

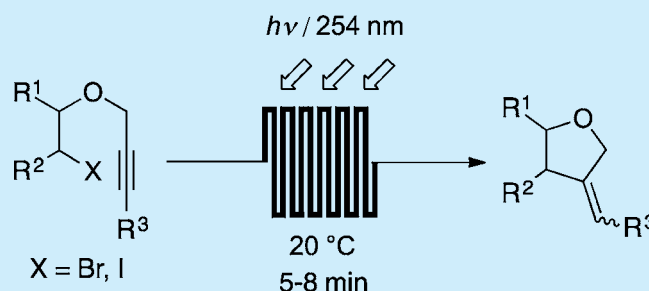
Flow Update for a Cossy Photocyclization

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S Supporting Information

ABSTRACT: A Cossy 5-exo-dig photocyclization of organohalides (X = Br, I) onto a C–C triple bond was studied using a flow photomicroreactor, which proceeded in a minute order of residence time. A deuterium labeling study supported the nonchain radical mechanism proposed by the Cossy group, in which a hydrogen source originates from a triethylamine cation radical. Scalable flow synthesis using a larger volume of flow reactor was also successful, providing 4 g of the product in high yield.



Radical addition onto an internal C–C triple bond provides a promising strategy for the construction of carbo- and heteroring molecules with an exomethylene moiety.¹ Cossy's photocyclization² is unique in this regard, since the system does not contain a typical H-donating radical mediator such as tributyltin hydride to achieve the same 5-exo-dig type of reductive radical cyclization (Scheme 1). The use of superstoichiometric amounts of triethylamine (TEA) is the key, which, with photoirradiation, delivers one electron to organohalides.³ The resultant radical anions undergo homolysis to generate the key alkyl radicals, which are ready to undergo 5-exo-dig cyclization with the liberation of halogenide anions. The hydrogen source of the Cossy reaction is thought to be the cation radical of TEA that arises from the one-electron transfer reaction.

By taking advantage of very narrow and shallow reactor channels, radical reactions are promptly carried out using flow microreactors.^{4,5} Thus, we believed that a photomicroreactor^{6,7} would help the speedy execution of Cossy radical cyclization, which is typically carried out using a batch reactor for 0.5 to 1 h.² In this paper, we report that (i) Cossy reaction using flow microreactors proceeds in residence times on the order of minutes, (ii) the labeling study using deuterated triethylamine lends support to the nonchain radical mechanism originally proposed by Cossy, and (iii) the scalable reaction was carried out

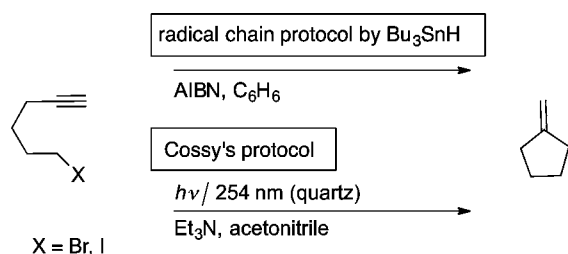
Table 1. Flow Radical Cyclization of Bromoacetal 1a in the Presence of Triethylamine^a

entry	conc. (M)	residence time (min)	conv. (%) ^b	yield (%) ^b
1	0.01	5	100	60
2	0.01	3.8	100	90
3	0.01	1	59	37
4	0.1	5	98	92
5	0.1	3	67	60
6 (batch) ^c	0.1	5	13	8

^aThe reactions were conducted with **1a** (1 mmol), NEt₃ (10 mmol), and CH₃CN using a flow photomicroreactor (YMC Co. Ltd., inner volume 0.11 mL, width 1 mm, length 560 mm, depth 200 μm, quartz).

^bGC yields using *n*-decane as an internal standard. ^cThe reaction was carried out in a quartz test tube with an i.d. of 1.3 cm.

Scheme 1. Cossy Cyclization and Tin Hydride-Mediated Cyclization



using a larger-volume flow photoreactor, which allowed a 4 g synthesis of cyclized product.

As a model to establish a flow Cossy reaction, the photocyclization of *trans*-3-bromo-2-(propargyloxy)-tetrahydropyran (**1a**) to give **2a** was chosen. An acetonitrile solution of **1a** and TEA was irradiated using a flow photomicroreactor (YMC Co. Ltd.; inner volume 0.11 mL, width 1 mm, length 560 mm, depth 200 μm, quartz) and a compact light source consisting of a low-pressure Hg lamp (254 nm, 1.2 W). We tested different conditions wherein the residence time and concentrations were systematically varied (Table 1). The flow reaction ([**1a**] = 0.01 M) with a residence time of 6 min gave the

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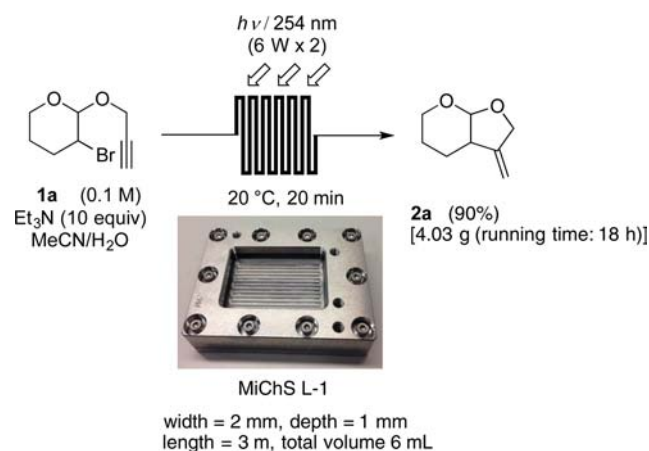
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Table 2. Flow Radical Photocyclization of Alkynyl Halides 1^a

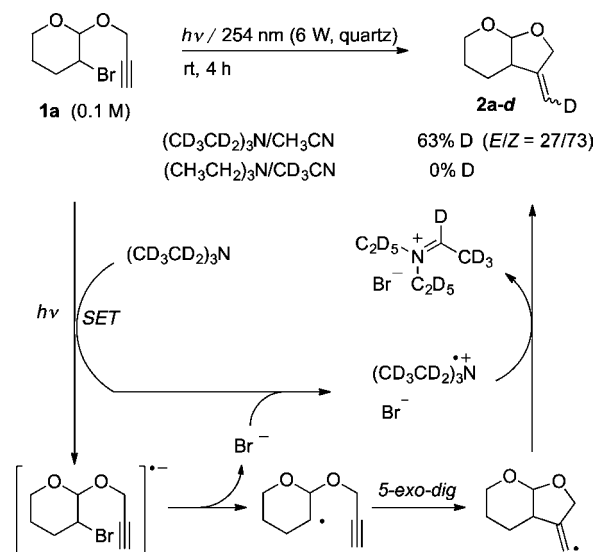
entry	substrate, 1	residence time (min)	product, 2	yield (%) ^b
1		5		93
2		5		91
3		5		75
4		6		70
5		5		62
6		7		66
7		7		45
8		5		71
9		8		63
10		7		60 (E/Z = 53/47)

^aThe reactions were conducted with **1** (1.0 mmol), Et₃N (10 mmol), and CH₃CN (10 mL) using a flow photomicroreactor (YMC Co. Ltd., inner volume 0.11 mL, width 1 mm, length 560 mm, depth 200 μ m, quartz) with residence times of 5–8 min. ^bIsolated yields after purification by chromatography on SiO₂ or Al₂O₃ (entries 3 and 5).

desired product **2a** in 60% yield, whereas starting **1a** was completely consumed (Table 1, entry 1). A shorter residence time of 3.8 min gave **2a** in 90% yield (Table 1, entry 2). Further reducing the residence time (1 min) resulted in a low conversion of **1a** (Table 1, entry 3). The flow radical cyclization of **1a** proceeded well even at a higher **1a** concentration (0.1 M) with residence time of 5 min (Table 1, entry 4). It should be noted that the batch reaction using a quartz test tube (1.3 cm internal

Scheme 2. Gram-Scale Synthesis of **2a** Using a Large-Volume Flow Photoreactor

Scheme 3. Deuterium Labeling Experiment To Support a SET-Based Reaction Mechanism



diameter) with the same UV source gave only an 8% yield of **2a** with 13% conversion (Table 1, entry 6).

After the initial observation of the effective conversion of **1a** into **2a** in times on the order of minutes, we next examined the radical cyclization of various haloacetals under the optimized conditions (Table 2). Irradiation of a 0.1 M acetonitrile solution of iodoacetal **1a'** in the presence of TEA at 254 nm proceeded rapidly to afford the cyclized product **2a** in 93% yield (Table 2, entry 1). In a similar manner and under otherwise identical conditions, irradiation of bromoacetals **1b** and **1c** resulted in the formation of exocyclic alkenes **2b** and **2c** in 91 and 75% yield, respectively (Table 2, entries 2 and 3). In the case of bromooxanorboranone **1d**, the desired tricyclic compound **2d** was obtained in 70% yield (Table 2, entry 4). The reaction of bromoalkyne **1e** gave the corresponding tricyclic product **2e** in 62% yield (Table 2, entry 5). In a similar manner, bromoalkyne **1f** was converted to the bicyclic compound **2f** in 66% yield (Table 2, entry 6). The reaction of bromoether **1g** gave a lower yield of the product **2g** (45%), which was probably due to a Norrish type 1 decomposition that is inherent in a ketone moiety (Table 2, entry 7). The photochemical reaction of bromoalkynes **1h** and **1i** resulted in the formation of tetrasubstituted alkenes **2h**

and **2i** in 71 and 63% yield, respectively (Table 2, entries 8 and 9). In these cases, an exocyclic double bond was isomerized to form conjugated esters. The internal alkyne **1j** gave **2j** in 60% yield as a 53/47 E/Z mixture (Table 2, entry 10).

We next executed the scalable synthesis of **2a** using an MiChS L1 flow photoreactor, which has a large inner volume (6 mL, width 2 mm, depth 1 mm, length 3 m), and two 6 W low-pressure Hg lamps were used for photoirradiation. The reaction was carried out with a residence time of 20 min using CH₃CN containing 10% H₂O as the solvent to suppress the influence of insoluble material, which stuck to the glass surface during the long-time operation. After continuous operation for 18 h, we obtained 4 g of **2a** in 90% isolated yield after column chromatography on silica gel (Scheme 2).

As for the mechanism, Cossy and co-workers already proposed a photoelectron-transfer mechanism for the generation of alkyl radicals, wherein TEA serves as a sacrificial electron source.² Labeling experiments using deuterated TEA were carried out in a batch reaction. The results reasonably supported Cossy's nonchain single electron transfer (SET) mechanism, since deuterium incorporation was observed only for the experiment using deuterated TEA and nonlabeled acetonitrile (Scheme 3).

In summary, we have demonstrated that the Cossy 5-exo-dig photocyclization of organohalides onto a C–C triple bond can be successfully carried out using a flow photomicroreactor and requires a relatively short residence time. Deuterium labeling experiments supported the nonchain radical mechanism proposed by Cossy, in which a vinyl radical abstracts hydrogen from a triethylamine cation radical. Scalable flow synthesis using a large-volume flow reactor was also successful.

■ ASSOCIATED CONTENT

■ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02727.

General experimental procedures and spectroscopic data of products (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

- (1) For a leading review, see: Gilmore, K.; Alabugin, I. V. *Chem. Rev.* **2011**, *111*, 6513.
- (2) (a) Cossy, J.; Ranaivosata, J.-L.; Bellosta, V. *Tetrahedron Lett.* **1994**, *35*, 8161. (b) Cossy, J.; Bellosta, V.; Ranaivosata, J.-L.; Gille, B. *Tetrahedron* **2001**, *57*, 5173.

- (3) For reviews of photoinduced electron transfer from amines, see: (a) Cossy, J. Photoinduced Electron Transfer in Radical Reactions. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds.; Wiley-VCH: Weinheim, Germany, 2001; Vol. 1, pp 229–249. (b) Cossy, J.; Belotti, D. *Tetrahedron* **2006**, *62*, 6459. (c) Griesbeck, A. G.; Hoffmann, N.; Warzecha, K.-D. *Acc. Chem. Res.* **2007**, *40*, 128.

- (4) For selected reviews of flow synthesis, see: (a) Mason, B. P.; Price, K. E.; Steinbacher, J. L.; Bogdan, A. R.; McQuade, D. T. *Chem. Rev.* **2007**, *107*, 2300. (b) Fukuyama, T.; Rahman, M. T.; Sato, M.; Ryu, I. *Synlett* **2008**, *2008*, 151. (c) Webb, D.; Jamison, T. F. *Chem. Sci.* **2010**, *1*, 675. (d) Suga, S.; Yamada, D.; Yoshida, J. *Chem. Lett.* **2010**, *39*, 404. (e) Yoshida, J.; Kim, H.; Nagaki, A. *ChemSusChem* **2011**, *4*, 331. (f) Wegner, J.; Ceylan, S.; Kirschning, A. *Adv. Synth. Catal.* **2012**, *354*, 17. (g) Ley, S. V. *Chem. Rec.* **2012**, *12*, 378. (h) Wiles, C.; Watts, P. *Green Chem.* **2012**, *14*, 38. (i) McQuade, D. T.; Seeberger, P. H. *J. Org. Chem.* **2013**, *78*, 6384. (j) Newman, S. G.; Jensen, K. F. *Green Chem.* **2013**, *15*, 1456. (k) Fukuyama, T.; Totoki, T.; Ryu, I. *Green Chem.* **2014**, *16*, 2042. (l) Gutmann, B.; Cantillo, D.; Kappe, C. O. *Angew. Chem., Int. Ed.* **2015**, *54*, 6688. (m) Porta, R.; Benaglia, M.; Puglisi, A. *Org. Process Res. Dev.* **2016**, *20*, 2.

- (5) For reviews of photoreaction using flow microreactors, see: (a) Matsushita, Y.; Ichimura, T.; Ohba, N.; Kumada, S.; Sakeda, K.; Suzuki, T.; Tanibata, H.; Murata, T. *Pure Appl. Chem.* **2007**, *79*, 1959. (b) Oelgemöller, M. *Chem. Eng. Technol.* **2012**, *35*, 1144. (c) Cambie, D.; Bottecchia, C.; Straathof, N. J. W.; Hessel, V.; Noel, T. *Chem. Rev.* **2016**, *116*, 10276.

- (6) For a review of flow radical reactions, see: (a) Fukuyama, T.; Ryu, I. Radical Chemistry by Using Flow Microreactor Technology. In *Encyclopedia of Radicals in Chemistry, Biology, and Materials*; Studer, A.; Chatgililoglu, C., Eds.; Wiley: Chichester, U.K., 2012; Vol. 2, pp 1243–1258. Also see our recent work: (b) Fukuyama, T.; Kawamoto, T.; Kobayashi, M.; Ryu, I. *Beilstein J. Org. Chem.* **2013**, *9*, 1791. (c) Manabe, Y.; Kitawaki, Y.; Nagasaki, M.; Fukase, K.; Matsubara, H.; Hino, Y.; Fukuyama, T.; Ryu, I. *Chem. - Eur. J.* **2014**, *20*, 12750.

- (7) For our work on photoreactions using microreactors, see: (a) Fukuyama, T.; Hino, Y.; Kamata, N.; Ryu, I. *Chem. Lett.* **2004**, *33*, 1430. (b) Sugimoto, A.; Fukuyama, T.; Sumino, Y.; Takagi, M.; Ryu, I. *Tetrahedron Lett.* **2006**, *47*, 6197. (c) Sugimoto, A.; Fukuyama, T.; Sumino, Y.; Takagi, M.; Ryu, I. *Tetrahedron* **2009**, *65*, 1593. (d) Tsutsumi, K.; Terao, K.; Yamaguchi, H.; Yoshimura, S.; Morimoto, T.; Kakiuchi, K.; Fukuyama, T.; Ryu, I. *Chem. Lett.* **2010**, *39*, 828. (e) Fukuyama, T.; Kajihara, Y.; Hino, Y.; Ryu, I. *J. Flow Chem.* **2011**, *1*, 40. (f) Matsubara, H.; Hino, Y.; Tokizane, M.; Ryu, I. *Chem. Eng. J.* **2011**, *167*, 567. Also see ref 6c.