Received: 30 March 2020 | Revised: 18 May 2020 | Accepted: 26 May 2020

DOI: 10.1002/aoc.5876

FULL PAPER

Applied Organometallic Chemistry WILEY

Allyl palladium complexes bearing carbohydrate-based *N*-heterocyclic carbenes: Anticancer agents for selective and potent *in vitro* cytotoxicity

Thomas Scattolin[1] | **Enrica Bortolamiol**[2] | **Flavio Rizzolio**[2,3] | **Nicola Demitri**[4] | **Fabiano Visentin**[2]

[1]Department of Chemistry and Center for Sustainable Chemistry, Ghent University, Krijgslaan 281 (S-3), Ghent, 9000, Belgium

[2]Dipartimento di Scienze Molecolari e Nanosistemi, Università Ca' Foscari, Campus Scientifico Via Torino 155, Venezia-Mestre, 30174, Italy

[3]Pathology unit, Centro di Riferimento Oncologico di Aviano (CRO) IRCCS, via F. Gallini 2, Aviano, 33081, Italy

[4]Hard X-ray Diffraction Beamlines, Elettra Sincrotrone Trieste, S.S. 14 Km 163.5 in Area Science Park, Basovizza, Trieste, 34149, Italy

Correspondence
Thomas Scattolin, Department of Chemistry and Center for Sustainable Chemistry, Ghent University, Krijgslaan 281 (S-3), 9000, Ghent, Belgium.
Email: thomas.scattolin@ugent.be

Fabiano Visentin, Dipartimento di Scienze Molecolari e Nanosistemi, Università Ca' Foscari, Campus Scientifico Via Torino 155, 30174 Venezia-Mestre, Italy.
Email: fvise@unive.it

Novel allyl palladium compounds stabilized by carbohydrate-based *N*-heterocyclic carbenes (NHCs) were prepared and characterized by nuclear magnetic resonance, high-resolution mass spectrometry and elemental analysis. The antiproliferative activity of the compounds was tested on a panel of different tumor lines, especially ovarian cancer and MRC-5 human lung fibroblasts (nontumor cells). These experiments showed that both mixed NHC/PPh_3 and NHC/PTA (PTA = 1,3,5-triaza-7-phosphaadamantane) allyl complexes have IC_{50} (half maximal inhibitory concentration) values comparable and sometimes even significantly lower than cisplatin. Moreover, the mixed NHC/PTA allyl complexes exhibit good activity toward the seven tumor lines tested with a substantial inactivity against normal cells, a necessary condition to avoid the general cytotoxicity of a metallo-drug. Furthermore, this subclass of compounds proved particularly active on the A549 lung cancer tumor line (up to 100-fold more cytotoxic than cisplatin) and exhibited satisfactory cytotoxicity against KURAMOCHI and OVCAR3 cell lines, which are currently considered the best *in vitro* models for serous ovarian cancer, the most lethal tumor for women worldwide.

KEYWORDS

carbohydrate-based NHC, metallo-drugs, ovarian and lung cancer, palladium allyl complexes

1 | INTRODUCTION

The discovery of the amazing antitumor properties of cisplatin, especially for the treatment of genitourinary neoplasm, has probably produced an excessive enthusiasm about the possibility of a generalized use of metal compounds as anticancer agents.[1] However, many collateral problems remain unsolved ever since. Cisplatin entails important side effects and resistance can occur during the therapeutic treatment.[2] Platinum complexes with minor contraindications, which appeared later in the market (i.e. carboplatin and oxaliplatin), also did not overcome the ineffectiveness toward some types of tumors, as they work with the same mechanism of action proposed for cisplatin.[3]

For this reason, many research groups have focused their attention on the synthesis and evaluation of the anticancer properties of compounds containing metals different from platinum.[4] In the last decade, palladium derivatives have been considered as feasible alternatives to platinum-based drugs.[5] Palladium compounds are generally more soluble in water[6] and show structure–activity relationships and mechanisms of action generally different from their platinum counterparts.[7] However, a

potential limitation of palladium complexes lies in their fast dissociation pattern compared with their platinum counterparts (10^4–10^5 times higher).[8]

This feature can compromise the possibility for the palladium compounds to selectively reach the biotarget, thereby increasing their general toxicity.[9] To cope with this counterindication, the most promising strategy seems to be the use of polydentate ligands and/or organometallic structures in which the strong carbon–palladium bond prevents or slows down the hydrolysis processes.[10]

An important class of strong and generally bulky ligands recently employed in the biomedical field is the *N*-heterocyclic carbenes (NHCs), which were first isolated by Arduengo and co-workers in 1991.[11a]

As recently reported by our research group and other authors, several NHC–palladium complexes exhibit an interesting antiproliferative activity *in vitro* and, in the few cases studied, tumor growth suppression even *in vivo*.[7a-b,12]

These encouraging results have prompted us to investigate for the first time the anticancer activity of palladium complexes stabilized by carbohydrate-based NHCs, which are an interesting category of ligands recently studied in homogenous catalysis,[13] especially for enantioselective processes.[14]

The reasons for this choice are multiple. First, carbohydrates and their derivatives (i.e. glycolipids, glycoproteins, and nucleic acids) are the most abundant class of biological molecules on earth and represent often the key species in the biological processes of living organisms (i.e. the storage and transport of energy and structural components of cellulose and cartilage). Furthermore, they play a fundamental role in the immune and reproductive systems.[15] On these bases it is plausible that the introduction of these biologically active residues in the skeleton of our complexes could increase their compatibility with the biological environment and possibly their activity and/or selectivity toward cancer cells.[16]

Second, the ability of carbohydrates to act as active sites for molecular recognition taking advantage of the hydrogen bonding,[17] their high water-solubility, and above all their more efficient uptake by tumor cells, compared with healthy ones,[18] make them very attractive for the design of new chemotherapeutic agents.

In particular, the preferential accumulation of glycoconjugates in tumor tissues, a phenomenon known as the Warburg effect, besides promoting their extensive use in diagnostics (i.e. positron emission tomography) and in the treatment of important forms of arthritis (i.e. Auranofin-based therapy for rheumatoid arthritis[19]), has become an appealing tool for the targeted delivery of anticancer drugs.[18]

All these considerations have motivated us to carry out the synthesis of the new palladium complexes bearing carbohydrate-based NHCs (Scheme 1).

The choice of combining the new carbohydrate-based carbene ligands with PPh_3 or PTA (1,3,5-triaza-7-phosphaadamantane) and the Pd(II)-η^3-allyl organometallic fragment stems from the encouraging results obtained with an analogous assembly. As a matter of fact, we have recently shown that a class of complexes with this pattern but bearing purine-based NHC ligands is endowed with good antiproliferative activity against ovarian cancer lines.[12a]

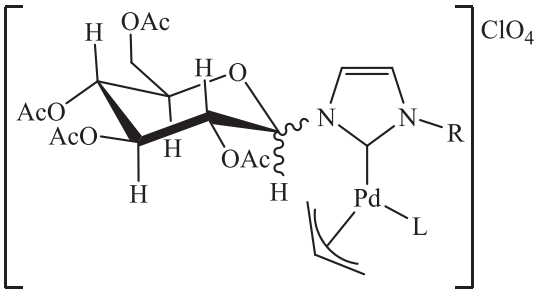
Remarkably, the Pd(II)-η^3-allyl organometallic fragment, whose reactivity[20] and importance in catalytic processes[21] have been extensively investigated, is probably the most promising among the palladium organometallic substrates examined by our research group[12a–d] for the preparation of new, efficient, and selective anticancer agents.

In this work, we examine the antiproliferative activity of the compounds detailed in Scheme 1 against a panel of different human tumor cell lines and human lung fibroblasts (normal cells).

2 | EXPERIMENTAL

2.1 | Solvents and reagents

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 first treated with 3-Å molecular sieves and then distilled over P_2O_5. All the other chemicals were commercially available grade products (Sigma-Aldrich, Italy) and were used as purchased.



4a, 5a R = CH_3 L= PPh_3, PTA
4b, 5b R = n-Bu L= PPh_3, PTA
4c, 5c R = Mes L= PPh_3, PTA

SCHEME 1 η^3-Allyl palladium complexes bearing carbohydrate-based NHCs and phosphines (PPh_3 or PTA). NHC, *N*-heterocyclic carbene; PTA, 1,3,5-triaza-7-phosphaadamantane

2,3,4,6-Tetra-O-acetyl-⟨-D-glucosyl bromide,[22] 2,3,4,6-tetra-O-acetyl-β-D-glucosyl imidazole,[13b] and 1-(2′,3′,4′,6′-tetra-O-acetyl-β-D-glucosyl)-3-mesityl imidazolium triflate[14b] were synthesized according to the published procedures.

2.2 | Infrared, nuclear magnetic resonance, high-resolution mass spectrometry, and elemental analysis

The infrared (IR), ^{1}H, and ^{13}C and ^{31}P nuclear magnetic resonance (NMR) spectra were recorded on a Perkin-Elmer Spectrum One spectrophotometer and on a Bruker 400 AVANCE spectrometer. Elemental analysis was carried out using an Elemental CHN "CUBO Micro Vario" analyzer. High-resolution mass spectra were obtained from Bruker Compact electrospray ionization (ESI)-time of flight with the following settings: source type ESI ion polarity, positive; set nebulizer pressure 0.3 bar; focus, active; capillary voltage, 4500 V; dry heater 200 °C; scan begin, 50 *m/z*; scan end 800 *m/z*, end plate offset −500 V; dry gas flow rate, 3.5 L/min; and collision cell Radio-Frequency (RF), 2500.0 Vpp.

A solution of complexes **4–5** in acetonitrile (1 mg/mL) was diluted 1:10,000 with acetonitrile. This solution was directly injected into the spectrometer.

2.3 | Synthesis of the imidazolium salts 1a–c

2.3.1 | Synthesis of 1a

About 0.9330 g of 1-(2,3,4,6-tetra-O-acetyl-β-D-glucosyl) imidazole and 2.8 g (1 mL, 0.02 mol) of methyl iodide were dissolved in 25 mL of anhydrous acetonitrile. The mixture was stirred at reflux for 4 hr and subsequently the solvent was removed under reduced pressure. The brownish solid obtained was dissolved in approximately 3 mL of dichloromethane. Addition of diethyl ether induced the precipitation of the final product which was filtered off on a Gooch crucible. About 1.07 g of **1a** was obtained (yield 85%)

^{1}H-NMR (300 MHz, $CDCl_3$, T = 298 K, ppm) δ: 2.03 (s, 3H, OCH_3), 2.07 (s, 3H, OCH_3), 2.11 (s, 3H, OCH_3), 2.12 (s, 3H, OCH_3), 4.21 (s, 3H, N–CH_3), 4.22–4.43 (m, 3H, H^5 + $CH_2{}^6$), 5.26 (t, 1H, J = 9.2 Hz, H^4), 5.34 (t, 1H, J = 9.2 Hz, H^2), 5.48 (t, 1H, J = 9.2 Hz, H^3), 6.61 (d, 1H, J = 9.2 Hz, H^1), 7.42 (d, 1H, J = 2.0 Hz, H^{Im}), 7.60 (t, 1H, J = 2.0 Hz, H^{Im}), 10.57 (s, 1H, NCHN).

$^{13}C\{^{1}H\}$-NMR ($CDCl_3$, T = 298 K, ppm) δ: 20.5 (CH_3, OCH_3), 20.6 (CH_3, OCH_3), 20.9 (CH_3, OCH_3), 21.1 (CH_3, OCH_3), 37.7 (CH_3, NCH_3), 61.1 (CH_2, $CH_2{}^6$), 67.3 (CH, CH^4), 71.2 (CH, CH^2), 72.4 (CH, CH^3), 75.0 (CH, CH^5), 83.7 (CH, CH^1), 119.6 (CH, CH^{Im}), 123.8 (CH, CH^{Im}), 137.7 (CH, NCHN), 169.4 (C, C=O), 169.5 (C, C=O), 169.9 (C, C=O), 170.5 (C, C=O).

Anal. Calcd for $C_{18}H_{25}IN_2O_9$ (%): C, 40.01; H, 4.66; N, 5.18. Found (%):C, 40.13; H, 4.81; N, 4.99.

2.3.2 | Synthesis of 1b

Imidazolium salt **1b** was synthesized according to published procedures.[13b]

2.3.3 | Synthesis of 1c

About 0.405 g (0.608 mmol) of 1-(2,3,4,6-tetra-O-acetyl-β-D-glucosyl)-3-(mesityl)imidazolium triflate, synthesized according to published procedures,[14b] was dissolved in 25 mL of methanol. To this solution 2 g of DOWEX-21K Cl exchange resin was added and the system was stirred for 24 hr at room temperature (RT). Subsequently, the solvent of the filtered solution was removed under reduced pressure and the solid obtained was dissolved in approximately 3 mL of dichloromethane. The addition of diethyl ether induced the precipitation of the final product which was filtered off on a Gooch crucible. About 0.2454 g of **1c** was obtained (yield 73%)

β Anomer (60%)

^{1}H-NMR (300 MHz, $CDCl_3$, T = 298 K, ppm) δ: 2.02–2.13 (m, 18H, 4 OCH_3 + 2 o-$CH_3{}^{Mes}$), 2.37 (s, 3H, p-$CH_3{}^{Mes}$), 4.19–4.44 (m, 3H, H^5 + $CH_2{}^6$), 5.27–5.36 (m, 2H, H^2 + H^4), 5.60 (t, 1H, J = 9.3 Hz, H^3), 7.30 (d, 1H, J = 9.3 Hz, H^1), 7.66 (d, 1H, J = 2.0 Hz, H^{Im}), 7.84 (t, 1H, J = 2.0 Hz, H^{Im}), 11.12 (s, 1H, NCHN).

$^{13}C\{^{1}H\}$-NMR ($CDCl_3$, T = 298 K, ppm) δ: 17.3 (CH_3, o-$CH_3{}^{Mes}$), 20.4 (CH_3, OCH_3), 20.5 (CH_3, OCH_3), 20.6 (CH_3, OCH_3), 20.7 (CH_3, OCH_3), 21.1 (CH_3, p-$CH_3{}^{Mes}$), 61.2 (CH_2, $CH_2{}^6$), 67.5 (CH, CH^4), 71.1 (CH, CH^2), 72.4 (CH, CH^3), 75.0 (CH, CH^5), 83.8 (CH, CH^1), 120.0 (CH, CH^{Im}), 123.5 (CH, CH^{Im}), 129.9 (CH, m-CH^{Mes}), 134.3 (C, o-C^{Mes}), 139.3 (CH, NCHN), 141.6 (C, i-C^{Mes}), 141.8 (C, p-C^{Mes}), 169.2 (C, C=O), 169.7 (C, C=O), 170.1 (C, C=O), 170.4 (C, C=O).

α Anomer (40%):

^{1}H-NMR (300 MHz, $CDCl_3$, T = 298 K, ppm) δ: 2.02–2.13 (m, 18H, 4 OCH_3 + 2 o-$CH_3{}^{Mes}$), 2.39 (s, 3H, p-$CH_3{}^{Mes}$), 4.19–4.44 (m, 3H, H^5 + $CH_2{}^6$), 5.27–5.36 (m, 2H, H^2 + H^4), 5.60 (t, 1H, J = 9.3 Hz, H^3), 7.30 (d, 1H, J = 9.3 Hz, H^1), 7.15 (d, 1H, J = 2.0 Hz, H^{Im}), 7.19 (t, 1H, J = 2.0 Hz, H^{Im}), 8.36 (s, 1H, NCHN).

$^{13}C\{^1H\}$-NMR ($CDCl_3$, T = 298 K, ppm) δ: 17.3 (CH_3, o-CH_3^{Mes}), 20.4 (CH_3, OCH_3), 20.5 (CH_3, OCH_3), 20.6 (CH_3, OCH_3), 20.7 (CH_3, OCH_3), 21.1 (CH_3, p-CH_3^{Mes}), 61.2 (CH_2, CH_2^6), 67.5 (CH, CH^4), 71.1 (CH, CH^2), 72.4 (CH, CH^3), 75.0 (CH, CH^5), 83.8 (CH, CH^1), 121.1 (CH, CH^{Im}), 122.3 (CH, CH^{Im}), 130.2 (CH, m-CH^{Mes}), 133.6 (CH, NCHN), 134.3 (C, o-C^{Mes}), 141.6 (C, i-C^{Mes}), 141.8 (C, p-C^{Mes}), 169.2 (C, C=O), 169.7 (C, C=O), 170.1 (C, C=O), 170.4 (C, C=O).

Anal. Calcd for $C_{26}H_{33}ClN_2O_9$ (%): C, 56.47; H, 6.02; N, 5.07. Found (%):C, 56.10; H, 5.90; N, 4.95.

2.4 | Synthesis of the Ag(I) complexes 2a–c

2.4.1 | Synthesis of the complex 2a

Approximately 0.2020 g (0.374 mmol) of **1a** was dissolved in 25 mL of anhydrous CH_2Cl_2 in a two-necked flask and 0.0524 g (0.226 mmol) of Ag_2O was added under inert atmosphere (Ar).

The mixture was stirred for 5 hr at RT in the dark and subsequently transferred to a 250-mL flask with the addition of about 150 mL of CH_2Cl_2. The solution was filtered on a Millipore membrane filter, concentrated under vacuum, and the complex precipitated by addition of diethyl ether. The brownish complex was filtered off on a Gooch crucible, repeatedly washed with diethyl ether and n-pentane, and dried under vacuum. About 0.1878 g of **2a** was obtained (yield 78%)

^{1}H-NMR (300 MHz, $CDCl_3$, T = 298 K, ppm) δ: 1.99 (s, 3H, OCH_3), 2.03 (s, 3H, OCH_3), 2.09 (s, 3H, OCH_3), 2.11 (s, 3H, OCH_3), 3.91 (s, 3H, NCH_3), 4.16–4.38 (m, 3H, H^5 + CH_2^6), 5.16 (t, 1H, J = 9.3 Hz, H^4), 5.25 (t, 1H, J = 9.3 Hz, H^2), 5.38 (t, 1H, J = 9.3 Hz, H^3), 6.12 (d, 1H, J = 9.2 Hz, H^1), 7.01 (d, 1H, J = 1.8 Hz, H^{Im}), 7.24 (d, 1H, J = 1.8 Hz, H^{Im}).

$^{13}C\{^1H\}$-NMR ($CDCl_3$, T = 298 K, ppm) δ: 20.5 (CH_3, OCH_3), 20.6 (CH_3, OCH_3), 20.7 (CH_3, OCH_3), 20.8 (CH_3, OCH_3), 39.1 (CH_3, NCH_3), 61.5 (CH_2, CH_2^6), 67.8 (CH, CH^4), 70.8 (CH, CH^2), 72.9 (CH, CH^3), 74.4 (CH, CH^5), 86.5 (CH, CH^1), 118.1 (CH, CH^{Im}), 122.7 (CH, CH^{Im}), 169.4 (C, C=O), 169.5 (C, C=O), 169.6 (C, C=O), 170.5 (C, C=O), 185.8 (C, carbene).

IR (KBr): $\nu_{C=O}$ = 1752 cm^{-1}, ν_{C-O} = 1228 cm^{-1}.

Anal. Calcd for $C_{18}H_{24}AgIN_2O_9$ (%):C, 33.41; H, 3.74; N, 4.33. Found (%):C, 33.22; H, 3.62; N, 4.23.

2.4.2 | Synthesis of the complex 2b

Complex **2b** was prepared in an analogous manner to that described for **2a** starting from 0.2020 g of **1b** and 0.0524 g of Ag_2O. About 0.2159 g (yield 89%) of **2b** was obtained as a pale yellow solid

^{1}H-NMR (300 MHz, $CDCl_3$, T = 298 K, ppm) δ: 0.96 (t, 3H, J = 7.3 Hz, $CH_3^{4\prime}$), 1.33 (m, 2H, $CH_2^{3\prime}$), 1.79 (m, 2H, $CH_2^{2\prime}$), 1.96 (s, 3H, OCH_3), 2.02 (s, 3H, OCH_3), 2.08 (s, 3H, OCH_3), 2.11 (s, 3H, OCH_3), 4.11–4.37 (m, 5H, H^5 + $CH_2^{1\prime}$ + CH_2^6), 5.21–5.29 (m, 2H, H^2 + H^4), 5.44 (t, 1H, J = 9.3 Hz, H^3), 6.62 (d, 1H, J = 9.3 Hz, H^1), 7.04 (d, 1H, J = 1.8 Hz, H^{Im}), 7.25 (d, 1H, J = 1.8 Hz, H^{Im}).

$^{13}C\{^1H\}$-NMR ($CDCl_3$, T = 298 K, ppm) δ: 13.6 (CH_3, $CH_3^{4\prime}$), 19.5 (CH_2, $CH_2^{3\prime}$), 20.4 (CH_3, OCH_3), 20.5 (CH_3, OCH_3), 20.6 (CH_3, OCH_3), 20.7 (CH_3, OCH_3), 33.2 (CH_2, $CH_2^{2\prime}$), 55.3 (CH_2, $CH_2^{1\prime}$), 61.6 (CH_2, CH_2^6), 67.7 (CH, CH^4), 71.0 (CH, CH^2), 72.5 (CH, CH^3), 74.9 (CH, CH^5), 87.5 (CH, CH^1), 118.4 (CH, CH^{Im}), 121.9 (CH, CH^{Im}), 169.1 (C, C=O), 169.5 (C, C=O), 169.6 (C, C=O), 170.5 (C, C=O), 179.9 (C, carbene). IR (KBr): $\nu_{C=O}$ = 1754 cm^{-1}, ν_{C-O} = 1230 cm^{-1}.

Anal. Calcd for $C_{21}H_{30}AgBrN_2O_9$ (%):C, 39.27; H, 4.71; N, 4.36. Found (%):C, 39.50; H, 4.90; N, 4.21.

2.4.3 | Synthesis of the complex 2c

Complex **2c** was prepared in an analogous manner to that described for **2a** starting from 0.1073 g of **1c** and 0.0270 g of Ag_2O. About 0.0661 g (yield 52%) of **2c** was obtained as a pale yellow solid

^{1}H-NMR (300 MHz, $CDCl_3$, T = 298 K, ppm) δ: 1.92 (s, 3H, p-CH_3^{Mes}), 1.98 (s, 3H, o-CH_3^{Mes}), 2.02 (s, 3H, o-CH_3^{Mes}), 2.05 (s, 3H, OCH_3), 2.11 (s, 3H, OCH_3), 2.15 (s, 3H, OCH_3), 2.35 (s, 3H, OCH_3), 4.07 (m, 1H, H^5), 4.21–4.42 (m, 2H, CH_2^6), 5.25–5.37 (m, 2H, H^2 + H^4), 5.45 (t, 1H, J = 9.4 Hz, H^3), 5.77 (d, 1H, J = 9.3 Hz, H^1), 6.99 (m, 2H, m-CH^{Mes}), 7.02 (t, 1H, J = 1.9 Hz, H^{Im}), 7.44 (t, 1H, J = 1.9 Hz, H^{Im}).

$^{13}C\{^1H\}$-NMR ($CDCl_3$, T = 298 K, ppm) δ: 17.3 (CH_3, p-CH_3^{Me}), 20.4 (CH_3, o-CH_3^{Mes}), 20.5 (CH_3, OCH_3), 20.6 (CH_3, OCH_3), 20.8 (CH_3, OCH_3), 21.1 (CH_3, OCH_3), 61.5 (CH_2, CH_2^6), 67.6 (CH, CH^4), 71.1 (CH, CH^2), 72.3 (CH, CH^3), 75.1 (CH, CH^5), 87.8 (CH, CH^1), 118.5 (CH, CH^{Im}), 124.0 (CH, CH^{Im}), 129.6–140.0 (Ph), 169.0 (C, C=O), 169.4 (C, C=O), 169.6 (C, C=O), 170.5 (C, C=O), 180.4 (C, carbene). IR (KBr): $\nu_{C=O}$ = 1754 cm^{-1}, ν_{C-O} = 1231 cm^{-1}. Anal. Calcd for $C_{26}H_{32}AgClN_2O_9$ (%):C, 47.33; H, 4.89; N, 4.25. Found (%):C, 47.58; H, 4.94; N, 4.13.

2.5 | Synthesis of neutral Pd allyl complexes 3a–c

2.5.1 | Synthesis of the complex 3a

Approximately 0.0243 g (0.0664 mmol) of the dimer [Pd(μ-Cl)(η^3-C_3H_5)]$_2$ was dissolved in about 25 mL of

anhydrous dichloromethane in a 50-mL two-necked flask under an inert atmosphere (Ar). The resulting mixture was treated with 0.0860 g (0.133 mmol) of the silver complex **2a** and stirred at RT for approximately 30 min.

The precipitated AgBr was removed by filtration on a Millipore membrane filter.

Addition of diethyl ether and *n*-hexane to the concentrated solution caused the precipitation of the complex **3a** as a brownish solid which was filtered off on a Gooch crucible and washed with *n*-pentane. About 0.0566 g of **3a** was obtained (yield 72%)

(α Anomer + β anomer)

^{1}H-NMR (300 MHz, $CDCl_3$, T = 298 K, ppm) δ: 1.97 (s, 3H, OCH_3), 1.98 (s, 3H, OCH_3), 2.03 (s, 3H, OCH_3), 2.04 (s, 3H, OCH_3), 2.07 (s, 3H, OCH_3), 2.08 (s, 3H, OCH_3), 2.09 (s, 3H, OCH_3), 2.11 (s, 3H, OCH_3), 2.45 (d, 2H, J = 13.2 Hz, *anti* allyl-H *trans*-Cl), 2.48 (d, 2H, J = 13.2 Hz, *anti* allyl-H *trans*-Cl), 3.38 (d, 1H, J = 13.4 Hz, *anti* allyl-H *trans*-C), 3.42 (d, 1H, J = 13.4 Hz, *anti* allyl-H *trans*-C), 3.48 (d, 2H, J = 5.4 Hz, 2*syn* allyl-H *trans*-Cl), 3.83 (s, 3H, NCH_3), 3.88 (s, 3H, NCH_3), 3.98 (m, 2H, $2H^5$), 4.14–4.30 (m, 4H, $2CH_2^6$), 4.38 (d, 1H, J = 5.3 Hz, *syn* allyl-H *trans*-C), 4.41 (d, 1H, J = 5.3 Hz, *syn* allyl-H *trans*-C), 5.20 (t, 2H, J = 9.7 Hz, $2H^3$), 5.41–5.44 (m, 6H, 2*central* allyl-H + $2H^2$ + $2H^4$), 6.18 (d, 1H, J = 8.6 Hz, H^1), 6.24 (d, 1H, J = 8.6 Hz, H^1), 6.96 (d, 1H, J = 2.1 Hz, H^{Im}), 6.98 (d, 1H, J = 2.1 Hz, H^{Im}), 7.20 (d, 2H, J = 2.1 Hz, $2H^{Im}$).

(α Anomer + β anomer)

$^{13}C\{^1H\}$-NMR ($CDCl_3$, T = 298 K, ppm) δ: 20.4 (CH_3, OCH_3), 20.5 (CH_3, OCH_3), 20.6 (CH_3, OCH_3), 20.7 (CH_3, OCH_3), 38.5 (CH_3, NCH_3), 48.8 (CH_2, allyl *trans*-Cl), 49.1 (CH_2, allyl *trans*-Cl), 61.8 (CH_2, CH_2^6), 61.9 (CH_2, CH_2^6), 68.0 (CH, CH^4), 68.1 (CH, CH^4), 69.9 (CH, CH^2), 70.0 (CH, CH^2), 73.0 (CH, CH^3), 73.1 (CH, CH^3), 73.4 (CH_2, allyl *trans*-C), 73.8 (CH_2, allyl *trans*-C), 74.6 (CH, CH^5), 74.7 (CH, CH^5), 86.4 (CH, CH^1), 86.5 (CH, CH^1), 115.2 (CH, *central* allyl), 118.3 (CH, CH^{Im}), 118.4 (CH, CH^{Im}), 123.2 (CH, CH^{Im}), 123.4 (CH, CH^{Im}), 169.4 (C, C=O), 169.5 (C, C=O), 169.7 (C, C=O), 170.5 (C, C=O), 183.1 (C, carbene), 183.6 (C, carbene).

IR (KBr): $\nu_{C=O}$ = 1752 cm^{-1}, ν_{C-O} = 1230 cm^{-1}.

Anal. Calcd for $C_{21}H_{29}ClN_2O_9Pd$ (%):C, 42.37; H, 4.91; N, 4.71. Found (%):C, 42.43; H, 4.84; N, 4.76.

2.5.2 | Synthesis of the complex 3b

Complex **3b** was prepared in an analogous manner to that described for **3a** starting from 0.0243 g of [Pd(μ-Cl)(η^3-C_3H_5)]$_2$ and 0.0853 g of **2a**. About 0.0703 g (yield 76%) of **3b** was obtained as a white solid.

(α Anomer + β anomer)

^{1}H-NMR (300 MHz, $CDCl_3$, T = 298 K, ppm) δ: 0.95–1.00 (m, 6H, $2CH_3^{4\prime}$), 1.33–1.42 (m, 4H, $2CH_2^{3\prime}$), 1.79–1.88 (m, 4H, $2CH_2^{2\prime}$), 1.95 (s, 3H, OCH_3), 1.97 (s, 3H, OCH_3), 2.03 (s, 3H, OCH_3), 2.04 (s, 3H, OCH_3), 2.07 (s, 3H, OCH_3), 2.08 (s, 3H, OCH_3), 2.09 (s, 3H, OCH_3), 2.10 (s, 3H, OCH_3), 2.45 (d, 2H, J = 12.1 Hz, 2*anti* allyl-H *trans*-Cl), 3.32 (d, 1H, J = 12.2 Hz, *anti* allyl-H *trans*-C), 3.36 (d, 1H, J = 12.2 Hz, *anti* allyl-H *trans*-C), 3.48 (d, 2H, J = 6.7 Hz, 2*syn* allyl-H *trans*-Cl), 4.02 (m, 2H, $2H^5$), 4.15–4.32 (m, 10H, 2*syn* allyl-H *trans*-C + $2CH_2^{1\prime}$ + $2CH_2^6$), 5.22 (t, 2H, J = 9.7 Hz, $2H^3$), 5.38–5.48 (m, 6H, 2*central* allyl-H + $2H^2$ + $2H^4$), 6.15 (d, 1H, J = 8.5 Hz, H^1), 6.20 (d, 1H, J = 8.5 Hz, H^1), 7.05 (d, 1H, J = 2.1 Hz, H^{Im}), 7.07 (d, 1H, J = 2.1 Hz, H^{Im}), 7.24 (d, 2H, J = 2.1 Hz, $2H^{Im}$).

(α Anomer + β anomer)

$^{13}C\{^1H\}$-NMR ($CDCl_3$, T = 298 K, ppm) δ: 13.4 (CH_3, $CH_3^{4\prime}$), 13.5 (CH_3, $CH_3^{4\prime}$), 19.6 (CH_2, $CH_2^{3\prime}$), 19.7 (CH_2, $CH_2^{3\prime}$), 20.2 (CH_3, OCH_3), 20.3 (CH_3, OCH_3), 20.4 (CH_3, OCH_3), 20.5 (CH_3, OCH_3), 32.7 (CH_2, $CH_2^{2\prime}$), 32.8 (CH_2, $CH_2^{2\prime}$), 48.9 (CH_2, allyl *trans*-Cl), 49.3 (CH_2, allyl *trans*-Cl), 51.0 (CH_2, $CH_2^{1\prime}$), 51.1 (CH_2, $CH_2^{1\prime}$), 61.8 (CH_2, CH_2^6), 61.9 (CH_2, CH_2^6), 67.9 (CH, CH^4), 68.0 (CH, CH^4), 70.0 (CH, CH^2), 70.1 (CH, CH^2), 72.0 (CH_2, allyl *trans*-C), 72.4 (CH_2, allyl *trans*-C), 72.8 (CH, CH^3), 72.9 (CH, CH^3), 74.6 (CH, CH^5), 74.7 (CH, CH^5), 86.7 (CH, CH^1), 86.8 (CH, CH^1), 115.1 (CH, *central* allyl), 118.0 (CH, CH^{Im}), 118.1 (CH, CH^{Im}), 122.0 (CH, CH^{Im}), 122.1 (CH, CH^{Im}), 169.2 (C, C=O), 169.5 (C, C=O), 169.6 (C, C=O), 170.3 (C, C=O), 182.7 (C, carbene), 183.0 (C, carbene). IR (KBr): $\nu_{C=O}$ = 1754 cm^{-1}, ν_{C-O} = 1231 cm^{-1}. Anal. Calcd for $C_{24}H_{35}ClN_2O_9Pd$ (%): C, 45.22; H, 5.53; N, 4.39. Found (%):C, 45.31; H, 5.46; N, 4.30.

2.5.3 | Synthesis of the complex 3c

Complex **3c** was prepared in an analogous to that described for **3a** starting from 0.0112 g of [Pd(μ-Cl)(η^3-C_3H_5)]$_2$ and 0.0400 g of **2c**. About 0.0290 g (yield 68%) of **3c** was obtained as a white solid.

β Anomer (60%)

^{1}H-NMR (300 MHz, $CDCl_3$, T = 298 K, ppm selected peaks) δ: 1.46 (d, 1H, J = 12.0 Hz, *anti* allyl-H *trans*-C), 1.89–2.84 (21H, $3CH_3^{Mes}$ + $4OCH_3$), 2.95–3.10 (m, 2H, 3.32 (d, 3H, *anti* allyl-H *trans*-Cl + *syn* allyl-H *trans*-C + *anti* allyl-H *trans*-Cl), 4.26 (d, 1H, J = 3.2 Hz, *syn* allyl-H *trans*-C), 5.12 (m, 1H, *central* allyl-H), 6.94–6.99 (m, 3H, Ph + H^{Im}), 7.40 (d, 1H, J = 1.9 Hz, H^{Im}).

$^{13}C\{^1H\}$-NMR ($CDCl_3$, T = 298 K, ppm selected peaks) δ: 17.4 (CH_3, *p*-CH_3^{Mes}), 18.8 (CH_3, *m*-CH_3^{Mes}), 20.3–21.1 (CH_3, OCH_3), 49.5 (CH_2, allyl *trans*-Cl), 74.5 (CH_2, allyl *trans*-C), 86.1 (CH, CH^1), 114.8 (CH, *central*

allyl), 128.6–139.3 (Ph), 168.9–170.5 (C, C=O), 183.0 (C, carbene).

α Anomer (40%):

^{1}H-NMR (300 MHz, $CDCl_3$, T = 298 K, ppm selected peaks) δ: 1.46 (d, 1H, J = 12.0 Hz, *anti* allyl-H *trans*-C), 1.89–2.84 (21H, $3CH_3^{Mes}$ + $4OCH_3$), 2.95–3.10 (m, 2H, 3.32 (d, 3H, *anti* allyl-H *trans*-Cl + *syn* allyl-H *trans*-C + *anti* allyl-H *trans*-Cl), 4.22 (d, 1H, J = 3.0 Hz, *syn* allyl-H *trans*-C), 4.87 (m, 1H, *central* allyl-H), 6.94–6.99 (m, 3H, Ph + H^{Im}), 7.42 (d, 1H, J = 1.9 Hz, H^{Im}).

$^{13}C\{^1H\}$-NMR ($CDCl_3$, T = 298 K, ppm selected peaks) δ: 17.6 (CH_3, *p*-CH_3^{Mes}), 18.5 (CH_3, *m*-CH_3^{Mes}), 20.3–21.1 (CH_3, OCH_3), 49.5 (CH_2, allyl *trans*-Cl), 74.6 (CH_2, allyl *trans*-C), 86.4 (CH, CH^1), 114.8 (CH, *central* allyl), 128.6–139.3 (Ph), 168.9–170.5 (C, C=O), 183.1 (C, carbene). IR (KBr): $\nu_{C=O}$ = 1752 cm^{-1}, ν_{C-O} = 1230 cm^{-1}. Anal. Calcd for $C_{29}H_{37}ClN_2O_9Pd$ (%): C, 49.80; H, 5.33; N, 4.00. Found (%): C, 49.72; H, 5.41; N, 4.09.

2.6 | Synthesis of mixed NHC/PPh_3 Pd allyl complexes

2.6.1 | Synthesis of the complex 4a

Approximately 0.0442 g (0.0742 mmol) of the allyl complex **3a** and 0.0196 g (0.0747 mmol) of PPh_3 were dissolved in about 12 mL of anhydrous CH_2Cl_2 and stirred at RT for about 30 min in a 50-mL two-necked flask under an inert atmosphere (Ar).

The resulting mixture was treated with 0.0236 g (0.193 mmol) of $NaClO_4{\cdot}H_2O$ dissolved in approximately 4 mL of methanol and stirred for further 20 min, dried under vacuum, and treated with CH_2Cl_2 and activated carbon. The inorganic salts were filtered off on a Celite filter and repeatedly washed with CH_2Cl_2, and the filtrate concentrated under vacuum. Addition of diethyl ether to the concentrated solution caused the precipitation of complex **4a** as a pale orange solid which was filtered off on a Gooch crucible and washed with *n*-pentane. About 0.0519 g of **4a** was obtained (yield 85%).

2 *Exo* isomers (α anomer + β anomer) (67%)

^{1}H-NMR (300 MHz, $CDCl_3$, T = 298 K, ppm) δ: 1.95 (s, 3H, OCH_3), 1.98 (s, 3H, OCH_3), 2.00 (s, 3H, OCH_3), 2.02 (s, 3H, OCH_3), 2.03 (s, 3H, OCH_3), 2.04 (s, 3H, OCH_3), 2.05 (s, 3H, OCH_3), 2.06 (s, 3H, OCH_3), 3.05 (s, 3H, NCH_3), 3.31 (s, 3H, NCH_3), 3.17 (d, 2H, J = 12.7 Hz, 2*anti* allyl-H *trans*-C), 3.39 (m, 2H, 2*anti* allyl-H *trans*-P), 3.59–3.92 (m, 4H, 2*syn* allyl-H *trans*-C + $2H^5$), 4.01–4.58 (m, 2H, 2*syn* allyl-H *trans*-P), 4.01–4.58 (m, 2H, 2*syn* allyl-H *trans*-P), 5.04–5.54 (m, 10H, $2CH_2^6$ + $2H^3$ + $2H^2$ + $2H^4$), 5.74 (d, 2H, J = 8.6 Hz, H^1), 5.92 (m, 2H, 2*central* allyl-H), 6.82 (d, 1H, J = 2.1 Hz, H^{Im}), 6.85 (d, 1H, J = 2.1 Hz, H^{Im}), 7.20–7.53 (m, 32H, 6Ph + $2H^{Im}$).

$^{31}P\{^1H\}$-NMR ($CDCl_3$, T = 298 K, ppm) δ: 26.0, 25.6.

$^{13}C\{^1H\}$-NMR ($CDCl_3$, T = 298 K, ppm selected peaks) δ: 20.0 (CH_3, OCH_3), 20.4 (CH_3, OCH_3), 20.5 (CH_3, OCH_3), 20.7 (CH_3, OCH_3), 20.7 (CH_3, OCH_3), 20.8 (CH_3, OCH_3), 20.8 (CH_3, OCH_3), 20.9 (CH_3, OCH_3), 37.6 (CH_3, NCH_3), 38.0 (CH_3, NCH_3), 69.7 (d, CH_2, J_{C-P} = 38.8 Hz, allyl *trans*-P), 60.2 (CH_2, CH_2^6), 60.5 (CH_2, CH_2^6), 74.1 (CH_2, allyl *trans*-C), 86.5 (CH, CH^1), 86.6 (CH, CH^1), 118.9 (CH, CH^{Im}), 119.0 (CH, CH^{Im}), 122.2 (CH, *central* allyl), 124.9 (CH, CH^{Im}), 125.0 (CH, CH^{Im}), 129.2–133.4 (Ph), 169.1 (C, C=O), 169.2 (C, C=O), 169.4 (C, C=O), 169.5 (C, C=O), 169.8 (C, C=O), 169.9 (C, C=O), 170.1 (C, C=O), 170.2 (C, C=O), 180.4 (d, J_{C-P} = 19.5 Hz, C, carbene), 181.0 (d, J_{C-P} = 19.5 Hz, C, carbene).

2 *Endo* isomers (α anomer + β anomer) (33%)

^{1}H-NMR (300 MHz, $CDCl_3$, T = 298 K, ppm) δ: 1.98 (s, 3H, OCH_3), 1.99 (s, 3H, OCH_3), 2.07 (s, 3H, OCH_3), 2.09 (s, 3H, OCH_3), 2.10 (s, 3H, OCH_3), 2.11 (s, 3H, OCH_3), 2.12 (s, 3H, OCH_3), 2.19 (s, 3H, OCH_3), 2.95 (d, 2H, J = 12.7 Hz, 2*anti* allyl-H *trans*-C), 2.99 (s, 3H, NCH_3), 3.23 (s, 3H, NCH_3), 3.39 (m, 2H, 2*anti* allyl-H *trans*-P), 3.59–3.92 (m, 4H, 2*syn* allyl-H *trans*-C + $2H^5$), 4.01–4.58 (m, 2H, 2*syn* allyl-H *trans*-P), 5.04–5.54 (m, 10H, $2CH_2^6$ + $2H^3$ + $2H^2$ + $2H^4$), 5.76 (d, 2H, J = 8.6 Hz, H^1), 5.92 (m, 2H, 2*central* allyl-H), 6.95 (d, 1H, J = 2.1 Hz, H^{Im}), 6.98 (d, 1H, J = 2.1 Hz, H^{Im}), 7.20–7.53 (m, 32H, 6Ph + $2H^{Im}$).

$^{31}P\{^1H\}$-NMR ($CDCl_3$, T = 298 K, ppm) δ: 25.4, 25.1.

$^{13}C\{^1H\}$-NMR ($CDCl_3$, T = 298 K, ppm selected peaks) δ: 20.4 (CH_3, OCH_3), 20.5 (CH_3, OCH_3), 20.6 (CH_3, OCH_3), 20.7 (CH_3, OCH_3), 37.5 (CH_3, NCH_3), 37.8 (CH_3, NCH_3), 60.2 (CH_2, CH_2^6), 60.5 (CH_2, CH_2^6), 73.0 (CH, CH^3), 69.3 (d, CH_2, J_{C-P} = 27.4 Hz, allyl *trans*-P), 74.2 (CH_2, allyl *trans*-C), 86.0 (CH, CH^1), 86.2 (CH, CH^1), 121.8 (CH, CH^{Im}), 121.9 (CH, CH^{Im}), 122.1 (CH, *central* allyl), 122.6 (CH, CH^{Im}), 122.7 (CH, CH^{Im}), 129.2–133.4 (Ph), 169.0 (C, C=O), 169.3 (C, C=O), 169.4 (C, C=O), 169.7 (C, C=O), 169.8 (C, C=O), 169.9 (C, C=O), 170.3 (C, C=O), 170.4 (C, C=O), 180.2 (d, J_{C-P} = 19.5 Hz, C, carbene), 181.1 (d, J_{C-P} = 19.5 Hz, C, carbene). IR (KBr): $\nu_{C=O}$ = 1752 cm^{-1}, ν_{C-O} = 1231 cm^{-1}; high-resolution mass spectrometry (HRMS; ESI^+): calcd for $C_{39}H_{44}N_2O_9PPd$ $[M]^+$: 821.1814. Found: 821.1823; Anal. Calcd for $C_{39}H_{44}ClN_2O_{13}PPd$ (%): C, 50.83; H, 4.81; N, 3.04. Found (%):C, 50.87; H, 4.74; N, 3.00.

2.6.2 | Synthesis of the complex 4b

Complex **4b** was prepared in an analogous manner to that described for **4a** starting from 0.0365 g of **3b**,

0.0138 g of PPh_3, and 0.0155 g of $NaClO_4{\cdot}H_2O$. About 0.0423 g (yield 83%) of **4b** was obtained as a white solid.

2 *Exo* isomers (α anomer + β anomer) (73%)

^{1}H-NMR (300 MHz, CD_2Cl_2, T = 298 K, ppm) δ: 0.79–0.89 (m, 6H, $2CH_3^{4\prime}$), 1.05–1.49 (m, 8H, $2CH_2^{3\prime} + 2CH_2^{2\prime}$), 1.89 (s, 3H, OCH_3), 1.94 (s, 3H, OCH_3), 1.98 (s, 3H, OCH_3), 2.01 (s, 3H, OCH_3), 2.02 (s, 3H, OCH_3), 2.03 (s, 3H, OCH_3), 2.05 (s, 3H, OCH_3), 2.07 (s, 3H, OCH_3), 3.65 (d, 2H, J = 12.7 Hz, 2*anti* allyl-H *trans*-C), 3.01–3.42 (m, 4H, 2*anti* allyl-H *trans*-P + $2H^5$), 3.82 (d, 1H, J = 3.9 Hz, *syn* allyl-H *trans*-C), 3.86 (d, 1H, J = 3.9 Hz, *syn* allyl-H *trans*-C), 4.30–4.41 (m, 2H, 2*syn* allyl-H *trans*-P), 5.03–5.77 (m, 12H, $2CH_2^6 + 2H^3 + 2H^2 + 2H^4 + 2H^1$), 5.93 (m, 2H, 2*central* allyl-H), 6.93 (d, 1H, J = 2.1 Hz, H^{Im}), 6.98 (d, 1H, J = 2.1 Hz, H^{Im}), 7.13–7.58 (m, 32H, 6Ph + $2H^{Im}$).

^{31}P{^{1}H}-NMR (CD_2Cl_2, T = 298 K, ppm) δ: 25.6, 25.5.

^{13}C{^{1}H}-NMR ($CDCl_3$, T = 298 K, ppm selected peaks) δ: 13.6 (CH_3, $CH_3^{4\prime}$), 13.7 (CH_3, $CH_3^{4\prime}$), 19.5 (CH_2, $CH_2^{3\prime}$), 19.6 (CH_2, $CH_2^{3\prime}$), 20.4–20.7 (CH_3, OCH_3), 31.4 (CH_2, $CH_2^{2\prime}$), 31.5 (CH_2, $CH_2^{2\prime}$), 50.5 (CH_2, $CH_2^{1\prime}$), 51.0 (CH_2, $CH_2^{1\prime}$), 60.4 (CH_2, CH_2^6), 60.7 (CH_2, CH_2^6), 67.2 (CH, CH^4), 67.3 (CH, CH^4), 68.3 (d, CH_2, J_{C-P} = 29.6 Hz, allyl *trans*-P), 68.4 (d, CH_2, J_{C-P} = 27.7 Hz, allyl *trans*-P), 69.3 (CH_2, allyl *trans*-C), 69.7 (CH_2, allyl *trans*-C), 86.4 (CH, CH^1), 86.5 (CH, CH^1), 119.3 (CH, CH^{Im}), 119.4 (CH, CH^{Im}), 122.0 (d, CH, J_{C-P} = 5.3 Hz, *central* allyl), 122.4 (d, CH, J_{C-P} = 4.8 Hz, *central* allyl), 123.0 (CH, CH^{Im}), 123.2 (CH, CH^{Im}), 129.2–133.4 (Ph), 169.1 (C, C=O), 169.2 (C, C=O), 169.4 (C, C=O), 169.5 (C, C=O), 169.6 (C, C=O), 169.7 (C, C=O), 170.1 (C, C=O), 170.2 (C, C=O), 179.7 (d, J_{C-P} = 19.1 Hz, C, carbene), 179.9 (d, J_{C-P} = 15.1 Hz, C, carbene).

2 *Endo* isomers (α anomer + β anomer) (27%)

^{1}H-NMR (300 MHz, CD_2Cl_2, T = 298 K, ppm) δ: 0.79–0.89 (m, 6H, $2CH_3^{4\prime}$), 1.05–1.49 (m, 8H, $2CH_2^{3\prime} + 2CH_2^{2\prime}$), 1.43 (s, 3H, OCH_3), 1.45 (s, 3H, OCH_3), 1.94 (s, 3H, OCH_3), 1.98 (s, 3H, OCH_3), 2.00 (s, 3H, OCH_3), 2.10 (s, 3H, OCH_3), 2.11 (s, 3H, OCH_3), 2.12 (s, 3H, OCH_3), 2.84 (d, 2H, J = 12.7 Hz, 2*anti* allyl-H *trans*-C), 3.01–3.42 (m, 4H, 2*anti* allyl-H *trans*-P + $2H^5$), 3.65 (d, 1H, J = 3.9 Hz, *syn* allyl-H *trans*-C), 3.73 (d, 1H, J = 3.9 Hz, *syn* allyl-H *trans*-C), 4.12–4.16 (m, 2H, 2*syn* allyl-H *trans*-P), 5.03–5.77 (m, 12H, $2CH_2^6 + 2H^3 + 2H^2 + 2H^4 + 2H^1$), 5.93 (m, 2H, 2*central* allyl-H), 7.03 (d, 1H, J = 2.1 Hz, H^{Im}), 7.08 (d, 1H, J = 2.1 Hz, H^{Im}), 7.13–7.58 (m, 32H, 6Ph + $2H^{Im}$).

^{31}P{^{1}H}-NMR (CD_2Cl_2, T = 298 K, ppm) δ: 25.2, 25.4.

^{13}C{^{1}H}-NMR ($CDCl_3$, T = 298 K, ppm selected peaks) δ: 13.5 (CH_3, $CH_3^{4\prime}$), 13.6 (CH_3, $CH_3^{4\prime}$), 19.6 (CH_2, $CH_2^{3\prime}$), 19.7 (CH_2, $CH_2^{3\prime}$), 20.1–20.9 (CH_3, OCH_3), 31.6 (CH_2, $CH_2^{2\prime}$), 31.7 (CH_2, $CH_2^{2\prime}$), 51.0 (CH_2, $CH_2^{1\prime}$), 51.1 (CH_2, $CH_2^{1\prime}$), 62.2 (CH_2, CH_2^6), 62.4 (CH_2, CH_2^6), 67.6 (CH, CH^4), 67.8 (CH, CH^4), 68.3 (d, CH_2, J_{C-P} = 29.6 Hz, allyl *trans*-P), 68.4 (d, CH_2, J_{C-P} = 27.7 Hz, allyl *trans*-P), 68.8 (CH_2, allyl *trans*-C), 69.0 (CH_2, allyl *trans*-C), 86.0 (CH, CH^1), 86.1 (CH, CH^1), 119.9 (CH, CH^{Im}), 119.9 (CH, CH^{Im}), 121.7 (d, CH, J_{C-P} = 5.8 Hz, *central* allyl), 122.6 (CH, CH^{Im}), 122.8 (CH, CH^{Im}), 129.2–133.4 (Ph), 169.2 (C, C=O), 169.2 (C, C=O), 169.3 (C, C=O), 169.3 (C, C=O), 169.9 (C, C=O), 170.0 (C, C=O), 170.3 (C, C=O), 170.4 (C, C=O), 180.1 (d, J_{C-P} = 18.0 Hz, C, carbene), 181.1 (d, J_{C-P} = 19.2 Hz, C, carbene). IR (KBr): $\nu_{C=O}$ = 1754 cm^{-1}, ν_{C-O} = 1231 cm^{-1}.

HRMS (ESI$^+$): calcd for $C_{42}H_{50}N_2O_9PPd$ $[M]^+$: 863.2283. Found: 863.2277. Anal. Calcd for $C_{42}H_{50}ClN_2O_{13}PPd$ (%): C, 52.35; H, 5.23; N, 2.91. Found (%):C, 52.27; H, 5.14; N, 2.98.

2.6.3 | Synthesis of the complex 4c

Complex **4c** was prepared in an analogous manner to that described for **4a** starting from 0.0369 g of **3c**, 0.0143 g of PPh_3, and 0.0150 g of $NaClO_4{\cdot}H_2O$. About 0.0488 g (yield 88%) of **4c** was obtained as a white solid.

2 *Exo* isomers (α anomer + β anomer) (55%)

^{1}H-NMR (300 MHz, $CDCl_3$, T = 298 K, ppm selected peaks) δ: 1.28 (s, 3H, p-CH_3^{Mes}), 1.76 (s, 3H, OCH_3), 1.90 (s, 6H, 2 o-CH_3^{Mes}), 2.03 (s, 3H, OCH_3), 2.07 (s, 3H, OCH_3), 2.37 (s, 3H, OCH_3), 2.84 (d, 2H, J = 12.7 Hz, 2*anti* allyl-H *trans*-C), 3.32 (d, 2H, J = 7.4 Hz, 2*syn* allyl-H *trans*-C), 3.60 (m, 2H, 2*anti* allyl-H *trans*-P), 4.40 (m, 2H, 2 *syn* allyl-H *trans*-P), 5.11 (m, 2H, 2*central* allyl-H), 6.62–7.62 (m, 34H, 6Ph + $4H^{Im}$).

^{31}P{^{1}H}-NMR ($CDCl_3$, T = 298 K, ppm) δ: 23.0, 22.3.

^{13}C{^{1}H}-NMR ($CDCl_3$, T = 298 K, ppm selected peaks) δ: 16.6–17.6 (CH_3, CH_3^{Mes}), 20.5–21.1 (CH_3, OCH_3), 71.5 (d, CH_2, J_{C-P} = 28.4 Hz, allyl *trans*-P), 74.2 (CH_2, allyl *trans*-C), 86.4 (CH, CH^1), 119.7 (CH, CH^{Im}), 120.0 (CH, CH^{Im}), 122.8 (d, CH, J_{C-P} = 3.2 Hz, *central* allyl), 126.4 (CH, CH^{Im}), 126.6 (CH, CH^{Im}), 128.9–140.2 (Ph), 169.3–170.4 (C, C=O), 181.8 (d, J_{C-P} = 14.7 Hz, C, carbene).

2 *Endo* isomers (α Anomer + β Anomer) (45%)

^{1}H-NMR (300 MHz, $CDCl_3$, T = 298 K, ppm selected peaks) δ: 1.09 (s, 3H, p-CH_3^{Mes}), 1.77 (s, 3H, OCH_3), 1.90 (s, 6H, 2 o-CH_3^{Mes}), 2.06 (s, 3H, OCH_3), 2.09 (s, 3H, OCH_3), 2.34 (s, 3H, OCH_3), 2.84 (d, 2H, J = 12.7 Hz, 2*anti* allyl-H *trans*-C), 3.32 (d, 2H, J = 7.4 Hz, 2*syn* allyl-H *trans*-C), 3.60 (m, 2H, 2*anti* allyl-H *trans*-P), 4.32 (m, 2H, 2 *syn* allyl-H *trans*-P), 6.06 (m, 2H, 2*central* allyl-H), 6.62–7.62 (m, 34H, 6Ph + $4H^{Im}$).

^{31}P{^{1}H}-NMR ($CDCl_3$, T = 298 K, ppm) δ: 21.8, 21.8.

^{13}C{^{1}H}-NMR ($CDCl_3$, T = 298 K, ppm selected peaks) δ: 16.6–17.6 (CH_3, CH_3^{Mes}), 20.5–21.1 (CH_3, OCH_3), 71.5 (d, CH_2, J_{C-P} = 28.4 Hz, allyl *trans*-P), 74.1 (CH_2, allyl *trans*-C), 86.5 (CH, CH^1), 119.7 (CH, CH^{Im}), 120.0 (CH, CH^{Im}), 120.8 (d, CH, J_{C-P} = 5.3 Hz, *central* allyl), 126.4 (CH, CH^{Im}), 126.6

(CH, CH^{Im}), 128.9–140.2 (Ph), 169.3–170.4 (C, C=O), 181.8 (d, J_{C-P} = 14.7 Hz, C, carbene).

IR (KBr): $\nu_{C=O}$ = 1752 cm^{-1}, ν_{C-O} = 1230 cm^{-1}.

HRMS (ESI^+): calcd. for $C_{47}H_{52}N_2O_9PPd$ $[M]^+$: 925.2440. Found: 925.2445.

Anal. Calcd for $C_{47}H_{52}ClN_2O_{13}PPd$ (%):C, 55.03; H, 5.11; N, 2.73. Found (%):C, 55.11; H, 5.18; N, 2.81.

2.7 | Synthesis of mixed NHC/PTA Pd allyl complexes

2.7.1 | Synthesis of the complex 5a

Approximately 0.0502 g (0.0843 mmol) of the allyl complex **3a** and 0.0132 g (0.0843 mmol) of PTA were dissolved in about 12 mL of anhydrous CH_2Cl_2 and stirred at RT for about 30 min in a 50-mL two-necked flask under an inert atmosphere (Ar).

The resulting mixture was treated with 0.0268 g (0.219 mmol) of $NaClO_4{\cdot}H_2O$ dissolved in 4 mL of methanol and stirred for further 20 min, dried under vacuum, and treated with CH_2Cl_2 and activated carbon. The inorganic salts were filtered off on a Celite filter and repeatedly washed with CH_2Cl_2, and the filtrate concentrated under vacuum. Addition of diethyl ether to the concentrated solution caused the precipitation of complex **5a** as a white solid which was filtered off on a Gooch crucible and washed with *n*-pentane. About 0.0619 g of **5a** was obtained (yield 90%).

2 *Exo* isomers (α anomer + β anomer) (75%)

^{1}H-NMR (300 MHz, $CDCl_3$, T = 298 K, ppm) δ: 1.92–2.10 (24H, 8 OCH_3), 2.95 (d, H, J = 13.3 Hz, *anti* allyl-H *trans*-C), 3.17 (m, 2H, 2*anti* allyl-H *trans*-P), 3.41 (d, H, J = 13.4 Hz, *anti* allyl-H *trans*-C), 3.58 (s, 3H, NCH_3), 3.80 (s, 3H, NCH_3), 3.90–4.62 (32H, 2*syn* allyl-H *trans*-C + $2H^5$ + 2*syn* allyl-H *trans*-P + 2*syn* allyl-H *trans*-P + $6NCH_2N$ + $6NCH_2P$), 5.11–5.70 (12H, 2*central* allyl-H + $2CH_2{}^6$ + $2H^3$ + $2H^2$ + $2H^4$), 5.89 (d, 2H, J = 9.2 Hz, H^1), 7.20 (d, 1H, J = 2.0 Hz, H^{Im}), 7.22 (d, 1H, J = 2.0 Hz, H^{Im}), 7.35 (d, 1H, J = 2.1 Hz, H^{Im}), 7.38 (d, 1H, J = 2.1 Hz, H^{Im}).

$^{31}P\{^1H\}$-NMR ($CDCl_3$, T = 298 K, ppm) δ: −56.1, −56.2.

$^{13}C\{^1H\}$-NMR ($CDCl_3$, T = 298 K, ppm selected peaks) δ: 20.4–20.8 (CH_3, OCH_3), 38.2 (CH_3, NCH_3), 38.4 (CH_3, NCH_3), 52.5 (d, CH_2, J_{C-P} = 12.5 Hz, NCH_2N), 62.1 (CH_2, allyl *trans*-C), 68.0–68.4 (CH_2, allyl *trans*-P), 72.8–74.0 (CH_2, NCH_2P), 85.4 (CH, CH^1), 119.8 (CH, CH^{Im}), 119.9 (CH, CH^{Im}), 122.4 (CH, *central* allyl), 124.6 (CH, CH^{Im}), 124.8 (CH, CH^{Im}), 169.0–170.7 (C, C=O), 178.7 (d, J_{C-P} = 21.5 Hz, C, carbene).

2 *Endo* isomers (α anomer + β anomer) (25%)

^{1}H-NMR (300 MHz, $CDCl_3$, T = 298 K, ppm) δ: 1.92–2.10 (24H, 8 OCH_3), 2.97 (d, H, J = 13.2 Hz, *anti* allyl-H *trans*-C), 3.06 (m, 2H, 2*anti* allyl-H *trans*-P), 3.33 (d, H, J = 13.3 Hz, *anti* allyl-H *trans*-C), 3.62 (s, 3H, NCH_3), 3.83 (s, 3H, NCH_3), 3.90–4.62 (32H, 2*syn* allyl-H *trans*-C + $2H^5$ + 2*syn* allyl-H *trans*-P + 2*syn* allyl-H *trans*-P + $6NCH_2N$ + $6NCH_2P$), 5.11–5.70 (12H, 2*central* allyl-H + $2CH_2{}^6$ + $2H^3$ + $2H^2$ + $2H^4$), 5.87 (d, 2H, J = 9.2 Hz, H^1), 7.25–7.30 (2H, $2H^{Im}$), 7.35–7.40 (2H, $2H^{Im}$).

$^{31}P\{^1H\}$-NMR ($CDCl_3$, T = 298 K, ppm) δ: −56.6, −56.8.

$^{13}C\{^1H\}$-NMR ($CDCl_3$, T = 298 K, ppm selected peaks) δ: 20.4–20.8 (CH_3, OCH_3), 38.2 (CH_3, NCH_3), 38.3 (CH_3, NCH_3), 52.8 (d, CH_2, J_{C-P} = 12.7 Hz, NCH_2N), 63.4 (CH_2, allyl *trans*-C), 68.0–68.4 (CH_2, allyl *trans*-P), 72.8–74.0 (CH_2, NCH_2P), 85.4 (CH, CH^1), 119.8 (CH, CH^{Im}), 119.9 (CH, CH^{Im}), 122.3 (CH, *central* allyl), 124.6 (CH, CH^{Im}), 124.7 (CH, CH^{Im}), 169.0–170.7 (C, C=O), 178.4 (d, J_{C-P} = 20.5 Hz, C, carbene).

IR (KBr): $\nu_{C=O}$ = 1754 cm^{-1}, ν_{C-O} = 1230 cm^{-1}.

HRMS (ESI^+): calcd for $C_{27}H_{41}N_5O_9PPd$ $[M]^+$: 716.1671. Found: 716.1648.

Anal. Calcd for $C_{27}H_{41}ClN_5O_{13}PPd$ (%):C, 39.72; H, 5.06; N, 8.58.. Found (%): C, 39.81; H, 5.01; N, 8.47.

2.7.2 | Synthesis of the complex 5b

Complex **5b** was prepared in an analogous manner to that described for **5a** starting from 0.0468 g of **3b**, 0.0115 g of PTA, and 0.0206 g of $NaClO_4{\cdot}H_2O$. About 0.0553 g (yield 88%) of **5b** was obtained as a white solid.

2 *Exo* isomers (α anomer + β anomer) (74%)

^{1}H-NMR (300 MHz, $CDCl_3$, T = 298 K, ppm) δ: 0.88–1.00 (m, 6H, $2CH_3{}^{4\prime}$), 1.21–1.69 (m, 8H, $2CH_2{}^{3\prime}$ + $2CH_2{}^{2\prime}$), 1.70–2.13 (24H, 8 OCH_3), 2.92 (d, H, J = 13.2 Hz, *anti* allyl-H *trans*-C), 3.25 (m, 2H, 2*anti* allyl-H *trans*-P), 3.48 (d, H, J = 13.4 Hz, *anti* allyl-H *trans*-C), 3.80–4.66 (34H, 2*syn* allyl-H *trans*-C + $2H^5$ + 2*syn* allyl-H *trans*-P + 2*syn* allyl-H *trans*-P + $6NCH_2N$ + $6NCH_2P$ + $2CH_3{}^{1\prime}$), 5.11–5.77 (12H, 2*central* allyl-H + $2CH_2{}^6$ + $2H^3$ + $2H^2$ + $2H^4$), 5.91 (d, 2H, J = 9.2 Hz, H^1), 7.19 (d, 1H, J = 2.0 Hz, H^{Im}), 7.22 (d, 1H, J = 2.0 Hz, H^{Im}), 7.38 (d, 1H, J = 2.1 Hz, H^{Im}), 7.40 (d, 1H, J = 2.1 Hz, H^{Im}).

$^{31}P\{^1H\}$-NMR ($CDCl_3$, T = 298 K, ppm) δ: −56.4, −56.5.

$^{13}C\{^1H\}$-NMR ($CDCl_3$, T = 298 K, ppm selected peaks) δ: 13.6 (CH_3, $CH_3{}^{4\prime}$), 13.7 (CH_3, $CH_3{}^{4\prime}$), 19.5 (CH_2, $CH_2{}^{3\prime}$), 19.5 (CH_2, $CH_2{}^{3\prime}$), 20.3–20.8 (CH_3, OCH_3), 32.4 (CH_2, $CH_2{}^{2\prime}$), 32.4 (CH_2, $CH_2{}^{2\prime}$), 51.1 (CH_2, $CH_2{}^{1\prime}$), 51.1 (CH_2, $CH_2{}^{1\prime}$), 52.6 (d, CH_2, J_{C-P} = 12.0 Hz, NCH_2N), 52.6 (d, CH_2, J_{C-P} = 12.0 Hz, NCH_2N), 61.1 (CH_2, $CH_2{}^6$), 61.1

(CH_2, CH_2^6), 63.5 (CH_2, allyl *trans*-C), 67.8 (CH, CH^4), 67.8 (CH, CH^4), 69.3 (d, CH_2, J_{C-P} = 27.8 Hz, allyl *trans*-P), 72.9 (d, CH_2, J_{C-P} = 27.0 Hz, NCH_2P), 73.0 (d, CH_2, J_{C-P} = 26.8 Hz, NCH_2P), 85.5 (CH, CH^1), 120.0 (CH, CH^{Im}), 120.2 (CH, CH^{Im}), 120.9 (d, CH, J_{C-P} = 5.3 Hz, *central* allyl), 122.7 (CH, CH^{Im}), 123.0 (CH, CH^{Im}), 169.0–170.7 (C, C=O), 177.2 (d, J_{C-P} = 18.6 Hz, C, carbene), 177.6 (d, J_{C-P} = 19.0 Hz, C, carbene).

2 *Endo* isomers (α anomer + β anomer) (26%)

^{1}H-NMR (300 MHz, $CDCl_3$, T = 298 K, ppm) δ: 0.88–1.00 (m, 6H, $2CH_3^{4\prime}$), 1.21–1.69 (m, 8H, $2CH_2^{3\prime}$ + $2CH_2^{2\prime}$), 1.70–2.13 (24H, 8 OCH_3), 2.93 (d, H, J = 13.2 Hz, *anti* allyl-H *trans*-C), 3.31 (m, 2H, 2*anti* allyl-H *trans*-P), 3.46 (d, H, J = 13.3 Hz, *anti* allyl-H *trans*-C), 3.80–4.66 (34H, 2*syn* allyl-H *trans*-C + $2H^5$ + 2*syn* allyl-H *trans*-P + 2*syn* allyl-H *trans*-P + $6NCH_2N$ + $6NCH_2P$ + $2CH_3^{1\prime}$), 5.11–5.77 (12H, 2*central* allyl-H + $2CH_2^6$ + $2H^3$ + $2H^2$ + $2H^4$), 5.90 (d, 2H, J = 9.2 Hz, H^1), 7.17–7.22 (2H, $2H^{Im}$), 7.36–7.41 (2H, $2H^{Im}$).

^{31}P{^{1}H}-NMR ($CDCl_3$, T = 298 K, ppm) δ: −57.0, −57.1.

^{13}C{^{1}H}-NMR ($CDCl_3$, T = 298 K, ppm selected peaks) δ: 13.8 (CH_3, $CH_3^{4\prime}$), 13.8 (CH_3, $CH_3^{4\prime}$), 19.6 (CH_2, $CH_2^{3\prime}$), 19.6 (CH_2, $CH_2^{3\prime}$), 20.3–20.8 (CH_3, OCH_3), 32.6 (CH_2, $CH_2^{2\prime}$), 32.6 (CH_2, $CH_2^{2\prime}$), 51.3 (CH_2, $CH_2^{1\prime}$), 51.3 (CH_2, $CH_2^{1\prime}$), 52.5 (d, CH_2, J_{C-P} = 12.0 Hz, NCH_2N), 52.8 (d, CH_2, J_{C-P} = 12.1 Hz, NCH_2N), 61.0 (CH_2, CH_2^6), 61.0 (CH_2, CH_2^6), 63.0 (CH_2, allyl *trans*-C), 67.7 (CH, CH^4), 67.7 (CH, CH^4), 69.4 (d, CH_2, J_{C-P} = 27.5 Hz, allyl *trans*-P), 73.1 (d, CH_2, J_{C-P} = 27.0 Hz, NCH_2P), 73.6 (d, CH_2, J_{C-P} = 26.8 Hz, NCH_2P), 85.6 (CH, CH^1), 120.1 (CH, CH^{Im}), 120.2 (CH, CH^{Im}), 121.1 (d, CH, J_{C-P} = 5.5 Hz, *central* allyl), 122.5 (CH, CH^{Im}), 122.9 (CH, CH^{Im}), 169.0–170.7 (C, C=O), 177.2 (d, J_{C-P} = 18.6 Hz, C, carbene), 177.6 (d, J_{C-P} = 19.0 Hz, C, carbene).

IR (KBr): $\nu_{C=O}$ = 1753 cm^{-1}, ν_{C-O} = 1231 cm^{-1}.

HRMS (ESI^+): calcd for $C_{30}H_{47}N_5O_9PPd$ $[M]^+$: 758.2146. Found: 758.2138.

Anal. Calcd for $C_{30}H_{47}ClN_5O_{13}PPd$ (%):C, 41.97; H, 5.52; N, 8.16. Found (%): C, 42.08; H, 5.44; N, 8.10.

2.7.3 | Synthesis of the complex 5c

Complex **5c** was prepared in an analogous manner to that described for **4a** starting from 0.0521 g of **3c**, 0.0117 g of PTA, and 0.0209 g of $NaClO_4$. About 0.0631 g (yield 92%) of **4c** was obtained as a white solid.

2 *Exo* isomers (α anomer + β anomer) (55%)

^{1}H-NMR (300 MHz, $CDCl_3$, T = 298 K, ppm selected peaks) δ: 1.86–2.38 (42H, 8 OCH_3, $6CH_3^{Mes}$), 3.16 (bd, 1H, *anti* allyl-H *trans*-C), 3.32 (m, 2H, 2*anti* allyl-H *trans*-P), 3.41 (d, H, J = 13.4 Hz, *anti* allyl-H *trans*-C), 3.88–4.88 (32H, 2*syn* allyl-H *trans*-C + $2H^5$ + 2*syn* allyl-H *trans*-P + 2*syn* allyl-H *trans*-P + $6NCH_2N$ + $6NCH_2P$), 5.09–5.88 (8H, 2*central* allyl-H + $2H^3$ + $2H^2$ + $2H^4$), 6.07 (d, 2H, J = 9.2 Hz, H^1), 6.93–7.85 (8H, Ar-H + 4 H^{Im}).

^{31}P{^{1}H}-NMR ($CDCl_3$, T = 298 K, ppm) δ: −58.5, −56.6.

^{13}C{^{1}H}-NMR ($CDCl_3$, T = 298 K, ppm selected peaks) δ: 17.4–18.5 (CH_3, CH_3^{Mes}), 20.5–21.2 (CH_3, OCH_3), 52.4–52.7 (CH_2, NCH_2N), 62.6 (CH_2, allyl *trans*-C), 69.9 (d, CH_2, J_{C-P} = 28.0 Hz, allyl *trans*-P), 73.0–73.2 (CH_2, NCH_2P), 85.4 (CH, CH^1), 119.9 (CH, CH^{Im}), 120.1 (CH, CH^{Im}), 122.9 (CH, *central* allyl), 125.6 (CH, CH^{Im}), 125.8 (CH, CH^{Im}), 129.3–140.4 (Ph), 169.2–170.8 (C, C=O), 181.6 (C, carbene).

2 *Endo* isomers (α anomer + β anomer) (45%)

^{1}H-NMR (300 MHz, $CDCl_3$, T = 298 K, ppm selected peaks) δ: 1.86–2.38 (42H, 8 OCH_3, $6CH_3^{Mes}$), 3.16 (bd, 1H, *anti* allyl-H *trans*-C), 3.32 (m, 2H, 2*anti* allyl-H *trans*-P), 3.43 (d, H, J = 13.4 Hz, *anti* allyl-H *trans*-C), 3.88–4.88 (32H, 2*syn* allyl-H *trans*-C + $2H^5$ + 2*syn* allyl-H *trans*-P + 2*syn* allyl-H *trans*-P + $6NCH_2N$ + $6NCH_2P$), 5.09–5.88 (8H, 2*central* allyl-H + $2H^3$ + $2H^2$ + $2H^4$), 6.19 (d, 2H, J = 9.1 Hz, H^1), 6.22 (d, 2H, J = 9.1 Hz, H^1), 6.93–7.85 (8H, Ar-H + 4 H^{Im}).

^{31}P{^{1}H}-NMR ($CDCl_3$, T = 298 K, ppm) δ: −59.5, −55.4.

^{13}C{^{1}H}-NMR ($CDCl_3$, T = 298 K, ppm selected peaks) δ: 17.4–18.5 (CH_3, CH_3^{Mes}), 20.5–21.2 (CH_3, OCH_3), 52.4–52.7 (CH_2, NCH_2N), 62.6 (CH_2, allyl *trans*-C), 69.9 (d, CH_2, J_{C-P} = 28.0 Hz, allyl *trans*-P), 73.0–73.2 (CH_2, NCH_2P), 85.4 (CH, CH^1), 119.9 (CH, CH^{Im}), 120.1 (CH, CH^{Im}), 122.9 (CH, *central* allyl), 125.6 (CH, CH^{Im}), 125.8 (CH, CH^{Im}), 129.3–140.4 (Ph), 169.2–170.8 (C, C=O), 181.6 (C, carbene).

IR (KBr): $\nu_{C=O}$ = 1750 cm^{-1}, ν_{C-O} = 1233 cm^{-1}.

HRMS (ESI^+): calcd for $C_{35}H_{49}N_5O_9PPd$ $[M]^+$: 820.2297. Found: 820.2296.

Anal. Calcd for $C_{35}H_{49}ClN_5O_{13}PPd$ (%):C, 45.66; H, 5.36; N, 7.61. Found (%): C, 45.58; H, 5.40; N, 7.70.

2.8 | 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 plated in 96 wells and grown for 96 hr. Cell viability was measured with a CellTiter-Glo 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.

2.9 | Computational details

The geometrical optimization of the complexes was carried out without symmetry constraints, using the hyper-GGA functional MO6,[26] in combination with polarized triple-ζ-quality basis sets [LAN2TZ(f)][27] and relativistic pseudopotential for the Pd atoms, polarized double-ζ-quality basis sets (LANL2DZdp)[28] with diffuse functions for the halogens, and polarized double-ζ-quality basis sets [6-31G(d,p)] for the other elements. Solvent effects (CH_2Cl_2) were included using CPCM.[29] The *restricted* formalism was applied in all the calculations. The zero-point vibrational energies and thermodynamic parameters were obtained by means of the stationary points characterized by IR simulation.[30] All the computational work was carried out on Intel based x86–64 workstations.

3 | RESULTS AND DISCUSSION

3.1 | Synthesis of carbohydrate-based imidazolium salts 1a–c

The protection of the α-D-glucose hydroxyl groups in positions 2, 3, 4, and 6 with acetyl groups and the simultaneous activation of the anomeric carbon (position 1) by bromination represent the first step of the synthesis of the carbohydrate-based imidazolium salts. The reaction was carried out at RT by reacting α-D-glucose, acetic anhydride, and acetyl bromide in the presence of a small amount of $HClO_4$ (Scheme 2).[22]

The imidazolium salts **1a–c** have been prepared from the 2,3,4,6-tetra-*O*-acetyl-α-D-glucosyl bromide following two different approaches (Scheme 3):

i. by reacting the 2,3,4,6-tetra-*O*-acetyl-α-D-glucosyl bromide with imidazole and subsequent alkylation of the imidazole derivative with methyl iodide or *n*-butyl bromide (compounds **1a** and **b**).[13b]
ii. by direct reaction of 2,3,4,6-tetra-*O*-acetyl-α-D-glucosyl bromide with mesityl-imidazole in the presence of AgOTf[14b] and subsequent OTf^-/Cl^- exchange on the DOWEX-21KCl resin (compound **1c**).

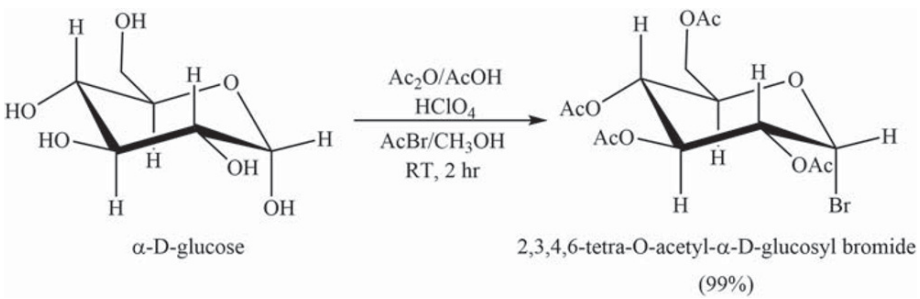
It is noteworthy that imidazolium salts **1a** and **b** were obtained as unique species characterized by β configuration of the anomeric carbon (Figures S1–S4), whereas the derivative **1c** was isolated as a 60:40 mixture of the α and β anomers; the anomerization process being probably promoted by interaction between the triflate species and the acid sites of the DOWEX-21KCl resin. The co-presence of the two anomers is unequivocally confirmed by the duplication of all the signals in the ^{1}H-NMR and ^{13}C-NMR spectra (Figures S5 and S6). Finally, the exchange between the triflate and chloride ions was confirmed by the disappearance of the signals at 639 cm^{-1} (S=O bending) and at 1200–1300 cm^{-1} (S=O and C–F triflate stretching) in the IR spectra (Figure S7).

3.2 | Synthesis of Ag(I) complexes with carbohydrate-based NHCs

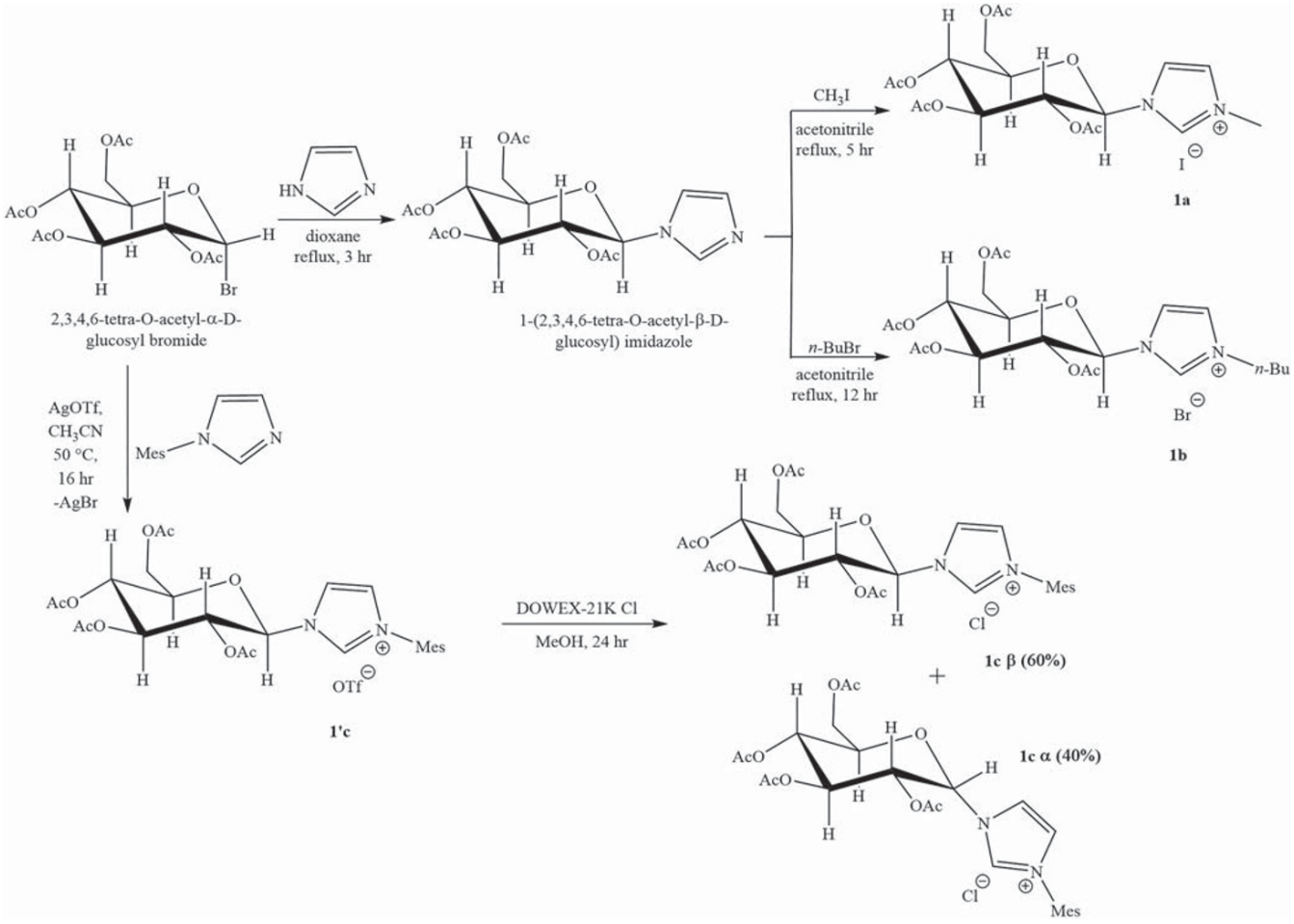
The silver(I) carbene complexes **2a–c** were obtained by reacting the imidazolium salts **1a–c** with silver oxide according to Scheme 4.

The reactions were carried out in anhydrous dichloromethane under an inert atmosphere (Ar) and in the dark for a time ranging from 5 to 12 hr depending on the R substituent. In all cases, the reaction progress was revealed by the gradual dissolution of the silver oxide. The products were isolated in good yields by precipitation with diethyl ether from the reaction mixture. All the synthesized complexes (**2a–c**) have been characterized by NMR and IR spectroscopy and are present as one single isomer, independent of the presence of one or two anomers in the starting imidazolium salts.

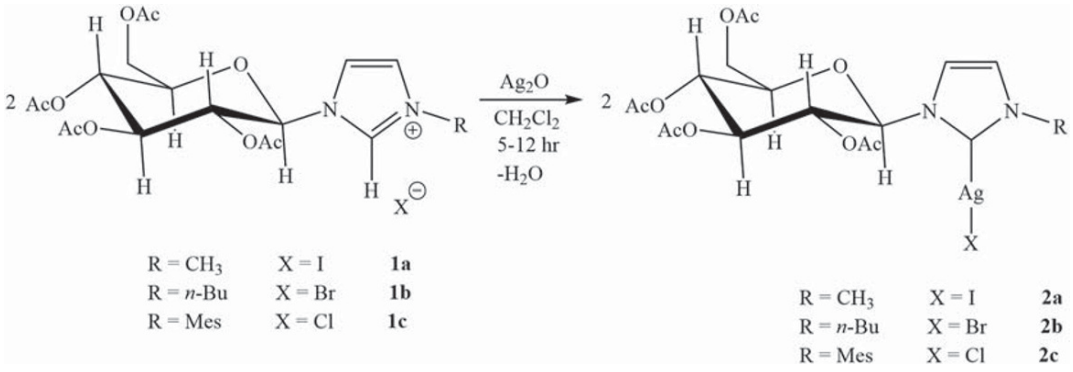
In more detail, we can observe the disappearance of the peak ascribable to the imidazolic proton NCHN between 8 and 11 ppm in the ^{1}H-NMR spectra (Figure S8) and the presence of the typical coordinated carbenic carbon signal between 180 and 190 ppm in the ^{13}C{^{1}H}-NMR spectra (Figures S9 and S12).



SCHEME 2 Functionalization of α-D-glucose. RT, room temperature



SCHEME 3 Synthesis of carbohydrate-based imidazolium salts (**1a–c**)



SCHEME 4 Synthesis of Ag(I)–NHC complexes (**2a–c**). NHC, *N*-heterocyclic carbene

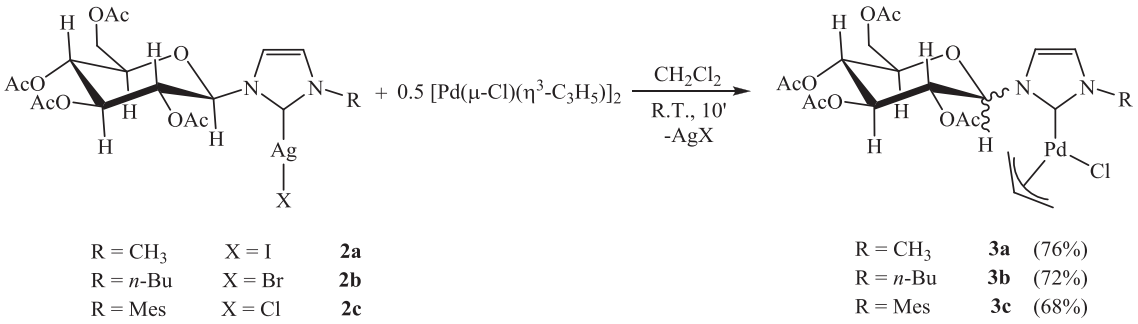
3.3 | Synthesis of the η³-allyl Pd(II) complexes

3.3.1 | Neutral η³-allyl Pd(II) complexes

The reaction between the precursor $[Pd(\mu\text{-}Cl)(\eta^3\text{-allyl})]_2$ and the silver complexes **2a–c** yields the neutral complexes **3a–c** and the relative silver halide whose formation and consequent precipitation represent the driving force of the whole process (Scheme 5).

The final complexes were separated in good yields by adding a diethyl ether/*n*-hexane mixture to the reaction residue.

^{1}H-NMR spectra at 298 K reveal that each product consists of two anomers. The anomerization is most likely promoted by the presence of the metal



SCHEME 5 Synthesis of neutral of η^3-allyl Pd complexes bearing carbohydrate-based NHCs (**3a–c**). NHC, *N*-heterocyclic carbene; RT, room temperature

centers Pd (II) and Ag(I) in the reaction mixture, which can act as Lewis acids, as already observed by other authors.[15,23]

The complexes under examination, having two different spectator ligands (Cl^- and NHC), exhibit for each anomer five different allylic proton signals in addition to the signals ascribable to the carbenic moiety.

Thus, in the ^{1}H-NMR spectra (Figures S13–S15) it is possible to identify for each anomer:

i. The acetyl OCH_3 signals resonant as singlets within 2 and 2.1 ppm.
ii. The $H^{anti}_{t\text{-}Cl}$ and $H^{anti}_{t\text{-}C}$ protons as doublets ($J \approx 12$–13 Hz) within 2.5 and 3.4 ppm, respectively.
iii. The $H^{syn}_{t\text{-}Cl}$ and $H^{syn}_{t\text{-}C}$ protons as doublets ($J \approx 5$–7 Hz) within 3.5 and 4.4 ppm, respectively.
iv. The $H^{central}$ signal as a multiplet at about 5.5 ppm.
v. The CH and CH_2 glycosidic signals within 4 and 6.3 ppm. In particular, the two doublets at about 6.2 ppm ($2H^1$) indicate the two different anomeric species.
vi. The signal of the methyl, *n*-butyl, and mesityl substituents slightly displaced with respect to those of the starting Ag(I) complexes.

The assignment of the proton signals for each species was achieved by means of the two-dimensional COSY technique (Figure S16). Moreover, from the NOESY spectra using the H^1 protons as reference, it was possible to attribute the proton signals to the two different anomeric species. In particular, as shown by DFT theoretical calculations, the spatial distance between the protons H^1 and H^2 (Figure S17) is different in the two anomers (about 2.9 and 2.3 Å for anomer β and α, respectively). Thus, the less intense cross-peak was assigned to the α anomer as reported in Figure 1.

By recording the ^{1}H-NMR spectra at low temperature (193–233 K) it was possible to freeze the rotation about the Pd–carbene bond with the consequent visualization of the signals related to four different species, two atropoisomers (*exo* and *endo*) for each anomer (α e β; Figure 2).

The two atropoisomers are distinguishable as a consequence of the mutual position of the R substituent (i.e. *n*-butyl for the compound **3b**) with respect to the central proton of the allyl group. As a matter of fact, the central allyl proton and the R group may be on the same or opposite side with respect to the main coordination plane that is identified by the palladium, the carbenic carbon, and the chloride ligand. As can be seen in Figure 3, atropoisomers *exo* are characterized by a reduced steric hindrance and therefore will be the most abundant in solution. For instance, the ratio between the *exo* and *endo* species in complex **3b** is *exo:endo* ≈ 80/20, as can be deduced from the spectra recorded at 193 K (see Figure 2).

The NMR characterization was completed by the analysis of the $^{13}C\{^1H\}$-NMR spectra (Figure S18–S20), where it is possible to observe for each anomer the signal of the carbenic carbon at 180–185 ppm, the signal of the central allyl carbon at about 115 ppm, and the signals of the allyl carbon *trans* to carbene and *trans* to chloride at about 73 and 49 ppm, respectively.

3.3.2 | Mixed NHC/PPh_3 and NHC/PTA η^3-allyl Pd(II) complexes

The cationic complexes, which represent the main synthetic target of this article, were prepared according to the procedure depicted in Scheme 6.

The reactions were carried out by adding to a dichloromethane solution of the complexes **3a–c** one equivalent of PPh_3 or PTA and subsequently, an excess of $NaClO_4 \cdot H_2O$ (dissolved separately in a 3:1 mixture of dichloromethane/methanol).

The precipitation of NaCl indicates the progress of the reaction. After the removal of the solvent, the residue was dissolved in dichloromethane and the inorganic salts were filtered off on a Celite filter. The final products were

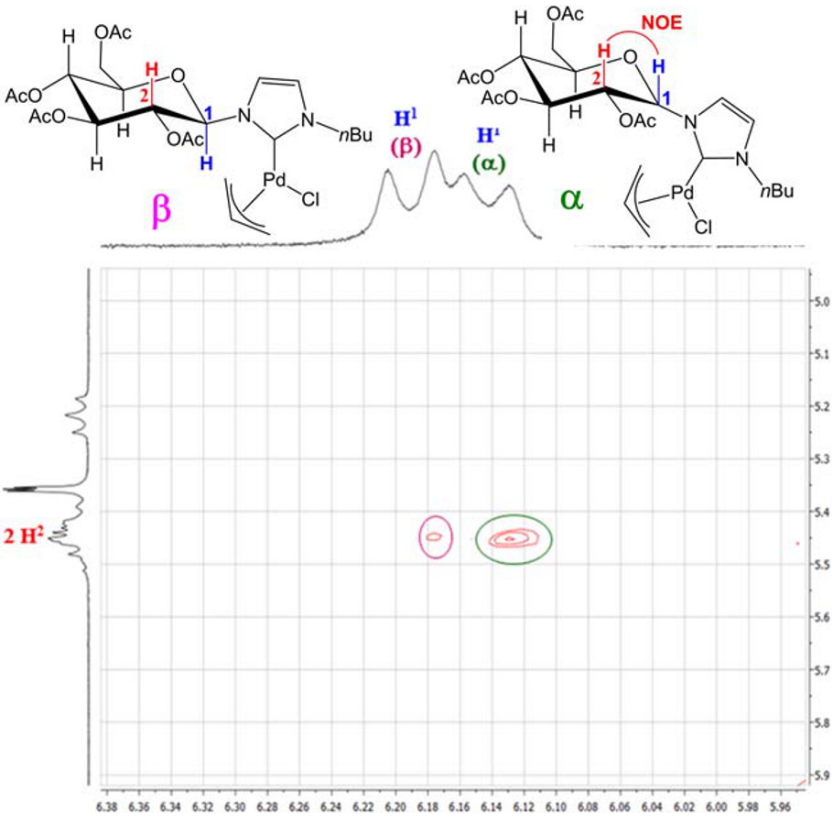


FIGURE 1 Relevant part of the NOESY spectrum of the complex **3b** (T = 298 K, $CDCl_3$)

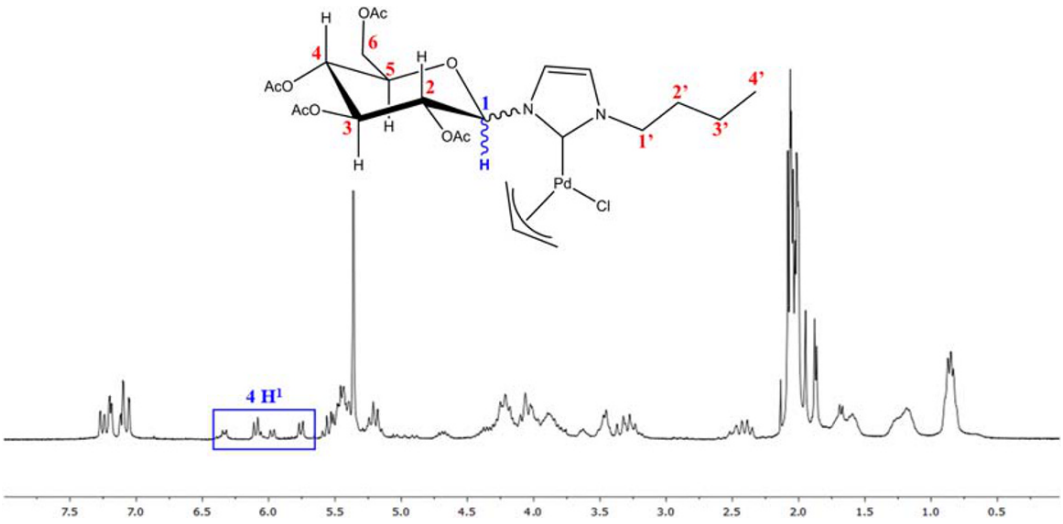


FIGURE 2 ^{1}H-NMR spectrum of the complex **3b** (T = 193 K, CD_2Cl_2). NMR, nuclear magnetic resonance

then easily isolated by precipitation induced by the addition of diethyl ether and *n*-hexane.

At variance with the neutral compounds **3a–c**, the presence in solution of the four different isomers (two atropoisomers for each anomer) is observed already at RT, because the triphenylphosphine or PTA prevents rotation about the Pd–C bond of the NHC ligand. Therefore, in the $^{31}P\{^1H\}$-NMR spectra (Figures S22–S27) the four signals, located at 23–27 ppm (for compounds **4a–c**) or about −57 ppm (for compounds **5a–c**), are always observed. The $^{31}P\{^1H\}$-NMR spectra indicate that the abundance of the anomeric species is about the same, whereas the atropoisomers present different concentrations.

In the ^{1}H-NMR spectra (Figure 4 and Figures S28–S33) for each species we can identify the $H^{anti}_{t\text{-}C}$ signal as doublet ($J \approx 12$–13 Hz) at about 3 ppm, the $H^{anti}_{t\text{-}P}$ signal as multiplet at about 3.4–3.6 ppm, the $H^{syn}_{t\text{-}C}$ signal as

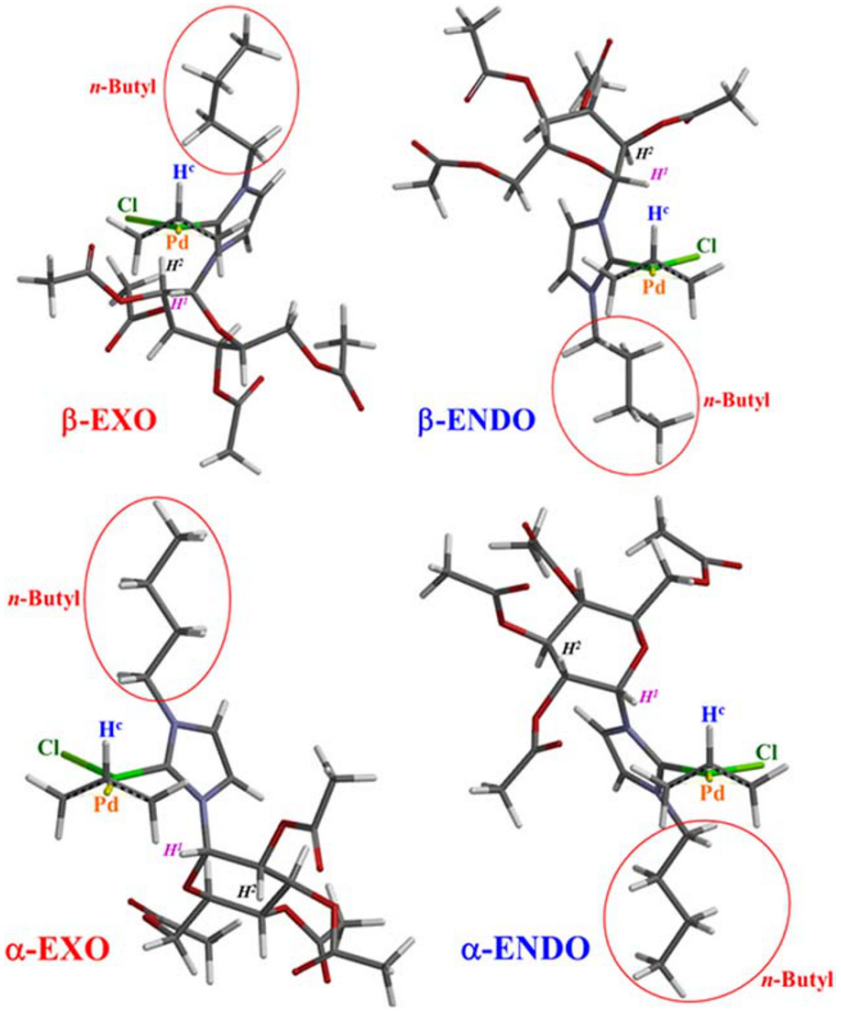
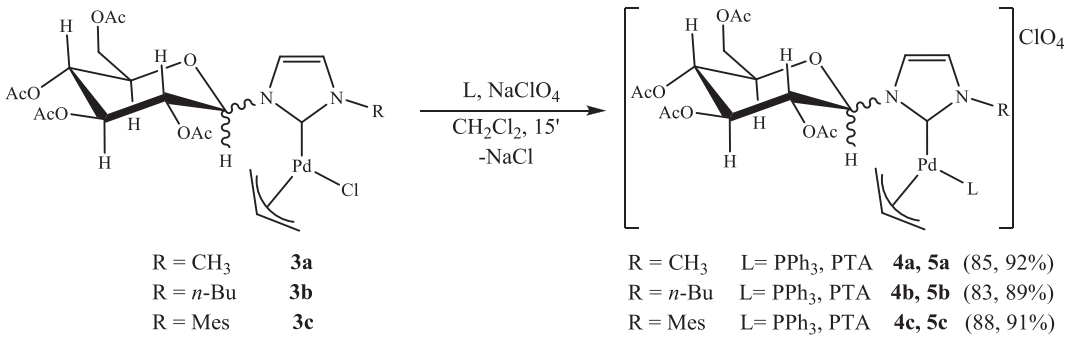


FIGURE 3 Representation of the four atropoisomers of the complex **3b** (density functional theory calculations)



SCHEME 6 Synthesis of mixed NHC/PPh_3 and NHC/PTA η^3-allyl Pd complexes (**4–5**). NHC, *N*-heterocyclic carbene; PTA, 1,3,5-triaza-7-phosphaadamantane

doublet ($J \approx 4$–7 Hz) at 3.5–3.8 ppm, the $H^{syn}_{t\text{-}P}$ signal as multiplet between 4.0 and 4.4 ppm, and the $H^{central}$ signal as multiplet at 5–6 ppm.

Moreover, in the $^{13}C\{^1H\}$-NMR spectra (Figure 5 and Figures S34–S39), we can observe for each isomer, a doublet ($J_{CP} \approx 20$ Hz) at about 180 ppm attributable to the carbenic carbon, a doublet ($J_{CP} \approx 25$–30 Hz) at about 69 ppm related to the CH_2 allyl *trans* to the phosphine, a singlet at about 74 ppm derived from the CH_2 allyl *trans* to the carbene, and a singlet at about 120–125 ppm ascribable to the central allyl carbon.

All the compounds were also characterized by HRMS, in which a single molecular ion of general formula $[(NHC)LPd(\eta^3\text{-allyl})]^+$ is observed (Figures S40 and S41

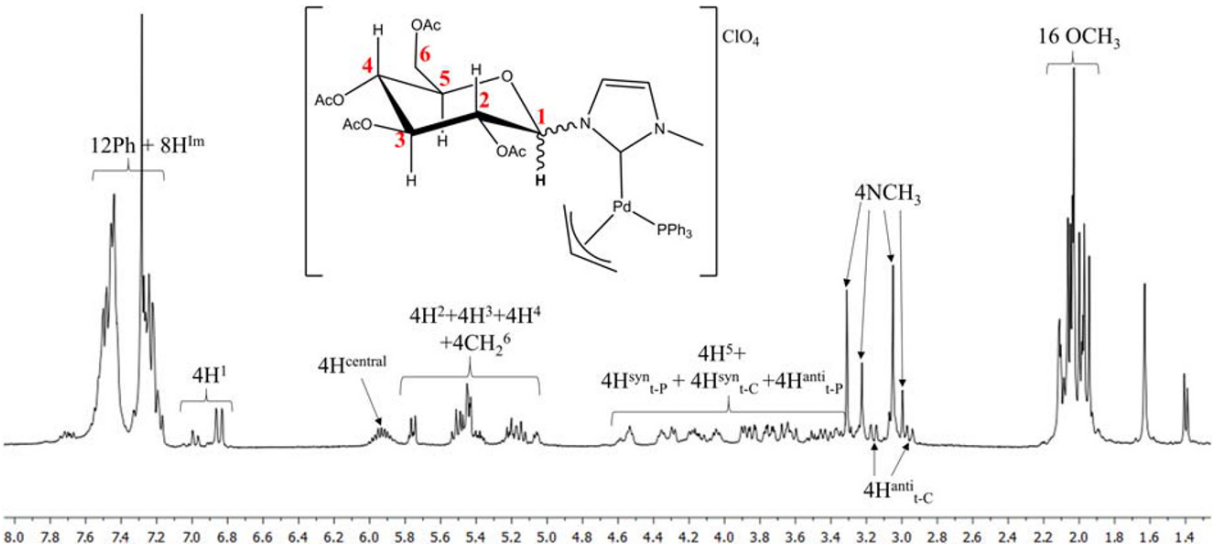


FIGURE 4 ^{1}H-NMR spectrum of the complex **4a** (T = 298 K, $CDCl_3$). NMR, nuclear magnetic resonance

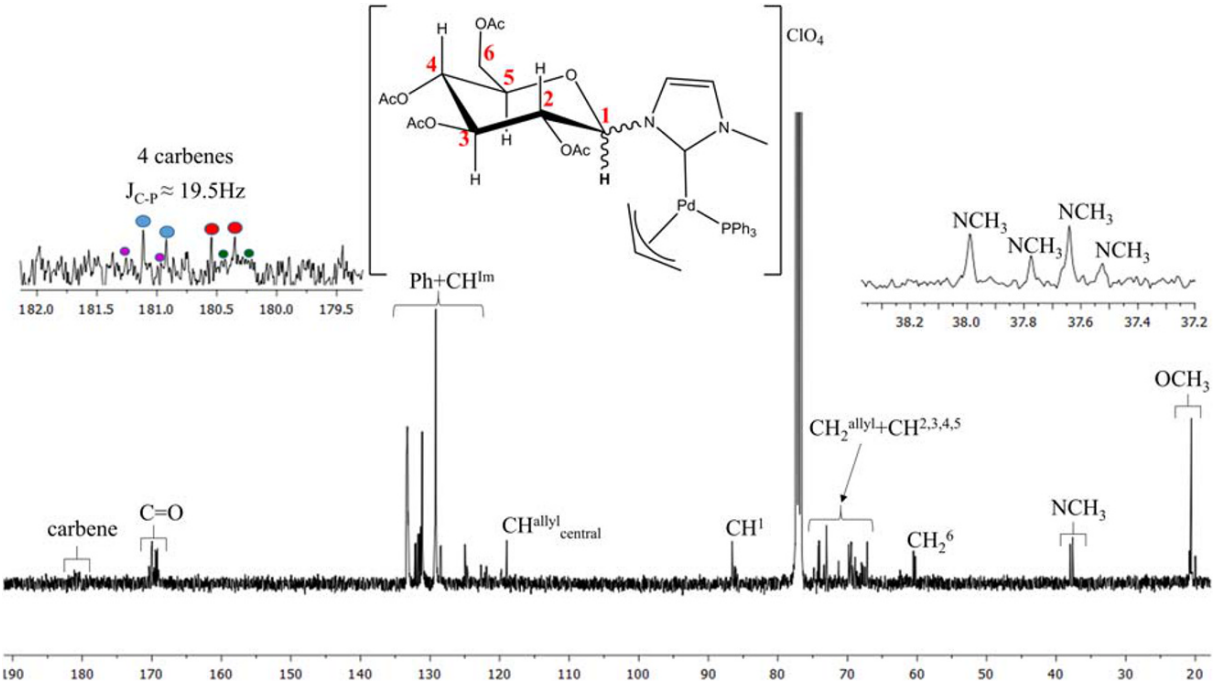


FIGURE 5 ^{13}C{^{1}H}-NMR spectrum of the complex **4a** (T = 298 K, $CDCl_3$). NMR, nuclear magnetic resonance

and see the "Experimental" section). Furthermore, it is possible to detect the fragment $[(NHC)Pd(\eta^3\text{-allyl})]^+$ which is formed after release of the phosphinic ligand (PPh_3 or PTA).

Finally, in the IR spectra (Figure S42), the C=O stretching and C–O stretching at about 1750 and 1231 cm^{-1} are observed, respectively, whereas the Cl–O stretching of the perchlorate counterion is detected at approximately 1100 cm^{-1}.

3.4 | *In vitro* antiproliferative activity toward human cancer and normal cell lines

The antiproliferative activity of the mixed NHC/PPh_3 (**4a–c**) and NHC/PTA (**5a–c**) allyl palladium complexes was assayed on a panel of five different human tumor cell lines (ovarian cancer cells OVCAR5 and A2780, its cis-platin resistant clone A2780*cis*, lung cancer cell A549,

TABLE 1 Effects of the Pd complexes on the proliferation of several cancer and normal cell lines[a]

	IC_{50} (μM)					
Complex	**A2780**	**A2780*cis***	**OVCAR5**	**A549**	**A375**	**MRC-5**
CisPt	0.81 ± 0.06	43 ± 5	5.2 ± 0.8	6 ± 2	4.7 ± 0.4	14 ± 1
4a	0.8 ± 0.2	3.6 ± 0.2	1.2 ± 0.2	1.8 ± 0.2	7.8 ± 0.8	2.6 ± 0.4
4b	0.20 ± 0.08	3 ± 1	1.6 ± 0.6	2.3 ± 0.2	3.2 ± 0.2	3.6 ± 0.6
4c	0.31 ± 0.03	0.46 ± 0.08	0.35 ± 0.09	0.49 ± 0.02	1.0 ± 0.1	3.9 ± 0.2
5a	0.28 ± 0.02	0.30 ± 0.03	1.7 ± 0.4	0.041 ± 0.007	4.5 ± 0.8	>100
5b	0.40 ± 0.01	0.50 ± 0.03	4 ± 1	0.06 ± 0.02	5.1 ± 0.7	>100
5c	0.48 ± 0.01	1.0 ± 0.1	9 ± 1	0.295 ± 0.007	13 ± 2	>100

[a]Data after 96-hr incubation. Stock solutions of all complexes in dimethyl sulfoxide (10 mM) were diluted in the culture medium; stock solution of cisplatin in H_2O (3 mM) was diluted in the culture medium.
IC_{50}, half maximal inhibitory concentration.

and malignant melanoma A375) and MRC-5 normal cells (human fibroblasts).

Preliminarily, the stability of the all examined compounds was checked in a 1:1 dimethyl sulfoxide-*d*6/D_2O solution by NMR spectroscopy; after 48 hr at RT no significant degradation was observed. The half inhibitory concentration (IC_{50}) induced by the palladium compounds and cisplatin (positive control) is reported in Table 1.

From the list of antiproliferative activity reported in Table 1, it is possible to infer a number of interesting considerations.

a. All complexes exhibit good/excellent activity on all examined tumor lines, with IC_{50} values comparable and in several cases markedly lower than cisplatin.
b. It is noteworthy that all our complexes show a comparable level of cytotoxicity toward cisplatin-sensitive (A2780) and the cisplatin-resistant (A2780*cis*) cell lines. This fact seems to imply a molecular target and/or mechanism of action other than cisplatin and its derivatives.
c. Among the complexes coordinating PPh_3 (**4a–c**), the derivatives with the mesityl substituent on NHC ligand (**4c**) show the highest antiproliferative activity against all tumor cell lines. Conversely, among complexes with PTA (**5a–c**) the homologous derivative (**5c**) is the least active. This fact suggests that, for a given organometallic fragment, even the choice of the ancillary ligands is crucial in defining the cytotoxicity of the complex.
d. The mixed NHC/PTA complexes **5a–c** are particularly active toward the A549 tumor line (lung cancer) with IC_{50} values up to 100 times lower than cisplatin.
e. Despite their high cytotoxicity against cancer cells, the antiproliferative activity of the mixed NHC/PTA complexes **5a–c** toward normal cells (MRC-5 human lung fibroblasts) is poor (IC_{50} > 100 μM). Therefore, these compounds are significantly more selective than the mixed NHC/PPh_3 complexes **4a–c** and cisplatin which show a non-negligible cytotoxicity ($3 < IC_{50} < 14$ μM) toward the same normal cells.

The last feature makes the mixed NHC/PTA complexes particularly promising, and therefore, we have decided to test their activity against two other ovarian cancer lines (KURAMOCHI and OVCAR3). Notably, these two lines are considered by recent studies as among the most indicative models for this pathology.[24] Again, these derivatives show comparable or lower IC_{50} values than cisplatin (Table 2).

Finally, it is important to underline that data on the neutral allyl compounds **3a–c** have shown a poor antiproliferative activity toward all the tested cancer lines (IC_{50} > 50–100 μM), which highlights the great

TABLE 2 Antiproliferative activity of mixed NHC/PTA complexes toward OVCAR3 and KURAMOCHI cell lines[a]

	IC_{50} (μM)	
Complex	**KURAMOCHI**	**OVCAR3**
CisPt	1.7 ± 0.3	2.2 ± 0.1
5a	0.46 ± 0.05	6 ± 4
5b	0.7 ± 0.1	7 ± 2
5c	2.5 ± 0.8	6.36 ± 0.07

[a]Data after 96-hr incubation. Stock solutions of all complexes in dimethyl sulfoxide (10 mM) were diluted in the culture medium; stock solution of cisplatin in H_2O (3 mM) was diluted in the culture medium.
IC_{50}, half maximal inhibitory concentration; NHC, *N*-heterocyclic carbene; PTA, 1,3,5-triaza-7-phosphaadamantane

importance assumed by the charge of complexes for their biological activity.

4 | CONCLUSIONS

In this work, we described the synthesis and the complete characterization of novel Pd(II) allyl complexes bearing carbohydrate-based NHCs and phosphinic ligands (i.e. PPh_3 or PTA). In particular, the choice to equip strong coordinating ligands as NHCs with a glycosyl group arises from the idea of taking advantage of the capability of these substituents to interact with the biological environment as well as their tendency to be preferentially absorbed by cancer cells. Actually, most of our palladium complexes, tested on different tumor lines, have often shown a better antiproliferative activity than cisplatin. Moreover, their cytotoxicity appears very similar on the A2780 (cisplatin-sensitive ovarian cancer) and A2780*cis* (cisplatin-resistant ovarian cancer) cell lines, suggesting a mechanism of action alternative to that of cisplatin and derivatives. This property is particularly attractive for the design of chemotherapeutical drugs to employ on cancer cells with cisplatin-acquired resistance.

The mixed NHC/PTA allyl compounds seem to be particularly promising because they are very active on the seven examined tumor lines (with a particularly relevant performance on A549 lung cancer cells) and poorly cytotoxic toward cells obtained from healthy tissues (MRC-5 human lung fibroblasts). This *in vitro* selectivity is a necessary prerequisite to prevent a generalized toxicity of a metallo-drug.

We have devoted particular attention to the antiproliferative activity of our compounds against serous ovarian cancer, testing five different tumor cell lines, which also included KURAMOCHI and OVCAR3, the most reliable *in vitro* models for this neoplasia.

The research on new chemotherapeutic agents is still of fundamental importance for the treatment of high-grade serous ovarian cancer, because this is one of the most lethal tumors for women worldwide. The platinum-based therapy is currently the main first-line treatment,[25] but unfortunately almost all patients relapse with a 5-year survival rate of less than 30%. In the near future, starting from these first encouraging results, we plan to carry out in-depth studies to evaluate the real possibility of using these compounds as new chemotherapeutic agents, especially for the treatment of this often lethal pathology.

ORCID

Fabiano Visentin https://orcid.org/0000-0001-9513-1182

REFERENCES

[1] B. Rosenberg, L. Vancamp, J. E. Trosko, V. H. Mansour, *Nature* **1969**, *222*, 385.
[2] L. Kelland, *Nat. Rev. Cancer* **2007**, *7*, 573.
[3] A. Bergamo, P. J. Dyson, G. Sava, *Coord. Chem. Rev.* **2018**, *360*, 17.
[4] (a) M. J. Clarke, F. Zhu, D. R. Frasca, *Chem. Rev.* **1999**, *99*, 2511. (b) S. Komeda, A. Casini, *Curr. Top. Med. Chem.* **2012**, *12*, 219. (c) S. M. Meier-Menches, C. Gerner, W. Berger, C. G. Hartinger, B. K. Keppler, *Chem. Soc. Rev.* **2018**, *47*, 909. (d) A. Casini, C. Gabbiani, F. Sorrentino, M. P. Rigobello, A. Bindoli, T. J. Geldbach, A. Marrone, N. Re, C. G. Hartinger, P. J. Dyson, L. Messori, *J. Med. Chem.* **2008**, *51*, 6773. (e) A. Casini, L. Messori, *Curr. Top. Med. Chem.* **2011**, *11*, 2647.
[5] A. R. Kapdi, I. J. Fairlamb, *Chem. Soc. Rev.* **2014**, *43*, 4751.
[6] M. D. Coskun, F. Ari, A. Y. Oral, M. Sarimahmut, H. M. Kutlu, V. T. Yilmaz, E. Ulukaya, *Bioorg. Med. Chem.* **2013**, *21*, 4698.
[7] (a) S. Ray, R. Mohan, J. K. Singh, M. K. Samantaray, M. M. Shaikh, D. Panda, P. Ghosh, *J. Am. Chem. Soc.* **2007**, *129*, 15042. (b) T.-H. Fong, C.-N. Lok, C. Y.-S. Chung, Y.-M. E. Fong, P.-K. Chow, P.-K. Wan, C.-M. Che, *Angew. Chem. Int. Ed.* **2016**, *55*, 11935.
[8] M. M. Shoukry, A. A. Shoukry, M. N. Hafez, *J. Coord. Chem.* **2010**, *63*, 652.
[9] A. S. Abu-Surrah, M. Kettunen, *Curr. Med. Chem.* **2006**, *13*, 1337.
[10] (a) Z. D. Matovic, E. Mrkalic, G. Bogdanovic, V. Kojic, A. Meetsma, R. Jelic, *J. Inorg. Biochem.* **2013**, *121*, 134. (b) E. S. Koumousi, M. Zampakou, C. P. Raptopoulou, V. Psycharis, C. M. Beavers, S. J. Teat, G. Psomas, T. C. Stamatatos, *Inorg. Chem.* **2012**, *51*, 7699. (c) J. Albert, J. Granell, J. A. Durán, A. Lozano, A. Luque, A. Mate, J. Quirante, M. K. Khosa, C. Calvis, R. Messeguer, L. Baldomà, J. Badia, *J. Organomet. Chem.* **2017**, *839*, 116.
[11] (a) A. J. Arduengo, R. L. Harlow, M. Kline, *J. Am. Chem. Soc.* **1991**, *113*, 361. (b) L. Oehninger, R. Rubbiani, I. Ott, *Dalton Trans.* **2013**, *42*, 3269.
[12] (a) T. Scattolin, I. Caligiuri, L. Canovese, N. Demitri, R. Gambari, I. Lampronti, F. Rizzolio, C. Santo, F. Visentin, *Dalton Trans.* **2018**, *47*, 13616. (b) T. Scattolin, L. Canovese, F. Visentin, S. Paganelli, P. Canton, N. Demitri, *Appl. Organomet. Chem.* **2018**, *32*, e4034. (c) T. Scattolin, S. Giust, P. Bergamini, I. Caligiuri, L. Canovese, N. Demitri, R. Gambari, I. Lampronti, F. Rizzolio, F. Visentin, *Appl. Organomet. Chem.* **2019**, *33*, e4902. (d) T. Scattolin, N. Pangerc, I. Lampronti, C. Tupini, R. Gambari, L. Marvelli, F. Rizzolio, N. Demitri, L. Canovese, F. Visentin, *J. Organomet. Chem.* **2019**, *899*, 120857. (e) T. Scattolin, I. Caligiuri, N. Mouawad, M. El Boustani, N. Demitri, F. Rizzolio, F. Visentin, *Eur. J. Med. Chem.* **2019**, *179*, 325. (f) T. Scattolin, E. Bortolamiol, F. Visentin, S. Palazzolo, I. Caligiuri, T. Perin, V. Canzonieri, N. Demitri, F. Rizzolio, A. Togni, *Chem. A Eur. J.* **2020**. https://doi.org/10.1002/chem.202002199 (g) T. Scattolin, E. Bortolamiol, I. Caligiuri, F. Rizzolio, N. Demitri, F. Visentin, *Polyhedron* **2020**, *186*, 114607.
[13] (a) B. K. Keitz, R. H. Grubbs, *Organometallics* **2010**, *29*, 403. (b) Z. Zhou, J. Qiu, L. Xie, F. Du, G. Xu, Y. Xie, Q. Ling, *Catal.*

Lett. **2014**, *144*, 1911. (c) C. Yang, P. Lin, F. Liu, I. J. B. Lin, G. Lee, S. Peng, *Organometallics* **2010**, *29*, 5959.

[14] (a) A. S. Henderson, J. F. Bower, M. C. Galan, *Biomol. Chem.* **2014**, *12*, 9180. (b) F. Tewes, A. Schlecker, K. Harms, F. Glorius, *J. Organomet. Chem.* **2007**, *692*, 4593.

[15] M. Miljkovic, *Carbohydrates: Synthesis, mechanisms and stereoelectronic effects*, Springer, New York **2009** 1.

[16] (a) B. Bertrand, L. Stefan, M. Pirrotta, D. Monchaud, E. Bodio, P. Richard, P. Le Gendre, E. Warmerdam, M. H. de Jager, G. M. M. Groothuis, M. Picquet, A. Casini, *Inorg. Chem.* **2014**, *53*, 2296. (b) C. V. Maftei, E. Fodor, P. G. Jones, M. Freytag, M. H. Franz, G. Kelter, H. H. Fiebig, M. Tamm, I. Neda, *Eur. J. Med. Chem.* **2015**, *101*, 431. (c) W. Niu, X. Chen, W. Tan, A. S. Veige, *Angew. Chem. Int. Ed.* **2016**, *55*, 8889.

[17] M. S. Taylor, E. N. Jacobsen, *Angew. Chem. Int. Ed.* **2006**, *45*, 1520.

[18] (a) M. G. Vander Heiden, L. C. Cantley, C. B. Thompson, *Science* **2009**, *324*, 1029. (b) O. Warburg, *Science* **1956**, *123*, 309. (c) Q. Wang, Z. Huang, J. Ma, X. Lu, L. Zhang, X. Wang, P. G. Wang, *Dalton Trans.* **2016**, *45*, 10366. (d) A. Annunziata, A. Amoresano, M. E. Cucciolito, R. Esposito, G. Ferraro, I. Iacobucci, P. Imbimbo, R. Lucignano, M. Melchiorre, M. Monti, C. Scognamiglio, A. Tuzi, D. M. Monti, A. Merlino, F. Ruffo, *Inorg. Chem.* **2020**, *59*, 4002. (e) A. Annunziata, M. E. Cucciolito, R. Esposito, P. Imbimbo, G. Petruk, G. Ferraro, V. Pinto, A. Tuzi, D. M. Monti, A. Merlino, F. Ruffo, *Dalton Trans.* **2019**, *48*, 7794. (f) M. E. Cucciolito, M. Trinchillo, R. Iannitti, R. Palumbo, D. Tesauro, A. Tuzi, F. Ruffo, A. D'Amora, *Eur. J. Inorg. Chem.* **2017**, *2017*, 4955.

[19] C. Roder, M. J. Thomson, *Drugs R&D* **2015**, *15*, 13.

[20] (a) B. Crociani, S. Antonaroli, F. Di Bianca, L. Canovese, F. Visentin, P. Uguagliati, *J. Chem. Soc. Dalton Trans.* **1994**, *n/a*, 1145. (b) L. Canovese, F. Visentin, P. Uguagliati, G. Chessa, A. Pesce, *J. Organomet. Chem.* **1998**, *566*, 61. (c) L. Canovese, G. Chessa, C. Santo, F. Visentin, P. Uguagliati, *Organometallics* **2002**, *21*, 4342. (d) F. Visentin, A. Togni, *Organometallics* **2007**, *26*, 3746. (e) L. Canovese, F. Visentin, C. Santo, G. Chessa, V. Bertolasi, *Organometallic* **2010**, *29*, 3027. (f) L. Canovese, F. Visentin, C. Levi, A. Dolmella, *Dalton Trans.* **2011**, *40*, 966. (g) L. Canovese, F. Visentin, C. Levi, C. Santo, V. Bertolasi, *J. Organomet. Chem.* **2013**, *732*, 27. (h) L. Canovese, F. Visentin, C. Santo, V. Bertolasi, *Organometallics* **2014**, *33*, 1700. (i) L. Canovese, F. Visentin, T. Scattolin, C. Santo, V. Bertolasi, *Polyhedron* **2016**, *119*, 377.

[21] (a)J. Tsuji, in *Handbook of Organopalladium Chemistry for Organic Synthesis*, (Ed: E. Negishi), Wiley-Interscience, New York **2002** 1669. (b)C. M. Zinser, F. Nahra, M. Brill, R. E. Meadows, D. B. Cordes, A. M. Z. Slawin, S. P. Nolan, C. S. J. Cazin, *Chem. Commun.* **2017**, *53*, 7990. (c)F. Izquierdo, A. Chartoire, S. P. Nolan, *ACS Catal.* **2013**, *3*, 2190.

[22] M. Hunsen, D. A. Long, C. R. D'Ardenne, A. L. Smith, *Carbohydr. Res.* **2005**, *340*, 2670.

[23] (a)E. Pacsu, *Chem. Ber.* **1928**, *61*, 1508. (b)B. Lindberg, *Arkiv Kemi, Mineral. Geol. Ser. B* **1944**, *18*, 1.

[24] S. Domcke, R. Sinha, D. A. Levine, C. Sander, N. Schultz, *Nat. Commun.* **2013**, *4*, 2126.

[25] (a)J. Ferlay, I. Soerjomataram, R. Dikshit, S. Eser, C. Mathers, M. Rebelo, D. M. Parkin, D. Forman, F. Bray, *Int. J. Cancer* **2015**, *136*, E359. (b)P. B. Ottevanger, *Semin. Cancer Biol.* **2017**, *44*, 67.

[26] (a) C. J. Cramer, *Essentials of Computational Chemistry*, 2nd ed., Wiley, Chichester **2004**. (b) F. Jensen, *Introduction to Computational Chemistry*, 2nd ed., Wiley, Chichester **2007**.

[27] (a) Y. Zhao, D. G. Truhlar, *Acc. Chem. Res.* **2008**, *41*, 157. (b) Y. Zhao, D. G. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215.

[28] (a) P. J. Hay, W. R. Wadt, *J. Chem. Phys.* **1985**, *82*, 270. (b) P. J. Hay, W. R. Wadt, *J. Chem. Phys.* **1985**, *82*, 299. (c) L. E. Roy, P. J. Hay, R. L. Martin, *J. Chem. Theory Comput.* **2008**, *4*, 1029.

[29] C. E. Check, T. O. Faust, J. M. Bailey, B. J. Wright, T. M. Gilbert, L. S. Sunderlin, *J. Phys. Chem. A* **2001**, *105*, 8111.

[30] (a) V. Barone, M. Cossi, J. Tomasi, *J. Chem. Phys.* **1997**, *107*, 3210. (b) V. Barone, M. Cossi, *J. Phys. Chem. A* **1998**, *102*, 1995.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Scattolin T, Bortolamiol E, Rizzolio F, Demitri N, Visentin F. Allyl palladium complexes bearing carbohydrate-based *N*-heterocyclic carbenes: Anticancer agents for selective and potent *in vitro* cytotoxicity. *Appl Organomet Chem*. 2020;e5876. https://doi.org/10.1002/aoc.5876