Organic LETTERS

Letter

pubs.acs.org/OrgLett

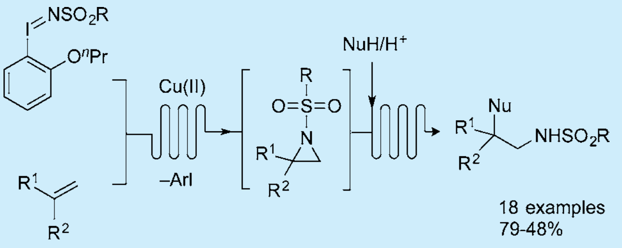
Functionalization of Alkenes through Telescoped Continuous Flow Aziridination Processes

Nathanael Hsueh, Guy J. Clarkson, and Michael Shipman*

Department of Chemistry, University of Warwick, Gibbet Hill Road, Coventry, CV4 7AL, U.K.

Supporting Information

ABSTRACT: Alkenes can be efficiently aziridinated using highly soluble iminoiodane derivatives under continuous flow conditions. By combining the aziridine generation with nucleophilic ring opening reactions, a variety of products can be made without the need to handle or isolate these potentially hazardous intermediates. Additionally, this chemistry can be used to make and use aziridines that are difficult to isolate and purify because of their high reactivity.

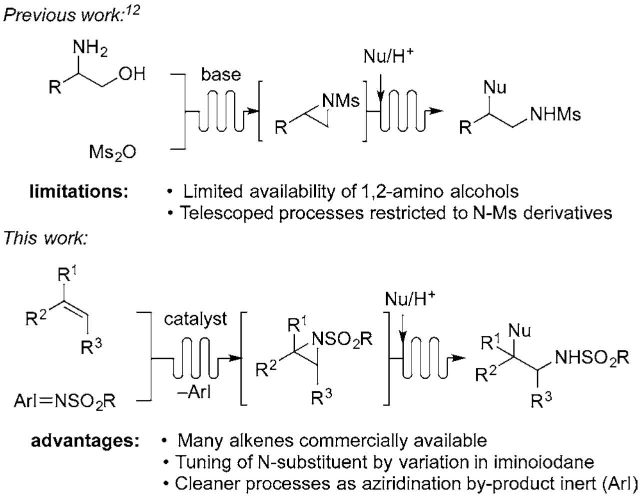


No need to handle or isolate the potentially hazardous intermediates

Aziridines are valuable building blocks widely used for the production of nitrogen containing molecules.[1,2] In particular, they serve as "spring-loaded" electrophiles that, upon nucleophilic ring opening, facilitate the formation of a variety of C−C and C−heteroatom bonds. These processes have such broad scope, efficiency, selectivity, and atom economy that they have been categorized as "click" reactions.[3] However, the high reactivity of these nitrogen heterocycles makes them potentially hazardous to human health.[4] For example, aziridine (ethylenimine) is a powerful alkylating agent with both mutagenic and genotoxic activity.[4a] Although the toxicity of other aziridines is less well established, considerable caution should be exercised when working with them to limit harmful exposure.

Continuous flow chemistry provides a way to generate and handle hazardous and reactive reagents in a safe manner.[5] Thus, we reasoned that this technology might allow us to generate and use aziridines in telescoped processes without recourse to handling or purifying them. The synthesis[6−12] and utilization[13−15] of these electrophilic species in laboratory-scale flow chemistry have recently attracted considerable attention although just two reports have explored their use as transient intermediates in telescoped processes. In 2016, Gaunt, Lapkin and co-workers described the continuous-flow synthesis and derivatization of a bicyclic aziridine by way of Pd-catalyzed C(sp^3)−H activation.[11] In the only other report, we described a simple flow synthesis of aziridines by ring closure of 1,2-amino alcohols and their further telescoped ring opening reactions (Scheme 1).[12] Unfortunately, the applicability of our chemistry was limited by the range of 1,2-amino alcohols that are commercially available or readily prepared. Moreover, aryl sulfonyl chlorides (e.g., TsCl) could not be used as activators for the ring closure as the derived chloride ion competed as a nucleophile leading to unwanted side products in the subsequent ring openings. This problem was solved through application of methanesulfonic anhydride as an activator in the telescoped reactions; however, this further limited the range of products that could be made by this approach.

Scheme 1. Concept for the Generation and Ring Opening of Aziridines in Continuous Flow by Metal-Catalyzed Nitrene Transfer from Iminoiodanes



Among methods developed for the preparation of aziridines, the metal catalyzed addition of nitrenes to C═C double bonds is especially general offering high levels of chemo-, regio- and stereocontrol.[1] Arylsulfonylimino phenyliodanes such as PhI═NTs have emerged as a particularly useful and practical nitrene precursor for such chemistry.[16] This encouraged us to explore the aziridination/ring opening of alkenes under continuous flow conditions using this methodology (Scheme 1). Potential benefits include the fact that (i) a very wide range of alkenes are

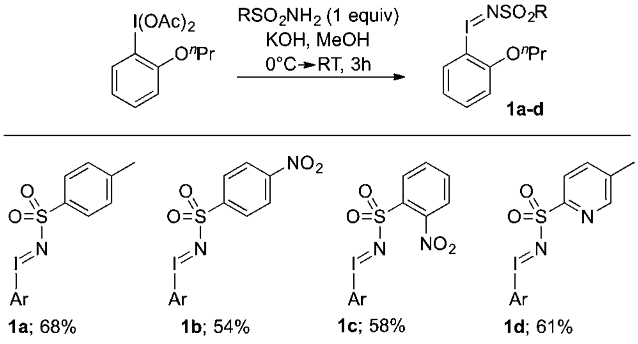
Received: August 10, 2016
Published: September 13, 2016

DOI: 10.1021/acs.orglett.6b02349
Org. Lett. 2016, 18, 4908−4911

commercially available and are known to participate in such metal catalyzed aziridinations; (ii) many ArI═NSO$_2$R are accessible, making it possible to tune the aziridine *N*-substituent; and (iii) an inert byproduct is generated in the form of an aryl iodide which should not interfere in the telescoped ring opening reactions.

At the outset of this work, we faced a significant practical obstacle insofar as most common iminoiodane derivatives such as PhI═NTs and PhI═NNs are extremely insoluble in organic solvents. To solve this problem, we turned to a report by Yoshimura and co-workers who described highly soluble and reactive *N*-tosyl nitrene precursors derived from *o*-propoxyiodobenzene.[17] We prepared iminoiodane **1a** from (2-propoxyphenyl)-λ^3-iodanediyl diacetate according to the published method (Scheme 2). Additionally, three new iminoiodanes namely **1b−d** were synthesized from the corresponding electron-deficient sulfonamides in good yields. These electron-withdrawing substituents were introduced to enhance the reactivity of the aziridines and make it easier to remove the sulfonyl groups from the nitrogen atom in the end products.[18] While iminoiodanes **1c** and **1d** exhibited good solubility in chlorinated solvents, **1b** proved to be only sparingly soluble making it unsuitable for further use in the flow aziridinations reported herein.

Scheme 2. Synthesis of Iminoiodanes 1a−d



The structure of **1d** was unambiguously established by X-ray crystallography which also provides possible insights into why it is more soluble (Figure 1 and Supporting Information). Unlike PhINTs which has a polymeric structure stabilized by short intermolecular I···N bonds (2.482 Å),[19] there are no such interactions in **1d**. Instead, the iodine benefits from a strong intramolecular interaction with the appended pyridine nitrogen atom (2.814 Å) as well as the ether oxygen (2.872 Å). The absence of strong intermolecular interactions presumably aids solubility.

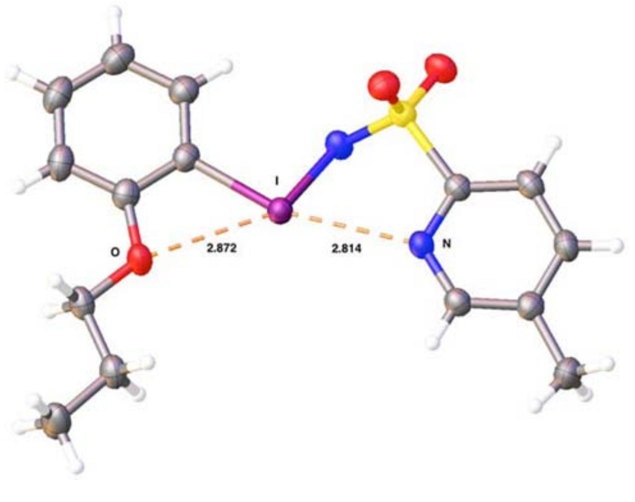
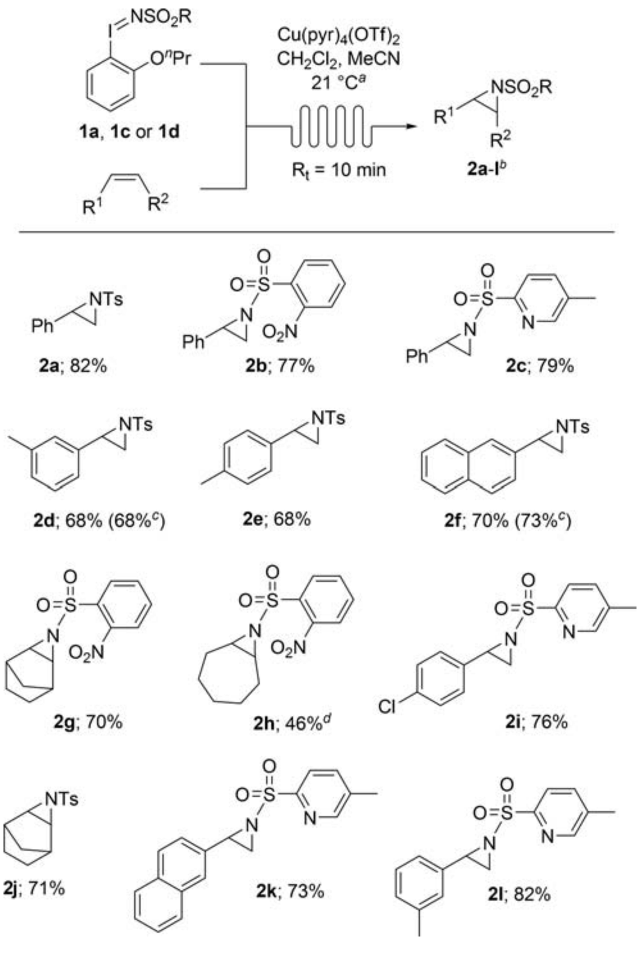


Figure 1. ORTEP depiction of the X-ray structure of **1d** highlighting the key interactions with the iodine atom.

Using soluble iminoiodanes **1a**, **1c**, and **1d**, we next explored the synthesis of aziridines in flow. A commercial microreactor (total reactor volume = 4.5 cm^3) connected to computer controlled syringe pumps was used (see Supporting Information for setup). The reactions were performed by combining tetrakis(pyridine)copper(II) triflate (10 mol %) and the alkene (10 equiv) in MeCN, with the iminoiodane (1 equiv) dissolved in CH$_2$Cl$_2$.[20] The addition rates were controlled to achieve a residence time (R_t) of 10 min in the reactor. In this way, aziridines **2a−l** were produced in good yields after column chromatography (Scheme 3). All three iminoiodanes were effective nitrene transfer reagents under flow conditions. Similar results were achieved using an inexpensive, tube reactor in place

Scheme 3



[a]ArI═NSO$_2$R (0.1 mmol) in CH$_2$Cl$_2$ (2 mL) and the alkene (1 mmol, 10 equiv) and (pyr)$_4$Cu(OTf)$_2$ (0.01 mmol) in MeCN (2 mL) were combined in a two-channel microreactor; flow rate = 0.45 mL min^{-1} (see Supporting Information). [b]Isolated yield after column chromatography. [c]Using an inexpensive tube reactor made from PTFE tubing; flow rate = 0.50 mL min^{-1} (see Supporting Information). [d]Conducted using cycloheptene (20 equiv).

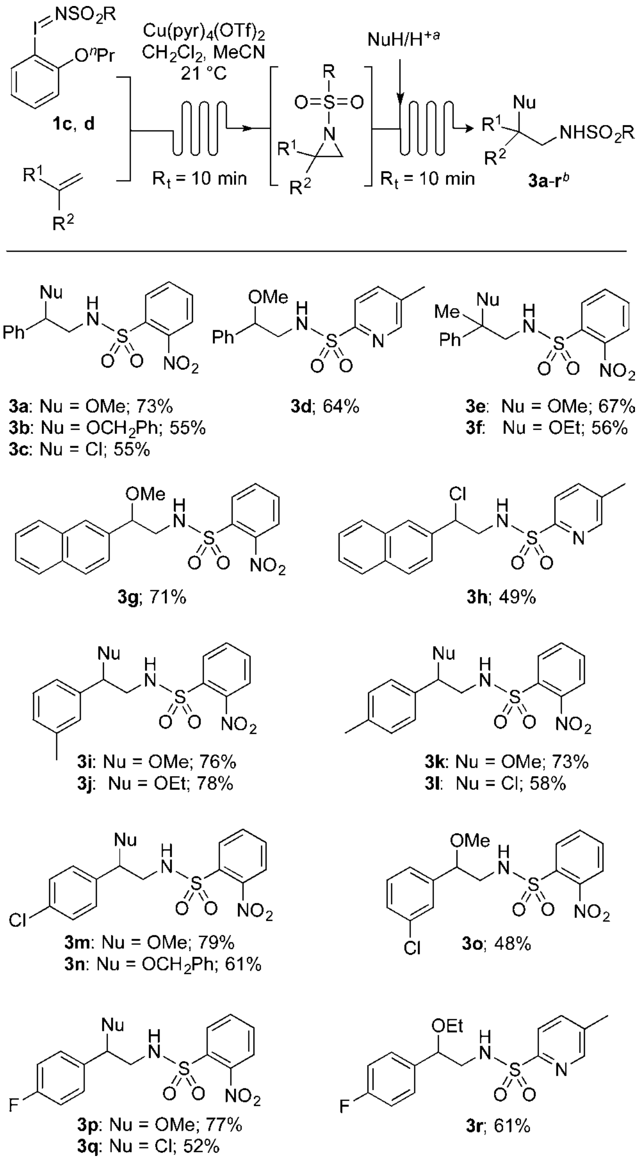
DOI: 10.1021/acs.orglett.6b02349
Org. Lett. 2016, 18, 4908−4911

of the chip reactor, as illustrated by the synthesis of **2d** and **2f** in comparable yields.

Next, we sought to ascertain if telescoped reactions could be undertaken whereby the aziridine is made and directly ring opened without recourse to handling or isolation. For these reactions, a three-input tube reactor was constructed with a total residence time of 20 min (see Supporting Information). First, the iminoiodane, alkene, and catalyst were combined at room temperature to produce the aziridine, whereupon the nucleophile and acid activator were introduced to effect ring opening. Better results in these telescoped reactions were achieved by reducing the quantities of the alkene (5 equiv). Through the synthesis of amines **3a–r** in moderate to good overall yields, it is apparent that this three-component process tolerates good variation in the alkene, nucleophile, and iminoiodane (Scheme 4).[21] For example, by using alcohol nucleophiles this chemistry provides rapid access to 1,2 amino alcohol motifs.[22] An unexpected benefit is that it can be used to make and use aziridines that are difficult to isolate and purify because of their high reactivity. For example, this telescoped process can be used to efficiently make **3e** and **3f** derived from α-methylstyrene, despite the fact that attempts to isolate the corresponding aziridine were unsuccessful. Regiospecific opening at the more hindered benzylic carbon of the intermediate aziridines was seen in all cases. This was established by HMBC 3-bond couplings[23] and, in the case of **3h**, further verified by X-ray crystallography (see Supporting Information).

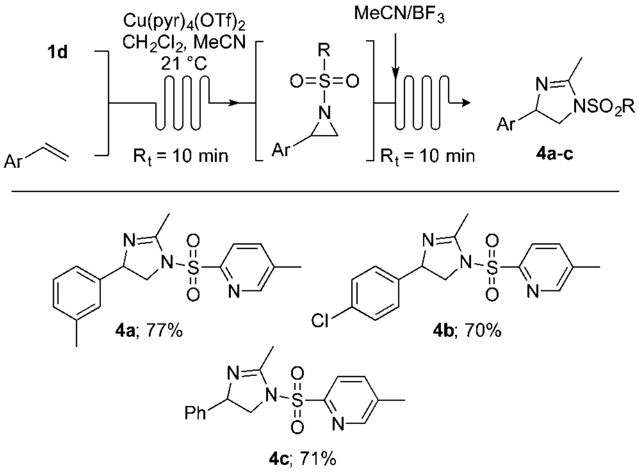
Additionally, the feasibility of making imidazolines has been demonstrated through the synthesis of **4a–c** by reaction of **1d** with a selection of styrenes, followed by boron trifluoride induced ring expansion in the presence of acetonitrile (Scheme 5).[24] In each case, a single regioisomer was observed.

Scheme 4



[a] H_2SO_4 in MeOH (Nu = OMe); H_2SO_4 in EtOH (Nu = OEt); MsOH in BnOH (Nu = OBn); HCl in Et_2O/CH_2Cl_2 (1:3) (Nu = Cl), flow rate = 1.0 mL min^{-1}. For full details, see Supporting Information. [b] Isolated yield after column chromatography.

Scheme 5. Flow Synthesis of Imidazolines by a Telescoped Aziridination/Ring Expansion Sequence



In conclusion, we have devised a general route to aziridines from a variety of alkenes using new, soluble iminoiodanes under continuous flow conditions. By telescoping their generation with further chemistry of the aziridines, it is possible to produce a wide range of valuable products by way of regiocontrolled openings. As well as limiting exposure to these potentially hazardous heterocycles, this has the added benefit that it can be used to make aziridines that are rather reactive and difficult to isolate. The application of these soluble iminoiodanes in other processes including the asymmetric aziridination of alkenes under continuous flow is ongoing in our laboratory and will be disclosed in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02349.

> Details of continuous flow apparatus, experimental procedures, characterization data for all compounds, copies of ^{1}H and ^{13}C NMR spectra (PDF)
>
> X-ray data for **1d** (CIF)
>
> X-ray data for **3h** (CIF)

AUTHOR INFORMATION

Corresponding Author

*E-mail: m.shipman@warwick.ac.uk.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank the University of Warwick for financial support. The Oxford Diffraction Gemini XRD system was obtained, through the Science City Advanced Materials project: Creating and Characterizing Next Generation Advanced Materials. We thank Dr. Andrew J. Clark (University of Warwick) for the generous loan of equipment.

REFERENCES

(1) For a monograph, see: Yudin, A. K., Ed. *Aziridines and Epoxides in Organic Synthesis*; Wiley-VCH: Weinheim, 2006.

(2) For reviews, see: (a) Degennaro, L.; Trinchera, P.; Luisi, R. *Chem. Rev.* **2014**, *114*, 7881−7929. (b) Callebaut, G.; Meiresonne, T.; De Kimpe, N.; Mangelinckx, S. *Chem. Rev.* **2014**, *114*, 7954−8015. (c) Cardoso, A. L.; Pinho e Melo, T. M. V. D. *Eur. J. Org. Chem.* **2012**, 6479−6501. (d) Stanković, S.; D'hooghe, M.; Catak, S.; Eum, H.; Waroquier, M. l.; Van Speybroeck, V.; De Kimpe, N.; Ha, H.-J. *Chem. Soc. Rev.* **2012**, *41*, 643−665. (e) Florio, S.; Luisi, R. *Chem. Rev.* **2010**, *110*, 5128−5157.

(3) (a) Moses, J. E.; Moorhouse, A. D. *Chem. Soc. Rev.* **2007**, *36*, 1249−1262. (b) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2001**, *40*, 2004−2021.

(4) (a) IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. *71* (1999); WHO press: Lyon, France. (b) Ismail, F. M. D.; Levitsky, D. O.; Dembitsky, V. M. *Eur. J. Med. Chem.* **2009**, *44*, 3373−3387.

(5) For leading references, see: (a) Gutmann, B.; Cantillo, D.; Kappe, C. O. *Angew. Chem., Int. Ed.* **2015**, *54*, 6688−6728. (b) Ager, D. J. *ACS Symp. Ser.* **2014**, *1181*, 285−351. (c) Degennaro, L.; Carlucci, C.; De Angelis, S.; Luisi, R. *J. Flow Chem.* **2016**, http://dx.doi.org/10.1556/1846.2016.00014.

(6) Maskill, K. G.; Knowles, J. P.; Elliott, L. D.; Alder, R. W.; Booker-Milburn, K. I. *Angew. Chem., Int. Ed.* **2013**, *52*, 1499−1502.

(7) Rossi, S.; Puglisi, A.; Benaglia, M.; Carminati, D. M.; Intrieri, D.; Gallo, E. *Catal. Sci. Technol.* **2016**, *6*, 4700−4704.

(8) Scholz, S. O.; Farney, E. P.; Kim, S.; Bates, D. M.; Yoon, T. P. *Angew. Chem., Int. Ed.* **2016**, *55*, 2239−2242.

(9) Baumann, M.; Baxendale, I. *Synlett* **2015**, *27*, 159−163.

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

(11) Zakrzewski, J.; Smalley, A. P.; Kabeshov, M. A.; Gaunt, M. J.; Lapkin, A. A. *Angew. Chem., Int. Ed.* **2016**, *55*, 8878−8883.

(12) Hsueh, N.; Clarkson, G. J.; Shipman, M. *Org. Lett.* **2015**, *17*, 3632−3635.

(13) Nagaki, A.; Takizawa, E.; Yoshida, J.-I. *Chem. Lett.* **2009**, *38*, 1060−1061.

(14) Giovine, A.; Musio, B.; Degennaro, L.; Falcicchio, A.; Nagaki, A.; Yoshida, J.-I.; Luisi, R. *Chem. - Eur. J.* **2013**, *19*, 1872−1876.

(15) Salice, P.; Rossi, E.; Pace, A.; Maity, P.; Carofiglio, T.; Menna, E.; Maggini, M. *J. Flow Chem.* **2014**, *4*, 79−85.

(16) (a) Karila, D.; Dodd, R. H. *Curr. Org. Chem.* **2011**, *15*, 1507−1538. (b) Chang, J. W. W.; Ton, T. M. U.; Chan, P. W. H. *Chem. Rec.* **2011**, *11*, 331−357.

(17) Yoshimura, A.; Nemykin, V. N.; Zhdankin, V. V. *Chem. - Eur. J.* **2011**, *17*, 10538−10541.

(18) (a) Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373−6374. (b) Pak, C. S.; Lim, D. S. *Synth. Commun.* **2001**, *31*, 2209−2214. (c) Han, H.; Bae, I.; Yoo, E. J.; Lee, J.; Do, Y.; Chang, S. *Org. Lett.* **2004**, *6*, 4109−4112.

(19) Mishra, A. K.; Olmstead, M. M.; Ellison, J. J.; Power, P. P. *Inorg. Chem.* **1995**, *34*, 3210−3214.

(20) Cu(pyridine)$_4$(OTf)$_2$ proved to be a superior catalyst to Cu(OTf)$_2$ which was used by Yoshida and co-workers for batch aziridinations using **1a** (ref 14). No attempts were made to recover the excess alkene from these reactions. Further details of the process optimization are provided in the Supporting Information.

(21) *N*-Tosyl derivatives made from **1a** were much less effective in these ring openings. Moreover, extending the residence time for ring opening with MeOH/H$_2$SO$_4$ to 20 min did not lead to any significant improvement.

(22) Bergmeier, S. C. *Tetrahedron* **2000**, *56*, 2561−2576.

(23) Furuta, Y.; Kumamoto, T.; Ishikawa, T. *Synlett* **2004**, 362−364.

(24) Prasad, B. A. B.; Pandey, G.; Singh, V. K. *Tetrahedron Lett.* **2004**, *45*, 1137−1141.