Novel Catalytic and Asymmetric Process for Aziridination Mediated by Sulfur Ylides

Varinder K. Aggarwal,*,† Alison Thompson,† Ray V. H. Jones,‡ and Mike C. H. Standen‡

Department of Chemistry, University of Sheffield, Sheffield S3 7HF, U.K., and Zeneca Manufacturing Partnership, Process Technology Department, Earls Road, Grangemouth, Stirlingshire FK3 8XG, U.K.

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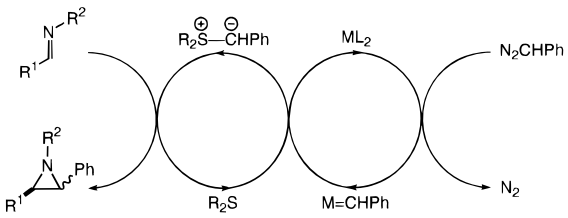
Like epoxides, aziridines are versatile synthetic intermediates.[1] However, only a limited number of methods for asymmetric aziridination exist: addition of carbenoids to imines[2] or copper-catalyzed additions of nitrenoids to alkenes.[3] Superior results have been obtained by the latter method, although high enantioselectivity is still limited to a small subset of alkenes and only *N*-Ts aziridines are accessible. This is a severe limitation of this methodology, especially as harsh conditions are required for cleavage of the strong sulfonamide bond. Despite recent advances, the tosyl group remains a difficult group to remove from sensitive substrates.[4]

An alternative strategy for aziridination involves the addition of sulfur ylides to imines.[5] However, this reaction normally[5e] requires stoichiometric amounts of reagents and is currently racemic. We have previously shown that in related epoxidation reactions such limitations can be overcome: sulfur ylides can be generated by the reaction of a sulfide with a carbenoid in the presence of an aldehyde and so only catalytic amounts of sulfides are required.[6] Furthermore, the use of chiral sulfides gives non racemic epoxides.[7] We now report the development of a novel, catalytic, and asymmetric route to aziridines based on this methodology.

Our proposed catalytic cycle for aziridination is shown in Scheme 1 and involves the slow addition of a diazo compound[8] to a solution of a suitable metal salt, sulfide, and imine. From our previous work, we knew that sulfur ylides could be generated in the presence of aldehydes by this method and that direct reaction between the diazocompound or carbenoid and aldehyde did not occur. For aziridination, direct reaction between the carbenoid and imine needed to be avoided and this could be achieved by employing electron-withdrawing groups on the imine nitrogen.[9] Such groups would also enhance the rate of addition of the sulfur ylide to the imine. Thus, we initially chose *N*-tosylbenzaldimine and carried out the reaction shown in Scheme 2. We were delighted to find that the corresponding aziridine was formed in excellent yield (Table 1, entry 1). Even with catalytic quantities of sulfide (0.2 equiv), high yields of aziridine were obtained (Table 1, entry 2). We confirmed that the reactions were occurring *via* the sulfur ylide as in the absence of sulfide no aziridine was isolated. This experiment confirmed that we had successfully eliminated the direct coupling between the metal carbenoid and imine.

Scheme 1



Scheme 2

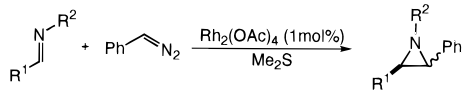


Table 1. Preparation of Aziridines from Imines and Phenyldiazomethane

entry	R^1	R^2	equiv of Me_2S	yield[a]/%	ratio *(trans:cis)*
1	Ph	Ts	1.0	90	4:1
2	Ph	Ts	0.2	91	4:1
3	Ph	DPP	0.2	83	3:1
4	Ph	SES	0.2	92	3:1
5	*p*-ClC_6H_4	SES	0.2	88	3:1
6	*p*-MeC_6H_4	SES	0.2	96	3:1

[a] The yield refers to the total yield of *trans* and *cis* isomers.

Having successfully shown that *N*-tosylimines participated in the aziridination process, we wanted to test alternative groups on nitrogen[10] that similarly activated the imine toward nucleophilic attack but were easier to remove. Thus, *N*-(diphenylphosphinyl)benzaldimines (DPP))[11] and *N*-[*β*-(trimethylsilyl)ethanesulfonyl]benzaldimines (*β*-(trimethylsilyl)ethanesulfonyl = (SES))[12] were prepared and subjected to the catalytic cycle. Again, using just catalytic quantities of sulfides, high yields of the corresponding aziridine were obtained (Table 1, entries 3 and 4). As the SES imines were more easily prepared than the DPP imines, several aryl imines with this group were prepared and tested in the cycle, and again, high yields of the corresponding aziridines were obtained (Table 1, entries 5 and 6). In all cases a 3:1

† University of Sheffield.

‡ Zeneca Manufacturing Partnership.

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(6) Aggarwal, V. K.; Abdel-Rahman, H.; Jones, R. V. H.; Lee, H. Y.; Reid, B. D. *J. Am. Chem. Soc.* **1994**, *116*, 5973−5974.

(7) Aggarwal, V. K.; Ford, J. G.; Thompson, A.; Jones, R. V. H.; Standen, M. C. H. *J. Am. Chem. Soc.* **1996**, *118*, 7004−7005.

(8) Slow addition is required to limit the extent of dimerisation of the diazocompound: Doyle, M. P.; Griffin, J. H.; Bagheri, V.; Dorow, R. L. *Organometallics* **1984**, *3*, 53−61.

(9) It has been shown that the nature of the group on nitrogen determines the efficiency of the addition of carbenoids to imines. Electron-donating groups result in high yields; electron-withdrawing groups result in low yields. See ref 2b. This issue would become important in the development of an asymmetric process.

(10) Neither silyl nor phenyl groups on nitrogen are sufficiently electron withdrawing to activate the imine toward nucleophilic attack by the sulfur ylide.

(11) Jennings, W. B.; Lovely, C. J. *Tetrahedron* **1991**, *47*, 5561−5568. The DPP group may be easily removed from aziridines by treatment with $MeOH/BF_3.OEt_2$: Osborn, H. M. I.; Sweeney, J. B. *Synlett* **1994**, 145−147.

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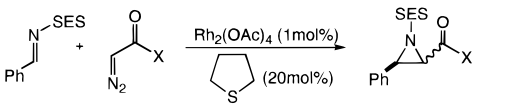
Table 2. Asymmetric Aziridination of *N*-SES-aldimine (Scheme 4)

entry	R^1	equiv of **1**	ML_2	yield[a]/%	ratio (*trans:cis*)	ee[b,c]/%
1	Ph	1.0	$Rh_2(OAc)_4$	55	3:1	97 (*R,R*)[d]
2	Ph	1.0	$Cu(acac)_2$	83	3:1	95 (*R,R*)[d]
3	Ph	0.2	$Cu(acac)_2$	62	3:1	90 (*R,R*)[d]
4	*p*-MeC_6H_4	1.0	$Rh_2(OAc)_4$	88	3:1	95 (*R,R*)[e]
5	*p*-MeC_6H_4	0.2	$Cu(acac)_2$	50	3:1	88 (*R,R*)[e]
6	*p*-ClC_6H_4	1.0	$Rh_2(OAc)_4$	70	3:1	88 (*R,R*)[e]
7	*p*-ClC_6H_4	0.2	$Cu(acac)_2$	44	3:1	85 (*R,R*)[e]

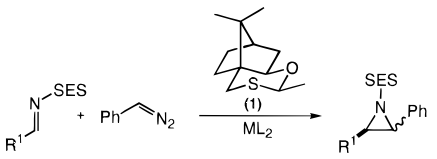
[a] The yield refers to the total yield of *trans* and *cis* isomers. [b] Enantiomeric excess determined by HPLC using a Chiralcel OD column. [c] All aziridines had a positive optical rotation. [d] The absolute configuration of *trans N*-[*β*-(trimethylsilyl)ethanesulfonyl]-2,3-diphenylaziridine was deduced by correlation to stilbene oxide (see ref 20). [e] By analogy with benzaldimine it is assumed that the absolute configuration is the same.

Scheme 3



X	Yield (%)	Ratio (*trans:cis*)
NEt_2	91	2:1
OEt	57	1:3

Scheme 4



mixture of *trans*:*cis* aziridines was obtained.[13] Deprotection[12] of *trans*-*N*-[*β*-(trimethylsilyl)ethanesulfonyl]-2,3-diphenylaziridine using CsF was facile and furnished *trans*-2,3-diphenylaziridine in 89% yield. This demonstrated the advantage of the current catalytic process over existing methods.

Encouraged by these results, we explored alternative diazo compounds (*N*,*N*-diethyldiazoacetamide[14] and ethyl diazoacetate) in the catalytic cycle. Higher temperatures (60 °C) were required for the decomposition of these more stable diazo compounds, and so tetrahydrothiophene was used instead of Me_2S. As shown in Scheme 3, good to excellent yields of the corresponding aziridines were obtained. While the diazoacetamide gave predominantly the *trans* aziridine, the diazoester gave the *cis* aziridine as the major product. These results show that the new methodology may be applied to the preparation of functionalized aziridines. We believe that the reaction employing the diazoester-derived sulfur ylide is under thermodynamic control and that the *cis* isomer is the thermodynamic product.[15]

In preliminary studies we have tested chiral sulfides derived from (+)-camphorsulfonyl chloride in the catalytic cycle for aziridination (Scheme 4, Table 2). We were delighted to find that the use of sulfide **1**[16] gave the required aziridine with high enantiomeric excess (97%), although in modest yield (55%) (Table 2, entry 1). In related studies, it was found that, using hindered sulfides, $Cu(acac)_2$ gave superior yields of epoxides with less dimerization of the diazo compound compared to $Rh_2(OAc)_4$.[17] Thus, $Cu(acac)_2$[18] was used in the catalytic cycle in place of $Rh_2(OAc)_4$, and a higher yield (83%) of the corresponding aziridine was obtained (Table 2, entry 2). Use of a catalytic amount of sulfide **1** (20 mol %) also furnished the correspnding aziridine but in slightly lower yield (Table 2, entry 3). Other aldimines were tested in the aziridination process using both rhodium and copper salts, and high enantioselectivity was maintained (Table 2, entries 4−7). The small reduction in the enantiomeric excess observed when $Cu(acac)_2$ was used in place of $Rh_2(OAc)_4$ is presumably due to limited, but competing, direct reaction between the imine and copper carbenoid, a pathway that became more pronounced when catalytic amounts of sulfides were used. From our previous experiments little or no direct coupling occurred between the *rhodium* carbenoid and imine. This is the first example of the preparation of nonracemic aziridines by the addition of chiral sulfur ylides to imines. Furthermore, *the levels of asymmetric induction for aziridination are the highest reported to date.*

In summary, we have developed a new method for the preparation of aziridines from imines and diazo compounds that requires catalytic amounts of metal salts and sulfides and operates under neutral conditions. Using enantiomerically pure sulfides, high enantioselectivity has been achieved in the aziridination process.

Acknowledgment. We gratefully thank Zeneca Manufacturing Partnership and Sheffield University for financial support.

Supporting Information Available: Experimental details for the preparation and analytical data of sulfide **1**, method for the asymmetric aziridination process, and assay methods for the product aziridines (12 pages).

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(12) Weinreb, S. M.; Demko, D. M.; Lessen, T. A. *Tetrahedron Lett.* **1986**, *27*, 2099−2102. The SES group has been shown to be easily removed from amines by fluoride.

(13) From cross-over experiments, we have shown that these reactions are under kinetic control. Full details will be published elsewhere.

(14) *N*,*N*-Diethyldiazoacetamide was prepared according to the method of Regitz for the preparation of *tert*-butyl diazoacetate. *N*,*N*-Diethylacetoacetamide was used in place of *tert*-butyl acetoacetate: Regitz, M.; Hocker, J.; Liedhegener, A. *Organic Synthesis*; Wiley: New York, 1973; Collect. Vol. V, pp 179−183. Rando, R. R. *J. Am.Chem. Soc.* **1972**, *94*, 1629−1631.

(15) This is presumably because the 1,2 steric interaction on the three-membered ring between the SES group (this is the largest group) and either of the substituents is greater than the 1,2 steric interaction between the substituents themselves. It has also been found that, under equilibrating conditions, *cis*-unsaturated *N*-tosylaziridines were formed in preference to the *trans* isomers: Mimura, N.; Ibuka, T.; Akaji, M.; Miwa, Y.; Taga, T.; Nakai, K.; Tamamura, H.; Fujii, N.; Yamamoto, Y. *J. Chem. Soc., Chem. Commun.* **1996**, 351−352.

(16) In related epoxidation reactions (ref 7), sulfide **1** was found to give high enantioselectivity in reactions with PhCHO (93% ee).

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(18) The quality of the $Cu(acac)_2$ is critical to the success of the reaction. Use of commercial $Cu(acac)_2$ was ineffective, but use of $Cu(acac)_2$ prepared by the method of Cervelló followed by sublimation was successful: Cervelló, J.; Marquet, J.; Moreno-Mañas, M. *Synth. Commun.* **1990**, *20*, 1931−1941.

(19) (*R*,*R*)-Stilbene oxide (94% ee) was treated with sodium azide followed by triphenylphosphine to yield (*S*,*S*)-*trans*-2,3-diphenylaziridine ($[\alpha]_D$ −320 (*c* 0.25 EtOH)). Deprotection of *N*-SES-*trans*-2,3-diphenylaziridine (97% ee) ($[\alpha]_D$ 9 (*c* 1.0 EtOH)) using CsF (see ref 12) gave *trans*-2,3-diphenylaziridine in 89% ($[\alpha]_D$ +311 (*c* 0.53 EtOH)). The absolute configuration of the *N*-SES-*trans*-2,3-diphenylaziridine could thus be deduced to be *R*,*R*.