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Highly stereoselective aziridination of imines with (*S*)-dimethylsulfonium-(*p*-tolylsulfinyl)methylide

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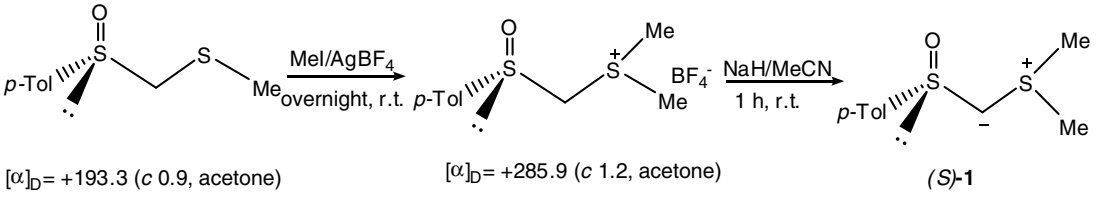
Abstract—Addition of (*S*)-dimethylsulfonium-(*p*-tolylsulfinyl)methylide to *N*-tosyl imines afforded the corresponding sulfinyl aziridines with full enantio- and diastereoselectivity. The chiral sulfinyl substituent was removed without ring opening leading to enantiopure 2-substituted aziridines.

Chiral aziridines form an attractive class of compounds, since they are versatile synthetic intermediates and easily undergo ring opening reactions with different nucleophiles.[1] While racemic aziridines are readily available, procedures for their synthesis in enantiomerically pure form are limited. An efficient strategy for their synthesis is the reaction of sulfur ylides with imines. This was accomplished using optically active sulfinimines in the reaction with dimethyloxosulfonium methylide described independently by Davis and Garcia-Ruano,[2] and with dimethylsulfonium methylide as developed by Stockman.[3] In another approach, developed independently by the groups of Aggarwal and Dai,[4] an asymmetric process for generating aziridines was mediated by chiral sulfur ylides.

Continuing our work on the utilization of optically active sulfinyl compounds in asymmetric synthesis, we designed a new type of chiral sulfur ylide, containing an enantiopure sulfinyl group bonded to the ylidic carbon atom. Dimethylsulfonium *p*-tolylsulfinylmethylide **1** was prepared by methylation of readily available (−)-(*S*)-*p*-tolyl methylthiomethyl sulfoxide and sub sequent deprotonation (Scheme 1). Its reaction with aldehydes gave α,β-epoxy sulfoxides with full enantioselectivity and moderate diastereoselectivity.[5] A high facial stereoselectivity was also observed in the reaction of **1** with vinylic phosphonates leading to cyclopropanes.[6] Encouraged by these results we decided to apply ylide **1** to the aziridination of imines.

When ylide **1** was reacted with *N*-phenyl benzaldimine no aziridine was produced (entry 1), only starting materials were recovered. The failure of this attempt was probably caused by the low reactivity of the imine used and may be overcome by its activation. It is known that the presence of a tosyl group on an imine nitrogen enhances electrophilicity considerably[7] facilitating nucleophilic attack by the sulfonium ylide. Indeed, the reaction of (*S*)-dimethylsulfonium-(*p*-tolylsulfinyl)methylide **1**



Scheme 1.

Keywords: Asymmetric reaction; Chiral auxiliaries; Ylides; Aziridination; Sulfoxides.
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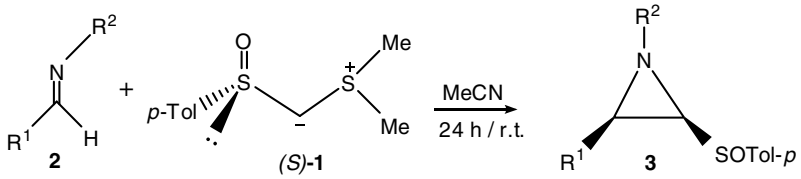
Table 1. Aziridination of imines using ylide **1**



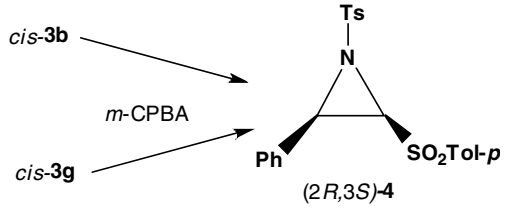
Entry	Imine	R^1	R^2	Product	Yield (%)	cis/trans[a]	de (%)
1	**2a**	Ph	Ph	**3a**	n.r.	—	—
2	**2b**	Ph	Ts	**3b**	88	100:0	100
3	**2c**	*p*-BrC_6H_4	Ts	**3c**	92	100:0	100
4	**2d**	*p*-$NO_2C_6H_4$	Ts	**3d**	93	100:0	100
5	**2e**	*n*-Bu	Ts	**3e**	72	100:0	100
6	**2f**	*i*-Pr	Ts	**3f**	81	100:0	100
7	**2g**[b]	Ph	TolS(O)	**3g**[c]	76[a]	90:10	100

[a] Determined by ^{1}H NMR spectroscopy of the crude reaction mixture.
[b] Racemic sulfinimine.
[c] Obtained as a mixture of four diastereomers.

with *N*-tosyl aldimines **2** occurred smoothly affording the corresponding aziridines in high yields (Table 1). The aziridination[8] was performed simply by the addition of ylide **1** generated in acetonitrile solution to the appropriate imine and stirring the reaction mixture for 24 h at room temperature. For all the *N*-tosyl imines (entries 2–6) the reaction afforded the desired aziridines **3** as single diastereomers (as seen from ^{1}H NMR spectra of the crude reaction mixtures).

According to the literature, the $^3J_{H-H}$ values of the coupling constants of the aziridine CH signals for trans isomers are smaller (4–5 Hz, dihedral angle 120°) than for cis isomers (7–8 Hz, dihedral angle 0°).[9] On this basis, the cis geometry was assigned to the isomers obtained of **3** having $^3J_{H-H} = 6.3$ Hz. This value is consistent with the $^3J_{H-H} = 6.5$ Hz value observed for the *cis*-*N*-(*p*-toluenesulfinyl)-2-carbomethoxyaziridines, reported by Davis et al.[10]

It is interesting to note that *N*-*p*-tolylsulfinyl imine reacts with stabilized ylide **1** (entry 7). In this case a complicated mixture of diastereomers was obtained due to the presence of an additional stereogenic center on the *N*-sulfinyl sulfur atom. Moreover, the reaction was less stereoselective and 10% of *trans*-**3g** was found in the crude reaction mixture.[11] However, oxidation of isolated *cis*-**3g** and *N*-tosyl analogue *cis*-**3b** gave the same sulfone **4**,[12] which confirmed the same facial selectivity in both cases (Scheme 2).



Scheme 2.

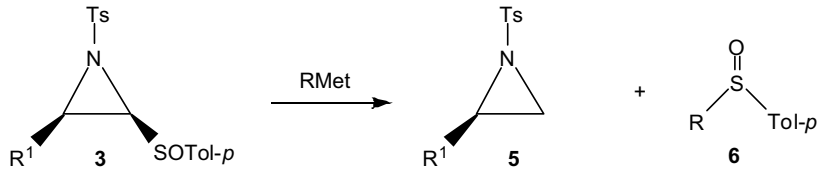
Next, we performed desulfinylation reactions of *N*-phenyl 2-sulfinyl-3-arylaziridines **3** using different alkyl metals (Table 2) under the conditions described by Satoh[13] for 2-sulfinyl-2,3-disubstituted aziridines. In contrast to their results, we observed desulfinylation in each case as indicated by the presence of signals for RS(O)Tol **6** in the ^{1}H NMR spectra of the crude reaction mixture. Although only a trace amount of the desired aziridine **3c** was detected from the reaction with MeMgI, the use of EtMgI considerably improved the yield. As shown in Table 2, the reaction was most effective when conducted with an excess of methyllithium.

Desulfinylation of (*N*-*p*-toluenesulfonyl-2-*p*-toluenesulfinyl)-3-phenylaziridine **3b** was useful for the assignment of absolute stereochemistry, since the absolute configuration of the resulting (*N*-*p*-toluenesulfonyl)-2-phenylaziridine **5b** was firmly established.[2,14] Hence, the absolute configuration of enantiomer **5b** obtained ($[\alpha]_D^{22}$ −65.4 (*c* 0.9, benzene)) was determined as *R*. Taking into account the cis configuration of **3** obtained in the aziridination reaction, it is possible to assign the 2*S*,3*R* configuration for aziridines **3**.

The high facial selectivity observed in the aziridination reactions can be explained by the reasonable assumption that ylide **1** adopts the conformation (A), which determines the stereochemical course of the process. The generally accepted mechanism for aziridine formation from sulfur ylides and imines[15] with the *transoid* approach can be applied (Scheme 3).

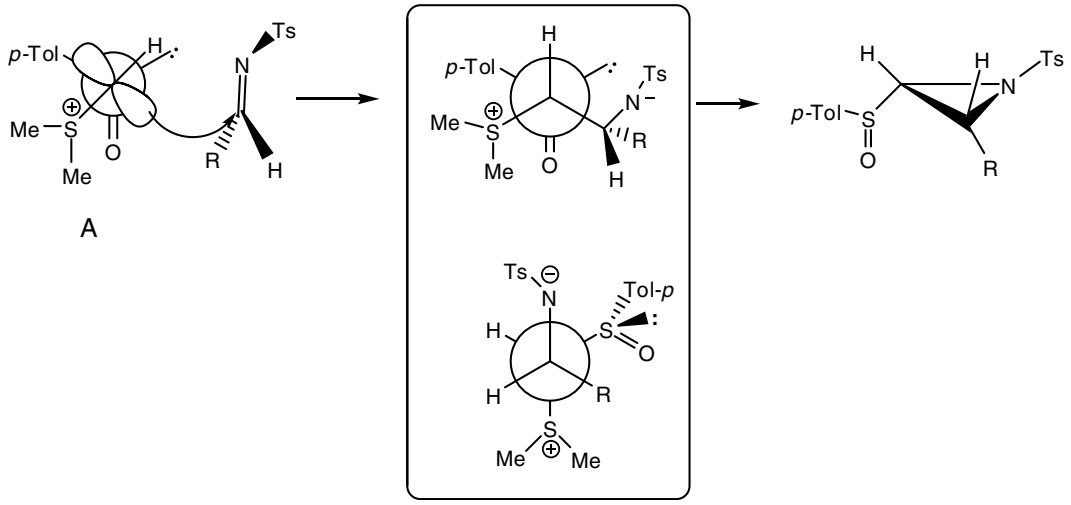
Although low cis selectivity was predicted by computational calculations for stabilized ylides,[16] exclusive formation of cis isomers in our case is probably caused by the difference in the ease of betaine formation. Transition state T2 leading to an *anti* betaine is disfavored due to repulsive interactions between the sulfinyl moiety of the ylide and the tosyl substituent on nitrogen. This interaction in T2 must be much stronger than the interaction between the sulfinyl group and the R-group of the

Table 2. Desulfinylation of 2*S*,3*R*,S_S-(*N*-*p*-toluenesulfonyl-2-*p*-toluenesulfinyl)-3-arylaziridines **3**

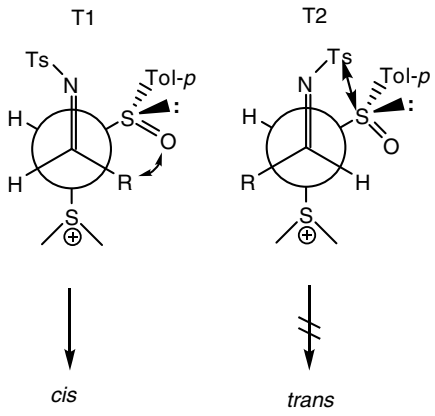


Entry	3	Conditions	Yield (%)	
			5	6
1	**b**	MeMgI/−35 °C/0.5 h	Trace	60[a]
2	**c**	EtMgI/−35 °C/1.5 h	60[b]	95
3	**b**	MeLi/−70 °C/10 min	75[b]	80
4	**e**	MeLi/−70 °C/10 min	76	83
5	**f**	MeLi/−70 °C/10 min	72	80

[a] Determined by ^{1}H NMR of the crude reaction mixtures.
[b] Isolated yield.



Scheme 3.



Scheme 4.

imine in the transition state T1 leading to a *syn* betaine (Scheme 4).

In conclusion, the asymmetric synthesis described herein provides enantiopure aziridines in high yields. Since the tosyl group can be cleaved with sodium naphthalenide,[17] the present approach using (*S*)-dimethylsulfonium-(*p*-tolylsulfinyl)methylide appears highly stereoselective and efficient for the synthesis of 2-substituted aziridines.

Acknowledgements

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8. *Typical procedure for aziridination*: To a solution of (*S*)-dimethylsulfonium-(*p*-tolylsulfinyl)methylide (1 mmol, 0.3 g) in 5 mL of dry MeCN, NaH (1.1 mmol, 0.03 g) was added at rt under an argon atmosphere. The resulting mixture was stirred for 30 min. The resulting precipitate was filtered off and 1 mmol of *N*-tosyl *p*-bromobenzaldimine (0.34 g) dissolved in 5 mL of dry MeCN was added. After stirring at rt for 24 h, the reaction was quenched with 20 mL of water, extracted with CH_2Cl_2 (4×5 mL) and the combined organics dried over $MgSO_4$. After filtration, the solvent was evaporated under reduced pressure affording **3** as a single isomer. A pure sample was obtained by column chromatography on silica gel ($CHCl_3$–acetone, 30:1).
2S,3R,S$_S$-(N-p-Toluenesulfonyl-2-p-toluenesulfinyl)-3-p-bromophenylaziridine **3c**. $[\alpha]_D^{22}$ −153.5 (*c* 0.9, CH_2Cl_2); mp 161–162 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.41 (3H, s, CH_3C$_6$H$_4$S); 2.48 (3H, s, CH_3C$_6$H$_4$S) 4.05 (1H, d, $J = 6.3$ Hz, CHC$_6$H$_5$); 4.32 (1H, d, $J = 6.3$ Hz, CHS); 7.13 and 7.40 (4H, A_2B_2 system, Ar); 7.22 and 7.55 (4H, A_2B_2, system, Ar); 7.37 and 7.57 (4H, A_2B_2, system, Ar); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.5; 21.7; 44.8; 62.6; 123.2; 124.5; 128.2; 129.5; 129.6; 129.7; 129.8; 131.9; 133.1; 137.8; 142.2; 145.3. Anal. Calcd for $C_{22}H_{20}BrNO_3S_2$: C, 53.88; H, 4.11; N, 2.86. Found: C, 54.64; H, 4.12; N, 2.99.
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12. *2S,3R-(N-p-Toluenesulfonyl-2-p-toluenesulfonyl)-3-phenylaziridine* **4**. $[\alpha]_D^{22}$ −67.7 (*c* 0.9, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.40 (3H, s, CH_3C$_6$H$_4$S); 2.47 (3H, s, CH_3C$_6$H$_4$S) 4.08 (1H, d, $J = 6.3$ Hz, CHC$_6$H$_5$); 4.41 (1H, d, $J = 6.3$ Hz, CHS); 7.13 and 7.50 (4H, A_2B_2 system, Ar); 7.21 and 7.58 (4H, A_2B_2, system, Ar); 7.28–7.43 (5H, m, Ph). ^{13}C NMR (125 MHz, $CDCl_3$) δ: 21.5; 21.7; 45.5; 62.9; 124.5; 127.9; 128.1; 128.4; 128.9; 129.7; 129.8; 130.4; 133.3; 138.1; 142.1; 145.1. Anal. Calcd for $C_{22}H_{21}NO_4S_2$: C, 61.80; H, 4.95; N, 3.28. Found: C, 61.73; H, 5.02; N, 3.30.
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