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Synthesis of α-Phenyl Proline Derivatives *via* 1,3-Dipolar Cycloaddition of Chiral Stabilised Azomethine Ylids.

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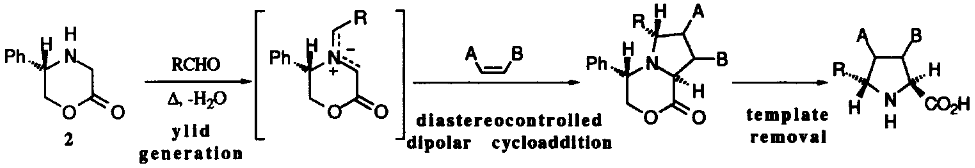
Abstract: The preparation of (3*S*, 5*R*)–3,5–diphenylmorpholinone **1** and subsequent diastereoselective 1,3– dipolar cycloaddition of its formaldehyde derived azomethine ylid is described. Removal of the chiral template furnishes α–phenyl proline derivatives.

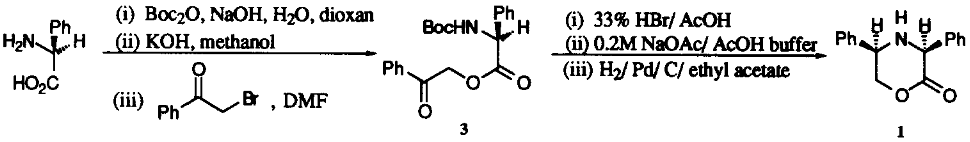
In a series of papers we have reported that 5-phenylmorpholin-2-one **2** reacts with aldehydes under both thermal[1] and catalysed conditions,[2] generating azomethine ylid species capable of undergoing highly diastereocontrolled cycloadditions. Subsequent removal of the chiral template permits the generation of proline derivatives in high enantiomeric purity. Intramolecular reactions in which the dipolarophile is tethered to the aldehyde used to generate the ylid proceed with high control of the reacting ylid geometry;[3] whilst intermolecular reactions of alkene dipolarophiles with aldehydes other than formaldehyde show moderate selectivity for reaction *via* the *E*–azomethine ylid (**Scheme 1**).[1c]



Scheme 1

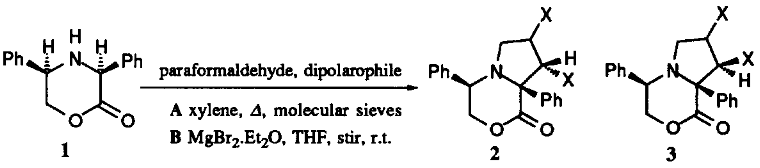
We now wish to report the results of our investigations into the diastereoselectivity of the cycloaddition reactions of the azomethine ylid derived from the condensation of the diphenyl substituted morpholinone **1**. The starting template is conveniently prepared in 6 steps from (*S*)–phenyl glycine following the method of Sunjic.[4] *N*–Boc protection (Boc$_2$O, NaOH, H$_2$O, Dioxan, 89%), potassium salt formation (KOH, methanol, quant), followed by alkylation with α-bromoacetophenone in DMF (74%) afforded the *N*-Boc protected ester **3**. Subsequent deprotection (33% HBr/ AcOH, 81%), cyclisation (0.2M NaOAc/ AcOH buffer, 89%), followed by stereoselective hydrogenation (86%) afforded the morpholinone **1** (**Scheme 2**).[5] In contrast to the observation of Sunjic that hydrogenation of the imine resulted in destruction of the template we have only ever observed clean stereoselective hydrogenation to furnish the desired morpholinone.

Dedicated to the memory of Professor Hidemasa Takaya, deceased on 5 October 1995

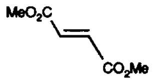
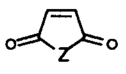


Scheme 2

(3*S*, 5*R*)–3,5–diphenylmorpholinone **1**, paraformaldehyde and a representative range of alkene dipolarophiles were heated to reflux in xylene, with azeotropic removal of water.[1c] Removal of solvent and column chromatography allowed the cycloadducts to be isolated and analysis of the 2–dimensional and n.O.e difference spectra permitted unambiguous configurational assignment in each instance (**Scheme 3, conditions A**).[5] Having demonstrated that paraformaldehyde would react with **1** to form an ylid capable of undergoing diastereocontrolled intermolecular trapping under thermal conditions with various dipolarophiles, the same conversions were studied under Lewis acid catalysis.[2] Accordingly the same reactions were repeated at room temperature in sonicated THF in the presence of $MgBr_2.Et_2O$ and molecular sieves. Standard work–up and purification furnished the same cycloadducts as in the thermal conditions, albeit in different yields (**Scheme 3, conditions B**).



a, **c**, **d**, X groups *syn* **b**, X groups *anti*

dipolarophile		isolated yield (%)			
		2		3	
		A	B	A	B
	a	89	56	0	0
	b	95	65	0	0
 Z=NPh	c	44	17	28	23
Z=NMe	d	53	36	29	25

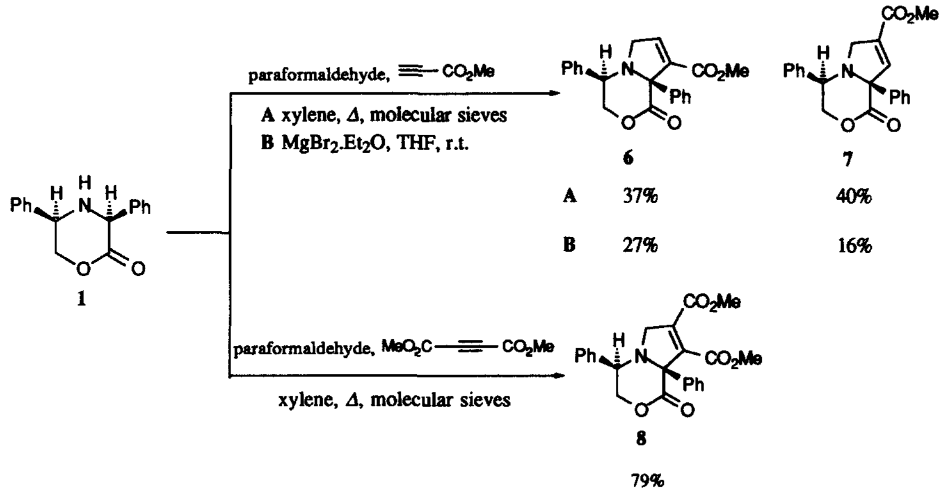
Scheme 3

In keeping with our previous observations and rationale, the major (or sole) products **2a** – **d** from the thermal reaction were shown to result from *endo*– approach of the dipolarophile to the least–hindered face of the templated ylid locked in a conformation in which the phenyl group is equatorial. Catalysis results in a uniform reduction in material yield of adducts and reduced diastereocontrol leading to the formation of a greater proportion of *exo*– adducts **3c**, **d** in the case of the cyclic dipolarophiles.

Although a higher temperature is required to effect reaction (refluxing xylene *vs* refluxing toluene), the diastereocontrol is better than previously found for intermolecular trapping of both substituted and unsubstituted ylids and the combined yields of cycloadducts are higher than those observed in the corresponding reactions of the 5-phenylmorpholin-2-one derived ylid.[1c] These observations presumably reflect the lower reactivity of the ylid due to the additional steric crowding and electronic stability imparted by the phenyl substituent. Notably, dimethyl fumarate and dimethyl maleate both furnish a single cycloadduct, **2a**, **2b** respectively, under thermal and catalysed conditions.

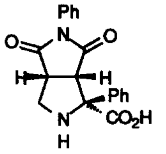
Cycloadducts with alkyne dipolarophiles are free from stereochemical complications arising from *exo*– or *endo*– attack. Accordingly dimethyl acetylenedicarboxylate and methyl propiolate were heated with (3*S*, 5*R*)–3,5–diphenylmorpholinone **1** and paraformaldehyde in refluxing xylene with azeotropic removal of water. Dimethyl acetylenedicarboxylate was found to give a single cycloadduct under these conditions, while methyl propiolate was found to give two products corresponding to the two regioisomers of the cycloadduct (**Scheme 4**). The stereo– and regiochemistry of the two regioisomers were determined by COSY and n.O.e difference experiments.

Under the catalysed conditions, dimethyl acetylenedicarboxylate was found not to produce the desired cycloadduct. However, methyl propiolate did react to give the two regioisomers in reduced yield.



Scheme 4

Subjecting cycloadducts **2b**, **2c**, and **3d** to catalytic hydrogenolysis (Pearlman's catalyst, H_2 5 bar, MeOH, TFA)[6] resulted in the isolation of the amino acids **9** 78%, **10** 70%, **11** 75%, although amino acid **10** was found to be insoluble in a range of solvents and was therefore isolated as the hydrochloride salt. Notably the efficiency of the hydrogenolysis was highly dependent on the cycloadduct involved, with cycloadduct **8** giving cycloadduct **2a** quantitatively, which along with cycloadduct **2d** was unchanged after lengthy exposure to the hydrogenolysis conditions.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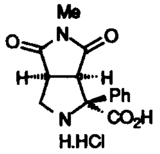
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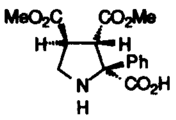
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Acknowledgements

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5 All novel compounds isolated had spectroscopic data in accord with their assigned structures. Selected data: (**1**) m.p=93-96 °C. found C, 75.6, H, 6.1, N, 5.5 %, $C_{16}H_{15}NO_2$ requires C, 75.9, H, 6.3, N, 5.5 %; υ_{max} (KBr) 3301, 1733, 1201 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.65-7.36 (10H, m, $\underline{Ph}$), 4.96 (1H, s, NC$\underline{H}$CO), 4.39-4.52 (3H, m, NC$\underline{H}$ + C$\underline{H}_2$O), 2.2 (1H, s, N$\underline{H}$); $^m/_z$ (CI, NH_3) 254 (100%, M+1), 209 (75%), 104 (75%). (**2a**) M.p.=110-114°C. found C, 67.47, H, 5.63, N, 3.40 %, $C_{23}H_{23}NO_6$ requires C, 67.47, H, 5.66, N, 3.42 %; υ_{max} (KBr) 1750, 1742, 1720 cm^{-1}; δ_H (500MHz, $CDCl_3$) 8.04-8.06 (m, 2H, Ph), 7.60-7.62 (m, 2H, Ph), 7.37-7.50 (m, 6H, Ph), 4.54 (dd, 1H, *J* 10.6, *J'* 3.3 Hz, 2α-H), 4.10-4.19 (m, 2H, 3α-H + 3β-H), 3.81 (s, 3H, Me), 3.66 (d, 1H, *J* 6.5 Hz, 7β-H), 3.62 (s, 3H, Me), 3.41 (dd, 1H, *J* 9.2, *J'* 7.5 Hz, 9β-H), 3.33 (dd, 1H, *J* 11.9, *J'* 9.2 Hz, 9α-H), 3.06-3.11 (m, 1H, 8β-H); nOe expt 4.55 **2α–H**–Ph (10.5%), –9α–H (6.1%), 3.4 **9β–H**–9α–H (21.7%), –8β–H (13.4%), –Ph (3.9%), –Ph (2.2%), 3.3 **9α–H**–9β–H (12.8%), –2α–H (10.7%), 3.1 **8β–H**–7β–H (10.9%), –9β–H (6.2%), –Ph (3.1%); m/z (CI, NH_3) 410 (100%, M+1), 378 (10%), 365 (10%), 104 (15%); $[\alpha]_D^{22}$ -27.6 (c 0.25, $CHCl_3$). (**2b**) M.p.=203-206°C; found C, 67.53, H, 5.50, N, 3.26 %, $C_{23}H_{23}NO_6$ requires C, 67.47, H, 5.66, N, 3.42 %; υ_{max} (KBr) 1741, 1725, 1720 cm^{-1}; δ_H (500MHz, C_6D_6), 8.11-8.13 (m, 2H, $\underline{Ph}$), 7.31-7.33 (m, 2H, $\underline{Ph}$), 6.96-7.13 (m, 6H, $\underline{Ph}$), 4.29 (dd, 1H, *J* 11.3, *J'* 3.4 Hz, 2α-H), 4.27 (d, 1H, *J* 2.7 Hz, 7β-H), 3.81 (dd, 1H, *J* 9.8, *J'* 2.6 Hz, 9β-H), 3.80 (t, 1H, *J* 11.3 Hz, 3β-H), 3.64 (dd, 1H, *J* 11.3, *J'* 3.4 Hz, 3α-H), 3.44 (s, 3H, $\underline{Me}$), 2.97 (dd, 1H, *J* 9.8, *J'* 7.0, 9α-H), 2.85 (s, 3H, $\underline{Me}$), 2.59-2.84 (m, 1H, 8α-H); nOe expt 3.8 **3β–H+9β–H**–9α–H (29%), –3α–H (24.7%), –8α–H (4.3%), –Ph (10%), –Ph (6%), 2.9 **9α–H**–9β–H (29.8%), –8α–H (12%), –2α–H (10.9%), 2.6 **8α–H**–7β–H (6.7%), –9α–H (6.2%); m/z (CI, NH_3) 410 (100%, M+1), 137 (35%), 104 (40%), 81 (45%), 61 (30%); $[\alpha]_D^{23}$ -27.8 (c 0.32, $CHCl_3$). (**9**) M.p. = 232-235°C (dec); υ_{max} (KBr) 3200-2800, 1780, 1718 cm^{-1}; δ (200MHz, CD_3OD) 7.2-7.8 (m, 10H, $\underline{Ph}$), 4.10-4.42 (m, 3H, 4α–H + 5α–H + 5β–H), 3.48 (d, *J* 7.0 Hz, 3α–H), 3.25 (d, *J* 9.0 Hz, N$\underline{H}$); m/z (DCI, NH_3) 337 (5%, M+1), 291 (100%), 102 (75%), 94 (75%); $[\alpha]_D^{20}$ -12.9 (c 0.75, 1 M HCl).

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