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PAPER

Synthesis and characterization of novel chiral NHC–palladium complexes and their application in copper-free Sonogashira reactions†

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A new series of chiral *N*-heterocyclic carbene (NHC) palladium complexes were synthesized from a relatively inexpensive amino acid, L-phenylalanine. All these compounds were fully characterized by ^{1}H-NMR, ^{13}C-NMR and elemental analysis. The X-ray molecular structures of two of the complexes were reported. The catalytic activity of the four palladium complexes was successfully tested in the Sonogashira reaction under copper free conditions in air. The palladium complex **3a** provided good activity in the Sonogashira coupling reaction.

Introduction

The Sonogashira cross-coupling reaction has become one of the most important methods in the synthesis of aryl alkynes from aryl halides or triflates.[1] Compounds bearing carbon–carbon triple bonds are often encountered in natural products, pharmaceuticals, and biologically important molecules, as well as in molecules with materials related applications.[2] In a typical Sonogashira procedure, the reaction is conducted using a phosphane-including palladium complex with a catalytic amount of copper (I) salt as catalyst in the presence of an amine. Although copper would greatly increase the reaction rate, it induces unwanted homo-coupled products of terminal alkynes through a Hay–Glaser-type reaction.[3] Moreover, Cu-acetylide generated *in situ* is extremely sensitive to air and moisture, so inert atmospheric conditions are required.[4] A solution to this problem is to eliminate copper in the reaction. In the last few decades, more and more efficient palladium catalysts containing hindered phosphane[5] and NHC ligands[6] have been developed working in the absence of Cu. Although the *N*-heterocyclic carbenes have been used widely in organometallic chemistry and catalysis,[7] Sonogashira coupling based on *N*-heterocyclic carbenes is relatively rarer compared to phosphine based precatalysts. Most of the copper-free Sonogashira reactions suffer from problems due to the high catalyst loadings,[8] and the use of unstable, expensive and toxic phosphine ligands.[5] Consequently, it is necessary to develop air-stable, robust and well-defined Pd-complexes with inexpensive ligands. We have developed an interest in exploring the utility of N/O-functionlized *N*-heterocyclic carbenes in chemical catalysis, with special emphasis on developing inexpensive, user-friendly, and highly efficient precatalysts for C–C cross-coupling reactions.[9] To explore new efficient catalysts for Sonogashira coupling reactions, we prepared a series of novel chiral NHC–palladium complexes from the relatively inexpensive L-phenylalanine and reported on the use of these complexes to catalyze the copper-free Sonogashira coupling reaction under aerobic conditions.

Results and discussion

Imidazolium salts

The optically pure imidazoline **1** was prepared by a 5-step sequence starting from L-phenylalanine according to the literature procedure (Scheme 1).[10] Although all five steps provided from moderate to good yield in the formation of all the reaction intermediates, the overall yield in the formation of **1** was *ca.* 30%. The imidazolium bromides **2** were synthesized by direct substitution reaction of imidazoline **1** with the readily available corresponding alkyl bromides in good yield. The reaction for compound **2a** was performed in toluene at 65 °C for 5 h, whereas the reactions for **2(b–d)** were conducted in acetonitrile at 110 °C for 10 h.

Synthesis of NHC–palladium complexes

The synthesis of NHC–palladium complexes **3(a–d)** was achieved by the procedure shown in Scheme 2. The reaction of **2** with one equiv. of $PdCl_2$ in pyridine in the presence of K_2CO_3 as a base and NaBr as the provider of bromide ion afforded

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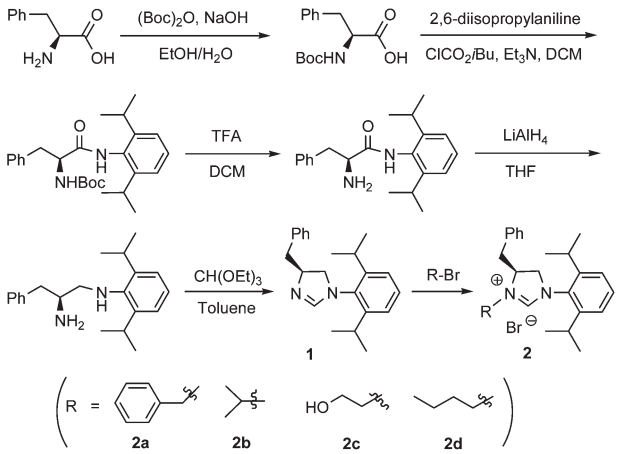
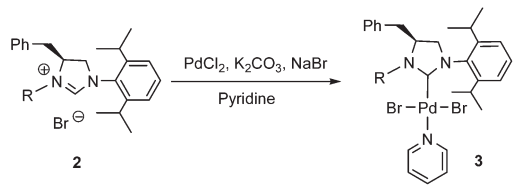
†CCDC reference numbers 858709 and 858710 for **3a** and **3c**, respectively. For crystallographic data in CIF or other electronic format see DOI: 10.1039/c2dt12391f



Scheme 1 Synthesis of compounds **2**.



Scheme 2 Synthesis of complexes **3**.

complexes **3** in moderate to good yield. All of these complexes were characterized by NMR spectroscopy and gave satisfactory elemental analyses. The complexes are air and moisture stable and can be stored in an air atmosphere in the solid state for more than 6 months without any noticeable decomposition.

The proton signal of NC*H*N from the imidazolium bromides **2** (9.99 ppm for **2a**; 9.18 ppm for **2b**; 8.76 ppm for **2c**; 9.73 ppm for **2d**) was absent in the ^{1}H NMR of the palladium complexes, confirming carbene generation. In addition, the formation of the metal complexes was evident from the distinctive Pd–$C_{carbene}$ peak (182.8 ppm for **3a**, 182.7 ppm for **3b**, 182.6 ppm for **3c** and 182.1 ppm for **3d**), which significantly shifted downfield relative to that of the imidazolinium N*C*HN peak of the starting ligand precursor (158.6 ppm for **2a**, 157.3 ppm for **2b**, 159.1 ppm for **2c**, 158.7 ppm for **2d**).

Single crystals for the solid-state structure determination of **3a** and **3c** could be obtained by slow diffusion of diethyl ether into a saturated DCM solution. The molecular structures of **3a** and **3c** were determined by means of X-ray diffraction studies. The molecular diagrams of **3a** and **3c** are shown in Figs 1 and 2 and selected crystallographic data are shown in Table 1. Two complexes show slightly distorted square-planar geometries around palladium center, which are surrounded by imidazolylidene, two bromo ligands in a *trans* configuration, and a pyridine. The Pd–$C_{carbene}$ distance is 1.965(45) Å for **3a** and 1.967(8) Å for **3c**, similar to those shown by other palladium-related species, *i.e.* (1-(mesityl)-3-(pyrimidine)imidazole-2-ylidend)$PdCl_2$ [1.964(3) Å].[11] The Pd–$N_{pyridine}$ distance in complex **3a** [2.114(4) Å], **3c** [2.111(7) Å] is comparable to that observed in other related palladium carbene analogues.[9] All other distances and angles lie in the expected range.

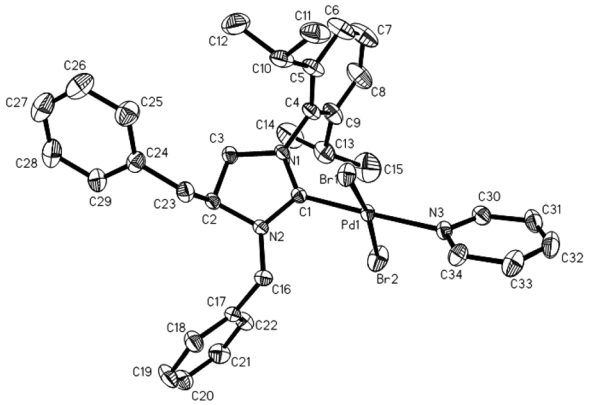


Fig. 1 The ORTEP structure of complex **3a** showing 30% probability ellipsoids; hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and bond angles (°): Pd1–C1 1.965(4), Pd1–Br1 2.4309(67), Pd1–Br2 2.4339(7), Pd1–N3 2.114(4), C1–N1 1.328(5), C1–N2 1.349(5), C1–Pd1–Br1 85.64(3), C1–Pd1–Br2 91.93(13), Br1–Pd1–N3 91.73(10), Br2–Pd1–N3 90.81(10), N1–C1–N2 109.2(4).

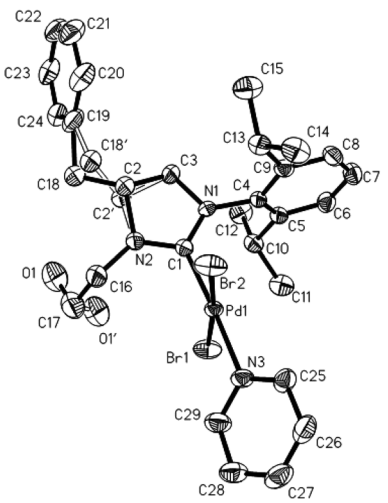


Fig. 2 The ORTEP structure of complex **3c** showing 30% probability ellipsoids; hydrogen atoms are omitted for clarity. Selected bond lengths (Å) and bond angles (°): Pd1–C1 1.967(8), Pd1–Br1 2.4311(12), Pd1–Br2 2.4256(12), Pd1–N3 2.111(7), C1–N1 1.332(9), C1–N2 1.333(10), C1–Pd1–Br1 91.1(2), C1–Pd1–Br2 87.4(2), Br1–Pd1–N3 90.4(2), Br2–Pd1–N3 90.7(2), N1–C1–N2 109.8(7).

As optically pure L-phenylalanine was used as a starting material, we suggested that all of these palladium complexes were chiral because the chiral center would survive in all the experimental processes. The X-ray structure of **3a** and **3c** confirmed there is a stereogenic center with *S* configuration in the back bone of imidazoline ring. The specific rotation of these Pd complexes in DCM is 6.3° for **3a**; 104.8° for **3b**; 78.9° for **3c** and 72.4° for **3d**.

Sonogashira coupling reaction

To evaluate the catalytic activity of **3a–3d** in the Cu-free Sonogashira coupling reactions under aerobic conditions, we performed the reaction of 1-iodo-2-methoxybenzene with

Table 1 Crystal data and structure refinement details for **3a** and **3c**

Complex	**3a**	**3c**
Formula	$C_{34}H_{39}Br_2N_3Pd$	$C_{29}H_{37}Br_2N_3OPd$
Formula weight	755.90	709.84
Temperature of measurement (K)	298(2)	298(2)
Crystal system	Triclinic	Monoclinic
Space group	$P\bar{1}$	$P2(1)/n$
a (Å)	10.6900(10)	10.4260(11)
b (Å)	11.0661(11)	17.3900(18)
c (Å)	14.7279(15)	16.7852(15)
α (°)	109.010(2)	90.00
β (°)	90.6700(10)	95.8990(10)
γ (°)	96.2090(10)	90.00
Volume (Å^3)	1635.5(3)	3027.2(5)
Z	2	4
Crystal size	0.45 × 0.43 × 0.38	0.43 × 0.40 × 0.30
F(000)	760	1424
Theta range for data collection (°)	2.576–27.954	2.287–24.529
Goodness-of-fit on F^2	1.038	1.079
Final R indices [$I > 2\sigma(I)$]	R_1 = 0.0400 wR_2 = 0.0964	R_1 = 0.0630 wR_2 = 0.1253
R indices (all data)	R_1 = 0.0686 wR_2 = 0.1103	R_1 = 0.0894 wR_2 = 0.1334

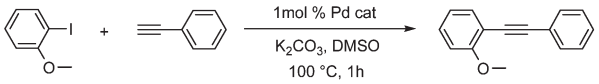
phenylacetylene in DMSO in the presence of K_2CO_3 as base at 100 °C for 1 h, using 1 mol% catalyst loading. As can be seen from the results shown in Table 2 (entries 1–4), complex **3a** is the one that provides the best activity (69% yield), whereas the other complexes (**3b–3d**) do not show good activity, especially **3d**, leading to only 31% yield.

The solvent is normally a very important parameter determining cross-coupling efficiency, so we tested the reaction catalyzed by **3a** in different solvents (Table 2, entries 1 and 5–9). The results showed that DMSO is the best solvent tested, and a relatively low yield was observed in DMF or a mixed solvent of DMF with water (3 : 1). No product was even observed in THF, toluene or dioxane as solvent at all. Therefore, solvent does play a very important role in this catalytic reaction.

To probe the substrate scope of the reaction, more aryl iodides and bromides were chosen to react with phenylacetylene using 1 mol% catalyst **3a** with 2 equiv. K_2CO_3 in DMSO (2 mL) in air (Table 3). The results showed that **3a** could not only catalyze the cross-coupling reaction of phenylacetylene with more reactive aryl iodides, but also could catalyze the reaction in good to moderate yield (55%–86%) with less reactive aryl bromides in the absence of copper co-catalysis. Unfortunately, the catalyst was not effective for aryl chloride (entry 12). The higher yield was obtained for aryl bromides with a strong electron-withdrawing group compared to those with a weaker electron-withdrawing group (like entry 1 *vs.* entry 5). The aryl bromides with *para*-substitution led to lower yields than the bromides with substitution at the *ortho*- or *meta*-position (entry 5 *vs.* entry 6; entry 7 *vs.* entry 9). Furthermore, the reaction went well with aliphatic alkyne as well (entries 13–18), for example the reaction of 1-hexyne with *para*-nitrobromobenzene gave 91% yield. All of the reactions were very fast, and they can be completed within 1 h.

As all the Pd complexes are chiral complexes, it is interesting to test them in an asymmetric reaction. Initially, asymmetric Suzuki reaction of 1-bromonaphthalene (1 mmol) with

Table 2 Coupling reactions under different reactions



Entry[a]	Pd cat.	Solvent	Yield[b] (%)
1	**3a**	DMSO	69
2	**3b**	DMSO	36
3	**3c**	DMSO	49
4	**3d**	DMSO	31
5	**3a**	DMF : H_2O = 3 : 1	45
6	**3a**	DMF	23
7	**3a**	THF	0
8	**3a**	Toluene	0
9	**3a**	Dioxane	0

[a] Reaction conditions: 0.5 mmol of aryl iodides, 1 mmol phenylacetylene and 1 mmol of K_2CO_3 in 2 mL solvents. [b] Average of two runs with dodecane as an internal standard.

naphthalen-1-ylboronic acid (1.2 mmol) catalyzed by 0.5 mol% of **3a** was investigated. The reaction was carried out in dioxane with KOH (3 mmol) as base at 100 °C for 24 h. The product was isolated in 99% yield, unfortunately, with only 5% ee. We are currently optimizing the conditions to further improve the catalytic results. Further reactivity studies of these and related catalyst systems in various reactions are on going in our laboratories and we hope to discover an efficient universal catalyst system.

Conclusion

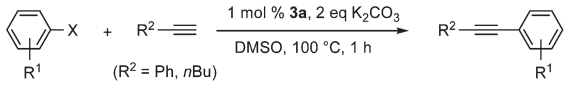
In summary, we have designed and synthesized a series of novel *N*-heterocyclic carbene (NHC) palladium complexes from a relatively inexpensive amino acid. They are highly stable to air and moisture. Complex **3a** appears to have good activity in the Sonogashira cross-coupling reaction under the much desired copper free and phosphine free conditions in air. The yields of the Sonogashira reactions catalyzed by **3a** ranging from 55–91%. The reaction can be completed in a short time (*ca*. 1 h) with low catalyst loading (1 mol%).

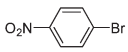
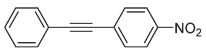
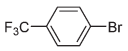
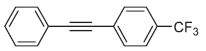
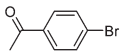
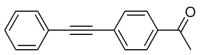
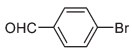
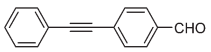
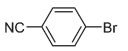
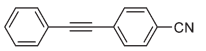
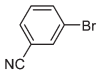
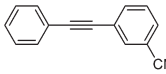
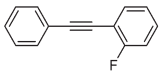
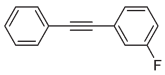
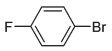
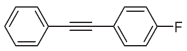
Experimental

General procedures

The chiral imidazolinium bromides were prepared according to our previous procedure.[10] Pyridine was distilled from calcium hydride under an argon atmosphere. Potassium carbonate was ground to a fine powder prior to use. All other reagents were commercially available and were used without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DPX 400 MHz spectrometer at room temperature and referenced to the residual signals of the solvent. Elemental analyses were performed on a EuroVektor Euro EA-300 elemental analyzer. GC-MS was performed on an Agilent 6890-5973N system with electron ionization (EI) mass spectrometry. Optical rotation was measured with Autopol IV automatic polarimeter in DCM solution. X-ray crystallography was conducted on a Rigaku

Table 3 Sonogashira coupling reactions of phenylacetylene with aryl halides



Entry[a]	Aryl halides	Alkyne	Product	Yield[b] (%)
1				84
2				78
3				76
4				71
5				79
6				84
7				60
8				59
9				55
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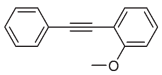
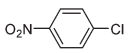
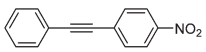
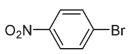
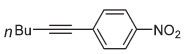
11				63
12				0
13				91
14				90
15				77
16				88
17				95
18				72

[a] Reaction conducted with 1 mmol of aryl halides, 2 mmol of alkyne and 2 mmol of K_2CO_3 in 2 mL of DMSO. [b] Isolated yield on average of two runs.

mercury CCD device with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). The crystal data collection and refinement parameters are summarized in Table 1. Absorption correction was performed by SADABS program. The structure was solved by direct methods using the SHELXS-97 program and refined by full-matrix least squares techniques on F^2.

Data for product 2

2a Yield: 94%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.99 (s, 1H), 7.56 (d, J = 4.0 Hz, 2H), 7.34–7.46 (m, 7H), 7.13–7.18 (m, 4H), 6.13 (d, J = 12.0 Hz, 1H), 4.64–4.75 (m, 2H), 3.95 (t, J = 12.0 Hz, 1H), 3.77–3.82 (m, 1H), 3.27 (dd, J = 12.0 Hz, J = 4.0 Hz, 1H), 3.13–3.18 (m, 1H), 2.69–2.76 (m, 1H), 2.26–2.31 (m, 1H), 1.31 (d, J = 4.0 Hz, 3H), 1.17 (t, J = 8.0 Hz, 6H), 1.11 (d, J = 8.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): 158.6, 146.3, 146.0, 133.5, 132.9, 130.9, 129.7, 129.5, 129.3, 129.1, 128.9, 127.8, 124.7, 60.2, 56.8, 49.7, 36.5, 28.8, 28.3, 25.2, 25.1, 23.8, 23.7.

2b Yield: 55%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.18 (s, 1H), 7.31–7.38 (m, 4H), 7.25 (d, J = 8.0 Hz, 2H), 7.16 (t, J = 8.0 Hz, 2H), 5.22–5.30 (m, 1H), 4.44–4.47 (m, 1H), 4.24 (t, J = 12.0 Hz, 1H), 3.77–3.82 (m, 1H), 3.48 (dd, J = 12.0 Hz, J = 12.0 Hz, 1H), 3.09–3.15 (m, 1H), 2.81 (br, 1H), 2.41 (br, 1H), 1.68 (d, J = 8.0 Hz, 3H), 1.61 (d, J = 4.0 Hz, 3H), 1.26 (d, J = 4.0 Hz,

3H), 1.22 (d, J = 8.0 Hz, 3H), 1.15–1.18 (m, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): 157.3, 146.4, 146.2, 133.9, 131.0, 129.9, 129.7, 129.3, 127.8, 124.9, 124.7, 61.3, 57.2, 50.0, 38.2, 28.8, 28.5, 25.1, 25.0, 24.2, 24.1, 22.9, 21.9.

2c Yield: 90%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.76 (s, 1H), 7.35–7.42 (m, 4H), 7.20 (d, J = 8.0 Hz, 3H), 7.10 (d, J = 8.0 Hz, 1H), 5.18–5.26 (m, 1H), 5.03–5.06 (m, 1H), 4.51–4.59 (m, 1H), 4.27 (t, J = 12.0 Hz, 1H), 3.92–4.06 (m, 2H), 3.79–3.84 (m, 1H), 3.69–3.73 (m, 1H), 3.08–3.24 (m, 3H), 1.97–2.03 (m, 1H), 1.23–1.27 (m, 6H), 1.04 (t, J = 8.0 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): 159.1, 147.1, 146.1, 133.6, 131.0, 129.8, 129.4, 129.3, 127.8, 125.0, 124.5, 60.5, 57.0, 56.5, 48.0, 36.5, 28.4, 28.2, 25.2, 25.0, 24.0.

2d Yield: 91%. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.73 (s, 1H), 7.34–7.39 (m, 4H), 7.21 (d, J = 4.0 Hz, 2H), 7.15 (t, J = 8.0 Hz, 2H), 4.90 (s, br, 1H), 4.72 (br, 1H), 4.07 (t, J = 12.0 Hz, 1H), 3.78–3.82 (m, 1H), 3.66–3.73 (m, 1H), 3.29 (dd, J = 12.0 Hz, J = 4.0 Hz, 1H), 3.08–3.13 (m, 1H), 2.78 (s, br, 1H), 2.28 (s, br, 1H), 1.77–1.82 (m, 2H), 1.65–1.71 (m, 2H), 1.27–1.29 (m, 3H), 1.18–1.23 (m, 6H), 1.09–1.11 (m, 3H), 1.01 (t, J = 8.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): 158.7, 146.5, 146.3, 133.6, 130.9, 129.8, 129.6, 129.3, 127.8, 124.7, 60.4, 56.6, 45.7, 36.6, 29.4, 28.8, 28.3, 25.2, 25.1, 24.0, 23.9, 19.4, 13.6.

Synthesis of complex 3a

To an oven-dried 50 mL r.b.f. containing **2a** (0.147 g, 0.3 mmol), $PdCl_2$ (0.053 g, 0.3 mmol), K_2CO_3 (0.415 g, 3 mmol) and NaBr (0.155 g, 1.5 mmol) with a septum, was injected pyridine (5 mL) under argon. The reaction mixture was stirred at 80 °C for 12 h, then 90 °C for 6 h. After cooling to room temperature, the mixture was filtered through a plug of Celite and washed with DCM. After the volatile was removed under vacuum, the solid was recrystallized by DCM–ether to give **3a** as a yellow solid (0.19 g, 85%). $[\alpha]_D^{25}$ = 6.3°; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.74 (d, J = 4.0 Hz, 2H), 7.68 (d, J = 4.0 Hz, 2H), 7.62 (t, J = 8.0 Hz, 1H), 7.47 (t, J = 8.0 Hz, 2H), 7.40 (t, J = 8.0 Hz, 2H), 7.31 (d, J = 8.0 Hz, 1H), 7.25–7.17 (m, 6H), 6.98 (d, J = 8.0 Hz, 2H), 6.72 (d, J = 12.0 Hz, 1H), 4.82 (d, J = 12.0 Hz, 1H), 4.02–3.95 (m, 1H), 3.89–3.77 (m, 2H), 3.54 (dd, J = 12.0 Hz, J = 4.0 Hz, 1H), 3.38–3.27 (m, 2H), 2.79–2.73 (m, 1H), 1.53 (d, J = 8.0 Hz, 3H), 1.48 (d, J = 8.0 Hz, 3H), 1.21 (d, J = 8.0 Hz, 3H), 1.07 (d, J = 8.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): 182.8, 152.3, 148.3, 148.2, 137.5, 135.9, 135.3, 134.1, 129.6, 129.2, 129.1, 128.9, 128.2, 127.0, 124.6, 124.5, 124.3, 59.1, 58.5, 53.7, 37.9, 28.6, 28.3, 27.2, 27.1, 24.6, 24.4. Anal. Calc. for $C_{34}H_{39}Br_2N_3Pd$ (756.93 g mol^{-1}): C, 53.95; H, 5.33; N, 5.55. Found: C, 53.56; H, 5.21; N, 5.72%.

Synthesis of complex 3b

To an oven-dried 50 mL r.b.f. containing **2b** (0.133 g, 0.3 mmol), $PdCl_2$ (0.053 g, 0.3 mmol), K_2CO_3 (0.415 g, 3 mmol) and NaBr (0.155 g, 1.5 mmol) with a septum, was injected pyridine (5 mL) under argon. The reaction mixture was stirred at 80 °C for 12 h. After cooling to room temperature, the mixture was filtered through a plug of Celite and washed with DCM. After the volatile was removed under vacuum, the solid was recrystallized by DCM–ether to give **3b** as a yellow solid (0.13 g, 59%). $[\alpha]_D^{25}$ = 104.8°; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.72 (d, J = 8.0 Hz, 2H), 7.61 (t, J = 8.0 Hz, 1H), 7.36 (t, J = 8.0 Hz, 1H), 7.32–7.16 (m, 9H), 6.17–6.10 (m, 1H), 4.48–4.40 (m, 1H), 3.81 (t, J = 8.0 Hz, 1H), 3.62–3.56 (m, 2H), 3.50 (dd, J = 12.0 Hz, J = 4.0 Hz, 1H), 3.44–3.38 (m, 1H), 2.84 (t, J = 12.0 Hz, 1H), 1.76 (d, J = 8.0 Hz, 3H), 1.62 (d, J = 4.0 Hz, 3H), 1.50 (d, J = 8.0 Hz, 3H), 1.42 (d, J = 8.0 Hz, 3H), 1.20 (d, J = 4.0 Hz, 3H), 1.04 (d, J = 8.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): 182.7, 152.4, 148.4, 148.3, 137.5, 136.2, 134.3, 129.5, 129.0, 127.2, 124.6, 124.5, 124.3, 59.0, 58.3, 53.1, 41.2, 28.5, 27.5, 27.1, 24.7, 24.3, 23.7, 20.3. Anal. Calc. for $C_{30}H_{39}Br_2N_3Pd$ (707.88 g mol^{-1}): C, 50.90; H, 5.58; N, 5.94. Found: C, 50.55; H, 5.47; N, 6.12%.

Synthesis of complex 3c

To an oven-dried 50 mL r.b.f. containing **2c** (0.133 g, 0.3 mmol), $PdCl_2$ (0.053 g, 0.3 mmol), K_2CO_3 (0.415 g, 3 mmol) and NaBr (0.155 g, 1.5 mmol) with a septum, was injected pyridine (5 mL) under argon. The reaction mixture was stirred at 80 °C for 12 h. After cooling to room temperature, the mixture was filtered through a plug of Celite and washed with DCM. After the volatile was removed under vacuum, the solid was recrystallized by DCM–ether to give **3c** as a yellow solid (0.16 g, 73%). $[\alpha]_D^{25}$ = 78.9°; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.68 (d, J = 8.0 Hz, 2H), 7.64 (t, J = 8.0 Hz, 1H), 7.38 (t, J = 8.0 Hz, 1H), 7.33–7.18 (m, 9H), 5.36–5.29 (m, 1H), 4.55–4.47 (m, 1H), 4.36–4.22 (m, 2H), 3.97–3.89 (m, 2H), 3.64–3.55 (m, 2H), 3.41–3.29 (m, 2H), 2.99–2.96 (m, 1H), 2.86–2.80 (m, 1H), 1.48 (d, J = 4.0 Hz, 3H), 1.42 (d, J = 4.0 Hz, 3H), 1.16 (d, J = 8.0 Hz, 3H), 1.07 (d, J = 8.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): 182.6, 152.3, 148.3, 148.2, 137.7, 135.8, 134.0, 129.7, 129.3, 129.0, 127.2, 124.6, 124.4, 60.9, 59.8, 58.5, 50.4, 38.5, 28.5, 28.4, 27.3, 27.2, 24.4. Anal. Calc. for $C_{29}H_{37}Br_2N_3OPd$ (709.85 g mol^{-1}): C, 49.07; H, 5.25; N, 5.92. Found: C, 48.76; H, 5.06; N, 6.12%.

Synthesis of complex 3d

To an oven-dried 50 mL r.b.f. containing **2d** (0.137 g, 0.3 mmol), $PdCl_2$ (0.053 g, 0.3 mmol), K_2CO_3 (0.415 g, 3 mmol) and NaBr (0.155 g, 1.5 mmol) with a septum, was injected pyridine (5 mL) under argon. The reaction mixture was stirred at 80 °C for 12 h. After cooling to room temperature, the mixture was filtered through a plug of Celite and washed with DCM. After the volatile was removed under vacuum, the solids was recrystallized by DCM–ether to give **3d** as a yellow solid (0.18 g, 82%). $[\alpha]_D^{25}$ = 72.4°; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.72 (d, J = 8.0 Hz, 2H), 7.62 (t, J = 8.0 Hz, 1H), 7.39–7.27 (m, 4H), 7.24–7.17 (m, 6H), 5.19–5.11 (m, 1H), 4.39–4.32 (m, 1H), 3.89 (t, J = 8.0 Hz, 1H), 3.79–3.72 (m, 1H), 3.69–3.62 (m, 1H), 3.60–3.55 (m, 1H), 3.37–3.26 (m, 2H), 2.84–2.78 (m, 1H), 2.06–1.91 (m, 2H), 1.58–1.52 (m, 2H), 1.48 (d, J = 8.0 Hz, 3H), 1.43 (d, J = 4.0 Hz, 3H), 1.16 (d, J = 8.0 Hz, 3H), 1.07 (t, J = 8.0 Hz, 6H). ^{13}C NMR ($CDCl_3$, 100 MHz): 182.1, 152.3, 148.3, 137.5, 135.9, 134.2, 129.5, 129.2, 129.0, 127.1, 124.5, 124.3, 59.9, 58.3, 49.0, 38.2, 30.0, 28.5, 28.3, 27.2, 24.5, 24.4, 20.3, 14.1. Anal. Calc. for $C_{31}H_{41}Br_2N_3Pd$ (721.07 g mol^{-1}): C, 51.58; H, 5.72; N, 5.82. Found: C, 51.33; H, 5.54; N, 6.03%.

General procedure for the Sonogashira coupling reaction

In a typical run, a 5 mL vial equipped with a magnetic bar was charged with a mixture of aryl halide (1 mmol), alkyne (2 mmol), Pd catalyst (0.01 mmol), K_2CO_3 (2 mmol) and 2 mL of DMSO in air. The reaction was heated at 100 °C for 1 h, after which time the mixture was cooled to room temperature and brine was added to it. The resulting mixture was extracted with ethyl acetate 3 times, and the crude oil was obtained by removing the volatile. The product was purified by flash column chromatography on silica gel.

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