Supporting Information: Enantioselective Rhodium-Catalysed 1,4-Additions of 2-Heteroarylzinc Donors Using Me-DUPHOS

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General Remarks

All reactions were performed under nitrogen atmosphere in pre-dried glassware. All solvents were purified by passing through a neutral alumina column under argon (Pure-Solv^{TM} by Innovative Technology). All chemicals were purchased from Fisher Scientific (Acros), Lancaster or Aldrich and used as received. $[Rh(COD)Cl]_2$ was synthesized following the literature procedure.[1] Flash chromatography was carried out using Fisher silica 60A (35-70 micron). TLC was performed using Alugram® silica G/UV_{254} coated plates. Mass spectra were carried out by using a Bruker microTOF spectrometer at the mass spectrometry services in Bath. IR spectra were recorded as thin films (DCM) using a Perkin- Elmer 1600 series FT – IR spectrophotometer in the range 4000- 600 cm^{-1}, with internal background scan, absorption maxima (ν) are recorded in wavenumbers (cm^{-1}). ^1H NMR spectra were recorded in $CDCl_3$ on a Bruker AM 300 instrument at 300 MHz. Chemical shifts are reported in ppm using residual $CHCl_3$ as an internal reference. Coupling constants are measured in hertz. ^{13}C NMR spectra were recorded in $CDCl_3$ on the same instrument at 75 MHz. HPLC analyses (Chiralcel OD-H or OJ, and Chiralpack AS column from Daicel, IPA-Hexane as eluent) were performed using a Agilent Technologies 1100 Series with Agilent Technologies 1100 Series Variable Wavelength Detector.

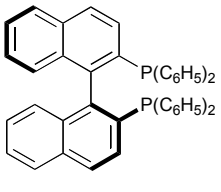
General synthesis of 0.5 M solution of 2-thenylzinc reagents[2]:

To a nitrogen flushed solution of 2-methylthiophene (0.98 g, 10 mmol) in dry THF (10 mL), n-butyllithium (6.25 mL of a 1.6 M solution in hexanes) was added dropwise at -78°C. The resulting mixture was allowed to slowly warm to 0°C. After stirring for 4 h at 0°C, $ZnCl_2$ (21 ml of a 0.5 M solution in THF) was added slowly. The mixture was stirred for additional 1 hour and then concentrated under vacuum to a volume of 20ml.

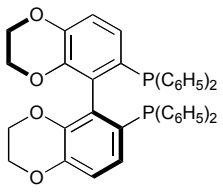
General synthesis of 0.5 M solution of 2-furanylzinc reagents[3]:

To a nitrogen flushed solution of furan (0.68 g, 10 mmol) in dry THF (10 mL), n-butyllithium (6.25 mL of a 1.6 M solution in hexanes) was added dropwise at 0°C. After stirring for 3 h at 0°C, $ZnCl_2$ (21 ml of a 0.5 M solution in THF) was added slowly. The mixture was stirred for additional 30 min and then concentrated under vacuum to a volume of 20ml.

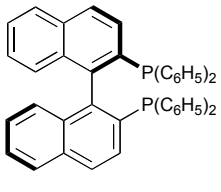
Ligands used in optimisation of enantioselectivity:



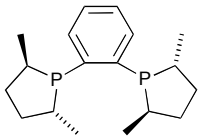
(*S*)-BINAP



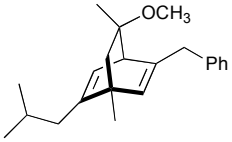
(*S*)-SYNPHOS



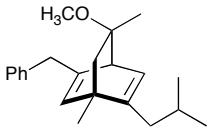
(*R*)-BINAP



(*R*,*R*)-Me-DUPHOS



(*R*,*R*,*R*)-DOLEFIN

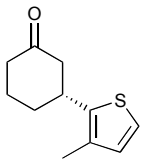


(S,S,S)-DOLEFIN

General procedure for the 1,4-addition reaction:

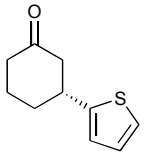
To a solution of $[Rh(ethylene)_2Cl]_2$ (2.9 mg, 3 mol% of Rh), (*R*,*R*)-Me-DUPHOS (5.5 mg, 3.6 mol%), in tetrahydrofuran (1 mL), stirred 15 minutes at room temperature, was added 2-cyclohexen-1-one (0.05 mL, 0.5 mmol, 1 equiv.), chlorotrimethylsilane (0.095 mL, 0.75 mmol, 1.5 equiv.) and the aryl zinc chloride solution (1.5 mL, 0.75 mmol, 0.5 M in tetrahydrofuran, 1.5 equiv.). The reaction mixture was stirred overnight (18 h) at room temperature. The reaction was quenched with brine, extracted twice with ethyl acetate and the combined organic layers were washed with water, dried over $MgSO_4$, filtered, and concentrated under vacuum. The crude mixture was then purified by silica gel chromatography using ethyl acetate/petroleum ether (1/10 then 1/4) as eluent to afford the product.

3-(3-Methylthiophen-2-yl)cyclohexanone (3a):



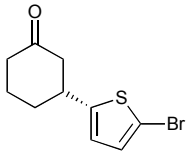
IR (ν_{max} (thin film)/cm^{-1}): 1709.5; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.73-1.90 (m, 2 H), 2.10-2.21 (m, 2 H), 2.16 (s, 3 H), 2.31-2.50 (m, 3 H), 3.26-3.37 (m, 1 H), 6.81 (d, *J* = 5.1 Hz, 1 H), 7.08 (d, *J* = 5.1 Hz, 1 H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 13.5, 25.5, 33.4, 38.4, 41.0, 49.6, 121.4, 130.1, 132.1, 141.6, 209.9; **HRMS** (ESI): calculated for $C_{11}H_{14}OS$ $[M+H]^+$ 195.0844, found 195.0830. **HPLC** (Chiracel OJ column, hexane:^{i}PrOH = 98:2, flow rate 1.0 mL/min), t_R 9.0 (major) and 11.7 (minor) min.

3-(Thiophen-2-yl)cyclohexanone (3b)[4]:



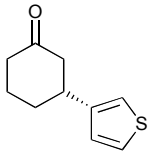
IR (ν_{max} (thin film)/cm^{-1}): 1712.0; **1H NMR** (300 MHz, $CDCl_3$): δ 1.71-1.94 (m, 2 H), 2.07-2.59 (m, 5 H), 2.69-2.79 (m, 1 H), 3.29-3.39 (m, 1 H), 6.84 (d, *J* = 1.4 Hz, 1 H), 6.94 (t, *J* = 3.5 Hz, 1 H), 7.18 (d, *J* = 3.9 Hz, 1 H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 24.9, 33.8, 39.7, 41.1, 49.4, 122.8, 123.3, 126.7, 148.3, 209.9; **HRMS** (ESI): calculated for $C_{10}H_{12}OS$ $[M+Na]^+$ 203.0507, found 203.0501. **HPLC** (Chiracel OJ column, hexane:^{i}PrOH = 98:2, flow rate 1.0 mL/min), t_R 11.1 (major) and 12.6 (minor) min.

3-(5-Bromothiophen-2-yl)cyclohexanone (3c):



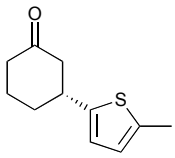
IR (ν_{max} (thin film)/cm^{-1}): 1711.5; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.68-1.88 (m, 2 H), 2.05-2.24 (m, 2 H), 2.28-2.53 (m, 3 H), 2.66-2.75 (m, 1 H), 3.20-3.30 (m, 1 H), 6.57-6.61 (m, 1 H), 7.87 (d, *J* = 3.7 Hz, 1 H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 24.7, 33.4, 40.0, 41.0, 48.9, 109.8, 123.3, 129.5, 149.9, 209.4; **HRMS** (ESI): calculated for $C_{10}H_{11}BrOS$ $[M+Na]^+$ 280.9612, found 280.9595. **HPLC** (Chiralpack AS column, hexane:^{i}PrOH = 98:2, flow rate 1.0 mL/min), t_R 21.7 (major) and 25.9 (minor) min.

3-(Thiophen-3-yl)cyclohexanone (3d)[5]:



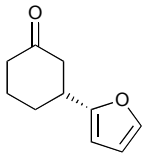
IR (ν_{max} (thin film)/cm^{-1}): 1711.4; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.69-1.89 (m, 2 H), 2.04-2.21 (m, 2 H), 2.30-2.55 (m, 3 H), 2.65-2.72 (m, 1 H), 3.11-3.21 (m, 1 H), 6.98-7.00 (m, 2 H), 7.28-7.31 (m, 1 H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 25.0, 32.4, 39.8, 41.2, 48.5, 119.5, 125.9, 126.4, 145.4, 210.7; **HRMS** (ESI): calculated for $C_{10}H_{12}OS$ $[M+Na]^+$ 203.0497, found 203.0506. **HPLC** (Chiralpack OD-H column, hexane:^{i}PrOH = 99:1, flow rate 0.5 mL/min), t_R 34.8 (minor) and 36.5 (major) min.

3-(5-Methylthiophen-2-yl)cyclohexanone (3e):



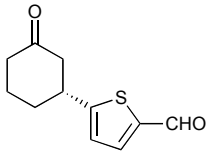
IR (ν_{max} (thin film)/cm^{-1}): 1710.6; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.72-1.89 (m, 2 H), 2.04-2.55 (m, 5 H), 2.68-2.75 (m, 1 H), 2.44 (s. 3H), 3.19-3.29 (m, 1 H), 6.57-6.60 (m, 1 H), 7.87 (d, *J* = 3.4 Hz, 1 H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 15.3, 24.8, 33.7, 39.8, 41.1, 19.3, 122.6, 124.6, 146.0, 210.1; **HRMS** (ESI): calculated for $C_{11}H_{14}OS$ $[M+Na]^+$ 217.0663, found 217.0666. [Not included in main text as could not fully resolve enantiomers by hplc]

3-(Furan-2-yl)cyclohexanone (3f)[4]:



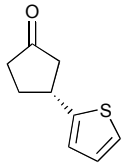
IR (ν_{max} (thin film)/cm^{-1}): 1710.4; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.68-2.19 (m, 4 H), 2.27-2.55 (m, 3 H), 2.63-2.70 (m, 1 H), 3.13-3.22 (m, 1 H), 6.00 (dm, *J* = 3.2 Hz, 1 H), 6.25-6.29 (m, 1 H), 7.30 (d, *J* = 1.8 Hz, 1 H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 24.4, 29.9, 37.5, 41.3, 45.6, 104.5, 110.0, 141.3, 157.1, 210.2; **HRMS** (ESI): calculated for $C_{10}H_{12}O_2$ $[M+Na]^+$ 187.0735, found 187.0728. **HPLC** (Chiralpack AS column, hexane:^{i}PrOH = 98:2, flow rate 1.0 mL/min), t_R 13.2 (minor) and 15.1 (major) min.

5-(3-oxocyclohexyl)thiophene-2-carbaldehyde (3g):



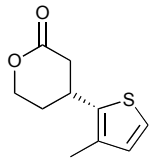
IR (ν_{max} (thin film)/cm^{-1}): 1664.3, 1722.3; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.70-1.93 (m, 2 H), 2.06-2.56 (m, 5 H), 2.68-2.76 (m, 1 H), 3.30-3.40 (m, 1 H), 6.93 (d, *J* = 3.8 Hz, 1 H), 7.60 (d, *J* = 3.8 Hz, 1 H), 9.81 (s, 1 H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 24.7, 33.3, 40.3, 40.8, 48.6, 124.6, 136.7, 141.8, 159.2, 182.7, 208.8; **HRMS** (ESI): calculated for $C_{11}H_{12}O_2S$ $[M+H]^+$ 209.0636, found 209.0629. [Not included in main text as could not fully resolve enantiomers by hplc]

3-(Thiophen-2-yl)cyclopentanone (4b)[4]:



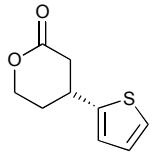
IR (ν_{max} (thin film)/cm^{-1}): 1742.6; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.97-2.08 (m, 1 H), 2.19-2.54 (m, 4H), 2.71 (dd, *J* = 18.3 Hz, 7.6 Hz, 1 H), 3.60-3.71 (m, 1 H), 6.84 (dm, *J* = 3.5 Hz, 1 H), 6.94 (t, *J* = 5.1 Hz, 1 H), 7.17 (dd, *J* = 5.1 Hz, 1.2 Hz, 1 H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 29.7, 32.1, 37.6, 38.5, 46.7, 123.2, 123.3, 126.8, 147.2, 217.4; **HRMS** (ESI): calculated for $C_9H_{10}OS$ $[M+Na]^+$ 189.0350, found 189.0333. **HPLC** (Chirapack AS column, hexane:^{i}PrOH = 99:1, flow rate 1.0 mL/min), t_R 24.7 (minor) and 26.2 (major) min.

4-(3-Methylthiophen-2-yl)tetrahydropyran-2-one (5a):



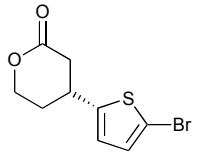
IR (ν_{max} (thin film)/cm^{-1}): 1728.7; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.95-2.08 (m, 1 H), 2.14-2.23 (m, 1 H), 2.18 (s, 3 H), 2.56 (dd, *J* = 17.6 Hz, 11.2 Hz, 1 H), 2.92 (ddd, *J* = 17.6 Hz, 5.8 Hz, 1.7 Hz, 1 H), 3.46-3.57 (m, 1 H), 4.39 (ddd, *J* = 11.6 Hz, 10.5 Hz, 3.8 Hz, 1 H), 4.48-4.55 (m, 1 H), 6.79 (d, *J* = 5.1 Hz, 1 H), 7.09 (d, *J* = 5.1 Hz, 1 H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 13.6, 30.8, 31.5, 38.2, 68.5, 121.9, 130.4, 133.0, 139.6, 169.9; **HRMS** (ESI): calculated for $C_{10}H_{12}O_2S$ $[M+H]^+$ 197.0636, found 197.0621. **HPLC** (Chiralcel OD-H column, hexane:^{i}PrOH = 90:10, flow rate 1.0 mL/min), t_R 20.8 (minor) and 24.6 (major) min.

4-(Thiophen-2-yl)tetrahydropyran-2-one (5b):



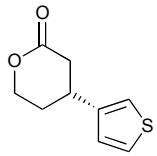
IR (ν_{max} (thin film)/cm^{-1}): 1729.0; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.97-2.15 (m, 1 H), 2.23-2.32 (m, 1 H), 3.01 (ddd, *J* = 17.6 Hz, 5.9 Hz, 1.6 Hz, 1 H), 3.46-3.57 (m, 1 H), 4.33-4.52 (m, 2 H), 6.85 (dm, *J* = 3.5 Hz, 1 H), 6.95 (t, *J* = 3.5 Hz, 1 H), 7.20 (d, *J* = 5.1 Hz, 1 H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 31.3, 33.0, 38.1, 68.2, 123.3, 123.9, 127.0, 146.2, 169.8; **HRMS** (ESI): calculated for $C_9H_{10}O_2S$ $[M+H]^+$ 183.0480, found 183.0469. **HPLC** (Chiralcel OD-H column, hexane:^{i}PrOH = 90:10, flow rate 1.0 mL/min), t_R 27.5 (minor) and 29.9 (major) min.

4-(5-Bromothiophen-2-yl)tetrahydropyran-2-one (5c):



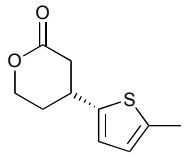
IR (ν_{max} (thin film)/cm^{-1}): 1728.5; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.93-2.08 (m, 1 H), 2.20-2.29 (m, 1 H), 2.63 (dd, *J* = 17.6 Hz, 10.3 Hz, 1 H), 2.98 (ddd, *J* = 17.6 Hz, 5.9 Hz, 1.6 Hz, 1 H), 3.38-3.49 (m, 1 H), 4.37 (ddd, *J* = 11.6 Hz, 10.0 Hz, 3.8 Hz, 1 H), 4.46-4.55 (m, 1 H), 6.61 (dm, *J* = 3.8 Hz, 1 H), 6.90 (d, *J* = 3.8 Hz, 1 H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 30.9, 33.3, 37.6, 68.0, 110.5, 123.8, 129.7, 147.8, 169.3; **HRMS** (ESI): calculated for $C_9H_9Br_1O_2S$ $[M+H]^+$ 260.9585, found 260.9554. **HPLC** (Chiralcel OD-H column, hexane:^{i}PrOH = 80:20, flow rate 1.0 mL/min), t_R 18.7 (minor) and 20.5 (major) min.

4-(Thiophen-2-yl)tetrahydropyran-2-one (5d)[5]:



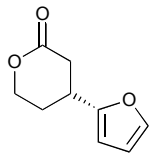
IR (ν_{max} (thin film)/cm^{-1}): 1731.4; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.93-2.06 (m, 1 H), 2.18-2.28 (m, 1 H), 2.63 (dd, *J* = 17.3 Hz, 10.2 Hz, 1 H), 2.96 (ddd, *J* = 17.7 Hz, 6.0 Hz, 1.5 Hz, 1 H), 3.30-3.41 (m, 1 H), 4.37 (dd, *J* = 9.8 Hz, 3.8 Hz, 1 H), 4.43-4.51 (m, 1 H), 6.98 (dd, *J* = 5.1 Hz, 1.5 Hz, 1 H), 7.02-7.04 (m, 1 H), 7.34 (dd, *J* = 5.1 Hz, 2.6 Hz, 1 H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 30.1, 32.9, 37.1, 68.4, 120.0, 126.0, 126.8, 143.6, 170.3; **HRMS** (ESI): calculated for $C_{10}H_{10}O_3S$ calculated for $C_9H_{10}O_2S_1$ $[M+Na]^+$ 205.0299, found 209.0282. **HPLC** (Chiralcel OD-H column, hexane:^{i}PrOH = 95:5, flow rate 1.0 mL/min), t_R 48.8 (minor) and 52.3 (major) min.

4-(5-Methylthiophen-2-yl)tetrahydropyran-2-one (5e)



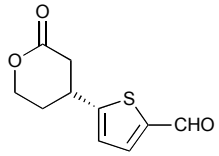
IR (ν_{max} (thin film)/cm^{-1}): 1728.6; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.94-2.07 (m, 1 H), 2.19-2.29 (m, 1 H), 2.44 (s, 3 H), 2.65 (dd, *J* = 17.3 Hz, 10.2 Hz, 1 H), 2.98 (ddd, *J* = 17.3 Hz, 6.0 Hz, 1.5 Hz, 1 H), 3.38-3.48 (m, 1 H), 4.36 (ddd, *J* = 11.7 Hz, 9.8 Hz, 3.8 Hz, 1 H), 4.44-4.51 (m, 1 H), 6.59 (m, 1 H), 6.63 (d, *J* = 3.8 Hz, 1 H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 15.2, 32.2, 33.1, 37.9, 68.2, 123.0, 124.8, 138.5, 143.9, 169.9; **HRMS** (ESI): calculated for $C_{10}H_{12}O_2S$ $[M+Na]^+$ 219.0443, found 219.0455. **HPLC** (Chiralcel OD-H column, hexane:^{i}PrOH = 94:6, flow rate 1.0 mL/min), t_R 28.7 (minor) and 30.4 (major) min.

4-(Furan-2-yl)tetrahydropyran-2-one (5f):



IR (ν_{max} (thin film)/cm^{-1}): 1710.3; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.98-2.10 (m, 1 H), 2.17-2.29 (m, 1 H), 2.70 (dd, *J* = 17.5 Hz, 9.2 Hz, 1 H), 2.91 (ddd, *J* = 17.6 Hz, 6.3 Hz, 1.1 Hz, 1 H), 3.32-3.42 (m, 1 H), 4.42-4.47 (m, 2 H), 6.09 (d, *J* = 3.2 Hz, 1 H), 6.32-6.53 (m, 1 H), 7.38 (d, *J* = 1.2 Hz, 1 H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 27.8, 31.0, 34.4, 67.9, 105.0, 110.2, 142.0, 155.4, 170.0; **HRMS** (ESI): calculated for $C_9H_{10}O_3$ $[M+H]^+$ 167.0708, found 167.0700. **HPLC** (Chiralcel OD-H column, hexane:^{i}PrOH = 90:10, flow rate 1.0 mL/min), t_R 26.1 (minor) and 27.2 (major) min.

5-(2-oxo-tetrahydro-*2H*-pyran-4-yl)thiophene-2-carbaldehyde (5g):



IR (ν_{max} (thin film)/cm^{-1}): 1713.1; **^{1}H NMR** (300 MHz, $CDCl_3$): δ 1.99-2.12 (m, 1 H), 2.25-2.35 (m, 1 H), 2.67 (dd, *J* = 17.5 Hz, 10.4 Hz, 1 H), 3.01 (ddd, *J* = 17.5 Hz, 5.9 Hz, 1.7 Hz, 1 H), 3.51-3.61 (m, 1 H), 4.43 (ddd, *J* = 11.6 Hz, 10.0 Hz, 3.8 Hz, 1 H), 4.48-4.55 (m, 1 H), 6.98 (dm, *J* = 3.8 Hz, 1 H), 7.64 (d, *J* = 3.8 Hz, 1 H), 9.82 (s, 1 H); **^{13}C NMR** (75 MHz, $CDCl_3$): δ 30.7, 33.7, 37.4, 67.9, 124.9, 136.7, 142.3, 156.8, 168.8, 182.6; **HRMS** (ESI): calculated for $C_{10}H_{10}O_3S$ $[M-H]^+$ 209.0272, found 209.0282. [Not included in main text as could not fully resolve enantiomers by hplc]

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