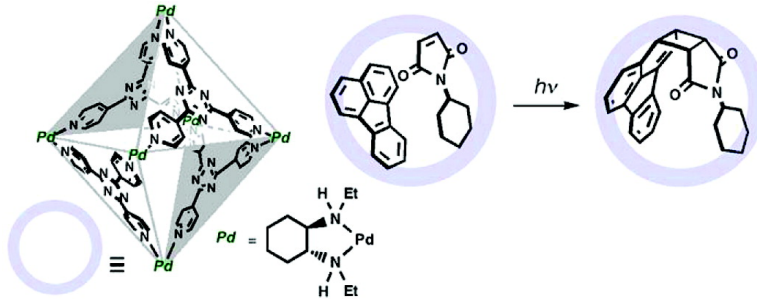
Communication

Asymmetric [2 + 2] Olefin Cross Photoaddition in a Self-Assembled Host with Remote Chiral Auxiliaries

Yuki Nishioka, Takumi Yamaguchi, Masaki Kawano, and Makoto Fujita

J. Am. Chem. Soc., **2008**, 130 (26), 8160-8161 • DOI: 10.1021/ja802818t • Publication Date (Web): 10 June 2008



More About This Article

Additional resources and features associated with this article are available within the HTML version:

- Supporting Information
- Links to the 3 articles that cite this article, as of the time of this article download
- Access to high resolution figures
- Links to articles and content related to this article
- Copyright permission to reproduce figures and/or text from this article

View the Full Text HTML

J|A|C|S
COMMUNICATIONS

Published on Web 06/10/2008

Asymmetric [2 + 2] Olefin Cross Photoaddition in a Self-Assembled Host with Remote Chiral Auxiliaries

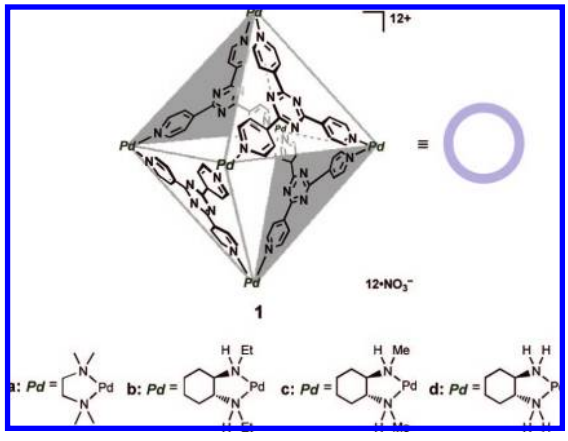
Yuki Nishioka, Takumi Yamaguchi, Masaki Kawano, and Makoto Fujita*

Department of Applied Chemistry, School of Engineering, The University of Tokyo, CREST, Japan Science and Technology Agency (JST), 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8656, Japan

Received April 22, 2008; E-mail: mfujita@appchem.t.u-tokyo.ac.jp

Similar to the pockets of enzymes, cavities of synthetic hosts can activate unreactive compounds to promote reactions in selective ways.[1] Recent self-assembled cages and capsules are showing an improved ability to accelerate and promote reactions with high regio- and stereoselectivity within their cavities.[2–5] However, asymmetric synthesis in chiral cavities still remains relatively unexplored, mainly because of the difficulty in preparing large chiral cages and capsules in optically pure forms.

We have developed a variety of thermal and photochemical reactions within the cavity of the self-assembled M_6L_4 cage **1**.[5] Simply replacing the ethylenediamine end-cap on each Pd center with chiral diamines result in chiral derivatives of **1** while maintaining the cavities' electronic nature, size, and T symmetry element. Here, we report that such a simple chiral modification at the periphery of the cage is sufficient for remotely controlling the previously unknown, chiral [2 + 2] olefin cross photoaddition between fluoranthene and maleimide derivatives (**2** and **3**, respectively) (Figure 1a). For related studies, Stang and co-workers reported modification of an M_6L_4 cage with chiral diphosphine auxiliaries, but the reactions within the cavity have not been reported.[6] Raymond and co-workers used a racemic cage to induce moderate diastereoselectivity in an organometallic transformation.[7] Inoue and co-workers have extensively studied asymmetric anthracene photodimerization and cyclooctene photoisomerization within cyclodextrins.[8,9]



Fluoranthene (**2a**) is an inert aromatic compound and its thermal or photochemical pericyclic reactions have never been reported. However, its cross [2 + 2] photoaddition with a maleimide derivative proceeded efficiently in the cavity of **1a**. Suspending **2a** (15.0 μmol) and *N*-cyclohexylmaleimide (**3**, 15.0 μmol) in a D_2O solution of **1a** (5.0 mM, 1.0 mL) formed the ternary complex **1a**•(**2a**•**3**) in 60% yield (by NMR) (Figure 1b). After filtering off the excess substrate, the solution was irradiated with an ultra high pressure Hg lamp. After 5 min at room temperature, a single product was formed in 55% yield (Figure 1c). The product was extracted with chloroform and identified as [2 + 2] adduct **4a** by NMR and MS analyses (see Supporting Information).

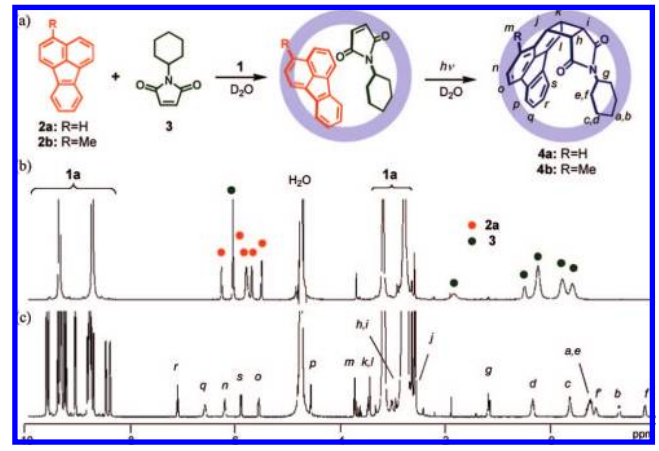


Figure 1. (a) [2 + 2] Photoaddition reaction of **2** with **3** in cage **1**. ^{1}H NMR spectra of (b) ternary complex **1a**•(**2a**•**3**) and (c) product **1a**•**4a** (500 MHz, D_2O, 27 °C).

Given the number of potential reactive sites, it is surprising that only the C2−C3 double bond undergoes photoaddition. Analysis of the calculated LUMO coefficients of **2a** reveals no particular localization on C2 or C3. Thus, the high regio-selectivity is ascribed to the steric control within the confined cavity rather than orbital control.

After establishing that cage **1a** promotes the unusual [2 + 2] cross addition of **2a**, chiral induction within chiral cavities was investigated. Chiral cage **1b** (with chiral auxiliary (1*R*, 2*R*)-*N*,*N*′-diethyl-1,2-diaminocyclohexane) was treated with **2a** and **3** to give the ternary complex **1b**•(**2a**•**3**). Upon irradiation for 30 min, the [2 + 2] adduct **4a** is again formed. After isolation, the enantiomeric excess (ee) of **4a** was determined to be 40% by chiral HPLC. The considerable asymmetric induction is remarkable as the presence of the chiral auxiliary is at the remote peripheral positions of the cage. Even though there is only a minor geometry change between the diastereomeric orientation of the substrates in the chiral cavity (**A** and **B** in Figure 2), it is this small energy difference that is presumably the origin of the asymmetric induction.

The absolute configuration of **4a** was determined by X-ray anomalous scattering method. The major enantiomer was obtained in optically pure form by resolving racemic **4a** with preparative chiral HPLC and recrystallization from chloroform. On the basis of the Flack parameter, the major enantiomer has a 1*S*,2*R*,2a*R*,10a*R* configuration (Figure 3).[10]

When 3-methylfluoranthene (**2b**) was used, the asymmetric induction was further enhanced (50% ee). The reaction is again

10.1021/ja802818t CCC: $40.75

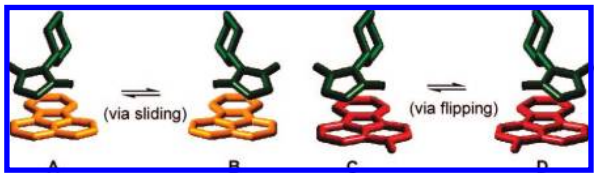


Figure 2. Schematic representation of the enantiomeric orientations of the substrates (which are diastereomeric in chiral cages).

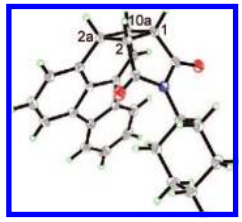


Figure 3. X-ray structure of (1*S*,2*R*,2a*R*,10a*R*)-**4a** (30% probability level). The absolute configuration was determined by X-ray anomalous scattering method.

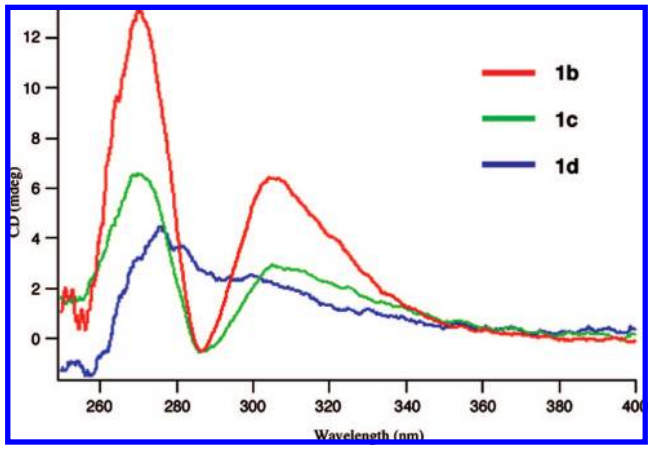


Figure 4. CD spectra of cage **1b**−**d** (0.05 mM) in H_2O at room temperature with 1 mm cell.

regiospecific and only the regioisomer involving reaction of the C4−C5 bond is formed. The subtle energy difference between the two diastereomeric orientations of the substrates within the cage (**C** and **D** in Figure 2) determines the enantioselectivity of the reaction. Interconversion of two orientations now requires that the fluoranthene flips. This process is rapid on the NMR time scale and the diastereomeric pairs were not distinguishable.

The steric bulk of the N-substituent (R) on the chiral diamine auxiliaries is responsible for the asymmetric induction. Cages **1c** (R = Me) and **1d** (R = H) promote the production of **4a**, but give dramatically reduced ee, 20% and 5%, respectively. The CD spectra of cages **1b**−**d** are sensitive to the steric bulk of the auxiliary ligand; the intensity of the Cotton effect at 270 nm (due to the triazine ligand) increases with steric bulk, R (H < Me < Et). The chirality of the auxiliary diamino ligands is communicated to the Pd center and then induces to the chiral deformation of the cavity. In the crystal structure of the achiral cage **1a**, the triazine ligand is perfectly coplanar. In contrast, molecular mechanics calculation of **1b** predicts that the pyridine rings on the triazine ligand are tilted by 17°, creating a chiral cavity (Figure 5). The deformation of the triazine panel is determined by the steric bulk and the tilt angle is reduced to 13° and 5° for **1c** and **1d**, which is consistent with the degree of asymmetric induction as well as that of the Cotton effect.

Figure 5. The deformation of the triazine panel in cages **1b**−**d** to create chiral cavities.

In summary, enantiomeric excesses of up to 50% were achieved in the [2 + 2] cross photoaddition of fluoranthenes within modified chiral cages. The peripheral chiral auxiliaries induce only a minor deformation of the triazine panel, yet this subtle difference is sufficient to produce considerable asymmetric induction. In sharp contrast with common asymmetric reactions, where direct involvement with the reaction sites by chiral catalysts is the crucial step for chiral induction, the reaction site is not directly activated in this reaction. The present results confirm that, similar to enzymes in nature, indirect cavity-control will be an important and achievable strategy for chiral synthesis.

Acknowledgment. We are grateful to Dr. D. Hashizume (RIKEN) for X-ray analysis and to Dr. H. Izumi (AIST) for vibrational circular dichromism (VCD) study. This research was partially supported by the Ministry of Education, Culture, Sports, Science, and Technology of Japan.

Supporting Information Available: Experimental procedures, physical properties, DFT calculation of **2a**, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Numerous examples with small covalent hosts have been reported. Breslow, R.; Dong, S. D. *Chem. Rev* **1998**, *98*, 1997–2011. (b) Warmuth, R.; Yoon, J. *Acc. Chem. Res.* **2001**, *34*, 95–105. (c) Jon, S. Y.; Ko, Y. H.; Park, S. H.; Kim, H.-J.; Kim, K. *Chem. Commun.* **2001**, 1938–1939. (d) Nakash, M.; Clyde-Watson, Z.; Feeder, N.; Davies, J. E.; Teat, S. J.; Sanders, J. K. M. *J. Am. Chem. Soc.* **2000**, *122*, 5286–5293.

(2) (a) Kang, J.; Rebek, J., Jr. *Nature* **1997**, *385*, 50–52. (b) Kang, J.; Hilmersson, G.; Santamaría, J.; Rebek, J., Jr *J. Am. Chem. Soc.* **1998**, *120*, 3650–3656. (c) Kang, J.; Santamaría, J.; Hilmersson, G.; Rebek, J., Jr *J. Am. Chem. Soc.* **1998**, *120*, 7389–7390. (d) Chen, J.; Rebek, J., Jr *Org. Lett.* **2002**, *4*, 327–329. (e) Iwasawa, T.; Hooley, R. J.; Rebek, J., Jr. *Science* **2007**, *317*, 493–496.

(3) (a) Fiedler, D.; Bergman, R. G.; Raymond, K. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 6748–6751. (b) Pluth, M. D.; Bergman, R. G.; Raymond, K. N. *Science* **2007**, *316*, 85–88. (c) Pluth, M. D.; Bergman, R. G.; Raymond, K. N. *Angew. Chem., Int. Ed.* **2007**, *46*, 8587–8589.

(4) (a) Kaanumalle, L. S.; Gibb, C. L. D.; Gibb, B. C.; Ramamurthy, V. *Org. Biomol. Chem.* **2007**, *5*, 236–238. (b) Natarajan, A.; Kaanumalle, L. S.; Jockusch, S.; Gibb, C. L. D.; Gibb, B. C.; Turro, N. J.; Ramamurthy, V. *J. Am. Chem. Soc.* **2007**, *129*, 4132–4133.

(5) (a) Kusukawa, T.; Nakai, T.; Okano, T.; Fujita, M. *Chem. Lett.* **2003**, *32*, 284–285. (b) Yoshizawa, M.; Fujita, M. *Pure Appl. Chem.* **2005**, *77*, 1107–1112. (c) Yoshizawa, M.; Tamura, M.; Fujita, M. *Science* **2006**, *312*, 251–254. (d) Nishioka, Y.; Yamaguchi, T.; Yoshizawa, M.; Fujita, M. *J. Am. Chem. Soc.* **2007**, *129*, 7000–7001. (e) Furusawa, T.; Kawano, M.; Fujita, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 5717–5719. (f) Yamaguchi, T.; Fujita, M. *Angew. Chem., Int. Ed.* **2008**, *47*, 2067–2069.

(6) Stang, P. J.; Olenyuk, B.; Muddiman, D. C.; Smith, R. D. *Organometallics* **1997**, *16*, 3094–3096.

(7) (a) Leung, D. H.; Fiedler, D.; Bergman, R. G.; Raymond, K. N. *Angew. Chem., Int. Ed.* **2004**, *43*, 963–966. (b) Leung, D. H.; Bergman, R. G.; Raymond, K. N. *J. Am. Chem. Soc.* **2006**, *128*, 9781–9797.

(8) (a) Nakamura, A.; Inoue, Y. *J. Am. Chem. Soc.* **2003**, *125*, 966–972. (b) Nakamura, A.; Inoue, Y. *J. Am. Chem. Soc.* **2005**, *127*, 5338–5339. (c) Yang, C.; Nakamura, A.; Fukuhara, G.; Origane, Y.; Mori, T.; Wada, T.; Inoue, Y. *J. Org. Chem.* **2006**, *71*, 3126–3136.

(9) (a) Inoue, Y.; Dong, F.; Yamamoto, K.; Tong, L.-H.; Tsuneishi, H.; Hakushi, T.; Tai, A. *J. Am. Chem. Soc.* **1995**, *117*, 11033–11034. (b) Inoue, Y.; Wada, T.; Sugahara, N.; Yamamoto, K.; Kimura, K.; Tong, L.-H.; Gao, X.-M.; Hou, Z.-J.; Liu, Y. *J. Org. Chem.* **2000**, *65*, 8041–8050. (c) Lu, R.; Yang, C.; Cao, Y.; Wang, Z.; Wada, T.; Jiao, W.; Mori, T.; Inoue, Y. *Chem. Commun.* **2008**, 374–376.

(10) X-ray diffraction study using Cu Kα radiation showed the Flack parameter of 0.02(13) for the correct absolute structure. The absolute configuration was also examined by VCD measurement coupled with DFT calculation (B3LYP/6-31G* level), which indicated the same absolute configuration for the major enantiomer (see Supporting Information).

JA802818T