Asymmetric Synthesis of Functionalised Pyrrolidines. Highly Diastereoselective Cyclisations Mediated by Sulfide and Sulfoxide Ligands

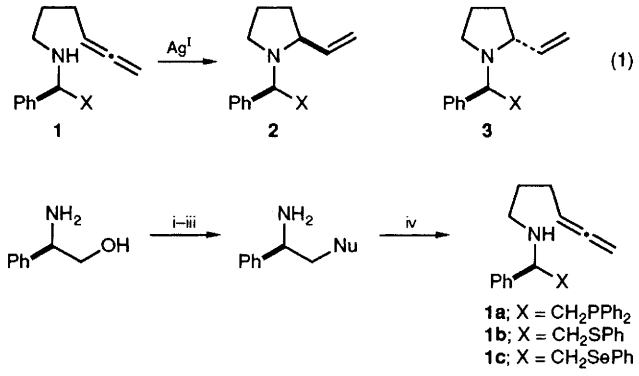
Ian W. Davies,[a] Timothy Gallagher,[a] R. Brian Lamont[b] and David I. C. Scopes[c]

[a] *School of Chemistry, Bath University, Bath BA2 7AY, UK*
[b] *Structural Chemistry Department, Glaxo Group Research Ltd, Greenford UB6 0HE, UK*
[c] *Medicinal Chemistry Department, Glaxo Group Research Ltd, Ware, Hertfordshire SG12 0DP, UK*

Silver(I)-catalysed cyclisation of sulfide **1b** and sulfoxides **4** and **5** to give the corresponding 2-vinylpyrrolidines **2b**, **6a** and **7a**, respectively proceeds with a high (up to 99% diastereoisomeric excess) level of diastereoselectivity; in all of these cases the sense of asymmetric induction observed has been shown to be the same.

The use of the allene π-system as a vehicle for electrophile-mediated heteroatom cyclisation reactions has developed rapidly over the last few years. While our goals in this area have been varied, lately we have focused on some of the fundamental stereochemical issues that pertain to this and related cyclisation processes.[1,2]

Recently, we described the use of a stereogenic benzylic residue as a means of controlling the outcome of the Ag^{I}-catalysed cyclisation of allenic amine **1** in terms of the distribution of the two diastereoisomeric pyrrolidines **2** and **3** [eqn. (1)]. The direct involvement of the X-substituent in this process provides a mechanism for effective asymmetric induction and the observed level of diastereoselectivity [expressed as % diastereoisomeric excess (d.e.)] correlated with the ability of X to act as a ligand for Ag^{I}. In the examples reported the highest selectivities obtained (80% d.e.; 9:1



Scheme 1 *Reagents and conditions*: i, $(Bu^tO)_2CO$, EtOAc, room temp.; ii, *p*-$MeC_6H_4SO_2Cl$, pyridine, room temp., then Nu^- (solvent) [Nu = PPh_2 (tetrahydrofuran, 0 °C), SPh (EtOH, room temp.), SePh (EtOH, room temp.)]; iii, CF_3CO_2H, 0 °C; iv, hexa-4,5-dienal, $NaBH(OAc)_3$, AcOH, $ClCH_2CH_2Cl$, room temp.

mixture of **2** and **3**) were for nitrogen-containing substrates **1** (X = CO·NHMe, CH_2NHMe).[2] Given these earlier observations, we reasoned that the incorporation of ligands based on second or third row elements into the benzylic stereocontrol unit should provide a higher level of stereodifferentiation. Accordingly, we have prepared allenic amines **1a–c**, starting from (*R*)-phenylglycinol, carrying a phosphine, sulfide and selenide ligand, respectively (Scheme 1).†

Cyclisation of phosphine **1a** using $AgOSO_2CF_3$ (100 mol%) in CH_2Cl_2 proceeded smoothly and the diastereoisomeric pyrrolidines **2a** and **3a** (X = CH_2PPh_2) were isolated in 68% yield, however, the level of diastereoselectivity obtained (59% d.e.) in this cyclisation reaction was surprisingly modest. Using the same conditions, cyclisation of selenide **1c** gave a similar result and **2c** and **3c** (X = CH_2SePh) were produced in 62% yield and 55% d.e. Given the relatively low level of selectivity observed, no effort was made in either case to determine the configuration of the major component.

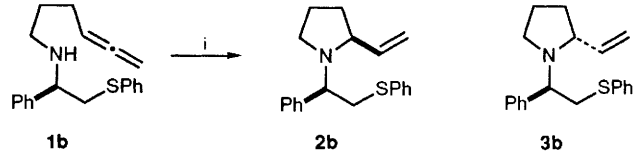
Sulfide **1b**, however, behaved quite differently. Cyclisation of **1b** (Scheme 2) was examined under a variety of conditions and these are summarised in Table 1. The highest selectivity obtained was achieved using $AgOSO_2CF_3$ (100 mol%) in 1,2-dichloroethane which gave **2b** and **3b** (X = CH_2SPh) in 90% isolated yield and 96% d.e. (as determined by HPLC and ^1H NMR of the crude reaction mixture).‡ The configuration of the major isomer **2b** resulting from this reaction was established unequivocally (see below).

We have also examined the corresponding sulfoxides **4**§ and **5**§ which have the possibility of ligating to Ag^I *via* sulfur or oxygen.[3] The Ag^I-mediated cyclisation of **4** and **5** was studied using both a stoichiometric and substoichiometric amount of $AgOSO_2CF_3$ and the results are shown in Scheme 3 and Table 2.‡ Once again, cyclisations were highly diastereoselective as determined by HPLC as well as being high yielding. In order

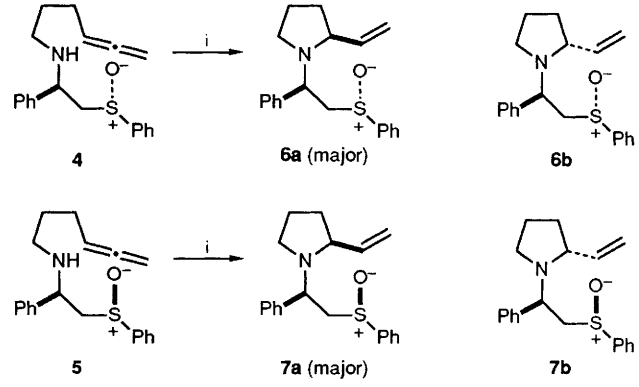
Table 1

Ag^I (mol%)	Solvent	D.e. (%)	Yield (%)
60	CH_2Cl_2	87	93
100	CH_2Cl_2	82	86
70	EtOAc	89	[a]
100	$ClCH_2CH_2Cl$	96	90

[a] Yield not determined.



Scheme 2 *Reagents and conditions*: i, $AgOSO_2CF_3$ (60–100 mol%), solvent (see Table 1), room temp.



Scheme 3 *Reagents and conditions*: i, $AgOSO_2CF_3$ (60–100 mol%), solvent (see Table 2), room temp.

to unambiguously ascertain the sense of asymmetric induction, as well as the configuration of the sulfoxide moiety, the structure of **6a** (the major diastereoisomer generated from cyclisation of **4**) was established by X-ray crystallographic analysis (Fig. 1).¶ We were also able to assign the structure of **7a**, the major diastereoisomer derived from sulfoxide **5**, by a straightforward chemical correlation. Sulfoxide reduction[4] (PBr_3, CH_2Cl_2, 0 °C) of **6a** and **7a** gave the same sulfide **2b** which was also identical, in terms of the stereochemistry at C-2 of the pyrrolidine ring, to the major diasteroisomer obtained by cyclisation of sulfide **1b**. Thus, in all cases involving sulfur-containing substrates the sense of asymmetric induction observed has been shown to be the same.

† All new compounds gave satisfactory spectral data (IR, ^1H and ^{13}C NMR) and were further characterised by elemental analysis and/or high resolution mass measurement; all yields refer to isolated material.

‡ The results shown in Schemes 2 and 3 have been reproduced (±1% d.e.) in duplicate runs. Increasing the amount of $AgOSO_2CF_3$ (to 500 mol%) did not significantly change the selectivity observed in the cyclisation of **1b** but the diastereoselectivity of this reaction was dramatically reduced by addition of small amounts of water or by the use of a hydroxylic solvent, such as methanol.

§ Sulfoxides **4** and **5** were obtained by oxidation of the *N*-(*tert*-butoxycarbonyl) derivative of **1b** (which gave a 1:1 mixture) which was followed by chromatographic separation of the diastereoisomers and carbamate cleavage (using CF_3CO_2H). Spectroscopic studies (FTIR) indicate that sulfoxide **4** ligates to Ag^I *via* oxygen: Δν(S=O) −16 cm^{-1} (CH_2Cl_2).

¶ *Crystal data* for **6a**: $C_{20}H_{23}NOS$, M = 325.47, trigonal, $a = b$ = 9.793(11), c = 16.749(5) Å, U = 1391(1) Å^3, λ = 1.5418 Å, space group $P3_2$ (No. 145), Z = 3, D_c = 1.17 g cm^{-3}, $F(000)$ = 522, μ(Cu-Kα) = 15.3 cm^{-1}, crystal size: 0.56 × 0.32 × 0.06 mm. Siemens R3m/V diffractometer, 2109 reflections measured ($3 < 2\theta < 115°$) of which 765 reflections had $I > 3.0\sigma(I)$. Full matrix least-squares refinement with anisotropic thermal parameters was used for all non-hydrogen atoms. Hydrogen atoms were refined in riding mode. Individual weights were applied according to the scheme $w = [\sigma^2(F_o) + 0.0005|F_o|^2]^{-1}$, refinement converged at R 0.035, R_w 0.035, goodness of fit = 0.98. The space group and hence the absolute structure were determined by refining Rogers' η parameter [η = 1.0(2)] [D. Rogers, *Acta Crystallogr., Sect. A*, 1981, **37**, 734]. All computations were carried out using the SHELXTL PLUS (μ-VAX II) system of programs (G. M. Sheldrick, SHETXTL release 4.11/V. Copyright 1990 Siemens Analytical X-ray Instruments). Atomic coordinates bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1.

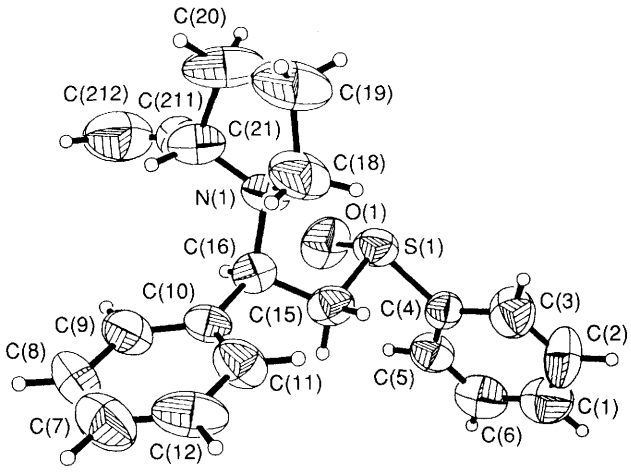


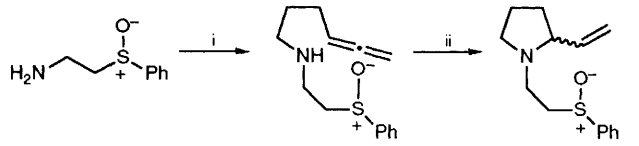
Fig. 1 ORTEP diagram of sulfoxide **6a**

Table 2

Sulfoxide	Ag^I (mol%)	Solvent	D.e. (%)	Yield (%)
4	94	CH_2Cl_2	95	81
4	67	CH_2Cl_2	97	85
4	100	EtOAc	91	[a]
4	98	$ClCH_2CH_2Cl$	99[b]	90
5	97	CH_2Cl_2	95	83
5	60	CH_2Cl_2	96	82
5	84	EtOAc	96	[a]

[a] Yield not determined. [b] This represents the limit of detection and no trace of the other diastereoisomer was observed.

Nevertheless, we were surprised that there was not a more substantial 'matched *vs.* mismatched' effect[5] involving an interaction between the two stereocentres present in both **4** and **5**. This prompted a closer examination of the role of the sulfoxide stereocentre itself in exerting an influence over the diastereoselectivity of the cyclisation reaction (Scheme 4). Using similar methodology to that described above, reductive amination of hexa-4,5-dienal with (±)-2-aminoethyl phenyl sulfoxide **8**[6] gave (±)-**9** in 47% yield. If the stereochemistry of the sulfoxide moiety plays a part in determining the level of asymmetric induction observed with **4** and **5**, then cyclisation of **9** should lead to a predominance of one of the two possible *racemic* diastereoisomeric pyrrolidines **10**. In the event, cyclisation of **9** proceeded in 91% yield, but showed a negligible level of diastereoselectivity (9% d.e.). It is apparent from this result, as well as from other studies that we have carried out, that the presence of a stereocentre close to the



Scheme 4 *Reagents and conditions*: i, hexa-4,5-dienal, $NaBH(OAc)_3$, AcOH, $ClCH_2CH_2Cl$, room temp., 47%; *ii*, $AgOSO_2CF_3$, (100 mol%), CH_2Cl_2, room temp., 91%

nucleophilic nitrogen atom is a prerequisite for high π-facial diastereoselectivity. However, establishing the origin of the extremely high selectivities observed with **4** and **5** will require further investigation.

Finally, one of our longer term goals is to build on these observations, in terms of the requirements for effective ligation and the relationship of stereocentres, to enable the design of a truly catalytic reaction that would encompass alkenyl, as well as allenyl substrates.[7] With this objective in mind it is important to note that a stereochemically, as well as chemically efficient cyclisation still takes place *using a substoichiometric amount of* Ag^I, even in the presence of sulfide or sulfoxide residues (Tables 1 and 2). Reaction times are longer under these conditions (days rather than hours) but this is a significant finding in terms of development of the catalytic process and work towards this end is continuing.

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References

1 D. N. A. Fox, D. Lathbury, M. F. Mahon, K. C. Molloy and T. Gallagher, *J. Chem. Soc., Chem. Commun.*, 1989, 1073.
2 For leading references to earlier work in this area of asymmetric induction, see D. N. A. Fox and T. Gallagher, *Tetrahedron*, 1990, **46**, 4697.
3 J. A. Davies, *Adv. Inorg. Chem. Radiochem.*, 1981, **24**, 115.
4 D. H. R. Barton, D. G. T. Greig, G. Lucente, P. G. Sammes, M. V. Taylor, C. M. Cooper, G. Hewitt and W. G. E. Underwood, *J. Chem. Soc., Chem. Commun.*, 1970, 1683; C. V. Kaiser, R. D. G. Cooper, R. E. Koehler, C. F. Murphy, J. A. Webber, I. G. Wright and E. M. Van Heyningen, *J. Org. Chem.*, 1970, **35**, 2430.
5 A. Horeau, H. B. Kagan and J. P. Vigneron, *Bull. Soc. Chim. Fr.*, 1968, 3795; S. Masamune, W. Choy, J. S. Petersen and L. R. Sita, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 1.
6 A. E. Senear, M. M. Rapport and J. B. Koepfli, *J. Biol. Chem.*, 1947, **167**, 229.
7 For a catalytic process based on Pd^{II}, see T. Hosokawa, C. Okuda and S. I. Murahashi, *J. Org. Chem.*, 1985, **50**, 1282.