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Organometallic palladium and platinum complexes with strongly donating alkyl coligands – Synthesis, structures, chemical and cytotoxic properties

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ABSTRACT

The synthesis, spectroscopy, and structures of organometallic complexes [(COD)M(R)X] and [(COD)M(R)(R′)] (COD = 1,5-cyclooctadiene, M = Pd or Pt; R = methyl, neopentyl (2,2-dimethylpropyl), neosilyl (trimethylsilylmethyl), or benzyl; X = Cl, Br, or I; R′ = 2-phenyl-ethynyl, *p*-fluoro-2-phenyl-ethynyl, *p*-methyl-2-phenyl-ethynyl or *p*-nitro-2-phenyl-ethynyl) has been explored. Selected samples of organo-platinum complexes show strikingly high cytotoxicity when tested against HT-29 and MCF-7 tumour cells.

1. Introduction

Organo-platinum(II) and -palladium(II) complexes [(COD)M(R)(L)] (M = Pt or Pd; R = alkyl, alkynyl or aryl; L = other ligands) with COD (1,5-cyclooctadiene) as an easily exchangeable ligand have been known for decades and are used as precursors for mono and polynuclear organometallic platinum(II) [1–5] or palladium(II) [6–8] compounds with applications in the field of catalysis [9–11] or chemical vapour deposition (CVD) of platinum [12]. Another interesting application of such complexes is their potential use as anti-tumour agents. Some years ago Komiya et al. investigated a series of complexes [(COD)Pt(Me)(Nuc)](NO_3) (Nuc = guanosine, cytosine or adenosine nucleosides), revealing that also in these organometallic complex fragments platinum binds preferentially guanosine (as found for most platinum complexes) [13]. Recently we have demonstrated the suitability of the [(COD)M(Me)] (M = Pt [14–16] or Pd [16,17]) fragments to coordinate various ligands. This moiety allows detailed insight into the binding properties of the ligands to platinum or palladium by ^{1}HNMR spectroscopy (especially for M = Pt) or molecular structure determination [14–17]. Also, we found that while the organometallic platinum(II) complexes [(COD)Pt(Me)Cl] and [(COD)Pt(Me)(Cyt)](SbF_6) (Cyt = cytosine) exhibit high toxicity against HT-29 and MCF-7 cancer cell lines, [(COD)$PtCl_2$] is virtually not toxic [16]. Superior toxicity of organometallic derivatives over non-organometallic complexes can be also concluded from Komiya's work [13] Takesawa's work [18] or a recent report by Deacon et al. [19]. We also found that the M–CH_3 bond is rather stable under physiological conditions, and that the solubility of the compounds can be drastically enhanced using the more bulky neopentyl (2,2-dimethyl-1-methyl = neop) coligand [16].

The aim of the here presented work was to extend this study by introducing various electron-rich alkyl coligands to COD platinum (II) and also COD palladium(II) complexes (Scheme 1, top, reaction (1)) using not only the neopentyl coligand but also neosilyl (trimethylsilylmethyl = neoSi) and benzyl, which were comparable to neopentyl in bulkiness and σ-donating properties [20].

As Scheme 1 reveals the synthetic protocol to achieve such potentially cytotoxic complexes comprises two steps. In reaction (1) the R coligand is introduced applying transmetallation reactions, while in reaction (2) further ligands L can be introduced by abstracting the halide X from the complexes [(COD)M(R)X] using silver or thallium salts [14–17].

A closer look in to the preparation routes to the desired complexes [(COD)M(R)X] following reaction (1) reveals two marked difficulties. The first occurs for the platinum complexes.

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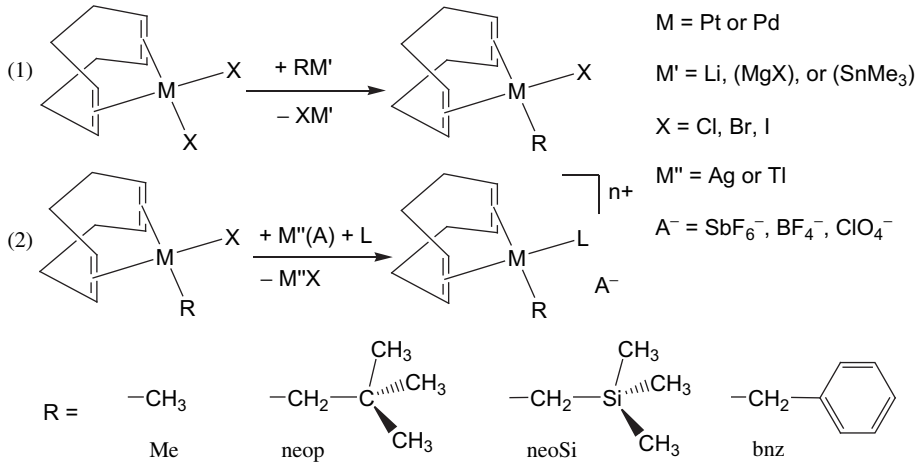


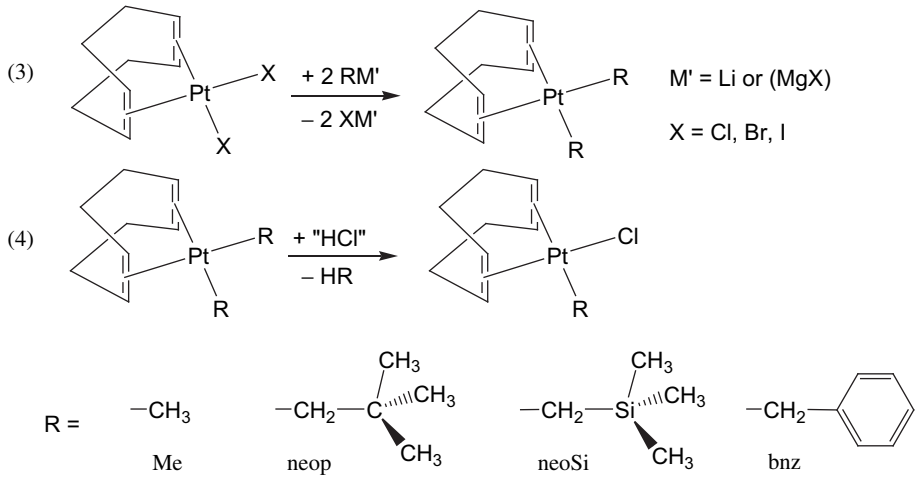
Scheme 1. COD organo-platinum(II) and -palladium(II) complexes investigated in this study (X = Cl, Br, or I; R = Me (methyl); neop (neopentyl = 2,2-dimethylpropyl); neoSi (neosilyl = trimethylsilylmethyl); bnz (benzyl); L = any monodentate ligand, for examples see refs [14–17].

[(COD)PtX_2] (X = Cl or I) can be alkylated using a Grignard reagent (R)MgX. However, for the preparation of methyl derivatives the use of one equivalent (Me)MgX leads to a mixture of [(COD)Pt$(Me)_2$], [(COD)Pt(Me)X] and [(COD)PtX_2]. The same holds also for the other alkyl coligands and the separation of the products is difficult in all cases. Therefore, the mono-alkylated complexes [(COD)Pt(R)X] were best obtained from the reaction of [(COD)Pt$(R)_2$] using HX (Scheme 2) [1]. So far the platinum(II) [(COD)Pt(neop)Cl] [5a], [(COD)Pt(neoSi)Cl] [4a] and [(COD)Pt(bnz)Cl] [1,3a,3c] have been reported.

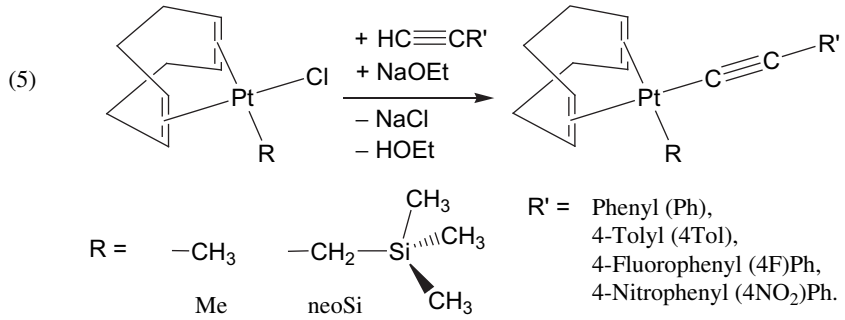
The second problem is encountered for the organo-palladium complexes [(COD)Pd(R)X] (R = alkyl). Here the transmetallation reaction using Grignard reagents (R)MgX or lithium derivatives (R)Li often fails, instead palladium(II) is reduced to palladium(0), even at very low temperatures. Thus, there is a small number of reports on complexes [(COD)Pd(R)Cl] (R = alkyl) prepared from [(COD)$PdCl_2$] and corresponding Grignard reagents (R)MgCl [8g, 21], or (R)Li [8d,22,23], while in most of the other reports the corresponding stannanes $Sn(R)_4$ were used as transmetallating agents [6d,7,8c,16,24]. As an example [(COD)Pd(Me)Cl] is usually prepared from [(COD)$PdCl_2$] and $Sn(Me)_4$ [6d]. However, this method (more generally applicable than the Grignard route) has two main disadvantages. First, the highly toxic $ClSn(R)_3$ compounds are molar co-products. Secondly, the transmetallating agent transfers only one R equivalent but has to be prepared from $SnCl_4$ and four equivalents (R)MgX, which makes the whole procedure quite ineffective. The latter drawback might be overcome by recycling the chlorostannane $ClSn(R)_3$. So far the synthesis of the complexes [(COD)Pd(neoSi)Cl] (using (neoSi)MgCl) [8g, 21], or(R)Li [(COD)Pd(bnz)Cl] [7c,8d] and [(COD)Pd(neop)Br] [16] (both using stannanes) was described. Also a number of related compounds [(COD)Pd$(CH_2CMe_2Ph)Cl$] [8g, 21,24]], [(COD)Pd$(CH_2CMe_2Tol)_2$] [8g], [(COD)Pd$(CH_2SO_2Tol)_2$] [22], [(COD)Pd$(CH_2SO_2Ph)Cl$] [23] and [(COD)Pd$(CH(SiMe_3)PPhMe_2)Cl]^+$ [25] have been reported. In most of these cases the stannane route was used, however a comparison of the two methods was never aspired.

In this paper we will report on a comprehensive study on feasible preparative routes to the complexes [(COD)M(R)X] (R = alkyl) applying both routes and alternatively lithium alkyls as transmetallating agents. Also, we will report on first examples of exchange reactions (2) introducing alkynyl coligands (Scheme 3).

The characterisation of the products and byproducts by multinuclear NMR and IR spectroscopy will be reported for all complexes and in many cases structural data from XRD on single crystals was collected. Selected samples have been tested concerning their antiproliferative properties.



Scheme 2. Two-step synthesis of organo-platinum(II) complexes [(COD)Pt(R)X] R = Me (methyl); neop (neopentyl = 2,2-dimethylpropyl); neoSi (neosilyl = trimethylsilylmethyl) or bnz (benzyl).



Scheme 3. Synthesis of organo-platinum(II) complexes [(COD)Pt(R)(C≡CR′)$_2$] (R = Me or neoSi; R′ = Ph, (4Me)Ph, (4NO$_2$)Ph or (4F)Ph.

2. Results and discussion

2.1. Preparations and analytical characterisation

2.1.1. Transmetallation reactions

The dihalido complexes [(COD)MX$_2$] can be all submitted to a transmetallation reaction (Scheme 1, reaction (1)). For palladium (II) derivatives the reaction using Grignard reagents (R)MgX yields exclusively the monosubstituted complexes [(COD)Pd(R)X] (Scheme 1) even if an excess of RMgX is applied (up to 2-fold). The yields were acceptable (R = bnz, 25%) to good (R = neop, 70%), the most frequent byproducts are bibenzyl (1,2-diphenylethane) and 2,2,5,5-tetramethylhexane, resulting from the C–C-coupling (Grignard homocoupling) reaction. The corresponding organolithium derivatives (R)Li cannot be used. Reactions at temperatures even below −30 °C gave precipitated elemental palladium. Since for R = methyl or benzyl the yields were not good, we used the corresponding stannanes Sn(R)$_4$ [6c,6d,26] and obtained far better yields of 42% of [(COD)Pd(bnz)Cl] and 92% for [(COD)Pd(Me)Cl]. One disadvantage of this method lies in the high toxicity of the byproducts XSn(R)$_3$. This makes thorough recrystallisations mandatory, which often lower the yield. The second disadvantage lies in the excessive consumption of transmetallating agents to produce the stannanes. E.g. five equivalents of (bnz)MgCl were required for the preparation of one equivalent of Sn(bzl)$_4$, while only one benzyl group is finally transferred onto the palladium atom.

The behaviour of the corresponding platinum derivatives differs largely from the above described palladium analogues. Both organolithium and Grignard reagents (R = neop, neoSi, bnz) can be used, the yields are fair to good (70–90%). However, the reactions were not selective. Applying one equivalent of transmetallation agent leads to a mixture of the three complexes [(COD)Pt(R)X], [(COD)Pt(R)$_2$] and [(COD)PtX$_2$], which are virtually inseparable. This phenomenon has been described already by Clark and Manzer [1] and the selective preparation of the mono-alkylated product can only be achieved via the di-alkylated derivatives as depicted in Scheme 2. According to this Scheme, first the di-alkylated derivatives [(COD)Pt(R)$_2$] have to be synthesised, which usually requires slightly more than 2 equivalents of transmetallation agent. One of the two alkyl coligands is cleaved in a second step using hydrochloric acid (HCl), generated in situ from acetyl chloride and methanol.

Table 1
Selected ^{1}H and ^{195}Pt NMR data of palladium and platinum complexes.[a]

	δ, H$_{1,2COD}$ *trans* L	$^2J_{Pt-H}$, H$_{1,2COD}$ *trans* L	δ, H$_{5,6COD}$ *trans* R	$^2J_{Pt-H}$, H$_{5,6COD}$ *trans* R	δ, M–CH$_2$–	$^2J_{Pt-H}$, Pt–CH$_2$–	δ, ^{195}Pt
[(COD)PtCl$_2$]	5.51	68	5.51	68	–	–	−3332
[(COD)PtI$_2$]	5.78	66	5.78	66	–	–	−3543
[(COD)Pt(Me)$_2$]	4.77	42	4.77	42	0.64	83	−3572
[(COD)Pt(Me)Cl]	4.54	75	5.42	36	0.78	73	−3501
[(COD)Pt(Me)Br]	4.59	74	5.43	34	0.78	73	−3627
[(COD)Pt(Me)I]	4.73	75	5.46	39	1.01	73	−3888
[(COD)Pt(neoSi)$_2$]	4.71	41	4.71	41	0.87	94	−3568
[(COD)Pt(neoSi)Cl]	4.59	74	5.35	38	0.95	76	−3456
[(COD)Pt(neoSi)Br]	4.66	79	5.37	40	1.12	77	−3586
[(COD)Pt(bnz)$_2$]	4.68	42	4.68	42	2.87	114	−3646
[(COD)Pt(bnz)Cl]	4.45	75	5.48	38	3.06	102	−3507
[(COD)Pt(neop)$_2$]	4.92	38	4.92	38	1.90	92	−3523
[(COD)Pt(neop)Cl]	4.53	75	5.47	33	1.72	81	−3460
[(COD)Pt(neop)Br]	4.62	76	5.50	35	1.90	82	−3580
[(COD)Pt(neoPh)$_2$]	4.14	38	4.14	38	2.21	90	−3541
[(COD)Pt(neoPh)Cl]	3.76	75	5.44	30	2.05	81	−3454
[(COD)Pt(Me)(C≡CPh)][b]	4.92	49	5.47	36	0.95	77	−3112
[(COD)Pt(Me)(C≡C(4Me)Ph)][b]	4.91	50	5.46	37	0.94	78	−3108
[(COD)Pt(Me)(C≡C(4F)Ph)][b]	4.92	49	5.43	36	0.94	78	−3115
[(COD)Pt(Me)(C≡C(4NO$_2$)Ph)][b]	5.00	50	5.46	35	0.96	77	−3124
[(COD)Pt(neoSi)(C≡CPh)][b]	4.95	48	5.36	38	1.08	89	−3166
[(COD)Pt(neoSi)(C≡C(4F)Ph)][c]	4.95	48	5.41	38	1.15	88	−2985
[(COD)Pd(Me)Cl]	5.21	–	5.77	–	1.00	–	–
[(COD)Pd(bnz)Cl][c]	4.87	–	5.89	–	3.59	–	–
[(COD)Pd(neop)Br]	5.34	–	5.81	–	2.34	–	–

[a] ^{1}H or ^{195}Pt NMR shifts [ppm] and selected ^{195}Pt–H coupling constants [Hz], measured in acetone-d_6.
[b] Measured in CD_2Cl_2.
[c] Measured in $CDCl_3$.

Table 2
Selected parameter of crystal structure measurements and refinements of palladium(II) and platinum(II) complexes [(COD)M(R)X].[a]

	[(COD)Pd (bnz)Cl]	[(COD)Pd (neop)Br]	[(COD)Pt (Me)Cl]	[(COD)Pt (bnz)Cl]	[(COD)Pt $(bnz)_2$]	[(COD)Pt (neoSi)Cl]	[(COD)Pt (neop)Cl]	[(COD)Pt (neop)Br]
Formula	$C_{15}H_{19}Cl_1Pd_1$	$C_{13}H_{23}$ Br_1 Pd_1	C_9H_{15} Cl_1Pt_1	$C_{15}H_{19}Cl_1Pt_1$	$C_{22}H_{26}$ Pt_1	$C_{12}H_{23}Cl_1Si_1Pt_1$	$C_{13}H_{23}$ I_1Pt_1	$C_{13}H_{23}$ Br_1Pt_1
Weight (g mol^{-1})	341.17	365.63	353.76	429.86	485.52	425.93	409.85	454.31
Crystal system	Triclinic	Monoclinic	Orthorhombic	Monoclinic	Monoclinic	Monoclinic	Monoclinic	Monoclinic
Space group	*P*-1[b]	$P2_1/c$	$P2_12_12_1$[c]	$P2_1/c$	$P2_1/c$	$P2_1/c$	$P2_1/c$	$P2_1/c$
Temperature (K)	293(2)	293(2)	293(2)	293(2)	203(2)	173(2)	293(2)	293(2)
cell *a* (Å)	6.640(1)	6.6560(9)	6.9618(7)	9.466(1)	11.170(2)	6.574(1)	6.4982(9)	6.612(1)
b (Å)	14.109(3)	12.244(1)	11.162(2)	11.345(1)	8.105(2)	12.233(2)	12.220(2)	12.253(3)
c (Å)	15.512(3)	18.056(3)	12.561(1)	14.378(3)	19.576(4)	18.054(5)	17.959(3)	18.054(5)
α	81.234(17)	90	90	90	90	90	90	90
β	89.633(15)	105.721(16)	90	118.43(1)	94.39(3)	101.10(3)	104.06(2)	105.39(3)
γ	79.452(16)	90	90	90	90	90	90	90
V ($Å^3$)	1411.7(5)	1416.5(3)	976.1(2)	1357.9(4)	1767.2(6)	1472.5(5)	1383.4(4)	1410.2(5)
Z	2	4	2	4	4	4	4	4
ρ_{calc} (g cm^{-3})	1.605	1.714	2.407	2.103	1.825	1.921	1.968	2.140
μ (mm^{-1})	1.480	4.101	14.585	10.505	7.938	9.763	10.306	12.754
F(*000*)	688	728	656	816	944	816	784	856
Goof. on F^2	0.586	0.796	0.982	0.878	0.894	1.010	0.537	0.582
Final R_1, wR_2 [$I > 2\sigma(I)$]	0.0463, 0.0640	0.0362, 0.0604	0.0689, 0.1618	0.0368, 0.0792	0.0513, 0.1360	0.0233, 0.0543	0.0466, 0.0633	0.0335, 0.0513
R_1, wR_2 (all data)	0.1697, 0.0806	0.0865, 0.0689	0.0784, 0.1693	0.0678, 0.0870	0.0701, 0.1502	0.0318, 0.0562	0.1390, 0.0788	0.1074, 0.0623
Larg. diff. peak/hole (e·$Å^{-3}$)	1.038/0.892	0.609/0.918	4.413/6.333	1.462/1.977	3.252/3.445	0.610/1.089	1.332/1.343	1.030/1.366
CCDC No.	764339	764340	764341	764342	764343	764344	764345	764346

[a] Radiation wavelength $\lambda = 0.71073$ Å; Refinement method: Full-matrix least-squares on F^2.
[b] [(COD)Pd(bnz)Cl] has also been found to crystallise in $P2_12_12_1$[7c].
[c] [(COD)Pt(Me)Cl] is also reported to crystallise in monoclinic *C*2/c [14].

2.1.2. Ligand exchange reactions

Alkynyl coligands C≡CR′ (R′ = Ph, (4Me)Ph, $(4NO_2)$Ph or (4F)Ph) were introduced by reacting the corresponding alkynes HC≡CR′ with the mono-alkylated platinum complexes [(COD)Pt(R)Cl] (R = Me or neoSi) in the presence of NaOEt (generated from sodium and ethanol) or KO^{t}Bu in excellent yields (Reaction 5, Scheme 3).

2.2. NMR spectroscopy

Apart from being an important analytical tool in our study, detailed multinuclear NMR spectroscopy allowed us to address a number of important questions concerning the constitution of the complexes in solution, their reactivity and in case of the platinum derivatives enabled us also to determine relative bond strengths of the (co)ligands R, R′ and L. It is well established since the 1970s that the *trans*-influence of a ligand and thus its strength correlates well with metal–ligand coupling constants. For platinum complexes coupling of the ^{195}Pt isotope to ^{1}H, ^{31}P, ^{13}C, or ^{15}N nuclei has been widely used [15,16,27]. We successfully applied this correlation for a large number of complexes $[(COD)Pt(Me)L]^{n+}$ [14–16], mainly by using the $^2J_{Pt-H(COD)}$ coupling constant as a measure for the bond strength of the corresponding *trans*-oriented coligand R or ligand L. In Table 1 these values were collected for the new complexes, revealing almost uniform values around 30 Hz for the olefinic protons *trans* to strong σ-donor coligands R. The corresponding coupling constants of the olefinic protons *trans* to the halide co-ligand X lie about 75–80 Hz, while for alkynyl coligands about 50 Hz were found, which means that alkynyl coligands can also be considered to be relatively strongly σ-donating, since principally feasible π-contribution is probably not very large [28]. The chemical shifts of the olefin protons $H_{1,2}$ nicely reflect the spatial proximity of the electron-rich alkyl ligands showing upfield-shifted resonances compared to the $H_{5,6}$ protons. The latter experience the π-electron density of the alkynyl (or halido) coligand, leading to a downfield shift. Strong downfield shifts were also found for the coligands $-CH_2-$ protons facing a phenyl group in the Cβ position (bnz, or neoPh) due to the diamagnetic ring current, while the C≡CPh phenyl groups are remote and do not exert any influence. ^{1}H NOESY results completely confirm these considerations.

2.3. Crystal and molecular structures

From the compounds [(COD)Pd(bnz)Cl], [(COD)Pd(neop)Br], [(COD)Pt(Me)Cl], [(COD)Pt(bnz)Cl], [(COD)Pt$(bnz)_2$], [(COD)Pt

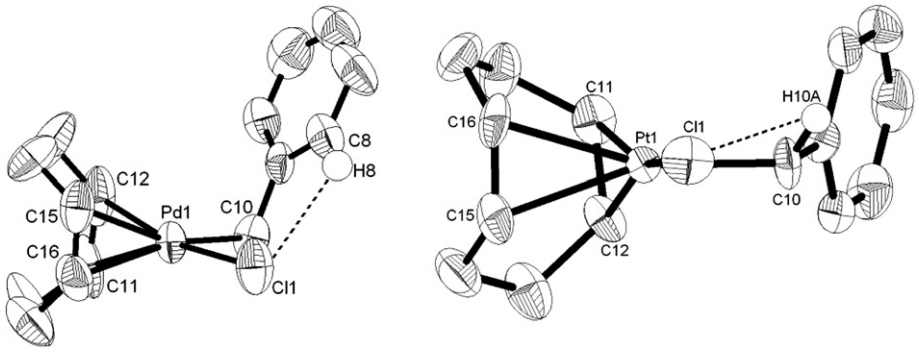


Fig. 1. Molecular structures of one of the two independent molecules of [(COD)Pd(bnz)Cl] (left) and of [(COD)Pt(bnz)Cl] (right). All atoms at 50% probability level; protons not involved in intramolecular H bonding were omitted for clarity.

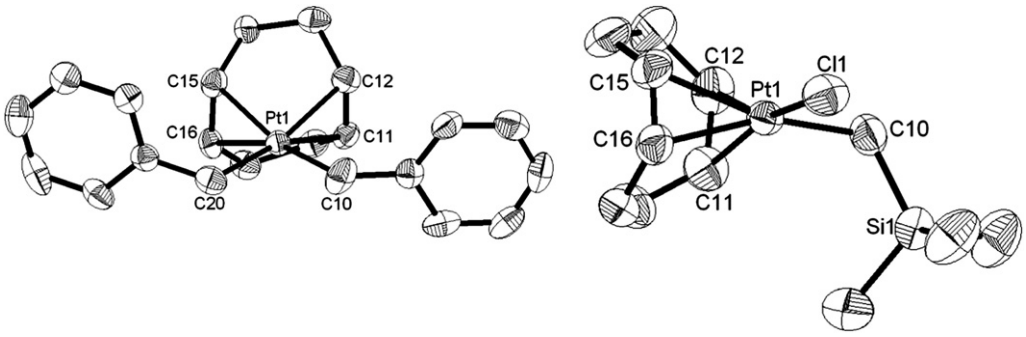


Fig. 2. Molecular structures of [(COD)Pt(bnz)$_2$] (left) and [(COD)Pt(neoSi)Cl] (right). All atoms at 50% probability level; all protons were omitted for clarity.

(neoSi)Ph], [(COD)Pt(neoSi)Cl], [(COD)Pt(neop)Cl], and [(COD)Pt (neop)Br] single crystals could be obtained during the preparations in solvents mentioned in the Experimental Section. The structures were solved and refined in various symmetries and space groups ranging from triclinic *P*-1 to orthorhombic $P2_12_12_1$ (Table 2). Although some of the structures could not be refined satisfactorily (large residual electron densities, small Goofs) the high similarity of all the structures makes us confident that the solution and refinement for all compounds was carried out correctly and only poor crystal quality and insufficient absorption correction is responsible for the low quality of some of the structure determinations.

A number of weak intermolecular contacts were observed, most of them are H···X hydrogen bridges. An examination of the H···X distances reveals values all exceeding 2.8 Å, which classifies them as very weak H bonds. In the crystal structure of [(COD)Pt(bnz)Cl] a packing of the benzyl coligands can be observed with close C–H···π contacts of about 3.1 Å (distance H···centroid). Such C–H···π contacts might have an impact on the crystal structure [29,30], marked influence on the molecular structure is only reported for molecules showing far shorter distances around 2.5 Å [29]. Other C–H···π or π–π interactions were not observed. Also no Pt···Pt contacts were observed, which is probably due to a shielding effect by the COD ligand. Figures of crystal structures can be found in the Supplementary Material. Figs. 1 and 2 show representative examples of the molecular structures and Table 3 summarises the essential bonding parameters for the neutral complexes.

The central palladium or platinum atoms all lie in a perfect plane defined by the centroids Y(1) and Y(2), the metal-binding carbon atom of the coligand (–CH_2–) and the second coligand (either X or C) as can be seen e.g. from the Σ of angles around M, (Table 3). The phenyl, CMe_3 and $SiMe_3$ cores of the coligands are bent away by a constant angle (M–CH_2–R″) of usually about 120°, only for [(COD) Pd(bnz)Cl] this angle is markedly smaller (Fig. 1, Table 3). However, an inspection of a big number of benzyl palladium(II) or platinum(II) complexes reveals angles varying from about 103° [31] to 120° [32] for palladium(II) and 112° [33] to 119° [34] for platinum(II). Thus all values lie in the typical range. Furthermore, the complex [(COD)Pd (bnz)Cl] has been previously reported in different space group $P2_12_12_1$ with a corresponding angle of 112.1(4)° [7c]. Another peculiar finding is that the centre of the phenyl core lies approximately within the coordination plane of the metal (in plane) for the two Pt complexes [(COD)Pt(bnz)Cl] and [(COD)Pt(bnz)$_2$], while for the Pd derivative [(COD)Pd(bnz)Cl] the benzyl coligand points away in a direction almost perpendicular to the coordination plane. The latter situation is also found for the other coligands neop and neoSi. Since this has no precedent in the crystal/molecular structures of benzyl platinum complexes we had thus a closer look on intra and intermolecular interactions. First, in the structure of [(COD)Pt(bnz)Cl] an intramolecular hydrogen bond C(8)–H8A···Cl1 of 2.835(2) Å (angle C–H···Cl = 92.30(5)°) is observed, however, for the Pd derivative [(COD)Pd(bnz)Cl] a hydrogen bond of approximately the same strength is found (2.868(4) Å). Next we examined intramolecular

Table 3
Selected distances (Å) and angles (deg.) of complexes [(COD)Pd(bnz)Cl], [(COD)Pd(neop)Br], [(COD)Pt(Me)Cl], [(COD)Pt(bnz)Cl], [(COD)Pt(bnz)$_2$], [(COD)Pt(neoSi)Cl], [(COD)Pt (neop)Cl], and [(COD)Pt(neop)Br].

	[(COD)Pd (bnz) Cl][b]	[(COD)Pd (neop)Br]	[(COD)Pt (Me) Cl]	[(COD)Pt (bnz) Cl]	[(COD)Pt (bnz)$_2$]	[(COD)Pt (neoSi)Cl]	[(COD)Pt (neop)Cl]	[(COD) Pt (neop) Br]
Distances								
M–X	2.353(3), 2.350(3)	2.4586(7)	2.330(5)	2.323(2)	2.086(7) *C(20)*	2.3241(11)	2.356(3)	2.4447(12)
M–C(10)	2.040(8), 2.057(8)	2.062(5)	2.127(15)	2.106(7)	2.096(8)	2.065(5)	2.068(11)	2.064(10)
M–C(11)	2.091(15), 2.160(10)	2.163(5)	2.13(2)	2.145(8)	2.235(6)	2.134(4)	2.094(13)	2.123(9)
M–C(12)	2.164(9), 2.178(9)	2.173(5)	2.090(19)	2.130(7)	2.206(7)	2.135(4)	2.124(14)	2.109(8)
M–C(15)	2.391(15), 2.392(10)	2.379(5)	2.264(17)	2.290(8)	2.223(7)	2.307(5)	2.300(9)	2.344(9)
M–C(16)	2.431(10), 2.445(11)	2.476(5)	2.26(2)	2.275(8)	2.229(6)	2.282(5)	2.346(10)	2.286(10)
M–Y(1)[a]	2.031(1), 2.065(1)	2.057(5)	1.980(1)	2.018(1)	2.108(7)	2.013(5)	2.000(1)	1.995(9)
M–Y(2)[a]	2.318(1), 2.323(1)	2.334(5)	2.160(1)	2.175(1)	2.115(7)	2.189(5)	2.228(1)	2.217(10)
Angles								
C(10)–M–X	89.4(2), 88.7(3)	91.2(2)	86.0(7)	86.4(2)	83.5(3)	90.3 (2)	91.2(4)	89.9(3)
C(10)–M–Y(1)	90.2(2), 93.1(2)	92.8(2)	93.7(7)	95.6(2)	96.6(3)	91.8(2)	91.9(3)	93.7(4)
C(10)–M–Y(2)	176.0(2), 174.8(3)	175.5(2)	177.3(5)	177.9(3)	177.6(4)	176.2(2)	175.0(3)	176.1(4)
X–M–Y(1)	171.4(1), 173.0(1)	169.3(2)	179.7(6)	178.0(1)	178.4(3)	175.7(2)	172.3(1)	171.6(3)
X–M–Y(2)	94.5(1), 95.2(1)	92.9(2)	94.4(6)	92.0(1)	94.6(3)	92.0(2)	92.1(1)	92.4(3)
Y(1)–M–Y(2)	86.1(1), 83.4(1)	83.5(2)	85.9(5)	86.0(1)	85.2(3)	86.0(2)	85.3(1)	84.5(4)
M–CH_2–R′	110.7(6), 110.9(6)	119.3(3)	–	121.9(5)	122.3(5), 119.3(5)	115.7(3)	121.8(8)	122.4(7)
Σ of angles around M	360.2(1), 360.4(2)	360.4(2)	360.0(6)	360.0(1)	359.9(3)	360.1(2)	360.5(2)	360.5(4)

[a] Two independent molecules in the unit cell.
[b] Centroids Y(1) and Y(2) are defined as the averaged olefinic bonds between C(11) and C(12) or C(15) and C(16) respectively.

Table 4
Cytotoxicity of selected compounds in HT-29 and MCF-7 cells expressed as IC_{50} values obtained in 2 independent experiments (standard deviations are given as superscript numbers).

	IC_{50} HT-29 in μM	IC_{50} MCF-7 in μM	Reference
Cisplatin	$7.0^{\pm 2.0}$	$2.0^{\pm 0.3}$	34
[(COD)$PtCl_2$]	>100	>100	16
[(COD)Pt(Me)Cl]	$8.3^{\pm 3.0}$	$11.2^{\pm 1.4}$	16
[(COD)Pt(bnz)Cl]	$10.3^{\pm 3.3}$	$9.7^{\pm 1.0}$	This work
[(COD)Pt(neoSi)Cl]	$7.4^{\pm 2.7}$	$8.5^{\pm 0.5}$	This work
[(COD)Pt(Me)(C≡C(4F)Ph)]	$4.6^{\pm 0.2}$	$4.7^{\pm 0.7}$	This work
[(COD)Pt(Me)(C≡C(4Me)Ph)]	$0.2^{\pm 0.1}$	$0.3^{\pm 0.1}$	This work
[(COD)Pt(Me)(C≡C(4NO_2)Ph)]	$2.3^{\pm 0.7}$	$1.9^{\pm 0.6}$	This work
[(COD)Pt(Me)(C≡CPh)]	$9.0^{\pm 1.7}$	$10.5^{\pm 7.9}$	This work

(olefin)C–H···π(Ph–CH_2–) interactions. However, the shortest H···centroid distances were all around 3.1 Å, which is not significant for a strong C–H···π interaction [29]. This is in agreement with the NMR results showing a measurable but weak interaction. Thus, we conclude that in these neutral complexes the interplay of various weak intra- and intermolecular forces create a variety of slightly different crystal and molecular structures by varying essentially the Pt–C(10)–C/Si angle and direction of the coligands.

The distances of the olefin carbon atoms, also represented by the centroids Y, reflect the character of the *trans*-oriented coligands (in terms of the *trans*-influence). For *trans*-oriented halogenido coligands the M–Y distances are markedly shorter than the M–Y distances at the *trans*-position of the alkyl coligands in agreement with the differences in coupling constants observed in solution (NMR). Here it is interesting to note, that for the complex [(COD)Pt(Me)Cl], crystallised in this work in the orthorhombic space group $P2_12_12_1$, the bond distances and angles do not significantly deviate from the previously reported structure in monoclinic C2/c [14].

2.4. Cytotoxicity

In continuation of our previous work on the cytotoxicity of organo-platinum(II) and -palladium(II) complexes we evaluated some of the complexes selected for their antiproliferative effects in HT-29 colon carcinoma and MCF-7 breast adenocarcinoma cells (Table 4). Previous studies on platinum COD species had indicated that replacing one chlorido ligand of [(COD)$PtCl_2$] with methyl resulted in a considerable increase in cytotoxic potency,[16] which is in line with the early findings of Takesawa et al.[18] In good agreement with this the structural analogues [(COD)Pt(bnz)Cl] and [(COD)Pt(neoSi)Cl] showed promising activities in both cell lines in the range of 7–10 μM. Introducing different phenylalkynyl ligands in the position of the chlorido ligand led to species with activities in the range of 0.2–10 μM. The highest activities were observed with the Me substituted [(COD)Pt(Me)(C≡C(4Me)Ph)], which was substantially more active than the platinum anticancer lead compound cisplatin. The differences in biological activity between the different phenylalkynyl platinum derivatives can be attributed to different electronic, steric and lipophilic effects of the substituents. This in turn might lead to possible differences in their cellular accumulation and biodistribution, interaction with biological targets (such as binding to the DNA) or involvement in cellular redox biochemistry (e.g. alterations in the formation of reactive oxygen species) and suggests more detailed biochemical/pharmalogical investigations.

3. Conclusions and outlook

A big number of organo-palladium(II) and -platinum(II) complexes could be synthesised and thoroughly characterised concerning their molecular structures in solution (multinuclear NMR spectroscopy) and in the solid state (XRD). Furthermore focus was laid on the synthesis procedures revealing some differences between palladium(II) and platinum(II) homologues, which helped to optimise the yields. Selected samples were submitted to antiproliferative testing using HT-29 and MCF-7 tumour cells. For some of the samples, namely the mixed alkyl alkynyl complexes striking IC_{50} values below that of cisplatin suggest more detailed biological studies on this type of platinum bioorganometallics.

4. Experimental

4.1. General

All preparations were carried out in a dry argon atmosphere using Schlenk techniques. Solvents (CH_2Cl_2, THF, toluene, diethyl ether and MeCN) were dried using an MBRAUN MB SPS-800 solvent purification system.

4.2. Instruments

The NMR spectra were recorded on a Bruker Avance II 300 MHz (^{1}H: 300.13 MHz, ^{13}C: 75.47 MHz)/Bruker Avance 400 spectrometer (^{1}H: 400.13 MHz, ^{13}C: 100.61 MHz, ^{195}Pt: 86.01 MHz) using a triple resonance ^{1}H,^{19}F,BB inverse probehead or on a Bruker Avance II 600 spectrometer (^{1}H: 600.13 MHz). The broad band coil was tuned to either the carbon or the platinum frequency and the detection coil to the proton frequency, resulting in 90° pulses of 11.9 μs for ^{13}C, 12.5 μs for ^{195}Pt and 12.4 μs for ^{1}H. The unambiguous assignment of the ^{1}H, ^{13}C and ^{195}Pt resonances was obtained from ^{1}H TOCSY, ^{1}H COSY, ^{1}H NOESY, gradient selected ^{1}H, ^{13}C HSQC and HMBC and gradient selected ^{1}H, ^{195}Pt HMBC experiments. All 2D NMR experiments were performed using standard pulse sequences from the Bruker pulse program library. Chemical shifts were relative to TMS for ^{1}H and ^{13}C and $Na_2[PtCl_6]$ in D_2O for ^{195}Pt. The spectra analyses were performed by the *Bruker TopSpin 1.3* software. EI-MS spectra were measured using a Finnigan MAT 95. Elemental analyses were carried out on Hekatech CHNS EuroEA 3000 Analyzer. IR spectra were measured on Bruker IFS66vS.

4.3. Reagents

The complexes [(COD)$PtCl_2$] [1], [(COD)$PdCl_2$] [36], [(COD)$PdBr_2$] [36], [(COD)Pt($Me)_2$] [1], [(COD)Pt(Me)Cl] [1], [(COD)Pd(Me)Cl] [6c,6d], [(COD)Pt($neop)_2$] [20a], [(COD)Pt(neop)Cl] [5a] and [(COD)Pd(neop)Br] [16] were prepared according to published procedures. All other chemicals were purchased by commercial suppliers and were used without further purification.

4.4. Synthesis of [(COD)Pt($bnz)_2$] and [(COD)Pt(bnz)Cl]

The compounds were prepared according to the method described for [(COD)Pt($Me)_2$] and [(COD)Pt(Me)Cl] [1,3a]. For the preparation of [(COD)Pt($bnz)_2$] the precursor [(COD)$PtCl_2$] was reacted with (bnz)MgCl. Yield: 85%. Anal. Calc. for $C_{22}H_{26}Pt$ (485.54): C, 54.42; H, 5.40. Found: C, 54.41; H, 5.48. ^{1}H-NMR (δ, $CDCl_3$): 7.16–7.05 (m; 8H, H_{Phbnz}), 6.90 (m, 2H, H_{Phbnz}), 4.68 (s, 4H, $H_{1,2,5,6COD}$, $^2J_{PtH} = 42$ Hz), 2,87 (s, 4H, CH_{2bzl}, $^2J_{PtH} = 113$ Hz), 2.24 (m, 8H, $H_{3,4,7,8COD}$). ^{195}Pt NMR (δ, $CDCl_3$): −3647. For the preparation of [(COD)Pt(bnz)Cl] the starting material [(COD)Pt($bnz)_2$] was reacted with an appropriate amount of acetyl chloride in a mixture of acetone/methanol (5/1). Yield 95%: Anal. Calc. for $C_{15}H_{19}Cl_1Pt_1$ (429.86): C, 41.91; H, 4.46. Found: C, 41.88; H, 4.46. EI-MS: 430 $[M]^+$. ^{1}H-NMR (δ, $CDCl_3$): 7.16–6.98 (m, 5H, H_{Phbnz}), 5.58 (m, 2H, $H_{5,6COD}$, $^2J_{PtH} = 37$ Hz), 4.32 (m, 2H, $H_{1,2COD}$, $^2J_{PtH} = 75$ Hz), 3.15 (s,

2H, CH_{2bzl}, $^2J_{PtH}$ = 102 Hz), 2.41–2.16 (m, 8H, $H_{3,4,7,8COD}$). ^{195}Pt NMR (δ, $CDCl_3$): −3508.

4.5. Synthesis of [(COD)Pd(bnz)Cl]

To a suspension of 1.5 g (5.25 mmol) [(COD)$PdCl_2$] in 50 mL diethyl ether 1.03 g (6.83 mmol) of a freshly prepared solution of (bnz)MgCl in 20 mL diethyl ether were added within 30 min while stirring at 0 °C. After further stirring for 30 min the brownish suspension was treated with 30 mL of moist diethyl ether and filtered through Celite. The clear yellow filtrate was evaporated to dryness, the resulting yellow solid washed with 10 mL *n*-pentane and dried in vacuo. Yield: 448 mg (1.31 mmol, 25%). Anal. Calc. for $C_{15}H_{19}Cl_1Pd_1$ (341.17): C, 52.81; H, 5.61. Found: C, 52.79; H, 5.68. EI-MS: 338 $[M]^+$. ^{1}H-NMR (δ, CDCl3): 7.43 (m, 2H, H_{Phbnz}), 7.14 (m, 3H, H_{Phbnz}), 5.89 (m, 2H, $H_{5,6COD}$), 4.87 (m, 2H, $_{H1,2COD}$), 3.59 (s, 2H, H_{CH2bnz}), 2.62–2.27 (bm, 8H, $H_{3,4,7,8COD}$).

4.6. Synthesis of [(COD)Pt(neoSi)$_2$] and [(COD)Pt(neoSi)Cl]

To a suspension of 0.9 g (2.43 mmol) [(COD)$PtCl_2$] in 20 mL diethyl ether 3.58 g (24.33 mmol) of a freshly prepared solution of (neoSi)MgCl in 30 mL diethyl ether were added within 40 min while stirring at −55 °C. After further stirring for 3 h at ambient temperature the suspension was cooled to −20 °C and quenched with 10 mL saturated aqueous NH_4Cl solution. After phase separation the aqueous phase was extracted three times with 20 mL of CH_2Cl_2. The organic phases were combined, dried over $MgSO_4$, filtered and evaporated to dryness. Yield: 1123 mg (2.35 mmol; 96%). Anal. Calc. for. $C_{16}H_{34}Pt_1Si_2$ (477.72): C, 40.23; H, 7.17. Found: C, 40.29; H 7.20. EI-MS: 478 $[M]^+$. ^{1}H-NMR (δ, acetone-d_6): 4.73 (m, 4H, $^2J_{(Pt-H)}$ = 43 Hz, $H_{1,2,5,6cod}$), 2.32 (m, 8H, $H_{3,4,7,8cod}$), 0.87 (s, 4H, $^2J_{(Pt-H)}$ = 94 Hz, CH_{2neoSi}), 0.04 (s, 18H, Me_{neoSi}). ^{195}Pt-^{1}H-HMBC (δ, acetone-d_6): −3568.

To a solution of 1.0 g (2.06 mmol) [(COD)Pt(neoSi)$_2$] in 75 mL acetone an 2 mL methanol were added at −55 °C 207 μL (2.93 mmol) acetyl chloride. The mixture was stirred for 3 h at ambient temperature and evaporated to dryness. Recrystallisation from CH_2Cl_2/*n*-heptane 10/2 mL gave 813 mg gave colourless crystals. Yield: 813 mg (1.91 mmol, 92%) Anal. Calc. for. $C_{12}H_{23}Cl_1Pt_1Si_1$ (425.95): C, 33.83; H, 5.44. Found: C, 33.89; H 5.46. EI-MS: 426 $[M]^+$ 411 $[M-Me]^+$. ^{1}H-NMR (δ, acetone-d_6): 5.35 (m, 2H, $^2J_{(Pt-H)}$ = 38 Hz, $H_{5,6cod}$), 4.59 (m, 2H, $^2J_{(Pt-H)}$ = 74 Hz, $H_{1,2cod}$), 2.64–2.20 (m, 8H, $H_{3,4,7,8cod}$), 0.95 (s, 2H, $^2J_{(Pt-H)}$ = 76 Hz, CH_{2neoSi}), 0.09 (s, 9H, ^1J(C-H) = 118 Hz, ^2J(Si-H) = 6.5 Hz, Me_{neoSi}). ^{29}Si-^{1}H-HMBC (δ, acetone-d_6): 1.66. ^{195}Pt-^{1}H-HMBC (δ, acetone-d_6): −3456.

4.7. Synthesis of [(COD)Pt(Me)(C≡CR′)] and [(COD)Pt(neoSi)(C≡CR″)] (R′ = Ph, (4Me)Ph, (4F)Ph, (4NO$_2$)Ph; R″ = Ph, (4F)Ph

The compounds were prepared in a variation to the method described for [(COD)Pt(C≡CPh)$_2$] [37]: A suspension of 104 mg (0.29 mmol) [(COD)Pt(Me)Cl] or 124 mg (0.29 mmol) [(COD)Pt(neoSi)Cl] in 10 mL ethanol was maintained at −30 °C and a freshly prepared mixture of the alkyne (0.32 mmol, 1.1 eq) and sodium ethoxide (prepared from 7 mg sodium) or 36 mg (0.32 mmol, 1.1 eq) potassium tert-butoxide in 5 mL ethanol were added dropwise with constant stirring. The solutions became darker and after 2 h the colourless products were filtered off. Recrystallisation from CH_2Cl_2/*n*-heptane gave the pure products.

[(COD)Pt(Me)(C≡CPh)]: Yield: 94 mg (0.22 mmol, 77%). Anal. Calc. for $C_{17}H_{20}Pt_1$ (419.42): C, 48.68; H, 4.81. Found: C, 48.66; H, 4.82. EI-MS: 419 $[M]^+$. ^{1}H-NMR (δ, CD_2Cl_2): 7.30 (d, 2H, H_{o-Ph}), 7.21 (m, 3H, $H_{m-Ph, p-Ph}$), 5.47 (m, 2H, $^2J_{(Pt-H)}$ = 36 Hz, $H_{1,2cod}$), 4.92 (m, 2H, $^2J_{(Pt-H)}$ = 49 Hz, $H_{5,6cod}$), 2.47–2.42 (m, 8H, $H_{3,4,7,8cod}$), 0.95 (s, 3H, $^2J_{(Pt-H)}$ = 77 Hz, H_{Me}). ^{195}Pt-^{1}H-HMBC (δ, CD_2Cl_2): −3112. IR (KBr, in cm^{-1}): 3039, 3912, 2991 (w): $\upsilon_{C=CH\ COD}$; 2928, 2880 (s), 2833, 2798 (m): $\upsilon_{CH2\ COD}$; 2111 (s): $\upsilon_{C\equiv C}$; 1596, 1566, 1516, 1486 (s): $\upsilon_{C=C\ Ph}$.

[(COD)Pt(Me)(C≡C(4Me)Ph)]: Yield: 98 mg (0.22 mmol, 79%). Anal. Calc. for $C_{18}H_{22}Pt_1$ (433.45): C, 49.88; H, 5.12. Found: C, 49.88; H, 5.18. EI-MS: 433 $[M]^+$. ^{1}H-NMR (δ, CD_2Cl_2): 7.12 (d, 2H, H_{o-Ph}), 7.04 (d, 2H, H_{m-Ph}), 5.46 (m, 2H, $^2J_{(Pt-H)}$ = 37 Hz, $H_{1,2cod}$), 4.91 (m, 2H, $^2J_{(Pt-H)}$ = 50 Hz, $H_{5,6cod}$), 2.46–2.41 (m, 8H, $H_{3,4,7,8cod}$), 2.30 (s, 3H, $^2J_{(Pt-H)}$ = 78 Hz, H_{Me-Tol}), 0.94 (s, 3H, $^2J_{(Pt-H)}$ = 78 Hz, H_{Me}). ^{195}Pt-^{1}H-HMBC (δ, CD_2Cl_2): −3108. IR (KBr, in cm^{-1}): 3049, 3033, 3012 (w): $\upsilon_{C=CH\ COD}$; 2949, 2882 (s), 2835, 2802 (m): $\upsilon_{CH2\ COD}$; 2113 (s): $\upsilon_{C\equiv C}$; 1602, 1559, 1540 (w), 1501 (s): $\upsilon_{C=C\ Ph}$.

[(COD)Pt(Me)(C≡C(4F)Ph)]: Yield: 105 mg (0.24 mmol, 84%). Anal. Calc. for $C_{17}H_{19}Pt_1F_1$ (437.41): C, 46.68; H, 4.38. Found: C, 46.66; H, 4.41. EI-MS: 437 $[M]^+$. ^{1}H-NMR (δ, CD_2Cl_2): 7.29 (dd, 2H, H_{o-Ph}), 6.93 (t, 2H, H_{m-Ph}), 5.45 (m, 2H, $^2J_{(Pt-H)}$ = 36 Hz, $H_{1,2cod}$), 4.92 (m, 2H, $^2J_{(Pt-H)}$ = 49 Hz, $H_{5,6cod}$), 2.44 (m, 8H, $H_{3,4,7,8cod}$), 0.94 (s, 3H, $^2J_{(Pt-H)}$ = 78 Hz, H_{Me}). ^{19}F-NMR (δ, CD_2Cl_2): −116. ^{195}Pt-^{1}H-HMBC (δ, CD_2Cl_2): −3115. IR (KBr, in cm^{-1}): 3036, 3006, 2988 (w): $\upsilon_{C=CH\ COD}$; 2943, 2883 (s), 2837, 2803 (m): $\upsilon_{CH2\ COD}$; 2113 (s): $\upsilon_{C\equiv C}$; 1598, 1585, 1518 (w), 1500 (s): $\upsilon_{C=C\ Ph}$.

[(COD)Pt(Me)(C≡C(4NO$_2$)Ph)]: Yield: 88 mg (0.19 mmol, 67%). Anal. Calc. for $C_{17}H_{19}N_1O_2Pt_1$ (464.42): C, 43.96; H, 4.12; N, 3.02. Found: C, 43.99; H, 4.08; N,3.05. ^{1}H-NMR (δ, CD_2Cl_2): 8.08 (d, 2H, H_{m-Ph}), 7.43 (d, 3H, $H_{o-Ph,}$), 5.46 (m, 2H, $^2J_{(Pt-H)}$ = 35 Hz, $H_{1,2cod}$), 5.00 (m, 2H, $^2J_{(Pt-H)}$ = 50 Hz, $H_{5,6cod}$), 2.46 (m, 8H, $H_{3,4,7,8cod}$), 0.96 (s, 3H, $^2J_{(Pt-H)}$ = 77 Hz, H_{Me}). ^{195}Pt-^{1}H-HMBC (δ, CD_2Cl_2): −3124. IR (KBr, in cm^{-1}): 3108, 3068 (w): $\upsilon_{C=CH\ COD}$; 2960, 2927, 2885 (m): $\upsilon_{CH2\ COD}$; 2116 (s): $\upsilon_{C\equiv C}$; 1633, 1593, 1518 (m), 1513 (s): $\upsilon_{C=C\ Ph}$; 1342 (s): υ_{NO2}; 694 (w): δ_{NO2}.

[(COD)Pt(neoSi)(C≡CPh)]: Yield: 103 mg (0.21 mmol, 73%). Anal. Calc. for $C_{20}H_{28}Pt_1Si_1$ (491.61): C, 48.86; H, 5.74. Found: C, 48.85; H, 5.70. ^{1}H-NMR (δ, acetone-d_6): 7.30 (d, 2H, H_{o-Ph}), 7.18 (m, 3H, $H_{m-Ph, p-Ph}$), 5.36 (m, 2H, $^2J_{(Pt-H)}$ = 38 Hz, $H_{1,2cod}$), 4.95 (m, 2H, $^2J_{(Pt-H)}$ = 48 Hz, $H_{5,6cod}$), 2.42 (m, 8H, $H_{3,4,7,8cod}$), 1.08 (s, 2H, $^2J_{(Pt-H)}$ = 89 Hz, H_{CH2Si}), 0.11 (s, 9H, $^2J_{(Pt-H)}$ = 117 Hz, ^2J(Si-H) = 6 Hz, H_{Me3Si}). ^{195}Pt-^{1}H-HMBC (δ, acetone-d_6): −3166. ^{29}Si-^{1}H-HMBC (δ, acetone-d_6): 1.79. IR (KBr, in cm^{-1}): 3057, 3038, 3025, 3003 (w): $\upsilon_{C=CH\ COD}$; 2937, 2888, 2877, 2832 (s): $\upsilon_{CH2\ COD}$; 2118 (s): $\upsilon_{C\equiv C}$; 1595 (s), 1572, 1518 (w), 1482 (s): $\upsilon_{C=C\ Ph}$.

[(COD)Pt(neoSi)(C≡C(4F)Ph)]: Yield: 107 mmol (0.21 mmol, 71%). Anal. Calc. for $C_{20}H_{27}Pt_1F_1Si_1$ (509.59): C, 47.14; H, 5.34. Found: C, 47.11; H, 5.37. ^{1}H-NMR (δ, $CDCl_3$): 7.34 (m, 2H, H_{o-Ph}), 6.92 (t, 2H, H_{m-Ph}), 5.41 (m, 2H, $^2J_{(Pt-H)}$ = 38 Hz, $H_{1,2cod}$), 4.95 (m, 2H, $^2J_{(Pt-H)}$ = 48 Hz, $H_{5,6cod}$), 2.42 (m, 8H, $H_{3,4,7,8cod}$),1.15 (s, 2H, $^2J_{(Pt-H)}$ = 88 Hz, H_{CH2Si}), 0.14 (s, 9H, $^2J_{(Pt-H)}$ = 117 Hz, ^2J(Si-H) = 6 Hz, H_{Me3Si}). ^{19}F-NMR (δ, $CDCl_3$): −115. ^{195}Pt-^{1}H-HMBC (δ, $CDCl_3$): −2985. ^{29}Si-^{1}H-HMBC (δ, $CDCl_3$): 1.92.

4.8. Crystal structure determination

The data collection was performed at T = 173(2) or 293(2) K on a *STOE IPDS I* diffractometer with Mo-Kα radiation (λ = 0.71073 Å) employing ω–2θ scan technique. The structures were solved by direct methods using the SHELXTL package [38] or SHELX-97 and WinGX [39] and refinement was carried out with SHELXL97 employing full-matrix least-squares methods on F^2 [40] with $F_0^2 \geq 2\sigma(F_0^2)$ with the results shown in Table 1 (and Supporting Information). All non-hydrogen atoms were treated anisotropically, hydrogen atoms were included by using appropriate riding models. CCDC 764339–764346 contain the full crystallographic data. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ UK. Fax: +44 1223 336 033; Email: deposit@ccdc.cam.ac.uk.

4.9. Cytoxicity tests

The antiproliferative effects of the compounds were determined following an established procedure [35]. In short, cells were suspended in cell culture medium (HT-29: 2850 cells/mL, MCF-7: 10 000 cells/mL), and 100 μL aliquots thereof were plated in 96 well plates and incubated at 37 °C: 5% CO_2 for 48 h (HT-29) or 72 h (MCF-7). Stock solutions of the compounds in dimethylformamide (DMF) were freshly prepared and diluted with cell culture medium to the desired concentrations (final DMF concentration: 0.1% v/v). The medium in the plates was replaced with medium containing the compounds in graded concentrations (six replicates). After further incubation for 72 h (HT-29) or 96 h (MCF-7) the cell biomass was determined by crystal violet staining and the IC_{50} values were determined as those concentrations causing 50% inhibition of cell proliferation. Results were calculated from two independent experiments.

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Appendix. Supplementary material

Supplementary material associated with this article can be found in the online version, at doi:10.1016/j.jorganchem.2010.04.027.

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