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Selective Bromination

Revisiting the Bromination of C–H Bonds with Molecular Bromine by Using a Photo-Microflow System

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Abstract: The photobromination of C–H bonds by using molecular bromine was reinvestigated under microfluidic conditions. The continuous-flow method suppressed the production of dibrominated compounds and effectively produced the desired monobrominated products with high selectivity. Rapid bromination of benzylic substrates containing a photoaffinity azide group was achieved without any decomposition.

Organobromine compounds are among the most versatile intermediates in organic synthesis. They serve as precursors to carbanions, carbon radicals, carbocations, and organo–transition-metal species.[1] Among the various methodologies to prepare bromoalkanes, the most straightforward is the direct conversion of C–H bonds into C–Br bonds by using molecular bromine; this method originated a century ago.[2] Kharasch and coworkers established the reactivity of this method towards different C–H bonds and radical-chain mechanisms.[3] A bromine radical, arising from homolysis of molecular bromine by photoirradiation, abstracts a hydrogen atom from a C–H bond to form a carbon radical, liberating HBr. The resulting carbon radical then abstracts a bromine atom from molecular bromine to give a C–Br bond, liberating a bromine radical, which participates in the next radical chain.

The disadvantage of this synthetic procedure is that the side products include a significant amount of 1,2-dibromoalkanes. A recent study using a batch flask reported that photobromination of cyclohexane (**1a**) with a stoichiometric amount of molecular bromine in water gives a 3:2 mixture of desired bromocyclohexane (**2a**) and undesired *trans*-1,2-dibromocyclohexane (**3a**).[4,5]

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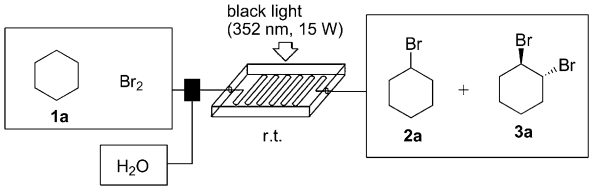
Recently, photoreactions have been investigated by using microreactors,[6,7] which enable efficient photoirradiation and realize a reproducible and energy-saving system. In general, microreactors suppress undesired over-reactions because the flow-reaction system allows the products to be rapidly transferred from the reactor. Consequently, various microfluidic processes for photoreactions, such as photoadditions, photorearrangements, photooxygenation, and specific examples of photohalogenation, have been examined.[8] This study aims to modernize the photoinduced C–H/C–Br conversion by molecular bromine by using microfluidic processes. Recent research has demonstrated that effective α-bromination of alkylbenzenes is possible based on microflow photobromination using bromine-related reagents, such as HBr–H_2O_2 and *N*-bromosuccinimide (NBS).[9]

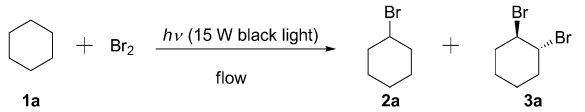
We examined the flow bromination of cyclohexane with molecular bromine under visible-light irradiation (15 W black light, peak wavelength 352 nm) by using microflow devices (Scheme 1, Table 1). When a cyclohexane solution of Br_2 (Br_2/**1a** = 1:5) was mixed with water by using a micromixer (diameter 500 μm), and the mixture subsequently introduced into a glass-made flow device with a residence photoirradiation time of 19 min, bromocyclohexane (**2a**) was formed in 42% yield, together with a 13% yield of 1,2-dibromocyclohexane (**3a**) (entry 1). A higher selectivity of **2a**/**3a** was attained when a larger excess of cyclohexane was used (entries 2–4). For example, an 80-fold excess of **1a** increased the selectivity of **2a**/**3a** to 96:4 (entry 5). The residence time could be reduced to 5.7 min (entry 7), whereas the reaction using a batch reactor (Pyrex, 3 cm internal diameter test tube) gave only 11% conversion. The use of two black-light bulbs (30 W) further increased the reaction rate with a residence time of 2.9 min (entry 8).



Scheme 1. Microflow devices for photobromination of cyclohexane (**1a**).

After successfully converting C–H bonds into C–Br bonds, microflow photobromination was then applied to various alkanes (Table 2). Continuous-flow bromination of cyclopentane

Table 1. Photoinduced continuous-flow bromination of cyclohexane (**1a**).



Entry[a]	Residence time [min]	Ratio of **1a**/Br_2	Yield [%][b] **2a**	**3a**	Selectivity for **2a** [%]
1	19	5:1	42	13	76
2	19	10:1	78	13	86
3	19	40:1	84	8	91
4	19	60:1	87	5	95
5	19	80:1	96	4	96
6	9.5	40:1	80	10	89
7	5.7	40:1	78	9	90
8[c]	2.9	40:1	77	7	92

[a] Reaction conditions: Br_2 (0.5 mmol), Mikroglas Dwel Device (channel size: 500 μm deep, 1000 μm wide, and 1.9 m long, Foturan® glass), Micromixer (500 μm) and 15 W black light (352 nm), room temperature. [b] Determined by GC analysis with chlorobenzene as an internal standard. [c] Two bulbs of black light (total 30 W) were used.

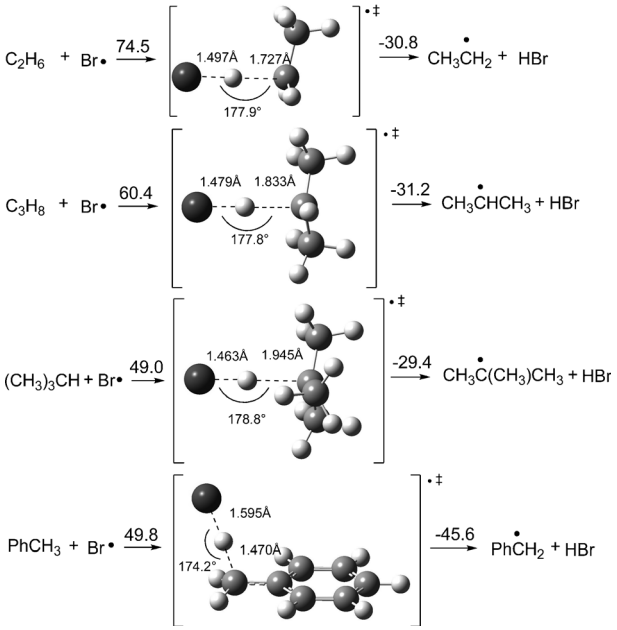
Table 2. Photoinduced flow bromination of various alkanes.

Entry[a]	Substrate	Product	Yield [%][b]	Selectivity for **2** [%]
1	**1a**	**2a**	84	91
2	**1b**	**2b**	92	93
3	**1c**	**2c**	99	99
4	**1d**	**2d**	93	94
5[c]	**1e**	**2e**	58	84
6[c,d]	**1f**	**2f**	76	87
7[c,e]	**1g**	**2g**	58	99

[a] Reaction conditions: Br_2 (0.5 mmol), **1** (40 equiv), Mikroglas Dwel Device (channel size: 500 μm deep, 1000 μm wide, 1.9 m long) Micromixer (500 μm) and 15 W black light (Toshiba, 352 nm), room temperature, residence time = 19 min. [b] Determined by GC analysis. [c] Alkanes were mixed with a FC-72 (perfluorohexanes) solution of molecular bromine by using a micromixer. The resulting solution was mixed with water by using a second micromixer (for details, see the Supporting Information). [d] Two stereoisomers of **2f** (product ratio = 4:1) were detected by GC analysis and ^1H NMR spectroscopy. [e] Residence time = 1.9 min.

(**1b**), cycloheptane (**1c**), and cyclooctane (**1d**) gave the corresponding bromocycloalkanes (**2b**, **2c**, and **2d**) in good yields with high selectivity (entries 2, 3, and 4). Bromination of substrates with a tertiary C–H bond, such as **1e**, **1f**, and **1g**, proceeded even under ambient light. Thus, a FC-72 (perfluorohexanes) solution of bromine with these alkanes was mixed by using an additional micromixer, and the resulting mixture was quickly mixed with water. These reactions occurred selectively at the tertiary C–H bond, giving corresponding tertiary alkyl bromides **2e**, **2f**, and **2g** in good yields (entries 5–7).

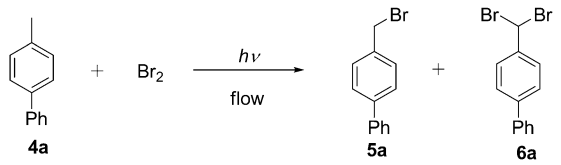
The ability of Br_2 to convert C–H bonds into C–Br bonds is much less than that of Cl_2 or F_2 for C–H/C–Cl or C–H/C–F conversion, respectively.[10] However, Br_2 provides site selectivity. The site selectivity of the photoinduced C–H/C–Br conversion is tertiary alkyl > secondary alkyl > primary alkyl. This trend can be rationalized by the low-barrier transition states for H-atom abstraction by the bromine radical, predicted by DFT calculations (Scheme 2).[11] It is interesting to compare H-atom abstraction, by the bromine radical, of trimethylmethane and toluene. Although both have almost identical activation energies, the energy barrier of the backward reaction with the tertiary butyl radical is more facile than that with the benzyl radical, predicting that benzylic bromination is more likely. Therefore, we then focused on flow photobromination of alkylarenes by using Br_2.



Scheme 2. Transition states for H-atom abstraction from C–H bonds by the bromine radical (energies (in kJ mol^{-1}) calculated at the BHandHLYP/6-311 + + G(d,p) + LanL2DZdp(Br) level).

α-Brominated alkylbenzenes have diverse applications in organic synthesis, especially as benzylation reagents. Consequently, numerous methods have been developed for bromination of the benzylic position, including using molecular bromine,[12] NBS,[13] H_2O_2/HBr,[14] or $NaBrO_3$/$NaHSO_3$.[15] Herein, we focused on flow photobromination using molecular bromine, which is a simple and cost-effective bromine source. Using 4-phenyltoluene (**4a**) as a model substrate, we examined flow photobromination (Table 3). A mixture of **4a** and 1.2 equivalents of Br_2 in CCl_4 was introduced into the microreactor

Table 3. Photoinduced flow bromination of **4a** under microfluidic conditions.



Entry[a]	Solvent	Light source	Residence time	Yield [%][b] 5a	6a	Selectivity for 5a [%]
1	CCl_4	black light[c]	43 s	72	11	86
2	CCl_4	LED lamp[d]	43 s	75	8	90
3	BTF	LED lamp[d]	3.6 min	74	9	89

[a] Reaction conditions: **4a** (0.1 M), Br_2 (1.2 equiv), microreactor (300 μm deep, 1000 μm wide, 2.35 m long), room temperature. [b] Determined by NMR spectroscopy. [c] 15 W black light (Toshiba, 352 nm). [d] LED lamp (YMC Co., Ltd., YMC-P-0049, 1.95 W 360 nm).

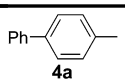
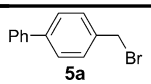
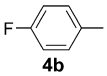
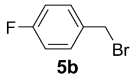
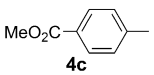
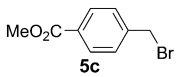
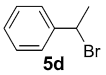
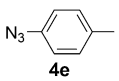
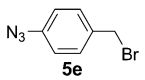
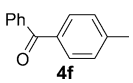
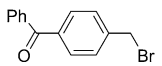
(MiChS L-1, 300 μm deep, 1000 μm wide, 2.35 m long, quartz) by means of a syringe pump, at a flow rate of 1.0 mL min^{-1}, under black-light (15 W) irradiation (entry 1). The resultant solution was quenched by aqueous saturated $Na_2S_2O_3$ and analyzed by NMR spectroscopy. The reaction gave desired monobrominated product **5a** in 72%, along with 11% of dibrominated byproduct **6a**. An experiment using an LED lamp (1.95 W, peak wavelength 360 nm) gave a slightly improved result (entry 2). CCl_4 could be substituted by benzotrifluoride (BTF)[16] as a solvent. In this case, the residence time was prolonged from 43 s to 3.6 min (entry 3).

Table 4 lists several examples of benzylic bromination under the microfluidic conditions. Bromination of *p*-fluorotoluene (**4b**) proceeded very smoothly with a residence time of 11 s to give corresponding benzylic bromide **5b** in good yield (entry 2). In contrast, methyl *p*-methyl benzoate (**4c**) required a prolonged residence time (7.5 min) to give corresponding monobrominated compound **5c** (entry 3). Interestingly, the flow bromination of ethylbenzene (**4d**) gave monobrominated compound **5d** with complete selectivity (entry 4).

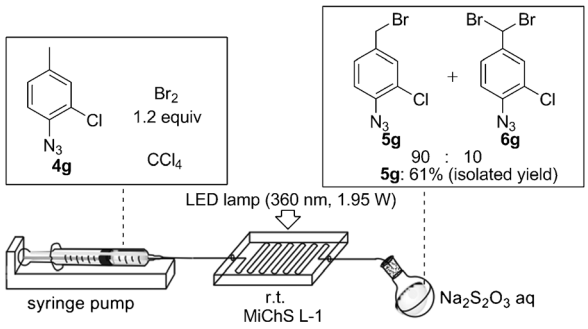
Next, to determine which functionalities were compatible with the rapid flow reaction, we examined the bromination of substrates with a photosensitive functionality. Thus, the benzylic positions of *p*-azidotoluene (**4e**) and *p*-benzoyltoluene (**4f**), which are sensitive to photoirradiation and widely used as photoaffinity groups,[17] were investigated. Compound **4e** was brominated, without decomposition of the parent structure, to give **5e** in 80% yield (entry 5). Although bromination of **4f** required a longer residence time (2.5 min), desired product **5f** was obtained in 61% yield. To the best of our knowledge, this is the first example of photobromination of substrates containing a photoaffinity group, such as an azide or benzoyl group, in its structure. These results demonstrate that judiciously controlled photoirradiation, coupled with a microflow reactor, enables a highly selective benzylic bromination reaction by using Br_2.

We previously reported that the 4-azido-3-chloro-benzyl group functions as a promising hydroxy protecting group, which can be selectively cleaved by a Staudinger reduction, followed by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) oxidation.[18] 4-Azido-3-chloro-benzylation of the hydroxy group was performed with 4-azido-3-chlorobenzyl bromide (**5g**) as a benzylating reagent. Originally **5g** was synthesized by a batch bromination of 4-azido-3-chlorotoluene (**4g**) by using NBS and 2,2′-azobis(isobutyronitrile) (AIBN) under reflux; however, this batch reaction produced a considerable amount of dibrominated product **6g** and a tedious chromatographic purification was necessary to remove the resultant succinimide. We then applied our flow conditions using Br_2 to obtain **5g** with high product selectivity, without decomposition of the photosensitive arylazide structure. Thus, 4-azido-3-chlorotoluene (**4g**) was reacted with 1.2 equivalents of molecular bromine under photomicrofluidic conditions at a flow rate of 0.05 mL min^{-1}, realizing a highly selective monobromination (**5g**/**6g** = 90:10, determined by ^{1}H NMR spectroscopy) without affecting the aryl azide structure (Scheme 3). The resultant HBr could be removed easily by an aqueous treatment, and product **5g** was easily isolated by recrystallization from methanol in 61% yield.

Table 4. Photoinduced flow benzylic bromination.

Entry[a]	Substrate	Product	Residence time	Yield [%][b]	Selectivity for 5 [%]
1	 4a	 5a	43 s	75	90
2	 4b	 5b	11 s	73	91
3	 4c	 5c	7.5 min	69	87
4	 4d	 5d	8.5 s	75	100
5	 4e	 5e	22 s	80	91
6[c]	 4f	 5f	2.5 min	61	87

[a] Reaction conditions: **4a**–**4f** (0.1 M), Br_2 (1.2 equiv), microreactor (300 μm deep, 1000 μm wide, 2.35 m long), LED lamp (YMC Co., Ltd., YMC-P-0049, 1.95 W 360 nm), room temperature. [b] Determined by ^{1}H NMR spectroscopy. [c] 1.5 equiv of Br_2 was used.



Scheme 3. Microflow photobromination of 4-azido-3-chlorotoluene (**4g**).

In summary, mild and selective bromination of a variety of C–H bonds with molecular bromine is possible by using a microflow system in combination with visible-light sources. This microfluidic method results in an excellent selectivity for monobrominated compounds, for both alkanes and benzylic substrates, enabling the scalable and efficient preparation of brominated compounds, including those with photosensitive functional groups.

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Keywords: bromination · bromine · microreactors · photoreactions

[1] a) *Halides, Pseudo-Halides and Azides in PATAI'S Chemistry of Functional Groups Vol 1 and 2* (Eds.: S. Patai, Z. Rappoport), Wiley, Chichester, **1983**; b) C. L. Hill, *Activation and Functionalization of Alkanes*, Wiley, New York, **1989**.

[2] For a review of earlier work on C–H halogenation, see: G. Egloff, E. S. R. E. Schaad, C. D. Lowry, Jr., *Chem. Rev.* **1931**, *8*, 1–80.

[3] a) M. S. Kharasch, P. C. White, F. R. Mayo, *J. Org. Chem.* **1938**, *3*, 33–47; b) M. S. Kharasch, W. Hered, F. R. Mayo, *J. Org. Chem.* **1941**, *6*, 818–829.

[4] H. Shaw, H. D. Perlmutter, C. Gu, S. D. Arcoo, T. O. Quibuyen, *J. Org. Chem.* **1997**, *62*, 236–237.

[5] For a mechanistic study, see: a) D. D. Tanner, T. Pace, T. Ochiai, *J. Am. Chem. Soc.* **1975**, *97*, 4303–4307; b) D. D. Tanner, T. C. S. Ruo, H. Takiguchi, A. Guillaume, *Can. J. Chem.* **1981**, *59*, 1368–1374. For bromination using CBr_4, see: c) Y. Nishina, B. Ohtani, K. Kikushima, *Beilstein J. Org. Chem.* **2013**, *9*, 1663–1667.

[6] For selected recent reviews, 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) B. P. Mason, K. E. Price, J. L. Steinbacher, A. R. Bogdan, D. T. McQuade, *Chem. Rev.* **2007**, *107*, 2300–2318; d) T. Fukuyama, M. T. Rahman, M. Sato, I. Ryu, *Synlett* **2008**, 151–163; e) D. Webb, T. F. Jamison, *Chem. Sci.* **2010**, *1*, 675–680; f) S. Suga, D. Yamada, J. Yoshida, *Chem. Lett.* **2010**, *39*, 404–406; g) J. Yoshida, H. Kim, A. Nagaki, *ChemSusChem* **2011**, *4*, 331–340; h) J. Wegner, S. Ceylan, A. Kirschning, *Adv. Synth. Catal.* **2012**, *354*, 17–57; i) S. V. Ley, *Chem. Rec.* **2012**, *12*, 378–390; j) C. Wiles, P. Watts, *Green Chem.* **2012**, *14*, 38–54; k) D. T. McQuade, P. H. Seeberger, *J. Org. Chem.* **2013**, *78*, 6384–6389; l) S. G. Newman, K. F. Jensen, *Green Chem.* **2013**, *15*, 1456–1472.

[7] For recent work on photoreactions and microreactors, see; a) A. Sugimoto, T. Fukuyama, Y. Sumino, M. Takagi, I. Ryu, *Tetrahedron* **2009**, *65*, 1593–1598; b) K. Tsutsumi, K. Terao, H. Yamaguchi, S. Yoshimura, T. Morimoto, K. Kakiuchi, T. Fukuyama, I. Ryu, *Chem. Lett.* **2010**, *39*, 828–829; c) S. Fuse, N. Tanabe, M. Yoshida, H. Yoshida, T. Doi, T. Takahashi, *Chem. Commun.* **2010**, *46*, 8722–8724; d) T. Fukuyama, Y. Kajihara, Y. Hino, I. Ryu, *J. Flow Chem.* **2012**, *1*, 40–45; e) S. Aida, K. Terao, Y. Nishiyama, K. Kakiuchi, M. Oelgemöller, *Tetrahedron Lett.* **2012**, *53*, 5578–5581. For recent reviews, see; f) Y. Matsushita, T. Ichimura, N. Ohba, S. Kumada, K. Sakeda, T. Suzuki, H. Tanibata, T. Murata, *Pure Appl. Chem.* **2007**, *79*, 1959–1968; g) M. Oelgemöller, *Chem. Eng. Technol.* **2012**, *35*, 1144–1152.

[8] For flow fluorination by molecular fluorine, see: a) R. D. Chambers, R. C. H. Spink, *Chem. Commun.* **1999**, 883–884. For flow alkane chlorination by molecular chlorine or sulfuryl chloride, see: b) H. Matsubara, Y. Hino, M. Tokizane, I. Ryu, *Chem. Eng. J.* **2011**, *167*, 567–571. For flow benzyl chlorination by molecular chlorine, see: c) H. Ehrich, D. Linke, K. Morgenschweis, M. Baerns, K. Jähnisch, *Chimia* **2002**, *56*, 647–653. For reviews on flow halogenation, see: d) P. Löb, H. Löwe, V. Hessel, *J. Fluorine Chem.* **2004**, *125*, 1677–1694.

[9] For recent work on flow benzyl bromination, see: a) (HBr-H_2O_2) W. Yu, D. Yu, M. Zheng, S. Shan, Y. Li, J. Gao, *J. Chem. Res.* **2012**, *36*, 258–260; b) (NBS) D. Šterk, M. Jukič, Z. Časar, *Org. process Res. Dev.* **2013**, *17*, 145–151; c) (NBS) D. Cantillo, O. de Frutos, J. A. Rincon, C. Mateos, C. O. Kappe, *J. Org. Chem.* ASAP, DOI: 10.1021/jo402409k.

[10] Z.-H. Li, K.-N. Fan, M. W. Wong, *J. Phys. Chem. A* **2001**, *105*, 10890–10898.

[11] N. Leplat, A. Wokaun, M. J. Rossi, *J. Phys. Chem. A* **2013**, *117*, 11383–11402.

[12] a) J. Snell, A. Weissberger, *Org. Synth. Coll.* **1955**, *3*, 788; b) E. F. M. Stephenson, *Org. Synth. Coll.* **1963**, *4*, 984.

[13] a) A. Wohl, *Ber. Dtsch. Chem. Ges.* **1919**, *52*, 51–63; b) K. Ziegler, A. Spath, E. Schaaf, W. Schumann, E. Winkelmann, *Justus Liebigs Ann. Chem.* **1942**, *551*, 80–119; c) C. Djerassi, *Chem. Rev.* **1948**, *43*, 271–317.

[14] a) A. Amati, G. Dosualdo, L. H. Zhao, A. Bravo, F. Fontana, F. Minisci, H. R. Bjorsvik, *Org. Process Res. Dev.* **1998**, *2*, 261–269; b) R. Mestres, J. Palenzuela, *Green Chem.* **2002**, *4*, 314–316.

[15] D. Kikuchi, S. Sakaguchi, Y. Ishii, *J. Org. Chem.* **1998**, *63*, 6023–6026.

[16] a) A. Ogawa, D. P. Curran, *J. Org. Chem.* **1997**, *62*, 450–451. Also, see reviews: b) J. J. Maul, P. J. Ostrowski, G. A. Ublacker, B. Linclau, D. P. Curran, *Top. Curr. Chem.* **1999**, *206*, 79–105; c) H. Matsubara, I. Ryu, *Top. Curr. Chem.* **2011**, *308*, 135–152.

[17] a) E. Leyva, M. S. Platz, G. Persy, J. Wirz, *J. Am. Chem. Soc.* **1986**, *108*, 3783–3790; b) G. Dorman, G. D. Prestwich, *Biochemistry* **1994**, *33*, 5661–5673.

[18] K. Egusa, K. Fukase, S. Kusumoto, *Synlett* **1997**, 675–676. 4-Azido-3-chlorobenzyl bromide (**5g**) can be purchased from Wako Pure Chemical Industries, Ltd.

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