Synlett M. Baumann, I. R. Baxendale Letter

Continuous-Flow Synthesis of 2*H*-Azirines and Their Diastereoselective Transformation to Aziridines

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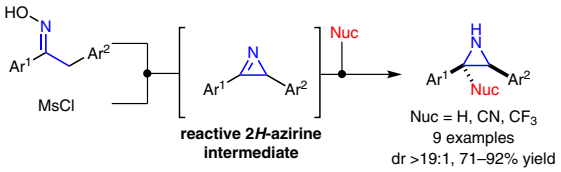
We dedicate the star of this paper to Prof. Steven V. Ley on the occasion of his 70th birthday



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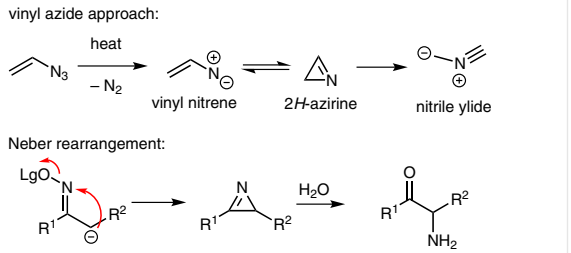
Abstract Using continuous-flow techniques, a small collection of 2*H*-azirines was prepared from oxime precursors via mesylation and base-promoted cyclisation. The 2*H*-azirines were either isolated after in-line purification or derivatised into a selection of 2-substituted aziridines through a telescoped reaction sequence involving nitrile, trifluoromethyl, or hydride nucleophilic addition. Importantly, these 2-substituted aziridines were produced with high *cis* diastereoselectivity providing access to small chiral heterocyclic entities that hold promise for medicinal chemistry programs because of their druglike features.

Key words flow synthesis, heterocycles, azirine, aziridine, microreactor, monolith, in-line purification

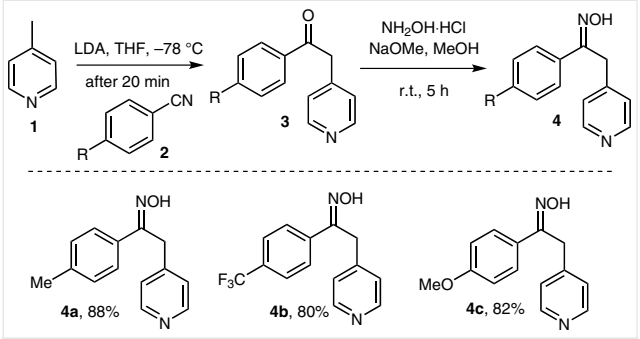
2*H*-Azirines and their saturated aziridine counterparts represent intriguing small heterocyclic components.[1] Synthesis of 2*H*-azirines commonly involves the photolysis of vinyl azides[2] or the Neber rearrangement of activated oximes.[3] Due to the inherently high ring strain of the 2*H*-azirine structures, their conversion into aziridines through nucleophilic attack at the imine carbon is a very thermodynamically favourable process accompanied by release of ~20 kcal/mol.[4] In addition 2*H*-azirines readily undergo ring opening into synthetically valuable nitrile ylide dipoles (Scheme 1).[5]



Scheme 1 Synthetic approaches towards 2*H*-azirines

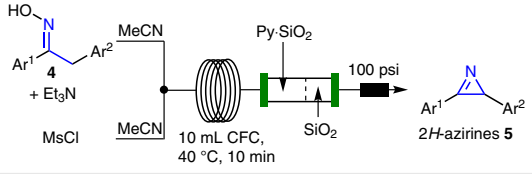
Current synthetic protocols towards 2*H*-azirines involve time- and labour-intensive batch manipulations where product instability results in decreased yield and the requirement for extensive purification. In the past we have successfully demonstrated several efficient flow processes yielding selections of chiral[6] and achiral[7] heterocyclic architectures displaying various versatile functionalization sites. We therefore aimed to harness the processing power of flow chemistry to deliver a stream of 2*H*-azirines based on an interrupted Neber rearrangement process. The intermediate 2*H*-azirines would be subsequently converted through a second reaction step involving addition of various nucleophiles to furnish di- and trisubstituted aziridines.[8]

We commenced our studies with the synthesis of different substrates bearing a 4-pyridyl moiety adjacent to the methylene carbon of the oxime motif that itself would be derived from the corresponding ketone precursor.[9] It was quickly established that these ketone structures **3** could be readily accessed through the addition of lithiated picolines **1** into nitriles **2** (Scheme 2, see Supporting Information for full details). The desired oximes **4** were subsequently prepared by condensation of the ketones **3** with hydroxylamine hydrochloride under basic conditions.



Scheme 2 Synthesis of oxime precusors **4a–c**

Having gained rapid entry to quantities of the oxime precursors we next turned our attention towards developing a flow process for their conversion into 2*H*-azirines and related aziridines. To this end we configured a Vapourtec E-series flow system so that a stream (stream A, Scheme 3) containing the oxime substrate (**4**, 0.1 M MeCN) and triethylamine (1.2 equiv) was mixed at a T-piece with a second stream containing methanesulfonyl chloride (0.12 M, MeCN; stream B, Scheme 3) before entering a tubular convection flow coil (CFC, 10 mL volume) maintained at 40 °C. The resultant mesylated oxime would then enter a packed glass column filled with silica-supported pyridine (2.5 g, 1.39 mmol/g functional loading[10]) as a base to promote displacement of the mesylate and thus formation of the desired *2H*-azirines via a 3-*exo*-trig cyclisation.



Scheme 3 Flow set-up generating 2*H*-azirines **5**

It was shown that this simple set-up was indeed suitable for delivering the desired 2*H*-azirine products **5** in a mild and efficient flow sequence within an overall residence time of 20 minutes (16 minutes mesylation in CFC and 4 minutes cyclisation in the glass column). ^{1}H NMR spectroscopic analysis of the crude output indicated >85% conversion of the oxime substrates to the 2*H*-azirine products. We therefore slightly modified the set-up to incorporate a small plug of silica gel (1 g) following the immobilised pyridine base in order to trap the triethylamine hydrochloride salt formed in the process. This not only resulted in a simple yet effective in-line purification, but also removed coloured impurities from the product stream. The set-up was used to rapidly generate a small selection of 2*H*-azirine products as depicted in Figure 1.

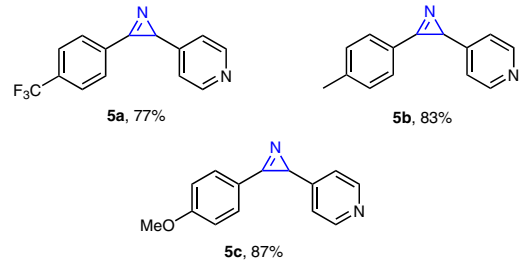
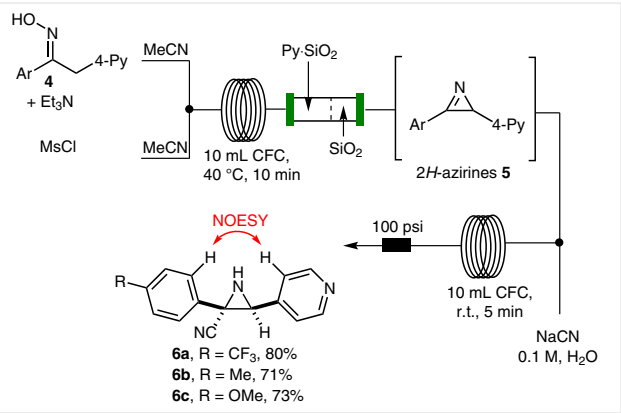


Figure 1 2*H*-Azirines **5a–c** prepared in flow (isolated yields).

Additional experiments also revealed that other solvents such as EtOAc or THF were also suitable for this transformation. However, the diminished solubility of the triethylamine hydrochloride generated presented a potential risk of clogging of the narrow-bore tubing connectors. It was found that although complete exclusion of triethylamine still yielded the desired 2*H*-azirines, they existed as their hydrochloride salts due to the embedded pyridyl moiety. As these required base treatment, this approach was not followed up further.

Next we explored the addition of various nucleophiles, such as nitrile, trifluoromethyl, and hydride onto the 2*H*-azirines **5**. To this end we designed an extended process that would merge the initial reaction stream containing the 2*H*-azirine product (ca. 0.05 M, MeCN) with an aqueous solution of sodium cyanide (0.1 M, H_2O) in order to generate the corresponding nitrile derivatives (Scheme 4). After passing through a second tubular reactor coil (10 mL) maintained at ambient temperature the desired nitrile product was isolated after evaporation and aqueous extraction. Pleasingly, it was quickly established that the desired adducts were formed not only in good yield but moreover with excellent diastereoselectivity (dr >19:1).



Scheme 4 Continuous synthesis of aziridine-2-carbonitriles **6**

Using NOESY NMR techniques it was shown that a *cis* relationship between the two aryl rings existed as a result of the nitrile approaching the azirine electrophile from the sterically least hindered face. In addition, single-crystal X-ray diffraction was used to confirm the stereochemical assignment (Figure 2).

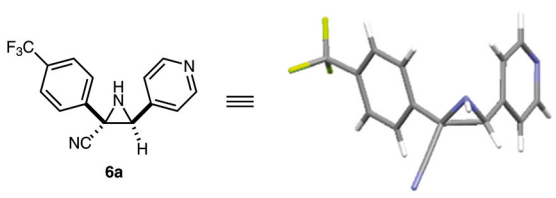
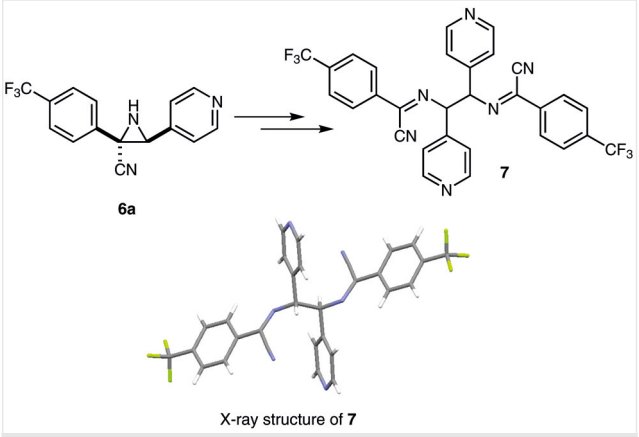


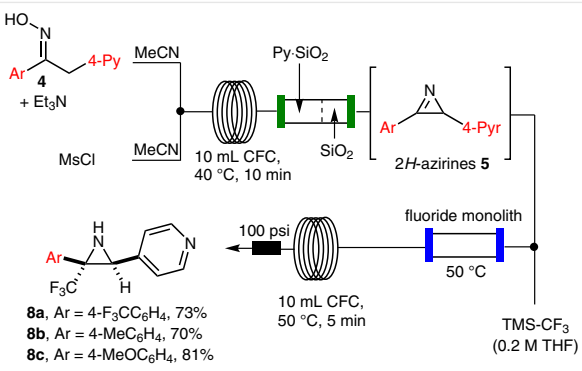
Figure 2 Relative stereochemistry of **6a** as established by X-ray crystallography

One interesting feature of these aziridines bearing a nitrile substituent is their distinct red colour when in solid form; whereas solutions possess an yellow-orange colouration. This is possibly indicative of a 'push–pull' interaction between the electron-withdrawing nitrile group and the electron-rich aziridine nitrogen atom. It was furthermore found that these products slowly undergo decomposition via a process likely to comprise a sequence of electrocyclic ring opening of **6a** and oxidative dimerization to generate biscyanoimine species **7**, the structure of which was confirmed by X-ray crystallography (Scheme 5).



Scheme 5 Decomposition of **6a**

Next, we decided to evaluate the viability of introducing a trifluoromethyl group by reacting the azirine flow stream with Ruppert's reagent ($TMSCF_3$) to yield the alternative trifluoromethylaziridines as such fluorinated heterocyclic structures are predisposed for potential applications in medicinal chemistry programs.[11] In order to achieve the synthesis of these entities we decided to draw from our previous studies that had shown how flow chemical processing offers a robust solution for safely and efficiently performing fluorination reactions with various reagents such as DAST,[12] Ruppert's reagent, and Selectfluor.[13] Of particular benefit in these studies was the successful development of a fluoride-containing ion-exchange monolith that previously had allowed us to activate $TMSCF_3$ towards addition into aldehydes without requiring TBAF as a solution-phase reagent that is often difficult to remove by chromatography. We therefore prepared a monolithic reactor cartridge and loaded it with fluoride as previously reported.[13a] The crude 2*H*-azirine flow stream was therefore mixed via a T-piece with a stream containing Ruppert's reagent (0.1 M, 2.0 equiv, THF) before passing through the fluoride monolith maintained at 50 °C. A CFC reactor (10 mL volume, 50 °C) was placed after the monolithic reactor to increase residence time for the trifluoromethylation reaction. Finally, a 100 psi back-pressure regulator was placed at the exit of the reactor to maintain the system pressure, and the product was isolated by direct evaporation of the output (Scheme 6).



Scheme 6 Telescoped flow approach towards trifluoromethylated aziridines **8a–c**

Pleasingly, this new set-up proved successful for the telescoped synthesis of a small selection of trifluoromethylated aziridines starting from the corresponding oxime precursors. Importantly, all final products where isolated as single diastereomers in good yield and high purity after column chromatography. In order to evaluate the relative stereochemistry of our products we firstly turned to 2D NMR techniques, specifically ^1H-^{19}F HOESY experiments, confirming the expected *cis* relationship between the CF_3 group and the adjacent proton. It was quickly established that there was a *cis* correlation between these groups by the observation of a through-space coupling at an estimated spatial distance of ca. 2.7 Å compared to ca. 4.1 Å for the *trans* diastereomer. Finally, a single-crystal X-ray structure of compound **8a** was secured and confirmed the assignment unambiguously (Figure 3).

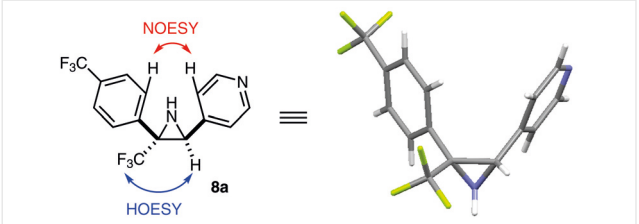


Figure 3 Relative stereochemistry of **8a** established by 2D NMR (^1H-^{19}F HOESY, left) and X-ray crystallography (right)

Finally, we elected to study the conversion of in situ prepared 2*H*-azirines into their corresponding aziridine derivatives. In order to achieve this reduction, several options were evaluated including flow-based hydrogenations with the H-Cube™ system.[14] In view of operational simplicity it was, however, established that collecting the 2*H*-azirine stream into a flask containing $NaBH_4$ (1.5 equiv, 0.1 M THF) would lead to the clean formation of the desired aziridine products **9a–c** that again were isolated as single diastereomers. After aqueous workup and column chromatography

the relative stereochemistry of these entities was established using NOESY NMR spectroscopy confirming the expected *cis* relationship (Figure 4).

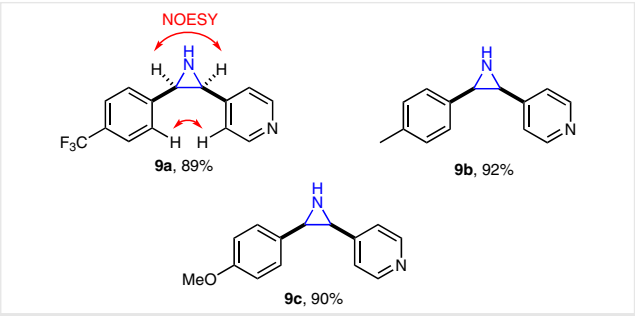


Figure 4 Disubstituted aziridines **9a–c** prepared in flow

In summary, we have developed a simple, yet robust flow process generating a selection of 2*H*-azirines from readily accessible oxime precursors.[15] The value of these species was furthermore demonstrated through a selection of telescoped reaction sequences showcasing the rapid formation of a number of aziridine derivatives accomplished by reaction with hydride, trifluoromethyl, and nitrile nucleophiles. Importantly, these structures were obtained in high yield and with exclusive *cis* diastereoselectivity presenting opportunities towards further exploitation of this versatile methodology.

Acknowledgment

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0035-1560391.

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(15) **Typical Flow Procedure for the Synthesis of 2*H*-Azirines**
Using a Vapourtec E-Series flow system, two streams containing the oxime substrate (**4**, 0.1 M MeCN, 1.0 equiv; stream A) and Et_3N (1.2 equiv; 0.3 mL/min; stream A) and MsCl (0.12 M MeCN, 1.2 equiv; 0.3 mL/min; stream B) were mixed in a T-piece prior to entering a tubular flow coil (10 mL volume, 40 °C) in which the mesylation occurred. The exiting flow stream was then directed into an Omnifit glass column (10 mm i.d., 150 mm length) filled with silica supported pyridine[10] (2.5 g, 1.39 mmol/g loading) and silica gel (1 g) that was maintained at ambient temperature. After exiting this column the crude reaction mixture passed a backpressure regulator (100 psi) before being collected. Final purification could be achieved via silica

column chromatography (20–50% EtOAc–hexanes) yielding the desired 2*H*-aziridines typically in high yield as yellow oils.

4-{3-[4-(Trifluoromethyl)phenyl]-2*H*-azirin-2-yl}pyridine (5a)

Yield 201 mg (0.77 mmol, 77%); yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.47 (2 H, d, *J* = 8.0 Hz), 7.97 (2 H, d, *J* = 8.0 Hz), 7.79 (2 H, d, *J* = 8.0 Hz), 7.02 (2 H, d, *J* = 8.0 Hz), 3.29 (1 H, s). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 161.9 (C), 149.5 (2 CH), 149.4 (C), 135.1 (C, q, *J* = 23 Hz), 130.3 (2 CH), 126.4 (2 CH, q, *J* = 4 Hz), 126.3 (C), 123.3 (CF_3, q, *J* = 271 Hz), 120.9 (2 CH), 33.6 (CH). ^{19}F NMR (376 MHz, $CDCl_3$): δ = –63.3 . IR (neat): ν = 1602 , 1413 , 1322 , 1168 , 1126 , 1065 , 1017 , 851 cm^{-1}. LC–MS (ESI-TOF): *m/z* = 263.1 [M + H]. HRMS (ESI-TOF): *m/z* calcd for $C_{14}H_{10}N_2F_3$: 263.0796; found: 263.0792 (Δ 0.4 mDa).