A convenient procedure for the catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides and alkenes

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General procedures. ¹H NMR and ¹³C NMR spectra were recorded in CDCl₃ at 400 MHz and 100 MHz, respectively. Chemical shifts are reported in ppm (δ) relative to residual protic solvent (δ 7.26 for ¹H NMR and δ 77.0 for ¹³C NMR, respectively). Column chromatography was carried out using Fluka silica gel 60 (0.04-0.063 mm particle size). Thin layer chromatography (TLC) was performed on Merck silica gel 60 F₂₅₄ plates and visualized by UV-light (254 nm) or by an aqueous mixture of KMnO₄, K₂CO₃ and NaOH. Optical rotations were measured on a Perkin-Elmer 241 polarimeter in dichloromethane solutions. The enantiomeric excess of the products was determined by HPLC using Daicel Chiralpack AS columns with 2-propanol/hexane mixtures as eluent. HRMS were recorded on a Micromass LC-TOF instrument.

Reagents and materials. CH₂Cl₂ HPLC grade (Chromasolv, Sigma-Aldrich) was used without further treatment. All reagents were used as purchased.

Representative procedure for the preparation of the imines. To a suspension of 5.78 g (46 mmol) glycine methyl ester hydrochloride in CH₂Cl₂ (70 mmol) was added 10 g anhydrous MgSO₄ and 7 mL (50 mmol) of Et₃N. The mixture was stirred for 1h at room

temperature. Then the aldehyde (40 mmol) was added and the resulting mixture stirred overnight. The reaction mixture was filtered and the organic phase washed with water (2 x 50 mL) and dried over anhydrous MgSO_4 , filtered and evaporated under reduced pressure. The imines were used without further purification.

General procedure for the silver fluoride-cinchonine catalyzed 1,3-dipolar cycloaddition. Silver fluoride (2.5 mg, 0.02 mmol), hydrocinchonine (5.9 mg, 0.02 mmol) and the imine **1** (0.40 mmol) were placed in a test tube. CH_2Cl_2 (3.2 mL) was added followed by *tert*-butyl acrylate (70 μL , 0.48 mmol). The tube was stopped with a rubber septum and stirred in a freezer at $-25\text{ }^\circ\text{C}$ for 4 days. After this time, the reaction mixture was chromatographed on silica gel using hexane-EtOAc or dichloromethane-diethyl ether mixtures containing 10 drops Et_3N /100 mL solvent to afford pyrrolidine **3**.

***tert*-Butyl (2*S*, 4*S*, 5*R*)-2-methoxycarbonyl-5-(4-methylphenyl)pyrrolidine-4-carboxylate (3c).**

Obtained after purification by column chromatography using CH_2Cl_2 - Et_2O (95:5) in 89% yield and 70% ee (Chiralpack AS, hexane/2-propanol 99:1, flow rate 1 mL/min, $t_{\text{R}(\text{major})} = 12.9$ min, $t_{\text{R}(\text{minor})} = 26.3$ min). $[\alpha]_{\text{D}}^{25} +23$ (c 0.53, CH_2Cl_2); HRMS $\text{C}_{18}\text{H}_{25}\text{NO}_4$ $[\text{M}+\text{Na}]^+$ calculated 342.1676, found 342.1674; ^1H NMR (400 MHz, CDCl_3) δ 7.21 (2H, d, $J = 8.0$ Hz), 7.09 (2H, d, $J = 8.0$ Hz), 4.42 (1H, d, $J = 7.6$ Hz), 3.91 (1H, t, $J = 8.4$ Hz), 3.79 (3H, s), 3.21 (1H, dd, $J = 14.4, 8.0$ Hz), 2.81 (1H, br s), 2.45-2.39 (1H, m), 2.30 (3H, s), 2.31-2.23 (1H, m), 1.02 (9H, s); ^{13}C NMR (100 MHz, CDCl_3) δ 173.7, 171.9, 136.8, 136.1, 128.6 (2C), 127.0 (2C), 80.4, 65.3, 59.8, 52.2, 50.2, 34.1, 27.4 (3C), 21.0.

***tert*-Butyl (2*S*, 4*S*, 5*R*)-2-methoxycarbonyl-5-(2-methylphenyl)pyrrolidine-4-carboxylate (3d).**

Obtained after purification by column chromatography using CH_2Cl_2 - Et_2O (95:5) in 97% yield and 64% ee (Chiralpack AS, hexane/2-propanol 95:5, flow rate 1 mL/min, $t_{\text{R}(\text{major})} = 5.6$ min, $t_{\text{R}(\text{minor})} = 21.2$ min). $[\alpha]_{\text{D}}^{25} +48$ (c 2.4, CH_2Cl_2); ^1H NMR and ^{13}C NMR were consistent with previously reported values for its enantiomer.¹

***tert*-Butyl (2*S*, 4*S*, 5*R*)-2-methoxycarbonyl-5-phenylpyrrolidine-4-carboxylate (3e).**

Obtained after purification by column chromatography using hexane-EtOAc (75:25) in 88% yield and 64% ee (Chiralpack AS, hexane/2-propanol 95:5, flow rate 1.0 mL/min, $t_{R(\text{major})}$ = 7.9 min, $t_{R(\text{minor})}$ = 12.5 min). $[\alpha]^{25}_D$ +24 (c 0.86, CH_2Cl_2); ^1H NMR and ^{13}C NMR were consistent with previously reported values for its enantiomer.¹

***tert*-Butyl (2*S*, 4*S*, 5*R*)-2-methoxycarbonyl-5-(2-methoxyphenyl)pyrrolidine-4-carboxylate (3f).**

Obtained after purification by column chromatography using hexane-EtOAc (65:35) in 63% yield and 56% ee (Chiralpack AS, hexane/2-propanol 99:1, flow rate 1 mL/min, $t_{R(\text{major})}$ = 14.5 min, $t_{R(\text{minor})}$ = 28.5 min). $[\alpha]^{25}_D$ +67 (c 0.41, CH_2Cl_2); HRMS $\text{C}_{18}\text{H}_{25}\text{NO}_5$ $[\text{M}+\text{Na}]^+$ calculated 358.1625, found 358.1623; ^1H NMR (400 MHz, CDCl_3) δ 7.33 (1H, d, J = 8.0 Hz), 7.24, t, J = 8.0 Hz), 6.93 (1H, t, J = 8.0 Hz), 6.84 (1H, d, J = 8.0 Hz), 4.51 (1H, d, J = 8.4 Hz), 3.90 (1H, t, J = 8.4 Hz), 3.85 (3H, s), 3.81 (3H, s), 3.43 (1H, td, J = 8.4, 4.0 Hz), 2.91 (1H, br s), 2.29-2.23 (1H, m), 0.98 (9H, s); ^{13}C NMR (100 MHz, CDCl_3) δ 173.5, 172.8, 156.8, 128.2, 126.6, 126.4, 120.2, 109.7, 79.9, 61.6, 59.6, 55.1, 52.1, 47.8, 34.5, 27.4 (3C).

***tert*-Butyl (2*S*, 4*S*, 5*R*)-2-methoxycarbonyl-5-(3-methoxyphenyl)pyrrolidine-4-carboxylate (3g).**

Obtained after purification by column chromatography using hexane-EtOAc (65:35) in 93% yield and 70% ee (2 x Chiralpack AS, hexane/2-propanol 99:1, flow rate 1 mL/min, $t_{R(\text{major})}$ = 53.6 min, $t_{R(\text{minor})}$ = 65.9 min). $[\alpha]^{25}_D$ +21 (c 2.4, CH_2Cl_2); HRMS $\text{C}_{18}\text{H}_{25}\text{NO}_5$ $[\text{M}+\text{Na}]^+$ calculated 358.1625, found 358.1630; ^1H NMR (400 MHz, CDCl_3) δ 7.20 (1H, t, J = 8.0 Hz), 6.92 (1H, d, J = 8.0 Hz), 6.91 (1H, d, J = 2.8 Hz), 6.77 (1H, dd, J = 2.8, 8.0 Hz), 4.43 (1H, d, J = 8.0 Hz), 3.92 (1H, t, J = 8.4 Hz), 3.79 (3H, s), 3.78 (3H, s), 3.23 (1H, dd, J = 7.6, 14.0 Hz), 2.80 (1H, br s), 2.45-2.38 (1H, m), 2.32-2.25 (1H, m), 1.04 (9H, s); ^{13}C NMR (100 MHz, CDCl_3) δ 173.6, 171.8, 159.3, 140.9, 129.0, 119.5, 112.9, 112.7, 80.5, 65.5, 59.8, 55.2, 52.2, 50.1, 34.0, 27.4 (3C).

***tert*-Butyl (2*S*, 4*S*, 5*R*)-2-methoxycarbonyl-5-(4-methoxyphenyl)pyrrolidine-4-carboxylate (3h).**

Obtained after purification by column chromatography using hexane-EtOAc (65:35) in 89% yield and 56 % ee (Chiralpack AS, hexane/2-propanol 95:5, flow rate 1 mL/min, $t_{R(\text{major})}$ = 9.8 min, $t_{R(\text{minor})}$ = 18.5 min). $[\alpha]_D^{25}$ + 19 (c 2.1, CH₂Cl₂); ¹H NMR and ¹³C NMR were consistent with previously reported values for its enantiomer.¹

***tert*-Butyl (2*S*, 4*S*, 5*R*)-2-methoxycarbonyl-5-(4-*N,N*-dimethylaminophenyl)-4-carboxylate (3i).**

Obtained after purification by column chromatography using hexane-EtOAc (65:3 5) in 86% yield and 67% ee (Chiralpack AS, hexane/2-propanol 99:1, flow rate 1 mL/min, $t_{R(\text{major})}$ = 20.4 min, $t_{R(\text{minor})}$ = 36.9 min). $[\alpha]_D^{25}$ +18 (c 0.53, CH₂Cl₂); HRMS C₁₉H₂₈N₂O₄ [M+Na]⁺ calculated 371.1941, found 371.1945; ¹H NMR (400 MHz, CDCl₃) δ 7.18 (2H, d, J = 8.0 Hz), 6.67 (2H, d, J = 8.0 Hz), 4.38 (1H, d, J = 7.6 Hz), 3.90 (1H, t, J = 8.4 Hz), 3.79 (3H, s), 3.19 (1H, dd, J = 7.6, 14.0 Hz), 2.89 (6H, s), 2.60 (1H, br s), 2.42-2.35 (1H, m), 2.31-2.24 (1H, m), 1.05 (9H, s); ¹³C NMR (100 MHz, CDCl₃) δ 173.7, 171.9, 150.0, 127.8 (2C), 127.3, 112.4 (2C), 80.3, 65.1, 59.8, 52.1, 50.4, 40.7, 34.1, 27.5 (3C). Part of the product (107 mg) was recrystallized from 5 mL of hexane and 1 mL CH₂Cl₂ at 0 °C. The mother liquors were concentrate to give 52 mg (48% yield, 41% overall yield) of enantiomerically enriched product (92% ee).

***tert*-Butyl (2*S*, 4*S*, 5*R*)-2-methoxycarbonyl-5-(4-bromophenyl)pyrrolidine-4-carboxylate (3j).**

Obtained after purification by column chromatography using CH₂Cl₂-Et₂O (80:20) in 88% yield and 66% ee (Chiralpack AS, hexane/2-propanol 95:5, flow rate 1 mL/min, $t_{R(\text{major})}$ = 7.8 min, $t_{R(\text{minor})}$ = 16.2 min). $[\alpha]_D^{25}$ +18 (c 0.76, CH₂Cl₂); ¹H NMR and ¹³C NMR were consistent with previously reported values for its enantiomer.¹

***tert*-Butyl (2*S*, 4*S*, 5*R*)-2-methoxycarbonyl-5-(4-cyanophenyl)pyrrolidine-4-carboxylate (3k).**

Obtained after purification by column chromatography using CH₂Cl₂-Et₂O (80:20) in 86% yield and 70% ee (Chiralpack AS, hexane/2-propanol 99:1, flow rate 1 mL/min, *t*_{R(major)} = 25.8 min, *t*_{R(minor)} = 42.9 min). [α]²⁵_D +23 (*c* 0.47, CH₂Cl₂); ¹H NMR and ¹³C NMR were consistent with previously reported values for its enantiomer.¹

***tert*-Butyl (2*S*, 4*S*, 5*R*)-2-methoxycarbonyl-5-(4-methoxycarbonylphenyl)pyrrolidine-4-carboxylate (3l).**

Obtained after purification by column chromatography using CH₂Cl₂-Et₂O (80:20) in 82% yield and 61% ee (Chiralpack AS, hexane/2-propanol 90:10, flow rate 1 mL/min, *t*_{R(major)} = 9.0 min, *t*_{R(minor)} = 17.3 min). [α]²⁵_D +20 (*c* 0.97, CH₂Cl₂); HRMS C₁₉H₂₅NO₆ [M+Na]⁺ calculated 386.1574, found 386.1579; ¹H NMR (400 MHz, CDCl₃) δ 7.99 (2H, d, *J* = 8.0 Hz), 7.45 (2H, d, *J* = 8.0 Hz), 4.50 (1H, d, *J* = 8.0 Hz), 3.96 (1H, t, *J* = 8.0 Hz), 3.91 (3H, s), 3.81 (3H, s), 3.28 (1H, dd, *J* = 7.0, 14.0 Hz), 2.50-2.42 (1H, m), 2.34-2.27 (1H, m), 1.02 (9H, s); ¹³C NMR (100 MHz, CDCl₃) δ 173.5, 171.5, 166.8, 144.5, 129.4 (2C), 129.0, 127.2 (2C), 80.9, 65.2, 59.8, 52.3, 52.1, 49.9, 34.0, 27.5 (3C). Part of the obtained product (113 mg) was recrystallized from 4 mL of hexane and 0.5 mL CH₂Cl₂ at 0 °C to give 57 mg (57% yield of crystals, 41% overall yield) of enantiomerically enriched product (85% ee).

***tert*-Butyl (2*S*, 4*S*, 5*R*)-2-methoxycarbonyl-5-(2-furyl)pyrrolidine-4-carboxylate (3m).**

Obtained after purification by column chromatography using hexane-EtOAc (60:40) in 86% yield and 73% ee (Chiralpack AS, hexane/2-propanol 90:10, flow rate 1 mL/min, *t*_{R(major)} = 5.8 min, *t*_{R(minor)} = 9.7 min); [α]²⁵_D -9 (*c* 1.5, CH₂Cl₂); HRMS C₁₅H₂₁NO₅ [M+Na]⁺ calculated 318.1312, found 318.1318; ¹H NMR (400 MHz, CDCl₃) δ 7.28 (1H, d, *J* = 2.0 Hz), 6.26 (1H, dd, *J* = 3.2, 2.0 Hz), 6.22 (1H, d, *J* = 3.2 Hz), 4.46 (1H, d, *J* = 8.0 Hz), 3.87 (1H, t, *J* = 8.0 Hz), 3.73 (3H, s), 3.19 (1H, q, *J* = 8.0 Hz), 2.65 (1H, br

s), 2.35 (2H, t, $J = 8.0$ Hz), 1.20 (9H, s); ^{13}C NMR (100 MHz, CDCl_3) δ 173.8, 170.8, 153.4, 141.5, 110.1, 107.0, 80.7, 59.2, 58.9, 52.2, 49.3, 32.5, 27.6 (3C).

***tert*-Butyl (2*S*, 4*S*, 5*R*)-2-methoxycarbonyl-5-(1-naphthyl)pyrrolidine-4-carboxylate (3n).**

Obtained after purification by column chromatography using hexane-EtOAc (70:30) in 88% yield and 64% ee (Chiralpack AS, hexane/2-propanol 90:10, flow rate 1 mL/min, $t_{\text{R}(\text{major})} = 7.6$ min, $t_{\text{R}(\text{minor})} = 17.1$ min). $[\alpha]_{\text{D}}^{25} +126$ (c 0.49, CH_2Cl_2); HRMS $\text{C}_{21}\text{H}_{25}\text{NO}_4$ $[\text{M}+\text{Na}]^+$ calculated 378.1676, found 378.1675; ^1H NMR (400 MHz, CDCl_3) δ 7.99 (1H, d, $J = 8.0$ Hz), 7.84 (1H, d, $J = 7.6$ Hz), 7.75 (1H, d, $J = 8.0$ Hz), 7.67 (1H, d, $J = 7.6$ Hz), 7.51 (1H, t, $J = 7.6$ Hz), 7.46 (1H, t, $J = 8$ Hz), 7.43 (1H, t, $J = 8.0$ Hz), 5.13 (1H, dd, $J = 8.0$ Hz), 3.82 (3H, s), 3.52 (1H, dd, $J = 8.0$, 13.6 Hz), 2.91 (1H, br s), 2.55-2.40 (2H, m), 0.60 (9H, s); ^{13}C NMR (100 MHz, CDCl_3) δ 173.3, 171.7, 134.4, 133.3, 131.4, 128.5, 127.8, 125.7, 125.3 (2C), 123.4 (2C), 79.8, 62.0, 59.4, 52.1, 48.7, 33.7, 26.9 (3C).

***tert*-Butyl (2*S*, 4*S*, 5*R*)-2-methoxycarbonyl-5-(2-naphthyl)pyrrolidine-4-carboxylate (3o).**

Obtained after purification by column chromatography using CH_2Cl_2 -Et₂O (80:20) in 86% yield and 62% ee (Chiralpack AS, hexane/2-propanol 95:5, flow rate 1 mL/min, $t_{\text{R}(\text{major})} = 8.9$ min, $t_{\text{R}(\text{minor})} = 16.8$ min). $[\alpha]_{\text{D}}^{25} +17$ (c 0.45, CH_2Cl_2); ^1H NMR and ^{13}C NMR were consistent with previously reported values for its enantiomer.¹

***tert*-Butyl (2*S*, 4*S*, 5*S*)-2-methoxycarbonyl-5-(1-naphthyl)pyrrolidine-4-carboxylate (3p).**

Obtained after purification by column chromatography using hexane-EtOAc (70:30) in 65% yield and 41% ee (2 x Chiralpack AS, hexane/2-propanol 99:1, flow rate 0.5 mL/min, $t_{\text{R}(\text{major})} = 21.8$ min, $t_{\text{R}(\text{minor})} = 26.4$ min). $[\alpha]_{\text{D}}^{25} -3$ (c 0.52, CH_2Cl_2); HRMS $\text{C}_{17}\text{H}_{29}\text{NO}_4$ $[\text{M}+\text{Na}]^+$ calculated 334.1989, found 339.1996; ^1H NMR (400 MHz, CDCl_3) δ 3.77

(1H, dd, $J = 10.4, 6.0$ Hz), 3.73 (3H, s), 2.81 (1H, td, $J = 6.0, 2.0$ Hz), 2.73 (1H, dd, $J = 10.0, 6.0$ Hz), 2.32-2.24 (2H, m), 2.11 (1H, ddd, $J = 13.6, 5.6, 2.0$ Hz), 2.06 (1H, br d, $J = 12.8$ Hz), 1.97 (1H, br d, $J = 12.8$ Hz), 1.75-1.61 (3H, m), 1.41 (9H, s), 1.40-0.95 (6H, m); ^{13}C NMR (100 MHz, CDCl_3) δ 173.9, 173.6, 80.7, 70.1, 59.6, 52.0, 46.5, 39.4, 34.9, 31.8, 31.0, 28.0 (3C), 26.2, 25.9, 25.8.

***tert*-Butyl (2*S*, 4*S*, 5*S*)-2-methoxycarbonyl-5-(2,2-dimethylethyl)pyrrolidine-4-carboxylate (3q).**

Obtained after purification by column chromatography using hexane-EtOAc (65:35) in 78% yield and 41% ee (2 x Chiralpack AS, hexane/2-propanol 99:1, flow rate 0.3 mL/min, $t_{\text{R(major)}}$ = 29.4min, $t_{\text{R(minor)}}$ = 32.5 min). $[\alpha]_{\text{D}}^{25} -14$ (c 0.87, CH_2Cl_2); HRMS $\text{C}_{16}\text{H}_{29}\text{NO}_4$ $[\text{M}+\text{Na}]^+$ calculated 322.1989, found 322.1996; ^1H NMR (400 MHz, CDCl_3) δ 3.73 (1H, dd, $J = 9.6, 7.2$ Hz), 3.71 (3H, s), 3.11 (1H, dd, $J = 10.8, 7.2$ Hz), 2.73 (1H, td, $J = 8.4, 3.6$ Hz), 2.29-2.21 (2H, m), 2.07 (1H, ddd, $J = 13.6, 6.4, 3.2$ Hz), 1.56 (1H, dd, $J = 14.4, 3.6$ Hz), 1.40 (9H, s), 1.43-1.29 (1H, m), 0.92 (9H, s); ^{13}C NMR (100 MHz, CDCl_3) δ 173.8, 173.5, 80.8, 60.5, 59.9, 52.0, 49.6, 44.3, 34.3, 30.2, 29.8 (3C), 28.1 (3C).

***tert*-Butyl (2*S*, 4*S*, 5*S*)-2-methoxycarbonyl-5-isopropylpyrrolidine-4-carboxylate (3r).**

Obtained after purification by column chromatography using hexane-EtOAc (70:30) in 67% yield and 52% ee (2 x Chiralpack AS, hexane/2-propanol 99:1, flow rate 0.3 mL/min, $t_{\text{R(major)}}$ = 31.3 min, $t_{\text{R(minor)}}$ = 38.6 min). $[\alpha]_{\text{D}}^{25} -8$ (c 1.1, CH_2Cl_2); HRMS $\text{C}_{14}\text{H}_{25}\text{NO}_4$ $[\text{M}+\text{Na}]^+$ calculated 294.1676, found 294.1681; ^1H NMR (400 MHz, CDCl_3) δ 3.81 (1H, dd, $J = 10.4, 5.6$ Hz), 3.75 (3H, s), 2.82 (1H, td, $J = 6.6, 2.0$ Hz), 2.67 (1H, dd, $J = 10.4, 6.0$ Hz), 2.36-2.28 (1H, m), 2.14 (1H, ddd, $J = 13.6, 6.6, 2.0$ Hz), 1.71-1.41 (1H, m), 1.42 (9H, s), 1.10 (3H, d, $J = 6.4$ Hz), 1.02 (3H, d, $J = 6.4$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 173.7, 173.5, 80.7, 71.6, 59.7, 52.0, 46.9, 35.1, 29.9, 28.0 (3C), 21.8, 20.8.

General procedure for the racemic 1,3 dipolar cycloaddition. The same procedure for the asymmetric reaction was carried out, using Et₃N instead of hydrocinchonine, at room temperature overnight. The reaction mixture was filtered through a pad of silica gel eluting with diethyl ether. Racemic products were used without further purification for comparing enantiomer retention times in HPLC.

(1)) Chen, C.; Li, X.; Schreiber, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 10174-10175.