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Carbamate Derived Stable Precursors for Generating Chiral Azomethine Ylids under Mild Conditions.

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Abstract: We describe the evolution of stable azomethine ylid precursors which avoid the need for an aldehyde in the ylid generation step. *tert*–Butyl carbamate derivative (**16**) demonstrates comparable efficiency to the standard method of ylid generation and trapping, but permits use of milder conditions.
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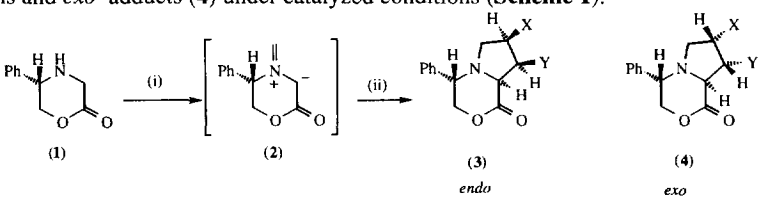
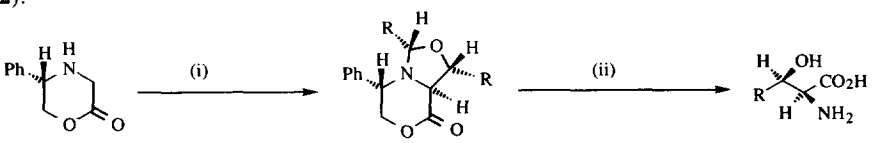
Much of the recent work on chiral azomethine ylids carried out within our group has involved the generation of an azomethine ylid from (5*S*)–5–phenylmorpholin–2–one (**1**) by condensation of this chiral template with an aldehyde under either thermal[1] or Lewis acid–catalyzed conditions.[2] Complete facial selectivity is observed in the cycloadditions of the ylids (**2**) with a range of dipolarophiles; *endo*–adducts (**3**) being favoured under thermal conditions and *exo*–adducts (**4**) under catalyzed conditions (**Scheme 1**).



(i) $[HCHO]_n$, benzene, molecular sieves , Δ, or $[HCHO]_n$, $MgBr_2.Et_2O$, THF, Δ; (ii) XCH=CHY.

Scheme 1

In addition, we have shown that, in the absence of any added dipolarophile, excess aldehyde may cycloadd stereoselectively to the ylid to generate adducts which can be converted into *threo*–β–hydroxy–α–amino acids (**Scheme 2**).[3]



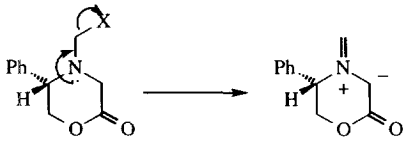
(i) RCHO (excess), toluene, Δ, $-H_2O$; (ii) $Pd(OH)_2/C$, H_2, 5 bar, aq. MeOH, TFA cat.

Scheme 2

However, efficient though the ylid generation process might be, it was found to have limited application with the more volatile aldehydes. This experimental limitation, and our goal of extending the scope of the aldehyde

cycloaddition reaction to the synthesis of complex β–hydroxy–α–amino acids, in which considerable synthetic effort would be involved in the preparation of the aldehyde component, made it desirable to develop methodology whereby the aldehyde would not be involved in the ylid generation step.

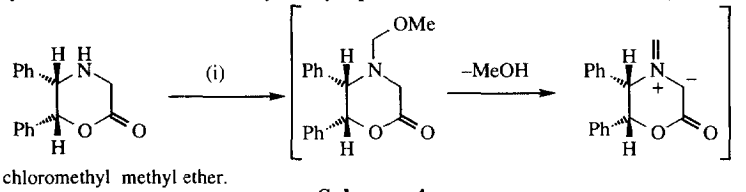
It was therefore decided to survey derivatives of (5*S*)–5–phenylmorpholin–2–one possessing a potential leaving group α–to nitrogen so that the ylid (**2**) could be generated *in situ* (**Scheme 3**). Furthermore, in attempting the rational design of alternative azomethine ylid precursors, it was considered imperative for them to be isolable and preferably crystalline.



(2)

Scheme 3

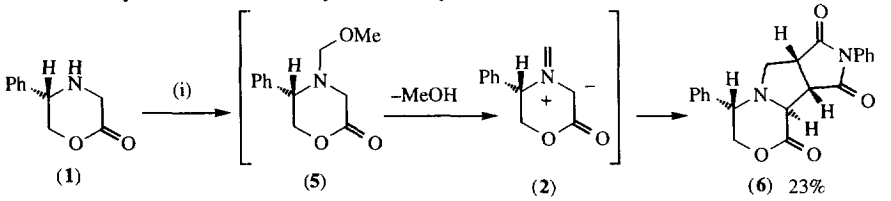
In a precedent for such an approach, Williams has generated a chiral morpholinone–derived ylid from a methoxymethyl precursor, but his method for obtaining this precursor requires highly carcinogenic chloromethyl methyl ether and the *N*–methoxymethyl species is not isolable (**Scheme 4**).[4]



(i) Triethylamine, chloromethyl methyl ether.

Scheme 4

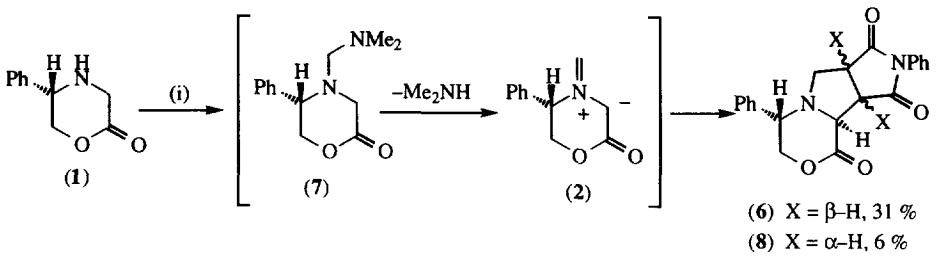
Avoiding the problem of carcinogenicity, we found that the analogous ylid precursor (**5**) could generated from (5*S*)–5–phenylmorpholin–2–one (**1**) using dimethoxymethane and magnesium bromide–etherate[2] in the presence of *N*–phenylmaleimide to permit *in situ* cycloaddition of the subsequently formed ylid (**2**). Gratifyingly, the procedure gave a single cycloadduct, albeit in a modest 23 % yield, shown by comparisonwith an authentic sample of cycloadduct showed this to be *exo*–adduct (**6**) (**Scheme 5**). This stereochemical *exo*–preference is in keeping with that observed in other room temperature cycloaddition reactions using this catalyst.[2] However, although indicating the feasibility of our approach, intermediate (**5**) was not isolable, although its intermediacy could be detected by NMR analysis of crude reaction mixtures.



(i) Dimethoxymethane, $MgBr_2.Et_2O$, *N*–phenylmaleimide, THF, rt.

Scheme 5

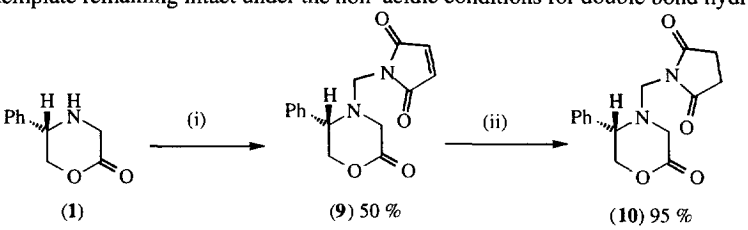
We then turned our attention to *N*–(*N*,*N*–dimethylamino)methyl derivative (**7**) formed from the reaction of (5*S*)–5–phenylmorpholin–2–one with Eschenmoser's salt in THF at room temperature. Although this adduct was also identifiable by NMR investigation, the isolated material proved to be unstable. However, adding *N*–phenylmaleimide to trap the ylid, generated *in situ* from (**7**) yielded both the *exo*– adduct (**6**) and the *endo*–adduct (**8**) in 37 % combined yield with the *exo*–adduct (**6**) being the major product (**Scheme 6**).



(i) $CH_2=N^+Me_2I^-$, *N*–phenylmaleimide, THF, rt.

Scheme 6

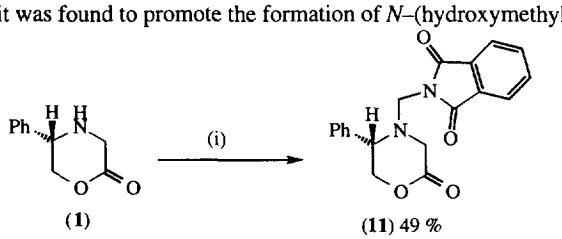
In associated studies, we observed that maleimide underwent nucleophilic addition to the iminium species formed from the morpholin–2–one and paraformaldehyde in the presence of magnesium bromide–etherate to form a stable derivative (**9**) in 50 % yield (**Scheme 7**). The stability of this adduct can be ascribed to the presence of the two electron withdrawing groups on the maleimide nitrogen. Although providing us with a stable crystalline intermediate, *N*–maleimidomethyl derivative (**9**) could not be a suitable cycloaddition precursor since generation of the ylid from this compound liberates a dipolarophile which could interfere with the desired cycloaddition. Consequently it was decided to prepare the *N*–succinimidomethyl derivative (**10**). Attempts to synthesise (**10**) by an analogous method to that used for (**9**) resulted in no trace of the desired product, presumably due to the significantly lower nucleophilicity of the succinimide nitrogen compared with that of maleimide. However, hydrogenation of *N*–maleimidomethyl derivative (**9**) led to (**10**) in 95 % yield, the morpholin–2–one template remaining intact under the non–acidic conditions for double bond hydrogenation.



(i) Maleimide, $[HCHO]_n$, $MgBr_2.Et_2O$, THF, molecular sieves, *Δ*; (ii) 5 %Pd/C (cat), H_2, EtOAc, stir.

Scheme 7

Repeated attempts to generate and trap the azomethine ylid from derivative (**10**) failed and so attention was turned to the *N*–phthalimidomethyl derivative (**11**), electronically analogous to (**9**) but no longer producing a dipolarophile on ylid generation. This was synthesised in 49 % purified yield (**Scheme 8**), although the Lewis acid catalyst was omitted as it was found to promote the formation of *N*–(hydroxymethyl)phthalimide.

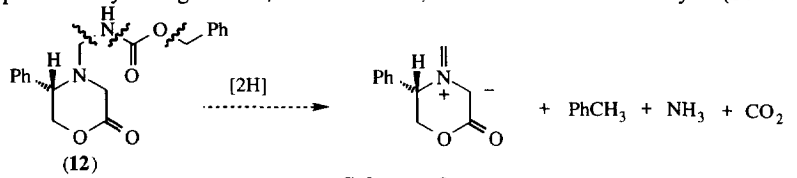


(i) Phthalimide, $[HCHO]_n$, THF, molecular sieves, *Δ*.

Scheme 8

Unfortunately, after an extensive survey of reaction conditions, the best results for ylid generation and trapping, did not furnish a yield of *exo*–adduct greater than 15 %.

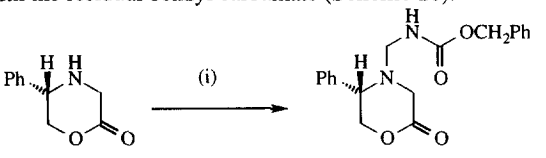
Reasoning that a single electron withdrawing group on the exocyclic nitrogen might provide the best compromise of stability *versus* reactivity it was decided to construct carbamate derivatives in which the additional refinement of an entropically favoured fragmentation would furnish the azomethine ylid. In the first instance it was envisaged that *N*–CBz–aminomethyl derivative (**12**) would be readily dismantled in a hydrogenolytic procedure yielding toluene, carbon dioxide, ammonia and the desired ylid (**Scheme 9**).



(**12**)

Scheme 9

The synthesis of (**12**) was first attempted following the method used to generate the *N*–(maleimidomethyl) analogue (**9**). (5*S*)–5–Phenylmorpholin–2–one (**1**), paraformaldehyde and benzyl carbamate were heated to reflux in dry THF in the presence of a catalytic amount of magnesium bromide–etherate over molecular sieves. After 4 hours t.l.c. analysis revealed the absence of starting material and chromatography afforded the desired adduct (**12**), contaminated with the residual benzyl carbamate (**Scheme 10**).

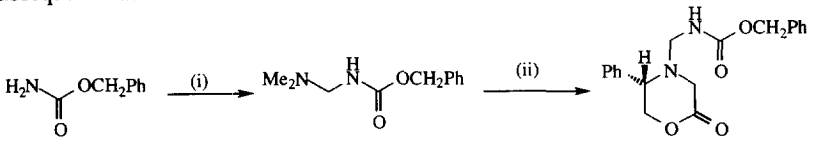


(**1**) (**12**)

(i) Benzyl carbamate, $[HCHO]_n$, $MgBr_2.Et_2O$, THF, molecular sieves, Δ.

Scheme 10

This contamination made characterisation of the product difficult and, subsequently, a two step approach was developed for the synthesis of this precursor. Initially benzyl carbamate was reacted with Eschenmoser's salt to form benzyl *N*–(*N*,*N*–dimethylaminomethyl)carbamate (**13**) in 80 % yield and this was then stirred overnight with morpholin–2–one (**1**) in the presence of pyridinium *p*–toluenesulfonate (**Scheme 11**). The solution was passed through a short silica pad to remove the acid catalyst and the solvent was removed *in vacuo* to give a colourless oil shown by spectroscopic analysis to be the desired product (**12**) in 88% yield of sufficient purity to be used in subsequent reactions.

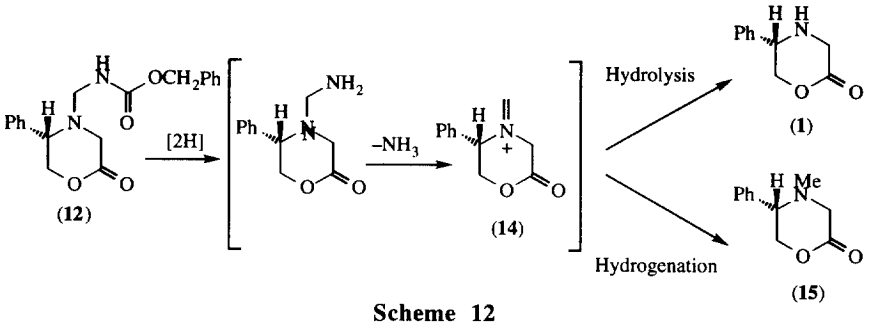


(**13**) 80 % (**12**) 88 %

(i) $CH_2{=}N^+Me_2I^-$, THF, rt.; (ii) (5*S*)–5–phenylmorpholin–5–one, PPTS, THF, rt.

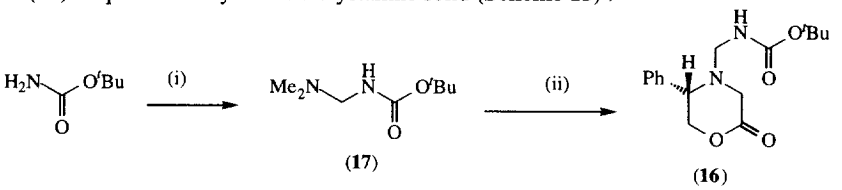
Scheme 11

This adduct was hydrogenated over 10 % Pd/C in the presence of *N*–phenylmaleimide to act as a trap resulting in the formation of two products which were separated and identified as morpholin–2–one (**1**) and (5*S*)–*N*–methyl 5–phenylmorpholin–5–one (**15**). The isolation of these materials can be rationalised by reaction proceeding initially as anticipated to form an iminium species (**14**), which is preferentially hydrogenated or hydrolysed, with no cycloaddition occurring (**Scheme 12**). Attempts at catalytic transfer hydrogenation equally proved unsuccessful.



Scheme 12

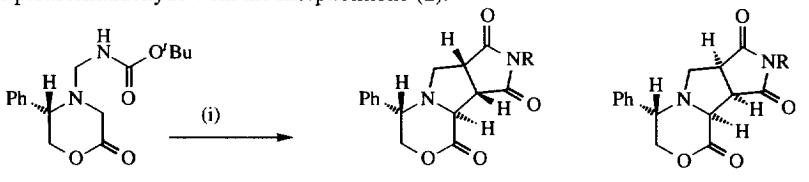
Despite the absence of cycloadducts, we were sufficiently encouraged by this result to prepare the analogous *N*–Boc derivative (**16**) in order to study acid–induced decomposition. Adduct (**16**) was initially synthesised in about 31% yield employing the method based on that used to prepare the phthalimido derivative (**11**), Lewis acid catalysts having been shown to be deleterious. However, as with *N*–CBz derivative (**12**) the desired adduct was difficult to separate from the residual *tert*–butyl carbamate The synthesis was therefore attempted *via* the two step method. Nucleophilic addition of *tert*–butyl carbamate to Eschenmoser's salt proceeded in quantitative yield to give the *N*–(dimethylaminomethyl) derivative (**17**) which reacted with morpholinone (**1**) to furnish the desired product (**16**) in quantitative yield as a crystalline solid (**Scheme 13**) .



(i) $CH_2=N^+Me_2I^-$, THF, rt.; (ii) morpholin–2–one, PPTS, THF, rt.

Scheme 13

While attempts at uncatalysed thermal decomposition of (**16**) led to recovery of starting material, reaction of (**16**) with trifluoroacetic acid in THF at room temperature in the presence of *N*–phenylmaleimide yielded the desired and *exo*– (**6**) and *endo*–cycloadduct (**8**) in 24 % and 33 % yield respectively (**Scheme 14**). Equally, *N*–methylmaleimide furnished the corresponding adducts in 19 % and 23 % yield respectively. The yields and *endo*– *exo*– ratios correspond closely to those obtained under the original thermal conditions utilising the condensation of paraformaldehyde with the morpholinone (**1**).[1]



(i) *N*–phenyl or *N*–methylmaleimide, TFA, THF, rt.

Scheme 15

In preparing *tert*–butyl carbamate derivative (**16**) we have at last achieved our goal of preparing a crystalline, storable material which will undergo azomethine ylid generation under mild conditions giving yields of

cycloadducts comparable to those obtained under standard conditions for azomethine ylid genration. This novel, entropically driven approach to azomethine ylid formation from an easy–to–use precursor has much potential and further work will be reported in due course.

ACKNOWLEDGEMENTS

We thank Pfizer Central Research, E.P.S.R.C. and DTI for financial support of this work under the auspices of the Asymmetric LINK Scheme (to C. E.W.).

EXPERIMENTAL

General Procedures Melting points were recorded using a Kofler heated–stage microscope and are uncorrected. Mass spectrometric data were recorded on a ZAB1F or TRIO–1 G.C. mass spectrometer under conditions of chemical ionisation (CI), or desorption chemical ionisation (DCI) using ammonia as the ionising source. Mass spectra are quoted in the form $^{m}/_{z}$ (relative intensity). Microanalyses were performed on a Carlo Erba 1106 elemental analyser in the Dyson Perrins Laboratory by Mrs V. Lamburn. Infra–red spectra were recorded on a Perkin Elmer 1750 FT–IR spectrometer as thin films or KBr discs as stated. ^{1}H NMR spectra were recorded in chloroform–*d*, benzene–d_6, methanol–d_4 or deuterium oxide. Instruments used were a Varian Gemini (200 MHz), a Bruker AC200 (200MHz) and a Bruker AM500 (500 MHz). Peak positions were recorded in δ p.p.m., with the abbreviations s, d, t, dd, dt, m and b denoting singlet, doublet, double doublet, double triplet, multiplet and broad respectively. Two–dimensional COSY spectra and nuclear Overhauser effect (n. O. e.) difference experiments were recorded on a Bruker AM500 spectrometer and were performed in the Dyson Perrins Laboratory by Mrs E. McGuinness. Optical rotation measurements were obtained using a Perkin Elmer 241 polarimeter. T. l. c. analysis refers to analytical thin layer chromatography, using Merck plastic–backed plates coated with 0.2 mm silica $60F_{254}$. Product spots were visualised either by quenching of UV fluorescence, or by staining with iodine vapour. Flash column chromatography refers to column chromatography using Merck 60 silica gel and head pressure by means of compressed air according to the method of Still.[5] THF and diethyl ether were obtained dry and oxygen–free by distillation from sodium benzophenone ketyl under nitrogen. Hexane and petroleum ether (b.p. 40–60 °C) were distilled before use. Identification of the cycloadducts was carried out by comparison of physical and spectroscopic data with those of the known diastereoisomers.[1]

Preparation of (5*S*)–*N*–(maleimidomethyl)–5–phenylmorpholin–2–one (9)

(5*S*)–5–Phenylmorpholin–2–one (**1**) (177 mg, 1.0 mmol, 1.0 equiv.), paraformaldehyde (150 mg, 5.0 mmol, 5.0 equiv.) and maleimide (110 mg, 1.1 mmol, 1.1 equiv.) were dissolved in THF, and $MgBr_2.Et_2O$ (1 mL) was added to the solution *via* syringe. The solution was heated to reflux in the presence of activated 3A molecular sieves for 2 hours. Purification by column chromatography, eluting with 3 : 1 hexane / ethyl acetate furnished (**9**) as a colourless solid (143 mg, 50 %), m.p. 158–160 °C; Found C, 62.79, H, 4.74, N, 10.01 %, $C_{15}H_{14}N_2O_4$ requires C, 62.92, H, 4.93, N, 9.79 %; ν_{max} (KBr disc) 1 756 and 1 707 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.47–7.35 (m, 5H), 6.73 (s, 2H), 4.48 (d, *J* 13.8 Hz), 4.30 (d, *J* 13.7 Hz, 1H), 4.26–4.20 (m, 2H), 4.10 (dd, *J* 4.4, *J'* 9.6 Hz), 3.94 (d, *J* 17.3 Hz, 1H), and 3.65 (d, *J* 17.3 Hz, 1H); $^{m}/_{z}$ CI (NH_3) 287 (100%, MH^+), 190, 104; $[\alpha]_D^{21}$ +18.6 (c 0.9, $CHCl_3$).

Preparation of (5*S*)–*N*–(succinimidomethyl)–5–phenylmorpholin–2–one (10)

(5*S*)–*N*–(Maleimidomethyl)–5–phenylmorpholin–2–one (**9**) (59 mg, 0.21 mmol) and a catalytic amount of 5 % Pd/C (6 mg) were suspended in ethyl acetate (15 mL). The solution was degassed and left stirring overnight under hydrogen at 1 atm.. The crude reaction mixture was passed through a short pad of Celite® to separate the catalyst and the solvent was then removed *in vacuo*. Crystallisation of the residual solid furnished (**10**) as colourless needles (57 mg, 95 %), m.p. 131–132 °C; Found C, 62.41, H, 5.73, N, 9.54 %, $C_{15}H_{16}N_2O_4$ requires C, 62.25, H, 5.60, N, 9.72 %; ν_{max} (KBr disc) 1 755 and 1 703 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.45–7.35 (m, 5H), 4.53 (d, *J* 13.4 Hz), 4.28 (d, *J* 13.3 Hz, 1H), 4.28 (m, 1H), 4.21 (m, 1H) 4.17 (m, 1H), 3.94 (d, *J* 17.2 Hz, 1H), 3.69 (d, *J* 17.2 Hz, 1H), and 2.66 (s, 4H); $^{m}/_{z}$ CI (NH_3) 289 (100%, MH^+), 190, 104; $[\alpha]_D^{20}$ +31.2 (c 0.9, $CHCl_3$).

Preparation of (5*S*)–*N*–(phthalimidomethyl)–5–phenylmorpholin–2–one (11)

(5*S*)–5–Phenylmorpholin–2–one (**1**) (189 mg, 1.1 mmol, 1.0 equiv.), paraformaldehyde (175 mg, 5.8 mmol, 1 equiv.) and phthalimide (220 mg, 1.5 mmol, 1.5 equiv.) were dissolved in THF (60 mL). The solution was heated to reflux in the presence of activated 3A molecular sieves for 1.5 hours. After cooling the

residual phthalimide was removed by filtration and the filtrate concentrated *in vacuo*. The crude material was purified using column chromatography eluting with 3 : 1 hexane / ethyl acetate to yield (**11**) as colourless needles from ethyl acetate / hexane (175 mg, 49 %), m.p. 129–131 °C; Found C, 67.68, H, 4.65, N, 8.31 %, $C_{19}H_{16}N_2O_4$ requires C, 67.83, H, 4.80, N, 8.33 %; ν_{max} (KBr disc) 1 758 1 713 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.87 (m, 2H), 7.77 (m, 2H), 7.49 (m, 2H), 7.43 (m, 2H), 7.37 (m, 1H), 4.66 (d, *J* 13.8 Hz, 1H), 4.47 (d, *J* 13.8 Hz, 1H), 4.29 (dd, *J* 4.0 , *J'* 10.9 Hz, 1H), 4.23 (dd, *J* 9.1, *J'* 10.9 Hz, 1H), 4.19 (dd, *J* 4.0, *J'* 9.1 Hz, 1H), 4.01 (d, *J* 17.3 Hz, 1H), and 3.75 (d, *J* 17.3 Hz, 1H); $^m/_z$ CI (NH_3) 337 (MH^+ 100%), 190, 104; $[\alpha]_D^{20}$ +97.8 (c 0.8, $CHCl_3$).

Cycloaddition involving ylid generation *via* phthalimido derivative (11)

Adduct (**11**) (165 mg, 0.5 mmol, 1 equiv.) and *N*–phenylmaleimide (433.0 mg, 2.5 mmol, 5 equiv.) were dissolved in dry THF (50 mL) under nitrogen. $MgBr_2.Et_2O$ (0.5 mL) was added and the solution was kept at reflux overnight. Removal of the solvent *in vacuo* and column chromatography, eluting with 3:1 hexane / ethyl acetate, yielded the *exo*–cycloadduct (**6**) as colourless crystals (26 mg, 15 %) and unreacted starting material (**11**) (71 mg, 42 %).

Preparation of (5*S*)–*N*–(Benzyloxycarbonylaminomethyl)–5–phenylmorpholin–2–one (12)

Method 1:

(5*S*)–5–Phenylmorpholin–2–one (**1**) (177 mg, 1.0 mmol, 1.0 equiv.), paraformaldehyde (35 mg, 1.2 mmol, 1.2 equiv.) and benzyl carbamate (227 mg, 1.5 mmol, 1.5 equiv.) were dissolved in THF (60 mL), and $MgBr_2.Et_2O$ (0.5 mL) was added to the solution *via* syringe. The solution was heated to reflux in the presence of activated 3A molecular sieves for 4 hours and allowed to cool to room temperature. The crude material was purified using column chromatography, eluting with 3 : 1 hexane / ethyl acetate to furnish a colourless oil (170 mg) which was shown to be (**12**), contaminated with residual benzyl carbamate.

Method 2:

Eschenmoser's salt (950 mg, 5 mmol, 1 equiv.) and benzyl carbamate (760 mg, 5 mmol, 1 equiv.) were dissolved in dry THF (150 mL) and stirred for 48 hours at room temperature. The solvent was removed *in vacuo*, the material taken up in dichloromethane (50 mL) and acidified with aq. HCl (20 mL). The salt was extracted with water (3 x 40 mL) and the aqueous layers were combined and neutralised with Na_2CO_3 (20 mL). The free amine was then extracted from the aqueous solution with dichloromethane (3 x 50 mL) and the solvent removed *in vacuo* to yield benzyl *N*–(*N*,*N*–dimethylaminomethyl)carbamate (**13**) as a colourless oil (800 mg, 80 %); ν_{max} (thin film) 3 338, 1 708,1 531 cm^{-1}; δ_H (200 MHz, $CDCl_3$) 7.38 (m, 5H), 5.13 (s, 2H), 4.02 (d, *J* 6.6 Hz, 2H), 2.29 (s, 6H); $^m/_z$ CI (NH_3) 209 (100%, MH^+), 58; $C_{11}H_{17}N_2O_2$ requires 209.1290, found 209.1304.

(5*S*)–5–Phenylmorpholin–2–one (**1**) (177 mg, 1.0 mmol, 1.0 equiv.), pyridinium *p*–toluenesulfonate (251 mg, 1.0 mmol, 1.0 equiv.) and benzyl *N*–(*N*,*N*–dimethylaminomethyl)carbamate (**13**) (210 mg, 1.0 mmol, 1.0 equiv.) were dissolved in dry THF (150 mL) and the mixture stirred for 16 hours at room temperature. The crude solution was passed through a silica pad to remove the acid catalyst and the solvent was removed *in vacuo* to afford (**12**) as a pale yellow oil (300 mg, 88 %); δ_H (500 MHz, $CDCl_3$) 7.43–7.30 (m, 10H), 5.12–5.07 (m, 2H) , 4.91 (bs, 1H), 4.31–4.24 (m, 2H), 4.20–4.16 (m, 1H), 3.92–3.87 (m, 2H), and 3.63 (d, 2H); $^m/_z$ CI (NH_3) 341 (70%, MH^+), 178; $[\alpha]_D^{20}$ +107.8 (c 0.85, $CHCl_3$).

Preparation of (5*S*)–*N*–methyl 5–phenylmorpholin–2–one (15)

(5*S*)–*N*–(Benzyloxycarbonylaminomethyl)–5–phenylmorpholin–2–one (**12**) (660 mg, 1.9 mmol, 1.0 equiv.) and a catalytic amount of palladium black were suspended in ethyl acetate (100 mL). The solution was degassed and stirred overnight under hydrogen at 1 atm.. The crude reaction mixture was passed through a short Celite® pad to separate the catalyst and the solvent removed *in vacuo*. Column chromatography, eluting with 2 : 1 hexane / ethyl acetate, afforded two products: (5*S*)–5–phenylmorpholin–2–one (**1**) (71 mg, 21 %) and (**15**) (153 mg, 42 %). ν_{max} (KBr disc) 1 750 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.37 (m, 5H), 4.32 (dd, *J* 10.3, *J'* 11.2 Hz, 1H), 4.27 (dd, *J* 4.1, *J'* 11.2 Hz, 1H), 3.85 (d, *J* 17.8 Hz, .1H), 3.43 (dd, *J* 4.1, *J'* 10.3 Hz, 1H), 3.15 (d, *J* 17.8 Hz, 1H), and 2.08 (s, 3H); $^m/_z$ DCI (NH_3) 192 (100%, MH^+), 104, $C_{11}H_{13}NO_2$ (M^+) requires 191.0946, found 191.0953; $[\alpha]_D^{20}$ +136 (c 0.3, $CHCl_3$).

Preparation of (5*S*)–*N*–(*tert*–butyloxycarbonylaminomethyl)–5–phenylmorpholin–2–one (16)

Method 1

(5*S*)–5–Phenylmorpholin–2–one (**1**) (370 mg, 2.1 mmol, 1.0 equiv.), paraformaldehyde (68 mg, 2.3 mmol, 1.0 equiv.) and *tert*–butyl carbamate (580 mg, 4.8 mmol, 2.5 equiv.) were dissolved in THF (60 mL). The solution was heated to reflux in the presence of activated 3A molecular sieves for 16 hours and allowed to cool

to room temperature. The crude material was purified using column chromatography, eluting with 3 : 1 hexane / ethyl acetate to give a colourless oil (493 mg), which was shown to be a 1 : 2 mixture of the desired adduct (**16**) (190 mg, 31 %) and excess *tert*–butyl carbamate.

Method 2

Eschenmoser's salt (190 mg, 1.0 mmol, 1.0 equiv.) and *tert*–butyl carbamate (120 mg, 1.0 mmol, 1.0 equiv.) were dissolved in dry THF (125 mL) and the mixture stirred for 24 hours at room temperature. The solvent was removed *in vacuo* and the material taken up in dichloromethane (20 mL) and acidified with aq. HCl (2 mL). The salt was then extracted with water (2 x 10 mL) and the aqueous layers were combined and neutralised with Na_2CO_3 (2 mL) . The free amine was then extracted from the aqueous solution with dichloromethane (2 x 20 mL) and the solvent removed *in vacuo* to yield the crude product. Crystallisation from ether / hexane afforded *tert*–butyl *N*–(*N*,*N*–dimethylaminomethyl)carbamate (**17**) as colourless flakes (172 mg, quant.), m.p. 94–96 °C; Found C, 55.10, H, 10.38, N, 15.99 %, $C_8H_{18}N_2O_2$ requires C, 55.13, H, 10.42, N, 16.08 %; ν_{max} (KBr disc) 3 207, 1 714 , 1 553 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 4.98 (bs, 1H), 3.93 (d, *J* 6.7 Hz, 2H), 2.27 (s, 6H), 1.46 (s, 9H);; $^m/_z$ CI (NH_3) 175 (100%, MH^+), 119, 58.

(5*S*)–2–Phenylmorpholin–2–one (**1**) (118 mg, 0.67 mmol, 1.0 equiv.), pyridinium *p*–toluenesulfonate (168 mg, 0.67 mmol, 1 equiv.) and *tert*–butyl *N*–(dimethylaminomethyl)carbamate (**17**) (116 mg, 0.67 mmol, 1.0 equiv.) were dissolved in dry THF (150 mL) and the mixture stirred for 16 hours at room temperature. The crude solution was passed through a silica pad to remove the acid catalyst and subsequent removal of solvent *in vacuo* afforded (**16**) as a colourless oil (304 mg, quant.); Found C, 62.33, H, 7.18, N, 9.14 %, $C_{16}H_{22}N_2O_4$ requires C, 62.73, H, 7.24, N, 9.14 %; ν_{max} (KBr disc) 1 751 1 707 cm^{-1}; δ_H (500 MHz, $CDCl_3$) 7.35 (m, 5H), 4.67 (bs, 1H), 4.29 (m, 2H), 4.11(dd, *J* 7.9, *J'* 13.7 Hz, 1H), 3.89 (dd, *J* 5.1, *J* 9.1 Hz, 1H), 3.85 (m, 1H), 3.81 (dd, *J* 5.9, *J'* 14.1 Hz, 1H), 3.61 (d, *J* 17.8 Hz, 1H), and 1.46 (s, 9H); $^m/_z$ FAB 327 (15%, MNa^+), 307 (10 %, MH^+), 251, 190, 104; $[\alpha]_D^{20}$ +143.4 (c 1.2, $CHCl_3$).

Cycloaddition involving ylid generation *via* *tert*–butyl carbamate derivative (16)

Adduct (**16**) (153 mg, 0.5 mmol, 1 equiv.) and *N*–phenylmaleimide (433.0 mg, 2.5 mmol, 5 equiv.) were dissolved in dry THF (20 mL) under nitrogen. TFA (0.5 mL) was added and the solution stirred under nitrogen overnight. Removal of the solvent *in vacuo* and column chromatography, eluting with 3:1 hexane / ethyl acetate, yielded the *exo*–cycloadduct (**6**) as colourless crystals (45 mg, 24 %) and the *endo*–adduct (**8**) as colourless crystals (55 mg, 30 %).

(The reaction was repeated with *N*–methylmaleimide to give 23 % *exo*–adduct and 19 % *endo*–adduct which were identified by comparison with recorded data).[1]

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