Sulfur Ylide Mediated Three-Component Aziridination and Epoxidation Reactions Using Vinyl Sulfonium Salts

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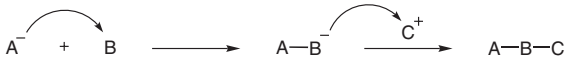
This paper is dedicated with deep respect to Prof. Sir Jack Baldwin on the occasion of his 70th birthday.

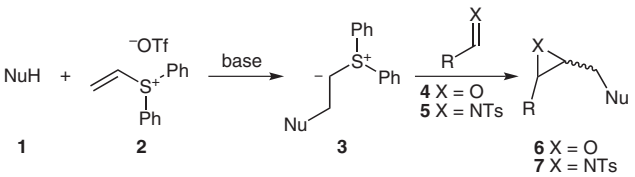
Abstract: Coupling of diphenylvinyl sulfonium triflate with nucleophiles and either aldehydes or imines gives epoxides and aziridines, respectively, in a three-component reaction. *cis*-Aziridines could be formed in good diastereomeric ratio, and the selectivity was correlated to the reactivity of the imine. This represents the first study of *cis*/*trans* selectivity in the reactions of imines with non-stabilized sulfur ylides.

Key words: sulfur ylides, epoxidations, aziridinations, multicomponent reactions, vinyl sulfonium salts

Three-component coupling reactions have not only been employed to enhance efficiency in organic synthesis but have also played a central role in diversity-oriented synthesis.[1] The key to success in the development of such reactions is controlled reactivity. Nucleophile **A** (e.g., a cuprate) should react selectively with electrophile **B** (e.g., an enone) generating an intermediate nucleophile **AB** which should then react selectively with electrophile **C** (e.g., an aldehyde), all other permutations (e.g. **A**+**C** or **AB**+**C**) should be slow or unproductive (Scheme 1). Our interest in vinyl sulfonium salts[2] led us to consider their potential use in these types of processes. In particular, the trapping of an intermediate ylide **3** with an aldehyde **4** or imine **5** would furnish an epoxide **6** or aziridine **7**, which are very useful products for further elaboration (Scheme 2).



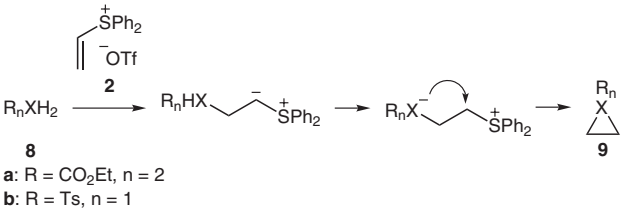
Scheme 1 General scheme for three-component reaction



Scheme 2 Proposed three-component epoxidation and aziridination reactions using vinyl sulfonium salt **2**

Although vinyl sulfonium salts such as **2** have been employed in two-component reactions (nucleophiles with tethered electrophiles) generating 5-, 6-, and 7-membered ring epoxides and aziridines and subsequently applied to the synthesis of mitomycins[3] and balanol,[2b,c] their use in three-component coupling reactions has not been investigated.[4]

However, initial experiments with *N*-methyl tosylamide (**1a**), diphenylvinylsulfonium salt **2**, and benzaldehyde in the presence of NaH were not promising – a large number of products were obtained, some of which were highly polar. We believed that the ylide intermediate **3** was preferentially reacting with the vinyl sulfonium salt instead of the aldehyde. To minimize this side reaction we needed to increase the concentration of the aldehyde and reduce the concentration of the vinyl sulfonium salt. Indeed, carrying out a slow addition of the vinyl sulfonium salt to a solution of the tosyl amide **1a**, NaH and five equivalents of benzaldehyde furnished the epoxide in good yield (Table 1, entry 1). Brief optimization of the reaction conditions showed that KO*t*-Bu in CH_2Cl_2 was optimal (entry 2). The reaction could be extended to a range of alternative nucleophiles including malonate **1b** (entry 3), an alcohol **1c** (entry 4), a thiol **1d** (entry 5), and an amine **1e** (entry 6). In all cases, the epoxides **6** were obtained in good yields but with poor diastereoselectivity. The low diastereoselectivities are typical of reactions of non-stabilized ylides with aldehydes,[5] but the moderate-to-high yields are not (they usually give low yields). We believe the high yields are a consequence of rapid (in situ) trapping of the ylide. The reaction, however, is limited to nucleophiles with only one acidic proton. A different pathway is followed in reactions of nucleophiles bearing two acidic protons (Scheme 3). Thus, in the case of diethyl malonate **8a**, following ylide formation 1,3-proton transfer occurred instead, followed by ring closure to give



Scheme 3 Reaction of vinyl sulfonium salt **2** with nucleophiles **8** bearing two acidic protons

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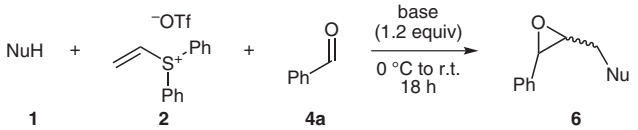
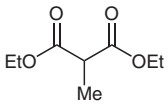
a cyclopropane **9a**. In the case of tosylamide **8b**, an aziridine **9b** was formed by the same process.[6]

Table 1 Three-Component Epoxidation Reaction Using Vinyl Sulfonium Salt **2** and Benzaldehyde



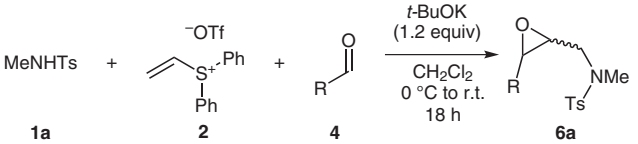
1 1 equiv | **2** 1.5 equiv | **4a** 5 equiv | **6**

Entry	NuH	Conditions	Yield (%)[a]	*cis*/*trans*[b]
1	MeNHTs	NaH, THF	74	1.8:1
2	MeNHTs	*t*-BuOK, CH_2Cl_2	87	1.5:1
3		*t*-BuOK, CH_2Cl_2	86	1.1:1
4	$PhCH_2OH$	*t*-BuOK, CH_2Cl_2	77	1:1.4
5	PhSH	*t*-BuOK, CH_2Cl_2	59	1:1.3
6	Pyrrolidine	*t*-BuOK, CH_2Cl_2	57	1:1

[a] Isolated yield after purification.
[b] Determined from ^{1}H NMR of the crude reaction mixture.

The reaction (demonstrated for *N*-methyl tosylamide) was easily extended to other aromatic and aliphatic aldehydes (Table 2), giving moderate-to-good yields but low diastereoselectivities.

Table 2 Three-Component Epoxidation of Various Aldehydes



1a 1 equiv | **2** 1.5 equiv | **4** 5 equiv | **6a**

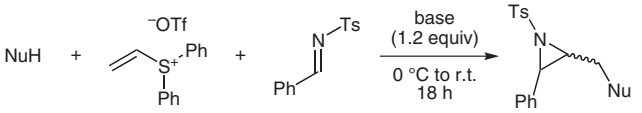
Entry	R	Yield (%)[a]	*cis*/*trans*[b]
1	Ph	87	1.5:1
2	4-$O_2NC_6H_4$	97	1.1:1
3	4-$MeOC_6H_4$	71	1.3:1
4	Bu	45	1.6:1
5	Cy	61	1.0:1

[a] Isolated yield after purification.
[b] Determined from ^{1}H NMR of the crude reaction mixture.

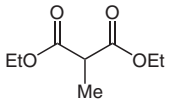
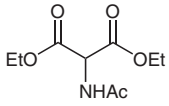
Related three-component coupling reactions with imines as electrophiles were also considered. Of particular interest were the diastereoselectivities of these processes as the reactions of imines with non-stabilized sulfur ylides had not been reported (except those of methylides).[7,8] Semi-stabilized ylides were known to react with *N*-Ts imines with moderate *trans* selectivity whilst stabilized ylides gave moderate *cis* selectivity.

In the event, application of our standard conditions with *N*-methyl tosylamide and **2** but replacing benzaldehyde for the corresponding *N*-Ts imine furnished aziridine **7a** in high yield as a 4:1 mixture of *cis*/*trans*-isomers (Table 3, entry 1). Further improvement in yield and diastereoselectivity was observed when using NaH in THF (entry 2, Table 3). The reaction could be extended to malonate derivatives (entries 3, 4), an alcohol (entry 5), and a thiol (entry 6) as before, but not amines (pyrrolidine was ineffective). Surprisingly, the major diastereomers derived from the alcohol and thiol reactions were now the *trans*-aziridines.

Table 3 Three-Component Aziridination Using Vinyl Sulfonium Salt **2** and *N*-Tosylbenzaldimine



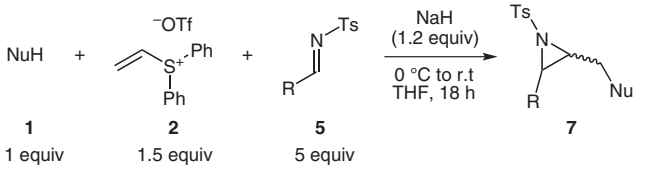
1 1 equiv | **2** 1.5 equiv | **5** 5 equiv | **7**

Entry	NuH	Conditions	Yield (%)[a]	*cis*/*trans*[b]
1	MeNHTs	*t*-BuOK, CH_2Cl_2	91	4:1
2	MeNHTs	NaH, THF	95	5:1
3		NaH, THF	89	3:1
4		NaH, THF	91	3:1
5	$PhCH_2OH$	NaH, THF	57	1:5
6	PhSH	NaH, THF	33	1:5

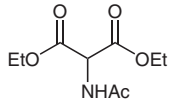
[a] Isolated yield after purification.
[b] Determined from ^{1}H NMR of the crude reaction mixture.

The aziridination reaction was extended to a range of imines (Table 4) with moderate-to-good yields being obtained in all cases. The diastereoselectivity was also found to be highly sensitive to the electronic nature of the imine: electron-rich imines gave very high *cis* selectivity whilst electron-poor imines gave low selectivity. In fact, the diastereoselectivities correlated well with σ^+ (Hammer substituent constant) (Figure 1). This observation is consistent with the development of positive charge in the transition states (TS) and a larger dependence on the imine's electronic properties in one of the two TS. More reactive imines show low selectivity while less reactive imines give better selectivity in line with the Hammond postulate. In the case of less reactive imines the later TS should lead to closer contacts between the imine and ylide

Table 4 Three-Component Aziridination of Various Imines



1 1 equiv | **2** 1.5 equiv | **5** 5 equiv | **7**

Entry	NuH	R	Yield (%)[a]	*cis*/*trans*[b]
1	MeNHTs	4-$O_2NC_6H_4$	99	1.5:1
2	MeNHTs	4-ClC_6H_4	94	3:1
3	MeNHTs	Ph	95	5:1
4	MeNHTs	4-MeC_6H_4	89	6:1
5	MeNHTs	4-$MeOC_6H_4$	95	15:1
6		4-$O_2NC_6H_4$	83	2:1
7	"	Ph	91	3:1
8	"	4-$MeOC_6H_4$	62	only *cis*

[a] Isolated yield after purification.
[b] Determined from ^{1}H NMR of the crude reaction mixture.

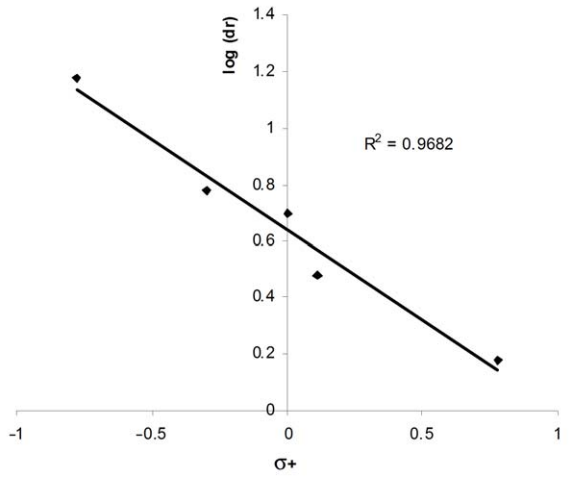
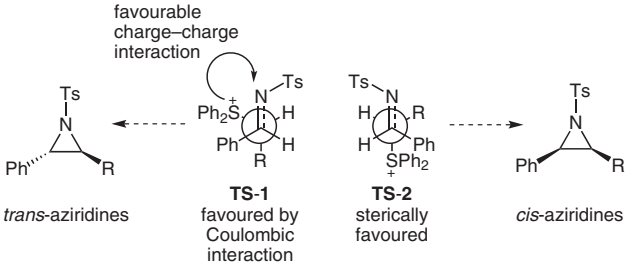


Figure 1 Plot of log (*cis*/*trans*) vs. σ^+ for the three-component aziridination using MeNHTs (**2**) and *p*-XC_6H_4C=NTs (see Table 4)

components and thus a more pronounced difference between the energies of the competing TS for the formation of the betaine intermediates that lead to *cis*- and *trans*-aziridines.

Semi-stabilized ylides have been shown to form betaine intermediates nonreversibly on reaction with *N*-tosylsulfonylimines[9] and so the selectivities in reactions of non-stabilized ylides should be determined by the relative energies of the TS for betaine formation. The unexpectedly high *cis* selectivity can be rationalized using the model derived by Robiette through DFT calculations.[10] In this model, approach of the ylide to the *N*-Ts imine is dominated by the steric interactions of the large sulfonamide



Scheme 4 Transition states proposed to lead to the betaine intermediates that give *cis*- and *trans*-aziridines

group which dictates that the only substituent 'allowed' in its vicinity is an H. Thus, two TS are believed to be responsible for product formation: **TS1**, in which the sulfonium and *N*-Ts groups are *gauche* to each other leading to the *trans*-aziridine and **TS2**, where the same two groups are *anti* to each other leading to the *cis*-aziridine (Scheme 4).

A possible explanation for the observed selectivity is that because of the Bürgi–Dunitz angle of approach of the nucleophile to the imine, one of the phenyl groups on the ylide comes into close proximity to the aryl group of the imine in **TS2** but not in **TS1**.[11] This π–π interaction (induced dipole or π-HAr hydrogen bond) will be stabilizing when the aryl group is electron rich since the Ph group attached to sulfur is electron deficient and so **TS2** will be favored, thus leading to the *cis*-aziridine. Subtle hydrogen-bonding interactions between the β-alkoxy group of the ylide component with the imine C–H may be responsible for favoring **TS1**, thus leading to the *trans*-aziridine.

In conclusion, it has been shown that vinyl sulfonium salt **2** participates in three-component coupling reactions with a variety of nucleophiles and aldehydes/imines. Key to the success of this transformation is to maintain a low concentration of the vinyl sulfonium salt (by slow addition) and a high concentration of the aldehyde/imine to ensure that the ylide intermediate reacts with the electrophile required and not with more vinyl sulfonium salt.

The scope of the reaction has been evaluated. Nucleophiles bearing one acidic proton give good results, whereas those bearing two acidic protons lead to three-membered rings without trapping the electrophile. Both aromatic and aliphatic aldehydes work well but, as expected, give low diastereoselectivity. In contrast, aromatic imines give high *cis* selectivity with electron-neutral/electron-rich aromatic imines. This work represents the first study of *cis*/*trans* diastereoselectivity in aziridination reactions of non-stabilized ylides with imines.

General Procedure for Three-Component Aziridinations

A solution of nucleophile (0.53 mmol) in THF (5 mL) was treated with NaH (0.64 mmol) at 0 °C under N_2 and stirred for 20 min while warming to r.t. as H_2 gas evolved. The reaction mixture was then cooled to 0 °C and treated with imine (2.65 mmol) followed by a solution of diphenyl(vinyl)sulfonium trifluoromethanesulfonate[2a] (0.80 mmol) in THF (10 mL) dropwise over 20 min. After stirring

for 18 h at r.t., H_2O (20 mL) was added and the mixture extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Purification by flash chromatography (SiO_2, EtOAc–PE) gave the product as a *cis*/*trans* mixture.[12–16]

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(12) The products were characterized by NMR, IR, MS, and mp (where appropriate). Satisfactory elemental analyses and/or HRMS were obtained for all compounds. Full details and spectra are available from the authors.

(13) ***N*,4-Dimethyl-*N*-{[1-(toluene-4-sulfonyl)-3-phenyl-2-aziridinyl]methyl}benzenesulfonamide (Table 2, Entry 2)**
cis-Isomer as a colourless oil; R_f = 0.40 (EtOAc–PE, 3:7). IR (film): 1598 (Ar), 1330 (SO_2), 1160 (SO_2) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.86 (2 H, d, *J* = 8.3 Hz, ArH), 7.50 (2 H, d, *J* = 8.3 Hz, ArH), 7.35 (2 H, d, *J* = 8.3 Hz, ArH), 7.27–7.16 (7 H, m, ArH), 3.93 (1 H, d, *J* = 7.0 Hz, NCHPh), 3.25–3.14 (2 H, m, NC*H*H and NC*H*CH_2), 2.53 (1 H, dd, *J* = 14.3, 7.0 Hz, NC*H*H), 2.44 (6 H, s, 2 × CH_3), 2.38 (3 H, s, CH_3). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 145.0 (C), 143.5 (C), 136.2 (C), 135.9 (C), 132.0 (C), 130.0 (CH), 129.9 (CH), 129.7 (CH), 128.6 (CH), 128.3 (CH), 127.4 (CH), 127.3 (CH), 47.6 (CH_2), 44.4 (CH), 44.1 (CH), 35.4 (CH_3), 21.7 (CH_3), 21.5 (CH_3). MS (CI): *m/z* (%) = 471 (14) [MH^+], 198 (100) [Ts(Me)NCH_2^+]; *trans*-isomer (obtained as a mixture with *cis*-isomer) as a colorless oil; R_f = 0.40 (EtOAc–PE, 3:7). IR (film): ν_{max} = 1599 (Ar), 1332 (SO_2), 1161 (SO_2) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.77 (2 H, d, *J* = 8.3 Hz, ArH), 7.69 (2 H, d, *J* = 8.3 Hz, ArH), 7.31 (2 H, d, *J* = 8.3 Hz, ArH), 7.26–7.19 (7 H, m, ArH), 3.85 (1 H, d, *J* = 3.8 Hz, NCHPh), 3.55 (1 H, dd, *J* = 14.6, 8.6 Hz, NC*H*H), 3.03 (1 H, ddd, *J* = 8.6, 8.6, 3.8 Hz, NC*H*CH_2N), 2.43 (6 H, s, 2 × CH_3), 2.42–2.38 (4 H, m, NC*H*H and CH_3). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 144.9 (C), 143.6 (C), 136.2 (C), 134.0 (C), 132.0 (C), 129.9 (CH), 129.8 (CH), 128.6 (CH), 128.5 (CH), 127.4 (CH), 127.3 (CH), 126.9 (CH), 49.6 (CH), 49.0 (CH_2), 48.8 (CH), 36.5 (CH_3), 21.7 (CH_3), 21.5 (CH_3). MS (CI): *m/z* (%) = 471 (14) [MH^+], 198 (100) [Ts(Me)NCH_2^+].

(14) **Diethyl 2-Methyl-2-({1-[(4-methylphenyl)sulfonyl]-3-phenyl-2-aziridinyl}methyl)malonate (Table 3, Entry 3)**
cis/*trans*-Isomers (3:1) as a colorless oil (89%); R_f = 0.30 (EtOAc–PE, 2:8). IR (film): 1761 (OCO), 1162 (SO_2) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ(*cis*) = 7.85 (2 H, d, *J* = 8.3 Hz, ArH), 7.32–7.17 (7 H, m, ArH), 4.19–4.02 (4 H, m, 2 × OCH_2), 3.87 (1 H, d, *J* = 7.2 Hz, NCHPh), 2.99–2.91 (1 H, m, $NCHCH_2$), 2.43 (3 H, s, CH_3), 1.87 (1 H, dd, *J* = 14.9, 5.8 Hz, C*H*H), 1.70 (1 H, dd, *J* = 14.9, 6.4 Hz, CH*H*), 1.31 (3 H, s, CH_3), 1.27–1.11 (6 H, m, 2 × CH_3). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 171.5 (C), 171.4 (C), 144.7 (C), 144.6 (C), 132.4 (C), 129.8 (CH), 129.6 (CH), 128.5 (CH), 128.2 (CH), 127.6 (CH), 61.8 (CH_2), 61.6 (CH_2), 52.4 (C), 45.1 (CH), 42.7 (CH), 31.1 (CH_2), 21.6 (CH_3), 19.5 (CH_3), 13.9 (CH_3), 13.8 (CH_3). ^1H NMR (400 MHz, $CDCl_3$): δ(*trans*) = 7.78 (2 H, d, *J* = 8.3 Hz, ArH), 7.32–7.17 (7 H, m, ArH), 4.19–4.02 (4 H, m, 2 × OCH_2), 3.78 (1 H, d, *J* = 4.2 Hz, NCHPh), 2.99–2.91 (1 H, m, $NCHCH_2$), 2.49–2.36 (5 H, m, CH_2 and CH_3), 1.31 (3 H, s, CH_3), 1.27–1.11 (6 H, m, 2 × CH_3). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 171.5 (C), 171.4 (C), 144.4 (C), 143.6 (C), 134.8 (C), 129.8 (CH), 128.8 (CH), 128.5 (CH), 127.4

(CH), 126.7 (CH), 61.8 (CH_2), 61.7 (CH_2), 52.9 (C), 46.2 (CH), 43.7 (CH), 31.9 (CH_2), 21.6 (CH_3), 20.7 (CH_3), 13.9 (CH_3), 13.8 (CH_3). MS (CI): *m/z* (%) = 460 (28) [MH^+] , 414 (17) [M^+ – EtO], 286 (100) [M^+ – $C(CO_2Et)_2Me$].

(15) **1-(4-Toluenesulfonyl)-2-phenyl-3-[(phenylsulfanyl)methyl]aziridine (Table 3, Entry 6)**

cis:*trans*-Isomers (1:5) as a colorless oil (33%); R_f = 0.45 (EtOAc–PE, 3:7). IR (film): 1347 (SO_2), 1164 (SO_2) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ(*cis*) = 7.58 (2 H, d, *J* = 8.3 Hz, ArH), 7.35–7.08 (12 H, m, ArH), 4.03 (1 H, d, *J* = 7.0 Hz, NCHPh), 3.29–3.19 (2 H, m, NC*H*C*H*H), 2.62 (1 H, dd, *J* = 14.2, 7.0 Hz, CH*H*), 2.36 (3 H, s, CH_3). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 143.5 (C), 137.0 (C), 135.2 (C), 134.6 (C), 129.8 (CH), 129.7 (CH), 129.1 (CH), 128.8 (CH), 128.1 (CH), 127.7 (CH), 127.1 (CH), 126.6 (CH), 46.2 (CH), 45.1 (CH), 35.4 (CH_2), 21.6 (CH_3). ^1H NMR (400 MHz, $CDCl_3$): δ(*trans*) = 7.81 (2 H, d, *J* = 8.3 Hz, ArH), 7.35–7.08 (12 H, m, ArH), 4.70 (1 H, d, *J* = 4.2 Hz, NCHPh), 3.73 (1 H, ddd, *J* = 7.0, 6.5, 4.2 Hz, NC*H*CH_2), 3.12 (1 H, dd, *J* = 14.1, 6.5 Hz, CH*H*), 2.81 (1 H, dd, *J* = 14.1, 7.0 Hz, C*H*H), 2.42 (3 H, s, CH_3). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 144.7 (C), 137.2 (C), 135.0 (C), 134.4 (C), 129.9 (CH), 129.7 (CH), 129.6 (CH), 129.2 (CH), 129.0 (CH), 128.9 (CH), 128.2 (CH), 127.4 (CH), 48.9 (CH), 46.3 (CH), 35.6 (CH_2), 21.7 (CH_3). MS (CI): *m/z* (%) = 396 (3) [MH^+], 224 (100) [MH^+ – $TsNH_2$], 155 (16) [Ts^+].

(16) **Diethyl 2-(Acetylamino)-2-{[3-(4-methoxyphenyl)-1-(4-toluene-sulfonyl)-2-aziridinyl]methyl}malonate (Table 4, Entry 8)**

cis-Isomer as a colorless oil (62%); R_f = 0.40 (EtOAc–PE, 4:6). IR (film): 1762 (OCO), 1160 (SO_2) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.79 (2 H, d, *J* = 8.3 Hz, ArH), 7.29 (2 H, d, *J* = 8.3 Hz, ArH), 7.21 (1 H, br s, NH), 6.95 (2 H, d, *J* = 8.7 Hz, ArH), 6.75 (2 H, d, *J* = 8.7 Hz, ArH), 4.41–4.09 (4 H, m, 2 × OCH_2), 3.74 (1 H, d, *J* = 7.2 Hz, NCHAr), 3.73 (3 H, s, OCH_3), 2.89 (1 H, ddd, *J* = 10.1, 7.2, 3.7 Hz, NC*H*CH_2), 2.53 (1 H, dd, *J* = 15.1, 3.7 Hz, C*H*H), 2.41 (3 H, s, CH_3), 2.10 (1 H, dd, *J* = 15.1, 10.1 Hz, CH*H*), 2.07 (3 H, s, CH_3), 1.33–1.15 (6 H, m, 2 × CH_3). ^{13}C NMR (100.5 MHz, $CDCl_3$): δ = 169.7 (C), 167.4 (C), 167.2 (C), 159.5 (C), 144.9 (C), 131.1 (C), 129.8 (CH), 128.5 (CH), 128.1 (CH), 123.8 (C), 114.0 (CH), 65.1 (C), 62.9 (CH_2), 62.7 (CH_2), 55.3 (CH_3), 45.1 (CH), 41.1 (CH), 28.9 (CH_2), 23.0 (CH_3), 21.8 (CH_3), 14.0 (CH_3), 13.9 (CH_3). MS (CI): *m/z* (%) = 533 (58) [MH^+], 320 (100) [MH^+ – TsNHAc].