*/*cis* geometry of the azobenzene. The catalytic activity of the pyridyl group was closely linked to the aggregation/dissociation state and hence photoirradiation could manipulate the catalytic performance.**

Catalysis plays a pivotal role in the efficient production of bulk and fine chemicals.[1] In practice, catalysts are specifically designed and fine-tuned for optimal execution in certain target reactions. Besides this reaction-oriented pursuit of catalysts, multistate catalytic systems, which produce differential catalytic functions and/or performance depending on the state of the catalyst, have received increased attention.[2,3] Various external triggers, such as photoirradiation and chemical additives, have been exploited to induce structural/conformational changes in the catalyst and hence different catalytic functions can be produced.[4]

Recently, we showed that bis(2-hydroxyphenyl)amide framework[5] **1a** exhibits heterochiral aggregation through a hydrogen bond in halogenated solvents, where (*R*)- and (*S*)-**1a** were mixed together to form insoluble precipitates while homochiral (*R*)- or (*S*)-**1a** remained in solution (Fig. 1a).[6] The two amide and phenol functionalities are responsible for the aggregation, and compound **1b** harnessed with a photochromic azobenzene unit allowed for reversible aggregation/dissociation by UV/Vis irradiation (Fig. 1b).[7] Herein, we envisaged that incorporation of a certain catalytic function into the photochromic diamide framework could produce a photoresponsive multistate catalyst (Fig. 1c). Aggregation/dissociation capability can be applied to the *in situ* manipulation of catalyst concentration in the solution phase, which should be directly linked to catalytic activity, and hence catalytic performance can be controlled by UV/Vis irradiation.

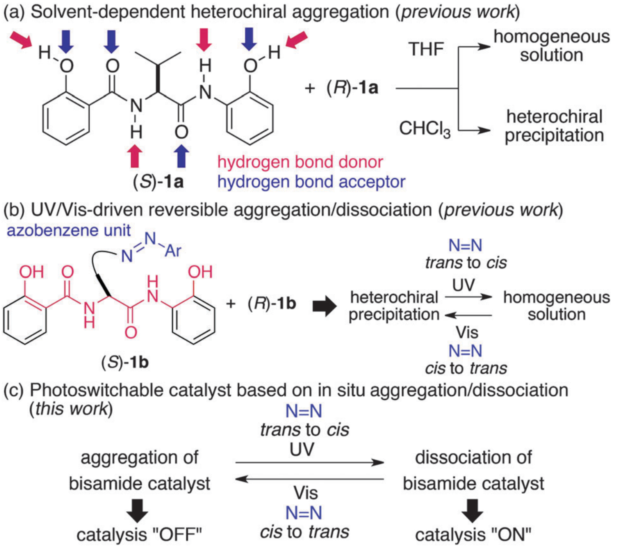

**Fig. 1** Background of aggregation/dissociation property of bis(2-hydroxyphenyl)-amide framework.

Design of the multistate catalyst (*S*)-**1c** is shown in Fig. 2a. The diamide framework and central α-amino acid residue part are engaged for aggregation/dissociation and photochromic control, respectively. Therefore, a catalytic function was introduced into the aromatic group located at both sides. We selected a nucleophilic pyridyl group as a catalytic part and replaced the anilide benzene ring on the right side with a 4-pyridyl group for highest nucleophilicity.[8] In the initial reaction screening, the presence of two phenol groups frequently impeded the target reactions. In contrast, two phenol groups were indispensable for the heterochiral aggregation of **1a** in halogenated solvent; the newly designed diamide *trans*-(*S*)-**1c** installed with a 4-pyridyl group lacking two phenol groups exhibited inherently lower solubility compared with **1b**, and even homochiral *trans*-(*S*)-**1c** formed the aggregates in acetonitrile. The aggregates were dissociated leading to a homogeneous solution when UV irradiation (365 nm) was used to photoisomerize the azobenzene unit from *trans* to *cis*. The contrast of the solubility difference between *trans*-**1c** and *cis*-**1c** was further enhanced in a mixed solvent

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[a] *Institute of Microbial Chemistry (BIKAKEN), 3-14-23 Kamiosaki, Shinagawa-ku, Tokyo 141-0021, Japan. E-mail: nkumagai@bikaken.or.jp, mshibasa@bikaken.or.jp; Fax: +81-3-3441-7589*

[b] *Graduate School of Pharmaceutical Sciences, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan*

[c] *JST, ACT-C, 3-14-23 Kamiosaki, Shinagawa-ku, Tokyo 141-0021, Japan*

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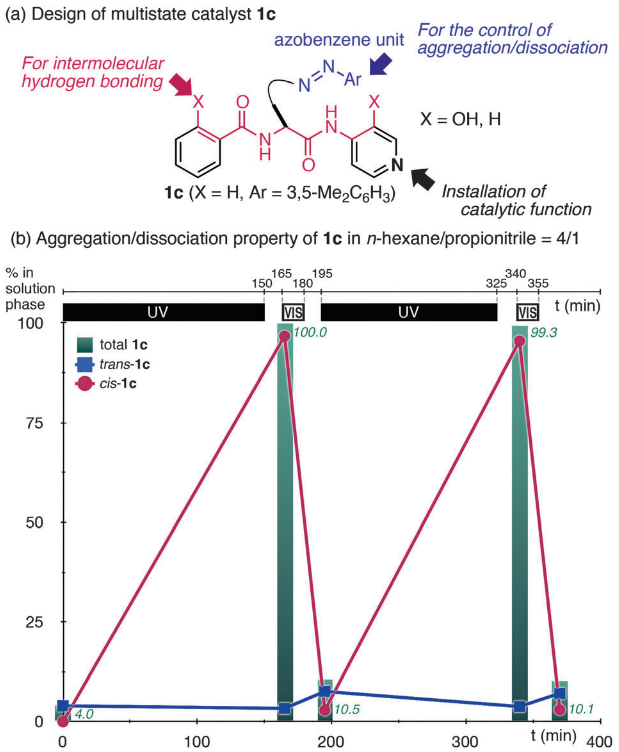

**Fig. 2** Design and property of multistate catalyst **1c**. UV (365 nm) irradiation was used during the period 0–150 min and 195–325 min. Visible light (>422 nm) irradiation was used during the period 165–180 min and 340–355 min. Green bars and numbers represent total amount of **1c** in solution phase.

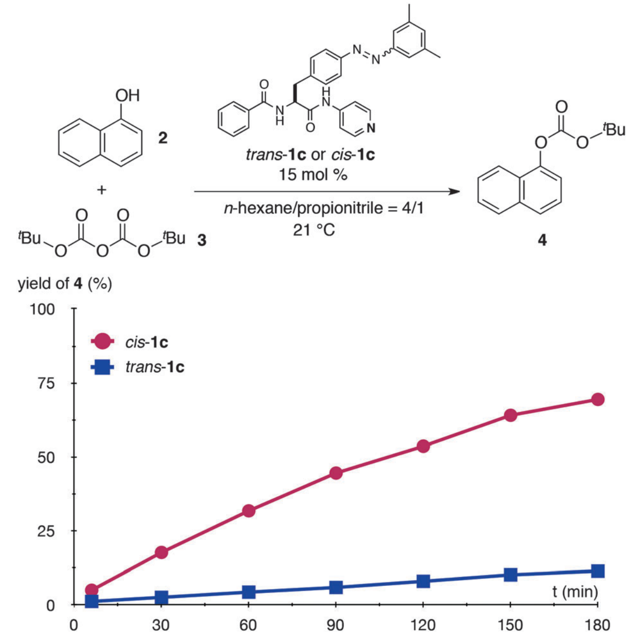

**Fig. 3** Profile of the reaction of **2** with **3** promoted by *trans*-**1c** (blue square) and *cis*-**1c**[9] (red circle). **2**: 0.1 mmol, **3**: 0.12 mmol, solvent 1.5 mL.

system of *n*-hexane–propionitrile = 4/1 (Fig. 2b). Only 4% of **1c** (*trans*/*cis* = 100/0, *trans*-**1c**: blue square) was present in the solution phase. Upon UV (365 nm) irradiation, the fraction of *cis*-**1c** (red circle) gradually increased and a homogeneous solution developed (at 165 min). Visible light (>422 nm) led to re-isomerization to *trans*-**1c** and 89.5% of **1c** aggregated to be excluded from the solution phase (at 195 min). Aggregation/dissociation could be repeated.

With diamide **1c** harnessed with a nucleophilic catalytic unit and reversible aggregation/dissociation capability, we explored the catalytic performance of **1c**. An initial trial was attempted in the reaction of 1-naphthol (**2**) with Boc$_2$O (**3**), which can be accelerated in the presence of a nucleophilic catalyst. To enhance the contrast of aggregation/dissociation states of **1c**, the reaction media were examined, which indicated that *n*-hexane–propionitrile = 4/1 was best suited in the present system; substrates **2**, **3**, and *cis*-**1c**[9] were perfectly miscible while the solubility of *trans*-**1c** was limited to only *ca.* 1 mM. Initially, the catalytic performance of *trans*-**1c** and *cis*-**1c**[9] was evaluated individually in the reaction of **2** with **3** with 15 mol% of catalyst loading (Fig. 3). With the soluble *cis*-**1c**,[9] the reaction profile showed steady progress at 21 °C to give carbonate **4**, and the reaction mixture remained homogeneous. In marked contrast, the reaction using *trans*-**1c** under otherwise identical conditions barely produced **4** in the same reaction period, because the extensive aggregation of *trans*-**1c** caused significant deterioration of the catalytic performance. *Trans*-**1c** and *cis*-**1c**[9] produced comparable catalytic performance in CHCl$_3$,[10] where both *trans*-**1c** and *cis*-**1c**[9] were miscible, indicating that the differential catalytic performance was ascribed to the aggregation/dissociation of the catalyst. This result led us to attempt the *in situ* manipulation of the catalytic performance of **1c** by a real-time transition of the aggregation/dissociation state of **1c** (Fig. 4). The reaction was initiated with 15 mol% of *cis*-**1c**[9] to promote the formation of **4** in a homogeneous mixture. At 30 min, analysis of the reaction mixture showed that **4** was produced in 19% yield (black square) and the content of *trans*-**1c** (blue bar) and *cis*-**1c** (red bar) in the solution phase was 5.6% and 94%, respectively. At this point, visible light irradiation (>422 nm) was used to induce photoisomerization from *cis*-**1c** to *trans*-**1c**. The reaction mixture gradually became turbid because of aggregation of *trans*-**1c**, and the reaction of **2** with **3** was retarded.

At 90 min, almost all of the *cis*-**1c** was isomerized to *trans*-**1c** and the irradiation was terminated. Catalyst **1c** was extensively aggregated, which shut off its catalytic activity and only 6.4% of **4** was produced over a 120 min period (from 90 min to 210 min). Next, the reaction mixture was irradiated with UV light (365 nm) to re-isomerize *trans*-**1c** to *cis*-**1c**, inducing the dissociation of the catalyst to revive its catalytic performance. After 90 min of irradiation (at 300 min), the content of *cis*-**1c** increased to 33% and the reaction rate of **2** with **3** gradually increased achieving steady production of **4**. UV or visible light failed to promote the reaction, confirming that the reaction progress was manipulated solely by the aggregation/dissociation state of **1c**. This catalytic system was applicable to the rearrangement of 2-acyloxybenzofuran **5** to 3-acyl-2-benzofuranone **6** that can be promoted by a nucleophilic catalyst (Fig. 5).[8c,11] In CHCl$_3$ at room temperature, where both *trans*-**1c** and *cis*-**1c**[9] were miscible, the rearrangement of **5** was promoted by 25 mol% of either *trans* or *cis*-**1c**[9] at nearly identical reaction rates.[10] In the *n*-hexane–ethyl acetate = 1/1 mixed solvent system, *trans*-**1c** showed limited solubility (*ca.* 1 mM) because of extensive aggregation and only 14% of rearranged product **6** was obtained after 100 min of reaction. On the other hand, with 25 mol% of *cis*-**1c**,[9] the reaction mixture was homogeneous and

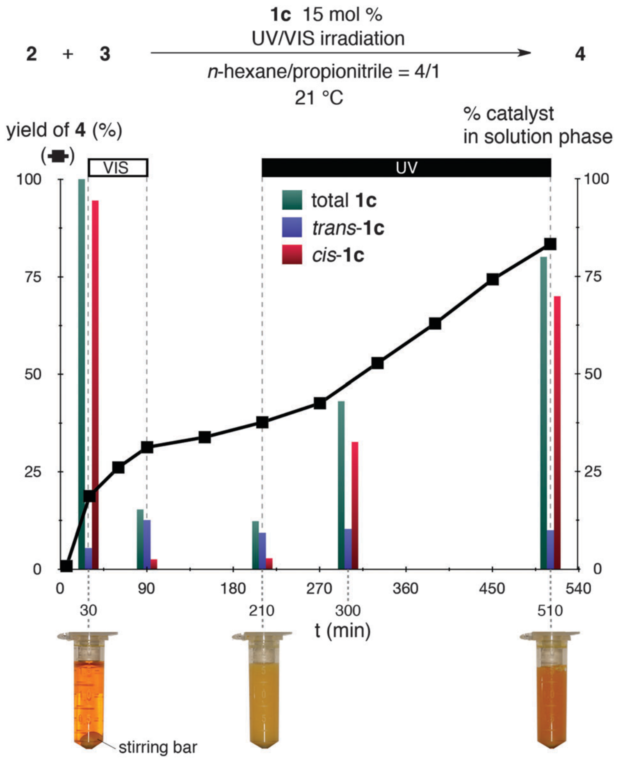

**Fig. 4** Profile of the reaction of **2** with **3** promoted by **1c**. Black squares represent yields of **4**. **2**: 0.1 mmol, **3**: 0.12 mmol, solvent 1.5 mL. Green, blue, and red bars represent the amount of *trans*-**1c** + *cis*-**1c**, *trans*-**1c**, and *cis*-**1c** in the solution phase, respectively. Visible light (>422 nm) irradiation was used during the period 30–90 min. UV light (365 nm) irradiation was used during the period 210–510 min.

rapid reaction progress was observed to afford 80% of **6** after 100 min.[12,13]

In conclusion, we developed a photoswitchable nucleophilic catalyst based on aggregation/dissociation of a diamide framework. The catalyst on–off state could be manipulated in the course of the reaction by UV/Vis irradiation. Installation of other catalytically active functional groups to produce distinct photoswitchable catalysts is currently underway.

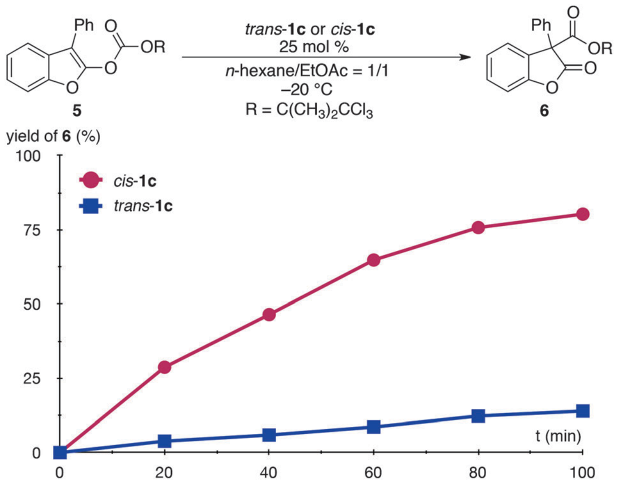

**Fig. 5** Profile of the rearrangement of **5** to **6** promoted by *trans*-**1c** (blue square) and *cis*-**1c**[9] (red circle). **5**: 0.06 mmol, solvent 1.5 mL.

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10 See ESI† for details.

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12 **6** was obtained in 7.8% ee and 14.5% ee by *trans*-(*S*)-**1c** and *cis*-(*S*)-**1c**, respectively (the (*S*)-isomer was obtained as a major product).

13 A small amount of 3-phenyl-2-benzofuranone was associated as a byproduct.