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Enantiocontrolled Construction of Bicyclic Proline Derivatives *via* One–Pot Generation and Intramolecular Trapping of Chiral Stabilised Azomethine Ylids

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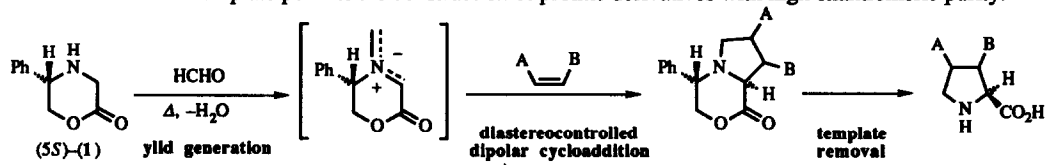
Abstract: Aldehydes possessing unsaturation at C–5 or C–6 condense with (5*S*)–phenylmorpholin–2–one (**1**), generating chiral stabilised azomethine ylids which undergo concommitant diastereospecific intramolecular 3+2 dipolar cycloaddition to furnish adducts (**2**), (**4**), and (**5**) which may be converted to homochiral bicyclic proline derivatives. Reductive desulfurisation of the thioether derivative (**5**) leads to (2*S*,4*R*,5*R*)–4,5–dimethylproline (**7**).

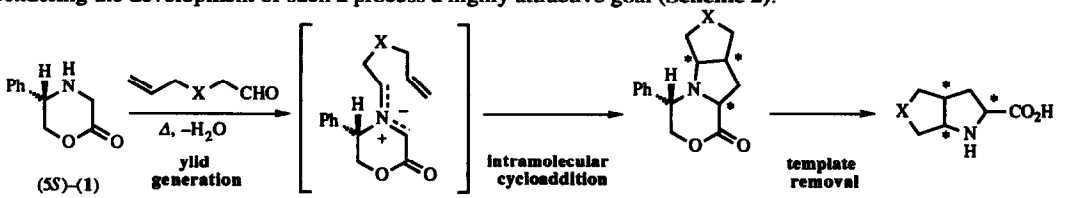
In a series of papers we have reported the results of our use of homochiral 5–phenylmorpholin–2–one templates to react with aldehydes, generating azomethine ylid species capable of undergoing highly diastereocontrolled intermolecular cycloadditions with electron deficient alkenes (**Scheme 1**).[1a–d] Subsequent removal of the chiral template permits the construction of proline derivatives with high enantiomeric purity.



(5*S*)-(1)

Scheme 1

Having established the efficacy of the intermolecular process, we now wish to report our investigations into the intramolecular variant of this sequence using aldehydes possessing appropriately positioned unsaturation. Combining ylid generation with an intramolecular 3+2 dipolar cycloaddition holds potential for diastereocontrolled construction of several stereocentres and rapid access to annelated proline derivatives, thus rendering the development of such a process a highly attractive goal (**Scheme 2**).

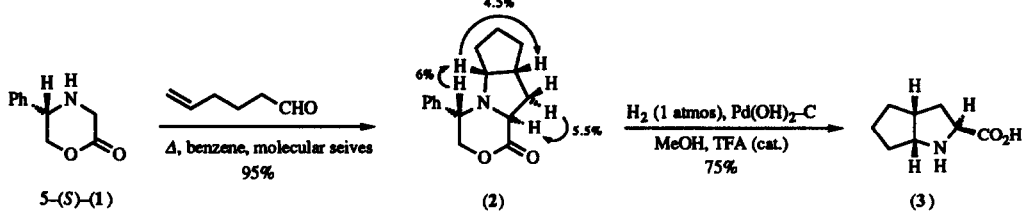


(5*S*)-(1)

Scheme 2

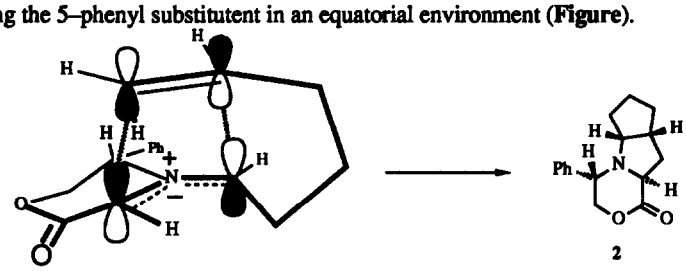
In addition to the features outlined above, there is literature precedent to suggest that the intramolecular nature of the process might permit dipolar cycloaddition to occur with less electron–deficient alkene dipolarophiles.[2] Herein we report the successful realisation of our aims and demonstrate the extension of this intramolecular cycloaddition methodology to the stereoselective construction of 4,5–dialkylated prolines.[3]

Treating (5*S*)–(**1**) with 2.5 equivalents of 5–hexenal in refluxing benzene, removing water using molecular sieves in a Soxhlet extractor as described previously,[1c] resulted in total disappearance of (**1**) within 3 hours to furnish a single adduct ($^{m}/_{z}$ 258, MH^{+}) as estimated by t.l.c. and spectroscopic analysis of the solid residue obtained after removal of volatiles. Recrystallisation of this material from ether / pentane furnished the adduct in 95% yield and analysis of the 2D ^{1}H n.m.r. and n.O.e. difference spectra enabled structure (**2**) to be assigned.[4] This assignment was further confirmed by removal of the template under standard hydrogenolytic conditions[1c] to furnish (1*R*, 3*S*, 5*R*)–2–azabicyclo[3.3.0^{1,5}]octane–3–carboxylic acid (**3**) in 75% recrystallised yield{$[\alpha]_D$ –45 (c 0.4, MeOH), m.p. 219–220°C; Lit.[5] $[\alpha]_D$ –47.2 (c 0.4, MeOH), m.p. 220°C} (**Scheme 3**).



Scheme 3

The stereocontrol in the formation of (**2**) may be rationalised by assuming axial approach of the dipolarophilic double bond to the *E*–configurated ylid in which the morpholin–2–one template is frozen in the conformation having the 5–phenyl substitutent in an equatorial environment (**Figure**).

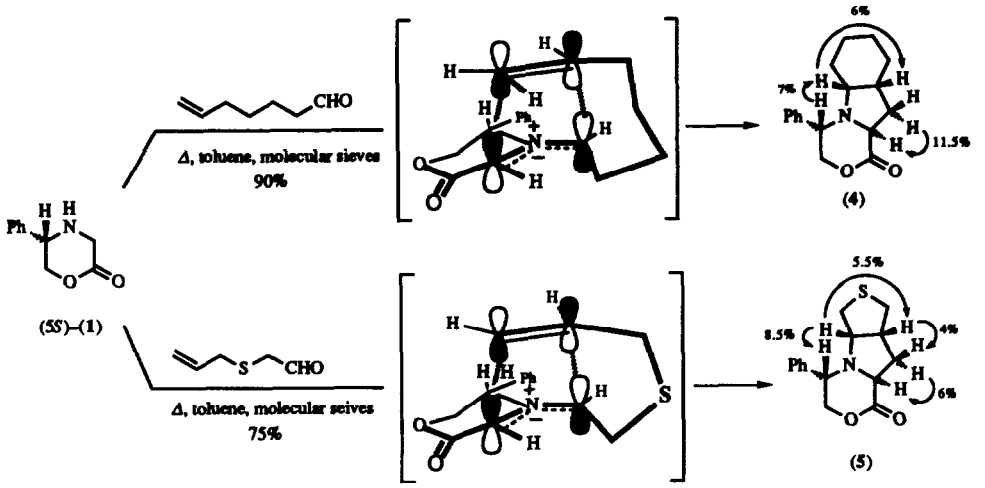


Figure

This rationale follows our earlier interpretation of diasterocontrol in intermolecular processes, when preferential cycloaddition of the *E*–ylid generated from 5–phenylmorpholin–2–one (**1**) and benzaldehyde was invoked to explain the observed product distribution.[1c] In the intramolecular reaction, the additional constraints of the linking chain are presumably responsible for the total selectivity of reaction *via* the *E*–ylid, as models indicate that the *Z*–ylid geometry does not permit effective proximity of dipole and dipolarophile.

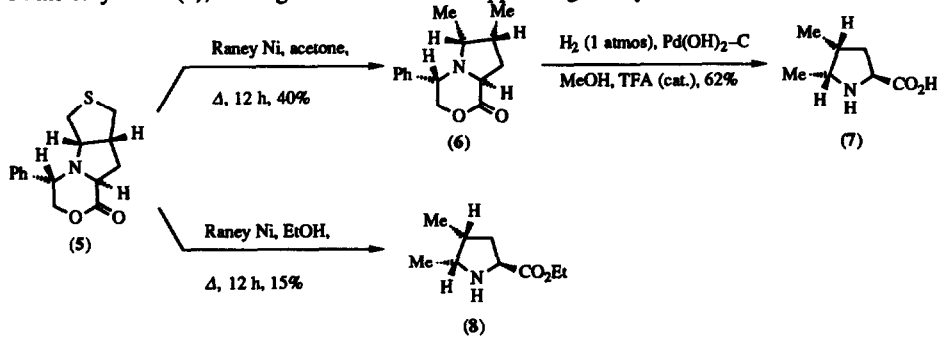
Using 6–heptenal under the above condensation / cycloaddition conditions furnished no new material after 24 hours. However, refluxing 1.1 equivalents of the aldehyde with (5*S*)–(**1**) in toluene for 12 hours led to a single cycloadduct which was obtained in 90% yield after recrystallisation from ether. Once again, detailed analysis of the crude reaction mixture did not indicate the presence of any other adducts, and examination of the 2D ^{1}H n.m.r. and n.O.e. difference spectra of the pure adduct allowed structure (**4**) to be assigned.[3] Similarly, use of 1.1 equivalents of 3–thia–5–hexenal[6] in refluxing toluene for 48 hours gave a single cycloadduct (**5**) (crude yield quantitative) which was isolated in 75% recrystallised yield (**Scheme 4**).

In each case the diastereocontrol observed in the condensation / intramolecular cycloaddition accords with the rationale proposed for the formation of (**2**); the original chiral centre at C–5 of the morpholinone template giving rise to three new asymmetric centres. It is worth noting the facility with which the intramolecular cycloaddition occurs, despite the fact that the double bond does not possess electron–withdrawing groups.



Scheme 4

Reductive cleavage of the thioether linkage in the cycloadduct (**5**) was readily achieved by heating a solution of (**5**) in acetone to reflux with excess Raney nickel for 12 hours to furnish (**6**) in 40% isolated yield. Hydrogenolytic degradation of the morpholin–2–one framework was then carried out using standard conditions to permit the isolation of (1*S*, 4*R*, 5*R*)–4,5–dimethylproline (**7**) in 62% yield (**Scheme 5**). Alternatively, desulfurisation and hydrogenolysis of the morpholin–2–one template with concommitant transesterification could be achieved in a one–pot process by refluxing an ethanolic solution of (**5**) with excess W–4 Raney nickel to furnish the ethyl ester (**8**), although in a somewhat disappointing 15% yield.



Scheme 5

In summary, the process of generating chiral ylids capable of undergoing diastereocontrolled dipolar cycloaddition described in this communication permits rapid access to both bicyclic and monocyclic 4,5–disubstituted derivatives of proline with high enantiocontrol over the new asymmetric centres generated. Investigations continue into the scope and applications of this useful variant of chiral azomethine ylid chemistry.

References

1. (a) A. S. Anslow, L. M. Harwood, H. Phillips, and D. Watkin, *Tetrahedron Asymmetry*, 1991, 2, 169. (b) A. S. Anslow, L. M. Harwood, H. Phillips, and D. Watkin, *Tetrahedron Asymmetry*, 1991, 2, 997. (c) A. S. Anslow, L. M. Harwood, D. Watkin, and L. F. Wong, *Tetrahedron Asymmetry*, 1991, 2, 1343. For reaction of these azomethine ylid species with aldehyde dipolarophiles see L. M. Harwood, J. Macro, D. Watkin, C. E. E. Williams and L. F. Wong, *Tetrahedron Asymmetry*, 1992, In the press. A brief mention of the use of 5,6–diphenylmorpholin–2–ones as azomethine ylid precursors

has now appeared (R. M. Williams, *Aldrichimica Acta*, 1992, **25**, 11). However, these compounds are not readily derived from naturally occuring amino acids and so are useless for the chiral memory system we have developed.

2. For a review of intramolecular cycloadditions involving azomethine ylids see P. A. Wade, in *'Comprehensive Organic Synthesis'*, 1991, vol. 4, chapter 10 pp. 1144–1150, Ed. in Chief, B. M. Trost, Pergamon Press; and references cited therein.

3. The work described herein forms part of G.B. Patent Application No. 9214932.7, 1992.

4. All substances isolated gave spectroscopic data in accord with their assigned structures. Selected spectroscopic data are given below:

(2*R*, 6*R*, 8*S*, 12*S*)–1–aza–10–oxo–12–phenyltricyclo[6.4.0^{1,8}.0^{2,6}]dodecan–9–one (**2**).Colourless crystals (Et_2O / hexane) m.p. 114.5–115.5°C. Requires C 74.7, H 7.40, N 5.4 %, found C 74.8, H 7.60, N 5.3 %; δ_H (500MHz, $CDCl_3$), 7.3-7.45 (5H, m), 4.3 (1H, dd, J=4.6Hz, J'=11.6Hz), 4.15 (1H, t, J=11.6Hz), 4.1 (1H, dd, J=3.3Hz, J'=7.3Hz), 3.95 (1H, dd, J=4.6Hz, J'=11.6Hz), 3.25-3.3 (1H, m), 2.6-2.7 (2H, m), 1.77-1.87 (1H, m), 1.57-1.7 (2H, m), 1.4-1.45 (1H, m), 1.37-1.42 (1H, m), 1.3-1.35 (2H, m); $^m/_z$ (C.I., NH_3), 258 (100%, MH^+), 213 (15%), 104 (35%); υ_{max} / cm^{-1} (Nujol®) 1750 (C=O); n.O.e. difference [Irradiation position δ, irradiated proton → enhanced proton (%)]: 3.95, $H_{12} \rightarrow H_2$ (6%), 3.3, $H_2 \rightarrow H_6$ (4.5%), 1.8, $H_{7\alpha} \rightarrow H_8$ (5.5%); $[\alpha]_D$ –44.0 (c 0.55, $CHCl_3$).

(2*R*, 7*R*, 9*S*, 13*S*)–1–aza–11–oxo–13–phenyltricyclo[7.4.0^{1,9}.0^{2,7}]tridecan–10–one (**4**) Colourless crystals (Et_2O), m.p. 186–187°C. Requires C 75.0, H 7.70, N 5.1%, found C 74.8, H 8.00, N 4.8%; δ_H (500MHz, $CDCl_3$) 7.3-7.5 (5H, m), 4.2-4.3 (3H, m), 3.7 (1H, dd, J=4.1Hz, J'=5.3Hz), 2.8 (1H, dd, J=4.1Hz, J'=4.4Hz), 2.5 (1H, m), 2.0 (1H, m), 1.9 (1H, m), 1.45-1.6 (3H, m), 1.3 (2H, m), 1.15 (2H, m), 0.95 (1H, m); $^m/_z$ (C.I., NH_3) 272 (100% MH^+), 227 (20%), 104 (35%); n.O.e. difference: 3.7, $H_{13} \rightarrow H_2$ (7%), 2.8, $H_2 \rightarrow H_{13}$, (7.5%), → H_7 (6%), 2.05, $H_7 \rightarrow H_2$ (8.5%), 1.9, $H_{8\alpha} \rightarrow H_9$ (11.5%); υ_{max} / cm^{-1} (Nujol®) 1760 (C=O), 1390 (C-O); $[\alpha]_D^{22}$ –44.3 (c 0.35, $CHCl_3$).

(2*R*,6*R*,8*S*,12*S*)–1–aza–10–oxo–12–phenyl–4–thiatricyclo[6.4.0^{1,8}.0^{2,6}]dodecan–9–one (**5**) Colourless rods (Et_2O), m.p.109–110°C. Requires C 65.4, H 6.20, N 5.4%, Found C 65.5, H 6.15, N 5.0%; δ_H (500MHz, $CDCl_3$), 7.3-7.5 (5H, m), 4.25-4.3 (2H, m), 4.2 (1H, t, J=11.5Hz), 4.0 (1H, dd, J=11.5 Hz, J'= 4.6Hz), 3.55 (1H, m), 3.0 (1H, m), 2.9 (1H, m), 2.7 (2H, m), 2.6 (1H, m), 2.4 (1H, m,), 2.1 (1H, m); n.O.e. difference, 3.0, $H_2 \rightarrow H_{12}$ (8.5%), → H_6 (5.5%), 3.0, $H_6 \rightarrow H_{7\beta}$ (4%), 2.1, $H_{7\alpha} \rightarrow H_8$ (6%); $^m/_z$ (C.I., NH_3), 276 (MH^+, 100%), 142 (20%),104 (25%), 80 (15%); υ_{max} /cm^{-1} (KBr disc) 1758 (C=O); $[\alpha]_D^{20}$ –33.0 (c 0.27, $CHCl_3$).

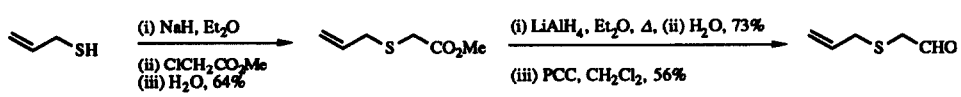
(2*S*, 6*S*, 8*R*, 9*R*)–1–aza–8,9–dimethyl–4–oxa–2–phenylbicyclo[4.3.0^{1,6}]nonan–5–one (**6**) Colourless needles (Et_2O / hexane) m.p. 98–101°C. Requires C 73.4, H 7.80, N 5.7 %, found C 73.1, H 7.85, N 5.3 %; δ_H (500MHz, $CDCl_3$), 7.3-7.5 (5H, m), 4.15-4.25 (3H, m), 3.85 (1H, t, J=7.6Hz), 2.9 (1H, quin, J=6.5Hz), 2.6 (1H, ddd, J=13.2Hz, J'=7.4Hz, J''=4.5Hz), 2.2 (1H, septet, J=6.7Hz), 1.87 (1H, m), 0.95 (3H, d, J=7.0Hz), 0.7 (3H, d, J=6.6Hz); n.O.e. difference: 4.2, $H_6 \rightarrow H_{7\alpha}$ (2.0%), 2.9, $H_9 \rightarrow H_2$ (8.2%), 2.2, $H_8 \rightarrow H_9$ (3.6%); $^m/_z$ (C.I., NH_3), 246 (100%, MH^+), 201 (20%), 104 (50%); υ_{max} / cm^{-1} (KBr disc), 1750 (C=O); $[\alpha]_D^{20}$ –28.0 (c 0.3, $CHCl_3$).

(2*S*, 4*R*, 5*R*)–4,5–dimethylproline ethyl ester (**7**) Oil. δ_H (500MHz, D_2O), 3.85 (1H, t, J=6.7Hz), 3.8 (1H, dd, J=4.2Hz J'=11.3Hz), 3.1 (2H, q, J=7.3Hz), 2.35 (1H, m), 2.1 (1H, q, J=11.3Hz), 2.0 (1H, m), 1.15 (3H, t, J=7.3Hz), 1.05 (3H, d, J=7.0Hz), 0.95 (3H, d, J=6.8Hz); $^m/_z$ (CI, NH_3), 172 (100%, MH^+), 126 (50%).

(1*S*, 4*R*, 5*R*)–4,5–dimethylproline (**8**) Colourless powder m.p. 204–207 dec. δ_H (500MHz, CD_3OD), 4.02 (1H, t, J=7.7Hz), 3.8 (1H, m), 2.4 (1H, m), 2.22 (1H, m), 2.15 (1H, m), 1.25 (3H, d, J=6.9Hz), 1.00 (3H, d, J=7.1Hz); $[\alpha]_D^{26}$ –22.0 (c 0.4, EtOH)

5. H. Urbach and R. Henning, *Heterocycles*, 1989, **28**, 957.

6. 3–Thia–5–hexenal was conveniently prepared by the following route:



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