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Flow assisted synthesis of bicyclic aziridines *via* photochemical transformation of pyridinium salts

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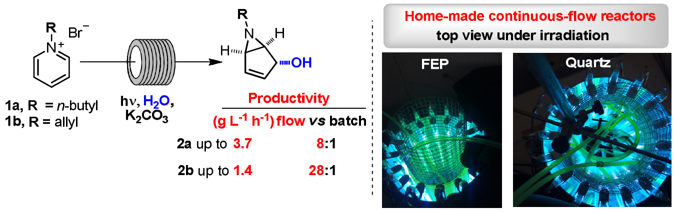
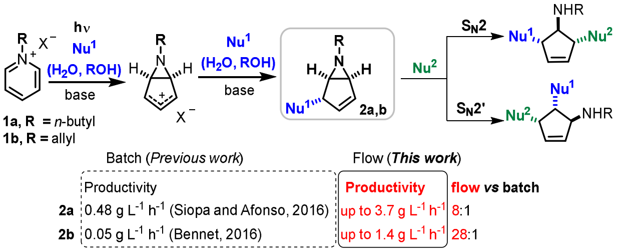


ABSTRACT: Here is described the development and comparison of home-made continuous-flow reactors, a fluorinated ethylene propylene tube (FEP) reactor (internal diameter of 0.4 cm) and two parallel quartz reactors containing two different internal diameters (0.4 and 0.2 cm) and their application on the photochemical transformation of 1-*n*-butyl and 1-allyl pyridinium bromide salts (**1a** and **1b**) to the corresponding α-hydroxycyclopenteno-aziridines **2a** and **2b** (6-azabicyclo[3.1.0]hex-3-en-2-ols). The FEP reactor allowed under recirculating conditions the production of more quantity of bicyclic-aziridine (3.2 g), while the quartz reactor with the same diameter furnished the best productivity results (3.7 g L^{-1} h^{-1}). In addition, the FEP reactor was operating efficiently under circulating conditions (1.75 L of **1a**) for 4.5 days (residence time of 17.9 h) allowing the production of **2a** in 2 g/day (62-93%).

KEYWORDS: Carbocycles; Photosynthesis; Flow chemistry; Continuous processing, Pyridinium; Aziridines

The discovery of potent biological properties of aminocyclopentitols and the promise that such effects might be exploited as an advantage in medicine have encouraged their synthesis.[1-4] An attractive approach for the synthesis of these compounds is the photochemical transformation of pyridinium salts to bicyclic-aziridines followed by aziridine ring-opening to afford aminocyclopentene derivatives (Scheme 1).[5-12] This photochemical rearrangement forms a *cis*-fused cyclopenten-aziridine allylic cation that reacts stereospecifically with poor nucleophiles Nu^1 (H_2O or alcohols) originating a *cis*-fused cyclopenten-aziridines **2** with a new C-Nu^1 bond in *trans*-position. This bicyclic-aziridine can react with other nucleophiles (Nu^2) *via* S_N2 or S_N2' pathways providing two trisubstituted cyclopentene isomers (Scheme 1). These aziridines are versatile intermediates for total synthesis of aminocyclopentitols,[5, 7] such as (+)-mannostantin A,[9] (+)-trehazolin, (-)trehazolin[8] and the aminocyclopentitol core of allosamidine[11].



Scheme 1. General route to aminocyclopentitols *via* photochemical transformation of pyridinium salts.[5, 7]

The synthesis of a range of aminocyclopentitols by this short route is limited to the photolysis which has been traditionally described under batch conditions.[5, 7] In general, the reported photochemical transformation of pyridinium salts to bicyclic-aziridines under batch (Tables S1 and S2) give low productivity 0.0027 - 1.33 g L^{-1} h^{-1} (Table S1) and 0.01- 0.36 g L^{-1} h^{-1} (Table S2), using water and methanol as nucleophile/solvent, respectively. Consequently, only a few milligrams (less than 100 mg) of bicyclic-aziridines (Tables S1 and S2) are produced, which constrains the subsequent synthetic pathways.[8, 10, 12-17]

Previously, we studied the ring-opening reaction of bicyclic-aziridines with a broad range of nucleophiles[16] under mild conditions. During this study it was noticeable that the amount of aziridine prepared by photochemical transformation of pyridinium salts was also a limiting issue. A quartz tube with 1.2 cm diameter and a home-made equivalent Rayonet reactor were used (Figure S4), and aziridines were prepared under batch conditions in only 0.02-0.13 g scale, corresponding to a productivity of 0.02-0.65 g L^{-1} h^{-1} (Table S1, entries 1, 15, 16.).[16] Nevertheless, Burger *et al*. were able to prepare 1.3 g of bicyclic-aziridine (Table S1, entry 1) using a Rayonet-RPR-100 reactor and achieved a productivity of 0.6 g L^{-1} h^{-1}. The same authors also reported the best productivity result of 1.3 g L^{-1} h^{-1} for the production of another aziridine (Table S1, entry 2).[14]

The major drawback of photochemical transformations is the limited scale-up options, due to the penetration of photons in the solution becoming less efficient with the increase of reactor dimensions. [18-20] Because of the attenuation effect of photon transport (Bouguer–Lambert–Beer law), the reaction time necessary to drive the reaction to completion increases considerably, which leads to over-irradiation of the reaction mixture that can potentiate the formation of byproducts.[18-20] In this sense, the use of continuous-flow reactors for photochemical reactions has focused the attention of researchers from both academia and industry, having an important impact in organic synthetic chemistry. The most important features of this approach are the reduced reaction times, straightforward scalability and possibility to safely use highly reactive and hazardous chemicals.[18-21] In addition, the use of a continuous-flow reactors in photoreactions will overcome the low efficiency under batch conditions that limited the scale-up.

Herein is presented the use of continuous-flow for the photochemical transformation of pyridinium salts **1a** and **1b** to the corresponding bicyclic-aziridine (Scheme 1).

Design of Flow Reactors:

We envisaged the use of continuous-flow for the photochemical transformation of pyridinium salts **1a,b** to the corresponding bicyclic-aziridines **2a,b**, to overcome the reported scale-up limitations of batch photochemical transformations.[18-20] In this context, three continuous-flow reactors were developed (Figures 1, 2 and S3). 1) A fluorinated ethylene propylene (FEP) reactor, as described previous by Booker-Milburn,[22] that consisted of a single length of UV transparent tubing wrapped closely around a metal grid (Figure 1). The FEP reactor is 2296 cm long and 0.4 cm of internal diameter (*d*), distributed by 40 turns of 57.4 cm/turn, FEP4: [2296 cm (*l*) × 0. 4 cm (*d*)](Figure 1); with a surface-to-volume ratio of 960 m^2/m^3. 2) A flow reactor that consisted of 24 parallel quartz tubes (PQT), with 22.5 cm of medium length and 0.4 cm of internal diameter PQT4: [24 tubes: 22.5 cm (*l*) × 0.4 cm (*d*)], (Figure 2); with a surface-to-volume ratio of 1003 m^2/m^3. 3) Another PQT that consisted of 32 parallel quartz tubes with 23 cm of medium length and 0.2 cm of internal diameter PQT2: [32 tubes: 23 cm (*l*) × 0.2 cm (*d*)], (Figure S3); with a surface-to-volume ratio of 1992 m^2/m^3. All the continuous-flow reactors were build to be placed inside the home-made equivalent Rayonet reactor (Model RPR-200), (Figure S4), near (1 cm) the UV lamps (16 Philips TUV lamps, 8W at 254 nm).

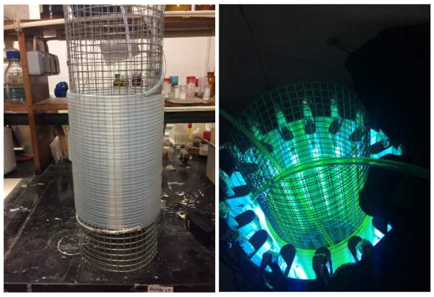


Figure 1. Home-made continuous-flow FEP4 reactor [(2296 cm (*l*) × 0.4 cm (*d*)], and top-view under irradiation.

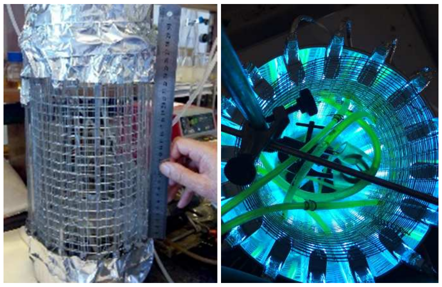


Figure 2. Home-made continuous-flow parallel tube quartz reactor PQT4 [24 tubes: 22.5 cm (*l*) × 0.4 cm (*d*)] and top-view under irradiation.

Batch Experiments: To assess the feasibility of using continuous-flow reactors for the phototransformation of pyridinium salts it was first evaluated the photoreaction of **1a**, under batch conditions. In this preliminary study we used quartz tubes (QT) and a FEP tube with the same length and diameter of the ones used in the continuous-flow reactors, *i.e.* QT4 and FEP tube [23 cm (*l*) × 0.4 cm (*d*)] (Table 2, entries 1,2 and entry 6), QT2: [22 cm (*l*) × 0.2 cm (*d*)] (Table 2, entries 3,4). A basic solution of pyridinium salt **1a** was prepared in a concentration *ca.* 60 mM (Table 2, entries 1, 3, 6) and conversion and productivity (g L^{-1} h^{-1}, determined by ^1H NMR) were compared after 8 h of photochemical irradiation. The results were similar (91% and 1.04 g L^{-1} h^{-1} for QT4 *vs* 88% and 0.96 g L^{-1} h^{-1} for QT2 *vs* 92% and 1.09 g L^{-1} h^{-1} for FEP - Table 2, entries 1, 3, 6; ^1H NMR in SI). Then, a concentration *ca.* 300 mM of **1a** was tested. The conversion, after 8 h of irradiation, was lower (17% for QT4 *vs* 33% for QT2 *vs* 13% for FEP - Table 2, entries 2, 4, 7; ^1H NMR in SI, Figure 3), which can be explained by the Bouguer–Lambert–Beer law, since the absorption of photons is strongly dependent on the reaction concentration.[18-20] Nevertheless, the productivity and conversion was better for QT2 than QT4 (1.81 g L^{-1} h^{-1}, 33% *vs* 0.97 g L^{-1} h^{-1}, 17%, respectively) because a shorter diameter allows a better penetration of the UV light.[18] Comparing the results obtained for QT4 and FEP tube with the same diameter, a lower productivity and conversion was observed for the FEP tube (0.73 g L^{-1} h^{-1}, 13% Table 2, entry 7, Figure 3). In spite of this reduction, which is probably due to its intrinsic characteristics, FEP is quite versatile and easy to handle, which outweighs the low productivity achieved..[18, 21-24] These preliminary results (Table 2) show that at a concentration *ca.* 300 mM the absorption of photons is already affected and the conversion and the productivity raises by the following order: QT2 > QT4 > FEP. Since at a concentration *ca.* 60 mM the absorption of photons is not affected, this concentration was chosen for the flow studies.

A scale-up experiment was also performed under batch conditions, using a higher diameter QT (Table 2, entry 5). In this case we isolated 0.55 g of **2a** (72 % yield) corresponding to a productivity of 0.25 g/h/L.

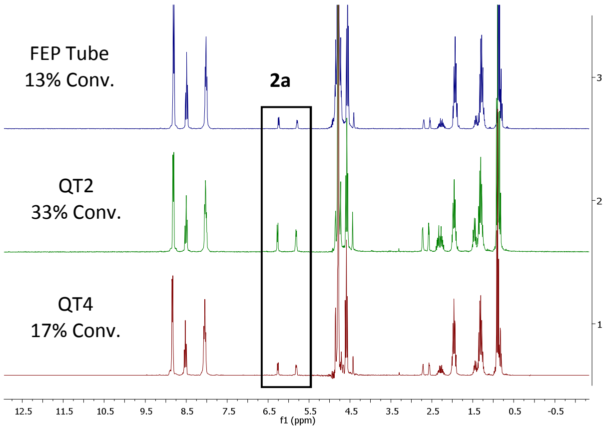
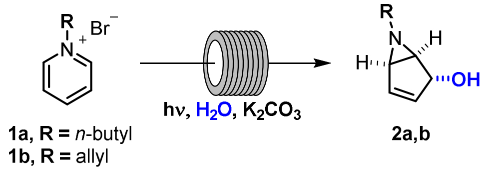


Figure 3. ^1H NMR spectra of the photoreaction under batch conditions of 1-*n*-butylpyridinium bromide **1a** (*ca.* Conc. 300mM), using the FEP tube, QT4 and QT2 (Table 2, entries 2,4,7).

Recirculating Continuous-Flow Experiments: We investigated the photochemical transformation of **1a,b** to **2a,b** (Tables 1, 3, 4) under comparable continuous-flow experimental conditions [concentration - 21-82 mM, temperature - rt and flow rate - 1.9 (for FEP4 and PQT4) and 0.5 (for PQT2) mL/min]. For the reactor PQT2 a flow of 0.5 mL/min was selected in order to maintain comparable fluid dynamics with the other reactors FEP4 and PQT4. All the reactions were followed by ^1H NMR (aliquots of 0.5 mL were analyzed at specific time), which allowed the determination of the conversion, as well as the product mass and the productivity (Table 1). The photoreaction of **1a** using PQT4 proceeded with high conversion (93-96%, Table 1, entries 1-3). In addition, the increase of the concentration led to a slight decrease in the conversion rate (Figure 4). At 42 mM and 62 mM (Figure 4 and Table 1, entries 1, 2) the reaction reached the best conversions after just 9 h (96% and 94%, respectively). At 82 mM, the conversion of 93% was only obtained after 17.7 h of reaction (Table 1, entry 3). At 42 and 82 mM the productivity was 2.5 g L^{-1} h^{-1}, allowing the maximum mass production of 2.9 g for 82 mM (Figure S8B and Table 1, entries 1, 3). The best productivity of 3.7 g L^{-1} h^{-1} was obtained at 62 mM (Figure 5 and Table 1, entry 2). This concentration was selected to test the reactors PQT2 and FEP4.

At 62 mM, PQT4 and PQT2 gave similar space-time yield (STY) of the process, 3.7 and 3.3 g L^{-1} h^{-1}, respectively (Table 1, entries 2, 4). It was expected that the large surface-to-volume ratio of PQT2 (1992 *vs* 1003 m^2/m^3) would give higher STY, due to the increased irradiation efficiency of the solution.[24] However, the amount of bicyclic-aziridine **2a** produced is smaller than PQT4 (0.7 g *vs* 2.2 g, respectively), due to the shorter internal surface area of PQT2 (0.046 m^2 *vs* 0.068 m^2 see SI)

Table 1. Selected results for the flow photochemical transformation of **1a,b** under recirculating continuous-flow conditions.



Entry	Flow Reactor	Py Salt, Conc.(mM)	Conv.(%), time[(a)]	Prod. Mass (g)	Productivity (g L^{-1} h^{-1})
1	PQT4	**1a**, 42	96, 9 h	1.5	2.5
2	PQT4	**1a**, 62	94, 9 h	2.2	**3.7**
3	PQT4	**1a**, 82	93, 17.7 h	2.9	2.5
4	PQT2	**1a**, 62	89, 10.0 h	0.8	3.3
5	FEP4	**1a**, 62	96, 19.5 h	**3.2**	0.5
6	PQT4	**1b**, 21	99, 7.5 h	0.7	1.4
7	PQT4	**1b**, 42	88, 15.7 h	1.3	1.2
8	PQT4	**1b**, 62	57, 20.7 h	1.2	0.9
9	PQT4	**1b**, 82	45, 23.7 h	1.3	0.8
10	FEP4	**1b**, 62	53, 19.5 h	1.6	0.3

[(a)] Reaction time at the presented conversion. All the data for each reaction is provided in the SI.

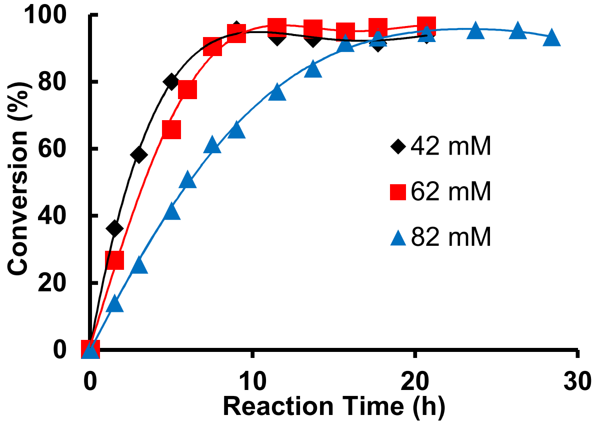


Figure 4. Conversion of **1a** at 42, 62 and 82 mM in the photochemical rearrangement using the home-made PQT4 under recirculating continuous-flow conditions.

For FEP4 the STY is much lower than for PQT4 (0.5 *vs* 3.7 $g\ L^{-1}\ h^{-1}$) (Figure 5). Since these reactors have comparable surface-to-volume ratios values (960 *vs* 1003 m^2/m^3), this result could be related to the geometry of FEP4 which probably reduces the radiation penetration in the inner side of the reactor. However, due to the highest internal surface area of FEP4 (0.290 m^2 see SI) the quantity of **2a** produced is the biggest (3.2 g; Table 1, entry 5 and Figure S10B).

The best productivity result of 3.7 $g\ L^{-1}\ h^{-1}$ (Figure 5) obtained with PQT4, shows a great improvement regarding all reported values under batch conditions (Tables S1 and S2) and, together with the shorter reaction time of 9 h, also shows the advantage of using continuous-flow reactor. In particular, for the pyridinium salt **1a** the best reported productivity under batch conditions was only 0.48 $g\ L^{-1}\ h^{-1}$ [16] which corresponds to 8 times less than under flow conditions.

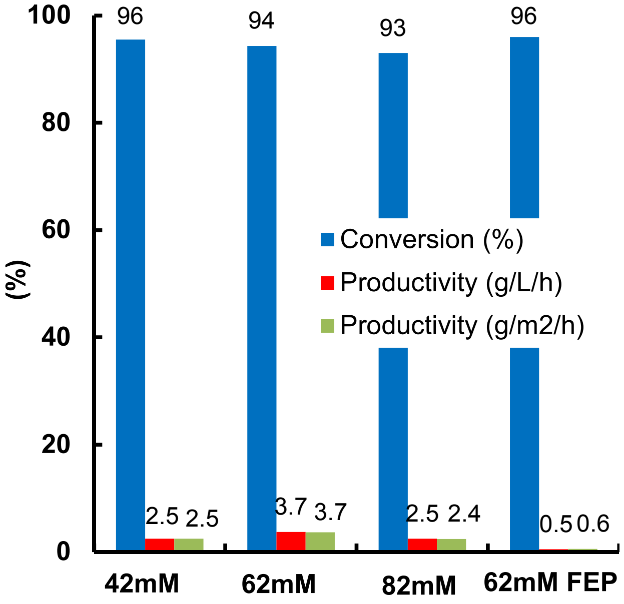


Figure 5. Conversion (%) and productivity ($g\ L^{-1}\ h^{-1}$ and $g\ m^{-2}\ h^{-1}$) of the photoreaction of pyridinium salt **1a**, at 42, 62 and 82 mM using PQT4 and FEP4 reactor at 62 mM under recirculating continuous-flow conditions.

The photochemical reaction of **1b** was evaluated using PQT4 and FEP4 reactors (Table 1, entries 6-10). This reaction gave lower productivity and conversion than **1a** (Table 1, entries 6-10), probably due to the effect of the allyl group. Using PQT4, at 21 mM was obtained the best productivity and conversion (1.4 $g\ L^{-1}\ h^{-1}$ and 99%, Table 1, entry 6) after 7.5 h. This productivity corresponds to an improvement of 28 times when compared to the literature value reported for batch reaction (0.05 $g\ L^{-1}\ h^{-1}$ [15]). Once more the FEP4 reactor gave less productivity (0.3 $g\ L^{-1}\ h^{-1}$, Table 1, entry 10) than PQT4 (0.9 $g\ L^{-1}\ h^{-1}$), but more quantity of **2b**. These results demonstrate again the value and usefulness of the continuous-flow reactors as a clear upgrade over the traditional batch conditions for the photochemical transformation of pyridinium salts to bicyclic-aziridines.

Continuous-Flow Experiment: The combined results show that for the photochemical transformation of substrates **1a** and **1b**, the flow reactor PQT4 is more efficient. However, due to construction limitations of the connections between the quart tubes, the PQT4 and PQT2 reactors have considerable dead volume which limits their use without recirculating the reaction medium. On the other hand, this limitations are absent for the FEP4 reactor, therefore, we explored the transformation of **1a** at 62 mM without recirculating the reaction media. The reaction crude was collect in different fractions (15 min/fraction) and the product conversion (%) calculated by ^1H NMR. First the reaction mixture was irradiated at a flow rate of 0.56 mL/min, corresponding to 8.9 h of residence time under irradiation (Figure 6). This flow rate was estimated based in the FEP tube batch experience for **1a** at 62 mM, in which after 8 h of irradiation was obtained 92 % conversion. However, after this time of irradiation the conversion was only 56 %. This low conversion, in opposition to the prediction by the batch experiment, is related to the geometry of the FEP4, due to the reaction mixture receiving less radiation, since the light penetration in the inner side of the reactor is reduced. The flow rate of 0.28 mL/min, which correspond to 17.9 h of residence time was then evaluated. This flow rate was estimated based on the FEP4 recirculated continuous-flow experiment for **1a** at 62 mM, in with at 1.9 flow rate after 16.3 h of reaction was obtained 89 % conversion and after 19.5 h of reaction was obtained 93 % conversion.

At 0.28 mL/min of flow rate the conversion increased to 93 % and remained above 60% throughout the operation period of 3.8 days (1.4 L of reaction mixture) (Figure 6). During the overall operating period (4.5 days), 1.75 L of reaction was irradiated allowing the synthesis of 9 g of **2a** in 3 days, which corresponds to 2 g/day.

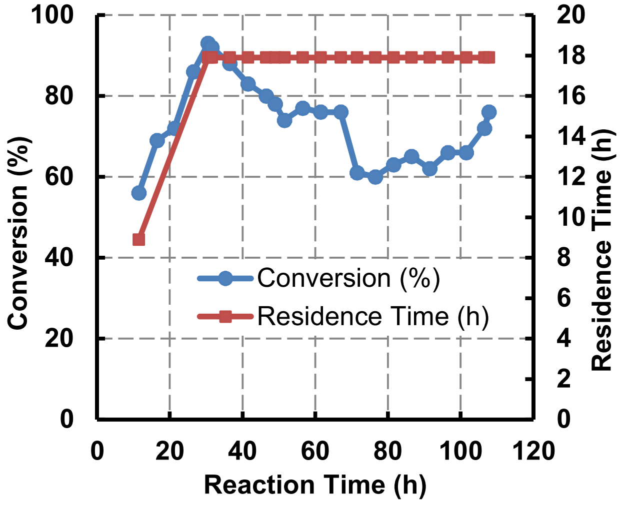


Figure 6. Conversion (%) and residence time (h) for the continuous-flow photoreaction of pyridinium salt **1a** at 62 mM using FEP4 reactor

In conclusion, this work reports an efficient photochemical transformation of 1-*n*-butyl and 1-allyl pyridinium salts to the corresponding bicyclic-aziridine under continuous-flow conditions. Three home-made continuous-flow reactors were developed, which overcome the scalable problem of this rearrangement and allowed the production of bicyclic-aziridines in gram scale. PQT4 gave the best productivity results (3.7 g L^{-1} h^{-1} for **1a** and 1.4 g L^{-1} h^{-1} for **1b)**, that revealed a huge improvement when compared with the reported literature under batch conditions (8 times and 28 times better, respectively). FEP4 allowed the production of higher quantities of bicyclic-aziridine, since it is a reactor with more capacity being efficient for long time operations under continuous-flow allowing the production of 2 g/day of **2a**. PQT2, the reactor with the smaller diameter, also gave a good productivity for **1a** (3.3 g L^{-1} h^{-1}), however the production is lower than PQT4. These powerful home-made reactors could also be explored in a wide variety of organic photochemistry reactions. The impact of continuous-flow in the field of organic synthesis as well as organic photochemistry is already high and it is still expected an increase of research in this topic, including for high scale production.

EXPERIMENTAL SECTION

General methods and materials: All the reagents were obtained commercially and were used without further purification. The solvents were obtained from commercial sources as pure grade and were distilled before.

^{1}H and ^{13}C NMR spectra were measured on a Bruker Fourier 300 spectrometer. Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad peak. The photochemical reactions were followed by ^{1}H NMR (D_2O). Low resolution mass spectroscopy was performed in a triple quadrupole mass spectrometer Micromass Quattro Micro API. Waters. The UV irradiation experiments were performed in a equivalent Rayonet reactor (Model RPR-200), containing 16 Philips TUV lamps (8W at 254 nm).

General procedure for synthesis of pyridinium salts: To an Aldrich ACE pressure tube (Z181064) at room temperature, was added pyridine (5.1 mL, 0.06 mol) and the respective brominated derivative (0.06 mol). The solution was heated at 100 ºC for 40 hours, unless stated. After cooling, the salt was dissolved in MeOH, transferred to a flask and evaporated under vacuum to obtain the pure salt.

1-*n*-butylpyridinium bromide (1a) The pyridinium salt **1a** was obtained in quantitative yield as a colourless solid. ^{1}H NMR (300 MHz, D_2O) δ 8.86 (d, *J* = 5.8 Hz, 2H), 8.58 – 8.52 (m, 1H), 8.09 (d, *J* = 6.9 Hz, 2H),4.62 (t, *J* = 7.4 Hz, 2H). 2.03 – 1.98 (m, 2H). 1.40 – 1.33 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H). Spectral data in accordance with the literature.[16]

1-allylpyridinium bromide (1b). The reaction mixture was stirred at 60 ºC overnight. The pyridinium salt **1b** was obtained in 82% yield as a brown solid. ^{1}H NMR (300 MHz, D_2O) δ 9.00 (d, *J* = 5.5 Hz, 2H), 8.72 – 8.67 (m, 1H), 8.22 (t, *J* = 7.0 Hz,2H), 6.34 – 6.21 (m, 1H), 5.67 – 5.59 (m, 2H). 5.37 (d, *J* = 6.0 Hz, 2H). ^{13}C NMR (75 MHz, D_2O) δ 148.3, 146.6, 132.3, 132.2, 130.6, 130.6, 125.4, 125.3, 65.8. MS(ESI) m/z: 120.2 $[M]^+$ ^{1}H NMR spectral data in accordance with the literature.[6]

General procedure for photochemical transformation of 1-*n*-butylpyridinium bromide to 6-*n*-butyl-6-azabicyclo[3.1.0]hex-3-en-2-ol *(2a)* under batch conditions: Inside a reactor tube (QT4: 23 cm (*l*) x 0.4 cm (*d*), QT2: 22 cm (*l*) x 0.2 cm (*d*) and FEP: 23 cm (*l*) x 0.4 cm (*d*), Table 2) was inserted an aqueous solution (Table 2) of pyridinium salt **1a** (Table 2) and potassium carbonate (1.2 mol equiv). The solution was deoxygenated under N_2 for 30 minutes and placed inside the Rayonet reactor (equivalent to Model RPR-200, containing 16 Philips TUV lamps (8W at 254 nm)) and the reaction mixture was irradiated at room temperature for 8 h, unless stated. To isolate the bicyclic-aziridine (Table 2, entry 5), the water was evaporated under vacuum and the solid dissolved in diethyl ether (3x100 mL). The solution was stirred for 15 minutes and filtered, the solvent was evaporated under vacuum to give the bicyclic vinyl aziridine **2a** as a brown oil.

6-*n*-Butyl-6-azabicyclo[3.1.0]hex-3-en-2-ol (*2a*) The compound was obtained as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.29 – 6.27 (m, 1H). 5.88 – 5.86 (m, 1H). 4.48 (d, *J* = 1.2 Hz,1H), 2.48 – 2.23 (m, 4H), 1.56 – 1.49 (m, 2H), 1.37 – 1.29 (m, 2H). 0.89 (t, *J* = 7.3 Hz, 3H). Spectral data in accordance with the literature.[16]

Table 2. Synthesis of **2a** under batch conditions.

Entry	Tube	S/V ratio [m^2/m^3]	Water (mL)	1a (mmol)/ (mM)	Conv.(%)	Productivity (g L^{-1} h^{-1})
1	QT4	1000	3	0.18/60	91	1.04
2	QT4	1000	3	0.89/296	17	0.97
3	QT2	2000	0.7	0.04/57	88	0.96
4	QT2	2000	0.7	0.20/285	33	1.81
5	QT25(a)	161	80	5/63	72(b)	0.25(0.65)(c)
6	FEP	1000	3	0.19/62	92	1.09
7	FEP	1000	3	0.89/296	13	0.73

(a)The reaction was irradiated during 28 h, internal diameter of the quartz tube: 2.5 cm. (b) Isolated yield (%), Isolated mass 0.55 g, (c) For a quartz tube with 1.2 cm diameter(*d*), using 1-*n*-butylpyridinium chloride (0.96 mmol) gave **2a** in 65% (0.131g of isolated mass) providing 0.65 g L^{-1} h^{-1} of productivity.[16]

General procedure for recirculating continuous-flow photochemical transformation of pyridinium salts to bicyclic-aziridines: In an Erlenmeyer was prepared an aqueous solution at specific concentrations (Tables 3 and 4) of pyridinium salt and potassium carbonate (1.2 mol equiv). Using a peristaltic pump (Watson Marlow 120U/DV, Internal diameter silicon tube (0.8 mm), 50 rpm, measured flow-rate 1.9 mL/min, unless otherwise stated), the reaction solution was circulated through the flow reactor and placed inside the Rayonet equivalent reactor. The reaction was irradiated by circulating the reaction mixture at room temperature, for the time specified in Tables 3 and 4. For each specific time, 0.5 mL of reaction mixture was collected, the solvent was evaporated under reduced pressure, the residue was dissolved in D_2O and the conversion determined by ^{1}H NMR using the average of integration of three different peak groups signals (see details in the SI document). In the end, the water was evaporated under vacuum, the solid was dissolved in dichloromethane (200 mL) and the solution was stirred for 15 minutes, filtered and evaporated under vacuum. This procedure was repeated 3 times, allowing the isolation of the corresponding bicyclic vinyl aziridines.

Table 3. Synthesis of **2a** under recirculating continuous-flow conditions.

Flow Reactor	S/V ratio [m^2/m^3]	Conc. (mM)	Water (mL)	1a (mmol)	Time (h)	Conv.(%)/ Isolated Yield (%)
PQT4	1003	42	250	10.5	20.7	94/90(1.4g)[(b)]
PQT4	1003	62	250	15.5	20.7	97/75(1.8g)[(b)]
PQT4	1003	82	250	20.5	28.4	93/76(2.4g)[(b)]
PQT2[(a)]	1992	62	90	5.6	10.0	89/ND
FEP4	960	62	350	21.7	26.0	97/63(2.1g)[(b)]

[(a)]Measured flow/rate of 0.5 mL/min, with the peristaltic pump at 13 rpm. [(b)]Isolated mass. All the data for each reaction are provided in the SI. ND – not determined

Table 4. Synthesis of **2b** under recirculating continuous-flow conditions.

Flow Reactor	Conc. (mM)	Water (mL)	1b (mmol)	Time (h)	Conv.(%)/Isolated Yield (%)
PQT4	21	250	5.3	9	97/ ND
PQT4	42	250	10.5	29.3	92/63(0.9g)[(a)]
PQT4	62	250	15.5	29.3	57/57(1.2g)[(a)]
PQT4	82	250	20.5	26.3	45/ ND
FEP4	62	350	21.7	26.0	54/ ND

[(a)]Isolated mass. All the data for each reaction are provided in the SI. ND – not determined

6-allyl-6-azabicyclo[3.1.0]hex-3-en-2-ol (2b) The bicyclic vinyl aziridine as obtained as a brown oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.27 (dt, *J* = 5.6, 1.2 Hz, 1H), 5.93 – 5.82 (m, 2H), 5.22 -5.09 (m, 2H), 4.48 (dd, *J* = 3.3, 2.0 Hz, 1H), 2.95 – 2.89 (m, 2H), 2.54 – 2.48 (m, 2H).^{13}C NMR (75 MHz, $CDCl_3$) δ 137.5, 135.6, 134.7, 116.8, 75.0, 60.2, 50.5, 46.8. MS(ESI) m/z: 138.2 $[M+H]^+$ HRMS-ESI m/z calcd. for $C_8H_{12}NO$ $[M+H]^+$: 138.09134; obtained 138.09069. Spectral data in accordance with the literature.[15]

Procedure for continuous-flow photochemical transformation of 1a to 2a using FEP4 reactor: In a FEP4 reactor (placed inside the Rayonet equivalent reactor) a 350 mL aqueous solution of **1a** and potassium carbonate (1.2 mol equiv) at 62 mM concentration was irradiated at 0.56 ml/min flow rate using a peristaltic pump (Watson Marlow 120U/DV, Internal diameter silicon tube (0.8 mm)), at 15 rpm, followed by the irradiation at 0.28 mL/min flow rate (peristaltic pump at 7 rpm) of 1400 mL of an aqueous solution **1a** and potassium carbonate (1.2 mol eq.) at 62 mM concentration. In the end a 350 mL of aqueous solution of potassium carbonate at 62 mM concentration was added to the FEP4 reactor at the same flow rate, in order to remove the last reaction mixture inside. During the reaction irradiation, the reaction mixture was collected from the outlet tube using a Büchi Fraction Collector C-660 set to 15 min/fraction (4.2 mL/fraction). Selected samples were concentrated in vacuum and submitted directly for ^{1}H NMR analysis (D_2O). Conversion to product (%) was calculated on the basis of the ratio of integrals of pyridinium salt **1a** [δ ^{1}H 8.60 (1H, t, H_{arm})] and the corresponding bicyclic vinyl aziridine **2a** [δ ^{1}H 6.36 (1H, d, CH)]. To isolated **2a**, the water was evaporated under vacuum, and the solid dissolved in dichloromethane (400 mL) and the solution stirred for 15 minutes, filtered and evaporated under vacuum. This procedure was repeated 3 times. The resulting oil was dissolved in THF (500 mL) and the solution stirred for 15 minutes, filtered and evaporated under vacuum, allowing the isolation of 9 g of **2a** in 54% yield.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge via the Internet at http://pubs.acs.org

Selected reported examples of photochemical transformations of pyridinium salts under bath conditions, using methanol and water as nucleophiles, details of home-made continuous-flow reactors and obtained results, copies of ^{1}H- and ^{13}C-NMR spectra of synthetized compounds and copies ^{1}H-. spectra of photochemical crude reactions.

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