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Biological and Catalytic Applications of Pd(II)-Indenyl Complexes Bearing Phosphine and *N*-Heterocyclic Carbene Ligands

Enrica Bortolamiol,[a] Giacomo Isetta,[a] Isabella Caligiuri,[b] Nicola Demitri,[c] Stefano Paganelli,[a] Flavio Rizzolio,[a, b] Thomas Scattolin,*[d] and Fabiano Visentin*[a]

A general synthetic entryway into novel cationic Pd(II) indenyl complexes bearing one alkyl/aryl phosphine and one *N*-heterocyclic carbene is reported. All metal complexes have been exhaustively characterized by spectroscopic and structural analyses, highlighting that the indenyl fragment has an hapticity intermediate between η^3 and η^5. Most of the target complexes are stable in solid state and in solution for a long time. Two different applications of these organopalladium compounds are proposed. Firstly, they have been tested as antiproliferative agents towards three different ovarian cancer cell lines, showing a cytotoxicity significantly higher than that of cisplatin, with a clear dependence on the nature of the coordinated phosphine. Moreover, the similar cytotoxicity towards cisplatin-sensitive and cisplatin-resistant cell lines suggests that these new palladium derivatives act with a different mechanism of action with respect to classical platinum-based drugs.
Finally, the water-soluble palladium complexes bearing 1,3,5-triaza-7-phosphaadamantane (PTA) have demonstrated interesting catalytic performances in Suzuki–Miyaura coupling in aqueous media, being, inter alia, readily and efficiently recyclable.

Introduction

The possibility to choose from a wide range of ancillary ligands is one of the most important opportunities offered to organometallic chemists to design novel compounds, giving them the best features for a specific use.[1] The nature of ancillary ligands can in fact contributes to predetermining the electronic density on the metal centre and consequently on the bonded organic fragment, creating the steric conditions to promote specific regio- and/or stereo-selective attacks to actor ligands and finally affecting the solubility of the complex in solvents with different polarity. It is beyond dispute that phosphines and *N*-heterocyclic carbenes (NHCs) are the ancillary ligands more widely employed to prepare organometallic complexes because of their large tunability. It is well-known that the proper selection of phosphorous substituents can finely determine the steric hindrance and electron-donating or electron-withdrawing character of monodentate phosphines, and many theoretical and experimental parameters have been defined for quantifying these features.[2] Even more numerous are the factors that allow to adjust the steric and electronic characteristics of *N*-heterocyclic carbenes. It is possible to act on the nature of *N*-substituents, the ring size and ring substituents as well as the aromaticity degree of the backbone.[3] Again, different methods have been also recently proposed to assess the steric and electronic properties of this important class of compounds.[4] Based on these assumptions, vast libraries of the two families of ligands have been set up and implemented over the time, by making it possible to choose the most suitable ligand for a certain purpose. However, phosphines and *N*-heterocyclic carbenes have almost always been considered as alternative ligands for the preparation of palladium organometallic complexes, and much more rarely have been used in combination seeking to take advantage from their respective qualities.[5] In recent times, our research group and other authors have addressed the issue of selectively obtain organopalladium derivatives coordinating both one phosphine and one *N*-heterocyclic carbene,[6] proving that in many cases this option is thermody-

[a] E. Bortolamiol, G. Isetta, Prof. Dr. S. Paganelli, Prof. Dr. F. Rizzolio, Prof. Dr. F. Visentin
Department of Molecular Sciences and Nanosystems
Università Ca' Foscari
Campus Scientifico Via Torino 155, 30174 Venezia-Mestre (Italy)
E-mail: fvise@unive.it
[b] I. Caligiuri, Prof. Dr. F. Rizzolio
Pathology Unit
Department of Molecular Biology and Translational Research
Centro di Riferimento Oncologico di Aviano (CRO) IRCCS
via Franco Gallini 2, 33081 Aviano (Italy)
[c] Dr. N. Demitri
Elettra-Sincrotrone Trieste
Area Science Park, S.S. 14 Km 163.5, Basovizza, 34149 Trieste (Italy)
[d] Dr. T. Scattolin
Dipartimento di Scienze Chimiche
Università degli Studi di Padova
via Marzolo 1, 35131 Padova (Italy)
E-mail: thomas.scattolin@unipd.it
http://www.organometallics.it

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namically preferred over the alternative consisting of the mixture of the two complexes bearing two phosphines and two *N*-heterocyclic carbenes, respectively. In Scheme 1 are depicted the classes of palladium compounds that we were able to successfully synthesize. As can be seen, when two mutually *cis*-coordination sites are occupied by an organic fragment, many combinations of phosphines and NHCs afforded stable Pd(II) and Pd(0) complexes.

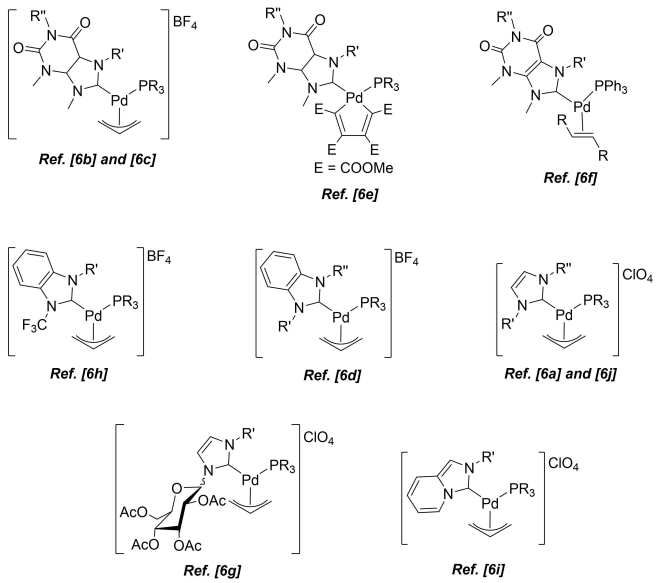
Many of the complexes reported in Scheme 1 have proven some interesting properties that could be exploited to promote catalytic processes or inhibit specific mechanisms of tumor cells proliferation. More in detail, palladium(II)-allyl complexes bearing one purine-based NHC and one TPPTS (3,3′,3′′-phosphinetriyltribenzenesulfonate), showed good catalytic performances in Suzuki–Miyaura coupling in aqueous media without the addition of any auxiliary organic solvent.[6b] Regarding instead the biological activity of the palladium complexes illustrated in Scheme 1, most of them have been tested *in vitro* as anticancer agents.[6c–i] Based on the results obtained, it could be established that, for the same organometallic fragment, the simultaneous presence of one phosphine and one NHC as ancillary ligands generally provides the most encouraging results. For example, palladium(II) allyl complexes coordinating one *N*-trifluoromethyl heterocyclic carbene and PTA (1,3,5-triaza-7-phosphaadamantane) can induce an high and selective antiproliferative activity towards ovarian cancer cells.[6h] Interestingly, an excellent cytotoxicity was also observed on more complex cellular structures such as tumoroids extracted from high-serous ovarian cancer patients. Notably, the mechanism of action of this peculiar family of palladium complexes seems to involve an early mitochondrial damage rather than the classical DNA metallation process. The particularly promising results obtained with palladium(II)-allyl derivatives have prompted us to turn our attention to the much less explored class of palladium(II) indenyl complexes that, while showing some undoubted similarities, nevertheless have some specific features that could differentiate their behaviour. The most significant difference between the two categories of organopalladium compounds is represented by the possibility of indenyl fragment to coordinate the metal centre with an η^5 hapticity (or at least intermediate between η^5 and η^3), an option that is obviously precluded to the allyl fragment.[7] For this reason, the Pd(II)-indenyl moiety presents an higher coordinative saturation and is less susceptible to nucleophilic attack than the Pd(II)-allyl one. In this context, we have recently reported the first systematic study dealing with the reactivity and antitumor activity of a large library of palladium(II) indenyl complexes bearing monodentate or bidentate phosphine ligands, showing the significant influence of steric and electronic parameters of the employed phosphines on the behaviour of the target organopalladium compounds.[8] We believe that the interesting biological results exposed in our first contribution can be a good starting point to make targeted changes in the coordinative sphere of palladium in order to improve the anticancer properties of Pd(II)-indenyl complexes. For this purpose, in this paper we have prepared a selection of palladium(II) indenyl complexes coordinating one phosphine and one *N*-heterocyclic carbene ligand. The novel complexes have been tested as antiproliferative agents towards different ovarian cancer cell lines and two of the synthesized complexes have been assessed as catalysts for Suzuki–Miyaura cross-coupling in aqueous media.

Results and Discussion

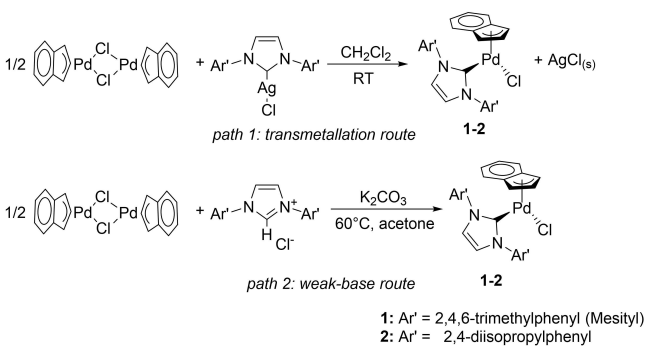
Synthesis of neutral palladium-indenyl complexes

The synthetic strategy used to prepare the desired mixed NHC/phosphine palladium(II) indenyl complexes includes the preliminary passage through the neutral species [PdCl(NHC)(indenyl)]. The latter can be easily obtained starting from the dimeric precursor $[Pd(\mu\text{-}Cl)(indenyl)]_2$ by alternatively choosing one of the two synthetic routes depicted in Scheme 2.

The first route (path 1) involves the "classical" transmetallation reaction, with a complete transfer of the NHC ligand from



Scheme 1. Classes of organopalladium complexes bearing phosphine and NHC ligands synthesized by our research group.



Scheme 2. Synthetic procedures to neutral [PdCl(NHC)indenyl] complexes.

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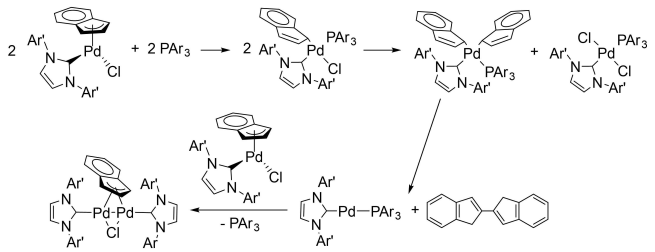
silver(I) to palladium(II) metal centres, which is thermodynamically favoured by silver chloride precipitation.[9] The second approach (path 2), known as *weak base route*,[10] is currently the most direct and sustainable method to achieve late transition metal-NHC complexes. With the sterically demanding IMes and IPr carbene ligands, we have verified that the two procedures give comparable yields, and therefore the second route should be preferable since avoids the use of expensive silver reactants and operates under aerobic conditions in the presence of non-anhydrous solvents and an inexpensive weak base such as potassium carbonate. Unlike [PdCl(IPr)(indenyl)] (**2**) (Figure S3 in Supporting Information), the complex [PdCl(IMes)(indenyl)] (**1**) has never been described in the literature, and so it is appropriate to report its complete characterization. As expected, 7 and 9 different signals ascribable to the indenyl fragment are present in ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra, respectively (Figures S1–S2 in Supporting Information). Also, the typical signals of coordinated IMes are easily identifiable and among them, that of the carbene carbon is located at 173 ppm in the $^{13}C\{^{1}H\}$ NMR spectrum. Remarkably, the presence of only one signal for the two *p*-methyl substituents, and only two for the four *o*-methyl substituents of the mesityl rings prove the free rotation around the Pd–NHC bond and the hindered rotation around *N*–$C_{mesityl}$ bonds.

Synthesis of mixed (hetero)aryl phosphine/NHC palladium(II) indenyl complexes

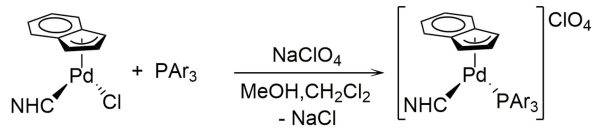
The easily synthesized neutral complexes [PdCl(IMes)(indenyl)] **1** and [PdCl(IPr)(indenyl)] **2** are definitely the most suitable intermediates to prepare the target complexes. However, the introduction of the phosphine in the palladium coordination sphere is not a trivial process and requires a few precautions. The main problem is that the simple stoichiometric addition of the phosphine to a solution of complexes **1** or **2** can activate a cascade process that ultimately generates the side-products displayed in Scheme 3.

This behaviour had already been observed by us and by Zargarian group in similar systems.[7a,8] In order to overcome this contraindication, it is necessary to remove the chloride ligand before adding the desired phosphine. In a previous work we had experienced the possibility to achieve this goal using sodium perchlorate ($NaClO_4$), dissolved in a dichloromethane/methanol solution, as dechlorinating agent in place of the classical silver salts.[8] Therefore, we tried to reproduce that synthetic protocol also in this case, obtaining good results (Scheme 4).

The library of the selected phosphines encompasses *para*-substituted phenyl and heteroaromatic derivatives. All complexes listed in Scheme 4 have been obtained in high yields, after being easily separated from the reaction mixture by precipitation with diethyl ether. Their identity can be promptly ascertained by examining their NMR spectra (Figures S4–S35 in Supporting Information). All $^{31}P\{^{1}H\}$ NMR spectra are characterized by the presence of only one peak that always falls at a higher chemical shift ($\Delta\delta \approx 20$–30 ppm) than that of the free phosphine, thus proving its coordination on palladium. The only exception to this general trend is represented by complex **3 g**, for which the coordination on the metal centre of 2-trifurylphosphine lowers the chemical shift of the peak in the $^{31}P\{^{1}H\}$ NMR spectrum of about 19 ppm, confirming a behaviour already previously observed in other contributions.[8,11] Moreover, the $^{19}F\{^{1}H\}$ NMR spectra of complexes **3 c**–**d**, equipped with fluorinated phosphines, show the signal of *para* substituents. In the ^{1}H and $^{13}C\{^{1}H\}$ NMR spectra, all the peaks attributable to coordinate *N*-heterocyclic carbene can be easily identified, with the signal of the carbene carbon that resonates as a doublet (at ca. 170 ppm) due to the coupling with phosphorus. The presence of two different ligands in the palladium coordination sphere differentiates the seven protons and the nine carbons of indenyl fragment. Remarkably, the signals of H^{1} and C^{1} (*trans* to the carbene) always fall at significant lower chemical shift than H^{3} and C^{3} (*trans* to the phosphine). The positions of the two ring junction carbons C^{3a} and C^{7a} are instead fundamental to define the hapticity of the indenyl fragment, according to the model proposed by Baker and Tulip.[12] The values of $\Delta\delta$ (difference between the average chemical shift of C^{3a} and C^{7a} and that of the reference compound NaInd, amounting to 130.7 ppm) are ranged between 3.6 and 4.7 ppm (see Table S11 in Supporting Information) proving that the hapticity of the indenyl fragment in this class of complexes can be deemed intermediate between η^3 and η^5, with a slight preference for the first one.[13] This binding mode is also supported by the structural data obtained



Scheme 3. Cascade reactions in absence of dechlorinating agent.



1: NHC = IMes
2: NHC = IPr

3a: $PAr_3 = PPh_3$	NHC = IMes
3b: $PAr_3 = P(p\text{-}Cl\text{-}C_6H_4)_3$	NHC = IMes
3c: $PAr_3 = P(p\text{-}F\text{-}C_6H_4)_3$	NHC = IMes
3d: $PAr_3 = P(p\text{-}CF_3\text{-}C_6H_4)_3$	NHC = IMes
3e: $PAr_3 = P(p\text{-}OMe\text{-}C_6H_4)_3$	NHC = IMes
3f: $PAr_3 = P(Ph)_2(2\text{-}Py)$	NHC = IMes
3g: $PAr_3 = P(2\text{-}furyl)_3$	NHC = IMes
4d: $PAr_3 = P(p\text{-}CF_3\text{-}C_6H_4)_3$	NHC = IPr

Scheme 4. Preparation of Pd(II)-indenyl complexes bearing monodentate (hetero)aryl phosphines and NHC ligands.

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by single crystal X-ray diffraction of complexes **3 b**, **3 c** and **3 e** (Figure 1 and Figures S45, S47 in Supporting Information). The resulting values of structural parameters such as ΔM–C, hinge and fold angles (HA and FA)[14] are always between 0.360–0.385 Å, 14.5°–15.2° and 13.9°–14.8°, respectively (see Tables S10, S4, S5 in Supporting Information), thus suggesting that the η^3/η^5 intermediate hapticity of the indenyl fragment is maintained also in the solid state. A more detailed description of the structural features of the three complexes is reported in Supporting Information. The fluxional behaviour of these new palladium derivatives deserves to be briefly described. At room temperature, complexes coordinating IMes (**3 a**–**f**) show a free rotation about the Pd–NHC bond and only by cooling at 243 K it can be completely hampered, as witnessed by the number of methyl group signals of mesityl substituents in ^{1}H NMR spectra, that increases from 3 to 6 (see Figures S5, S9, S13, S18, S23 in Supporting Information). In the case of complexes with the bulkier IPr ligand, this free rotation is already prevented at 298 K.

Finally, two intense bands at ca. 1080 and 620 cm^{-1} are present in the IR spectra of all synthesized compounds, thus confirming the presence of ClO_4^- counterion and indirectly the cationic nature of these organopalladium compounds.

Synthesis of mixed PTA/NHC and P(OEt)$_3$/NHC palladium(II) indenyl complexes

With the aim of verifying the versatility of the proposed synthetic procedure, we tried to prepare some new palladium(II) indenyl complexes bearing, in addition to the NHC, PTA (1,3,5-triaza-7-phosphaadamantane) or P(OEt)$_3$ as phosphorus-based ligands. Both ligands might confer to their complexes features appreciably different from those of the corresponding compounds with (hetero)aryl phosphines previously described. In particular, the water-soluble PTA could help to increase the hydrophilicity of the palladium derivatives, thus improving their compatibility with the biological environment[6e,h,15] or for their use as potential homogeneous catalysts in water.[16] Scheme 5 shows the reactions carried out and the obtained yields.

These new complexes have been readily isolated and easily characterized by NMR spectroscopy (Figures S36–S44 in Supporting Information). The $^{31}P\{^1H\}$ NMR spectra are all featured by the presence of only one peak always localised at chemical shift significantly higher than in the case of the corresponding free phosphine ($\Delta\delta \approx 50$ ppm for complexes **5** and **6** coordinating PTA, and $\Delta\delta \approx 20$ ppm for complex **7** bearing P(OEt)$_3$). Accordingly, the signals of methylene (PCH_2N and NCH_2N) protons and carbons in the case of complexes with PTA, and those ones of ethyl group for the complex with P(OEt)$_3$, are easily identifiable in the ^{1}H and $^{13}C\{1H\}$ NMR spectra. The coordination of the phosphines is also indirectly proven by the doubling of the peak ascribable to carbene carbon (resonating at ca. 170 ppm, due to the coupling with phosphorus). Again, the indenyl protons and carbons are all magnetically different but with respect to the cases discussed in the previous paragraph, the signals of H^3 and H^1 protons resonate at chemical shifts closer to each other (especially for the complexes with PTA), whereas the distance between the peaks of C^3 and C^1 increases, with the latter carbon that is particularly highfield shifted (ca. 75 ppm). Finally, also for these complexes the position of C^{3a} and C^{7a} suggests an hapticity intermediate between η^3 and η^5 for the indenyl fragment (see Table S11 in Supporting Information). The identity of the three synthesized compounds is further confirmed by their solid-state structures obtained by single crystal X-ray diffraction (Figure 2 and Figures S45–46 in Supporting Information), proving the attitude of the indenyl fragment to assume an hapticity between η^3 and η^5 (see Tables S3 and S6–S9 in Supporting Information).

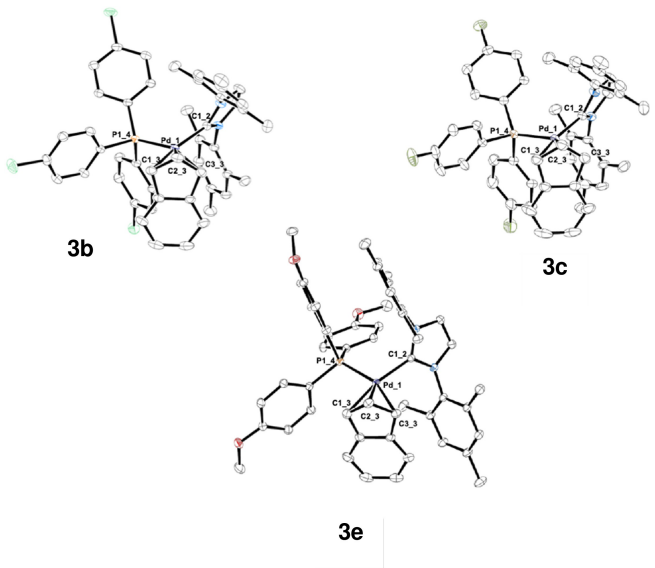
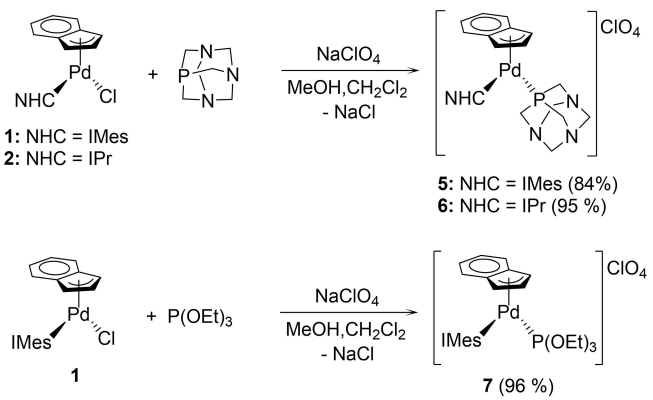


Figure 1. X-ray structures of **3 b** (left) and **3 c** (right) and **3 e** (down) with perchlorate counterions and hydrogen atoms omitted for clarity.



Scheme 5. Preparation of Pd(II)-indenyl complexes bearing PTA or P(OEt)$_3$ and NHC ligands.

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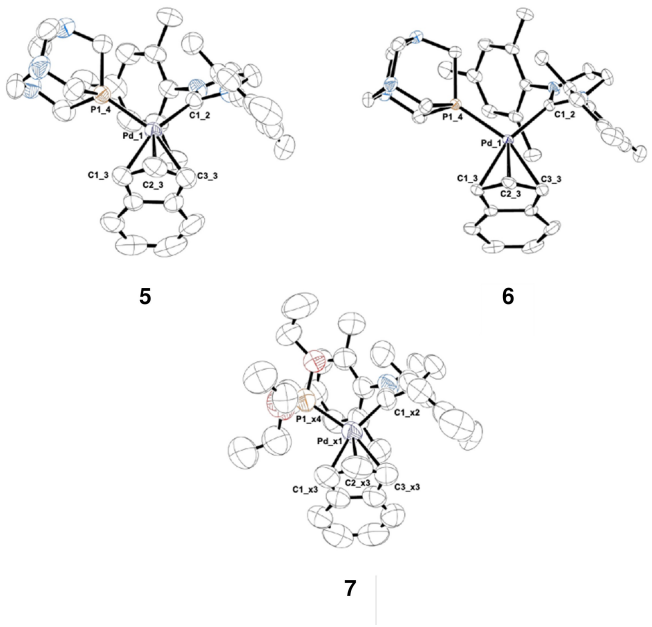

Figure 2. X-ray structures of **5** (left) and **6** (right) and **7** (down) with perchlorate counterions and hydrogen atoms omitted for clarity.

Table 1. IC_{50} (μM) on cancer and normal cell lines.

Complex	A2780	A2780*cis*	OVCAR-5	MRC-5
Cisplatin	1.6 ± 0.1	20 ± 3	3 ± 1	6.1 ± 0.2
3 b	0.28 ± 0.05	0.23 ± 0.09	1.3 ± 0.4	0.61 ± 0.04
3 d	0.08 ± 0.04	0.02 ± 0.01	1.3 ± 0.6	0.4 ± 0.1
3 e	0.015 ± 0.001	0.024 ± 0.003	0.22 ± 0.02	0.013 ± 0.002
3 f	0.025 ± 0.003	0.016 ± 0.008	0.13 ± 0.03	0.11 ± 0.07
3 g	0.004 ± 0.001	0.02 ± 0.01	0.21 ± 0.03	0.024 ± 0.006
4 d	0.11 ± 0.06	0.04 ± 0.01	3.7 ± 0.2	1.2 ± 0.2
5	0.30 ± 0.03	2.2 ± 0.1	3.1 ± 0.3	0.6 ± 0.1
6	0.32 ± 0.05	2.1 ± 0.3	2.8 ± 0.4	0.30 ± 0.03
7	0.008 ± 0.001	0.029 ± 0.007	0.027 ± 0.005	0.005 ± 0.001

Antiproliferative activity on ovarian cancer and normal cell lines

Organopalladium compounds begin to be taken into serious consideration as promising metallodrugs for the treatment of neoplastic pathologies.[17] The presence of the organic fragment usually confers them a further reactivity with potential target biomolecules, reactivity that could be added to the more predictable one with the metal centre. In recent time, also our research group has dealt with this research field, preparing and testing different classes of organopalladium derivatives.[6c–i] In particular, our recent study has revealed the promising anticancer activity of palladium(II) indenyl complexes,[8] and in this work we intend to deepen the issue, investigating the effect of the simultaneous presence of one phosphine and one *N*-heterocyclic carbene as ancillary ligands. Preliminarily to the biological tests, the stability of all complexes has been checked in a DMSO-d_6/D_2O solution by NMR spectroscopy: after 24 h no appreciable degradation has been observed with the only exception of complexes **3 a** and **3 c** that for this reason have been excluded from the screening.

The antitumoral activity of the synthesized complexes has been determined on a panel of three different type of human ovarian cancer cell lines (A2780, A2780*cis* and OVCAR-5) and on MRC-5 normal cells (see Supporting Information for the detailed procedures). It should be recalled that ovarian cancer is a particularly aggressive and lethal form of neoplasia.[18] The resulting half-inhibitory activities (IC_{50}) are summarised in Table 1, together with those obtained for cisplatin (positive control).

The results obtained are interesting and deserve some comments:

(a) All palladium complexes show a high cytotoxicity towards all three ovarian cancer cell lines, in most of the cases much greater than cisplatin, with IC_{50} values always within the micro/nano-molar range.

(b) There does not appear any significant difference between the antiproliferative activity of the complexes towards A2780 cisplatin-sensitive and A2780*cis* cisplatin-resistant cells. This fact suggests that our compounds act with a mechanism of action different from that of classical platinum-based antineoplastic drugs. Notably, the IC_{50} values related to OVCAR-5 cell line are systematically higher, as expected from these more aggressive ovarian tumor cells (classified as high-grade serous ovarian cancer).[19]

(c) Among the complexes bearing (hetero)aryl phosphines, the one bearing a *para*-chloro substituted phosphine (**3 b**), exhibit a slightly lower cytotoxicity on all cell lines tested.

(d) The presence of PTA in the coordination sphere of palladium(II) indenyl complexes (**5**–**6**) seems to induce a general lowering of their cytotoxicity. This effect had already been noted by us for other classes of organopalladium derivatives, and it was basically explained with the lower toxicity of PTA than that of (hetero)aryl phosphines. In fact, it is possible that the mechanism of action of palladium complexes might include the release of the phosphine ligand.

(e) The most active complex is that coordinating triethylphosphite **7**; the IC_{50} values of this compound are generally lower by about an order of magnitude than those recorded in the other cases.

(f) By retaining the same phosphine, a change of NHC ligand (from IMes to IPr) does not result in significant change in antiproliferative activity of the complexes.

(g) Unfortunately, all the new Pd(II) indenyl complexes exhibit an high toxicity even on non-tumor cells MRC-5, therefore showing not particularly selective for cancer cells.

Catalytic activity in Suzuki–Miyaura coupling in aqueous media

As anticipated in the introductory section, palladium–NHC complexes are widely used as well-defined pre-catalysts in several organic transformations.[20] In particular, Hazari and Nolan have recently studied complexes of the type

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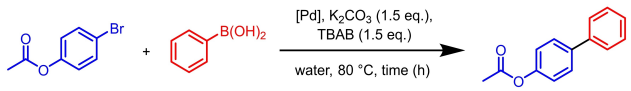
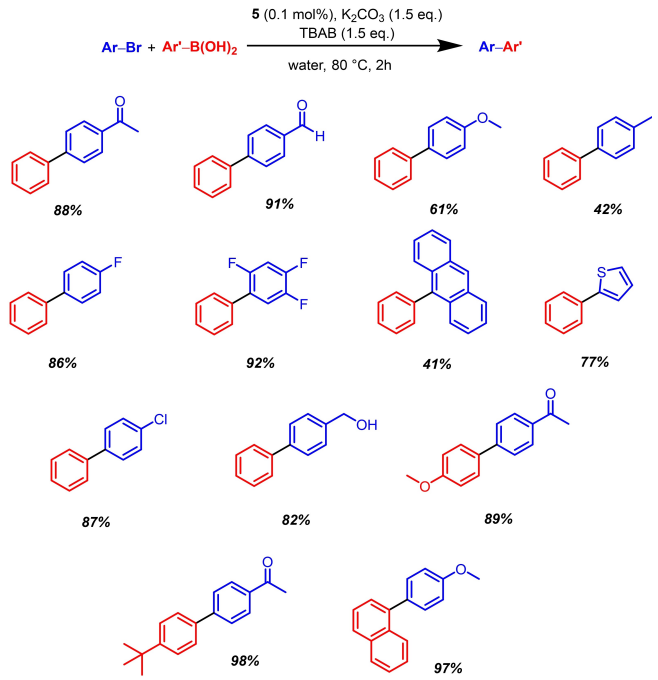
[PdCl(NHC)(1-^{t}Bu-indenyl)] with a wide scope of NHC ligands, as efficient precatalysts in Buchwald–Hartwig and Suzuki–Miyaura couplings in different organic solvents.[21] In this contribution we report the catalytic activity of [Pd(NHC)(PTA)(indenyl)]ClO_4 (NHC=IMes and IPr, **5**–**6**) in aqueous media, taking advantage of the well-known solubility in water of PTA derivatives. More in detail, the Suzuki–Miyaura coupling of aryl bromides was chosen as the model reaction to explore the catalytic activity of the synthesized complexes. Based on the conditions reported by our group in 2018,[6b] the reaction between phenylboronic acid and 4-bromoacetophenone in the presence of **5** or **6**, tetrabutylammonium bromide (TBAB, 1.5 equiv.) and K_2CO_3 (1.5 equiv.) as the base was investigated (Table 2).

Table 2. Reaction conditions for coupling of phenylboronic acid with 4-bromoacetophenone.



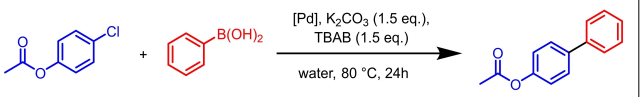
Entry	Cat.	Loading (mol%)	Time (h)	Yield[c] (%)
1[a]	**5**	1.0	21	94
2[a]	**6**	1.0	21	87
3[a]	**5**	0.1	2	88
4[b]	**5**	0.1	2	>99
5[b]	**5**	0.1	2	84
6[b]	**5**	0.1	2	83

[a] Reaction condition: 4-bromoacetophenone (0.5 mmol), phenylboronic acid (0.6 mmol), [Pd(NHC)(PTA)(indenyl)]ClO_4 **5**–**6**, K_2CO_3 (0.75 mmol), TBAB (0.75 mmol) and water (10 mL); [b] The catalyst was recycled from the previous entry, by extracting the target products with ethyl acetate and re-adding the substrates and TBAB; [c] GC yield from the ethyl acetate phase.



Scheme 6. Scope of the Suzuki–Miyaura coupling of aryl bromides catalysed by complex **5**.

Table 3. Reaction conditions for the reaction between phenylboronic acid and 4-chloroacetophenone.



Entry	Cat.	Loading (mol%)	Yield[c] (%)
1[a]	**5**	0.1	34
2[a]	**5**	1.0	77

[a] Reaction condition: 4-chloroacetophenone (0.5 mmol), phenylboronic acid (0.6 mmol), [Pd(IMES)(PTA)(indenyl)]ClO_4 **5**, K_2CO_3 (0.75 mmol), TBAB (0.75 mmol) and water (10 mL); [c] GC yield from the ethyl acetate phase.

When the reaction is carried out at 80 °C for 21 h with a 1% of catalyst loading, the best performance was obtained with complex **5** (yields: 94% vs 87%, see entries 1–2, Table 2). This catalyst was chosen for further tests to verify the efficiency of the system with higher substrate/catalyst ratios and reduced reaction times. Gratifyingly, by operating at 80 °C for 2 h, an excellent yield was achieved even in the presence of 0.1% of **5** (entry 3, Table 2). Because of the high price of palladium and in the aim at achieving a greener process, we investigated the catalyst recyclability. To this end, the target organic products were extracted with ethyl acetate and the catalytic aqueous phase was reused. Interestingly, the performance of the recycled catalyst has remained unaltered in three recycle experiments (entries 4–6, Table 2). Taking advantage of these optimal conditions, we examined the scope of substrates using 9 different aryl bromides and 4 different arylboronic acids (Scheme 6).

Although the reaction outcome is negatively influenced by the presence of electron-donor substituents in the aryl bromide moiety, most of the products were obtained in excellent yields, thus confirming the efficiency and versatility of this catalytic system in eco-friendly aqueous conditions. Preliminary results demonstrated the possibility of using the more challenging aryl chlorides as substrates. In fact, by operating at 80 °C for 24 h, discrete to excellent yields were obtained by reacting 4-chloroacetophenone and phenylboronic acid with 0.1% and 1% loadings of **5**, respectively (entries 1–2, Table 3).

Taking advantage of the conditions reported in Entry 2, we examined the scope of substrates using two additional aryl chlorides such as 4-chlorobenzaldehyde and 1-chloro-4-(trifluoromethyl)benzene. Operating at 80 °C for 24 h with 1% loading of **5**, the desired coupling products were obtained in good to excellent yields (95 and 58%, respectively).

Conclusions

In this work we have prepared a new class of cationic palladium complexes characterised by the presence of the Pd(II)-indenyl organometallic fragment, one *N*-heterocyclic carbene and one phosphine. The developed synthetic protocol has allowed to selectively obtain and in good yields the desired products, which have been completely characterised. In particular, structural and spectroscopic analyses have highlighted that in

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all compounds the indenyl fragment has always an hapticity intermediate between η^3 and η^5, a fact that together with the coordinative efficiency of the ancillary ligands ensures the elevate stability of the target complexes. These novel palladium-indenyl derivatives have shown some interesting biological and catalytic properties. More specifically, they have proven to be efficient antiproliferative agents towards three different ovarian cancer cell lines, with IC_{50} values always within the micro/nano-molar range, showing slightly better performances than palladium(II) indenyl complexes bearing two phosphine ligands previously studied.[8] The cytotoxicity seems to moderately depend on the type of the phosphine ligand with the lowest activity in the case of PTA derivatives and the highest for the complex bearing $P(OEt)_3$. Moreover, it should be emphasized that the antiproliferative activity of all complexes is practically the same towards A2780 (cisplatin-sensitive) and A2780*cis* (cisplatin-resistant) cells, suggesting a mechanism of action different from that of platinum-based drugs. Unfortunately, the synthesized complexes also exhibit a high cytotoxicity against MRC-5 normal cells, and therefore any possible therapeutic use of these compounds should include an efficient drug delivery system.

These palladium(II) indenyl complexes can also be harnessed to promote specific catalytic processes. In particular, compound **5**, which bears the water-soluble PTA as ancillary ligand, has been successfully applied as well-defined catalyst for Suzuki–Miyaura coupling in aqueous media. In addition to the good effectiveness shown on a large library of aryl bromides and, slightly forcing the working conditions, with the more challenging 4-chloroacetophenone, the catalyst is also readily recyclable.

In perspective, it may be interesting to deepen the study about the mechanism of action of this new class of complexes aimed at improving their performances as anticancer agents. These future experiments might suggest specific structural modifications of palladium compounds or verifying their effectiveness when used in combination with other anticancer drugs (e.g. doxorubicin, paclitaxel, etc.). Furthermore, it will be advisable to test the catalytic properties of these indenyl derivatives on other classes of organic reactions.

Experimental Section

Materials and methods

Dichloromethane was distilled over P_2O_5 and then maintained under an Argon atmosphere. All other reagents and solvents were employed as supplied. $[Pd(\mu\text{-}Cl)(indenyl)]_2$[22] and the silver complexes [AgCl(IMes)] and [AgCl(IPr)][23] were prepared according to the published synthesis. The neutral Pd(II)-indenyl complexes **1**–**2** were obtained following two different procedures as reported in Supporting Information. Notably, in the case of the weak base approach, the palladate intermediate can be isolated in the absence of potassium carbonate as recently reported by our group.[24] NMR spectra were obtained by Bruker 300 or 400 -MHz spectrometers. For IR measurements a PerkinElmer Spectrum One spectrophotometer was employed. HRMS data were collected by a Bruker Compact Q-TOF (Figures S48–S58 in Supporting Information).

General procedure for the synthesis of mixed NHC/PR_3 or NHC/$P(OEt)_3$ Pd(II)-indenyl complexes

To one equivalent of the neutral Pd(II)-indenyl complex **1** or **2** dissolved in 3 mL of anhydrous dichloromethane, a solution of $NaClO_4{\cdot}H_2O$ (4 equiv.) in 2 mL of methanol and one of the selected phosphine (or triethylphosphite) (1 equiv.) in 3 mL of CH_2Cl_2 were added.

The reaction mixture was stirred at room temperature for 15 min and the solvent was removed under vacuum. Afterwards, 4 mL of CH_2Cl_2 was added and the resulting mixture was filtered on Millipore apparatus. The clear solution obtained was concentrated under vacuum. and the final product was firstly precipitated by addition of diethyl ether and finally dried under vacuum.

The detailed procedures and characterizations for all the target complexes are reported in Supporting Information.

General procedure for Suzuki–Miyaura coupling

A round bottom flask was charged, with arylboronic acid (0.6 mmol), aryl bromide/chloride (0.5 mmol), potassium carbonate (0.75 mmol), tetrabutylammonium bromide (0.75 mmol), catalyst **5** (0.0005 or 0.005 mmol) and H_2O (10 mL). The mixture was then stirred at 80 °C for 2–24 h. Afterwards, the reaction mixture was extracted three times with ethyl acetate (3 × 5 mL) and analysed by GC-MS. The aqueous phase was recycled for additional experiments.

Crystal Structure Determination

3b, **3c**, **3e**, **5**, **6** and **7** crystals data (Tables S1–S2 in Supporting Information) were collected at the Elettra Synchrotron, Trieste (Italy).[25] The details of the procedure followed for the determinations of crystallographic data are reported in Supporting Information.[26–34]

Deposition Numbers 2226223 (for **7** at 298 K), 2226224 (**3c** at 100 K), 2226225 (**3e** at 100 K), 2226218 (**5** at 100 K), 2226219 (**5** at 298 K), 2226220 (**6** at 100 K), 2226221 (**6** at 200 K) and 2226222 (**3b** at 100 K) contain the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

Supporting Information

Additional references cited within the Supporting Info.[35–36]

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Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: anticancer activity · catalysis in aqueous media · *N*-heterocyclic carbene ligands · palladium · P ligands · Suzuki–Miyaura coupling

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