Preprint Title	A Sustainable Strategy for the Straightforward Preparation of 2*H*-azirines and Highly Functionalized NH-aziridines from Vinyl Azides Using a Single Solvent Flow-Batch Approach
Authors	Michael Andresini, Leonardo Degennaro and Renzo Luisi
Publication Date	16 Nov 2020
Article Type	Letter
Supporting Information File 1	NH-Aziridine-Thematic-BJOC-Supporting-Info.pdf; 2.8 MB
ORCID® iDs	Michael Andresini - https://orcid.org/0000-0003-4523-8488; Renzo Luisi - https://orcid.org/0000-0002-9882-7908

A Sustainable Strategy for the Straightforward Preparation of 2*H*-azirines and Highly Functionalized NH-aziridines from Vinyl Azides Using a Single Solvent Flow-Batch Approach

Michael Andresini, Leonardo Degannaro,* Renzo Luisi*

Flow Chemistry and Microreactor Technology FLAME-Lab

Department of Pharmacy – Drug Sciences University of Bari “A. Moro” Via E. Orabona 4, Bari, 70125 (Italy)

* Corresponding authors

Abstract

The reported flow-batch approach enables the easy preparation of 2*H*-azirines and their stereoselective transformation into highly functionalized NH-aziridines, starting from vinyl azides and organolithiums. The protocol has been developed using cyclopentylmethylether (CPME) as an environmentally responsible solvent, resulting into a sustainable, safe and potentially automatable method for the synthesis of interesting strained compounds.

Keywords

2H-Azirines; Aziridines; Flow Chemistry; Green Chemistry; Organolithiums.

Introduction

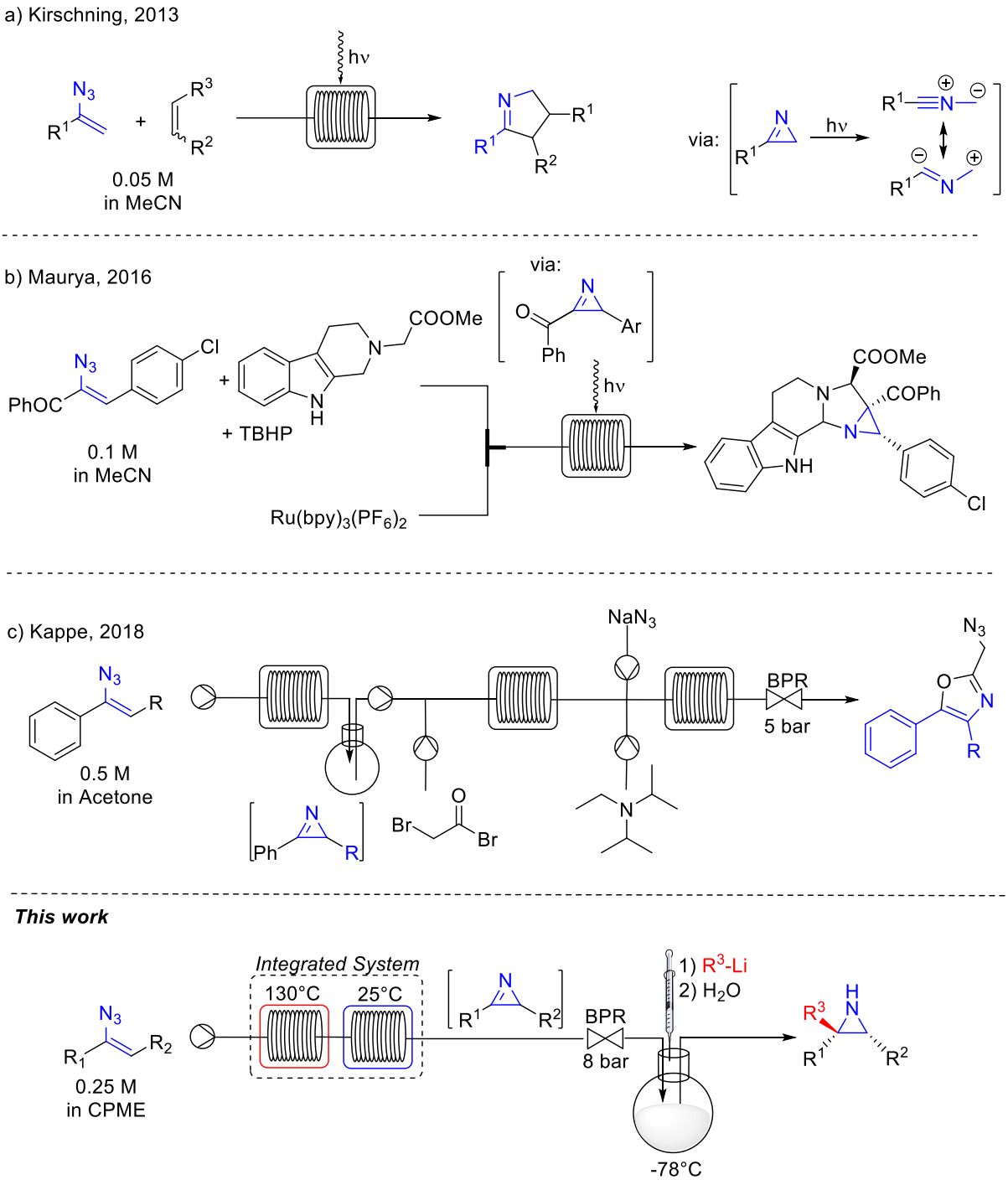
Since their conception in early 1990s, Green Chemistry Principles (GCP) have been applied with increasing effort towards the design of efficient production processes.[1-3]. As a result, a number of sustainable synthetic strategies have been recently developed, lowering the environmental impact and reducing the chemical hazards associated to the preparation of highly valuable compounds.[4] Among the elements that impact the sustainability of a synthetic method, the choice of the solvent is crucial.[5] In fact, chemical solvents represent most of the total amount of chemical species used in manufacturing processes, and therefore strongly affect waste disposal requirements and process related risks.[6] Recently, a variety of sustainable solvents have been therefore identified, and their use have been combined with those of enabling technologies. In this landscape, the development of continuous flow synthetic methodologies has found its fortune in the past two decades.[7-9] A number of chemical hazards can be effectively controlled through the use of microfluidic systems, because of the utilization of a reduced confined space and the exquisite control over heat and mass transfer.[10] As a consequence, efforts have been devoted to the development of synthetic processes combining GCP and enabling technologies[11].

Within the synthetic chemistry context, the preparation of aziridines still generates interest, mostly because of their importance as source for drug prototypes and drug discovery leads.[12] Interestingly, important advances have been recently addressed in the synthesis of NH-aziridines directly from olefins.[13,14] Aziridines are otherwise accessible from a variety of acyclic precursors,[15-17] even stereoselectively,[18-20] and through derivatization of 2*H*-azirines. The reactions using 2*H*-azirines as electrophiles proceed with several nitrogen, oxygen and sulfur nucleophiles, enabling to access aziridines with great structural variability.[21] The reaction of azirines with

Grignard and organolithium reagents has been poorly investigated, and without using green and renewable solvents. [22,23] In turn, 2H-azirines can be smoothly obtained through intramolecular cyclisation of vinyl azides, or by other strategies involving oximes, imines and oxazoles.[24]

One appealing strategy for the preparation of 2*H*-azirines involves the use of readily available vinyl azides. [25-30] However, the batch cyclisation of vinyl azides into the corresponding 2*H*-azirines could generate some risks, due to the explosive nature of organic azides, and possible overpressure issues caused by nitrogen generation at high temperatures. Consequently, scalability and control of this processes represents a real challenge. The exploitation of microfluidic technologies has therefore resulted into safer procedures for the preparation of 2*H*-azirines, offering valuable alternatives for production purposes. In 2013, Kirschning harnessed the photoinduced electrocyclisation of vinyl azides in a microfluidic photoreactor yielding 2*H*-azirines as precursors of 1,3-dipolarophiles (Scheme 1, a).[27] Similarly, Maurya developed a microfluidic photoreactor for the synthesis of a fused *β*-carboline from an α-keto vinyl azide and a 1,2,3,4-tetrahydro-β-carboline (Scheme 1, b).[30] More recently, Kappe reported the generation of 2*H*-azirines under continuous flow conditions, and their transformation into functionalized oxazoles using acetone as the solvent (Scheme 1, c).[28] Inspired by these recent reports, we became interested in the development of an eco-friendly strategy for the safe preparation of highly functionalized NH-aziridines from acyclic precursors. We report herein a sustainable mixed flow-batch approach, that enables the direct preparation of functionalized NH-aziridines from vinyl azides.

Scheme 1: Flow generation and transformation of 2*H*-azirines

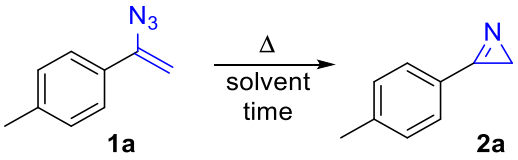


Results and Discussion

At the earliest stage of our research, we focused on the choice of the most suitable solvent for azides cyclisation and organolithium addition reactions. Most of the previously reported flow procedures involved acetonitrile, dichloromethane and acetone as solvents, however incompatibles with the utilization of reactive alkali

organometals. An exception is made for toluene, used by Kirschning for the photo-induced azirines formation.[27] Therefore, we investigated the thermally induced cyclisation of 1–(1–azidovinyl)–4–methylbenzene **1a** in refluxing 2-MeTHF and cyclopentylmethylether (CPME) as green solvents, and compared the results with the reaction conducted in toluene (Table 1).

Table 1: Thermally induced cyclisation of 1–(1–azidovinyl)–4–methylbenzene **1a** under batch conditions.



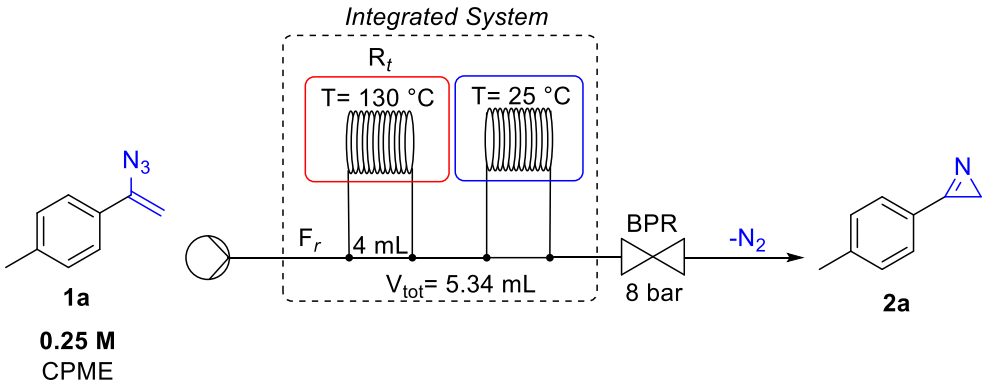
Solvent	Temperature	Time[a]
Toluene	110°C	1.5 h
2-MeTHF	80°C	4.0 h
CPME	106°C	45 min

[a] Time needed for complete consumption of **1a**

The reaction proceeded rapidly in CPME, while the use of 2-MeTHF resulted in longer reaction times if compared with toluene. We therefore selected CPME as the most suitable solvent for our purposes. Interestingly, besides being characterized by low toxicity, CPME has a very low affinity to water, making it suitable for moisture sensitive reactions, without previous distillation.[31-33] Subsequently, the process was examined under continuous flow conditions employing special integrated coil reactor with two different operating temperatures (see Supporting Information). A solution of 1–(1–azidovinyl)–4–methylbenzene **1a (**0.25M in CPME) was introduced, via a high pressure syringe pump, into the coil reactor maintained at the temperature of 130°C, and the residence time varied by adjusting the flow rate (Table 2). The reaction yield was calculated by ^{1}H NMR analysis of the crude. In details, conversion of **1a** in **2a**

increased from 33% to >99% by adjusting the residence time from 4 min to 16 min respectively. From a technical point of view, the pressure generated during the course of the reaction, due to nitrogen evolution, could be managed by using high pressure pump, a stainless-steel reactor and a back-pressure of 8 bar.

Table 2: Flow cyclisation of 1–(1–azidovinyl)–4–methylbenzene **1a**

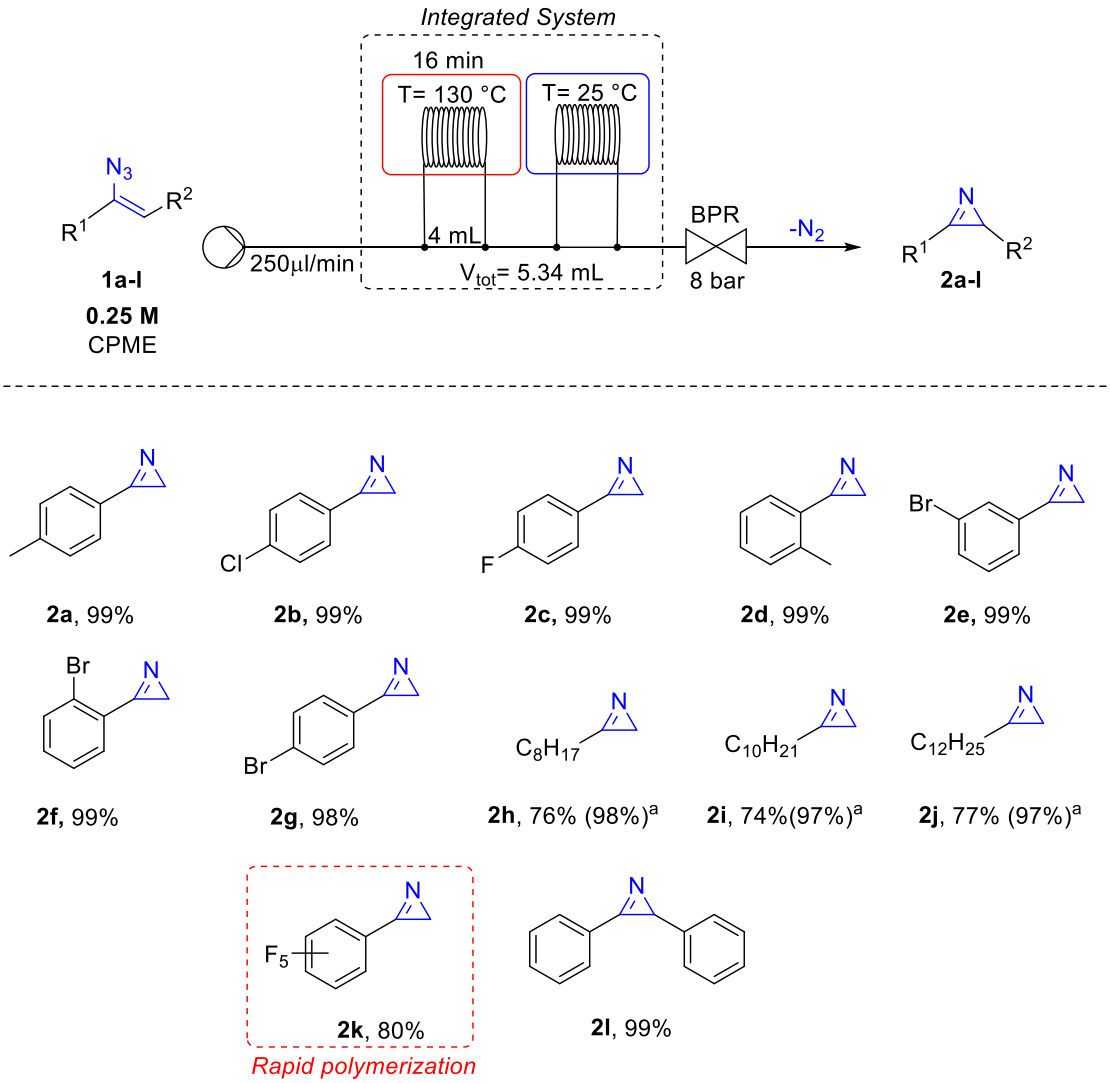


Entry	Flow rate (F_r)	Residence Time (R_t)	Yield of 2a
1	1.00 mL/min	4 min	33%
2	0.50 mL/min	8 min	65%
3	0.25 mL/min	16 min	>99%

Under the optimized conditions, the scope of the reaction was explored on vinyl azides **1a**–**l** that were transformed into the corresponding 2*H*–azirines **2a**–**l** (Scheme 2). The methodology was found to be efficient with vinlyazides carrying aryls substituted with chlorine (**2b**), fluorine (**2c**), and bromide (**2e**–**g**). In details, *ortho*–, *meta*–, and *para*–bromo phenyl derivatives were quantitively transformed into the corresponding 2*H*–azirines **2e-g** without substantial differences. Similarly, 3–(*o*–tolyl)–2*H*–azirine (**2d**) and 2,3–diphenyl–2*H*–azirine (**2l**) were also obtained in excellent yields. When 1–(1–azidovinyl)–2,3,4,5,6–pentafluorobenzene **1k** was reacted under optimal flow conditions, a mixture of **1k** and 2*H*–azirine **2k** (20:80 ratio respectively) was recovered.

Unfortunately, it was not possible to isolate **3**–(perfluorophenyl)–2*H*–azirine **2k** due to its rapid polymerization in the crude mixture.

Scheme 2: Flow synthesis of 2*H*–azirines from vinyl azides.

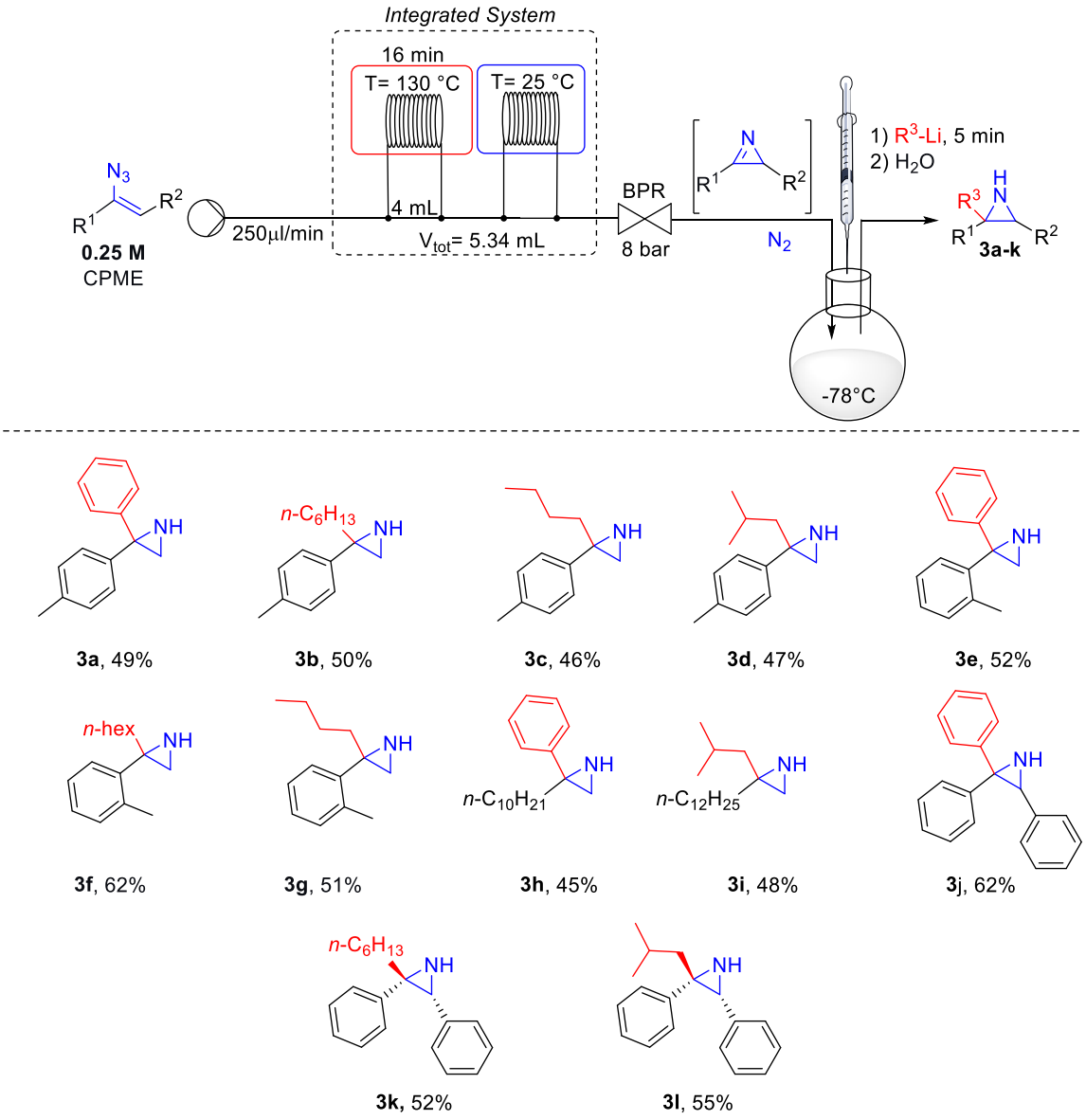


[a]The solution of vinyl azide was re-introduced twice into the flow system to achieve full conversion.

Interestingly, aliphatic vinyl azides **1h–j** were found less reactive, and the corresponding azirines **2h–j** were obtained in just 74–77% of yield, in mixture with unreacted starting materials. However, when the reaction crudes were re-introduced into the flow reactor under the same conditions, azirines **2h-j** were obtained quantitively (**2h**, 98%; **2i**, 97%; **2j**, 97%).

Pursuing in our aim to develop a green approach to prepare substituted NH-aziridines from vinyl azides in a single procedure, the solution of **2a** from the microfluidic system was collected in a round bottom flask cooled at -78°C, and reacted with1.2 equivalents of phenyllithium (PhLi). The mixture was stirred at the same temperature for 5 minutes, before quenching with water. With our delight, product **3a** was isolated in 49% yield. Next, the reaction of several commercially available organolithiums was examined. As shown in Scheme 3, the reaction of **2a**, generated in flow from **1a**, proceeded smoothly also with hexyllithium (HexLi), *n*–butyllithium (*n*-BuLi) and *iso*–butyllithium (*i*-BuLi) affording the corresponding NH-aziridines **3a-c** in good yields. Subsequently, other vinyl azides were tested for this flow-batch two-step procedure (Scheme 3).

Scheme 3: Mixed flow-batch approach for the preparation of functionalized *NH*-aziridines from vinyl azides.



Starting from vinyl azide **1d**, the corresponding 3–(*o*–tolyl)–2*H*–azirine **2d** was generated under flow conditions, and reacted with PhLi, HexLi and BuLi, furnishing NH-azirdines **3e**-**3g**. Aliphatic vinyl azides **1j** and **1k** were also subjected to this mixed flow-batch protocol, generating NH-aziridines **3h,i** in good yields (Scheme 3). The reaction was found to be efficient when PhLi was added to the collected solution of 2,3–diphenyl–2*H*–azirine **2m**, affording 2,2,3-triphenylaziridine **3j** in 62% yield. Moreover, the reaction was found highly stereoselective when HexLi or *i*-BuLi were added to **2m**. In fact, only products deriving from the attack of the organolithium on the

less hindered face (i.e. *anti* with respect to the phenyl substituent at C3), leading to **3k** (52%), and **3l** (55%), were observed. The relative stereochemistry was assigned by NOESY experiments (see Supporting Information). Unfortunately, when the protocol was applied to 1–(1–azidovinyl)–2,3,4,5,6–pentafluorobenzene **1l**, only a complex mixture was recovered likely because of the instability of the corresponding 2H-azirine **2k** (*vide infra*).

Conclusion

In summary, we have developed a sustainable mixed flow-batch approach for the synthesis of functionalized NH-aziridines starting from vinyl azides using a single green solvent for two reaction steps. Several vinyl azides have been quantitively transformed into the corresponding 2H-azirines in a microfluidic reactor, overcoming the hazards associated with this transformation under batch conditions. A small library of functionalized aryl and alkyl substituted NH-aziridines has been created under operationally simple conditions. Notably, the addition reaction was found to proceed stereoselectively when organolithiums were added to 2,3-diphenyl-2*H*-azirine. This is a fast, safe, green and convenient method to access this interesting structural motif without requiring protection/deprotection steps or long synthetic pathways.

Supporting Information

Supporting Information File 1: Description of general methods, general procedures, characterization data for all compounds and copies of ^{1}H,^{13}C,^{19}F, NOESY spectra.

Acknowledgements

We thank the CNR ICCOM section of Bari.

Funding

This research was supported by the project MISE, Horizon 2020 (PON 2014/2020 FARMIDIAB “code 338”) and the University of Bari (Fin. Ateneo Degennaro2019).

References

1. Chen, T.-L.; Kim, H.; Pan, S.-Y.; Tseng, P.-C.; Lin, Y.-P.; Chiang, P.-C. *Science of The Total Environment* **2020**, 716, 136998.

2. Ratti, R. *SN Appl. Sci.* **2020**, 2 (2).

3. Loste, N.; Roldán, E.; Giner, B. *Environ Sci Pollut Res* **2019**, 27 (6), 6215–6227.

4. Sharma, S.; Das, J.; Braje, W. M.; Dash, A. K.; Handa, S. *ChemSusChem* **2020**, 13 (11), 2859–2875.

5. Akito, C. O. *Industrial Applications of Green Solvents in Organic and Drug Synthesis for Sustainable Development of Chemical Process and Technologies*, Springer, **2020**, 14-40.

6. Häckl, K.; Kunz, W. *Comptes Rendus Chimie* **2018**, 21 (6), 572–580.

7. Fanelli, F.; Parisi, G.; Degennaro, L.; Luisi, R. *Beilstein J. Org. Chem.* **2017**, 13, 520–542.

8. Porta, R.; Benaglia, M.; Puglisi, A. *Org. Process Res. Dev.* **2015**, 20 (1), 2–25.

9. Degennaro, L.; Carlucci, C.; De Angelis, S.; Luisi, R. *J. Flow Chem.* **2016**, 6 (3), 136–166.

10. Plutschack, M. B.; Pieber, B.; Gilmore, K.; Seeberger, P. H. *Chem. Rev.* **2017**, 117 (18), 11796–11893.

11. Bogdan, A. R.; Dombrowski, A. W. *J. Med. Chem.* **2019**, 62 (14), 6422–6468.

12. Dembitsky, V. M.; Terent’ev, A. O.; Levitsky, D. O. Aziridine Alkaloids: Origin, Chemistry and Activity. In Natural Products; Springer Berlin Heidelberg, **2013**; pp 977–1006.

13. Jat, J. L.; Paudyal, M. P.; Gao, H.; Xu, Q.-L.; Yousufuddin, M.; Devarajan, D.; Ess, D. H.; Kürti, L.; Falck, J. R. *Science* **2014**, 343 (6166), 61–65.

14. Oseka, M.; Laudadio, G.; van Leest, N. P.; Dyga, M.; de Andrade Bartolomeu, A.; Goossen, L.; de Bruin, B.; Thiago de Oliveira, K.; Noel, T. Electrochemical Aziridination of Internal Alkenes with Primary Amines, 2020. doi:10.26434/chemrxiv.12824135.v1

15. Ielo, L.; Touqeer, S.; Roller, A.; Langer, T.; Holzer, W.; Pace, V. *Angew. Chem. Int. Ed.* **2019**, 58 (8), 2479–2484.

16. Ielo, L.; Pace, V.; Pillari, V.; Miele, M.; Castiglione, D. *Synlett* **2020**. doi:10.1055/s-0040-1706404

17. Monticelli, S.; Colella, M.; Pillari, V.; Tota, A.; Langer, T.; Holzer, W.; Degennaro, L.; Luisi, R.; Pace, V. *Org. Lett.* **2019**, 21 (2), 584–588.

18. Degennaro, L.; Trinchera, P.; Luisi, R. *Chem. Rev.* **2014**, 114 (16), 7881–7929.

19. de Ceglie, M. C.; Musio, B.; Affortunato, F.; Moliterni, A.; Altomare, A.; Florio, S.; Luisi, R. *Chem. Eur. J.* **2010**, 17 (1), 286–296.

20. Dammacco, M.; Degennaro, L.; Florio, S.; Luisi, R.; Musio, B.; Altomare, A. *J. Org. Chem.* **2009**, 74 (16), 6319–6322.

21. Alves, M. J.; Teixeira Costa, F. 2H-Azirines as electrophiles*, Heterocyclic Targets in Advanced Organic Synthesis First Edition*, **2010**, 1, 145-172.

22. Davis, F. A.; Linag, C.-H.; Liu, H. *J. Org. Chem.* **1997**, 62, 12, 3796–3797.

23. Carlson, R. M.; Lee, S. Y. *Tetrahedron Lett.* **1969**, 10 (45), 4001-4004.

24. Ramkumar, N.; Voskressensky, L. G.; Sharma, U. K.; Van der Eycken, E. V. *Chem Heterocycl Comp* **2019**, 55 (9), 795–801.

25. Tiwari, D. K.; Maurya, R. A.; Nanubolu, J. B. *Chem. Eur. J.* **2015**, 22 (2), 526–530; (b)

26. O'Brien, A. G.; Lévesque, F.; Seeberger, P. H. *Chem. Commun.* **2011**, 47 (9), 2688–2690.

27. Cludius-Brandt, S.; Kupracz, L.; Kirschning, A. *Beilstein J. Org. Chem.* **2013**, 9, 1745–1750.

28. Rossa, T. A.; Suveges, N. S.; Sá, M. M.; Cantillo, D.; Kappe, C. O*. Beilstein J. Org. Chem.* **2018**, 14, 506–514.

29. Koo, H.; Kim, H. Y.; Oh, K. *Org. Lett.* **2019**, 21 (24), 10063–10068.

30. Chandrasekhar, D.; Borra, S.; Nanubolu, J. B.; Maurya, R. A. *Org. Lett.* **2016**, 18 (12), 2974–2977.

31. Azzena, U.; Carraro, M.; Pisano, L.; Monticelli, S.; Bartolotta, R.; Pace, V. *ChemSusChem* **2018**, 12 (1), 40–70.

32. Perna, F. M.; Vitale, P.; Capriati, V. *Curr. Opin. Green Sustain. Chem.* **2020**, 21, 27–33.

33. Watanabe, K.; Yamagiwa, N.; Torisawa, Y. *Org. Process Res. Dev.* **2007**, 11 (2), 251–258.