FULL PAPER

Dialkylterphenyl Phosphine-Based Palladium Precatalysts for Efficient Aryl Amination of N-nucleophiles

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Dedicated to Professor Pablo Espinet on the occasion of his 70th birthday

Abstract: A series of 2-aminobiphenyl palladacycles supported by dialkylterphenyl phosphines, PR_2Ar' (R = Me, Et, *i*Pr, Cyp; Ar' = Ar^{Dipp2}, Ar^{Xyl2}) have been prepared and structurally characterized. Neutral palladacycles were obtained with less bulky terphenyl phosphines (i.e. Me and Et substituents) while the largest phosphines provided cationic palladacycles in which the phosphines adopted a bidentate hemilabile κ^1-P,η^1-C_{arene} coordination mode. The influence of the ligand structure on the catalytic performance of these Pd precatalysts was evaluated in aryl amination reactions. Cationic complexes bearing phosphines $PiPr_2Ar^{Xyl2}$ and $PCyp_2Ar^{Xyl2}$ were the most active of the series. These precatalysts have demonstrated a high versatility and efficiency in the coupling of a variety of N-nucleophiles, including secondary amines, alkyl amines, anilines and indoles, with electronically deactivated and *ortho*-substituted aryl chlorides at low catalyst loadings (0.25-0.75 mol% Pd) and without excess ligand.

Introduction

At present, palladium-catalyzed aryl amination is a general, versatile and reliable synthetic protocol for the formation of C(sp^2)-N bonds, which finds applications both in academic and industrial contexts.[1] Since its introduction, almost 25 years ago by the groups of Buchwald[2] and Hartwig,[3] the rapid evolution experienced by this catalytic transformation has been largely driven by the development of new ancillary ligands, leading to increasingly challenging couplings under milder conditions.[1d,4] Not surprisingly, the most widely employed supporting ligands in Pd-catalyzed cross-coupling reactions are tertiary phosphines,[5] since their electronic and steric properties can be conveniently tuned by changing the nature of the substituents attached to the phosphorous atom. Actually, phosphines that combine both electron-richness and bulkiness produce remarkably active Pd catalytic species for Buchwald-Hartwig aminations.[6] Examples include bisphosphines like Xantphos[7] or Josiphos,[8] hemilabile P,N-ligands[9] and Buchwald's biaryl monophosphines.[10]

The mentioned dialkylbiaryl phosphines constitute a broad family of ligands, with an outstandingly extensive applicability,[1e] as their modular synthesis enables the customization of the ligand for a particular coupling.[11] Besides, most of these ligands feature fair air-stability both in solution and in the solid state, facilitating their manipulation. Furthermore, these ligands adopt different coordination modes, where P-bonding is complemented by weak M···C_{arene} interactions with the non-phosphine-containing aryl ring.[10a,12] In the last decade, the use of well-defined Pd(II) precatalysts in cross-coupling reactions has been extended.[13] Precatalysts ensure a better control over the composition and stoichiometry of the catalytic species throughout the catalytic cycle, improving the efficiency and the economy of the process.[13b] In this regard, 2-aminobiphenyl palladacycles bearing larger dialkylbiaryl phosphine ligands have emerged as extremely powerful catalytic systems for aryl amination reactions.[14]

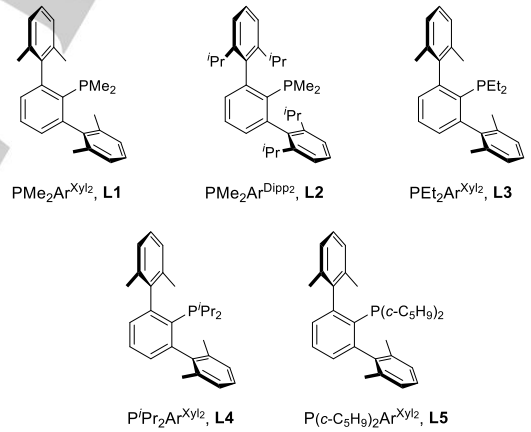

Figure 1. Structural formula, abbreviated names and numbering scheme for terphenyl phosphines employed in this work.

Contrary to Buchwald's biaryl phosphines, dialkylterphenyl phosphines, PR_2Ar' with Ar' = terphenyl radical, have been far less studied (Figure 1).[15] With the aim of investigating the properties of this type of ligands, we prepared a series of dialkylterphenyl phosphines with a variety of substituents both on the phosphorus and on the terphenyl moiety and evaluated their electronic and steric parameters.[16] These studies highlighted their strong basicity and their superior steric protection when compared to dicyclohexylbiaryl phosphines.[16b,c] Moreover, the coordination properties of terphenyl phosphines towards a variety of late transition metals including Rh, Ir, Ni, Pt and Au proved their ability to adopt different coordination modes involving the P atom

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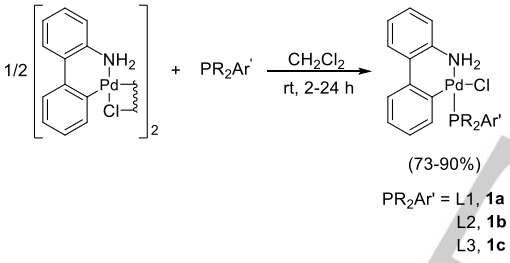
and one of the flanking aryl rings of the terphenyl fragment.[16,17] Herein, we describe the first application of terphenyl phosphines in Pd-catalyzed aryl amination reactions. With this aim, a series of 2-aminobiphenyl palladacycles stabilized by the ligands depicted in Figure 1 have been synthesized and structurally characterized. Their catalytic activities in the arylation of a variety of N-nucleophiles, including alkyl primary and secondary amines, anilines and indoles, with electronically deactivated methoxy-substituted aryl chlorides have been examined.

Results and Discussion

Synthesis and structural characterization of terphenyl phosphine-stabilized palladacycles

Palladacycles **1a-1c** were prepared in good yields following the procedure shown in Scheme 1,[14a,b] which involves the equimolar reaction between the 2-aminobiphenyl-Pd chloride-bridged dimer with the less bulky terphenyl phosphine ligands **L1**-**L3** in dichloromethane at room temperature. Whereas the reactions with PMe_2Ar' phosphines **L1**-**L2** were achieved in 2 h, that involving PEt_2Ar^{Xyl2}, **L3**, required a considerably longer reaction time (24 h) to reach completion.



Scheme 1. General synthesis of complexes **1a**-**1c**.

Complexes **1a**-**1c** were isolated as air-stable colorless crystals and were fully characterized by microanalysis and NMR spectroscopy. As opposed to those described for analogous palladacycles bearing bulky monophosphine ligands,[14a,18] the room temperature $^{31}P\{^1H\}$ NMR spectra of compounds **1a**-**1c** display single resonances at δ 1.7, 1.9 and 29.1, respectively, revealing shifts of about 40 ppm to higher frequencies with respect to the free phosphine ligands. The ^1H NMR spectrum of **1a** is consistent with a fast rotation of the phosphine ligand around the P-C_{ipso} bond at 25 ºC, since the four methyl substituents of the xylyl rings originate only one resonance at 2.25 ppm and the two methyl groups directly bound to the P atom appear as a doublet at 1.00 ppm (J_{HP} = 9 Hz). In addition, a broad singlet centered at 4.50 ppm is observed for the two protons of the amino group of the 2-aminobiphenyl moiety. Conversely, ^1H NMR spectra for **1b** and **1c** show broad resonances in the aliphatic region, indicating that for both species the above-mentioned fluxional process is somewhat slower at room temperature. Upon cooling at -30 °C, these signals resolve into the distinct pattern of resonances expected for non-equivalent substituents both on the aryl rings and on the phosphorus atom, indicating a hindered process of exchange of the flaking aryl rings (see Figs. S1 and S2). Furthermore, for the PEt_2Ar^{Xyl2} derivative **1c**, the resonance due to the NH_2 group splits into two signals at low temperature (δ 4.62 and 4.56). The ^1H-^{31}P heteronuclear correlation experiment recorded at 0 ºC for **1c** provides clear evidence of the coupling between the NH_2 protons and the phosphorus atom, supporting a mutually *trans* arrangement between the phosphine and the amino group in these molecules.

The solid-state structures of complexes **1a** and **1c** were confirmed by X-ray diffraction studies (Figures 2 and S3). In both complexes the Pd^{II} center is bonded to the 2-aminobiphenyl moiety, the phosphine and the chloride ligands in a slightly distorted square-planar geometry, with *cis* bond angles varying from *ca*. 83 to 95º. As in the cases of the solid-state structures reported for other 2-aminobiphenyl palladacycles,[18,19] the phosphorus atom in **1a** and **1c** is coordinated in *trans* position relative to the nitrogen atom of the amino group. The Pd-P distances of 2.2763(7) and 2.2596(7) Å for **1a** and **1c**, respectively, compare well with those found in similar complexes.[18,19]

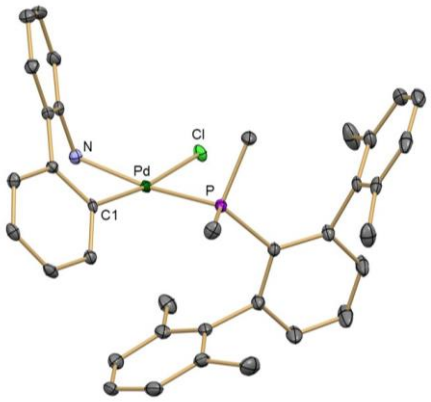
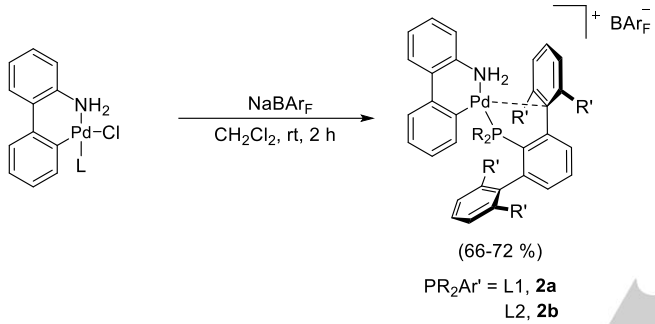


Figure 2. Molecular structure of **1a**. Hydrogen atoms are omitted for clarity. Thermal ellipsoids are shown at 50% probability. Selected bond lengths [Å] and angles [º]: Pd-P 2.2763(7), Pd-N 2.107(2), Pd-C1 2.005(2), Pd-Cl 2.4151(6); N-Pd-P 170.37(6), C1-Pd-Cl 171.36(7), C1-Pd-P 94.64(7), P-Pd-Cl 92.69(2).

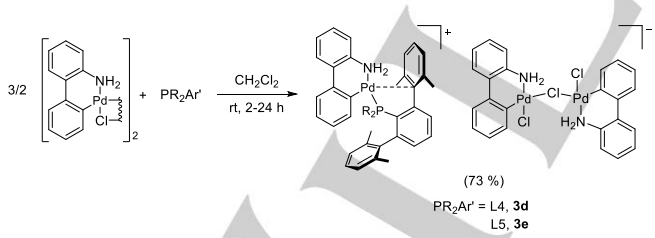
Treatment of dichloromethane solutions of **1a** and **1b** with $NaBAr_F$ promoted the abstraction of the chloride ligand and the quantitative formation of cationic species **2**. As outlined in Scheme 2, the resulting free coordination site in these complexes was occupied by one of the flanking aryl rings of the terphenyl group. The structures proposed for complexes **2** were based on analytical and spectroscopic data, as well as on molar conductivity measurements. The resonance due to the phosphorus nucleus in the cationic derivatives **2** experiences a shift to higher frequency ($\Delta\delta \approx 13$ ppm) with respect to that of the neutral complexes **1a** and **1b**. Such a shift may be indicative of a bidentate coordination mode of the phosphine ligand involving the P atom and one of the flanking aryl ring of terphenyl moiety.[16b] The complexity of ^1H and $^{13}C\{^1H\}$ NMR spectra of **2a** and **2b** at 25 ºC attests for the low symmetry exhibited by these compounds. Thus taking **2a** as an example, its ^1H NMR spectrum shows separate signals for each of the methyl groups of the xylyl

fragments. The methyl groups attached to the P atom give rise to two doublets at δ 1.47 and 0.87 (J_{HP} = 11 Hz). In addition, the two diasterotopic protons of the amino group resonate as a doublet of doublets at 4.37 (J_{HH} = 5.1 and J_{HP} = 9 Hz) and as broad doublet centered at 1.55 ppm. To confirm the cationic nature of complexes **2**, conductivity measurements were undertaken in nitromethane as the solvent. The molar conductivities of 1.0 mM solutions of **2a** and **2b** in nitromethane were measured at 46.8 and 36.0 Ω^{-1} cm^2 mol^{-1}, respectively. Both values are significantly lower than that of 82.2 Ω^{-1} cm^2 mol^{-1} gauged for [^{n}Bu]$_4$NI, a 1:1 electrolyte, in this solvent.[20] However, although low, they are comparable to that measured for tetraphenyl borate salts (i.e. 59.4 for [(^{i}C$_5$H$_{11}$)N][BPh$_4$])[20,21] in nitromethane, for which this anomalous conductivity behavior has been attributed to a low mobility of the tetraphenyl borate anion.[20]



Scheme 2. Synthesis of complex **2a** and **2b**.

The general reaction conditions depicted in Scheme 1 were applied to the bulkier terphenyl phosphines, namely P*i*Pr$_2$Ar^{Xyl2}, **L4** and PCyp$_2$Ar^{Xyl2}, **L5**. The monitoring of these reactions by ^{31}P{^{1}H} NMR revealed the formation of new species (δ 61.4 and 53.4, respectively) together with considerable amounts of free ligands. We found that reactions were completed when 3:1 Pd/phosphine molar ratios were used (Scheme 3).



Scheme 3. General synthesis of complexes **3d** and **3e**.

Complexes **3d** and **3e** were obtained as yellow crystalline solids by slow diffusion crystallization techniques. As stated above, their ^{31}P{^{1}H} NMR spectra contain only one ^{31}P resonance, which is shifted by *ca*. 47 ppm to higher frequencies relative to the uncoordinated phosphines. Again, such a change in ^{31}P δ seems to indicate that terphenyl phosphines in these compounds could be coordinated in a bidentate fashion.[16b] In fact, the NMR features of the phosphine ligands in complexes **3** seem to support this hypothesis, since, in both instances, the two flanking xylyl rings of the terphenyl fragment and the two P-R groups appear inequivalent at room temperature. On the other hand, the integration of the resonances in the aromatic region of their ^{1}H NMR spectra evidences the presence of three 2-aminobiphenyl units in these species. In light of the above and taking into account the stoichiometry of the reaction, it seems plausible that complexes **3** are not neutral compounds but salt-like derivatives, composed of a cationic palladacycle analogous to **2a** and a dinuclear aminobiphenyl-palladium anionic species containing no phosphine ligands; however, its structure could not be ascertained from the NMR data. To validate this proposal, HRMS experiments were undertaken, confirming the presence of the mentioned cationic palladacycles in compounds **3**. However, no information could be gathered from these experiments regarding the nature of the counterion. Additionally, the molar conductivities of **3d** and **3e** were gauged in nitromethane, obtaining values (47.3 and 45.8 Ω^{-1} cm^2 mol^{-1}, respectively) very close to that of the ionic compound **2a**.

The postulated ionic nature of **3d** and **3e** was further confirmed by X-ray diffraction analyses. As illustrated in Figures 3 and S4, both species consist of a [Pd(2-aminobiphenyl)(PR$_2$Ar')]$^+$ cation and a dinuclear {[Pd(2-aminobiphenyl)Cl]$_2$(μ-Cl)}$^-$ anionic species. In the cations, the metal ion exhibits a distorted square-planar geometry with bond angles varying from the ideal value by as much as *ca*. 10º. As anticipated by the analysis of the NMR data, one of the coordination sites on the Pd(II) center is occupied by a weak Pd···C$_{ipso}$ interaction with the closer xylyl ring of the terphenyl fragment. These interactions are characterized by Pd···C$_{ipso}$ bond lengths (Pd-C(19)) of *ca*. 2.41 Å, within the range of 2.22-2.45 Å found for the η^1-coordination of an arene moiety to a d^8-ML$_3$ fragment,[23] and comparable to those reported for analogous biaryl phosphine derivatives (ver comment).[14b] Additionally, in the case of complex **3d**, the Pd-C distance to the *ortho* carbon of the proximal ring is about 2.57 Å, significantly longer than that to the *ipso* carbon, but shorter than the sum of the van der Waals radii of the atoms involved (3.06 Å).[22] To facilitate these interactions, the central aryl ring of the terphenyl moiety bends in both cases towards the metal, resulting in a narrowing of the corresponding P-C$_{ipso}$-C$_{ortho}$ angle (115.4(3)° and 116.3(4)º for **3d** and **3e**, respectively) at the expense of the other (127.0(4)° and 125.4(5)º for **3d** and **3e**, respectively). Moreover, the bulky P-R groups are located on opposite sides of the plane defined by the central aryl ring of the terphenyl moiety. The Pd-P bond distances in both cationic species (2.26 and 2.28 Å, respectively, for **3d** and **3e**) match the value found in the analogous the BrettPhos complex (2.266 Å),[14b] but are substantially shorter than that of the bulkier *t*BuXPhos derivative (2.323 Å).[14b]

The structure of the counterion consists of two almost square-planar [Pd(2-aminobiphenyl)Cl] units linked together by a single bridging chlorine atom, with the two terminal chloride ions in pseudo-*trans* disposition. The coordination planes of the two Pd atoms cross with a dihedral angle of *ca*. 64º. The Pd-Cl-Pd angle (*ca*. 119º) is significantly deviated from the 90º expected for a single M-X-M bridge,[24] but falls within the range found for other

complexes containing the Pd–μ-Cl–Pd fragment supported by bidentate o π-coordinated ligands.[25] Consequently, the two metal centers are too far apart for any metal-metal interaction (Pd···Pd mean value *ca*. 4.28 Å). The Pd-μ-Cl bond lengths are nearly identical (mean value: 2.49 Å) but somewhat longer than those of terminal Pd-Cl bonds (mean value: 2.32 Å). Though rare, homo and heteronuclear systems with a single unsupported halide bridge have been structurally described for various d^8 transition metal ions.[23-26]

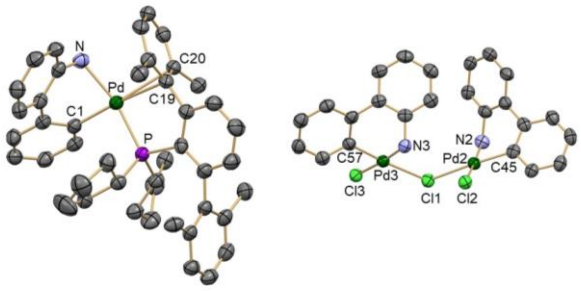
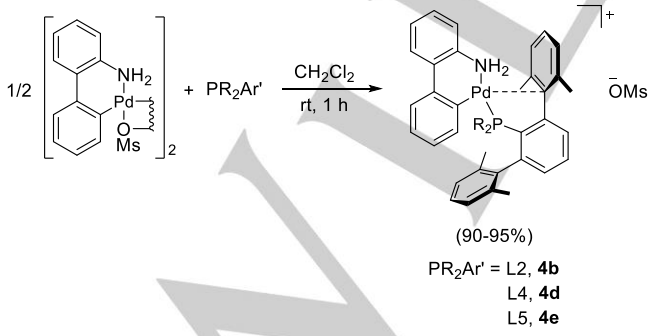


Figure 3. Molecular structure of **3e**. Hydrogen atoms are omitted for clarity. Thermal ellipsoids are shown at 50% probability. Selected bond lengths [Å] and angles [º]: Pd1-P 2.2646(15), Pd1-N1 2.144(5), Pd1-C1 2.024(6), Pd1-C19 2.422(6), Pd1-C20 2.617(6), Pd2-Cl1 2.4731(15), Pd2-Cl2 2.3101(15), Pd2-N2 2.052(5), Pd2-C45 1.977(6), Pd3-Cl1 2.4684(16), Pd3-Cl3 2.3232(15), Pd3-N3 2.053(5), Pd3-C57 1.980(6); N1-Pd1-P 163.02(14), C1-Pd1-C19 170.9(2), C1-Pd1-P 90.12(17), P-Pd1-C19 83.92(15), Pd2-Cl1-Pd3 118.34(6).

These results underline that, as was the case of larger biaryl phosphines,[14b] sterically demanding ligands **L4** and **L5** do not favor the formation of neutral 2-aminobiphenyl palladacycles but instead promote the isolation of cationic [Pd(2-aminobiphenyl)(PR_2Ar')]$^+$ species.

The cationic palladacycles described above could be easily isolated as methanesulfonate (mesylate) salts from the reaction of the 2-aminobiphenyl-Pd mesylate-bridged dimer with phosphines **L4** and **L5** in dichloromethane at room temperature[28] (Scheme 4). This method was also applied for the synthesis of complex **4b** with the less bulky ligand PMe_2Ar^{Dipp2}, **L2**.



Scheme 4. General synthesis of complexes **4b, 4d-4e**.

Compounds **4** were obtained in quantitative yields as air-stable, pale-yellow solids. They were characterized by microanalysis and NMR spectroscopy. Since the phosphine **L2** facilitates the formation of both neutral and cationic 2-aminobiphenyl palladacycles (**1b** and **4b**, respectively), it is interesting to comment the most significant differences in the NMR spectra of these two species. The ^{31}P resonance for the ligated phosphine in **4b** is shifted by *ca*. 11 ppm to higher frequency with respect to that of complex **1b** due to the change in the coordination mode of the phosphine from monodentate to bidentate. Accordingly, the ^1H and $^{13}C\{^1H\}$ NMR spectra of **4b** evidence the lack of exchange between the two flanking aryl rings of the terphenyl moiety at room temperature, giving rise to a distinct set of signals for each of the *i*Pr substituents on the Dipp rings and two different doublets for the methyl groups on the P atom.

The solid-state structures of **4b**, **4d** and **4e** were determined by X-ray diffraction studies (Figures 4, S5 and S6), confirming in all three cases the expected bidentate coordination mode of the terphenyl phosphines. Structural parameters (bond lengths and angles) obtained for the three complexes are essentially identical to those found for the cations of the salt-like compounds **3d** and **3e**.

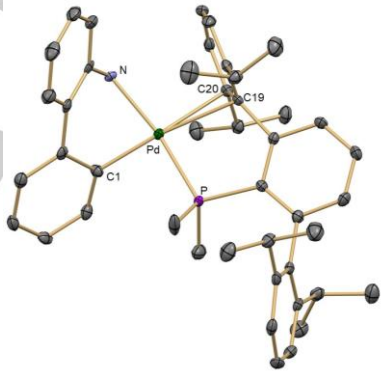


Figure 4. Molecular structure of **4b**. Hydrogen atoms and OMs^- counterion are omitted for clarity. Thermal ellipsoids are shown at 50% probability. Selected bond lengths [Å] and angles [º]: Pd-P 2.2577(9), Pd-N 2.113(3), Pd-C1 2.018(3), Pd-C19 2.406(3), Pd-C20 2.555(3); N-Pd-P 167.56(8), C1-Pd-C19 168.32(13), C1-Pd-P 88.80(11), P-Pd-C19 81.66(9).

Catalytic activity of terphenyl phosphine-stabilized palladacycles in C-N cross-coupling reactions

With a series of neutral and cationic Pd(II) precatalysts in hand, we analyzed their performance in aryl aminations reactions using a variety of N-nucleophiles.

Protocols for the N-arylation of secondary amines based on Pd are scarce.[29] On that basis, we evaluated complexes **1a-1c, 2a, 2b** and **4b-4d** as precatalysts in the coupling of 4-chlorotoluene with morpholine applying the conditions already reported for Pd catalyst systems based on RuPhos,[14b] an outstanding ligand for the arylation of secondary amines (Fig. 5). Indeed, for comparative purposes, the RuPhos-based 2-aminobiphenyl palladacycle was prepared and also tested in this study. As shown in Fig. 5, all terphenyl phosphine-stabilized precatalysts were active in the arylation of morpholine, observing

a direct correlation between the bulkiness of the substituents on the P atom and the catalytic efficiency of the resulting palladium complexes. Remarkably, precatalysts bearing PMe_2-containing phosphines, **1a**, **1b**, **2a**, **2b** and **4b**, afforded the coupling product in modest (30% for **1a**) to high (82% for **4b**) yields. This finding is particularly interesting considering that methyl-substituted phosphines are rarely used as ancillary ligands in cross-coupling reactions,[30] particularly those catalyzed by palladium, and emphasizes the significant steric encumbrance conferred by the terphenyl fragment.[31] We observed an interesting anion effect when compared the catalytic activity of **1b**, **2b** and **4b**. Precatalyst **2b**, with the weakly coordinating BAr_F anion, was the less efficient. Probably, the large size of BAr_F^- brings it close enough to the Pd(II) cationic species to slow the intermolecular interaction with the base rendering the LPd(0) catalytic species.[12b,14c] Overall, the best performances were obtained with palladacycles **4d** and **4e** bearing the bulkiest ligands **L4** and **L5**, which provided the highest yields of product at 0.5 mol% catalyst loading without using any excess phosphine ligand.[32] In our hands, under the same reaction conditions, Buchwald's RuPhos precatalysts resulted equally effective.

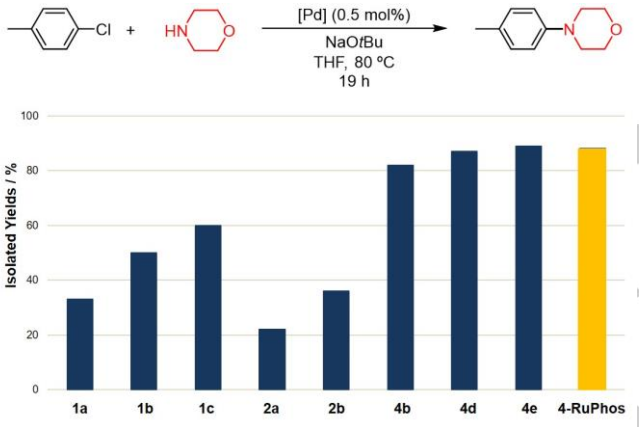
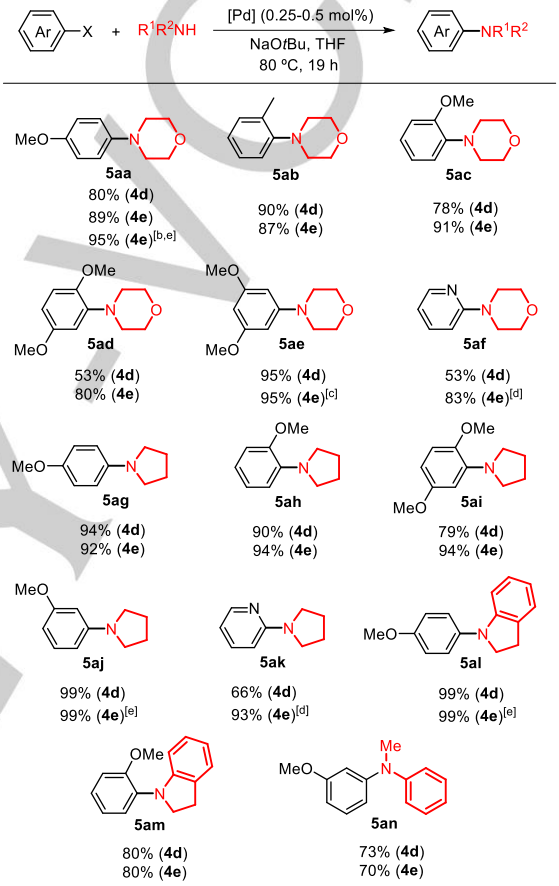


Figure 5. Catalytic performance of **1**, **2** and **4** in the N-arylation of morpholine with 4-chlorotoluene. Reaction conditions: 4-chlorotoluene (1 mmol), morpholine (1.2 mmol), [Pd] (0.005 mmol), NaO*t*Bu (1.2 mmol), THF (1 mL), T = 80 ºC, reaction time = 19 h (unoptimized). Yields of isolated products.

Having identified **4d** and **4e** as the most efficient Pd precatalysts of the series, we investigated their versatility in the N-arylation of secondary amines with various challenging aryl chlorides, e.g. electronically deactivated or sterically hindered substrates. Generally, both precatalysts displayed comparable activities in the studied reactions (Table 1). Thus, morpholine, pyrrolidine and indoline were effectively coupled with unactivated 4-chloroanisole with yields ranging from 80 to 98% (**5aa, 5ag, 5al**). Particularly, when 4-bromoanisole was used as the electrophilic coupling partner, the coupling with morpholine could be attained at even lower catalyst loading (0.25 mol%). *ortho*-Substituted aryl chlorides were successfully used as coupling partners under the standard reaction conditions (**5ab**-**5ad**, **5ah**, **5ai**, **5am**). Similarly, the coupling of 2-chloropyridine with pyrrolidine proceeded satisfactorily, with catalyst **4e** providing the corresponding products in high yields (**5ak**). However, the arylation of acyclic secondary amines proved more challenging with these two precatalysts and positive results could only be obtained in the reaction of N-methyl aniline with 3-chloroanisol (**5an**).

Table 1. Scope of N-arylation of secondary amines with aryl chlorides catalyzed by **4d** and **4e**.[a]



[a] Reaction conditions: aryl chloride (1 mmol), amine (1.2 mmol), [Pd] (0.005 mmol), NaO*t*Bu (1.2 mmol), THF (1 mL), T = 80 ºC, 19 h (unoptimized). Yields of isolated products. [b] Aryl bromide (1 mmol). [c] Reaction time: 1 h. [d] *t*BuOH (1 mL) as the solvent. [e] [Pd] 0.0025 mmol.

Next, we focused on primary amines as nucleophiles. Aniline and *n*-hexylamine were the model substrates for testing the reactivity of **4d** and **4e**. As in the previous case, the performance of our complexes was compared to that of the BrettPhos-based palladacycle, a highly efficient precatalyst for the N-arylation of primary amines.[14b] Applying the same reaction conditions as in the previous couplings, the three complexes produced quantitative yields of the product of the model reaction (Fig. 6). However, in the coupling of *n*-hexylamine with 3-chloroanisol the catalytic activity of **4d** was significantly lower than that of the precatalyst bearing $PCyp_2Ar^{Xyl2}$, **4e**. Under these conditions, Buchwald's BrettPhos precatalyst delivered the coupling product in almost quantitative yield. Increasing the

temperature up to 100 ºC enhanced the reaction yield achieved with precatalyst **4e**, matching that of the BrettPhos system.

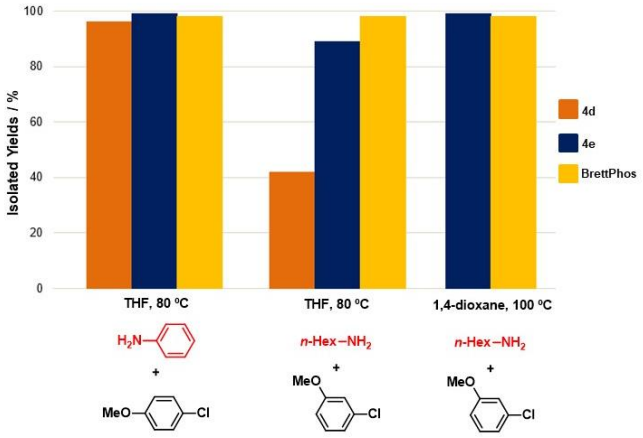


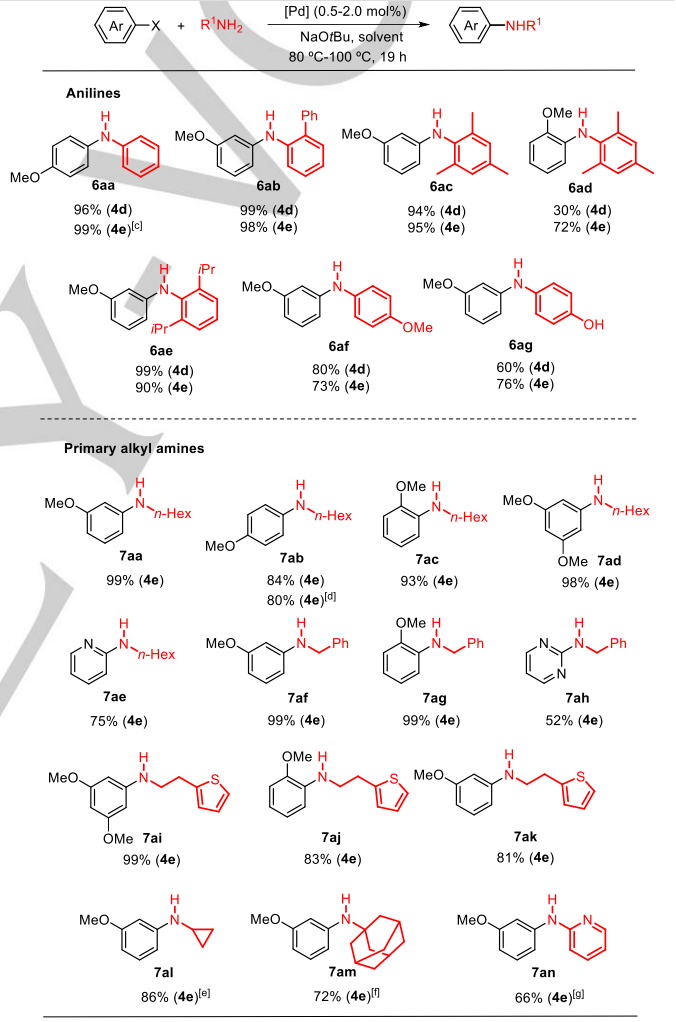
Figure 6. Catalytic performance of precatalysts **4d** and **4e** in the N-arylation of aniline with 4-chloroanisol and 3-chloroanisol, respectively. Reaction conditions: aryl chloride (1 mmol), amine (1.2 mmol), [Pd] (0.005 mmol), NaO*t*Bu (1.2 mmol), THF (1 mL), T = 80 ºC or 100 ºC, reaction time = 19 h (unoptimized). Yields of isolated products.

Under the standard conditions, the coupling of a variety of anilines with methoxy-substituted aryl chlorides proceeded well, providing products in good to high yields (Table 2). Steric hindrance in one or both of the coupling partners seemed not to be a major problem, particularly with precatalyst **4e**, leading to the corresponding products in good to quantitative yields (**6ab**-**6af**). The N-arylation of 4-aminophenol, a structural motif in compounds with potential biological activities,[33] was selectively achieved with both precatalysts (**6ag**).

Using the modified reaction conditions (reaction temperature = 100 ºC) precatalyst **4e** effectively accomplished the coupling of an array of aliphatic primary amines with electron-rich (**7ab**, **7ak**), electron neutral (**7aa**, **7ad**, **7af**, **7ai**) or *ortho*-substituted methoxy-chloroarenes (**7ac**, **7ag**, **7aj**) providing the products in high yields (Table 2). Interestingly, heteroaryl chlorides were also tolerated affording moderate to good yields of the coupling products (**7ae**, **7ah**). Cyclopropylamine, a substrate hardly used as cross-coupling partner, was efficiently coupled with 3-chloroanisol at 0.75 mol% catalyst loading, affording selectively the monoarylated product (**7al**). This result compares well with those reported by Colacot and co-workers using the [(BrettPhos)Pd(crotyl)]OTf] precatalyst.[34] The coupling reactions involving bulky adamantyl amine or 2-aminopyridine appeared to be more difficult and required an increase of the catalyst loading (1 mol% or 2 mol% Pd, respectively) to obtain reasonably good yields of N-arylated products (**7am, 7an**).

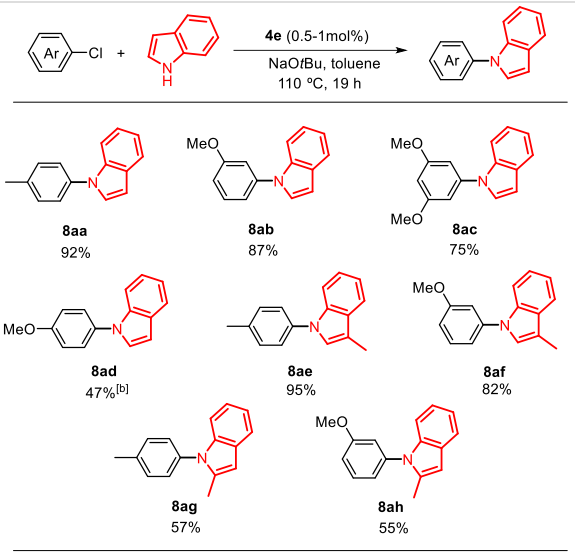
To further expand the scope of N-nucleophiles, we gauged the activity of precatalyst **4e** in the N-arylation of indoles (Table 3). Indole motifs are present in compounds with interesting medicinal applications.[35] However, scarce Pd-based catalytic systems exist which are able to effectively perform this challenging transformation.[36] As shown in Table 3, **4e** was a competent precatalyst for the N-arylation of indoles with simple-aryl chlorides at 110 ºC with 0.5 mol% catalyst loading and without adding excess ligand (**8aa**-**8ah**). Even the presence of a methyl substituent at the 2 position of the indole ring was tolerated, obtaining the coupling products in moderate yields (**8ag**, **8ah**). It is interesting to note that competing C-arylation products were not observed in these reactions.[36c]

Table 2. Scope of N-arylation of anilines and primary alkylamines with aryl chlorides catalyzed by **4d** and **4e**.[a],[b]



[[a] Reaction conditions for anilines: aryl chloride (1 mmol), aniline (1.2 mmol), [Pd] (0.005 mmol), NaO*t*Bu (1.2 mmol), THF (1 mL), T = 80 ºC, 19 h (unoptimized). [b] Reaction conditions for primary alkyl amines: aryl chloride (1 mmol), primary amine (1.2 mmol), **4e** (0.005 mmol), NaO*t*Bu (1.2 mmol), dioxane (1 mL), T = 100 ºC, 19 h (unoptimized). Yields of isolated products. [c] Reaction time: 1 h. [d] Aryl bromide (1 mmol), [Pd] 0.0025 mmol. [e] [Pd] 0.0075 mmol, T = 80 ºC. [f] [Pd] 0.01 mmol. [g] [Pd] 0.02 mmol.

Table 3. Scope of N-arylation of indoles with aryl chlorides catalyzed by **4e**.[a]

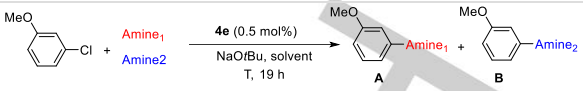


[a] Reaction conditions: aryl chloride (0.50 mmol), indole (0.53 mmol), [Pd] (0.0025 mmol), NaO*t*Bu (0.7 mmol), toluene (1 mL), T = 110 ºC, 18 h. Yields of isolated products. [b] 1 mol% Pd.

To assess the substrate preference of the more general precatalyst **4e**, competition experiments between the different N-nucleophiles used in this survey were undertaken. These experiments were conducted under the reaction conditions collected in Tables 1-3, using 3-chloroanisole as the electrophilic coupling partner. As illustrated in Table 4, precatalyst **4e** showed a clear preference for the arylation of the primary alkyl amine over the aromatic and the secondary amines. A striking result was found in the competition reaction between *n*-hexylamine and indole. When the experiment was carried out in toluene, a very low conversion of 3-chloroanisole was observed[37] (15%, entry 4), although with a high selectivity towards the N-arylation of indole over *n*-hexylamine. Since the arylation of indole proceeded efficiently in toluene (see Table 3), the coupling of *n*-hexylamine with 3-chloroanisole was examined in this solvent. Only 20% yield of the cross-coupling product was attained (110 ºC, 19 h), evincing an important solvent effect in this transformation. Complete conversion was observed when the reaction between these two competing N-nucleophiles was performed in dioxane, exhibiting a marked selectivity towards the product of the N-arylation of indole.

Finally, we examined the coupling between aniline and 3-chloroanisole using precatalyst **4e** in the presence of metallic mercury (see SI for details). No effect on the rate or product selectivity was observed during catalysis, suggestive evidence of homogenous catalysis.[38] However, to rule out the participation of nanoparticles or Pd clusters as the active catalyst species in the coupling processes described here, a detailed mechanistic study, involving synthetic studies to generate key intermediates and kinetic experiments, is presently under way in our laboratory.

Table 4. Amine competition experiments using precatalyst **4e**.[a]



Amine1	Amine2	T (ºC)	Solvent	Ar–Am1 (**A**)	Ar–Am2 (**B**)	Ratio (**A** : **B**)
		80	THF	43	54	(0.8:1)
	*n*-Hex–NH_2	80 100	THF dioxane	30 26	67 59	(1:2)
	*n*-Hex–NH_2	80 100	THF dioxane	28 25	63 72	(1:2) (1:3)
n-Hex–NH_2		110	dioxane toluene[b]	35 No reaction	65	(1:2)

[a] Reaction conditions: 3-chloroanisol (0.5 mmol), N-nucleophile (0.6 mmol), [Pd] (0.0025 mmol), NaO*t*Bu (0.6 mmol), solvent (1 mL), 19 h. Conversions were determined by GC analysis of the reaction mixtures using dodecane as internal standard. [b] The arylation of *n*-hexylamine with 3-chloroanisole proceeded in toluene, at 110 ºC, with only 20% yield.

Conclusions

In summary, we have described the first catalytic application of terphenyl phosphine ligands, PR_2Ar', a new family of electron-rich, sterically encumbered monophosphines, in cross-coupling chemistry. In this study, we have developed two classes of air- and moisture-stable neutral and cationic 2-aminobiphenyl-derived palladacycles bearing dialkylterphenyl phosphines. In the neutral Pd(2-aminobiphenyl)Cl(PR_2Ar') complexes, stabilized by the less bulky ligands (i.e. those with Me and Et substituents on the P atom), the phosphine adopts a classical, κ^1-P, coordination mode. However, in cationic [Pd(2-aminobiphenyl)(PR_2Ar')]$^+$ species, isolated with the most sterically hindered ligands, the phosphine is coordinated in a bidentate hemilabile fashion (κ^1-P, η-C_{arene}), featuring a weak M···C_{arene} interaction with one of the flanking aryl rings of the terphenyl fragment. These complexes have been evaluated as precatalysts in Pd-catalyzed aryl amination reactions, the most active being cationic **4d** and, notably, **4e**, bearing the phosphine $PCyp_2Ar^{Xyl2}$. Utilizing these two precatalysts, we have developed a practical, versatile and efficient protocol for the arylation of a variety of challenging N-nucleophiles, including secondary amines, primary alkyl amines and indoles, with problematic aryl chlorides, like those electronically deactivated or sterically encumbered. The couplings are conducted with low catalyst loading (0.25-0.75 mol% Pd) and without ligand excess.

Experimental Section

All preparations and manipulations were carried out under oxygen-free nitrogen, using conventional Schlenk. Solvents were rigorously dried and degassed before use. Ligands **L1**-**L5**,[16a-b] and [Pd(2-aminobiphenyl)X]$_2$ (X = Cl,[39a] OMs[39b]) were synthesized by following previously reported

procedures. Reagents were purchased from commercial suppliers and used without further purification. Solution NMR spectra were recorded on Bruker Avance DPX-300, Avance DRX-400, Avance DRX-500, and 400 Ascend/R spectrometers. The ^{1}H and ^{13}C resonances of the solvent were used as the internal standard and the chemical shifts are reported relative to TMS while ^{31}P was referenced to external H_3PO_4. Elemental analyses were performed by the Servicio de Microanálisis of the Instituto de Investigaciones Químicas (IIQ). High resolution mass spectra were registered on Orbitrap Elite Mass Spectrometer at the Centro de Investigación Tecnología e Innovación, CITIUS (Universidad de Sevilla). CITIUS. X-ray diffraction studies were accomplished at CITIUS and Centro de Investigación en Química Sostenible, CIQSO (Universidad de Huelva). Complete synthetic and catalytic procedures and characterization data for new compounds are provided in the Supporting Information. A selection of representative syntheses of Pd(II) complexes and catalytic reactions are reported below.

Synthesis of Pd(2-aminobiphenyl)Cl($PMe_2Ar^{Xyl_2}$), 1a. CH_2Cl_2 (6 mL) was added to a mixture of 2-aminobiphenyl-Pd chloride-bridged dimer (35.8 mg, 0.058 mmol) and PMe_2Ar^{Xyl2} (40 mg, 0.115 mmol). The reaction mixture was stirred at room temperature for 2 h. After removal of volatiles under vacuum, the white solid residue was extracted in CH_2Cl_2, filtered through a Celite plug and the solution was taken to dryness. The complex was purified by crystallization at -20 ºC from a diethyl ether: CH_2Cl_2 (2:1) mixture. Yield: 70 mg (93%). Elemental analysis calculated (found) for $C_{36}H_{37}ClNPPd$: C, 65.86 (65.74); H, 5.68 (5.86); N, 2.13 (2.22).

Synthesis of [Pd(2-aminobiphenyl)($PMe_2Ar^{Dipp_2}$)]OMs, 4b. CH_2Cl_2 (6 mL) was added to a mixture of 2-aminobiphenyl-Pd mesylate-bridged dimer (44.4 mg, 0.06 mmol), $PMe_2Ar^{Dipp_2}$ (55.0 mg, 0.12 mmol). The reaction mixture was stirred at room temperature for 1 h. After removal of volatiles under vacuum, the orange solid residue was extracted in CH_2Cl_2, filtered through a Celite plug and the solution was taken to dryness. The complex was purified by crystallization at -0 ºC from a petroleum ether: CH_2Cl_2 (2:1) mixture. Yield: 89.0 mg (90%). Elemental analysis calculated (found) for $C_{45}H_{56}NO_3PPdS$: C, 65.25 (65.15); H, 6.81 (6.45); N, 1.69 (1.61); S, 3.87 (3.77).

General catalytic procedure for aryl amination reactions. The precatalyst (0.5-1 mol%), the base NaO*t*Bu (1.2 mmol) and the solvent (1 mL) were added in turn to a vial equipped with a J Young tap and containing a magnetic bar. The *N*-nucleophile (1.2 mmol) and the aryl chloride (1 mmol) were added under a nitrogen atmosphere. The mixture was stirred at certain temperature (80 to 110 ºC) for 19 h in an oil bath. The reaction mixture was allowed to cool to room temperature, diluted with ethyl acetate (10 mL) and filtered through Celite. The resulting solution was evaporated to dryness and the residue was purified by column chromatography.

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Keywords: palladacycles • aryl amination • cross-coupling • phosphine complexes •

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[32] We also examined the catalytic performance of salt-like complexes **3d** and **3e** in the model reaction under the conditions listed in Table 1, obtaining similar yields of the coupling product (85% and 93%, respectively) to those attained with complexes **4d** and **4e**. However, on lowering the catalyst loading at 0.25 mol%, the yield was only 40% with precatalyst **3d**, with compares well to that found for complex **4d** at the same catalyst loading. These experiments suggest that the palladate(II) anion presented in **3** is not active in this particular cross-coupling reaction.

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[37] Stradiotto and co-workers observed no conversion in the competing N-arylation of *n*-octylamine and indole with chlorobenzene in toluene using a Pd/BippyPhos catalyst system, which was attributed to the inhibiting effect of the indole (see ref. 36g).

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Entry for the Table of Contents

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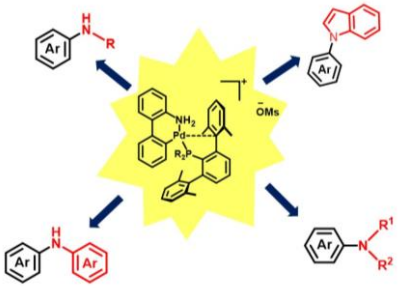
New ligands on the stage. Palladacycles bearing dialkylterphenyl phosphines mediated the arylation of a variety of N-nucleophiles efficiently at low catalyst loadings and without excess ligand.



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Page No. – Page No.

Dialkylterphenyl Phosphine-Based Palladium Precatalysts for Efficient Aryl Amination of N-nucleophiles