Expedient synthesis of substituted (*S*)-*N*-(α-methylbenzyl)aziridines†

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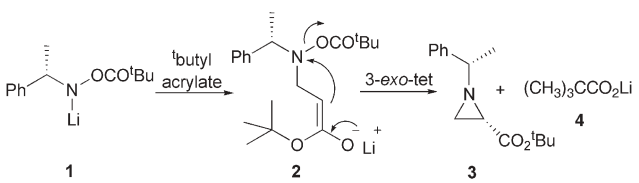
We report for the first time that after *O*-acylation the conjugate addition products of (*S*)-*N*-(α-methylbenzyl)hydroxylamine undergo an efficient diastereoselective 3-*exo*-tet ring-closure reaction affording 2- and 2,3-disubstituted-*N*-alkylaziridines in good to excellent yields.

Chiral non-racemic aziridines[1] are highly versatile chemical entities which readily undergo regio- and stereo-selective ring-opening reactions.[2] The synthesis of optically active aziridines has recently been reviewed.[3] The bioactive component of many aziridine containing natural products can usually be attributed to the presence of the strained, 3-membered heterocycle. The biological activities associated with many aziridines ensure that protocols for their efficient asymmetric synthesis are important.[4]

This *Communication* reports our preliminary studies towards an efficient, high yielding, one-pot asymmetric synthesis of optically active (*S*)-*N*-(α-methylbenzyl)-2- and -2,3-disubstituted aziridines. Our studies focused on undertaking a conjugate addition reaction between the readily synthesised lithium salt of *O*-pivaloyl-(*S*)-*N*-(α-methylbenzyl)hydroxylamine **1** and an acrylate ester. We pondered the possibility that enolate **2**, derived from the initial conjugate addition, would undergo nucleophilic attack, *via* a 3-*exo*-tet cyclisation, on to the nitrogen atom of the *O*-pivaloyl hydroxylamine to yield **3** with concomitant expulsion of **4**. Stereochemical control of the ring-closure by incorporating an optically active *N*-substituent intrigued us (Scheme 1).

Appending optically active *N*-substituents on *O*-acylated hydroxylamines for the asymmetric synthesis of chiral non-racemic aziridines has not, as far as we are aware, been reported. Encouraged by this, the reaction outlined in Scheme 1 was attempted. However to our disappointment all attempted conjugate addition reactions with **1** returned either protonated **1**, *O*- to *N*-pivaloyl migration products or decomposition products of **1**.



Scheme 1 Asymmetric synthesis of *N*-alkylaziridine **3**.

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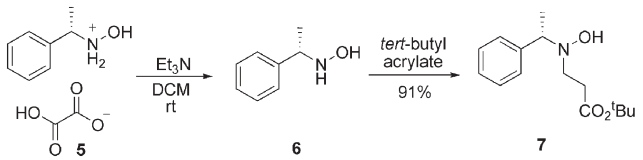
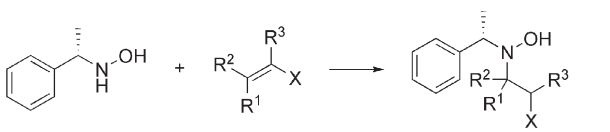


Scheme 2 Synthesis of conjugate addition product **7**.

Saito *et al.*[5] and Baldwin *et al.*[6] have demonstrated that **6** undergoes conjugate additions to activated C=C bonds. Replacing **1** with *in situ* generated **6** (Et_3N and **5**, Scheme 2) allowed the conjugate addition with *tert*-butyl acrylate. To our delight **7** was returned in a 91% yield.

Surveying and extending the reaction protocol outlined in Scheme 2 for the potential of **6** to undergo further conjugate addition reactions a number of alternative C=C activating groups and *trans*-1,2-disubstituted C=C bonds were explored. The reaction was fully amenable to variation on the alkyl group of the acrylate ester, *i.e. tert*-butyl, ethyl and benzyl returning β-[(*S*)-*N*-(α-methylbenzyl)aminohydroxy] alkyl esters in excellent yields (entries 1, 2 and 3, Table 1). Although phenyl acrylate (entry 4) underwent conjugate addition, the resulting adduct cyclised *via* the hydroxy group to yield an isoxazolidin-5-one.[7] Electron-rich 3,4,5-trimethoxyphenyl acrylate ester failed to react altogether and sterically hindered 2,4,6-trimethylphenyl acrylate ester afforded the desired conjugate addition adduct (49%), but similar to entry 4, isoxazolidin-5-one formation was observed (50%). Substituting the carboxylic ester for alternative activating groups, *i.e.* phenylsulfone, nitrile and nitro species, was very successful (entries 5–7 respectively, diastereoselectivity for entry 7 was 66 : 34), returning 91%–100% yields of the corresponding addition products. The

Table 1 Summary of conjugate addition products using **6**



N°	R^1	R^2	R^3	X	%
1	H	H	H	$-CO_2{}^tBu$	97
2	H	H	H	$-CO_2Et$	100
3	H	H	H	$-CO_2Bn$	100
4	H	H	H	$-CO_2Ph$	95[8]
5	H	H	H	$-SO_2Ph$	91
6	H	H	H	–CN	100
7	H	Ph	H	$-NO_2$	100
8	H	H	CH_3	$-CO_2Et$	100
9	H	CH_3	H	$-CO_2Et$	100
10	H	Ph	H	$-CO_2Ph$	57[8]
11	CH_3C=C	H	H	$-CO_2Et$	0

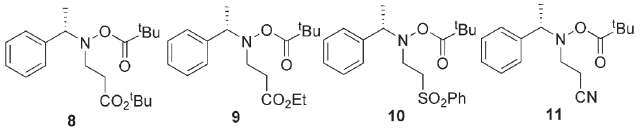


Fig. 1 *O*-acylated conjugate addition products of (*S*)-*N*-(α-methylbenzylamine)hydroxylamine.

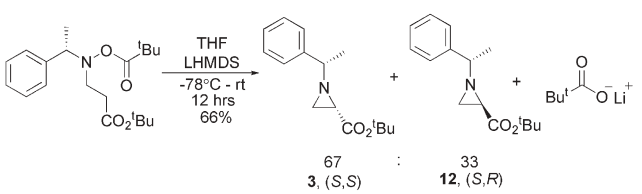
conjugate addition of **6** to ethyl methacrylate and ethyl *trans*-crotonate (entries 8 and 9, diastereoselectivity 63 : 37 and 82 : 18 respectively) proceeded in quantitative yields. Disappointingly our attempts at incorporating an amide functional group *via* the conjugate addition of **6** with *N*-acryloylmorpholine failed.

Employing our standard reaction protocol for the *in situ* synthesis of **6** (from **5**, Scheme 2) and either methyl, ethyl or *tert*-butyl cinnamate, yielded none of the desired conjugate addition products. Perhaps not surprisingly, given the lack of reactivity between **6** and the cinnamates mentioned, ethyl tiglate failed to react with **6**, even after prolonged periods of heating. Likewise the *trans*,*trans*-α,β,γ,δ-diene of ethyl 2,4-hexadienoate (entry 11) also failed to react with **6**, even after refluxing in THF for 72 hours. In contrast, phenyl cinnamate (entry 10), similar to phenyl acrylate (entry 4), underwent a conjugate addition reaction with **6** but, as observed for phenyl acrylate, the subsequent addition product underwent cyclisation.[7] Interestingly the C=C bonds of the *phenyl esters* of cinnamic and acrylic acid underwent conjugate addition reactions. This contrasts sharply with the lack of reactivity with the *alkyl esters*, *i.e.* methyl, ethyl or *tert*-butyl esters of cinnamic acid.

Acylation of the conjugate addition adducts with either pivaloyl chloride or cyanide of selected hydroxyamines (entries 1, 2, 5, and 6, Table 1) was attempted. The optically active (*S*)-*N*-(α-methylbenzylamine)-*O*-pivaloyl hydroxylamine adducts **8–11** (Fig. 1) were afforded in good to excellent yields (75–93%).

With *O*-pivaloyl hydroxylamines **8–11** in hand, our attention was directed to their transformation into chiral non-racemic aziridines *via* a diastereoselective 3-*exo*-tet cyclisation. A solution of **8** was cooled (−78 °C) and LHMDS added, presumably forming the corresponding enolate. The enolate attacks the nitrogen of **8** affording the desired optically active aziridines (Scheme 3). Gratifyingly a 66% yield of both **3** and **12** was returned as a partially separable mixture of diastereomers (67 : 33 respectively). Assignment of **3** and **12** as the (*S*,*S*) and (*S*,*R*) diastereomers respectively was based on reported ^{1}H-NMR and $[\alpha]_D$ values.[9]

Repeating the reaction protocol in Scheme 3 with *O*-pivaloyl hydroxylamines **9**, **10** and **11** the synthesis of the corresponding aziridines was attempted. We were delighted to find after aqueous work-up diastereomeric mixtures of aziridines **13–15** (**13**, 75 : 25; **14**, 78 : 22; **15**, 69 : 31) were afforded in 42–67% yields.



Scheme 3 Asymmetric synthesis of (*S*,*S*)-**3** and (*S*,*R*)-**12**.

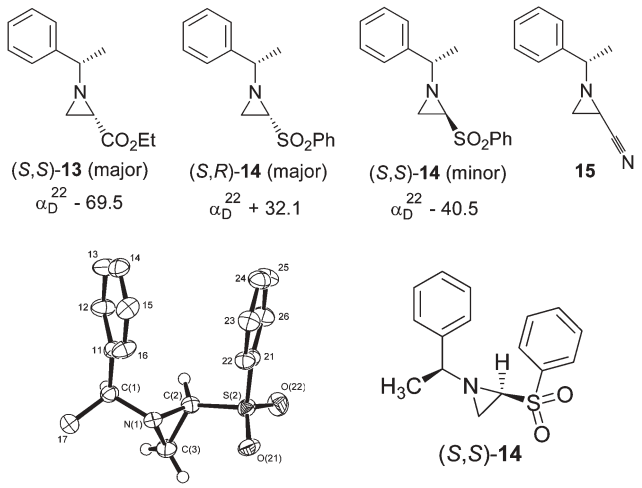


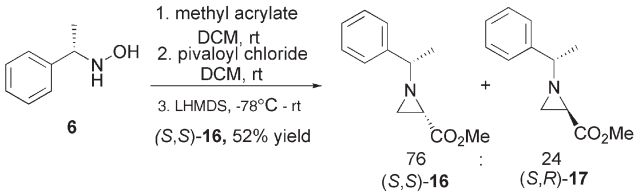
Fig. 2 Optically active aziridines synthesised from **9**, **10** and **11** and X-ray crystal structure of (*S*,*S*)-**14**.

The (*S*,*S*) and (*S*,*R*) diastereomers for **14** were readily separated using flash chromatography. In agreement with published data,[9] the absolute stereochemistry for the major diastereomer (**13**) was assigned (*S*,*S*). X-ray analysis of a crystal of the minor diastereomer of **14** conclusively proved that our assignment as the (*S*,*S*) configuration was correct (Fig. 2).‡ Attempts at purifying and or separating the diastereomers of **15** resulted in their decomposition.

Utilising **6** and methyl acrylate the conjugate addition product was synthesised in quantitative yield and *O*-acylated. Deprotonation afforded a diastereomeric mixture of separable aziridines (*S*,*S*)-**16** (52% yield) and (*S*,*R*)-**17** (76 : 24 respectively, Scheme 4). Physicochemical data for (*S*,*S*)-**16** and (*S*,*R*)-**17** were essentially the same as reported by Farooq *et al.*[10] and Seebach *et al.*[11]

Employing **8**, the conditions outlined in Scheme 3 and various temperatures we investigated the yield and diastereoselectivity of the reaction. At −100 °C or −78 °C the ratio of **3** : **12** was approximately the same (77 : 23). Conducting the cyclisation at −60 °C the yield of **3** : **12** fell to 45% but, interestingly, the diastereoselectivity increased. Remarkably, at −40 °C the diastereoselectivity increased still further to 91 : 9 and at −20 °C the diastereoselectivities and yields were both excellent (90 : 10, 93%).

Further studies, employing **8**, investigated the effect on the reaction when alternative bases[7] and solvents[7] were employed at −40 °C. Substituting LHMDS for either NaH, BEMP, n-BuLi or *t*-BuOK afforded **8** or poor yields of **3** and **12**. However LDA, LHMDS, NaHMDS, KHMDS or lithium diphenylamide returned excellent yields of **3** and **12** with poor (45 : 55 for LDA) to excellent (93 : 7 for LHMDS) diastereomeric ratios of **3** : **12** resulting.



Scheme 4

Utilising **8**, the effect on the yield and diastereoselectivity of the aziridination reaction in solvents of differing polarity was investigated. Employing LHMDS as the base, conducting the reactions at −40 °C and using a diverse selection of solvents,[7] it is clear that for **8**, THF is the optimum solvent affording a quantitative yield and excellent diastereoselectivity (93 : 7) for **3** : **12** respectively.

Undertaking a one-pot aziridination, we were delighted that stirring salt **5**, *tert*-butyl acrylate and triethylamine afforded **7**. Without work-up, *O*-acylation (pivaloyl cyanide), cooling to −40 °C and addition of LHMDS (3 eq) afforded a diastereomeric mixture of aziridines **3** : **12** (67 : 33 respectively) in a 64% yield.

In summary our preliminary results demonstrate for the first time that the *O*-acylated conjugate addition adducts of **6** afford (*S*)-*N*-(α-methylbenzyl)-2- and 2,3-disubstituted aziridines in good to excellent yields and good diastereoselectivity. These results reveal that optically active *N*-α-methylbenzyl groups are able to induce high levels of stereocontrol *via* 3-*exo*-tet ring-closure reactions on to *O*-acylated hydroxylamines, furthermore our innovative protocol is robust and amenable to a wide variety of alkene substrate types.

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Notes and references

‡ Crystal data for (*S*,*S*)-**14**: $C_{16}H_{17}NO_2S$, M = 287.4. Orthorhombic, space group $P2_12_12_1$ (no. 19), a = 8.587(3), b = 11.452(2), c = 15.080(4) Å, V = 1483.0(7) Å^3. Z = 4, D_c = 1.287 g cm^{-3}, $F(000)$ = 608, T = 293(2) K, μ(Mo-Kα) = 2.2 cm^{-1}, λ(Mo-Kα) = 0.71069 Å. Crystals are colourless, rectangular prisms. Intensity data were measured on a Nonius CAD4 diffractometer (with monochromated radiation); 2573 reflections to θ_{max} = 27.5°, 2394 unique reflections (R_{int} = 0.054), 2189 'observed' with $I > 2\sigma_I$. Corrections were applied for Lorentz-polarisation effects, absorption (by semi-empirical ψ-scan methods) and to eliminate negative net intensities (by Bayesian statistical methods). Structure determined by direct methods in SHELXS,[12] and refined by full-matrix least-squares, on F^2's, in SHELXL.[12] The Flack parameter, x, indicates that the correct absolute configuration has been refined, and is that shown in Fig. 2. At convergence, wR_2 = 0.094 and R_1 = 0.040 (A2) for all 2394 reflections weighted $w = [\sigma^2(F_o^2) + (0.0534P)^2 + 0.11P]^{-1}$ with $P = (F_o^2 + 2F_c^2)/3$; for the 'observed' data only, R_1 = 0.037. CCDC 606486. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b606033a

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