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Functionalisation of Alkenes Through Telescopied Continuous Flow Aziridination Processes

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Supporting Information Placeholder

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.

Aziridines are valuable building blocks widely used for the production of nitrogen containing molecules. 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. However, the high reactivity of these nitrogen heterocycles make them potentially hazardous to human health. For example, aziridine (ethylenimine) is a powerful alkylating agent with both mutagenic and genotoxic activity. 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. Thus, we reasoned that this technology might allow us to generate and use aziridines in telescopied processes without recourse to handling or purifying them. The synthesis and utilization of these electrophilic species in laboratory-scale flow chemistry has recently attracted considerable attention although just two reports have explored their use as transient intermediates in telescopied processes. In 2016, Gaunt, Lapkin and coworkers described the continuous-flow synthesis and derivatization of a bicyclic aziridine by way of Pd-catalyzed C(sp³)–H activation. In the only other report, we described a simple flow synthesis of aziridines by ring closure of 1,2-amino alcohols and their further telescopied ring opening reactions (Scheme 1). 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 activator in the telescopied 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 chemoselective control. Arylsulfonylimino phenyliodanes such as PhI=NTs have emerged as a particularly useful and practical nitrene precursors for such chemistry. 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 commercially available and are known to participate in such metal catalyzed aziridinations; (ii) many ArI=NSO-R are accessible, making it possible to tune the aziridine N-substituent; and (iii) an inert by-product 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 coworkers who described highly soluble and reactive N-tosyl nitrene precursors derived from o-propoxyiodobenzene. We prepared iminoiodane 1a from (2-propoxyphenyl)-iodane 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. Whilst iminoiodanes 1c and 1d had 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.

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

Scheme 3.
Using soluble iminoiodanes 1a, 1c and 1d, we next explored the synthesis of aziridines in flow. A commercial microreactor (total reactor volume = 4.5 cm³) connected to computer controlled syringe pumps was used (see Supporting Information for set-up). 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 CH₂Cl₂.²⁰ The addition rates were controlled to achieve a residence time (Rt) of 10 min in the reactor. In this way, aziridines 2a-1 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 of the chip reactor, as illustrated by the synthesis of 2d and 2f in comparable yields.

Scheme 4.

![Scheme 4](image)

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 regiosomer was observed.

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 α-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 α-alkenes under continuous flow is ongoing in our laboratory and will be disclosed in due course.

ASSOCIATED CONTENT

Supporting Information
Details of continuous flow apparatus, experimental procedures, characterisation data for all compounds, copies of 1H and 13C NMR spectra and X-ray data for 1d and 3h. This Supporting Information is available free of charge on the ACS Publications website.

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REFERENCES
(20) Cu(pyridine)3OTf2 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 optimisation 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/H2SO4 to 20 min did not lead to any significant improvement.