

Supplementary Materials: Aziridine- and Azetidine-Pd Catalytic Combinations. Synthesis and Evaluation of the Ligand Ring Size Impact on Suzuki-Miyaura Reaction Issues

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S1. Materials and Methods

Unless otherwise noted, all starting materials were obtained from commercial suppliers and used without purification. Petroleum ether was distilled under Argon. NMR spectra were recorded on a 300 MHz and 200 MHz Bruker spectrometers (Bruker BioSpin GmbH, Rheinstetten, Germany). Chemical shifts were reported in ppm relative to the residual solvent peak (7.27 ppm for CHCl_3) for ^1H spectra and (77.00 ppm for CDCl_3) for ^{13}C spectra. High Resolution Mass spectroscopy data were recorded on an Autospec Ultima (Waters/Micromass) device (Waters, Gyancourt, France,) with a resolution of 5000 RP at 5%. Thin-layer chromatography (TLC) was carried out on aluminium sheets precoated with silica gel 60 F254. Column chromatography separations were performed using silica gel (0.040–0.060 mm). (*N*-benzyl)-2-cyanoazetidone **1** and (*N*-benzyl)-2-cyanoaziridine **2** have been prepared according to references [24,25]

S1.1. General Procedure for Addition/Reduction Sequence

The phenylmagnesium chloride (2 mmol) was added to a solution of 2-cyanoderivative **1** or **2** (1 mmol) in dry THF (10 mL) at 0 °C under argon. After stirring for 20 min, MeOH (10 mL) and NaBH_4 (1.2 mmol) were successively added. After a further 1 h, the reaction was quenched with saturated aqueous NH_4Cl solution (5 mL), and extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine, dried with magnesium sulfate and concentrated under reduced pressure. Amines **3** and **4** were purified by silica gel column chromatography using cyclohexane/Et₂O 1:1 as the eluant.

Synthesis of azetidone **3**. ^1H NMR (300 MHz, CDCl_3) δ (ppm): 1.71 (m, 1H), 1.94 (brs, 2H, NH_2), 2.18 (quint., $J = 9.2$ Hz, 1H), 2.66 (m, 1H), 3.16–3.31 (m, 4H), 3.69 (d, $J = 5.2$ Hz, 1H), 7.11–7.26 (m, 10H). ^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 18.8, 51.1, 57.8, 62.4, 71.8, 127.1, 127.2, 127.3, 128.4, 128.5, 128.9, 138.6, 142.9. SM-HR (ESI, m/z): $[M + \text{H}]^+$ calcd for $\text{C}_{17}\text{H}_{21}\text{N}_2$: 253.1705; found: 253.1698.

Synthesis of aziridine **4**. ^1H NMR (300 MHz, CDCl_3) δ (ppm): 1.25 (d, $J = 6.4$ Hz, 1H), 1.62 (m, 1H), 1.79 (d, $J = 3.5$ Hz, 1H), 1.89 (brs, 2H, NH_2), 3.13 (d, $J = 13.3$ Hz, 1H), 3.33 (d, $J = 13.3$ Hz, 1H), 3.71 (d, $J = 5.4$ Hz, 1H), 7.07–7.19 (m, 10H). ^{13}C NMR (75 MHz, CDCl_3) δ (ppm): 30.9, 45.2, 56.0, 64.1, 126.6, 126.8, 127.0, 127.8, 128.0, 128.1, 138.8, 143.4. SM-HR (ESI, m/z): $[M + \text{H}]^+$ calcd for $\text{C}_{16}\text{H}_{18}\text{N}_2$: 239.1548; found: 239.1540.

S1.2. General Complexation Procedure

To a stirred solution of ligand **1–4** (0.25 mmol) in 5 mL of freshly distilled MeOH was added Na_2PdCl_4 (74 mg, 0.25 mmol). The mixture was stirred at room temperature for 1 to 16 h and filtered over a celite pad. The filtrate was removed by evaporation under vacuum. The residue was then purified over silica gel pad eluting first with cyclohexane/EtOAc 7:3 to remove traces of free ligand, then with EtOAc for ligands **3** and **4** and with AcOEt/MeOH 95:5 for ligands **1** and **2**. Complexes may be obtained as mixtures of diastereomers due to heterocyclic nitrogen lone pair inversion during complexation process.

Complex A. ^1H NMR (300 MHz, DMSO- d_6) δ (ppm): 1.86 (m, 1H), 2.89 (m, 1H), 3.20 (quint., $J = 9.9$ Hz, 1H), 3.44–3.56 (m, 2H), 4.14 (t, $J = 8.1$ Hz), 4.28 (m, 1H), 4.57 (d, $J = 11.6$ Hz, 1H), 5.49 (m, 1H, NH), 5.67 (t, $J = 11.0$ Hz, 1H, NH), 7.15 (d, $J = 7.7$ Hz, 2H), 7.26–7.32 (m, 3H), 7.57–7.64 (m, 3H), 8.29 (d, $J = 6.4$ Hz, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ (ppm): 17.3, 59.4, 63.8, 64.2, 75.0, 127.3, 128.4, 128.9, 129.2, 129.5, 132.0, 134.6, 135.2. SM-HR (ESI, m/z): $[\text{M}-\text{Cl}-\text{HCl}]^+$ calcd for $\text{C}_{17}\text{H}_{19}\text{N}_2\text{Pd}$: 357.0590; found: 357.0595.

Complex B. ^1H NMR (300 MHz, DMSO- d_6) δ (ppm): 2.67 (dd, $J = 2.1$ et 7.3 Hz, 1H), 2.79 (d, $J = 13.0$ Hz, 1H), 2.99 (m, 1H), 3.55 (dd, $J = 2.1$ and 5.2 Hz, 1H), 4.33 (m, 1H), 4.72 (d, $J = 13.0$ Hz, 1H), 5.02 (t, $J = 10.5$ Hz, 1H, NH), 5.39 (m, 1H, NH), 7.34–7.36 (m, 3H), 7.43–7.51 (m, 5H), 7.93–7.96 (m, 2H). ^{13}C NMR (75 MHz, DMSO- d_6) δ (ppm): 38.6, 48.3, 60.9, 61.2, 128.2, 128.6, 128.9, 129.0, 129.1, 130.4, 136.0, 136.2. SM-HR (ESI, m/z): $[\text{M}-\text{Cl}-\text{HCl}]^+$ calcd for $\text{C}_{16}\text{H}_{17}\text{N}_2\text{Pd}$: 343.0433; found: 343.0434.

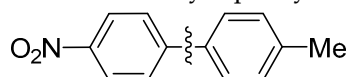
Complex C. ^1H NMR (300 MHz, DMSO- d_6) δ (ppm): 2.62 (m, 1H), 2.96 (quint., $J = 9.6$ Hz, 1H), 3.56 (d, $J = 11.8$ Hz, 1H), 3.65 (m, 4H), 4.18 (m, 1H), 4.28 (d, $J = 11.8$ Hz, 1H), 5.05 (t, $J = 8.6$ Hz, 1H), 7.47–7.53 (m, 3H), 8.07 (dd, $J = 1.9$ and 7.7 Hz, 2H), 8.37 (brs, 1H, NH). ^{13}C NMR (75 MHz, DMSO- d_6) δ (ppm): 22.6, 57.4, 59.4, 64.5, 71.2, 129.1, 129.4, 131.9, 134.0, 177.8. SM-HR (ESI, m/z): $[\text{M}-\text{Cl}-\text{HCl}]^+$ calcd for $\text{C}_{12}\text{H}_{15}\text{N}_2\text{OPd}$: 309.0024; found: 306.0238.

Complex D. ^1H NMR (300 MHz, DMSO- d_6) δ (ppm): 2.71 (d, $J = 12.9$ Hz, 1H), 2.89 (d, $J = 7.7$ Hz, 1H), 3.52 (d, $J = 4.2$ Hz, 1H), 3.86–3.89 (m, 4H), 4.62 (d, $J = 12.9$ Hz, 1H), 7.46–7.53 (m, 3H), 7.90 (d, $J = 7.5$ Hz, 2H), 8.43 (brs, 1H, NH). ^{13}C NMR (75 MHz, DMSO- d_6) δ (ppm): 44.4, 44.9, 58.1, 61.0, 129.0, 129.1, 130.9, 135.3, 175.3. SM-HR (ESI, m/z): $[\text{M}-\text{Cl}-\text{HCl}]^+$ calcd for $\text{C}_{11}\text{H}_{13}\text{N}_2\text{OPd}$: 295.0067; found: 295.0073.

S1.3. General Suzuki Coupling Procedure

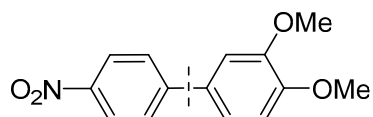
To a stirred solution of aromatic halide (0.5 mmol), boronic acid (0.6 mmol) and Cs_2CO_3 (407 mg, 1.25 mmol) in 1 mL of DMF/ H_2O (95:5) was added the palladium complex as a solid or in solution in DMF/ H_2O (95:5). The mixture was stirred at room temperature or 100 °C (refer to Table 1). 10 mL of EtOAc and 10 mL of water were then added and the aqueous phase was extracted with EtOAc (3×5 mL). The combined organic layers were dried (MgSO_4), filtered and concentrated under vacuum, the crude product was purified by flash chromatography on silica gel to give the biaryl product.

4-Nitro-4'-methylbiphenyl



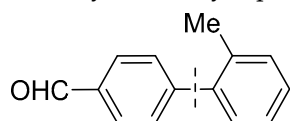
^1H NMR (200 MHz, CDCl_3) δ (ppm) 2.44 (s, 3H), 7.32 (d, $J = 8.0$ Hz, 2H), 7.54 (d, $J = 8.0$ Hz, 2H), 7.72 (d, $J = 9.0$ Hz, 2H), 8.28 (d, $J = 9.0$ Hz, 2H). Data in accordance with previously reported results [26].

2,4-Dimethoxy-4'-nitrobiphenyl



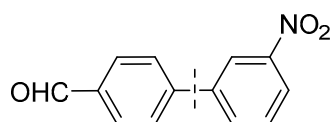
^1H NMR (200 MHz, CDCl_3) δ (ppm) 3.84 (s, 3H), 3.88 (s, 3H), 6.61 (m, 2H), 7.28 (d, $J = 8.8$ Hz, 1H), 7.67 (d, $J = 8.3$ Hz, 2H), 8.23 (d, $J = 8.3$ Hz, 2H). Data in accordance with previously reported results [27].

4-Formyl-2'-methylbiphenyl



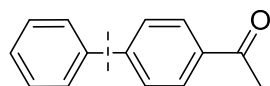
^1H NMR (200 MHz, CDCl_3) δ (ppm) 2.30 (s, 3H), 7.25–7.33 (m, 4H), 7.51 (d, $J = 8.6$ Hz, 2H), 7.95 (d, $J = 8.6$ Hz, 2H), 10.08 (s, 1H). Data in accordance with previously reported results [28].

4-Formyl-3'-nitrobiphenyl



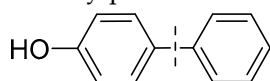
$^1\text{H NMR}$ (200 MHz, CDCl_3) δ (ppm) 7.67 (t, $J = 8.0$ Hz, 1H), 7.79 (d, $J = 8.3$ Hz, 2H), 7.94–8.03 (m, 3H), 8.22–8.28 (m, 1H), 8.47 (t, $J = 2.0$ Hz, 1H), 10.08 (s, 1H). Data in accordance with previously reported results [29].

4-Phenylacetophenone



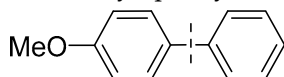
$^1\text{H NMR}$ (200 MHz, CDCl_3) δ (ppm) 2.64 (s, 3H), 7.37–7.53 (m, 3H), 7.60–7.72 (m, 4H), 8.05 (d, $J = 8.8$ Hz, 2H). Data in accordance with previously reported results [29].

4-Phenylphenol



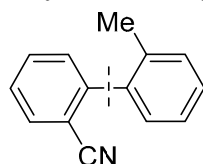
$^1\text{H NMR}$ (200 MHz, CDCl_3) δ (ppm) 4.99 (s, 1H), 6.92 (d, $J = 8.8$ Hz, 2H), 7.28–7.59 (m, 7H). Data in accordance with previously reported results [30].

4-Methoxybiphenyl



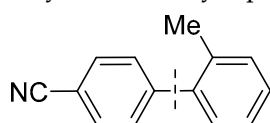
$^1\text{H NMR}$ (200 MHz, CDCl_3) δ (ppm) 3.91 (s, 3H), 7.06 (d, $J = 8.8$ Hz, 2H), 7.34–7.54 (m, 3H), 7.58–7.69 (m, 4H). Data in accordance with previously reported results [30].

2-Cyano-2'-methylbiphenyl



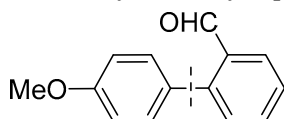
$^1\text{H NMR}$ (200 MHz, CDCl_3) δ (ppm) 2.22 (s, 3H), 7.21–7.42 (m, 5H), 7.47 (td, $J = 1.4$ and 7.6 Hz, 1H), 7.65 (td, $J = 1.4$ and 7.6 Hz, 1H), 7.77 (dd, $J = 1.4$ and 7.7 Hz, 1H). Data in accordance with previously reported results [31].

4-Cyano-2'-methylbiphenyl



$^1\text{H NMR}$ (200 MHz, CDCl_3) δ (ppm) 2.29 (s, 3H), 7.19–7.35 (m, 4H), 7.45 (d, $J = 8.7$ Hz, 2H), 7.72 (d, $J = 8.7$ Hz, 2H). Data in accordance with previously reported results [28].

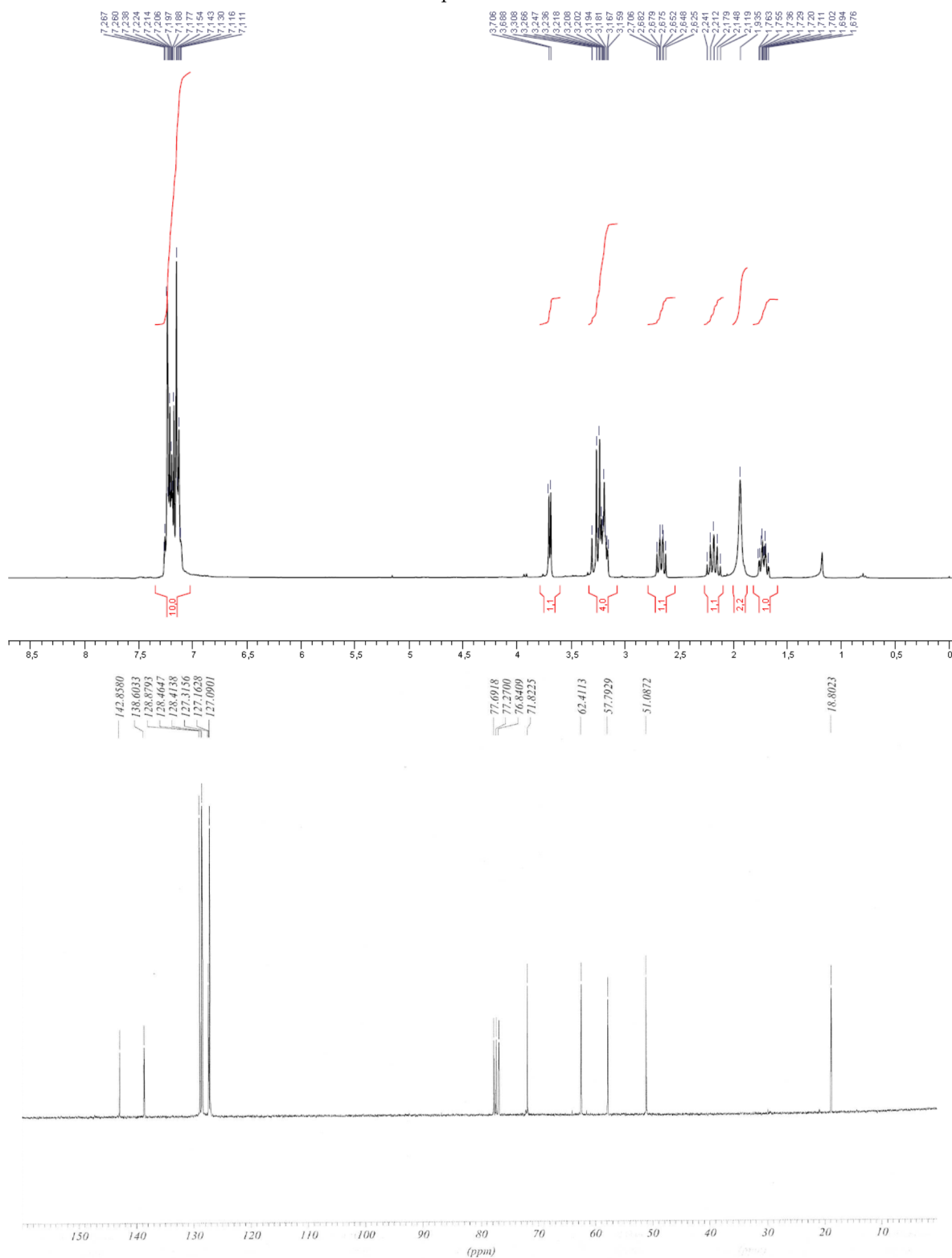
4-Methoxy-2'-formylbiphenyl



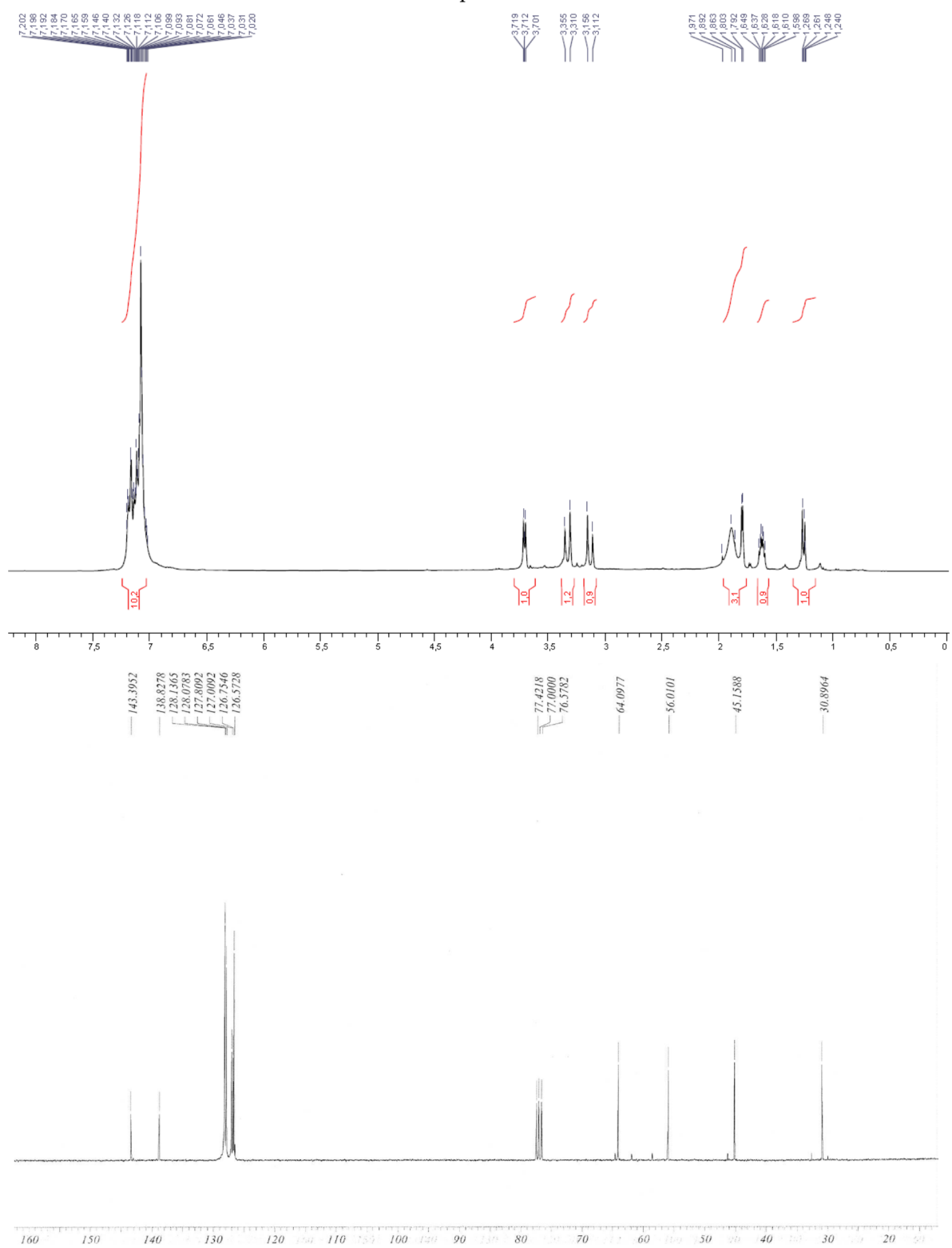
$^1\text{H NMR}$ (200 MHz, CDCl_3) δ (ppm) 3.86 (s, 3H), 7.00 (d, $J = 8.8$ Hz, 2H), 7.30 (d, $J = 8.8$ Hz, 2H), 7.47 (m, 2H), 7.61 (td, $J = 1.6$ and 7.3 Hz, 1H), 8.01 (m, 1H), 10.00 (s, 1H). Data in accordance with previously reported results [32].

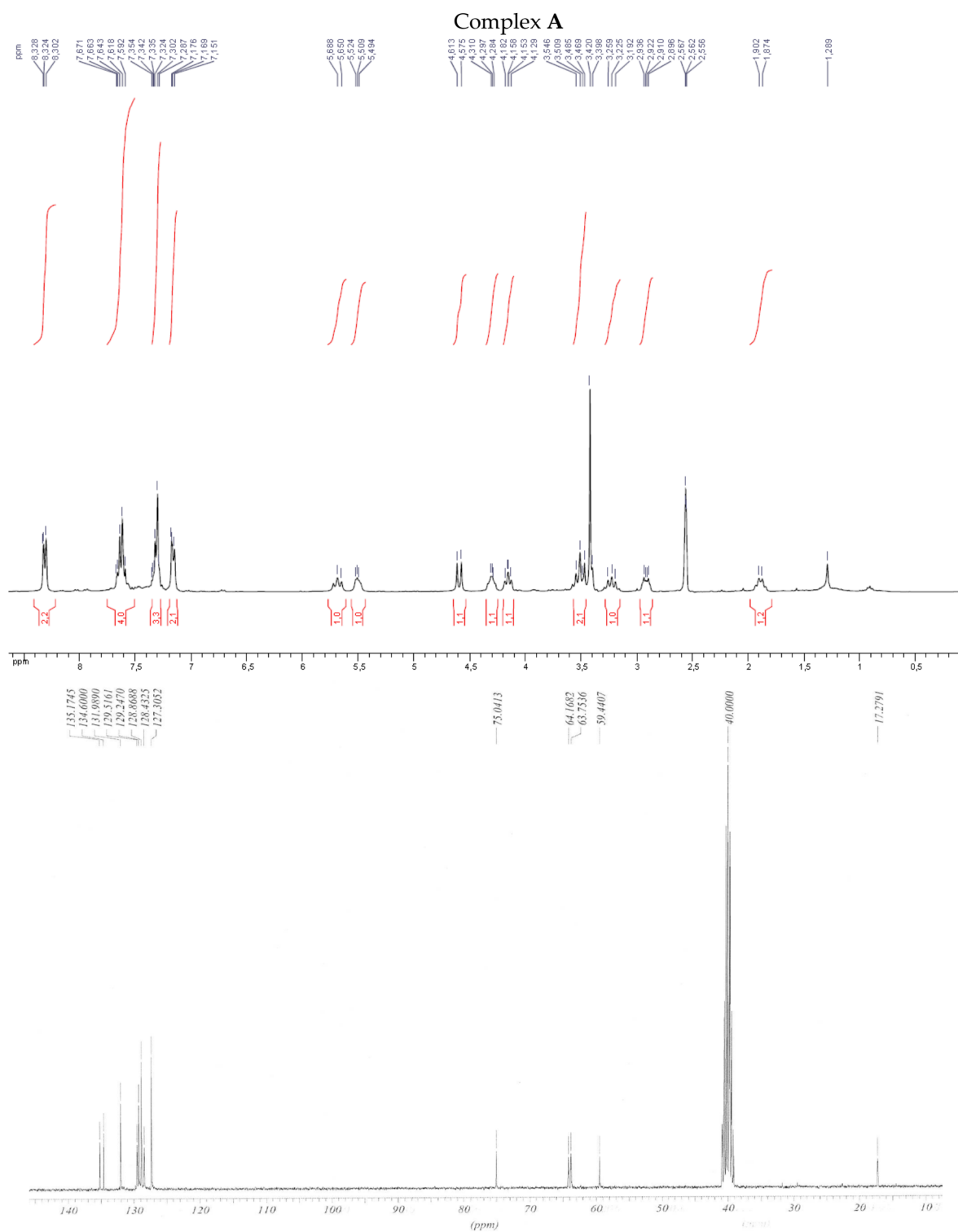
NMR spectra for compounds 3, 4 and complexes A–D

Compound 3

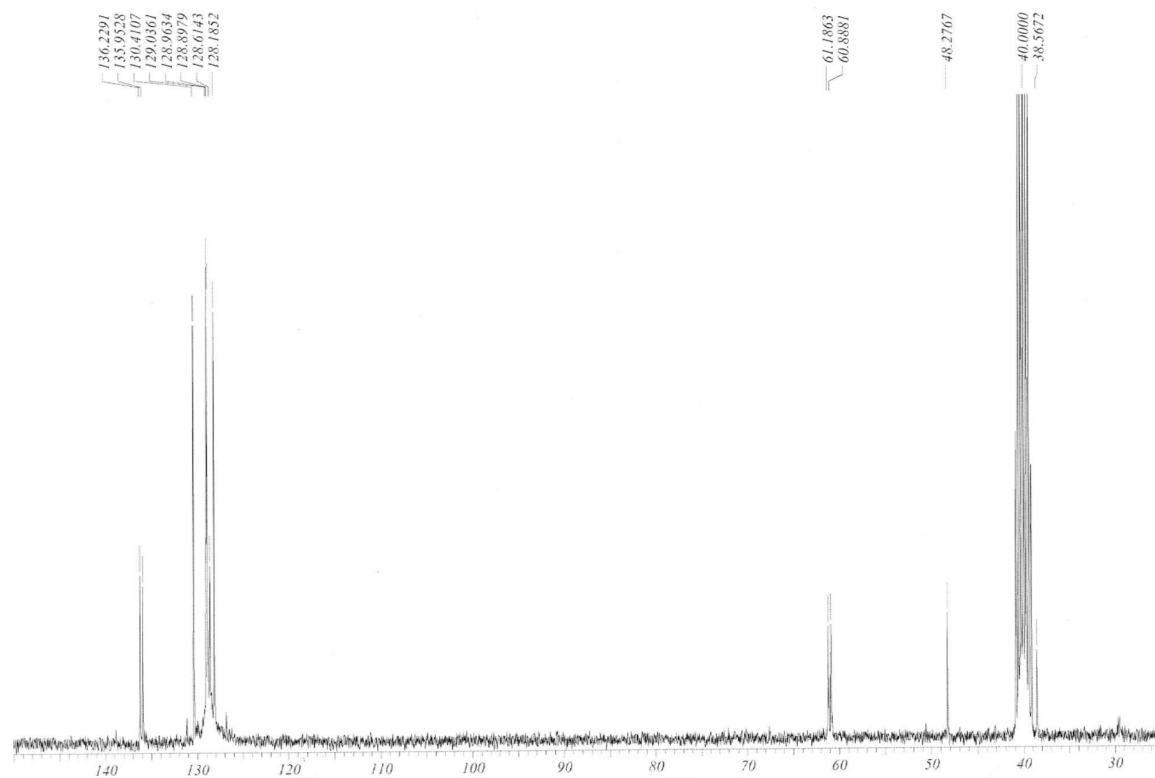
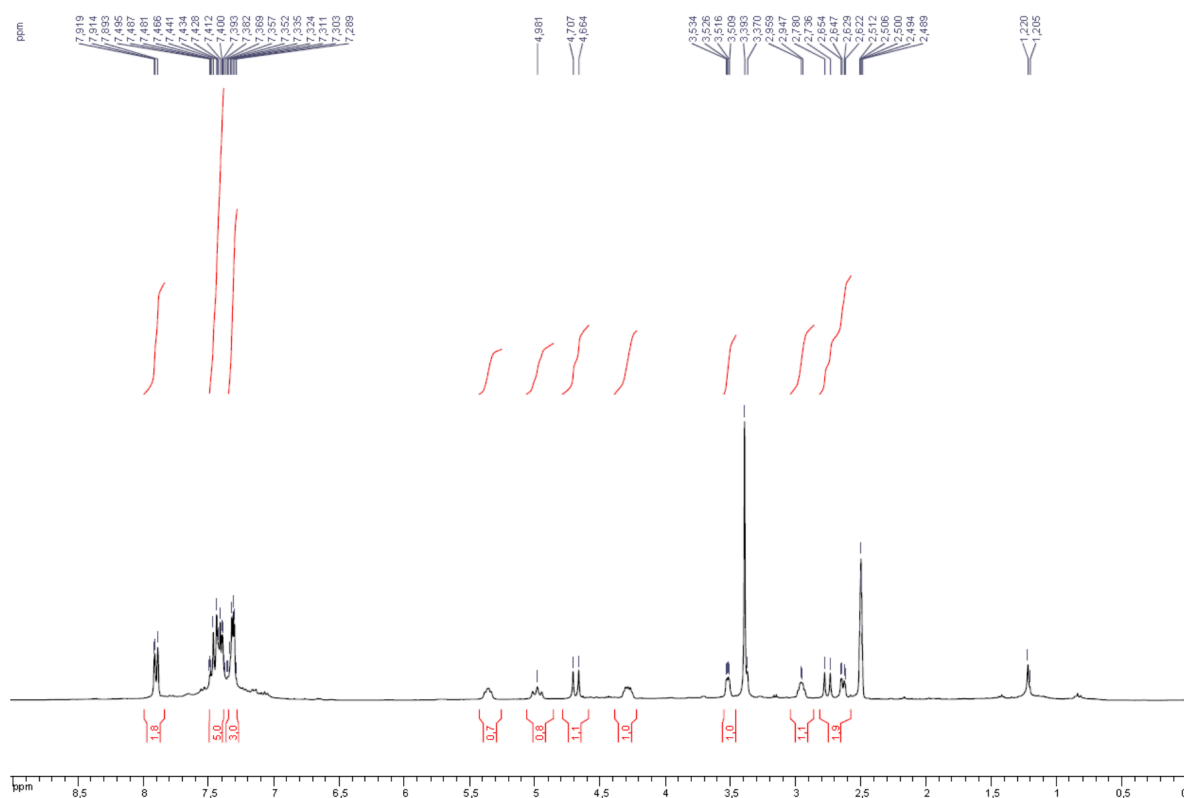


Compound 4





Complex B



Complex C

