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C–H Activation in Primary 3-Phenylpropylamines: Synthesis of Seven-Membered Palladacycles through Orthometalation. Stoichiometric Preparation of Benzazepinones and Catalytic Synthesis of Ureas

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Abstract

The dimeric cyclometalated complexes $[Pd_2\{\kappa^2C,N\text{-}C_6H_4CH_2CH_2C(R)(Me)NH_2\text{-}2\}_2(\mu\text{-}Cl)_2]$ (R = Me (**1a**), H (**1b**)) are prepared by reacting 1,1-dimethyl-3-phenylpropylammonium or 1-methyl-3-phenylpropylammonium triflate with $Pd(OAc)_2$ in a 1:1 molar ratio, and subsequent treatment with excess NaCl. The mononuclear derivatives $[Pd\{\kappa^2C,N\text{-}C_6H_4CH_2CH_2C(R)(Me)NH_2\text{-}2\}Cl(L)]$ (L = PPh_3, R = Me (**3a**), H (**3b**); L = 4-picoline (4-pic), R = Me (**4a**), H (**4b**)) were prepared from **1a**,**b**, by splitting the chloro-bridges with the neutral ligands L. A conformational analysis of the mononuclear

palladacycles in solution has been carried out. Insertion of CO takes place into the Pd–C bond of complexes **1a**,**b** affording Pd(0) and the tetrahydro-benzazepinone **5a** or **5b**, which possesses potential pharmacological interest. Additionally, the triflate salt **A** or **B** undergoes catalytic carbonylation with CO to afford the corresponding *N*,*N*'-dialkylurea, using $Pd(OAc)_2/Cu(OAc)_2$, in boiling acetonitrile. The crystal structures of **3a**·1/2H_2O, **3b**, **4b**·$CHCl_3$, and **5a** were determined by X-ray diffraction studies.

Introduction

It is well established that most palladium-catalyzed C–H functionalizations assisted by heteroatom-containing directing groups occur through cyclometalated intermediates.[1,2] Because of this, there has been an increasing interest in the study of ortho-palladated complexes as models to reach a deep understanding of the mechanism of these catalytic transformations.

The most common palladacycles are those that contain *N*-donor ligands and five- or six-membered rings.[3] Several methods are used in their synthesis. These include metalation, transmetalation, carbometalation, or oxidative addition reactions. The most interesting method, from a catalytic point of view, is the metalation since it involves the direct activation of a C–H bond by a palladium salt. Seven-membered palladacycles are relatively scarce and, to the best of our knowledge, only one of them has been obtained by metalation of an arene.[4] The synthesis of the reported seven-membered palladacycles comprises: (1) insertion of alkynes into the Pd–C bond of five-membered palladacycles,[5] or of RNC into the Pd–C bond of six-membered palladacycles,[6] (2) coordination of a donor atom of a functionalized ligand previously C-bonded to Pd(II),[7] (3) coordination to Pd(II) of bis-N-heterocyclic carbenes, bis-ylides, or phosphine-

carbene ligands usually generated in situ,[8] (4) oxidative addition of $Ar^{P,N,S}X$ ($Ar^{P,N,S}$ = PR_2, NR_2, py, or RS-functionalized aryl; X = Br, I) to Pd(0) compounds,[9] followed occasionally by a C–C coupling reaction,[10] and (5) C–H activation by a Pd(II) salt, where the metalated CH can belong to an allyl,[11] a phenyl,[4] or a methyl group.[12] It is worthy to note that the later are very uncommon processes: the allylic activation affords a pincer complex,[11] the C_{aryl}–H activation occurs in a tetraphenylcyclobutadiene complex of Co(II),[4] and the C(sp^3)–H palladation takes place in a di-*tert*-butyl(biaryl)phosphine coordinated to Pd(II).[12] Shi, Zhao et al. have also reported the sequential alkenylation of oxalyl amide protected phenylpropylamine derivatives via a seven-membered palladacycle, which can be detected in a stoichiometric reaction in an NMR tube.[13]

The initial work of Cope and Friedrich[14] on cyclopalladation of arylalkylamines stated that this type of ligand could only be ortho-metalated when (1) the amine was tertiary, (2) a five-membered metallacycle was formed, and (3) the aromatic ring was not deactivated towards electrophilic attack.[15] Since then, these rules have been partially or completely broken, and thus, ortho-metalated derivatives of a wide variety of primary benzyl- and phenethylamines containing electron withdrawing or releasing substituents on the aromatic ring have been obtained.[6,16,17,18,19-22] However, there are no precedents for the synthesis of the corresponding seven-membered palladacycles. In this work, the synthesis and isolation of these metallacycles, prepared by direct palladation of a C_{aryl}–H bond of phenylpropylamine derivatives, is described for first time. These examples may pave the way for the development of new palladium-catalyzed directed C–H functionalizations via these unusual rings.[23]

We also report the insertion of CO into the Pd–C bond of the cyclometalated complexes, affording Pd(0) and the tetrahydro-3-benzazepin-1-ones **5**, which possess

potential pharmacological interest.[24] This moiety constitutes the core structure of some pharmacologically relevant compounds that have been tested as modulators for dopamine (D_3),[25,26] and serotonin (5-HT_{2A}, 5-HT_{2C}, and 5-HT_6) receptors,[26,27] as well as inhibitors for glycogen synthase kinase (GSK-3)[28] or anaplastic lymphoma kinase (ALK).[29] According to these studies, these compounds could play important roles in the treatment of severe health disorders such as depression, anxiety, schizophrenia, pain, epilepsy, obesity, diabetes, cancer, and neurodegenerative diseases.

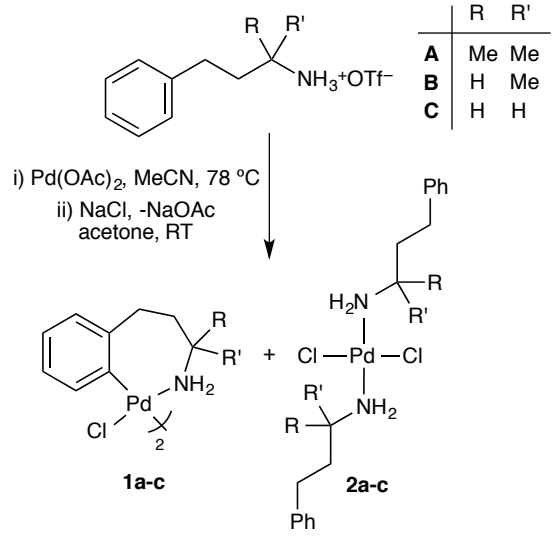
Results and Discussion

The Orthometalation Reaction: Synthesis of Seven-Membered Palladacycles. We have reported that a simple change in the starting materials usually employed in the orthometalation reactions of arylalkylamines can drastically affect the success of the reaction.[21] Thus, when using not the free amines but the corresponding ammonium triflates, (1) orthometalation of new arylalkylamines could be achieved,[22] and (2) the yields of previously reported orthopalladation reactions could be significatively improved.[21] These results were explained on the basis of the enhanced electrophilicity of the Pd(II) intermediate formed when the ammonium triflate is used as starting material. We planned to use this improved method to synthesize new seven-membered palladacycles derived from phenylpropylamines, as the free amines do not react with $Pd(OAc)_2$ to afford the corresponding ortho-metalated complexes.

Indeed, the chloro-bridged cyclopalladated complex [$Pd_2(\kappa^2C,N$-$C_6H_4CH_2CH_2CMe_2NH_2$-2)$_2(\mu$-Cl)$_2$] (**1a**), containing a novel seven-membered ring, was obtained in good yield (70%) by reacting the ammonium triflate derived from 1,1-dimethyl-3-phenylpropylamine with 1 equiv of $Pd(OAc)_2$, in acetonitrile at 78 ºC, followed

by treatment with NaCl (Scheme 1). No previous orthopalladation of any phenylpropylamine has been reported.

Scheme 1. Synthesis of Seven-Membered Palladacyles



	R	R'
A	Me	Me
B	H	Me
C	H	H

	R	R'	**1**	**2**
a	Me	Me	71%	--
b	H	Me	46%	33%
c	H	H	0%	70%

An analogous reaction sequence, starting from 1-methyl-3-phenylpropylammonium triflate, afforded a mixture, from which two different complexes could be isolated: $[Pd_2\{\kappa^2C,N\text{-}C_6H_4CH_2CH_2CH(Me)NH_2\text{-}2\}_2(\mu\text{-}Cl)_2]$ (**1b**; 46%), containing the ortho-metalated phenylpropylamine, and $[PdCl_2\{NH_2CH(Me)CH_2CH_2Ph\}_2]$ (**2b**; 33%). Complex **2b** could be independently prepared by reaction of $PdCl_2$ and two equiv of 1-methyl-3-phenylpropylamine. Other authors have reported the synthesis of complex **2b** from $[Pd_2\{\kappa^2C,N\text{-}C_6H_4CH_2CH_2CH(Me)NH_2\text{-}2\}_2(\mu\text{-}OAc)_2]$ and NaCl.[30] Finally, orthometalation of 3-phenylpropylammonium triflate was pursued under the same reaction conditions, but in this case only the coordination complex $[PdCl_2\{NH_2CH_2CH_2CH_2Ph\}_2]$ (**2c**; 70%) was isolated, i.e., orthometalation was not observed for the amine with no substituents in α-

position. It has previously been reported that α-substitution in arylalkylamines promotes the intramolecular C–H bond activation, an effect that was attributed to steric factors affecting the stability and reactivity of the reaction intermediates.[20,31,32]

Complexes **1a** and **1b** are insoluble in CH_2Cl_2 and $CHCl_3$ but very soluble in DMSO. Most likely, the DMSO splits the chloro-bridges, leading to mononuclear species in solution.[33,34] The ^1H and ^{13}C NMR spectra of **1a** and **1b** (in DMSO-d_6) confirm the metalation of the aromatic ring: in the ^1H spectra there are only four aromatic proton resonances, while in the aromatic region of their APT spectra, the expected resonances for two quaternary and four tertiary carbons can be observed. Interestingly, the ^1H NMR spectrum of **1a** (in DMSO-d_6, 25 ºC) reveals the diastereotopic nature of the hydrogen atoms of the NH_2 and CH_2 groups, as well as the Me groups of the CMe_2 moiety, an indication that the molecule is chiral in solution, i.e., either the seven-membered ring is not fluxional, or its fluxionality does not result in the equivalence of the two sides of the molecule. For **1b**, the ^1H and ^{13}C NMR spectra (in DMSO-d_6) reveal the presence of two diastereoisomers in solution, in ca. 2:1 molar ratio, being for each of them the hydrogen atoms of the NH_2 and CH_2 groups, as well as the Me groups of the CMe_2 moiety, again diastereotopic. These two diastereoisomers must arise from the presence in **1b** of two sources of chirality: the asymmetric carbon of the starting amine, and the (at least partial) rigidity of the chelate ring.

As expected, some of the ^1H and ^{13}C resonances of the non-chelate complex **2b** also show two sets of signals, in a 1:1 ratio, which belong to the two possible diastereoisomers (*RR* + *SS*, and the meso form *RS*). For each of them, the hydrogen atoms within each NH_2 and CH_2 group are again diastereotopic.

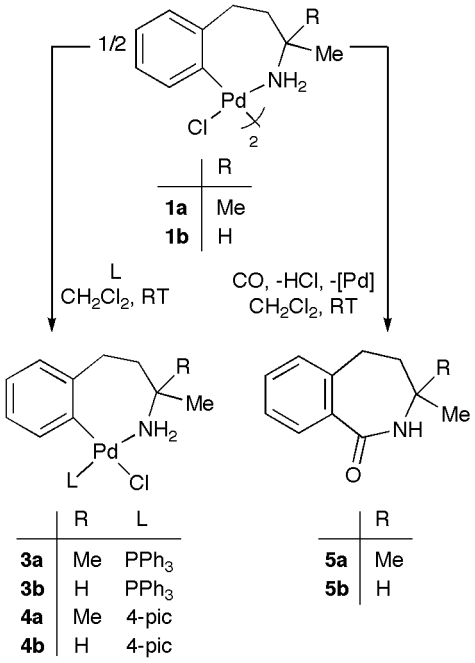
Finally, the ^1H and ^{13}C NMR spectra of complex **2c**, (R = R' = H), with neither chiral

centers nor cyclopalladated moieties, show the presence of only one isomer in solution, for which the protons of the NH_2 and CH_2 groups are not diastereotopic.

The IR spectra of **2b** and **2c** show one band at ca. 340 cm^{-1} (**2b**: 340; **2c**: 337 cm^{-1}) assigned to the ν(Pd–Cl) stretching vibration and consistent with a *trans*-Cl–Pd–Cl geometry,[35] as usual for this type of complexes.[32,33,36]

Reactions of Seven-Membered Palladacycles with Neutral Ligands. Chloro-bridges in dimeric ortho-palladated complexes containing primary arylalkylamines are easily split by neutral ligands, such as phosphines or pyridines,[16,19,37,38] to give mononuclear complexes. Thus, the reaction of the dimeric complexes **1a,b** with triphenyphosphine or 4-picoline (4-pic) in a 1:2 molar ratio, at room temperature in CH_2Cl_2, led to the mononuclear derivatives [Pd{κ^2*C,N*-$C_6H_4CH_2CH_2C(R)(Me)NH_2$-2}Cl(L)] (L = PPh_3, R = Me (**3a**), H (**3b**); L = 4-pic, R = Me (**4a**), H (**4b**)) (Scheme 2). In all the new complexes, the incoming ligand is coordinated trans to the amino group, as expected according to the greater transphobia between C-/P- and C-/N-donors than between N-/P- and N-/N-donor pairs, respectively.[38,39]

Scheme 2. Synthesis of Mononuclear Derivatives and Lactams



	R
1a	Me
1b	H

	R	L
3a	Me	PPh_3
3b	H	PPh_3
4a	Me	4-pic
4b	H	4-pic

	R
5a	Me
5b	H

Despite their apparent similarity, complexes **3a** (L = PPh_3) and **4a** (L = 4-pic) show quite different behaviors in solution, according to their ^{1}H NMR spectra in $CDCl_3$ (Figure 1). For **3a** the two protons of the NH_2 and CH_2 groups, as well as the Me groups of the CMe_2 moiety, are diastereotopic. In contrast, for **4a** there is only one ^{1}H resonance for each of these groups, an indication that in this complex the palladacycle ring is fluxional at room temperature, making both sides of the molecule equivalent in the NMR timescale. It is necessary to lower the temperature to –40 ºC to slow down this conformational fluxionality (Figure 2). A lineshape analysis of the VT ^{1}H NMR spectra, using the program gNMR (see Figure S13 in the Supporting Information), has revealed an Arrhenius activation energy for the fluxional process of 12.4 kcal mol^{-1}. This value is in the upper range of those reported for the exchange between different conformations in seven-membered DIOP chelate rings (between ca. 6 and 12 kcal mol^{-1}).[40]

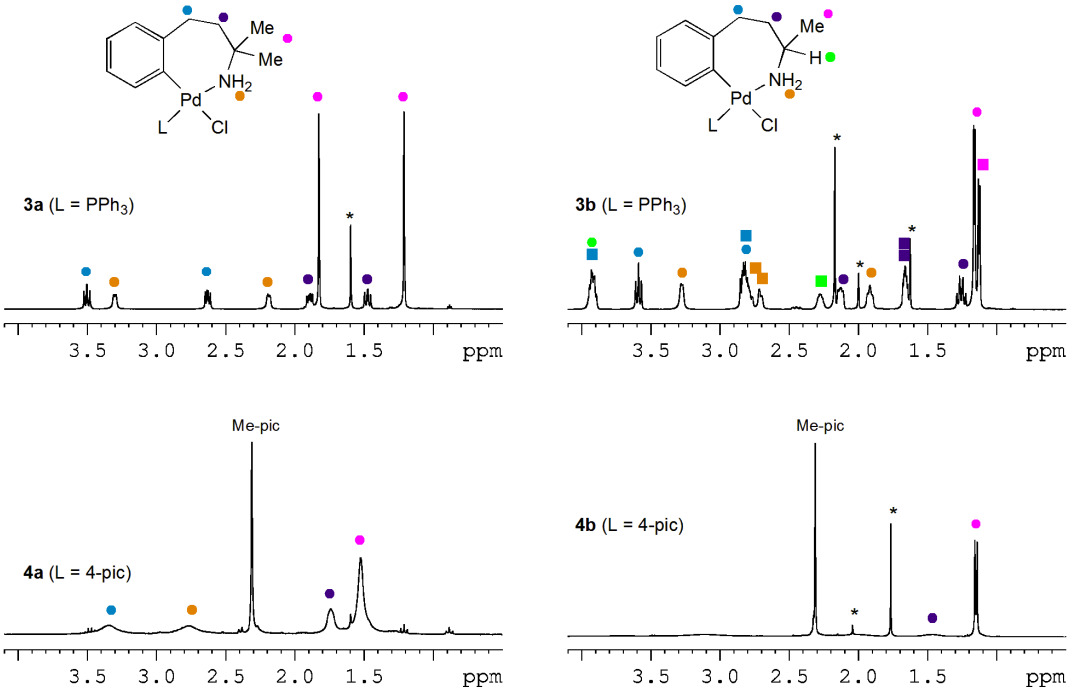


Figure 1. ^{1}H NMR spectra (0.5–4.1 ppm) of complexes **3a,b** (600 MHz) and **4a,b** (400 MHz) in $CDCl_3$ at room temperature. The asterisks indicate the signals corresponding to traces of solvents. For **3b**, the circles and squares correspond to the major and minor diastereoisomers, respectively.

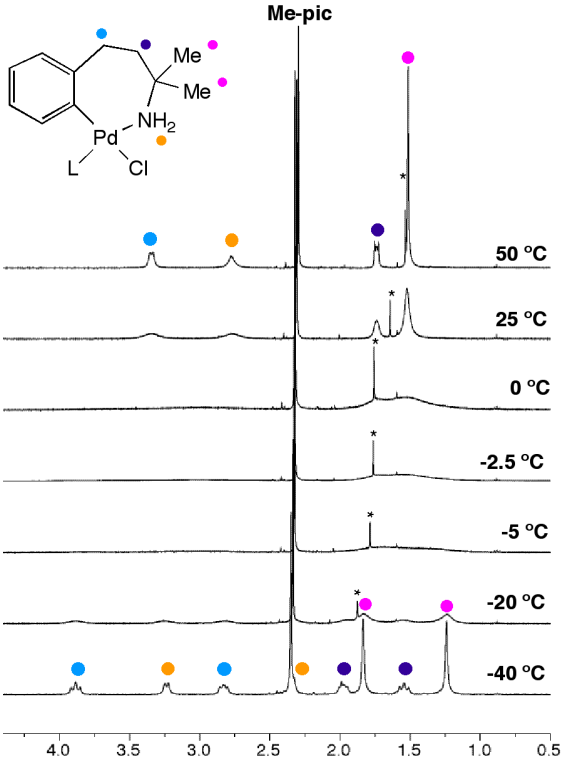


Figure 2. VT ^{1}H NMR spectra of complex **4a** in $CDCl_3$ (aliphatic region). The asterisks indicate the signals corresponding to traces of solvents.

Complexes **3b** and **4b** contain a chiral center in the asymmetric carbon of the starting amine, and thus, if the cyclopalladated ring is relatively rigid, two diastereoisomers are expected in their NMR spectra, as described above for **1b**. This is indeed the case for **3b** (L = PPh_3), which at room temperature shows the separate ^{1}H, ^{13}C, and ^{31}P NMR resonances of two diastereoisomers, in ca. 1.3:1 molar ratio (Figure 1). For each of them, the hydrogen atoms of the NH_2 and CH_2 groups are diastereotopic. An NMR sample of **3b** was heated to 55 ºC (in $CDCl_3$), to check if the ring became more fluxional at the higher temperature, but both diastereoisomers where still observed, with no significant line broadening. In contrast, complex **4b** (L = 4-pic), similarly to **4a**, is fluxional at room temperature and shows only one set of NMR resonances. The ^{1}H resonances of the $CH_2CH_2CH(Me)NH_2$ moiety are so broad that they are almost

imperceptible, with the exception of the Me group, which appears as a single doublet (Figure 1). When the temperature is decreased to –50 ºC, the ^{1}H and APT RMN spectra of **4b** show the expected two diastereoisomers in ca. 1.4:1 ratio, being, for each of them, the hydrogen atoms of the NH_2 and CH_2 groups diastereotopic.

Thus, there is a very significant difference in the fluxional behavior between complexes **3a**,**b** (L = PPh_3) and **4a**,**b** (L = pic), in $CDCl_3$. We suggest that the reason for this difference arises from the steric hindrance of the PPh_3 in **3a**,**b**, which hinders the conformational changes in the ring as a result of the proximity between the Ar ring of the metalated ligand and the Ph rings of the phosphine. This spatial proximity is confirmed by the ^{1}H NOESY spectra of **3a**,**b**, which show strong NOE contacts between the o-H's of the PPh_3 and the aryl H6 proton (see Figure S8 in the Supporting Information).

The crystal structures of complexes **3a**·1/2H_2O, **3b**, and **4b**·$CHCl_3$ (Figures 3–5) were determined by X-ray diffraction studies. For complexes **3b** and **4b**·$CHCl_3$, there are two independent molecules in the asymmetric unit (A and B). The three structures displayed the palladium atoms in square-planar or distorted square-planar geometries, with mean deviations of the Pd(II)-coordination plane between 0.001 and 0.062 Å (**3a**·1/2H_2O: 0.062 Å; **3b**: (A) 0.030 Å, (B) 0.030 Å; **4b**·$CHCl_3$: (A) 0.001 Å, (B) 0.001 Å), and dihedral angles of 0.3–6.4° between the planes N–Pd–C and Cl–Pd–X (**3a**·1/2H_2O, X = P: 6.4º; **3b**, X = P: (A) 3.0°, (B) 3.8°; **4b**·$CHCl_3$, X = N: (A) 0.3°, (B) 2.4°). The chelated ligand formed a seven-membered metallacycle, with a chair conformation[41] for complex **3a**·1/2H_2O. For complexes **3b** and **4b**·$CHCl_3$, one of the two molecules of the asymmetric unit is disordered over two positions (occupancy distribution: **3b**, ca. 82:12; **4b**·$CHCl_3$, ca. 73:27). The metallacycles in the non-disordered molecules adopt a chair (**3b**) or a boat conformation (**4b**·$CHCl_3$). In the disordered molecules, both conformations

are present, corresponding the major occupancy distribution to the same conformation as for the non-disordered molecule (i.e., chair for **3b** and boat for **4**·$CHCl_3$). The plane of the metalated aryl ring formed an angle of 55–67º with the coordination plane of the Pd atom (**3a**·1/2H_2O, 67º; **3b**, (A) 65°, (B) 66°; **4b**·$CHCl_3$, (A) 54.8°, (B) 62.1°). As expected, the nitrogen atom of the amine and the phosphorus or nitrogen atom of the monodentated ligand are mutually trans; for complex **4b**·$CHCl_3$, the picoline ring is rotated ca. 70º with respect to the metalated aryl ring to avoid steric hindrance (A, 65.9º; B, 74.6º).

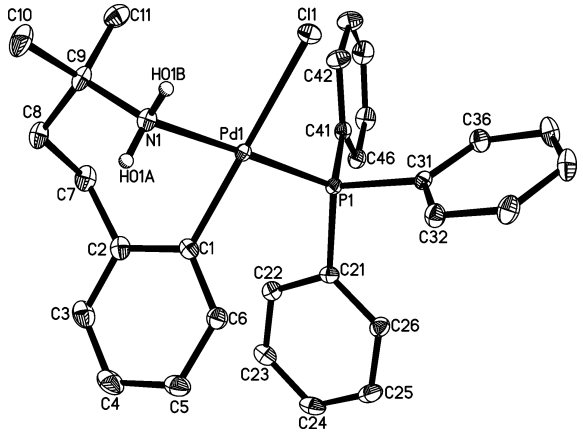


Figure 3. X-ray thermal ellipsoid plot of complex **3a**·1/2H_2O (50% probability). The solvent molecule and the hydrogen atoms bonded to carbon have been omitted for clarity. Selected bond lengths (Å) and angles (deg): Pd(1)–C(1) = 1.9969(14), Pd(1)–N(1) = 2.1112(12), Pd(1)–Cl(1) = 2.4334(4), Pd(1)–P(1) = 2.2570(4); C(1)–Pd(1)–N(1) = 85.83(5), N(1)–Pd(1)–Cl(1) = 89.08(4), Cl(1)–Pd(1)–P(1) = 92.633(13), P(1)–Pd(1)–C(1) = 92.55(4).

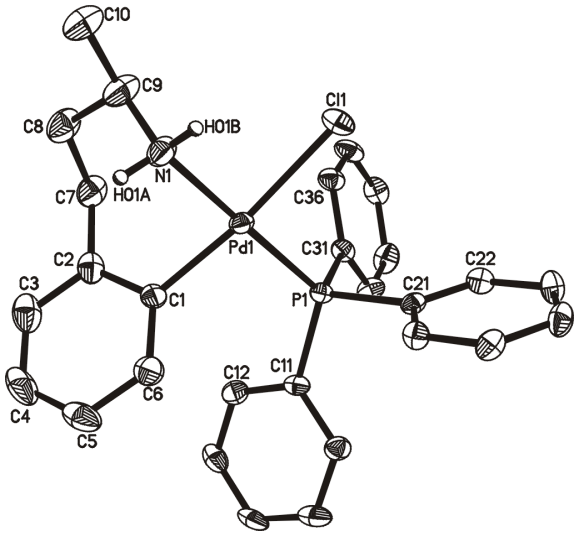


Figure 4. X-ray thermal ellipsoid plot of one (A) of the two independent molecules of complex **3b** (50% probability). The hydrogen atoms bonded to carbon have been omitted for clarity. Selected bond lengths (Å) and angles (deg) are given for both independent molecules present in the asymmetric unit (A and B): (A) Pd(1)–C(1) = 1.998(4), Pd(1)–N(1) = 2.101(3), Pd(1)–Cl(1) = 2.4051(12), Pd(1)–P(1) = 2.2413(11); C(1)–Pd(1)–N(1) = 86.11(15), N(1)–Pd(1)–Cl(1) = 88.05(11), Cl(1)–Pd(1)–P(1) = 91.28(4), P(1)–Pd(1)–C(1) = 94.59(11). (B) Pd(2)–C(41) = 1.992(4), Pd(2)–N(2) = 2.115(4), Pd(2)–Cl(2) = 2.4052(10), Pd(2)–P(2) = 2.2535(11); C(41)–Pd(2)–N(2) = 85.81(17), N(2)–Pd(2)–Cl(2) = 87.81(14), Cl(2)–Pd(2)–P(2) = 93.55(4), P(2)–Pd(2)–C(41) = 92.84(10).

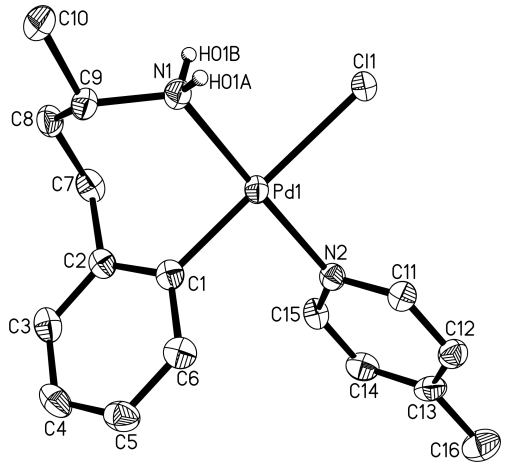


Figure 5. X-ray thermal ellipsoid plot of one (A) of the two independent molecules of complex **4b**·$CHCl_3$ (50% probability). The solvent molecule and the hydrogen atoms have been omitted for clarity. Selected bond lengths (Å) and angles (deg) are given for both independent molecules present in the asymmetric unit (A and B): (A) Pd(1)–C(1) = 1.990(4), Pd(1)–N(1) = 2.066(3), Pd(1)–Cl(1) = 2.4408(10), Pd(1)–N(2) = 2.044(3); C(1)–Pd(1)–N(1) = 93.99(15), N(1)–Pd(1)–Cl(1) = 86.68(10), Cl(1)–Pd(1)–N(2) = 92.03(9), N(2)–Pd(1)–C(1) = 87.30(14). (B) Pd(2)–C(21) = 1.983(4), Pd(2)–N(3) = 2.055(15), Pd(2)–Cl(2) = 2.4361(12), Pd(2)–N(4) = 2.029(3); C(21)–Pd(2)–N(3) = 94.6(2), N(3)–Pd(2)–Cl(2) = 85.45(19), Cl(2)–Pd(2)–N(4) = 90.65(9), N(4)–Pd(2)–C(21) = 89.22(14).

Conformational Investigation in Solution. We have investigated the structure in solution of the palladacycles **1a**,**b** (in DMSO-d_6) and **3a**,**b** (in $CDCl_3$) which, as described above, appear to have a relatively rigid cyclopalladated ring in solution. The relatively scarce reports that have dealt with the conformational behavior of seven-membered rings concern mainly organic molecules,[42,41,43] and describe the possibility of several chair and boat conformations.[41] Although there are investigations concerning complexes with seven-membered *P*,*P*-chelates, no studies have been performed on seven-membered *C*,*N*-metallacycles, such as those described in this article. In contrast, there are some reports on the conformations of five- or six-membered palladacycles.[44,45]

To try to elucidate the structures in solution, we have measured ^{1}H NOESY spectra of **1a**,**b** (in DMSO-d_6) and **3a**,**b** (in $CDCl_3$). These experiments have revealed an interesting difference between these pairs of complexes: in **1a**,**b** there *is* actually a slow fluxional process that exchanges the diastereotopic nuclei within each CH_2, CMe_2, and NH_2 group,[47] while for **3a**,**b** no such slow exchange has been detected (see Figure 6 and Figures S7,S9 in the Supporting Information for some sections of these ^{1}H NOESY

spectra). This observation is in agreement with our supposition (see above) that the steric hindrance between the PPh_3 and the Ph group of the amine is the source of the rigidity of the cyclopalladated ring in **3a**,**b**. For **1a**,**b** in DMSO-d_6 solution, the steric hindrance of the coordinated DMSO would be lower, although the influence of the solvating polar solvent molecules should also be considered, and could account for the relative rigidity of **1a**,**b** (in DMSO-d_6) when compared with the very fluxional picoline complexes **4a**,**b** (in $CDCl_3$). Thus, we can now establish the following order of ring fluxionality (in solution) for our palladacycles: **4a**,**b** ($CDCl_3$) > **1a**,**b** (DMSO-d_6) > **3a**,**b** ($CDCl_3$).

The ^1H NOESY spectrum of **3a** in $CDCl_3$ (Figure 6) has revealed quite selective NOE contacts within the molecule, confirming its relative rigidity in solution. Thus, the *ortho* protons of the PPh_3 show NOE contacts with only one of the Me groups of the CMe_2 moiety, and only one of the methylenic protons of the CH_2Ar group and, very significantly, not with the other methylenic group (CH_2CMe_2). There are also selective NOE contacts between one NH_2 proton and only one methylenic proton of the CH_2CMe_2 group, and not with the CH_2Ar group. If the cyclopalladated ring was fluxional in solution in the NMR timescale, we would see more indiscriminate intramolecular NOE contacts. Based on the observed contacts we propose a chair-like conformation (C) in solution for **3a** in $CDCl_3$, as shown in Figure 6. This conformation would give rise to two enantiomers, δ and λ (see Figures S10-S11 in the Supporting Information for a graphic representation of both conformations). Interestingly, this conformation is very similar to that found in the solid state (Figure 3). It is also the more stable conformation according to a molecular modeling performed using the software Spartan 14.

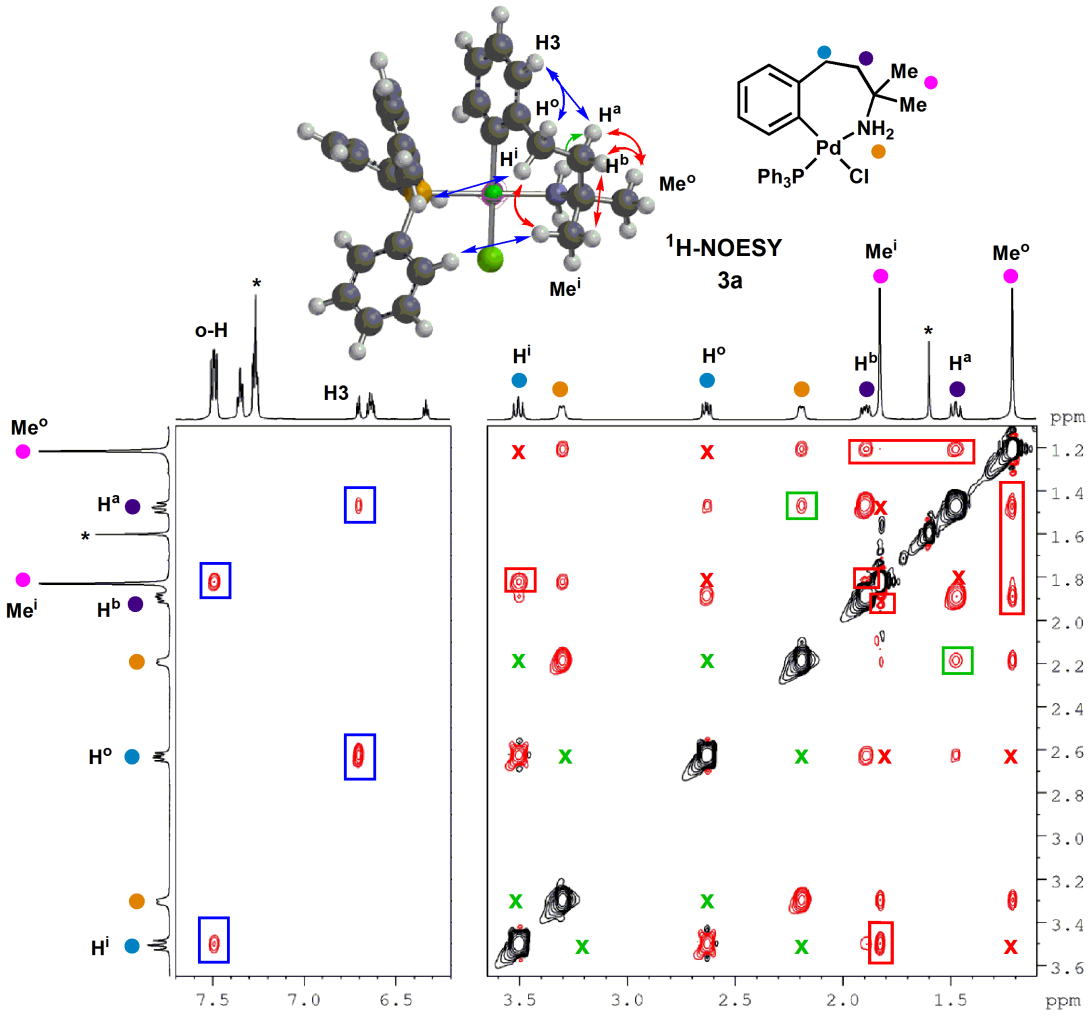


Figure 6. Sections of the ^{1}H NOESY spectrum of **3a** (600 MHz, $CDCl_3$), together with a minimized 3D molecular model of the molecule obtained with Spartan 14, which displays a chair conformation (the δ enantiomer, C^{δ}, is depicted). This conformation is in agreement with the observed NOE's. Thus, NOE contacts (blue rectangles and arrows) are found between the o-H's of the PPh_3 and only one of the Me groups (Me^{i}, pointing "inwards"), as well as one methylenic proton of the CH_2Ar group (H^{i}). There is also an NOE contact between the aryl H3 proton and the other methylenic proton of the CH_2Ar group (H^{o}, pointing "outwards"), as well as a weak contact between H3 and one CH_2C proton (H^{a}). Both are depicted in blue. In the aliphatic region, the red rectangles mark the NOE contacts between Me^{i} and both H^{i} (CH_2Ar) and H^{b} (CH_2C), as well as between

Me^{o} and both $H^{a,b}$ (CH_2C). The red crosses mark the *absence* of NOE contacts between Me^{i} and H^{a} (CH_2C) or H^{o} (CH_2Ar), as well as between Me^{o} and both $H^{i,o}$ (CH_2Ar). The green rectangles mark the NOE contacts between one NH_2 proton and H^{a} (CH_2C), while the green crosses mark the *absence* of NOE contacts between the NH_2 protons and both CH_2Ar protons. The asterisks indicate the signals corresponding to traces of solvents.

In principle, one would expect that the two diastereoisomers of **3b** in $CDCl_3$ solution would have a similar chair-like ring conformation as the one found for **3a**, differing only in the *R* or *S* conformation of the chiral CHMe carbon. Thus, the two diastereomeric pairs of enantiomers of **3b** would be $C^{\delta}R/C^{\lambda}S$ and $C^{\lambda}R/C^{\delta}S$. However, the ^{1}H NOESY spectrum of **3b** (see Figure S9 in the Supporting Information) shows very similar intramolecular NOE contacts for both diastereoisomers, which would not be possible if both would have the chair-like conformation. Thus, as shown in Figure 6, in **3a** the Me group in axial position is close to the CH_2Ar methylene group, while the Me group in equatorial position is close to the CH_2CMe_2 methylene, and indeed those are the NOE contacts found for **3a**. For **3b**, however, the Me group of *both* diastereoisomers shows a strong NOE contact with the CH_2C methylene group, and not with the CH_2Ar (see Figure S9 in the Supporting Information), indicating that both of them are in equatorial position and thus, that the $C^{\delta}R/C^{\lambda}S$ conformation (with the Me group in axial position) does not actually exist in solution. We suggest instead a boat-like conformation, $B^{\lambda}R/B^{\delta}S$, with the Me group in equatorial position (Figure 7). The preference of Me substituents to occupy equatorial positions has been described before.[45]

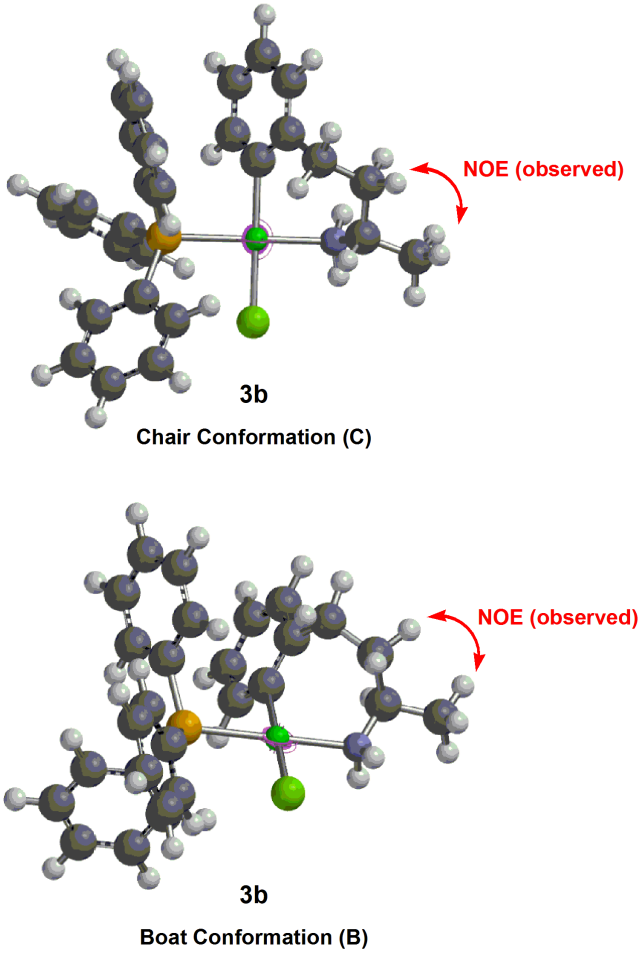


Figure 7. Chair (C) and boat (B) conformations for **3b**. The $C^{\delta}S$ and $B^{\lambda}R$ enantiomers are drawn (the other enantiomers would be $C^{\lambda}R$ and $B^{\delta}S$). Both conformations place the Me group in equatorial position, as suggested by the ^{1}H NOESY spectrum of **3b** ($CDCl_3$, 25 ºC, Figure S9 in the Supporting Information), which shows for both diastereoisomers strong NOE contacts between the Me group and the CH_2C methylenic protons, and not between the Me group and the CH_2Ar methylenic protons (as would be expected for a $C^{\delta}R/C^{\lambda}S$ conformation (depicted in Figure S12 in the Supporting Information).

The observation of the ^{1}H chemical shifts of **3a**,**b** in $CDCl_3$ (Table 1) confirms the proposed conformations. Thus, while for **3a** the two diastereomeric Me groups (one equatorial and the other axial) show quite different chemical shifts (1.21 and 1.83 ppm),

for **3b** the Me groups of the two diastereoisomers show almost the same chemical shift (1.16 and 1.13 ppm) indicating that both have a similar (equatorial) disposition within the molecule (Figure 7). Moreover, there is a very significant difference in the chemical shift of the methine CHMe proton between the two diastereoisomers of **3b** (ca. 3.9 ppm for the major isomer *vs* ca. 2.3 ppm for the minor isomer), which can be explained by the different spatial situation of this ^{1}H in both conformations (Figure 7). While in the chair conformation ($C^{\lambda}R/C^{\delta}S$) the methine proton is almost on the same plane as the Ph ring of the amine, in the boat conformation ($B^{\lambda}R/B^{\delta}S$) this proton is almost over the Ph ring, in a region shielded by the aromatic anisotropic effect. Thus, the minor diastereoisomer would be the one with a $B^{\lambda}R/B^{\delta}S$ boat conformation, and the major diastereoisomer the one with a $C^{\lambda}R/C^{\delta}S$ chair conformation. These results are also in agreement with the data from the X-ray solid structure of **3b** (see above), where the molecules display the $C^{\lambda}R$, $C^{\delta}S$, (major) and $B^{\lambda}R$, $B^{\delta}S$ (minor) conformations.

Table 1. Some ^{1}H chemical shifts (ppm) for **3a** and **3b**, in $CDCl_3$.

		CMe	CH
3a		1.83 1.21	
3b	Major	1.16	3.96–3.88
	Minor	1.13	2.32–2.22

Insertion of CO into the Pd–C bond of Seven-Membered Palladacycles. Synthesis of 2,3,4,5-Tetrahydro-2-benzazepin-1-ones and *N,N'*-Phenylpropyl-ureas. Lactams and esters can be synthesized through oxidative Pd(II)-catalyzed carbonylation of *N*-protected arylalkylamines.[2,48,49] Two key steps in this process are (1) the directed C–H aryl activation of the aryl ring by a Pd(II) salt, and (2) the insertion of

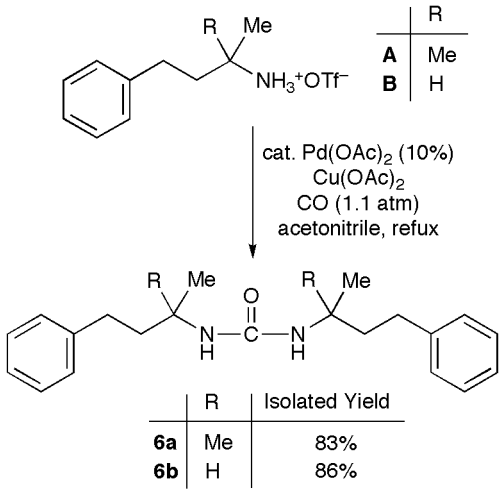
CO into the Pd–C bond of the ortho-metalated intermediate to give an acyl-derivative, which subsequently decomposes. However, with the exception of a few α-alkyl-substituted benzyl-[50] or phenethylamines,[51] primary arylalkylamines cannot be used as starting materials, because in the presence of an excess of the amine, orthometalation of the aromatic ring (i.e., the C–H activation) does not occur (or it is extremely slow).[17,19] Nevertheless, it has been possible to convert primary arylalkylamines to benzolactams through stoichiometric processes, and thus we have prepared tetrahydroisoquinolones,[6,20,22] or tetrahydrobenzazocinones[52,53] by reaction with CO of six- or eight-membered palladacycles containing primary arylalkylamines.

Following this line of research, we have carried out the reaction of the palladacycle **1a** or **1b** with CO in CH_2Cl_2 at room temperature, obtaining Pd(0) and the lactam **5a** or **5b** in moderate yield (Scheme 2; **5a**: 47%, **5b**: 44%). We also attempted the reaction with CO of one family of mononuclear complexes, **4a** and **4b**, obtaining the lactams as well, along with 4-methylpyridinium chloride. Nevertheless, they could be easily purified by crystallization from Et_2O/*n*-pentane.

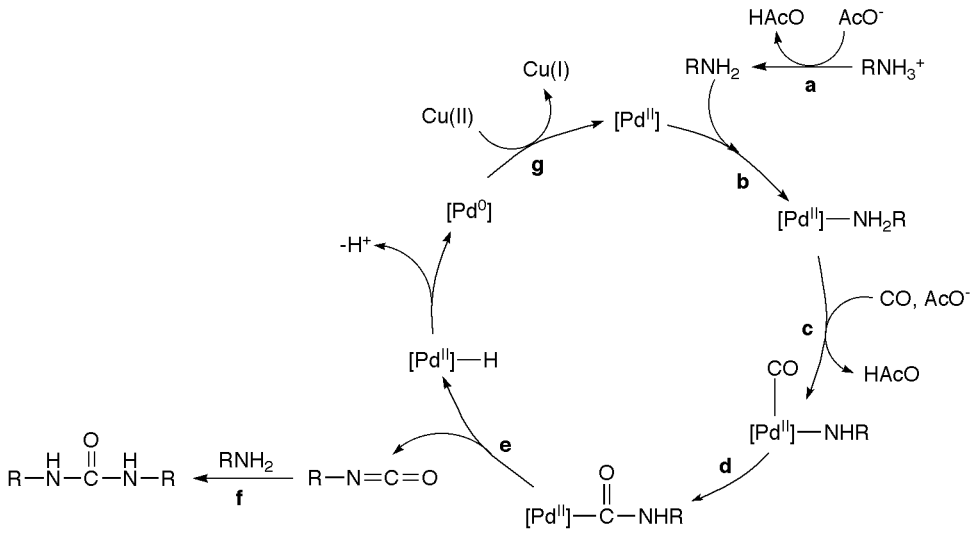
We have also tried the synthesis of the lactams through catalytic carbonylation with the triflate salts **A** and **B**, which seemed the most promising starting materials for this reaction, since they undergo the orthometalation reaction. Each of these salts was dissolved in acetonitrile, $Pd(OAc)_2$ (10%) and $Cu(OAc)_2$ (100%) were added, and the mixtures were heated at reflux under a CO atmosphere (1.1 atm). However, instead of the lactams **5a**,**b**, these reactions afforded the corresponding ureas, *N*,*N*'-bis(2,2-dimethyl-3-phenylpropyl)-urea (**6a**) and *N*,*N*'-bis(1-methyl-3-phenylpropyl)-urea (**6b**), in good yields (Scheme 3). This result is in agreement with previous reports by Orito et al.[49] The reaction pathway proposed for this transformation involves the following steps

(Scheme 4):[49,52] (a) deprotonation of the ammonium salt with AcO^- to give the free amine, (b) coordination of the amine to Pd(II) to form an amino-complex, (c) coordination of CO to Pd(II), and deprotonation of the coordinated amine to give an amido-compound, (d) insertion of CO into the Pd–N bond to afford a carbamoyl intermediate, (e) β-hydride elimination to give an isocyanate and a hydride complex of Pd(II), which decomposes to Pd(0), (f) reaction of the isocyanate with the free amine to form the urea, and (g) regeneration of $Pd(OAc)_2$ by oxidation of Pd(0) with $Cu(OAc)_2$.

Scheme 3. Catalytic Carbonylation of Triflate Salts **A** and **B**.



Scheme 4. Proposed Catalytic Cyclic for the Synthesis of Ureas



The ^{1}H and ^{13}C NMR spectra of **5a**, **6a**, and **6b** are in agreement with the proposed structures, and those of **5b**, with the data reported in the literature.[54] In the lactams **5a**,**b**, the anisotropic influence of the C=O double bond results in a deshielding of the aryl H9 proton, which is shifted to higher frequencies (7.75 ppm, **5a**; 7.61 ppm, **5b**) with respect the other aromatics protons, which resonate between 7.4–7.1 ppm.[6] Compounds **5a** and **6a** do not have chiral centers, and thus the protons and Me substituents of the CH_2 and CMe_2 groups are not diastereotopic, and afford a single resonance for each group. In the lactam **5b** the chiral center makes the methylenic protons diastereotopic, while for the urea **6b** the two chiral centers result in two diastereoisomers (*RR* + *SS*, and a meso form, *RS*). The crystal structure of **5a**, determined by X-ray diffraction studies shows that the azepinone ring adopts a twisted boat conformation (Figure 8). The molecules are associated through N–H···O hydrogen bonds, forming dimers (see the Supporting Information).

To the best of our knowledge, no synthesis of **5a** has been reported before. Previous syntheses of compound **5b** involve the intramolecular cyclization of *N*-hydroxy-2-methyl-4-phenylbutanamide with polyphosphoric acid (PPA),[55] and the reaction of 2-

methyl-3,4-dihydro-2*H*-1-naphthalenone with NaN_3 in aqueous HCl.[54] In the first case, **5b** (3-methyl-2,3,4,5-tetrahydro-1*H*-2-benzazepin-1-one) was obtained in 29% yield along with its regioisomer 3-methyl-2,3,4,5-tetrahydro-1-benzazepin-2-one,[55] while in the second report,[54] the Schmidt reaction was incomplete, and the product was isolated in only 34% yield. Moreover, this reaction[54] involved the use of hydrazoic acid (prepared *in situ* from sodium azide and hydrochloric acid), which is both explosive and toxic, and should be handled with extreme care.

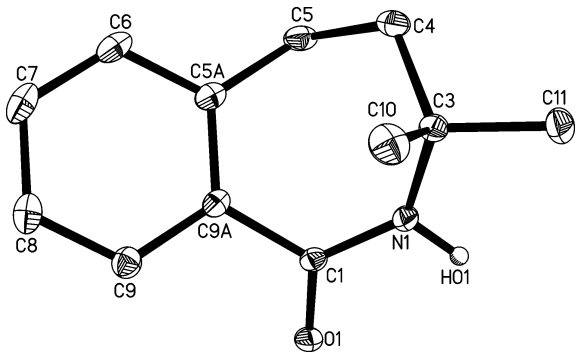


Figure 8. X-ray thermal ellipsoid plot of compound **5a** (50% probability). The hydrogen atoms bonded to carbon have been omitted for clarity. Selected bond lengths (Å) and angles (deg): N(1)–C(3) = 1.4842(10); N(1)–C(1) = 1.3474(11), C(1)–O(1) = 1.2444(10), C(1)–C(9A) = 1.4937(11); C(3)–N(1)–C(1) = 129.02(7), N(1)–C(1)–O(1) = 121.18(7), N(1)–C(1)–C(9A) = 119.19(7), O(1)–C(1)–C(9A) = 119.62(7).

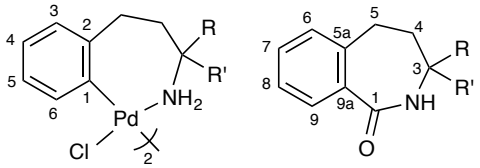
Experimental Section

General Considerations, Materials and Instrumentation. Unless otherwise noted, all preparations were carried out at room temperature under atmospheric conditions. Reagents and synthesis grade solvents were obtained from commercial sources and used as received.

NMR spectra were recorded in $CDCl_3$ at 298 K, unless otherwise stated. Chemical shifts are referenced to TMS (^1H, ^{13}C) or H_3PO_4 (^{31}P). Signals in the ^1H and ^{13}C NMR spectra of all complexes were assigned with the help of APT, HMQC and HMBC techniques. The ^1H NOESY experiments were measured in a 600 MHz Bruker spectrometer, with a mixing time of 400 ms. The 1,2-C_6H_4 arylene group is denoted by Ar. Melting points were determined on a Reichert apparatus and are uncorrected. Infrared spectra were recorded in the range 4000–200 cm^{-1}, using Nujol mulls between polyethylene sheets.

Chart 1 gives the numbering schemes for the new palladacycles and the organic lactams.

Chart 1. Numbering Schemes for the New Palladadium(II) Complexes and the Lactams



Synthesis of ($PhCH_2CH_2CMe_2NH_3$)(CF_3SO_3) (A). 1,1-Dimethyl-3-phenylpropylamine hydrochloride (2.04 g, 10.20 mmol) and Na_2CO_3 (2.56 g, 24.2 mmol) were stirred in water (90 mL) for 30 min, and the resulting 1,1-dimethyl-3-phenylpropylamine was extracted with CH_2Cl_2 (3 × 40 mL). The combined extracts were dried over anhydrous Na_2SO_4, the suspension was filtered and the solvent removed from the filtrate. The resulting oil was dissolved in Et_2O (30 mL), and triflic acid (1 mL, 11.46 mmol) was slowly added. The mixture was stirred for 15 min and kept in the freezer overnight. The suspension was filtered, and the solid washed with Et_2O (3 × 5 ml) and vacuum-dried to give **A** as a colorless solid. Yield: 2.69 g, 8.58 mmol, 84%. Anal. Calcd

for $C_{12}H_{18}F_3NO_3S$ (313.34): C, 46.00; H, 5.79; N, 4.47; S, 10.23. Found: C, 46.09; H, 5.91; N, 4.57; S, 10.33. Mp: 120 ºC. Λ_M: 124 Ω^{-1} cm^2 mol^{-1} (5.07 × 10^{-4} M in acetone). IR (cm^{-1}): ν(NH), 3109 (br vs); δ(NH_2), 1626 (s); ν and δ(TfO), 1269 (br, vs), 1166 (s), 1034 (s), 762 (m), 701 (m), 634 (s), 580 (w), 519 (s). ESI-HRMS: exact mass calcd for $C_{11}H_{18}N$, 164.1434 [(M–CF_3SO_3)$^+$]; found, 164.1439. ^{1}H NMR (400.9 MHz, DMSO-d_6): δ 7.78 (br s, 3 H, NH_3), 7.32–7.28 (m, 2 H, Ph), 7.21–7.17 (m, 3 H, Ph), 2.62–2.58 (m, 2 H, CH_2Ph), 1.80–1.75 (m, 2 H, CH_2CMe$_2$), 1.28 (s, 6 H, Me). ^{13}C{^{1}H} NMR (100.8 MHz, DMSO-d_6): δ 141.2 (s, *i*-C, Ph), 128.5 (s, *o*-CH, Ph), 128.2 (s, *m*-CH, Ph), 126.0 (s, *p*-CH, Ph), 53.6 (s, *C*Me$_2$), 41.8 (s, *C*H$_2$CMe$_2$), 29.3 (s, CH_2Ph), 25.0 (s, Me). The ^{13}C resonance corresponding to the CF_3 group was not observed.

Synthesis of (PhCH$_2$CH$_2$CH(Me)NH$_3$)(CF$_3$SO$_3$) (B). Triflic acid (1.1 mL, 12.3 mmol) was slowly added to a solution of 1-methyl-3-phenylpropylamine (2.0 ml, 12.4 mmol) in Et_2O (50 mL) at 0 ^{o}C, and the mixture was stirred in an ice-bath for 15 min. The resulting suspension was filtered, and the solid washed with Et_2O (2 × 5 ml) and vacuum-dried to give **B** as a colorless solid. Yield: 3.28 g, 11.0 mmol, 89%. Anal. Calcd for $C_{11}H_{16}F_3NO_3S$ (299.31): C, 44.14; H, 5.39; N, 4.68; S, 10.71. Found: C, 44.15; H, 5.48; N, 4.71; S, 10.85. Mp: 124 ºC. Λ_M: 114 Ω^{-1} cm^2 mol^{-1} (7.22 × 10^{-4} M in acetone). IR (cm^{-1}): ν(NH), 3234 (s), 3167 (s), 3088 (s); δ(NH_2), 1626 (m), 1591 (m); ν and δ(TfO), 1279 (s), 1238 (s), 1171 (s), 1033 (s), 748 (m), 699 (m), 640 (s), 582 (m), 516 (m). ESI-HRMS: exact mass calcd for $C_{10}H_{16}N$, 150.1283 [(M–CF_3SO_3)$^+$]; found, 150.1279. ^{1}H NMR (300.1 MHz, DMSO-d_6): δ 7.50 (br s, 3 H, NH_3), 7.32–7.27 (m, 2 H, Ph), 7.22–7.16 (m, 3 H, Ph), 3.13 (m, 1 H, CH), 2.63 (m, 2 H, CH_2Ph), 1.90–1.78 (m, 1 H, CH_2CH), 1.76–1.70 (m, 1 H, CH_2CH), 1.20 (d, 3 H, Me, $^3J_{HH}$ = 6.6 Hz). ^{13}C{^{1}H} NMR (75.4 MHz, DMSO-d_6): δ 140.9 (s, *i*-C, Ph), 128.5 (s, *o*-CH, Ph), 128.2 (s, *m*-CH, Ph), 126.1 (s, *p*-

CH, Ph), 46.5 (s, CH), 36.0 (s, *C*H_2CH), 30.8 (s, CH_2Ph), 18.1 (s, Me). The ^{13}C resonance corresponding to the CF_3 group was not observed.

Synthesis of ($PhCH_2CH_2CH_2NH_3$)(CF_3SO_3) (C). Triflic acid (1.5 mL, 17.0 mmol) was slowly added to a solution of 3-phenylpropylamine (2.0 ml, 14.1 mmol) in Et_2O (50 mL) at 0 °C, and the mixture was stirred in an ice-bath for 15 min. The resulting suspension was filtered, and the solid washed with Et_2O (2 × 5 ml) and vacuum-dried to give **C** as a colorless solid. Yield: 2.66 g, 9.32 mmol, 66%. Anal. Calcd for $C_{10}H_{14}F_3NO_3S$ (285.065): C, 42.10; H, 4.95; N, 4.91; S, 11.24. Found: C, 42.18; H, 4.98; N, 4.72; S, 10.99. Mp: 119 ºC. Λ_M: 137 Ω^{-1} cm^2 mol^{-1} (4.7 × 10^{-4} M in acetone). IR (cm^{-1}): ν(NH), 3169 (br vs); δ(NH_2), 1620 (s); ν and δ(TfO), 1243 (br vs), 1170(s), 1035 (s), 744 (m), 700 (m) 640 (s), 516 (m). ESI-HRMS: exact mass calcd for $C_9H_{14}N$, 136.1126 [$(M–CF_3SO_3)^+$]; found, 136.1126. ^{1}H NMR (400.9 MHz, DMSO-d_6): δ 7.63 (br s, 3 H, NH_3), 7.32–7.28 (m, 2 H, *m*-H, Ph), 7.21–7.17 (m, 3 H, *o*- and *p*-H, Ph), 2.78 (m, 2 H, CH_2N), 2.63 ("t", 2 H, CH_2Ph, $^3J_{HH}$ = 7.6 Hz), 1.82 ("q", 2 H, C*H*$_2$CH, $^3J_{HH}$ = 7.6 Hz). ^{13}C{^{1}H} NMR (100.8 MHz, DMSO-d_6): δ 140.8 (s, *i*-C, Ph), 128.4 (s, *m*-CH, Ph), 128.3 (s, *o*-CH, Ph), 126.1 (s, *p*-CH, Ph), 120.7 (q, CF_3, $^1J_{CF}$ = 322.2 Hz), 38.5 (s, CH_2N), 31.8 (s, CH_2Ph), 28.8 (s, *C*H_2CH).

Synthesis of [Pd_2(κ^2*C,N*-$C_6H_4CH_2CH_2CMe_2NH_2$-2)$_2$(μ-Cl)$_2$] (1a). The ammonium triflate **A** (1.02 g, 3.26 mmol) was added to a suspension of $Pd(OAc)_2$ (731 mg, 3.26 mmol) in acetonitrile (60 mL) and the resulting solution was heated at 60 ºC for 2 h, and then at 78 ºC for 24 h. The mixture was filtered through a plug of Celite/Na_2CO_3, and the solvent was removed from the filtrate. NaCl (2.30 g, 39.4 mmol) and acetone (30 mL) were added and the mixture was stirred for 3 h. The solvent was removed, and Et_2O (20 mL) added to the residue. The yellow suspension was stirred for 30 min, and filtered.

The solid was washed with Et_2O (4 x 5 ml), water (5 x 10 ml) and Et_2O (4 x 5 ml), and vacuum-dried to give **1a** as a yellow solid. An analytically pure sample of **1a** was obtained by recrystallization from CH_2Cl_2/*n*-pentane. Yield: 691 mg, 1.14 mmol, 70%. Anal. Calcd for $C_{22}H_{32}Cl_2N_2Pd_2$ (608.25): C, 43.44; H, 5.30; N, 4.61. Found: C, 43.25; H, 5.36; N, 4.53. Dec pt: 190 ºC. IR (cm^{-1}): $\nu(NH_2)$, 3290 (w), 3215 (m). ^{1}H NMR (400.9 MHz, DMSO-d_6): δ 7.25–7.22 (m, 1 H, H6, C_6H_4). 6.88–6.84 (m, 3 H, H3 + H4 + H5, C_6H_4), 3.98 (br d, 1 H, NH_2, $^2J_{HH}$ = 10 Hz), 3.41 ("t", 1 H, CH_2Ar, J_{HH} = 12.5 Hz), 3.32 (br d, 1 H, NH_2, $^2J_{HH}$ = 10 Hz), 2.65–2.59 (m, 1 H, CH_2Ar), 1.79–1.73 (m, 1 H, CH_2CMe), 1.53 (s, 3 H, Me), 1.41 ("t", 1 H, CH_2CMe, J_{HH} = 12.6 Hz), 1.11 (s, 3 H, Me). ^{13}C{^{1}H} NMR (100.8 MHz, DMSO-d_6): δ 148.1 (s, C2, C_6H_4), 147.0 (s, C1, C_6H_4), 134.3 (s, CH6, C_6H_4), 127.2 (s, CH3, C_6H_4), 125.1 (s, CH5, C_6H_4), 124.5 (s, CH4, C_6H_4), 55.4 (s, *C*Me_2), 41.8 (s, *C*H_2CMe), 33.3 (s, Me), 31.9 (s, CH_2Ar), 29.1 (s, Me).

Synthesis of [Pd_2{κ^2*C,N*-$C_6H_4CH_2CH_2CH(Me)NH_2$-2}$_2$(μ-Cl)$_2$] (1b). The ammonium triflate **B** (500 mg, 1.67 mmol) was added to a suspension of $Pd(OAc)_2$ (417 mg, 1.85 mmol) in acetonitrile (25 mL), and the resulting solution was stirred at room temperature for 24 h and then at 78 ºC for 8 h. The mixture was filtered through a plug of Celite, and the solvent was removed from the filtrate. NaCl (1.00 g, 17.1 mmol) and acetone (15 mL) were added and the mixture was stirred for 6 h. The solvent was removed, and CH_2Cl_2 (10 mL) added. The yellow suspension was filtered, and the solid washed with water (3 x 5 ml) and Et_2O (3 x 5 ml), and vacuum-dried to give **1b** as a yellow solid. An analytically pure sample of **1b** was obtained by recrystallization from CH_2Cl_2/Et_2O. Yield: 221 mg, 0.38 mmol, 46%. Anal. Calcd for $C_{20}H_{26}Cl_2N_2Pd_2$ (580.16): C, 41.40; H, 4.86; N, 4.83. Found: C, 41.23; H, 4.80; N, 4.87. Mp: 200 ºC. IR (Nujol, cm^{-1}): $\nu(NH_2)$, 3288 (m), 3242 (m), 3213 (m). The NMR spectra of this complex showed two

sets of signals in approximately 2:1 ratio (determined by ^{1}H integration), corresponding to the two possible diastereomeric pairs of enantiomers. ^{1}H NMR (600.1 MHz, DMSO-d_6): Major diastereoisomer: δ 7.26 (d, 1 H, H6, C_6H_4, $^3J_{HH}$ = 7.5 Hz). 6.94–6.82 (m, 3 H, H3 + H4 + H5, C_6H_4, overlapped with the corresponding resonance of the minor isomer), 4.45 (d, 1 H, NH_2, $^3J_{HH}$ = 10.8 Hz), 3.73–3.65 (m, 1 H, CH_2Ar), 3.56–3.50 (m, 1 H, NH_2, overlapped with the corresponding resonance of the minor isomer), 2.78–2.72 (m, 1 H, CH_2Ar), 1.95–1.85 (m, 1 H, CH), 1.70–1.62 (m, 1 H, CH_2CH), 1.47–1.38 (m, 1 H, CH_2CH), 0.97 (d, 3 H, Me, $^3J_{HH}$ = 6.3 Hz). Minor diastereoisomer: δ 7.19–7.17 (m, 1 H, H6, C_6H_4), 6.94–6.82 (m, 3 H, H3 + H4 + H5, C_6H_4, overlapped with the corresponding resonance of the major isomer), 3.65–3.61 (m, 1 H, NH_2), 3.56–3.50 (m, 1 H, NH_2, overlapped with the corresponding resonance of the major isomer), 3.50–3.44 (m, 1 H, CH_2Ar), 3.44–3.36 (m, 1 H, CH), 2.87–2.81 (m, 1 H, CH_2Ar), 2.0–1.95 (m, 1 H, CH_2CH), 1.28–1.20 (m, 1 H, CH_2CH), 1.02 (d, 3 H, Me, $^3J_{HH}$ = 6.2 Hz). ^{13}C{^{1}H} NMR (75.4 MHz, DMSO-d_6): Major diastereoisomer: δ 150.8 (s, C1, C_6H_4), 142.8 (s, C2, C_6H_4), 133.4 (s, CH6, C_6H_4), 126.7 (s, CH3, C_6H_4), 124.7 (s, CH5, C_6H_4), 124.6 (s, CH4, C_6H_4), 45.7 (s, CH), 34.3 (s, *C*H_2CH), 32.9 (s, CH_2Ar), 23.1 (s, Me). Minor diastereoisomer: δ 147.9 (s, C2, C_6H_4), 147.7 (s, C1, C_6H_4), 134.2 (s, CH6, C_6H_4), 127.4 (s, CH3, C_6H_4), 125.1 (s, CH5, C_6H_4), 124.4 (s, CH4, C_6H_4), 54.0 (s, CH), 36.7 (s, *C*H_2CH), 36.0 (s, CH_2Ar), 25.6 (s, Me).

Synthesis of [$PdCl_2${$NH_2CH(Me)CH_2CH_2Ph$}$_2$] (2b). 1-Methyl-3-phenylpropylamine (0.5 mL, 2.81 mmol) was added to a suspension of $PdCl_2$ (249 mg, 1.40 mmol) in acetone (20 mL). The mixture was stirred for 48 h and filtered through a plug of Celite. The solvent was removed from the orange filtrate, *n*-pentane (10 mL) was added to the residue, and the mixture vigorously stirred for 24 h. The resulting

suspension was filtered, and the solid washed with *n*-pentane (2 x 3 mL) and vacuum-dried to give **2b** as a yellow solid. Yield: 488 mg, 1.03 mmol, 73%. Anal. Calcd for $C_{20}H_{30}Cl_2N_2Pd$ (475.80): C, 50.49; H, 6.36; N, 5.89. Found: C, 50.73; H, 6.41; N, 5.88. Mp: 116 ºC. IR (cm^{-1}): $\nu(NH_2)$, 3227 (m), 3137 (m), 3209 (m); $\delta(NH_2)$, 1576 (s); ν(Cl–Pd), 340 (m). Some of the NMR resonances of this complex showed two sets of signals in approximately 1:1 ratio (determined by ^{1}H integration), corresponding to two diastereoisomers. ^{1}H NMR (300.1 MHz): All resonances correspond to both diastereoisomers, except the Me resonances, which can be distinguished for each of them: δ 7.30–7.17 (m, 10 H, Ph), 3.32–3.15 (m, 4 H, 2 H of NH_2 + 2 H of CH), 2.91–2.65 (m, 6 H, 2 H of NH_2 + 4 H of CH_2Ph), 2.13–1.99 (m, 2 H, CH_2CH), 1.89–1.78 (m, 2 H, CH_2CH), 1.46 and 1.45 (d, 3 H, Me, $^3J_{HH}$ = 6.4 Hz, one isomer each), 1.45 (d, 3 H, Me, $^3J_{HH}$ = 6.3 Hz). ^{13}C{^{1}H} NMR (75.4 MHz): All resonances correspond to both diastereoisomers, except the CH and *C*H_2CH resonances, which can be distinguished for each of them: δ 141.3 (s, *i*-C, Ph), 128.7 (s, *o*-CH, Ph), 128.6 (s, *m*-CH, Ph), 126.3 (s, *p*-CH, Ph), 50.84 and 50.83 (s, CH, one isomer each), 40.17 and 40.15 (s, *C*H_2CH, one isomer each), 32.4 (s, CH_2Ph), 22.2 (s, Me).

Synthesis of [$PdCl_2(NH_2CH_2CH_2CH_2Ph)_2$] (2c). 3-Phenylpropylamine (0.2 mL, 1.41 mmol) was added to a suspension of $PdCl_2$ (125 mg, 0.71 mmol) in acetone (20 mL), the mixture was stirred for 18 h and filtered through a plug of $MgSO_4$. The solvent was removed from the filtrate, and *n*-pentane (20 mL) was added. The resulting suspension was filtered, and the solid washed with *n*-pentane (2 x 3 mL) and vacuum-dried to give complex **2c** as a yellow solid. Yield: 192.0 mg, 0.429 mmol, 61%. Anal. Calcd for $C_{18}H_{26}Cl_2N_2Pd$ (447.738): C, 48.29; H, 5.85; N, 6.26. Found: C, 48.10; H, 5.77; N, 6.19. Mp: 169 ºC. IR (cm^{-1}): $\nu(NH_2)$, 3272 (s), 3224 (s), 3140 (m); $\delta(NH_2)$, 1587 (m);

ν(Cl–Pd), 337 (m). ^{1}H NMR (400.9 MHz): δ 7.31–7.26 (m, 2 H, *m*-H, Ph), 7.22–7.17 (m, 3 H, *o*- and *p*-H, Ph), 2.90 (br m, 2 H, NH_2), 2.77 (q, 2 H, CH_2N, $^3J_{HH}$ = 7.2 Hz), 2.70 (t, 2 H, CH_2Ph, $^3J_{HH}$ = 7.6 Hz), 2.03 (q, 2 H, CH_2CH, $^3J_{HH}$ = 7.6 Hz). $^{13}C\{^1H\}$ NMR (100.8 MHz): δ 140.7 (s, *i*-C, Ph), 128.5 (s, CH, Ph), 128.3 (s, CH, Ph), 126.2 (s, *p*-CH, Ph), 44.6 (s, CH_2N), 33.0 (s, CH_2CH), 32.8 (s, CH_2Ph). Spectroscopic data are in agreement to those reported in the literature (^{1}H and ^{13}C NMR).[30]

Synthesis of [Pd(κ^2*C,N*-$C_6H_4CH_2CH_2CMe_2NH_2$-2)Cl(PPh_3)] (3a). PPh_3 (57.0 mg, 0.217 mmol) was added to a solution of complex **1a** (65.6 mg, 0.108 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred for 30 min and filtered through a plug of $MgSO_4$. The filtrate was concentrated to ca. 2 mL, and *n*-pentane (20 mL) was added. The suspension was filtered, and the solid washed with *n*-pentane (2 x 3 ml) and vacuum-dried to give **3a** as a pale yellow solid. Yield: 88.0 mg, 0.155 mmol, 72%. Anal. Calcd for $C_{29}H_{31}ClNPPd$ (566.40): C, 61.50; H, 5.52; N, 2.47. Found: C, 61.14; H, 5.48; N, 2.65. Mp: 233–234 ºC (dec). IR (cm^{-1}): ν(NH_2), 3496 (br), 3300 (w), 3208 (m). ^{1}H NMR (600.1 MHz): δ 7.52–7.46 (m, 6 H, *o*-CH, PPh_3), 7.37–7.33 (m, 3 H, *p*-CH, PPh_3), 7.29–7.23 (m, 6 H, *m*-CH, PPh_3), 6.70 (d, 1 H, H3, C_6H_4, $^3J_{HH}$ = 7.3 Hz), 6.66–6.61 (m, 2 H, H4 + H6, C_6H_4), 6.33 (br t, 1 H, H5, C_6H_4, $^3J_{HH}$ = 7.4 Hz), 3.51 (“t”, 1 H, CH_2Ar, $^3J_{HH}$ = $^2J_{HH}$ = 12.6 Hz), 3.30 (br d, 1 H, NH_2, $^2J_{HH}$ = 8.9 Hz), 2.63 (dd, 1 H, CH_2Ar, $^3J_{HH}$ = 8.4, $^2J_{HH}$ = 13.8 Hz), 2.19 (br d, 1 H, NH_2, $^2J_{HH}$ = 8.9 Hz), 1.89 (dd, 1 H, CH_2CMe, $^3J_{HH}$ = 8.2, $^2J_{HH}$ = 14.4 Hz), 1.83 (s, 3 H, Me), 1.47 (dd, 1 H, CH_2CMe, $^3J_{HH}$ = 12.0, $^2J_{HH}$ = 14.2 Hz), 1.21 (s, 3 H, Me). $^{13}C\{^1H\}$ NMR (75.4 MHz): δ 152.0 (s, C1, C_6H_4), 147.7 (s, C2, C_6H_4), 136.8 (d, CH6, C_6H_4, $^3J_{CP}$ = 9.2 Hz), 134.4 (d, *o*-CH, PPh_3, $^2J_{CP}$ = 11.5 Hz), 131.1 (d, *i*-C, PPh_3, $^1J_{CP}$ = 49.7 Hz), 130.1 (d, *p*-CH, PPh_3, $^4J_{CP}$ = 2.1 Hz), 128.0 (d, *m*-CH, PPh_3, $^3J_{CP}$ = 10.6 Hz), 126.8 (s, CH3, C_6H_4), 125.3 (d, CH5, C_6H_4, $^4J_{CP}$ = 3.2 Hz), 123.5 (s, CH4, C_6H_4), 56.1 (s,

*C*Me$_2$), 43.1 (s, *C*H$_2$CMe$_2$), 35.5 (d, Me, $^4J_{CP}$ = 5.1 Hz), 33.5 (d, CH$_2$Ar, $^4J_{CP}$ = 1.6 Hz), 28.8 (s, Me). ^{31}P{^{1}H} NMR (121.5 MHz): δ 31.9. Single crystals of **3a**·H$_2$O suitable for an X-ray diffraction study were obtained by slow evaporation of a solution of **3a** in CHCl$_3$/*n*-pentane.

Synthesis of [Pd(κ^2*C,N*-C$_6$H$_4$CH$_2$CH$_2$CH(Me)NH$_2$-2)Cl(PPh$_3$)] (3b). PPh$_3$ (114 mg, 0.432 mmol) was added to a suspension of complex **1b** (125 mg, 0.216 mmol) in CH$_2$Cl$_2$ (15 mL). The mixture was stirred for 30 min and filtered through a plug of MgSO$_4$. The filtrate was concentrated to ca. 2 mL, and a 1:4 mixture of Et$_2$O/*n*-pentane (25 mL) was added. The suspension was filtered, and the solid washed with a 1:4 mixture of Et$_2$O/*n*-pentane (2 x 5 ml) and vacuum-dried to give **3b** as a pale yellow solid. Yield: 182 mg, 0.328 mmol, 76%. Anal. Calcd for C$_{28}$H$_{32}$ClNPPd (552.38): C, 60.88; H, 5.29; N, 2.54. Found: C, 60.57; H, 5.15; N, 2.64. Mp: 203 ºC. IR (cm^{-1}): ν(NH$_2$), 3276 (m), 3305 (m), 3185 (m); ν and δ(PPh$_3$), 3044 (m), 1578 (m), 11098 (m), 751 (m), 692 (m), 508 (m), 498 (m). The NMR spectra of this complex showed two sets of signals in approximately 1.3:1 ratio (determined by ^{1}H integration), corresponding to the two possible diastereomeric pairs of enantiomers. The resonances marked with an asterisk are overlapped for both diastereoisomers. ^{1}H NMR (600.1 MHz): Major diastereoisomer: δ 7.54–7.46* (m, 6 H, *o*-CH, PPh$_3$), 7.37–7.32* (m, 3 H, *p*-CH, PPh$_3$), 7.29–7.23* (m, 6 H, *m*-CH, PPh$_3$), 6.72–6.68* (m, 1 H, H3, C$_6$H$_4$), 6.68–6.62* (m, 1 H, H4, C$_6$H$_4$), 6.53–6.50 (m, 1 H, H6, C$_6$H$_4$), 6.36–6.32 (m, 1 H, H5, C$_6$H$_4$), 3.96–3.88 (m, 1 H, CH, overlapped with one H of CH$_2$Ar of the minor isomer), 3.59 ("t", 1 H, CH$_2$Ar, J_{HH} = 12.4 Hz), 3.28 (br d, 1 H, NH$_2$, $^2J_{HH}$ = 7.0 Hz), 2.87–2.79* (m, 1 H, CH$_2$Ar), 2.16–2.10 (m, 1 H, C*H*$_2$CH), 1.96–1.88 (m, 1 H, NH$_2$), 1.30–1.21 (m, 1 H, C*H*$_2$CH), 1.16 (d, 3 H, Me, $^3J_{HH}$ = 6.0 Hz). Minor diastereoisomer: δ 7.54–7.46* (m, 6 H, *o*-CH, PPh$_3$), 7.37–7.32* (m, 3 H,

p-CH, PPh_3), 7.29–7.23* (m, 6 H, PPh_3 *m*-CH, PPh_3), 6.72–6.68* (m, 1 H, H3, C_6H_4), 6.68–6.62* (m, 1 H, H4, C_6H_4), 6.56–6.53 (m, 1 H, H6, C_6H_4), 6.36–6.32 (m, 1 H, H5, C_6H_4), 3.96–3.88 (m, 1 H, CH_2Ar, overlapped with the CH of the major isomer), 2.87–2.79* (m, 1 H, CH_2Ar), 2.79–2.74 (m, 1 H, NH_2), 2.74–2.68 (m, 1 H, NH_2), 2.32–2.22 (m, 1 H, CH), 1.69–1.63 (m, 2 H, CH_2CH), 1.13 (d, 3 H, Me, $^3J_{HH}$ = 6.0 Hz). $^{13}C\{^1H\}$ NMR (75.4 MHz): Major diastereoisomer: δ 152.9 (s, C1, C_6H_4), 147.3 (s, C2, C_6H_4), 136.5 (d, CH6, C_6H_4, $^3J_{CP}$ = 7.8 Hz), 134.6 (d, *o*-CH, PPh_3, $^2J_{CP}$ = 11.7 Hz), 130.7 (d, *i*-C, PPh_3, $^1J_{CP}$ = 50.4 Hz), 130.1 (d, *p*-CH, PPh_3, $^4J_{CP}$ = 2.5 Hz), 127.9 (d, *m*-CH, PPh_3, $^3J_{CP}$ = 10.6 Hz), 126.9 (s, CH3, C_6H_4), 125.5 (d, CH5, C_6H_4, $^4J_{CP}$ = 2.9 Hz), 123.5 (s, CH4, C_6H_4), 54.1 (s, CH), 38.1 (s, *C*H_2CH), 37.4 (s, CH_2Ar), 27.5 (d, Me, $^4J_{CP}$ = 4.0 Hz). Minor diastereoisomer: δ 153.8 (s, C1, C_6H_4), 142.6 (s, C2, C_6H_4), 136.6 (d, CH6, C_6H_4, $^3J_{CP}$ = 9.5 Hz), 134.5 (d, *o*-CH, PPh_3, $^2J_{CP}$ = 11.5 Hz), 131.1 (d, *i*-C, PPh_3, $^1J_{CP}$ = 50.5 Hz), 130.1 (d, *p*-CH, PPh_3, $^4J_{CP}$ = 2.5 Hz), 127.9 (d, *m*-CH, PPh_3, $^3J_{CP}$ = 10.6 Hz), 126.2 (s, CH3, C_6H_4), 125.2 (d, CH5, C_6H_4, $^4J_{CP}$ = 3.4 Hz), 123.4 (s, CH4, C_6H_4), 45.7 (s, CH), 35.5 (s, *C*H_2CH), 34.0 (s, CH_2Ar), 25.1 (d, Me, $^4J_{CP}$ = 3.7 Hz). $^{31}P\{^1H\}$ NMR (162.29 MHz): Major diastereoisomer: δ 33.3 (s). Minor diastereoisomer: δ 33.6 (s). Single crystals suitable for an X-ray diffraction study were obtained by slow diffusion of *n*-pentane into a solution of **3b** in CH_2Cl_2.

Synthesis of [Pd(*κ*^{2}*C,N*-$C_6H_4CH_2CH_2CMe_2NH_2$-2)Cl(pic)] (4a). 4-Picoline (26 μl, 0.267 mmol) was added to a suspension of complex **1a** (78.4 mg, 0.129 mmol) in CH_2Cl_2 (15 mL) and the mixture was stirred for 30 minutes. The solution was filtered through a plug of $MgSO_4$, and the solvent was evaporated from the filtrate. The residue was dissolved in Et_2O (10 mL) and *n*-pentane (35 mL) was added. The suspension was filtered, and the solid washed with *n*-pentane (3 x 5 ml) and vacuum-dried to give **4a** as

a colorless solid. Yield: 65.0 mg, 0.164 mmol, 63%. Anal. Calcd for $C_{17}H_{23}ClN_2Pd$ (397.251): C, 51.40; H, 5.84; N, 7.05. Found: C, 51.44; H, 5.65; N, 7.19. Dec pt: 177 ºC. IR (cm^{-1}): $\nu(NH_2)$, 3251 (w), 3197 (w); ν(C=N), 1619 (m). ^{1}H NMR (400.9 MHz): δ 8.46 (d, 2 H, *o*-H, pic, $^3J_{HH}$ = 6.4 Hz), 7.00 (d, 2 H, *m*-H, pic, $^3J_{HH}$ = 6.0 Hz), 6.90–6.85 (m, 2 H, H3 + H4, C_6H_4), 6.81 ("d", 1 H, H6, C_6H_4, $^3J_{HH}$ = 7.2 Hz), 6.74–6.69 (m, 1 H, H5, C_6H_4), 3.50–3.10 (br s, 2 H, CH_2Ar), 2.90–2.60 (br s, 2 H, NH_2), 2.31 (s, 3 H, Me, pic), 1.74 (br s, 2 H, C*H*$_2$CMe$_2$), 1.52 (br s, 6 H, Me). ^{1}H NMR (400.9 MHz, –50 ºC): δ 8.43 (d, 2 H, *o*-H, pic, $^3J_{HH}$ = 6.0 Hz), 7.06 (d, 2 H, *m*-H, pic, $^3J_{HH}$ = 5.6 Hz), 6.96–6.90 (m, 2 H, H3 + H4, C_6H_4), 6.82 ("d", 1 H, H6, C_6H_4, $^3J_{HH}$ = 7.2 Hz), 6.78–6.74 (m, 1 H, H5, C_6H_4), 3.88 ("t", 1 H, CH_2Ar, $^2J_{HH}$ = $^3J_{HH}$ = 12.4 Hz), 3.23 (d, 1 H, NH_2, $^2J_{HH}$ = 10.4 Hz), 2.84 (dd, 1 H, CH_2Ar, $^2J_{HH}$ = 13.2, $^3J_{HH}$ = 8.4 Hz), 2.36 (br s, 1 H, NH_2, obscured by the signal of the Me of pic), 2.36 (s, 3 H, Me, pic), 1.98 (dd, 1 H, C*H*$_2$CMe$_2$, $^2J_{HH}$ = 13.2, $^3J_{HH}$ = 8.4 Hz), 1.83 (s, 3 H, Me), 1.55 ("t", 1 H, C*H*$_2$CMe$_2$, $^2J_{HH}$ = $^3J_{HH}$ = 12.8 Hz), 1.25 (s, 3 H, Me). ^{13}C{^{1}H} NMR (75.4 MHz): δ 152.7 (s, *o*-CH, pic), 149.4 (s, *p*-C, pic), 148.1 (s, C1, C_6H_4), 147.7 (s, C2, C_6H_4), 135.3 (s, CH6, C_6H_4), 127.3 (s, CH3, C_6H_4), 125.4 (s, *m*-CH, pic), 124.8 (s, CH5, C_6H_4), 124.3 (s, CH4, C_6H_4), 55.8 (s, *C*Me$_2$), 42.8 (s, *C*H$_2$CMe), 32.1 (s, CH_2Ar), 21.0 (s, Me, pic). The Me resonances of the CMe_2 group are not observed. ^{13}C{^{1}H} NMR (100.8 MHz, –50 ºC): δ 152.2 (s, *o*-CH, pic), 149.5 (s, *p*-C, pic), 148.2 (s, C1, C_6H_4), 147.5 (s, C2, C_6H_4), 135.2 (s, CH6, C_6H_4), 127.2 (s, CH3, C_6H_4), 125.4 (s, *m*-CH, pic), 124.6 (s, CH5, C_6H_4), 124.1 (s, CH4, C_6H_4), 55.7 (s, *C*Me$_2$), 42.0 (s, CH_2 *C*H$_2$CMe), 34.6 (s, Me), 31.6 (s, *C*H$_2$Ar), 28.1 (s, Me), 21.2 (s, Me, pic).

Synthesis of [Pd(κ^2*C,N*-$C_6H_4CH_2CH_2CH(Me)NH_2$-2)Cl(pic)] (4b). 4-Picoline (44 μl, 0.448 mmol) was added to a suspension of complex **1b** (130 mg, 0.224 mmol) in CH_2Cl_2 (10 mL) and the mixture was stirred for 30 minutes. The resulting solution was

filtered through a plug of $MgSO_4$, the filtrate was concentrated to ca. 1 mL, and *n*-pentane (15 mL) was added. The suspension was filtered, and the solid washed with *n*-pentane (2 x 5 ml) and vacuum-dried to give **4b** as a yellow solid. Yield: 97.0 mg, 0.253 mmol, 54%. Anal. Calcd for $C_{16}H_{21}ClN_2Pd$ (383.22): C, 50.15; H, 5.52; N, 7.31. Found: C, 49.96; H, 5.51; N, 7.01. Mp: 112 ºC. IR (cm^{-1}): $\nu(NH_2)$, 3273 (w), 3197 (w); ν(C=N), 1617 (m). At –50 ºC, the NMR spectra of this complex showed two sets of signals in approximately 1.4:1 ratio (determined by ^1H integration), corresponding to the two possible diastereomeric pairs of enantiomers. ^1H NMR (400.9 MHz): δ 8.42 (d, 2 H, *o*-H, pic, $^3J_{HH}$ = 5.9 Hz), 7.00 (d, 2 H, *m*-H, pic, $^3J_{HH}$ = 5.9 Hz), 6.91–6.85 (m, 2 H, H3 + H4, C_6H_4), 6.81 ("d", 1 H, H6, C_6H_4, $^3J_{HH}$ = 7.5 Hz), 6.76–6.69 (m, 1 H, H5, C_6H_4), 2.31 (s, 3 H, Me, pic), 1.15 (d, 3 H, Me, $^3J_{HH}$ = 6.3 Hz). The ^1H resonances of the $CH_2CH_2CHMeNH_2$ chain (except the Me resonance) are too broad to be assigned. ^1H NMR (400.9 MHz, –50 °C): The ^1H and ^{13}C resonances marked with an asterisk are overlapped for both isomers. Major diastereoisomer: δ 8.40 (d, 2 H, *o*-H, pic, $^3J_{HH}$ = 6.4 Hz). 7.06* (d, 2 H, *m*-H, pic, $^3J_{HH}$ = 6.4 Hz), 6.97–6.91* (m, 2 H, H3 + H4, C_6H_4), 6.88 ("d", 1 H, H6, C_6H_4, $^3J_{HH}$ = 7.6 Hz), 6.83–6.77 (m, 1 H, H5, C_6H_4), 3.98 ("t", 1 H, CH_2Ar, $^2J_{HH} = {}^3J_{HH}$ = 12.4 Hz), 3.78 (br s, 1 H, CH), 3.25 (br d, 1 H, NH_2, $^2J_{HH}$ = 9.6 Hz), 3.04 (dd, 1 H, CH_2Ar, $^2J_{HH}$ = 13.2, $^3J_{HH}$ = 7.6 Hz), 2.99–2.87* (m, 1 H, CH_2CH), 2.35 (s, 3 H, Me, pic), 2.29–2.18 (m, 1 H, CH_2CH), 2.02 (br t, 1 H, NH_2, $^2J_{HH} = {}^3J_{HH}$ = 11.2 Hz), 1.17 (d, 3 H, Me, $^3J_{HH}$ = 6.0 Hz). Minor diastereoisomer: δ 8.37 (d, 2 H, *o*-H, pic, $^3J_{HH}$ = 6.4 Hz). 7.06* (d, 2 H, *m*-H, pic, $^3J_{HH}$ = 6.4 Hz), 6.97–6.91* (m, 2 H, H3 + H4, C_6H_4), 6.74 (br td, 1 H, H5, C_6H_4, $^3J_{HH}$ = 7.2, $^4J_{HH}$ = 2.0 Hz), 6.68 ("d", 1 H, H6, C_6H_4, $^3J_{HH}$ = 7.2 Hz), 4.24–4.12 (m, 1 H, NH_2), 2.99–2.87* (m, 1 H, CH_2CH), 2.72–2.50 (br s, 1 H, NH_2), 2.36 (s, 3 H, Me, pic), 1.83–1.70 (m, 1 H, CH_2Ar), 1.70–1.57 (m, 1 H, CH_2Ar), 1.39–1.22 (m, 1 H,

C*H*$_2$CH, partially obscured by traces of pentane), 1.11 (very br s, 3 H, Me). The resonance of the *C*HMe carbon could not be identified. $^{13}C\{^1H\}$ NMR (100.8 MHz): δ 152.5 (s, *o*-CH, pic), 149.5 (s, *p*-C, pic), 134.6 (s, CH6, C_6H_4), 127.2 (s, CH3, C_6H_4), 125.5 (s, *m*-CH, pic), 124.8 (s, CH, C_6H_4), 124.2 (s, CH, C_6H_4), 38.0 (s, *C*H_2CH), 31.3 (s, CH_2Ar), 21.0 (s, Me, pic). The resonances of the aryl quaternary carbons and the CHMe group are not observed. $^{13}C\{^1H\}$ NMR (100.8 MHz, –50 ^oC): Major diastereoisomer: δ 152.1 (s, *o*-CH, pic), 149.5 (s, *p*-C, pic), 149.4* (s, C1, C_6H_4), 147.3* (s, C2, C_6H_4), 134.8 (s, CH6, C_6H_4), 127.4 (s, CH3, C_6H_4), 125.5 (s, *m*-CH, pic), 124.8 (s, CH, C_6H_4), 124.0 (s, CH, C_6H_4), 54.8* (s, CH), 37.2* (s, *C*H_2CH), 35.7 (s, CH_2Ar), 26.9* (s, Me), 21.2* (s, Me, pic). Minor diastereoisomer: δ 152.3 (s, *o*-CH, pic), 149.5 (s, *p*–C, pic), 149.4* (s, C1, C_6H_4), 147.3* (s, C2, C_6H_4), 134.2 (s, CH6, C_6H_4), 126.7 (s, CH3, C_6H_4), 125.6 (s, *m*-CH, pic), 124.2 (s, CH, C_6H_4), 123.9 (s, CH, C_6H_4), 54.8* (s, CH), 37.2* (s, *C*H_2CH), 35.2 (s, CH_2Ar), 26.9* (s, Me), 21.2* (s, Me, pic). Single crystals of **4b**·$CHCl_3$ suitable for an X-ray diffraction study were obtained by slow evaporation of a solution of **4b** in $CHCl_3$.

Synthesis of 3,3-dimethyl-2,3,4,5-tetrahydrobenzo[*c*]azepin-1-one (5a). Method A. CO was bubbled for 5 min through a suspension of the palladacycle **1a** (153 mg, 0.251 mmol) in CH_2Cl_2 (20 mL) in a Carius tube. The pressure of CO was increased to 1 atm, the tube sealed, and the mixture was stirred for 2 h. Decomposition to metallic palladium was observed. The resulting suspension was filtered through a plug of $MgSO_4$, the solvent was removed from the filtrate, and the residue vacuum-dried to give **5a** as a colorless solid. Yield: 45.0 mg, 0.238 mmol, 47%. **Method B.** CO was bubbled for 5 min through a solution of **4a** (50.0 mg, 0.126 mmol) in CH_2Cl_2 (15 mL) in a Carius tube. The pressure of CO was increased to 1 atm, the tube sealed, and the mixture was

stirred for 18 h. Decomposition to metallic palladium was observed. The resulting suspension was filtered through a plug of $MgSO_4$, the solvent was removed from the filtrate, and the residue vacuum-dried. This residue proved to be a mixture of the lactam **5a** and 4-methylpyridinum (by ^{1}H NMR). Et_2O (10 mL) was added to the residue, and the suspension was filtered. The solvent was removed from the filtrate, and the residue vacuum-dried to give **5a** as a colorless solid. Yield: 12.9 mg, 0.068 mmol, 54%. Mp: 173 ºC. IR (cm^{-1}): ν(NH), 3270 (w), 3186 (m), 3040 (m); ν(CO), 1649 (s). ESI-HRMS: exact mass calcd for $C_{12}H_{16}NO$, 190.1232 [$(M+H)^+$]; found, 190.1234. ^{1}H NMR (300.1 MHz): δ 7.75 (dd, 1 H, H9, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 1.5 Hz), 7.39 (td, 1 H, H7, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 1.5 Hz), 7.32 (td, 1 H, H8, $^3J_{HH}$ = 7.5, $^4J_{HH}$ = 1.5 Hz), 7.10 (m, 1 H, H6), 6.11 (br s, 1 H, NH), 2.90 ("t", 2 H, CH_2Ar, $^3J_{HH}$ = 6.9 Hz), 2.04 ("t", 2 H, CH_2CMe_2, $^3J_{HH}$ = 6.6 Hz), 1.11 (s, 6 H, Me). $^{13}C\{^1H\}$ NMR (75.4 MHz): δ 171.8 (s, CO, C1), 139.6 (s, C5a), 135.0 (s, C9a), 131.4 (s, CH7), 129.2 (s, CH9), 128.4 (s, CH6), 126.9 (s, CH8), 52.3 (s, CMe_2), 43.6 (s, CH_2CMe_2), 32.3 (s, Me), 31.4 (s, CH_2Ar). Single crystals suitable for an X-ray diffraction study were obtained by slow evaporation of a solution of **5a** in $CHCl_3$/*n*-pentane.

Synthesis of 3-methyl-2,3,4,5-tetrahydrobenzo[*c*]azepin-1-one (5b). Method A. CO was bubbled for 5 min through a suspension of the palladacycle **1b** (190 mg, 0.328 mmol) in CH_2Cl_2 (20 mL) in a Carius tube. The pressure of CO was increased to 1 atm, the tube sealed, and the mixture was stirred for 24 h. Decomposition to metallic palladium was observed. The resulting suspension was filtered through a plug of $MgSO_4$, the filtrate was concentrated to ca. 1 mL, and *n*-pentane (15 mL) added. The suspension was filtered, and the solid washed with *n*-pentane (2 x 5 mL) and air-dried to afford compound **5b** as a colorless solid. Yield: 49.9 mg, 0.285 mmol, 44%. **Method B.** CO was bubbled for 5 min through a solution of **4b** (50.0 mg, 0.130 mmol) in CH_2Cl_2 (15

mL) in a Carius tube. The pressure of CO was increased to 1.1 atm, the tube sealed, and the mixture was stirred for 18 h. Decomposition to metallic palladium was observed. The resulting suspension was filtered through a plug of $MgSO_4$, the solvent was removed from the filtrate, and the residue vacuum-dried. This residue proved to be a mixture of the lactam **5b** and 4-methylpyridinum (by ^{1}H NMR). Et_2O (10 mL) was added to the residue, and the suspension was filtered. The solvent was removed from the filtrate, and the residue vacuum-dried to give **5b** as a colorless solid. Yield: 20.6 mg, 0.117 mmol, 90%. Mp: 143.2 ºC. IR (cm^{-1}): ν(NH), 3277 (w), 3189 (m), 3059 (w); ν(CO), 1601 (s). ESI-HRMS: exact mass calcd for $C_{11}H_{14}NO$, 176.1075 [$(M+H)^+$]; found, 176.1061. ^{1}H NMR (400.9 MHz): δ 7.61 (dd, 1 H, H9, $^3J_{HH}$ = 7.2, $^4J_{HH}$ = 1.2 Hz), 7.30 (td, 1 H, H7, $^3J_{HH}$ = 7.2, $^4J_{HH}$ = 1.2 Hz), 7.24 (td, 1 H, H8, $^3J_{HH}$ = 7.6, $^4J_{HH}$ = 1.2 Hz), 7.10 (br d, 1 H, H6, $^3J_{HH}$ = 7.2 Hz), 7.01 (br s, 1 H, NH), 3.20 (m, 1 H, CH), 2.92 (m, 1 H, CH_2Ar), 2.60 (dd, 1 H, CH_2Ar, $^2J_{HH}$ = 13.6, $^3J_{HH}$ = 6.0 Hz), 1.96–1.85 (m, 1 H, CH_2CH), 1.85–1.74 (m, 1 H, CH_2CH), 1.18 (d, 3 H, Me, $^3J_{HH}$ = 6.8 Hz). ^{13}C{^{1}H} NMR (100.8 MHz): δ 172.5 (s, CO, C1), 138.7 (s, C5a), 135.1 (s, C9a), 131.1 (s, CH7), 128.6 (s, CH9), 128.5 (s, CH6), 126.9 (s, CH8), 46.8 (s, CH3), 38.8 (s, *C*H_2CH, C4), 30.7 (s, CH_2Ar, C5), 19.9 (s, Me). Spectroscopic data are in agreement to those reported in the literature (^{1}H and ^{13}C NMR).[54]

General Procedure for Preparation of Ureas 6a,b. A Carius tube was charged with the triflate salt (**A** or **B**, 0.30 mmol), $Pd(OAc)_2$ (6.7 mg, 0.03 mmol, 10 mol%), $Cu(OAc)_2$ (18.1 mg, 0.30 mmol), and acetonitrile (3.0 mL). The tube was evacuated, refilled with CO (1.1 atm) and sealed. The reaction mixture was heated in an oil-bath at 100 °C for 16 h. After cooling the Carius tube to RT, the crude was diluted with CH_2Cl_2 (15 mL) and washed with 10% aq NH_3 (50 mL). The aqueous layer was extracted with

CH_2Cl_2 (3 x 30 mL). The organic layers were combined, dried with anhydrous $MgSO_4$ and filtered. The solvent was removed from the filtrate, and *n*-pentane (15 mL) was added to the residue. The suspension was filtered, and the solid air-dried to give the lactam as a colorless solid.

Data for 6a. Yield: 44.6 mg, 0.125 mmol, 83%. IR (cm^{-1}): ν(NH), 3364 (m); ν(CO), 1638 (s). ESI-HRMS: exact mass calcd for $C_{23}H_{33}N_2O$, 353.2593 [$(M+H)^+$]; found, 353.2580. ^1H NMR (400.9 MHz): δ 7.26–7.13 (m, 5 H, Ph), 4.00 (s, 1 H, NH), 2.61–2.57 (m, 2 H, CH_2Ph), 2.03–1.99 (m, 2 H, CH_2CMe_2), 1.33 (s, 6 H, Me). $^{13}C\{^1H\}$ NMR (100.8 MHz): δ 155.9 (s, CO), 142.1 (s, *i*-C, Ph), 128.0 (s, CH, Ph), 127.8 (s, CH, Ph), 125.1 (s, *p*-CH, Ph), 52.2 (CMe_2), 42.2 (s, CH_2CMe_2), 30.5 (s, CH_2Ph), 27.5 (s, Me).

Data for 6b. Yield: 41.8 mg, 0.129 mmol, 86%. IR (cm^{-1}): ν(NH), 3318 (m); ν(CO), 1619 (s). ESI-HRMS: exact mass calcd for $C_{21}H_{29}N_2O$, 325.2280 [$(M+H)^+$]; found, 325.2286. Some of the NMR resonances of this compound showed two sets of signals in approximately 1:1 ratio, corresponding to two diastereoisomers. ^1H NMR (300.1 MHz): All resonances correspond to both diastereoisomers, except the Me resonances, which can be distinguished for each of them: δ 7.29–7.24 (m, 2 H, Ph), 7.18–7.15 (m, 3 H, Ph), 4.16 (m, 1 H, NH), 3.76 (m, 1 H, CH), 2.65 ("t", 2 H, CH_2Ph, $^3J_{HH}$ = 8.1 Hz), 1.72 (m, 2 H, CH_2CH), 1.148 and 1.145 (d, 3 H, Me, $^3J_{HH}$ = 6.6 Hz, one isomer each). $^{13}C\{^1H\}$ NMR (75.4 MHz): When not specified, the resonances correspond to both diastereoisomers: δ 157.4 (br s, CO); 142.2 and 142.1 (s, *i*-C, Ph, one isomer each), 128.64 (s, CH, Ph), 128.55 (s, CH, Ph), 126.1 (s, *p*-CH, Ph), 45.9 (br s, CH), 39.51 and 39.46 (s, CH_2CH, one isomer each), 32.70 and 32.67 (s, CH_2Ph, one isomer each), 21.91 and 21.88 (s, Me, one isomer each).

Single Crystal X-ray Structure Determinations. Relevant crystallographic data, details of the refinements, complete set of cartesian coordinates and details (including symmetry operators) of hydrogen bonds, and CIF files for compounds **3a**·1/2H_2O, **3b**, **4b**·$CHCl_3$, and **5a** are given in the Supporting Information. *Data Collection*. Crystals suitable for X-ray diffraction were mounted in inert oil on a glass fiber and transferred to a Bruker D8 QUEST (**3a**·1/2H_2O, **4b**·$CHCl_3$, **5a**) or a Bruker SMART (**3b**) diffractometer. Data were recorded at 100(2) K, using graphite-monochromated Mo-Ka radiation (λ = 0.71073 Å), and ω-scan (**3a**·1/2H_2O, **3b**) or ω- and ϕ-scan (**4b**·$CHCl_3$, **5a**) mode. Multiscan absorption corrections were applied for all complexes. *Structure Solution and Refinements*. Crystal Structures were solved by Patterson (**4b**·$CHCl_3$) or direct methods (**3a**·1/2H_2O, **3b**, **5a**) and all non hydrogen atoms refined anisotropically on F^2 using the program SHELXL-2014/7.[56] Hydrogen atoms were refined as follows: Complex **3a**·1/2H_2O: H_2O, free with DFIX; methyl, rigid group; all others, riding. Complexes **3b** and **4b**·$CHCl_3$: NH_2 (in the non-disordered molecule), free with SADI; ordered methyl, rigid group; all others, riding. Compound **5a**: NH, free; methyl, rigid group; all others, riding. *Special features*: For **3b**: The $NH_2CH(Me)CH_2$ part is disordered over two positions, with a ca. 82:18 occupancy distribution; the two hydrogen atoms on NH_2 in the minor part were not located, so they were not used in the refinement. For **4b**·$CHCl_3$: The atoms C29, C30 and N3 were disordered over two positions, with a ca. 73:27 occupancy distribution; the two hydrogen atoms at N3 were not located so they were not used in the refinement; one chloroform molecule is disordered over two positions, with a ca. 51:49 occupancy distribution.

CONCLUSIONS

Seven-membered palladacycles can be synthesized by unprecedented C–H activation of phenylpropylamine derivatives. The presence of substituents in the α-carbon of the arylalkylamine is essential for the orthometalation to take place. The structure in solution and dynamic behavior of the palladacycles has been investigated by NMR. The reaction of the palladacycles with CO affords Pd(0) and the corresponding 2,3,4,5-tetrahydro-2-benzazepin-1-ones. Catalytic attempts to perform the carbonylation, using the system $Pd(OAc)_2/Cu(OAc)_2$ as catalyst, rendered *N,N'*-phenylpropyl-ureas.

ASSOCIATED CONTENT

Supporting Information Available: Copies of ^{1}H and ^{13}C-APT NMR spectra of all compounds, ^{1}H NOESY and ^{1}H-^{13}C HMQC and HMBC spectra of selected complexes, details on the conformations found for **3a**,**b** in solution, details on the NMR line shape analysis of the fluxional process taking place in complex **4a**, crystallographic data, details of hydrogen bonds (including symmetry operators), and CIF files for compounds **3a**·1/2H_2O, **3b**, **4b**·$CHCl_3$, and **5a**. CCDC 1457218–1457221. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

1. Chu, J.-H.; Chen, C.-C.; Wu, M.-J. *Organometallics* **2008**, *27*, 5173-5176. Chu, J.-H.; Huang, H.-P.; Hsu, W.-T.; Chen, S.-T.; Wu, M.-J. *Organometallics* **2014**, *33*, 1190-1204. Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147-1169. Omae, I. *Coord. Chem. Rev.* **2011**, *255*, 139-160. Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788-802. Liang, Z.; Zhang, J.; Liu, Z.; Wang, K.; Zhang, Y. *Tetrahedron* **2013**, *69*, 6519-6526. Péron, F.; Fossey, C.; Sopkova-de Oliveira Santos, J.; Cailly, T.; Fabis, F. *Chem. Eur. J.* **2014**, *20*, 7505-7513. Boyarskiy, V. P.; Bokach, N. A.; Luzyanin, K. V.; Kukushkin, V. Y. *Chem. Rev.* **2015**, *115*, 2698-2779. Li, G.; Wan, L.; Zhang, G.; Leow, D.; Spangler, J.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015**, *137*, 4391-4397.
2. Aguilar, D.; Cuesta, L.; Nieto, S.; Serrano, E.; Urriolabeitia, E. P. *Curr. Org. Chem.* **2011**, *15*, 3441-3464.
3. Bosque, R.; Maseras, F. *Eur. J. Inorg. Chem.* **2005**, 4040-4047. Dupont, J.; Pfeffer, M., *Palladacycles. Synthesis, Characterization and Applications*. Wiley-VCH: Weinheim, Germany, 2008.
4. Singh, J.; Kumar, D.; Singh, N.; Elias, A. J. *Organometallics* **2014**, *33*, 1044-1052.
5. Arlen, C.; Pfeffer, M.; Bars, O.; Grandjean, D. *J. Chem. Soc., Dalton Trans.* **1983**, 1535-1544. Maassarani, F.; Pfeffer, M.; Le Borgne, G.; Grandjean, D. *Organometallics* **1986**, *5*, 1511-1513. Maassarani, F.; Pfeffer, M.; Le Borgne, G. *Organometallics* **1987**, *6*, 2029-2043. Arsenault, G. J.; Ferguson, G.; McAlees, A.

J.; McCrindle, R.; Ruhl, B. L. *Acta Crystallogr., Sect. C* **1991**, *47*, 1729-1730. Spencer, J.; Pfeffer, M.; Kyritsakas, N.; Fischer, J. *Organometallics* **1995**, *14*, 2214-2224. Vicente, J.; Abad, J. A.; Fernández-de-Bobadilla, R.; Jones, P. G.; Ramírez de Arellano, M. C. *Organometallics* **1996**, *15*, 24-34. Hashmi, A. S. K.; Rivas Nass, A.; Bats, J. W.; Bolte, M. *Angew. Chem. Int. Ed.* **1999**, *38*, 3370-3373. Benito, M.; López, C.; Morvan, X.; Solans, X.; Font-Bardía, M. *J. Chem. Soc., Dalton Trans.* **2000**, 4470-4478. Bosque, R.; Benito, M.; López, C. *New J. Chem.* **2001**, *25*, 827-833. Gül, N.; Nelson, J. H.; Wilis, A. C.; Rae, A. D. *Organometallics* **2002**, *21*, 2041-2048. Kelly, A. E.; Macgregor, S. A.; Willis, A. C.; Nelson, J. H.; Wenger, E. *Inorg. Chim. Acta* **2003**, *352*, 79-97. Vicente, J.; Saura-Llamas, I.; Turpín, J.; Bautista, D.; Ramírez de Arellano, C.; Jones, P. G. *Organometallics* **2009**, *28*, 4175-4195. Luo, D.; Li, Y.; Pullarkat, S. A.; Cockle, K. E.; Leung, P.-H. *Organometallics* **2010**, *29*, 893-903. Chen, S.; Pullarkat, S. A.; Li, Y.; Leung, P.-H. *Organometallics* **2011**, *30*, 1530-1550. Chen, S.; Pullarkat, S. A.; Li, Y.; Leung, P.-H. *Eur. J. Inorg. Chem.* **2011**, 3111-3121. Chen, S.; Pullarkat, S. A.; Li, Y.; Leung, P.-H. *Eur. J. Inorg. Chem.* **2012**, 1823-1831. Chen, S.; Chiew, J. X.; Pullarkat, S. A.; Li, Y.; Leung, P.-H. *Eur. J. Inorg. Chem.* **2013**, 5487-5494. Frutos-Pedreño, R.; González-Herrero, P.; Vicente, J.; Jones, P. G. *Organometallics* **2013**, *32*, 4664-4676.

6. Vicente, J.; Saura-Llamas, I.; García-López, J. A.; Bautista, D. *Organometallics* **2009**, *28*, 448-464.
7. Widenhoefer, R. A.; Zhong, H. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 6787-6795. Motti, E.; Della Ca', N.; Xu, D.; Piersimoni, A.; Bedogni, E.; Zhou, Z.-M.; Catellani, M. *Org. Lett.* **2012**, *14*, 5792-5795. Peng, H. M.; Song, G.; Li, Y.; Li,

X. *Inorg. Chem.* **2008**, *47*, 8031-8043. Frutos-Pedreño, R.; González-Herrero, P.; Vicente, J.; Jones, P. G. *Organometallics* **2013**, *32*, 1892-1904.

8. Douthwaite, R. E.; Green, M. L.; Silcock , P. J.; Gomes, P. T. *J. Chem. Soc., Dalton Trans.* **2002**, 1386-1390. Lee, H. M.; Lu, C. Y.; Chen, C. Y.; Chen, W. L.; Lin, H. C.; Chiu, P. L.; Cheng, P. Y. *Tetrahedron* **2004**, *60*, 5807-5825. Vignolle, J.; Donnadieu, B.; Bourissou, D.; Soleilhavoup, M.; Bertrand, G. *J. Am. Chem. Soc.* **2006**, *128*, 14810-14811. Wanniarachchi, Y. A.; Slaughter, L. M. *Chem. Commun.* **2007**, 3294-3296. Wanniarachchi, Y. A.; Kogiso, Y.; Slaughter, L. M. *Organometallics* **2008**, *27*, 21-24. Sabouncheia, S. J.; Panahimehra, M.; Ahmadia, M.; Akhlaghia, F.; Boscovic, C. *C. R. Chimie* **2014**, *17*, 81-90.
9. Ma, L.; Woloszynek, R. A.; Chen, W.; Ren, T.; Protasiewicz, J. D. *Organometallics* **2006**, *25*, 3301-3304. Ma, L.; Wobser, S. D.; Protasiewicz, J. D. *J. Organomet. Chem.* **2007**, *692*, 5331-5338. Schroder, P. M.; Spilker, T. F.; Luu, W.; Updegraff III, J. B.; Kwan, M. L.; Challen, P. R.; Protasiewicz, J. D. *Inorg. Chem. Commun.* **2009**, *12*, 1171-1174.
10. Nicasio-Collazo, J.; Álvarez, E.; Alvarado-Monzón, J. C.; Andreu-de-Riquer, G.; Jimenez-Halla, J. O. C.; De León-Rodríguez, L. M.; Merino, G.; Morales, U.; Serrano, O.; López, J. A. *Dalton Trans.* **2011**, *40*, 12450-12453.
11. Bennett, M. A.; Johnson, R. N.; Robertson, G. B.; Tomkins, I. B.; Whimp, P. O. *J. Am. Chem. Soc.* **1976**, *98*, 3514-3523.
12. Jimeno, C.; Christmann, U.; Escudero-Adán, E. C.; Vilar, R.; Pericàs , M. A. *Chem. Eur. J.* **2012**, *18*, 16510-16516.
13. Wang, Q.; Han, J.; Wang, C.; Zhang, J.; Huang, Z.; Shi, D.; Zhao , Y. *Chem. Sci.* **2014**, *5*, 4962-4967.

14. Cope, A. C.; Friedrich, E. C. *J. Am. Chem. Soc.* **1968**, *90*, 909-913.

15. Dunina, V. V.; Zalevskaya, O. A.; Potapov, V. M. *Russ. Chem. Rev.* **1988**, *57*, 250-269. Ryabov, A. D. *Chem. Rev.* **1990**, *90*, 403-424.

16. Fuchita, Y.; Tsuchiya, H.; Miyafuji, A. *Inorg. Chim. Acta* **1995**, *233*, 91-96.

17. Vicente, J.; Saura-Llamas, I.; Palin, M. G.; Jones, P. G.; Ramírez de Arellano, M. C. *Organometallics* **1997**, *16*, 826-833. Kurzeev, S. A.; Kazankoz, G. M.; Ryabov, A. D. *Inorg. Chim. Acta* **2002**, *340*, 192-196.

18. Vicente, J.; Saura-Llamas, I.; Cuadrado, J.; Ramírez de Arellano, M. C. *Organometallics* **2003**, *22*, 5513-5517. Fuchita, Y.; Yoshinaga, K.; Ikeda, Y.; Kinoshita-Kawashima, J. *J. Chem. Soc., Dalton Trans.* **1997**, 2495-2499. Vicente, J.; Saura-Llamas, I.; Palin, M. G.; Jones, P. G. *J. Chem. Soc., Dalton Trans.* **1995**, 2535-2539.

19. Vicente, J.; Saura-Llamas, I. *Comments Inorg. Chem.* **2007**, *28*, 39-72.

20. Vicente, J.; Saura-Llamas, I.; García-López, J. A.; Calmuschi-Cula, B.; Bautista, D. *Organometallics* **2007**, *26*, 2768-2776.

21. Vicente, J.; Saura-Llamas, I.; Oliva-Madrid, M. J.; García-López, J. A.; Bautista, D. *Organometallics* **2011**, *30*, 4624-4631.

22. Oliva-Madrid, M.-J.; García-López, J.-A.; Saura-Llamas, I.; Bautista, D.; Vicente, J. *Organometallics* **2012**, *31*, 3647-3660.

23. Alsters, P. L.; Boersma, J.; Smeets, W. J. J.; Spek, A. L.; Van Koten, G. *Organometallics* **1993**, *12*, 1639-1647. Cámpora, J.; López, J. A.; Palma, P.; del Rio, D.; Carmona, E.; Valerga, P.; Graiff , C.; Tiripicchio, A. *Inorg. Chem.* **2001**, *40*, 4116-4126. Rousseaux, S.; Davi, M.; Sofack-Kreutzer, J.; Pierre, C.; Kefalidis, C. E.; Clot, E.; Fagnou, K.; Baudoin, O. *J. Am. Chem. Soc.* **2010**, *132*, 10706-10716.

Giri, R.; Lam, J. K.; Yu, J.-Q. *J. Am. Chem. Soc.* **2010**, *132*, 686-693. Piou, T.; Bunescu, A.; Wang, Q.; Neuville, L.; Zhu, J. *Angew. Chem. Int. Ed.* **2013**, *52*, 12385-12389. Yan, J.-X.; Li, H.; Liu, X.-W.; Shi, J.-L.; Wang, X.; Shi, Z.-J. *Angew. Chem. Int. Ed.* **2014**, *53*, 4945-4949. Cong, X.; You, J.; Gao, G.; Lan, J. *Chem. Commun.* **2013**, *49*, 662-664.

24. Murakami, Y.; Hara, H.; Okada, T.; Hashizume, H.; Kii, M.; Ishihara, Y.; Ishikawa, M.; Shimamura, M.; Mihara, S.-i.; Kato, G.; Hanasaki, K.; Hagishita, S.; Fujimoto, M. *J. Med. Chem.* **1999**, *42*, 2621-2632. Miller, W. H.; Alberts, D. P.; Bhatnagar, P. K.; Bondinell, W. E.; Callahan, J. F.; Calvo, R. R.; Cousins, R. D.; Erhard, K. F.; Heerding, D. A.; Keenan, R. M.; Kwon, C.; Manley, P. J.; Newlander, K. A.; Ross, S. T.; Samanen, J. M.; Uzinskas, I. N.; Venslavsky, J. W.; Yuan, C. C.-K.; Haltiwanger, R. C.; Gowen, M.; Hwang, S.-M.; James, I. E.; Lark, M. W.; Rieman, D. J.; Stroup, G. B.; Azzarano, L. M.; Salyers, K. L.; Smith, B. R.; Ward, K. W.; Johanson, K. O.; Huffman, W. F. *J. Med. Chem.* **2000**, *43*, 22-26. Kamimura, A.; So, M.; Kuratani, T.; Matsuura, K.; Inui, M. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3193-3195. Feytens, D.; De Vlaeminck, M.; Cescato, R.; Tourwé, D.; Reubi, J. C. *J. Med. Chem.* **2009**, *52*, 95-104. Lee, S.-J.; Heo, I.-J.; Cho, C.-W. *Bull. Korean Chem. Soc.* **2012**, *33*, 739-741. So, M.; Kotake, T.; Matsuura, K.; Inui, M.; Kamimura, A. *J. Org. Chem.* **2012**, *77*, 4017-4028. Quick, M. P.; Fröhlich, R.; Schepmann, D.; Wünsch, B. *Org. Biomol. Chem,* **2015**, *13*, 7265-7281.

25. Braje, W.; Geneste, H.; Haupt, A.; Lubisch, W. Keto lactam compounds and use thereof. PCT Int. Appl. WO 2005056546 A1, 2005. López, L.; Selent, J.; Ortega, R.; Masaguer, C. F.; Domínguez, E.; Areias, F.; Brea, J.; Loza, M. I.; Sanz, F.; Pastor,

M. *ChemMedChem* **2010**, *5*, 1300-1317. Ortega, R.; Hübner, H.; Gmeiner, P.; Masaguer, C. F. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2670-2674.

26. Ortega, R.; Raviña, E.; Masaguer, C. F.; Areias, F.; Brea, J.; Loza, M. I.; López, L.; Selent, J.; Pastor, M.; Sanz, F. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1773-1778.
27. Akritopoulou-Zanze, I.; Braje, W.; Djuric, S. W.; Wilson, N. S.; Turner, S. C.; Kruger, A. W.; Relo, A. L.; Shekhar, S.; Welch, D. S.; Zhao, H. Modulators of 5-HT receptors and methods of use thereof. U.S. Patent US8846951 B2, 2014.
28. Sivaprakasam, P.; Han, X.; Civiello, R. L.; Jacutin-Porte, S.; Kish, K.; Pokross, M.; Lewis, H. A.; Ahmed, N.; Szapiel, N.; Newitt, J. A.; Baldwin, E. T.; Xiao, H.; Krause, C. M.; Park, H.; Nophsker, M.; Lippy, J. S.; Burton, C. R.; Langley, D. R.; Macor, J. E.; Dubowchik, G. M. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 1856-1863.
29. Kang, G. A.; Lee, M.; Song, D.; Lee, H. K.; Ahn, S.; Park, C. H.; Lee, C. O.; Yun, C. S.; Jung, H.; Kim, P.; Ha, J. D.; Cho, S. Y.; Kim, H. R.; Hwang, J. Y. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 3992-3998.
30. Karami, K.; Naeini, N. H.; Eigner, V.; Dusek, M.; Lipkowski, J.; Hervés, P.; Tavakol, H. *RSC Adv.* **2015**, *5*, 102424-102435.
31. Cockburn, B. N.; Howe, D. V.; Keating, T.; Johnson, B. F. G.; Lewis, J. *J. Chem. Soc., Dalton Trans.* **1973**, 404-410. Dunina, V. V.; Kuz'mina, L. G.; Kazakova, M. Y.; Gorunova, O. N.; Grishin, Y. K.; Kazakova, E. I. *Eur. J. Inorg. Chem.* **1999**, 1029-1039. Laga, E.; García-Montero, A.; Sayago, F. J.; Soler, T.; Moncho, S.; Cativiela, C.; Martínez, M.; Urriolabeitia, E. P. *Chem. Eur. J.* **2013**, *19*, 17398–17412.
32. Vicente, J.; Saura-Llamas, I.; Bautista, D. *Organometallics* **2005**, *24*, 6001-6004.

33. Vicente, J.; Saura-Llamas, I.; García-López, J.-A.; Bautista, D. *Organometallics* **2010**, *29*, 4320-4338.

34. Vicente, J.; Arcas, A.; Fernández-Hernández, J. M.; Bautista, D. *Organometallics* **2001**, *20*, 2767-2774. Vicente, J.; Arcas, A.; Borrachero, M. V.; Hursthouse, M. B. *J. Chem. Soc., Dalton Trans.* **1987**, 1655-1658.

35. Vassileva, V.; Gencheva, G.; Russeva, E.; Varbanov, S.; Scopelliti, R.; Tashev, E. *Inorg. Chim. Acta* **2005**, *358*, 3671-3679. Nakamoto, K., *Infrared and Raman Spectra of Inorganic and Coordination Compounds, Part B.* 5th ed.; Wiley: New York, 1997.

36. Sui-Seng, C.; Zargarian, D. *Acta Cryst.* **2003**, *E59*, m957-m958. Sabater, S.; Mata, J. A.; Peris, E. *Organometallics* **2013**, *32*, 1112-1120.

37. Albert, J.; Granell, J.; Tavera, R. *Polyhedron* **2003**, *22*, 287-291.

38. Oliva-Madrid, M.-J.; García-López, J.-A.; Saura-Llamas, I.; Bautista, D.; Vicente, J. *Organometallics* **2014**, *33*, 33-39.

39. Vicente, J.; Arcas, A.; Gálvez-López, M.-D.; Juliá-Hernández, F.; Bautista, D.; Jones, P. G. *Organometallics* **2008**, *27*, 1582-1590. Vicente, J.; Abad, J. A.; Hernández-Mata, F. S.; Rink, B.; Jones, P. G.; Ramírez de Arellano, M. C. *Organometallics* **2004**, *23*, 1292-1304. Rodríguez, N.; Cuenca, A.; Ramírez de Arellano, C.; Medio-Simón, M.; Peine, D.; Asensio, G. *J. Org. Chem.* **2004**, *69*, 8070-8076. Vicente, J.; Abad, J. A.; Frankland, A. D.; López-Serrano, J.; Ramírez de Arellano, M. C.; Jones, P. G. *Organometallics* **2002**, *21*, 272-282. Larraz, C.; Navarro, R.; Urriolabeitia, E. P. *New J. Chem.* **2000**, *24*, 623-630. Vicente, J.; Arcas, A.; Bautista, D.; Jones, P. G. *Organometallics* **1997**, *16*, 2127-2138.

40. Kadyrov, R.; Börner, A.; Selke, R. *Eur. J. Inorg. Chem.* **1999**, 705-711.

41. Entrena, A.; Campos, J. M.; Gallo, M. A.; Espinosa, A. *ARKIVOC* **2005**, *(iv)*, 88-108.

42. Hart, H.; Corbin, J. L. *J. Am. Chem. Soc.* **1965**, *87*, 3135-3139. Christl, M.; Roberts, J. D. *J. Org. Chem.* **1972**, *37*, 3443-3452. Canuel, L.; St-Jacques, M. *Can. J. Chem.* **1974**, *52*, 3581-3588. Flapper, W. M. J.; C. Romers, C. *Tetrahedron* **1975**, *31*, 1705-1713. Bocian, D. F.; Pickett, H. M.; Rounds, T. C.; Strauss, H. L. *J. Am. Chem. Soc.* **1975**, *97*, 687-695. A. Blanchette; F. Sauriol-Lord; St.-Jacques, M. *J. Am. Chem. Soc.* **1978**, *100*, 4055-4062.

43. De Clercq, P. J. *J. Org. Chem.* **1981**, *46*, 667-675. Sauriol-Lord, F.; Grindley, T. B. *J. Am. Chem. Soc.* **1981**, *103*, 936-938. Dionne, P.; St- Jacques, M. *Can. J. Chem.* **1990**, *68*, 513-521. Allen, F. H.; Howard, J. A.; Pitchford, N. A.; Vinter, J. G. *Acta Cryst.* **1995**, *B50*, 382-395. Entrena, A.; Campos, J.; Gómez, J. M.; Gallo, M. A.; Espinosa, A. *J. Org. Chem.* **1997**, *62*, 337-349. Leong, M. K.; Mastryukov, V. S.; Boggs, J. E. *J. Mol. Struct.* **1998**, *445*, 149-160. Hassner, A.; Amit, B.; Marks, V.; Gottlieb, H. E. *J. Org. Chem.* **2003**, *68*, 6853-6858. Groenewald, F.; Mateura, M.; Dillen, J. *Struct. Chem.* **2013**, *24*, 243-250.

44. Bookham, J. L.; McFarlane, W. *J. Chem. Soc., Chem. Commun.* **1993**, 1352-1354. McFarlane, W.; D., S. J.; Bookham, J. L. *J. Chem. Soc., Daton Trans.* **1998**, 3233-3238. Li, Y.; Ng, K.-H.; Selvaratnam, S.; Tan, G.-K.; Vittal, J. J.; Leung, P.-H. *Organometallics* **2003**, *22*, 834-842. Dunina, V. V. *Curr. Org. Chem.* **2011**, *15*, 3415-3440. Mawo, R. Y.; Mustakim, S.; Young, J., V. G.; Hoffmann, M. R.; Smoliakova, I. P. *Organometallics* **2007**, *26*, 1801-1810. Mawo, R. Y.; Johnson, D. M.; Wood, J. L.; Smoliakova, I. P. *J. Organomet. Chem.* **2008**, *693*, 33-45. Gopi, K.; Thirupathi, N.; Nethaji, M. *Organometallics* **2011**, *30*, 572-583.

45. Espinet, P.; Casares, J. A., *Conformational Mobility in Chelated Square-Planar Rh, Ir, Pd, and Pt Complexes*. Fluxional Organometallic and Coordination Compounds: Physical Organometallic Chemistry; John Wiley & Sons, Ltd,: Chichester, UK, 2005; Vol. 4.

46. Brown, J. M.; Chaloner, P. A. *J. Am. Chem. Soc.* **1978**, *100*, 4307-4309. Brown, K.; Chaloner, P. A. *J. Organomet. Chem.* **1981**, *217*, C25-C28. Toriumi, K.; Ito, T.; Takaya, H.; Souchi, T.; Noyori, R. *Acta Cryst.* **1982**, *B38*, 807-812. Kawano, H.; Ikariya, T.; Ishii, Y.; Kodama, T.; Saburi, M.; Yoshikawa, S.; Uchida, Y.; Akutagawa, S. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1595-1602. Toth, I.; Hanson, B. E. *Organometallics* **1993**, *12*, 1506-1513. RajanBabu, T. V.; Radetich, B.; You, K. K.; Ayers, T. A.; Casalnuovo, A. L.; Calabrese, J. C. *J. Org. Chem.* **1999**, *64*, 3429-3447. Raskatov, J. A.; Thompson, A. L.; Brown, J. M. *Tetrahedron: Asymmetry* **2010**, *21*, 1737-1744.

47. For **1b** the exchange peaks within each CH_2, NH_2, and CMe_2 group are found between diastereomers (one proton of the major diastereomer exchanges with a proton of the same group of the minor diasteromer, and viceversa). This is not surprising, as the exchange process intercoverts the diastereromers.

48. Orito, K.; Horibata, A.; Nakamura, T.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Tokuda, M. *J. Am. Chem. Soc.* **2004**, *126*, 14342-14343. Li, H.; Cai, G.-X.; Shi, Z.-J. *Dalton Trans.* **2010**, *39*, 10442-10446 . Haffemayer, B.; Gulias, M.; Gaunt, M. J. *Chem. Sci.* **2011**, *2*, 312-315. Wu, X.-F.; Neumann, H.; Beller, M. *Chem. Rev.* **2013**, *113*, 1-35.

49. Orito, K.; Miyazawa, M.; Nakamura, T.; Horibata, A.; Ushito, H.; Nagasaki, H.; Yuguchi, M.; Yamashita, S.; Yamazaki, H.; Tokuda, M. *J. Org. Chem.* **2006**, *71*, 5951-5958.

50. Nieto, S.; Sayago, F. J.; Laborda, P.; Soler, T.; Cativiela, C.; Urriolabeitia, E. P. *Tetrahedron* **2011**, *67*, 4185-4191.

51. López, B.; Rodriguez, A.; Santos, D.; Albert, J.; Ariza, X.; Garcia, J.; Granell, J. *Chem. Commun.* **2011**, *47*, 1054-1056. Albert, J.; Ariza, X.; Calvet, T.; Font-Bardia, M.; Garcia, J.; Granell, J.; Lamela, A.; López, B.; Martinez, M.; Ortega, L.; Rodriguez, A.; Santos, D. *Organometallics* **2013**, *32*, 649-659.

52. García-López, J.-A.; Oliva-Madrid, M.-J.; Saura-Llamas, I.; Bautista, D.; Vicente, J. *Organometallics* **2012**, *31*, 6351-6364.

53. García-López, J.-A.; Oliva-Madrid, M.-J.; Saura-Llamas, I.; Bautista, D.; Vicente, J. *Organometallics* **2013**, *32*, 1094-1105. Oliva-Madrid, M.-J.; García-López, J.-A.; Saura-Llamas, I.; Bautista, D.; Vicente, J. *Organometallics* **2014**, *33*, 6420-6430.

54. Grunewald, G. L.; Dahanukar, V. H. *J. Heterocycl. Chem.* **1994**, *31*, 1609-1617.

55. Potapov, V. M.; Dem'yanovich, V. M.; Vendrova, O. E.; Khlebnikov, V. A. *Khim. Geterotsikl. Soedin.* **1983**, 655-660.

56. Sheldrick, G. M. SHELXL-2014; University of Göttingen, Göttingen, Germany, 2014.

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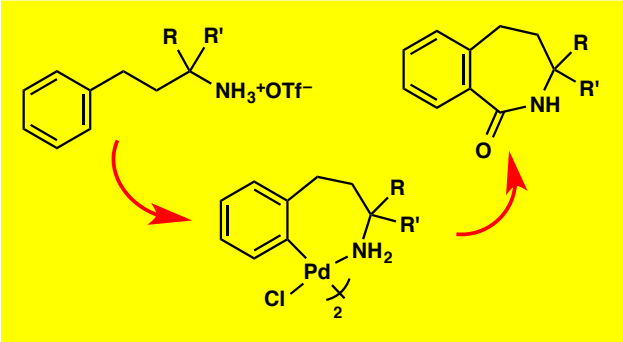

Synopsis

The first cyclopalladations of primary arylalkylamines leading to seven-membered rings are reported. Stoichiometric carbonylation of the palladacycles give 2-benzazepinones. Catalytic carbonylation of the starting amonium salts with CO, using as catalyst the system $Pd(OAc)_2/Cu(OAc)_2$, affords the corresponding ureas instead the lactams.