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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 Ph_3P, Cy_3P, and $(Ph_2PCH_2)_2$, 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, palladacycle-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] Cyclophanyl-derived 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-

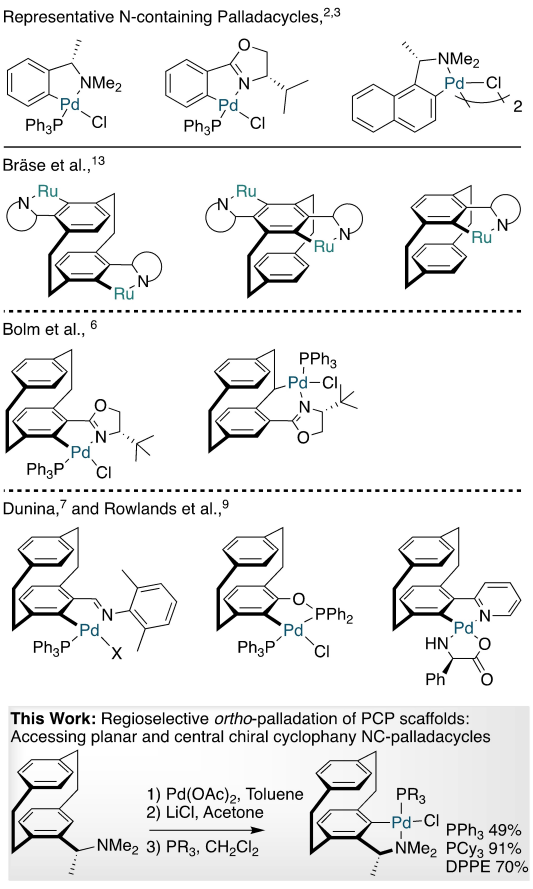

Figure 1. Representative previous work on non-cyclophanyl and cyclophanyl-derived cyclometallated complexes.

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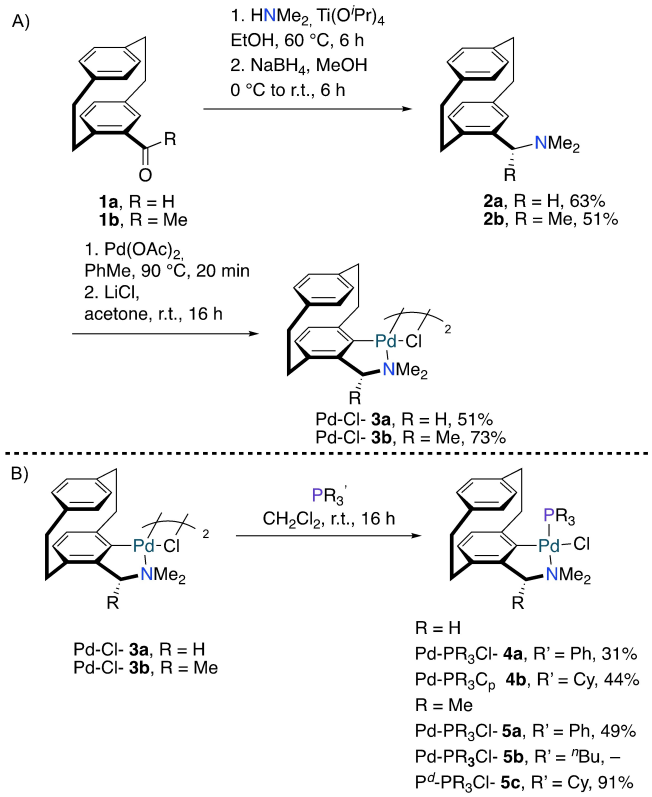
phosphide enabled access to PCP-derived planar chiral phosphines. Later, Dunina and co-workers reported direct cyclopalladation of a PCP-derived imine to afford *ortho*-palladated imine complexes,[7] and a phosphinite-P,C-palladacycle.[8] Rowlands and co-workers have reported pyridine-based cyclophanyl palladacycles that mediate Suzuki–Miyaura reaction of aryl chlorides..[9] Some other PCP-derived palladacycles have also been reported.[10]

Cyclophanyl-derived chelates enable the formation of precatalysts and as intermediate synthons in various molecular systems have been demonstrated.[11] 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.[12] Previously, a series of oxazolinyl substituted and PCP bearing pyridines located on different decks that display various regioisomers for their ability in mono- and dinuclear regioselective cycloruthenation complexes with $[RuCl_2(p\text{-cymene})]_2$ were introduced that hold two Ru-metal centers with defined distance and spatial orientation.[13] 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_3P, Cy_3P, and $(Ph_2PCH_2)_2$ (dppe). The dimethylethylamine derivative **2b** was prepared by reductive amination starting from 4-acetyl[2.2]paracyclophane (**1**, Scheme 1A).



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).

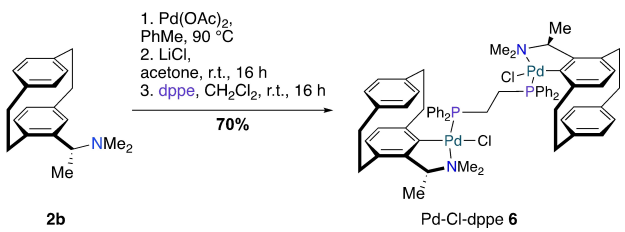
Following a previously established procedure, **2b** was obtained with a d.r. >99:1 in 51% yield.[14] A similar procedure was followed for the preparation of dimethylmethylamine derivative **2a**, which gave the product in 63% yield. We had previously investigated the crucial role of the *N*,*N*-dimethylethylamino group grafted onto **2b** in a directed and regioselective lithiation at pseudo-*ortho* position of the PCP scaffold.[14] This ultimately furnished pseudo-*ortho* functionalized PCP-derivatives upon reaction with electrophiles. The *ortho*-palladated N,C-dimer **3a** using **2a** (previously established by Dunina and co-workers) as well as its transformation into the monometallic derivative **4a** were performed under our modified reaction conditions (Scheme 1).[15]

Combining two or more chiral elements into a ligand or catalyst system could enable stereochemical cooperativity, which provides a powerful strategy for the optimization and tuning of the stereochemical outcome. Therefore we incorporated an additional central-chiral element into the PCP scaffold which exhibits the innate element of planar chirality. The PCP derivative **2b** was reacted with palladium(II) acetate in hot toluene. By treatment of the mixture with lithium chloride in acetone, the dimeric structure **3b** could be isolated and transformed into the mono-metallic N,C-palladacycles **5a** and **5c** by reaction with 1.0 equiv. of either PPh_3 or PCy_3 (Scheme 1B). Reaction with $^nBu_3P$ led to no conversion and only the dimeric compound **3b** was reisolated. The formation of other regioisomers, for instance, the bridgehead-palladated species (benzylic 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 detailed spectroscopic techniques, and mass spectrometry. The PPh_3, PCy_3 and $(Ph_2PCH_2)_2$ 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



Scheme 2. Synthesis of the binuclear Pd-complex PCP-Pd-Cl-dppe **6**.

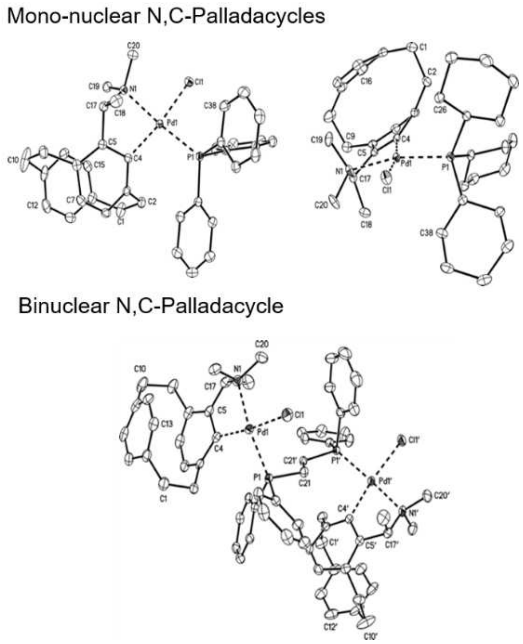


Figure 2. Molecular structure of **5 a**, **5 c**, and **6**. Solvent molecules and hydrogen atoms are omitted for clarity, displacement parameters are drawn at 50 % probability level.

Table 1, selected structural data is reported. Bond distances [Å] and angles [°] are in the expectancy range of palladacycles compared to the related literature values (which are fully described in the Supporting Information).

For the formation of enantiomerically pure palladacycles, chiral resolution of 4-formyl-PCP (**1 a**) and 4-acetyl-PCP (**1 b**) to access enantiomerically pure planar and central chiral precursors has been the crucial step.[16] Starting from enantiomerically pure (S_p)-**1 b**, the corresponding enantiomerically pure palladacycles (S_p)-**5 a** and (S_p)-**5 c** 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.

Table 1. Selected bond distances and angles of the PCP-derived mono- and dinuclear N,C-palladacycles.

Bond type	**5 a**	**5 c**	**6**[a]
Pd–C	2.0216(14)	2.019(2)	2.009(2) 2.007(2)
Pd–Cl	2.4072(4)	2.4068(6)	2.4102(7) 2.3823(7)
Pd–P	2.2651(4)	2.2847(6)	2.2555(7) 2.2550(7)
Pd–N	2.1475(13)	2.1447(18)	2.133(2) 2.140(2)
C–Pd–N	81.56(4)	80.88(8)	81.96(9) 80.78(9)
C–Pd–P	98.53(4)	97.60(6)	98.28(7) 95.67(7)
C–Pd–Cl	167.94(4)	169.21(6)	172.52(7) 172.60(7)
N–Pd–P	160.62(4)	165.72(5)	165.11(6) 167.16(6)
N–Pd–Cl	92.61(4)	91.66(5)	93.91(6) 94.23(6)
P–Pd–Cl	90.476(16)	91.24(2)	87.32(2) 90.37(3)

[a] Two Pd-moieties.

Experimental Section

Crystallographic data: Deposition Numbers 1048638 (for **5 a**), 1048639 (for **5 c**), 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.

Keywords: Cyclometallation · Palladacycles · Planar chirality · [2.2]Paracyclophane · Regioselectivity

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