# Intramolecular Photocycloaddition of 2-(2-Alkenyloxymethyl)-naphthalene-1-carbonitriles Using Glass-Made Microreactors

**Hirofumi Mukae, Hajime Maeda,* Satoshi Nashihara, and Kazuhiko Mizuno***

Department of Applied Chemistry, Graduate School of Engineering, Osaka Prefecture University,
1-1 Gakuen-cho, Naka-ku, Sakai, Osaka 599-8531

Received September 21, 2006; E-mail: mizuno@chem.osakafu-u.ac.jp

Intramolecular [2 + 2] and [2 + 3] photocycloadditions of 2-(2-alkenyloxymethyl)naphthalene-1-carbonitriles and their photocycloreversion using glass-made microreactors were investigated in comparison with photoreactions under conventional batch conditions. Both the efficiency and regioselectivity were improved by use of glass-made microreactors. These results can be explained by thorough absorption of light and outflow of primary product from the reaction system.

Recently, microreactors with narrow channel space, where the width and depth are micrometer-size, have attracted much attention as a new reaction vessel in organic synthesis.[1] There are many reports concerning thermal reactions and catalytic reactions using the characteristics of microreactors.[2] However, preparative photoreactions conducted in microreactors have not been reported as much as thermal reactions.[3–9] To the best of our knowledge, photochemical formation of benzopinacol,[3] the addition of photochemically generated singlet oxygen to $\alpha$-terpinene,[4] the photocyanation of pyrene,[5] the intramolecular photocycloaddition of enones with vinyl acetates,[6] the photochlorination of arenes,[7] the photoacid generation,[8] the $TiO_2$-catalyzed photoreactions,[9] have been investigated in microreactors. We have recently reported the intramolecular [2 + 2] photocycloaddition of a 1-naphthalenecarbonitrile derivative using PDMS-made microreactors as a preliminary communication.[10] In the study presented here, we investigated the effects of substituents, solvents, residence time and flow rate, width and depth of microreactors on intramolecular photocycloaddition and photocycloreversion using Pyrex-glass-made microreactors comparing with photoreactions under conventional batch conditions. Especially, it is noteworthy that the efficiency of the photoreaction dramatically increased and the selectivity of products increased by suppression of the secondary reaction using Pyrex-glass-made microreactors.

## Experimental

**Materials.** All solvents were reagent grade and were distilled before use. Benzene was carefully fractionated from calcium hydride and then from sodium. Acetonitrile was carefully distilled with $P_2O_5$. 2-(2-Alkenyloxymethyl)naphthalene-1-carbonitriles **1a**–**1c** were synthesized according to the reported procedure and purified before use.[11]

**Photoreaction: Batch-Scale Experiments.** Irradiation was carried out using a 500-W Xenon lamp (M. Watanabe & Co., Ltd., WACOM Hx-500) under argon in Pyrex tube, of which the diameter was 8 mm.

**Photoreaction: Micro-Flow System.** The micro-flow system used in this study is shown in Fig. 1. The microreactors were Pyrex-glass-made microchannel chips. Type A was purchased from Institute of Microchemical Technology (IMT Co., Ltd., ICCDI05), and its two channels were connected by a fluororesin tube (diameter = 0.3 mm). The width of the Type A microreactor was 100 µm, the depth was 40 µm, and the length was 120 mm. The Type B microreactor was hand-made by attaching an ionomer resin film with a bored hole (2.5 mm × 60 mm) in the center by two Pyrex glass plates (Matsunami Co., Ltd., Microslide glass S-1111, 76 mm × 26 mm, thickness: 0.8–1.0 mm). The sample solutions were injected by using a syringe pump (KD Scientific Inc., IC3100) equipped with a gastight syringe (Hamilton, 81520, 1005TLL 5.0 mL SYR). Fluororesin tubes (diameter = 0.3 mm) were used to connect the gastight syringe, microreactors, and outlet containers. The flowed solutions were irradiated with a Xenon lamp. The irradiation time (min) was calculated from the volume of microchannel chip (mL) divided by flow rate ($mL\,h^{-1}$). The flow rate was controlled by the syringe pump.

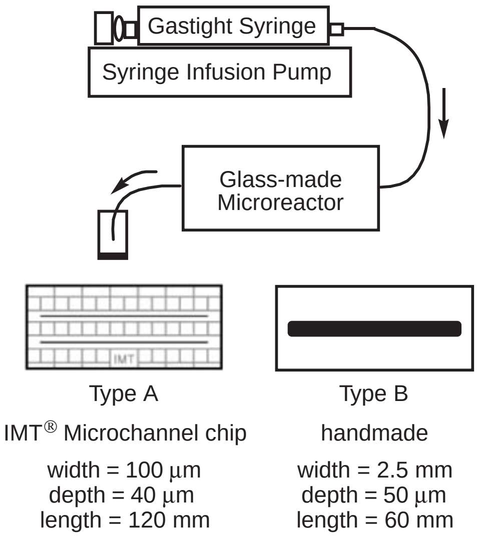


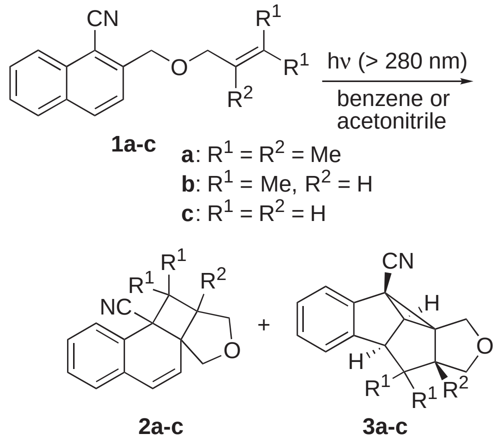
Fig. 1. Apparatus for the photoreaction in the micro-flow system.

Published on the web June 13, 2007; doi:10.1246/bcsj.80.1157

Table 1. Effect of Micro-Flow System on the Intramolecular [2 + 2] and [2 + 3] Photocycloaddition of **1a**–**1c**

| Entry | Reactant | Condition$^{a)}$ | Solvent | Irradiation time$^{b)}$ /min | Product ratio$^{c)}$/% | | Conversion$^{c)}$/% |
|---|---|---|---|---|---|---|---|
| | | | | | **2a–2c** | **3a–3c** | |
| 1 | **1a** | Batch | benzene | 240 | 55 | 45 | 65 |
| 2 | **1a** | Flow | benzene | 1 | 96 | 4 | 69 |
| 3 | **1b** | Batch | benzene | 180 | 73 | 27 | 74 |
| 4 | **1b** | Flow | benzene | 1 | 93 | 7 | 75 |
| 5 | **1b** | Batch | acetonitrile | 50 | 72 | 28 | 77 |
| 6 | **1b** | Flow | acetonitrile | 2.9 | 90 | 10 | 72 |
| 7 | **1c** | Batch | acetonitrile | 90 | 3 | 97 | 33 |
| 8 | **1c** | Flow | acetonitrile | 2.9 | 10 | 90 | 40 |

a) Irradiated by Xenon lamp. Pyrex tubes (diameter = 8 mm) were used under batch conditions, where micro-flow photoreactions were carried out with Glass-made microchannel chip (Type A). Irradiated by Xenon lamp, $[\mathbf{1a}\text{–}\mathbf{1c}]_0 = 30\,\text{mM}$. b) In the case of flow system, the irradiation time (min) was calculated by the volume of microchannel chip (mL) per flow rate ($\text{mL}\,\text{h}^{-1}$). c) Determined by $^1$H NMR.

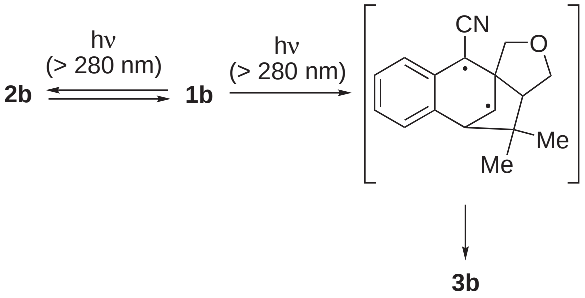


Scheme 1. Intramolecular photocycloaddition of **1a**–**1c**.

For examples, in Entries 2 and 4 in Table 1, volume = $4.8 \times 10^{-4}$ mL, flow rate = $0.03\,\text{mL}\,\text{h}^{-1}$, and irradiation time = 1 min. In Entries 6 and 8 in Table 1, volume = $4.8 \times 10^{-4}$ mL, flow rate = $0.01\,\text{mL}\,\text{h}^{-1}$, and irradiation time = 2.9 min. The flow rates in Figs. 3 and 4 are in the range of $0.01$–$0.2\,\text{mL}\,\text{h}^{-1}$ as shown in Figs. 3 and 4.

**Product Analysis.** Photoproducts were analyzed by nuclear magnetic resonance (NMR) spectra obtained using a Varian Mercury 300 spectrometer. Chemical shifts of **1a**–**1c**, **2a** and **2b**, and **3a**–**3c** were compared with those of the reported data.[11] Compound **2c** is a new compound (See below). The structures of **3a**–**3c** were also determined by X-ray analysis. Molar ratios of substrates **1a**–**1c** and photoproducts **2a**–**2c** and **3a**–**3c** were determined on a GC (Shimadzu GC-2014) equipped with a capillary column (Quadrex corporation, No. 007-17) using dodecane as an internal standard and the $^1$H NMR spectra.

**Data for 1-Cyano-5-oxabenzo[10,11]tricyclo[5.4.0.0$^{3,7}$]-undec-8-ene (2c).** Colorless solid; mp 154–157 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ 2.70–2.83 (m, 2H), 3.07–3.13 (m, 1H), 3.49 (d, $J = 10.4$ Hz, 1H), 3.70 (dd, $J = 9.7$ Hz, 4.7 Hz, 1H), 3.87 (d, $J = 9.5$ Hz, 1H), 4.58 (d, $J = 10.4$ Hz, 1H), 5.58 (d, $J = 10.0$ Hz, 1H), 6.42 (d, $J = 9.9$ Hz, 1H), 7.04–7.07 (m, 1H), 7.22–7.36 (m, 3H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 36.6, 42.4, 49.5, 52.3, 74.0, 77.3, 121.1, 125.6, 127.7, 127.9 (two aromatic carbon signals are overlapped), 128.7, 129.4, 130.2, 132.9; IR (KBr) 2228 cm$^{-1}$; MS (EI) $m/z = 223$ ($M^+$).



Scheme 2. Mechanism for the formation of **2b** and **3b**.

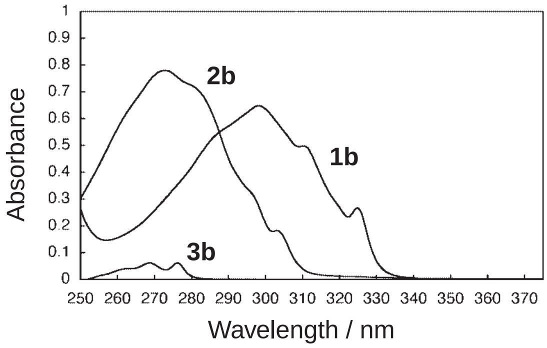


Fig. 2. UV–vis absorption spectra of **1b**, **2b**, and **3b** in $10^{-4}$ M acetonitrile solution.

## Results and Discussion

**Products and Reversibility.** McCullough et al. and we have previously reported that the photoirradiation of benzene and acetonitrile solutions containing 2-(2-alkenyloxymethyl)-naphthalene-1-carbonitriles (**1a**–**1c**) afforded photocycloadducts at 1,2-position (**2a**–**2c**) and 2,4-position (**3a**–**3c**) of the naphthalene ring (Scheme 1).[11–13] Compound **2b** was predominantly obtained at the initial stage of the reaction, but prolonged irradiation afforded [3 + 2] photocycloadduct **3b** as a major product, because photocycloreversion from **2b** to **1b** takes place, but that from **3b** to **1b** does not occur (Scheme 2). This reversibility is supported by the UV absorption spectra of **1b**, **2b**, and **3b** measured in acetonitrile (Fig. 2). Under the present irradiation conditions using Pyrex filter (>280 nm), **1**

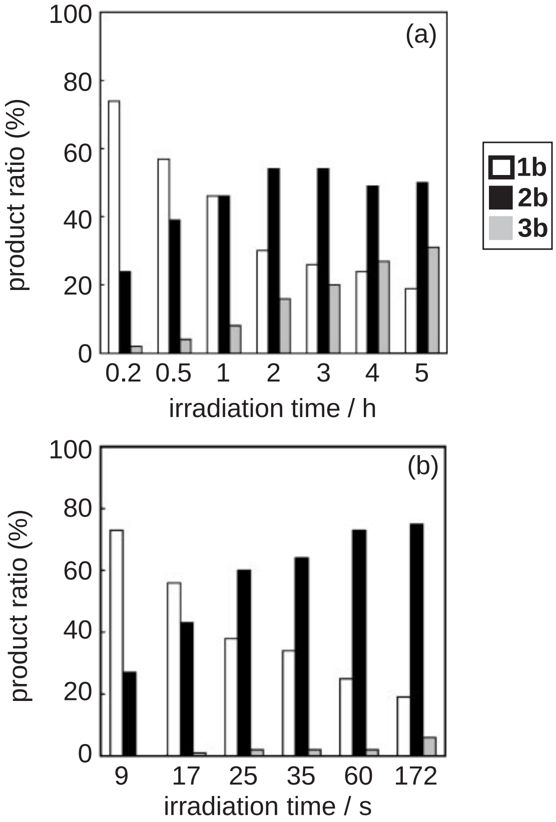


Fig. 3. Product ratios upon photoirradiation of benzene solutions of **1b** (a) under batch conditions and (b) in micro-flow system Type A.

and **2** competitively absorbed UV light, but **3** did not absorb the incident light.

**The Effects of Substrates, Solvents, and Micro-Flow System.** The experimental results concerning the effects of substrates, solvents, and conditions are summarized in Table 1. In order to compare the efficiency and product ratio between batch and flow conditions, irradiation was ceased when conversion of **1a**–**1c** under both conditions reached similar values. Photoirradiation of a benzene solution containing **1a** by a Xenon lamp through a Pyrex filter (>280 nm) for 240 min under batch conditions gave intramolecular photocycloadducts **2a** and **3a** in 55:45 ratio (Table 1, Entry 1). However, we found that, when the photoreaction was carried out in a microreactor with a flow system, both the regioselectivity of the products and the efficiency were higher than those under batch conditions. For example, only a one minute irradiation of a benzene solution of **1a** in microreactor Type A gave **2a** and **3a** in 96:4 ratio (Entry 2). A similar enhancement effect was also observed in the photoreaction of **1b**, in which both the efficiency and selectivity increased by using micro-flow system in benzene and acetonitrile solutions (Entries 3–6). Photoreactions of unsubstituted allyl derivative **1c** in acetonitrile predominantly afforded **3c** (Entries 7 and 8). The ratio of **2c** (3%) under batch conditions increased up to 10% in the micro-flow system.

The effects of substituents and solvents represented in Table 1 can be interpreted as follows. As we previously suggested,[11,12d] in the photocycloaddition between electron-donating molecules (D) and electron-accepting molecules (A), charge-transfer interaction in the singlet exciplex is important for the photocycloaddition. Since decreasing the number of methyl groups on the alkenyl group (**1a** > **1b** > **1c**) makes the electron-donating character of the alkene moiety lower, the relative reactivity decreases. Charge-transfer nature of the exciplex is especially important for the formation of **3**, but contribution of exciton resonance is involved for the formation of **2**. Indeed, dependency of the solvent polarity for the formation of **2a** and **3a** was not observed among less polar solvents, such as benzene, and polar solvents, such as acetonitrile. The formation of **2b** was also independent of the solvent polarity, but that of **3b** increased with increasing solvent polarity. In benzene, photoreaction of **1c** did not afford the intramolecular photocycloadducts at all, but in acetonitrile slowly gave **3c**.

**Time-Dependency on the Photoreaction of 1b.** Time dependency on the ratio of **1b** and photoproducts **2b** and **3b** in the photoreaction of **1b** in benzene solutions is shown in Fig. 3. Under batch conditions, after 1 h irradiation, about half of the amount of **1b** was consumed, and **2b** and **3b** were formed in 46 and 8% yields, respectively (Fig. 3a). After 5 h irradiation, **1b** decreased to 19%, and the ratio of **2b** and **3b** became about 3:2. On the other hand, in micro-flow system Type A, when the residence time was 25 s, **1b** decreased to less than half amount and **2b** and **3b** formed in 60 and 2% yields, respectively (Fig. 3b). When the residence time of the solution was prolonged to 172 s by reducing the flow rate to 0.01 mL h$^{-1}$, the conversion of **1b** became nearly equal to that after 5 h of irradiation under batch conditions, but the ratio of **2b** and **3b** was about 12:1. These data suggest that difficulty in obtaining only the initial photoproduct under conventional batch condition can be overcome by using micro-flow system.

**Time-Dependency on the Photocycloreversion from 2b.** As mentioned above, photocycloreversion from **2b** to **1b** competitively took place in the photoreaction of **1b**. Thus, we turned our attention to the time-dependency on the photocycloreversion from isolated **2b** (Fig. 4). Under batch conditions, after irradiation for 3 h, the yields of **2b** and **3b** were 65 and 18%, respectively (Fig. 4a). After 5 h irradiation, recovery of **2b** decreased to 47%, and **1b** and **3b** were produced in 13 and 40% yield, respectively. On the other hand, after irradiation of a benzene solution containing **2b** in micro-flow system Type A, only a trace amount of **3b** was formed after 60 s irradiation, whereas **1b** was obtained in 13% yield (Fig. 4b). Moreover, after 172 s irradiation, the conversion of **2b** was nearly equal to that of photoreaction of **2b** for 1 h under batch conditions, and the yield of **3b** was only 3% in micro-flow system.

**Effects of Width in Microreactors.** One of the weak points of the microreactors is that quantity of products obtained is too small. In order to overcome this problem, microreactor Type B having wider width (2.5 mm) than Type A was developed without significant change of the depth. A comparison of the width of the microreactors is shown in Table 2. To keep irradiation time even with the Type A reactor, a flow rate of 0.45 mL h$^{-1}$ was used for the Type B reactor. As a result, a 25-fold quantity of products with a similar regioselectivity

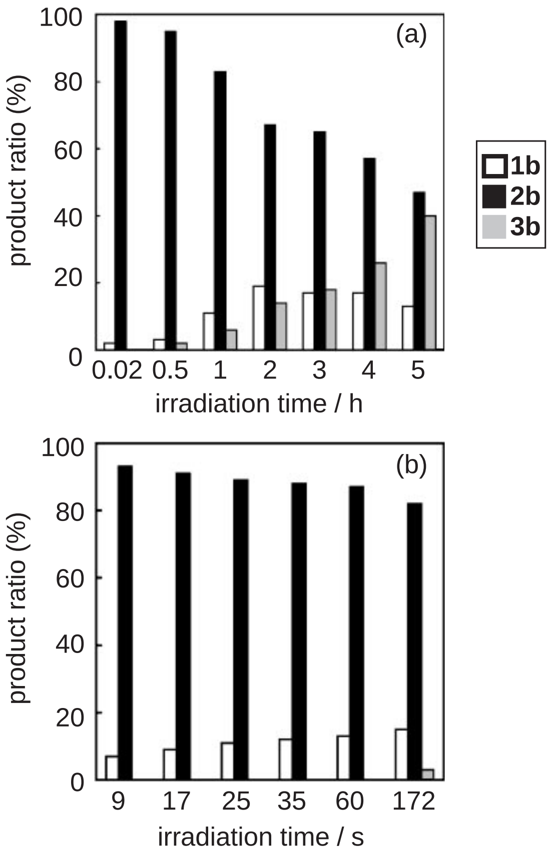


Fig. 4. Product ratios upon photoirradiation of benzene solutions containing **2b** (a) under batch conditions and (b) in micro-flow system Type A.

Table 2. Comparison of Width of Microchannels on the Photoreaction of **1b**[a)]

| Entry | Condition[a)] | Width /mm | Flow rate /mL h$^{-1}$ | Product ratio[b)]/% | | |
|---|---|---|---|---|---|---|
| | | | | **2b** | **3b** | recovery of **1b** |
| 1 | Flow (Type A) | 0.1 | 0.03 | 73 | 2 | 25 |
| 2 | Flow (Type B) | 2.5 | 0.45 | 69 | 2 | 29 |

a) Irradiated by Xenon lamp for 1 min, $[\mathbf{1b}]_0 = 30$ mM, in benzene, rt. b) Determined by $^1$H NMR.

was obtained when Type B reactor was used with a similar rate and the same irradiation time (1 min) as those in Type A reactor.

**Effects of Microreactors.** These results can be explained by the inherent characteristics of micro-flow system. On the basis of Lambert–Beer's law ($A = \log(I_0/I) = \varepsilon cl$) using values of $c = 3.0 \times 10^{-2}$ mol L$^{-1}$ and $\varepsilon_{326\text{nm}} = 2.43 \times 10^4$ mol$^{-1}$ L cm$^{-1}$ of **1b**, 99.9% of the incident light is absorbed by the solution from the surface of the vessel to the depth of 40 µm. This means that the greater part of solution in 8 mm$\phi$ Pyrex tube under batch conditions cannot absorb the light. The increase in reaction efficiency can be attributed to the thorough absorption of the incident light. It is also a notable effect of microreactors that the flow rates can be liberaly chosen on the basis of the reactivity of the substrates. As shown in Figs. 3 and 4, slower flow rate increased the conversion, and faster flow rate decreased the conversion.

As noted above, the pathway for producing **2b** is a fast reversible process, whereas the pathway giving **3b** is a relatively slow irreversible process. Relative reaction rates of these pathways were calculated from the data at the lowest conversion, shown in Figs. 3 and 4, as follows: $k_{(1\to2)}:k_{(2\to1)}:k_{(1\to3)} = 100:26:1$. Namely, under batch condition without stirring, initial product **2b** is produced only near the surface of vessel at the initial stage of the photoreaction, then a secondary reaction giving **3b** proceeds faster than diffusion of **2b**, which has already accumulated near the surface. On the other hand, in the flow system, selectivity of products can be improved by a quick outflow of the initial product **2b** from the reaction system. From small Reynolds number of these microreactors, it is also thought that the laminar flow is predominant in microreactors, meaning the mixing effect arising from turbulent flow is negligible. Thus, in a reaction system, in which both fast reversible process and slow irreversible process coexist, a micro-flow system is appropriate for the selective formation of the initial product.

## Conclusion

In conclusion, the efficiency and regioselectivity on the intramolecular [2 + 2] and [2 + 3] photocycloaddition of alkenylnaphthalene derivatives was increased using the micro-flow system. The increase in efficiency was explained by the thorough absorption of the incident light. Improved regioselectivity was attributed to the flow system. The quantity of products can be increased by widening the width without deepening the depth. It seems that glass-made micro-flow reactors are useful for the preparative photoreactions, in which an undesired secondary reaction competitively takes place.

The authors thank to Prof. Noboru Kitamura (Hokkaido University), Associate Professor Haeng-Boo Kim (The University of Tokyo), and Professor Minoru Seki (Osaka Prefecture University) for helpful discussion. This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas (417) (No. 17029058) and (432) (No. 17034056), Exploratory Research (No. 16655018), and Young Scientists (B) (No. 16750039) from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan.

### References

1 a) S. H. DeWitt, *Curr. Opin. Chem. Biol.* **1999**, *3*, 350. b) S. J. Haswell, P. Watts, *Green Chem.* **2003**, *5*, 240.

2 a) V. Skelton, G. M. Greenway, S. J. Haswell, P. Styring, D. O. Morgan, B. Warrington, S. Y. F. Wong, *Analyst* **2001**, *126*, 7. b) S. Suga, M. Okajima, K. Fujiwara, J. Yoshida, *J. Am. Chem. Soc.* **2001**, *123*, 7941. c) E. Garcia-Egido, S. Y. F. Wong, B. H. Warrington, *Lab Chip* **2002**, *2*, 31. d) P. Watts, C. Wiles, S. J. Haswell, E. Pombo-Villar, *Lab Chip* **2002**, *2*, 141. e) T. Fukuyama, M. Shinmen, S. Nishitani, M. Sato, I. Ryu, *Org. Lett.* **2002**, *4*, 1691. f) P. Watts, C. Wiles, S. J. Haswell, E. Pombo-Villar, *Tetrahedron* **2002**, *58*, 5427. g) S. Suga, A. Nagaki, J. Yoshida, *Chem. Commun.* **2003**, 354. h) M. Ueno, H. Hisamoto, T. Kitamori, S. Kobayashi, *Chem. Commun.* **2003**, 936. i) M. Brivio, R. E. Oosterbroek, W. Verboom, M. H. Goedbloed, A. van den Berg, D. N. Reinhoudt, *Chem. Commun.* **2003**,

1924. j) C. Wiles, P. Watts, S. J. Haswell, E. Pombo-Villar, *Tetrahedron* **2003**, *59*, 10173. k) C. Wiles, P. Watts, S. J. Haswell, E. Pombo-Villar, *Org. Process Res. Dev.* **2004**, *8*, 28. l) P. He, S. J. Haswell, P. D. I. Fletcher, *Lab Chip* **2004**, *4*, 38. m) C. Wiles, P. Watts, S. J. Haswell, E. Pombo-Villar, *Lab Chip* **2004**, *4*, 171. n) S. Y. Lu, P. Watts, F. T. Chin, J. Hong, J. L. Musachio, E. Briard, V. W. Pike, *Lab Chip* **2004**, *4*, 523. o) N. Kitamura, Y. Hosoda, K. Ueno, S. Iwata, *Anal. Sci.* **2004**, *20*, 783. p) J. Kobayashi, Y. Mori, K. Okamoto, R. Akiyama, M. Ueno, T. Kitamori, S. Kobayashi, *Science* **2004**, *304*, 1305. q) C. Basheer, F. Shahitha, J. Hussain, H. K. Lee, S. Valiyaveettil, *Tetrahedron Lett.* **2004**, *45*, 7297. r) C. Jönsson, S. Lundgren, S. J. Haswell, C. Moberg, *Tetrahedron* **2004**, *60*, 10515. s) T. Kawaguchi, H. Miyata, K. Ataka, K. Mae, J. Yoshida, *Angew. Chem., Int. Ed.* **2005**, *44*, 2413. t) C. Wiles, P. Watts, S. J. Haswell, *Tetrahedron* **2005**, *61*, 5209. u) C. Wiles, P. Watts, S. J. Haswell, E. Pombo-Villar, *Tetrahedron* **2005**, *61*, 10757. v) A. Nagaki, M. Togai, S. Suga, N. Aoki, K. Mae, J. Yoshida, *J. Am. Chem. Soc.* **2005**, *127*, 11666. w) N. T. S. Phan, J. Khan, P. Styring, *Tetrahedron* **2005**, *61*, 12065. x) P. He, P. Watts, F. Marken, S. J. Haswell, *Angew. Chem., Int. Ed.* **2006**, *45*, 4146. y) J. Kobayashi, Y. Mori, S. Kobayashi, *Chem. Asian J.* **2006**, *1*, 22.

3 a) B. Borderie, D. Lavabre, G. Levy, J. P. Laplante, J. C. Micheau, *J. Photochem. Photobiol., A* **1991**, *56*, 13. b) H. Lu, M. A. Schmidt, K. F. Jensen, *Lab Chip* **2001**, *1*, 22.

4 R. C. R. Wootton, R. Fortt, A. J. de Mello, *Org. Process Res. Dev.* **2002**, *6*, 187.

5 K. Ueno, F. Kitagawa, N. Kitamura, *Lab Chip* **2002**, *2*, 231.

6 T. Fukuyama, Y. Hino, N. Kamata, I. Ryu, *Chem. Lett.* **2004**, *33*, 1430.

7 H. Ehrich, D. Linke, K. Morgenschweis, M. Baerns, K. Jähnisch, *Chimia* **2002**, *56*, 647.

8 S. Takahashi, S. Machida, K. Horie, *Macromol. Symp.* **2001**, *175*, 299.

9 a) R. Gorges, S. Meyer, G. Kreisel, *J. Photochem. Photobiol., A* **2004**, *167*, 95. b) H. Nakamura, X. Li, H. Wang, M. Uehara, M. Miyazaki, H. Shimizu, H. Maeda, *Chem. Eng. J.* **2004**, *101*, 261. c) S. Teekateerawej, J. Nishino, Y. Nosaka, *J. Photochem. Photobiol., A* **2006**, *179*, 263. d) Y. Matsushita, S. Kumada, K. Wakabayashi, K. Sakeda, T. Ichimura, *Chem. Lett.* **2006**, *35*, 410.

10 H. Maeda, H. Mukae, K. Mizuno, *Chem. Lett.* **2005**, *34*, 66.

11 Y. Yoshimi, S. Konishi, H. Maeda, K. Mizuno, *Synthesis* **2001**, 1197.

12 a) J. J. McCullough, W. K. MacInnis, C. J. L. Lock, R. Faggiani, *J. Am. Chem. Soc.* **1980**, *102*, 7780. b) J. J. McCullough, W. K. MacInnis, C. J. L. Lock, R. Faggiani, *J. Am. Chem. Soc.* **1982**, *104*, 4644. c) K. Mizuno, S. Konishi, T. Takata, H. Inoue, *Tetrahedron Lett.* **1996**, *37*, 7775. d) Y. Yoshimi, S. Konishi, H. Maeda, K. Mizuno, *Tetrahedron Lett.* **2001**, *42*, 3475. Structures of the photoproducts at 3,4-position of naphthalene rings reported in Refs. 10–12 were corrected to $[3+2]$ photocycloadducts at 2,4-position. See: H. Mukae, H. Maeda, K. Mizuno, *Angew. Chem., Int. Ed.* **2006**, *45*, 6558.

13 A similar intramolecular $[2+2]$ photocycloaddition was reported by Gilbert et al. a) A. Kashoulis, A. Gilbert, G. Ellis-Davies, *Tetrahedron Lett.* **1984**, *25*, 2905. b) A. Gilbert, P. Heath, A. Kashoulis-Koupparis, G. C. R. Ellis-Davies, S. M. Firth, *J. Chem. Soc., Perkin Trans. 1* **1988**, 31.