Corey–Chaykovsky Reaction of Chiral Sulfinyl Imines: A Convenient Procedure for the Formation of Chiral Aziridines

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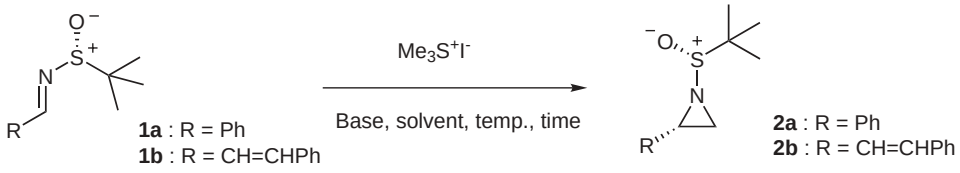
Abstract: The reaction of dimethylsulfonium methylide with a range of aromatic, heterocyclic and aliphatic *tert*-butylsulfinyl imines is presented. Aziridines were formed in 63–84% yield and 77–95% diastereomeric excess.

Key words: aziridine, ylide, sulfinyl imine, Corey–Chaykovsky, imine

As part of a programme directed at the exploitation of aziridines as versatile synthetic intermediates in total synthesis, we wished to synthesise a range of chiral non-racemic aziridines. We were drawn to the reports by Garcia-Ruano[1] and Davis[2] of the use of chiral sulfinyl imines to direct a Corey–Chaykovsky[3] type ylide aziridination. Davis' report studied the addition of dimethyloxosulfonium methylide with *p*-toluenesulfinyl imines, derived from benzaldehyde, 1-napthaldehyde and butanal, and found that the best conditions gave 51–68% yield and 50–70% diastereomeric excess. Garcia-Ruano reported on the use of *p*-toluenesulfinyl and *tert*-butyl sulfinyl imines, derived from benzaldehyde and cinnamaldehyde, with both dimethyloxosulfinium methylide and dimethylsulfonium methylide reactants. The best results obtained were for the *tert*-butylsulfinyl imines, with yields of 72% (70% de) and 72% (64% de) for the benzaldehyde and cinnamaldehyde derived substrates respectively, on reaction with dimethylsulfonium methylide. Herein we report our findings on the scope of this reaction, using chiral *tert*-butylsulfinyl imines derived from a range of aromatic and aliphatic aldehydes.

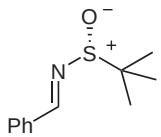
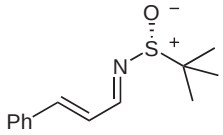
Initially, we investigated the aziridination of benzyl and cinnamyl *tert*-butylsulfinyl imines, as these had previously been studied (Table 1). These sulfinyl imines were formed using Ellman's procedure.[4] The best conditions for the reaction of these imines with trimethylsulfonium iodide were found to be sodium

Table 1 Reaction of Benzaldehyde and Cinnamaldehyde Sulfinyl Imines with Dimethylsulfonium Methylide under a Range of Conditions[a]



1a : R = Ph
1b : R = CH=CHPh

2a : R = Ph
2b : R = CH=CHPh

Entry	Substrate	Solvent	Base	Temp (°C)	Time (hours)	Yield	De
1		DMSO	NaH	20	5	84%	86%
2		MeCN	NaH	20	14	0%[b]	–
3		THF	*n*-BuLi	–20	24	56%	85%
4		THF	*n*-BuLi	–78	28	30%	79%
5		DMSO	NaH	20	4	75%	91%
6		MeCN	NaH	20	96	60%	77%
7		THF	*n*-BuLi	20	6	20%	61%
8		THF	*n*-BuLi	–20	48	55%	70%

[a] In all reactions three equivalents of trimethylsulfonium iodide and base were used. Diastereomeric excess was determined by ^{1}H NMR of the crude reaction mixture. Yields quoted are of isolated pure products.
[b] Complex mixture of products.

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hydride in anhydrous DMSO (entries 1 and 5), which gave good yields and excellent diastereoselectivities. Use of acetonitrile as a solvent gave a complex mixture of products with the benzaldimine, although results for cinnimaldimine were fair. Use of butyl lithium in THF, as favoured by Davis[2] for dimethyloxosulfonium methylide, was found to give lower yields and diastereoselectivities with the dimethylsulfonium methylide employed in our studies.

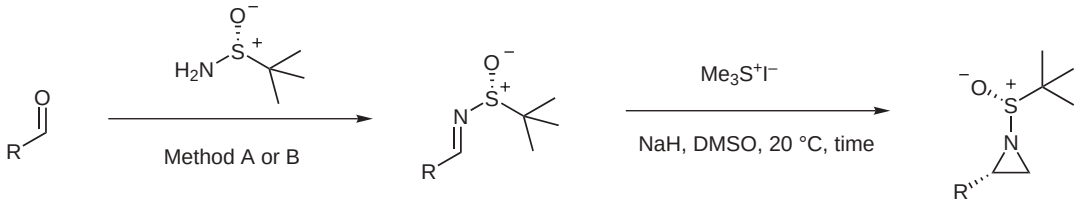
The stereochemistry generated at the aziridine C(2) was confirmed as (*S*) by comparison of the optical rotation of **2a**, $[\alpha]_D^{20}$ +298 (*c* 0.88, $CHCl_3$), with the literature value of it's enantiomer[1b] {$[\alpha]_D^{20}$ –320 (*c* 0.5, $CHCl_3$)}. An X-ray crystal structure (Figure 1) of the major (R_S, 2*S*) diastereomer of **2b** obtained in entry 5, Table 1, also confirms this assignment.

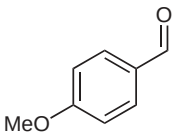
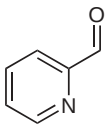
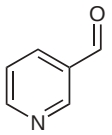
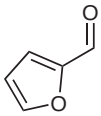
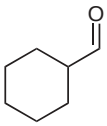
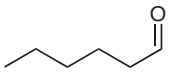
The stereochemistry of the reaction appears to be controlled on steric grounds, with the more open *Re*-face being attacked. The use of more polar solvents would stabilise the betaine intermediate, and thus favour kinetic products, and this is borne out in the diastereoselectivities.

Having established that the use of sodium hydride in DMSO gave the best yields and diastereoselectivities, we turned our attention to the scope of the reaction. Table 2 shows the results of the formation and aziridination of a range of sulfinyl imines derived from aromatic and aliphatic aldehydes.[5] The sulfinyl imines were synthesised from the aldehydes and (*R*)-*tert*-butylsulfinamide using either anhydrous copper sulfate in dichloromethane at 20 °C (Method A) or titanium(IV) ethoxide in THF at 0 °C (Method B).

The aziridination of the sulfinyl imines proceeded in generally good yields (63–77%).[6] The two aliphatic sulfinyl

Table 2 Sulfinyl Imine Formation and Subsequent Aziridine Formation of a Range of Aldehydes[a]



Entry	Substrate	Imine Formation	Yield of Imine	Time (h) for Aziridination	Yield of Aziridine	de of Aziridine
1		Method A	85%	3	65%	87%
2		Method A	72%	3	77%	90%
3		Method B	82%	5	74%	77%
4		Method B	78%	4	72%	91%
5		Method B	85%	10	63%	>95%
6		Method B	68%	6	65%	80%

[a] Method A: 3 equiv $CuSO_4$, CH_2Cl_2, r.t., 18 h. Method B: 1.5 equiv $Ti(OEt)_4$, 0 °C to r.t., 6 h. In all aziridination reactions 3.0 equivalents of trimethylsulfonium iodide and sodium hydride were used. Diastereomeric excess was determined by ^1H NMR of the crude reaction mixture. Yields quoted are of isolated pure products.

imines gave slightly decreased yields, which may be attributable to their ability to enolise under the basic reaction conditions. The increased steric bulk of the cyclohexyl imine is probably responsible for the higher selectivity in this case (Table 2, entry 5).

In conclusion, the *tert*-butylsulfinyl group is a successful acivating group/directing group for the synthesis of aziridines from imines. Electron rich, electron poor, sterically hindered and primary alkyl imines are all successful substrates. Reports of our findings on the conversion of these aziridines into functionalised heterocyclic scaffolds will be reported in due course.

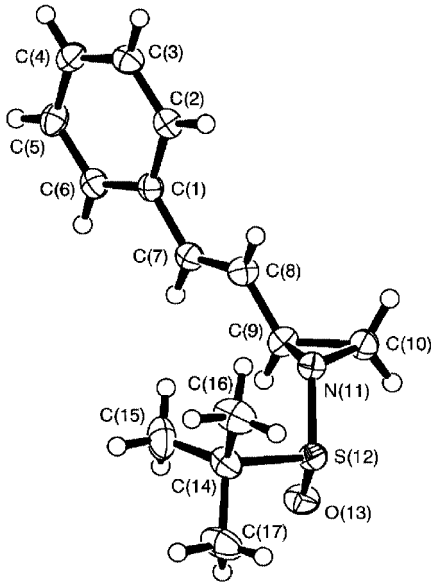


Figure 1 X-ray crystal structure of **2b**

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References

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(5) **Representative Procedure as follows:** To a solution of prewashed sodium hydride, (pentane, 3 equiv, 60% in mineral oil), in DMSO, dry, (3 mL), was added trimethylsulfonium iodide, (3 equiv). This was stirred at ambient temperature under argon, and stirred for 10 min, until the cloudy mixture went clear. At this point a solution of sulfinylimine, (1 equiv), in dry DMSO, (2 mL), was added dropwise to the mixture. The reaction was then stirred at r.t. and the progress monitored by thin layer chromatography. Once complete, ice-cold brine (3 mL) was added, and the reaction stirred for 5 min. The resulting mixture was filtered through a pad of celite, and the solution extracted with EtOAc (5 × 20 mL), and concentrated under reduced pressure. The residue was partitioned between 1:1 hexanes–Et_2O and H_2O, and the organic fraction dried over Na_2SO_4, and concentrated under reduced pressure. Purification by column chromatography on alumina (Brockmann grade 3) eluting with hexanes–EtOAc gave the products.

(6) Data for aziridines: ***N*-[*tert*-Butyl-(*R*)-sulfinyl]-2-(*S*)-phenylaziridine**: $[\alpha]_D^{20}$ +298 (*c* 0.88, $CHCl_3$). IR: 1080, 2330, 2350, 2923 cm^{-1}. MS: *m/z* (%) = [M + H] 224.1(5), 104.0(100). HRMS: Calcd for $C_{12}H_{17}NOS$ [M + H] 224.1109. Found: 224.1111. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.18 (s, 9 H), 2.18 (d, 1 H, *J* = 3.6 Hz), 2.46 (d, 1 H, *J* = 6.8 Hz), 3.61 (dd, 1 H, *J* = 3.6, 6.8 Hz), 7.30 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.9, 31.5, 31.9, 57.0, 126.9, 128.0, 128.8, 137.2. ***N*-[*tert*-Butyl-(*R*)-sulfinyl]-2-(*S*)-(2′-phenylvinyl)-aziridine**: $[\alpha]_D^{20}$ +185 (*c* 0.5, $CHCl_3$). IR: 1070, 2360, 2918 cm^{-1}. MS: *m/z* (%) = [M + H] 250.0(42), 96.1(100). HRMS: Calcd for $C_{14}H_{19}NOS$ [M + H]: 250.1256. Found: 250.1263. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.18 (s, 9 H), 2.17 (broad, 1 H), 2.35 (d, 1 H, *J* = 9.0 Hz), 3.20–3.30 (m, 1 H), 5.80–6.00 (dd, 1 H, *J* = 11.4, 21.2 Hz), 6.80 (d, 1 H, *J* = 21.2 Hz), 7.30 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.1, 29.9, 35.0, 57.2, 126.6, 128.2, 128.9, 136.5. ***N*-[*tert*-Butyl-(*R*)-sulfinyl]-2-(*S*)-(4′-methoxyphenyl)-aziridine**: $[\alpha]_D^{20}$ +68 (*c* 0.5, $CHCl_3$). IR, 2924, 1516, 1449, 1250, 1086 cm^{-1}. MS: *m/z* (%) = [M + H] 254.2(82), 149.2(100). HRMS: Calcd for $C_{13}H_{19}NO_2S$ [M + H]: 254.1209. Found: 254.1209. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.20 (s, 9 H), 2.08 (d, 1 H, *J* = 4 Hz), 2.36 (d, 1 H, *J* = 6.8 Hz), 3.50 (dd, 1 H, *J* = 4.0, 6.8 Hz), 3.74 (s, 3 H), 6.80 (s, 2 H), 7.12 (s, 2 H). ^{13}C NMr (101 MHz, $CDCl_3$): δ = 23.1, 31.4, 31.9, 55.5, 57.1, 114.2, 114.3, 128.0. ***N*-[*tert*-Butyl-(*R*)-sulfinyl]-2-(*S*)-(2′-pyridyl)-aziridine**: $[\alpha]_D^{20}$ +102 (*c* 1, $CHCl_3$). IR: 1080, 1450, 1475, 2923 cm^{-1}. MS: *m/z* (%) = [M + H] 225.0(100). HRMS: Calcd for $C_{11}H_{16}N_2OS$: 225.1056. Found: 225.1058. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.18 (s, 9 H), 2.417 (d, 1 H, *J* = 6.8 Hz), 2.443 (d, 1 H, *J* = 4.0 Hz), 3.70 (dd, 1 H, *J* = 4.0, 6.8 Hz), 7.14 (dd, 1 H, *J* = 4.8, 7.6 Hz), 7.22 (d, 1 H, *J* = 8.0 Hz), 7.60 (dd, 1 H, *J* = 7.6, 8.0 Hz), 8.52 (d, 1 H, *J* = 4.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.9, 28.7, 29.4, 56.1, 121.1, 121.9, 135.8, 149.1, 155.5. ***N*-[*tert*-Butyl-(*R*)-sulfinyl]-2-(*S*)-(3′-pyridyl)-aziridine**: $[\alpha]_D^{20}$ +116 (*c* 1, $CHCl_3$). IR: 1078, 1455, 1585, 2910 cm^{-1}. MS: *m/z* (%) = [M + H] 225.1(4), 106.1(100). HRMS: Calcd for $C_{11}H_{16}N_2OS$ [M + H]: 225.1061. Found: 225.1061. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.18 (s, 9 H), 2.23 (d, 1 H, *J* = 4.0 Hz), 2.52 (d, 1 H, *J* = 6.8 Hz), 3.66 (1 H, *J* = 4.0, 6.8 Hz), 7.32 (m, 1 H), 7.58 (m, 1 H), 8.60 (broad, 2 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.0, 29.5, 32.1, 57.2, 134.2, 148.9, 149.4. ***N*-[*tert*-Butyl-(*R*)-sulfinyl]-2-(*S*)-(2′-furyl)-aziridine**: $[\alpha]_D^{20}$ +66 (*c* 0.5, $CHCl_3$). IR: 1089, 2338, 2358, 2920 cm^{-1}. MS: *m/z* (%) = [M + H] 214.2(100). HRMS: Calcd for $C_{10}H_{15}NO_2S$ [M + H]: 214.0896. Found: 214.0896. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.14 (s, 9 H), 2.35 (dd, 1 H, *J* = 1.2, 7.2 Hz),

2.44 (d, 1 H, *J* = 4.4 Hz), 3.6 (dd, 1 H, *J* = 4.4, 7.2 Hz), 6.27 (m, 2 H), 7.20 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.6, 25.8, 28.5, 57.1, 108.7, 110.7, 142.7. ***N*-[*tert*-Butyl-(*R*)-sulfinyl]-2-(*S*)-cyclohexylaziridine**: $[\alpha]_D^{20}$ –62 (*c* 0.5, $CHCl_3$). IR: 1080, 1460, 2920 cm^{-1}. MS: *m/z* (%) = [M + H] 230.0 (18), 56.9 (100). HRMS: Calcd for $C_{12}H_{23}NOS$ [M + H]: 230.1573. Found: 230.1573. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (m, broad, 4 H), 1.25 (s, 9 H), 1.50 (m, 1 H), 1.60–1.80 (m, 6 H), 1.92 (d, 1 H, *J* = 4.4 Hz), 1.94 (dd, 1 H, *J* = 1.2, 7.2 Hz), 2.58 (m, 1 H, *J* = 7.2 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.7, 22.9, 25.9, 26.1, 26.4, 28.4, 29.8, 21.2, 37.9, 56.5. ***N*-[*tert*-Butyl-(*R*)-sulfinyl]-2-(*S*)-pentylaziridine**: $[\alpha]_D^{20}$ –80 (*c* 0.5, $CHCl_3$). IR: 2920, 1741, 1505, 1357, 1260, 1086 cm^{-1}. MS: *m/z* = [M + H] 218.0 (12), 191.0(100). HRMS: Calcd for $C_{11}H_{23}NOS$ [M + H]: 218.1573. Found: 218.1572. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (m, 3 H), 1.18 (s, 9 H), 1.32 (m, 8 H), 1.82 (d, 1 H, *J* = 4.0 Hz), 2.03 (d, 1 H, *J* = 6.8 Hz), 2.65 (m, 1 H, *J* = 4.0, 6.8 Hz). ^{13}C NMR (101 MHz, $CDCl_3$): δ = 14.2, 22.8, 23, 25.8, 26.2, 28.8, 31.8, 36.3, 57.

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