High Yielding Direct Intramolecular Arylation Reactions of Inactivated Arenes with Aryl Chlorides

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Supporting Information

General Methods:

All experiments were carried out under an atmosphere of nitrogen. ^1H and ^{13}C NMR were recorded in CDCl_3 or $(\text{CD}_3)_2\text{O}$ solutions using a Bruker AVANCE 300 spectrometer with Me_4Si as an internal standard. High-resolution mass spectra were obtained on a Kratos Concept IIH. Infra-Red analysis was performed with a Bruker EQUINOX 55. HPLC Grade THF, Et_2O , benzene, toluene and CH_2Cl_2 are dried and purified via MBraun SP Series solvent purification system. Triethylamine was freshly distilled from NaOH before every use. Dimethylacetamide was degassed with N_2 before every use. Imidazolium salts were either synthesized according to literature procedures, as described in the supporting information, or purchased from Strem and used without further purification and stored in a dessicator and were weighed out to air unless otherwise specified. Palladium, copper and NHC-Pd complexes were stored in a dessicator and were weighed out to air unless otherwise specified. All other reagents and solvents were used as is from commercial sources. Unless noted below, all other compounds have been reported in the literature or are commercially available.

Tables of Content

Synthesis and characterization of unknown NHC-Pd complexes	S2
General procedures and characterization for unknown starting materials	S6
General procedure and characterization for unknown products	S9
General procedure for Stille reaction using NHC-Pd complex	S10

PdCl_2 (0.25mmol), iPrHCl (0.505mmol) and Cs_2CO_3 (2.5mmol) were weighed out to air and placed in a 50mL round bottom flask. The flask was fitted with a condenser and then purged with nitrogen. THF (25mL) was then added via syringe and the reaction was refluxed overnight.

Heating was discontinued and volatiles were evaporated under reduced pressure. The residue was then purified by silica gel chromatography using 1:1 CH_2Cl_2 :hexane affording an off-white solid in 51% yield. Single crystals of the complex were then grown from slow evaporation of a saturated ether solution. Crystal structure deposited to the Cambridge Crystallographic Data Center – CCDC 261497

^1H NMR (300MHz, CDCl_3 , 293K, TMS): 0.87 (24H, d, $J=7\text{Hz}$), 0.93 (24H, d, $J=7\text{Hz}$), 2.90 (8H, sept, $J=7\text{Hz}$), 6.71 (4H, s), 7.78 (8H, d, $J=8\text{Hz}$), 7.33 (2H, s), 7.36 (4H, t, $J=8\text{Hz}$);

^{13}C NMR (75MHz, CDCl_3 , 293K, TMS): 22.9, 26.0, 28.1, 123.7, 129.1, 136.3, 146.4, 172.5;

$\text{Pd}(\text{OAc})_2$ (0.25mmol), $i\text{PrHCl}$ (0.505mmol) and were weighed out open to air and placed in a 50mL round bottom flask. The flask was fitted with a condenser and purged with nitrogen. THF (25mL) was then added via syringe and the reaction was refluxed overnight. Heating was discontinued and the volatiles were evaporated under reduced pressure. The residue was then

purified by silica gel chromatography using 1:1 CH_2Cl_2 :hexane affording a pale yellow solid in 71% yield. Single crystals of the complex were then grown from slow evaporation of a saturated DCM/Hexane solution. Crystal structure deposited to the Cambridge Crystallographic Data Center – CCDC 261499

^1H NMR (300MHz, CDCl_3 , 293K, TMS): 0.83 (6H, d, $J=6.9\text{Hz}$), 0.91 (6H, d, $J=6.6\text{Hz}$), 1.01 (18H, m), 1.22(18H, m), 2.43 (2H, sept, $J=6.8\text{Hz}$), 2.73 (2H, sept, $J=6.8\text{Hz}$), 3.14 (4H, sept, $J=6.8\text{Hz}$), 6.52 (1H, d, $J=1.4$), 6.89 (2H, s), 7.08 (2H, d, $J=7.7\text{Hz}$), 7.22 (6H, t, $J=7.7\text{Hz}$), 7.38 (4H, m), 7.53 (1H, d, $J=1.4\text{Hz}$);

^{13}C NMR (75MHz, CDCl_3 , 293K, TMS): 22.8, 23.2, 24.7, 24.8, 26.0, 26.5, 28.0, 28.1, 28.3, 123.4, 123.6, 123.6, 124.0, 124.1, 126.1, 129.2, 129.4, 130.5, 131.4, 133.0, 134.8, 136.2, 145.9, 146.3, 146.5, 152.3, 178.0;

Prepared from corresponding iMes chloride dimer¹ using a method adapted from the Sigman protocol using AgOAc in reagent grade CH₂Cl₂.² Single crystals were grown by slow evaporation of a saturated hexanes/dichloromethane solution. Crystal structure deposited to the Cambridge Crystallographic Data Center – CCDC 261498

¹H NMR (300MHz, CDCl₃, 293K, TMS): 1.69 (6H, s), 2.16 (12H, s), 2.42 (6H, s), 7.05 (2H, s), 7.08 (4H, s);

¹³C NMR (75MHz, CDCl₃, 293K, TMS): 17.6, 21.2, 23.3, 123.5, 129.4, 134.4, 135.6, 139.7, 149.6, 181.5;

Prepared from corresponding the SiPr chloride dimer³ using a method adapted from the Sigman protocol using AgOAc in reagent grade CH₂Cl₂.² Single crystals were grown by slow evaporation of a saturated hexanes/dichloromethane solution. Crystal structure deposited to the Cambridge Crystallographic Data Center – CCDC 261500

¹H NMR (300MHz, CDCl₃, 293K, TMS): 1.26 (12H, d, *J*=6.7Hz), 1.43 (12H, d, *J*=6.7Hz), 1.75 (6H, s), 3.25 (4H, sept, *J*=6.7Hz), 4.05 (4H, s), 7.36 (4H, d, *J*=7.7Hz), 7.49 (2H, t, *J*=7.7Hz);

¹³C NMR (75MHz, CDCl₃, 293K, TMS): 23.9, 24.6, 26.4, 28.5, 53.6, 124.8, 129.8, 134.4, 147.0, 182.0, 183.0

Starting Materials

Complexes **3-IPr**¹, **4-IPr**¹, **4-SIPr**³, **5-IPr**² and **7**⁴ were previously reported.

Compounds **1**⁵, **11**⁶, **13**⁷, **17**⁸, **20**⁹, **23**¹⁰, **25**¹¹, exhibited spectral data identical to that reported in the literature.

General Procedure for the Synthesis of Compounds **11**, **13** and **15**:

The appropriate phenol or methanesulfonaniline (2 equiv.), K₂CO₃ (3 equiv.) and NaI (0.5 equiv.) were placed in a round bottom flask equipped with a magnetic stir bar. Reagent grade acetone was added (0.5M) and the flask was fitted with a reflux condenser. Addition of the 2-chlorobenzylchloride (1 equiv.) was followed by heating (50°C) of the reaction overnight. The reaction was allowed to cool and was extracted using Et₂O/Brine. The organics were dried using MgSO₄, filtered and the volatiles were evaporated under reduced pressure. The residues were then purified via column chromatography using ethyl acetate/hexanes mixtures.

N-(2-Chloro-benzyl)-*N*-phenyl-methanesulfonamide

¹H NMR (300MHz, CDCl₃, 293K, TMS): 2.99 (3H, s), 5.03 (2H, s), 7.26 (8H, m), 7.49 (1H, m);

¹³C NMR (75MHz, CDCl₃, 293K, TMS): 37.9, 51.8, 127.0, 128.1, 128.3, 129.0, 129.4, 130.3, 133.3, 133.7, 139.1;

IR (ν_{max} /cm⁻¹): 3065(w), 1595(w), 1492(m), 1342(s), 1154(s), 1048(m), 873(m);

HRMS calculated for C₁₄H₁₄ClNO₂S (M⁺) 295.0403; Found: 295.0415

m.p. = 98-99°C (EtOAc/Hex)

Indole (1 equiv.) and crushed KOH (4 equiv.) were placed in a round bottom flask equipped with a magnetic stir bar. DMSO was added (0.5M) and the reaction was left stirring at room temperature for 30 minutes. The appropriate benzyl chloride was then

1-(2-Chloro-benzyl)-1*H*-indole added in one portion and the reaction was left stirring at room temperature for 2 hours. The reaction mixture was then extracted with H₂O and Et₂O. The organics were washed with NH₄Cl and re-extracted with Et₂O and the organic residue was dried over MgSO₄ and evaporated under reduced pressure. The product was purified by silica gel column chromatography using hexanes as the eluent.

¹H NMR (300MHz, CDCl₃, 293K, TMS): 5.34 (2H, s), 6.52 (1H, dd, *J*=7.7 & 0.5Hz), 6.56, (1H, dd, *J*=3.2 & 0.7Hz), 7.00 (1H, td, *J*=7.5 & 1.2Hz), 7.15 (5H, m), 7.36, (1H, dd, *J*=7.9 & 1.2Hz);

¹³C NMR (75MHz, CDCl₃, 293K, TMS): 48.1, 105.5, 110.1, 120.2, 121.6, 122.4, 127.7, 128.4, 128.9, 129.1, 129.3, 129.4, 132.8, 135.6, 136.7;

IR ($\nu_{\max}$ /cm⁻¹): 3057(s), 2925(m), 1574(m), 1462(s), 1319(s), 1050(s), 740(s)

HRMS calculated for C₁₅H₁₂ClN (M⁺) 241.0658; Found: 241.0652

1-(2-(2-chlorophenyl)ethynyl)-4-methoxybenzene

4-Iodoanisole (1.05 equiv.), CuI (0.02 equiv.) and Pd(PPh₃)Cl₂ (0.02 equiv.) were weighed to open air and placed in a round bottom flask equipped with a magnetic stir bar.

The flask was purged with nitrogen and THF (0.2M) and NEt₃ (5% volume to THF) were added. To this stirring mixture was added 2-chlorophenylacetylene dropwise and the reaction was allowed to stir overnight under positive nitrogen pressure. The volatiles were then evaporated under reduced pressure and the residue was extracted using EtOAc/Et₂O/Brine. The organics were dried using MgSO₄, filtered and the volatiles were evaporated under reduced pressure. The residue was then purified via silica gel column chromatography using hexane to afford the diarylacetylene.

¹H NMR (300MHz, CDCl₃, 293K, TMS): 3.84 (s, 3H), 6.87-6.92 (m, 2H), 7.22-7.25 (m, 2H), 7.41-7.44 (m, 1H), 7.49-7.51 (m, 1H), 7.53-7.56 (m, 2H);

¹³C NMR (75MHz, CDCl₃, 293K, TMS): 55.3, 94.7, 114.0, 115.0, 123.5, 126.4, 128.9, 129.2, 133.0, 133.2, 135.7;

IR ($\nu_{\max}$ /cm⁻¹): 2954(s), 2925(s), 2854(s), 1458(m);

HRMS calculated for C₁₅H₁₁ClO (M⁺): 242.0498; Found: 242.0488;

m.p. = 65–66°C (ether)

19

1-(2-chlorophenethyl)-4-methoxybenzene

The 1-(2-(2-chlorophenyl)ethynyl)-4-methoxybenzene (1 equiv.) and *p*-toluenesulfonylhydrazine (20 equiv.) were then dissolved in DME (0.1M) and heated to 85°C. To this stirring mixture was added a solution of NaOAc (20 equiv.) in

water over 8 hours via syringe pump. The reaction was stirred for an additional 4 hours and the heat source was removed. The reaction mixture was then extracted with hexane/ethyl acetate and brine. The organic extracts were dried using MgSO₄, and concentrated under reduced pressure. Purification was done by flash chromatography using hexanes.

¹H NMR (300MHz, CDCl₃, 293K, TMS): 2.82-2.88 (m, 2H), 2.96-3.02 (m, 2H), 3.79 (s, 3H), 6.81-6.86 (m, 2H), 7.11-7.17 (m, 5H), 7.34-7.37 (m, 1H);

¹³C NMR (75MHz, CDCl₃, 293K, TMS): 35.1, 36.1, 55.2, 113.7, 126.7, 127.4, 129.4, 129.4, 130.5, 133.6, 133.9, 139.3, 157.8;

IR (ν_{max} /cm⁻¹): 2933 (w), 2834 (w), 1512 (s), 1246 (s), 1037 (m);

HRMS calculated for C₁₅H₁₅ClO (M⁺): 246.0811; Found: 246.0811

General Procedure for synthesis of aryl amines 25, 27 and 29:

Diarylamines were synthesized using the appropriate 2-chloroaniline and iodobenzene using amination conditions described by Buchwald.¹²

(2-Chloro-4-fluoro-phenyl)-phenyl-amine

¹H NMR (300MHz, CDCl₃, 293K, TMS): 5.87 (s, 1H), 6.89 (td, J = 8.6 Hz & 2.7 Hz, 1H), 7.01 (t, 1H), 7.08 (d, 2H), 7.14 (dd, J=8.1 Hz & 2.7 Hz, 1H), 7.21-7.33 (m, 3H);

¹³C NMR (75MHz, CDCl₃, 293K, TMS): 114.2, 114.5, 116.7, 117.0, 117.3, 117.5, 119.1, 122.2, 129.5, 129.5;

IR (ν_{max} /cm⁻¹): 3412 (m), 1599 (s), 1516 (s), 1478 (s), 860 (m);

HRMS calculated for C₁₂H₉ClFN (M⁺): 221.0408; Found: 221.0389

(2-Chloro-5-trifluoromethyl-phenyl)-phenyl-amine

¹H NMR (300MHz, CDCl₃, 293K, TMS): 6.25 (s, 1H), 7.00-7.03 (m, 1H), 7.11-7.21 (m, 3H), 7.35-7.46 (m, 4H);

¹³C NMR (75MHz, CDCl₃, 293K, TMS): 110.9 (q, J=3.9 Hz), 116.2 (q, J=3.9 Hz), 121.3, 123.8 (q, J=273.1 Hz), 124.0, 129.8, 130.0 (q, J=32.5 Hz), 130.1, 140.1, 141.1;

IR (ν_{max} /cm⁻¹): 2855 (s), 1454 (s), 1065 (m);

HRMS calculated for C₁₃H₉ClF₃N (M⁺): 271.0376; Found: 271.0377

Products

Compounds **2**¹³, **12**¹⁴, **16**¹⁵, **18**¹⁶, **22**¹⁷, **24**¹⁸, **26**¹⁹ exhibited spectral data identical to that reported in the literature.

General procedure for intramolecular direct arylation:

Crushed K₂CO₃ (0.72mmol), substrate (0.36mmol), iPr-HCl (0.0036mmol) and complex **5-iPr** (0.0036mmol) were placed in a 2mL screw-cap vial equipped with a magnetic stir. The vial was purged with nitrogen and 1.8mL of *N,N*-dimethylacetamide (DMA) was added. The reaction was heated to 130°C overnight. After the reaction was judged complete by TLC or GC/MS analysis, the heat source was removed and the reaction mixture was allowed to cool. The crude mixture was then loaded directly onto silica and purified by flash chromatography using ethyl acetate/hexanes mixtures as the eluent.

¹H NMR (300MHz, CDCl₃, 293K, TMS): 5.27 (s, 2H), 7.06 (d, *J*=9 Hz, 1H), 7.20 (d, *J*=7.5 Hz, 1H), 7.42 (m, 2H), 7.80 (d, *J*=7.8 Hz, 1H), 8.13 (dd, *J*=9.0 Hz & 2.7 Hz, 1H), 8.65 (d, *J*=2.7 Hz, 1H);

¹³C NMR (75MHz, CDCl₃, 293K, TMS): 68.8, 118.0, 119.3, 122.4, 123.0, 124.8, 125.0, 127.9, 129.0, 129.1, 130.3, 142.6, 142.6, 159.8;

IR (ν_{max}/cm⁻¹): 2954 (s), 2924 (s), 2854 (s), 1339 (m);

HRMS calculated for C₁₃H₉NO₃ (M⁺): 227.0580; Found: 227.0582

m.p. = 158-159°C (EtOAc/Hex)

¹H NMR (300MHz, CDCl₃, 293K, TMS): 7.12-7.25 (m, 2H), 7.35 (dd, *J*=8.7 Hz & 4.5 Hz, 1H), 7.44 (d, *J*=3.6 Hz, 2H), 7.73 (dd, *J*=9.0 Hz & 2.7 Hz, 1H), 8.03 (d, *J*=7.8 Hz, 2H);

¹³C NMR (75MHz, CDCl₃, 293K, TMS): 105.8, 106.1, 109.3, 110.8, 111.0, 111.1, 113.4, 113.8, 119.4, 120.5, 126.4;

IR (ν_{max}/cm⁻¹): 3418 (m), 2925 (s), 2854 (s), 1457 (s), 1168 (m);

HRMS calculated for C₁₂H₈FN (M⁺): 185.0641; Found: 185.0632

m.p. = 211-212°C (EtOAc/Hex)

¹H NMR (300MHz, (CD₃)O, 293K, TMS): 7.26 (1H, t, *J*=7.4Hz), 7.50 (2H, m), 7.60 (1H, m), 7.89 (1H, s), 8.21 (1H, d, *J*=7.8Hz), 8.30 (1H, d, *J*=8.1Hz), 10.57 (1H, s, broad)

¹³C NMR (75MHz, (CD₃)O, 293K, TMS): 109.9 (q, *J*=4.3Hz), 113.2, 117.0 (q, *J*=3.7Hz), 121.4, 122.6, 122.7, 123.9, 127.2 (q, *J*=271.1Hz), 127.7, 128.5 (q, 31.6Hz), 128.9, 141.0, 143.0;

IR (ν_{max} /cm⁻¹): 3418 (m), 2925 (s), 2854 (s), 1457 (s), 1168 (m);

HRMS calculated for C₁₃H₈F₃N (M⁺): 235.0609; Found: 235.0589

m.p. = 210-211°C (EtOAc/Hex)

General Procedure for Stille Reaction:

CsF (2 equiv.), iPr-Pd complex **5** (0.05 equiv.) and iPr-HCl (0.05 equiv.) are placed in a 5mL round bottom flask equipped with reflux condenser, magnetic stir bar and rubber septa. The vessel is purged with argon. Dioxane (1M), 1,3-dimethoxybenzene (1 equiv. *internal standard*), *p*-chlorotoluene (1 equiv.) and phenyl(trimethyltin) (1.1 equiv.) are added via syringe and the reaction is heated to 100°C for 12 hours. Aliquot are then taken via syringe and conversion to **31**²⁰ was determined via GC/MS analysis.

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