Supporting Information for

Highly Enantioselective Copper(I)-Fesulphos Catalyzed 1,3-Dipolar Cycloaddition of Azomethine Ylides

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Experimental Section

General methods

All the reactions were carried out in anhydrous solvents and under argon atmosphere. Melting points were taken in open-end capillary tubes. NMR spectra were recorded at 200 MHz (^1H), 50 MHz (^{13}C) or at 300 MHz (^1H), 75 MHz (^{13}C), at room temperature in CDCl_3 [calibrated at 7.26 ppm (^1H), and 77.0 ppm (^{13}C)]. Mass spectra (MS) were determined at an ionizing voltage of 70 eV. HPLC experiments were conducted using Daicel Chiralcel OD and Chiralpak AS-H columns. Flash column chromatography was performed using silica gel Merk-60 (230-400 mesh). Ethyl *N*-(diphenylmethylene)glycinate was purchased from Aldrich.

General procedure for the synthesis of α -imino esters: To a suspension of the corresponding amino acid ester hydrochloride (23.9 mmol) and MgSO_4 (25.0 mmol) in CH_2Cl_2 (25 mL) was added Et_3N (3.4 mL, 23.9 mmol). The mixture was stirred at room temperature for 1 h, then the corresponding aldehyde (20.0 mmol) was added. The reaction was stirred at room temperature overnight, and then the resulting precipitate was removed by filtration. The filtrate was washed with water (15 mL), the aqueous phase was extracted with CH_2Cl_2 (10 mL) and the combined organic phase was washed with brine, dried over MgSO_4 and concentrated. The resulting iminoesters were obtained pure and used in 1,3-dipolar cycloadditions without further purification.

General procedure for the synthesis of α -ketimino esters: A mixture of the glycine methyl ester hydrochloric salt (879.0 mg, 7.0 mmol) in dichloromethane was neutralized with concentrated aqueous ammonia solution. The organic phase was separated, dried (MgSO_4) and concentrated partially to remove most of CH_2Cl_2 (due to the volatility of the aminoester). The resulting concentrated amino ester solution was added to a mixture of the corresponding ketone (6.6 mmol) and molecular sieves 4 Å (15 gr) in dry benzene (50 mL). The reaction was stirred at room temperature for 12 h, it was filtered and the filtrate was concentrated to give a mixture of the corresponding ketone and ketimine (around 70:30 ratio).

Methyl *N*-(1-phenylethylidene)glycinate:¹ Addition of hexane to the crude mixture induced precipitation of the ketimine. After filtration, the product was obtained as a white solid (203 mg, 16% isolated yield, 83% converted). The unreacted acetophenone

¹ Selva, M.; Tundo, P.; Marques, C. A. *Synthetic Communications* **1995**, 25, 369.

was recovered after flash chromatography (hexano/EtOAc 6:1). Mp= 57-58 °C. ¹H NMR (200 MHz): δ 7.97-7.92 (m, 2H), 7.21-7.17 (m, 3H), 4.13 (s, 2H), 3.44 (s, 3H), 1.66 (s, 3H).

Methyl *N*-[1-(*p*-chlorophenyl)ethylidene]glycinate: The crude 31:69 mixture of ketimine-ketone was used without further purification due to the rapid imine-enamine isomerization. Representative data for the imine product: ¹H NMR (200 MHz): δ 7.65 (d, *J*= 8.6 Hz, 2H), 7.14 (d, *J*= 8.6 Hz, 2H), 4.07 (s, 2H), 3.43 (s, 3H), 1.53 (s, 3H).

General procedure for asymmetric 1,3-dipolar cycloaddition of azomethine ylides:

To a solution of Fesulphos ligand² (2.7 mg, 0.006 mmol) and Cu(CH₃CN)₄ClO₄ (2.0 mg, 0.006 mmol) in CH₂Cl₂ (0.5 mL) or THF (0.5 mL), at the optimal temperature (indicated in each case), were successively added a solution of the imine (0.20 mmol) in CH₂Cl₂ (1.0 mL) or THF (0.5 mL), Et₃N (5.0 μL, 0.035 mmol) and the corresponding dipolarophile (0.30 mmol). Once the starting material was consumed (monitored by TLC) the mixture was filtered through Celite[®] and the filtrate was concentrated to dryness. The residue was analyzed by ¹H NMR to determine the endo/exo ratio and purified by flash chromatography (the eluent is indicated in each case).

(1*S*,3*R*,3*aS*,6*aR*)-Methyl-4,6-dioxo-3,5-diphenyl-octahydropyrrole[3,4-*c*]pyrrole-1-carboxylate (endo-3a**).**³ Following the general procedure, the reaction of methyl (*E*)-*N*-benzylideneglycinate (35.5 mg, 0.20 mmol) with *N*-phenylmaleimide (51.9 mg, 0.30 mmol) in CH₂Cl₂ at -10 °C afforded, after chromatography (*n*-hexane-EtOAc 1:1), endo-**3a** as a white solid; yield: 56.7 mg, 81%; mp = 180-181 °C (lit.^{3b} mp= 160-162 °C). [α]_D²⁰ = +114 (*c* 1.22, CH₂Cl₂), >99% *ee*; Lit.^{3b} [α]_D²⁰ = +91.1 (*c* 1.22, CH₂Cl₂) for a 71% *ee* sample. HPLC: Daicel Chiralpak AS-H, *i*-PrOH-hexane 50/50, flow rate 0.8

² a) Priego, J.; García Mancheño, O.; Cabrera, S.; Gómez Arrayás, R.; Llamas, T.; Carretero, J. C. *Chem. Commun.* **2002**, 2512-2513; b) García Mancheño, O.; Priego, J.; Cabrera, S.; Gómez Arrayás, R.; Llamas, T.; Carretero, J. C. *J. Org. Chem.* **2003**, *68*, 3679.

³ a) Oderaotoshi, Y.; Cheng, W.; Fujitomi, S.; Kasano, Y.; Minakata, S.; Komatsu, M. *Org. Lett.* **2003**, *5*, 5043; b) Longmire, J. M.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* **2002**, *124*, 13400, c) Grigg, R.; Gunaratne, H. Q. N.; Sridharan, V. *Tetrahedron* **1987**, *43*, 5887.

mL/min, t_R : 13.6 min (1*S*,3*R*,3*aS*,6*aR*)-isomer and 29.2 min (1*R*,3*S*,3*aR*,6*aS*)-isomer, 220 nm. ^1H NMR (200 MHz): δ 7.50-7.32 (m, 8H), 7.17-7.12 (m, 2H), 4.63 (dd, J = 8.6, 5.1 Hz, 1H), 4.16 (dd, J = 6.5, 5.1 Hz, 1H), 3.88 (s, 3H), 3.78-3.71 (m, 1H), 3.58 (t, J = 8.2 Hz, 1H), 2.55-2.50 (m, 1H).

endo-**3b**

(1*S*,3*R*,3*aS*,6*aR*)-Methyl-4,6-dioxo-3-naphthyl-5-phenyl-octahydropyrrole[3,4-*c*]pyrrole-1-carboxylate (endo-3b**).** Following the general procedure, the reaction of methyl (*E*)-*N*-(2-naphthylmethylene)glycinate (45.5 mg, 0.20 mmol) with *N*-phenylmaleimide (51.9 mg, 0.30 mmol) in CH_2Cl_2 at $-10\text{ }^\circ\text{C}$ afforded, after chromatography (*n*-hexane-EtOAc 1:1), endo-**3b** as a white solid; yield: 64.8 mg, 81%; mp= 226-227 $^\circ\text{C}$. $[\alpha]_D^{20} = +165$ (c 0.11, CH_2Cl_2), >99% *ee*. HPLC: Daicel Chiralpak AS-H, *i*-PrOH-hexane 50/50, flow rate 0.8 mL/min, t_R : 16.9 min (1*S*,3*R*,3*aS*,6*aR*)-isomer and 60.1 min (1*R*,3*S*,3*aR*,6*aS*)-isomer, 220 nm. ^1H NMR (300 MHz): δ 7.98 (s, 1H), 7.88-7.83 (m, 3H), 7.57-7.46 (m, 3H), 7.39-7.28 (m, 3H), 7.15-7.11 (m, 2H), 4.78 (dd, J = 8.6, 5.0 Hz, 1H), 4.21 (dd, J = 6.4, 5.0 Hz, 1H), 3.92 (s, 3H), 3.80 (t, J = 6.4 Hz, 1H), 3.68 (t, J = 8.6 Hz, 1H), 2.65-2.62 (m, 1H). ^{13}C NMR (75 MHz): δ 175.1, 173.6, 170.1, 134.3, 133.4, 133.3, 131.6, 129.0, 128.5, 128.2, 128.0, 127.9, 126.3, 126.1, 126.0, 125.6, 125.3, 64.3, 61.9, 52.4, 49.4, 48.4. IE^+ MS m/z 400 (M^+ , 18), 227 (78), 196 (33), 167 (100).

endo-**3c**

(1*S*,3*R*,3*aS*,6*aR*)-Methyl 4,6-dioxo-3-(*p*-fluorophenyl)-5-phenyl-octahydropyrrole [3,4-*c*]pyrrole-1-carboxylate (endo-3c**).** Following the general procedure, the reaction

of methyl (*E*)-*N*-(4-fluorobenzylidene)glycinate (39.0 mg, 0.20 mmol) with *N*-phenylmaleimide (51.9 mg, 0.30 mmol) in CH₂Cl₂ at -10 °C afforded, after chromatography (*n*-hexane-EtOAc 1:1), endo-**3c** as a white solid; yield: 60.3 mg, 82%; mp= 179-180 °C. $[\alpha]_D^{20} = +118$ (*c* 0.11, CH₂Cl₂), >99% *ee*. HPLC: Daicel Chiralpak AS-H, *i*-PrOH-hexane 50/50, flow rate 0.8 mL/min, *t*_R: 13.6 min (1*S*,3*R*,3*aS*,6*aR*)-isomer and 28.5 min (1*R*,3*S*,3*aR*,6*aS*)-isomer, 220 nm. ¹H NMR (300 MHz): δ 7.38-7.23 (m, 5H), 7.09-7.05 (m, 2H), 7.00-6.95 (m, 2H), 4.53 (d, *J*= 8.7 Hz, 1H), 4.07 (d, *J*= 6.6 Hz, 1H), 3.80 (s, 3H), 3.65 (dd, *J*= 7.8, 6.6 Hz, 1H), 3.47 (dd, *J*= 8.7, 7.9 Hz, 1H), 2.42 (bs, 1H). ¹³C NMR (75 MHz): δ 174.9, 173.5, 169.9, 162.6 (d, *J*_{F-C}= 245.5 Hz), 132.4, 131.6, 129.1, 128.8 (d, *J*_{F-C}= 8.2 Hz), 128.6, 128.0, 115.5 (d, *J*_{F-C}= 21.3 Hz), 63.5, 61.8, 52.3, 49.2, 48.1. IE⁺ MS *m/z* 368 (M⁺, 7), 309 (53), 195 (100), 162 (68), 135 (96), 108 (22). Anal. Calcd. for C₂₀H₁₇FN₂O₄: C, 62.21; H, 4.65; N, 7.60. Found: C, 64.82; H, 4.86; N, 7.23.

(1*S*,3*R*,3*aS*,6*aR*)-Methyl 4,6-dioxo-3-(*p*-methoxyphenyl)-5-phenyl-octahydropyrrole [3,4-*c*]pyrrole-1-carboxylate (endo-3d**).**^{3a} Following the general procedure, the reaction of methyl (*E*)-*N*-(4-methoxybenzylidene)glycinate (41.5 mg, 0.20 mmol) with *N*-phenylmaleimide (51.9 mg, 0.30 mmol) in CH₂Cl₂ at -10 °C afforded, after chromatography (*n*-hexane-EtOAc 1:1), endo-**3d** as a white solid; yield: 61.6 mg, 81%; mp= >200 °C (decomp) (Lit.^{3a} (±)-endo-**3d** mp= 194-196 °C). $[\alpha]_D^{20} = +106$ (*c* 0.16, CH₂Cl₂), >99% *ee*. HPLC: Daicel Chiralpak AS-H, *i*-PrOH-hexane 50/50, flow rate 0.8 mL/min, *t*_R: 18.3 min (1*S*,3*R*,3*aS*,6*aR*)-isomer and 36.9 min (1*R*,3*S*,3*aR*,6*aS*)-isomer, 220 nm. ¹H NMR (200 MHz): δ 7.45-7.32 (m, 5H), 7.19-7.14 (m, 2H), 6.91-6.87 (m, 2H), 4.58 (dd, *J*= 8.6, 5.8 Hz, 1H), 4.13 (dd, *J*= 6.4, 4.8 Hz, 1H), 3.87 (s, 3H), 3.79 (s, 3H), 3.73 (t, *J*= 6.6 Hz, 1H), 3.53 (t, *J*= 8.4 Hz, 1H), 2.49 (bs, 1H).

endo-**3e**

(1*S*,3*R*,3*aS*,6*aR*)-Methyl 4,6-dioxo-3-(*o*-methylphenyl)-5-phenyl-octahydropyrrole [3,4-*c*]pyrrole-1-carboxylate (endo-3e**).** Following the general procedure, the reaction of methyl (*E*)-*N*-(2-methylbenzylidene)glycinate (38.2 mg, 0.20 mmol) with *N*-phenylmaleimide (51.9 mg, 0.30 mmol) in CH₂Cl₂ at -10 °C afforded, after chromatography (*n*-hexane-EtOAc 1:1), endo-**3e** as a white solid; yield: 62.6 mg, 85%; mp= 154-155 °C. $[\alpha]_D^{20} = +136$ (*c* 0.11, CH₂Cl₂), >99% *ee*. HPLC: Daicel Chiralpak AS-H, *i*-PrOH-hexane 50/50, flow rate 0.8 mL/min, *t*_R: 10.9 min (1*S*,3*R*,3*aS*,6*aR*)-isomer and 50.5 min (1*R*,3*S*,3*aR*,6*aS*)-isomer, 220 nm. ¹H NMR (300 MHz): δ 7.69-7.63 (m, 1H), 7.38-7.19 (m, 6H), 7.09-7.04 (m, 2H), 4.75-4.73 (m, 1H), 4.16-4.14 (m, 1H), 3.88 (s, 3H), 3.74 (t, *J* = 6.2 Hz, 1H), 3.65 (t, *J* = 8.6 Hz, 1H), 2.45 (s, 3H). ¹³C NMR (75 MHz): δ 175.1, 173.3, 170.0, 135.8, 135.3, 131.6, 130.0, 128.9, 128.4, 128.0, 126.1 (2C), 125.3, 61.6, 60.6, 52.3, 48.3, 47.0, 19.4. IE⁺ MS *m/z* 368 (M⁺, 7), 364 (7), 305 (41), 191 (100), 158 (50), 131 (86). Anal. Calcd. for C₂₁H₂₀N₂O₄: C, 69.22; H, 5.53; N, 7.69. Found: C, 68.82; H, 5.57; N, 7.34.

endo-**4a**

(1*S*,3*R*,3*aS*,6*aR*)-Methyl 5-methyl-4,6-dioxo-3-phenyl-octahydropyrrole[3,4-*c*]pyrrole-1-carboxylate (endo-4a**).**^{3a,b,4} Following the general procedure, the reaction of methyl (*E*)-*N*-benzylideneglycinate (35.5 mg, 0.20 mmol) with *N*-methylmaleimide (33.0 mg, 0.30 mmol) in CH₂Cl₂ at room temperature afforded, after chromatography (*n*-hexane-EtOAc 1:1), endo-**4a** as a white solid; yield: 97%; mp= 166-167 °C (Lit.^{3b} mp= 176-177 °C). $[\alpha]_D^{20} = +51$ (*c* 0.14, CH₂Cl₂), >99% *ee*; Lit.^{3b} $[\alpha]_D^{20} = +61.0$ (*c* 1.18, CH₂Cl₂) for a 79% *ee* sample. HPLC: Daicel Chiralcel OD, *i*-PrOH-hexane 50/50, flow

rate 0.6 mL/min, t_R : 31.3 min (1*S*,3*R*,3*aS*,6*aR*)-isomer and 36.8 min (1*R*,3*S*,3*aR*,6*aS*)-isomer, 220 nm. ^1H NMR (200 MHz): δ 7.37-7.33 (m, 5H), 4.51 (dd, J = 8.3, 5.4 Hz, 1H), 4.07 (dd, J = 6.5, 4.4 Hz, 1H), 3.89 (s, 3H), 3.64-3.54 (m, 1H), 3.48-3.39 (m, 1H), 2.89 (s, 3H), 2.44(bs, 1H).

(1*S*,3*R*,3*aS*,6*aR*)-Methyl 1-methyl-4,6-dioxo-3,5-diphenyl-octahydropyrrole[3,4-*c*]pyrrole-1-carboxylate (endo-5a**).**⁵ Following the general procedure, the reaction of methyl (*E*)-*N*-benzylidenealaninate (38.2 mg, 0.20 mmol) with *N*-phenylmaleimide (51.9 mg, 0.30 mmol) in CH_2Cl_2 at -10 °C afforded, after chromatography (*n*-hexane-EtOAc 1:1), endo-**5a** as a white solid; yield: 36.4 mg, 50%; mp= 199-200 °C. $[\alpha]_D^{20}$ = +73 (c 0.12, CH_2Cl_2), 80% *ee*. HPLC: Daicel Chiralcel OD, *i*-PrOH-hexane 50/50, flow rate 0.6 mL/min, t_R : 17.3 min (1*R*,3*S*,3*aR*,6*aS*)-isomer and 28.4 min (1*S*,3*R*,3*aS*,6*aR*)-isomer, 210 nm. ^1H NMR (300 MHz): δ 7.37-7.18 (m, 8H), 7.01-6.98 (m, 2H), 4.81 (d, J = 9.1 Hz, 1H), 3.80 (s, 3H), 3.61 (dd, J = 9.1, 7.7 Hz, 1H), 3.37 (d, J = 7.6 Hz, 1H), 2.59 (bs, 1H), 1.58 (s, 3H). ^{13}C NMR (75 MHz): δ 174.8, 173.5, 172.7, 136.8, 131.5, 129.0, 128.5, 128.4 (2C), 127.1, 126.0, 67.6, 62.4, 55.7, 52.7, 50.2, 23.9. FAB⁺ MS m/z 365 (M+H, 100), 305 (43), 154 (64), 149 (62), 136 (67), 69 (60).

(1*S*,3*R*,3*aS*,6*aR*)-Methyl 1-methyl-3-naphthyl-4,6-dioxo-5-phenyl-octahydropyrrole [3,4-*c*]pyrrole-1-carboxylate (endo-5b**).** Following the general procedure, the reaction of methyl (*E*)-*N*-(2-naphthylmethylene)alaninate (48.2 mg, 0.20 mmol) with *N*-

⁴ Tsuge, O.; Kanemasa, S.; Yoshioka, M. *J. Org. Chem.* **1988**, 53, 1384.

⁵ Amornraksa, K.; Grigg, R.; Gurantne, H. Q. N.; Kemp, J.; Sridharan, V. *J. Chem. Soc. Perkin Trans. 1* **1987**, 10, 2285.

phenylmaleimide (51.9 mg, 0.30 mmol) at -10 °C afforded, after chromatography (*n*-hexane-EtOAc 1:1), endo-**5b** as a white solid; yield: 64.6 mg, 78%; mp= >210 (decomp) °C. $[\alpha]_D^{20} = +105$ (*c* 0.12, CH₂Cl₂), 92% *ee*. HPLC: Daicel Chiralpak AS-H, *i*-PrOH-hexane 50/50, flow rate 0.7 mL/min, *t*_R: 13.2 min (1*S*,3*R*,3*aS*,6*aR*)-isomer and 15.9 min (1*R*,3*S*,3*aR*,6*aS*)-isomer, 220 nm. ¹H NMR (300 MHz): δ 7.84 (s, 1H), 7.77-7.71 (m, 3H), 7.44-7.37 (m, 3H), 7.23-7.18 (m, 3H), 6.96-6.93 (m, 2H), 4.98-4.93 (m, 1H), 3.83 (s, 3H), 3.68 (dd, *J*= 9.1, 7.6 Hz, 1H), 3.41 (d, *J*= 7.6 Hz, 1H), 2.65 (d, *J*= 6.5 Hz, 1H), 1.61 (s, 3H). ¹³C NMR (75 MHz): δ 174.9, 173.6, 172.8, 134.5, 133.4, 133.3, 131.5, 129.0, 128.4, 128.2, 128.0, 127.8, 126.3, 126.1, 126.0, 125.5, 67.6, 62.4, 55.7, 52.7, 50.1, 23.9. IE⁺ MS *m/z* 414 (M⁺, 17), 355 (84), 241 (100), 208 (40), 181 (96).

endo-**5c**

(1*S*,3*aS*,6*aR*)-Ethyl 1-methyl-4,6-dioxo-3,3,5-triphenyl-octahydropyrrole [3,4-*c*]pyrrole-1-carboxylate (endo-5c**).** Following the general procedure, the reaction of ethyl *N*-(diphenylmethylene)glycinate (53.5 mg, 0.20 mmol) with *N*-phenylmaleimide (51.9 mg, 0.30 mmol) in CH₂Cl₂ at -10 °C afforded, after chromatography (*n*-hexane-EtOAc 1:1), endo-**5c** as a white solid; yield: 81.0 mg, 92%; mp= 185-186 °C. $[\alpha]_D^{20} = +161$ (*c* 0.14, CH₂Cl₂), 93% *ee*. HPLC: Daicel Chiralpak AS-H, *i*-PrOH-hexane 30/70, flow rate 0.8 mL/min, *t*_R: 12.9 min (1*S*,3*aS*,6*aR*)-isomer and 19.1 min (1*R*,3*aR*,6*aS*)-isomer, 220 nm. ¹H NMR (300 MHz): δ 7.57-7.54 (m, 2H), 7.46-7.43 (m, 2H), 7.30-7.01 (m, 1H), 4.40-4.29 (m, 1H), 4.23-4.12 (m, 1H), 3.85 (t, *J*= 7.7 Hz, 1H), 3.69 (d, *J*= 7.7 Hz, 1H), 3.12-3.07 (m, 2H), 1.18 (t, *J*= 7.2 Hz, 3H). ¹³C NMR (75 MHz): δ 174.8, 173.9, 170.2, 144.5, 141.4, 131.7, 129.0, 128.9, 128.5, 128.0, 127.7, 127.6, 127.2, 126.4, 126.3, 73.8, 61.7, 60.3, 53.0, 49.1, 14.1. FAB⁺ MS *m/z* 441 (M+H, 100), 367 (14), 154 (18).

endo-**5d**

(1*S*,3*R*,3*aS*,6*aR*)-Methyl 3-methyl-4,6-dioxo-3,5-diphenyl-octahydropyrrole [3,4-*c*]pyrrole-1-carboxylate (endo-5d**).** Following the general procedure, the reaction of methyl (*E*)-*N*-(1-phenylethylidene)glycinate (38.3 mg, 0.20 mmol) with *N*-phenylmaleimide (51.9 mg, 0.30 mmol) in CH₂Cl₂ at -10 °C afforded, after chromatography (*n*-hexane-EtOAc 1:1), endo-**5d** as a white solid; yield: 56.7 mg, 78%; mp= 185-186 °C. $[\alpha]_D^{20} = +87$ (*c* 0.27, CH₂Cl₂), 94% *ee*. HPLC: Daicel Chiralpak AS-H, *i*-PrOH-hexane 50/50, flow rate 0.7 mL/min, *t*_R: 11.7 min (1*S*,3*R*,3*aS*,6*aR*)-isomer and 24.6 min (1*R*,3*S*,3*aR*,6*aS*)-isomer, 210 nm. ¹H NMR (300 MHz): δ 7.70-7.66 (m, 2H), 7.43-7.28 (m, 6H), 6.98-6.95 (m, 2H), 4.45 (t, *J*= 6.7 Hz, 1H), 3.90 (s, 3H), 3.82-3.77 (m, 1H), 3.40 (d, *J*= 7.7 Hz, 1H), 2.41 (d, *J*= 6.5 Hz, 1H), 1.74 (s, 3H). ¹³C NMR (75 MHz): δ 174.8, 173.7, 170.7, 141.8, 131.4, 129.1, 128.9, 128.4, 128.2, 127.7, 126.2, 126.0, 67.3, 60.0, 56.1, 52.4, 49.4, 29.1. EI⁺ MS *m/z* 364 (*M*⁺, 10), 349 (100), 305 (81), 191 (67), 158 (71).

endo-**5e**

(1*S*,3*R*,3*aS*,6*aR*)-Methyl 3-(*p*-chlorophenyl)-3-methyl-4,6-dioxo-5-phenyl-octahydropyrrole [3,4-*c*]pyrrole-1-carboxylate (endo-5e**).** Following the general procedure, the reaction of a 31:69 mixture of *p*-chloroacetophenone and methyl (*E*)-*N*-[1-(*p*-chlorophenyl)ethylidene]glycinate (143 mg, which correspond to 45.0 mg, 0.20 mmol of pure ketimine) with *N*-phenylmaleimide (51.9 mg, 0.30 mmol) in CH₂Cl₂ at -10 °C afforded, after chromatography (*n*-hexane-EtOAc 1:1), endo-**5e** as a white solid; yield: 63.8 mg, 80%; mp= >210 °C (decomp.). $[\alpha]_D^{20} = +151$ (*c* 0.16, CH₂Cl₂), >99% *ee*. HPLC: Daicel Chiralpak AS-H, *i*-PrOH-hexane 50/50, flow rate 0.7 mL/min, *t*_R: 12.6 min (1*S*,3*R*,3*aS*,6*aR*)-isomer and 37.8 min (1*R*,3*S*,3*aR*,6*aS*)-isomer, 220 nm. ¹H

NMR (300 MHz): δ 7.61-7.58 (m, 2H), 7.36-7.29 (m, 5H), 6.97-6.94 (m, 2H), 4.41 (t, J = 6.7 Hz, 1H), 3.87 (s, 3H), 3.77 (t, J = 7.7 Hz, 1H), 3.37 (d, J = 7.7 Hz, 1H), 2.29 (d, J = 6.3 Hz, 1H), 1.68 (s, 3H). ^{13}C NMR (75 MHz): δ 174.7, 173.6, 170.6, 140.5, 133.7, 131.4, 129.0, 128.6, 128.3, 127.8, 126.0, 66.8, 60.0, 55.8, 52.5, 49.0, 29.1.

endo-6

(2S,3R,4S,5R)-Trimethyl 5-phenylpyrrolidine-2,3,4-tricarboxylate (endo-6).^{3b}

Following the general procedure, the reaction of methyl (*E*)-*N*-benzylideneglycinate (35.5 mg, 0.20 mmol) with dimethyl maleate (37.0 μL , 0.30 mmol) in THF at room temperature afforded, after chromatography (*n*-hexane-EtOAc 4:1), endo-6 as a white solid; yield: 30.2 mg, 47%; mp= 94-95 $^{\circ}\text{C}$ (lit.^{3b} mp= 91-93 $^{\circ}\text{C}$). $[\alpha]_{\text{D}}^{20}$ = +100 (*c* 0.05, CH_2Cl_2), 94% *ee*; Lit.^{3b} $[\alpha]_{\text{D}}^{20}$ = +64.7 (*c* 1.07, CH_2Cl_2) for a 87% *ee* sample. HPLC: Daicel Chiralpak AS-H, *i*-PrOH-hexane 50/50, flow rate 0.8 mL/min, t_{R} : 7.1 min (2*S*,3*R*,4*S*,5*R*)-isomer and 12.6 min (2*R*,3*S*,4*R*,5*S*)-isomer, 220 nm. ^1H NMR (300 MHz): δ 7.28-7.18 (m, 5H), 4.41 (d, J = 6.8 Hz, 1H), 4.09 (d, J = 8.9 Hz, 1H), 3.74 (s, 3H), 3.66 (d, J = 8.2 Hz, 1H), 3.62 (s, 3H), 3.53-3.48 (m, 1H), 3.29 (bs, 1H), 3.16 (s, 3H).

endo-7

(2S,3S,4S,5R)-Trimethyl 5-phenylpyrrolidine-2,3,4-tricarboxylate (endo-7).^{3b,6}

Following the general procedure, the reaction of methyl (*E*)-*N*-benzylideneglycinate (35.5 mg, 0.20 mmol) with dimethylfumarate (43.2 mg, 0.30 mmol) in THF at -10 $^{\circ}\text{C}$ afforded, after chromatography (*n*-hexane-EtOAc 4:1), endo-7 as a colorless oil; yield: 57.1 mg, 89%. $[\alpha]_{\text{D}}^{20}$ = +43 (*c* 0.10, CH_2Cl_2), >99% *ee*; Lit.⁶ $[\alpha]_{\text{D}}^{20}$ = +20 (*c* 0.35, CH_2Cl_2) for a 76% *ee* sample. HPLC: Daicel Chiralcel OD, *i*-PrOH-hexane 30/70, flow rate 0.8 mL/min, t_{R} : 16.1 min (2*S*,3*S*,4*S*,5*R*)-isomer and 26.6 min (2*R*,3*R*,4*R*,5*S*)-isomer,

⁶ Gothelf, A. S.; Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 4236.

210 nm. ^1H NMR (200 MHz): δ 7.33-7.27 (m, 5H), 4.65 (d, J = 7.8 Hz, 1H), 4.20 (d, J = 7.3 Hz, 1H), 3.84 (s, 3H), 3.78 (s, 3H), 3.73-3.52 (m, 2H), 3.20 (s, 3H), 2.76 (bs, 1H).

exo-8

(2*S*,3*R*,4*R*,5*R*)-Methyl 3,4-dicyano-5-phenylpyrrolidine-2-carboxylate (exo-8).^{3a}

Following the general procedure, the reaction of methyl (*E*)-*N*-benzylideneglycinate (35.5 mg, 0.20 mmol) with fumarodinitrile (23.4 mg, 0.30 mmol) in THF at -30 °C afforded, after chromatography (*n*-hexane-EtOAc 4:1), exo-8 as a white solid; yield: 39.8 mg, 78%; mp = 120-121 °C (lit.^{3a} mp = 128-130 °C). $[\alpha]_{\text{D}}^{20}$ = +356 (*c* 1.0, CH₂Cl₂), 76% *ee*. HPLC: Daicel Chiralcel OD, *i*-PrOH-hexane 40/60, flow rate 0.7 mL/min, t_{R} : 21.9 min (2*S*,3*R*,4*R*,5*R*)-isomer and 28.7 min (2*R*,3*S*,4*S*,5*S*)-isomer, 210 nm. ^1H NMR (300 MHz): δ 7.44-7.30 (m, 5H), 4.32 (t, J = 8.5 Hz, 1H), 4.22 (t, J = 7.3 Hz, 1H), 3.84 (s, 3H), 3.61 (t, J = 8.4 Hz, 1H), 3.15 (t, J = 8.6 Hz, 1H), 2.73 (bs, 1H).

endo-9

(2*S*,4*S*,5*R*)-Dimethyl 5-phenylpyrrolidine-2,4-dicarboxylate (endo-9).^{3b,5}

Following the general procedure, the reaction of methyl (*E*)-*N*-benzylideneglycinate (35.5 mg, 0.20 mmol) with methyl acrylate (27.0 μL , 0.30 mmol) in THF at room temperature afforded, after chromatography (*n*-hexane-EtOAc 4:1), endo-9 as a colorless oil; yield: 32.6 mg, 62%. $[\alpha]_{\text{D}}^{20}$ = +36 (*c* 0.08, CH₂Cl₂), 95% *ee*; Lit.⁵ $[\alpha]_{\text{D}}^{20}$ = +38 (*c* 0.10, CH₂Cl₂) for a 88% *ee* sample. HPLC: Daicel Chiralpak AS-H, *i*-PrOH-hexane 10/90, flow rate 1.0 mL/min, t_{R} : 15.0 min (2*S*,4*S*,5*R*)-isomer and 24.5 min (2*R*,4*R*,5*S*)-isomer, 210 nm. ^1H NMR (200 MHz): δ 7.27-7.16 (m, 5H), 4.47 (d, J = 7.8 Hz, 1H), 3.92 (t, J = 8.1 Hz, 1H), 3.76 (s, 3H), 3.25 (q, J = 6.9 Hz, 1H), 3.15 (s, 3H), 2.72 (bs, 1H), 2.35 (dd, J = 8.1, 6.9 Hz, 2H).

exo-10

(2*S*,3*S*,4*R*,5*S*)-Methyl 4-nitro-3,5-diphenylpyrrolidine-2-carboxylate (exo-10).⁷

Following the general procedure, the reaction of methyl (*E*)-*N*-benzylideneglycinate (35.5 mg, 0.20 mmol) with trans β-nitrostyrene (44.7 mg, 0.30 mmol) in THF at -10 °C afforded, after chromatography (*n*-hexane-EtOAc 4:1), exo-10 as a white solid; yield: 39.8 mg, 61%; mp= 105-106 °C (lit.⁷ (±)-exo-10 mp= 113-115 °C). $[\alpha]_D^{20} = +105$ (*c* 0.11, CH₂Cl₂), 94% *ee*. HPLC: Daicel Chiralpak AS-H, *i*-PrOH-hexane 20/80, flow rate 0.4 mL/min, *t*_R: 25.2 min (2*S*,3*S*,4*R*,5*S*)-isomer and 27.1 min (2*R*,3*R*,4*S*,5*R*)-isomer, 220 nm. ¹H NMR (200 MHz): δ 7.56-7.52 (m, 2H), 7.45-7.18 (m, 8H), 5.19 (t, *J*= 8.0 Hz, 1H), 4.73 (d, *J*= 7.8 Hz, 1H), 4.48 (d, *J*= 9.1 Hz, 1H), 4.35 (t, *J*= 7.8 Hz, 1H), 3.26 (s, 3H), 2.71 (bs, 1H).

exo-11

(2*S*,4*S*,5*S*)-Methyl 4-formyl-3-methyl-5-phenylpyrrolidine-2-carboxylate (exo-11).

Following the general procedure, the reaction of methyl (*E*)-*N*-benzylideneglycinate (35.5 mg, 0.20 mmol) with methacrolein (25.0 μL, 0.30 mmol) in CH₂Cl₂ at room temperature afforded, after chromatography (*n*-hexane-EtOAc 2:1), exo-11 as a colorless oil; yield: 23.7 mg, 48%. $[\alpha]_D^{20} = -8$ (*c* 0.36, CH₂Cl₂), 69% *ee*. HPLC: Daicel Chiralpak AS-H, *i*-PrOH-hexane 30/70, flow rate 0.5 mL/min, *t*_R: 15.7 min (2*S*,4*S*,5*S*)-isomer and 29.5 min (2*R*,4*R*,5*R*)-isomer, 210 nm. ¹H NMR (300 MHz): δ 9.16 (s, 1H), 7.40-7.28 (m, 5H), 4.13 (s, 1H), 4.05 (dd, *J*= 9.1, 6.5 Hz, 1H), 2.62 (dd, *J*= 13.4, 6.5 Hz, 1H), 2.01 (dd, *J*= 13.4, 9.1 Hz, 1H), 1.28 (s, 3H). ¹³C NMR (75 MHz): δ 203.8, 174.0, 136.9, 128.6, 128.2, 127.2, 72.7, 57.9, 55.3, 52.3, 37.3, 19.1. EI⁺ MS *m/z* 247 (*M*⁺, 8), 177 (65), 117 (100), 106 (32). EI⁺ HRMS Calcd. for C₁₄H₁₇NO₃: 247.1208. Found: 247.1205.

⁷ Vivanco, S.; Lecea, B.; Arrieta, A.; Prieto, P.; Morao, I.; Linden, A.; Cossío, F. P. *J. Am. Chem. Soc.* **2000**, *122*, 6078.

Stereochemical assignment of 1,3-dipolar cycloadducts

Endo/exo stereochemistry

Many of the pyrrolidine cycloadducts described here were known either in optically active or racemic form. Thus, the endo/exo stereochemical assignment was established by comparison of the corresponding NMR and physical data with those previously reported for compounds endo-**3a**,^{3a,3b} endo-**3d**,^{3a} endo-**4a**,^{3a,3b} endo-**5a**,⁵ endo-**6**,^{3b} endo-**7**,⁵ exo-**8**,^{3a} endo-**9**⁵ and exo-**10**.⁷ The endo-stereochemistry of the new compounds **3b**, **3c**, **3e**, **5b-e** and **11** was established by chemical analogy and by NMR, mainly by a combination of careful examination of ¹H NMR data and NOESY/ NOE experiments.

In the case of maleimide cycloadducts, characteristic differences between the endo- and exo-isomers in chemical shift and coupling constants of key protons were of great diagnostic value.⁸ For instance, the coupling constants between the proton couples H⁴-H⁵ in all endo-adducts are significantly higher (typically 7-9 Hz) than those observed in the exo-adducts (typically 4-5.5 Hz).

Also, the cone anisotropy effect of the phenyl ring at C-5 causes a characteristic upfield shift on the protons of substituents at C-4 that are cis with regard to that phenyl group. For example, the proton signals of the methoxycarbonyl group at C-4 in compounds endo-**6**, endo-**7** and endo-**9** appears 0.6 ppm more shielded (around 3.0 ppm) than that of the methoxycarbonyl groups at C-2 or C-3 (typically at 3.6-3.8 ppm). This effect is also observed in the proton of the formyl group at C-4 of endo-**11**, which appears shielded (9.1 ppm) in comparison to the expected chemical shift (typically around 9.7 ppm).⁹

In addition, in the case of the new compounds having a quaternary stereocenter at C-2, C-5 or C-4 (endo-**5a**, endo-**5d** and endo-**11**) the stereochemical assignment was confirmed by NOE experiments. The most diagnostic values are shown in Figure 1.

⁸ For similar effects observed in related 1,3-dipolar cycloadducts, see: (a) Woller, P. B.; Cromwell, N. H. *J. Org. Chem.* **1970**, 35, 888.

⁹ See, for instance, Shirahase, M.; Kanemasa, S.; Oderaotoshi, Y. *Org. Lett.* **2004**, 6, 675.

Figure 1

Absolute configuration

Five of the endo adducts described here were known in optically active form. Thus, the absolute stereochemistry of the cycloadducts (+)-endo-**3a**,^{3b} (+)-endo-**4a**,^{3b} (+)-endo-**6**,^{3b} (+)-endo-**7**⁶ and (+)-endo-**9**⁶ was assigned by comparison of the optical rotation values with those previously reported in the literature. The same facial selectivity in the approach of the dipolarophile to the azomethine ylide was assumed for assigning the absolute configuration of the rest of the endo and exo-cycloadducts.

NMR Spectra