doi:10.1246/cl.2010.828

Published on the web June 26, 2010

Diastereoselective [2 + 2] Photocycloaddition of Chiral Cyclic Enone and Cyclopentene Using a Microflow Reactor System

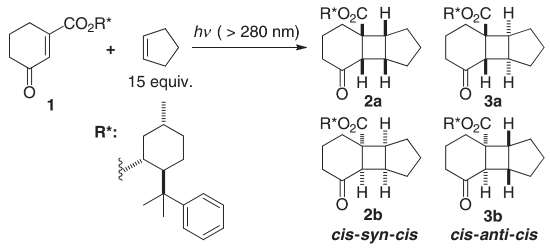
Ken Tsutsumi,[1] Kimitada Terao,[1] Hiroki Yamaguchi,[1] Syogo Yoshimura,[1] Tsumoru Morimoto,[1] Kiyomi Kakiuchi,*[1] Takahide Fukuyama,[2] and Ilhyong Ryu*[2]
[1]*Graduate School of Materials Science, Nara Institute of Science and Technology (NAIST), 8916-5 Takayama, Ikoma, Nara 630-0101*
[2]*Department of Chemistry, Graduate School of Science, Osaka Prefecture University, Sakai, Osaka 599-8531*

(Received May 11, 2010; CL-100457; E-mail: tsutsumi@ms.naist.jp, kakiuchi@ms.naist.jp)

Diastereoselective [2 + 2] photocycloaddition of chiral cyclohexenone **1** with cyclopentene was conducted using a continuous microflow reactor. This reaction led to photoadducts **2** and **3** in a shorter reaction time and with a higher diastereoselectiviy than the corresponding reaction in a batch reactor. The effect of temperatures on the selectivities of both reaction systems is also discussed.

Photochemical [2 + 2] cycloadditions, particularly asymmetric photoreactions, have received a greate deal of interest due to the formation of potentially versatile synthons for the synthesis of biologically active natural products and various unique structural compounds.[1] In this context, asymmetric [2 + 2] photocycloadditions of α,β-unsaturated ketones with olefins have been investigated.[2,3] Previous studies have found that menthyl derivatives are effective chiral auxiliaries for achieving a high degree of asymmetric induction.[3] However, large-scale applications of photochemical reactions remain problematic because it is difficult to effectively irradiate all reactants in a large-scale apparatus with conventional photoirradiation. Recently, microflow reactor systems have received a great deal of attention. In such systems, reactions can be easily scaled up using a microreactor that is running continuously or by operating several microreactors in parallel, typically referred to as numbering-up.[4] A number of photoreactions have already been successfully performed in microreactors,[5–7] including asymmetric reactions.[6a] Thus we decided to investigate a diastereoselective [2 + 2] photocycloaddition in a flow system using a microreactor. This study discusses the utility of microflow systems in photoinduced asymmetric reactions, and compares our results with those obtained using a large volume batch reactor system.

Diastereoselective [2 + 2] photocycloaddition of the cyclohexenonecarboxylate derivative **1**, which includes a (−)-8-(phenyl)menthyl group as a chiral auxiliary, with an excess of cyclopentene was carried out in both a microflow system and a batch reactor system (Scheme 1).[8] These studies were conducted using a Dainippon Screen Mfg. microreactor composed of a stainless-steel plate with a single-lane microchannel (1000 µm wide, 100 µm deep, 2.2 mm long, and with a holdup volume of 0.2 mL), and a Pyrex glass plate. The microdevice and the Pyrex test tube for the batch reaction (13 mm inner diameter × 17 mm outer diameter) were positioned next to a high-pressure mercury lamp (500 W) attached to a quartz cooling jacket (Figure 1). The reactors were immersed in the ethanol-containing cooling bath. A solution of **1** (0.05 M in toluene or dichloromethane) and cyclopentene (0.75 M) was introduced into the microchannel



Scheme 1. Diastereoselective [2 + 2] photocycloaddition.

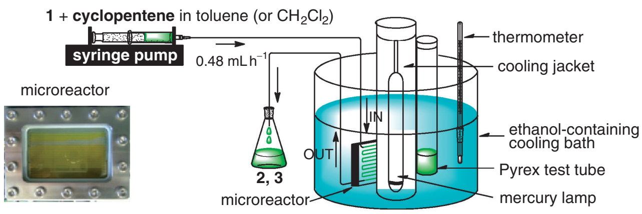


Figure 1. Schematic diagram of the photoreaction system comprising a microflow reactor and a batch reactor.

using a syringe pump at a flow rate of 0.48 mL h^{-1} (residence time: 0.5 h). In the case of the batch reaction, a test tube containing a 2 mL solution of **1** (0.05 M in toluene or dichloromethane) and cyclopentene (0.75 M) was used under nitrogen atmosphere. In both cases, photoirradiation was performed with a Pyrex-filtered light ($\lambda > 280$ nm) obtained from a high-pressure mercury lamp.

The photoreactions in toluene proceeded smoothly and produced four diastereomeric isomers of [2 + 2] adducts, i.e., *cis–syn–cis* **2a** and **2b** and *cis–anti–cis* **3a** and **3b**, in both the microflow system and the batch system (Scheme 1, Table 1). Note that the photoreactions using the microflow system reached completion in a shorter reaction time (0.5 h) than the reaction using the batch system (1 h). The microreactor system allowed complete conversions in both toluene and CH_2Cl_2 at low temperatures, e.g., −40 °C (Table 1, Entries 1–3 and 7–9). Both reaction systems yielded **3** as the major product at 0 °C (Table 1, Entries 1, 4, 7, and 10). Lange reported that a similar reaction at room temperature in a batch reactor system led to four photoadducts of compounds **2** and **3**, with the major product being the *cis–anti–cis* compound **3**.[2a] Almost identical ratios of **2** and **3** were obtained in both reaction systems. On the other hand, the diastereoselectivity was increased at lower temperatures and the use of toluene resulted in a higher diastereoselectivity. The highest d.e. (diastereomeric excess) values were observed in the microflow reaction at −40 °C using toluene as the solvent

Table 1. Diastereoselective [2 + 2] photocycloaddition of **1** with cyclopentene

Entry	Reactor	Temp[a] /°C	Solvent	Time[b] /h	Ratio[c] **2**:**3**	d.e./%[c] **2**	d.e./%[c] **3**
1	Micro[d]	0	Toluene	0.5[e]	39:61	71	53
2		−20		0.5[e]	41:59	72	53
3		−40		0.5[e]	50:50	82	54
4	Batch	0		1	38:62	60	37
5		−20		1	41:59	70	42
6		−40		1	50:50	72	44
7	Micro[d]	0	CH_2Cl_2	0.5[e]	38:62	65	30
8		−20		0.5[e]	50:50	70	32
9		−40		0.5[e]	51:49	71	34
10	Batch	0		1	35:65	57	27
11		−20		1	46:54	60	30
12		−40		1	50:50	67	33

[a]The temperature of ethanol was measured as the reaction temperature. [b]Time required for full conversion of **1**, as determined by ^{1}H NMR analysis of samples. [c]Determined by HPLC (CHIRALPAK AD). [d]The microreactor was offered as a gift by Dainippon Screen Mfg. Co., Ltd. [e]Reaction time was calculated according to the following equation: time (h) × flow rate (mL h^{-1}) = volume of microreactor (mL).

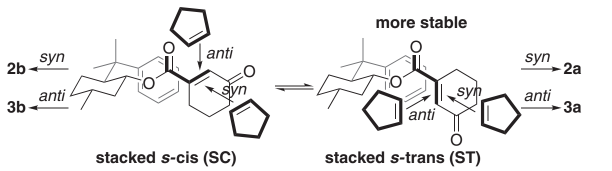


Figure 2. Equilibration between the stacked *s-cis* (SC) and the stacked *s-trans* (ST) conformations of **1**.

(Table 1, Entry 3). In a previous work, we reported that the selectivity of the reaction relates to the populations of two stable conformers of **1**, a stacked *s-cis* (SC) and a stacked *s-trans* (ST) (Figure 2).[3] The diastereoface of cyclohexenone is shielded by the phenyl ring. Thus, **2a** and **3a** are presumably produced from the stable ST conformer as a major product, while **2b** and **3b** are produced from the SC conformer. As the ST conformer is enthalpically stable, the conformational equilibrium is shifted towerd the ST conformer at low temperatures. The better diastereoselectivities achieved by the microflow system may be the result of an accurate temperature control associated with a very large surface area to volume ratio in the reaction chamber.[4]

Because photoreactions depend to a large degree on the irradiation power, [2 + 2] photocycloadditions are generally carried out using a high-power mercury lamp.[2,3] In the microreactor however, a low-power light source is sufficient to perform the photoreaction.[7] Indeed, as indicated by our preliminary results, photocycloaddition can be carried out using a black light (15 W); the reaction in toluene at 25 °C for 1 h resulted in 51% conversion, and almost no by-products were formed (**2**:**3** = 44:56, **2**: 49%de, **3**: 32%de).[8]

In summary, this study has shown that a flow microreactor can be effectively used for asymmetric photoreactions. Interestingly, the diastereoselectivities of the reactions in the microflow reactor were slightly superior to those obtained in the batch reactor. This may be due to the accurate control of the reaction temperature in the small volume of the microreactor. We have also found that a low-power, black light can effectively supply photons to the microreactor system.

The microreactor was offered as a gift by Dainippon Screen Mfg. Co., Ltd. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) and the Japan Society for the Promotion of Science (JSPS) in Japan, and by the Foundation for Nara Institute of Science and Technology.

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