Direct synthesis of chiral aziridines from *N-tert*-butyl-sulfinylketimines

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The direct preparation of a range of variously substituted chiral *tert*-butylsulfinylketimines was achieved in good yield (41–90%), with relatively rapid reaction times (4–15 hours); their synthetic application was examined through the reaction with the ylides derived from trimethylsulfonium iodide and *S*-allyl tetrahydrothiophenium bromide, affording convenient access to a diverse range of highly substituted chiral aziridines in up to 78% yield and > 90% d.e.

Amines, and particularly chiral amines, are key structural functionalities throughout natural products and drug candidates. Perhaps the most direct method of synthesis of functionalised amines is through 1,2-nucleophilic addition to imines. What makes this avenue particularly attractive is the vast pool of readily available inexpensive aldehydes and ketones which can be easily transformed into imines. However, the reactive nature of imines is such that an electron withdrawing *N*-substituent is required to domesticate their character. In this role the *N*-sulfonyl substituent has found widespread application.[1] A significant limitation to the chemistry of *N*-sulfonylimines is the problematic preparation of sulfonyl ketimines.[2] Thus, while sulfonyl-aldimines have enjoyed facile preparation and reaction, the chemistry of their more substituted counterparts is significantly less developed.

Recent reports have detailed the emergence and application of chiral sulfoxides as *N*-protecting groups for imines.[3] Methods have been developed for the direct preparation of these enantiopure building blocks. Both the *p*-tolyl- and *tert*-butyl- chiral sulfinyl moieties have been demonstrated to be successful directing/protecting groups for a large variety of transformations,[4] in addition both the sulfinyl-aldimines and sulfinyl-ketimines are readily accessible.[4]

A particular class of asymmetric amines that has great potential for further elaboration are chiral aziridines.[5] Our previous investigations have focused on the suitability of *tert*-butyl sulfinyl-aldimines as substrates for aziridination *via* reaction with both dimethylsulfonium methylide[6] and allylic sulfur ylides.[7]

We report the extension of the scope of this methodology by demonstrating the suitability of *tert*-butyl-sulfinyl-ketimines as aziridination substrates (Fig. 1).

Using an adaptation of the methods established by Ellman *et al.* for the condensation of *tert*-butyl-sulfinamide with carbonyl compounds[8] provided direct access to a comprehensive range of

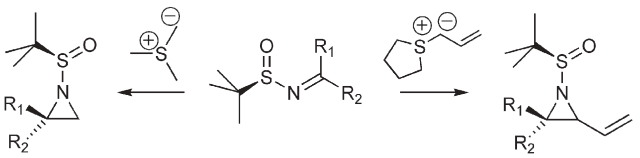


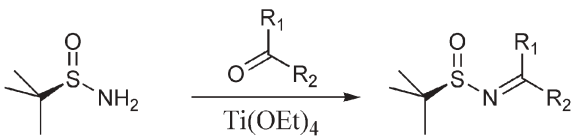
Fig. 1 Synthesis of chiral aziridines from *tert*-butyl-sulfinylketimines.

tert-butyl-sulfinyl-ketimines in good yield. Our results are summarized in Table 1.

At room temperature the condensation of many of the substrates was observed to be sluggish. The formation of *tert*-butyl-sulfinyl-ketimines is known to be accelerated at elevated temperatures.[5] The extent of warming was found to be dependent on the thermal stability of the product; in many of our preliminary investigations thermal decomposition of the ketimine was observed. The temperatures reported in Table 1 reflect the optimum conditions found for the synthesis of the ketimines. Thus the *tert*-butyl-sulfinyl-ketimines were prepared in good yield (41–90%), with the ketimines found to be stable to flash column chromatography.

The high propensity for the *tert*-butyl-sulfinyl-aldimines to reside in the *E*-conformation has been observed throughout the plethora of publications within this field.[1,2] This tendency is also evident for the *tert*-butyl-sulfinyl-ketimines, albeit to a lesser extent, particularly in substrates with less pronounced steric differentiation between the substituents. Our findings were in agreement with this literature precedent; the *E*-isomer predominated in all instances. There were only two cases where the

Table 1 Summary of the preparation of a range of chiral *tert*-butyl-sulfinylketimines



Entry	R_1, R_2	Temp./°C	Time/h	Yield (%)	*E*/*Z*	Prod.
1	Ph, Ph	55	4	69	—	**1a**
2	Me, Ph	55	6	90	> 10/1	**1b**
3	Me, Et	45	6	41	> 10/1	**1c**
4	–$(CH)_4$–	55	4	61	—	**1d**
5	–$(CH)_5$–	55	5	55	—	**1e**
6	–$(CH)_6$–	55	8	62	—	**1f**
7	Et, 2-methyl Bu	45	12	48	> 10/1	**1g**
8	Et, 2-thiophene	45	7	51	~ 5/1	**1h**
9	Et, Cy	45	15	60	> 10/1	**1i**
10	Et, 2-thiazole	50	7	44	~ 6/1	**1j**
11	Me, *n*-hexyl	45	10	51	> 10/1	**1k**

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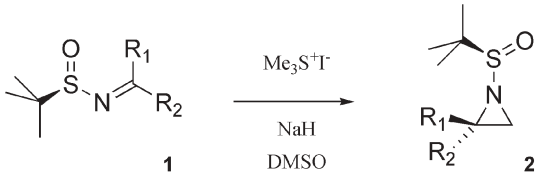
Table 2 Summary of the reaction of *tert*-butyl-sulfinyl-ketimines with dimethylsulfonium methylide



1 **2**

Entry	Substrate	Time/h	Yield (%)	d.e. (%)	Prod.
1	**1a**	4	73	> 95	**2a**
2	**1a**	12	69	> 95	**2a**
3	**1c**	24	trace	—	**2c**
4	**1d**	24	—	—	**2d**
5	**1f**	8	—	—	**2f**
6	**1g**	5	—	—	**2g**
7	**1h**	8	—	—	**2h**
8	**1i**	8	47	> 95	**2i**
9	**1j**	4	trace	—	**2j**
10	**1k**	12	36	> 95	**2k**

Z-isomer was present to any significant extent (entries 8 and 10, Table 1), and in these instances the major isomer could be isolated.

We have previously demonstrated the suitability of *tert*-butyl-sulfinyl-aldimines as substrates for the Corey–Chaykovsky aziridination with dimethylsulfonium methylide, furnishing the aziridines in high yield, and in addition with high stereocontrol gained through the influence of the chiral sulfinyl group.[6] Table 2 summarises our investigations into the suitability of *tert*-butyl-sulfinyl-ketimines as substrates for the optimized Corey–Chaykovsky aziridination procedure.

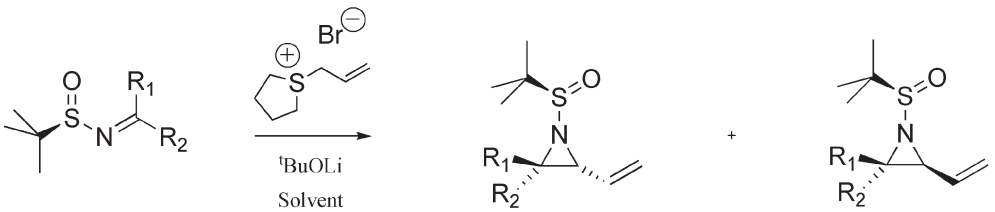
In contrast to our previous findings with the *tert*-butyl-sulfinyl-aldimines, the ketimines were, in general, found not to be suitable substrates for reaction with dimethylsulfonium methylide. Only three of the nine ketimines exposed to the reaction conditions furnished significant amounts of the desired aziridines. While many of the reactions yielded little or none of the desired aziridine, those that were synthesised were formed in excellent diastereoselectivity. It is thought that the low yields observed in the reaction of dimethylsulfonium methylide and the *tert*-butyl-sulfinyl-ketimines are due to the harsh reaction conditions employed; the strained, relatively unstable nature of the ketimines led to a multitude of undesired side reactions upon exposure to sodium hydride, hence we chose to investigate the use of the less basic ylide derived from *S*-allyl tetrahydrothiophenium bromide accessible under much milder conditions.

The reaction of *tert*-butyl-sulfinyl-aldimines with the allylic ylide during previous studies was optimised to provide efficient access to chiral vinyl aziridines.[8] The aziridines were synthesised in high yield[9] with excellent diastereoselectivities and good stereocontrol when the reaction was carried out in THF. However, it was found that by employing DMSO as the solvent aziridines were synthesised in higher yield, albeit with lower stereocontrol. Consideration of the reduced reactivity caused by the greater steric presence inherent in the *tert*-butyl-sulfinyl-ketimines prompted us to investigate the use of both THF and DMSO as the solvent for aziridination. Our results are summarised in Table 3.

The implementation of the allylic ylide proved to provide a more substituent tolerant procedure.[10] The highly strained vinyl aziridines were prepared in good yield (42–85%), excellent diastereoselectivity (between 90– > 95%) and reasonable *cis*/*trans* selectivity. In comparison to the reaction of ketimines with dimethylsulfonium methylide, the yields are significantly improved, with the distinction particularly pronounced for ketimines bearing an enolisable proton.

There are many routes for the elaboration of aziridines,[11] a good proportion of which require deprotection of the aziridine nitrogen.

Table 3 Summary of the reaction of chiral *tert*-butyl-sulfinyl-ketimines with the ylide derived from *S*-allyl tetrahydrothiophenium bromide



1 ***cis* - 3** ***trans* - 3**

Entry	Substrate	Solvent	Time/h	Yield (%)	*trans*/*cis*	d.e. (%)[a]	Prod.
1	**1a**	THF	2	52	—	> 95	**3a**
2	**1a**	DMSO	1.5	85	—	> 95	**3a**
3	**1b**	THF	2.5	72	80/20	> 95	**3b**
4	**1b**	DMSO	2	78	75/25	> 95	**3b**
5	**1d**	THF	6	trace	—	—	**3d**
6	**1d**	DMSO	4	55	—	> 95	**3d**
7	**1e**	DMSO	48	—	—	—	**3e**
8	**1f**	DMSO	48	—	—	—	**3f**
9	**1h**	THF	3	55	72/28	> 95	**3h**
10	**1h**	DMSO	3	72	60/40	> 95	**3h**
11	**1j**	THF	4	42	50/50	—	**3j**
12	**1j**	DMSO	2	56	55/45	90	**3j**
13	**1k**	DMSO	3	55	69/31	> 95	**3k**

[a] Diastereomeric excess stated is that measured of the major *trans*-isomer determined from the ^{1}H NMR of the crude reaction mixture.

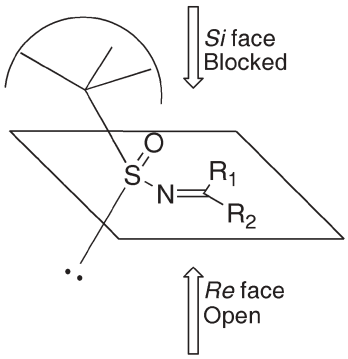


Fig. 2 Influence of the *tert*-butyl-sulfinyl group on the topicity of attack of nucleophiles on sulfinimines.

Encouraged by our previous results[7] and further reports detailing the deprotection of tri-substituted *tert*-butyl-sulfinyl-aziridines[10] we investigated the removal of the sulfinyl group. Deprotection of tri-substituted aziridine **3a** using saturated HCl in diethyl ether was successful, yielding the corresponding aziridinium salt in 83% yield with the remaining mass balance accounted for by the ring-opened product, wherein chloride ion has attacked the aziridine ring on the carbon bearing the vinyl group (15%).

The exceptional diastereoselectivity observed in the formation of the aziridines is thought to be due to the high stereo-directing nature of the chiral *tert*-butyl-sulfinyl group (Fig. 2). The nucleophilic sulfur ylide can approach the ketimine from either face, however, the large *tert*-butyl group effectively blocks one face of the imine to attack from the nucleophile, directing the addition of the sulfur ylide.

The origins of the *cis*/*trans* selectivity observed in sulfur ylide addition to carbonyls and imines has been the focus of much work. In a series of enlightening articles Aggarwal *et al.* and others outline the key factors contributing to the selectivity of this reaction. Our observations are in agreement with the trends detailed within.[12]

Overall we have demonstrated the suitability of *tert*-butyl-sulfinylketimines as substrates for ylide mediated aziridination. While the reaction of *tert*-butyl-sulfinylketimines under Corey–Chaykovsky conditions was disappointing, with more sensitive, enolisable substrates not forming the desired aziridine, high diastereoselectivities for those synthesised were observed. The reaction with the ylide derived from *S*-allyl tetrahydrothiophenium bromide was found to furnish the desired chiral vinyl aziridines for a much wider range of substrates and in improved yield. Both excellent diastereoselectivities and good stereocontrol were observed. Studies of the exploitation of these highly substituted aziridines as chiral building blocks for synthesis of complex molecules are ongoing, and our results will be reported in due course.

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8 G. Liu, D. A. Cogan and J. A. Ellman, *J. Am. Chem. Soc.*, 1997, **119**, 9913.
9 **Representative procedure for the synthesis of *tert*-butyl sulfinyl vinyl aziridines**: An oven-dried 25 mL round-bottomed flask was charged with a 0.1 M solution of *S*-allyl tetrahydrothiophenium bromide, (2.5 eq.), in anhydrous DMSO, and the solution stirred at ambient temperature under an atmosphere of argon. To which was added a solution of *N-[tert-butyl-(R_S)-sulfinyl]-ketimine*, (1 eq.), in anhydrous DMSO, portionwise, and the reaction allowed to stir for 30 minutes. To the clear reaction mixture was added lithium *tert*-butoxide, (2.5 eq.), and the progress was monitored by TLC. Once the reaction was complete, ice-cold brine was added, and the biphasic mixture stirred for 10 minutes. Filtration of the cloudy mixture through Celite, and extraction of the solids with EtOAc, afforded a biphasic solution which was separated, the aqueous layer extracted with EtOAc and the combined organic fractions concentrated under reduced pressure. The organic residues were then partitioned between a 1 : 1 petrol/Et_2O solution and brine. The organic fractions were then dried over sodium sulfate, and concentrated under reduced pressure to yield the crude aziridine. Purification was achieved through column chromatography over alumina. ***N*-[*tert*-butyl-(R_S)-sulfinyl]-2-diphenyl-3-vinyl-aziridine**: R_f 0.54 (4 : 1 petrol/EtOAc); m.p. 81–83 °C (from hexane/EtOAc); ν_{max} (Nujol)/ cm^{-1} 2921, 1450, 1370, 1282, 1089 (s) (*S=O stretch*); δ_H (400 MHz; $CDCl_3$) 7.80–7.20 (10H, m, *Ar-H*), 5.49–5.43 (1H, m, *–CH C-4*), 5.25 (1H, d, J = 16.8, *C-5-H_A*), 5.19 (1H, d, J = 10.1, *C-5-H_B*), 3.68 (1H, d, J = 6.4, *–CH C-3*), 1.23 (9H, s, *^{t}butyl-H*); δ_C (100 MHz; $CDCl_3$) 139.6, 137.1, 133.3 (*2 × C*), 130.3 (*2 × C*), 128.8 (*2 × C*), 128.2 (*2 × C*), 127.5 (*2 × C*), 121.5, 120.9, 58.3, 57.1, 49.8, 23.2 (*3 × C*); MS (CI): *m/z* $[M + H]^+$ 326.2 (100%); HRMS calculated for $C_{20}H_{24}NOS$ (M + H) 326.1573, found 326.1572.
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