Organic LETTERS

Letter

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Asymmetric Synthesis of Trisubstituted Aziridines via Aza-Darzens Reaction of Chiral Sulfinimines

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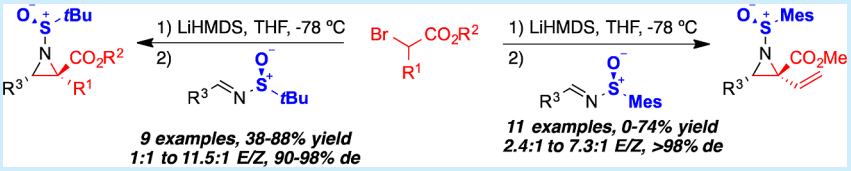
Supporting Information



ABSTRACT: The aza-Darzens reaction of substituted 2-bromoesters with chiral *tert*-butane- and mesitylsulfinimines provides a rapid access to a range of highly substituted aziridines in good yields and excellent levels of stereoselectivity. The synthetic potential of this protocol is further enhanced by the successful removal of the sulfinyl motif, yielding simple access to chiral N−H aziridines in just three steps from commercial aldehyde precursors.

Chiral aziridines are of great interest as powerful synthetic building blocks in organic synthesis, as their inherent chemical reactivity allows for a wide variety of transformations for the preparation of different nitrogen-containing compounds.[1] In this regard, numerous efforts have been directed toward the synthesis of this class of substrates in a stereoselective fashion.[2] Of those methods, the addition of carbenoids onto chiral imines represents one of the most common strategies to access asymmetric aziridines. Given the simplicity of chiral sulfinimine preparation, and the ready availability of aldehydes, their synthetic precursors, chiral sulfinimines have become one of the most promising intermediates for the asymmetric construction of chiral amines.[3]

Over the past decade, several groups have exploited the potential of sulfinimines for the asymmetric synthesis of aziridines.[2] Despite the advances realized within this field, there persists to be a number of issues that still need to be addressed. For instance, a general and reliable method for the synthesis of highly functionalized aziridines from chiral aldimines and disubstituted carbenoids still remains a challenge. While the synthesis of trisubstituted aziridines has been successfully achieved with the use of ketimines,[4] there is only one example on the use of carbenoids with high levels of substitution.[5a]

Prompted by the preliminary work of Davis on the use of substituted 2-bromoesters in aza-Darzens reactions,[5] and given the better stereodirecting ability of *tert*-butane and mesitylsulfinimines,[4a,6] we decided to explore their potential in their reaction with substituted 2-bromoesters, taking particular interest in the synthesis of 2-vinylaziridine 2-carboxylates, given their synthetic potential as chiral precursors to α- and β-amino acids.[7] Herein, we describe our initial findings on the aza-Darzens reaction of *tert*-butane- and mesitylsulfinimines for the preparation of 2,2′,3-trisubstituted aziridines.

Drawn by their previous success in aziridination reactions, we initially turned our attention to the use of Ellman's *tert*-butanesulfinimines for the synthesis of aziridines. Using standard protocols,[8] we prepared a range of *tert*-butanesulfinimines, which were subjected to previously developed aza-Darzens conditions[4a,5] of LHMDS in THF at −78 °C, with different substituted 2-bromoesters (**2**). The results of these investigations are summarized in Table 1.

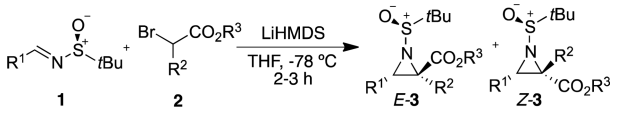
Initially, a range of substituted *tert*-butanesulfinimines were reacted with rather electron-defficient and bulky **2a**, which gave aziridines *E*-**3** as major diastereomers in good yields and excellent stereoselectivities (entries 1−4). Both alkyl (entry 2) and aryl groups (entries 1, 3, and 4) were tolerated under our regular aza-Darzens conditions. While a slight increased yield was found with alkyl and electron-deficient aryl sulfinimines (entries 2 and 4), erosion of the *cis*/*trans* selectivity was also observed. Additionally, we were able to confirm the absolute configuration of the products by X-ray crystallographic analysis of *E*-**3a** (Figure 1). We next examined the reaction with the less bulky methyl 2-bromobutenoate **2b** (entries 2−9). In general, moderate to good yields of aziridines **3** were obtained in all cases using alkyl and aromatic imines. However, the use of aliphatic imines resulted in an almost complete loss of *cis*/*trans* selectivity (entries 6, 8, and 9).

As previously proposed by Davis,[5] the stereoselective outcome of the reaction is dictated by a six-membered transition state (Scheme 1),[9] where the enolate approaches from the less hindered face of the sulfinimine. The locked *E*-

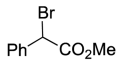
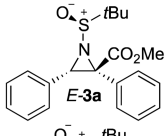
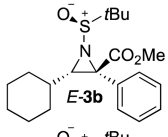
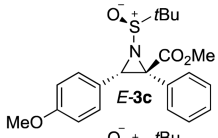
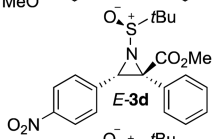
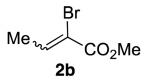
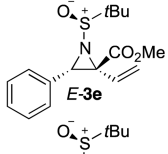
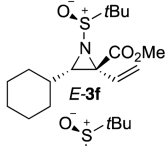
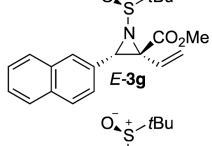
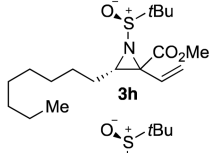
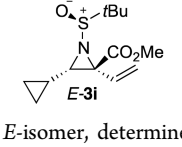
Received: October 10, 2014

   dx.doi.org/10.1021/ol502967x | *Org. Lett.* XXXX, XXX, XXX−XXX

Table 1. Aza-Darzens Reaction of *tert*-Butanesulfinyl Aldimines with Substituted 2-Bromoesters



1 2 *E*-3 *Z*-3

entry	2	3[a]	yield (%)	*E*/*Z*[b]	*de* (%)[b]
1	 **2a**	 *E*-**3a**	63	92 / 8	>98%
2	**2a**	 *E*-**3b**	75	81 / 19	>98%
3	**2a**	 *E*-**3c**	62	92 / 8	>98%
4	**2a**	 *E*-**3d**	76	80 / 20	90%
5	 **2b**	 *E*-**3e**	72	86 / 14	>98%
6	**2b**	 *E*-**3f**	88	52 / 48	>98%
7	**2b**	 *E*-**3g**	64	87 / 13	>98%
8	**2b**	 **3h**	54	50 / 50	>98%
9	**2b**	 *E*-**3i**	38	67 / 33	>98%

[a]Major isomer. [b]de of *E*-isomer, determined by ^{1}H NMR analysis of the crude mixture.

geometry of both the sulfinimine and the enolate accounts for the *cis*/*trans* selectivity.

While the chiral auxiliary group provided excellent levels of stereocontrol in all cases, the poor *cis*/*trans* ratios obtained using aliphatic sulfinimines limited the generality of this protocol. To circumvent this, we envisioned that the use of mesitylsulfinimines could result in better diastereoselectivities given their observed tolerance for large nucleophiles.[6]

Therefore, a range of mesitylsulfinimines were prepared following a one-pot methodology established by our group.[10] Given our interest in 2-vinyl aziridine 2-carboxylates, compounds **4** were subjected to our aza-Darzens conditions using methyl 2-bromobutenoate **2b** (Table 2). In general, aziridines **5** were obtained in good yields and with outstanding levels of stereocontrol. Interestingly, the same sense of

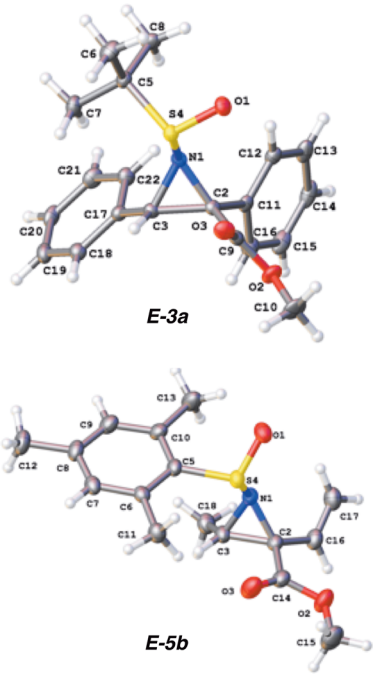
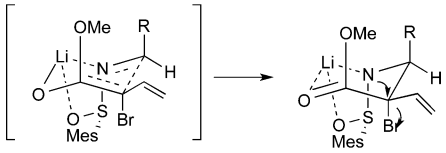


Figure 1. X-ray structures of *E*-**3a** and *E*-**5b**.

Scheme 1. Proposed Transition State Leading to the Major Diastereomer



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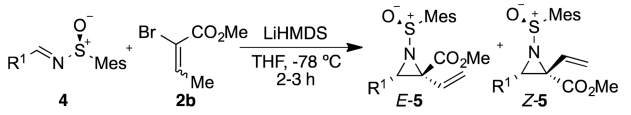
stereoinduction was observed as the *tert*-butanesulfinimines, and thus it appears a closed transition state is in operation, which is contrary to reactivity observed with these sulfinimines in reactions with Grignard reagents[6] (Scheme 1). Unfortunately, no product could be obtained when aromatic sulfinimine **4a** was used (entry 1), probably due to the less nucleophilic character of the corresponding negatively charged sulfinamide intermediate, which prevents the ring-closing step. Nevertheless, the reaction appears to be general to the use of aliphatic imines **4**. Aziridines **5b** and **5c**, with linear chains at the C3 position, can be obtained in good yields and excellent stereoselectivities (entries 2 and 3). We were fortunate to obtain aziridine **5b** as a crystalline structure, which allowed us to perform X-ray analysis, confirming its expected structure. The steric bulk also plays a crucial role in the outcome of the reaction: while rather bulky aziridine **5d** could be accessed (entry 4), no product was observed with the use of *tert*-butane sulfinimine **4e** (entry 5), showing the limitations of this strategy.[11] The reaction also tolerates different functionalities such as protected alcohols (entry 9), alkenes (entry 10), and alkynes (entry 11). Remarkably, even aziridine **5h** (entry 8), bearing a chloride motif, could be prepared (albeit in low yield).

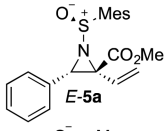
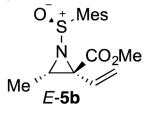
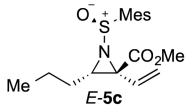
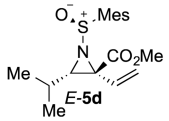
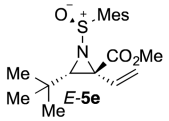
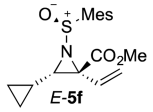
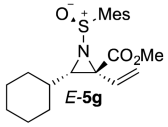
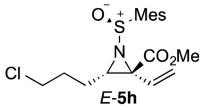
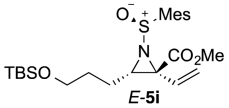
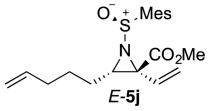
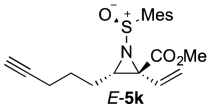
For our program aimed at the utilization of aziridines **5** as chiral building blocks, we required the successful removal of the sulfinyl directing group (Scheme 2). The challenge associated with this transformation arises from the possible aziridine ring-

dx.doi.org/10.1021/ol502967x | *Org. Lett.* XXXX, XXX, XXX−XXX

Table 2. Aza-Darzens Reaction of Mesitylsulfinyl Aldimines with Methyl 2-Bromo-2-butenoate

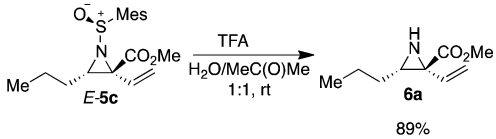


4 2b E-5 Z-5

entry	4[a]	yield (%)[b]	E/Z[c]	de (%)[c]
1	 E-5a	0	-	-
2	 E-5b	74	80 / 20	>98%
3	 E-5c	61	83 / 17	>98%
4	 E-5d	67	81 / 19	>98%
5	 E-5e	0	-	-
6	 E-5f	57[a]	88 / 12	>98%
7	 E-5g	43	71 / 29	>98%
8	 E-5h	14	76 / 24	>98%
9	 E-5i	52	80 / 20	>98%
10	 E-5j	59	79 / 21	>98%
11	 E-5k	63[a]	82 / 12	>98%

[a]Major isomer. [b]As a mixture of diastereomers. [c]Determined by ^{1}H NMR analyses of the crude mixture.

Scheme 2. Removal of the Sulfinyl Group



E-5c 6a 89%

opening reaction due to the harsh acidic conditions usually employed for the removal of sulfinyl groups.[3] However, the deprotection of the mesitylsulfinyl group proved facile, as a milder TFA treatment successfully cleaved the sulfinyl moiety and compound **6a** could be obtained without the need for chromatographic purification.

In conclusion, we have expanded the aza-Darzens methodology using *tert*-butane- and mesitylsulfinimines for the synthesis of highly substituted 2,2′,3-substituted aziridines. The use of Ellman's auxiliary proved suitable for aromatic imines, whereas better *cis*/*trans* ratios were obtained by employment of the mesitylsulfinyl group for aziridines bearing an aliphatic chain at the C3 position. The applicability of this protocol was further illustrated by the successful removal of both chiral auxiliaries. Studies to expand the scope of the aziridination to more heavily functionalized substrates, and toward the use of aziridines **3** and **5** as building blocks, are currently ongoing within our laboratories and will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

General synthetic procedures and characterization and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors wish to thank GlaxoSmithKline (T.M.) and EPSRC (RAS, EP/015078) for funding. Justine Dutton and Jose Souto are thanked for investigating the aziridination of *p*-tolylsulfinimines.

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(9) See Supporting Information.
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(11) The two *p*-toluenesulfinimines derived from benzaldehyde and acetaldehyde were also investigated in the vinyl aziridination reaction, but gave aziridines in yields of <30%, with poor *E*/*Z* selectivity (around 2:1) and low thermal stability (they were found to decompose over a period of several hours). These substrates were therefore not investigated further.

dx.doi.org/10.1021/ol502967x | *Org. Lett.* XXXX, XXX, XXX−XXX