Chirality Transfer in Azetidinium Ylides: An Enantioselective Route to α-Quaternary Azetidines

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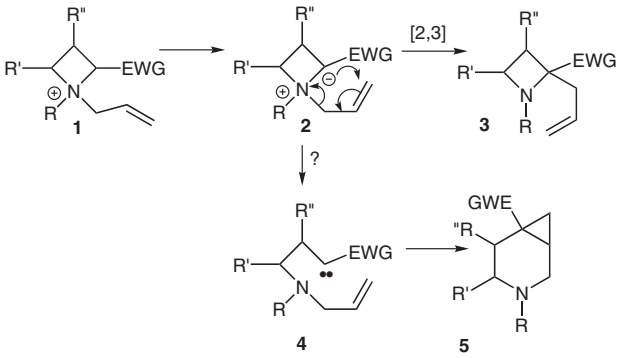
Abstract: Enantiomerically pure *N*-allyl azetidinium ions undergo a stereoselective [2,3]-sigmatropic shift to give azetidines with an α-quaternary center. These compounds are direct precursors of 2-alkyl-2-carboxy-azetidines, a new class of constrained α-amino acids.

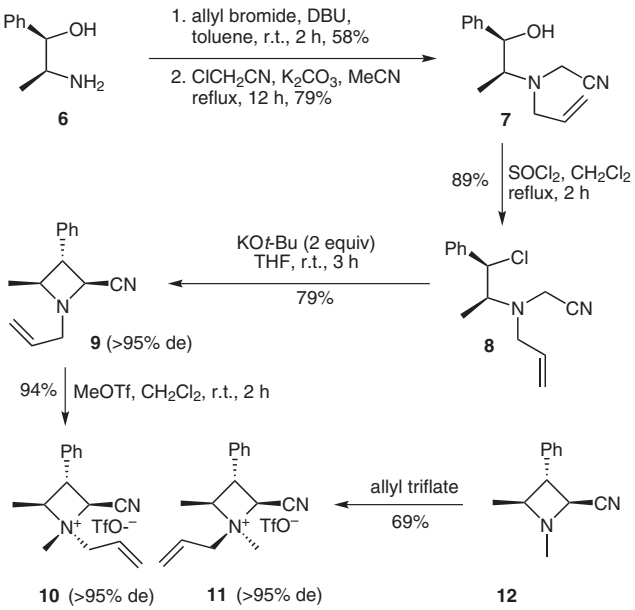
Key words: azetidines, nitrogen ylides, α-quaternary amino acids

The synthesis of enantiopure α-substituted prolines is a field of great interest, due to the exceptional role of proline in the control of the secondary structures of peptides. Asymmetric syntheses of such amino acids can be achieved through well-established procedures,[1] and among these, the method based on the concept of self-reproduction of chirality developed by Seebach et al. is probably the most popular.[2] In contrast, the asymmetric synthesis of α-quaternary 2-carboxyazetidine (i.e., the lower homologue of proline) is almost uncovered. Besides, in these cyclic amino acids, the geometrical constraint brought by the four-membered ring is of special interest since it was recently demonstrated that these amino acids are efficient scaffolds for the induction of γ-turns in short peptides.[3] To the best of our knowledge, the asymmetric synthesis of such amino acids has been achieved only quite recently through two different methodologies. The first one relies on the chemoselective reduction[4] of a suitably functionalized homochiral azetidin-2-one, itself prepared through chiral-auxiliary-mediated asymmetric synthesis,[5] and the second one is based on the elegant concept of memory of chirality.[6] This restricted availability of synthetic methodologies reflects the difficulties encountered in the asymmetric synthesis of azetidines,[7] which also hampers the growing interest in 2-carboxyazetidine derivatives.[8]

In continuation of our interest in the chemistry of azetidinic amino acids,[9] and in the reactivity of azetidinium ylides,[10] we decided to investigate whether enantiopure α-quaternary azetidines **3** would be accessible through a [2,3]-sigmatropic shift involving azetidinium ylide **2** (Scheme 1). Such a transformation has been studied by West with homologous proline derivatives, and he was able to demonstrate that an efficient N→C chirality transfer was in operation.[11] The introduction of an allyl group is also particularly interesting since it can give rise to a number of derivatives through cross-metathesis of the double bond.[12] Apart from the stereoisomeric considerations, we were also intrigued to see if the strain of the four-membered ring would unveil a carbenoid-like reactivity of the azetidinium ylide to give **4**, that would logically evolve to piperidine **5** through intramolecular cyclopropanation of the double bond.[13]



Scheme 1 Is a stereoselective [2,3]-sigmatropic shift of *N*-allyl azetidinium ions a viable route to azetidines with an α-quaternary center?



Scheme 2 Synthesis of epimeric azetidinium ions **10** and **11**

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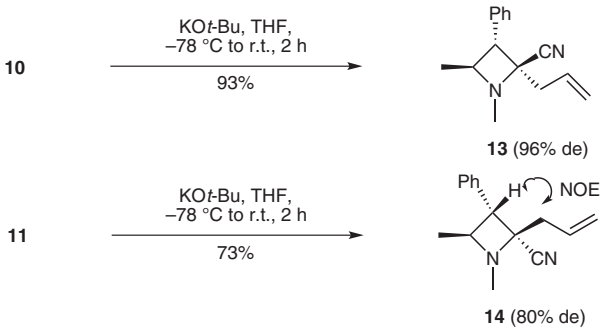
In order to address the question of reactivity, and for a convenient examination of the stereoselectivity, we first synthesized *N*-allyl azetidinium ions **10** and **11**, epimeric at the nitrogen stereocenter (Scheme 2). The former compound was prepared from (1*R*,2*S*)-norephedrine (**6**) which was first N-allylated and next reacted with chloroacetonitrile. The resulting amino alcohol was chlorinated and cyclized into **9**. It should be noted, as shown by TLC, that the stereoselectivity of this reaction results from thermodynamic control, favoring the depicted isomer **9**, which was isolated in 79% yield. Methylation of this compound with methyltrifluoromethylsulfonate then gave azetidinium ion **10** with high stereoselectivity, similarly to related substrates.[14] On the other hand, N-allylation of known[15] azetidine **12** with a freshly prepared solution of allyltrifluoromethylsulfonate[16] gave epimeric azetidinium ion **11** with high diastereoselectivity.

In order to test the viability of the sigmatropic shift, these epimers were reacted with KO*t*-Bu in THF and afforded the expected azetidines **13** and **14** with high yields and selectivities. The absolute configuration of the newly created quaternary stereocenter in **14** was determined by NOE experiments, as depicted in Scheme 3, and this configuration agrees with the work of West et al. in the homologous series, who observed a delivery of the allyl group to the same face, in a concerted manner.[11] We were not able to isolate under various experimental conditions [use of other bases, addition of Cu(II) or Rh(II) catalyst] any cyclopropyl piperidine **5** that would be diagnostic of the carbenoid character of the intermediate ylide.



Scheme 3 An efficient N→C chirality transfer in azetidinium ylides

Encouraged by these results, and in order to examine the scope of this rearrangement, a small series of stereodefined azetidines was synthesized and transformed into azetidinium salts by quaternarization with either methyl- or allyltrifluoromethanesulfonate. These salts were next reacted with KO*t*-Bu following the conditions depicted in Scheme 3. Table 1 summarizes the outcome of these reactions.

Entries 1–3 in Table 1 illustrate some important points. First, the relative configuration of the amino nitrile moiety in the starting azetidinium ions does not influence at all the stereochemical outcome of the rearrangement, since exactly the same distribution of epimers is obtained starting from **11** and **16** on one hand and **18** and **21** on the other hand. This is indicative of a rapid inversion of the corresponding anion, prior to rearrangement. Secondly, although the configuration of the nitrogen atom is indeed the main parameter which controls diastereoselectivity, this latter can be influenced by the substitution of the alkene, since **19** was obtained as a mixture of epimers. In this particular case, we assume that this mixture corresponds to epimers at C-2 since they are produced exclusively from a [2,3]-sigmatropic shift and not a Stevens rearrangement.[21] As a matter of fact, this [2,3]-sigmatropic rearrangement is expected to control the configuration of the benzylic carbon, due to the defined stereochemistry of the starting alkene. This possibility could not, however, be ruled out unambiguously by NOE experiments. The unexpected absence of the reaction in the case of substrate **23** also reflects the sensitivity of this reaction towards steric crowding. In this case, either the ylide is not produced, or it does not react and gives back **23** by subsequent protonation. Entries 5 and 6 demonstrate that other anion-stabilizing moieties, such as an ester, can also be used successfully in this reaction, but the azetidinium **25** was obtained only in low yield, accompanied by undesired β-elimination product, a side reaction which can only occur with 2-alkyl-substituted azetidines.[22] In the case of compound **29**, the absolute configuration of the newly created stereocenter was confirmed by X-ray crystallography of the derived azetidinium salt, whose structure[23] is depicted in Figure 1. Finally, entry 7 shows that an attempt to transfer a benzyl group through a Stevens rearrangement led only to an intractable mixture of products.

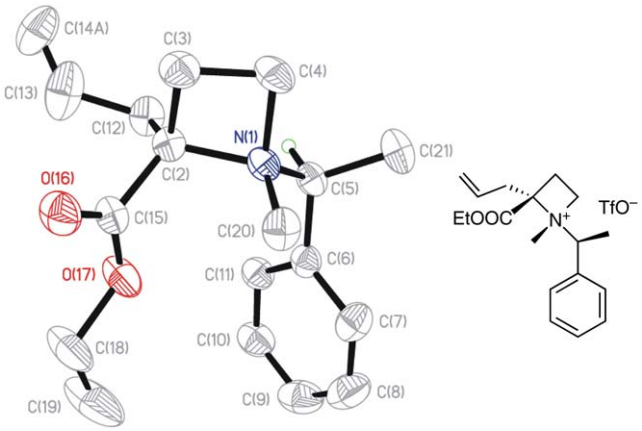
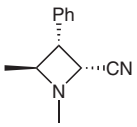
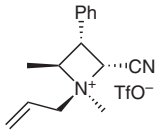
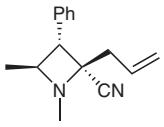
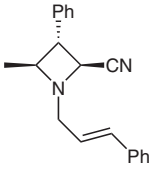
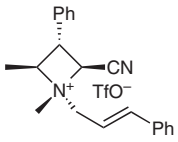
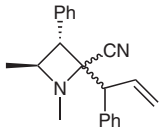
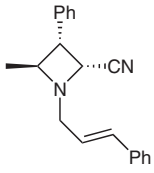
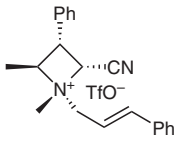
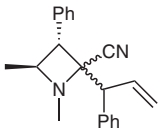
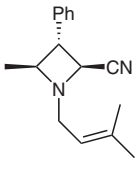
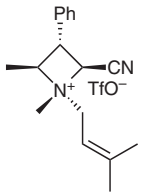
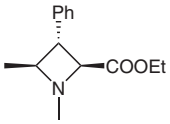
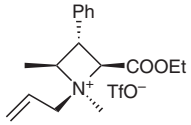
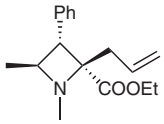
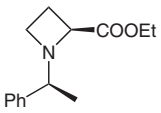
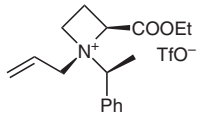
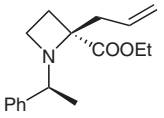
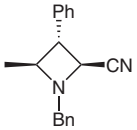
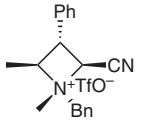


Figure 1 The ORTEP structure of azetidinium triflate derived from **29**

The reactivity of the produced azetidines with a quaternary stereocenter was also briefly examined. First, we were intrigued to know whether the strained amino nitrile moiety in **13** could be reduced.[24] As a matter of fact, compound **12**, in which a secondary amino nitrile is present, does not react at all with $NaBH_4$ to give the corresponding reduced product, and this was attributed to the difficult generation of an iminium ion in 2-cyano azetidines. On the other hand, compound **13** reacted sluggishly with $NaBH_4$ under the same conditions to give a 1:1 mixture of **33** and **14**, the epimerized starting compound at the amino

Table 1 Scope of the [2,3]-Sigmatropic Rearrangement of *N*-Allyl Azetidinium Trifluoromethanesulfonates

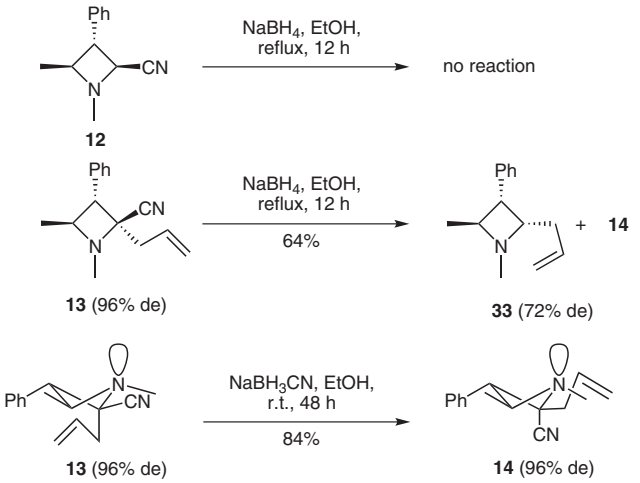
Entry	Starting azetidine	Azetidinium salts	Product(s)	Yield (%)[a]
1	 **15**[15]	 **16** (69%)	 **14**	74
2	 **17**[17]	 **18** (89%)	 **19**	50[b]
3	 **20**[17]	 **21** (78%)	 **19**	71[b]
4	 **22**[17]	 **23** (77%)	no reaction	–
5	 **24**[18]	 **25** (37%)[c]	 **26**	68
6	 **27**[19]	 **28** (58%)	 **29**	64
7	 **30**[20]	 **31** (95%)	decomposition	–

[a] Yield of isolated product.
[b] This compound was obtained as a 1:1 mixture of epimers (see text).
[c] Elimination product (52%) was isolated in this experiment (see text).

nitrile stereocenter (Scheme 4). This unexpected epimerization was confirmed by a third experiment: reaction of **13** with sodium cyanoborohydride resulted in complete epimerization of this stereocenter to give **14** in good isolated yield. This last transformation can only be explained by the formation of an intermediate iminium ion from the quaternary amino nitrile, which is probably easier to form here than from **12**.

The epimerization of **13** to **14** reflects the greater stability of **14** compared to **13**. As a matter of fact, in **14**, the *trans* diaxial disposition of the nitrile group and the lone pair of the nitrogen atom allows a stabilizing anomeric effect to occur by overlap of the n orbital at the nitrogen atom and the σ* orbital of the C–CN bond.

In summary, we have developed an efficient synthesis of stereodefined α-quaternary azetidines,[25] which are direct precursors of a new class of constrained α-amino acids.



Scheme 4 An iminium ion can be generated from α-quaternary amino nitriles in azetidines

Acknowledgment

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(23) The crystal structure data have been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 703601.
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(25) **General Procedure for Rearrangement of Azetidinium Triflates**
The following procedure for the preparation of azetidine **13** is representative. To a solution of azetidinium triflate **10** (823 mg, 2.19 mmol) in dry THF (40 mL), cooled at –78 °C was added in one portion KO*t*-Bu (300 mg, 2.67 mmol). The reaction mixture was allowed to reach 0 °C over 3 h and was quenched by addition of H_2O and Et_2O. The reaction mixture was extracted with Et_2O, the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude residue was examined by ^1H NMR and showed a diastereomeric ratio of 98:2. Purification by flash chromatography (cyclohexane–EtOAc, 8:2) gave **13** as a colorless oil (461mg, 93%).
Selected Data
Compound **13**: R_f = 0.48 (cyclohexane–EtOAc, 8:2); $[\alpha]_D^{25}$ –13.1 (*c* 0.33, $CHCl_3$). ^1H NMR (300 MHz,$CDCl_3$): δ = 1.42 (d, *J* = 6.6 Hz, 3 H, Me), 2.01–2.12 (m, 1 H, C*H*HCH=CH_2), 2.21–2.32 (m, 1 H, CH*H*CH=CH_2), 2.42 (s, 3 H, NMe), 3.65 (d, *J* = 5.4 Hz, 1 H, H3), 3.80 (q, *J* = 5.5 Hz, 1 H, H4), 4.85–5.03 (m, 2 H, CHHCH=CH_2), 5.35–5.52 (m, 1 H, CHHC*H*=CH_2), 7.23–7.35 (m, 5 H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.2 (CH_3), 33.9 (NMe), 36.3 (CH_2), 53.3 (C3), 61.9 (C4), 64.9 (C2), 119.9 (CN), 121.1 (CH=*C*H_2), 126.9, 128.3, 129.1 (CHAr), 131.0 (*C*H=CH_2), 135.6 (CqAr). MS (CI, NH_3): *m/z* = 227.1 (100) [MH^+], 200.2 (50) [MH^+ – HCN].
Compound **14**; yield 73%, colorless oil; R_f = 0.34 (pentane–EtOAc, 9:1); $[\alpha]_D^{25}$ –64 (*c* 1, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.17 (d, *J* = 5.8 Hz, 3 H, Me), 2.38 (s, 3 H, NMe), 2.58 (appt. d, *J* = 5.3 Hz, 2 H, CH_2CH=CH_2), 3.15 (d, *J* = 9.1 Hz, 1 H, H3), 3.35 (q, *J* = 5.8 Hz, 1 H, H4), 5.11–5.22 (m, 2 H, CHHCH=CH_2), 5.70–5.84 (m, 1 H, CHHC*H*=CH_2), 7.12–7.21 (m, 5 H, Ar). ^{13}C NMR (75 MHz, $CDCl_3$ MHz): δ = 19.6 (CH_3), 37.9 (NMe), 43.8 (CH_2), 53.9 (C3), 63.5 (C4), 71.2 (C2), 117.2 (CN), 120.2 (CH=*C*H_2), 127.8, 128.3, 128.6 (CHAr), 130.9 (*C*H=CH_2), 135.3 (CqAr). MS (CI, NH_3): *m/z* = 227.1 (100) [MH^+], 200.2 (35) [MH^+ – HCN].