# From Anilines to Aziridines: A Two-Step Synthesis under Continuous-Flow Conditions

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The Sandmeyer reaction of anilines to generate aryl azides, followed by the Ru(porphyrin)CO-catalyzed addition to styrenes affording *N*-aryl aziridines was successfully performed for the first time in mesoreactors, under continuous-flow conditions. Mesofluidic technology allowed for a rapid screening of different parameters and a quick identification of the optimized reaction conditions for the two separate steps. The two optimized reactions were then combined in a single continuous process that allowed a safe and efficient synthesis of *N*-arylaziridines from convenient commercially available starting materials.

**Keywords:** azides, aziridines, ruthenium catalyst, mesoreactors, flow chemistry

## 1. Introduction

Nitrogen containing molecules, which can be found widespread in nature, can be conveniently prepared starting from aziridines as valuable building blocks [1]. Among the different available synthetic strategies [2], the metal-catalyzed addition of nitrenes to alkenes represents one of the most popular and established methodology for the preparation of aziridines [3]. Organic azides ($RN_3$) [4] are largely used in this process as convenient nitrene sources, thanks to their high atom efficiency resulting in the formation of eco-friendly $N_2$ as the sole byproduct of nitrene transfer reactions. Organic azide-based aziridinations are well catalyzed by several classes of metal transition complexes, and efficient stereoselective synthetic protocols have also been developed [5].

However, this useful synthetic methodology suffers from the handling of hazardous organic azides as starting material, due to their propensity to vigorous decomposition. It is not surprising, then, that the synthesis [6] and manipulation [7] of organic azides under continuous-flow conditions have been the object of extensive investigation since the dawning of flow chemistry. In the last few years, flow chemistry technologies [8] have become very popular in the synthesis of organic molecules [9], including complex natural products [10] or active pharmaceutical ingredients (APIs) [11]. Attractive features of continuous processes are short reaction times and improved reagent mixing as well as mass and heat transfer. Moreover, given the small volumes involved, a safer handling of hazardous reagents or very reactive intermediates may also be positively addressed.

In particular, the Sandmeyer reaction of anilines with $NaNO_2$ to afford diazonium compounds followed by reaction with $NaN_3$ is a convenient and atom-economic method to prepare aromatic azides. The continuous-flow preparation of reactive diazonium intermediates was reported in 2003 by de Mello and coworkers [12]. The formation of diazonium salt starting from anilines, followed by addition of $NaN_3$ to afford aryl azides, was extensively studied by researchers at Sigma-Aldrich under continuous-flow conditions; this flow process allows the manipulation of labile and potentially hazardous intermediate in a reduced volume and in a safe manner [13]. The proposed setup represents a batch-to-continuous adaptation from the batch synthesis of aromatic azides proposed by Tsuritani, Mizuno, and coworkers, who also made a risk assessment study of aryl azides [14]. This is also the Sigma-Aldrich current method to prepare commercial azide solutions.

Considering that some of us have extensively studied nitrene transfer reactions promoted by ruthenium porphyrin complexes from both experimental [15] and theoretical point of view [16], and given our experience in flow chemistry [17], we decided to investigate the continuous-flow synthesis of aryl azides followed by the Ru(porphyrin)CO-catalyzed aziridination of styrenes in mesoreactors in an attempt to develop a two-step, simple, efficient, and safe synthesis of aziridines starting directly from anilines [18]. In order to expand our recent study on the Ru(porphyrin)CO-catalyzed addition of aryl azides to styrenes to afford *N*-aryl aziridines in mesoreactors under continuous-flow conditions [19, 20], we here report the reaction of prepared azide with alkene in the presence of the ruthenium catalyst in a reaction. We felt that the continuous-flow synthesis of aryl azides could represent an improvement of the known methodology both from the safety and efficiency point of view.

## 2. Results and Discussion

To assess the feasibility of our idea, we first focused on the synthesis of aryl azides starting from the corresponding anilines via the Sandmeyer reaction under continuous-flow conditions [13]. The schematic representation of the system is illustrated in Scheme 1. The reaction between the aniline and $NaNO_2$ was conducted into coil-reactor 1, a mesoreactor immersed in cooling bath (10 °C). The reactor output, containing the diazonium salt, entered coil-reactor 2, where the salt was diluted with an organic solvent (methyl *t*-butyl ether [MTBE] or α-methylstyrene). Finally, the diazonium salt was reacted with $NaN_3$ into coil-reactor 3 affording the desired azide, which was completely extracted by the organic solvent, while the unreacted material remained in the aqueous phase.

For initial optimization studies, we chose the synthesis of 4-$NO_2$-phenylazide **2a** starting from 4-$NO_2$-aniline **1a** under continuous-flow conditions as a model reaction. The reaction was conducted in a mesoreactor composed by three coil-reactors made of commercially available polytetrafluoroethylene (PTFE) tubing (see Table 1 and Supporting Information for further details) that were coiled in a bundle and immersed in cooling bath (10 °C). A Chemix Fusion 100 syringe pump equipped with two Hamilton gastight 5 mL syringes was used in order to feed the reagents into coil-reactor 1 (PTFE tubing; inner diameter, 0.58 mm; length, 189 cm; total volume, 500 μL). Solution A contained 4-$NO_2$-aniline dissolved in freshly prepared 2.5 M HCl solution and solution B contained $NaNO_2$ solution in water. The reactor output entered a second

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**Scheme 1.** Schematic representation of flow setup for the conversion of anilines into azides

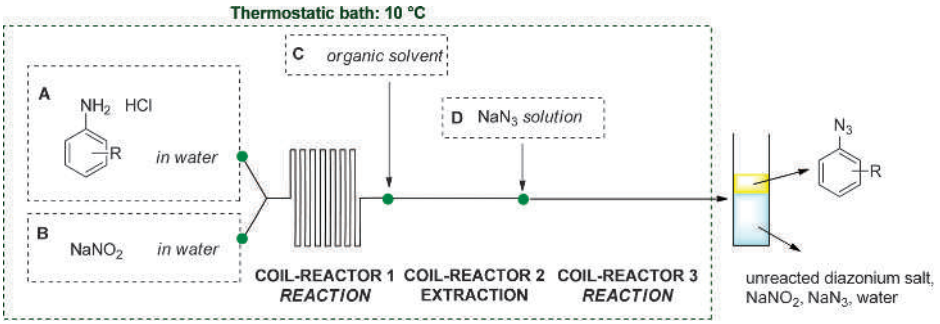
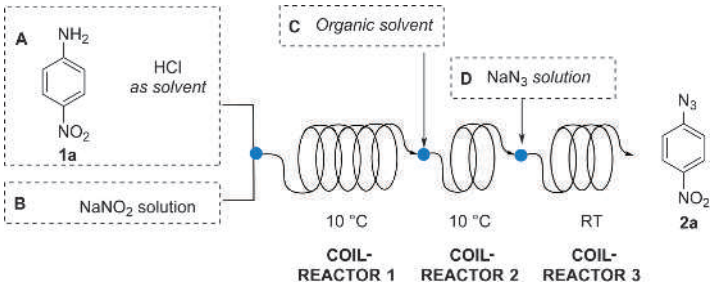



**Table 1.** Reaction of 4-$NO_2$-aniline **1a** to afford 4-$NO_2$-phenylazide **2a** in a PTFE mesoreactor




| Entry | 1a (M)[a] | $NaNO_2$ (M)[a] | $NaN_3$ (M)[a] | Flow rate[b] (mL/min) | Residence time[c] (min) | Yield[d,e] (%) |
|---|---|---|---|---|---|---|
| 1 | 0.8 | 0.816 | 1.2 | 0.1 | 5 | 81 |
| 2 | 0.8 | 0.816 | 1.2 | 0.05 | 10 | 84 |
| 3[f] | 0.8 | 0.816 | 1.2 | 0.05 | 10 | 82[g] |
| 4 | 0.8 | 0.816 | 1.2 | 0.025 | 20 | 87 |
| 5 | 0.4 | 0.408 | 0.6 | 0.1 | 5 | 74 |
| 6 | 0.4 | 0.408 | 0.6 | 0.05 | 10 | 92 |
| 7 | 0.4 | 0.408 | 0.6 | 0.025 | 20 | 98 |

[a] Molarity values correspond to the concentration inside the syringe.
[b] Total flow rate at T-junction (flow rate of syringe A + flow rate of syringe B).
[c] Residence time inside coil-reactor 1.
[d] Four reactor volumes were discarded before collection.
[e] Monitored by GC using biphenyl as the internal standard. Calculated as (mmol/min product) / (mmol/min reactant) × 100.
[f] MTBE was used as the organic solvent (see ref. 8).
[g] Isolated yield.

T-junction together with α-methylstyrene as an extracting solvent (solution C) into coil-reactor 2 (PTFE tubing; inner diameter, 0.58 mm; length, 19 cm; total volume, 50 μL) cooled to 10 °C. Finally, the $NaN_3$ solution in water was added into coil-reactor 3 (PTFE tubing; inner diameter, 0.58 mm; length, 55 cm; total volume, 145 μL) at room temperature, in order to convert the diazonium salt into aryl azide **2a**. Conversions and yields were determined by gas chromatography (GC) using biphenyl as the internal standard (see Supporting Information for further details). α-Methylstyrene was chosen as an extracting solvent with the aim of using it as the reaction partner in the following reaction, the aziridination promoted by Ru catalyst. α-Methylstyrene is a readily available and cheap alkene, much less prone to polymerization than styrene. The reaction output containing the desired azide was recovered in a vial in order to collect about 2 mL of 1 M azide solution into the organic solvent (the collection time depending on the α-methylstyrene flow rate — solution C; see Supporting Information for further details). Results are reported in Table 1.

Data in Table 1 show that 4-$NO_2$-aniline **1a** was efficiently converted into 4-$NO_2$-phenylazide **2a** in very short reaction times using small excess of $NaNO_2$ and $NaN_3$, using α-methylstyrene as the extraction solvent for the azide. We observed that some time was necessary for the system to reach the steady state, so four reactor volumes were discarded before collecting and analyzing the reactor output [21]. This operation guaranteed reproducible yields during time. α-Methylstyrene was as efficient as MTBE to extract the product, as shown by entry 2 vs. entry 3, and this is very convenient when aiming at the two-step synthesis of aziridines. After 10 min residence time inside the 500 μL mesoreactor, most of the aniline was converted into the diazonium salt which was trapped by $NaN_3$ (Table 1, entry 2). The reaction efficiency was slightly affected by the concentration of the aniline HCl salt. The use of a high concentration of the clorohydrate could be convenient to obtain a high amount of the final azide; however, solubility issues should be considered, so more diluted solutions have to be used, in some cases, to reach satisfactory final yields (see, for example, entry 2 vs. entry 6). It is noteworthy that we demonstrated that the fluidic dynamics inside the round-section PTFE 500 μL mesoreactor was as favorable as inside a square-section glass microreactor [13].

We next extended the scope of the reaction to differently substituted anilines to verify the general applicability of the methodology. For convenience, in this screening, we used MTBE to extract the aryl azides and provide isolated yields. The concentration of the aniline was adjusted to the maximum to prevent the salt precipitation inside the syringe, and the concentration of the reactants was changed accordingly. Based on the previous results, 10 min residence time inside the coil-reactor 1 was chosen (total flow rate at the T-junction 0.05 mL/min). Halogen-derived anilines were screened [13] as well as anilines

bearing electron-donating or electron-withdrawing groups. The flow system setup was the same as in Table 1, and results of this screening are reported in Table 2.

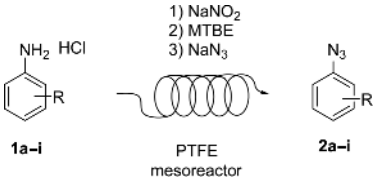
We were pleased to find that, as shown in Table 2, the reaction can tolerate different functionalization on the aromatic ring. Aniline was used in the reaction at a high concentration and afforded phenylazide **2b** in 71% yield (Table 2, entry 2). High azide yields were obtained by using halogen derived anilines (entries 3–5), and both electron-donating (entries 6–8) and electron-withdrawing groups (entries 1 and 9) on the phenyl ring were very well tolerated, leading to the desired products in very high yields (>82%). Due to solubility issues, 4-$CF_3$-aniline **1h** required a higher dilution with respect to other anilines (0.2 M vs. 0.4 M) but afforded 4-$CF_3$-phenylazide **2h** in 95% yield (entry 9); on the other hand, 4-*t*Bu-aniline **1i** gave 4-*t*Bu-phenylazide **2i** in 65% yield (entry 10). Again, by using simple PTFE tubing and common connections, and by adjusting reactants concentrations according to solubility, it was possible to obtain aryl azides in short reaction times with a safe and efficient process. It is noteworthy that the organic phase recovered at the end of the process only contained aryl azide (>95% purity by $^1$H-NMR analysis).

Having established the best reaction conditions for the azide synthesis and extraction, and proved the reaction versatility, we examined the possibility of using the prepared azides into the Ru(porphyrin)CO-catalyzed addition to styrenes to afford *N*-aryl aziridines. The schematic representation of the two-step process is illustrated in Scheme 2.

After the first step, the azide synthesis, the organic phase was manually separated and used in the next step, the Ru(porphyrin)CO-catalyzed addition to α-methylstyrene affording corresponding *N*-aryl aziridine. At this stage, we were interested in demonstrating that the product outcome of the first reaction could be used in the next catalyzed step without further purification of the azide. In principle, by adding a continuous extracting unit after the azide synthesis, it could be possible to realize a two-step process in continuo.

Based on our previous experience [19], the aziridination reaction was conducted in a mesoreactor, made of commercially available PTFE tubing (coil-reactor 4; inner diameter, 0.58 mm; length, 189 cm; total volume, 500 μL) that was coiled in a bundle and immersed in a 120 °C preheated oil bath. A Chemix Fusion 100 syringe pump equipped with two Hamilton gastight 2.5 mL syringes was used to feed the reagents into the mesoreactor through a T-junction (syringe E: [Ru(TPP)(CO)] **3** (2% mol) dissolved in α-methylstyrene; TPP = dianion of tetraphenyl porphyrin; syringe F: the azide solution, in α-methylstyrene coming from the first step). The mesoreactor was kept at 120 °C, and 30 min was chosen as a residence time. In order to stop the reaction, products were collected at −30 °C. The reaction output was collected for 30 min (see Supporting Information for further details). Results are summarized in Table 3.

**Table 2.** Reaction of anilines **1a–i** affording aryl azides **2a–i** in a PTFE mesoreactor




| Entry[a] | R | **1a–i** (M)[b] | **$NaNO_2$** (M)[b] | **$NaN_3$** (M)[b] | Yield[c,d] (%) |
|---|---|---|---|---|---|
| 1 | $NO_2$ **1a** | 0.8 | 0.816 | 1.2 | 82 |
| 2 | H **1b** | 1.69 | 1.73 | 2.5 | 71 |
| 3 | 4-Cl **1c** | 0.4 | 0.408 | 0.6 | 86 |
| 4[e] | 4-Cl **1c** | 0.4 | 0.408 | 0.6 | 88[f] |
| 5 | 4-Br **1d** | 0.4 | 0.408 | 0.6 | 79 |
| 6 | 4-$OCH_3$ **1e** | 0.4 | 0.408 | 0.6 | 99 |
| 7 | 4-$CH_3$ **1f** | 0.4 | 0.408 | 0.6 | 95 |
| 8 | 3,4,5-$(OCH_3)_3$ **1g** | 0.4 | 0.408 | 0.6 | 89 |
| 9 | 4-$CF_3$ **1h** | 0.2 | 0.204 | 0.3 | 95 |
| 10 | 4-$^t$Bu **1i** | 0.2 | 0.204 | 0.3 | 65 |

[a] Total flow rate at the T-junction: 0.05 mL/min, corresponding to 10 min residence time inside coil-reactor 1.
[b] Molarity values correspond to the concentration inside the syringe.
[c] Four reactor volumes were discarded before collection.
[d] Isolated yield; calculated as (mmol/min product) / (mmol/min reactant) × 100.
[e] α-Methylstyrene was used as the extracting solvent.
[f] Monitored by GC using biphenyl as the internal standard. Calculated as (mmol/min product) / (mmol/min reactant) × 100.

As already demonstrated [19], Ru(TPP)(CO) promoted the addition of aryl azides to α-methylstyrene under continuous-flow conditions in a PTFE tubing, working at 120 °C and 30 min residence time. 4-$NO_2$-aniline **1a** was efficiently converted into 4-$NO_2$-phenylazide **2a** (83% yield) and then into the corresponding aziridine **4a**. However, this second step proved to be less efficient than expected, and aziridine **4a** was obtained in 27% yield rather than 64% as we reported previously (Table 3, entry 1) [19]. We reasoned that the aqueous environment of the first reaction affected the catalyst performances. After the manual separation of the organic phase, the α-methylstyrene containing azide **2a** was treated with $Na_2SO_4$ and used in the aziridination reaction. We were pleased to find that aziridine **4a** was formed in 44% yield (Table 3, entry 2). Considering that HCl can have a deactivating catalytic role, we treated the α-methylstyrene solution of the azide with $Na_2SO_4$ and $Na_2CO_3$ in order to eliminate traces of water and HCl. After this treatment, we were able to improve aziridine **4a** yield up to 54% (Table 3, entry 3). The same treatment was applied to all the azides we screened.

The tested anilines readily reacted to afford *N*-aryl azides in high yields. The so-synthesized azides were converted in the presence of the ruthenium catalyst into the corresponding *N*-arylaziridines in very good yields (Table 3). It is noteworthy that by using this methodology we were able to prepare and react the potentially explosive phenylazide **2b** in a safe and efficient process, by handling very small volume of its solution in a continuous process without purification [22]. By using a dilute solution of aniline **1b** (0.4 M), it was possible to obtain azide **2b** in 64% and, consequently, *N*-phenylaziridine **4b** in 64% yield. As demonstrated previously, a more concentrated solution leads to a higher yield (see Table 2, entry 2). Halogens were also very well tolerated in both reactions. 4-Cl-phenylazide **2c** was obtained in 88% yield, and the corresponding aziridine **4c** in 71% yield after the second step (Table 3, entry 5). Similarly, 4-Br-phenylazide **2d** was obtained in 74% yield, and the corresponding aziridine **4d**, in 76% yield (Table 3, entry 6). Collected data are in good agreement with (and in some cases superior to) those reported in our previous work on the continuous-flow synthesis of *N*-arylaziridines promoted by Ru(TPP)CO catalyst [19].

It is noteworthy that the *N*-aryl azides prepared with this methodology and extracted by α-methylstyrene did not show any trace of triazoline, a typical byproduct of the spontaneous additions of azides to alkenes [18b, 23]. The formation of this byproduct was hampered by mixing the solution containing Ru(TPP)CO catalyst with the α-methylstyrene–azide mixture immediately after the azide extraction. This procedure limited the occurrence of the uncatalyzed reaction of azide with α-methylstyrene forming the corresponding triazoline.

It is important to underline that α-methylstyrene plays the double role, the reaction solvent and the reagent, allowing to form the desired aziridine product in a two-step procedure. The sustainability of the reported synthesis is assured by the recovery and recycle of α-methylstyrene by a simple distillation process at the end of the catalytic reaction.

**Scheme 2.** The two-step synthesis of aziridines starting from anilines under continuous-flow conditions

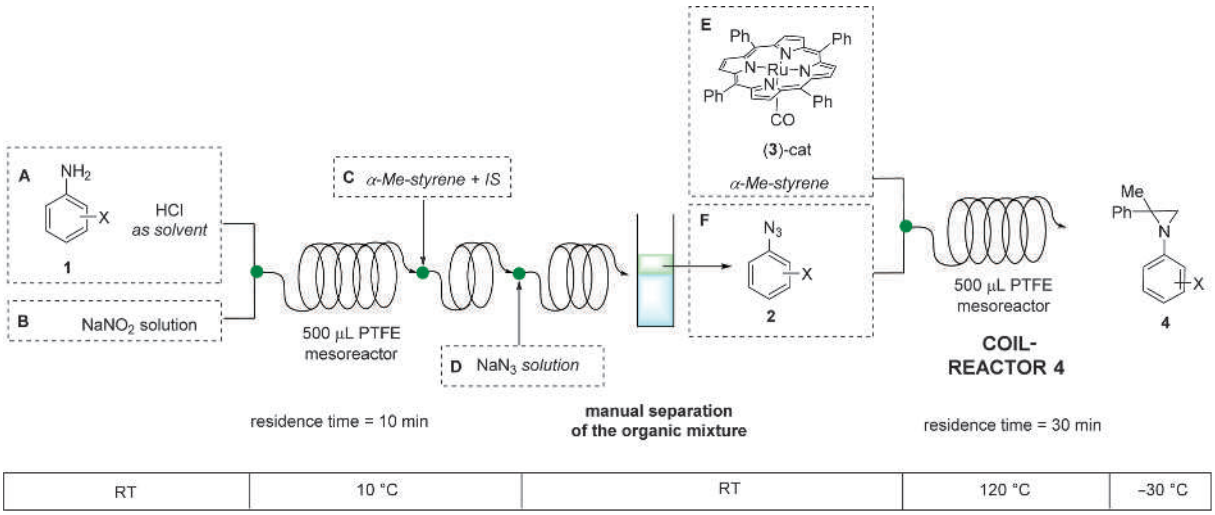
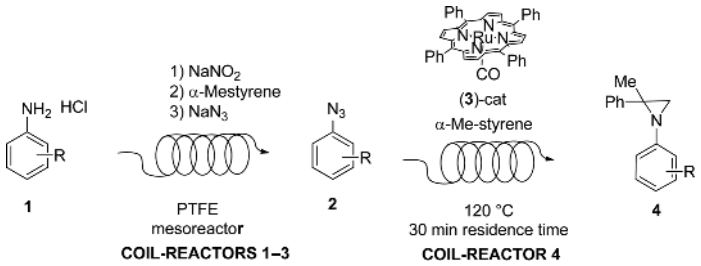



**Table 3.** Reaction of anilines **1** to afford *N*-arylaziridines **4**




| Entry[a] | R | Organic phase treatment | 1st Step yield[b,c] (%) | 2nd Step yield[d,e] (%) |
|---|---|---|---|---|
| 1 | $NO_2$ **1a** | – | 83 | 27 |
| 2 | $NO_2$ **1a** | $Na_2SO_4$ | 83 | 44 |
| 3 | $NO_2$ **1a** | $Na_2SO_4$ + $Na_2CO_3$ | 83 | 54 |
| 4 | H **1b** | $Na_2SO_4$ + $Na_2CO_3$ | 64 | 61[f] |
| 5 | 4-Cl **1c** | $Na_2SO_4$ + $Na_2CO_3$ | 88 | 71[f] |
| 6 | 4-Br **1d** | $Na_2SO_4$ + $Na_2CO_3$ | 74 | 76 |
| 7 | 4-$CF_3$ **1h** | $Na_2SO_4$ + $Na_2CO_3$ | 55[g] | 33[g] |

[a] [**1**] = 0.4 M except for entry 7 ([**1h**] = 0.2 M). Molarity values correspond to the concentration inside the syringe; concentration of reactants was calculated accordingly.
[b] Monitored by GC using biphenyl as the internal standard. Calculated as (mmol/min azide **2**) / (mmol/min aniline **1**) × 100.
[c] Total flow rate at the T-junction: 0.05 mL/min, corresponding to 10 min residence time inside coil-reactor 1.
[d] Monitored by GC using biphenyl as the internal standard. Calculated as (mmol/min aziridine **4**) / (mmol/min azide **2**) × 100.
[e] Total flow rate at the T-junction: 0.0168 mL/min, corresponding to 30 min residence time inside coil-reactor 4.
[f] Calculated by $^1$H-NMR using 2,5-dinitrotoluene as an internal standard.
[g] Monitored by IR.

## 3. Conclusions

In conclusion, a straightforward two-step synthesis of *N*-arylaziridines starting from anilines was efficiently performed in mesoreactors under continuous-flow conditions. The synthesis and extraction of aryl azides were studied and quickly optimized, thanks to the fluidic device. The combination with the continuous-flow Ru(porphyrin)CO-catalyzed addition of the prepared azides to styrenes to afford *N*-arylaziridines was also successfully accomplished. The combination of the two steps into a single process allowed for a safe and efficient synthesis of aziridines, useful building blocks for organic synthesis. The use of α-methylstyrene as an extracting solvent for the azides was the key feature of this system: α-methylstyrene can act both as the reaction partner and the solvent in the aziridination step, thus, realizing a sustainable process where the α-methylstyrene excess can be easily recovered by distillation and recycled. This study shows the potentiality of the multistep synthesis performed in home-made mesoreactors with a very simple equipment, commonly available in organic laboratories. Even if this system needs some improvements, we believe that it can be considered a good starting point to develop multistep, efficient, and sustainable processes.

## 4. Experimental

Proton NMR spectra were recorded on spectrometers operating at 300 MHz (Bruker Fourier 300 or AMX 300) or at 500 MHz (Bruker Avance 500). Proton chemical shifts are reported in ppm ($\delta$) with the solvent reference relative to tetramethylsilane (TMS) employed as the internal standard ($CDCl_3$ $\delta$ = 7.26 ppm). $^{13}$C NMR spectra were recorded operating at 75 MHz, with complete proton decoupling. Carbon chemical shifts are reported in ppm ($\delta$) relative to TMS with the respective solvent resonance as the internal standard ($CDCl_3$, $\delta$ = 77.0 ppm). $^{19}$F NMR spectra were recorded operating at 282 MHz. Fluorine chemical shifts are reported in ppm ($\delta$) relative to $CF_3Cl$. GC analysis was performed using Agilent 6850 single channel GC system with a flame

ionization detector (FID). Infrared (IR) analysis was performed using a Varian Scimitar FTS 1000 spectrophotometer. Mesoreactor was prepared using PTFE tubing for HPLC connections purchased from Supelco.

Solvents were freshly distilled under $CaH_2$ prior to use by standard procedures and stored under nitrogen. All starting anilines were commercial products and were purified by distillation or crystallization. [Ru(β-$Ph_4$TPP)(CO)] [18a] was synthesized according to literature procedure.

Caution: Although no safety problems were encountered during work with azides, precautions against possible explosion should be implemented when handling it dry or suspended in solution. A plastic spatula is used to weigh out sodium azide; the use of metal spatulas should be avoided. Azides and their intermediates were handled with adequate shielding and standard protective equipment.

**4.1. General Procedure for the Synthesis of 4-$NO_2$-phenylazide 2a under Continuous-Flow Conditions.** A fluidic device composed by coil-reactor 1, coil-reactor 2, and coil-reactor 3 was used.

In a typical experiment, syringe A was filled with a solution obtained by dissolving 2 mmol (276.2 mg) of 4-$NO_2$-aniline in 5 mL of fresh prepared 2.5 M HCl. The final mixture (0.4 M for 4-$NO_2$-aniline) was sonicated for 20 min prior to use. Syringe B was filled with a solution obtained by dissolving 2.04 mmol (140.7 mg) of $NaNO_2$ in 5 mL of water. The syringe was then connected to a syringe pump, and the reagents were fed into the coil-reactor 1 cooled to 10 °C at the desired flow rate (0.025 mL/min for 10 min residence time).

Syringe C containing 0.08 mmol of biphenyl (internal standard, 12.36 mg) dissolved in 10 mL of α-methylstyrene (0.008 M) was connected at the end of coil-reactor 1 with a T-junction, and the reagents were fed into the coil-reactor 2 cooled to 10 °C at the desired flow rate (0.1 mL/min). The presence of internal standard (IS) was omitted when the solvent is methyl *t*-butyl ether (MTBE).

Syringe D containing 6 mmol (390.1 mg) of $NaN_3$ dissolved in 10 mL of water was connected at the end of coil-reactor 2 with a T-junction, and the reagents were fed into the coil-reactor 3 at the desired flow rate (0.1 mL/min) at room temperature. The biphasic reaction outcome was then collected at the end of coil-reactor 3 into a vial. After the desired time, the mixture was separated and the organic phase was collected, dried with $Na_2SO_4$, treated with $Na_2CO_3$, filtered using a CHROMAFIL® syringe filter (0.45 μm NYLON), and analyzed through GC. Four reactor volumes were discarded before starting sample collections in order to achieve steady-state conditions.

**4.2. General Procedure for the Two-Step Synthesis of Aziridines under Continuous-Flow Conditions.** A fluidic device composed by coil-reactor 1, coil-reactor 2, coil-reactor 3, and coil-reactor 4 was used.

In a typical experiment, syringe A was filled with a solution obtained dissolving 2 mmol of the desired aniline in 5 mL of freshly prepared 2.5 M HCl. The final solution (0.4 M in aniline) was sonicated for 20 min prior to use. Syringe B was filled with a solution obtained dissolving 2.04 mmol (140.7 mg) of $NaNO_2$ in 5 mL of water. The syringe was then connected to a syringe pump, and the reagents were fed into the coil-reactor 1 cooled to 10 °C with 0.025 mL/min as flow rate (10 min residence time).

Syringe C containing 0.08 mmol of biphenyl (internal standard, 12.36 mg) dissolved in 10 mL of α-methylstyrene (0.008 M) was connected at the end of coil-reactor 1 with a T-junction, and the reagents were fed into the coil-reactor 2 cooled to 10 °C with 0.1 mL/min as flow rate. Syringe D containing 6 mmol (390.1 mg) of $NaN_3$ dissolved in 10 mL of water was connected at the end of coil-reactor 2 with a T-junction, and the reagents were fed into the coil-reactor 3 with 0.1 mL/min as flow rate at room temperature. The biphasic reaction outcome was then collected at the end of coil-reactor 3 into a vial. After the desired time, the mixture was manually separated and the organic phase was collected, dried with $Na_2SO_4$, treated with $Na_2CO_3$, filtered using a CHROMAFIL® syringe filter (0.45 μm NYLON), and analyzed by GC or IR. The same mixture was then loaded into syringe F. Four reactor volumes were discarded before starting sample collections in order to achieve steady-state conditions.

Syringe E was filled with a solution obtained dissolving 0.005 mmol of [Ru(β-$Ph_4$TPP)(CO)] (3.78 mg, 1:50 [catalyst]:[azide] ratio) in 2.5 mL of α-methylstyrene. The mixture was sonicated for 10 min and heated until a complete dissolution of the catalyst. Syringes E and F were connected to a syringe pump, and the reagents were pumped into PTFE mesoreactor through a T-junction at 0.0084 mL/min as flow rate (30 min as residence time). One reactor volume was discarded before starting sample collection in order to achieve steady-state conditions. Reaction outcome was collected into a vial cooled at −30 °C and directly analyzed by GC or $^1$H NMR (using 2,5-dinitrotoluene as an internal standard).

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## Supporting Information

Electronic Supplementary Material (ESM) (details for the flow setup, catalytic experiments, analysis, and characterization of the reaction products, GC traces) associated with this article can be found in the online version at doi: 10.1556/1846.2016.00027.

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