Asymmetric Synthesis of Functionalised Pyrrolidines. The Role of a Stereogenic Centre on Nitrogen

David N. A. Fox, David Lathbury, Mary F. Mahon, Kieran C. Molloy, and Timothy Gallagher*

School of Chemistry, Bath University, Bath BA2 7AY, U.K.

The diastereoselectivity available during the silver(I)-catalysed aminocyclisation of a series of allenic amines (**1a—e**) bearing a stereogenic residue on nitrogen, to give the 2-substituted pyrrolidines (**2a—e**), has been evaluated; the ability of this residue to co-ordinate Ag^I is important to the success of the process.

Activation of a π-bond by interaction with an electrophile (metal^{n+}, RS^+, I^+ *etc.*), followed by cyclisation of either an oxygen or nitrogen nucleophile provides a flexible entry into a range of substituted oxygen- or nitrogen-containing heterocycles.[1]

Considerable progress has also been made on controlling the orientation of the new stereocentre that is generated on cyclisation, with respect to other substituents present on the newly-formed heterocycle.[2] However, efforts to control the stereochemistry of this newly-created centre in an absolute rather than in a relative sense, have met with more limited success.[3]

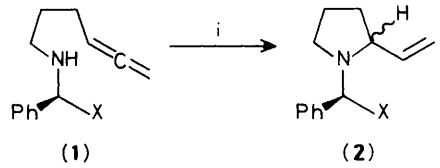
As part of a more general study[4] into the synthesis of nitrogen heterocycles utilising aminocyclisation to a metal ion-activated allene, we have addressed this stereochemical issue. A series of optically active allenic amines (**1a—e**) have been examined and in this Communication we describe how the presence of a stereogenic centre adjacent to nitrogen may be used to achieve a good level of asymmetric induction in the Ag^I-mediated cyclisation sequence shown in Scheme 1.

Amines (**1a—e**) were readily prepared by a reductive sequence (using 4,5-hexadienal and the appropriate amine or amino acid derivative)† and the results of the cyclisation study, in terms of the distribution of diastereoisomeric products (**2**), are shown in Table 1. Diastereoselectivities of up to 80% have been observed (entries 5 and 7) and in the case of (**1e**), the major diastereoisomer obtained was converted to the crystalline derivative (**3**) (m.p. 197 °C, CH_2Cl_2/$MeCO_2Et$/cyclohexane),‡ whose structure was then determined by *X*-ray crystallographic analysis (Figure 1).§ The structure of (**2d**) has

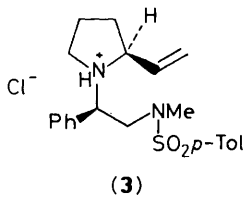
† 4,5-Hexadienal was obtained by DiBAl reduction of the corresponding nitrile which was in turn prepared from 3,4-pentadienol (tosyl chloride/pyridine, followed by NaCN/dimethyl sulphoxide).

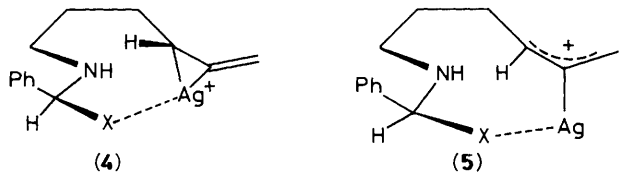
‡ Hydrochloride (**3**) was prepared by treating the major isomer of (**2e**) with tosyl chloride in pyridine, followed by reaction with HCl in ether.

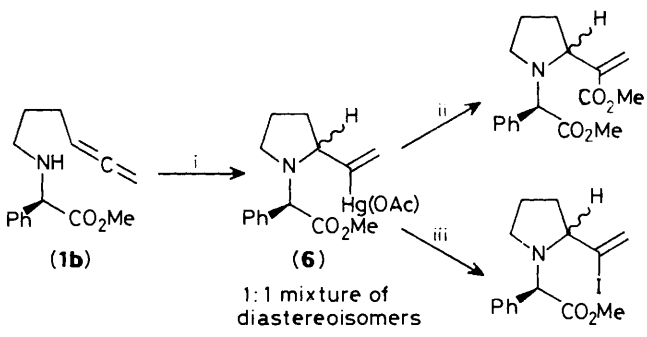
§ *Crystal data*: $C_{22}H_{29}ClN_2O_2$, M = 388.5, orthorhombic, a = 10.818(5), b = 13.841(4), c = 15.198(4) Å, U = 2,271.3 Å^3, space group $P2_12_12_1$, Z = 4, D_c = 1.231 g cm^{-3}, μ(Mo-K_α) = 2.7 cm^{-1}, F(000) = 896. Data were measured at room temperature on a Hilger and Watts Y290 four-circle diffractometer in the range $2 < \theta < 22°$. 1499 Reflections were collected of which 1198 were unique with $I \geq 3\sigma I$. Data were corrected for Lorentz and polarisation effects but not for absorption. The structure was solved by conventional direct methods. In the final stages of full matrix refinement the S(1), Cl(1), O(1), O(2), C(17), C(18), C(19), C(20), and C(21) atoms were refined anisotropically, all other atoms isotropically. Hydrogen atoms were included at calculated positions. The chirality of the space group was examined by inversion of the z co-ordinates of all atoms, but no significant difference in the final R values for the two models based on the Hamilton significance test was found. The configuration chosen was based on the stereocentre at C(10), derived from (*R*)-phenylglycine. Final residuals were R = 0.0749, R_w = 0.0787 for 163 parameters. Atomic co-ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors Issue No. 1.



Scheme 1. *Reagents*: i, $AgBF_4$ or $AgOSO_2CF_3$ (0.1—1.0 equiv.), CH_2Cl_2, 20 °C.







Scheme 2. *Reagents*: i, $Hg(OAc)_2$ or $Hg(OCOCF_3)_2$, tetrahydrofuran (THF), H_2O; ii, Li_2PdCl_4, CO, CH_3OH (58%); iii, KI, I_2 (53%).

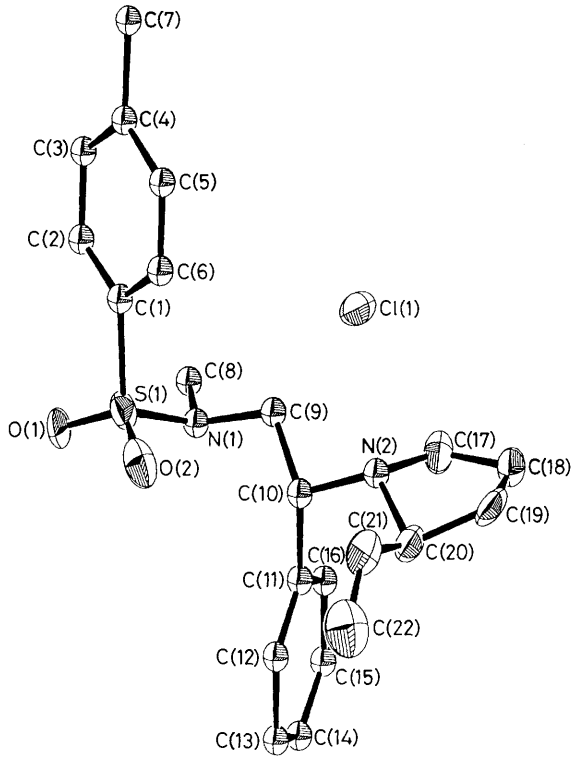


Figure 1. The asymmetric unit of (**3**) showing the atomic labelling scheme used. The thermal ellipsoids enclose 33% probability.

Table 1.

Entry	Allenic amine (**1**)	Product (**2**) (% yield, % diastereoisomeric excess)
1	(**1a**), X = Me	(**2a**) (82%, 33%)
2	(**1b**), X = CO_2Me	(**2b**) (80%, 60%)
3	(**1c**), X = CH_2OH	(**2c**) (90%, 60%)
4	(**1d**), X = CO·NHMe	(**2d**) (90%, 70%)[a]
5	(**1d**), X = CO·NHMe	(**2d**) (90%, 80%)[b]
6	(**1d**), X = CO·NHMe	(**2d**) (90%, 66%)[c]
7	(**1e**), X = CH_2NHMe	(**2e**) (97%, 80%)

[a] Using $AgOSO_2CF_3$ (0.1 equiv.). [b] Using $AgOSO_2CF_3$ (0.5 equiv.). [c] Using $AgOSO_2CF_3$ (1.0 equiv.).

also been correlated to this absolute configuration; reduction, using di-isobutylaluminium hydride (DiBAl), of the major isomer of (**2d**) gave the same diastereoisomer that predominated in (**2e**).

The degree of asymmetric induction achieved during cyclisation would appear to correlate with the ability of the stereogenic residue on nitrogen (X) to co-ordinate the incoming electrophile, Ag^I. This suggests that a chelating interaction is important if effective transmission of information from the otherwise remote stereocentre to the C-2 position of the incipient pyrrolidine is to be effective.

The exact process by which the asymmetric induction shown in Scheme 1 is achieved is still unclear; however two basic mechanistic pathways may be distinguished.[5] Firstly, a chelate involving the nitrogen atom and the residue (X) could serve as a template from which the electrophile, Ag^I, is delivered preferentially to one of the enantiotopic faces of the allene.[6] Reaction of the amine nucleophile with the resulting chiral metallocyclopropane/π-complex (**4**) would lead to the observed product. Alternatively, Ag^I could react with the allenic π-system to give, *via* a π-complex, a σ-silver species (**5**) (a planar allyl cation), again stabilised by co-ordination involving the remote ligand X. The observed asymmetric induction would then be a consequence of this interaction delivering the amine nucleophile in a face-selective fashion to the allenic residue.

The absolute stereochemistry of pyrrolidine (**2**) could therefore be set either at the stage that the electrophile interacts with the allene or during the cyclisation step itself.

The dependence on Ag^I concentration that is also observed (see entries 4—6 Table 1) may suggest the intermediacy of a species other than a simple 1 : 1 complex of the amine (**1**) and Ag^I. We are currently investigating the mechanism of this process to gain a more complete understanding of how this approach to asymmetric induction may be more fully controlled. Interestingly, the corresponding mercury(II)-induced

cyclisation reactions, which would normally be expected to parallel the related silver(I) pathway, do not show a comparable level of diastereoselectivity (Scheme 2). To date this has been a more limited study but clearly, efficient asymmetric induction in this area would be desirable given the established synthetic value of alkenyl mercury derivatives such as (**6**).[7]

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