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COMMUNICATION

Stereoselective aza-Darzens reactions of *tert*-butanesulfinimines: convenient access to chiral aziridines†

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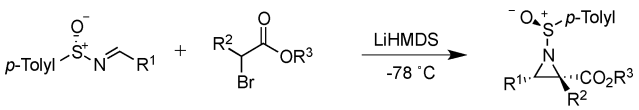
Stereoselective synthesis of 2,3-di- and 2,2′,3-tri-substituted aziridines in good yields and excellent diastereoselectivities are achieved through aza-Darzens reactions of a range of *tert*-butanesulfinyl aldimines and ketimines with ethyl bromoacetate.

Synthetic interest in aziridines as potentially versatile intermediates has increased over the past decade,[1] prompted by the increasing numbers of methods for the stereoselective synthesis of chiral functionalised aziridines.[2] A number of methodologies have been developed for the synthesis of chiral aziridines, including many catalytic asymmetric methods.[3] However, one of the simplest methodologies for the stereoselective synthesis of aziridines is the addition of a carbenoid to chiral sulfinimines.[4] Sulfinimines are simple to synthesise from the commercially available *tert*-butanesulfinamide and aldehydes under simple dehydrating conditions,[5] or can be synthesised in a few steps from commodity chemicals using auxiliary-based methodologies.[6] Two main variants of sulfinimines are commonly used: the *p*-toluenesulfinimines developed by Davis and the *tert*-butanesulfinimines introduced by Ellman. The *p*-toluenesulfinimines have the advantage that they are UV active, and thus enable easy monitoring of the reaction, whilst the *tert*-butanesulfinimines generally have been found to confer a greater degree of stereoselectivity due to their increased steric bulk.[4]

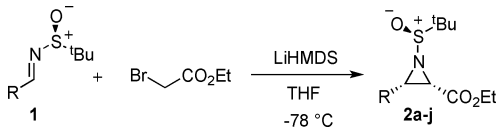
As part of a programme aimed at the exploitation of aziridines as versatile synthetic intermediates for the synthesis of a range of amino acid derivatives, we required an efficient and concise access to chiral aziridines bearing an ester at the 2-position. We were drawn to the reports of Davis on the aza-Darzens reactions of *p*-toluenesulfinimines with α-bromoesters (Scheme 1),[7] and wondered if the increased steric bulk of *tert*-butanesulfinimines would provide an increase in stereoselectivity. We herein report our initial findings in this area, the publication of which has been prompted by Njardarson's recent report of similar work on the synthesis of vinyl aziridines.[8]



12 examples, 20-85% yield, 2:1 to 11:1 *cis/trans*, 52-98% de

Scheme 1 Davis's aza-Darzens reactions of *p*-tolylsulfinimines.

Table 1 Aza-Darzens reaction of *tert*-butanesulfinyl aldimines



Entry	*R*	Time (h)	Yield[a] (%)	de (%)[a]	*Z*/*E*[b]	Product
1	Ph	2.75	79	>98	91 : 9	**2a**
2	Cyclohexyl	2	81	>98	92 : 8	**2b**
3	4-MeOPh	3[c]	69	>98	98 : 2	**2c**
4	4-NO_2Ph	2.5	56	>98	71 : 29	**2d**
5	2-Pyridyl	3[d]	55	>98	83 : 17	**2e**
6	2-Furanyl	3[c]	86	>98	86 : 14	**2f**
7	Cyclopropyl	2	56	>98	90 : 10	**2g**
8	*n*-Octyl	2	66	>98	80 : 20	**2h**
9	Methyl	2	49	>98	90 : 10	**2i**
10	*tert*-Butyl	2.5	77	>98	95 : 5	**2j**

[a] Major isomer. [b] *cis*/*trans* Ratio determined from the ^{1}H NMR of the crude mixture. [c] After 2 h solution was allowed to reach r.t. [d] Solution was allowed to reach r.t. after imine addition.

We first thought to look at the synthesis of 1,2-disubstituted aziridines through the reaction of sulfinyl aldimines with ethyl-bromoacetate under basic conditions. The *tert*-butanesulfinimines were synthesised by Ellman's protocol,[5] using commercially purchased *tert*-butanesulfinamide. The results of our investigation into the scope of the aza-Darzens reaction of sulfinylaldimines is summarised in Table 1.

We found that in all cases, good *Z* : *E* ratios (4 : 1 to 19 : 1) and outstanding diastereoselectivities were achieved (judged by ^{1}H NMR of the crude reaction product). This compares favourably with the *p*-toluenesulfinimines which gave diastereoselectivities in the range of 52–98%, and *Z* : *E* ratios in the range 2 : 1 to 11 : 1,[7] confirming our hypothesis that the *tert*-butanesulfinimines would confer a greater sense of stereocontrol. We were fortunate that several of the products were crystalline, and thus we obtained an X-ray crystallographic analysis of **2c** to confirm the absolute stereochemistry (Fig. 1). Yields in general were good, with the

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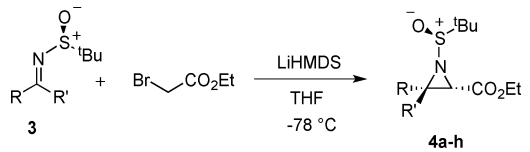
† Electronic supplementary information (ESI) available: Experimental procedures for the synthesis of aziridines. See DOI: 10.1039/c1ob05561e

Table 2 Aziridination of *tert*-butanesulfinyl ketimines



Entry	R, R′	Time (h)	Yield[a] (%)	de[a] (%)	*Z*/*E*[b]	Product
1	Ph, Ph	2	95	96	—	**1a**
2	-$(CH_2)_5$-	3.5[c]	36	76	—	**1b**
3	-$(CH_2)_6$-	4[c]	23	62	—	**1c**
4	Ph, Me	2.5[d]	65	>98	85 : 15	**1d**
5	2-thiophene, Et	5[c]	43	>98	93 : 7	**1e**
6	Heptyl, Me	3	50	>98	71 : 29	**1f**
7	Cyclohexyl, Et	6[c]	—	—	—	—

[a] Major isomer. [b] *cis*/*trans* Ratio determined from the ^{1}H NMR of the crude mixture. [c] Reaction at r.t. [d] Solution was allowed to reach r.t. after 2.5 h.

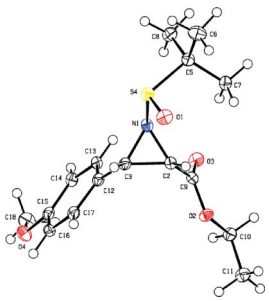


Fig. 1 X-Ray structure of **2c**.

more sterically encumbered substrates giving the best yields. We found no examples that failed to give the expected aziridine product. The major product in each case was the *cis* aziridine, in line with Davis's findings on the *p*-toluenesulfinimines, suggesting that the closed-transition state model put forward by Davis is operating in these examples (Fig. 2).[7]

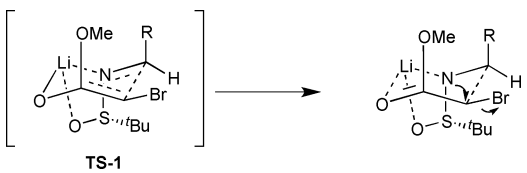


Fig. 2 Closed transition state.

We next decided to look at a class of substrates not investigated by Davis: sulfinylketimines. These substrates should yield trisubstituted aziridines, and we were keen to discover if the decreased reactivity of ketimines *vs.* aldimines would be tolerated. Our results are summarised in Table 2.

Once again, we were pleased to find that most substrates prepared gave aziridines in high diastereoselectivity. Yields were predictably lower than for the aldimines substrates, due to increased steric interactions and lower reactivity of the ketimines. The bulky cyclohexylketimine, **3h**, was found not to react, showing the limitations of the method. The two cyclic ketimines were also relatively poor substrates, again presumably due to steric hindrance.

Conclusions

In conclusion we have found that the aza-Darzens reaction of *tert*-butanesulfinyl aldimines and ketimines is a reliable and stereoselective method for the synthesis of 2,3-disubstituted and 2,2′,3-trisubstituted aziridines. Our investigations into the synthesis of even more highly substituted aziridines using this method, and the use of these as chiral building-blocks for synthesis are on-going and will be reported in due course.

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