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Asymmetric photosensitized addition of methanol to (*R*)-(+)-(*Z*)-limonene in a microreactor

Kosaku Sakeda[a], Kazuhito Wakabayashi[a], Yoshihisa Matsushita[a], Teijiro Ichimura[a,*], Tadashi Suzuki[a], Takehiko Wada[b], Yoshihisa Inoue[b]

[a] *Department of Chemistry and Materials Science, Tokyo Institute of Technology, 2-12-1 Ohokayama, Meguro-ku, Tokyo 152-8551, Japan*
[b] *Department of Applied Chemistry, Graduate School of Engineering, Osaka University, 2-1 Yamadaoka, Suita, Osaka 565-0871, Japan*

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Abstract

Photosensitized diastereodifferentiating addition of methanol to (*R*)-(+)-(*Z*)-limonene in a microreactor was investigated. The quantity of photoproducts, *cis*- and *trans*-4-isopropenyl-1-methoxy-1-methylcyclohexane, increases with increasing period of irradiation by a mercury lamp, and the diastereomeric excess (de) of the photoadduct is slightly larger than that obtained in a batch reaction system. The reaction rate constants for the production of the *cis* and *trans* isomers were successfully obtained by using the steady state approximation. The larger de value in the microreactor was found to result from the suppression of the sequential side reaction processes. The feasibility of microreaction system for the photoreaction will be discussed.

Keywords: Microreactor; Asymmetric reaction; (*R*)-(+)-(*Z*)-Limonene; Photosensitized reaction; Diastereomeric excess

1. Introduction

Recently, there has been a rapid growth in the development of microreaction technology. Microreaction systems have been successfully applied to a wide variety of chemical transformations utilizing the features unique to microspace, for instance short molecular diffusion distance, excellent heat transfer characteristics, large surface-to-volume ratio and laminar flow [1–5]. However, only a small number of studies have been made so far on photochemical reactions in microreactors [6–16].

Because microreaction systems are expected to have several advantages on photoreactions, *e.g.* higher spatial illumination homogeneity, better light penetration through the entire reactor depth, and larger illuminated surface area per unit volume in comparison with large-scale reactors, we have applied microreactors to photochemistry [17,18]. We also developed a photocatalytic microreaction system immobilizing a TiO_2 layer on inner walls of microfabricated channels and examined photocatalytic oxidation [19], reduction [20], and alkylation processes [21] as model reactions.

It has been widely accepted that the chirality of molecules is crucial to the functions of biological system, and the development of new methodology to control this property has been an important target of a number of researches. Numerous efforts have been devoted to thermally driven catalytic and enzymatic asymmetric syntheses. On the other hand, the area of photochemical asymmetric synthesis is still relatively new, although it has already been shown to possess several advantages over its thermal and enzymatic counterparts [22–25]. Kropp et al. reported *m*-xylene-sensitized photoreaction of (*R*)-(+)-(*Z*)-limonene in methanol, and found addition products: diastereomeric *cis*- and *trans*-4-isopropenyl-1-methoxy-1-methylcyclohexane (*cis* and *trans* isomers) and exocyclic isomer (exo isomer) [26] (see Scheme 1). Shim et al. investigated the internal and external factors for the asymmetric photoreaction to achieve high diastereomeric excess (de) of the photoproduct [25]. In this study, we examined the photosensitized diastreodifferentiating addition of methanol to (*R*)-(+)-(*Z*)-limonene as a model reac-

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[*] Corresponding author. Tel.: +81 3 5734 2225; fax: +81 3 5734 2331.
E-mail address: tichimur@cms.titech.ac.jp (T. Ichimura).

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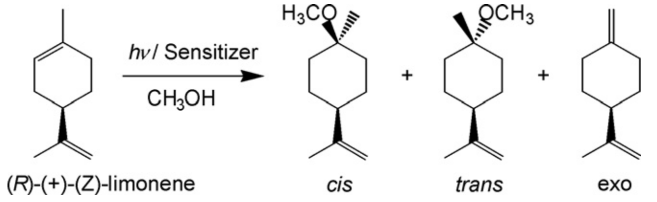


Scheme 1. Diastereodifferentiating photosensitized addition of methanol to (*R*)-(+)-(*Z*)-limonene.

tion in a microreactor. The advantages of a microreactor on the asymmetric photochemical reaction will be discussed.

2. Experimental

(*R*)-(+)-(*Z*)-Limonene (Aldrich), toluene (Kanto Chemical Co., Inc.), and dodecane (Kanto Chemical Co., Inc.) were used as received. Methanol (Kanto Chemical Co., Inc.; UGR grade) and cyclohexane (Kanto Chemical Co., Inc.; GR grade) were used as solvents without further purification.

Three kinds of microreactors made of quartz (Shimadzu Co.) were prepared. The channel sizes of the microreactors were 500 μm × 300 μm × 60 mm, 400 μm × 40 μm × 100 mm, and 200 μm × 20 μm × 100 mm (width × depth × length). A solution containing (*R*)-(+)-(*Z*)-limonene (25 mM), toluene (10 mM), dodecane (10 mM, internal standard), and methanol (solvent) was injected into a microreactor channel with a syringe pump. The solution irradiated with a low-pressure mercury lamp (40 W, 253.7 nm) in a microreactor was collected, and photoproducts were analyzed by a gas chromatograph (Shimadzu GC-14B and GC-2014) with a 30 m-capillary column (Shimadzu CBP1-M25-025 PEG). Irradiation time was controlled by the injection rate of the syringe pump. A schematic experimental setup is shown in Fig. 1.

An experimental setup for transient absorption spectrum measurement has been described elsewhere [27]. A KrF excimer laser was used as an excitation light source. The laser beam was focused loosely into a flow cell (NSG T-59FL-10; 10 mm optical path length) with a cylindrical lens. A Xe lamp (Ushio UXL-300DO; 300 W) was used as a monitoring light source. The fresh sample solution was consistently fed into the cell to eliminate the influence of the photoproduct. All the measurements were carried out at room temperature.

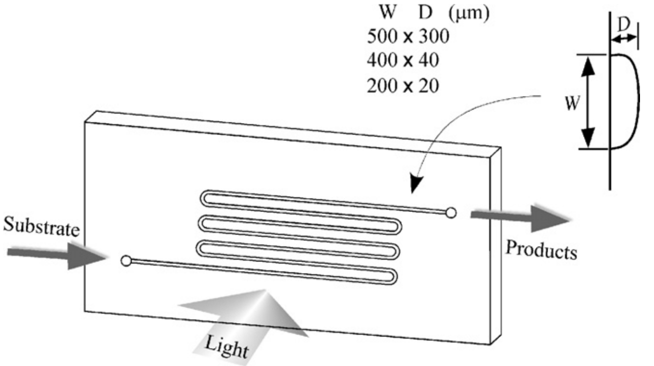
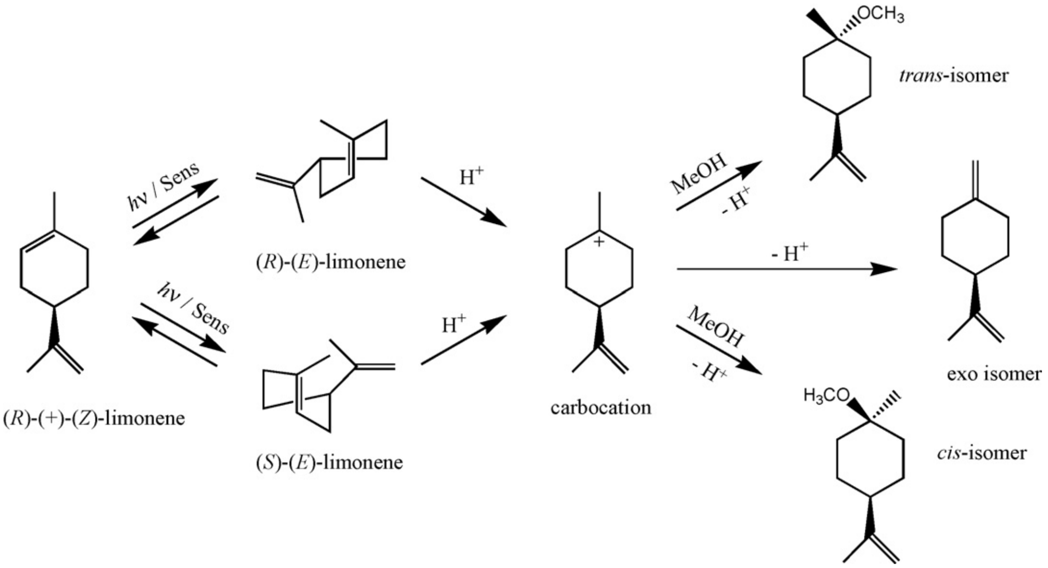


Fig. 1. A schematic description of the photoreaction system with a microreactor, which is made of quartz glass for UV irradiation. The product is analyzed with a gas chromatograph.

3. Results and discussion

The reaction mechanism proposed for photosensitized diastereodifferentiating addition of methanol to (*R*)-(+)-(*Z*)-limonene is shown in Scheme 2 [25]. The (*E*)-isomer of limonene, produced upon triplet sensitization by toluene, is protonated in the polar solvent to give the carbocation, which is either deprotonated to afford the exocyclic isomer or attached by methanol to produce the diastereomeric *cis*- and *trans*-adducts. The stereoselective key is the conformation of the carbocation



Scheme 2. The proposed mechanism of photosensitized addition reaction of methanol to (*R*)-(+)-(*Z*)-limonene. The diastereomeric *cis* and *trans* isomers and the exo isomer are produced through a carbocation intermediate. Sens indicates a sensitizer. For details, see Ref. [25].

Table 1
Conversion of limonen and yields of *cis*, *trans* and exo isomers against the irradiation time

Irradiation time (s)	36	72	135
Conversion (%)			
Limonene	2.5	7.9	12.0
Yield (%)			
cis	0.37	0.95	1.54
trans	0.71	1.76	2.71
exo	0.90	2.10	3.70

produced. Diastereomeric excess (de) is defined as follows:

$$\mathrm{de} = \frac{[trans] - [cis]}{[trans] + [cis]}$$

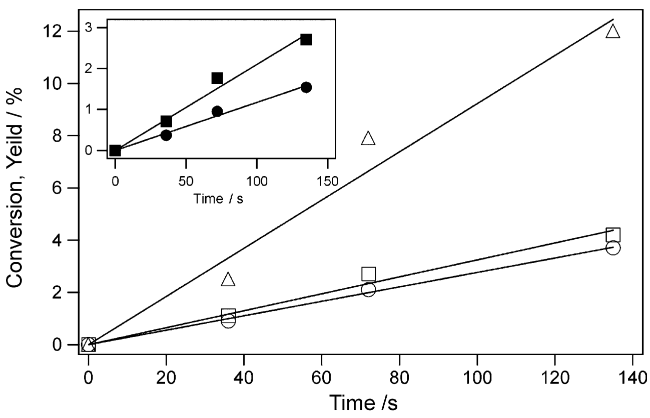
where [*trans*] and [*cis*] denote the concentration of the *trans* and the *cis* isomers of the methanol adducts, respectively.

A methanol solution of (*R*)-(+)-(*Z*)-limonene (25 mM) and toluene (10 mM) as a sensitizer was fed into a microreactor of 500 μm (width) × 300 μm (depth), and irradiated with a 40 W Hg lamp. As a reference, the control experiment was carried out in a quartz batch cell (3 mm light path length, 1 mL volume). Fig. 2 shows the yields of photoproducts and the conversion of (*R*)-(+)-(*Z*)-limonene plotted against the irradiation time. In the microreactor the yield of the *cis* and *trans* isomers increased linearly during the irradiation period examined as shown in the inset of the figure and Table 1 (135 s), while in the batch cell the yield increased linearly only for the initial time region of up to 20 min and reached a plateau. To our surprise, the yields of *cis* and *trans* isomers against the photon number absorbed by the sensitizer per second, namely photon efficiency, in the microreactor was much higher than that in the batch cell. The photon efficiency is defined as follows.

$$\text{Photon efficiency} = \frac{[\text{number of product molecules}]}{[\text{number of absorbed photons}]}$$

The number of absorbed photon was evaluated from the light power (J/s) at 253.7 nm of the Hg lamp, the irradiation time controlled by the flow rate, and the absorbance of the sample solution, which was calculated from the absorption coefficient at 253.7 nm and concentration of the photosensitizer toluene in methanol and the light path length (3 mm for the batch cell and 300 μm for the microreactor). In the microreactor, the photon efficiency was 0.11, while it was 0.05_9 in the batch cell. Furthermore, the de value was as high as 30.6% (36 s irradiation) in the microreactor while it was 28.7% de (15 min irradiation) in the batch cell. The enhancement of stereoselectivity and the drastic increase of the reaction quantum yield indicate the distinct properties of a microreactor applied to asymmetric photochemistry.

(a) microreactor (500 μm x 300 μm)



(b) cell (3 mm light path length)

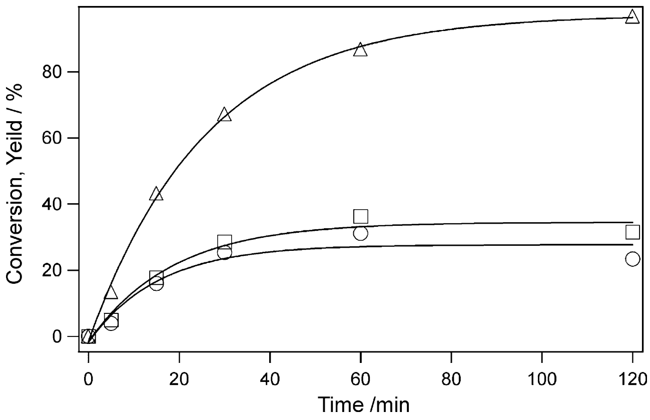
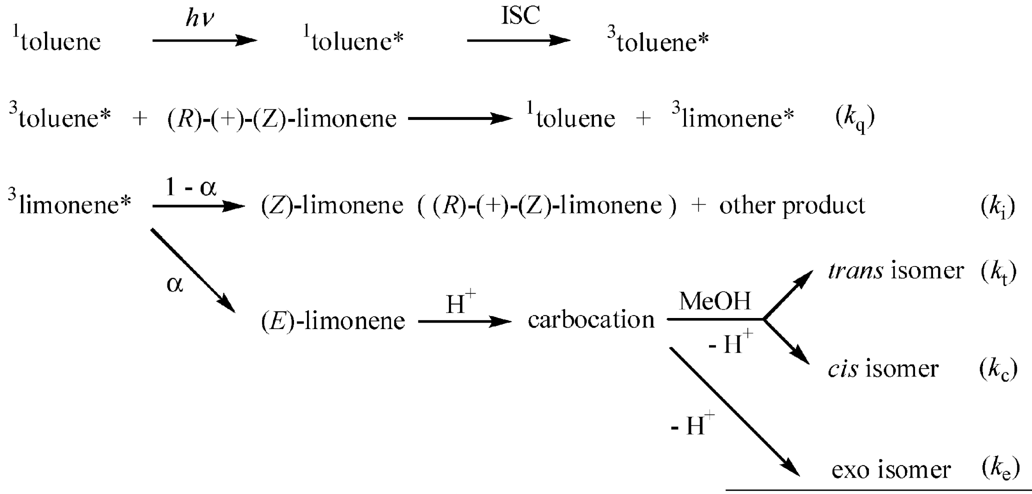


Fig. 2. The plots of yield of *cis* and *trans* isomer (□), yield of exo product (○), and conversion of (*R*)-(+)-(*Z*)-limonene (△) against the irradiation time of a 40 W Hg lamp (a) in the microreactor of 500 μm (width) × 300 μm (depth) and (b) in a quartz cell. The inset shows the plots of yield of *cis* (●) and *trans* (■) against the irradiation time.

To clarify the origin of the difference in de observed in the microreactor *versus* the batch cell, the reaction rate constants for the *cis* and *trans* isomer formation were estimated. From the reaction mechanism proposed (Scheme 2 and ref. [25]),

Table 2
Photon efficiency, formation rate constants for *cis* (k_c) and *trans* (k_t) isomers, and de values of photosensitized addition of methanol to (*R*)-(+)-(*Z*)-limonene in a batch cell and microreactors

Reactor	Size	Photon efficiency	Formation rate constants		
			k_t ($\times 10^8$ M^{-1} s^{-1})	k_c (10^7 M^{-1} s^{-1})	de (%)
Batch cell	100 mm × 3 mm	0.06	0.29	1.6	28.7
Microreactor	500 μm × 300 μm	0.11	0.55	2.9	30.6
Microreactor	400 μm × 40 μm	0.27	1.0	5.6	29.4
Microreactor	200 μm × 20 μm	0.29	1.4	7.4	30.0



the rate equations can be expressed as follows:

$$\frac{d[^3\text{toluene}^*]}{dt} = I_0[^1\text{toluene}] - (k_0 + k_q[\text{limonene}])[^3\text{toluene}^*]$$
$$= I_0[^1\text{toluene}] - k_T[^3\text{toluene}^*]$$
$$(k_T = k_0 + k_q[\text{limonene}]) \qquad (1)$$

$$\frac{d[\text{limonene}]}{dt} = -k_q[^3\text{toluene}^*][\text{limonene}] \qquad (2)$$

$$\frac{d[\textit{trans}]}{dt} = k_t[^3\text{toluene}^*][\text{limonene}] \qquad (3)$$

$$\frac{d[\textit{cis}]}{dt} = k_c[^3\text{toluene}^*][\text{limonene}] \qquad (4)$$

$$\frac{d[\text{exo}]}{dt} = k_e[^3\text{toluene}^*][\text{limonene}] \qquad (5)$$

where [^{1}toluene], [^{3}toluene*], and [limonene] denote concentrations of toluene in the ground state and in the triplet state, and concentration of (*R*)-(+)-(*Z*)-limonene, respectively. I_0 is the light intensity, and α the branching ratio of production of the reaction intermediate, (*E*)-limonene. k_q is the bimolecular deactivation rate constant of ^{3}toluene* by limonene. k_t, k_c, and k_e are the rate constants for the production of *trans*, *cis*, and exo isomers from ^{3}limonene*, respectively. The ratio of the formation quantity for *cis* and *trans* isomers ([*cis*]:[*trans*]) is equal to k_c:k_t. With the ratio of the slopes of the solid lines in the inset of Fig. 2, the k_c/k_t value was successfully determined to be 0.555 in the batch cell and 0.531 in the microreactor. The difference of the k_c/k_t value obviously results in the higher de value and also better stereoselectivity in the microreactor.

The quenching rate constant, k_q, was determined to be $k_q = 1.1 \times 10^8\ \text{M}^{-1}\ \text{s}^{-1}$ by Stern–Volmer plots with transient absorption measurements in the cell. With the relation of Eqs. (2)–(5), the yield of *cis*, *trans*, and exo isomers, and conversion of (*R*)-(+)-(*Z*)-limonene, the rate constants of *cis* and *trans* isomers and exo product in the batch cell were obtained to be $k_t = 2.9 \times 10^7\ \text{M}^{-1}\ \text{s}^{-1}$, $k_c = 1.6 \times 10^7\ \text{M}^{-1}\ \text{s}^{-1}$, $k_e = 4.1 \times 10^7\ \text{M}^{-1}\ \text{s}^{-1}$. Here, we regarded the ratio of the slopes of the best-fitted lines in Fig. 2 as the ratio of the reaction rate constants. Thus, the apparent reaction rate constants for the isomer formation were successfully obtained for the first time.

In order to compare the formation rate constants for the *cis* and *trans* photoproducts in the different types of the reactors we tried to precisely determine the k_q value in the microreactor, which however turned out to be very difficult because of the detection limit of the transient absorption technique. The photon efficiency, which should relate to the reaction rate constant, was determined to be 0.11 in the microreactor, while it was 0.059 in the batch cell, as shown in Table 2. Thus, the photon efficiency in the microreactor is much larger than that in the conventional reactor or cell. These results indicate the higher efficiency of the reaction in the microreactor, namely, the higher formation efficiency of the *cis* and *trans* isomers from triplet toluene. The net reaction rate constant in a microreactor from triplet toluene ($k_r = k_t + k_c + k_e + k_i$) should be 1.8 times lager than that in the cell, revealing the characteristic feature of the microspace and the flow. Since the k_r value was evaluated as $2.0 \times 10^8\ \text{M}^{-1}\ \text{s}^{-1}$, eventually we could successfully determine the formation rate constants: $k_t = 5.5 \times 10^7\ \text{M}^{-1}\ \text{s}^{-1}$, $k_c = 2.9 \times 10^7\ \text{M}^{-1}\ \text{s}^{-1}$, $k_e = 7.3 \times 10^7\ \text{M}^{-1}\ \text{s}^{-1}$. In the microreactor, the formation rate constant was larger than that in the batch cell. The difference in the relative rate constant (k_c/k_t) between the batch cell and the microreactor affects the difference in de. The diastereoselective reaction is known to be sensitive to the reaction temperature. The experiment in the batch cell and the microreactor was carried out at the room temperature. With the power of the Hg lamp, the absorbance of the sample solution, and the heat capacity of methanol considered, the temperature rise caused by the irradiation should be negligible. Furthermore, the differential activation parameters for diastereodifferentiating photoaddition of methanol to (*R*)-(+)-(*Z*)-limonene sensitized by toluene in methanol at 25 °C were reported to be relatively small: $\Delta\Delta H = -0.11$ kcal/mol and $\Delta\Delta S = -0.16$ kcal/mol [25]. These results also suggest that the effect on de of the temperature rise should be negligible under our experimental condition. In the batch cell, it is likely that the rate constant observed should contain the effect of side reactions, whilst that in the microreactor contributes little. In the microreactor, side reactions can be suppressed because of not only the nature of the flow system, where the residence time of the substrate is very short and the reac-

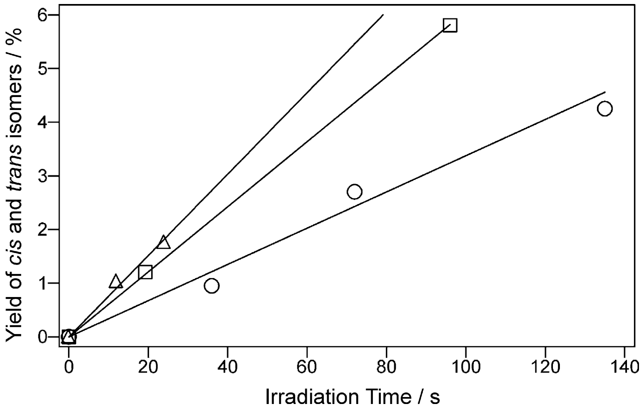


Fig. 3. The plots of the yield of *cis* and *trans* isomers *vs.* the irradiation time in various size of microreactors: 500 μm × 300 μm (○), 400 μm × 40 μm (□), and 200 μm × 20 μm (△).

tion vessel does not retain the reaction products, but also unique properties of the microspace.

Fig. 3 shows the effect of microchannel size on the reaction yield. The yield of the photoproduct increased linearly with the irradiation time for each microreactor. In addition, the slope of the best-fitted line is larger, namely the photon efficiency increases with decreasing channel size of the microreactor. As described above, the photon efficiencies in the microreactors of 400 μm × 40 μm and 200 μm × 20 μm cross section were determined to be 0.27 and 0.29, respectively. The estimated formation rate constants were $k_t = 1.0 \times 10^8\ \mathrm{M^{-1}\,s^{-1}}$, $k_c = 5.6 \times 10^7\ \mathrm{M^{-1}\,s^{-1}}$, $k_e = 1.2 \times 10^8\ \mathrm{M^{-1}\,s^{-1}}$ (400 μm × 40 μm), and $k_t = 1.4 \times 10^8\ \mathrm{M^{-1}\,s^{-1}}$, $k_c = 7.4 \times 10^7\ \mathrm{M^{-1}\,s^{-1}}$, $k_e = 1.6 \times 10^8\ \mathrm{M^{-1}\,s^{-1}}$ (200 μm × 20 μm). These results are summarized in Table 2. The de value is not very dependent on the dimension of microreactor (30.6% de with 500 μm × 300 μm, 29.4% de with 400 μm × 40 μm, and 30.0% de with 200 μm × 20 μm). The error for the de value is less than 1%. Although the side reactions may also occur in a microreactor, the reactions will not proceed so effective. Therefore, 30% de is regarded as the intrinsic de value for this reaction. These results indicate that the microreaction system would be useful on controlling side reaction.

To probe the nature of the side reactions, the *trans* isomer was isolated from the photoproduct solution by chromatography with silicagel. However, the *cis* and exo isomers could not be obtained. A solution of the *trans* isomer with toluene (1 mM) in methanol was irradiated with the Hg lamp in a quartz batch cell. Small amounts of *cis* and exo isomers were detected by the gas chromatographic analysis after irradiation for several minutes. This reveals the existence of equilibrium among the *cis*, *trans*, and exo isomers. Such an equilibrium should result in the decrease in de upon prolonged irradiations. A solution of (*R*)-(+)-(*Z*)-limonene (25 mM) and toluene (10 mM) in methanol was irradiated by the Hg lamp in the batch cell. Fig. 4 shows the time evolution of the de value against the irradiation time. The de value decreased at the beginning of the irradiation, and then reached to a nearly constant value. The same experiment in the microreactor was carried out. The long irradiation period (several minutes) led to a saturation of the product yield and a decrease in de. This strongly suggests that a micro-flow system, which does not retain reaction products, should enable us to obtain a better de value of the asymmetric photoreaction.

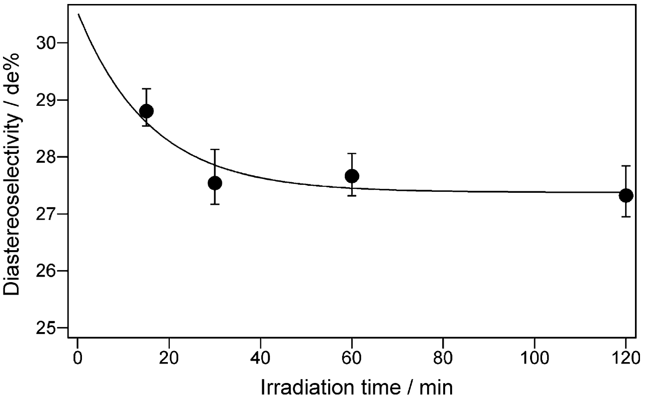


Fig. 4. The plots of the de value against the irradiation time of the Hg lamp.

In the present study, the asymmetric photosensitized diastereodifferentiating addition of methanol to (*R*)-(+)-(*Z*)-limonene in a microreactor was investigated. The enhancement of stereoselectivity and the drastic increase of the quantum yield of the photoreaction in the microspace were probably brought by the distinct properties of microreactors on photoreactions, high spatial illumination homogeneity and excellent light penetration throughout the reactor. Moreover, in the micro-flow system, the residence time of the substrate is very short and the reaction vessel does not retain the reaction products. These features may prevent sequential side reactions and increase the quantum yield of the photoreaction.

Acknowledgments

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