Supporting Information

for

$C_{sp2}$-Br Bond Activation of Br-Pyridine by Neophylpalladacycle: Formation of Binuclear Seven-Membered Palladacycle and Bipyridine Species

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General Information

All reactions were carried out in oven-dried glassware under nitrogen atmosphere unless otherwise noted. Except as otherwise indicated, all reactions were magnetically stirred and monitored by analytical thin layer chromatography (TLC) using Fluka pre-coated silica gel on TLC plates (0.2 mm) with fluorescent indicator 254 nm. The developed chromatography was visualized under UV lamp (254 nm). Flash column chromatography was performed according to the method of Still using silica gel 60 (70-230 mesh) supplied by Aldrich. Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Ultra Shield 500 MHz and Advanced 400 MHz spectrometer at ambient temperature. $^1$H and $^{13}$C chemical shifts (δ) are given in parts per million (ppm) relative to TMS. The solvent signal was used as reference and the chemical shifts converted to the TMS scale. The proton spectra are reported as follows δ (position of proton, multiplicity, coupling constant J, number of protons). Multiplicity is indicated by s (singlet), d (doublet), t (triplet), q (quartet), p (quintet), h (septet), m (multiplet) and bs (broad singlet). Complete assignment of each compound were aided using $^1$H-$^1$H COSY, $^1$H-$^1$H NOESY, $^1$H-$^{13}$C($^1$H) HSQC, and $^1$H-$^{13}$C($^1$H) HMBC.

A high resolution, electrospray ionization–quadrupole-time of flight mass spectrometer maXis impact ESI-QTOFMS equipped with Data Analysis 4.1 (Bruker Daltonics) was used with sample introduction by direct infusion (3 µL/min). ESI was operated in a positive mode with ion spray voltage 4500 V, dry gas 4 L/min, drying temperature 180 °C and nebulizing gas pressure 0.4 bar. Spectra were acquired in the m/z range 80–800, using a lock-mass standard m/z 299.2945 (methyl stearate) in the ion source. Before infusion, the samples were diluted with acetonitrile: 0.1% v/v aqueous formic acid (80:20). N,N-dimethylformamide, 1,5-cyclooctadiene, neophyl chloride, triphenylphosphine, magnesium, palladium acetate, sodium hydroxide, K$_2$CO$_3$, Cs$_2$CO$_3$, Et$_2$O, toluene, dichloromethane, and all 2-halo-pyridines were purchased from Sigma-Aldrich. Palladium chloride was purchased from Pressure Chemical Co. Neophyl-Mg-Cl Grignard reagent,¹ palladacycle I,² [PdCl$_2$(COD)],³ [PdCl(Me)(COD)],⁴ [PdCl(Neophyl)(COD)]⁵ and [PdCl$_2$(PPh$_3$)$_2$],⁶ were synthesized according to the procedure described in the literature. All commercial available compounds (Aldrich) were used as received.
**General procedure for the synthesis of seven-membered Pd(II) binuclear complexes.**

To a solution of 0.1 mmol of palladacycle 1 in 5 mL of benzene, 0.1 mmol of the 2-bromopyridine derivative was added, the reaction mixture was stirred at room temperature for 30 minutes. The corresponding solid was filtered and washed twice with hexanes, and dried under reduced pressure, to get the palladacycle without any further purification.

**Compound 1**: Prepared following the general procedure to afford a yellow pale solid (22 mg, 56%).

\[
\begin{align*}
\text{^1H NMR} & (500 \text{ MHz, DMSO-}d_6) \delta = 8.86 (d, J=5.5, 1H), 8.14 (td, J=7.7, 1.6, 1H), 7.75 (d, J=7.8, 1H), 7.66 – 7.64 (m, 1H), 7.62 (d, J=8.4, 1H), 7.51 (td, J=7.6, 1.6, 1H), 7.40 (td, J=7.4, 1.1, 1H), 7.33 (dd, J=7.5, 1.6, 1H), 2.45 (bs, 1H), 2.24 (bs, 1H), 1.44 (s, 3H), 0.61 (s, 3H).
\end{align*}
\]

\[
\begin{align*}
\text{^{13}C NMR} & (126 \text{ MHz, DMSO-}d_6) \delta = 160.81, 151.89, 139.76, 138.78, 131.38, 129.29, 126.17, 125.46, 125.43, 124.88, 124.11, 52.41, 32.50, 32.22.
\end{align*}
\]

**Compound 2**: Prepared following the general procedure to afford a yellow pale solid (25 mg, 53%).

\[
\begin{align*}
\text{^1H NMR} & (500 \text{ MHz, DMSO-}d_6) \delta = 8.23 (t, J=7.8, 1H), 7.82 (d, J=7.9, 1H), 7.78 (d, J=7.3, 1H), 7.62 (d, J=7.9, 1H), 7.52 (td, J=7.7, 1.6, 1H), 7.41 (td, J=7.4, 1.1, 1H), 7.35 (m, 1H), 6.90 (s, 1H), 4.36 – 4.27 (m, 1H), 4.17 – 4.05 (m, 3H), 2.47 (d, J=7.5, 1H), 2.41 (d, J=7.3, 1H), 1.41 (s, 3H), 0.57 (s, 3H).
\end{align*}
\]

\[
\begin{align*}
\text{^{13}C NMR} & (126 \text{ MHz, DMSO-}d_6) \delta = 160.49, 156.78, 146.57, 140.87, 139.18, 131.40, 129.38, 126.24, 125.46, 124.55, 121.95, 103.58, 66.03, 64.89, 45.62, 32.44, 32.35.
\end{align*}
\]
Compound 3: Prepared following the general procedure to afford a yellow pale solid (19 mg, 44%)

$^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ = 11.17 (s, 1H), 8.40 (t, $J=7.7$, 1H), 8.17 (dd, $J=7.7$, 1.3, 1H), 8.07 (dd, $J=7.8$, 1.3, 1H), 7.67 (d, $J=7.9$, 1H), 7.56 (td, $J=7.7$, 1.7, 1H), 7.45 (t, $J=7.4$, 1H), 7.40 (dd, $J=7.5$, 1.6, 1H), 2.54 (bs, 2H), 1.45 (s, 3H), 0.67 (s, 3H).

$^{13}$C NMR (126 MHz, DMSO) $\delta$ = 190.58, 161.47, 148.97, 146.51, 141.50, 138.77, 131.73, 129.70, 129.34, 126.40, 124.90, 123.39, 46.51, 32.67, 32.35.

Compound 4: Prepared following the general procedure to afford a yellow pale solid (22 mg, 51%).

$^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ = 8.45 – 8.37 (m, 1H), 8.14 (dd, $J=6.7$, 2.6, 1H), 7.68 (d, $J=8.0$, 1H), 7.57 (td, $J=7.6$, 1.6, 1H), 7.45 (t, $J=7.4$, 1H), 7.44 – 7.38 (m, 1H), 2.47 (d, $J=8.1$, 1H), 2.38 (d, $J=7.9$, 2H), 1.44 (s, 3H), 0.61 (s, 3H).

$^{13}$C NMR (126 MHz, DMSO-$d_6$) $\delta$ = 162.63, 146.31, 141.39, 137.38, 133.47, 131.45, 130.15, 130.09, 129.01, 126.48, 125.21, 116.07, 46.97, 32.60, 32.49.
Figure S1. $^1$H NMR spectra for reaction of I and BrPy. From bottom to top, palladacycle I, reaction I and BrPy 10 min, 20 min and 30 min at CDCl$_3$ at r.t.
Figure S2. Upper Box: High resolution mass spectrum for compound 1 in CH$_3$CN solution. Lower boxes: Theoretical isotopic patterns and molecular structures of the two ions detected.
**Figure S3.** Upper box: Selected region of ESI-HRMS spectrum acquired for the liquor crude solution; Lower box: theoretical isotopic pattern for compound 1a.
Figure S4. $^1$H NMR spectrum of 1 in dms-o-$d_6$ at rt.
Figure S5. $^{13}$C NMR spectrum of 1 in dms-o-$d_6$ at rt.
Figure S6. $^{13}$C DEPT NMR spectrum of 1 in dmsø-$d_6$ at rt.
Figure S7. $^1$H–$^1$H COSY NMR spectrum of 1 in dmso-$d_6$ at rt.
Figure S8. $^1$H-$^1$H NOESY NMR spectrum of 1 in dms-o-$d_6$ at rt.
Figure S9. $^1$H-$^{13}$C HMQC NMR spectrum of 1 in dmso-$d_6$ at rt.
Figure S10. $^1$H-$^{13}$C HSQC NMR spectrum of 1 in dmsø-d$_6$ at rt.
Figure S11. $^1$H NMR spectrum of 2 in dms-o-$d_6$ at rt.
Figure S12. $^{13}$C NMR spectrum of 2 in dmsø-$d_6$ at rt.
Figure S13. $^{13}$C DEPT NMR spectrum of 2 in dmso-$d_6$ at rt.
Figure S14. $^1$H-$^1$H COSY NMR spectrum of 2 in dmoso-$d_6$ at rt.
Figure S15. $^1$H-$^1$H NOESY NMR spectrum of 2 in dmsø-$d_6$ at rt.
Figure S16. $^1$H-$^{13}$C HSQC NMR spectrum of 2 in dms-o-$d_6$ at rt.
Figure S17. $^1$H-$^{13}$C HMQC NMR spectrum of 2 in dmso-$d_6$ at rt.
Figure S18. $^1$H NMR spectrum of 3 in dmso-$d_6$ at rt.
Figure S19. $^{13}$C NMR spectrum of 3 in dms-$d_6$ at rt.
Figure S20. $^{13}$C DEPT NMR spectrum of 3 in dmoso-$d_6$ at rt.
Figure S21. $^1$H-$^1$H COSY NMR spectrum of 3 in dms-o-d$_6$ at rt.
Figure S22. $^1$H-$^1$H NOESY NMR spectrum of 3 in dmso-$d_6$ at rt.
Figure S23. $^1\text{H}-^{13}\text{C}$ HSQC NMR spectrum of 3 in dms-o-d$_6$ at rt.
Figure S24. $^1$H-$^{13}$C HMQC NMR spectrum of 3 in dmoso-$d_6$ at rt.
Figure S25. $^1$H NMR spectrum of 4 in dms-o-$d_6$ at rt.
Figure S26. $^{13}$C NMR spectrum of 4 in dmso-$d_6$ at rt.
Figure S27. $^{13}$C DEPT NMR spectrum of 4 in dmso-$d_6$ at rt.
Figure S28. $^1$H-$^1$H COSY NMR spectrum of 4 in dmso-$d_6$ at rt.
Figure S29. $^1$H-$^1$H NOESY NMR spectrum of 4 in dmsO-$d_6$ at rt.
Figure S30. $^1$H-$^{13}$C HSQC NMR spectrum of 4 in dmso-$d_6$ at rt.
Figure S31. $^1$H-$^1$C HMQC NMR spectrum of 4 in dmsO-$d_6$ at rt.
Figure S32. Comparative $^1$H spectra of compounds 1-4 in dms-o-$d_6$ at rt.
Figure S33. Comparative $^1$H spectra of compounds 1-4 in dmso-$d_6$ at rt.
General procedure for the reactivity of seven-membered Pd(II) complexes 1-4 with PPh₃: formation of compound 5-8.

In a NMR tube complexes 1-4 (0.01 mmol) were charged and dissolved in 500 µL. Then a proton NMR spectral was acquired and PPh₃ was added (0.022 mmol), at room temperature. According to the proton NMR spectra a spontaneous reaction take place with the concomituated formation of 5-8, respectively.
Table S1.  
Selected data for:

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<th>Compound</th>
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<th>-CH₃</th>
<th>³¹P</th>
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<th>Compound</th>
<th>δ (ppm)</th>
<th>Mult. (Hz)</th>
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<td>d (8.9)</td>
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Figure S34. Comparative $^1$H spectra of compounds 3 and 7 in dmso-$d_6$ at rt.
Figure S35. Left side: Comparative $^1$H NMR spectra of compounds 1-4 on the aliphatic region from a-d, respectively (in DMSO-d$_6$ at r.t.). Right side: Comparative $^1$H NMR spectra of compounds 5-8 on
Figure S36. Comparative $^1$H spectra of compounds 5-8 in dms-o-$d_6$ at rt.
Figure S37. Comparative $^1$H spectra in dms$\text{O-d}_6$ at rt. a) Compound synthesized in this work b) bipyridine and c) crude reaction.
**Figure S38.** $^1$H spectrum of 5 in dmso-$d_6$ at rt.
Figure S39. $^{31}$P spectrum of 5 in dms-o-d$_6$ at rt
Figure S40. $^1$H spectrum of 6 in dms-o-6 at rt.
Figure S41. $^{31}$P spectrum of 6 in dmoso-$d_6$ at rt.
Figure S42. $^1$H spectrum of 7 in dmso-$d_6$ at rt.
Figure S43 $^{31}$P spectrum of 7 in dmoso-$d_6$ at rt.
Figure S44. $^1$H spectrum of 8 in dmsol$_6$ at rt.
Figure S45. $^{31}$P spectrum of 8 in dmsos-$d_6$ at rt.
Figure S46. $^{31}$P spectra of compounds 5-8 in dmsO-$d_6$ at rt.
Figure S47. $^{31}$P spectra of compounds 7 and 8 in dms-o-$d_6$ at rt.
**Figure S48.** Upper Box: High resolution mass spectrum for compound 1 in CH₃CN solution. Lower boxes: Theoretical isotopic patterns and molecular structures of the two ions detected.

**Figure S49.** Upper Box: High resolution mass spectrum for compound 6 in CH₃CN solution.
Symmetric and Asymmetric Bipyridine Synthesis through Direct 2-X-Pyridine Coupling (X= Cl or Br) Catalyzed by Palladium in Water.

Thus, palladacycle I react easy and cleanly with an excess of X-Py (Ratio 1:3) at room temperature to give the BiPy complexes \([Pd(BiPy)X_2]\), 10 (Eq. 1). Additionally, complexes 10a-b can be obtained by the reaction of BiPy with the appropriate palladium source.\(^7\)\(^-\)\(^8\) At this point, we found ourselves into the next question: Could be possible obtain BiPy species using I as catalytic precursor? To found an answer to this question we carried out the next experiments.

After an initial screen we found that 11 could be isolated in good yield after 24 h of reaction by using \(N,N´\)-dimethylformamide (DMF) as solvent (Table S2, entries 1-2). However, high temperature must be reached to get this conversion. Below this temperature, only a negligible amount of BiPy was detected (Table S2, entries 3-4). Also, the use of different base types like Cs\(_2\)CO\(_3\) or K\(_2\)CO\(_3\) clearly does not affect the conversion and yield of compound 11, but without base addition into the reaction mixture compound 11 is not formed (Table S2, entry 5-6). Finally, the control experiment was carried out without a palladium source and bipyridine specie was not formed (Table S2, entry 7).
Table S2.

From this knowledge, we decided to test a commercial available coordination palladium complexes (\([\text{PdCl}_2(\text{PPh}_3)_2]\), \([\text{Pd(OAc)}_2]\), \([\text{PdCl}_2(\text{COD})]\) and \(\text{PdCl}_2\)), easy handled and cheapest that compounds I, as catalytic precursors into the synthesis of 11. Rewarding, these compounds can convert the 2-X-Py into BiPy (Table S3). Additionally, where we found that using toluene as solvent the reaction do not take place, even if water is added as co-solvent into the reaction mixture (Table S3, entries 7-9 and 10-11). Interestingly, addition of DMF into the reaction mixture plays a critical role in the reaction efficiency, and a complete conversion and formation of 11 was observed (Table S3, entries 13-17). These suggest that DMF might act as an auxiliary ligand increasing the solubility and stabilizing the catalytic specie. In this regard, the minimum amount of palladium required to catalyzed the complete conversion was found to be 1.5 mol% (Table S3, entries 18-21).
Prompted by these results, we tested the coupling reaction using water as solvent (2 mL) and DMF as additive, observing again completed consumption of 2-halo-pyridines and formation of 10 (Table S3, entry 22). Finally, at this point, we found that the best catalytic conditions to carry out the conversion of 2-halo-pyridine to 11, is using 1.5 mol % of [Pd(OAc)2], water (2 mL), DMF (500 µL) and K2CO3 (Table S3, entry 22). Recently, Duan et al. reported homocoupling using Ni as catalyst with a stoichiometric amount of Zn for the classic pre-formation of organozinc-pyridine derivative.14
Table S3.

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<th>Entry</th>
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<td>15</td>
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<td>Pd(OAc)₂</td>
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<td>Toluene/H₂O/DMF(10:2:1)</td>
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<tr>
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<td>Toluene/H₂O/DMF(10:2:1)</td>
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<td>DMF</td>
<td>K₂CO₃</td>
<td>210</td>
<td>24</td>
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<tr>
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<td>DMF</td>
<td>K₂CO₃</td>
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<td>87</td>
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<td>H₂O/DMF(additive)</td>
<td>K₂CO₃</td>
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<td>24</td>
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n.r. means no reaction
Table S4

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<td>CHO</td>
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<tr>
<td>2</td>
<td>H</td>
<td>OMe</td>
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<td>CHO</td>
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</tr>
<tr>
<td>4</td>
<td>H</td>
<td>1,3-dioxolan</td>
<td>17 13% (1) 11 45% (3) 18 30% (2)</td>
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<tr>
<td>5</td>
<td>CHO</td>
<td>1,3-dioxolan</td>
<td>19 20% (5) 12 5% (1) 18 65% (33)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Ration determined by 1H NMR in the reaction crude (In parenthesis).

<sup>b</sup>Yield obtained after purification by column chromatography.
General procedure for the asymmetric coupling reaction.

The reactions were conducted under nitrogen atmosphere, in 150 mL J. Young glass-tube with Teflon stopper. In a typical experiment, 1 mmol of the corresponding 2-halo-pyridine, catalyst, additive, and water were loaded into the tube. The tube was placed in a sand bath preheated to the desired temperature and the stirrer was started. After a suitable reaction time, the reactor was cooled at room temperature. The products were extracted with dichloromethane. Additionally, the BiPys 12-19, were fully characterized after purification in chromatographic column on silica.

**Compound 16**: Prepared following the general procedure.

\(^1\text{H NMR}\) (500 MHz, CDCl\(_3\)) \(\delta = 8.32\) (d, \(J=7.3, 1\text{H}\)), 8.03 (d, \(J=6.9, 1\text{H}\)), 7.79 (td, \(J=8.0, 2.7, 1\text{H}\)), 7.70 (dt, \(J=9.1, 4.6, 1\text{H}\)), 7.20 (d, \(J=7.1, 1\text{H}\)), 6.78 (d, \(J=7.8, 1\text{H}\)), 4.81 (s, 2H), 4.11 (sb, 1H), 4.04 (s, 3H).

\(^{13}\text{C NMR}\) (126 MHz, CDCl\(_3\)) \(\delta = 163.70, 158.16, 154.93, 153.04, 139.46, 137.60, 120.30, 119.71, 113.82, 111.44, 64.04, 53.35.\)
**Compound 17**: Prepared following the general procedure.

\[ \text{\textsuperscript{1}H NMR (500 MHz, CDCl}_3 \delta = 8.61 \ (d, J=5.0, 1H), 8.44 \ (dd, J=8.1, 4.1, 1H), 8.37 \ (dd, J=7.9, 3.3, 1H), 7.80 \ (dd, J=9.1, 6.5, 1H), 7.73 \ (dddd, J=9.7, 7.8, 5.1, 1.9, 1H), 7.55 – 7.48 \ (m, 1H), 7.22 \ (ddt, J=8.9, 4.8, 1.5, 1H), 6.10 – 5.47 \ (m, 1H), 4.22 – 4.10 \ (m, 2H), 4.09 – 3.96 \ (m, 2H).} \]

\[ \text{\textsuperscript{13}C NMR (126 MHz, CDCl}_3 \delta = 156.60, 155.69, 155.58, 148.98, 137.62, 136.76, 123.73, 121.31, 121.17, 120.42, 103.94, 65.54.} \]

**Compound 19**: Prepared following the general procedure.

\[ \text{\textsuperscript{1}H NMR (500 MHz, CDCl}_3 \delta = 8.46 – 8.34 \ (m, 2H), 7.86 \ (t, J=7.8, 1H), 7.79 \ (t, J=7.8, 1H), 7.56 \ (dd, J=7.7, 1.1, 1H), 7.23 \ (d, J=7.6, 1H), 5.94 \ (s, 1H), 4.81 \ (s, 2H), 4.29 – 4.19 \ (m, 2H), 4.18 – 4.09 \ (m, 2H), 4.04 \ (sb, 1H).} \]

\[ \text{\textsuperscript{13}C NMR (126 MHz, CDCl}_3 \delta = 158.26, 156.91, 155.28, 154.68, 137.79, 137.70, 121.28, 120.76, 120.62, 120.19, 104.14, 65.78, 64.11.} \]
\[ \text{Br}_2 \overset{\text{Pd(OAc)}_2 / \text{K}_2\text{CO}_3}{\text{Water / DMF / 210 \degree C}} \overset{\text{HO}}{\text{O}} \]

\[ \text{1H NMR (500 MHz, CDCl}_3\text{) for reaction crude.} \]

**Figure S50.** \(^1\text{H NMR spectrum of reaction crude in CDCl}_3\text{ at rt.} \)
**Figure S51.** $^1$H NMR spectrum of reaction crude in CDCl$_3$ at rt.
$^1$H NMR (500 MHz, CDCl$_3$) reaction crude.

Figure S52. $^1$H NMR spectrum of reaction crude in CDCl$_3$ at rt.
Figure S53. $^1$H NMR spectrum of 16 in CDCl$_3$ at rt.
Figure S54. $^{13}$C NMR spectrum of 16 in CDCl$_3$ at rt.
Figure S55. $^1$H NMR spectrum of 17 in CDCl$_3$ at rt.
Figure S56. $^{13}$C NMR spectrum of 17 in CDCl$_3$ at rt.
Figure S57. $^1$H NMR spectrum of 19 in CDCl$_3$ at rt.
Figure S58. $^{13}$C NMR spectrum of 19 in CDCl$_3$ at rt.
Figure S59. Molecular structure of the compound 10 (thermal ellipsoids are show with a 30 % probability level).
References.


