doi.org/10.1002/hlca.202300078

RESEARCH ARTICLE

HELVETICA chimica acta

Towards Platinum(II) Complexes for *in cellulo* Applications: Synthesis, Characterization, Biological and Catalytic Evaluation

Lisa Gourdon-Grünewaldt[+,a] Marija Bakija[+,b] Lara Wild[+,a] Berislav Perić,[b] Gilles Gasser,[a] Srećko I. Kirin,*[b] and Kevin Cariou*[a]

[a] Chimie ParisTech, CNRS, PSL University, Institute of Chemistry for Life and Health Sciences, Laboratory for Inorganic Chemical Biology, FR-75005 Paris, France, e-mail: kevin.cariou@chimieparistech.psl.eu

[b] Ruđer Bošković Institute, Division of Materials Chemistry,, Laboratory for solid state and complex compounds chemistry, Bijenička cesta 54, HR-10 000 Zagreb, Croatia, e-mail: srecko.kirin@irb.hr

Dedicated to Prof. *Roger Alberto* on the occasion of his retirement

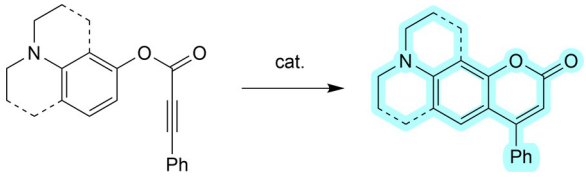
With the aim of achieving bioorthogonal intracellular catalysis, a library of platinum(II) complexes was synthesized. Their non-toxicity to living cells was demonstrated and their catalytic activity was evaluated on a cyclization reaction leading to a highly fluorescent coumarin. None of the platinum complexes showed any catalytic activity for coumarin synthesis. Still, we demonstrated that the silver salt $AgSbF_6$ commonly used to 'activate' metal catalysts by removing a chloride is a very efficient catalyst for the studied intramolecular cyclization reaction.

Keywords: chemical biology, catalysis, cyclization, platinum, silver.

Introduction

In cellulo metal-based catalysis is an emerging research field that bears promises for developing alternative therapies. In recent decades, much attention has been paid to developing processes that take place within the cell without interfering with natural biological processes: this is referred to as biorthogonal chemistry.[1] Profluorogenic substrates are often used for intracellular reaction studies since the fluorescence occurs after the catalytic reaction and can be easily localized in the cell by confocal microscopy.[2] A good starting point for intracellular reaction studies are coumarins, which have broad pharmaceutical applications: they have antibacterial,[3] cyclooxygenase inhibition,[4] antimutagenic and anti-cancer activities.[5,6] More importantly, they are highly fluorescent compounds, whose formation can be monitored *in cellulo* from a non-fluorescent coumarin precursor by cyclization. This was demonstrated by the group of *Mascareñas* and coworkers using gold catalysis to activate the alkyne moiety of the precursor (*Scheme 1*).[7]

Many efforts have recently been dedicated to the development of biorthogonal and bio-compatible catalysts based on various metals; some critical reviews deal with the state of the art of the subject.[8–14] Most examples are based on ruthenium, iridium, palladium, gold or copper. However, only a few examples of



Scheme 1. Intramolecular cyclization to form fluorescent coumarins.

[+] Those authors contributed equally to the work.

Supporting information for this article is available on the WWW under https://doi.org/10.1002/hlca.202300078

metal-catalyzed intracellular reactions involve platinum.[15] This might be due to the inherent toxicity of many platinum(II) compounds, such as the well-known anticancer drug Cisplatin.[16] To try to fill this gap, we have investigated the catalytic potential of a series of Pt^{II} complexes. Platinum complexes can act as soft *Lewis* acids to chemoselectively activate π-bonds, the same way as gold complexes, which display catalytic activity.[17] Therefore, a range of Pt^{II} complexes was synthesized and characterized, their non-toxicity demonstrated in living cells, and their catalytic activity investigated.

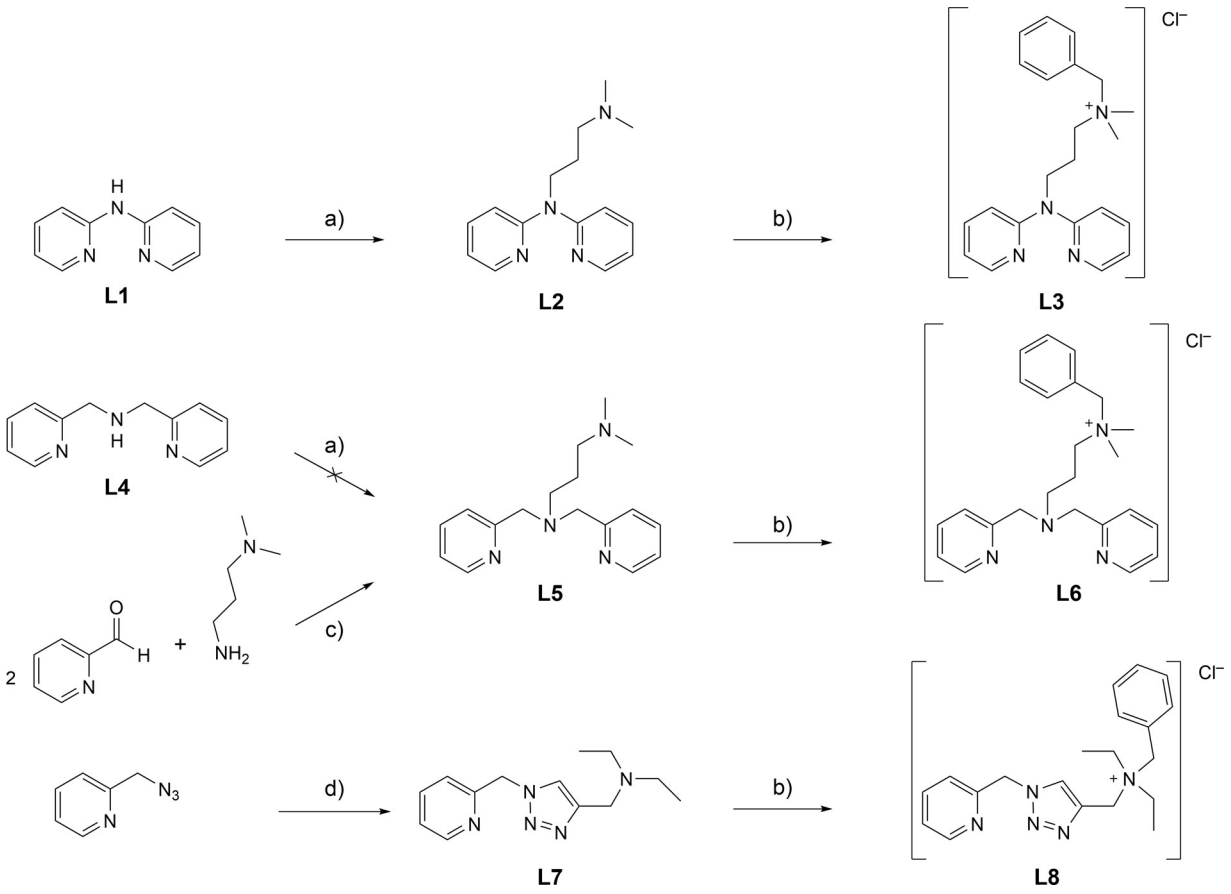
Results and Discussion

Synthesis and Characterization

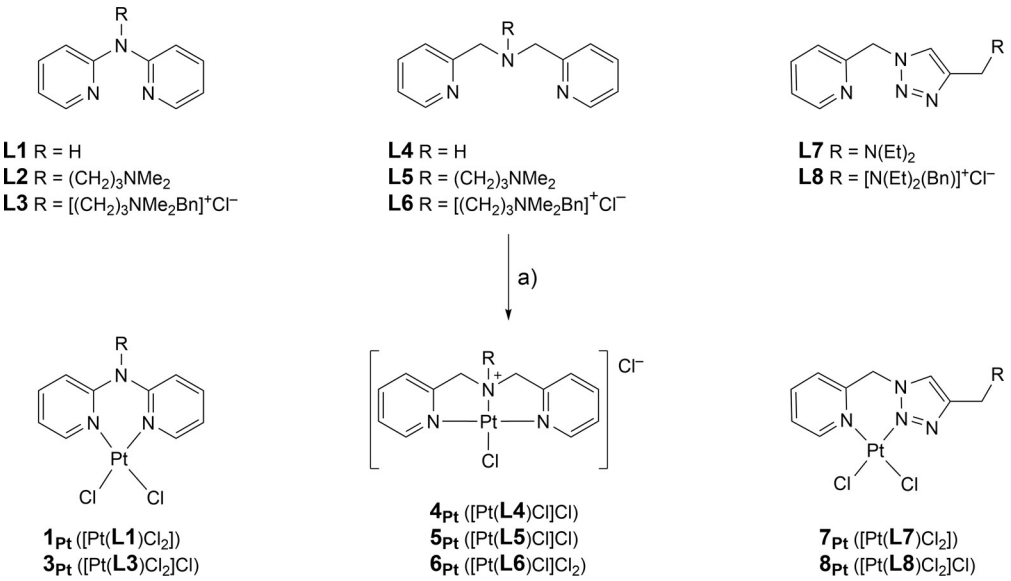
A series of bidentate and tridentate nitrogen ligands were considered, while ligands **L1** and **L4** are commercially available, **L2**, **L5** and **L7** were synthetized (*Scheme 2*). In addition to neutral ligands (**L1**, **L2**, **L4**, **L5**, **L7**), quaternary ammonium salt analogues were also prepared (**L3**, **L6**, **L8**), in order to achieve better solubility of their Pt complexes in polar solvents, namely water.

Ligand **L2** was prepared by a modified literature procedure[18] reacting **L1** with *N*,*N*-dimethylaminopropyl chloride, potassium iodide and potassium hydroxide in DMSO, under microwave irradiation (150 W, 100 °C). In contrast to the synthesis of **L2** from **L1**, attempts for the direct preparation of **L5** from **L4** were not successful. The synthesis of **L5** was accomplished according to a known procedure[19] from (2-pyridinyl)carboxaldehyde and *N*,*N*-dimethylaminopropylamine by reductive amination. Copper-catalyzed dipolar cycloaddition was utilized for the preparation of the triazolic **L7**.[20] The quaternary ammonium salt analogues (**L3**, **L6**, **L8**) were obtained by stirring in acetonitrile with benzyl chloride and potassium iodide with high yields.

Neutral and cationic Pt^{II} complexes were synthesized (**1**–**8**), using **L1**–**L8** (*Scheme 3*). To do so, K_2PtCl_4



Scheme 2. Synthetic routes for ligands **L2**, **L3** and **L5**–**L8**. a) *N*,*N*-Dimethylaminopropyl chloride, KI, KOH, DMSO, microwave irradiation (150 W, 100 °C), 2 h. b) Benzyl chloride, KI, acetonitrile, r.t., 24 h. c) Glacial acetic acid, $NaBH(OAc)_3$, argon atmosphere, dry THF, r.t., 2 d. d) *N*,*N*-diethylpropargylamine, copper(II) acetate (1 % mmol), methanol, 24 h.



Scheme 3. Synthetic route for platinum(II) complexes $\mathbf{1_{Pt}}$–$\mathbf{8_{Pt}}$. a) K_2PtCl_4, H_2O, 60 °C, 24 h.

was stirred in H_2O for 15 min before adding a suspension of the ligand (1 equiv.) in H_2O dropwise followed by stirring overnight at 60 °C. The resulting complex either precipitated ($\mathbf{1_{Pt}}$, $\mathbf{4_{Pt}}$, $\mathbf{6_{Pt}}$, $\mathbf{8_{Pt}}$) or could be isolated by column chromatography ($\mathbf{3_{Pt}}$, $\mathbf{5_{Pt}}$, $\mathbf{7_{Pt}}$). The complexes as well as the ligands were characterized by NMR, IR and HR-MS.

Single crystals were obtained for complexes $\mathbf{3_{Pt}}$ and $\mathbf{5_{Pt}}$ by slow diffusion of diethyl ether into a MeOH solution (*Figure 1*). In both structures the Pt^{2+} cation has square planar coordination. As anticipated from the structure of **L3**, in the X-ray structure of $\mathbf{3_{Pt}}$, the central Pt^{2+} ion is coordinated by two pyridyl nitrogen atoms and two chlorides, yielding a N_2Cl_2 coordination. On the other hand, in $\mathbf{5_{Pt}}$, Pt^{2+} has a N_3Cl

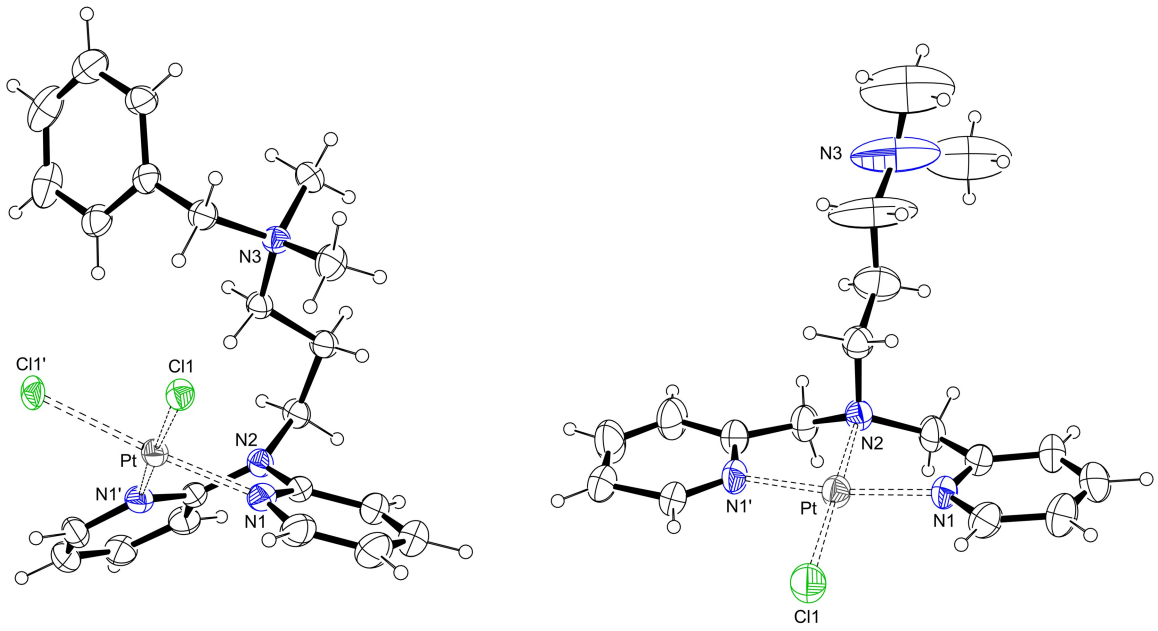


Figure 1. X-Ray structures of compounds $\mathbf{3_{Pt}}$ (left) and $\mathbf{5_{Pt}}$ (right), with labeled heteroatoms. The chlorine anions in both structures and the solvent molecules are omitted for clarity. Please see the *Supporting Information* for details.

coordination. An additional difference between the two complexes is visible in the side chain amino group. Complex $\mathbf{5_{Pt}}$ contains a tertiary amine function in the side chain. On the contrary, $\mathbf{3_{Pt}}$ has a quaternary ammonium group, substituted with an additional benzyl group. Structural parameters, *e.g.*, bond lengths and angles, are similar to crystal structures of related complexes already published in the literature.[18,21,22]

Biological Evaluation

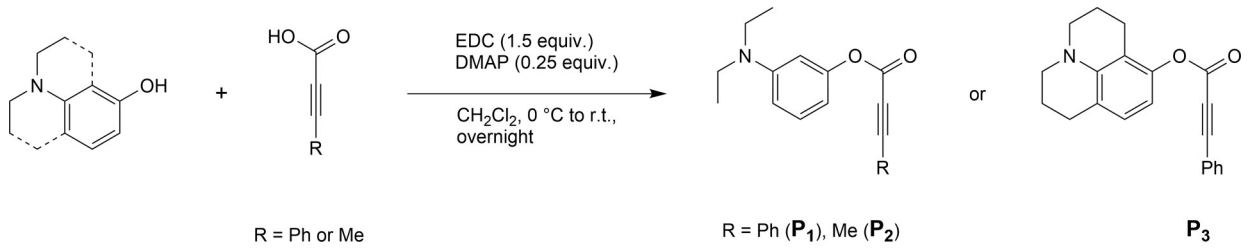
As we aimed for intracellular catalysis, we first had to ensure the compounds were not toxic to living cells. To do so, we evaluated the cytotoxicity on 2D monolayers of the murine colorectal cancer cell line CT-26 (see *Supporting Information* for details). After 48 hours of incubation of $\mathbf{1_{Pt}}$–$\mathbf{8_{Pt}}$, the cytotoxicity was evaluated by resazurin fluorescence assay in triplicates. All compounds showed no toxicity towards this cell line ($IC_{50} > 100$ μM) except for the dicationic complex $\mathbf{6_{Pt}}$ that was very moderately toxic with an IC_{50} of 57.9 ± 2.5 μM.

Catalytic Evaluation

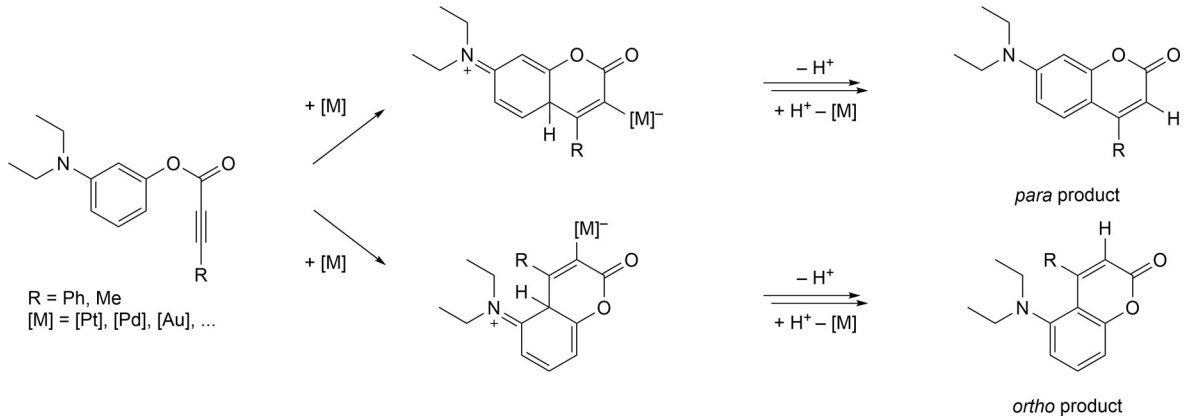
Encouraged by these results, we investigated the catalytic activity of all Pt complexes on cyclization of a coumarin precursors with the aim, in a second time, to follow this reaction by fluorescence *in cellulo*. A previously published synthetic route was chosen to produce three different coumarin precursors: $\mathbf{P_1}$, $\mathbf{P_2}$, and $\mathbf{P_3}$ (*Scheme 4*).[7,23]

Two of them contained a NEt_2 substituent ($\mathbf{P_1}$ and $\mathbf{P_2}$, *Scheme 4*), which could lead to two isomeric products (*ortho* and *para* cyclization). The proposed reaction mechanism of precursor cyclization involves π-*Lewis* acid catalysis of the platinum(II) complex: the triple bond would coordinate to the metal complex, which would be followed by cyclization, rearomatization and protodemetallation (*Scheme 5*). To avoid *ortho* cyclization and obtain a single coumarin, an *ortho* substituted coumarin precursor, derived from 8-hydroxyjulolidine, was also prepared ($\mathbf{P_3}$, *Scheme 4*).

The reaction was carried out with all Pt complexes and compared to the gold catalyst – described by *Mascareñas* and coworkers – [AuCl(PTA)] (**3**, PTA = 1,3,5-triaza-7-phosphaadamantane).[7] We followed the reaction conversion by integration of characteristic ^{1}H-NMR signals. In this first attempt, no catalytic activity



Scheme 4. Synthesis scheme for coumarin precursors $\mathbf{P_1}$, $\mathbf{P_2}$ and $\mathbf{P_3}$.



Scheme 5. Proposed mechanism for the metal-catalyzed coumarin synthesis.

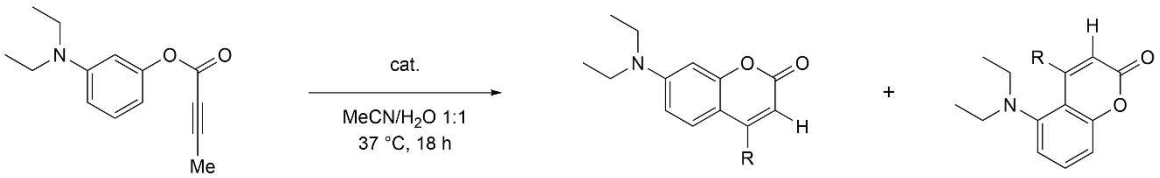
of the cyclization of $\mathbf{P_1}$ was observed – except in the case of the positive control with the Au complex. Since we expected the metal complex, a *Lewis* acid, to coordinate to the triple bond, we assumed that this inactivity could be due to the steric hindrance of the phenyl ring. To reduce this steric hindrance, the phenyl substituent was replaced by a methyl substituent ($\mathbf{P_2}$, *Scheme 4*).[24,25] However, no cyclization was ever observed with any of the Pt^{II} complexes. Therefore, various silver (I) salts were used as additives with the intention of activating the catalyst by abstracting a chloride. No conversion was observed when $AgPF_6$ (3 mol-%) was used. We then investigated catalytic activity using $AgSbF_6$ as the additive.[24]

In this case, we began to observe conversion up to 22% (*Table 1*, *Entries 1–7*) and a strong visible blue fluorescence, even for very little conversion. However, the conversion was higher when using $AgSbF_6$ only (up to 74% conversion overall after 10 h, *Entry 8*), which proved even better than the gold catalyst (*Entry 9*). This was surprising as *Sames* and coworkers did not report any conversion using silver salts only.[24] In the presence of $\mathbf{1_{Pt}}$ only, a product conversion of less than 2% only and a slight blue fluorescence could be observed. It can be concluded that this series of platinum(II) complexes show no catalytic activity for this reaction, while $AgSbF_6$ appears to be an efficient catalyst. Yet when $AgSbF_{6\ is}$ used in conjunction with Pt complexes, a strong decrease in activity is observed. This can be due to the rapid formation of the Pt hexafluoroantimonate complexes – which appear to be all less active than the corresponding silver salt – and of the inactive AgCl.It is worth noting that Ag(I)-catalyzed reactions involving the activation of triple bonds has previously been reported in the literature.[26–29]

Conclusions

A library of new platinum(II) complexes was synthesized and characterized. In view of their application for intracellular catalysis, we have first demonstrated their cellular innocuity on a murine cancer cell line. Then, their catalytic activity for the cyclization of coumarin precursors was evaluated. Although the Pt^{II} complexes themselves were found to be catalytically inactive for this reaction, considering their low toxicity, their activity towards other reactions should be evaluated. We also demonstrated that the salt $AgSbF_6$, sometimes used to activate *Lewis* acid complexes by chloride abstraction, was itself highly catalytically active towards the coumarin formation reaction. This result highlights the potential of silver catalysts for coumarin synthesis and possibly opens new opportunities for the design of silver complexes able to trigger *in cellulo* reactions.

Table 1. Catalytic activity of platinum(II) complexes for the cyclization of **P2**.



P2 → ***p*-C3** *para* coumarin + ***o*-C3** *ortho* product

Entry	Catalyst/additives	***p*-C3** conv.	***o*-C3** conv.	Fluorescence, observations
1	$\mathbf{1_{Pt}}/AgSbF_6$	14%	0.9%	Blue
2	$\mathbf{3_{Pt}}/AgSbF_6$	0.9%	0.9%	weakly blue
3	$\mathbf{4_{Pt}}/AgSbF_6$	0.9%	0.9%	weakly blue
4	$\mathbf{5_{Pt}}/AgSbF_6$	19%	3%	blue
5	$\mathbf{6_{Pt}}/AgSbF_6$	11%	0.9%	blue
6	$\mathbf{7_{Pt}}/AgSbF_6$	4%	0.9%	blue
7	$\mathbf{8_{Pt}}/AgSbF_6$	0.9%	0.9%	weakly blue
8	Only $AgSbF_6$	60%	14%	blue
9	[AuCl(PTA)]	47%	8.2%	blue
10	Only $\mathbf{1_{Pt}}$	0.9%	0.9%	weakly blue

Conditions: $MeCN/H_2O$ 1:1, 37 °C, overnight, inert atmosphere, protection from light, conversion calculated from ^{1}H-NMR.

Experimental Section

General Remarks

Reactions were carried out in ordinary glassware and chemicals were used as purchased from commercial suppliers without further purification. Microwave reactions were carried out in a microwave reactor (*CEM Discover*). Reactions were monitored by thin-layer chromatography on *Silica Gel 60* F_{254} plates and detected with a UV lamp (254 nm); ligands were purified using automated *flash* chromatography (*Teledyne Isco CombiFlash Rf*) equipped with a UV detector (254 nm) and prepacked silica (12 g)/aluminum oxide (30 g) columns. Platinum complexes were purified using column chromatography packed with aluminum oxide powder (Aluminum oxide Standardized 90, particle size 63–200 μm, neutral). NMR Spectra were obtained on *Bruker Avance 300*, *400* or *600* spectrometers at room temperature, operating at 300, 400 or 600 MHz for ^{1}H and 150 MHz for ^{13}C, at room temperature. The chemical shifts, δ, are reported in ppm (parts per million). The residual solvent peaks have been used as internal references. The abbreviations for the peak multiplicities are as follows: *s* (*singlet*), *d* (*doublet*), *t* (*triplet*), *q* (*quartet*), *quint.* (*quintet*), *m* (*multiplet*). Coupling constants, *J*, are given in Hertz. IR Spectra were recorded using CsI pellets with an *ABB Bomem MB102* instrument, with DTGS detector and CsI optics in the 4000–200 cm^{-1} region.

X-Ray Crystallography

X-Ray intensity data for $\mathbf{3_{Pt}}$ and $\mathbf{5_{Pt}}$ were collected at 146 K or 293 K, respectively, on an *XtaLAB Synergy* diffractometer with a *HyPix* detector using monochromatic Cu-K_α radiation ($\lambda = 1.54184$ Å). The data were processed by the CrysAlis Pro program[30] used for unit cell determination and data reduction. The structures were solved by the program SXELXT[31] and refined according to the least-squares procedure (F^2 on all data) by the program SHELXL.[32] Basic experimental data are given in *Table S1* of the *Supporting Information*. For $\mathbf{3_{Pt}}$, all non-hydrogen atoms were found from the first solution obtained from the SHELXT program,[31] while for $\mathbf{5_{Pt}}$, Pt^{2+} cation, two types of Cl^- anions (coordinated and uncoordinated) and majority of atoms of the ligand were recognized from the first SHELXT solution.[31] Beside these interpreted electron density peaks (atoms), an additional peak was found in the vicinity of one coordinated pyridyl ring, most probably coming from the second, disordered position of the uncoordinated Cl^- anion, with refined occupancy of 20%. Atoms from the $N(CH_3)_2$ group in $\mathbf{5_{Pt}}$ showed very large atomic displacement parameters (ADP) and they were recognized only among residual peaks in the subsequent calculation of difference electron density. Also, two additional peaks in difference electron density were interpreted as one disordered solvent water molecule. Using strong rigid-body restraints for the -$N(CH_3)_2$ group and additional restraint that sums of the occupancies for two positions of uncoordinated Cl^- anions and two water molecules are equal to 1, satisfactory model of $\mathbf{5_{Pt}}$ structure is obtained. Bearing in mind these restraints for disordered parts of $\mathbf{5_{Pt}}$ structure, both structures were finally refined in the anisotropic model of the ADP parameters for all non-hydrogen atoms, while hydrogen atoms were treated in a riding rigid body model, *i.e.*, their positions were calculated from the positions of atoms to which they are bonded. Torsion angles of methyl groups in the $\mathbf{3_{Pt}}$ complex and in its solvent methanol molecule were determined according to the best fit to difference electron density. Due to the lower quality of the $\mathbf{5_{Pt}}$ data structure and inherent disorder, positions of the solvent water hydrogen atoms were not determined. The CCDC-2262575 and −2262576 reference codes contain the supplementary crystallographic data for this paper. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre through https://www.ccdc.cam.ac.uk/structures/. Deposition Number(s) 2262575 (for $\mathbf{3_{Pt}}$), 2262576 (for $\mathbf{5_{Pt}}$), contain(s) 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.

Ligand Synthesis (**L1**–**L8**)

Ligands **dpaH** (**L1**) and **bpaH** (**L4**) were purchased from commercial suppliers and used without further purification.

DMAPr-dpa (**L2**). A mixture of dpaH (171 mg, 1.00 mmol), KOH (2.24 g, 40.0 mmol), *N*,*N*′-dimethyl-3-aminopropyl chloride hydrochloride (197 mg, 1.20 mmol), and KI (199 mg, 1.20 mmol) in DMSO (15 mL) was heated in a microwave reactor for 30 min (150 W, 75 °C). The mixture was cooled to room temperature and then diluted aq. HCl solution was gradually added (40.0 mmol, 3.38 mL of conc. HCl in 10 mL of dist. water) until a slightly basic pH was reached (pH was monitored using a universal indica-

tor). A saturated solution of $NaHCO_3$ (50 mL) was added to the reaction mixture, and the product was extracted using Et_2O (3×50 mL). The organic extracts were combined and dried using anhydrous Na_2SO_4, filtered, and evaporated. The crude product was purified using automated *flash* chromatography in 1:1 AcOEt/EtOH + 1% TEA solvent mixture on a prepacked silica gel column (12 g). Yield: 193.4 mg (0.8 mmol, 75%), yellow solid. ^{1}H-NMR (300 MHz, DMSO-d_6): 8.33–8.25 (m, 2H), 7.69–7.57 (m, 2H), 7.18–7.09 (m, 2H), 6.98–6.88 (m, 2H), 4.17–4.06 (m, 2H), 2.22 (t, J = 7.0, 2H), 2.08 (s, 6H), 1.72 (quint., J = 7.1, 2H). ^{13}C-NMR (75 MHz, DMSO-d_6): 156, 148, 137, 117, 114, 99.5, 56.5, 45.8, 45.10, 40.0, 39.8, 39.5, 39.2, 38.9, 38.6, 25.7. HR-ESI-MS: 257.1769 ([M+H]$^+$, $C_{15}H_{20}N_4H^+$; calc. 257.1761; error: 3.2 ppm). 256.17. ESI-MS: 257.25 ([M+H]$^+$, 100%).

[Bn-DMAPr-dpa]$^+$Cl$^-$ (**L3**). A mixture of DMAPr-dpa (**L2**; 153 mg, 0.60 mmol), benzyl chloride (71.9 mg, 0.60 mmol), and KI (99.6 mg, 0.60 mmol) was stirred overnight in MeCN at r.t. The solvent was evaporated, and the product was purified using automated *flash* chromatography, 2.5% MeOH in CH_2Cl_2, on a prepacked aluminum oxide column (30 g). Yield: 246 mg (0.60 mmol, >99%), yellow solid. ^{1}H-NMR (300 MHz, DMSO-d_6): 8.40–8.31 (m, 2H), 7.74–7.62 (m, 2H), 7.57–7.43 (m, 5H), 7.20–7.11 (m, 2H), 7.07–6.96 (m, 2H), 4.50 (s, 2H), 4.21 (t, J = 6.7, 2H), 3.49–3.17 (m, 2H), 2.93 (s, 6H), 2.18 (quint., J = 6.0, 2H). ^{13}C-NMR (151 MHz, DMSO-d_6): 156, 148, 137, 132, 130, 128, 127, 117, 114, 66.2, 60.9, 49.2, 44.4, 21.4. HR-ESI-MS: 347.2231 (M^+, $C_{22}H_{27}N_4^+$; calc. 347.2230; error: 0.2 ppm). IR (CsI): 3330 (w), 3003 (m),1601 (s), 1584 (s), 1566 (s), 1471 (s), 1455 (s),1385 (s), 1325 (s), 1250 (s), 772 (s), 726 (s), 700 (s).

DMAPr-bpa (**L5**). 2-Pyridinecarboxaldehyde (0.476 ml, 5.00 mmol), *N*,*N*′-dimethyl-3-aminopropanamine (0.315 ml, 2.60 mmol), and glacial acetic acid (0.286 ml, 5.00 mmol) were dissolved in dry THF (30 ml) under argon. Sodium triacetoxyborohydride (1.41 g, 6.70 mmol) was added, and the mixture was stirred at room temperature for 2 d. After removing the solvent under reduced pressure, the residue was dissolved in CH_2Cl_2 (30 ml) and washed with saturated aq. $NaHCO_3$ solution (3×30 ml), dried over $NaSO_4$, filtered, and evaporated. The crude product was purified using automated *flash* chromatography on a prepacked aluminum oxide column (30 g), 0.5% MeOH in CH_2Cl_2. Yield: 299 mg (1.10 mmol, 42%), yellow oil. ^{1}H-NMR (600 MHz, DMSO-d_6): 8.52–8.46 (m, 2H), 7.81–7.74 (m, 2H), 7.54–7.47 (m, 2H), 7.30–7.22 (m, 2H), 3.74 (s, 4H), 3.11 (overlapped with water peak, m, 2H), 2.34–2.31 (m, 2H), 2.18 (s, 6H), 1.68–1.61 (m, 2H). ^{13}C-NMR (151 MHz, DMSO-d_6): 159.14, 148.80, 136.55, 122.75, 122.12, 59.54, 56.68, 51.57, 44.06. HR-ESI-MS: 285.2081 ([M+H]$^+$, $C_{17}H_{24}N_4H^+$; calc. 285.2074; error: 2.5 ppm). IR (CsI): 3060 (w), 2765 (w), 1590 (m), 1569 (m), 1475 (m), 1436 (m), 1367 (m), 1261 (m), 1251 (m), 845 (m), 764 (s).

[Bn-DMAPr-bpa]$^+$Cl$^-$ (**L6**). The same synthesis protocol as for the **L3** ligand was employed. DMAPr-bpa (**L5**; 142.1 mg, 0.6 mmol), benzyl chloride (63.3 mg, 0.50 mmol), KI (99.6 mg, 0.60 mmol). The crude product was purified using automated *flash* chromatography on a prepacked aluminum oxide column (30g), 1% MeOH in CH_2Cl_2. Yield: 193 mg (0.50 mmol, >99%), yellow oil. ^{1}H-NMR (300 MHz, DMSO-d_6): 8.53–8.45 (m, 2H), 7.77–7.75 (m, 2H), 7.55–7.53 (m, 5H), 7.47–7.38 (m, 2H), 7.34–7.22 (m, 2H), 4.52 (s, 2H), 3.75 (s, 4H), 3.26–3.13 (m, 2H), 2.93 (s, 6H), 2.11–1.89 (m, 2H), 1.39–1.14 (m, 2H). ^{13}C-NMR (151 MHz, DMSO-d_6): 148, 136, 132, 130, 128, 128, 122.87, 122, 66.8, 61.51, 59.2, 50.2, 49.2, 19.5. HR-ESI-MS: 375.2544 (M^+, $C_{24}H_{31}N_4^+$; calc. 375.2543; error: 0.2 ppm). IR (CsI): 3069 (w), 2992 (m), 2927 (m), 2833 (m), 1594 (s), 1586 (s), 1569 (s), 1494 (s), 1477 (s), 1471 (s), 1455 (s), 1436 (s), 1407, 1378 (m), 1218 (m), 1147 (m), 869 (s), 773 (s), 766 (s), 720 (s), 702, 656, 632, 620, 598, 569, 515, 502, 488, 466, 458, 448, 436, 429, 419, 406, 320, 314, 303, 281, 276, 254, 247, 228, 214, 210.

DEt-pytaz (**L7**). *Step 1.* Picolyl chloride hydrochloride (1.00 g, 6.10 mmol) and NaN_3 (1.20 g, 18.3 mmol) were dissolved in water (25 mL) and stirred for 24 h at 80 °C. Sat. aq. $NaHCO_3$ solution (100 mL) was added to the mixture, and the aqueous layer was extracted with CH_2Cl_2 (3×100 mL). The organic extracts were combined and dried using anhydrous Na_2SO_4, filtered and evaporated (the product was evaporated under pressure at 30 °C due to high volatility). The crude product was used without further purification. Yield: 868.1 mg (4.6 mmol, 75%), colorless oil.

Step 2. Picolyl azide (709 mg, 3.70 mmol), propargyldiethylamine (0.648 mL, 3.70 mmol), and Cu(OAc)$_2$·H$_2$O (68.1 mg, 0.40 mmol) were stirred in MeOH at room temperature for 2 d. The solvent was evaporated, and the crude product was directly purified using automated *flash* chromatography on a prepacked silica gel column (12g), 5% →9% MeOH in

CH_2Cl_2. Yield: 584 mg (2.40 mmol, 64%), yellow oil. ^{1}H-NMR (300 MHz, DMSO-d_6): 8.58–8.50 (m, 1H), 8.02 (s, 1H), 7.87–7.75 (m, 1H), 7.39–7.29 (m, 1H), 5.68 (s, 2H), 3.67 (s, 2H), 2.41 (q, J=7.1, 4H), 0.99 (t, J=7.1, 6H). ^{13}C-NMR (151 MHz, DMSO-d_6): 155, 149, 143, 137, 124, 123, 121, 54.2, 46.6, 46.0, 11.9. HR-ESI-MS: 246.1718 ([M+H]$^+$, $C_{13}H_{19}N_5H^+$; calc. 246.1713; error: 1.9 ppm). IR (CsI): 3138 (w), 3055 (w), 2971 (m), 2823 (w), 1594 (m), 1575 (m), 1557 (m), 1475 (m), 1472 (m), 1464 (m), 1456 (m), 1439 (m), 1436 (m), 1387 (m), 1373 (m), 1330 (s), 1293 (s), 1220 (m), 1150 (m), 1121 (m), 1050 (s), 802 (m), 758 (s), 718 (m).

[Bn-DEtA-pytaz]$^+$Cl$^-$ (**L8**). The same synthesis protocol as for the **L3** ligand was used. DEtA-pytaz (**L7**; 122 mg, 0.50 mmol), benzyl chloride (63.3 mg, 0.50 mmol), KI (99.6 mg, 0.60 mmol). The crude product was purified using automated *flash* chromatography on a prepacked silica gel column (12 g), 5% MeOH in CH_2Cl_2. Yield: 87.4 mg (0.20 mmol, 47%), yellow solid. ^{1}H-NMR (600 MHz, DMSO-d_6): 8.58 (s, 1H), 8.56–8.52 (m, 1H), 7.88–7.83 (m, 1H), 7.77–7.71 (m, 2H), 7.57–7.50 (m, 3H), 7.38–7.38 (m, 2H), 5.81 (s, 2H), 4.57 (s, 2H), 4.57 (s, 2H), 3.14 (q, J=7.1, 4H), 1.42 (t, J=7.2, 6H). ^{13}C-NMR (151 MHz, DMSO-d_6): 154, 149, 137, 135, 132, 130, 129, 129, 127, 123, 122, 60.2, 54.5, 52.8, 51.1, 7.92. HR-ESI-MS: 336.2182 (M^+, $C_{20}H_{26}N_5^+$; calc. 336.2183; error: −0.2 ppm). IR (CsI): 3481 (w), 3059 (m), 2988 (m), 1630 (m), 1595 (m), 1572 (m), 1475 (m), 1456 (m), 1439 (m), 1394 (m), 1387 (m), 1367 (m), 1233 (m), 1175 (m), 1151 (m), 1131 (m), 1057 (m), 758 (s), 725 (s), 710 (s).

*Platinum Complex Synthesis (**1$_{Pt}$**–**8$_{Pt}$**)*

K_2PtCl_4 (1 equiv.) was dissolved in distilled H_2O (20 mL) and stirred for 15 min. A ligand (**L1**–**L8**; 1 equiv.) was suspended in 1 mL of water and added to the mixture dropwise. The mixture was then stirred overnight at 60 °C. If a precipitate had formed (**1$_{Pt}$**, **4$_{Pt}$**, **6$_{Pt}$**, **8$_{Pt}$**), the mixture was centrifugated, the solvent filtered off, and the precipitate washed twice with water and acetone. The residual solvent was evaporated. If no precipitate formed (**3$_{Pt}$**, **5$_{Pt}$**, **7$_{Pt}$**), the water was evaporated from the mixture, and the product was purified using column chromatography.

[Pt(L1)Cl$_2$] (**1$_{Pt}$**). DpaH (**L1**; 34.3 mg, 0.20 mmol), K_2PtCl_4 (83.0 mg, 0.20 mmol). A greenish-yellow precipitate was formed after stirring overnight, and the product was purified by centrifuging and washing with water and acetone and evaporating to dryness. Yield: 48.5 mg (0.10 mmol, 54%). ^{1}H-NMR (300 MHz, DMSO-d_6): 11.04 (s, 1H), 8.84–8.75 (m, 2H), 8.04–7.92 (m, 2H), 7.30–7.23 (m, 2H), 7.17–7.06 (m, 2H). IR (CsI): 3458 (m), 3239 (m), 3088 (m), 1662 (s), 1635 (s), 1584 (s), 1525 (s), 1475 (s), 1436 (s), 1358 (m), 1235 (s), 1160 (s), 1035 (s), 770 (s), 449 (m), 337 (s), 325 (s).

[Pt(L3)Cl$_2$]$^+$Cl$^-$ (**3$_{Pt}$**). **L3** (86.8 mg, 0.25 mmol), K_2PtCl_4 (104 mg, 0.25 mmol). Water was evaporated from the mixture after stirring overnight. The product was purified by column chromatography, packed with aluminum oxide powder (10 g) in 8% MeOH in a CH_2Cl_2 solvent mixture. Yield: 95.3 mg (0.1 mmol, 60%), yellow solid. Single crystals were obtained by slow diffusion of diethyl ether into a MeOH solution of **3$_{Pt}$** (10 mg in 0.5 mL). ^{1}H-NMR (300 MHz, DMSO-d_6): 8.86–8.78 (m, 2H), 8.23–8.11 (m, 2H), 7.74–7.61 (m, 2H), 7.59–7.42 (m, 5H), 7.42–7.31 (m, 2H), 4.51 (s, 2H), 4.29 (t, J=6.4, 2H), 3.91–3.80 (m, 2H), 2.92 (s, 6H), 2.23–2.17 (m, 2H). HR-ESI-MS: 613.1243 (M^+, $C_{22}H_{27}Cl_2N_4Pt^+$; calc. 613.1242; error: 0.2 ppm). IR (CsI): 3442 (m), 3025 (m),1603 (s), 1575 (m), 1488 (s), 1463 (s), 1347 (s), 1240 (s), 778 (s), 771 (s), 753 (s), 708 (s), 339 (s), 329 (s).

[Pt(L4)Cl]Cl$^-$ (**4$_{Pt}$**). BpaH (**L4**; 39.9 mg, 0.20 mmol), K_2PtCl_4 (83.0 mg, 0.20 mmol). After stirring, no precipitation was present, so the solvent was reduced to 5 mL, and after one week, yellow crystals formed. The crystals were filtered off, washed twice with water and acetone, and evaporated to dryness. Yield: 69.4 mg (0.10 mmol, 75%). ^{1}H-NMR (300 MHz, DMSO-d_6): 8.86–8.77 (m, 3H), 8.30–8.18 (m, 2H), 7.81–7.72 (m, 2H), 7.68–7.58 (m, 2H), 4.99–4.85 (m, 2H), 4.67–4.55 (m, 2H). HR-ESI-MS: 430.0427 (M^+, $C_{12}H_{13}ClN_3Pt^+$; calc. 430.0432; error: −1.2 ppm). IR (CsI): 3468 (w), 2988 (m), 2813 (m), 2496 (w), 1612 (s), 1567 (m) 1482 (s), 1472 (s), 1439 (s), 1277 (s), 1151 (s), 1059 (s), 1026 (s), 811 (s), 773 (s), 726 (s), 348 (m), 322 (m), 288 (m), 268 (m).

[Pt(L5)Cl]Cl$^-$ (**5$_{Pt}$**). **L5** (71.1 mg, 0.25 mmol), K_2PtCl_4 (103 mg, 0.25 mmol). Water was evaporated from the mixture after stirring overnight. The product was purified by column chromatography twice, packed with aluminum oxide powder (13 g) in 9% MeOH in a CH_2Cl_2 solvent mixture. Single crystals were obtained by slow diffusion of diethyl ether into a methanol solution. Yield: 47.2 mg (0.10 mmol, 34%), red solid. ^{1}H-NMR (600 MHz, DMSO-d_6): 8.85–8.76 (m, 2H), 8.36–8.25 (m, 2H), 7.85–7.78 (m, 2H), 7.70–7.62 (m, 2H), 5.07 (dd, J=299.3, 15.8, 4H), 4.09 (q, J=5.2, 1H), 3.08–2.99 (m, 2H), 2.13 (t, J=6.6, 2H), 1.96 (s, 6H), 1.67–1.57

(m, 2H). HR-ESI-MS: 514.1333 (M^+, $C_{17}H_{24}ClN_4Pt^+$; calc. 514.1332; error: 0.2 ppm). IR (CsI): 3458 (w), 2944 (m), 1615 (s), 1480 (s), 1450 (s), 1385 (w), 1286 (m), 1161 (m), 775 (s), 446 (w), 329 (w), 324 (w).

[Pt(L6)Cl]Cl_2^- (**6_{Pt}**). **L6** (93.8 mg, 0.25 mmol), K_2PtCl_4 (103 mg, 0.25 mmol). A white precipitate was formed after stirring overnight, and the product was purified by centrifuging and washing with water and acetone and evaporating to dryness. Yield: 29.7 mg (0.04 mmol, 18%). ^{1}H-NMR (300 MHz, DMSO-d_6): 8.84–8.76 (m, 2H), 8.36–8.24 (m, 2H), 7.79–7.68 (m, 2H), 7.72–7.63 (m, 2H), 7.57–7.43 (m, 5H), 5.31 (d, J=15.9, 2H), 4.84 (d, J=15.9, 2H), 4.42 (s, 2H), 3.08 (s, 4H), 2.83 (s, 6H), 2.01 (s, 2H). HR-ESI-MS: 303.0936 (M^{2+}, $C_{24}H_{31}ClN_4Pt^{2+}$; calc. 303.0935; error: −0.3 ppm). ESI-MS (pos): 514.3 ([Pt(**L5**)Cl]$^+$, 12%). IR (CsI): 3065 (w), 2938 (w), 1616 (m), 1486 (m), 1455 (m), 1065 (s), 842 (s), 771 (s), 728 (s), 598 (w), 559 (s), 358 (w), 329 (w), 325 (w).

[Pt(L7)Cl_2] (**7_{Pt}**). **L7** (61.3 mg, 0.25 mmol), K_2PtCl_4 (103 mg, 0.25 mmol). The solvent was evaporated, and the crude product was directly purified using chromatography on a column packed with aluminum oxide powder (15 g) in solvent solution: 5% →9% MeOH in CH_2Cl_2. Yield: 17.0 mg (0.03 mmol, 13%). ^{1}H-NMR (600 MHz, MeOD): 9.07 (ddd, J=5.8, 1.7, 0.6, 1H), 8.96 (s, 1H), 8.08 (td, J=7.7, 1.6, 1H), 7.93–7.88 (m, 1H), 7.52 (ddd, J=7.5, 5.7, 1.6, 1H), 6.12 (dd, J=295.5, 14.7, 2H), 3.98 (dd, J=119.4, 17.0, 2H), 3.05–2.82 (m, 2H), 1.38 (dt, J=8.5, 7.1, 6H). IR (CsI): 3448 (m), 3073 (m), 2974 (m), 2929 (m), 2855 (m), 1611 (s), 1573 (m), 1489 (m), 1451 (s), 1382 (s), 1234 (m), 1154 (s), 1107 (s), 1040 (s), 845 (s), 804 (s), 774 (s), 343 (m), 392 (w).

[Pt(L8)Cl_2]Cl (**8_{Pt}**). **L8** (74.3 mg, 0.20 mmol), K_2PtCl_4 (83.0 mg, 0.20 mmol). A greenish-yellow precipitate had formed after stirring overnight, and the product was purified by centrifuging and washing with water and acetone and evaporating to dryness. Yield: 54.7 mg (0.09 mmol, 43%). ^{1}H-NMR (600 MHz, DMSO-d_6): 8.58 (s, 1H), 8.54 (ddd, J=4.8, 1.8, 1.0, 1H), 7.85 (dd, J=7.7, 1.8, 1H), 7.75 (dd, J=7.9, 1.7, 2H), 7.58–7.50 (m, 4H), 7.39 (d, J=7.9, 1H), 5.81 (s, 2H), 4.57 (s, 2H), 4.57 (s, 2H), 3.17–3.13 (m, 4H), 1.41 (t, J=9.3, 7.1, 6H). ^{13}C-NMR (151 MHz, DMSO-d_6): 154, 149, 137, 135, 132, 130, 129, 129, 127, 123, 122, 60.2, 54.5, 52.8, 51.1, 39.9, 39.8, 39.6, 39.5, 39.3, 39.2, 39.1, 7.89. HR-ESI-MS: 602.1211 (M^+, $C_{20}H_{26}Cl_2N_5Pt^+$; calc. 602.1194; error: 2.8 ppm). IR (CsI): 3467 (m), 2986 (m), 2360 (w), 1611 (m), 1478 (m), 1456 (m),1308 (m), 1231 (m), 1160 (m), 1034 (m), 779 (s), 759 (s), 723 (s), 707 (s), 350 (s), 337 (s).

Coumarin Precursor Synthesis **P_1–P_3** *Gold Complex [AuCl(PTA)] and coumarin* **p-C2**

3-(Diethylamino)phenyl 3-Phenylprop-2-ynoate (**P_1**). The procedure was adapted from the literature.[7] 3-Diethylaminophenol (991 mg, 6.00 mmol), 3-phenylpropiolic acid (730 mg, 5.00 mmol), EDC (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide, 1.44 g, 7.50 mmol) and DMAP (4-(dimethylamino)pyridine, 152 mg, 1.25 mmol) were dissolved in CH_2Cl_2 (6 mL) at 0 °C and stirred overnight within warming up from 0 °C to room temperature. The organic phase was washed with aq. HCl (0.1 M, 40 mL), sat. aq. $NaHCO_3$ (40 mL) and brine (40 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (SiO_2, cyclohexane/ethyl acetate 4:1, R_f 0.57,) yielding the product (498 mg, 1.70 mmol, 34%) as yellowish oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.66–7.59 (m, 2H), 7.52–7.44 (m, 1H), 7.42–7.36 (m, 2H), 7.20 (t, J=8.3, 1H), 6.58–6.52 (m, 1H), 6.48–6.39 (m, 2H), 3.34 (q, J=7.1, 4H), 1.16 (t, $^3J_{HH}$=7.1, 6H). Data are in accordance with the literature.[7]

7-(Diethylamino)-4-phenyl-2*H*-chromen-2-one (***p*-C1**) *through Gold Catalysis*. The procedure was adapted from the literature.[7] [AuCl(PTA)] (6.64 mg, 17.0 µmol) and **P_1** (50.0 mg, 170 µmol) were dissolved in a solution of acetonitrile and water (1:1, 20 mL) and stirred overnight at 37 °C. The aqueous phase was extracted with CH_2Cl_2 (3×30 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by preparative TLC (SiO_2, cyclohexane/AcOEt 4:1, R_f 0.62), yielding the product (40 mg, 136 µmol, 80%) as yellowish oil exhibiting a blue fluorescence. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.52–7.47 (m, 3H), 7.47–7.43 (m, 2H), 6.59 (d, $^3J_{HH}$=2.6, 1H), 6.53 (dd, J=9.1, 2.6, 1H), 6.03 (s, 1H), 3.43 (q, J=7.1, 4H), 1.22 (t, J_H=7.1, 6H). Data are in accordance with the literature.[7]

[AuCl(PTA)]. The procedure was adapted from the literature.[7] Under inert atmosphere [AuCl(SMe_2)] (100 mg, 0.339 mmol) was dissolved in CH_2Cl_2 (5.0 mL), and a solution of PTA (1,3,5-triaza-7-phosphaadamantane, 55.0 mg, 0.339 mmol) in CH_2Cl_2 (5.0 mL) was added. After stirring for 4 h at r.t., the solution was concentrated under reduced pressure to *ca.* 3 mL, hexane (150 mL) was added, and the precipitate was

filtered and washed with hexane (3×15 mL) and diethyl ether (3×15 mL). The product (105 mg, 0.271 mmol, 80%) was obtained as a white solid, dried *in vacuo*, and stored under nitrogen. ^{1}H-NMR (400 MHz, CD_2Cl_2): 4.59–4.43 (m, 6H), 4.29 (s, 6H).

3-(Diethylamino)phenyl But-2-ynoate (**P_2**). The procedure was adapted from the literature.[7] 3-Diethylaminophenol (994 mg, 6.00 mmol, 1.2 equiv.), trifluoromethanesulfonic acid (420 mg, 5.00 mmol, 1.0 equiv.), EDC (1-ethyl-3-(3-dimethylaminopropyl)carbodiimide,1.44 g, 7.50 mmol, 1.5 equiv.) and DMAP (4-(dimethylamino)pyridine, 152 mg, 1.25 mmol, 0.25 equiv.) were dissolved in CH_2Cl_2 (20 mL) at 0 °C and stirred overnight within warming up from 0 °C to room temperature. The organic phase was washed with aq. HCl (0.1 M, 40 mL), sat. aq. $NaHCO_3$ (40 mL) and brine (40 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure, and the crude product was purified by column chromatography (SiO_2, cyclohexane/AcOEt 9:1, R_f 0.57), yielding the product (382 mg, 1.65 mmol, 33%) as violet oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.17 (t, $^3J_{HH}$=8.2, 1H), 6.55–6.49 (m, 1H), 6.40–6.34 (m, 2H), 3.32 (q, J=7.1, 4H), 2.05 (s, 3H), 1.15 (t, J=7.1, 6H). Data are in accordance with the literature.[25]

2,3,6,7-Tetrahydro-1*H*,5*H*-pyrido[3,2,1-*ij*]quinolin-8-yl 3-Phenylprop-2-ynoate (**P_3**). The procedure was adapted from the literature.[7] Under inert atmosphere, phenyl propiolic acid (800 mg, 4.23 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (6.5 mL) at 0 °C and stirred for 5 min. After the addition of DIC (*N,N*-dicyclohexylcarbodiimide, 1.31 g, 6.34 mmol, 1.5 equiv.), a solution of 8-hydroxyjulolidine (803 mg, 5.50 mmol, 1.3 equiv.) in CH_2Cl_2 (10 mL) and a solution of DMAP (4-(dimethylamino)pyridine, 129 mg, 1.06 mmol, 0.25 equiv.) in CH_2Cl_2 (1.0 mL) were added. The mixture was stirred overnight, warming up from 0 °C to room temperature. The residue was filtered over *Celite*, the solvent was removed under reduced pressure, and the crude product was purified by column chromatography (SiO_2, hexane/diethyl ether 5:1, R_f 0.5) yielding the product (160 mg, 0.423 mmol, 12%) as pink oil. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.67–7.57 (m, 2H), 7.52–7.45 (m, 1H), 7.43–7.37 (m, 2H), 6.81 (d, J=8.1, 1H), 6.34 (d, J=8.1, 1H), 3.23–3.03 (m, 4H), 2.76 (t, J=6.5, 2H), 2.65 (t, J=6.6, 2H), 2.03–1.91 (m, 4H). Data are in accordance with the literature.[7]

7-(Diethylamino)-4-methyl-2*H*-chromen-2-one (***p*-C_2**). Representative procedure withgold catalysis, adapted from the literature.[7] **[AuCl(PTA)]** (8.42 mg, 21.6 µmol, 0.1 equiv.) and **P_2** (50.0 mg, 216 µmol) were dissolved in a solution of acetonitrile and water (1:1, 20 mL) and stirred overnight at 37 °C. The aqueous phase was extracted with CH_2Cl_2 (3×30 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. The crude product was purified by preparative TLC (SiO_2, cyclohexane/AcOEt 3:1, R_f 0.59), yielding the product (25 mg, 108 µmol, 50%) as yellowish oil with blue fluorescence. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.36 (d, J=9.0, 1H), 6.56 (dd, J=9.0, J=2.6, 1H), 6.47 (d, J=2.6, 1H), 5.91 (d, J=1.0, 1H), 3.39 (q, J=7.1, 4H), 2.31 (d, J=1.1, 3H), 1.18 (t, J=7.1, 6H). Data are in accordance with the literature.[7]

Biological Experiments

Cell Culture. CT26 cells were cultured in DMEM medium (*Gibco*, *Life Technologies*, USA) supplemented with 10% of fetal calf serum (*Gibco*) complemented with 1% penicillin-streptomycin mixture (*Gibco*) and maintained in a humidified atmosphere at 37 °C and 5% of CO_2.

Cytotoxicity. Cells were seeded at a 4,000 cells/well density in 96-well plates (100 µL/well) and were incubated at 37 °C, 5% CO_2 for 24 h. The medium was replaced by test compound dilutions in fresh medium (100 µL/well), and cells were incubated at 37 °C, 5% CO_2 for 48 h. The medium was then replaced with 100 µL of fresh medium containing resazurin (0.2 mg/mL). After 4 h of incubation at 37 °C, 5% CO_2, plates were read using a *SpectraMaxM2* Microplate Reader (λ_{exc}=540 nm; λ_{read}=590 nm). Fluorescence data were normalized, data were fitted using GraphPad Prism Software, and IC_{50} was calculated by non-linear regression.

Supporting Information

NMR spectra, MS spectra, IR spectra, SCXRD, overlapped NMR spectra, fluorometric cell viability assays.

Acknowledgements

L. G.-G. thanks the ENS-PSL for a Ph.D. fellowship. This work was also financially supported by an ERC Consolidator Grant PhotoMedMet to *G. G.* (GA 681679), has received support under the program 'Investissements d'Avenir' launched by the French

Government and implemented by the ANR with the reference ANR-10-IDEX-0001–02 PSL (*G. G.*). The authors acknowledge the Croatian-French bilateral grant program, COGITO. *M. B.* acknowledges the Croatian Science Foundation for a doctoral scholarship (DOK-2021–02-7366). This work was partially supported by CAT Pharma (KK.01.1.1.04.0013), a project co-financed by the Croatian Government and the European Union through the European Regional Development Fund – the Competitiveness and Cohesion Operational Program.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contribution Statement

L. G.-G. performed all biological experiments and drafted the manuscript, *M. B.* prepared the ligands and the Pt complexes, *L. W.* prepared the coumarin precursors and Au catalyst and performed the catalysis tests; *L. G.-G.*, *M. B.* and *L. W.* contributed equally to the work. *B. P.* performed the crystallography studies. *G. G.*, *S. I. K.* and *K. C.* conceived the study, supervised the experiments and finalized the manuscript. All authors have approved the manuscript and have no conflict of interest to declare.

References

[1] T. Liang, Z. Chen, H. Li, Z. Gu, 'Bioorthogonal catalysis for biomedical applications', *Trends Chem.* **2022**, *4*, 157–168.
[2] D. P. Nguyen, H. T. H. Nguyen, L. H. Do, 'Tools and Methods for Investigating Synthetic Metal-Catalyzed Reactions in Living Cells', *ACS Catal.* **2021**, *11*, 5148–5165.
[3] M. J. Matos, S. Vazquez-Rodriguez, L. Santana, E. Uriarte, C. Fuentes-Edfuf, Y. Santos, A. Munoz-Crego, 'Looking for New Targets: Simple Coumarins as Antibacterial Agents', *Med. Chem.* **2012**, *8*, 1140–1145.
[4] A. Nargotra, S. Sharma, M. I. Alam, Z. Ahmed, A. Bhagat, S. C. Taneja, G. N. Qazi, S. Koul, 'In silico identification of viper phospholipaseA2 inhibitors: validation by in vitro, in vivo studies', *J. Mol. Model.* **2011**, *17*, 3063–3073.
[5] A. Thakur, R. Singla, V. Jaitak, 'Coumarins as anticancer agents: A review on synthetic strategies, mechanism of action and SAR studies', *Eur. J. Med. Chem.* **2015**, *101*, 476–495.
[6] M. Basanagouda, V. B. Jambagi, N. N. Barigidad, S. S. Laxmeshwar, V. Devaru, Narayanachar, 'Synthesis, structure–activity relationship of iodinated-4-aryloxymethyl-coumarins as potential anti-cancer and anti-mycobacterial agents', *Eur. J. Med. Chem.* **2014**, *74*, 225–233.
[7] C. Vidal, M. Tomás-Gamasa, P. Destito, F. López, J. L. Mascareñas, 'Concurrent and orthogonal gold(I) and ruthenium(II) catalysis inside living cells', *Nat. Commun.* **2018**, *9*, 1913.
[8] M. Martínez-Calvo, J. L. Mascareñas, 'Organometallic catalysis in biological media and living settings', *Coord. Chem. Rev.* **2018**, *359*, 57–79.
[9] J. G. Rebelein, T. R. Ward, '*In Vivo* catalyzed new-to-nature reactions', *Curr. Opin. Biotechnol.* **2018**, *53*, 106–114.
[10] A. H. Ngo, S. Bose, L. H. Do, 'Intracellular Chemistry: Integrating Molecular Inorganic Catalysts with Living Systems', *Chem. Eur. J.* **2018**, *24*, 10584–10594.
[11] A. Seoane, J. L. Mascareñas, 'Exporting Homogeneous Transition Metal Catalysts to Biological Habitats', *Eur. J. Org. Chem.* **2022**, e202200118.
[12] A. Gutiérrez-González, F. López, J. L. Mascareñas, 'Ruthenium Catalysis in Biological Habitats', *Helv. Chim. Acta* **2023**, *106*, e202300001.
[13] J. Miguel-Ávila, M. Tomás-Gamasa, J. L. Mascareñas, 'Metal-promoted synthetic chemistry within living cells', *Trends Chem.* **2023**, *5*, 474–485.
[14] H. Madec, F. Figueiredo, K. Cariou, S. Roland, M. Sollogoub, G. Gasser, 'Metal complexes for catalytic and photocatalytic reactions in living cells and organisms', *Chem. Sci.* **2023**, *14*, 409–442.
[15] B. L. Oliveira, B. J. Stenton, V. B. Unnikrishnan, C. R. de Almeida, J. Conde, M. Negrão, F. S. S. Schneider, C. Cordeiro, M. G. Ferreira, G. F. Caramori, J. B. Domingos, R. Fior, G. J. L. Bernardes, 'Platinum-Triggered Bond-Cleavage of Pentynoyl Amide and *N*-Propargyl Handles for Drug-Activation', *J. Am. Chem. Soc.* **2020**, *142*, 10869–10880.
[16] B. Rosenberg, L. Vancamp, J. E. Trosko, V. H. Mansour, 'Platinum Compounds: a New Class of Potent Antitumour Agents', *Nature* **1969**, *222*, 385–386.
[17] E. Soriano, J. Marco-Contelles, 'Mechanistic Insights on the Cycloisomerization of Polyunsaturated Precursors Catalyzed by Platinum and Gold Complexes', *Acc. Chem. Res.* **2009**, *42*, 1026–1036.
[18] M. J. Rauterkus, S. Fakih, C. Mock, I. Puscasu, B. Krebs, 'Cisplatin analogues with 2,2′-dipyridylamine ligands and their reactions with DNA model nucleobases', *Inorg. Chim. Acta* **2003**, *350*, 355–365.
[19] S. I. Kirin, C. M. Happel, S. Hrubanova, T. Weyhermüller, C. Klein, N. Metzler-Nolte, 'Synthesis, structure and comparison of the DNA cleavage ability of metal complexes M(II)L with the *N*-(2-ethoxyethanol)-bis(2-picolyl)amine ligand L (M=Co, Ni, Cu and Zn)', *Dalton Trans.* **2004**, 1201–1207.
[20] S. Jakopec, L. Gourdon-Grünewaldt, I. Čipor, A. M. Macan, B. Perić, I. Piantanida, K. Cariou, G. Gasser, S. I. Kirin, S. Raić-Malić, 'Synthesis, Characterisation and Biological Evaluation of Monometallic Re(I) and Heterobimetallic Re(I)/Fe(II) Complexes with a 1,2,3-Triazolyl Pyridine Chelating Moiety', *Dalton Trans.* **2023**, DOI 10.1039/D3DT01070H.
[21] Q.-P. Qin, B.-Q. Zou, Z.-F. Wang, X.-L. Huang, Y. Zhang, M.-X. Tan, S.-L. Wang, H. Liang, 'High *In Vitro* and *In Vivo* antitumor activities of luminecent platinum(II) complexes with jatrorrhizine derivatives', *Eur. J. Med. Chem.* **2019**, *183*, 111727.

[22] D. Urankar, B. Pinter, A. Pevec, F. De Proft, I. Turel, J. Košmrlj, 'Click-Triazole N2 Coordination to Transition-Metal Ions Is Assisted by a Pendant Pyridine Substituent', *Inorg. Chem.* **2010**, *49*, 4820–4829.
[23] J. H. Do, H. N. Kim, J. Yoon, J. S. Kim, H.-J. Kim, 'A Rationally Designed Fluorescence Turn-On Probe for the Gold(III) Ion', *Org. Lett.* **2010**, *12*, 932–934.
[24] P. A. Vadola, D. Sames, 'Catalytic Coupling of Arene C–H Bonds and Alkynes for the Synthesis of Coumarins: Substrate Scope and Application to the Development of Neuroimaging Agents', *J. Org. Chem.* **2012**, *77*, 7804–7814.
[25] H. J. Kim, 'Aminophenyl alkynyl ester compound, preparation of the same, selective detection probe and detection method of gold using the same', Patent KR101130492B1, 2012.
[26] S. Gujarathi, G. Zheng, '$AgSbF_6$-catalyzed efficient propargylation/cycloisomerization tandem reaction for the synthesis of fully substituted furans and new insights into the reaction mechanism', *Tetrahedron* **2015**, *71*, 6183–6188.
[27] R. Maeda, R. Ishibashi, R. Kamaishi, K. Hirotaki, H. Furuno, T. Hanamoto, '$AgSbF_6$-Promoted Cycloaddition Reaction of 2-Trifluoromethyl-*N*-tosylaziridine with Aldehydes', *Org. Lett.* **2011**, *13*, 6240–6243.
[28] R. Mamidala, V. K. Pandey, A. Rit, '$AgSbF_6$-Catalyzed *anti*-Markovnikov hydroboration of terminal alkynes', *Chem. Commun.* **2019**, *55*, 989–992.
[29] F. Jaroschik, A. Simonneau, G. Lemière, K. Cariou, N. Agenet, H. Amouri, C. Aubert, J.-P. Goddard, D. Lesage, M. Malacria, Y. Gimbert, V. Gandon, L. Fensterbank, 'Assessing Ligand and Counterion Effects in the Noble Metal Catalyzed Cycloisomerization Reactions of 1,6-Allenynes: a Combined Experimental and Theoretical Approach', *ACS Catal.* **2016**, *6*, 5146–5160.
[30] CrysAlis Pro (version 1.171.39.46), Rigaku Oxford Diffraction Ltd., Yarnton, Oxfordshire, England, 2018.
[31] G. M. Sheldrick, '*SHELXT* – Integrated space-group and crystal-structure determination', *Acta Crystallogr. Sect. A* **2015**, *71*, 3–8.
[32] G. M. Sheldrick, 'Crystal structure refinement with *SHELXL*', *Acta Crystallogr. Sect. C* **2015**, *71*, 3–8.

Received May 30, 2023
Accepted June 27, 2023

