Highly regioselective ring-opening of trisubstituted aziridines by sulfur-stabilised carbanions†

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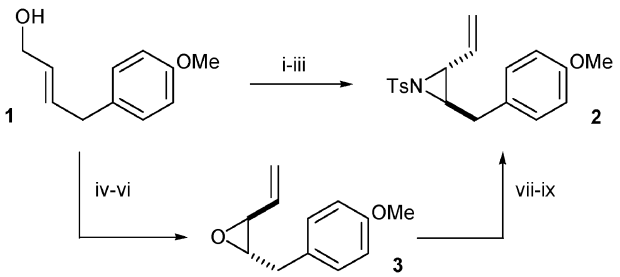
The highly regioselective, stereospecific ring-opening of trisubstituted *N*-tosylaziridines possessing vinyl and hydroxymethyl groups by sulfone- and sulfide-stablised carbanions is reported.

Aziridines are valuable intermediates for the synthesis of nitrogen-containing molecules.[1] In general, 1,2-disubstituted aziridines suffer attack by anionic nucleophiles at the less substituted 3-position. When both carbon atoms are substituted, competing steric and electronic effects may be such that the regioselectivity of nucleophilic ring-opening is eroded. This Communication reports a series of ring-opening reactions of 1,2,3-trisubstituted aziridines by sulfur-stabilised carbanionic nucleophiles, and demonstrates that vinyl and lithiated hydroxymethyl groups are effective directing groups for highly regioselective C–C bond-forming transformations.

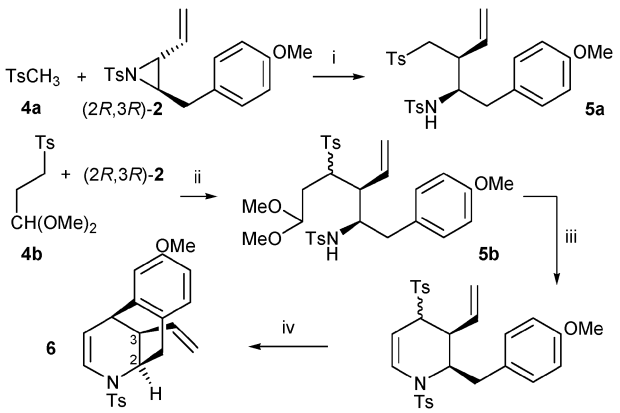
We began by investigating the reactivity of aziridine **2**. This was readily synthesised as the racemic *trans*-(2*R**,3*R**) isomer from *E*-4-(4-methoxyphenyl)-2-buten-1-ol **1**[2] by the routes shown in Scheme 1. The more direct sequence involved aziridination of **1**,[3] oxidation and Wittig methylenation. Problems of irreproducibility[4] of the Wittig reaction on scale-up led to the development of a more robust route, in which epoxidation of **1**, Swern oxidation and methylenation gave vinylepoxide **3**. Ammonolysis, *N*-tosylation and cyclisation under Mitsunobu conditions gave **2** in 51% overall yield for the six-step sequence from **1**. Enantiomerically pure (2*R*,3*R*)-**2** was made using the same sequence, carrying out the epoxidation of **1** using Sharpless AE instead of *m*-CPBA.

Reaction of enantiomerically pure aziridine (2*R*,3*R*)-**2** with the lithio-anion of **4a** gave a single product. Assignment of structure **5a** followed from the TsNHC*H* methine *δ*-value of 3.74 ppm, indicative of its non-allylic nature. Reaction of the conjugate base of **4b** with (2*R*,3*R*)-**2** in similar fashion gave in excellent yield a 3 : 1 mixture of diastereoisomeric sulfonamides **5b**. Treatment of **5b** with $BF_3{\cdot}OEt_2$ gave in high yield a mixture of tetrahydropyridines, which upon exposure to $SnCl_4$ gave in 56% yield a single tricyclic product **6**.[5] The structure of **6**, and therefore that of **5b** followed from the absence of coupling between H-2 and the ethenyl methine proton (Scheme 2).



Scheme 1 Synthesis of (±)-**2**. *Reagents and conditions*: (i) Chloramine-T®, $PhNMe_3Br_3$, MeCN, rt, 24 h: 77%; (ii) Dess–Martin periodinane, wet CH_2Cl_2, rt, 2 h: 60%; (iii) Ph_3PCH_3Br, $KN(SiMe_3)_2$, THF, −20 °C, 35 min, then rt, 10 min: 71%; (iv) *m*-CPBA, CH_2Cl_2, −78 °C → rt, 4 h: 96%; (v) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −78 °C → rt, 1 h; (vi) Ph_3PCH_3Br, KHMDS, THF, −20 °C, 1.5 h: 83% over two steps from epoxyalcohol; (vii) aq. NH_4OH (28% NH_3), 110 °C (microwave), 35 min: 84%; (viii) TsCl, DMAP, Et_3N, CH_2Cl_2, −5 °C → 0 °C, 3 h: 81%; (ix) DIAD, PPh_3, THF, −25 °C then −5 °C, 13 h: 94%.

Further studies showed that the anion of allylic sulfone **4c** combined with (±)-**2** to give **5c** as a single regio- and stereoisomer, as evidenced by X-ray crystallographic analysis



Scheme 2 Ring-opening reactions of (2*R*,3*R*)-**2**. *Reagents and conditions*: (i) **4a** + *n*BuLi, THF, −50 °C → −20 °C, then (*R*,*R*)-**2**, −20 °C → rt, 12 h: 74% based on (*R*,*R*)-**2**; (ii) **4b** + *n*BuLi, THF, −30 °C, then (*R*,*R*)-**2**, −30 °C → −15 °C → rt, 12 h: 90% based on **2**; (iii) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C → −50 °C, 2.5 h: 83%; (iv) $SnCl_4$, CH_2Cl_2, −78 °C → 0 °C, 5 h: 56%.

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(Fig. 1). Upon lithiation and reaction with (±)-**2**, allylic sulfide **4d** gave a 5 : 1 diastereoisomeric mixture of adducts **5d**.[6] The major isomer was again assigned by X-ray crystallography, of the *N*-methyl derivative **7** (Fig. 1); this was made in 82% yield by treatment of the separated major (2*R**,3*S**,4*S**) diastereoisomer of **5d** with *t*BuOK and CH_3I in THF. Propargylic sulfide **4e** was doubly deprotonated[7] and combined with (±)-**2** to give the terminal alkyne **5e** as a 2 : 1 mixture of isomers. Finally, reaction of the potassium enolate of methyl 2-tosylacetate with (±)-**2** resulted in regioselective ring-opening followed by cyclisation *in situ* to give the *N*-tosyl-γ-lactam **8** (Scheme 3, Table 1).

These results demonstrate the powerful directing effect of the vinyl group on the regiochemistry of aziridine ring-opening. This may be rationalised in terms of selective weakening of the allylic C–N bond of the aziridine by πC=C–σ*C–N overlap. Aryl groups have been reported to show analogous directing effects, in ring-opening reactions of arylaziridines by electron-rich arenes proceeding through S_EAr-type mechanisms,[8–13] by sulfoxonium ylides,[14] and by organometallic reagents.[15] In contrast, reaction of vinylaziridines with organomagnesium[16] and organocopper[17–19] reagents frequently gives predominantly the allylic amine products of S_N2'-type ring-opening.

The second part of this investigation focused on the regioselective ring-opening of hydroxymethyl-substituted aziridines. Prior to our work, a single example of such a process had been reported.[20] Two hydroxymethyl-substituted aziridines were selected for our study. Substrate (±)-**9** had already been prepared by direct aziridination of **1**; *syn*-configured indole-containing aziridine (±)-**12** was assembled in good overall yield from racemic aziridine **10**[21,22] by KH-mediated aza-Payne rearrangement,[23] $BF_3{\cdot}OEt_2$-assisted ring-opening of the resultant epoxide **11** by 1-methylindole,[24] and cyclisation of product alcohol **13** under Mitsunobu conditions followed by silyl deprotection (Scheme 4).

Reaction of *O*-lithiated **9** with lithio-**4c** gave a 10 : 1 mixture of diastereoisomers of tosamide **14** in 52% yield. Similar reaction of *O*-lithio-**12** with **4b** gave a 1 : 1 mixture of adducts **16** in 83% yield. No products corresponding to aza-Payne rearrangement of **9** or of **12** were detected in their ring-opening reactions. Treatment of the major isomer of **14** with paraformaldehyde under acidic conditions gave *N*-tosylaminal **15**, whose identity was firmly estabilised by X-ray crystallographic

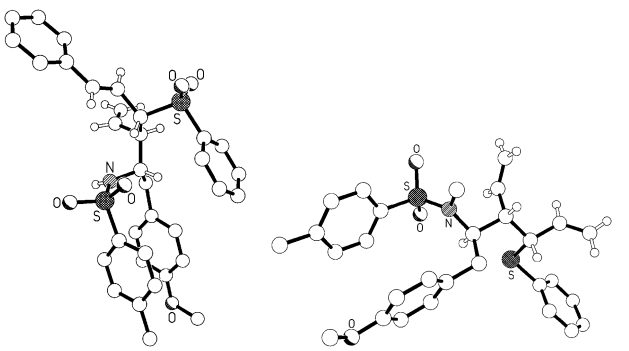
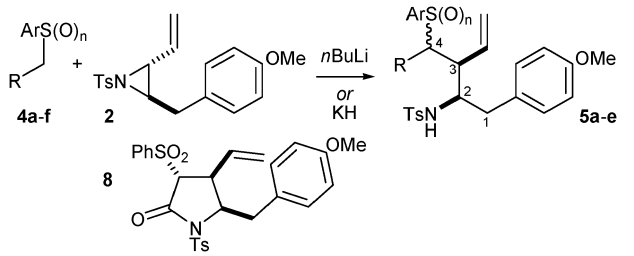


Fig. 1 The molecular structures of (±)-**5c** (left, major isomer) and (±)-**7** (right).

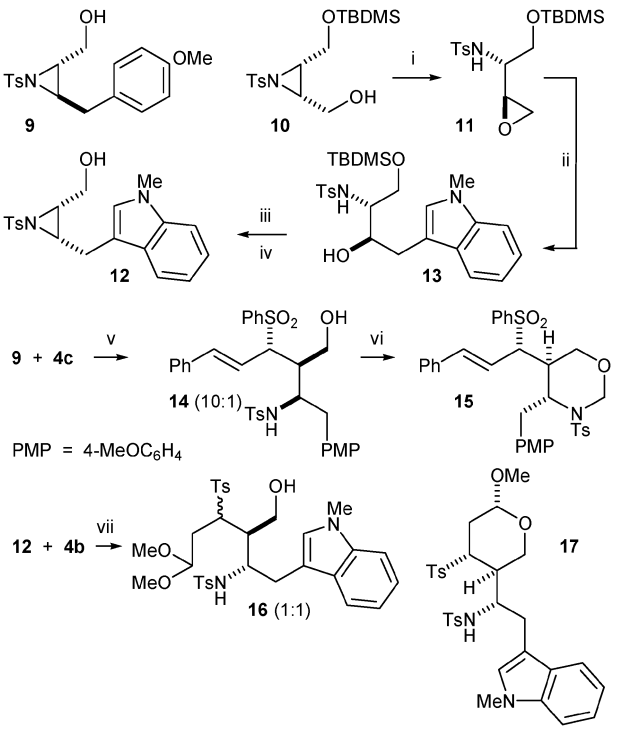


Scheme 3 Ring-opening reactions of **2** by sulfur-stabilised carbanions **4**.

Table 1 Ring-opening reactions of **2**

Entry	Ar	R	*n*	Ratio **4** : **2**	Yield of **5** (%)	dr
a[a]	Tol	H	2	2	74	—
b[a]	Tol	$(MeO)_2CHCH_2$	2	1.5	90	3 : 1[b]
c[c]	Ph	*E*-PhCH=CH	2	1.3	45	10 : 1[d]
d[c]	Ph	H_2CCH	0	1.1	76	5 : 1[e]
e[cf]	Ph	HCC	0	1.2	76	2 : 1[g]
f[ch]	Ph	MeO_2C	2	1	89[i]	1 : 0

[a] Enantiomerically pure (2*R*,3*R*)-**2** was used. [b] The major diastereoisomer had (2*R*,3*S*,4*R*) configuration. [c] Racemic (2*R**,3*R**)-**2** was used. [d] The major diastereoisomer had (2*R**,3*S**,4*R**) configuration. [e] The major diastereoisomer had (2*R**,3*S**,4*S**) configuration. [f] 2 Equiv. of *n*BuLi with respect to **4e** was used. [g] The major/minor diastereoisomer structures were not assigned. [h] 1.1 Equiv. of KH with respect to **4f** was used. [i] The product was lactam **8**.



Scheme 4 Synthesis of **12** and ring-opening reactions of **9** and **12**. *Reagents and conditions*: (i) NaH, THF, 0 °C, 3 h: 100%; (ii) 1-methylindole, $BF_3{\cdot}OEt_2$, $NaHCO_3$ (anhyd. solid), CH_2Cl_2, −70 °C: 85%; (iii) PPh_3, DIAD, THF, rt, 1 h: 97%; (iv) TBAF, THF, 0 °C 10 min: 91%; (v) *n*BuLi added to **9**, THF, −78 °C, 5 min, then PhCH=CHCHLiSO_2Ph (generated from **4c** + *n*BuLi, THF), −78 °C → rt: 52%; (vi) $(HCHO)_n$, cat. *p*-TsOH·H_2O, benzene, 90 °C, 6 h: 62%; (vii) *n*BuLi added to **4b**, THF, −78 °C, 30 min, then *O*-Li-**12** in THF added, −78 °C → rt, 16 h: 83%.

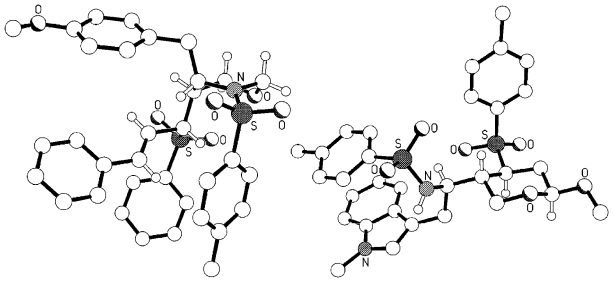


Fig. 2 The molecular structures of (±)-**15** (left) and (±)-**17** (right).

analysis. Structural assignment of **16** followed from the conversion of one of the diastereoisomers into tetrahydropyran **17** on brief treatment with acid (Scheme 4). The X-ray structures of **15** and **17** are shown in Fig. 2.[25]

It seems likely that the lithiated oxygen moiety in **9** and **12** interacts in an attractive sense with lithiated **4**, directing ring-opening to the proximal aziridine carbon.[20] Supporting this idea is the observation that reaction of the *O*-MOM analogue of **12** with lithio-**4b** gave a mixture of regiosiomeric products, corresponding to non-selective aziridine ring-opening.

In summary, we have shown that functionally diverse sulfur-stabilised carbanionic species react stereospecifically with both vinyl- and hydroxymethyl-containing 1,2,3-trisubstituted aziridines with complete regioselectivity. We anticipate that these transformations will be useful in the synthesis of alkaloids and related structures, and we are currently investigating the total synthesis of several natural product targets based on this chemistry.

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24 We thank Mr Niels Tholen (Imperial College) for optimisation of this reaction. This transformation also may be carried out using 1-methylindole (1.25 equiv. with respect to **11**) in the presence of $ZnCl_2$ (0.35 equiv.) under microwave irradiation conditions (CH_2Cl_2 [0.8 M], 80 °C, 2 × 30 min; 95%).

25 *Crystal data for* **5c**: $C_{34}H_{35}NO_5S_2$, M = 601.75, orthorhombic, *Pbca* (no. 61), a = 16.4954(2), b = 13.9284(3), c = 26.6078(5) Å, V = 6113.26(19) Å^3, Z = 8, D_c = 1.308 g cm^{-3}, μ(Mo-Kα) = 0.217 mm^{-1}, T = 173 K, colourless tablets, Oxford Diffraction Xcalibur 3 diffractometer; 7155 independent measured reflections (R_{int} = 0.050), F^2 refinement, R_1(obs) = 0.067, wR_2(obs) = 0.141, 5780 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta_{max}$ = 57°], 394 parameters. CCDC 698819. *Crystal data for* **7**: $C_{29}H_{33}NO_3S_2$, M = 507.68, orthorhombic, *Pbca* (no. 61), a = 15.6552(2), b = 12.3842(2), c = 28.0436(4) Å, V = 5437.01(14) Å^3, Z = 8, D_c = 1.240 g cm^{-3}, μ(Cu-Kα) = 2.009 mm^{-1}, T = 173 K, colourless tablets, Oxford Diffraction Xcalibur PX Ultra diffractometer; 3002 independent measured reflections (R_{int} = 0.038), F^2 refinement, R_1(obs) = 0.042, wR_2(obs) = 0.076, 1958 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta_{max}$ = 104°], 318 parameters. CCDC 698820. *Crystal data for* **15**: $C_{34}H_{35}NO_6S_2$, M = 617.75, orthorhombic, *Pccn* (no. 56), a = 15.99842(7), b = 30.52231(13), c = 12.73593(6) Å, V = 6219.07(5) Å^3, Z = 8, D_c = 1.320 g cm^{-3}, μ(Cu-Kα) = 1.932 mm^{-1}, T = 173 K, colourless tablets, Oxford Diffraction Xcalibur PX Ultra diffractometer; 6002 independent measured reflections (R_{int} = 0.050), F^2 refinement, R_1(obs) = 0.038, wR_2(obs) = 0.105, 4796 independent observed absorption-corrected reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta_{max}$ = 142°], 390 parameters. CCDC 698821. *Crystal data for* **17**: $C_{31}H_{36}N_2O_6S_2$, M = 596.74, monoclinic, $C2/c$ (no. 15), a = 15.217(9), b = 15.731(3), c = 26.981(5) Å, β = 101.78(3)°, V = 6323(4) Å^3, Z = 8, D_c = 1.254 g cm^{-3}, μ(Mo-Kα) = 0.212 mm^{-1}, T = 213 K, colourless blocks, Bruker P4 diffractometer; 4093 independent measured reflections (R_{int} = 0.046), F^2 refinement, R_1(obs) = 0.070, wR_2(obs) = 0.141, 2042 independent observed reflections [$|F_o| > 4\sigma(|F_o|)$, $2\theta_{max}$ = 45°], 383 parameters. CCDC 699430.