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Fusion of Photochromic Reaction and Synthetic Reaction: Photoassisted Cyclization to Highly Strained Chiral Azobenzenophanes

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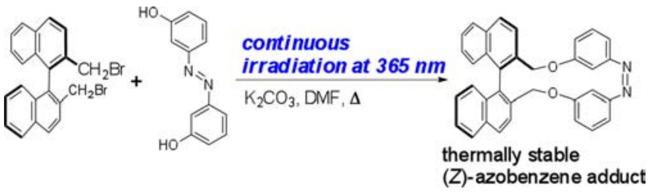
ABSTRACT



A method for synthesizing highly strained cyclic structures by combining photochromic and synthetic reactions is described. Tightly linked azobenzene–binaphthyl dyads (*R*)-4 and (*R*)-6 could not be obtained by conventional cyclization, but continuous application of photoirradiation, which induced (*E*)→(*Z*) isomerization of the azobenzene moiety, allowed the cyclization reaction to proceed, affording the desired chiral azobenzenophanes.

The synthesis, conformation, and optical properties of smaller cyclophanes and nano rings are beginning to attract attention because these molecules often have unusual properties not shared by larger macrocycles and linear analogues.[1,2] Meanwhile, azobenzenes are widely used as molecular switches because they undergo dramatic, reversible, and facile photoisomerization between the (*Z*)- and (*E*)-forms.[3] In general, UV light induces (*E*)→(*Z*) isomerization, whereas visible light or heat induces (*Z*)→(*E*) isomerization. Recently, azobenzenes incorporated into cyclic compounds, so-called azobenzenophanes, have attracted particular interest because isomerization of the azobenzene moiety can efficiently and dramatically change the conformation of the whole molecule.[4] We have previously investigated the configuration and the photoswitching of chiroptical properties of axially chiral

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(1) Recent examples: (a) Kawase, T.; Nishiyama, Y.; Nakamura, T.; Ebi, T.; Matsumoto, K.; Kurata, H.; Oda, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 1086–1088. (b) Forgan, R. S.; Sauvage, J.-P.; Stoddart, J. F. *Chem. Rev.* **2011**, *111*, 5434–5464. (c) Zhang, F.; Goetz, G.; Mena-Osteritz, E.; Weil, M.; Sarkar, B.; Kaim, W.; Baeuerle, P. *Chem. Sci.* **2011**, *2*, 781–784. (d) Sprafke, J. K.; Kondratuk, D. V.; Wykes, M.; Thompson, A. L.; Hoffmann, M.; Drevinskas, R.; Chen, W.-H.; Yong, C. K.; Karnbratt, J.; Bullock, J. E.; Malfois, M.; Wasielewski, M. R.; Albinsson, B.; Herz, L. M.; Zigmantas, D.; Beljonne, D.; Anderson, H. L. *J. Am. Chem. Soc.* **2011**, *133*, 17262–17273.

(2) Highly strained cycloparaphenylenes were synthesized: (a) Jasti, R.; Bhattacharjee, J.; Neaton, J. B.; Bertozzi, C. R. *J. Am. Chem. Soc.* **2008**, *130*, 17646–17647. (b) Yamago, S.; Watanabe, Y.; Iwamoto, T. *Angew. Chem., Int. Ed.* **2010**, *49*, 757–759. (c) Sisto, T. J.; Golder, M. R.; Hirst, E. S.; Jasti, R. *J. Am. Chem. Soc.* **2011**, *133*, 15800–15802.

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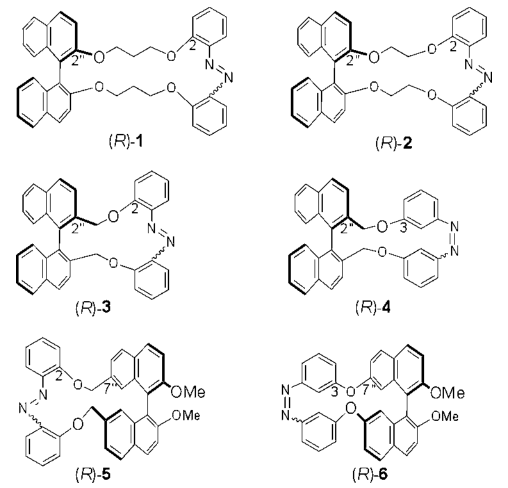

Figure 1. Azobenzene–binaphthyl dyads (*R*)-**1**–**6**.

binaphthyl–azobenzene cyclic dyads, mainly **1**, **2**, and their benzylated analogues (Figure 1).[5] In most molecular switches, including these dyads, the distance between the stimulus-driven moiety and the effector site and the nature of the linkers are very important. Nevertheless, the synthesis of not only cyclic molecular switches but also almost all small cyclic compounds with short linkers is difficult and sometimes impossible because of the large molecular strain. In fact, the shortest linkers that have so far been successfully used to connect a binaphthyl moiety and an azobenzene moiety consist of four atoms, –O–C–C–O–, as in (*R*)-**2**.[5e] Strained azobenzenophanes were previously synthesized by means of N=N forming reaction of two nitro or amino groups under stringent conditions.[6] Here, we focus on the development of a versatile, mild, and simple method for synthesis of small cyclic compounds, and we also investigate their conformations. Initially, (*R*)-**3**–**6**, linked by two atoms (–O–C–) or one atom (–O–), were selected as model compounds, and we examined the feasibility of using simple cyclization by means of tandem Williamson ether synthesis to generate them with the aid of continuous photoirradiation during the reaction to relieve strain as required.

Synthesis of dyads (*R*)-**3**–**6** was first attempted as shown in Scheme 1. (*R*)-**3** and (*R*)-**5** were successfully synthesized as follows. Compound (*R*)-**3** was prepared in moderate yield by coupling of 2,2′-bis(bromomethyl)binaphthyl (*R*)-**7**[7] and 1.0 equiv of 2,2′-dihydroxyazobenzene (**8**). (*R*)-**5** was synthesized similarly, using 7,7′-bis(bromomethyl)binaphthyl (*R*)-**9**. However, attempts to synthesize (*R*)-**4** and (*R*)-**6** from 3,3′-disubstituted azobenzenes **10**[8] and **12**[9] were unsuccessful, affording complex mixtures including larger macromolecules. Under these conditions, the azobenzenes **8**, **10**, and **12** should exist completely in (*E*)-form, which is thermally stable. Therefore, it was considered that the two hydroxy groups of (*E*)-**10** and the fluorinated carbons of (*E*)-**12**, i.e., the reactive points, are too distant from each other, compared with the those of binaphthyls (*R*)-**7** and (*R*)-**11**.[10] In the optimized structures obtained by DFT calculation at the B3LYP/6-31G(d,p) level, the O–O distance is 3.9 Å for (*E*)-**8** and 9.0 Å for (*E*)-**10**, and the C_{sp3}–C_{sp3} distance of the bromomethyl groups in (*R*)-**7** is 4.1 Å.[11] The O–O distance of (*Z*)-**10** is 5.9 Å. Therefore, we envisioned that the coupling of (*Z*)-**10** with (*R*)-**7** might be a feasible route to (*R*)-**4**. In order to drive the reaction, we decided to employ continuous photoirradiation, inducing (*E*)→(*Z*) isomerization, throughout the reaction period.

Table 1 shows the results of the photoassisted synthesis of (*R*)-**4**, conducted as illustrated in Figure 2. The half-life, $T_{1/2}$, of (*Z*)-**10** was 21 min at 80 °C (rate constant $k = 5.6 \times 10^{-4}\ \mathrm{s}^{-1}$, DMF, 1×10^{-5} M). This is sufficiently long to be applicable for the synthesis because (*E*)→(*Z*) photoisomerization occurs at the picosecond or subpicosecond time

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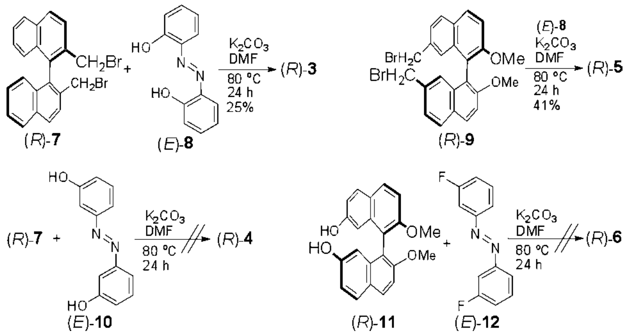
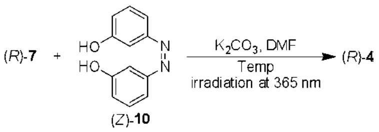
Scheme 1. Reactions of Binaphthyls and Azobenzenes[a]



[a] Conditions: 22.7 mM for **7**–**12** and 227 mM for K_2CO_3.

Table 1. Synthesis of (*R*)-**4** under Photoirradiation at 365 nm[a]



entry	temp (°C)	conc of (*R*)-**7** (mM)	light	yield[b] (%)
1	80	22.7	ON	8
2	20	22.7	ON	0
3	80	2.27	ON	20
4	50	2.27	ON	14
5	20	2.27	ON	0
6	80	2.27	OFF	0

[a] Conditions: a DMF solution of compound **10** was pre-photoirradiated for 1 h, except in the case of entry 6. Reaction time was 24 h. Reaction mixtures were photoirradiated throughout the reaction period; 365 nm, 10 mW/cm^2. Molar ratio of (*R*)-**7**/**10**/K_2CO_3 = 1:1:10. [b] Isolated yield. No detectable starting materials remained at the end of the reaction.

scale.[12] Under the conditions shown in Scheme 1, including photoirradiation, the reaction afforded (*R*)-**4**, although in low yield (8% yield, entry 1). A high dilution condition promoted the intramolecular second etherification (20% yield, entry 3). The side products were complex mixtures including cyclic and acyclic macromolecules. The use of lower temperatures gave a larger proportion of polymerized macromolecules, even though the (*Z*)→(*E*) thermal isomerization of **10** is suppressed (entries 2, 4, and 5). We cannot yet explain this phenomenon. However, one possibility is that the reaction is one of the Curtin–Hammet controlled reactions,[13] being linked to the (*Z*)–(*E*) equilibrium and $\Delta\Delta G^{\ddagger}$. This would be consistent with the fact that synthesis of (*R*)-**4** requires photoirradiation at 365 nm, heat, and the use of the highest feasible dilution. The application of photoirradiation increased the yield from 0% (entry 6) to 20%. Similarly, in the synthesis of (*R*)-**6** from (*R*)-**11** and **12**, photoirradiation increased the yield from 0% to 10% (for details, see the Supporting Information). The cyclization using (*R*)-**7** and 4,4′-dihydroxyazobenzene was also examined, but we could not obtain the 1:1 reaction product even when the azobenzene was in the (*Z*)-form.

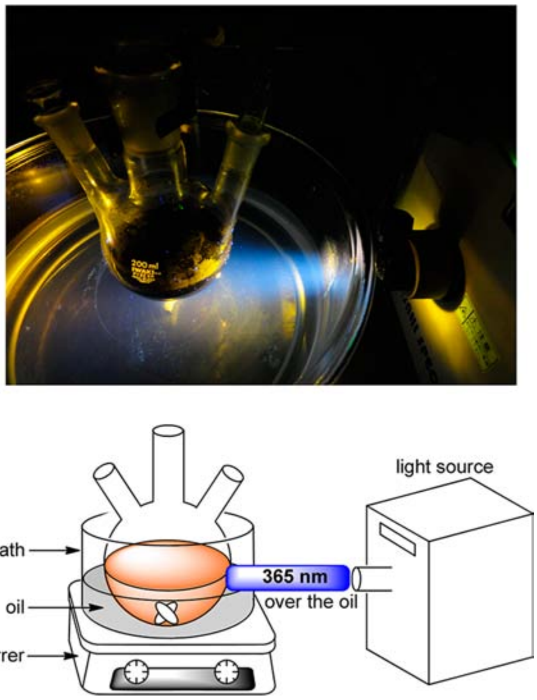


Figure 2. Photograph of the apparatus and schematic illustration of photoassisted cyclization. Irradiation conditions: 365 nm, 10 mW/cm^2 using a 120 W high-pressure mercury lamp (Asahi Spectra REX-120). The reaction was conducted under an atmosphere of N_2 and the apparatus was surrounded by a blackout curtain.

Next, we analyzed fundamental optical properties and conformations of the synthesized dyads, especially (*R*)-**3** and (*R*)-**4**. Figure 3a,b shows absorption spectra obtained after photoirradiation. In both (*R*)-**3** and (*R*)-**4**, judging from the absorption at over 300 nm which is derived from azobenzene,[3] photoirradiation at 365 nm induced (*E*)→(*Z*) isomerization, whereas photoirradiation at 436 nm led to (*Z*)→(*E*) isomerization. Photoisomerization ratios after irradiation at 365 nm were 0.86 and 0.78 for (*R*,*Z*)-**3** and (*R*,*Z*)-**4**, respectively, and those after irradiation at 436 nm were 0.80 and 0.58 for (*R*,*E*)-**3** and (*R*,*E*)-**4**, respectively. We also examined thermal isomerization of these compounds. In the case of (*R*)-**3**, the (*Z*)-form showed a typical pattern of change into the (*E*)-form (Figure 3c). Intriguingly, however, (*R*,*E*)-**4** thermally isomerized to (*R*,*Z*)-**4** (Figure 3d).[14] This is consistent with the fact that synthesis of (*R*)-**4** required photoirradiation, as described above. In addition, thermal isomerizations of both (*R*)-**3** and **4** were

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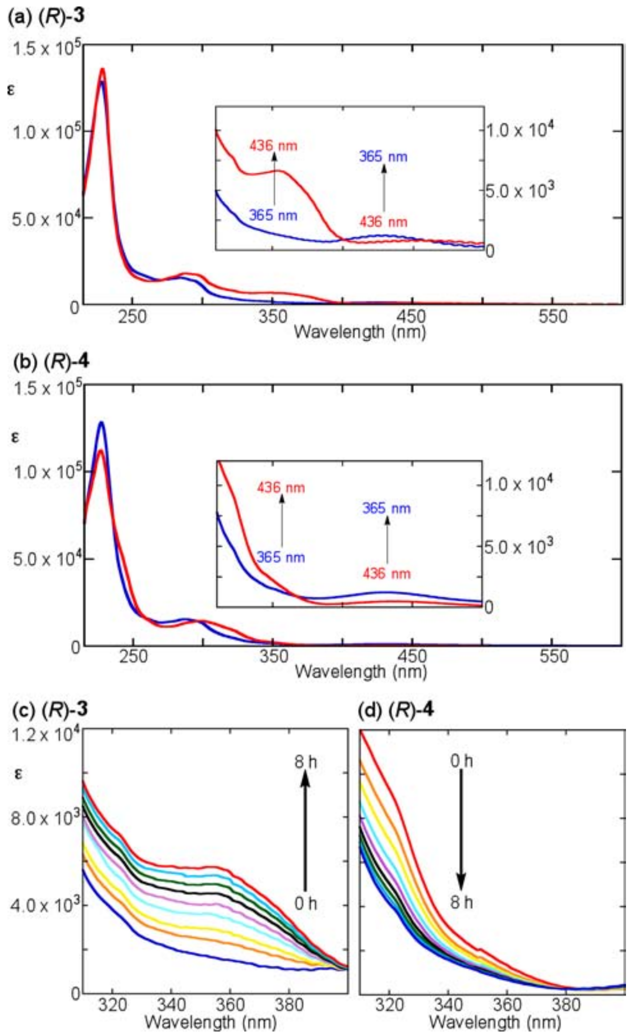

Figure 3. (a,b) Absorption spectra of (*R*)-**3** and (*R*)-**4** after irradiation at 365 nm (blue, rich in (*Z*)-form) and after irradiation at 436 nm (red, rich in (*E*)-form) at 20 °C. Inset: expanded version of part of the spectra. (c) Time-dependent change of absorption spectra of (*R*)-**3** after irradiation at 365 nm at 65 °C. (d) Time-dependent change of absorption spectra of (*R*)-**4** after irradiation at 436 nm at 35 °C. Common conditions: 1,4-dioxane, 1.0×10^{-5} M, light path length = 10 mm, irradiation at 10 mW/cm^2 for 100 s).

first-order reactions, and the entropies of activation, $\Delta S^{\ddagger}$, were −19.7 cal/mol·K for (*R*)-**3** and +5.2 cal/mol·K for (*R*)-**4**. The apparent $\Delta S^{\ddagger}$ difference would be consistent with heterogeneous isomerization depending on the compounds. (*R*)-**5** showed the same tendency as (*R*)-**3**. Meanwhile, in the case of (*R*,*Z*)-**6**, neither photo- nor thermal isomerization occurred, and only degradation was observed. Unisomerizable (*Z*)-azobenzenes are limited largely to 5,6-diazaphenanthrene structures,[15] and (*R*,*Z*)-**6** is structurally quite different from them. Therefore, **4** as well as **6** should be useful in studies on (*Z*)-azobenzene structure.

To compare the conformations and stability, optimized structures of (*R*)-**3** and (*R*)-**4** were calculated (Figure S8, Supporting Information).[16] (*R*,*E*)-**3** was significantly more stable than (*R*,*Z*)-**3**, while in contrast, (*R*,*Z*)-**4** was more stable than (*R*,*E*)-**4**, in accordance with the experimental results. The (*E*)-azobenzene moiety of (*R*,*E*)-**4** was strained in the direction of the linkers owing to the limited movement of the binaphthyl. In fact, the dihedral angles of C−N−N−C were 176° for (*R*,*E*)-**3** and 157° for (*R*,*E*)-**4**, whereas 180° is expected for the unstrained structure.

The properties of these dyads indicate that they would make excellent chiroptical photoswitches; for example, $\Delta\Delta\varepsilon$ of CD at 227 nm of (*R*)-**4** was 165 and $\Delta[\alpha]_D$ of (*R*)-**3** was 1226 (Table S1, Supporting Information).

In conclusion, we have developed a method for synthesizing highly strained cyclic structures by combining a photochromic reaction with the synthetic reaction. Thus, we were able to synthesize azobenzene−binaphthyl dyads with extremely short linkers by means of photoassisted cyclization, making use of the photoinduced (*E*)→(*Z*) isomerization of the azobenzene moiety, which allows the cyclization reaction to proceed. This novel synthetic method should provide convenient access to a variety of strained functionalized molecules that have previously been inaccessible or very difficult to synthesize. Studies on optimization and work to establish the range of application of this photoassisted synthesis are continuing.

Acknowledgment. We thank Dr. D. Hashizume and members of the molecular characterization team at RIKEN for single-crystal X-ray analysis and the spectral measurements. The calculations were performed using the RIKEN Integrated Cluster of Clusters (RICC).

Supporting Information Available. Synthesis, spectra, computational details, and thermodynamic parameters of novel compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) According to time-dependent ^{1}H NMR spectra, the (*E*)→(*Z*) thermal isomerization of (*R*)-**4** was completed within 96 h at 20 °C, and the stationary state included no (*E*)-form (Figure S10, Supporting Information). Stationary states of (*R*)-**3** and (*R*)-**5** were the (*E*)-form and that of (*R*)-**6** was the (*Z*)-form; see the NMR spectra in the Supporting Information.

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(16) The (*Z*)-forms have helical chirality, (*P*) or (*M*); the calculated energy values suggested that (*R*,*Z*,*M*)-**3** and (*R*,*Z*,*P*)-**4** were preferred over the opposite helical isomers (Table S3, Supporting Information). Judging the helicity of (*Z*)-azobenzenes from CD spectra is difficult because of the influence of induced CD related to the binaphthyl moiety and residual (*Z*)-form. (a) Kobayashi, N.; Higashi, R.; Titeca, B. C.; Lamote, F.; Ceulemans, A. *J. Am. Chem. Soc.* **1999**, *121*, 12018–12028. (b) Ma, X.; Wang, Q.; Qu, D.; Xu, Y.; Ji, F.; Tian, H. *Adv. Funct. Mater.* **2007**, *17*, 829–837. (c) Helical (*Z*)-azobenzenes were reported; see: ref 5d and: Haberhauer, G.; Kallweit, C. *Angew. Chem., Int. Ed.* **2010**, *49*, 2418–2421.