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Asymmetric Cycloadditions of Aldehydes to Stabilised Azomethine Ylids: Enantiocontrolled Construction of β–Hydroxy–α–amino acid Derivatives

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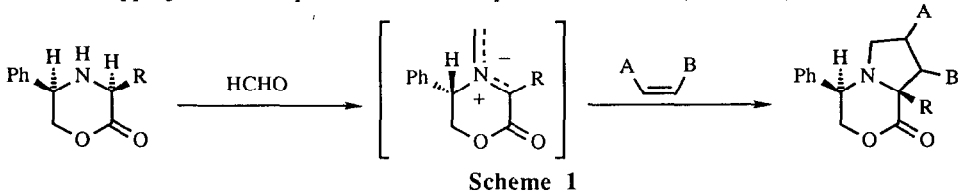
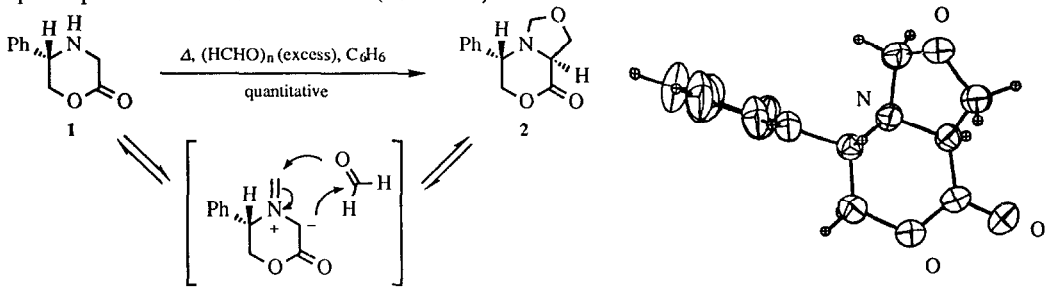
Abstract: In the absence of added dipolarophile, chiral stabilised azomethine ylids derived from the reaction of 5–(*S*)–phenylmorpholin–2–one (**1**) with aldehydes undergo efficient and highly enantiocontrolled cycloaddition with a second molecule of aldehyde to furnish products which may be converted into β–hydroxy–α–amino acids.

In a series of papers we have reported the results of our use of 5–phenylmorpholin–2–one templates with the aim of relaying chiral information at C–3 of the precursor through the sequence of azomethine ylid generation and trapping, in order to produce homochiral proline derivatives (**Scheme 1**).[1]



Scheme 1

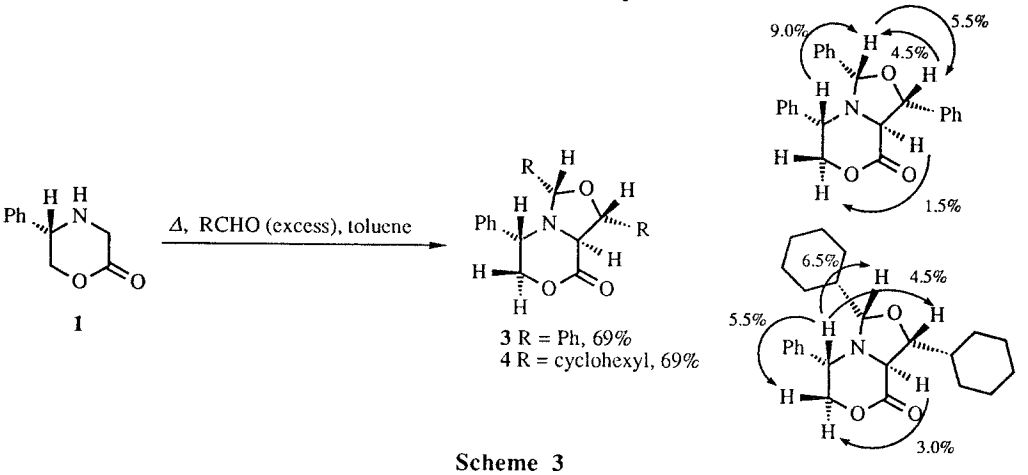
During our studies we found that, with decreasing dipolarophile reactivity, traces of a second product could be detected by t.l.c. analysis which did not correspond to the product of thermal dimerisation of **1**.[2] Subsequently we were able to demonstrate that heating 5–(*S*)–phenylmorpholinone (**1**) in benzene, in the presence of excess paraformaldehyde but with no additional dipolarophile, led to the exclusive production of this new material. Mass spectrometric analysis indicated this product to have resulted from addition of two molecules of formaldehyde to **1** in quantitative yield. Spectroscopic[3] and X–ray crystallographic analysis[4] showed this bis–adduct to have structure **2** {$[\alpha]_D^{20}$ –5.3 (c 1.0, $CHCl_3$)}formally derived by a second molecule of formaldehyde acting as the dipolarophile and undergoing cycloaddition with the azomethine ylid, although a stepwise process cannot be discounted (**Scheme 2**).[5]



Scheme 2

The regiochemical control is in keeping with that expected for the addition of aldehyde dipolarophiles to stabilised azomethine ylids.[5] Formation of **2** appears not to compete with trapping of the azomethine ylid by electron poor alkenes or alkynes, even those which only furnish low yields (*ca.* 30%) of cycloaddition material, indicating that reaction with a second molecule of formaldehyde is appreciably slower.

Reaction of of **1** in a similar manner with 3 equivalents of benzaldehyde in toluene (lower yields were observed in benzene) gave a single detectable cycloadduct (**3**), isolated in 69% yield {$[\alpha]_D^{20}$ –87.5 (c 1.0, $CHCl_3$)}. In this instance 3 chiral centres have been constructed with high stereocontrol. The relative stereochemistry was deduced by n.O.e difference measurements as shown in **Scheme 3**. Likewise, cyclohexane carboxaldehyde furnished an analogous cycloadduct (**4**) {$[\alpha]_D^{12}$ –26.8 (c 0.62, $CHCl_3$)}, also in 69% isolated yield. Once again n.O.e. difference studies enabled unambiguous assignment of the relative stereochemistry of the product. However, the less nucleophilic 4–hydroxybenzaldehyde furnished no cycloadduct and no reaction was detected when **1** was heated in the presence of ketones.



Scheme 3

The stereocontrol in the formation of **3** and **4** can be rationalised as shown in **Figure 1**. The favoured addition pathway involves the dipolarophile approaching the azomethine ylid in an axial manner from the least hindered side, with the aldehyde substituent positioned in the sterically least demanding environment. The whole process may well be reversible and such a rationale is entirely in keeping with previously observed stereochemistries in earlier work.[1,5] In the resultant cycloadducts **3** and **4** three new centres of absolute sterochemistry are derived from the single controlling centre at C–5 of the original morpholinone template.

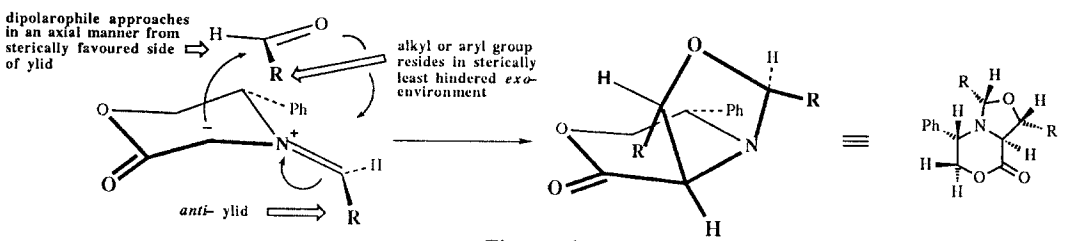
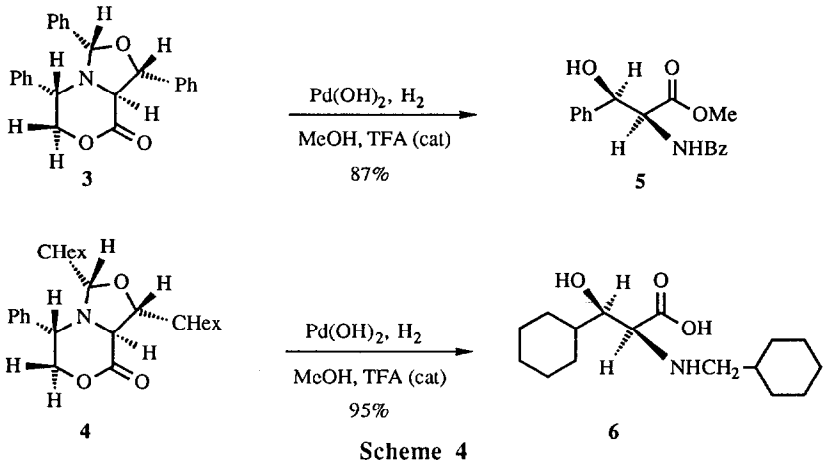


Figure 1

Adduct **2** is a fully and differentially protected derivative of (*S*)–serine, and adducts **3** and **4** are 2(*S*),3(*R*)–3–hydroxyamino acid derivatives. Subsequent removal of the morpholinone template of adduct **3**

under standard conditions with concommitant preferential hydrogenolytic cleavage of the *O*–benzyl bond of the oxazolidine ring[6] ($Pd(OH)_2/C$ catalyst, MeOH, trifluoroacetic acid) was accompanied by transesterification to furnish the methyl ester of *N*–benzyl 2(*S*),3(*R*)–(3–hydroxy)phenylalanine (**5**) in 87% isolated yield {$[\alpha]_D^{30}$ –10.4 (c 1.50, MeOH)}; whereas similar treatment of **4** furnished the *N*–cyclohexymethyl derivative of the free acid (**6**) in 95% yield {$[\alpha]_D^{21}$ –8.9 (c 1.05, MeOH)}(**Scheme 4**). In both cases, traces of the corresponding phenethyl esters were detectable by mass spectrometric analysis of the crude reaction mixture, and in the case of hydrogenolysis of **4**, traces of the methyl ester were also found.



Scheme 4

It is noteworthy that, under the hydrogenolysis conditions, cleavage of the *N*–benzyl bond of the oxazolidine ring of **3** is not observed.

In summary, we have found that the stabilised azomethine ylid (**1**) can react with excess aldehyde in the absence of added dipolarophile to furnish cycloadducts in which up to 3 new chiral centres have been generated with extremely high stereocontrol. Removal of the morpholinone template of such adducts is accompanied by hydrogenolysis of the *O*–benzyl bond of the oxazolidine ring to furnish homochiral β–hydroxy–α–amino acid derivatives in high overall yield. We will report further studies on the synthetic applications of this system in due course.

References

1 For the latest paper in this series see: A. S. Anslow, L. M. Harwood, H. Phillips, D. W. Watkin and L. F. Wong, *Tetrahderon Asymmetry*, 1991, **2**, 1343 and references cited therein.

2 5–Phenylmorpholinone has been reported to show a propensity to dimerise (J. Dellaria and B. D. Santarsiero, *J. Org. Chem.*, 1989, **54**, 3916.), but we have found the recrystallised material to be stable for indefinite periods at 0°C and to withstand refluxing toluene temperatures for 48 hours, although chromatographically pure material is more labile; presumably due to traces of acid present which are removed by recrystallisation.

3 All novel compounds isolated gave spectroscopic and/or analytical data in accord with their assigned structures. **2** mp 122°C; (Found C, 65.4, H, 5.80, N, 6.2 %; $C_{12}H_{13}NO_3$ requires C, 65.7, H, 6.00, N, 6.4 %; IR (KBr disk) ν_{max} 1739 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.35-7.45 (m, 5H,), 4.42 (d, J 7.0 Hz, 1H), 4.36 (t, J 11.0 Hz, 1H), 4.27 (dd, J 11.0 Hz, 3.0 Hz, 1H), 4.27 (dd, J 9.0 Hz, 7.0

Hz,1H), 4.20 (d, J 7.0 Hz, 1.0H), 4.13 (dd, J 12.0 Hz, 8.0 Hz, 1H), 4.11 (dd, J 14.0 Hz, 8.0 Hz, 1H), 4.00 (dd, J 11.0 Hz, 3.0 Hz, 1H); $^{m}/_{z}$ (CI {NH3}) 220 (MH^+), 104; $[\alpha]_D^{20}$ -5.3 (c 1.0, $CHCl_3$); **3** mp 152°C; (Found C, 78.0, H, 5.40, N, 3.4 %; $C_{24}H_{21}NO_3$ requires C, 77.6, H, 5.70, N, 3.8 %; IR (KBr disk) ν_{max} 1748 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 6.80-7.70 (m, 15H), 5.60 (d, J 7.0 Hz, 1H), 5.02 (s, 1H), 3.84 (d, J 7.0 Hz, 1H), 3.66 (dd, J 12.0 Hz, 11.0 Hz, 1H), 3.65 (dd, J 12.0 Hz, 4.0 Hz, 1H), 3.49 (dd, J 10.0 Hz, 5.0 Hz, 1H); $^{m}/_{z}$ (DCI {NH_3}) 372 (MH^+), 266, 104; $[\alpha]_D^{20}$ -87.5 (c 1.0, $CHCl_3$); **4** mp 164°C; (Found C, 75.1, H, 9.00, N, 3.5 %; $C_{24}H_{33}NO_3$ requires C, 75.2, H, 8.65, N, 3.6 %); IR (KBr disk) ν_{max} 1752 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34-7.40 (m, 5H), 4.34 (dd, J 11.0 Hz, 1.0 Hz, 1H), 4.24 (dd, 11 Hz, 4 Hz, 1H), 4.12 (dd, J 7.0 Hz, 5.0 Hz, 1H), 4.03 (d, J 5.0 Hz, 1H), 3.92 (d, J 7.0 Hz, 1H), 3.89 (dd, J 11.0 Hz, 4.0 Hz, 1H), 0.7-1.9 (m, 22H, **Cx**); $^{m}/_{z}$ (DCI {NH_3}) 384 (MH^+), 300, 272, 104; $[\alpha]_D^{12}$ -26.8 (c 0.615, $CHCl_3$); **5** IR (film) ν_{max} 3032, 1674 cm^{-1}; ^1H NMR (200 MHz, CD_3OD) δ 7.10-7.55 (m, 10 H), 4.94 (d, J 7.0 Hz, 1 H), 4.53 (d, J 14.0 Hz, 1 H), 4.27 (d, J 14.0 Hz, 1 H), 4.16 (d, J 7.0 Hz, 1 H), 3.57 (s, 3 H); $^{m}/_{z}$ (DCI {NH_3}) 286 (MH^+), 178, 108, 91, 88; $[\alpha]_D^{30}$ -10.4 (c 1.50, MeOH); **6** IR (film) ν_{max} 3080, 1720 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 2.1–3.1 (m, 22 H), 3.95–4.05 (m, 1 H), 4.10–4.15 (m, 1 H), 4.85–5.10 (m, 2 H); $^{m}/_{z}$ (DCI {NH_3}) 388 (MH^+), 298, 284, 268; $[\alpha]_D^{21}$ -8.9 (c 1.05, MeOH)

4 **Crystal data for 2:** $C_{12}H_{13}NO_3$, orthorhombic, $P2_12_12_1$, a = 5.452, b = 21.910, c = 9.229Å, α = 90, β = 90, γ = 90°, V = 1102.43 $Å^3$, Z = 4, D_c = 1.321 g cm^{-3}, $F(000)$ = 464, $\mu(Cu–K_\alpha)$ = 0.750 cm^{-1}. 1975 Independent reflections with $I > \sigma(I)$ were used in the analysis. Final R = 3.02, final Hamiltonian weighted R = 3.83. 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.

5 For example see: H. Ardill, X. L. R. Fontaine, R. Grigg, D. Henderson, J. Montgomery, V. Sridharan and S. Surendrakumar, *Tetrahedron*, 1990, **46**, 6449; H. Ardill, R. Grigg, V. Sridharan, S. Surendrakumar and S. Thianpataganagal, *J. Chem. Soc., Chem. Commun.*, 1986, 602.

6 M. Senkus, *J. Am. Chem. Soc*,. 1945, **67**, 126.