



# Continuous-Flow Divergent Lithiation of 2,3-Dihalopyridines: Deprotolithiation versus Halogen Dance

Thibaud Brégent, Maria Ivanova, Thomas Poisson, Philippe Jubault, Julien Legros

## ► To cite this version:

Thibaud Brégent, Maria Ivanova, Thomas Poisson, Philippe Jubault, Julien Legros. Continuous-Flow Divergent Lithiation of 2,3-Dihalopyridines: Deprotolithiation versus Halogen Dance. Chemistry - A European Journal, In press, <10.1002/chem.202202286>. <hal-03838955>

**HAL Id: hal-03838955**

**<https://hal.science/hal-03838955v1>**

Submitted on 3 Nov 2022

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



HAL Authorization

# Continuous Flow Divergent Lithiation of 2,3-Dihalopyridines, Deprotolithiation versus Halogen Dance

This manuscript is dedicated to Professor Guy Quéguiner for his outstanding contribution to the chemistry of pyridine.

Thibaud Brégent,<sup>[a]</sup> Maria V. Ivanova,<sup>[a]</sup> Thomas Poisson,<sup>\*,[a],[b]</sup> Philippe Jubault<sup>\*,[a]</sup> and Julien Legros<sup>\*,[a]</sup>

[a] Dr. T. Brégent, Dr. M. V. Ivanova, Prof. Dr. T. Poisson, Prof. Dr. P. Jubault, Dr. J. Legros  
Normandie Univ., INSA Rouen, UNIROUEN, CNRS, COBRA (UMR 6014), 76000 Rouen, France.  
[thomas.poisson@insa-rouen.fr](mailto:thomas.poisson@insa-rouen.fr); [philippe.jubault@insa-rouen.fr](mailto:philippe.jubault@insa-rouen.fr); [julien.legros@univ-rouen.fr](mailto:julien.legros@univ-rouen.fr)

[b] Prof. Dr. T. Poisson  
Institut Universitaire de France, 1 rue Descartes, 75231 Paris, France.

Supporting information for this article is given via a link at the end of the document.

**Abstract:** We describe herein the first Halogen Dance (HD) in continuous flow on 2-chloro-3-bromopyridine by trapping selectively (pyridin-4-yl)lithium species that is known to undergo halogen dance process. In addition, this lithiated intermediate was trapped at lower temperature before the HD occurs. The HD process has been extended to fluoro-iodopyridines using various electrophiles to afford 28 examples with yields ranging from 42% to 97% with very short residence times. Finally, the scale up of the reaction was demonstrated, affording a promising space-time yield (STY) of 4.2 kg.h<sup>-1</sup>.L<sup>-1</sup>.

## Introduction

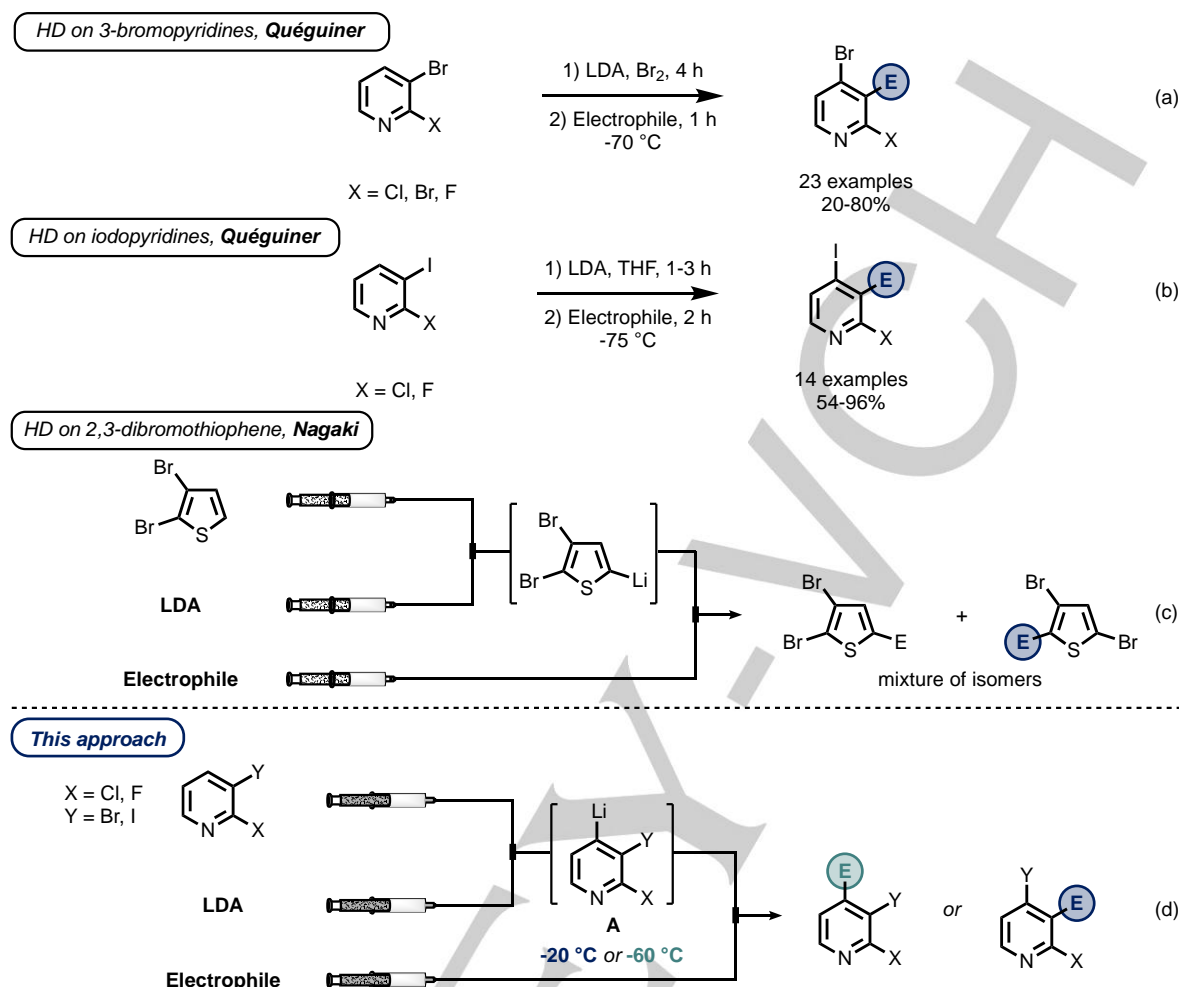
Pyridine motifs are important building blocks for organic chemists and is a prominent scaffold found in plethora of bioactive molecules (e.g. Lansoprazole, Crizotinib or Regorafenib).<sup>[1]</sup> Indeed, many pyridine derivatives have been shown to be efficient in the treatment of cancer, for instance.<sup>[2]</sup> Hence, the development of efficient methods to synthesize or to build-up polyfunctionalized pyridine derivatives is still of high demand to broaden the current arsenal of synthetic tool available to the organic practitioners.

Continuous flow chemistry<sup>[3]</sup> is a well-recognized manifold to address transformations that are tedious to control in batch such as reactions involving highly reactive species (e.g. radicals, carbene or organolithium reagents). Among these reactions, tackling the formation of highly reactive and sensitive organometallic intermediates remains a challenge for organic chemists and within this context continuous flow process appears as a tool of choice. Indeed, the continuous flow conditions allow an easier and better control of the formation of these highly reactive species by adjusting thoroughly the residence time and the temperature of the reactor. This fine-control of the parameters is facilitated with microreactors rather than with batch reactors.<sup>[4,5]</sup> Over the last few years, Yoshida and others studied the formation of organolithium species in microflow reactors and their subsequent trapping with various electrophiles, addressing major synthetic challenges.<sup>[6]</sup>

Among these transformations involving highly reactive organolithium species, the halogen dance (HD),<sup>[7]</sup> which was widely studied on haloaromatics,<sup>[8]</sup> and heterocycles<sup>[9]</sup> is an appealing transformation to increase the molecular complexity. This particular reaction required a careful control of the reaction time and temperature, and is therefore an excellent candidate to develop under continuous flow to facilitate its scale-up and possible use in large scale. Indeed, the deprotolithiation of halogenated (hetero)aromatic derivatives provides access to different organolithium intermediates (kinetic or thermodynamic), depending on the reaction conditions, since the dance of the halogen atom is driven by the stability of the resulting organolithium species. Herein, we aimed at controlling the selective formation of these species by taking advantage of the continuous flow chemistry, which would allow a perfect control of the residence time and the reaction temperature. Concerning pyridine derivatives, the halogen dance reaction was mostly studied by Quéguiner and co-workers on halopyridines (Scheme 1 eq. (a) & (b)).<sup>[10,11]</sup> The reaction with 2-halo-3-bromo and 2-halo-3-iodopyridine, carried out in batch with LDA (lithium diisopropylamide) as the base, required very low reaction temperature (-70 °C) to minimize the side-products formation. Indeed, the products resulting from the HD (i.e. the 4-halopyridines) were highly sensitive to the presence of the base at higher temperature. These prerequisites to succeed in the HD reaction on pyridines, strongly hamper its application on a large scale, despite its undisputable synthetic interest in the elaboration of polyfunctionalized pyridine derivatives.

It is also important to mention the recent report from Nagaki, who reported the continuous flow deprotolithiation using LDA on 2,3- and 2,5-dibromothiophene derivatives (Scheme 1, eq (c)).<sup>[12]</sup> This report clearly highlighted the challenging and tedious control of the formation of lithiated species, even in continuous flow at very low temperature and with very short residence times.

As a part of our ongoing interest in the development of continuous flow transformations,<sup>[13]</sup> we sought to develop an efficient and general method to control the lithiation on halopyridines in continuous flow, either by trapping the initial lithiated species **A** or by promoting the HD event (Scheme 1, eq (d)).

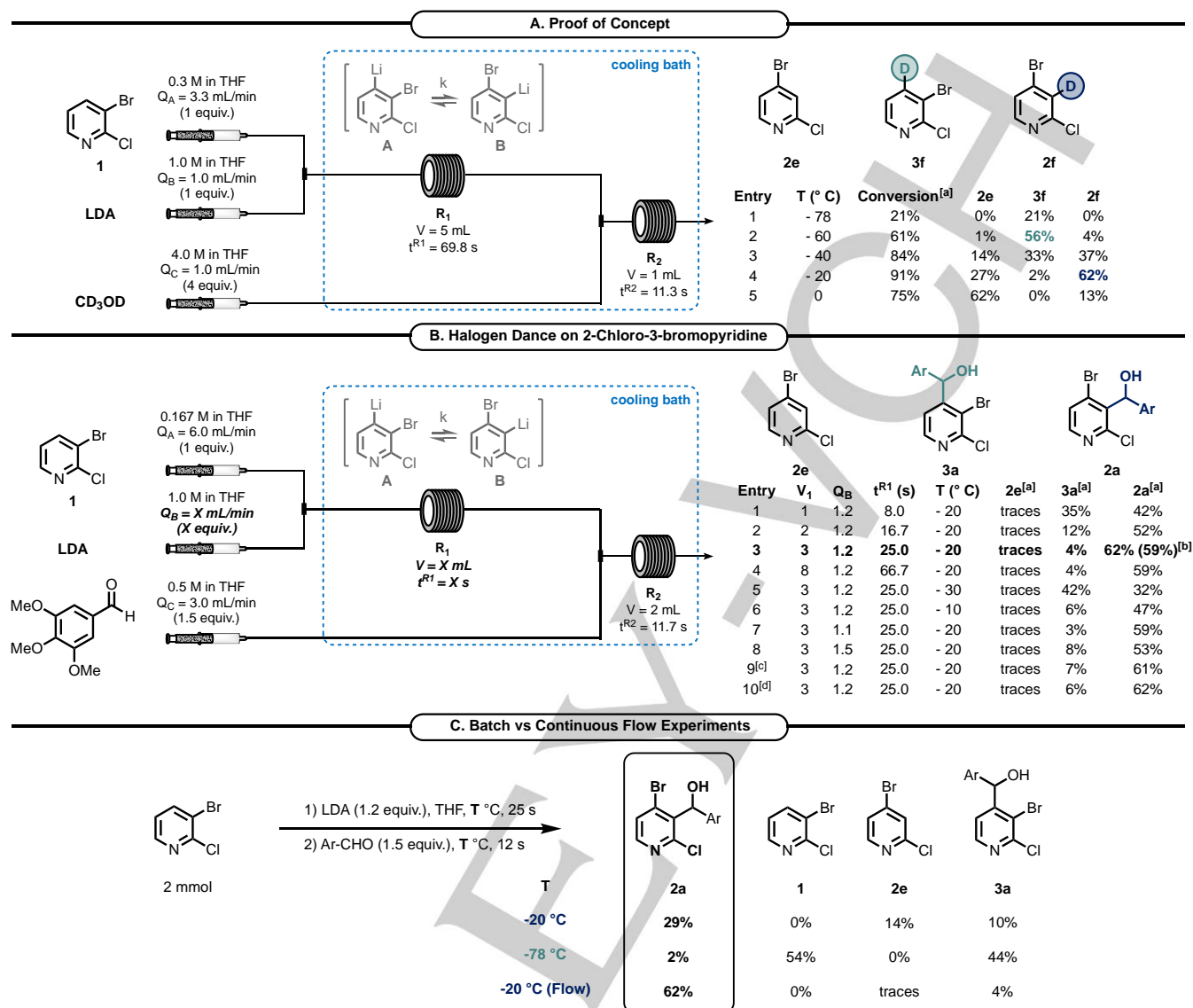


Scheme 1. State of the art and Present work.

## Results and Discussion

At the beginning of this project, we selected the commercially available 2-chloro-3-bromopyridine **1** as the model substrate to study the deprotometalation reaction. At the outset of our investigations, we paid attention on the effect of the reaction temperature and of the residence time, which are known as crucial parameters in organolithium chemistry.<sup>[14]</sup> Indeed, we conjectured that these two crucial parameters would permit to finely control the selectivity of the reaction toward either the HD product or the product resulting from the deprotolithiation, *i.e.* the most difficult to access. First, the temperature of the reaction with **1** and LDA was studied. We investigated the formation of the intermediate **A**, in equilibrium with the product **B**, generated in the presence of LDA and its subsequent trapping with deuterated methanol as the electrophile at various temperatures

to control the selectivity of the metalation reaction **2f** (Scheme 2A). As initial conditions to start our endeavor, we fixed the flow rate of the 0.3 M solution of 2-chloro-3-bromopyridine in THF to 3.3 mL/min. The freshly prepared 1.0 M solution of LDA was setting to a flow rate of 1.0 mL/min (1.0 equiv.) and the 4.0 M deuterated methanol solution in THF to 1.0 mL/min (4 equiv.). First, the temperature of the reactor was set at -78 °C and a 21% conversion into the 4-*D*-pyridine **3f**, resulting from the *ortho*-lithiation of the starting material **1**, was measured without trace of the expected compound **2f** (Scheme 2A, entry 1). Then, we screened different temperatures from -60 to 0 °C. We noticed that the selectivity of this reaction was highly temperature dependent. Indeed, at lower temperature (-60 °C) the major product was the 2-chloro-3-bromo-4-*d*-pyridine **3f** (Scheme 2A, entry 2), while at -20 °C the desired HD product **2f**, resulting from the halogen dance turned out to be the major one,



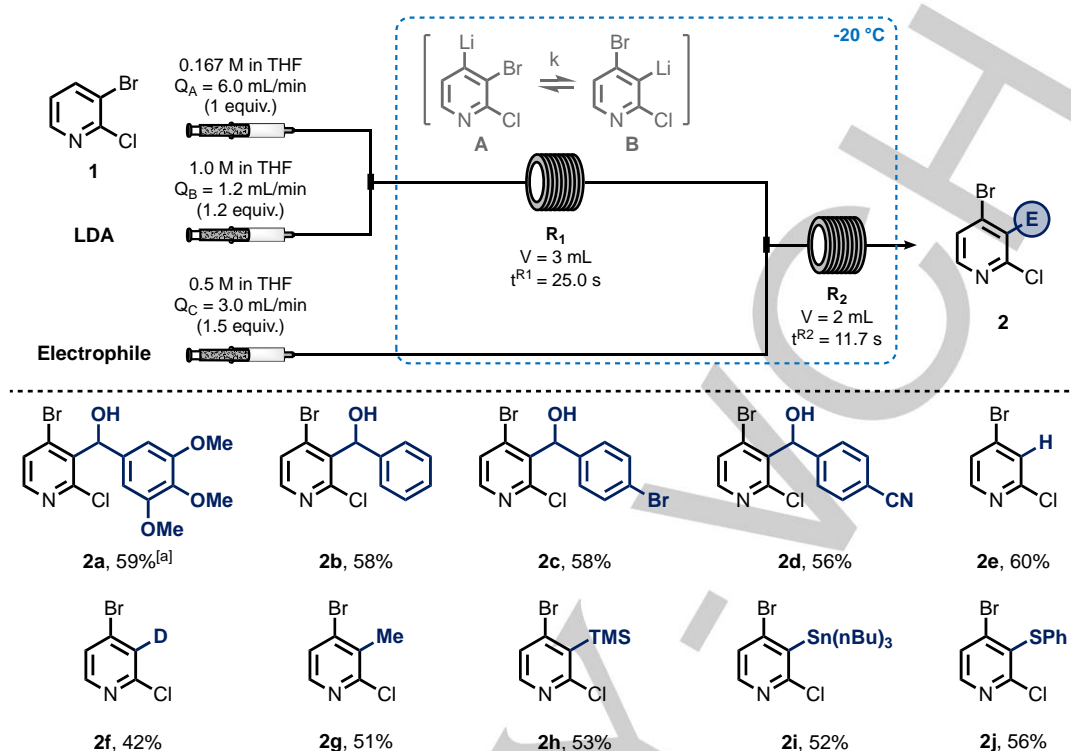
**Scheme 2.** A. Study of the temperature effect – Proof of concept. Ø1 mm PFA tubing. <sup>a</sup> Determined by <sup>1</sup>H NMR using nitromethane as internal standard. B. Optimization of halogen dance on 2-chloro-3-bromopyridine. <sup>[a]</sup> Determined using MeNO<sub>2</sub> as <sup>1</sup>H NMR internal standard. <sup>[b]</sup> Isolated yield. <sup>[c]</sup> [Electrophile] = 0.3 M, Q<sub>C</sub> = 5 mL/min, V<sub>C</sub> = 3 mL. <sup>[d]</sup> Q<sub>C</sub> = 4 mL/min (2 equiv.). C. Batch vs continuous flow experiments. Ar = 3,4,5-(OMe)<sub>3</sub>-C<sub>6</sub>H<sub>2</sub>.

clearly showcasing the deprotonated product as the kinetic product and the HD product as the thermodynamic one (Scheme 2A, entry 4). Encouraged by this promising result, we thought to develop a divergent process allowing either access to the functionalized 3-halo or to the 4-halo regioisomer by adjusting the reaction temperature. Following the proof of concept obtained with methanol-*D*<sub>4</sub> (Scheme 2A, entry 4), we moved on the optimization of the halogen dance reaction conditions by adjusting several parameters such as the residence time, concentrations, and flow rates as well as the stoichiometry of the electrophile (Scheme 2B). As part of the development of a divergent process, we also have optimized the reaction conditions allowing access to the 4-regioisomer **3**.<sup>[15]</sup> The flow rate of the 2-chloro-3-bromopyridine solution (0.167 M in THF) was set at a 6.0 mL/min flow rate. The concentration of the LDA solution was unchanged and the 0.5 M electrophile solution

in THF (1.5 equiv.) was set to 3.0 mL/min flow rate. For practical reasons, the 3,4,5-trimethoxybenzaldehyde was chosen as a model electrophile. The variation of the residence time (*t*<sup>R1</sup>) allowed us to demonstrate that the formation of the desired HD product **2a** as well as the complete conversion of the starting material was favored with a residence time of 25 seconds (Scheme 2B, entries 1-4). Then, a survey of the temperature of the reaction was achieved. The optimal temperature was -20 °C, since experiments carried out at -10 °C or -30 °C did not improve the conversion of **1** into the HD product **2a** (Scheme 2B, entries 5-6). Similarly, the variation of the LDA or electrophile stoichiometry did not improve the efficiency of the process (Scheme 2B, entries 7-10).

Prior the extension and the evaluation of the scope of the reaction, we decided to showcase the efficiency and the added

value of the developed reaction through the comparison of the reactions carried out in continuous flow vs batch conditions to



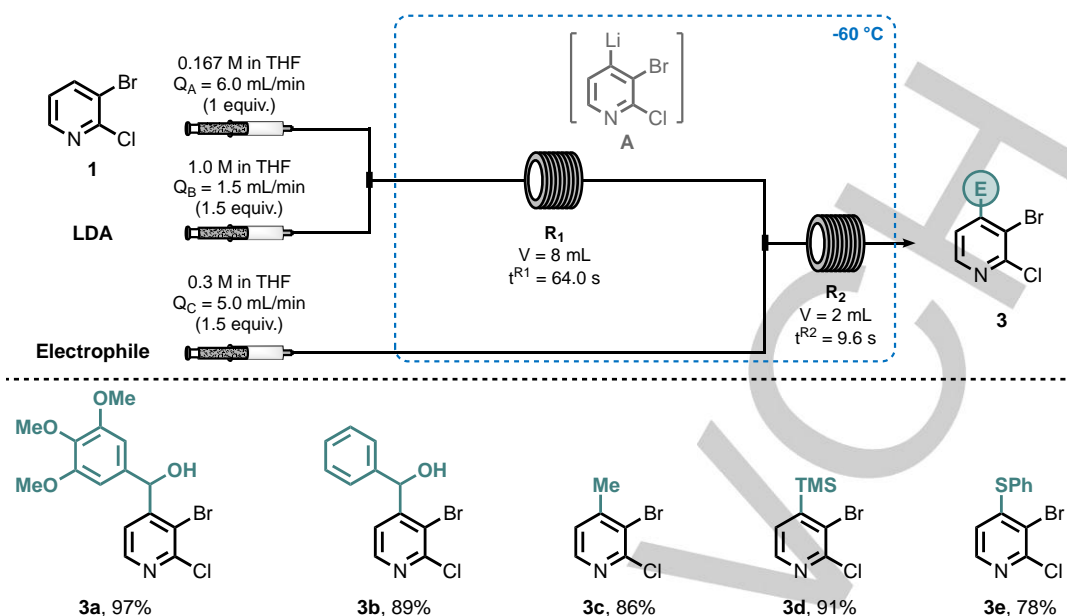
**Scheme 3.** Continuous flow halogen dance on 2-chloro-3-bromopyridine. <sup>[a]</sup> The same yield was obtained using commercially available LDA 1.0 M in THF/hexanes.

access the product **2a** (Scheme 2C). In that purpose, we ran two experiments at  $-78\text{ }^{\circ}\text{C}$  and  $-20\text{ }^{\circ}\text{C}$  (the most efficient temperature in flow conditions, see Scheme 2B, entry 3) in batch keeping the same reaction times as those in flow ( $t_{R1} = 25\text{ s}$  and  $t_{R2} = 12\text{ s}$ ).<sup>[15]</sup> At  $-20\text{ }^{\circ}\text{C}$ , a mixture of 29% of **2a** with 14% of **2e** and 10% of **3a** (total conversion of **1**) was obtained. Moreover, the crude reaction mixture was quite messier than the one resulting from the reaction conducted under continuous flow. At  $-78\text{ }^{\circ}\text{C}$ , merely 46% conversion was observed with 2% of the expected pyridine **2a** and 44% of the 4-functionalized 3-halopyridine **3a**. These observations highlighted two major points: 1) the regioselectivity of the process is dependent of the reaction temperature, even in batch, and 2) the use of continuous flow chemistry is significantly powerful for such transformation, shortening the reaction time, while allowing an increase of the reaction temperature ( $-20\text{ }^{\circ}\text{C}$  compared to  $-78\text{ }^{\circ}\text{C}$  used in the literature for HD processes), which allows a possible implementation of the process at a larger scale.

Then, having these optimized flow conditions in hand, we evaluated the scope of this continuous flow halogen dance protocol (Scheme 3). The use of different benzaldehyde derivatives as the electrophile was well tolerated to afford corresponding HD products with moderate to good yields, as a

single regioisomer (**2a-d**). The presence of other functional groups such as a bromine atom or a nitrile group did not affect the efficiency of the reaction, and no side-product resulting from the presence of these substituents was identified in the crude reaction mixture. It is also important to note that commercially available 1.0 M LDA in THF/hexanes could be used without loss of efficiency instead of freshly prepared LDA. Methanol and methanol- $d_4$  were used to protonate or deuterate, respectively, the pyridine-3-yl lithiated species **A** in moderate to good yields (**2e-f**). Thereafter, other electrophiles were tested like iodomethane, trimethylsilyl chloride, tri-*n*-butyltin chloride as well as diphenyldisulfide to access the corresponding pyridines **2g-j** with good yields. It is important to mention that the presence of a chlorine atom at the 2 position on the pyridine ring is known to alter the halogen dance reaction, as proved by Quéguiner and co-workers.<sup>[11b]</sup> Indeed, in contrast to the 2-fluoro analogue, the pyridine-3-yl lithiated species is less stable, since it is prone to form the corresponding 2,3-pyridyne, which could explain some moderate yields on this 2-chloropyridine series.

To pursue our work on 2-chloro-3-bromopyridine, we extended the process to the formation of other regioisomer, *i.e.* the 4-substituted-3-bromo-2-chloropyridines by performing the reaction at  $-60\text{ }^{\circ}\text{C}$  (Scheme 4).

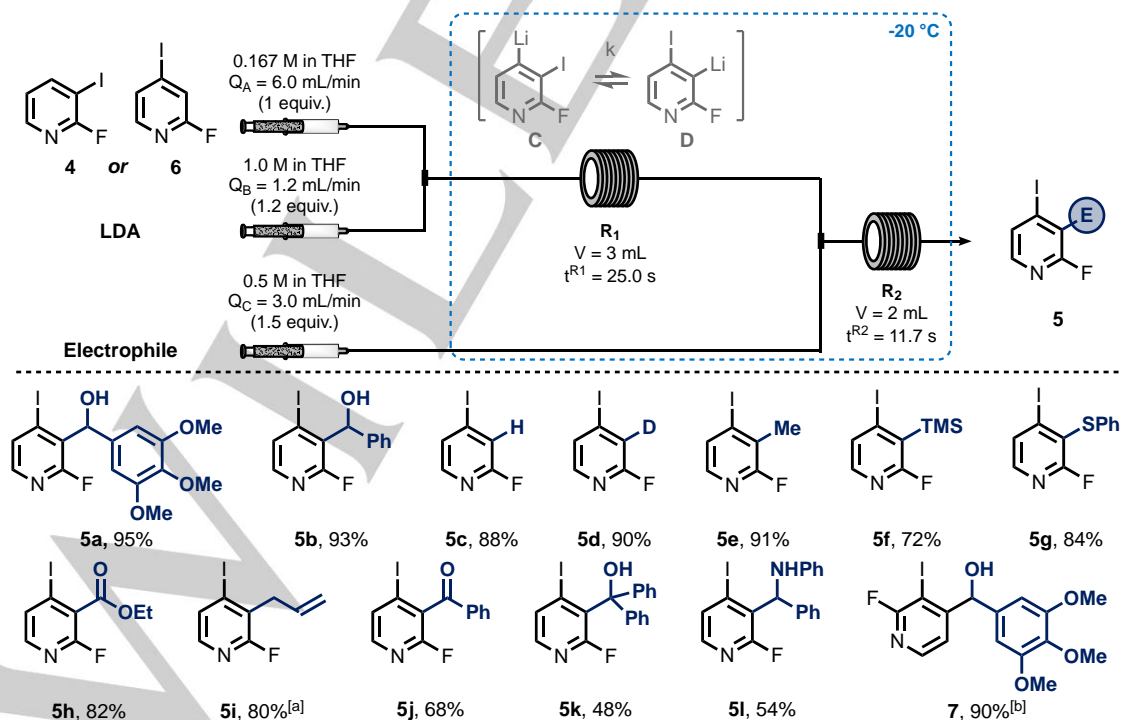


**Scheme 4.** Continuous flow deprotonation with LDA on 2-chloro-3-bromopyridine.

Thus, to conduct this reaction we have slightly modified the previously optimized conditions (Table 2, entry 3). The residence time  $t^{R1}$  has been increased to 64 seconds and the concentration of the electrophile decreased to 0.3 M to avoid any issue of crystallization in the tubes at  $-60$  °C for solid electrophiles such as 3,4,5-trimethoxybenzaldehyde and

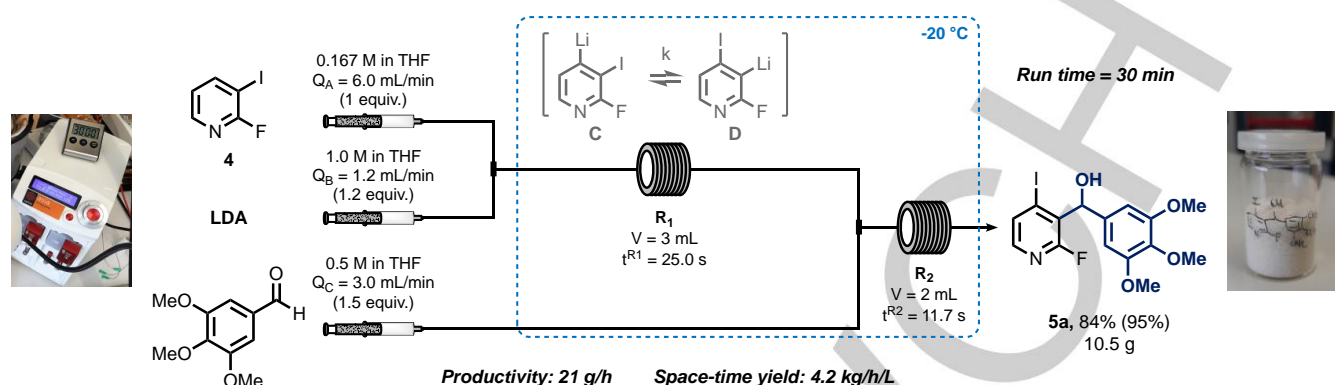
diphenyldisulfide. To keep the same pyridine/electrophile ratio, the flow rate ( $Q_C$ ) was adjusted to 5.0 mL/min (1.5 equiv.) without loss of efficiency.

With this set of conditions in hand, we were able to demonstrate the robustness of our methodology with a selection of electrophiles to trap the pyridin-4-yllithium A.



**Scheme 5.** Continuous flow halogen dance on 2-fluoro-3-iodopyridine (4) and 3-fluoro-4-iodopyridine (6). <sup>[a]</sup> [Electrophile] = 1.67 M,  $t^{R2} = 29.4$  s. <sup>[b]</sup> 6 was used.





**Scheme 6.** Large scale continuous flow halogen dance on 2-fluoro-3-iodopyridine trapped with 3,4,5-trimethoxybenzaldehyde.

The corresponding pyridines derivatives were obtained in good (**3e**) to excellent yields (**3a-d**) as a single regioisomer.

To further expand our methodology, we moved on to the study of the continuous flow lithiation of the 2-fluoro-3-iodopyridine **4** (Scheme 5). To start our investigations, we trapped the pyridine-3-yllithium species **D** with the electrophile which has previously proven to be the most efficient, the 3,4,5-trimethoxybenzaldehyde. Interestingly, the result turned out to be excellent, giving access to the corresponding pyridine **5a** with 95% isolated yield. Subsequently, to evaluate the efficiency of our protocol, the reaction was extended to the introduction of other electrophiles. We tested some electrophiles previously used in the functionalization of pyridine **1** such as benzaldehyde (**5b**), methanol (**5c**), methanol- $d_4$  (**5d**), iodomethane (**5e**), trimethylsilyl chloride (**5f**) and diphenyldisulfide (**5g**). All yields were very good to excellent (84-95%) except for the silylated derivative **5f**, for which a good yield of 72% was obtained. Afterward, we selected other electrophiles like ethyl cyanoformate (**5h**) and allyl bromide (**5i**) to further broaden the scope of the reaction. While the yield of the ethyl 2-fluoro-3-iodonicotinate **5h** was fairly good, we had to slightly adjust the reaction conditions to obtain **5i** with a decent yield of 80%. In fact, the concentration of the electrophile solution in THF was increased to 1.67 M and the volume of the second reactor was changed to 5 mL ( $t^{R2} = 29.4$  s) to avoid as much as possible the formation of an impurity resulting from the protonation of the lithiated intermediate **D** (product **5c**). Finally, we tested the reaction of the 3-fluoro-4-iodopyridine **6** as a new substrate with the 3,4,5-trimethoxybenzaldehyde as the electrophile. The desired product was isolated with an excellent 90% isolated yield (**7**). As with the 2-chloro-3-bromopyridine, we tried to trap the intermediate **C** at  $-60\text{ }^\circ\text{C}$ , prior the halogen dance, using the previously optimized conditions (Scheme 4). Unfortunately, we have not been able to promote the direct trapping of the kinetic lithiated species. This reaction demonstrated that the HD process was much faster on the 2-fluoro-3-iodopyridine affording to a mixture of the starting pyridine **4** (22%), the HD product **5a** as the major product (68%) and the expected compound in a very low amount (10%). Unfortunately, all attempts to favor the trapping of the kinetic lithiated species were unsuccessful,

clearly highlighting the fast formation of the thermodynamically favored lithiated species **5a**, even at very low temperature, within short residence time. This result showcases a limitation of the reported methodology under continuous flow conditions.

Finally, we aimed at demonstrating the synthetic interest of our methodology. Indeed, it is well recognized that the implementation of process on large scale using lithiated species might be tedious, particularly due to the use of drastic cryogenic conditions and the accumulation of highly reactive and/or pyrophoric species. Hence, we showcased the possible implementation of this protocol on a larger scale. In order to ensure the practicality of our new method, we investigated the continuous halogen dance with a run time of 30 min (equivalent to 30 mmol,  $Q_A = 1$  mmol/min) with our optimized flow conditions on 2-fluoro-3-iodopyridine trapped by 3,4,5-trimethoxybenzaldehyde (Scheme 6). In that purpose, we took advantage of Syrris ASIA pumps in order to engage a larger amount of solution, unlike the syringe pumps used up previously.<sup>[15]</sup> Pleasingly, we were able to obtain the desired pyridine **5a** with an excellent  $^1\text{H}$  NMR yield of 95% and a very good isolated yield of 84% (10.5 g in 30 minutes). Note that no clogging, nor leak within the reaction setup has been witnessed. Pleasingly, using these conditions the production is 21 g per hour and the space-time ratio is 4.2 kg per hour per liter. It also should be noted that the THF used here is commercially available dry THF and not the freshly distilled THF previously used, without loss of efficiency.<sup>[15]</sup>

## Conclusion

In conclusion, we developed herein the selective lithiation of 2,3-dihalopyridines, under continuous flow conditions. Pleasingly, depending on the reaction conditions, we have been able to selectively trap the thermodynamically favored pyridine-4-yllithium species, resulting from the halogen dance, with various electrophiles. The products were isolated with good to excellent yields as single regioisomers. A simple adjustment of the reaction temperature allowed the trapping of the kinetically favored lithiated species, which after trapping with various electrophiles led to the 4-functionalized-2,3-dihalopyridine

derivatives in excellent yields. In summary, we took advantage of the continuous flow chemistry to control the selectivity of the lithiation of 2,3-dihalo-pyridine toward either the deprotonolithiation product or the HD product. This methodology represents a unique example of selective lithiation of pyridine derivatives under continuous flow. We believe that this novel protocol will find application in process and inspire further developments in the field to forge compounds of interest.

## Acknowledgements

This work is part of the API program supported by the European Community through the operational program FEDER/FSE 2014-2020 (n°20E04976) and FNADT-DRAC CAR E program 2020-2023 (N)15179). It has been partially supported by University of Rouen Normandy, INSA Rouen Normandy, the Centre National de la Recherche Scientifique (CNRS), Labex SynOrg (ANR-11-LABX-0029), Carnot Institute I2C, the graduate school for research XL-Chem (ANR-18-EURE-0020 XL CHEM), and by Région Normandie. T. P. thanks the Institut Universitaire de France (IUF) for support.

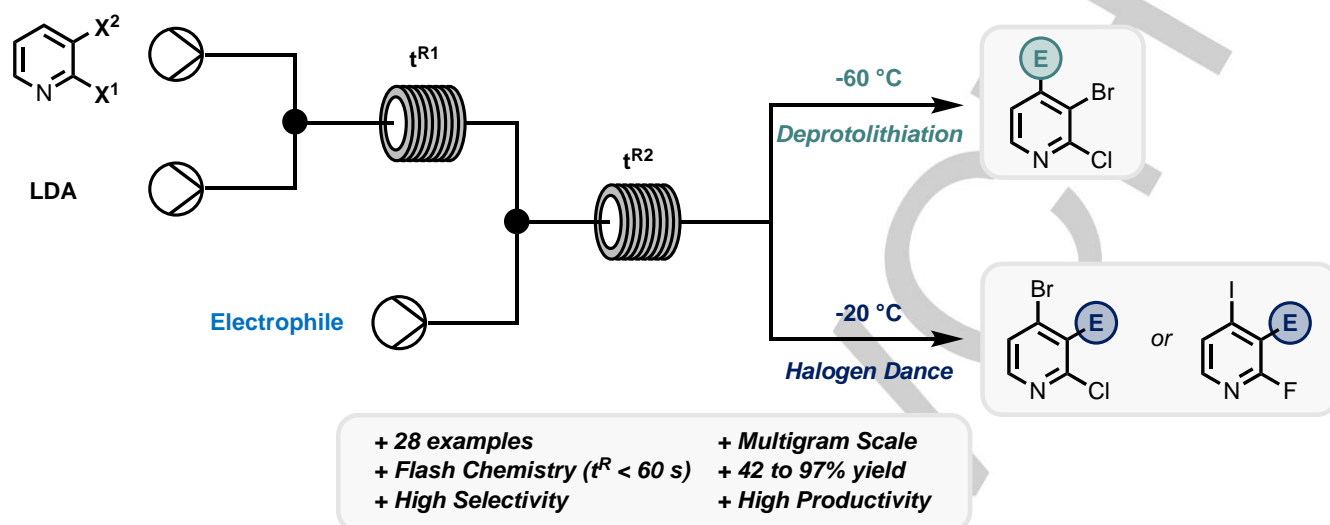
**Keywords:** lithiation • continuous flow • flash chemistry • pyridines • halogen dance

- [1] a) El-Sayed, H. A.; Moustafa, A. H.; El-Torky, A. E.; Abd El-Salam, E. A. *Russ. J. Gen. Chem.* **2017**, *87*, 2401-2408. b) Gerloff, J.; Mignot, A.; Barth, H.; Heintze, K. *Eur. J. Clin. Pharmacol.* **1996**, *50*, 293-297. c) Zou, H. Y.; Li, Q.; Lee, J. H.; Arango, M. E.; McDonnell, S. R.; Yamazaki, S.; Koudriakova, T. B.; Alton, G.; Cui, J. J.; Kung, P.-P.; Nambu, M. D.; Los, G.; Bender, S. L.; Mroczkowski, B.; Christensen, J. G. *Cancer Res.* **2007**, *67*, 4408-4417. d) Strumberg, D.; Scheulen, M. E.; Schulteis, B.; Richly, H.; Frost, A.; Büchert, M.; Christensen, O.; Jeffers, M.; Heinig, R.; Boix, O.; Mross, K. *Regorafenib Br. J. Cancer* **2012**, *106*, 1722-1727.
- [2] Sahu, R.; Mishra, R.; Kumar, R.; Salahuddin; Majee, C.; Mazumder, A.; Kumar, A. *Mini Rev. Med. Chem.* **2022**, *22*, 248-272.
- [3] For selected reviews on flow chemistry: a) Wegner, J.; Ceylan, S.; Kirschning, A. *Adv. Synth. Catal.* **2012**, *354*, 17-57. b) Kirschning, A.; Kupracz, L.; Hartwig, J. *Chem. Lett.* **2012**, *41*, 562-570. c) Pastre, J. C.; Browne, D. L.; Ley, S. V. *Chem. Soc. Rev.* **2013**, *42*, 8849-8869. d) McQuade, D. T.; Seeberger, P. H. *J. Org. Chem.* **2013**, *78*, 6384-6389. e) Baxendale, I. R. *J. Chem. Technol. Biotechnol.* **2013**, *88*, 519-552. f) Cambié, D.; Bottecchia, C.; Straathof, N. J. W.; Hessel, V.; Noël, T. *Chem. Rev.* **2016**, *116*, 10276-10341. g) Porta, R.; Benaglia, M.; Puglisi, A. *Org. Process Res. Dev.* **2016**, *20*, 2-25. h) Gemoets, H. P. L.; Su, Y.; Shang, M.; Hessel, V.; Luque, R.; Noël, T. *Chem. Soc. Rev.* **2016**, *45*, 83-117. i) Plutschack, M. B.; Pieber, B.; Gilmore, K.; Seeberger, P. H. *Chem. Rev.* **2017**, *117*, 11796-11893. j) Britton, J.; Raston, C. L. Multi-step Continuous-flow Synthesis. *Chem. Soc. Rev.* **2017**, *46*, 1250-1271. k) Guidi, M.; Seeberger, P. H.; Gilmore, K. How to Approach Flow Chemistry. *Chem. Soc. Rev.* **2020**, *49*, 8910-8932.
- [4] For selected reviews on flash chemistry: a) Yoshida, J.-I.; Nagaki, A.; Yamada, T. *Chem. Eur. J.* **2008**, *14*, 7450-7459. b) Yoshida, J.-I.; Takahashi, Y.; Nagaki, A. *Chem. Commun.* **2013**, *49*, 9896-9904. c) Nagaki, A.; Ashikari, Y.; Takumi, M.; Tamaki, T. *Chem. Lett.* **2021**, *50*, 485-492.
- [5] a) Wong, J. Y. F.; Tobin, J. M.; Vilela, F.; Barker, G. *Chem. Eur. J.* **2019**, *25*, 12439-12445. b) Colella, M.; Nagaki, A.; Luisi, R. *Chem. Eur. J.* **2020**, *26*, 19-32. c) Kuhwald, C.; Kirschning, A. *Org. Lett.* **2021**, *23*, 4300-4304.
- [6] For selected examples of flow lithiation and sodiation reactions under continuous flow, see: a) Usutani, H.; Tomida, Y.; Nagaki, A.; Okamoto, H.; Nokami, T.; Yoshida, J.-I. *J. Am. Chem. Soc.* **2007**, *129*, 3046-3047. b) Nagaki, A.; Takahashi, Y.; Yoshida, J.-I. *Chem. Eur. J.* **2014**, *20*, 7931-7934. c) Nagaki, A.; Ichinari, D.; Yoshida, J.-I. *J. Am. Chem. Soc.* **2014**, *136*, 12245-12248. d) Nagaki, A.; Imai, K.; Ishiuchi, S.; Yoshida, J.-I. *Angew. Chem. Int. Ed.* **2015**, *54*, 1914-1918. e) Kupracz, L.; Kirschning, A. *Adv. Synth. Catal.* **2013**, *335*, 3375-3380. f) Wu, J.; Yang, X.; He, Z.; Mao, X.; Hatton, T. A.; Jamison, T. F. *Angew. Chem. Int. Ed.* **2014**, *53*, 8416-8420. g) Kim, H.; Lee, H.-J.; Kim, D.-P. *Angew. Chem. Int. Ed.* **2015**, *54*, 1877-1880. h) Nagaki, A.; Yamashita, H.; Hirose, K.; Tsuchihashi, Y.; Yoshida, J.-I. *Angew. Chem. Int. Ed.* **2019**, *58*, 4027-4030. i) M. R. Becker, P. Knochel, *Angew. Chem. Int. Ed.* **2015**, *54*, 12501-12505; *Angew. Chem.* **2015**, *127*, 12681-12685; j) M. Ketels, M. A. Ganiek, N. Weidmann, P. Knochel, *Angew. Chem. Int. Ed.* **2017**, *56*, 12770-12773; *Angew. Chem.* **2017**, *129*, 12944-12948; k) M. A. Ganiek, M. V. Ivanova, B. Martin, P. Knochel, *Angew. Chem. Int. Ed.* **2018**, *57*, 17249-17253; *Angew. Chem.* **2018**, *130*, 17946-17500. l) N. Weidmann, M. Ketels, P. Knochel, *Angew. Chem. Int. Ed.* **2018**, *57*, 10748-10751; *Angew. Chem.* **2018**, *130*, 10908-10911; m) J. H. Harenberg, N. Weidmann, K. Karaghiosoff, P. Knochel, *Angew. Chem. Int. Ed.* **2021**, *60*, 731-735; *Angew. Chem.* **2021**, *133*, 742-746; n) J. H. Harenberg, N. Weidmann, P. Knochel, *Angew. Chem. Int. Ed.* **2020**, *59*, 12321-12325; *Angew. Chem.* **2020**, *132*, 12419-12424; o) P. Musci, M. Colella, A. Sivo, G. Romanazzi, R. Luisi, L. Degennaro, *Org. Lett.* **2020**, *22*, 3623-3627; p) M. Colella, A. Tota, Y. Takahashi, R. Higuma, S. Ishikawa, L. Degennaro, R. Luisi, A. Nagaki, *Angew. Chem. Int. Ed.* **2020**, *59*, 10924-10928; *Angew. Chem.* **2020**, *132*, 11016-11020; q) S. Monticelli, M. Colella, V. Pillari, A. Tota, T. Langer, W. Holzer, L. Degennaro, R. Luisi, V. Pace, *Org. Lett.* **2019**, *21*, 584-588.
- [7] For selected reviews on halogen dance, see: (a) Duan, X.-F.; Zhang, Z.-B. *Heterocycles* **2005**, *65*, 2005-2012. (b) De Souza, M. V. N. *Curr. Org. Chem.* **2007**, *11*, 637-646. (c) Schnürch, M.; Spina, M.; Khan, A. F.; Milhovilovic, M. D.; Stanetty, P. *Chem. Soc. Rev.* **2007**, *36*, 1046-1057. (d) Schnürch, M. *Recent Progress on the Halogen Dance Reaction on Heterocycles*. In *Halogenated Heterocycles: Synthesis, Application and Environment*, Vol. 27; Iskra, J., Ed; Springer, **2012**; pp 185-218.
- [8] a) Mongin, F.; Desponds, O.; Schlosser, M. *Tetrahedron Lett.* **1996**, *37*, 2767-2770. b) Erb, W.; Mongin, F. *Tetrahedron* **2016**, *72*, 4973-4988.
- [9] a) Sammakia, T.; Stangeland, E. L.; Whitcomb, M. C. *Org. Lett.* **2002**, *4*, 2385-2388. b) Saitton, S.; Kihlberg, J.; Luthman, K. A. *Tetrahedron* **2004**, *60*, 6113-6120. c) Miller, R. E.; Rantanen, T.; Ogilvie, K. A.; Groth, U.; Snieckus, V. *Org. Lett.* **2010**, *12*, 2198-2201. d) Miyagawa, N.; Murase, Y.; Okano, K.; Mori, A. *Synlett* **2017**, *28*, 1106-1110. e) Mari, D.; Miyagawa, N.; Okano, K.; Mori, A. *J. Org. Chem.* **2018**, *83*, 14126-14137.
- [10] a) Mallet, M.; Quéguiner, G. *Tetrahedron* **1979**, *35*, 1625-1631. b) Mallet, M.; Quéguiner, G. *Tetrahedron* **1982**, *38*, 3035-3042. c) Mallet, M.; Quéguiner, G. *Tetrahedron* **1985**, *41*, 3433-3440. d) Cochenec, C.; Rocca, P.; Marsais, F.; Godard, A.; Quéguiner, G. *Synthesis* **1995**, 321-324. e) Mongin, F.; Trécourt, F.; Gervais, B.; Mongin, O.; Quéguiner, G. *J. Org. Chem.* **2002**, *67*, 3272-3276.
- [11] a) Mallet, M.; Branger, G.; Marsais, F.; Quéguiner, G. *J. Organomet. Chem.* **1990**, *382*, 319-322. b) Rocca, P.; Cochenec, C.; Marsais, F.; Thomas-dit-Dumont, L.; Mallet, M.; Godard, A.; Quéguiner, G. *J. Org. Chem.* **1993**, *58*, 7832-7838.
- [12] Okano, K.; Yamane, Y.; Nagaki, A.; Mori, A. *Synlett* **2020**, *31*, 1913-1918.
- [13] a) Ivanova, M.; Legros, J.; Poisson, T.; Jubault, P. *J. Flow. Chem.* **2021**, *12*, 147-151. b) Mougeot, R.; Jubault, P.; Legros, J.; Poisson, T. *Molecules* **2021**, *26*, 7183-7189. c) Ivanova, M.; Legros, J.; Poisson, T.; Jubault, P. *J. Flow. Chem.* **2022**, *10.1007/s41981-022-00223-3*. d) Desrues, T.; Legros, J.; Jubault, P.; Poisson, T. *React. Chem. Eng.* **2022**, *7*, 1285-1288.
- [14] Power, M.; Alcock, E.; McGlacken, G. P. *Org. Process Res. Dev.* **2020**, *24*, 1814-1838.
- [15] See Supporting Information for details.



## Entry for the Table of Contents

Insert graphic for Table of Contents here.



The divergent lithiation of 2,3-dihalopyridines is reported. Taking advantage of the continuous flow technology, either the deprotolithiation or the halogen dance is carried out. After a subsequent trapping with various electrophiles both regioisomers were obtained in excellent yields and selectivities on 25 examples. Finally, the scale up of this methodology was performed and promising space-time yield was obtained.

Institute and/or researcher Twitter usernames: @LabPoisson