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Development of a Chiral Stabilised Azomethine Ylid. A Chiral Relay System.

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Abstract: The chiral, stabilised azomethine ylid (2) derived from (*R*)-2-phenylglycinol has been demonstrated to undergo enantioselective 1,3-dipolar cycloaddition reactions with a range of alkene and alkyne dipolarophiles.

Azomethine ylids are readily accessible from α-amino acid precursors,[1] but are not capable of expressing their original chirality, as this information is necessarily lost in the process of ylid generation (**Figure 1**). Previous investigations into carrying out enantioselective cycloadditions with azomethine ylids have focussed upon the use of chiral auxiliaries on the dipolarophile.[2]

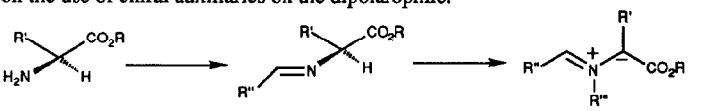


Figure 1

We reasoned that derivatisation of the α-amino acid, with the generation of additional chiral centres, could result in a template with an infrastructure capable of relaying the original absolute stereochemical information held in the amino acid precursor. Thus, by using the original α-chiral centre to control the formation of new chiral sites within a cyclic template (the 'chiral memory') prior to generation of the azomethine ylid, a relay system would be generated (**Figure 2**).[3]

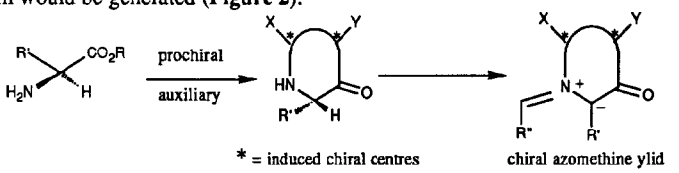


Figure 2

In this communication we report the realisation of stereocontrol in the 1,3-dipolar cycloaddition of the templated azomethine ylid system (2), derived from (5*R*)-phenylmorpholin-2-one (1) prepared in 75% yield from (*R*)-2-phenylglycinol by the method of Dellaria[4] (**Figure3**).

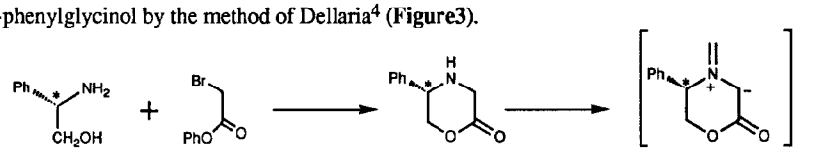
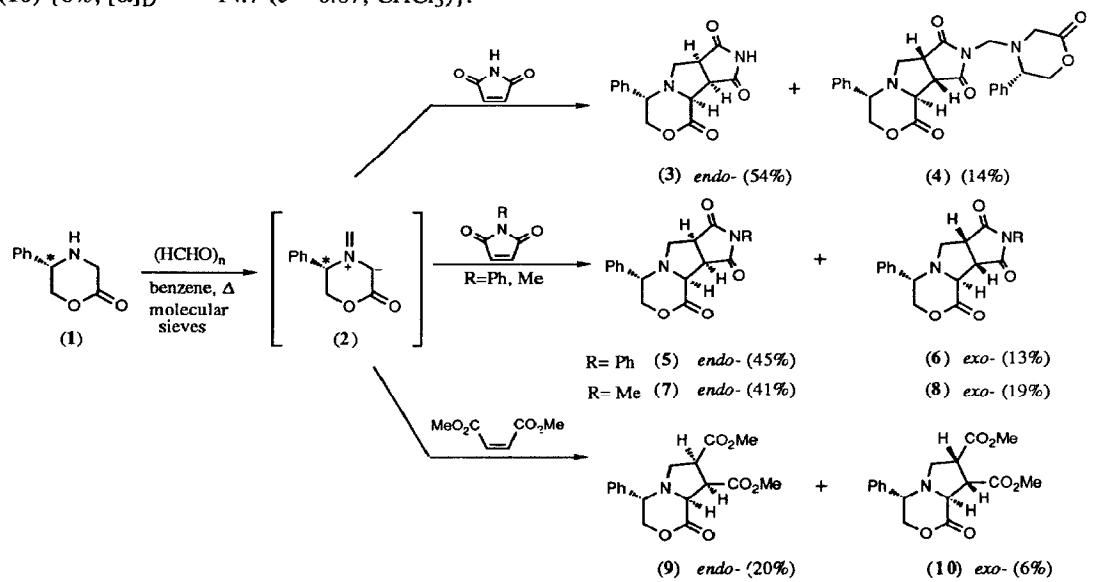


Figure 3

The azomethine ylid (2) was prepared by treating **1** with paraformaldehyde and reacted *in situ* with

various dipolarophiles in refluxing benzene. In a modification of the method of Tsuge[1c] a solution of **1** in sodium–dried benzene was added dropwise *via* a cannula[5] to refluxing dry benzene containing paraformaldehyde (10 equivalents) and the requisite dipolarophile (3 – 5 equivalents) under an atmosphere of nitrogen (**Scheme 1**). It was found most efficient to remove water produced during condensation by means of molecular sieves contained in a Soxhlet extractor. Reactions were monitored by t.l.c. (2 : 1 ethyl acetate : hexane) indicating absence of starting morpholinone within 2 h. Removal of the unreacted paraformaldehyde by filtration followed by evaporation of the solvent yielded a mixture of products together with excess dipolarophile which could be separated either by crystallisation or column chromatography.[6] Following this procedure, reaction of **2** with maleimide yielded the *endo*– adduct (**3**) in 54% yield {$[\alpha]_D^{20}$ = +45.3 (c = 1.0, $CHCl_3$)}whilst the *exo*– adduct was found to have reacted with a further molecule of **2** to yield **4** in 14% yield {$[\alpha]_D^{20}$ = +13.0 (c = 1.0, $CHCl_3$)}. Presumably the *endo*–analogue of compound **4** was not obtained since approach to the NH would be more hindered in this case. In order to circumvent this subsequent condensation, *N*–phenyl maleimide was used to trap the ylid (**2**). Two identifiable products were isolated, after column chromatography of the crude material, and were assigned structures of the *endo*– adduct (**5**) {45%, $[\alpha]_D^{20}$ = –42.3 (c = 0.6, $CHCl_3$)} and *exo*– adduct (**6**) {13%, $[\alpha]_D^{20}$ = +88.0 (c = 0.25, $CHCl_3$)}. Similarly, *N*–methyl maleimide was coupled with **2** to furnish only two products; the *endo*– adduct (**7**) {41%, $[\alpha]_D^{20}$ = +45.0 (c = 1.0, $CHCl_3$)} and the *exo*– adduct (**8**) {19%, $[\alpha]_D^{20}$ = +30.9 (c = 1.0, $CHCl_3$)}. Reaction of **2** with dimethyl maleate likewise furnished the *endo*– adduct (**9**) {20%, $[\alpha]_D^{20}$ = +6.0 (c = 0.73, $CHCl_3$)} and *exo*– adduct (**10**) {6%, $[\alpha]_D^{20}$ = –14.7 (c = 0.87, $CHCl_3$)}.

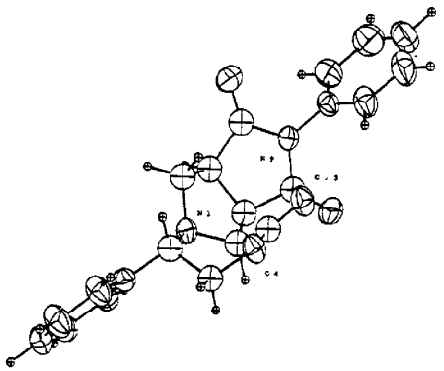


Scheme 1

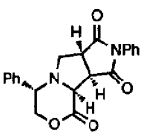
Although the material yields of adducts were variable, careful analysis of the crude mixtures gave no evidence for the presence of additional monomeric compounds other than excess dipolarophile. Heating **1** in refluxing benzene with excess paraformaldehyde for 2h in absence of dipolarophile and sieves, led to the recovery of 34% of starting material with unchanged optical rotation; indicating that the absolute configuration at C–5 is unaffected in the generation of the azomethine ylid (**2**). Thus, despite the observation of both *exo*– and

endo– cycloadducts when using alkene dipolarophiles, only ***one*** absolute stereochemistry is observed at C–3 of the morpholin–2–one ring for all cycloadducts **(3) – (10)**.

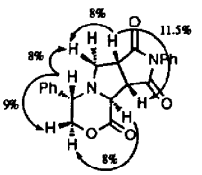
The structure of **5** was confirmed by X-ray analysis,[7] showing the morpholinone ring in a boat conformation in agreement with an earlier X–ray structure determination of a morpholin–2–one derivative.[4] The relative stereochemistry of the minor adduct was determined to be that of the *exo*– isomer (**6**) by COSY and NOE difference studies (**Figure 4**).



X–ray crystal structure of *endo*– adduct (**5**)



(**5**)

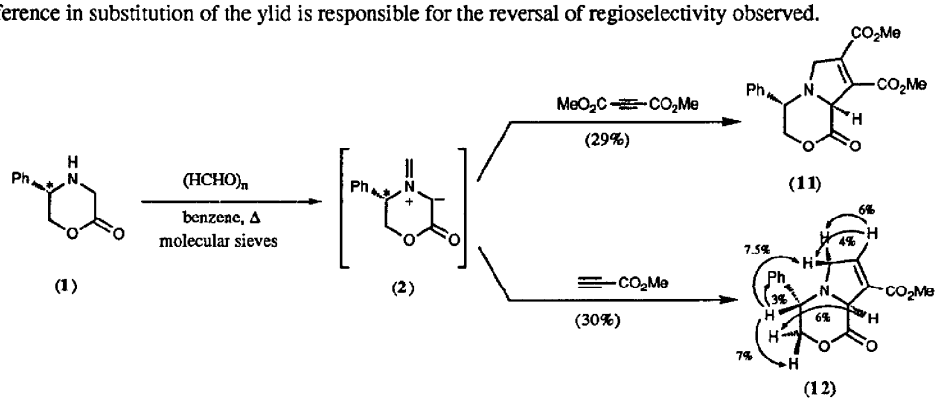


(**6**)

NOE enhancements for *exo*– isomer (**6**)

Figure 4

As alkene dipolarophiles furnished mixtures of *exo*– and *endo*– cycloadducts with a unique absolute stereochemistry at C–3 of the morpholinone ring, we reasoned that a symmetrical alkyne should result in a single cycloadduct. Indeed, cycloaddition between **2** and dimethyl butyne–1,4–dicarboxylate (5 equivalents), furnished a single cycloadduct in 29% yield which was identified as **11** {$[\alpha]_D^{20} = -76.0$ (c = 0.82, $CHCl_3$)} (**Scheme 2**).[6] To evaluate regiocontrol with this chiral azomethine ylid system, **2** was reacted with methyl propynoate to furnish a single product in 30% isolated yield, indentified as **12** {$[\alpha]_D^{20} = -32.8$ (c = 0.83, $CHCl_3$)} by COSY and NOE difference studies. This result is the inverse of the regioselectivity usually observed for cycloadditions of stabilised azomethine ylids with unsymmetrical dipolarophiles.[8] However, these previous studies concentrated upon stabilised ylids derived from aromatic aldehydes and it may be that this difference in substitution of the ylid is responsible for the reversal of regioselectivity observed.



Scheme 2

The stereochemical control at C–3 of the morpholin–2–one ring can be rationalised by envisaging an axial approach of the dipolarophile to the morpholin–2–one ylid in a chair conformation in which the phenyl group is equatorial (**Figure 5**). Subsequently, on completion of the cycloaddition, flipping the morpholinone ring to a boat conformation results in all substituents lying in the sterically least demanding environments.

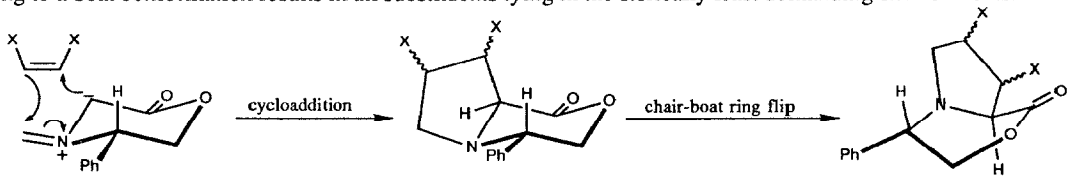


Figure 5

In conclusion, this work demonstrates high stereocontrol in the 1,3–dipolar cycloaddition of azomethine ylids constrained within a chiral morpholin–2–one template to generate adducts with total control over the absolute stereochemistry at the asymmetric centre α– to nitrogen. We are now investigating the application of this approach to the chiral relay system which is our ultimate goal. Within this context it is worthy of note that homochiral 3,5–disubstituted morpholin-2-ones may also be obtained *via* highly stereoselective hydrogenation of imine lactones obtained by the condensation of α–amino acids with α–bromoketones.[9]

Acknowledgement We gratefully acknowledge support for this work from the S.E.R.C. (A.S.A).

References

1. For example see: (a) S. Husinec, A. E. A. Porter and V. Savic, *Tetrahedron Lett.*, 1988, 6649; (b) H. Ardill, R. Grigg, V. Sridharan and S. Surendrakumar, *Tetrahedron*, 1988, **44**, 4953; (c) O. Tsuge, S. Kanemasa, M. Ohe and S. Takenaka, *Chem. Lett.*, 1986, 973; (d) M. Joucla and J. Mortier, *J. Chem. Soc., Chem. Comm.*, 1985, 1566 and references therein.
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3. For other examples of chiral relay systems see: H. Poisel and U. Schmidt, *Chem. Ber.*, 1972, **105**, 625; U. Schollkopf, R. Wick, R. Hinrichs and M. Lange, *Liebigs Ann. Chem.*, 1988, 1025; U. Schollkopf, U. Groth, K.-O. Westphalen and C. Deng, *Synthesis*, 1981, 969; J. Rouden, J. Royer and H.-P. Husson, *Tetrahedron Lett.*, 1989, 5133.
4. J.F. Dellaria, Jr. and B.D. Santarsiero, *J. Org. Chem.*, 1989, **54**, 3916. In this paper we use the trivial morpholin–2–one nomenclature to describe the 2,3,5,6–tetrahydro–*4H*–oxazinone ring system.
5. Slow addition of **1** and dilute conditions were necessary as the morpholinone exhibits a propensity to dimerise.[4] Consequently, **1** was prepared as required and stored below 0 °C for a maximum of 24 hours.
6. In all instances the products cited in this communication were the only identifiable monomeric materials. All novel compounds isolated gave spectroscopic and combustion analytical data in accord with their assigned structures
7. *Crystal data* for (7): $C_{21}H_{18}N_2O_4$, monoclinic, $P2_1$, a =6.767, b = 12.275, c = 10.822 Å, α = 83.62, β = 89.97, γ = 89.97°, V = 893.3 Å^3, Z = 1, D_c = 0.6736 g cm^{-3}, $F(000)$ = 190, μ(Cu–K_α) = 3.675 cm^{-1}. 1956 Independent reflections with $I > 3\sigma(I)$ were used in the analysis. Final R = 4.9, final Hamiltonian weighted R = 6.1. Data for crystallographic analysis were measured ($2\theta_{max}$ = 150°) on an Enraf–Nonius CAD 4 diffractometer using Cu–K_α radiation and ω–2θ scans. Structures were solved by direct methods and refined by least squares using the CRYSTAL package. Atomic co–ordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre.
8. For example see: D. A. Barr, R. Grigg, H. Q. Gunaratne, J. Kemp, P. McMeekin and V. Sridharan, *Tetrahedron*, 1988, **44**, 557. Grigg has reported instances of the alternative regioselectivity when the cycloaddition is carried out in the presence of Ti(IV) complexes: D. A. Barr, R. Grigg and V. Sridharan, *Tetrahedron Lett.*, 1989, 4727.
9. V. Caplar, A. Lisini, F. Kajfez, D. Kalbah and V. Sunjic, *J.Org.Chem.* , 1978, **43**, 1355.