Synthesis, characterization and anticancer activity of palladium allyl complexes bearing benzimidazole-based *N*-heterocyclic carbene (NHC) ligands

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ABSTRACT

The synthesis of twelve new palladium allyl complexes bearing benzimidazole-based NHC (NHC = *N*-heterocyclic carbene) ligands is reported. All the complexes were characterized by NMR and elemental analysis and, in the case of complex **5c**, it was possible to confirm the connectivity by single crystal X-ray diffraction.

The cationic palladium allyl complexes were tested toward 5 different cancer lines, with IC_{50} values generally lower than cisplatin and similar antiproliferative activity in the two ovarian cancer cell lines (A2780 and A2780*cis*), suggesting a different mechanism of action from classical platinum-based anticancer drugs.

Compounds equipped with a pyridine arm or with the NHC/PTA combination (PTA = 1,3,5-triaza-7-phosphaadamantane) showed a lower cytotoxicity on normal cells with respect to cancer ones.

By comparing the IC_{50} values of mixed NHC/PTA complexes reported in this work and their trifluoromethyl congeners recently published by our group, it appears evident that they have very similar antiproliferative activity against cancer cells but the absence of the CF_3 group significantly decreases the selectivity toward them.

1. Introduction

Benzimidazole derivatives are among the most common heterocyclic compounds in the U.S. FDA-approved pharmaceutical drugs [1]. In particular, they exhibit a wide range of biological properties such as anti-inflammatory [2], anti-ulcer [3], antihypertensive [4] and anticancer [5].

For instance, Candesartan [6] and omeprazole [7] are used for the treatment of hypertension and stomach ulcers, respectively, whereas Nocodazole and Dovotininb are well-established antineoplastic drugs [8,9].

The therapeutic potential of these derivatives has prompted researchers to design and synthesize new organic and organometallic compounds containing the benzimidazole scaffold for a wide selection of pharmacological applications.

In this context, organometallic chemists wondered if the remarkable advances obtained in the field of *N*-heterocyclic carbenes (NHCs) as privileged ancillary ligands in homogeneous catalysis [10] could be exploited for the preparation of benzimidazole-based NHC metal complexes with biological properties.

It should be noted that the use of ligands with a biologically active framework is a well-recognized strategy for the development of new potential metallodrugs. In fact, in numerous contributions a synergy between the biologically active ligand and the organometallic fragment was proved and in the most favourable cases, the ligand has become a real targeting vector of the metal compound [11].

On this basis, a number of gold, silver and ruthenium complexes equipped with benzimidazole-based NHCs have been prepared and tested as potential antibacterial and antitumor agents, showing interesting results [12].

Among the metal complexes studied as alternative to classical platinated antineoplastic drugs, palladium organometallic compounds have received growing interest in the last two decades because of their remarkable *in vitro* cytotoxicity toward different cancer cell lines and

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their good stability in physiological conditions [13].

In this context, some palladium complexes bearing benzimidazole-based NHCs, mainly of general formula $[Pd(NHC)_2X_2]$ or $[Pd(NHC)X_2L]$ (X = I, Br, Cl; L = Py, PR_3 etc.), have been previously synthesized and tested as potential anticancer agents. Unfortunately, only few derivatives have shown a satisfactory cytotoxicity (Scheme 1) [14].

Conversely, a category of organopalladium compounds that has recently produced some promising results is represented by Pd-allyl derivatives [15]. These complexes have shown a good/excellent antiproliferative activity against different cisplatin-sensitive and cisplatin-resistant cell lines.

In particular, in our recent study we proved the potent *in vitro* anticancer activity of palladium-allyl complexes stabilized by trifluoromethyl benzimidazolylidenes and phosphine ligands [14]. The mixed NHC/PTA (PTA = 1,3,5-triaza-7-phosphaadamantane) palladium complexes were particularly interesting as they combine excellent cytotoxicity toward cancer cells with low toxicity toward normal ones.

These results were confirmed on more complex biological systems such as 3D organoids and tumoroids extracted from real patients. Moreover, detailed immunofluorescence assays revealed cell death *via* mitochondrial disfunction rather than the classical interaction with DNA observed in cisplatin and its derivatives.

However, an important question has been left open: is the presence of the trifluoromethyl group necessary to ensure the uncommon selectivity of these palladium derivatives toward cancer cells?

As a matter of fact, the importance of fluorinated substituents in the biological activity of organic molecules is well documented [16] but, at the best of our knowledge, this issue has been scarcely explored in metal-based compounds.

With the main goal to address this problem herein we report the synthesis and anticancer activity of palladium allyl complexes bearing benzimidazole-based NHCs in which the trifluoromethyl group, present in these compounds, has been replaced by a methyl substituent.

The easier access to these derivatives compared to their trifluoromethyl congeners makes the latter decidedly less expensive and rapid to prepare.

2. Results and discussion

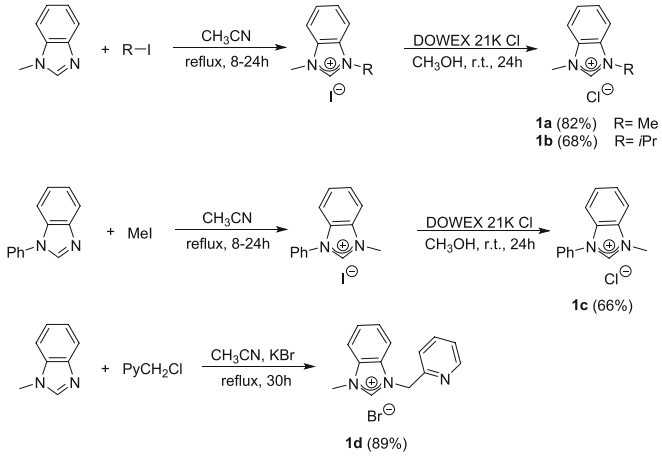
2.1. Synthesis of benzimidazolium and bis-benzimidazolium salts (1a-f)

The benzimidazolium salts **1a-d** used as precursors of the monodentate carbene ligands were prepared by alkylation of the N-3 of methyl-benzimidazole (for **1a-b** and **1d**) or phenyl-benzimidazole (for **1c**) under the operating conditions reported in Scheme 2.

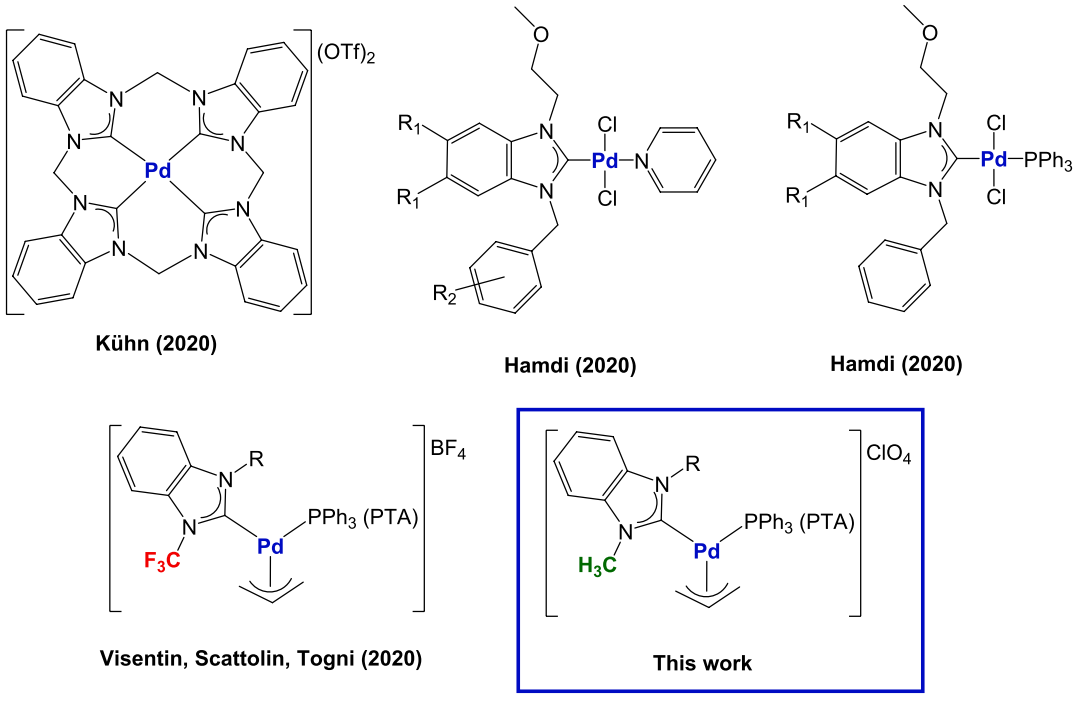
In all ^1H NMR spectra of the products it is possible to observe a considerable increase of the H^2 proton chemical shift ($\Delta\delta \approx 2$ ppm) with respect to the starting materials, due to the quaternization of benzimidazole nitrogen.

For needs connected to the subsequent synthetic steps, the azolium salts **1a-c** were synthesized in the chloride version, suspending the intermediate iodide derivatives in methanol in the presence of the DOWEX 21 K Cl ion-exchange resin.

Bis-benzimidazolium salts **1e-f** were synthesized by reacting methyl-benzimidazole or adamantyl-benzimidazole with dibromomethane in



Scheme 2. Synthesis of benzimidazolium salts **1a-d.**



Scheme 1. Examples of palladium complexes bearing benzimidazole-based NHCs with potent anticancer activity.

tetrahydrofuran or in neat conditions, as reported in Scheme 3. Unfortunately, the bisbenzimidazolium bromides obtained are scarcely soluble and therefore it was necessary to exchange the halide with the perchlorate anion, in order to facilitate the following synthetic steps. The metathesis was carried out using $AgClO_4$ as a dehalogenating agent.

The ^1H NMR spectra of **1e-f** exhibit in addition to the methyl or adamantyl substituents signals the methylene bridge NCH_2N singlets at 7.4–8.5 ppm and the diagnostic peaks of the H^2 proton at 9–10 ppm.

2.2. Synthesis of silver-NHC complexes (2a-d)

The classical transmetallation route from silver-NHC precursors was chosen as the synthetic strategy for the synthesis of the palladium compounds reported in this work.

To this end, the silver-NHC complexes **2a-d** were prepared in good yields by reaction between benzimidazolium salts **1a-d** and Ag_2O. Each reaction is completed in a few hours at room temperature in dichloromethane (Scheme 4).

The successful outcome of the reaction is proved by the disappearance of the benzimidazole proton H^2 and by the downfield shift of the corresponding carbon (C^2) in the ^1H and ^{13}C NMR spectra, respectively, in addition to a general shift of all other signals with respect to the starting imidazolium salts. In particular, the C^2 carbon resonates at ca. 190 ppm which is typical of a coordinated carbene carbon.

2.3. Synthesis of palladium-allyl complexes bearing chelating C—N or C—C ligands (3d-f)

The first category of palladium-allyl complexes taken into consideration includes those containing picolyl-carbene (**3d**) and biscarbene (**3e-f**) as chelating ligands.

These classes of compounds have recently exhibited a promising *in vitro* anticancer activity when classical imidazolylidenes were used as spectator ligands [15] and for this reason we believe that synthesis and biological investigations of their benzimidazolylidene congeners could be interesting.

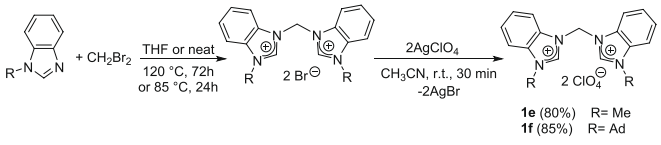
As illustrated in Scheme 5, complex **3d** was synthesized by reacting the picolyl-NHC silver precursor **2d** with $[Pd(\mu\text{-}Cl)(\eta^3\text{-allyl})]_2$, in the presence of $NaClO_4{\cdot}H_2O$ as the dehalogenating agent.

The latter is perfectly soluble in these optimal conditions unlike other alternative dehalogenants (eg. KPF_6 or $NaBF_4$) and ensures the obtainment of products with a high degree of purity and stability both in the solid state and in solution.

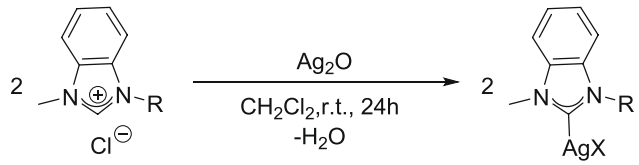
The desired complex was obtained in high yield and purity and its NMR characterization is straightforward.

In particular, the coordination of the pyridine arm is confirmed by the downfield shift of the proton *ortho* to the pyridine nitrogen ($\Delta\delta \approx$ 0.3 ppm) with respect to the silver precursor and by the presence of an AB system attributable to the diastereotopic methylene protons N-CH_2.

As for the allyl fragment, we can observe that the protons *trans* to pyridine are significantly broadened at room temperature, suggesting a selective η^3-η^1-η^3 fluxionality. By lowering the temperature to 243 K it is possible to block this fluxional phenomenon and observe five sharp allyl signals, with those *trans* to the carbene resonating at higher chemical shifts due to the greater *trans* effect of NHC ligands compared to pyridine. For the same reason, the terminal allyl carbon *trans*-N occurs at 49 ppm whereas that *trans*-C falls at 75 ppm. In the ^{13}C NMR spectrum the coordinate carbene carbon peak at 187 ppm is also well recognizable.



Scheme 3. Synthesis of bisbenzimidazolium salts **1e-f.**



1a R= Me X = Cl
1b R= *i*Pr X = Cl
1c R= Ph X = Cl
1d R= CH_2Py X = Br

2a (70%)
2b (93%)
2c (72%)
2d (79%)

Scheme 4. Synthesis of silver-NHC complexes **2a-d.**

Palladium allyl complexes bearing chelating bisNHC ligands (**3e-f**) were synthesized by a one-pot procedure. More in detail, the bisimidazolium salts **1e-f** were reacted with Ag_2O for 18–48 h in acetonitrile at room temperature and then the dimeric precursor $[Pd(\mu\text{-}Cl)(\eta^3\text{-allyl})]_2$ was added, affording the desired complexes **3e-f** in good yields and purity (Scheme 6).

The ^1H NMR spectrum of **3e** is characterized by three different allyl protons (H_{syn}, H_{anti} and $H_{central}$), an AB system at ca. 6.5 ppm and a singlet at 4 ppm ascribable to methylene protons NCH_2N and methyl substituents, respectively.

In the ^{13}C NMR spectrum, the signal at ca. 60 ppm for the terminal allyl carbons, the carbene carbon (187 ppm) and the methylene bridge signal at 57 ppm are particularly worth of mention.

The presence of a single set of signals suggests that in solution the rearrangement of the methylene spacer above and below the main coordination plane (ring inversion of chelating ligand) is free and therefore the two possible diastereoisomers are not distinguishable at room temperature.

Conversely, complex **3f**, which contains the higher steric demanding adamantyl wing-type substituents, is present in solution as a mixture of two atropoisomers (in a 1:2 ratio).

Also in this case, for each isomer the two terminal allyl protons (*syn* and *anti*), the central allyl proton and the AB systems of the NCH_2N methylene protons can be identified in the ^1H NMR spectrum.

2.4. Synthesis of neutral palladium-allyl complexes bearing monodentate NHC ligands (4a-c)

The neutral allyl complexes of the type $[Pd(NHC)Cl(\eta^3\text{-allyl})]$ [17], which will be used as precursors of the mixed NHC/PR_3 derivatives, were synthesized by reaction between $[Pd(\mu\text{-}Cl)(\eta^3\text{-allyl})]_2$ and the silver-NHC complexes **2a-c**. Each reaction is completed within 30 min, in which the progressive precipitation of AgCl was observed (Scheme 7).

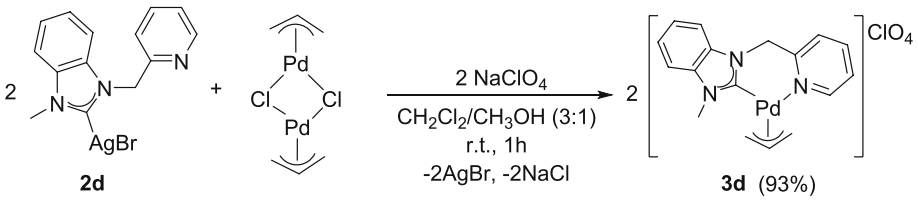
In the ^1H NMR spectra of the final products **4a-c** it is possible to observe, in addition to the signals ascribable to carbene ligand, five different allyl protons, with those *trans* to chloride having a lower chemical shift than those *trans* to the carbene ligand.

This effect is confirmed in the ^{13}C NMR spectra in which the terminal allyl carbon *trans* to chloride resonates at chemical shifts lower than 20 ppm compared to that *trans* to the carbene.

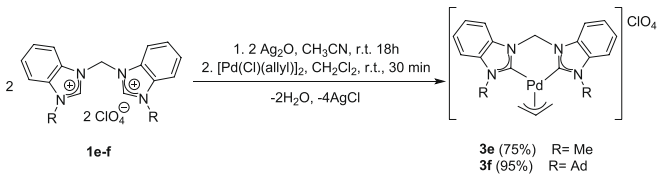
In these neutral derivatives the carbene carbon singlet resonates at ca. 180 ppm.

2.5. Synthesis of mixed NHC/PR_3 palladium-allyl complexes (5a-d and 6a-b)

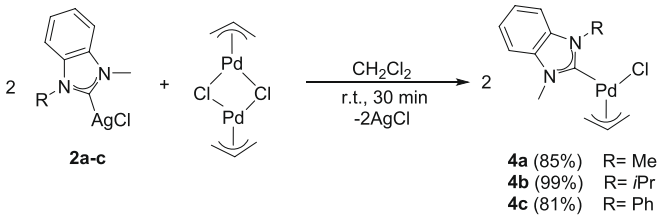
With the aim of indirectly evaluate the importance of the trifluoromethyl group in the antitumor activity of the mixed NHC/PR_3 (PR_3 = PPh_3 and PTA) palladium allyl complexes recently reported by our group [14], we synthesized their methyl congeners by reaction between triphenylphosphine or 1,3,5-triaza-7-phosphaadamantane (PTA) and the neutral palladium allyl complexes **4a-c** in the presence of



Scheme 5. Synthesis of palladium-allyl complexes bearing a picolyl-NHC ligand **(3d)**.



Scheme 6. Synthesis of palladium-allyl complexes bearing chelating bisNHC ligands **(3e-f)**.

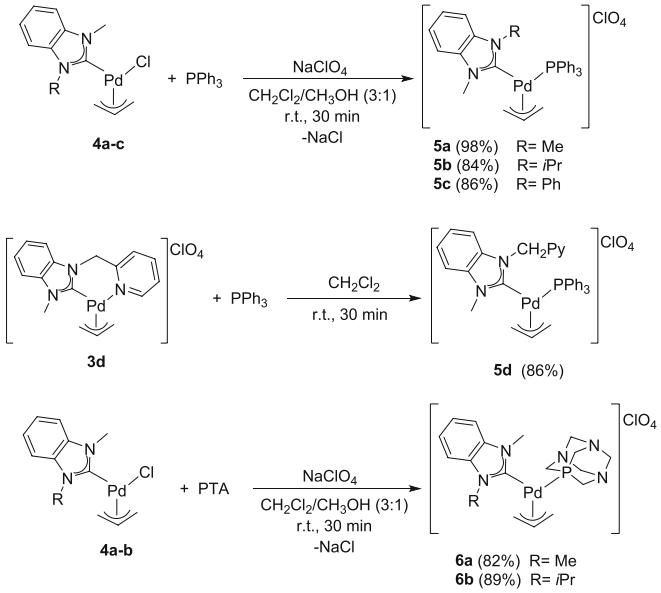


Scheme 7. Synthesis of neutral palladium-allyl complexes **(4a-c)**.

$NaClO_4$ or, in the case of complex **5d**, by addition of triphenylphosphine to complex **3d** bearing the chelate carbene-picolyl ligand (Scheme 8).

It should be noted that, unlike the trifluoromethyl derivatives, the complexes reported in this work are easier to isolate and purify using $NaClO_4$ instead of $NaBF_4$ (or $AgBF_4$) as a dehalogenating agent.

Complexes **5a-b** and **6a-b**, which contain symmetrical benzimidazole-based NHC ligands, show a single peak at ca. 25 ppm (for **5a-b**) and −55 ppm (for **6a-b**) in ^{31}P NMR spectra, with a remarkable downfield shift with respect to the uncoordinated PPh_3 or PTA.



Scheme 8. Synthesis of mixed NHC/PR_3 palladium-allyl complexes **(5a-d** and **6a-b)**.

The ^1H NMR spectra display five different allyl signals and, among them, those attributable to the terminal protons *trans* to the phosphine ligand are distinguishable by coupling with the phosphorus nucleus.

The concomitant presence of phosphine and NHC ligands is confirmed by the ^{13}C NMR spectra, in which the carbene carbon signal resonates as a doublet ($J_{C\text{-}P} \approx 20$ Hz) at 180–190 ppm.

As regards the complexes **5c-d**, which bear unsymmetrical benzimidazole-based NHC ligands, the presence of two different atropoisomers is observed because of the hindered rotation about the Pd-C_{NHC} bond. In particular, two singlets at ca. 25 ppm are distinguishable in the ^{31}P NMR spectra.

Consistently, in the ^1H and ^{13}C NMR spectra we also observe the presence of two sets of signals, one for each atropoisomer.

It should be noted that every attempt at synthesizing complexes **6c-d** led to the formation of significant amounts of bisNHC (**3c-d**) and bisPTA complexes, in addition to the desired mixed NHC/PTA species. This phenomenon had already been observed previously in attempts at synthesizing Pd(0) olefin complexes bearing one xanthine-based NHC and one PTA molecule [13].

As a definitive confirmation of the nature of mixed NHC/PR_3 complexes, we report the structure of complex **5c** obtained by single crystal X-ray diffraction (Fig. 1).

The crystalline form of **5c** contains one crystallographically independent palladium complex.

The palladium centers adopt square planar coordination spheres with bond lengths and angles in agreement with literature structural data of similar complexes, like CCDC 1,992,549 [14] (Table S2). The complex bears a positive charge which is balanced by a ClO_4 counterion, located close to the allyl ligand, which represent the area where the metal is more exposed (shortest O···Pd contacts are 4.530(4) Å in **5c** and 3.88(1) Å in CCDC 1992549). The molecular model of **5c** is well

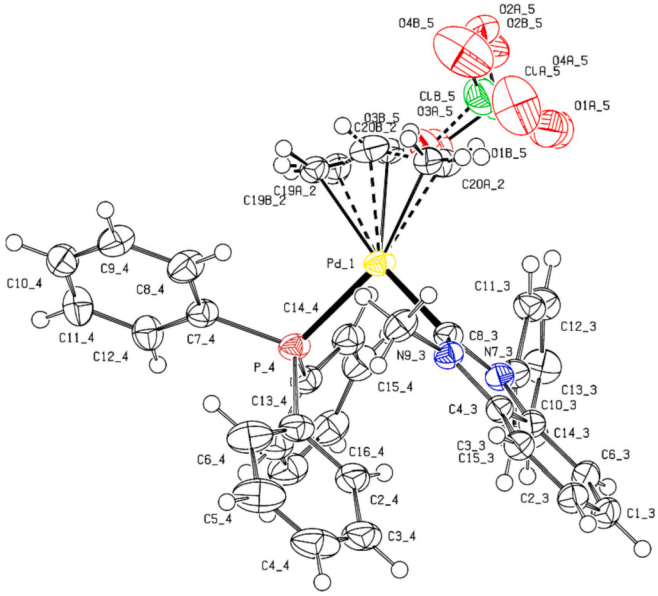


Fig. 1. Ellipsoid representation of **5c** crystal ASU content (ellipsoids radii corresponding to 50% probability). Atom labels in use are reported.

superimposable with CCDC 1,992,549 (Fig. S2) with minimal shifts of atoms directly bound to the metal and equivalent benzimidazole and allyl arrangements. This comparison highlights the phosphine ligand conformational freedom, which is influenced by crystal packing contacts and relative bulkiness of benzimidazole substituents.

The crystal packing of **5c** shows hydrophobic contacts among neighbour molecules, involving weak intermolecular interactions: π···π (i.e. $d_{\pi\cdots\pi} = 3.710(1)$ Å with 1.00 Å slippage between benzimidazole ring centroids) and CH···π (i.e. $d_{CH\cdots\pi} = 3.477(3)$ Å with 63° between CH and π-plane), among the allyl ligand and neighbour aromatic sidechains. The η^3-allyl instead can adopt two equally probable conformations specular respect to the Pd coordination plane.

2.6. Cytotoxicity studies on cationic palladium allyl complexes *3d-f, 5a-d* and *6a-b*

The antiproliferative activity of the cationic palladium(II) derivatives **3d-f, 5a-d** and **6a-b** was assayed toward MRC-5 normal cells (human fibroblasts) and five different human tumor cell lines: ovarian cancer (A2780, with its cisplatin resistant clone A2780*cis*), lung cancer (A549), colon cancer (DLD-1) and glioblastoma (U87 cells).

Preliminarily, the stability of all the compounds examined was checked in 1:1 DMSO-d_6/D_2O solution by NMR spectroscopy: after 24 h at room temperature no noticeable degradation was observed.

The half-inhibitory concentrations (IC_{50}) induced by the palladium (II) compounds and cisplatin (positive control) are summarized in Table 1.

The IC_{50} values display a marked cytotoxicity of all compounds in the different tumor lines tested. In most cases, the complexes exhibit a higher antiproliferative activity than cisplatin, which is generally also maintained in the A2780*cis* (cisplatin-sensitive) cell line, suggesting a different mechanism of action compared to cisplatin. In this respect, in our previous contribution, their trifluoromethyl congeners showed inducing mitochondrial dysfunction as primary damage [14].

An important result obtained concerns the cytotoxicity of our compounds toward MRC-5 normal cells. In this context, complexes **3d**, **3e**, **5d**, **6a** and **6b** show IC_{50} values on average an order of magnitude higher on normal cells with respect to those obtained on cancer ones. Among these few derivatives, compound **3d** is the most promising as it is substantially inactive against normal cells ($IC_{50} > 100$ μM).

Table 1
Cytotoxicity of Pd-complexes toward several cancer and normal cell lines*.

Complex	IC_{50} (μM)					
	A2780	A2780cis	A549	DLD-1	U87	MRC-5
CisPt	0.16 ± 0.02	5.8 ± 0.6	5.2 ± 0.8	4 ± 1	31 ± 4	2.4 ± 0.2
3d	0.71 ± 0.03	3.0 ± 0.04	3.4 ± 0.2	2.3 ± 0.2	0.57 ± 0.04	>100
3e	0.23 ± 0.03	0.9 ± 0.3	2.8 ± 0.3	0.5 ± 0.3	1.8 ± 0.4	4.4 ± 0.4
3f	0.035 ± 0.008	0.029 ± 0.003	0.015 ± 0.003	0.04 ± 0.02	0.022 ± 0.001	0.32 ± 0.04
5a	0.16 ± 0.05	0.17 ± 0.02	0.44 ± 0.03	0.28 ± 0.02	0.19 ± 0.03	0.9 ± 0.3
5b	0.030 ± 0.007	0.18 ± 0.06	0.10 ± 0.02	0.104 ± 0.003	0.028 ± 0.009	0.38 ± 0.02
5c	0.026 ± 0.006	0.019 ± 0.003	0.035 ± 0.003	0.014 ± 0.003	0.0183 ± 0.0004	0.22 ± 0.03
5d	0.13 ± 0.06	1.5 ± 0.4	0.80 ± 0.06	0.13 ± 0.03	0.30 ± 0.03	2.3 ± 0.2
6a	0.017 ± 0.002	0.19 ± 0.03	3.4 ± 0.5	0.32 ± 0.05	0.5 ± 0.1	2.1 ± 0.3
6b	0.10 ± 0.03	0.25 ± 0.03	0.59 ± 0.07	0.3 ± 0.1	0.36 ± 0.06	2.8 ± 0.1

* Data after 96 h of incubation. Stock solutions in DMSO for all complexes; stock solutions in H_2O for cisplatin. A2780 (cisplatin-sensitive ovarian cancer cells), A2780*cis* (cisplatin-resistant ovarian cancer cells), A549 (lung cancer cells), DLD1 (colon cancer cells), U87 (glioblastoma cells), MRC-5 (normal lung fibroblasts).

As already observed in some previous works [14,15], two combinations that seem in general to guarantee a certain selectivity toward cancer cells are the presence of a pyridine arm on the NHC or the NHC/PTA motif.

Although mixed NHC/PTA complexes **6a-b** showed some selectivity toward cancer cells, their cytotoxicity toward MRC-5 fibroblasts is significantly higher than mixed NHC/PTA palladium allyl complexes bearing *N*-trifluoromethyl benzimidazolylidenes [14], suggesting that the presence of the CF_3 group is crucial for an *in vitro* selective antitumor activity.

3. Conclusions

In summary, we reported the synthesis and characterization of 12 new palladium allyl complexes bearing benzimidazole-based NHC ligands. Compounds **3f** and **5c-d** appear as a mixture of two atropoisomers and for **5c** it was possible to unequivocally establish the connectivity of the atoms by single crystal X-ray diffraction.

The nine cationic compounds were tested as potential anticancer agents against five different types of tumors (cisplatin-sensitive and cisplatin-resistant ovarian cancers, lung cancer, colon cancer and glioblastoma), exhibiting excellent cytotoxicity in the sub-micromolar range.

In particular, they are generally more active than cisplatin and showed similar IC_{50} values in the two of ovarian cancer lines (A2780 and A2780*cis*), suggesting a different mechanism of action with respect to classical platinated chemotherapeutic agents.

Compounds with a pyridine arm or the NHC/PTA combination showed a significant selectivity toward cancer cells, in which compound **3d** was the most promising by virtue of its poor cytotoxicity against MRC-5 normal cells.

On comparing the IC_{50} values of complexes **6a-b** and their trifluoromethyl congeners recently published by our group, it appears evident that they have very similar cytotoxicity toward cancer cells but the presence of the CF_3 group guarantees a greater selective anticancer activity, with a substantial inactivity toward MRC-5 lung fibroblasts ($IC_{50} > 100$ μM vs approx. 2 μM).

4. Experimental section

4.1. Materials and characterization techniques

All syntheses of complexes were carried out using standard Schlenk techniques under an atmosphere of dry nitrogen. Solvents were dried and distilled according to standard methods: CH_2Cl_2 was firstly treated with 3 Å molecular sieves and then distilled over P_2O_5. All other chemicals were commercially available grade products and were used as purchased.

The palladium(II) precursor 1-methylbenzimidazole [18], 1-phenylbenzimidazole [19] and 1-adamantylbenzimidazole [20], were synthesized according to published procedures.

The IR and NMR spectra were recorded on a Perkin-Elmer Spectrum One spectrophotometer and on a Bruker 400 Avance spectrometer, respectively.

Elemental analysis was carried out using an Elemental CHN "CUBO Micro Vario" analyzer.

Safety note: Perchlorate salts (eg. $NaClO_4$) are potentially explosive and should only be handled in small quantities with care.

4.2. Synthesis of the compound *1a*

In a 100 mL flask, 1.3 g (10 mmol) of 1-methylbenzimidazole was solubilized in 15 mL of acetonitrile and 0.87 mL (13.5 mol) of iodomethane was added to the resulting solution.

The reaction mixture was kept at 90 °C for ca. 8 h and then cooled down to room temperature.

The solvent was removed under vacuum and the iodide azolium salts was solubilized in 100 mL of methanol. Then, 20 g of DOWEX 21KCl resin was added. The system was then stirred at room temperature for 24 h. After filtration of the resin, the solvent was removed under vacuum and the final white product **1a** was obtained in excellent yield (1.80 g, 82%).

^{1}H NMR (300 MHz, DMSO-d_6, T = 298 K, ppm) δ: 9.62 (s, 1H, NCHN), 8.01 (dt, J = 6.7, 3.4 Hz, 2H, Ar-H), 7.72 (dt, J = 6.2, 3.3 Hz, 2H, Ar-H), 4.08 (s, 6H, CH_3).

Anal. Calc. for $C_9H_{11}ClN_2$: C, 59.18; H, 6.07; N, 15.34. Found: C, 59.30; H, 6.00; N, 15.27%.

4.3. Synthesis of the compound *1b*

In a 100 mL flask, 1.3 g (10 mmol) of 1-methylbenzimidazole was solubilized in 15 mL of acetonitrile and 2.0 mL (20 mol) of 2-iodopropane was added to the resulting solution.

The reaction mixture was kept at 90 °C for ca. 24 h and then cooled down to room temperature.

The solvent was removed under vacuum and the iodide azolium salts recrystallized using a 1:2 acetonitrile/methanol mixture. The purified solid was dissolved in 100 mL of methanol and 20 g of DOWEX 21KCl resin was added. The system was then stirred at room temperature for 24 h. After filtration of the resin, the solvent was removed under vacuum and the final white product **1b** was obtained in good yield (1.44 g, 68%).

^{1}H NMR (300 MHz, DMSO-d_6, T = 298 K, ppm) δ: 9.80 (s, 1H, NCHN), 8.18 – 8.07 (m, 1H, Ar-H), 8.07 – 7.98 (m, 1H, Ar-H), 7.76 – 7.65 (m, 2H, Ar-H), 5.06 (p, J = 6.7 Hz, 1H, isopropyl-CH), 4.07 (s, 3H, N-CH_3), 1.62 (d, J = 6.7 Hz, 6H, isopropyl-CH_3).

Anal. Calc. for $C_{11}H_{15}ClN_2$: C, 62.70; H, 7.18; N, 13.30. Found: C, 62.54; H, 7.28; N, 13.17%.

4.4. Synthesis of the compound *1c*

In a 100 mL flask, 2.2 g (11 mmol) of 1-phenylbenzimidazole was dissolved in 20 mL of tetrahydrofuran and 1.1 mL (17 mol) of iodomethane was added to the resulting solution.

The reaction mixture was kept at 90 °C for ca. 24 h and then cooled down to room temperature.

The iodide azolium salts was filtered off and dried under vacuum. This white intermediate was dissolved in 100 mL of methanol and 20 g of DOWEX 21KCl resin was added. The system was then stirred at room temperature for 24 h. After filtration of the resin, the solvent was removed under vacuum and the final white product **1c** was obtained in good yield (1.81 g, 66%).

^{1}H NMR (300 MHz, DMSO-d_6, T = 298 K, ppm) δ: 10.10 (s, 1H, NCHN), 8.15 (d, J = 7.7 Hz, 1H, Ar-H), 7.95 – 7.60 (m, 8H, Ar-H), 4.17 (s, 3H, CH_3).

Anal. Calc. for $C_{14}H_{13}ClN_2$: C, 68.71; H, 5.35; N, 11.45. Found: C, 68.89; H, 5.30; N, 11.38%.

4.5. Synthesis of compound *1d*

In a 100 mL flask, 1.98 g (15.6 mmol) of 2-chloromethylpyridine was dissolved in 70 mL of anhydrous acetonitrile. 2.7 g (22 mmol) of 1-methylbenzimidazole was added to the resulting solution.

The reaction mixture was kept at 90 °C for ca. 30 h and then cooled down to room temperature.

The solvent was removed under vacuum, the resulting solid resuspended in dichloromethane (50 mL) and the mixture was filtered in order to remove inorganic salts.

The solution was concentrated and the title compound precipitated by addition of diethylether.

The red solid (4.12 g, 89%) was filtered off on a gooch filter, repeatedly washed with diethylether and *n*-pentane and dried under vacuum.

^{1}H NMR (300 MHz, DMSO-d_6, T = 298 K, ppm) δ: 9.87 (s, 1H, NCHN), 8.54 – 8.44 (m, 1H, Ar-H), 8.04 (dd, J = 7.0, 1.5 Hz, 1H, Ar-H), 7.98 – 7.85 (m, 2H, Ar-H), 7.75 – 7.58 (m, 2H, Ar-H), 7.38 (dd, J = 6.6, 4.9 Hz, 2H, Ar-H), 5.92 (s, 2H, NCH_2N), 4.15 (s, 3H, CH_3).

Anal. Calc. for $C_{14}H_{14}BrN_3$: C, 55.28; H, 4.64; N, 13.81. Found: C, 55.16; H, 4.71; N, 13.88%.

4.6. Synthesis of compound *1e*

In a 10 mL flask, 1.5 g (11 mmol) of 1-methylbenzimidazole was solubilized in 5 mL of tetrahydrofuran and 1.1 g (5 mol) of dibromomethane was added to the resulting solution.

The reaction mixture was kept at 120 °C for ca. 72 h and then cooled down to room temperature.

The solid was filtered off (1.98 g) and suspended in a 250 mL flask with 150 mL of methanol. Then 1.87 g (9 mmol) of $AgClO_4$ was added and AgBr was removed by filtration on a millipore membrane filter.

The solution was concentrated and the title compound precipitated by addition of diethylether.

The white product (2.0 g, 80%) was filtered off on a gooch filter, repeatedly washed with diethylether and *n*-pentane and dried under vacuum.

^{1}H NMR (300 MHz, DMSO-d_6, T = 298 K, ppm) δ: 10.28 (s, 1H, NCHN), 8.39 (dd, J = 6.7, 2.0 Hz, 2H, Ar-H), 7.88 – 7.68 (m, 6H, Ar-H), 7.48 (s, 2H, NCH_2N), 4.15 (s, 6H, NCH_3).

Anal. Calc. for $C_{17}H_{18}Cl_2N_4O_8$: C, 42.78; H, 3.80; N, 11.74. Found: C, 42.61; H, 3.86; N, 11.83%.

4.7. Synthesis of compound *1f*

In a 5 mL vial, 543.1 mg (2.16 mmol) of 1-adamanylbenzimidazole was suspended in 1.5 mL (21.5 mmol) of dibromomethane.

The reaction mixture was kept at 85 °C for ca. 24 h and then cooled down to room temperature.

The solid was filtered off (0.6 g) and suspended in a 100 mL flask with 50 mL of methanol. Then 0.37 g (1.8 mmol) of $AgClO_4$ was added and AgBr was removed by filtration on a millipore membrane filter.

The solution was concentrated and the title compound precipitated by addition of diethylether.

The white product (0.66 g, 85%) was filtered off on a gooch filter, repeatedly washed with diethylether and *n*-pentane and dried under vacuum.

^{1}H NMR (300 MHz, CD_3CN, T = 298 K, ppm) δ: 12.08 (s, 2H, NCHN), 9.07 (d, J = 8.4 Hz, 2H, Ar-H), 8.52 (s, 2H, NCH_2N), 8.06 (d, J = 8.5 Hz, 3H, Ar-H), 7.84 – 7.60 (m, 4H, Ar-H), 2.55 (d, J = 2.7 Hz, 12H, CH_2), 2.45 (s broad, 6H, CH), 1.92 (s broad, 12H, CH_2).

Anal. Calc. for $C_{35}H_{42}Cl_2N_4O_8$: C, 58.58; H, 5.90; N, 7.81. Found: C, 58.70; H, 5.81; N, 7.75%.

4.8. Synthesis of silver-NHC complexes *2a-d*

4.8.1. Synthesis of complex *2a*

0.4012 g (2.2 mmol) of **1a** was dissolved in 30 mL of anhydrous dichloromethane in a two-necked flask and 0.2790 g (1.2 mmol) of Ag_2O was added under inert atmosphere (Ar).

The mixture was stirred for 24 h at RT in the dark and subsequently transferred to a 250 mL flask with the addition of ca. 100 mL of CH_2Cl_2. The solution was filtered on a millipore membrane filter, concentrated under vacuum and the title complex precipitated by addition of diethylether.

The brownish complex was filtered off on a gooch filter, repeatedly washed with diethylether and *n*-pentane and dried under vacuum.

0.3994 g of **2a** was obtained (yield 60%).

^{1}H NMR (300 MHz, $CDCl_3$, T = 298 K, ppm) δ: 7.58 – 7.42 (m, 4H, Ar-

H), 4.06 (s, 6H, NCH_3).

$^{13}C\{^1H\}$ (75,5 MHz, $CDCl_3$, ppm): 189.7 (C, carbene), 134.3 (C, Ar-C), 124.3 (CH, Ar-CH), 111.2 (CH, Ar-CH), 35.8 (CH_3, NCH_3).

Anal. Calc. for $C_9H_{10}AgClN_2$: C, 37.34; H, 3.48; N, 9.68. Found: C, 37.21; H, 3.56; N, 9.61%.

4.8.2. Synthesis of complex **2b**

Complex **2b** was prepared by a procedure analogous to that described for **2a** starting from 0.4049 g (1.92 mmol) of **1b** and 0.2364 g (1.02 mmol) of Ag_2O.

0.5733 g (yield 93%) of **2b** was obtained.

^1H NMR (300 MHz, $CDCl_3$, T = 298 K, ppm) δ: 7.69 – 7.58 (m, 1H, Ar-H), 7.54 – 7.37 (m, 4H, Ar-H), 5.07 (p, J = 7.0 Hz, 1H, isopropyl-CH), 4.05 (s, 3H, NCH_3), 1.74 (d, J = 7.0 Hz, 6H, isopyl-CH_3).

$^{13}C\{^1H\}$-NMR ($CDCl_3$, T = 298 K, ppm) δ: 187,6 (C, carbene), 134.9 (C, Ar-C), 132.4 (C, Ar-C), 124.2 (CH, Ar-CH), 123.8 (CH, Ar-CH), 112.4 (CH, Ar-CH), 111.5 (CH, Ar-CH), 53.7 (CH, isopropyl-CH), 36.1 (NCH_3), 22.6 (CH_3, isopropyl-CH_3).

Anal. Calc. for $C_{11}H_{14}AgClN_2$: C, 41.60; H, 4.44; N, 8.82. Found: C, 41.72; H, 4.39; N, 8.75%.

4.8.3. Synthesis of complex **2c**

Complex **2c** was prepared by a procedure analogous to that described for **2a** starting from 0.2720 g (1.66 mmol) of **1c** and 0.1355 g (0.58 mmol) of Ag_2O.

0.2834 g (yield 72%) of **2c** was obtained.

^1H NMR (300 MHz, $CDCl_3$, T = 298 K, ppm) δ: 7.66 – 7.55 (m, 6H, Ar-H), 7.47 – 7.42 (m, 3H, Ar-H), 4.17 (s, 3H, NCH_3).

$^{13}C\{^1H\}$-NMR ($CDCl_3$, T = 298 K, ppm) δ: 188,2 (C, carbene), 137.6 (C, Ar-C), 134.4 (C, Ar-C), 134.2 (C, Ar-C), 130.2 (CH, Ar-CH), 129.6 (CH, Ar-CH), 129.5 (CH, Ar-CH), 126.0(CH, Ar-CH), 124.7 (CH, Ar-CH), 112.2 (CH, Ar-CH), 111.4 (CH, Ar-CH), 36.1 (CH_3, NCH_3).

Anal. Calc. for $C_{14}H_{12}AgClN_2$: C, 47.83; H, 3.44; N, 7.97. Found: C, 47.96; H, 3.39; N, 7.88%.

4.8.4. Synthesis of complex **2d**

Complex **2d** was prepared by a procedure analogous to that described for **2a** starting from 0.3997 g (1.31 mmol) of **1d** and 0.1658 g (0.715 mmol) of Ag_2O.

0.4222 g (yield 79%) of **2d** was obtained.

^1H NMR (300 MHz, $CDCl_3$, T = 298 K, ppm) δ: 8.58 (m, 1H, 6-py-H), 7.66 (td, J = 7.7, 1.8 Hz, 1H, 4-py-H), 7.57 – 7.31 (m, 6H, Ar-H, 5-pyr-H) 7.24 (dd, J = 7.0, 5.4 Hz, 1H, 3-pyr-H), 5.75 (s, 2H, NCH_2), 4.11 (s, 3H, NCH_3).

$^{13}C\{^1H\}$-NMR ($CDCl_3$, T = 298 K, ppm) δ: 191.2 (C, carbene), 154.84 (C, 2-pyr-C), 149.8 (CH, 6-pyr-CH), 137.3 (CH, 4-pyr-CH), 134.5 (C, Ar-C), 133.9 (C, Ar-C), 124.3 (CH, 3-pyr-CH), 124.2 (CH, Ar-CH), 123.3 (CH, Ar-CH), 122.2 (CH, 5-pyr-CH), 112.3 (CH, Ar-CH), 111.1 (CH, Ar-CH), 54,9 (s, NCH_2), 35.9 (s, NCH_3).

Anal. Calc. for $C_{14}H_{13}AgBrN_3$: C, 40.91; H, 3.19; N, 10.22. Found: C, 41.06; H, 3.11; N, 10.17%.

4.9. Synthesis of palladium allyl complexes bearing chelating C—C and C—N ligands

4.9.1. Synthesis of complex **3d**

0.0653 g (0.17 mmol) of the precursor $[Pd(\mu\text{-}Cl)(\eta^3\text{-allyl})]_2$ was dissolved in 15 mL of anhydrous dichloromethane in a 50 mL two-necked flask under inert atmosphere (Ar) and 0.1471 g (0.35 mmol) of the silver complex **2d** was added to this solution.

Subsequently, 0.1000 g (0.70 mmol) of $NaClO_4{\cdot}H_2O$, dissolved in 4 mL of methanol, was added and the mixture was stirred at room temperature for ca. 1 h.

Then the solvent was removed under vacuum and the residue was suspended in dichloromethane (15 mL). The inorganic salts were filtered off on a Celite filter and repeatedly washed with CH_2Cl_2, whereas the filtrate was concentrated under vacuum. Addition of diethylether caused the precipitation of complex **3d** as a white solid which was filtered off on a gooch and washed with *n*-pentane. 0.1562 g of **3d** was obtained (yield 93%).

^1H NMR (300 MHz, CD_3CN, T = 243 K, ppm) δ: 8.96 – 8.85 (m, 1H, 6-py-H), 8.05 (td, J = 7.7, 1.6 Hz, 1H, 4-py-H), 7.92 (d, J = 7.5 Hz, 1H, Ar-H), 7.88 – 7.80 (m, 1H, Ar-H), 7.68 – 7.57 (m, 2H, Ar-H), 7.55–7.39 (m, 3H, Ar-H, 3-py-H, 5-pyr-H), 5.88 – 5.70 (m, 1H, *central* allyl), 5.67 – 5.36 (AB system, J = 15.3 Hz, 2H, NCH_2Py), 4.50 (dd, J = 7.7, 1.8 Hz, 1H, *syn* allyl-H *trans*-C), 4.08 (dd, J = 4.9, 1.8 Hz, 1H, *syn* allyl-H *trans*-N), 3.97 (s, 3H, NCH_3), 3.74 (d, J = 13.7 Hz, 1H, *anti* allyl-H *trans*-C), 3.10 (d, J = 12.2 Hz, 1H, *anti* allyl-H *trans*-N).

$^{13}C\{^1H\}$-NMR (CD_3CN, T = 243 K, ppm) δ: 186.66 (C, carbene), 155.7 (C, 2-py-C), 153.4 (CH, 6-py-CH), 140.5 (CH, 4-py-CH), 134.1 (C, Ar-C), 133.5 (C, Ar-C), 126.2 (CH, Ar-CH), 125.3 (CH, Ar-CH), 124.00 (CH, 3-py-CH), 123.9 (CH, 5-py-CH), 121.2 (CH, *central* allyl), 111.7 (CH, Ar-CH), 110.9 (CH, Ar-CH), 74.5 (CH_2, allyl *trans*-C), 50.9 (CH_2, NCH_2py), 49.2 (CH_2, allyl *trans*-N), 35.0 (CH_3, NCH_3).

Anal. Calc. for $C_{17}H_{18}ClN_3O_4Pd$: C, 43.42; H, 3.86; N, 8.94. Found: C, 43.29; H, 3.92; N, 8.99%.

4.9.2. Synthesis of complex **3e**

0.0941 g (0.20 mmol) of **1e** was dissolved in 20 mL of anhydrous acetonitrile in a two-necked flask and 0.0550 g (0.24 mmol) of Ag_2O was added under inert atmosphere (Ar).

The mixture was stirred for 18 h at RT in the dark and subsequently 0.0361 g (0.10 mmol) of the precursor $[Pd(\mu\text{-}Cl)(\eta^3\text{-allyl})]_2$ was added. After 30 min at RT, the solution was filtered on a millipore membrane filter, concentrated under vacuum and the title complex precipitated by addition of diethylether.

The brownish complex was filtered off on a gooch filter, repeatedly washed with dichloromethane (2x0.5 mL), diethylether (2x3mL) and *n*-pentane (2x3mL) and dried under vacuum.

0.0771 g of **2a** was obtained (yield 75%).

^1H NMR (300 MHz, CD_3CN, T = 298 K, ppm) δ: 7.98 (dt, J = 8.5, 0.8 Hz, 2H, Ar-H), 7.69 – 7.65 (m, 2H, Ar-H), 6.55 (AB system, J = 13.9 Hz, 2H, NCH_2N), 5.64 – 5.49 (m, 1H, *central* allyl-H), 4.46 (d, J = 7.4 Hz, 2H, *syn* allyl-H), 4.02 (s, 6H, NCH_3) , 3.15 (d, J = 13.4 Hz, 2H, *anti* allyl-H).

$^{13}C\{^1H\}$-NMR (CD_3CN, T = 298 K, ppm) δ: 186.8 (C, carbene), 134.3 (C, Ar-C), 133.4 (C, Ar-C), 124.3 (CH, Ar-CH) 124.1 (CH, Ar-CH), 120.6 (CH, *central* allyl), 111.7 (CH, Ar-CH), 110.5 (CH, Ar-CH), 60.0 (CH_2, *terminal* allyl), 56.8 (CH_2, NCH_2), 35.4 (CH_3, NCH_3).

Anal. Calc. for $C_{20}H_{21}ClN_4O_4Pd$: C, 45.91; H, 4.05; N, 10.71. Found: C, 46.07; H, 3.98; N, 10.60%.

4.9.3. Synthesis of complex **3f**

Complex **3f** was prepared by a procedure analogous to that described for **3e** starting from 0.1006 g (0.14 mmol) of **1e**, 0.0354 mg (0.15 mmol) of Ag_2O and 0.0231 g (0.07 mmol) of $[Pd(\mu\text{-}Cl)(\eta^3\text{-allyl})]_2$.

Reaction time: 48 h.

0.1019 g (yield 95%) of **3f** was obtained.

Isomer A/isomer B ≈ 1: 2.

^1H NMR (300 MHz, CD_3CN, T = 298 K, ppm) δ: 8.03, 7.96, 7.89 (d, J = 8.4, Hz, 2H, Ar-H), 7.47 – 7.32 (m, 2H, Ar-H), 6.94, 6.79 (d, J = 14.3 Hz, 1H, NCH_2N), 6.51, 6.22 (d, J = 14.3 Hz, 1H, NCH_2N), 6.00, 5.51 (m, 1H, *central* allyl-H), 4.32,4.04 (d, J = 7.2 Hz, 2H, *syn* allyl-H), 3.08, 2.88 (d, J = 13.3 Hz, 2H, *anti* allyl-H), 2.28–2.67 (m, 16H, Adamantyl-H), 1.84–1.90 (m, 12H, Adamantyl-H).

$^{13}C\{^1H\}$-NMR (CD_3CN, T = 298 K, ppm) δ: 188.1 (C, carbene), 187.8 (C, carbene), 134.9 (C, Ar-C), 134.7 (C, Ar-C), 133.4 (C, Ar-C), 133.3 (C, Ar-C), 123.9 (CH, Ar-CH), 123.8 (CH, Ar-CH), 122.9 (CH, Ar-CH), 122.8 (CH, Ar-CH), 119.1 (CH, *central* allyl), 117.5 (CH, *central* allyl), 116.2 (CH, Ar-CH), 116.1 (CH, Ar-CH), 110.4(CH, Ar-CH), 110.3 (CH, Ar-CH), 62.8 (CH_2, *terminal* allyl), 62.6 (CH_2, *terminal* allyl), 61.2 (C, Adamantyl-C), 61.1 (C, Adamantyl-C), 58.2 (CH_2, NCH_2), 57.9 (CH_2, NCH_2), 42.5 (CH_2, Adamantyl-CH_2), 42.3 (CH_2, Adamantyl-CH_2), 35.6 (CH_2,

Adamantyl-CH_2), 35.5 (CH_2, Adamantyl-CH_2), 29.3 (CH, Adamantyl-CH), 29.3 (CH, Adamantyl-CH).

Anal. Calc. for $C_{38}H_{45}ClN_4O_4Pd$: C, 59.77; H, 5.94; N, 7.34. Found: C, 59.61; H, 6.02; N, 7.40%.

4.10. Synthesis of neutral palladium complexes (**4a-c**)

4.10.1. Synthesis of complex **4a**

0.0597 g (0.16 mmol) of $[Pd(\mu\text{-}Cl)(\eta^3\text{-allyl})]_2$ was dissolved in ca. 15 mL of anhydrous CH_2Cl_2. 0.0934 g (0.32 mmol) of the silver complex **2a** was added and the mixture was stirred at room temperature for ca. 30 min in a 50 mL two necked flask under inert atmosphere (Ar).

The precipitated AgCl was filtered off on a Celite filter and repeatedly washed with CH_2Cl_2, whereas the filtrate was concentrated under vacuum. Addition of diethylether caused the precipitation of complex **4a** as a white solid which was filtered off on a gooch and washed with *n*-pentane.

0.0898 g of **4a** was obtained (yield 85%).

^{1}H NMR (300 MHz, $CDCl_3$, T = 298 K, ppm) δ: 7.37 (dtd, *J* = 13.0, 6.7, 3.4 Hz, 4H, Ar-H), 5.47 (tt, *J* = 13.8, 7.4 Hz, 1H, *central* allyl-H), 4.43 (dd, *J* = 7.9, 1.7 Hz, 1H, *syn* allyl-H *trans*-C), 4.06 (s, 6H, NCH_3), 3.53 (d, *J* = 6.5 Hz, 1H, *syn* allyl-H *tran*-Cl), 3.45 (d, *J* = 13.7 Hz, 1H, *anti* allyl-H *trans*-C), 2.58 (d, *J* = 11.9 Hz, 1H, *anti* allyl-H *trans*-Cl).

^{13}C{^{1}H}-NMR ($CDCl_3$, T = 298 K, ppm) δ: 192.6 (C, carbene), 135.1 (C, Ar-C), 123.0 (CH, Ar-CH), 115.6 (CH, *central* allyl), 110.0 (CH, Ar-CH), 74.1 (CH_2, allyl *trans*-C), 48.4 (CH_2, allyl *trans*-Cl), 35.0 (CH_3 NCH_3).

Anal. Calc. for $C_{12}H_{15}ClN_2Pd$: C, 43.79; H, 4.59; N, 8.51. Found: C, 43.92; H, 4.50; N, 8.57%.

4.10.2. Synthesis of complex **4b**

Complex **4b** was prepared by a procedure analogous to that described for **4a** starting from 0.0531 g (0.15 mmol) of $[Pd(\mu\text{-}Cl)(\eta^3\text{-allyl})]_2$ and 0.0922 g (0.30 mmol) of **2b**.

0.1032 g (yield 99%) of **4b** was obtained.

^{1}H NMR (300 MHz, $CDCl_3$, T = 298 K, ppm) δ: 7.57 (dd, *J* = 6.1, 2.6 Hz, 1H, Ar-H), 7.43 – 7.20 (m, 3H, Ar-H), 5.66–5.32 (m, 2H, isopropyl-CH e *central*-allyl-H), 4.40 (d, *J* = 7.6 Hz, *syn* allyl-H *trans*-C), 4.04 (s, 3H, NCH_3), 3.49 (d, *J* = 5.3 Hz, 1H, *syn* allyl-H *trans*-Cl), 3.44 (d, *J* = 13.7 Hz, 1H, *anti* allyl-H *trans*-C), 2.52 (d, *J* = 11.8 Hz, 1H, *anti* allyl-H *trans*-Cl), 1.70 (d, *J* = 6.8 Hz, 6H, isopropyl-CH_3).

^{13}C{^{1}H}-NMR ($CDCl_3$, T = 298 K, ppm) δ: 190.5 (C, carbene), 136.2 (C, Ar-C), 132.7 (C, Ar-C), 122.8 (CH, Ar-CH), 122.5 (CH, Ar-CH), 115.3 (CH, *central* allyl), 112.0 (CH, Ar-CH), 110.4 (CH, Ar-CH), 73.7 (CH_2, allyl *trans*-C), 53.9 (CH, isopropyl-CH), 48.1 (CH_2, allyl *trans*-Cl), 34.9 (CH_3, NCH_3), 21.6 (CH_3 , isopropyl-CH_3).

Anal. Calc. for $C_{14}H_{19}ClN_2Pd$: C, 47.08; H, 5.36; N, 7.84. Found: C, 47.20; H, 5.29; N, 7.77%.

4.10.3. Synthesis of complex **4c**

Complex **4c** was prepared by a procedure analogous to that described for **4a** starting from 0.0605 g (0.16 mmol) of $[Pd(\mu\text{-}Cl)(\eta^3\text{-allyl})]_2$ and 0.1165 g (0.33 mmol) of **2c**.

0.1060 g (yield 81%) of **4c** was obtained.

^{1}H NMR (300 MHz, $CDCl_3$, T = 298 K, ppm) δ: 7.82 (d, *J* = 7.4 Hz, 2H, Ar-H), 7.67 – 7.44 (m, 4H, Ar-H and Ar-H), 7.43 – 7.24 (m, 3H, Ar-H), 5.06 (tt, *J* = 13.7, 7.4 Hz, 1H, *central*-allyl-H), 4.26 (d, *J* = 1.7 Hz, 1H, *syn* allyl-H *trans*-C), 4.24 (s, 3H, NCH_3), 3.18 (d, *J* = 13.6 Hz, 1H, *syn* allyl-H *trans*-Cl), 3.02 (d, *J* = 6.4 Hz, 1H, *anti* allyl-H *trans*-C), 1.84 (d, *J* = 11.9 Hz, 1H, *anti* allyl-H *trans*-Cl).

^{13}C{^{1}H}-NMR ($CDCl_3$, T = 298 K, ppm) δ: 192.2 (C, carbene), 138.4 (C, Ar-C), 135.3 (C, Ar-C), 134.8 (C, Ar-C), 129.3 (CH, Ar-CH), 126.8 (CH, Ar-CH), 123.6 (CH, Ar-CH), 123.5 (CH, Ar-CH), 117.2 (CH, Ar-CH), 115.1 (CH, *central* allyl), 111.1 (CH, Ar-CH), 110.4 (CH, Ar-CH), 72.7 (CH_2, allyl *trans*-C), 49.5 (s CH_2, allyl *trans*-Cl), 35.1 (CH_3, NCH_3).

Anal. Calc. for $C_{17}H_{17}ClN_2Pd$: C, 52.19; H, 4.38; N, 7.16. Found: C, 52.08; H, 4.43; N, 7.27%.

4.11. Synthesis of mixed NHC/PPh_3 palladium complexes

4.11.1. Synthesis of complex **5a**

0.0509 g (0.15 mmol) of **4a** was dissolved in ca. 12 mL of anhydrous CH_2Cl_2 and 0.0405 g (0.15 mmol) of PPh_3 was added. Subsequently, 0.0450 g (0.32 mmol) of $NaClO_4{\cdot}H_2O$, dissolved in 4 mL of methanol, was added and the mixture was stirred at room temperature for ca. 30 min in a 50 mL two necked flask under inert atmosphere (Ar).

Then the solvent was removed under vacuum and the residue was suspended in dichloromethane (15 mL). The inorganic salts were filtered off on a Celite filter and repeatedly washed with CH_2Cl_2, whereas the filtrate was concentrated under vacuum. Addition of diethylether caused the precipitation of the complex **5a** as a yellow solid which was filtered off on a gooch and washed with *n*-pentane. 0.0990 g of **5a** was obtained (yield 98%).

^{1}H NMR (300 MHz, $CDCl_3$, T = 298 K, ppm) δ: 7.49 – 7.14 (m, 33H, Ar-H), 5.92 (tt, *J* = 13.5, 7.3 Hz, 1H, *central*-allyl-H), 4.54 (m, 1H, *syn* allyl-H *trans*-P), 4.15 (d, *J* = 7.3 Hz, 1H, *syn* allyl-H *trans*-P), 3.65 (s, 3H, NCH_3), 3.49 (s, 3H, CH_3), 3.48 (m, 1H, *syn* allyl-H *trans*-P), 3.29 (d, *J* = 13.5 Hz, 1H, *syn* allyl-H *trans*-C).

^{31}P{^{1}H}-NMR ($CDCl_3$, T = 298 K, ppm) δ: 25.9.

^{13}C{^{1}H}-NMR ($CDCl_3$, T = 298 K, ppm) δ: 189.6 (d, J_{CP} = 19.1 Hz, carbene), 135.2 (C, Ar-C), 135.2 (C, Ar-C), 123.4 (CH, Ar-CH), 123.4 (CH, Ar-CH), 122.2 (d, J_{CP} = 5.3 Hz, CH, *central* allyl), 110.1 (CH, Ar-CH), 110.0 (CH, Ar-CH), 70.2 (d, *J* = 2.0 Hz, CH_2, allyl *trans*-C), 67.1 (d, , J_{CP} = 27.1 Hz, CH_2, allyl *trans*-P), 34.8 (CH_3, NCH_3), 34.5 (CH_3, NCH_3).

Anal. Calc. for $C_{30}H_{30}ClN_2O_4PPd$: C, 54.98; H, 4.61; N, 4.27. Found: C, 55.12; H, 4.54; N, 4.21%.

4.11.2. Synthesis of complex **5b**

Complex **5b** was prepared by a procedure analogous to that described for **5a** starting from 0.0885 g (0.25 mmol) of **4b**, 0.0649 g (0.25 mmol) of PPh_3 and 0.0700 g (0.50 mmol) of $NaClO_4{\cdot}H_2O$.

0.1437 g (yield 84%) of **5b** was obtained.

Isomer A/isomer B ≈ 1: 1.25.

^{1}H NMR (300 MHz, $CDCl_3$, T = 298 K, ppm) δ: 7.85 – 7.08 (m, 19H, Ar-H), 6.08 – 5.78 (m, H, *central* allyl-H), 5.08 and 4.77 (sept, *J* = 7.0 Hz, 1H, isopropyl-H), 4.52 and 4.44 (d, *J* = 6.3 Hz, 1H, *syn* allyl-H *trans*-C), 4.10 and 4.00 (dd con J_{HP}, *J* = 8.3 Hz, 1H, *syn* allyl-H *trans*-P), 3.45 – 3.20 (m, 2H, *anti* allyl-H *trans*-C and *anti* allyl-H *trans*-P), 3.47 and 3.26 (s, 3H, NCH_3), 1.62 and 1.55 (d, *J* = 7.0 Hz, 3H, isopropyl-CH_3), 1.15 and 1.08 (d, *J* = 7.0 Hz, 3H, isopropyl-CH_3).

^{31}P{^{1}H}-NMR ($CDCl_3$, T = 298 K, ppm) δ: 25.1 and 25.0

^{13}C{^{1}H}-NMR ($CDCl_3$, T = 298 K, ppm) δ: 187.8 (C, J_{CP} = 18.8 Hz, carbene), 187.7 (C, J_{CP} = 18.7 Hz, carbene), 136.6 (C, Ar-C), 136.5 (C, Ar-C), 132.7 (C, Ar-C), 132.5 (C, Ar-C), 128.4 (CH, Ar-CH), 128.3 (CH, Ar-CH), 123.1 (CH, Ar-CH), 123.0 (CH, Ar-CH), 123.3 (d, J_{CP} = 5.2 Hz, CH, *central* allyl), 112.2 (CH, Ar-CH), 112.1 (CH, benzyl-CH), 110.7 (CH, Ar-CH), 110.6 (CH, Ar-CH), 71.8 (d, J_{CP} = 2.8 Hz, CH_2, allyl *trans*-C), 70.3 (d, J_{CP} = 2.8 Hz, CH_2, allyl *trans*-C), 66.6 (d, J_{CP} = 28.6 Hz, CH_2, allyl *trans*-P), 66.1 (d, J_{CP} = 27.1 Hz, CH_2, allyl *trans*-P), 55.6 (CH, isopropyl-CH), 54.2 (CH, isopropyl-CH), 34.5 (CH_3, NCH_3), 34.2 (CH_3, NCH_3), 21.7 (CH_3, isopropyl-CH_3), 21.5 (CH_3, isopropyl-CH_3), 20.3 (CH_3, isopropyl-CH_3), 20.3 (CH_3, isopropyl-CH_3).

Anal. Calc. for $C_{32}H_{34}ClN_2O_4PPd$: C, 56.23; H, 5.01; N, 4.10. Found: C, 56.09; H, 5.08; N, 4.15%.

4.11.3. Synthesis of complex 5c

Complex **5c** was prepared by a procedure analogous to that described for **5a** starting from 0.0397 g (0.10 mmol) of **4c**, 0.0286 g (0.10 mmol) of PPh_3 and 0.0306 g (0.21 mmol) of $NaClO_4{\cdot}H_2O$.

0.0653 g (yield 86%) of **5c** was obtained.

Isomer A/isomer B ≈ 1: 1.

^{1}H NMR (300 MHz, $CDCl_3$, T = 298 K, ppm) δ: 7.78 – 7.12 (m, 12H, PPh_3, Ar-H), 7.08 – 6.83 (m, 12H, Ar-H), 6.08 and 5.29 (m, 1H, *central* allyl-H), 4.78 and 4.46 (dd, $J_{HH} = J_{HP}$ 5.2 Hz, 1H, *syn* allyl-H *trans*-P), 4.01 and 3.72 (d, $J = 6.3$ Hz, 1H, *syn* allyl-H *trans*-C), 3.87 and 3.78 (s, 3H, NCH_3), 3.72 and 3.25 (d, $J = 13.5$ Hz, 1H, *anti* allyl-H *trans*-C), 2.88 and 2.51 (dd, $J_{HH} = 13.0$, $J_{HP} = 10.0$ Hz, 1H, *anti* allyl-H *trans*-P)).

^{31}P{^{1}H}-NMR ($CDCl_3$, T = 298 K, ppm) δ: 25.2, 25.1.

^{13}C{^{1}H}-NMR ($CDCl_3$, T = 298 K, ppm) δ: 188.9.0, (C, carbene, from HMBC), 189.8 (C, carbene, from HMBC), 137.2 (C, Ar-C), 137.0 (C, Ar-C), 135.3 (C, Ar-C), 135.3 (C, Ar-C), 124.2 (C, Ar-C), 124.1 (CH, Ar-CH), 124.0 (CH, Ar-CH), 123.9 (CH, Ar-CH), 122.3 (d, $J_{CP} = 4.8$ Hz, CH, *central* allyl), 121.3 (CH, d, $J_{CP} = 5.3$ Hz, *central* allyl), 110.8 (CH, Ar-CH), 110.8 (CH, Ar-CH), 110.7 (CH, Ar-CH), 69.4 (CH_2, d, $J_{CP} = 27.8$, allyl *trans*-P), 69.3 (CH_2, allyl *trans*-C), 69.2 (CH_2, allyl *trans*-C), , 68.0 (d, $J_{CP} = 28.8$, CH_2, allyl *trans*-P), 35.4 (CH_3, NCH_3), 35.4 (CH_3, NCH_3).

Anal. Calc. for $C_{35}H_{32}ClN_2O_4PPd$: C, 58.59; H, 4.50; N, 3.90 Found: C, 58.77; H, 4.42; N, 3.95%.

4.11.4. Synthesis of complex 5d

Complex **5d** was prepared by a procedure analogous to that described for **5a** (no further addition of $NaClO_4 \cdot H_2O$ was necessary) starting from 0.0550 g (0.12 mmol) of **3d** and 0.0315 g (0.12 mmol) of PPh_3.

0.0740 g (yield 86%) of **5d** was obtained.

Isomer A/isomer B = 1: 1.25.

^{1}H NMR (300 MHz, $CDCl_3$, T = 243 K, ppm) δ: 8.27 and 8.16 (d, $J =$ 4.1 Hz, 1H, m, 1H, 6-py-H), 7.69 – 7.08 (m, 22H, PPh_3, 4-py-H, 5-py-H, 3-py-H and Ar-H), 5.81 and 5.59 (m, 1H, *central* allyl-H), 5.39 (AB system, $J = 16.2$ Hz, 1H, NCH_2Py) and 5.19 (AB system, $J = 16.2$ Hz, 1H, NCH_2Py), 5.17 (s, 2H, NCH_2Py), 4.44 (dd, $J_{HH} = J_{HP} = 5.8$ Hz, *syn* allyl-H *trans*-P), 4.18 (d, $J = 7.3$ Hz, *syn* allyl-H *trans*-C), 4.16 – 4.06 (m, *syn* allyl-H *trans*-P, *syn* allyl-H *trans*-C), 3.47 and 3.35 (s, 3H, NCH_3), 3.26 and 2.94 (dd, $J_{HH} = 13.4$, $J_{HP} = 9.6$ Hz, 1H, CH *anti* allyl-H *trans*-P), 3.14 and 2.98 (d, $J = 13.4$ Hz, 1H, *anti* allyl-H *trans*-C).

^{31}P{^{1}H}-NMR ($CDCl_3$, T = 243 K, ppm) δ: 26.4, 26.2

^{13}C{^{1}H}-NMR ($CDCl_3$, T = 243 K, ppm) δ: 191.1 (d, $J_{CP} = 8.0$ Hz, C, carbene), 190.0 (d, $J_{CP} = 8.0$ Hz, C, carbene), 155.0 (C, 2-py-C), 154.9 (C, 2-py-C), 149.3 (CH, 6-py-CH), 149.2 (CH, 6-py-CH), 137.2 (CH, 4-py-CH), 137.2 (CH, 4-py-CH), 135.4 (C, Ar-C), 135.2 (C, Ar-C), 135.1 (C, Ar-C), 134.7(C, Ar-C), 131.7 (CH, 3-py-CH), 131.6 (CH, 3-py-CH), 131.2 (CH, 5-py-CH), 131.0 (CH, 5-py-CH), 123.2 (CH, Ar-CH), 122.2 (CH, Ar-CH), 123.9 (CH, Ar-CH), 122.1 (d, CH, $J_{CP} = 4.5$ Hz, *central* allyl), 110.98 (CH, Ar-CH), 110.86 (CH, Ar-CH), 110.58 (CH, Ar-CH), 110.49 (CH, Ar-CH), 68.87 (CH_2, allyl *trans*-C), 68.10 (CH_2, allyl *trans*-C), 67.14 (d, $J_{CP} = 23.0$ Hz, CH_2, allyl *trans*-P), 66.75 (d, $J_{CP} = 23.0$ Hz, CH_2, allyl *trans*-P), 52.96 (CH_2, NCH_2), 52.70 (CH_2, NCH_2), 34.38 (CH_3, NCH_3), 34.27 (CH_3, NCH_3).

Anal. Calc. for $C_{35}H_{33}ClN_3O_4PPd$: C, 57.39; H, 4.54; N, 5.74 Found: C, 57.22; H, 4.48; N, 5.80%.

4.11.5. Synthesis of complex 6a

Complex **6a** was prepared by a procedure analogous to that described for **5a** starting from 0.0561 g (0.17 mmol) of **4a**, 0.0270 g (0.17 mmol) of 1,3,5-triaza-7-phosphaadamantane (PTA) and 0.0490 g (0.34 mmol) of $NaClO_4 \cdot H_2O$.

0.0778 g (yield 82%) of **6a** was obtained.

^{1}H NMR (300 MHz, $CDCl_3$, T = 298 K, ppm) δ: 7.59 – 7.40 (m, 4H, Ar-H), 5.55 (ddd, $J = 21.0$, 13.6, 7.5 Hz, 1H, *central*-allyl-H), 4.67 – 4.43 (m, 6H, PCH_2N), 4.42–4.30 (m, 2H, *syn* allyl-H *trans*-C and *syn* allyl-H *trans*-P), 4.27 (s, 6H, NCH_2N), 4.01 (s, 3H, NCH_3), 3.81 (s, 3H, NCH_3), 3.21–3.02 (m, 2H, *anti* allyl-H *trans*-C and *anti* allyl-H *trans*-P).

^{31}P{^{1}H}-NMR ($CDCl_3$, T = 298 K, ppm) δ: −55.7.

^{13}C{^{1}H}-NMR ($CDCl_3$, T = 298 K, ppm) δ: 187.8 (d, C, $J_{CP} = 20.6$ Hz, carbene), 135.4 (C, Ar-C), 135.3 (C, Ar-C), 123.8 (CH, Ar-CH), 123.8 (CH, Ar-CH), 121.7 (d, $J_{CP} = 5.3$ Hz, CH, *central* allyl), 110.5 (CH, Ar-CH), 110.4 (CH, Ar-CH), 73.1 (d, $J_{CP} = 7.2$ Hz, CH_2, PCH_2N), 67.7 (d, $J_{CP} = 27.4$ Hz, CH_2, allyl *trans*-P), 63.00 (CH_2, allyl *trans*-C), 52.8 (d, $J_{CP} = 12.4$ Hz, NCH_2N), 35.1 (CH_3, NCH_3), 34.8 (CH_3, NCH_3).

Anal. Calc. for $C_{18}H_{27}ClN_5O_4PPd$: C, 39.29; H, 4.95; N, 12.73 Found: C, 39.44; H, 4.87; N, 12.64%.

4.11.6. Synthesis of complex 6b

Complex **6b** was prepared by a procedure analogous to that described for **6a** starting from 0.0547 g (0.15 mmol) of **4b**, 0.0242 g (0.15 mmol) of 1,3,5-triaza-7-phosphaadamantane (PTA) and 0.0460 g (0.30 mmol) of $NaClO_4 \cdot H_2O$.

0.0786 g (yield 89%) of **6b** was obtained.

Isomer A/isomer B ≈ 1: 1.

^{1}H NMR (300 MHz, $CDCl_3$, T = 298 K, ppm) δ: 7.73 – 7.30 (m, 4H, Ar-H), 5.68–5.41 (m, 1H, *central* allyl-H), 5.06 (sept, $J = 6.9$ Hz, 1H, isopropyl-H), 4.83 – 4.66 (m, 1H, isopropyl-H), 4.68 – 4.46 (m, 6H, PCH_2N), 4.40–4.30 (m, 2H, *syn* allyl-H *trans*-P, *syn* allyl-H *trans*-C), 4.31 (s, 6H, NCH_2N), 4.01 and 3.79 (s, 3H, NCH_3), 3.25 – 3.00 (m, 2H, *anti* allyl-H *trans*-P, *anti* allyl-H *trans*-C), 1.83 and 1.71 (d, $J = 7.0$ Hz, 3H, isopropyl-CH_3), 1.62 and 1.55 (d, $J = 6.9$ Hz, 3H, isopropyl-CH_3).

^{31}P{^{1}H}-NMR ($CDCl_3$, T = 298 K, ppm) δ: −56.3, −56.6.

^{13}C{^{1}H}-NMR ($CDCl_3$, T = 298 K, ppm) δ: 186.2 (C, carbene, from HMBC), 186.1 (C, carbene, from HMBC), 136.6 (C, Ar-C), 136.4 (C, Ar-C), 132.9 (C, Ar-C), 132.7 (C, Ar-C), 123.6 (CH, Ar-CH), 123.5 (CH, Ar-CH), 123.4 (CH, Ar-CH), 121.8 (d, $J_{CP} = 5.1$ Hz, CH, *central* allyl), 121.5 (d, $J_{CP} = 5.2$ Hz, CH, *central* allyl), 112.6 (CH, Ar-CH), 112.2 (CH, Ar-CH), 111.0 (CH, Ar-CH), 110.9 (CH, Ar-CH), 73.1 (d, $J_{CP} = 7.1$ Hz, CH_2, NCH_2N), 67.9 (d, $J_{CP} = 5.3$ Hz, CH_2, allyl *trans*-P), 67.6 (d, $J_{CP} = 5.5$ Hz, CH_2, allyl *trans*-P), 63.2 (CH_2, allyl *trans*-C), 63.0 (CH_2, allyl *trans*-C), 54.8 (CH, isopropyl-CH), 54.1 (CH, isopropyl-CH), 53.0 (d, $J_{CP} = 12.2$ Hz, PCH_2N), 35.2 (CH_3, NCH_3), 34.8 (CH_3, NCH_3), 21.7 (CH_3, isopropyl-CH_3), 21.7 (CH_3, isopropyl-CH_3), 21.6 (CH_3, isopropyl-CH_3), 21.5 (CH_3, isopropyl-CH_3).

Anal. Calc. for $C_{20}H_{31}ClN_5O_4PPd$: C, 41.54; H, 5.40; N, 12.11 Found: C, 41.69; H, 5.28; N, 12.03%.

4.12. Cell viability assays

Cells were grown in accordance with the supplier and maintained at 37 °C in a humidified atmosphere of 5% carbon dioxide. Five hundred cells were placed in 96 wells and treated with six different concentrations (0.001, 0.01, 0.1, 1, 10 and 100 μM) of palladium(II) compounds. After 96 h from the treatment cell viability was measured with a CellTiter glow assay (Promega, Madison, WI, USA) with a Tecan M1000 instrument. IC_{50} values were calculated from logistical dose response curves. Averages were obtained from triplicates and error bars are standard deviations.

4.13. Crystal structure determination

The **5c** crystal data were collected at 100 K at the XRD2 beamline of the Elettra Synchrotron, Trieste (Italy) [21], using a monochromatic wavelength of 0.620 Å. The data sets were integrated and corrected for Lorentz, absorption and polarization effects using XDS package [22]. The structures were solved by direct methods using SHELXT program [23] and refined using full-matrix least-squares implemented in SHELXL–2018/3 [24].

Thermal motions for all non-hydrogen atoms have been treated anisotropically and hydrogens have been included on calculated positions, riding on their carrier atoms. Geometric restrains (SAME) have been applied to disordered ClO_4^- counterions. No solvent molecules have been found in the crystal packing. The Coot program was used for structure building [25]. The crystal data are given in Table S1. Pictures were prepared using Ortep3 [26] and Pymol [27] softwares.

Crystallographic data has been deposited at the Cambridge Crystallographic Data Centre and allocated the deposition number CCDC 2091479. These data can be obtained free of charge via https://www.

5. Authorship statement

Manuscript title: Synthesis, characterization and anticancer activity of Palladium allyl complexes bearing benzimidazole-based *N*-heterocyclic carbene (NHC) ligands

- Conception and design of study: Thomas Scattolin, Fabiano Visentin and Flavio Rizzolio
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- Drafting the manuscript: Thomas Scattolin
- Revising the manuscript critically for important intellectual content: Fabiano Visentin and Flavio Rizzolio

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] E. Vitaku, D.T. Smith, J.T. Njardarson, J. Med. Chem. 57 (2014) 10257–10274.
[2] M. Gaba, S. Singh, C. Mohan, Eur. J. Med. Chem. 76 (2014) 494–505.
[3] A.M. Ganie, A.M. Dar, F.A. Khan, B.A. Dar, Mini-Rev. Med. Chem. 19 (2019) 1292–1297.
[4] U.J. Ries, G. Mihm, B. Narr, K.M. Hasselbach, H. Wittneben, M. Entzeroth, J.C. van Meel, W. Wienen, N.H. Hauel, J. Med. Chem. 36 (1993) 4040–4051.
[5] M.J. Akhtar, Y.M. Shahar, V.K. Sharma, A.A. Khan, Z. Ali, M.R. Haider, A. Pathak, Curr. Med. Chem. 27 (2020) 5970–6014.
[6] D.J. Carini, J.V. Duncia, P.E. Aldrich, A.T. Chiu, A.L. Johnson, M.E. Pierce, W. A. Price, J.B. Santella III, G.J. Wells, R.R. Wexler, P.C. Wong, S.-E. Yoo, P.B.M.W. M. Timmermans, J. Med. Chem. 34 (1991) 2525–2547.
[7] D.S. Strand, D. Kim, D.A. Peura, Gut Liver 11 (2017) 27–37.
[8] J. Li, X. Chen, X. Ding, Y. Cheng, B. Zhao, Z.-C. Lai, K. Al Hezaimi, R. Hakem, K.-L. Guan, C.-Y. Wang, Cell Rep. 5 (2013) 1650–1663.
[9] B. B. Hasinoff, X. Wu, J. L. Nitiss, R. Kanagasabai, J. C. Yalowich.
[10] Biochem. Pharmacol. 84 (2012) 1617–1626.
[11] (a) T. Scattolin, S.P. Nolan, Trends Chem. 2 (2020) 721–736;
(b) S. Díez-González, N. Marion, S.P. Nolan, Chem. Rev. 109 (2009) 3612–3676;
(c) K.V.S. Ranganath, S. Onitsuka, A.K. Kumar, J. Inanaga, Catal. Sci. Technol. 3 (2013) 2161–2181.
[12] (a) A. Valentini, F. Conforti, A. Crispini, A. De Martino, R. Condello, C. Stellitano, G. Rotillo, M. Ghedini, G. Federici, S. Bernardini, D. Pucci, J. Med. Chem. 52 (2009) 484–491;
(b) A. Monney, M. Albrecht, Coord. Chem. Rev. 257 (2013) 2420–2433;
(c) M. Tanaka, H. Kataoka, S. Yano, H. Ohi, K. Kawamoto, T. Shibahara, T. Mizoshita, Y. Mori, S. Tanida, T. Kamiya, T. Joh, BMC Cancer 13 (2013) 237–245.
[13] (a) P.N. Muskawar, P. Karthikeyan, S.A. Aswar, P.R. Bhagat, S.S. Kumar, Arab. J. Chem. 9 (2016) S1765–S1778;
(b) U.F.M. Haziz, R.A. Haque, A.-A.-A. Abdullah, M.R. Razali, J. Coord. Chem. 73 (2020) 2698–2717;
(c) T.A.C.A. Bayrakdar, T. Scattolin, X. Ma, S.P. Nolan, Chem. Soc. Rev. 49 (2020) 7044–7100.
[14] (a) T. Scattolin, V.A. Voloshkin, F. Visentin, S.P. Nolan, Cell Rep. Phys. Sci. (2021), https://doi.org/10.1016/j.xcrp.2021.100446;
(b) T. Scattolin, E. Bortolamiol, S. Palazzolo, I. Caligiuri, T. Perin, V. Canzonieri, N. Demitri, F. Rizzolio, L. Cavallo, B. Dereli, M.V. Mane, S.P. Nolan, F. Visentin, Chem. Commun. 56 (2020) 12238–12241;
(c) T. Scattolin, N. Pangerc, I. Lampronti, C. Tupini, R. Gambari, L. Marvelli, F. Rizzolio, N. Demitri, L. Canovese, F. Visentin, J. Organomet. Chem. 899 (2019), 120857;
(d) T. Scattolin, S. Giust, P. Bergamini, I. Caligiuri, L. Canovese, N. Demitri, R. Gambari, I. Lampronti, F. Rizzolio, F. Visentin, Appl. Organomet. Chem. 33 (2019), e4902;
(e) T. Scattolin, I. Caligiuri, N. Mouawad, M. El Boustani, N. Demitri, F. Rizzolio, F. Visentin, Eur. J. Med. Chem. 179 (2019) 325–334.
[15] (a) I. Al Nasr, N. Touj, W. Koko, T. Khan, I. Özdemir, S. Yasar, N. Hamdi, Catalysts 10 (2020), 1190; (b) M. A. Bernd, E. B. Bauer, J. Oberkofler, A. Bauer, R. M. Reich, F. E. Kühn, Dalton Trans. 49 (2020) 14106–14114; (c) T. Scattolin, E. Bortolamiol, F. Visentin, S. Palazzolo, I. Caligiuri, T. Perin, V. Canzonieri, N. Demitri, F. Rizzolio, A. Togni, Chem. Eur. J. 26 (2020) 11868–11876.
[16] (a) T. Scattolin, I. Caligiuri, L. Canovese, N. Demitri, R. Gambari, I. Lampronti, F. Rizzolio, C. Santo, F. Visentin, Dalton Trans. 47 (2018) 13616–13630;
(b) T. Scattolin, E. Bortolamiol, F. Rizzolio, N. Demitri, F. Visentin, Appl. Organomet. Chem. 34 (2020), e5876;
(c) T. Scattolin, E. Bortolamiol, I. Caligiuri, F. Rizzolio, N. Demitri, F. Visentin, Polyhedron 186 (2020), 114607.
[17] (a) N.A. Meanwell, J. Med. Chem. 54 (2010) 2529–2591;
(b) J. Wang, M. Sánchez-Roselló, J.L. Aceña, E. Al, Chem. Rev. 114 (2014) (2014) 2432–2506;
(c) S. Purser, P.R. Moore, S. Swallow, V. Gouverneur, Chem. Soc. Rev. 37 (2008) 320–330.
[18] A. Simoens, T. Scattolin, T. Cauwenbergh, G. Pisanó, C.S.J. Cazin, C.V. Stevens, S. P. Nolan, Chem. Eur. J. 27 (2021) 5653–5657.
[19] M.J. Saif, K.R. Flower, Transit. Met. Chem. 38 (2013) 113–118.
[20] M. Takashi, H. Yoshikazu, S. Hiroaki, S. Masami, F. Tsutomu, Synlett. 4 (2008) 614–620.
[21] G.F. Raenko, N.I. Korotkikh, T.M. Pekhtereva, O.P. Shvaika, Russ. J. Org. Chem. 37 (2001) 1153–1157.
[22] A. Lausi, M. Polentarutti, S. Onesti, J. R. Plaisier, E. Busetto, G. Bais, L. Barba, A. Cassetta, G. Campi, D. Lamba, A. Pifferi, S. C. Mande, D. D. Sarma, S. M. Sharma, G. Paolucci, Eur. Phys. J. Plus 130 (2015) 1–8.
[23] W. Kabsch, XDS, Acta Crystallographica Section D 66 (2010) 125–132.
[24] G.M. Sheldrick, Acta Crystallogr. Section A 71 (2015) 3–8.
[25] P. Emsley, B. Lohkamp, W. Scott, K. Cowtan, Acta Crystallogr. Section D 66 (2010) 486–501.
[26] L. Farrugia, J. Appl. Crystallogr. 45 (4) (2012) 849+854.
[27] L. Schrodinger, The PyMOL Molecular Graphics System (2015), http://www.pymol.org.