Supporting Information

A New Highly Asymmetric Chelation-Controlled Heck Arylation

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Experimental Section

General. ¹H- and ¹³C NMR spectra were obtained in CDCl₃ solution at 400 MHz and 100 MHz, respectively. Low resolution mass spectra were recorded on a GC-MS instrument equipped with a 25 m HP-1 capillary column operating at an ionization potential of 70 eV. The oven temperature was 40-315 °C (gradient 30 °C/min). Elemental analyses were performed by Mikro Kemi AB, Uppsala, Sweden or Analytische Laboratorien, Lindlar, Germany. Silica gel 60 (0.040-0.063 mm, E. Merck, no. 9385) was used for column chromatography. Enantiomeric purities were analyzed by chiral HPLC (*Chiracel OD-H* or *OB-H*; 0.46 × 25 cm, PS = 5 μm, degassed isohexane/2-propanol, flow rate 0.4 or 0.5 mL/min, detection at 220 nm) or chiral GC (25 m 6-O-TBDMS-2,3-di-O-methyl-β-cyclodextrin capillary at 140 °C from Macherey-Nagel). The chiral HPLC column was protected by a guard column (*Chiracel OD* 0.46 × 5 cm, PS = 10 μm). Optical rotation was measured in CHCl₃ (c = 1, T = 23 °C). All reactions were conducted under air in vials fitted with teflon-lined screw caps and all isolated compounds were >95% pure as deduced by GC-MS.

Materials. Palladium(II)acetate was obtained from Strem Chemicals. 2-Methylcyclopentanone **5**; trimethyl orthoformate; *N,N*-dimethylethanolamine; (*S*)-(-)-1-methyl-2-pyrrolidine-methanol, were purchased from Aldrich Co and used as received. All other reagents obtained from commercial sources were also used as received. Compounds **4a**, **4b**, **4d**, **4e**, are known compounds (with reported elemental analysis) and spectral data were in agreement with the proposed

structures. Synthesized compounds lacking elemental analysis in the literature or compounds without adequate spectroscopic characterization exhibited spectral and analytical properties as summarized below.

Synthesis of Dimethyl-[2-(2-methyl-cyclopent-1-enyloxy)-ethyl]-amine (1).

1,1-Dimethoxy-2-methyl-cyclopentane¹ (8.00 g) was added to a mixture of *N,N*-dimethylethanolamine (35.7 mmol, 3.17 g) and Me₃NHCl (42.8 mmol, 4.09 g). The oil-bath temperature was set to 130 °C and the mixture was slowly distilled by repeated addition of toluene (5 mL). The reaction was interrupted after two days when GC-MS analysis of the residue showed complete consumption of the amino alcohol. Addition of NaOH (5 M, 30 mL) and subsequent extraction with diethyl ether provided, after drying (K₂CO₃) and evaporation a red brown crude product. Purification on a large silica column (10 × 50 cm) using 95:5 hexane/triethylamine separated the two double bond isomers and provided pure **1** (1.65 g, 27%) as a colorless oil (second eluting isomer).

¹H NMR (400 MHz, CDCl₃) δ 3.81 (t, *J* = 6.0 Hz, 2H), 2.52 (t, *J* = 6.0 Hz, 2H), 2.38-2.30 (m, 2H), 2.26 (s, 6H), 2.18-2.12 (m, 2H), 1.82-1.73 (m, 2H), 1.56-1.52 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 149.9, 112.4, 67.1, 58.9, 45.9, 33.8, 29.4, 19.8, 11.8; MS (70 eV) *m/z* (relative intensity) 169 (M⁺, 2), 72 (63), 58 (100). Anal calcd for C₁₀H₁₉NO: C, 70.96; H, 11.31. Found: C, 70.82; H, 11.48.

(rac)-Dimethyl-[2-(5-methyl-cyclopent-1-enyloxy)-ethyl]-amine.

First eluting isomer (1.51 g, 25%). ¹H NMR (400 MHz, CDCl₃) δ 4.40-4.35 (m, 1H), 3.85-3.75 (m, 2H), 2.72-2.56 (m, 3H), 2.35-2.04 (m, 9H), 1.45-1.35 (m, 1H), 1.02 (d, *J* = 6.9 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 163.3, 92.9, 67.4, 58.1, 45.9, 38.4, 30.8, 27.1, 18.9; MS (70 eV) *m/z* (relative intensity) 169 (M⁺, 2), 72 (22), 58 (100). Anal calcd for C₁₀H₁₉NO: C, 70.96; H, 11.31. Found: C, 70.81; H, 11.44.

Synthesis of 1-Methyl-2-(S)-(2-methyl-cyclopent-1-enyloxymethyl)-pyrrolidine (6a).

2-Methylcyclopentanone (152.8 mmol, 15.0 g) and trimethylorthoformate (168.1 mmol, 17.8 g) were stirred with 4-toluenesulfonic acid monohydrate (0.764 mmol, 0.145 g) at 0 °C for 30 min. The reaction mixture was allowed to warm to room temperature and after another 30 min a distillation was performed to remove methyl formate at 45 °C. (*S*)-(-)-1-Methyl-2-pyrrolidine-methanol (50.9 mmol, 5.87 g) was dissolved in 15 mL toluene and precipitated with HCl (g). The slurry was transferred to the distillation residue and heated at 100 °C for 16 h. The oil-bath temperature was raised to 130 °C to facilitate a slow distillation. Toluene (15 mL), forming an azeotrope with methanol, was added once a day during 3 days. The distillation was stopped when GC-MS analysis of the residue showed complete consumption of the amino

alcohol. Addition of sodium hydroxide (10 M, 50 mL) and subsequent extraction with diethyl ether provided a red brown crude product after drying (K_2CO_3) and evaporation. Purification on a large silica column (10 × 50 cm) using 95:5 hexane/triethylamine separated the two double bond isomers (**6a** and **6b**) and provided pure **6a** (3.90 g, 39%) as a colorless oil (second eluting isomer). 1H NMR (400 MHz, $CDCl_3$) δ 3.77-3.71 (m, 1H), 3.63-3.57 (m, 1H) 3.05-2.98 (m, 1H), 2.47-2.27 (m, 6H), 2.23-2.10 (m, 3H), 1.97-1.88 (m, 1H), 1.81-1.49 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 111.7, 72.2, 64.9, 57.8, 41.7, 33.7, 29.5, 28.8, 22.9, 19.8, 11.7; MS (70 eV) m/z (relative intensity) 195 (M^+ , 1), 98 (19), 84 (100). Anal calcd for $C_{12}H_{21}NO$: C, 73.8; H, 10.8. Found: C, 73.5; H, 10.4. $[\alpha]_D^{23} = -47^\circ$

1-Methyl-2-(*S*)-(5-(*R,S*)-methyl-cyclopent-1-enyloxymethyl)-pyrrolidine (**6b**).

First eluting isomer (3.45 g, 35%). 1H NMR (400 MHz, $CDCl_3$) δ 4.39-4.33 (m, 1H), 3.75-3.50 (m, 2H) 3.07-2.99 (m, 1H), 2.65-2.45 (m, 2H), 2.44-2.37 (m, 3H), 2.25-1.50 (m, 8H), 1.41-1.30 (m, 1H), 1.05-0.95 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 163.3, 92.7, 92.7, 72.8, 72.0, 64.3, 64.1, 57.9, 57.8, 41.8, 41.6, 38.4, 30.9, 29.0, 28.5, 27.1, 23.1, 23.0, 18.9, 18.8; MS (70 eV) m/z (relative intensity) 195 (M^+ , 1), 42 (26), 84 (100). Anal calcd for $C_{12}H_{21}NO$: C, 73.80; H, 10.84. Found: C, 73.63; H, 11.01.

General Procedure for Heck Arylation of **1** and Subsequent Hydrolysis Producing **4**.

The reactants were added to a reaction vial in the following order: aryl iodide **2** (0.60 mmol), enol ether **1** (0.78 mmol, 0.132 g), $Pd(OAc)_2$ (0.018 mmol, 0.004 g), NaOAc (0.72 mmol, 0.059 g), LiCl (1.20 mmol, 0.051 g), K_2CO_3 (0.72 mmol, 0.100 g), DMF (2 mL) and water (0.2 mL). The tube was closed and the contents were magnetically stirred and heated for 1-7 days (**2a** 42 h, 70 °C, **2c** 72 h, 80 °C, **2e** 42 h, 70 °C). The reaction was interrupted when GC-MS analysis showed complete conversion. After cooling, 0.5 mL concd HCl was added and the contents stirred for 30 min. After complete hydrolysis of **3** (GC-MS) the reaction mixture was diluted with 10 mL 0.5 M HCl and extracted five times with diethyl ether. The ethereal phases were washed twice with 0.1 M NaOH and dried with $K_2CO_3(s)$. Evaporation of the solvent and silica column chromatography afforded pure products.

(*rac*)-2-(2-Methoxy-phenyl)-2-methyl-cyclopentanone (**4a**)²

Compound **4a** was obtained in 49% yield after silica column chromatography (hexane-diethyl ether, 70:30).

(rac)-2-Methyl-2-*o*-tolyl-cyclopentanone (4c)

Compound **4c** was obtained after silica column chromatography (hexane-diethyl ether, 95:5) in 49% yield.

(rac)-2-(3-Methoxy-phenyl)-2-methyl-cyclopentanone (4e)⁵

Compound **4e** was obtained in 57% yield after silica column chromatography (hexane-diethyl ether, 90:10).

General Procedure for the Asymmetric Heck Arylation of 6a and Subsequent

Hydrolysis Producing 4.

The reactants were added to a reaction vial in the following order: aryl iodide or aryl bromide **2** (0.60 mmol), enol ether **6a** (0.78 mmol, 0.152 g), Pd(OAc)₂ (0.018 mmol, 0.004 g), NaOAc (0.72 mmol, 0.059 g), LiCl (1.20 mmol, 0.051 g), K₂CO₃ (0.72 mmol, 0.100 g), DMF (2 mL) and water (0.2 mL). The tube was closed and the contents were magnetically stirred and heated for 1-3 days at 70-100 °C (Table 1). The reaction was interrupted when GC-MS analysis showed no further improvements in conversion. After cooling, 0.5 mL concd HCl was added and the contents stirred for 30 min. After full hydrolysis (GC-MS) the reaction mixture was diluted with 10 mL 0.5 M HCl and extracted five times with diethyl ether. The ethereal phases were washed twice with 0.1 M NaOH and dried with K₂CO₃(s). Evaporation of the solvent and silica column chromatography afforded pure products **4**.

(R)-2-(2-Methoxy-phenyl)-2-methyl-cyclopentanone (4a)²

Compound **4a** was obtained in 67% yield and 98% ee after silica column chromatography (hexane-diethyl ether, 70:30). HPLC OD-H (isohexane/2-propanol 99.5:0.5): t_r = 52 min (+), t_r = 57 min (-); flowrate = 0.4 mL/min. [α]_D²³ = +39°

(R)-2-Methyl-2-*p*-tolyl-cyclopentanone (4b)³

Compound **4b** was obtained in 54% yield and 93% ee after silica column chromatography (hexane-diethyl ether, 95:5). HPLC OD-H (isohexane/2-propanol 98:2): t_r = 18.2 min (+), t_r = 23.3 min (-); flowrate = 0.5 mL/min. [α]_D²³ = +88°

(R)-2-Methyl-2-*o*-tolyl-cyclopentanone (4c)

Compound **4c** was obtained in 50% yield and 94% ee after silica column chromatography (hexane-diethyl ether, 95:5). ¹H NMR (400 MHz, CDCl₃) δ 7.32-7.28 (m, 1H), 7.19-7.15 (m, 3H), 2.56-2.50 (m, 2H), 2.45-2.40 (m, 1H), 2.25 (s, 3H), 2.09-1.91 (m, 3H), 1.48 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 221.5, 141.4, 135.7, 132.4, 127.3, 127.1, 126.0, 53.9, 38.5, 36.9, 22.4, 22.1, 19.1; MS (70 eV) m/z (relative intensity) 188 (M⁺, 49), 132 (100), 117 (63). Anal calcd for C₁₃H₁₆O: C, 82.94; H, 8.57. Found: C, 82.70; H, 8.72. HPLC OD-H (isohexane/2-propanol 99.5:0.5): t_r = 41 min (+), t_r = 45 min (-); flowrate = 0.4 mL/min. [α]_D²³ = +60°

(R)-2-Methyl-2-phenyl-cyclopentanone (4d)⁴

Compound **4d** was obtained in 61% yield and 94% ee after silica column chromatography (hexane-diethyl ether, 95:5). HPLC OD-H (isohexane/2-propanol 99.5:0.5): t_r = 18.5 min (+), t_r = 22.7 min (-); flowrate = 0.5 mL/min. [α]_D²³ = +54°

(R)-2-(3-Methoxy-phenyl)-2-methyl-cyclopentanone (4e)⁵

Compound **4e** was obtained in 68% yield and 93% ee after silica column chromatography (hexane-diethyl ether, 90:10). Chiral GC 25 m capillary with 6-O-TBDMS-2,3-di-O-methyl-β-cyclodextrin at 140 °C. [α]_D²³ = +88°

(R)-2-Methyl-2-naphthalen-1-yl-cyclopentanone (4f)

Compound **4f** was obtained after silica column chromatography (hexane-diethyl ether, 95:5) in 49% yield and 91% ee via **2g** and 45% yield and 90% ee via **2f**. ¹H NMR (400 MHz, CDCl₃) δ 7.90-7.85 (m, 1H), 7.84-7.74 (m, 2H) 7.52-7.45 (m, 2H), 7.42-7.38 (m, 2H), 2.93-2.82 (m, 1H), 2.78-2.66 (m, 1H), 2.63-2.52 (m, 1H), 2.15-1.96 (m, 3H), 1.67 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 221.8, 139.0, 135.2, 130.4, 129.8, 128.4, 125.6, 125.5, 125.2, 125.2, 125.2, 54.2, 39.1, 36.9, 23.3, 19.0; MS (70 eV) m/z (relative intensity) 224 (M⁺, 69), 168 (50), 153 (100). Anal calcd for C₁₆H₁₆O: C, 85.7; H, 7.2. Found: C, 86.0; H, 7.4. HPLC OB-H (isohexane/2-propanol 90:10): t_r = 26 min (-), t_r = 29 min (+); flowrate = 0.5 mL/min. [α]_D²³ = +80° (via **2g**), [α]_D²³ = +77° (via **2f**)

(R)-2-(4-Benzoyl-phenyl)-2-methyl-cyclopentanone 4g

Compound **4g** was obtained after silica column (hexane-diethyl ether, 90:10) in 78% yield and 94% ee using 4-bromobenzophenone **2i** as starting material. ^1H NMR (400 MHz, CDCl_3) δ 7.81-7.74 (m, 4H), 7.61-7.55 (m, 1H), 7.51-7.44 (m, 4H), 2.60-2.52 (m, 1H), 2.43-2.36 (m, 2H), 2.13-1.86 (m, 3H), 1.43 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 220.1, 196.3, 147.7, 137.6, 136.0, 132.5, 130.4, 130.1, 128.4, 126.4, 53.3, 38.1, 37.8, 25.0, 18.9; MS (70 eV) m/z (relative intensity) 278 (M^+ , 38), 145 (100), 105 (57). Anal calcd for $\text{C}_{19}\text{H}_{18}\text{O}_2$: C, 82.0; H, 6.5. Found: C, 82.4; H, 6.7. HPLC OD-H (isohexane/2-propanol 95:5); t_r = 29 min (+), t_r = 33 min (-); flowrate = 0.5 mL/min. $[\alpha]_D^{23} = +45^\circ$

Synthesis of {4-[1-(R)-Methyl-2-(1-methyl-pyrrolidin-2-(S)-ylmethoxy)-cyclopent-2-enyl]-phenyl}-phenyl-methanone (7g).

The reactants were added to the reaction vial in the following order: 4-iodobenzophenone **2h** (0.60 mmol, 0.185 g), enol ether **6a** (0.78 mmol, 0.152 g), $\text{Pd}(\text{OAc})_2$ (0.018 mmol, 0.004 g), NaOAc (0.72 mmol, 0.059 g), LiCl (1.20 mmol, 0.051 g), K_2CO_3 (0.72 mmol, 0.100 g), DMF (2 mL) and water (0.2 mL). The vial was closed and the contents were magnetically stirred and heated for 24 h. After cooling, the reaction mixture was diluted with diethyl ether and was washed five times with NaOH (0.1 M). The combined aqueous phases were additionally extracted twice with diethyl ether. The ethereal phases were combined and dried with K_2CO_3 (s). Evaporation of the solvent and silica column chromatography (hexane/diethyl ether/triethylamine, 1:1:0.05) yielded 0.119 g pure product **7g** (53%).

^1H NMR (400 MHz, CDCl_3) δ 7.81-7.72 (m, 4H), 7.58-7.38 (m, 5H), 4.66-4.64 (m, 1H), 3.87-3.81 (m, 1H), 3.69-3.62 (m, 1H), 3.06-2.99 (m, 1H), 2.58-2.50 (m, 1H), 2.38 (s, 3H), 2.31-2.19 (m, 3H), 2.17-1.99 (m, 2H), 1.95-1.84 (m, 1H), 1.81-1.64 (m, 2H), 1.57-1.44 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 196.6, 163.0, 153.2, 138.0, 135.1, 132.2, 130.2, 130.1, 128.3, 126.2, 95.1, 73.1, 64.0, 57.8, 51.2, 41.7, 41.0, 29.0, 26.0, 25.2, 22.9; MS (70 eV) m/z (relative intensity) 375 (M^+ , 0.5), 84 (100), 42 (4). Anal calcd for $\text{C}_{25}\text{H}_{29}\text{NO}_2$: C, 79.96; H, 7.78. Found: C, 79.84; H, 7.67.

(R)-2-(4-Benzoyl-phenyl)-2-methyl-cyclopentanone (4g)

The enol ether **7g** (0.032 g) was carefully placed in a vial together with 1 mL concentrated HCl and 3 mL diethyl ether. The vial was closed and stirred at room temperature over night. The ether layer was separated and the acidic aqueous layer extracted three times with diethyl ether. The organic phases were combined and dried with K_2CO_3 (s). Evaporation of the solvent furnished 0.021 g pure product **4g** (88%) in 97% ee. $[\alpha]_D^{23} = +48^\circ$

Competitive Phenylation Experiment with **1** and **6a**

The reactants were added to the reaction vial in the following order: iodobenzene (0.80 mmol, 0.163 g), **1** (0.20 mmol, 0.034 g), **6a** (0.20 mmol, 0.039 g), Pd(OAc)₂ (0.012 mmol, 0.0027 g), LiCl (0.8 mmol, 0.0339 g), K₂CO₃ (0.48 mmol, 0.0664 g), NaOAc (0.48 mmol, 0.0394 g) and water (0.2 mL) in 2 mL of DMF. The reaction was heated at 50 °C for 45 h. After cooling, the reaction mixture was diluted with diethyl ether and washed five times with NaOH (0.1 M). The combined aqueous phases were additionally extracted twice with diethyl ether. The ethereal phases were combined and dried with K₂CO₃ (s). Evaporation of the solvent afforded a clear yellow oil. Crude H NMR was taken. The ratio between **3d** and **7d** was determined to 50/50 by integration.

Proposed Structure of π -Complex **D**

Intermediate **D** was constructed from a low energy conformation of the enol ether **6a** and a σ -phenylpalladium(II) complex. The in-plane and metal-chelating geometry was selected to allow the four-center transition state for the migratory insertion affording Heck product **7d**.⁶ Furthermore, the nitrogen-palladium and sp²-carbon-palladium distances were adjusted to agree with related reported X-ray structures.^{6b,7} Principal bond lengths of the proposed π -intermediate **D** in Chart 1 were Pd-N (2.18 Å), Pd-C(-O) (2.27 Å), Pd-C(-CH₃) (2.16 Å).

Diastereoselectivity

Small amounts of the diastereoisomers (*S,S*)-**7a-g** were produced in the arylations (Table 1). As deduced from modeling the complex **E** in Chart 2 seems to be the most reasonable structure of a N-coordinated complex that could deliver (*S,S*)-**7d**. However, this highly distorted π -intermediate with a mean Pd-C(-O) distance of ~2.8 Å (considerably longer than the corresponding bonds in the X-ray π -structures reported in the literature^{6b,7}) is not expected to undergo a facile *Re*-face insertion, unless the Pd-N distance is strongly truncated (Chart 2).

Clearly, the metal is not positioned above the double bond, but above the methyl substituted sp²-carbon in a canonical form.^{7c} We therefore suggest that it is more likely that the minor diastereoisomers (*S,S*)-**7a-g** are results of non-chelated insertions.

Chart 2. Complex E.

References and Notes for the Supporting Information

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