

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/258826786>

ChemInform Abstract: A Scalable Procedure for Light-Induced Benzylic Brominations in Continuous Flow.

ARTICLE *in* THE JOURNAL OF ORGANIC CHEMISTRY · NOVEMBER 2013

Impact Factor: 4.72 · DOI: 10.1021/jo402409k · Source: PubMed

CITATIONS

17

READS

112

5 AUTHORS, INCLUDING:



David Cantillo

Karl-Franzens-Universität Graz

40 PUBLICATIONS 431 CITATIONS

SEE PROFILE



Juan A. Rincón

Eli Lilly

22 PUBLICATIONS 249 CITATIONS

SEE PROFILE



Carlos Mateos

Eli Lilly

18 PUBLICATIONS 217 CITATIONS

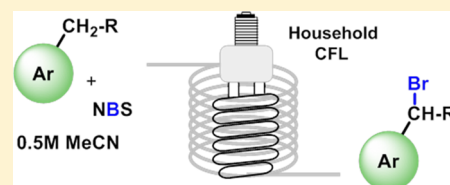
SEE PROFILE

A Scalable Procedure for Light-Induced Benzylic Brominations in Continuous Flow

David Cantillo,[†] Oscar de Frutos,[‡] Juan A. Rincon,[‡] Carlos Mateos,^{*,‡} and C. Oliver Kappe^{*,†}[†]Institute of Chemistry, University of Graz, Heinrichstrasse 28, A-8010 Graz, Austria[‡]Centro de Investigación Lilly S.A., Avda. de la Industria 30, 28108 Alcobendas-Madrid, Spain

S Supporting Information

ABSTRACT: A continuous-flow protocol for the bromination of benzylic compounds with *N*-bromosuccinimide (NBS) is presented. The radical reactions were activated with a readily available household compact fluorescent lamp (CFL) using a simple flow reactor design based on transparent fluorinated ethylene polymer (FEP) tubing. All of the reactions were carried out using acetonitrile as the solvent, thus avoiding hazardous chlorinated solvents such as CCl₄. For each substrate, only 1.05 equiv of NBS was necessary to fully transform the benzylic starting material into the corresponding bromide. The general character of the procedure was demonstrated by brominating a diverse set of 19 substrates containing different functional groups. Good to excellent isolated yields were obtained in all cases. The novel flow protocol can be readily scaled to multigram quantities by operating the reactor for longer time periods (throughput 30 mmol h⁻¹), which is not easily possible in batch photochemical reactors. The bromination protocol can also be performed with equal efficiency in a larger flow reactor utilizing a more powerful lamp. For the bromination of phenylacetone as a model, a productivity of 180 mmol h⁻¹ for the desired bromide was achieved.



INTRODUCTION

Benzylic brominations represent a rather important class of transformations in organic chemistry, as the resulting brominated derivatives are useful and versatile intermediates in synthesis.¹ The classical Wohl–Ziegler bromination² using *N*-bromosuccinimide (NBS) in refluxing CCl₄ in the presence of a radical initiator such as benzoyl peroxide or 2,2'-azobis(isobutyronitrile) has traditionally been used for the bromination of benzylic groups³ and nowadays is still often the method of choice for substitutions of this type.⁴ Although NBS is a relatively safe and user-friendly brominating agent compared with liquid bromine (Br₂), the classical Wohl–Ziegler bromination protocol suffers from the use of the toxic and ozone-depleting solvent CCl₄.⁵ Because of these properties, this solvent has been internationally banned by the so-called Montreal Protocol, and its use is therefore prohibited on an industrial scale.⁶

In the past few years, important efforts have been made to develop greener bromination procedures, mainly focusing on the substitution of hazardous CCl₄ by more benign solvents. Thus, several bromination protocols using nonchlorinated solvents such as methyl acetate,⁷ ethyl acetate and pivalate,⁸ trifluoromethylbenzene,⁹ acetonitrile,¹⁰ water,¹¹ or ionic liquids¹² or even solvent-free conditions^{12,13} have been described. Alternative brominating agents such as the bromide/hydrogen peroxide^{8,11b,14} and the bromide/bromate¹⁵ systems have also been studied, as well as different activation methods, in particular UV- or visible-light-induced brominations,^{7a,8,11a,b,13b,16} to avoid the use of hazardous and potentially explosive radical initiators such as benzoyl peroxide.¹⁷ It can be argued that light-induced protocols are among the cleanest, safest, and most economical methods of activation in organic chemistry. Photochemistry in

general is a powerful and versatile synthetic technique that can be used to generate complex structures otherwise difficult to obtain.¹⁸ Despite the large potential of organic photochemistry, it has generally been underutilized both in academic laboratories and the pharmaceutical industry. The main difficulties reside in the problems associated with large-scale synthesis using UV or visible light. Photochemical transformations are difficult to scale because of the low penetration of light into the reaction mixture, which, according to the Beer–Lambert law, decreases exponentially with the path length.¹⁹ In addition, the heat typically generated by the light source is difficult to control on a large scale, and efficient cooling methods are required. Moreover, in a batch reaction the time during which the substances are irradiated cannot be sufficiently controlled. Thus, the ensuing products are irradiated together with the remaining substrates for long periods, often producing side reactions and undesired materials.

Recently it has been demonstrated that microreactor/continuous-flow technology can overcome the problems associated with larger-scale photochemical transformations.^{20–22} In addition to the benefits derived from the microfluidics approach such as enhanced heat and mass transfer,²³ the relatively low reactor volume and especially the high surface area to volume ratio of capillary flow reactors have proven to be key advantages for light-initiated reactions, as intense and uniform irradiation of the reaction mixture can be assured. Because of the short path length of the light in a capillary microreactor, higher substrate concentrations can be used, and therefore, the reaction throughput can be significantly increased. In a photochemistry

Received: October 29, 2013

Published: November 21, 2013

flow setup, the light exposure can be very precisely controlled by the pump flow rate, which minimizes overirradiation of the mixture, avoiding undesired side products. Importantly, the optimized reaction conditions can be readily scaled to multigram quantities by a simple scale-out or numbering-up of the reactor.²⁴ Not surprisingly, therefore, in the past few years an increasing amount of scientific work has appeared describing photochemical transformations enhanced by a continuous-flow device.²¹ In this context, examples describing photocycloadditions,^{24,25} photorearrangements,²⁶ singlet oxygen reactions,²⁷ and photoredox catalysis²⁸ have been reported.

As a result of the above-mentioned importance of benzylic bromination in organic synthesis and the unique advantages that microreactor/continuous-flow technology offers to photochemical transformations, we envisaged that the development of a general continuous-flow protocol for the light-induced bromination of benzylic positions would be highly desirable. Only very few examples of general bromination reactions performed in continuous flow exist in the literature. Electrophilic bromination of aromatic rings with NBS²⁹ and brominations of alkenes³⁰ or acetophenone³¹ using Br₂ in flow have been described. One very recent published example discusses the benzylic bromination of a 5-methylpyrimidine precursor to rosuvastatin in continuous flow. In that paper, Ćasar and co-workers³² utilized a 150 W UV lamp and NBS to obtain the desired benzyl bromide intermediate in good purity, significantly improving on the corresponding batch procedure.

Herein we present a general protocol for the continuous-flow visible-light-induced bromination of benzylic compounds with NBS. The radical reaction is activated with a simple household compact fluorescent lamp (CFL) under mild conditions using acetonitrile as the solvent. With this straightforward procedure, several substituted toluenes as well as other substrates containing benzylic groups have been transformed into the corresponding bromides with excellent selectivities and very good yields. The process is readily scalable and, to the best of our knowledge, constitutes the first general protocol for the bromination of benzylic compounds in a continuous-flow regime.

RESULTS AND DISCUSSION

Flow Reactor Setup. Our flow reactor was designed so that different types of household CFLs could be used as the light source and easily exchanged, thus providing the reactor with high flexibility. The materials used are readily available in any organic chemistry lab, and all of the domestic lamps were purchased from standard commercial vendors (details about the lamps used are contained in the Supporting Information). The reactor design (Figure 1 and Figure S1 in the Supporting Information) followed the general concept described by Booker-Milburn^{24a} and consisted of fluorinated ethylene propylene (FEP) tubing (ϕ 1/8") coiled around a standard 300 mL Pyrex beaker. The inner volume of the tubing exposed to the light source was 13 mL, and the reaction mixture was pumped through the reactor with an HPLC pump (flow rate 0.1–10.0 mL min⁻¹). The outer surface of the reactor was wrapped with aluminum foil to enhance the light irradiation, and the reactor was immersed in an external thermostatted bath. Thus, the reaction temperature could be controlled by setting the bath to the desired value. Furthermore, an air cooling device was installed inside the reactor to ensure that the heat generated by the lamp would not influence the reaction. During our initial set of experiments, three different household CFLs were evaluated for the benzylic bromination: a

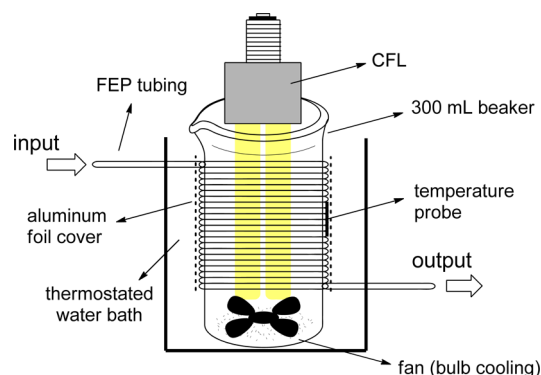
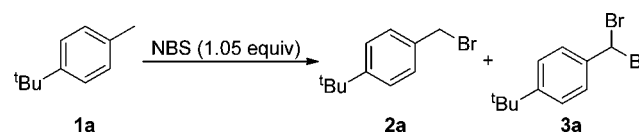


Figure 1. Schematic diagram of the flow setup employed for the continuous-flow photochemical benzylic brominations.

30 W cool-white lamp (A), a 15 W plant-growing lamp (B), and a 25 W black-light lamp (C).

Model Reaction Optimization. We initiated our investigation by studying the bromination of 4-*tert*-butyltoluene (**1a**) (Scheme 1) as a model reaction. This substituted toluene has

Scheme 1. Bromination of 4-*tert*-Butyltoluene, Selected as a Model Substrate



frequently been used as a model in previous studies of benzylic brominations.^{11,13} Variable amounts of the dibrominated product (**3a**) are typically observed during the benzylic bromination of toluene derivatives. Tetrahydrofuran (THF) and acetonitrile were initially selected as solvents, as both NBS and the ensuing succinimide are relatively well soluble in these solvents;³³ this avoided workup issues related to handling of polar high-boiling-point solvents (e.g., DMF, DMSO). The set of optimization reactions was performed on a 2 mmol scale. Thus, 2.1 mmol (1.05 equiv) of NBS, 2 mmol of 4-*tert*-butyltoluene, and acetonitrile (0.5 M **1a**) were placed into a vial and stirred for a few seconds until the mixture was completely homogeneous. The solution was then pumped through the reactor, and the crude reaction mixture collected from the output was analyzed by GC–MS.

When THF was used as the solvent, poor conversions of the substrate were obtained (Table 1, entries 1–3), even when the reaction was carried out at 40 °C and a residence time of 50 min was used (entry 3). Notably, much better performance was observed in MeCN, and the conversion dramatically increased when this solvent was used. The temperature was also an important parameter and had an influence on the efficiency of the bromination. Thus, when the temperature was increased from 20 to 60 °C (entries 4–6), the conversion improved from 69% to 96% using the 30 W white lamp. Excellent selectivity (99%) for the monobrominated product was observed at 20 and 40 °C, but the selectivity significantly decreased (to 93%) when the reaction was performed at 60 °C (entry 6). Apart from the solvent and temperature employed, the type of CFL utilized to irradiate the reactor had an important influence on the bromination. The efficiency of the light source for the reaction was C > B > A (see Table 1), and therefore, the 25 W CFL black-light lamp was the preferred choice and the light

Table 1. Optimization of the Reaction Conditions for the Photochemical Bromination of 4-*tert*-Butyltoluene with NBS under Continuous-Flow Conditions (Scheme 1)^a

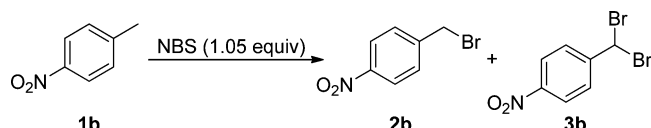
entry	solvent	light source ^b	<i>t</i> [min]	<i>T</i> [°C]	conv. [%] ^c	selectivity [%] ^{c,d}
1	THF	A	25	20	<10	99
2	THF	A	50	20	<10	99
3	THF	A	50	40	<10	99
4	MeCN	A	25	20	69	99
5	MeCN	A	25	40	91	99
6	MeCN	A	25	60	96	93
7	MeCN	B	25	20	98	96
8	MeCN	B	13	20	68	99
9	MeCN	B	25	40	98	96
10	MeCN	C	25	20	98	97
11	MeCN	C	13	20	98	97
12 ^e	MeCN	C	25	20	99	94
13 ^e	MeCN	C	13	20	99	94
14	MeCN	none ^f	45	20	—	—
15	MeCN	none ^f	45	50	—	—
16	MeCN	none ^f	45	70	—	—

^aConditions: 2 mmol of **1a**, MeCN (0.5 M), NBS (1.05 equiv). ^bA = 30 W cool-white lamp; B = 15 W plant lamp; C = 25 W black-light lamp. ^cMeasured by GC–MS. ^dSelectivity for the monobrominated product. ^e1.1 equiv of NBS was used. ^fThe reaction mixture was placed in a sealed vial covered with aluminum foil and kept at room temperature or heated in an oven.

source employed for all of the substrates. In this case, only 13 min (1 mL min^{−1} flow rate) was necessary to obtain excellent conversion and selectivity without the need to apply heat to the reaction (entry 11). When the amount of NBS was increased to 1.1 equiv (entries 12 and 13), full conversion was obtained but the selectivity was lower, with higher amounts of the dibrominated product **3a** being detected. In the absence of light the reaction does not proceed, as demonstrated by runs in which a sample of the reaction mixture was kept in a sealed vial covered with aluminum foil for 45 min at room temperature, 50 °C, or 70 °C (entries 14–16, respectively). In each case, no significant conversion of the substrate was observed.

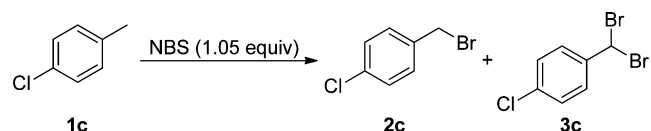
We next turned our attention to the benzylic bromination of two further substrates, 4-nitrotoluene (**1b**) and 4-chlorotoluene (**1c**), to test the versatility of our flow reactor. The bromination of 4-nitrotoluene was expected to proceed very slowly relative to that for 4-*tert*-butyltoluene, while the reaction with 4-chlorotoluene is prone to yield large amounts of the double-brominated side product. Gratifyingly, both reactions could be successfully carried out with good conversion and selectivity by tuning the reactor temperature and residence time (see Tables 2 and 3). Thus, 90% conversion and excellent selectivity (99%) could be achieved for the bromination of 4-nitrotoluene using the standard procedure (1.05 equiv of NBS, 0.5 M in acetonitrile) by exposing the reaction mixture to light for 50 min (flow rate 0.25 mL min^{−1}) at 60 °C (Table 2, entry 4). In the case of the chlorinated substrate, employing the optimal conditions for 4-*tert*-butyltoluene (13 min, 20 °C) provided a relatively low selectivity (92%), and unreacted starting material was detected in the crude reaction mixture (Table 3, entry 1). However, very good control of the selectivity for this reaction could be obtained by irradiating the sample at low temperature (0 °C; Table 3, entries 2 and 3).

Therefore, it appeared that the bromination of a wide range of substrates could be efficiently performed using this

Table 2. Optimization of the Reaction Conditions for the Photochemical Bromination of 4-Nitrotoluene (1b**) with NBS under Flow Conditions^a**


entry	light source	<i>t</i> [min]	<i>T</i> [°C]	conv. [%] ^b	selectivity [%] ^{b,c}
1	C	13	20	—	—
2	C	25	40	13	99
3	C	25	60	67	99
4	C	50	60	90	99
5 ^d	C	25	60	71	99
6 ^e	C	25	60	87	98

^aConditions: 2 mmol of substrate, MeCN (0.5 M), NBS (1.05 equiv), 25 W black-light irradiation. ^bMeasured by GC–MS. ^cSelectivity for the monobrominated product **2b**. ^d1.2 equiv of NBS. ^e1.5 equiv of NBS.

Table 3. Optimization of the Reaction Conditions for the Photochemical Bromination of 4-Chlorotoluene (1c**) with NBS under Flow Conditions^a**


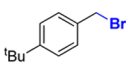
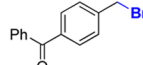

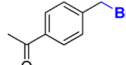

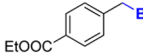

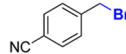
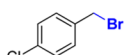
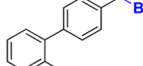

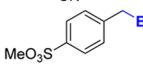
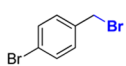


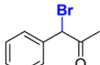
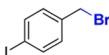

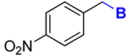
entry	light source ^b	<i>t</i> [min]	<i>T</i> [°C]	conv. [%] ^c	selectivity [%] ^{c,d}
1	C	13	20	96	92
2	C	13	0	60	99
3	C	25	0	99	96
4	A	13	20	97	94
5	A	25	0	97	94
6	none ^e	50	20	—	—

^aConditions: 2 mmol of substrate, MeCN (0.5 M), NBS (1.05 equiv). ^bA = 30 W white lamp; C = 25 W black-light lamp. ^cMeasured by GC–MS. ^dSelectivity for the monobrominated product **2c**. ^eThe reaction mixture was placed in a sealed vial covered with aluminum foil and kept at room temperature.

procedure by tuning of the reactor temperature and residence time. Thus, unreactive substrates could be transformed to the corresponding bromides by increasing the temperature of the reactor to 40 or 60 °C. In the case of more reactive substrates, where considerable amounts of the dibromide product are expected, the selectivity could be controlled by operating the reactor at low temperature (0 °C).

Reaction Scope. To demonstrate the scope and general applicability of our continuous-flow bromination procedure, a series of substituted toluenes and other benzylic substrates were transformed into the corresponding bromides (Table 4). All of the reactions were carried out on a 5 mmol scale (see the Experimental Section for details), and the method showed very good conversions and selectivities for a wide range of substrates containing alkyl chains or halogen, ketone, ester, nitro, or cyano functionalities. In some cases, small amounts of the dibrominated product were detected by GC–MS analysis, but gratifyingly, selectivities above 90% were obtained for all of the substrates. Full details on the conversions and selectivities (GC–MS analysis) observed for all transformations are collected in Table S1 in the Supporting Information.

Table 4. Photochemical Bromination of Benzylic Positions under Continuous-Flow Conditions^a

$\text{Ar}-\text{CH}_2-\text{R} \xrightarrow[\text{MeCN (0.5 M), CFL light (25W)}]{\text{NBS (1.05 equiv)}} \text{Ar}-\text{CH}(\text{Br})-\text{R}$									
Entry	Product	T [°C]	t [min]	Yield ^b [%]	Entry	Product	T [°C]	t [min]	Yield ^b [%]
1		20	13	91	11		20	25	76
2		20	25	92	12		20	13	77
3		20	13	85	13		20	25	82 ^d
4		0	25	70 ^d	14		40	13	80
5		0	25	87	15		40	13	91
6		40	13	88	16		40	25	70
7		20	13	78	17		20	13	94 ^c
8		60	13	82	18		40	13	93
9		60	13	79	19		60	25	92
10		60	50	86					

^aConditions: 5 mmol of substrate **1**, MeCN (0.5 M), NBS (1.05 equiv). ^bIsolated yields after silica gel column chromatography. ^cPurified by extraction in water/diethyl ether. ^dIsolated with small impurities (5–10%) of the dibrominated product.

The brominated products were purified by silica gel flash chromatography using hexane/ethyl acetate as the eluent to remove small amounts of unreacted starting material and dibrominated side products. In all cases, good to excellent yields were obtained after purification (Table 4). When full conversion and complete selectivity were obtained, alternative workup procedures were also evaluated. Thus, (1-bromoethyl)-benzene (entry 3) was additionally isolated by extraction with diethyl ether/water or by precipitation of the succinimide with a petroleum ether/Et₂O mixture, providing the pure bromide in yields of 97% and 95%, respectively.

Notably, very good selectivity was obtained in the case of halogenated toluenes (entries 5–9). It should be noted that iodine–bromine exchange had been reported during radical brominations of iodine-substituted toluenes.^{7a} With our flow protocol, no traces of halogen-exchanged products were observed (GC–MS), even when the reaction temperature was raised to 60 °C to shorten the reaction time (entry 9). As expected, a higher temperature was required for ortho-compared with para-substituted substrates (entries 5 and 6), and the reactivity toward benzylic bromination decreased in the order Cl > Br > I.

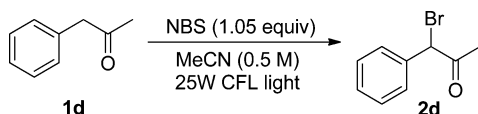
For the carbonyl-substituted toluenes (entries 11–13) and for methyl 4-methyltoluenesulfonate (entry 16), higher amounts of the dibrominated product were detected by GC–MS, with

selectivities in the range of 90–95% (Table S1 in the Supporting Information). However, the corresponding products could be readily separated by chromatography and isolated in good yields. 1-Indanone was brominated at the benzylic position at 20 °C (entry 17), but the corresponding bromide partially decomposed on the column, leading to significant amounts of the elimination product, 1-indenone. This compound was therefore purified by extraction with ether/water. A pyridine derivative was also successfully brominated in excellent yield at 60 °C and a residence time of 25 min (entry 19).

It must be pointed out that the continuous-flow protocol was typically not successful when applied to the benzylic bromination of electron-rich toluene derivatives (e.g., 4-methoxytoluene). Following the general flow reaction conditions, full conversion of the starting materials could readily be obtained. However, in these cases the bromination exclusively occurred on the aromatic ring instead of the benzylic position, as confirmed by GC–MS and ¹H NMR analyses. This clearly is the main limitation of light-induced NBS bromination procedures, as previously reported.^{11a,12,13b}

Reaction Scale-Out and Scale-Up. One of the main advantages of continuous-flow processing is the ease with which a reaction can be scaled to larger product quantities simply by operating the reactor for longer periods of time (scale-out), in contrast with batch chemistry, where a larger scale normally

Scheme 2. Bromination Reaction Selected as an Example for the Scale-Out and Scale-Up of the Continuous-Flow Protocol



requires a new reactor design. To test the robustness of our method, we selected as a representative example the bromination of phenylacetone (Scheme 2 and Table 4, entry 18) for a larger-scale experiment. Thus, a 50 mmol solution of the substrate and NBS (1.05 equiv) in acetonitrile (0.5 M, 100 mL) was pumped through the reactor (preheated to 40 °C) at a flow rate of 1.0 mL min⁻¹. The total operation time was therefore 100 min. Subsequently, the crude reaction mixture collected from the reactor output was evaporated under reduced pressure, and the residue was dissolved in diethyl ether and washed with distilled water. Evaporation of the organic phase after drying over magnesium sulfate provided 9.9 g (93% yield) of pure 1-bromo-1-phenylacetone. It is worth pointing out that larger quantities of the desired bromide can be obtained by operating the reactor for longer periods. This is not easily achieved in a batch photochemical reactor, where the effective reactor volume is limited by the penetration of light into the reaction mixture.

We next decided to scale up our bromination procedure by building a photochemical reactor with a larger internal volume and incorporating a more powerful light source. The principle of the new reactor design was the same as of the small-scale reactor (cf. Figure 1), but in the larger-volume reactor the FEP tubing was coiled around a glass cylinder, which allowed more efficient cooling of the lamp (see Figures S2 and S3 in the Supporting Information). This was important because the CFLs used for this reactor (100 W) generated a considerable amount of heat. The volume of the FEP tubing exposed to the light for this reactor was 28 mL, which is approximately 2-fold the volume of the reactor employed for the smaller-scale reactions.

Gratifyingly, our large-scale reactor showed a very high efficiency toward light-induced benzylic brominations. Thus, the model substrate 4-*tert*-butyltoluene (Scheme 1) could be fully converted into the corresponding bromide at a flow rate of 6 mL min⁻¹ at room temperature using the standard conditions (0.5 M in acetonitrile, 1.05 equiv of NBS) with a 100 W cool-white CFL. This flow rate corresponds to a residence time of less than 5 min. In addition, phenylacetone (Scheme 2) was brominated at room temperature at a flow rate of 4 mL min⁻¹. In a 50 mmol scale run at this flow rate, full conversion and complete selectivity were obtained for the desired brominated product, which could be isolated in pure form by extraction in 96% yield. This corresponds to a productivity of 25 g h⁻¹. When a black-light CFL of comparable power (105 W) was used instead of the cool-white lamp, the flow rate could be increased to 6 mL min⁻¹ without loss of selectivity, thus increasing the throughput of the desired 1-bromo-1-phenylacetone to 38 g h⁻¹.

CONCLUSIONS

We have developed a general protocol for the visible-light-induced bromination of benzylic compounds in continuous flow. The photochemical reactor was set up using readily available materials, and the light source is an inexpensive household CFL. With acetonitrile as the solvent, the reaction proceeds to completion within minutes under mild conditions, avoiding the use of

radical initiators or hazardous CCl₄ as the solvent. By careful tuning of the reactor temperature and residence time, several benzylic compounds were successfully transformed into the corresponding benzylic bromides in good to excellent yields. Multigram quantities of the desired bromides can easily be obtained simply by operating the reactor for longer periods of time, which is difficult to achieve in a batch photochemical procedure. Moreover, we successfully scaled up our continuous-flow protocol by building a larger photochemical reactor. Thus, higher flow rates of up to 6 mL min⁻¹ could be employed to carry out the bromination of phenylacetone, providing a productivity of 180 mmol h⁻¹.

EXPERIMENTAL SECTION

General Remarks. ¹H NMR spectra were recorded on a 300 MHz instrument. ¹³C NMR spectra were recorded on the same instrument at 75 MHz. Chemical shifts (δ) are expressed in parts per million downfield from TMS as an internal standard. The letters s, d, t, q, and m are used to indicate singlet, doublet, triplet, quadruplet, and multiplet, respectively. GC–MS monitoring was based on electron impact ionization (70 eV) using an HP/5MS column (30 m × 0.250 mm × 0.025 μm). After 1 min at 50 °C, the temperature was increased in 25 °C min⁻¹ steps up to 300 °C and kept at 300 °C for 1 min. The carrier gas was helium, and the flow rate was 1.0 mL min⁻¹ in constant-flow mode. HPLC-grade solvents were used in all experiments. Flash chromatography purifications were carried out on an automated flash chromatography system using cartridges packed with KP-SIL, 60 Å (32–63 μm particle size). *N*-Bromosuccinimide of 99% purity was purchased from Acros Organics (code 107451000, lot A0330482). Chemicals were obtained from standard commercial vendors and used without any further purification. In all of the flow experiments, the lamp was turned on at least 15 min prior use to ensure maximum and constant irradiation.

All of the compounds synthesized herein are known in the literature. Proof of purity and identity was obtained by ¹H NMR spectroscopy and mass spectrometry.

General Procedure for the Continuous-Flow Benzylic Bromination (Table 4). *N*-Bromosuccinimide (934 mg, 5.25 mmol, 1.05 equiv), HPLC-grade acetonitrile, and the corresponding substrate (5 mmol) were placed into a vial and stirred until the mixture was completely homogeneous. The solution was then pumped through the reactor at the desired flow rate. The reaction mixture collected from the reactor output was evaporated under reduced pressure, and the crude mixture was purified by flash column chromatography using petroleum ether/ethyl acetate as the eluent.

Alternative workup A: The reaction mixture collected from the reactor output was evaporated under reduced pressure, and the residue was treated with 30 mL of diethyl ether. The white precipitate was filtered off, and the solvent was extracted with distilled water (3 × 10 mL). Then the organic phase was dried over magnesium sulfate and evaporated under reduced pressure, providing the corresponding benzyl bromide.

Alternative workup B: The reaction mixture collected from the reactor output was evaporated under reduced pressure, and the residue was treated with 10 mL of 1:1 petroleum ether/diethyl ether and then stirred at room temperature. The white precipitate was filtered off, and the solvent was evaporated. The process was repeated until no new precipitate was observed.

4-*tert*-Butylbenzyl Bromide (Table 4, entry 1). Yield: 1032 mg (91%). ¹H NMR (300 MHz, CDCl₃): δ 7.42–7.35 (m, 4H), 4.53 (s, 2H), 1.35 (s, 9H). ¹³C NMR (75 MHz, CDCl₃): δ 151.57, 134.76, 128.77, 125.78, 34.66, 33.66, 31.27. MS-EI: *m/z* 147 (100%), 132 (40%), 117 (35%).

Benzyl Bromide (Table 4, entry 2). Yield: 787 mg (92%). ¹H NMR (300 MHz, CDCl₃): δ 7.44–7.32 (m, 4H), 4.53 (s, 2H). ¹³C NMR (75 MHz, CDCl₃): δ 137.8, 129.1, 128.8, 128.4, 33.6. MS-EI: *m/z* 91 (100%), 65 (22%).

(1-Bromoethyl)benzene (Table 4, entry 3). Yield: 786 mg (85%). ¹H NMR (300 MHz, CDCl₃): δ 7.48 (d, *J* = 12.0 Hz, 2H), 7.41–7.28

(m, 3H), 5.25 (q, $J = 8.0$ Hz, 20.0 Hz, 1H), 2.09 (d, $J = 12.0$ Hz). ^{13}C NMR (75 MHz, CDCl_3): δ 143.3, 128.7, 128.4, 126.8, 49.6, 26.9, 26.8. MS-EI: m/z 105 (100%), 79 (25%), 77 (25%).

2-Methylbenzyl Bromide (Table 4, entry 4). Yield: 647 mg (70%). ^1H NMR (300 MHz, CDCl_3): δ 7.30–7.18 (m, 4H), 4.55 (s, 2H), 2.45 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 137.3, 135.7, 130.8, 130.0, 129.0, 126.4, 32.4, 18.8. MS-EI: m/z 105 (100%), 103 (20%), 79 (22%), 77 (22%).

4-Chlorobenzyl Bromide (Table 4, entry 5). Yield: 894 mg (87%). ^1H NMR (300 MHz, CDCl_3): δ 7.34 (s, 4H), 4.48 (s, 2H). ^{13}C NMR (75 MHz, CDCl_3): δ 136.3, 134.3, 130.4, 129.0, 32.5. MS-EI: m/z 127 (30%), 125 (100%), 89 (45%).

2-Chlorobenzyl Bromide (Table 4, entry 6). Yield: 905 mg (88%). ^1H NMR (300 MHz, CDCl_3): δ 7.48–7.40 (m, 2H), 7.31–7.26 (m, 2H), 4.62 (s, 2H). ^{13}C NMR (75 MHz, CDCl_3): δ 135.4, 134.3, 131.3, 130.1, 130.0, 127.3, 30.6. MS-EI: m/z 127 (30%), 125 (100%), 89 (40%).

4-Bromobenzyl Bromide (Table 4, entry 7). Yield: 975 mg (78%). ^1H NMR (300 MHz, CDCl_3): δ 7.49 (d, $J = 12.0$ Hz, 2H), 7.28 (d, $J = 12.0$ Hz, 2H), 4.46 (s, 2H). ^{13}C NMR (75 MHz, CDCl_3): δ 136.81, 131.99, 130.71, 122.49, 32.46. MS-EI: m/z 171 (80%), 169 (90%), 90 (100%), 89 (75%).

3-Bromobenzyl Bromide (Table 4, entry 8). Yield: 1025 mg (82%). ^1H NMR (300 MHz, CDCl_3): δ 7.57 (s, 1H), 7.45 (d, $J = 8.0$ Hz, 1H), 7.34 (d, $J = 8.0$ Hz, 1H), 7.23 (t, $J = 8.0$ Hz, 1H), 4.45 (s, 2H). ^{13}C NMR (75 MHz, CDCl_3): δ 139.9, 132.1, 131.5, 130.3, 127.7, 122.6, 32.1. MS-EI: m/z 171 (80%), 169 (90%), 90 (100%), 89 (75%).

4-Iodobenzyl Bromide (Table 4, entry 9). Yield: 1175 mg (79%). ^1H NMR (300 MHz, CDCl_3): δ 7.70 (d, $J = 12.0$ Hz, 2H), 7.15 (d, $J = 12.0$ Hz, 2H), 4.44 (s, 2H). ^{13}C NMR (75 MHz, CDCl_3): δ 138.0, 137.4, 130.9, 94.2, 32.5. MS-EI: m/z 217 (99%), 90 (100%), 89 (75%).

4-Nitrobenzyl Bromide (Table 4, entry 10). Yield: 927 mg (86%). ^1H NMR (300 MHz, CDCl_3): δ 8.22 (d, $J = 12.0$ Hz, 2H), 7.58 (d, $J = 12.0$ Hz, 2H), 5.54 (s, 2H). ^{13}C NMR (75 MHz, CDCl_3): δ 147.7, 144.8, 129.9, 124.1, 31.0. MS-EI: m/z 136 (100%), 106 (20%), 90 (45%), 89 (60%), 78 (60%).

4-(Bromomethyl)benzophenone (Table 4, entry 11). Yield: 1047 mg (76%). ^1H NMR (300 MHz, CDCl_3): δ 7.83–7.79 (m, 4H), 7.62 (t, $J = 8.0$ Hz, 2H), 7.59–7.48 (m, 4H), 4.56 (s, 2H). ^{13}C NMR (75 MHz, CDCl_3): δ 196.0, 142.1, 137.5, 137.4, 132.6, 130.6, 130.0, 129.0, 128.4, 32.3. MS-EI: m/z 195 (90%), 167 (100%), 118 (20%), 105 (35%).

4-(Bromomethyl)acetophenone (Table 4, entry 12). Yield: 825 mg (77%). ^1H NMR (300 MHz, CDCl_3): δ 7.94 (d, $J = 12.0$ Hz, 2H), 7.50 (d, $J = 12.0$ Hz, 2H), 4.52 (s, 2H), 2.62 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 197.4, 142.8, 136.9, 129.2, 128.8, 32.1, 26.9. MS-EI: m/z 133 (100%), 118 (60%), 105 (70%), 90 (65%).

Ethyl 4-(Bromomethyl)benzoate (Table 4, entry 13). Yield: 995 mg (82%). ^1H NMR (300 MHz, CDCl_3): δ 8.03 (d, $J = 12.0$ Hz, 2H), 7.47 (d, $J = 12.0$ Hz, 2H), 4.52 (s, 2H), 4.39 (q, $J = 8.0$ Hz, 20.0 Hz, 2H), 1.41 (t, $J = 8.0$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 166.04, 142.49, 130.41, 130.03, 128.98, 61.11, 32.29, 14.32. MS-EI: m/z 163 (100%), 135 (40%), 118 (35%), 107 (50%).

4-Cyanobenzyl Bromide (Table 4, entry 14). Yield: 785 mg (80%). ^1H NMR (300 MHz, CDCl_3): δ 7.65 (d, $J = 12.0$ Hz, 2H), 7.51 (d, $J = 12.0$ Hz, 2H), 4.49 (s, 2H). ^{13}C NMR (75 MHz, CDCl_3): δ 142.8, 132.6, 129.7, 118.4, 112.2, 31.5. MS-EI: m/z 116 (100%), 89 (30%).

4'-Bromomethyl-2-cyanobiphenyl (Table 4, entry 15). Yield: 1240 mg (91%). ^1H NMR (300 MHz, CDCl_3): δ 7.79 (d, $J = 8.0$ Hz, 1H), 7.67 (t, $J = 8.0$ Hz, 1H), 7.59–7.45 (m, 6H), 4.57 (s, 2H). ^{13}C NMR (75 MHz, CDCl_3): δ 144.7, 138.3, 138.2, 133.8, 133.0, 130.0, 129.5, 129.2, 127.8, 118.6, 111.2, 32.9. MS-EI: m/z 193 (15%), 192 (100%), 190 (15%), 165 (17%).

Methyl 4-(Bromomethyl)benzenesulfonate (Table 4, entry 16). Yield: 929 mg (70%). ^1H NMR (300 MHz, CDCl_3): δ 7.89 (d, $J = 12.0$ Hz, 2H), 7.59 (d, $J = 12.0$ Hz, 2H), 4.52 (s, 2H), 3.78 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 144.0, 135.0, 129.9, 128.5, 56.5, 31.3. MS-EI: m/z 185 (100%), 121 (70%), 90 (72%), 89 (76%).

3-Bromoindan-1-one (Table 4, entry 17). Yield: 990 mg (94%). ^1H NMR (300 MHz, CDCl_3): δ 7.77–7.71 (m, 3H), 7.54–7.46 (m, 1H), 5.61 (dd, $J = 4.0$ Hz, 8.0 Hz, 1H), 3.37 (dd, $J = 8.0$ Hz, 28.0 Hz, 1H), 3.06 (dd, $J = 4.0$ Hz, 28.0 Hz, 1H). ^{13}C NMR (75 MHz, CDCl_3): δ 201.5, 154.3, 136.0, 135.6, 129.7, 127.5, 123.4, 48.1, 40.7, 40.7. MS-EI: m/z 131 (100%), 103 (60%), 77 (40%).

1-Bromo-1-phenylacetone (Table 4, entry 18). Yield: 992 mg (93%). ^1H NMR (300 MHz, CDCl_3): δ 7.48–7.36 (m, 5H), 5.46 (s, 1H), 2.32 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 199.2, 135.1, 129.2, 129.1, 128.7, 56.4, 26.3. MS-EI: m/z 171 (30%), 169 (35%), 133 (90%), 118 (25%), 105 (35%), 90 (95%), 89 (100%).

2-(1'-Bromoethyl)pyridine (Table 4, entry 19). Yield: 860 mg (92%). ^1H NMR (300 MHz, CDCl_3): δ 8.58 (d, $J = 4.0$ Hz, 1H), 7.70 (t, $J = 12.0$ Hz, 1H), 7.46 (d, $J = 8.0$ Hz, 1H), 7.21 (dd, $J = 8.0$ Hz, 12.0 Hz, 1H), 5.24 (q, $J = 8.0$ Hz, 1H), 2.08 (d, $J = 12.0$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 161.0, 149.3, 137.0, 123.0, 121.6, 49.4, 25.0, 25.0. MS-EI: m/z 105 (100%), 103 (20%), 79 (25%), 77 (25%).

■ ASSOCIATED CONTENT

Supporting Information

Supporting tables and figures and copies of ^1H NMR spectra of all prepared compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: mateos_gutierrez_carlos@lilly.com.

*E-mail: oliver.kappe@uni-graz.at.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by Eli Lilly and Company through the Lilly Research Award Program (LRAP). We thank Dr. Scott A. May for his contributions to this work.

■ REFERENCES

- (1) Larock, R. C. *Comprehensive Organic Transformations: A Guide to Functional Group Preparations*, 2nd ed.; Wiley-VCH: New York, 1999.
- (2) (a) Wohl, A. *Ber. Dtsch. Chem. Ges.* **1919**, 52, 51–63. (b) Ziegler, K.; Spath, A.; Schaaf, E.; Schumann, W.; Winkelmann, E. *Justus Liebigs Ann. Chem.* **1942**, 551, 80–119.
- (3) (a) Veisi, H.; Ghorbani-Vaghei, R.; Zolfigol, M. A. *Org. Prep. Proced. Int.* **2011**, 43, 489–540. (b) Djerassi, C. *Chem. Rev.* **1948**, 43, 271–317.
- (4) For some recent examples, see: (a) Haberhauer, G.; Tepper, C.; Wölper, C.; Bläser, D. *Eur. J. Org. Chem.* **2013**, 2325–2333. (b) Sreedharan, D. T.; Clive, D. L. J. *Org. Biomol. Chem.* **2013**, 11, 3128–3144. (c) Pallela, V. R.; Mallireddigari, M. R.; Cosenza, S. C.; Akula, B.; Subbaiah, D. R. C. V.; Reddy, E. P.; Reddy, M. V. R. *Org. Biomol. Chem.* **2013**, 11, 1964–1977. (d) Chen, J.; Sun, W.; Yang, J.; Sun, H.; Wang, Z.; Dong, L.; Qiao, C.; Xi, C.-M. *Bioorg. Med. Chem. Lett.* **2013**, 23, 3785–3787. (e) Kadam, H. K.; Tilve, S. G. *Eur. J. Org. Chem.* **2013**, 4280–4284. (f) Ruchelman, A. L.; Man, H. W.; Zhang, W.; Chen, R.; Capone, L.; Kang, J.; Parton, A.; Corral, L.; Schafer, P. H.; Babusis, D.; Moghaddam, M. F.; Tang, Y.; Shirley, M. A.; Muller, G. W. *Bioorg. Med. Chem. Lett.* **2013**, 23, 360–365. (g) Belluti, F.; Bartolini, M.; Bottegoni, G.; Bisi, A.; Cavalli, A.; Andrisano, V.; Rampa, A. *Eur. J. Med. Chem.* **2011**, 46, 1682–1693. (h) Lo Monte, F.; Kramer, T.; Gu, J.; Brodrecht, M.; Pilakowski, J.; Fuentes, A.; Dominguez, J. M.; Plotkin, B.; Eldar-Finkelman, H.; Schmidt, B. *Eur. J. Med. Chem.* **2013**, 61, 26–40. (i) Huang, J.; Xi, Z. *Tetrahedron Lett.* **2012**, 53, 3654–3657. (j) Fu, L.; Liu, X.; Ling, C.; Cheng, J.; Guo, X.; He, H.; Ding, S.; Yang, Y. *Bioorg. Med. Chem. Lett.* **2012**, 22, 814–819.
- (5) (a) Recknagel, R. O.; Glende, E. A.; Dolak, J. A.; Waller, R. L. *Pharmacol. Ther.* **1989**, 43, 139–154. (b) Rood, A. S.; McGavran, P. D.; Aanenson, J. W.; Till, J. E. *Risk Anal.* **2001**, 21, 675–695.

(c) WMO. *Scientific Assessment of Ozone Depletion: 2006 Global Ozone Research and Monitoring Project*; Report No. 50; World Meteorological Organization: Geneva, Switzerland, 2007.

(6) United Nations Environment Programme, Ozone Secretariat. *The Montreal Protocol on Substances that Deplete the Ozone Layer as either adjusted and/or amended in London 1990, Copenhagen 1992, Vienna 1995, Montreal 1997, and Beijing 1999*; United Nations Environment Programme: Nairobi, Kenya, 2000.

(7) (a) Amijs, C. H. M.; van Klink, G. P. M.; van Koten, G. *Green Chem.* **2003**, *5*, 470–474. (b) Offermann, W.; Vögtle, F. *Synthesis* **1977**, 272–273.

(8) Mestres, R.; Palenzuela, J. *Green Chem.* **2002**, *4*, 314–316.

(9) Suarez, D.; Laval, G.; Tu, S.-M.; Jiang, D.; Robinson, C. L.; Scott, R.; Golding, B. T. *Synthesis* **2009**, 1807–1810.

(10) Salama, T. A.; Novák, Z. *Tetrahedron Lett.* **2011**, *52*, 4026–4029.

(11) (a) Podgoršek, A.; Stavber, S.; Zupan, M.; Iskra, J. *Tetrahedron Lett.* **2006**, *47*, 1097–1099. (b) Podgoršek, A.; Stavber, S.; Zupan, M.; Iskra, J. *Tetrahedron Lett.* **2006**, *47*, 7245–7247. (c) Kikuchi, D.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **1998**, *63*, 6023–6026.

(12) Togo, H.; Hirai, T. *Synlett* **2003**, 702–704.

(13) (a) Rahman, A. N. M. M.; Bishop, R.; Tan, R.; Shan, N. *Green Chem.* **2005**, *7*, 207–209. (b) Jereb, M.; Zupan, M.; Stavber, S. *Helv. Chim. Acta* **2009**, *92*, 555–566. (c) Jiang, X.; Shen, M.; Tang, Y.; Li, C. *Tetrahedron Lett.* **2005**, *46*, 487–489.

(14) Amati, A.; Dosualdo, G.; Zhao, L.; Bravo, A.; Fontana, F.; Minisci, F.; Bjørsvik, H.-R. *Org. Process Res. Dev.* **1998**, *2*, 261–269.

(15) (a) Adimurthy, S.; Ramachandraiah, G.; Bedekar, A. V.; Ghosh, S.; Mehta, A. S.; Ranu, B. C.; Ghosh, P. K. *Green Chem.* **2006**, *8*, 916–922. (b) Adimurthy, S.; Ghosh, S.; Patoliya, P. U.; Ramachandraiah, G.; Agrawal, M.; Gandhi, M. R.; Upadhyay, S. C.; Ghosh, P. K.; Ranu, B. C. *Green Chem.* **2008**, *10*, 232–237.

(16) (a) Shaw, H.; Perlmutter, H. D.; Gu, C. *J. Org. Chem.* **1997**, *62*, 236–237. (b) Ghosh, S.; Das, J. *Tetrahedron Lett.* **2011**, *52*, 1112–1116.

(17) Material safety data sheet.

(18) CRC *Handbook of Organic Photochemistry and Photobiology*, 3rd ed.; Griesbeck, A.; Ghatti, F.; Oelgemöller, M., Eds.; CRC Press: Boca Raton, FL, 2012.

(19) Braun, A. M.; Maurette, M.; Oliveros, E. *Photochemical Technology*; Wiley: New York, 1991.

(20) For early pioneering work in the field of flow photochemistry, see: (a) Lu, H.; Schmidt, M. A.; Jensen, K. F. *Lab Chip* **2001**, *1*, 22–28. (b) Elrich, H.; Linke, D.; Morgenschweis, K.; Baerns, M.; Jähnisch, K. *Chimia* **2002**, *56*, 647–653. (c) Ueno, K.; Kitagawa, F.; Kitamura, N. *Lab Chip* **2002**, *2*, 231–234.

(21) For recent reviews of flow photochemistry, see: (a) Knowles, J. P.; Elliot, L. D.; Booker-Milburn, K. I. *Beilstein J. Org. Chem.* **2012**, *8*, 2025–2052. (b) Noel, T. *Chim. Oggi* **2013**, *31*, 10–15. (c) Oelgemöller, M. *Chem. Eng. Technol.* **2012**, *35*, 1144–1152. (d) Oelgemöller, M.; Shvydkiv, O. *Molecules* **2011**, *16*, 7522–7550. (e) Oelgemöller, M.; Murata, A. *Med. Chem. News* **2012**, *22*, 30–40.

(22) For a recent review of radical reactions using flow microreactor technology, see: Fukuyama, T.; Ryu, I. In *Encyclopedia of Radicals in Chemistry, Biology and Materials*; Chatgililoglu, C., Studer, A., Eds.; Wiley: Chichester, U.K., 2012; pp 1243–1258.

(23) For recent selected reviews of continuous-flow/microreactor chemistry, see: (a) Hessel, V.; Kralisch, D.; Kockmann, N.; Noel, T.; Wang, Q. *ChemSusChem* **2013**, *6*, 746–789. (b) Baxendale, I. R. *J. Chem. Technol. Biotechnol.* **2013**, *88*, 519–552. (c) Newman, S. G.; Jensen, K. F. *Green Chem.* **2013**, *15*, 1456–1472. (d) Wiles, C.; Watts, P. *Green Chem.* **2012**, *14*, 38–54. (e) Noël, T.; Buchwald, S. L. *Chem. Soc. Rev.* **2011**, *40*, 5010–5029. (f) Baumann, M.; Baxendale, I. R.; Ley, S. V. *Mol. Diversity* **2011**, *15*, 613–630. (g) Yoshida, J.-i.; Kim, H.; Nagaki, A. *ChemSusChem* **2011**, *4*, 331–340.

(24) (a) Hook, B. D. A.; Dohle, W.; Hirst, P. R.; Pickworth, M.; Berry, M. B.; Booker-Milburn, K. I. *J. Org. Chem.* **2005**, *70*, 7558–7564. (b) Lainchbury, M. D.; Medley, M. I.; Taylor, P. M.; Hirst, P.; Dohle, W.; Booker-Milburn, K. *J. Org. Chem.* **2008**, *73*, 6497–6505.

(c) Aggarwal, V. K.; Fang, G.; Kokotos, C. G.; Richardson, J.; Unthank, M. G. *Tetrahedron* **2006**, *62*, 11297–11303.

(25) (a) Nettekoven, M.; Püllmann, B.; Martin, R. E.; Wechsler, D. *Tetrahedron Lett.* **2012**, *53*, 1363–1366. (b) Pimparkar, K.; Yen, B.; Goodell, J. R.; Martin, V. I.; Lee, W.-H.; Porco, J. A., Jr.; Beeler, A. B.; Jensen, K. F. *J. Flow Chem.* **2011**, *2*, 53–55. (c) Horie, T.; Sumino, M.; Tanaka, T.; Matsushita, Y.; Ichimura, T.; Yoshida, J. *Org. Process Res. Dev.* **2010**, *14*, 405–410. (d) Fukuyama, T.; Kajihara, Y.; Hino, Y.; Ryu, I. *J. Flow Chem.* **2011**, *1*, 40–45.

(26) (a) Fuse, S.; Tanabe, N.; Yoshida, M.; Yoshida, H.; Doi, T.; Takahashi, T. *Chem. Commun.* **2010**, *46*, 8722–8724. (b) Mimieux Vaske, Y. S.; Mahoney, M. E.; Konopelski, J. P.; Rogow, D. L.; McDonald, W. J. *J. Am. Chem. Soc.* **2010**, *132*, 11379–11385. (c) Bou-Hamdan, F. R.; Lévesque, F.; O'Brien, A. G.; Seeberger, P. H. *Beilstein J. Org. Chem.* **2011**, *7*, 1124–1129.

(27) (a) Lévesque, F.; Seeberger, P. H. *Org. Lett.* **2011**, *13*, 5008–5011. (b) Lévesque, F.; Seeberger, P. H. *Angew. Chem., Int. Ed.* **2012**, *51*, 1706–1709. (c) Carofiglio, T.; Donnola, P.; Maggini, M.; Rossetto, M.; Rossi, E. *Adv. Synth. Catal.* **2008**, *350*, 2815–2822. (d) Park, C. P.; Maurya, R. A.; Lee, J. H.; Kim, D.-P. *Lab. Chip* **2011**, *11*, 1941–1945.

(28) (a) Bou-Hamdan, F. R.; Seeberger, P. H. *Chem. Sci.* **2012**, *3*, 1612–1616. (b) Tucker, J. W.; Zhang, Y.; Jamison, T. F.; Stephenson, C. R. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 4144–4147. (c) Kreis, L. M.; Krautwald, S.; Pfeiffer, N.; Martin, R. E.; Carreira, E. M. *Org. Lett.* **2013**, *15*, 1634–1637. (d) Nguyen, J. D.; D'Amato, E. M.; Narayanam, J. M. R.; Stephenson, C. R. J. *Nat. Chem.* **2012**, *4*, 854–859. (e) Andrews, R. S.; Becker, J. J.; Gagné, M. R. *Angew. Chem., Int. Ed.* **2012**, *51*, 4140–4143. (f) Wang, X.; Cuny, G. D.; Noel, T. *Angew. Chem., Int. Ed.* **2013**, *52*, 7860–7864.

(29) Pelleter, J.; Renaud, F. *Org. Process Res. Dev.* **2009**, *13*, 698–705. (30) Fukuyama, T.; Rahman, M. D.; Kamata, N.; Tokizane, M.; Fukuda, Y.; Ryu, I. *J. Flow Chem.* **2013**, *3*, 4–6.

(31) Becker, R.; van den Broek, S. A. M. W.; Nieuwland, P. J.; Koch, K.; Rutjes, F. P. J. T. *J. Flow Chem.* **2012**, *2*, 87–91.

(32) Šterk, D.; Jukić, M.; Časar, Z. *Org. Process Res. Dev.* **2013**, *17*, 145–151.

(33) Wang, K.; Hu, Y.; Yang, W.; Shi, Y.; Li, Y. *Thermochim. Acta* **2012**, *538*, 79–85.