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Scalable flow synthesis of [6,6]-phenyl-C_{61}-butyric acid methyl ester (PCBM) using a flow photo-reactor with a Na lamp

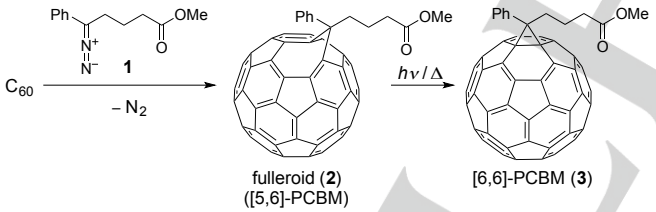
Mitsuhiro Ueda,[a] Naoyuki Imai,[b] Shunsuke Yoshida,[b] Hiroshi Yasuda,*[b] Takahide Fukuyama,*[a] and Ilhyong Ryu [a,c]

Dedication ((optional))

Abstract: An efficient flow system was constructed for the synthesis of PCBM, which involves flow [2+1] addition of C_{60} and the subsequent flow photo isomerization of the resulting fulleroid to PCBM by using a flow photo-reactor in combination with a Na lamp. With the present flow system, the scalable synthesis of PCBM (0.79 g/3.3 h) was achieved by the continuous operation for 3.3 h.

Introduction

PCBM ([6,6]-phenyl-C_{61}-butyric acid methyl ester) displays outstanding performance as a material of n-type organic semiconductor for organic photovoltaics (OPVs).[1,2] This necessitates the development of effective manufacturing protocol available for the synthesis of a large quantity of PCBM. A general synthetic method for PCBM is composed of two steps, (i) [2+1] cycloaddition to prepare fullenoid **2** from C_{60} and diazo-alkane **1** and (ii) its isomerization leading to PCBM **3** (Scheme 1).[3,4] The second isomerization step has options of thermal and photo isomerization. If we assume the latter option on scaling-up in a batch reactor, a huge light source capable of irradiating a large surface volume would be necessary, yet the solubility of C_{60} in organic solvent is very poor[5] (Scheme 1).

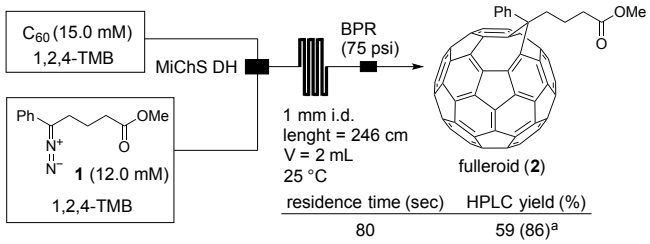


Scheme 1. General synthetic method of PCBM (**3**) via fulleroid (**2**)

Recently, the use of continuous flow system[6] for the synthesis of PCBM has attracted much attention. In 2011, Wong and Jones reported the gram scale synthesis of PCBM using one-flow system (2.6 g/ 8 h), in which heating to 250 °C was used for the isomerization step of fulleroid **2** to PCBM **3**.[7] Muccini and Maggini used the photo-irradiative flow synthesis of PCBM[8] using white LEDs at ambient temperature (25 °C). However, in their flow system, due to the low power of the employed white LEDs (1.35 W x 75), the long residence time (41 min) was required. As the result, the system allowed for only low product output (6 mg/ 1 h). Since our group has a long research experience in photo-flow synthesis,[9][10] we believed that a practical photo isomerization process would be possible with a judicious choice of a photo flow microreactor and a light source. Herein, we report that the scalable flow synthesis of PCBM is achieved in short residence time of minute order over two steps by using a serially connected flow system comprising thermal flow reactor and a photo flow reactor combined with a Na lamp as a light source.[11]

Results and Discussion

In the first investigation, we examined the flow synthesis of fulleroid **2** by the reaction of C_{60} with diazo-alkane **1** (Scheme 2). For this reaction, we used a MiChS's DH micromixer (channel width = 60 μm) as a micromixer and a residence time unit (i.d. = 1 mm, length = 2.46 m, inner volume: 2 mL). The flow reaction of C_{60} with **1** at 25 °C with a residence time of 80 sec gave fulleroid **2** in 59% yield, in which the yield based on the consumed C_{60} was 86%.[12] A shorter residence time of 40 sec gave **2** in 52% yield, in which the yield based on the consumed C_{60} was 83%.[13]



residence time (sec)	HPLC yield (%)
80	59 (86)[a]
40	52 (83)[a]

*1,2,4-TMB: 1,2,4-trimethylbenzene

[a] Values in parentheses were based on consumed C_{60}

Scheme 2. Flow synthesis of fulleroid (**2**) by the reaction of C_{60} and **1**

Encouraged by these nice results for flow synthesis of fulleroid **2**, we then moved on the isomerization of **2** to PCBM **3** using a flow photo-reactor (Scheme 3). A 1,2,4-trimethylbenzene solution of fulleroid (**2**, 4.1 mM) was irradiated using a flow photo-reactor (MiChS L-1; inner volume: 3 mL, width = 2 mm, length = 3 m,

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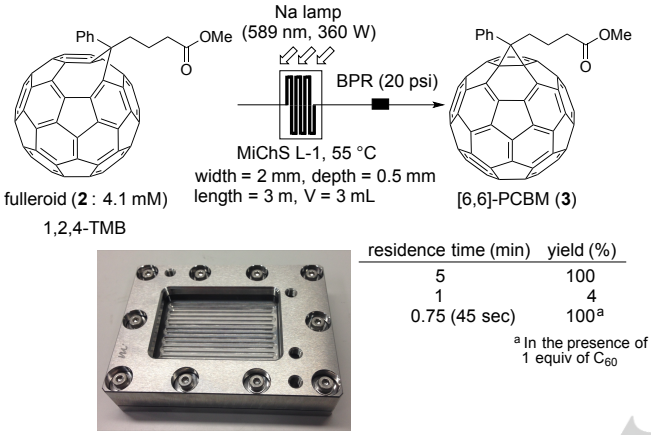
depth = 0.5 mm, quartz). After a survey of various light sources (See the Supporting Information), we were delighted to find that the use of a Na lamp (589 nm, 360 W) gave excellent results (Scheme 3).[4,14] For example, the flow photo isomerization of **2** to **3** with a residence time of 5 min gave the desired isomerization product **3** in 100% yield. Whereas a much shorter residence time of 1 min gave **3** in poor yield, we found that *even with the short residence time of 45 sec, in the presence of C_{60}, PCBM **3** was formed in excellent yield.* We assume that C_{60} would behave as a photo-sensitizer in the present photo isomerization reaction as well as the reported cases.[15]

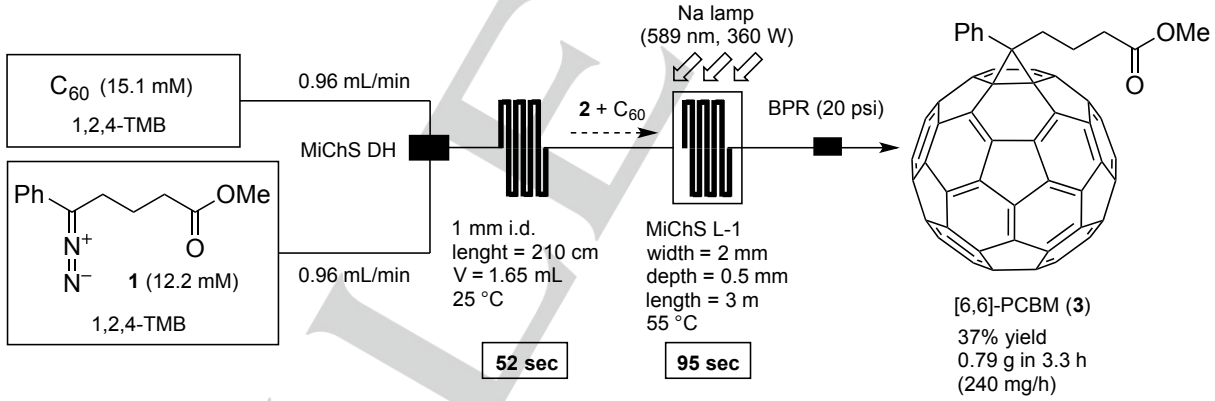


Scheme 3. Photo-isomerization of fulleroid (**2**) to PCBM (**3**).

Having promising results over two flow steps in hand, we then embarked on a challenge to develop the continuous one-flow two-step synthesis of PCBM **3** from C_{60} and diazo-alkane **1**, for which we used an automated flow reactor system (MiChS X-1)[16] combined with the photo flow reactor (MiChS L-1) and Na lamp (for details, see SI) (Scheme 4). A 1,2,4-trimethylbenzene solution of C_{60} (0.96 mL/min) and a 1,2,4-trimethylbenzene solution of **1** (0.96 mL/min) were mixed using a micromixer at 25 °C, and the resultant mixture was guided to the residence time unit at the same temperature with residence time of 52 sec. The reaction mixture including unconverted C_{60} was then passed through the flow photo-reactor (MiChS L-1) at 55 °C with residence time of 95 sec under Na lamp irradiation (589 nm, 360 W). Consequently, we obtained 0.79 g of PCBM (**3**) in 3.3 h (37% yield, PCBM/others/C_{60} = 30/28/42, Scheme 4).[17]

Conclusions

In summary, we demonstrated one flow synthesis of PCBM **3** from C_{60} and diazo-alkane **1**, in which photo-isomerization of in situ formed fulleroid **2** to PCBM **3** was successfully carried out in very short residence time by the irradiation of a Na lamp. The presence of excess C_{60} contributed to accelerate the photo-isomerization presumably as a photo-sensitizer and the obtained output (0.79 g/3.3 h) is promising for scalable synthesis of PCBM.



Scheme 4. Continuous one-flow synthesis of PCBM (**3**). Picture of the flow reactor system (MiChS® System XL-1)

Experimental Section

Flow synthesis of fulleroid (2): A 60 mL 1,2,4-trimethylbenzene solution of C_{60} (0.9 mmol, 0.65 g, 15.0 mM) and a 60 mL 1,2,4-trimethylbenzene solution of diazo-alkane **1** (12.0 mM, 0.8 equiv) were prepared and placed in glass-made bottles respectively. These two bottles were connected by PTFE tube to the HPLC pumps of the automated microflow reactor, MiChS® system X-1, equipped with a MiChS DH micromixer, a residence time unit (RTU, inner volume: 2 mL, 1 mm i.d., length: 246 cm, 25 °C), a back-pressure regulator (75 psi), and an automated fraction collector. The reaction mixtures for each conditions were sampled (1 mL) automatically in vials by a fraction collector, and the yields of product **2** were determined by HPLC analysis.

Photo-isomerization of fulleroid (2) to PCBM (3): An 80 mL 1,2,4-trimethylbenzene solution of fulleroid (**2**: 0.3 mmol, 0.3 g, 4.1 mM) was prepared and placed in a glass-made bottle. The bottle was connected by PTFE tube to the HPLC pumps of the automated microflow system, MiChS® system X-1, equipped with a MiChS L-1 as a flow photo-reactor (inner volume 3 mL, width 2 mm, length 3 m, depth 0.5 mm, quartz, 55 °C), which was irradiated with a Na lamp (589 nm, 360 W), a back-pressure regulator (20 psi), and an automated fraction collector. The reaction mixtures for each conditions were sampled (1 mL) automatically

in vials by a fraction collector, and the yields of product **3** were determined by HPLC analysis.

Continuous one-flow synthesis of PCBM (3): A 243 mL 1,2,4-trimethylbenzene solution of C_{60} (3.7 mmol, 2.6 g, 15.1 mM) and a 275 mL 1,2,4-trimethylbenzene solution of diazo-alkane **1** (12.2 mM, 0.8 equiv) were prepared and placed in bottles respectively. These two bottles were connected by PTFE tube to the HPLC pumps of the automated microflow system, MiChS® system X-1, equipped with a MiChS DH as a micromixer, a residence time unit (Inner volume: 1.65 mL, 1 mm i.d., length: 210 cm, 25 °C), MiChS L-1 as a flow photo-reactor (inner volume 3 mL, width 2 mm, length: 3 m, depth 0.5 mm, quartz, 55 °C), which was irradiated with Na lamp (589 nm, 360 W), a back-pressure regulator (20 psi), and an automated fraction collector. A 1,2,4-trimethylbenzene solution of C_{60} (0.96 mL/min) and a 1,2,4-trimethylbenzene solution of **1** (0.96 mL/min) were mixed using MiChS DH mixer at 25 °C, and the resultant mixture was guided to the residence time unit (residence time, 52 sec). The reaction mixture was then passed through the flow photo-reactor (MiChS L-1, 55 °C, residence time, 95 sec) under Na lamp irradiation (589 nm, 360 W) in the presence of unconverted C_{60}. The reaction mixture was collected during 3.3 h and the evaporation of the solvent gave a crude reaction mixture, which was purified by column chromatography on SiO_2 to give PCBM (**3**: 0.79 g, 37% yield).

Acknowledgements

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Keywords: Flow synthesis • PCBM • Isomerization • Photo-reactor • Na lamp

[1] For recent reviews, see: a) F. Giacalone, N. Martín, *Adv. Mater.* **2010**, *22*, 4220; b) J. Roncali, *Acc. Chem. Res.* **2009**, *42*, 1719; c) J. Chen, Y. Cao, *Acc. Chem. Res.* **2009**, *42*, 1709; d) Y. Matsuo, E. Nakamura, *Chem. Rev.* **2008**, *108*, 3016; e) N. Martín, *Chem. Commun.* **2006**, 2093; f) N. Martín, M. Altable, S. Filippone, A. Martín-Domenech, *Synlett* **2007**, 3077; g) E. Nakamura, H. Isobe, *Acc. Chem. Res.* **2003**, *36*, 807.

[2] Cyclobutane- and cyclopentane-annulated fullerenes also have attracted considerable attention as a material for organic photovoltaics. Recently, we found that the cyclobutane-annulated fullerene derivatives have high-lying LUMO levels, which gave a high open-circuit voltage compared with the PCBM-based devices in organic solar cell applications. see: M. Ueda, T. Sakaguchi, M. Hayama, T. Nakagawa, Y. Matsuo, A. Munechika, S. Yoshida, H. Yasuda, I. Ryu, *Chem. Commun.* **2016**, *52*, 13175.

[3] R. A. J. Janssen, J. C. Hummelen, F. Wudl, *J. Am. Chem. Soc.* **1995**, *117*, 544.

[4] J. C. Hummelen, B. W. Knight, F. LePeq, F. Wudl, *J. Org. Chem.* **1995**, *60*, 532.

[5] a) K. N. Semenov, N. A. Charykov, V. A. Keskinov, A. K. Piartman, A. A. Blokhin, A. A. Kopyrin, *J. Chem. Eng. Data* **2009**, *55*, 13; b) R. J. Doome, S. Dermaut, A. Fonseca, M. Hammida, J. B. Nagy, *Fullerene Sci. Technol.* **1997**, *5*, 1593; c) R. S. Ruoff, D. S. Tse, R. Malhotra, D. C. Lorents, *J. Phys. Chem.* **1993**, *97*, 3379.

[6] For selected reviews on flow chemistry, see: a) T. Wirth, *Microreactors in Organic Synthesis and Catalysis*, Wiley-VCH, Weinheim, **2013**; b) V. Hessel, A. Renken, J. C. Schouten, J. Yoshida, *Micro Process Engineering*, Wiley-VCH, Weinheim, **2009**; c) H. P. L. Gemoets, Y. Su, M. Shang, V. Hessel, R. Luque, T. Noel, *Chem. Soc. Rev.* **2016**, *45*, 83; d) R. Karande, A. Schmid, K. Buehler, *Org. Process Res. Dev.* **2016**, *20*, 361; e) B. Gutmann, D. Cantillo, C. O. Kappe, *Angew. Chem.* **2015**, *127*, 6788; *Angew. Chem. Int. Ed.* **2015**, *54,* 6688; f) T. Fukuyama, T. Totoki, I. Ryu, *Green Chem.* **2014**, *16*, 2042; g) D. T. McQuade, P. H. Seeberger, *J. Org. Chem.* **2013**, *78*, 6384; h) S. V. Ley, *Chem. Rec.* **2012**, *12*, 378; i) J. Wegner, S. Ceylan, A. Kirschning, *Chem. Commun.* **2011**, *47*, 4583; j) R. L. Hartman, J. P. McMullen, K. F. Jensen, *Angew. Chem.* **2011**, *123*, 7642; *Angew. Chem. Int. Ed.* **2011**, *50*, 7502; k) D. Webb, T. F. Jamison, *Chem. Sci.* **2010**, *1*, 675; l) T. Fukuyama, M. T. Rahman, M. Sato, I. Ryu, *Synlett* **2008**, 151; m) B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan, D. T. McQuade, *Chem. Rev.* **2007**, *107,* 2300.

[7] H. Seyler, W. W. H. Wong, D. J. Jones, A. B. Holmes, *J. Org. Chem.* **2011**, *76*, 3551.

[8] E. Rossi, T. Carofiglio, A. Venturi, A. Ndobe, M. Muccini, M. Maggini, *Energy Environ. Sci.* **2011**, *4*, 725.

[9] For reviews on photoreaction using flow microreactors, see: a) D. Cambie, C. Bottecchia, N. J. W. Staathof, V. Hessel, T. Noel, *Chem. Rev.* **2016**, *116*, 10276; b) K. Mizuno, Y. Nishiyama, T. Ogaki, K. Terao, H. Ikeda, K. Kakiuchi, *J. Photochem. Photobiol. C. Photochem. Rev.* **2016***, 29,* 107; c) M. Oelgemöller, *Chem. Eng. Technol.* **2012**, *35*, 114; d) Y. Matsushita, T. Ichimura, N. Ohba, S. Kumada, K. Sakeda, T. Suzuki, H. Tanibata, T. Murata, *Pure Appl. Chem.* **2007**, *79*, 195

[10] For our work on photoreactions using microreactor, see: a) S. Inuki, K. Sato, T. Fukuyama, I. Ryu, Y. Fujimoto, *J. Org. Chem.* **2017**, *82*, 1248; b) T. Fukuyama, Y. Fujita, M. A. Rashid, I. Ryu, *Org. Lett.* **2016**, *18*, 5444; c) T. Fukuyama, M. Tokizane, A. Matsui, I. Ryu, *React. Chem. Eng.* **2016**, *1*, 613; d) Y. Manabe, Y. Kitawaki, M. Nagasaki, K. Fukase, H. Matsubara, Y. Hino, T. Fukuyama, I. Ryu, *Chem. Eur. J.* **2014**, *20*, 12750; e) T. Fukuyama, Y. Kajihara, Y. Hino, I. Ryu, *J. Flow Chem.* **2011**, *1*, 40; f) H. Matsubara, Y. Hino, M. Tokizane, I. Ryu, *Chem. Eng. J.* **2011**, *167*, 567; g) K. Tsutsumi, K. Terao, H. Yamaguchi, S. Yoshimura, T. Morimoto, K. Kakiuchi, T. Fukuyama, I. Ryu, *Chem. Lett.* **2010**, *39*, 828; h) A. Sugimoto, T. Fukuyama, Y. Sumino, M. Takagi, I. Ryu, *Tetrahedron* **2009**, *65*, 1593; i) A. Sugimoto, T. Fukuyama, Y. Sumino, M. Takagi, I. Ryu, *Tetrahedron Lett.* **2006**, *47*, 1593; j) T. Fukuyama, Y. Hino, N. Kamata, I. Ryu, *Chem. Lett.* **2004**, *33*, 1430.

[11] Recently, synthesis of PCBM using one-flow system comprising thermal flow reactor (30 °C) and a photo flow reactor equipped with the fluorescent lamp was disclosed (total residence time: 27.5 min). see: T. Iwai, J. Murata, T. Iwasawa, F. Matsumoto, K. Moriwaki, Y. Takao, T. Ito, T. Mizuno, T. Ohno, Abstracts of Papers, the 95th Annual Meeting of the Chemical Society of Japan, Chiba, **2015**, 1PA-055.

[12] In reference 3, the reaction of **1** with C_{60} for 24 h gave fulleroid (**2**) in 50% yield. The yield of based on consumed C_{60} was 70% yield.

[13] Further reducing the residence time resulted in low yield (a residence time: 20 sec, 44% yield)

[14] In reference 3, the isomerization of **2** at 180 °C for 2 h gave PCBM (**3**) in 98% yield. In reference 4, under irradiation conditions with an Ar ion laser (488 nm, 50 mW), the isomerization of **2** for 1 h gave **3** in quantitative conversion.

[15] a) T. Hamano, K. Okuda, S. Mashino, M. Hirobe, K. Arakane, T. Nagano, *Chem. Commun.* **1997**, 21; b) T. Nagano, K. Arakane, A. Ryu, T. Masunaga, K. Shinmoto, S. Mashino, M. Hirobe, *Chem. Pharm. Bull.* **1994**, *42*, 2291; c) J. W. Arbogast, A. P. Darmanyan, C. S. Foote, Y. Rubin, F. N. Diederich, M. M. Alvarez, S. J. Anz, R. L. Whetten, *J. Phys. Chem.* **1991**, *95*, 11.

[16] http://www.michs.jp/index_en.html.

[17] Conventional batch reaction gave 32% yield of PCBM with similar product distribution.

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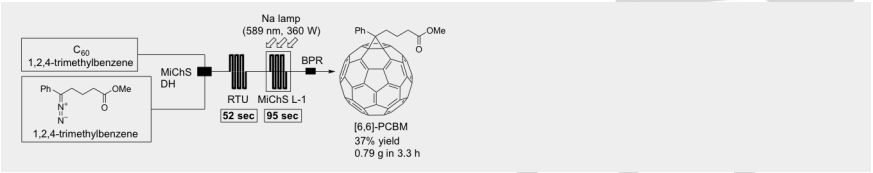

One-Flow synthesis*

Mitsuhiro Ueda, Naoyuki Imai, Hiroshi Yasuda, Takahide Fukuyama,* and Ilhyong Ryu*

We found that the photo-isomerization of fulleroid to PCBM proceed very efficiently by using a flow photo-reactor with a Na lamp. As the result, the scalable synthesis of PCBM was achieved by continuous-flow synthesis (0.79 g/3.3 h).

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Scalable flow synthesis of [6,6]-phenyl-C_{61}-butyric acid methyl ester (PCBM) using a flow photo-reactor with a Na lamp

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