Regioselective ortho-Palladation of [2.2]Paracyclophane Scaffolds: Accessing Planar and Central Chiral N, C-Palladacycles

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In this report, we describe a series of cyclophanyl-derived mono- and binuclear N,C-palladacycles by regioselective ortho-palladation of amine-functionalized [2.2]paracyclophanes. Employing Pd(OAc)₂ followed by LiCl and with the subsequent modular treatment of Ph₃P, Cy₃P, and (Ph₂PCH₂)₂, this strategy allows to prepare stable cyclophanyl-derived planar and central chiral N,C-palladacycles in a highly selective manner. The regioselective ortho-palladation mono- and bimetallic product formation was analyzed by detailed spectroscopic techniques, mass spectrometry and unambiguously confirmed by single-crystal X-ray analysis.

Cyclometallated complexes as precatalysts or intermediates in complex molecular architectures have seen tremendous progress in terms of synthetic advances, their versatile structural features, and emerging synthetic applications.[1] Among cyclometallated derivatives, palladacycles in particular have attracted much interest as an important class of catalysts that commonly contain one or more intramolecularly coordinated donor atoms (typically N, P) to give a stabilized five or six-membered Pd-chelated ring(s).[2] Coordination-capable ligands, for instance, amines, imines, pyridines, pyrimidines, oxazolines and other N-, O-, and P-containing derivatives are known that can form stable cyclopalladated systems.[3] From the application perspectives, palladacyle-directed diverse synthetic transformations, where it acts as an intermediate to controls regioselectivity, are well documented.[4]

[2.2]Paracyclophane (cyclophanyl; PCP) is a co-facially stacked prochiral scaffold that features unusual characteristics caused by transannular electronic effects of the stacked benzene rings and exhibits unique stereochemical features (planar chirality) on functionalization.[5] Cyclopalladated ligands bearing N-, O-, and P-containing moieties enable the installation of metal centers. Bolm and co-workers first described the regioselective palladation of 2-oxazolinyl-PCP.[6] The competing metalation in ortho-position and at the bridgehead of the PCP was observed (Figure 1). Furthermore, metal to phosphine exchange on treatment with potassium diphenyl-phosphate.

Figure 1. Representative previous work on non-cyclophanyl and cyclophanyl-derived cyclometallated complexes.
phosphide enabled access to PCP-derived planar chiral phosphines. Later, Dunina and co-workers reported direct cyclopalladation of a PCP-derived imine to afford ortho-palladated imine complexes, and a phosphinite-P,C-palladacycle. Rowlands and co-workers have reported pyridine-based cyclophanyl palladacycles that mediate Suzuki–Miyaura reaction of aryl chlorides. Some other PCP-derived palladacycles have also been reported.

Cyclophanyl-derived chelates enable the formation of precatalysts and as intermediate synths in various molecular systems have been demonstrated. We and others have a long-standing interest in the development of new and generally useful classes of PCP-based planar chiral ligands and catalysts, which are successfully employed as a toolbox for various stereo-controlled transformations. Previously, a series of oxazolinyl substituted and PCP bearing pyridines located on different decks that display various regioisomers for their ability to undergo ortho-palladation product formation were introduced that hold two Ru-metal centers with defined distance and spatial orientation. In this work, we sought to develop a series of new mono- and bimetallic N,C-palladacycles by regioselective ortho-palladation of amine- and imine-functionalized PCPs, employing Pd(OAc)$_2$, and LiCl followed by the modular treatment of Ph$_2$P, Cy$_2$P, and (Ph$_2$P)$_2$CH$_2$ (dppe). The dimethylammonium derivative was prepared by reductive amination starting from 4-acetyl[2,2]paracyclopehane (1, Scheme 1A).

Following a previously established procedure, 2b was obtained with a d.r. $>$ 99:1 in 51% yield. A similar procedure was followed for the preparation of dimethylamine derivative 2a, which gave the product in 63% yield. We had previously investigated the crucial role of the $N,N$-dimethylamino group (route A); subsequent treatment of the mixture with lithium chloride in acetone, the dimeric structure could be isolated and transformed into the mono-metallic N,C-palladacycle 5a and 5c by reaction with 1.0 equiv. of either PPh$_3$ or PCy$_3$ (Scheme 1B). Reaction with $^6$Bu$_3$P led to no conversion and only the dimeric compound 3b was reisolated. The formation of other regioisomers, for instance, the bridgehead-palladated species (benzyl position of the PCP skeleton) was not observed in any case.

Next, we introduced 1,2-bis(diphenylphosphino)ethane (dppe, Scheme 2) as bis-dentate ligand. The use of 0.5 equiv. dppe as ligand resulted in a binuclear N,C-palladacycle complex 6. In this scaffold, the bisphosphine acts as a bridge between the two metal centers showing that a binuclear complex can be formed on this sterically demanding scaffold. All cyclophanyl-derived complexes were purified by flash column chromatography and air stable. The regioselective ortho-palladation product formation was analyzed by spectroscopic techniques, and mass spectrometry. The PPh$_3$, PCy$_3$ and (Ph$_2$P)$_2$CH$_2$ containing monometallic 5a, 5c, and dinuclear N,C-palladacycles 6 were unambiguously characterized by single-crystal X-ray analysis as shown in Figure 2.

The coordination geometry of the Pd-moieties can be described as distorted square planar (distortion towards a compressed tetrahedral coordination), where C- and Cl- as well as N- and P-substituents are in trans-position, respectively. In the coordination sphere of the Pd-centers, the two ortho-palladated phosphines are in cis-compressed tetrahedral coordination), where C- and Cl- as well as N- and P-substituents are in trans-position, respectively. In the coordination sphere of the Pd-centers, the two ortho-palladated phosphines are in cis-

Scheme 1. Reductive amination of PCP-derivatives and dichloro-bridged dimers formation (route A); subsequent treatment of 3 with phosphines for the synthesis of N,C-palladacycles 4 and 5 (route B).

Scheme 2. Synthesis of the binuclear Pd-complex PCP-Pd-Cl-dppe 6.
cycles $(S)_5\alpha$ and $(S)_5\gamma$ could be obtained in good yields which are potential candidates for their application in cross-coupling as well as regio-controlled *ortho*-functionalization of the PCP scaffold. Controlling regioselectivity in transforming PCP scaffolds at a particular position poses notable drawbacks and limitations are associated with conventional approaches, for instance, multiple pre-functionalization steps, undesired side products, and a lack of selectivity due to the competing reactivity of the multiple C–H bonds of chemically very similar nature.[17] Employing cyclopalladated-PCPs for the regio-controlled transformations, might overcome these hurdles. Some further studies are certainly needed to demonstrate the synthetic utility of cyclopalladated-PCPs.

### Experimental Section

Crystallographic data: Deposition Numbers 1048638 (for $5\alpha$), 1048639 (for $5\gamma$), and 1048640 (for $6$) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

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### Conflict of Interest

The authors declare no competing financial interest.

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**Figure 2.** Molecular structure of $5\alpha$, $5\gamma$, and $6$. Solvent molecules and hydrogen atoms are omitted for clarity, displacement parameters are drawn at 50% probability level.

| Table 1. Selected bond distances and angles of the PCP-derived mono- and dinuclear N,C-palladacycles. |
|---|---|---|
| Bond type | $5\alpha$ | $5\gamma$ | $6^{[a]}$ |
| Pd–C | 2.0216(14) | 2.019(2) | 2.009(2) |
| Pd–Cl | 2.4072(4) | 2.4068(6) | 2.4102(7) |
| Pd–P | 2.2651(4) | 2.2847(6) | 2.2555(7) |
| Pd–N | 2.1475(13) | 2.147(18) | 2.133(2) |
| C–Pd–N | 81.56(4) | 80.88(8) | 81.96(9) |
| C–Pd–P | 98.53(4) | 97.60(6) | 98.28(7) |
| C–Pd–Cl | 167.94(4) | 169.21(6) | 172.53(7) |
| N–Pd–P | 160.62(4) | 165.72(5) | 165.11(6) |
| N–Pd–Cl | 92.61(4) | 91.16(5) | 93.91(6) |
| P–Pd–Cl | 90.476(16) | 91.24(2) | 87.32(2) |

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