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Full Paper

An Enantiomerically Pure Pyridine *NC*-Palladacycle Derived from [2.2]Paracyclophane

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An enantiomerically pure planar chiral pyridine-based palladacycle was prepared from [2.2]paracyclophane in just four steps. The palladacycle shows potential in catalysis, mediating the Suzuki coupling of an aryl chloride. It also permits the *ortho* bromination of [2.2]paracyclophane, a reaction that can be hard to achieve selectively.

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Introduction

[2.2]Paracyclophane (**1**; R = H; Fig. 1) is a robust molecule that comprises two aryl rings held in close proximity by two ethyl bridges. Its rigid structure has the potential to create well defined chiral scaffolds for use in asymmetric catalysis, medicinal chemistry, and materials science.[1–6] Yet [2.2]paracyclophane has only seen limited use in these areas. Two challenges curtail its exploitation, the resolution of planar chiral enantiomers and the functionalisation of substituted derivatives.[7–10] At present there are no enantioselective syntheses and all routes to [2.2]paracyclophane derivatives require a resolution step. Access to enantiopure forms of the common starting materials, such as mono- and dibromo[2.2]paracyclophane, are not trivial. The chemistry of [2.2]paracyclophane is littered with idiosyncrasies and it is not always possible to transfer simple aromatic chemistry to [2.2]paracyclophane without encountering unusual reactivity. One challenging example is the *ortho*-functionalisation of 4-substituted [2.2]paracyclophanes; a range of selectivity issues have been observed including reaction at the bridgehead (C2), at the *para*-position (C7), and at the 'directing' group itself.[11,12]

We are interested in developing methodology that permits the facile formation of enantiopure polysubstituted [2.2]paracylcophane derivatives. Previously we have used sulfoxides as traceless chiral auxiliaries for the formation of enantiopure monosubstituted [2.2]paracyclophane derivatives.[9,13–15] Frustratingly, our methodology was not compatible with our implementation of Fagnou's C–H activation chemistry,[16–18] which we had employed in the synthesis of planar chiral Lewis base catalysts.[19] In those studies we had to resolve dibromo[2.2]paracyclophane before arylation. As the formation of the pyridine *N*-oxide derivatives proceeded with only moderate yield precious resolved materials were wasted. We believed it would be advantageous to resolve the planar chiral pyridine-substituted [2.2]paracyclophanes themselves. As with our sulfoxide chemistry we were interested in achieving the resolution in a manner that would permit further functionalisation of the [2.2]paracyclophane framework.

Cyclopalladated complexes (CPCs) have found extensive use as pre-catalysts, catalysts,[20,21] and intermediates in several ligand transformations where the Pd–C bond is functionalised.[22,23] Chiral CPCs have been successfully employed as mild Lewis acids for asymmetric variants of the Overman rearrangement of allylic trichloroacetamides[24] and the hydrophosphination of methylidenemalonates[25] as well as in an example of an asymmetric Suzuki coupling.[26] The current interest in CPCs centres around their intermediacy in directed C–H activation chemistries. Either isolated CPCs or proposed CPC intermediates are readily transformed into a variety of C–O, C–X, C–P, and C–C bonds. Such reactions provide a mild and powerful method for the *ortho* functionalisation of aryl systems.[22]

Our initial goal was to develop a method that permitted the resolution of pyridyl [2.2]paracyclophanes and would allow us to modify the core of these molecules to form improved Lewis base catalysts[19] and sterically congested planar chiral monophosphanes for comparison with our planar chiral heterocyclic

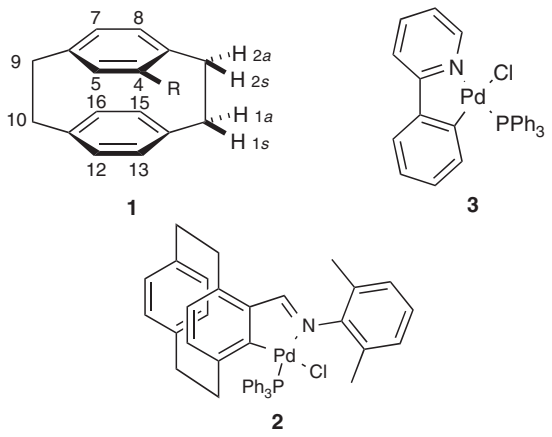


Fig. 1. [2.2]Paracyclophane (R = H; **1**) and cyclopalladated complexes **2** and **3**.

phosphanes.[27,28] Several [2.2]paracyclophane-based CPCs have previously been prepared: Dunina has reported the synthesis and resolution of both *C*,*P*-[29] and *C*,*N*-palladacycles **2**.[26,30] Richards demonstrated the elegant kinetic resolution of 4-*N*,*N*-dimethylaminomethyl[2.2]paracyclophane that proceeded by the selective formation of a CPC.[31] Bolm has highlighted the utility of CPCs to allow the problematic *ortho* (C5) functionalisation of [2.2]paracyclophanes first through the reaction of isolated *C*,*N*-CPC with potassium diphenylphosphide[11] and later through a catalytic process that permitted directed acetoxylations.[32]

In this paper, we report the synthesis of a CPC derived from 2-([2.2]paracyclophan-4-yl)pyridine, its resolution, and demonstrate its potential for the functionalisation of [2.2]paracyclophane and as a catalyst.

Results and Discussion

Racemic 2-([2.2]paracyclophan-4-yl)pyridine **4** was readily prepared from [2.2]paracyclophane **1** in three steps (Scheme 1):[33] bromination was followed by the direct arylation of pyridine *N*-oxide employing the chemistry of Fagnou.[16–18] The heterocyclic derivative was subjected to trichlorosilane-mediated reduction to furnish the pyridine **4**. This material can be obtained in 40–50 % yield after three steps and only one purification process, chromatographic separation of the *N*-oxide.

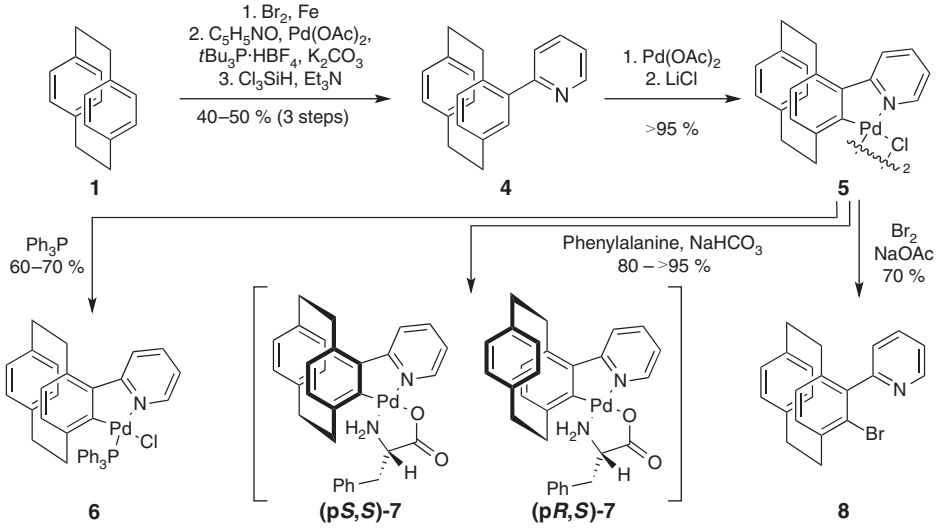
Formation of CPC **5** was achieved by heating a mixture of the pyridine **4** and palladium(II) acetate to 70°C overnight followed by ligand substitution with lithium chloride to give a yellow amorphous powder. It is assumed that the powder was a mixture of racemic and *meso* chloride-bridged diastereoisomers. No useful spectroscopic data could be obtained on this material except the high-resolution mass spectrum. This in conjunction with subsequent reactions implied that the desired CPC had been prepared.

In order to remove the issue of diastereoisomers and allow better characterisation of the CPC, the dimer was cleaved by treatment with triphenylphosphane. The resulting monomeric phosphane **6** was isolated in moderate yield (60–70 %). While it is possible that a regioisomeric mixture of CPCs containing both the *ortho*-palladated (aromatic C–H insertion) and the bridgehead-palladated (benzylic C–H insertion) species could have been formed,[11] analysis of the reaction mixture suggests that only the *ortho*-palladated molecule was prepared and the loss of material was a result of decomposition and not the formation of isomers.

The ^{1}H NMR spectrum indicates that the *ortho*-palladated CPC was isolated as a single isomer with the phosphane *trans* to the pyridine as expected. There are six discrete aromatic protons for the [2.2]paracyclophane backbone ranging from 6.90 to 5.66 ppm. Theses signals are distinct from the phenyl or pyridine aromatic protons' resonances, which range from 9.67 to 7.27 ppm. There are six well defined signals for ethylene protons and one multiplet with an integral of two protons confirming that no insertion into the bridging ethylene C–H bonds had occurred.

Interpretation of the NOESY spectrum for the CPC **6** permits identification of all the protons of the [2.2]paracyclophane backbone (Fig. 2).[34] The assignment was based on the strong interaction between H-9*s* and H-18, the proton *ortho* to the pyridine–[2.2]paracyclophane biaryl bond. A smaller interaction can be observed between H-10*s* and H-18. Each benzylic proton shows a strong interaction with the adjacent aromatic proton allowing simple interpretation. H-12, the proton *pseudo-gem* to the pyridine ring, displays a more shielded resonance than the analogous proton in the imine-based palladacycle[30] **2** (5.66 vs 6.49 ppm). Presumably this is the result of the anisotropic effect of the pyridine ring. The ring current of the pyridine ring can also be invoked to explain the deshielded resonance observed for H-9*s* that is at 3.89 ppm compared with 3.21–2.06 ppm for the other ethylene protons (and 3.07 ppm for [2.2]paracyclophane).

The *trans* (*P*,*N*)-geometry of the phosphane and the pyridine ligand was determined by NOE cross peaks between the *ortho* phenyl protons of the phosphane and both H-2*s* and H-1*s* of the PCP skeleton along with a weak interaction with H-2*a*. In addition, it is clear that H-2*a* is in a highly shielded environment with a resonance at 2.06 ppm compared with the other bridgehead protons that range between 2.58–3.89 ppm and H-2*s*, which is a multiplet between 2.91–2.98 ppm. A similar effect has been observed in the ^{1}H NMR spectra of the imine analogue and results from the proximity of the proton with the aromatic ring of the phosphane. For **6** the increased shielding for H-2*a* over H-2*s* is explained by the shorter distance of H-2*a* (on C2)



Scheme 1. Synthesis of pyridine-derived cyclopalladated complexes.

from the centroid of the nearest phenyl ring (2.97 Å) as compared with H-2*s* which is further away at 3.45 Å (Fig. 3). This correlation is comparable to the imine derivative in which the chemical shifts were 1.93 and 2.79 ppm and the distance between the analogous protons and the centroid were 2.81 and 3.34 Å for H-2*a* and H-2*s*, respectively.

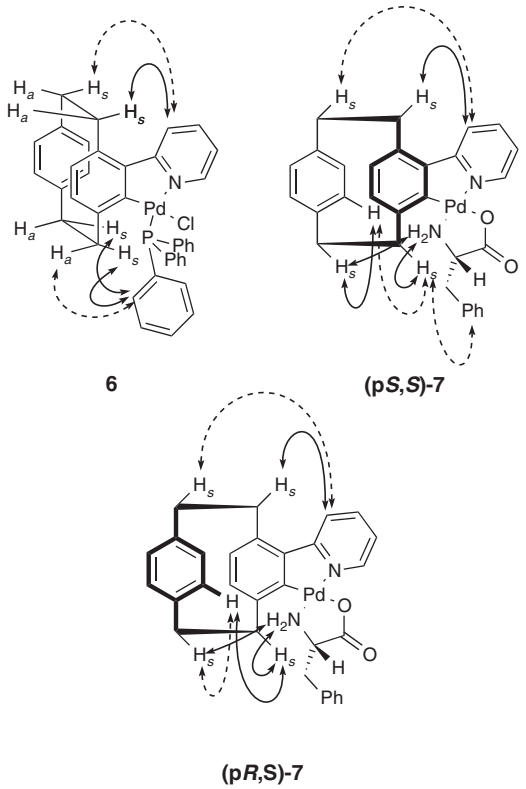


Fig. 2. Important NOESY interactions in the cyclopalladated complexes **6**, **(p*S*,*S*)-7**, and **(p*R*,*S*)-7**. Plain arrows indicate a strong NOESY interaction and dashed arrows a weak interaction.

Both the *ortho*-palladation and the relative orientations of the chloro and phosphane substituents were confirmed by X-ray crystallography (Fig. 3). The pyridine CPC is structurally similar to the previously reported imine-based CPC[30] and displays similar distortion of the palladium centre in comparison to the achiral phenyl derivative **3** (Fig. 1).[35] The key differences between the [2.2]paracyclophane-based CPC and the simple phenyl analogue **3** include the distortion of the geometry of the palladium and the elongation of the bonds to palladium. The achiral phenyl analogue **3** contains a planar palladium centre with an interplanar angle between the planes derived from the C–Pd–N and P–Pd–Cl atoms of 2.5°. The phosphane [2.2]paracyclophane complex **6** shows far greater distortion from the ideal planar system with the analogous interplanar angle of 22.0°. The imine-based CPC **2** displays a smaller distortion (16.9°) possibly reflecting a higher degree of conformational freedom for the imine substituent.

Bond lengths suggest a minimisation of steric interaction between the palladium substituents and the [2.2]paracyclophane backbone. The Pd–P bond length is longer in **6** (2.296(2) Å) than in either the imine-derivative (2.2703(7) Å)[30]or the achiral phenyl derivative (2.2510(5) Å) **3** (Fig. 1).[35] A similar elongation of the Pd–Cl bond is also observed for **6** (2.427 (1) Å) when compared with the analogous bond lengths for the imine and pyridine examples (2.3713(6) and 2.3707(7) Å, respectively).

The key step was the resolution of the racemic CPC and this was achieved by reacting the bridged chloro dimer **5** with the sodium salt of phenylalanine (Scheme 1). The reaction cleanly produces two complexes that were readily separated by column chromatography (SiO_2) and the structure, including absolute stereochemistry, of the first eluted material was determined by NMR spectroscopy and X-ray diffraction studies. It proved impossible to grow X-ray quality crystals of the second eluted molecule because of its reduced solubility and propensity for

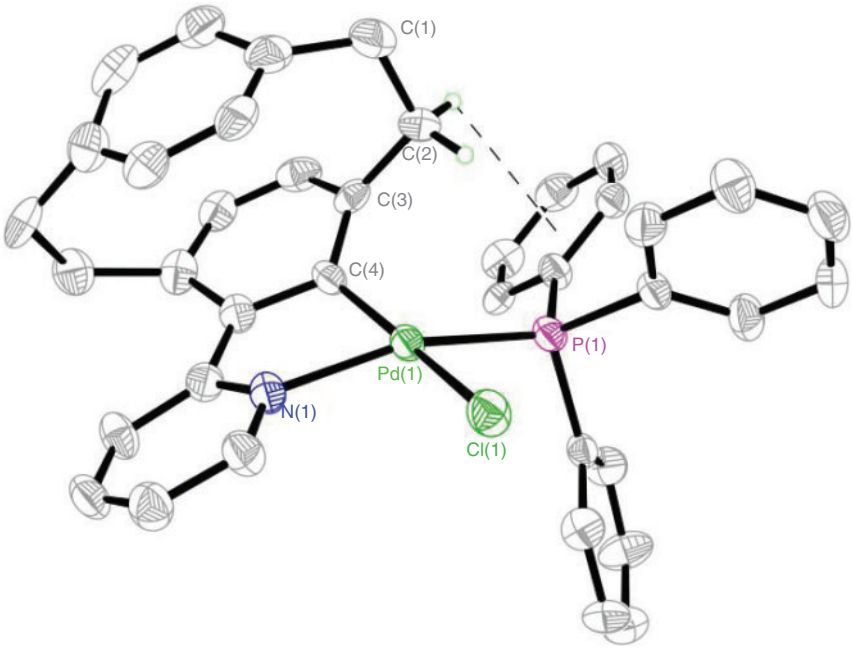


Fig. 3. X-ray structure of **6**. Solvent molecules and hydrogen atoms have been removed for clarity (except for H-2*a* and H-2*s*). The dashed line indicates the proximity of H-2*a* to the aryl ring of the phosphane. Ellipsoids are drawn at the 50 % probability level.[36]

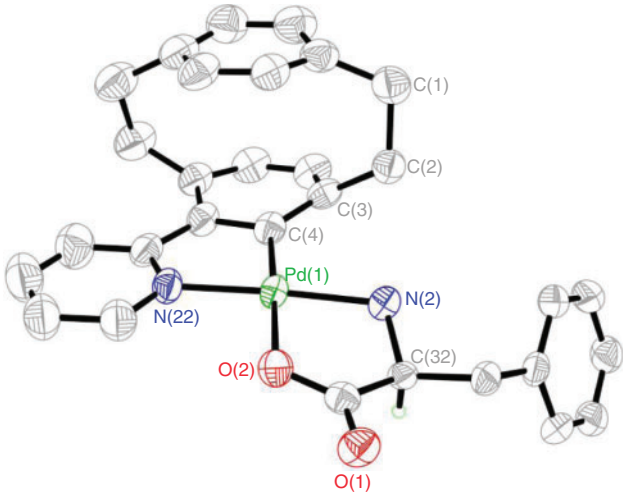


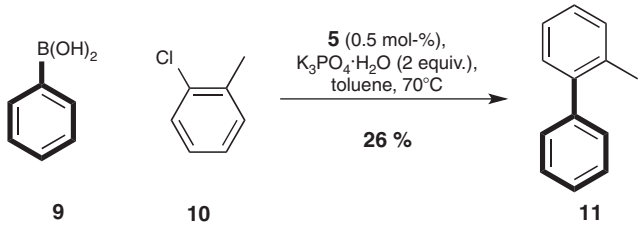
Fig. 4. X-ray structure of **(p*S*,*S*)-7**. Solvent molecules and hydrogen atoms have been removed for clarity (except for H32). Ellipsoids are drawn at the 50 % probability level.[37]

forming amorphous powders. Similarities in the ^{1}H NMR spectra, in conjunction with the mass balance for the reaction, indicate that the two complexes are diastereomeric, only differing by their planar chirality of the [2.2]paracyclophane backbone rather than geometry at the palladium centre.

The ^{1}H NMR spectrum of the reaction mixture indicates the formation of the expected 1 : 1 mixture of diastereomers.[34] The two complexes are very similar, only the resonances for the paracyclophane aromatic protons are differentiated in the two complexes; the alkyl protons of both [2.2]paracyclophane and phenylalanine occur between 3.95 and 2.53 ppm while the aromatic protons superimposed upon each other occur between 8.81 and 7.07 ppm. There are limited NOE interactions between the phenylalanine residue and the [2.2]paracyclophane backbone (Fig. 2). In both complexes the strongest of these interactions is found between H-2*s* and the axial and equatorial amine signals. This indicates that both isomers have the same geometry at the palladium centre with the amine *trans* to the pyridine. In the first complex eluted from the column there is a weak NOE interaction between the *ortho*-aromatic protons of the phenylalanine residue and H-2*s*. This suggests that this diastereomer has the phenylalanine 'inside' the [2.2]paracyclophane and determines that it is the (p*S*) diastereomer. This was confirmed by X-ray diffraction studies.

The ^{1}H NMR resonances for the bridgehead protons H-2*s* and H-2*a* for **(p*S*,*S*)-7** and **(p*R*,*S*)-7** are markedly different to those in the phosphane derivative. In the amino acid derivatives, H-2*s* is more shielded than H-2*a*, with a resonance of 2.54 and 2.53 ppm compared with 2.98–2.72 and 2.98–2.76 ppm. In the phosphane the pattern is reversed and H-2*a* has a lower resonance, 2.06 ppm compared with H-2*s*, which is 2.98–2.91 ppm. This dramatic change is a result of the anisotropic effect of the phenyl rings of the phosphane, which are orientated over the bridgehead. In the phenylalanine derivative neither H-2 proton is in close proximity to the phenyl ring.

The X-ray crystal structure of the first diastereomer eluted is shown in Fig. 4. It confirms the assignment of the (p*S*) stereochemistry of the [2.2]paracyclophane backbone and indicates that the *ortho*-hydrogen atoms of the phenyl ring are 3.156 Å from H-2*s* and could give rise to a weak NOE signal. The phenylalanine residue is free to rotate away from the [2.2] paracyclophane backbone reducing any steric interaction that would distort the palladium centre.



Scheme 2. Cyclopalladated complex-mediated Suzuki coupling of *p*-chlorotoluene.

We had three goals when we initially formed the CPCs, having shown that they could be used to resolve the planar chirality we then turned our attention to proving their competency as (pre)catalysts for coupling reactions and investigated the functionalisation of the *ortho*-position of the [2.2]paracyclophane ring. Our preliminary results, coupled with recent publications from other groups,[11,26,32] suggest that these palladacycles are useful materials. We only attempted the challenging coupling of an aryl chloride as it is clear that virtually all CPCs couple simple aryl bromides and iodides.[20] We were pleased to see that the simple chloride-bridged dimer **5** promoted the coupling of phenylboronic acid **9** and *para*-chlorotoluene **10** when the mixture was heated to 70°C in toluene to give the biaryl **11** in 26 % yield (Scheme 2). The yield is low but it shows that CPC **5** matches the efficiency of our best heterocyclic monophosphane while displaying the added advantage of being considerably easier to synthesise.[27] It should be noted that we cannot rule out the possibility that the dimer simply acts as a reservoir of active Pd^0 but the coupling of a chloride at a relatively low temperature (70°C) combined with the results of Dunina and co-workers for the analogous imine derivative[26] is encouraging.

CPC **5** also permits the *ortho*-functionalisation of the [2.2]paracyclophane backbone. Simple treatment with bromine gave the bromide **8** in excellent yield (Scheme 1) and we have no doubt that this material will be a useful precursor for the formation of functionalised planar chiral pyridine molecules. Based on the chemistry of Bolm and co-workers,[32] it is clear that the [2.2]paracyclophane-based palladacycles offer the opportunity to incorporate many different functional groups.

Conclusion

This paper describes the rapid preparation and resolution of a planar chiral palladacycle. The enantiomerically pure complex can be formed in just four steps from readily available [2.2]paracyclophane. The resulting complex shows potential in catalysis and is a suitable precursor for the further functionalisation of the notoriously problematic *ortho*-position of [2.2]paracyclophane. We are currently investigating the use of these complexes in the synthesis of new monophosphanes analogous to the successful (2-diphenylphosphino-1-naphthyl)isoquinoline (QUINAP) ligand[38–40] and research in this area will be published in due course.

Experimental

All starting compounds and solvents were used as received from commercial sources without further purification unless otherwise noted. 4-Bromo[2.2]paracyclophane was synthesised according a modification of the Cram and Day procedure

(Br_2/Fe in CH_2Cl_2); we have found that heating is unnecessary.[41] Column chromatography was carried out on silica gel (grade 60, mesh size 230–400, Scharlau). Visualisation techniques employed included using ultraviolet light (254 nm), potassium permanganate, ethanolic phosphomolybdic acid, or ninhydrin when applicable. NMR spectra were recorded at room temperature on Bruker-400 and Bruker-500 Avance instruments, with the use of the solvent proton as an internal standard. Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Mass spectra and high resolution mass spectrometry was performed at the Waikato Mass Spectrometry Facility, The University of Waikato, New Zealand.

2-([2.2]Paracyclophan-4-yl)pyridine N*-Oxide*

A suspension of 4-bromo[2.2]paracyclophane (1.50 g, 5.23 mmol, 1 equiv.), pyridine *N*-oxide (1.99 g, 20.91 mmol, 4.0 equiv.), K_2CO_3 (1.44 g, 10.45 mmol, 2.0 equiv.), *t*-$Bu_3P \cdot HBF_4$ (0.23 g, 0.78 mmol, 0.15 equiv.), and $Pd(OAc)_2$ (0.06 g, 0.26 mmol, 0.05 equiv.) in toluene (17.4 mL) was heated to reflux overnight. The reaction was cooled to room temperature and filtered through celite, washing with CH_2Cl_2/MeOH (1 : 1, 100 mL) and acetone/MeOH (1 : 1, 100 mL). The filtrate was concentrated and purified by gradient column chromatography (CH_2Cl_2/MeOH, 98 : 2 → 95 : 5 → 90 : 10). The resulting solid was placed on a sintered funnel and washed with Et_2O to remove the last traces of pyridine *N*-oxide and ligand by-products to give 2-([2.2]paracyclophan-4-yl)pyridine *N*-oxide (0.94 g, 66 %) as a white crystalline solid. mp 181–183°C. ν_{max} /cm^{-1} 3047, 2930, 1474, 1256, 1035, 765. δ_H (400 MHz, $CDCl_3$) 8.33 (1H, d, *J* 6.4, H-6pyr), 7.66 (1H, dd, *J* 7.8, 1.8, H-3pyr), 7.41 (1H, t, *J* 7.8, H-4pyr), 7.31–7.25 (1H, m, H-5pyr), 6.67 (1H, d, *J* 7.7, H-15/H-16), 6.64 (1H, d, *J* 8.4, H-16/H-15), 6.61 (2H, s, H-7, H-8), 6.57 (1H, s, H-5), 6.52 (2H, dd, *J* 12.0, 8.4 H-12, H-13), 3.35–3.04 (5H, m, CH_2), 2.99–2.92 (2H, m, CH_2), 2.85–2.79 (1H, m, CH_2). δ_C (125 MHz, $CDCl_3$) 150.9, 141.5, 140.3, 140.0, 139.6, 139.0, 135.1, 134.8, 133.6, 132.6, 132.4, 131.9, 130.9, 129.3, 128.1, 125.1, 124.4, 35.5, 35.4 (× 2), 35.0.*m/z* (HRMS EI) 324.1359; $C_{21}H_{19}NONa$ ($[M + Na]^+$) requires 324.1360.

2-([2.2]Paracyclophan-4-yl)pyridine ***4***

To a solution of 2-([2.2]paracyclophan-4-yl)pyridine *N*-oxide (0.94 g, 3.13 mmol, 1.0 equiv.) in CH_2Cl_2 (31.3 mL) at room temperature was added Cl_3SiH (4.74 mL, 46.89 mmol, 15.0 equiv.) and Et_3N (4.35 mL, 31.26 mmol, 10.0 equiv.) sequentially. The initial addition of Cl_3SiH causes considerable precipitate to form, hindering stirring of the suspension; addition of Et_3N results in a finer suspension that stirs more readily. The suspension was heated to reflux for 3 h and then cooled to 0°C and diluted with CH_2Cl_2 (20 mL). NaOH(aq) (1 M, 20 mL) was added cautiously. Further CH_2Cl_2 (20 mL) and NaOH(aq) (1 M, 20 mL) was added and the suspension stirred at room temperature until effervescence had ceased and most solid had dissolved (~2 h). The layers were separated and the aqueous layer extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give a residue that was purified by column chromatography (elution EtOAc/hexane, 3 : 2) followed by recrystallisation from hot CH_2Cl_2 to give 2-([2.2]paracyclophan-4-yl)pyridine **4** (0.71 g, 80 %). Mp 136–137°C. ν_{max} /cm^{-1} 3046, 2982, 2934, 2894, 2855, 1584, 1566, 1500, 1467, 1424, 1266, 1146. δ_H (400 MHz, $CDCl_3$) 8.77 (1H, d, *J* 4.8, H-6pyr), 7.79 (1H, td, *J* 7.7, 1.9, H-4pyr), 7.53 (1H, d, *J* 7.9, H-3pyr), 7.26–7.23 (1H, m, H-5pyr), 6.84 (1H, d, *J* 1.6, H-5), 6.64–6.55 (6H, m, H-7, H-8, H-12, H-13, H-15, H-16), 3.74–3.66 (1H, m, H-2), 3.24–3.15 (2H, m, 2 × C*H*H), 3.12–3.05 (2H, m, 2 × C*H*H), 3.03–2.91 (2H, m, 2 × C*H*H), 2.71–2.63 (1H, m, C*H*H). δ_C (125 MHz, $CDCl_3$) 159.1, 149.6, 140.6, 139.8, 139.6, 139.4, 138.2, 136.3, 136.2, 133.2, 132.9, 132.7, 132.6, 132.4, 130.7, 124.2, 121.4, 35.5, 35.3, 35.2, 34.5. *m/z* (HRMS ESI) 286.1591; $C_{21}H_{20}N$ ($[M + H]^+$) requires 286.1590.

*Racemic Di-μ-chlorobis{5-(pyridin-2-yl)[2.2] paracyclophan-4-yl-*C,N*}dipalladium(II) (±)-****5***

A suspension of 2-([2.2]paracyclophan-4-yl)pyridine **4** (0.47 g, 1.64 mmol, 1.0 equiv.) and palladium(II) acetate (0.39 g, 1.72 mmol, 1.05 equiv.) in toluene (16.4 mL) was heated to 70°C overnight. The solvent was removed and the residue dissolved in acetone (16.4 mL). To this was added lithium chloride (0.14 g, 3.28 mmol, 2.0 equiv.) and the resulting suspension was stirred at room temperature for 3 h. The solid was removed by filtration and washed with water to give **5** as an amorphous yellow powder (0.39 g). A second crop of **5** was obtained by adding water to the acetone filtrate and filtering the resulting precipitate, which was washed with water to give **5** (0.30 g; combined yield was 0.69 g; > 95 %). *m/z* (HRMS ESI) 815.0665; Anal. Calc. for $C_{42}H_{36}^{35}ClN_2Pd_2$ 815.0631. *m/z* (HRMS ESI) 390.0496; Anal. Calc. for $C_{21}H_{18}NPd$ ($[0.5M - Cl]^+$) 390.0469. *m/z* 817, 535, 390, 284.

*Racemic Chloro{5-(pyridin-2-yl)[2.2]paracyclophan-4-yl-*C,N*}(triphenylphosphane-*P*)palladium(II) (±)-****6***

To a yellow suspension of racemic di-μ-chlorobis{5-(pyridin-2-yl)[2.2]paracyclophan-4-yl-*C,N*}dipalladium(II) (±)-**5** (0.11 g, 0.13 mmol, 1.0 equiv.) in toluene (5 mL) was added triphenylphosphane (0.06 g, 0.25 mmol, 2.0 equiv.). The suspension was stirred at room temperature for 2.5 h. The volume of toluene was reduced to ~2 mL and hexane was added until no more precipitate formed. The solid was filtered off and the crude material purified by recrystallisation (CH_2Cl_2/Et_2O) to give **6** (0.05 g; 60 %). Mp 194–195°C (dec.). ν_{max} /cm^{-1} 3052, 2925, 2856, 1600, 1566, 1530, 1481, 1464, 1446, 1265, 1097, 739. δ_H (400 MHz, $CDCl_3$) 9.67 (1H, t, *J* 3.7, H-21), 7.96–7.89 (2H, m, H-18, H-19), 7.68–7.63 (6H, m, 6 × Ar-H_m), 7.40–7.36 (3H, m, 3 × Ar-H_p), 7.31–7.27 (7H, m, H-20, 6 × Ar-H_o), 6.90 (1H, dd, *J* 7.7, 1.6, H-13), 6.47 (1H, dd, *J* 7.8, 1.5, H-16), 6.39 (1H, dd, *J* 7.9, 1.6, H-15), 6.13 (1H, d, *J* 7.7, H-7), 5.71 (1H, d, *J* 7.0, H-8), 5.66 (1H, dd, *J* 7.7, 1.7, H-12), 3.89 (1H, dd, *J* 14.3, 8.2, H-9_s), 3.21 (1H, ddd, *J* 13.1, 10.5, 4.3, H-1_s), 3.03 (1H, dd, *J* 12.6, 9.5, H-10_a), 2.98–2.91 (1H, m, H-2_s), 2.86–2.74 (2H, m, H-1_a, H-9_a), 2.58 (1H, ddd, *J* 12.9, 8.7, 8.6, H-10_s), 2.06 (1H, ddd, *J* 13.8, 10.6, 4.4, H-2_a). δ_C (100 MHz, $CDCl_3$) 167.7, 167.6, 166.4, 166.3, 150.7, 147.2, 146.11, 146.1, 139.7, 138.2, 138.1, 135.9, 135.6, 135.3, 134.2, 133.0, 132.9, 132.6, 132.0, 131.9, 131.8, 131.5, 130.3, 130.2, 129.7, 127.8, 127.7, 122.9, 120.5, 120.5, 41.6, 36.4, 35.9, 33.6. δ_P (162 MHz, $CDCl_3$) 31.5. *m/z* (HRMS ESI) 652.1394; Anal. Calc. for $C_{39}H_{33}NPPd$ 652.1380. *m/z* 652, 390, 339, 284.

*(pS,S)-{5-(Pyridin-2-yl)[2.2]paracyclophan-4-yl-*C,N*} (phenylalaninato-*N,O*)palladium(II)* ***(pS,S)-7*** *and (p*R,S*)-{5-(Pyridin-2-yl)[2.2]paracyclophan-4-yl-*C,N*} (phenylalaninato-*N,O*)palladium(II)* ***(pR,S)-7***

To a yellow suspension of racemic di-μ-chlorobis{5-(pyridin-2-yl)[2.2]paracyclophan-4-yl-*C,N*}dipalladium(II) (±)-**5** (0.18 g, 0.21 mmol, 1.0 equiv.) in MeOH (21 mL) was added (*S*)-phenylalanine (0.07 g, 0.42 mmol, 2.0 equiv.) and $NaHCO_3$

(0.04 g, 0.42 mmol, 2.0 equiv.). The suspension was stirred at room temperature overnight. After 2 h a clear brown solution had formed. The solvent was removed under reduced pressure and the residue diluted with CH_2Cl_2 (3 mL). The solid was removed by filtration and the filtrate concentrated. The crude material was purified by column chromatography (acetone/CH_2Cl_2, 9 : 1). First eluted was (p*S*,*S*)-{5-(pyridin-2-yl)[2.2]paracyclophan-4-yl-*C*,*N*}(phenylalaninato-*N*,*O*)palladium(II) **(p*S*,*S*)-7** as a yellow powder (0.06 g; 55 % assuming racemic starting material). Mp 219–221°C (dec.). $[\alpha]_D$ −88.0 (*c* 0.85, $CHCl_3$). ν_{max} /cm^{-1} 3332, 3222, 3029, 2923, 2853, 1622, 1599, 1532, 1482, 1385, 1265, 1154, 1078, 935, 724. δ_H (400 MHz, $CDCl_3$) 8.79 (1H, s, H-21), 7.81 (2H, d, *J* 4.7, H-18, H-19), 7.45–7.31 (5H, m, Ar-H), 7.07 (1H, d, *J* 4.0, H-20), 6.80 (1H, d, *J* 6.8, H-13), 6.59 (1H, d, *J* 7.7, H-16), 6.54 (1H, d, *J* 7.7, H-15), 6.23–6.22 (1H, m, H-7), 6.13–6.11 (1H, m, H-8), 5.93 (1H, d, *J* 6.7, H-12), 3.98–3.89 (1H, m, H-23), 3.87–3.78 (1H, m, H-9*s*), 3.54 (1H, dd, *J* 14.6, 3.0, H-24), 3.38 (1H, br s, NH), 3.25 (1H, dd, *J* 14.0, 10.0, H-24), 3.18–3.03 (3H, m, H-1*s*, H-10*s*, NH), 2.98–2.72 (4H, m, H-1*a*, H-2*a*, H-9*a*, H-10*a*), 2.54 (1H, ddd, *J* 13.6, 8.9, 4.9, H-2*s*). δ_C (100 MHz, $CDCl_3$) 178.0, 165.8, 158.4, 150.3, 145.9, 144.4, 138.9, 138.7, 138.4, 136.7, 135.9, 134.3, 133.2, 132.6, 132.3, 131.7, 130.4, 129.3, 127.5, 122.1, 120.9, 60.9, 40.6, 36.6, 36.5, 35.9, 33.7. *m*/*z* (HRMS ESI) 577.1088; Anal. Calc. for $C_{30}H_{28}N_2NaO_2Pd$ 577.1078. *m*/*z* 577, 473, 381, 353, 284.

Second eluted was (p*R*,*S*)-{5-(pyridin-2-yl)[2.2]paracyclophan-4-yl-*C*,*N*}(phenylalaninato-*N*,*O*)palladium(II) **(p*R*,*S*)-7** as a yellow powder (0.05 g; 45 % assuming racemic starting material). Mp 206–209°C (dec.). $[\alpha]_D$ +91.7 (*c* 1.31, $CHCl_3$). δ_H (400 MHz, $CDCl_3$) 8.81 (1H, d, *J* 5.4, H-21), 7.86–7.83 (2H, m, H-18, H-19), 7.28–7.21 (3H, m, 2 × H-27, H-28), 7.19–7.16 (2H, m, 2 × H-26), 7.10 (1H, dd, *J* 9.0, 5.4, H-20), 6.90 (1H, dd, *J* 7.8, 1.4, H-13), 6.62 (1H, dd, *J* 7.9, 1.5, H-16), 6.57 (1H, dd, *J* 7.9, 1.6, H-15), 6.31 (1H, d, *J* 7.8, H-7), 6.22 (1H, d, *J* 7.8, H-8), 6.01 (1H, dd, *J* 7.8, 1.8, H-12), 3.95–3.83 (2H, m, H-9*s*, H-23), 3.69–3.62 (1H, m, NH), 3.49 (1H, dd, *J* 13.9, 3.2, H-24), 3.28 (1H, dd, *J* 13.9, 11.2, H-24), 3.20–3.12 (2H, m, H-1*s*, H-10*a*), 2.98–2.76 (5H, m, H-1*a*, H-2*a*, H-9*a*, H-10*s*, NH), 2.53 (1H, ddd, *J* 13.8, 9.7, 5.1, H-2*s*). δ_C (100 MHz, $CDCl_3$) 178.8, 165.9, 158.0, 151.3, 144.3, 138.9, 138.8, 138.4, 136.6, 135.8, 134.3, 133.3, 132.6, 132.4, 131.7, 130.6, 129.2, 129.2, 127.4, 122.1, 120.9, 62.4, 40.3, 36.6, 36.5, 35.9, 33.8. *m*/*z* (HRMS ESI) 577.1089; Anal. Calc. for $C_{30}H_{28}N_2NaO_2Pd$ 577.1078. *m*/*z* 577, 473, 390, 284.

*Racemic 4-Bromo-5-(pyridin-2-yl)[2.2] paracyclophane (±)-**8***

A suspension of Br_2 (0.015 mL, 0.29 mmol, 2.10 equiv.) and NaOAc (0.02 g, 0.27 mmol, 1.95 equiv.) in CCl_4 (3 mL) was added dropwise over 30 min to a yellow/green suspension of palladacycle **5** (0.12 g, 0.14 mmol, 1.00 equiv.) in CH_2Cl_2 (3.5 mL) at room temperature. As the Br_2 was added the suspension of palladacycle cleared to give a deep red solution. The solution was stirred at room temperature for 1 h and then poured into aqueous sat. $Na_2S_2O_3$ (10 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to give an orange solid. The crude material was purified by column chromatography (1 % EtOAc/CH_2Cl_2) to give **8** as a pale yellow powder (0.071 g; 70 %). δ_H (400 MHz, $CDCl_3$) 7.72 (1H, td, *J* 7.8, 1.5), 7.59 (1H, d, *J* 7.1), 7.19 (1H, dd, *J* 5.7, 1.1), 7.16 (1H, d, *J* 7.7), 6.86 (1H, d, *J* 7.7), 6.83–6.76 (3H, m), 6.49 (1H, d, *J* 7.8), 3.60 (1H, ddd, *J* 13.5, 8.1, 4.8), 3.35 (1H, dd, *J* 11.2, 10.0), 3.27–3.16 (1H, m), 3.13–3.06 (1H, m), 2.97–2.88 (1H, m), 2.86–2.82 (2H, m), 2.33–2.25 (1H, m). δ_C (100 MHz, $CDCl_3$) 159.4, 155.1, 145.2, 140.3, 139.5, 139.3, 137.5, 137.1, 136.6, 135.3, 134.0, 132.2, 129.2, 128.6, 127.5, 125.3, 123.2, 37.2, 36.3, 35.5, 33.4. *m*/*z* (HRMS ESI) 364.0695; Anal. Calc. for $C_{21}H^{79}_{19}BrN$ 364.0695.

2-Methyl-1,1′-biphenyl

A suspension of phenylboronic acid **9** (0.20 g, 1.64 mmol, 1.5 equiv.), *p*-chlorotoluene **10** (0.13 mL, 1.09 mmol, 1.0 equiv.), $K_3PO_4 \cdot H_2O$ (0.51 g, 2.20 mmol, 2.0 equiv.), and CPC **5** (0.005 g, 0.005 mmol, 0.005 equiv. (1 mol % Pd)) in toluene (5.5 mL) was heated to 70°C for 12 h. The solvent was removed and the crude material purified by column chromatography (hexane/EtOAc) to give **11** (0.05 g, 26 %). Two subsequent repeats produced similar results (21 and 29 %). All data were in agreement with the literature.[42]

X-Ray Crystallography

X-Ray data of the compounds **6** and **7** were recorded at low temperature with a Rigaku-Spider X-ray diffractometer, comprising a Rigaku MM007 microfocus copper rotating-anode generator, high-flux Osmic monochromating and focussing multilayer mirror optics ($Cu_{K\alpha}$ radiation, λ 1.5418 Å), and a curved image-plate detector. *CrystalClear*[43] was utilised for data collection and *FSProcess* in *PROCESS-AUTO*[44] for cell refinement and data reduction. All structures were solved employing direct methods and expanded by Fourier techniques.[45] Non-hydrogen atoms were refined anisotropically. Hydrogen atoms were placed in calculated positions and refined using a riding model with fixed isotropic *U* values. For compound **6** two of the chlorine atoms in the dichloromethane solvent molecule are positionally disordered in the ratio of (0.75 : 0.25 for Cl11 and Cl12 respectively).

Crystal data for **6**: $C_{39}H_{33}ClNPPd \cdot CH_2Cl_2$, *M* 771.39, *T* 153 (1) K, λ 1.5418 Å, monoclinic, space group $P2_1/n$, *a* 18.1862(3), *b* 9.9971(2), *c* 19.6312(14) Å, β 108.832(8)°, *V* 3378.1(3) Å^3, *Z* 4, D_c 1.517 mg m^{-3}, $\mu(Cu_{K\alpha})$ 7.293 mm^{-1}, *F*(000) 1568, crystal size 0.02 × 0.07 × 0.09 mm^3. 33 359 reflections measured, 5966 independent reflections (R_{int} 0.071), the final *R* was 0.0546 [$I > 2\sigma(I)$], and $wR(F^2)$ was 0.1420 (all data).

Crystal data for **(p*S*,*S*)-7**: $C_{30}H_{28}N_2O_2Pd \cdot CH_2Cl_2$, *M* 639.87, *T* 153(2) K, λ 1.5418 Å, monoclinic, space group $P2_1$, *a* 11.7563(4), *b* 9.3095(4), *c* 13.8116(10) Å, β 113.256(8)°, *V* 1388.80(15) Å^3, *Z* 2, D_c 1.530 mg m^{-3}, $\mu(Cu_{K\alpha})$ 7.408 mm^{-1}, *F*(000) 652, crystal size 0.1 × 0.2 × 0.2 mm^3. 15 212 reflections measured, 4562 independent reflections (R_{int} 0.041), the final *R* was 0.0397 [$I > 2\sigma(I)$], and $wR(F^2)$ was 0.0855 (all data).

Supplementary Material

^{1}H, ^{13}C, and ^{31}P NMR spectra for all new compounds are available on the Journal's website.

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[37] CCDC-956996 contains the supplementary crystallographic data for compound (p*S,S*)**-7**. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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