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Highly cytotoxic palladium(II) complexes with 1,2,4-triazole-derived carbene ligands

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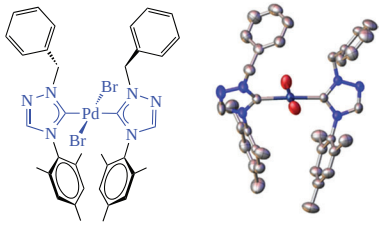
Two novel palladium(II) complexes, *trans*-[$PdBr_2$(tz-Mes)$_2$] and *trans*-[$PdBr_2$(tz-Dipp)$_2$] featuring less explored 1,2,4-triazole-derived N-heterocyclic carbene (tz) have been synthesized. In solution, they exist both as *trans-syn* and *trans-anti* rotamers while their *syn*/*anti* ratios can be determined by ^{1}H NMR harnessing the built-in aromatic rings as NMR probes. Complex *trans*-[$PdBr_2$(tz-Mes)$_2$] is highly cytotoxic toward A549, MCF-7, LNCaP and HT-29 cancerous cells.



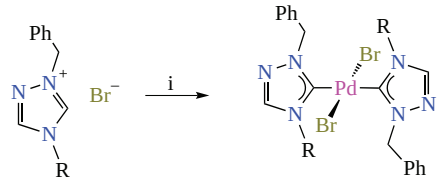
Keywords: 1,2,4-triazolin-5-ylidene ligands, palladium(II) complexes, palladium-NHC, anticancer activities, NMR probe.

N-Heterocyclic carbenes (NHCs) are among the most prominent ligands for organometallic chemistry.[1–6] Tuning of NHC stereoelectronic properties and consequently their metal complex reactivities can be reached by judicious choice of heterocycle backbones and/or wingtip substitutions.[7–9] Much success has been demonstrated by Pd^0/Pd^{II} NHC complexes in homogeneous catalysts.[10–14] Despite their popularity in catalysis, the exploitation of NHCs' advantage to develop biologically active palladium(II) complexes is far from well established. Notably, recent works[15–19] have revealed potent anticancer activities of Pd^{II}-NHC complexes, and some complexes offer cytotoxicity comparable to that of platinum(II)-based cousins or organic genres. However, reported works largely focus on the classical (benz)imidazole derived NHCs. Coordination chemistry and applications of palladium(II) complexes of 1,2,4-triazole derived NHCs (tz) are much less explored even though imidazole- and tz-based NHC share very similar structural features. To the best of our knowledge, cytotoxicity of Pd^{II}-tz complexes was only reported for [$PdBr_2$(tz*)$_2$] and [Pd(tfa)$_2$(tz*)$_2$], where tfa is trifluoroacetate and tz* carbenes are 1,2,4-triazole-derived carbenes bearing chiral substituents.[16] Interestingly, all of these complexes displayed anti-proliferative activities toward MCF-7 breast cancer cells and one of them even showed IC_{50} value lower than that of the benchmark cisplatin.

As part of our ongoing effort to explore the coordination chemistry and potential applications of 1,2,4-triazole derived carbene complexes,[20,21] we report in this work the syntheses, characterization and cytotoxicity study for palladium(II) bis(1,2,4-triazolin-5-ylidene) [$PdBr_2$(tz-R)$_2$] complexes (tz-R is 1-benzyl-4-mesityl-1,2,4-triazolin-5-ylidene (tz-Mes, **1**) and 1-benzyl-4-(1,6-diisopropylphenyl)-1,2,4-triazolin-5-ylidene (tz-Dipp, **2**).

Synthesis of 1,2,4-triazolium precursors (tz-Mes·HBr and tz-Dipp·HBr) was carried out following procedures reported previously.[21] Palladation of the salts was accomplished *via* the silver-carbene transfer pathway (Scheme 1). Accordingly, tz-R·HBr salts were treated with silver(I) oxide in dichloromethane in the dark, and then reacted with palladium(II) bromide.

The deprotonations of the salts occurred smoothly giving the product in excellent yields. It is in line with the fact that the C^5–H protons of triazolium salts are generally more acidic compared to the relative C^2–H proton in imidazolium salts due to the additional electronegative nitrogen atom. The obtained complexes were purified using silica-gel column chromatography and isolated as pale yellow solids. They are both stable under ambient conditions with high solubility in polar organic solvents, such as dichloromethane, chloroform, and dimethyl sulfoxide. In addition, complex **1** can be easily crystallized from the CH_2Cl_2/hexane solvent mixture while **2** often ended as powder during crystal growing processes. Identity of the complexes was confirmed by multinuclear (^{1}H and ^{13}C{^{1}H}) NMR spectroscopy, mass spectrometry, elemental analysis, and single crystal X-ray diffraction. In the NMR spectra of complexes **1** and **2**, two sets of signals were observed, suggesting the presence of two isomers in their solutions. Taking into account the unsymmetrical nature and the bulkiness of the tz-Mes and tz-Dipp ligands, the two isomers can be assigned to the *trans-syn* and *trans-anti* rotamers.



Scheme 1 *Reagents and conditions*: i, Ag_2O, CH_2Cl_2, dark, room temperature, 2 h, then $PdBr_2$, 10 h.

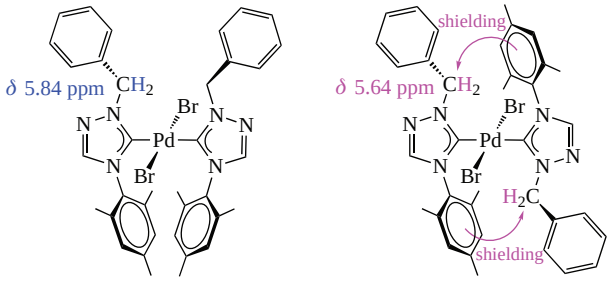


Figure 1 Structures of the two rotamers of compound **1** and their spectral assignments.

Interestingly, the ring current of the aromatic rings in mesityl (Mes) or 2,6-diisopropylphenyl (Dipp) wingtips can act as internal probes, facilitating the spectral assignments and allowing convenient determination of the *syn*/*anti* ratio in solutions. In the *trans-anti* complexes, the benzyl CH_2 protons are situated in the shielded region caused by the aromatic ring current of the Mes/Dipp and therefore they resonate significantly upfield compared to the respective signals in the *trans-syn* rotamers. For example, in the ^{1}H NMR spectrum of **1** (see Online Supplementary Materials, Figure S1), the benzyl CH_2 protons resonate at 5.84 ppm for the *syn* rotamer compared to 5.64 ppm for *anti* rotamers (Figure 1). Similarly, two signals at 6.02 (for *syn*-**2**) and 5.63 ppm (for *anti*-**2**) were also observed in its ^{1}H NMR spectrum. Moreover, the integration ratios also indicate that in chloroform solution, the *syn*/*anti* ratios are 1 : 0.6 and 1 : 0.5 for **1** and **2**, respectively.

The identity of the complexes was also unambiguously confirmed using single crystal X-ray diffraction (Figure 2).† Both complexes adopt square planar geometries, typically observed for d^8 metal complexes. The metal center in each of them is coordinated by two bromide and two NHC ligands. The two NHC moieties exist in *trans*-configuration. Complex **1** is crystallized in the *trans-syn* form, while the *trans-anti* configuration is observed for **2**.

Since complex **1** crystallized out easily, it was selected for cytotoxicity study (Table 1). The anti-proliferative activity of the complexes was tested against a collection of cancer cell lines, including lung carcinoma epithelial cell (A549), human breast cancer cell (MCF-7), human prostate adenocarcinoma cell (LNCaP), oral cancer cell (KB), human colorectal adenocarcinoma cell (HT-29), and the human embryonic kidney cell line (HEK-293A).

† Single crystals of **1** and **2** were obtained by slow evaporation of their solutions in CH_2Cl_2/hexane mixtures.

Crystal data for **1**. $C_{36}H_{38}Br_2N_6Pd$, M = 820.92, triclinic, space group $P\bar{1}$, at 298 K, a = 11.1327(8), b = 11.8266(9) and c = 15.8739(12) Å, α = 75.180(2)°, β = 73.070(2)°, γ = 65.577(2)°, V = 1798.4(2) Å^3, Z = 2, d_{calc} = 1.516 g cm^{-3}, $F(000)$ = 824. Intensity of 9213 were measured [λ(MoKα) = 0.71073 Å, μ(MoKα) = 11.42 cm^{-1}, ω-scans, $2\theta < 57.2°$], and 9150 independent reflections were used for the structure solution and refinement. Final R factors: R_1 = 0.0474 for 6073 reflection with $I > 2\sigma(I)$, wR_2 = 0.1313 and GOF = 1.039 for all independent reflections.

Crystal data for **2**. $C_{42}H_{50}Br_2N_6Pd$, M = 905.08, monoclinic, space group $P2_1/n$, at 298 K, a = 10.7357(6), b = 12.4858(7) and c = 16.4281(9) Å, α = 90°, β = 104.544(2)°, γ = 90°, V = 2131.5(2) Å^3, Z = 2, d_{calc} = 1.410 g cm^{-3}, $F(000)$ = 920. Intensity of 5343 were measured [λ(MoKα) = 0.71073 Å, μ(MoKα) = 11.42 cm^{-1}, ω-scans, $2\theta < 57.2°$], and 9150 independent reflections were used for the structure solution and refinement. Final R factors: R_1 = 0.0408 for 3899 reflection with $I > 2\sigma(I)$, wR_2 = 0.1098 and GOF = 1.071 for all independent reflections.

CCDC 2156068 and 2156071 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

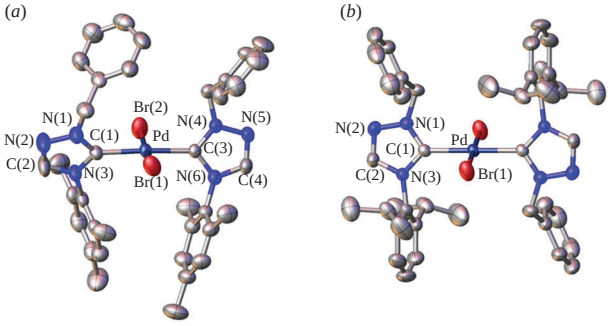


Figure 2 Molecular structure of (*a*) **1** and (*b*) **2**. Structural parameters for **1**: Pd–C(1), 2.023(5); Pd–C(2), 2.024(4); Pd–Br(1), 2.436(1); Pd–Br(3), 2.421(1) Å; C(1)–Pd–C(2), 176.4(2)°; C(1)–Pd–Br(1), 90.9(1)°; Br(1)–Pd–Br(2), 172.2(1)°; for **2**: Pd–C(1), 2.025(3); Pd(1)–Br(1), 2.424(1) Å; C(1)–Pd–C(1A), 180.0°; C(1)–Pd–Br(1), 92.4(1)°; Br(1)–Pd–Br(1A), 180.0(1)°.

Table 1 IC_{50} (μM) of the complexes after 72 h of incubation (values are expressed as mean ± standard deviation).

Cell lines	Complex **1**	Cisplatin
A549	7.61 ± 0.92	5.95 (ref. 22)
MCF-7	8.72 ± 0.83	8.30 (ref. 23)[a]
LNCaP	5.30 ± 0.53	>50 (ref. 24)[b]
KB	10.64 ± 0.68	2.4 (ref. 25)
HT-29	10.38 ± 0.94	75.8 (ref. 26)
HEK-293A	8.04 ± 0.24	16.3 (ref. 27)

[a] 96 h incubation. [b] 24 h incubation.

Notably, complex **1** demonstrates high cytotoxicity toward all the five cancerous cell lines tested (A549, MCF-7, LNCaP, KB and HT-29), showing the IC_{50} concentration in the micromolar range, varying from 6.30 to 10.64 μM. It also shows antiproliferative activity toward human embryonic kidney noncancerous cells (HEK-293A, IC_{50} = 8.04 ± 0.24 μM), suggesting limited selectivities. Note that, compared to the benchmark cisplatin, the complex is less potent to KB and A549 cancerous cells, showing IC_{50} values of 10.64 and 7.61 μM while that of cisplatin is 2.4 and 5.95 μM, respectively. Complex **1** activity toward MCF-7 is comparable with that of cisplatin, but is outperformed by the reported chiral $PdBr_2(tz^*)_2$ complex.[16] The compound, however, is much more effective toward the antiproliferation of LNCaP and HT-29 cells than cisplatin, displaying IC_{50} concentrations of 5.30 and 10.38 μM.

In conclusion, two palladium(II)-bisNHC complexes featuring the less explored NHC scaffold, 1,2,4-triazolin-5-ylidene, have been successfully synthesized. The identity of the complexes has been unambiguously confirmed by single crystal X-ray diffraction studies in addition to NMR spectroscopy and mass spectrometry. Moreover, structural characterization reveals the presence of two rotamers for each compound in solutions. Harnessing the built-in aromatic rings as NMR probes, the ratios of *syn*/*anti* rotamers were conveniently determined to be 1 : 0.6 (for **1**) and 1 : 0.5 (for **2**). In addition, complex **1** is highly cytotoxic toward A549, MCF-7, LNCaP, KB and HT-29 cancer cell lines, showing IC_{50} values in the micromolar range. The cytotoxicity toward LNCaP and HT-29 appears to be superior to the benchmark compound cisplatin.

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Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi: 10.1016/j.mencom.2022.09.008.

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