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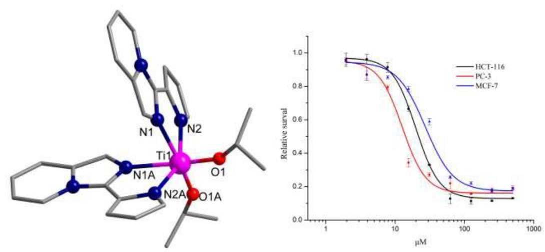

RSC Advances RSCPublishing

ARTICLE

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012, Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

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Titanium complexes supported by imidazo[1,5-*a*]pyridine-containing pyrrolyl ligand as catalysts for hydroamination and polymerization reactions, and as antitumor reagent

Jinna Liu,[a] Yuhua Cao,[b] Lei Li,[a] Hao Pei,[a] Yanmei Chen,[a,c] Jinfa Hu,[a] Yaru Qin,[a] Yahong Li,[*a] Wu Li[c] and Wei Liu[*a]

A new imidazo[1,5-a]pyridine-containing pyrrolyl ligand HL (HL = 3-(1*H*-pyrrol-2-yl)imidazo[1,5-*a*]pyridine) has been synthesized and employed to the organometallic chemistry of titanium. The syntheses, structures, catalytic properties and antitumor activity of three titanium complexes supported by HL are reported. Reactions of $Ti(NMe_2)_4$ and $Ti(NEt_2)_4$, respectively, with 2 equivalents of HL, lead to the production of titanium bisamido complexes $TiL_2(NMe_2)_2$ (**1**) and $TiL_2(NEt_2)_2$ (**2**). Treatment of $Ti(O^iPr)_4$ with **2** equivalents of HL results in the formation of $TiL_2(O^iPr)_2$ (**3**). All complexes have been characterized by elemental analyses and NMR studies. The solid-state structures of **2** and **3** have been further established by single X-ray crystallography. The titanium bisamido complexes **1** and **2** are shown to be good pre-catalysts for the hydroamination of alkynes. Complex **1** was found to be active catalyst for the ring-opening polymerization of ε-caprolactone. The cytotoxicity activities of **3** towards the tumor cells HCT-116, PC3 and MCF-7 were measured. Complex **3** exhibited good antitumor properties.

Introduction

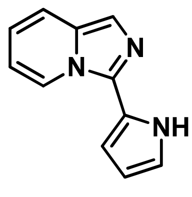
The organometallic chemistry of titanium has received growing attention from many groups around the world.[1] The efforts of these groups are driven by a number of impetuses, but the three most important factors are the development of precatalysts for alkyne and alkene hydroamination reactions,[2] the employment of titanium complexes as the initiators for the polymerization of olefin[3] and cyclic ester,[4] and the investigation of cytotoxicity of titanium compounds towards cancer cells.[5] Hydroamination is the addition of N-H bond across an unsaturated C-C bond. Since hydroamination of alkyne or alkene provides an important avenue for the efficient synthesis of imines, enamines and nitrogen-containing heterocycles with a 100% atom-economical fashion, hydroamination reaction has been the subject of ever-increasing scrutiny over the past two decades.[2] Numerous catalysts based on the elements stretched across the periodic table have been found to be able to catalyze this transformation.[6] Among which the titanium complexes have been proved particularly useful.[2a-c] The advantages of titanium catalysts over late transition metals are improved cost effectiveness and low toxicity. The titanium compounds are also preferred over rare-earth catalysts owing to their enhanced robustness and broad functional group scope.

The recent advances of titanium catalyzed hydroamination reveal that the regiochemical outcome of the reaction could be dramatically controlled by utilizing different ligands. Thus, a plethora of ancillary ligands, *e.g.*, Cp-based molecules,[7] pyrrolyl ligands,[8] amidate compounds,[9] imidazole-containing ligands[10] and phenolate,[11] *etc.*, are reported. However, employment of a multidentate ligand in which a pyrrolyl moiety and a N-containing heterocycle were incorporated in one molecule entity, has rarely been explored. Aiming at exploring the influences of the structure of the ligands on the regioselectivity of the hydroamination products and continuing our ongoing efforts on studying the hydroamination of alkynes catalyzed by titanium compounds supported by pyrrolyl ligands,[8a-b] we expand our efforts to synthesize titanium pre-catalysts coordinated by 3-(1*H*-pyrrol-2-yl)imidazo[1,5-*a*]pyridine (HL, Scheme 1), which contains both a pyrrolyl ring and an imidazo[1,5-*a*]pyridine moiety. The reactions of HL with $Ti(NMe_2)_4$, $Ti(NEt_2)_4$, and $Ti(O^iPr)_4$, respectively, gave complexes $TiL_2(NMe_2)_2$ (**1**), $TiL_2(NEt_2)_2$ (**2**) and $TiL_2(O^iPr)_2$ (**3**). Herein we report the syntheses and characterizations of these complexes. The catalytic activities of **1** and **2** towards the intermolecular hydroamination of alkynes, the ring-opening polymerization of ε-caprolactone initiated by **1**, and the cytotoxicity activities of **3** towards the tumor cells HCT-116, PC3 and MCF-7 were also investigated.

Results and discussion

Synthesis of the HL ligand

The ligand HL was prepared by the reaction of 1*H*-pyrrole-2-carbonyl chloride and 2-pyridylmethanamine in the presence of T_3P (50 wt% in DMF). The ligand HL was obtained in good yield and was characterized by ^{1}H and ^{13}C NMR spectra.



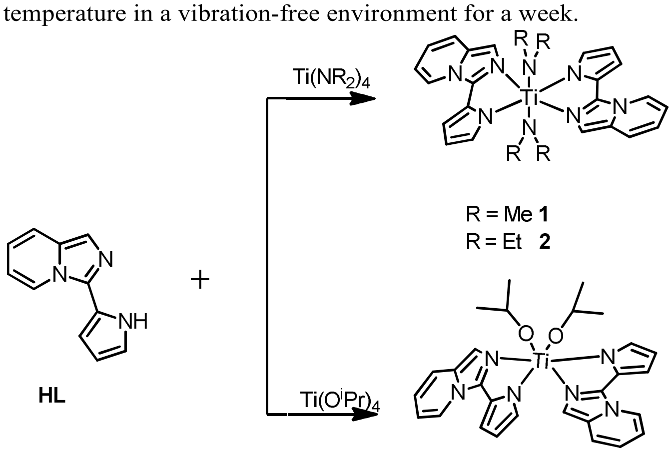
HL

Scheme 1 Structure of the ligand.

Syntheses of the titanium complexes

Treatment of HL with THF solution of $Ti(NMe_2)_4$ and $Ti(NEt_2)_4$, respectively, led to the formations of $TiL_2(NMe_2)_2$ (**1**) and $TiL_2(NEt_2)_2$ (**2**) (Scheme 2). The reaction of $Ti(O^iPr)_4$ with 2 equiv. of HL afforded $TiL_2(O^iPr)_2$ (**3**) (Scheme 2). Complexes **1-3** were readily obtained in good yields. They were also characterized by ^{1}H and ^{13}C NMR spectra and elemental analyses.

Crystals suitable for X-ray diffraction of **2** and **3** were grown from toluene solutions which were left standing at room temperature in a vibration-free environment for a week.



Scheme 2 Syntheses of $TiL_2(NMe_2)$ (**1**), $TiL_2(NEt_2)$ (**2**) and $TiL_2(OiPr)_2$ (**3**).

Structure descriptions of 2 and 3

The molecular structures of **2** and **3** in the solid state have been confirmed by X-ray analysis and are shown in Figs. 1, 2 and 3, respectively. The crystallographic data and experimental details for structural analyses are summarized in Table 1. Selected bond distances and angles are listed in Table 2.

The single crystal analysis revealed that **2** crystallizes in monoclinic crystal system of the $P2_1/c$ space group and displays several interesting features. The overall structure of **2** includes two molecules (Fig. 1), and the two individual molecules are not completely symmetrical. The central Ti(IV) atom is six-coordinated by four nitrogen atoms from two bidentate L^- ligands and two amides in *cis* arrangement, displaying a distorted octahedral coordination environment. The bond lengths between titanium atom and donor imidazopyridine nitrogen atoms (Ti1-N1 = 2.236(3) Å, and Ti1-N4 = 2.277(3) Å) are apparently longer than those of the Ti – N(pyrrolyl) distances (Ti1-N2 = 2.148(3) Å, and Ti1-N4 = 2.123(3) Å). One donor imidazopyridine nitrogen atom of the ligand and one amide atom are in *trans* arrangement, with bond angles of 87.69(10)º (N2-Ti1-N3) and 97.53(11)º (N5–Ti1–N2), summing to185.22º（Fig. 2）.

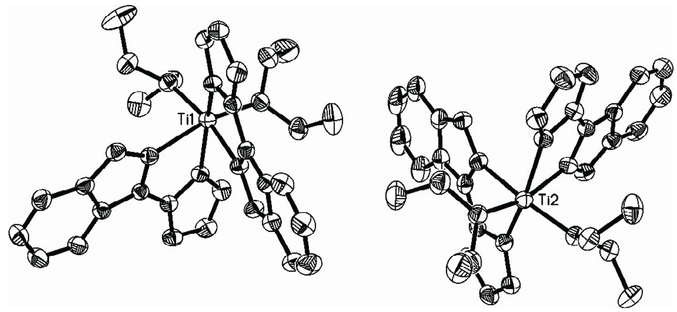


Fig. 1 ORTEP structural drawing of **2**.

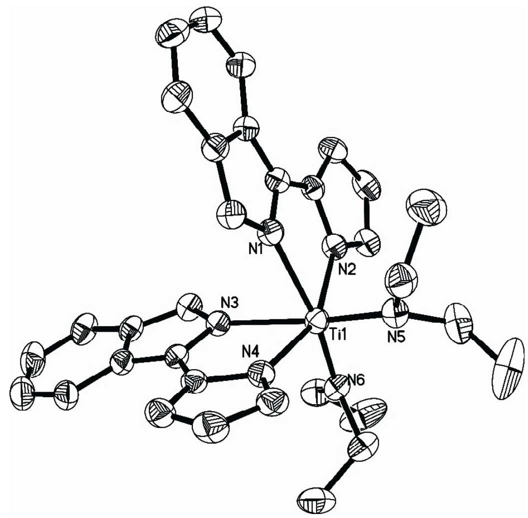


Fig. 2 Partially labeled structure of one of molecules of **2**.

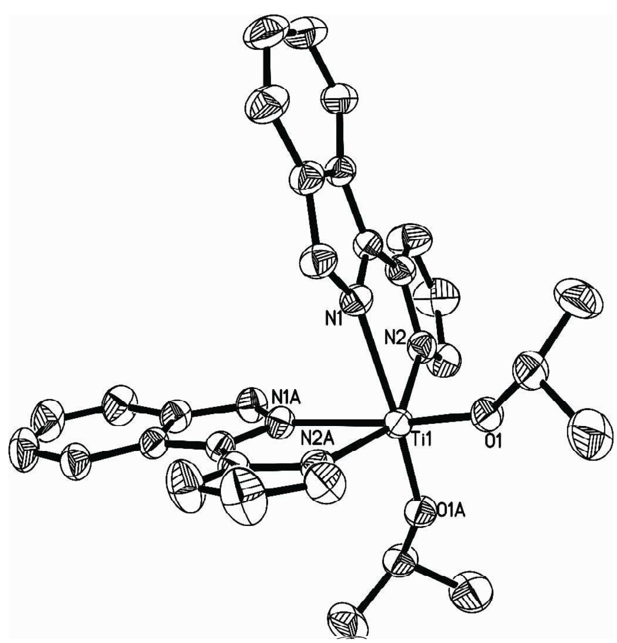


Fig. 3 ORTEP structural drawing of **3**.

Table 1 Crystal data and structure refinements for **2** and **3**

Complex	2	3
Empirical formula	$C_{30}H_{36}N_8Ti$	$C_{28}H_{30}N_6O_2Ti$
Formula weight	556.54	530.45
Temperature	296(2) K	293(2) K
Wavelength	0.71073 Å	0.71073 Å
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	C 2/c
Unit cell dimensions	a = 23.010(9) Å	a = 8.7336(17) Å
	b =13.712(5) Å	b =16.212(6) Å
	c = 21.228(9) Å	c = 18.952(4) Å
	α = 90°	α = 90°
	β =115.456(7)°	β =92.30(3) °
	γ = 90°	γ = 90°
Volume	6048(4) $Å^3$	2681.2(13) $Å^3$
Z	8	4
ρ(mg•m^{-3})	1.222	1.314
F(000)	2352	1112
Crystal size(mm^3)	0.60 x 0.40 x 0.40	0.60 x 0.40 x 0.40
θ range/°	1.78° to 26.22	3.31° to 27.49°
Limiting indices	-28 ≤ h ≤ 23	-9 ≤ h ≤ 11
	-25 ≤ l ≤ 26	-20 ≤ k ≤ 20
	-16 ≤ k ≤ 17	-24 ≤ l ≤ 24
Reflections collected/ unique	35810 / 12166	12023 / 3070
Data / restraints / parameters	12094 / 0 / 711	3048 / 0 / 170
GOF	0.950	1.076
R1,wR2[I> 2σ(I)]	R_1 = 0.0507	R_1 = 0.0456
	wR_2 = 0.1111	wR_2 = 0.1289
R1,wR2(all data)	R_1 = 0.1290	R_1 = 0.0578
	wR_2 = 0.1438	wR_2 = 0.1365
Largest diff. peak and hole(e•$Å^3$)	0.276 and -0.249	0.369 and -0.271

Table 2 Selected bond lengths (Å) and angles (°) for **2** and **3**

Ti(1)-N(1)	2.236(3)	Ti(1)-N(2)	2.148(3)
Ti(1)-N(3)	2.277(2)	Ti(1)-N(4)	2.123(3)
Ti(1)-N(5)	1.912(3)	Ti(1)-N(6)	1.910(3)
N(1)-Ti(1)-N(3)	76.45(9)	N(2)-Ti(1)-N(3)	87.69(10)
N(4)-Ti(1)-N(3)	74.90(10)	N(5)-Ti(1)-N(3)	167.17(11)
N(6)-Ti(1)-N(3)	88.51(10)	N(2)-Ti(1)-N(1)	73.82(10)
N(4)-Ti(1)-N(1)	84.61(9)	N(5)-Ti(1)-N(1)	93.69(11)
N(6)-Ti(1)-N(1)	162.79(10)	N(4)-Ti(1)-N(2)	155.02(10)
N(5)-Ti(1)-N(2)	97.53(11)	N(6)-Ti(1)-N(2)	97.57(11)
N(5)-Ti(1)-N(4)	96.26(11)	N(6)-Ti(1)-N(4)	99.70(11)
N(6)-Ti(1)-N(5)	102.32(12)		
3			
Ti(1)-O(1)	1.7799(13)	Ti(1)-N(1A)	2.2209(15)
Ti(1)-O(1A)	1.7798(13)	Ti(1)-N(2)	2.1003(16)
Ti(1)-N(1)	2.2209(16)	Ti(1)-N(2A)	2.1004(16)
O(1)-Ti(1)-N(1)	90.02(6)	O(1A)-Ti(1)-N(2A)	103.11(6)
O(1)-Ti(1)-N(1A)	167.20(6)	N(1A)-Ti(1)-N(1)	80.70(8)
O(1)-Ti(1)-N(2)	103.11(6)	N(2)-Ti(1)-N(1)	74.28(6)
O(1)-Ti(1)-N(2A)	95.96(6)	N(2)-Ti(1)-N(1A)	82.96(6)
O(1A)-Ti(1)-O(1)	100.41(9)	N(2A)-Ti(1)-N(1)	82.96(6)
O(1A)-Ti(1)-N(1)	167.20(6)	N(2A)-Ti(1)-N(1A)	74.28(6)
O(1A)-Ti(1)-N(1A)	90.02(6)	N(2A)-Ti(1)-N(2)	150.07(9)
O(1A)-Ti(1)-N(2)	95.96(6)		

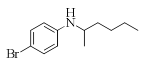
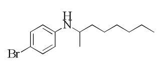
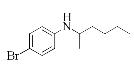
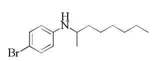
The single crystal X-ray diffraction determination indicates that the octahedral Ti(IV) ion of **3** is surrounded by four nitrogen atoms (N1, N2, N1A, and N2A) from two L^- ligands and two oxygen atoms (O1 and O1A) from isopropoxide groups. The N1, O1, N1A, and O1A atoms are equatorial coplanar, with the bond angles of 90.06(6)º, 100.41(9)º, 90.02(6)º and 80.70(8)º, respectively, summing to 361.19º, with the deviation being 1.19º compared with 360º. The bond lengths between titanium atom and donor imidazopyridine nitrogen atoms (Ti1-N1 = 2.2209(16) Å, and Ti1-N1A = 2.2209(15) Å) are apparently longer than those of the Ti–N(pyrrolyl) distances (Ti1-N2 = 2.1003(16) Å, and Ti1-N2A = 2.1004(16) Å).

Hydroamination of alkynes catalyzed by 1 and 2

To evaluate the catalytic activities of **1** and **2**, we investigated the reactions of aniline with a selection of alkynes (diphenylacetylene, 3-hexyne, 3-octyne, phenylacetylene, 1-hexyne, and 1-octyne) catalyzed by 10 mol% of **1** or **2**. The results are shown in Table 3. As we can see in Table 3, both **1** and **2** could catalyze the hydroamination of 1-hexyne and 1-octyne (entries 4, 5, 9 and 11). The Markovnikov product is favored product of hydroamination. No hydroamination product was determined for symmetric alkynes.

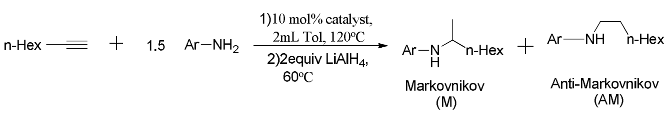
To further probe the scope of the catalysis, a larger selection of amines was screened in reactions with 1-octyne. The results are shown in Table 4. Again, the Markovnikov product is highly favored. In the presence of **1** or **2**, most arylamines hydroaminated 1-octyne in >60% yield and with high regioselectivities. This is in contrast to utilizing Me_2TiCp_2 as the precatalyst,[12] which yielded anti-Markovnikov products. In addition, most of substituted anilines gave better yields. However, when 2-chloroaniline was employed as the amine source, low yields with high regioselectivities were observed (Table 4, entries 5 and 6). 2-Methoxy-phenylamine can be used to hydroaminate 1-octyne with lower regioselectivities (Table 4, entries 17 and 18). In genrral, the yields of hydroamination of alkynes catalyzed by **2** are higher than that of **1**. This is probably due to the slightly larger steric impediment of the diethyl amide group. The yields of the hydroamination reactions by **1** or **2** are higher than that of Ti(imidazol-2-yl)$(NMe_2)_3$.[10]

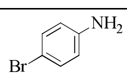
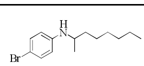
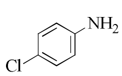
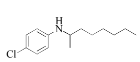
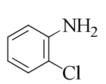
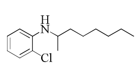
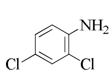
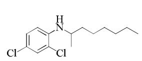
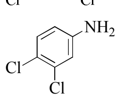
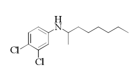
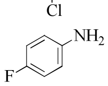
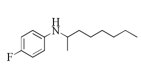
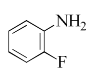
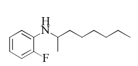
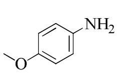
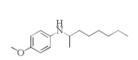
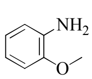
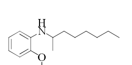
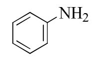
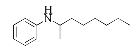
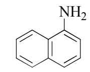
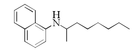
Table 3 Hydroamination of alkynes with 4-bromoaniline catalyzed by complexes **1** or **2**

Entry	Catalyst	Alkyne	Product	M/anti-M[b]	Yield (%)[a]
1	**1**	Ph—≡—Ph			
2		Et—≡—Et			
3		n-Pr—≡—n-Pr			
4		n-Bu—≡		88:12	38
5		n-Hex—≡		98:2	73
6	**2**	Ph—≡—Ph			
7		Et—≡—Et			
8		n-Pr—≡—n-Pr			
9		n-Bu—≡		92:8	47
10		n-Hex—≡		97:3	91

[a] Isolated yields after reduction by $LiAlH_4$. [b] By GC-MS analysis.

Table 4 Hydroamination of 1-octyne with amines catalyzed by **1** and **2**



Entry	Amine	Product	Cat.	M/anti-M	Yield (%)
1			**1**	92:8	73
2			**2**	97:8	91
3			**1**	97:3	70
4			**2**	95:5	77
5			**1**	94:6	22
6			**2**	91:9	21
7			**1**	96:4	65
8			**2**	94:4	79
9			**1**	99:1	93
10			**2**	87:13	85
11			**1**	92:8	52
12			**2**	100:0	79
13			**1**	94:6	72
14			**2**	96:4	59
15			**1**	92:8	68
16			**2**	89:11	86
17			**1**	75:25	62
18			**2**	62:38	77
19			**1**	94:6	78
20			**2**	91:9	83
21			**1**	99:1	84
22			**2**	99:1	95

[a] Isolated yields after reduction by $LiAlH_4$. [b] By GC-MS analysis.

Ring-opening polymerization of ε-caprolactone initiated by complex 1

Metal-catalyzed ring-opening polymerization (ROP) of lactones is one of the most promising processes for the preparation of environmentally friendly and biomedical polyesters, and it provides an alternative in the synthesis of well-characterized biodegradable polymers. While rare earth metal complexes were well known to efficiently catalyze the polymerization of lactones because of the highly electropositive nature of the lanthanides,[13] the titanium(IV) complexes have also been found to initiate the polymerization of ε-caprolactone over the past few years.[14] The titanium compounds chelated by alkoxide or aryloxide ligands have long been recognized to have significant applications in polymerization catalysis, [15] but the potential of titanium complexes supported by imidazopyridine-containing pyrrolyl ligands, has never been explored. Thus, we investigated the catalytic behavior of complexes **1, 2** and **3** towards ring-opening polymerization of ε-caprolactone.

The initial studies were performed using $TiL_2(O^iPr)_2$ (**3**) as the initiator. It was found that **3** showed low activity for the polymerization. The polymerization reaction proceeded very slowly and low yields of polymers were generated after 24 h at 60°C (Table S4, Supporting Information). Next, the polymerization recation was conducted by employing **1** as the initiator, and utilizing dimethyl ether (DME), tetrahydrofuran (THF), and toluene, respectively, as the solvents at 60°C and 80°C. To our delight, complex **1** can effectively initiate ε-caprolactone polymerization, and the obtained polymers have high molecular weights and relatively narrow molecular weight distributions (PDIs). The polymerization results are summarized in Table 5. The solvents have the obvious effect on the yields of the polymers. When the polymerization was conducted in THF, poor or moderate yields were afforded (68% and 60% in THF). However, no observable polymerization initiated by complex **2** occurred at 80°C after 24 h.

Cytotoxicity

Recently, titanium (IV) complexes have been studied as antitumor compounds with the expectation for substituting for platinum compounds.[17] The 'salan' isopropoxide titanium(IV) complexes, which are based on tetradentate diaminobis(phenolato) ligands were demonstrated high antitumor activity;[18] whereas the cytotoxicity of the 'pyrrolyl' isopropoxide titanium(IV) complexes was rarely studied.[19] In order to investigate the influences of the ligand structures on the properties of the Ti(IV) complexes, we studied the anticancer features of complex **3**.

The cytotoxic activity of **3** was studied on HCT-116, PC3 and MCF-7 cells, employing the methylthiazolyl-diphenyl-tetrazolium bromide (MTT) assay. Relative IC_{50} and maximal inhibition values are listed in Table 6. Cytotoxicity plots are given in Fig. 4.

It is evident that **3** exhibits variable cytotoxicity. Compared with cisplatin,[20] complex **3** shows an obvious cytotoxic effect towards HCT-116, PC3 and MCF-7 cells, with the IC_{50} values of 21.87, 31.37 and 14.17 μM, respectively. These IC_{50} data are close to or better than cisplatin (3.79, 33.3, and 46.9 μM towards HCT-116, PC3 and MCF-7 cells, respectively).

Table 5 Polymerization of ε-caprolactone initiated by **1**

Entry	Initiator	solvent	[M]/[I]	t/h	Yield/%[a]	T/°C	Mn(calc)[b](10^4)	Mn[c](10^4)	Mn(obsd)[d](10^4)	PDI	Efficiency/%
1	**1**	DME	200	5	82	80	1.87	2.67	1.49	1.39	70.0
2	**1**	DME	200	10	79	60	1.80	2.33	1.30	1.50	77.2
3	**1**	THF	200	12	68	80	1.55	2.48	1.39	1.49	53.4
4	**1**	THF	200	17	60	60	1.36	1.94	1.09	1.39	70.4
5	**1**	Tol	200	3	89	80	2.03	3.30	1.85	1.22	61.5
6	**1**	Tol	200	4	86	60	1.96	2.25	1.26	1.47	87.0

[a]Yield: weight of polymer obtained/weight of monomer used. [b]Mn(calc) = M_{mono}*[M]/[I] *Conv. [c]Measured by GPC relative to polystyrene standards. [d]Measured by GPC relative to standards with Mark-Houwink corrections[16] for Mn (obsd) = 0.56 Mn (GPC) for ε-caprolactone.

Table 6 Relative IC_{50} and maximal inhibition values for **3**

Compound	IC_{50}			maximal inhibition[a] (%)		
	HCT-116	PC3	MCF-7	HCT-116	PC3	MCF-7
Ti $(O^iPr)_2L_2$ (**3**)	21.87	31.37	14.17	89	81	83

[a] The concentrations of complex **3** are all 250 μM.

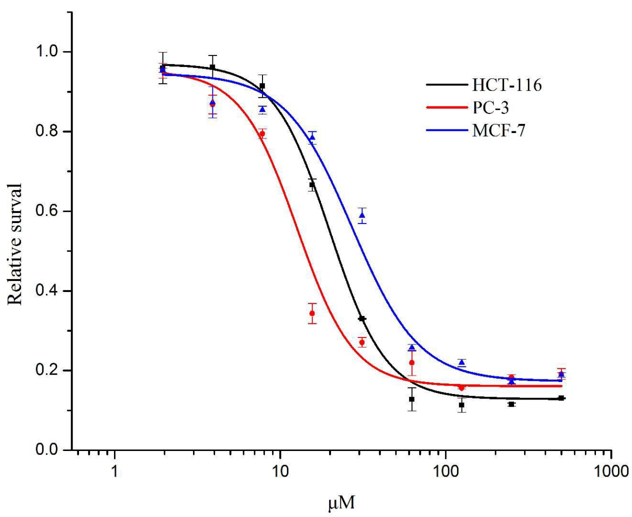


Fig. 4 Cell survivals in response to complex **3** towards cell HCT-116, PC-3, MCF-7.

Conclusions

In summary, three complexes $TiL_2(NMe_2)_2$ (**1**), $TiL_2(NEt_2)_2$ (**2**), and $TiL_2(O^iPr)_2$ (**3**) were synthesized and characterized. The catalytic behaviors of these complexes towards the hydroamination of alkynes, ring-opening polymerization of ε-caprolactone and their cytotoxicity were investigated. Complexes **1** and **2** were able to catalyze the hydroamination of alkynes, and showed higher catalytic activity and gave highly Markovnikov selective hydroamination of 1-octyne. Complex **1** also exhibited good catalytic activity for ring-opening polymerization of ε-caprolactone. High cytotoxicities were obtained for **3**, indicating that pyrrolyl–titanium(IV) complexes may serve as a new family of antitumor agents towards HCT-116, PC3 and MCF-7 cells.

Experimental section

General considerations

All manipulations of air-sensitive compounds were carried out in an MBraun glovebox in a purified nitrogen atmosphere. Anhydrous THF, DME and toluene were freshly distilled from purple sodium benzophenone ketyl for at least 4 days. ^{1}H and ^{13}C spectra were recorded on Innova-400 spectrometers at ambient temperature using TMS as an internal standard, and chemical shifts of carbon, hydrogen and nitrogen atoms were performed with a Carlo－Erba EA1110 CHNOS microanalyzer.

X-ray crystallography

Crystals grown from concentrated solutions at room temperature were quickly selected and mounted on a glass fiber in wax. The data collections were carried out with a Mercury CCD detector equipped with graphite-monochromated Mo-Kα radiation by using the φ/ω scan technique at room temperature. The structures were solved by direct methods with SHELXS-97.[21] The hydrogen atoms were assigned with common isotropic displacement factors and included in the final refinement by use of geometrical restraints. A full-matrix least-squares refinement on F^2 was carried out using SHELXL-97.

General procedure for hydroamination reactions

To a 30 mL pressure tube was added the pre-catalyst (0.1 mmol), amine (1.5 mmol), alkyne (1 mmol) and toluene (5 mL) in a drybox. The pressure tube was sealed with a Teflon screw cap, taken out of the drybox and heated at 120°C for 24 h. Then at 0°C the reaction solution was carefully added to a suspension of $LiAlH_4$ in toluene and the mixture was refluxed for 12 h at 60°C. After cooling the solution to 0°C, the excess $LiAlH_4$ was hydrolyzed with sodium sulphate decahydrate. The mixture was filtered to remove sodium sulphate decahydrate.The solvent was concentrated under vacuum. Column chromatography of the residue on silica gel afforded the pure amine derivatives.

Typical polymerization procedure

A THF solution of complex **1** (0.0250 g, 0.05 mmol) and ε-caprolactone (1.14 g, 10 mmol) was added to a 30 mL pressure tube equipped with a magnetic stirring bar in a glovebox. Afterwards, the pressure tube was taken out from the glovebox. The reaction mixture was heated to 80°C for 12 h and then terminated by addition of a mixture of conc. HCl/EtOH (1:5 V/V) (2 mL). Petroleum ether (20 mL) was added to give yellow solids. The solids were dissolved in THF (20 mL), column chromatography on Al_2O_3 to give a white solid. Yield: 0.78 g (68 %).

General considerations for cytotoxicity

Cytotoxicity was measured on colorectal cancer cell HCT-116, adenocarcinoma MCF-7 and PC-3 using the methylthiazolyldiphenyl tetrazolium bromide (MTT) assay. HCT 116 cells were cultured at 37°C in a 5% CO_2 atmosphere incubator in modified McCoy's 5A medium (sigma) complemented with 10% fetal bovine serum (FBS, Hyclone) containing 1% penicillin and 1% streptomycin (Sigma). MCF-7 was maintained in RPMI 1640 medium with 10% FBS and PC3 in F-12K medium with 10% FBS. For cytotoxicity assay, HCT 116, MCF-7 and PC-3 cells were seeded into 96-well plates at densities of 5000 cells per well and maintained for 24 h. Next, the cells were incubated with the reagents tested at different concentrations for another 72 h in modified McCoy's 5A medium containing 10% FCS. After that, MTT (5 mg/mL in 20 μL) was added and the cells were incubated for additional 4 h. The supernatant was removed, and the precipitates were dissolved in 150 mL of DMSO. The absorbance at 490 nm was measured. Relative IC_{50} values with standard error of means were determined by a nonlinear regression of a variable slope model.

Synthesis of the ligand and complexes 1-3

3-(1*H*-pyrrol-2-yl)imidazo [1,5-*a*]pyridine (HL). To a stirred solution of 1*H*-pyrrole-2-carbonyl chloride (10 mmol) in CH_2Cl_2 was added pyridine (2 mL) followed by substituted 2-pyridylmethanamine (10 mmol) at room temperature. The reaction mixture was stirred for 1 h and added 30 mL water. The reaction was neutralized by $NaHCO_3$ and extracted with ethylacetate; then the organic layer was dried and concentrated to give the amide (N-(pyridin-2-ylmethyl)-1*H*-pyrrole-2-carboxamide). To the amide added 9 mL of T_3P (50 wt% in DMF) and refluxed for 3 h at 125°C. This was poured into cold water and neutralized with ammonia solution. The water layer was extracted three times with ethylacetate. The combined organic phases were dried over anhydrous Na_2SO_4 and evaporated under vacuum. The residue, thus obtained was purified by column chromatography using ethylacetate and hexane as solvent system to get the product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.14 (s, 1H), 8.39 – 8.28 (m, 1H), 7.51 (s, 1H), 7.45 (d, 1H), 7.02 (d, 1H), 6.76 – 6.58 (m, 3H), 6.41 (dd, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.32, 130.71, 122.01, 119.86, 119.21, 118.72, 118.33, 113.31, 109.16, 106.07. Anal. Calc. for HL: C 72.11; H 4.95; N 22.94%. Found: C 71.79; H 5.06; N 22.61%.

$TiL_2(NMe_2)_2$ (1). To a solution of $Ti(NMe_2)_4$ (0.112 g, 0.5 mmol) in THF (2 mL) was added dropwise HL (0.1830 g, 1 mmol) in THF (5 mL). After stirring at room temperature for 24 h, the volatiles were removed under reduced pressure to give a red solid. Yield: 0.47 g (93%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, 2H, $C_7H_5N_2$), 7.54 (s, 2H, $C_7H_5N_2$), 7.06 (d, 2H, $C_7H_5N_2$), 6.62 (d, 2H, pyrrole-H), 6.53 – 6.39 (m, 6H, $C_7H_5N_2$ + pyrrole-H), 6.28 (s, 2H, pyrrole-H), 3.35 (s, 12H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.41, 130.93, 129.01, 128.70, 122.06, 119.09, 117.65, 115.87, 113.31, 108.90, 103.68, 68.17, 47.37. Anal. Calc. for $C_{26}H_{28}N_8Ti$: C 62.40; H 5.64; N 22.39%. Found: C 62.32; H 5.82; N 22.43%.

$TiL_2(NEt_2)_2$ (2). The synthesis of complex **2** was carried out in the same way as that described for complex **1**, but $Ti(NEt_2)_4$ (0.186 g, 0.5 mmol) was used instead of $Ti(NMe_2)_4$. The volatiles were removed under reduced pressure to give a red-brown solid. Yield: 0.50 g (89%). Red crystals were obtained in toluene. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, 2H, $C_7H_5N_2$), 7.61 (s, 2H, $C_7H_5N_2$), 7.06 (d, 2H, $C_7H_5N_2$), 6.62 (d, 2H, pyrrole-H), 6.47 (dd, 8H, $C_7H_5N_2$ + pyrrole-H), 4.22 – 3.74 (m, 8H, CH_2), 0.62 (t, 12H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.92, 131.65, 128.84, 128.25, 121.99, 118.92, 117.44, 115.76, 113.05, 108.71, 103.24, 45.21, 12.82. Anal. Calc. for $C_{30}H_{36}N_8Ti$: C 64.74; H 6.52; N 20.13%. Found: C 64.83; H 6.57; N 19.71%.

$Ti(O^iPr)_2L_2$ (3). To a solution of $Ti(O^iPr)_4$ (0.1421 g, 0.5 mmol) in tetrahydrofuran (2 mL), HL (0.1830 g, 1.0 mmol) in tetrahydrofuran was added at room temperature. After stirring at room temperature for at least 24 h, THF was evaporated completely under reduced pressure to give an orange solid. The product was obtained as light orange block crystals after crystallized from toluene. Yield: 80% (0.4135 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, 2H, $C_7H_5N_2$), 7.51 (d, 2H, $C_7H_5N_2$), 7.15 – 7.00 (m, 2H, $C_7H_5N_2$), 6.59 (d, 2H, pyrrole-H), 6.52 – 6.38 (m, 6H, $C_7H_5N_2$ + pyrrole-H), 6.20 (s, 2H, pyrrole-H), 4.79 – 4.58 (m, 2H, CH), 1.17 (d, 6H, CH_3), 1.00 (d, 3H, CH_3). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.63, 132.05, 128.74, 128.21, 121.92, 119.15, 117.76, 115.90, 113.49, 108.42, 103.41, 79.19, 25.55. Anal. Calc. for $C_{28}H_{30}N_6O_2Ti$: C 63.40; H 6.70; N 15.84%. Found: C 63.73; H 5.60; N 16.23%.

Acknowledgements

We thank Professor Zhijun Zhang of Suzhou Institute of Nanotech and Nano-bionics for assistance with cytotoxicity measurement. The authors appreciate the financial supports of Natural Science Foundation of China (21272167 and 21201127), A Project Funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions, and KLSLRC (KLSLRC-KF-13-HX-1).

Notes and references

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† Electronic Supplementary Information (ESI) available:Crystallography, ^{1}H and ^{13}C NMR data. CCDC reference numbers 1030010 and 990411 for complex **2** and **3**, respectively. For ESI and crystallographic data in CIF or other electronic see DOI: 10.1039/b000000x/

1 For selected examples, see: (*a*) N. Hazari and P. Mountford, *Acc Chem. Res.*, 2005, **38**, 839-849; (*b*) A. D. Schwarz, A. J. Nielson, N. Kaltsoyannis and P. Mountford, *Chem. Sci.*, 2012, **3**, 819–824; (*c*) Y. H. Li, Y. H. Shi and A. L. Odom, *J. Am. Chem. Soc.*, 2004, **126**, 1794-1803; (*d*) I. Prochnow, P. Zark, T. Müller and S. Doye, *Angew. Chem., Int. Ed.*, 2011, **50**, 1 – 6; (*e*) L. H. Gade, *Acc. Chem. Res.*, 2002, **35**, 575-582; (*f*) S. W. Hu, T. Shima and Z. M. Hou, *Nature*, 2014, **512**, 413-415; (*g*) T. Shima, S. W. Hu, G. Luo, X. H. Kang, Y. Luo and Z. M. Hou, *Science*, 2013, **340**, 1549-1552; (*h*) H. Shen and Z. W. Xie, *J. Am. Chem. Soc.*, 2010, **132**, 11473-11480; (*i*) V. N. Cavaliere, M. G. Crestani, B. Pinter, M. Pink, C. Chen, M. Baik and D. J. Mindiola, *J. Am. Chem. Soc.*, 2011, **133**, 10700–10703; (*j*) R. Thompson, C. Chen, M. Pink, G. Wu and D. J. Mindiola, *J. Am. Chem. Soc.*, 2014, **136**, 8197–8200.

2 For selected reviews and recent papers, see: (*a*) T. E. Müller, K. C. Hultzsch, M. Yus, F. Foubelo and M. Tada, *Chem. Rev.*, 2008, **108**, 3795; (*b*) A. L. Odom, *Dalton Trans.*, 2005, 225-233; (*c*) G. F. Zi, *J. Organomet. Chem.*, 2011, **696**, 68-75; (*d*) R. Severin, S. Doye, *Chem. Soc. Rev.*, 2007, **36**, 1407-1420; (*e*) H. Shigehisa, N. Koseki, N. Shimizu, M. Fujisawa, M. Niitsu and K. Hiroya, *J. Am. Chem. Soc.*,

2014, **136**, 13534-13537; (*f*) A. J. Musacchio, L. Q. Nguyen, G. H. Beard and R. R. Knowles, *J. Am. Chem. Soc.*, 2014, **136**, 12217-12220; (*g*) A. R. Ickes, S. C. Ensign, A. K. Gupta and K. L. Hull, *J. Am. Chem. Soc.*, 2014, **136**, 11256-11259. (*h*) A. Zhdanko and M. E. Maier, *Angew. Chem. Int. Ed.*, 2014, **53**, 7760-7764; (*i*) T. M. Nguyen, N. Manohar and D. A. Nicewicz, *Angew. Chem. Int. Ed.*, 2014, **53**, 6198-6201; (*j*) M. J. Goldfogel, C. C. Roberts and S. J. Meek, *J. Am. Chem. Soc.*, 2014, **136**, 6227-6230.

3 (*a*) F. Gornshtein, M. Kapon, M. Botoshansky and M. S. Eisen, *Organometallics*, 2007, **26**, 497-507; (*b*) I. Saeed, S. Katao and K. Nomura, *Organometallics*, 2009, **28**, 111-122; (*c*) K. H. Tam, M. C. W. Chan, H. Kaneyoshi, H. Makio and N. Zhu, *Organometallics*, 2009, **28**, 5877-5882; (*d*) W. H. Sun, S. Liu, W. Zhang, D. Wang and T. Liang, *Organometallics*, 2010 , **24**, 732-741; (*e*) M. Delferro and T. J. Marks, *Chem. Rev.*, 2011, **111**, 2450-2485; (*f*) L. Wang, Q. Wu, H. Xu and Y. Mu, *Dalton Trans.*, 2012, **41**, 7350-7357; (*g*) X. C. Shi and G. X. Jin, *Organometallics*, 2012, **31**, 7198-7205; (*h*) S. Liu, A. Motta, M. Delferro and T. J. Marks, *J. Am. Chem. Soc.*, 2013, **135**, 8830-8833; (*i*) S. Liu, A. Motta, A. R. Mouat, M. Delferro and T. J. Marks, *J. Am. Chem. Soc.*, 2014, **136**, 10460-10469; (*j*) J. G. M. Morton, H. Al-Shammari, Y. Sun, J. Zhu and D. W. Stephan, *Dalton Trans.*, 2014, **43**, 13219-13231.

4 (*a*) R. R. Gowda, D. Chakraborty and V. Ramkumar, *Inorg. Chem. Commun.*, 2011, **14**, 1777–1782; (*b*) E. L. Whitelaw, M. D. Jones, M. F. Mahon and G. Kociok-Kohn, *Dalton Trans.*, 2009, 9020–9025; (*c*) D. Deivasagayam and F. Peruch, *Polymer*, 2011, **52**, 4686-4693; (*d*) C. Y. Li, C. J. Yu and B. T. Ko, *Organometallics*, 2013, **32**, 172−180; (*e*) R. L. Webster, *RSC Adv.*, 2014, **4**, 5254–5260; (*f*) C. Y. Tsai, H. C. Du, J. C. Chang, B. H. Huang, B. T. Ko and C. C. Lin, *RSC Adv.*, 2014, **4**, 14527–14537.

5 (*a*) R. Hernandez, J. Mendez, J. Lamboy, M. Torres, F. R. Roman and E. Melendez, *Toxicol. in Vitro*, 2010, **24**, 178–183; (*b*) S. Gómez-Ruiz, B. Gallego, Ž. Žižak, E. Hey-Hawkins, Z. D. Juranić and G. N. Kaluđerović, *Polyhedron*, 2010, **29**, 354–360; (*c*) L. M. Gao, J. Matta, A. L. Rheingold and E. Meléndez, *J. Organomet. Chem.*, 2009, **694**, 4134–4139.

6 (*a*) S. D. Lee, J. C. Timmerman and R. A. Widenhoefer, *Adv. Synth. Catal.*, 2014, **356**, 3187-3192; (*b*) A. G. M. Barrett, C. Brinkmann, M. R. Crimmin, M. S. Hill, P. Hunt and P. A. Procopiou, *J. Am. Chem. Soc.*, 2009, **131**, 12906-12907; (*c*) M. A. Savolainen, X. P. Han and J. Wu, *Org. Lett.*, 2014, **16**, 4349-4351; (*d*) M. R. Crimmin, M. Arrowsmith, A. G. M. Barrett, I. J. Casely, M. S. Hill and P. A. Procopiou, *J. Am. Chem. Soc.*, 2009, **131**, 9670-9685; (*d*) Z. Chai, D. Z. Hua, K. Li, S. L. Zhou, J. Chu and G. S. Yang, *J. Organomet. Chem.*, 2014, **768**, 136-139; (*e*) A. Mukherjee, S. Nembenna, T. K. Sen, S. P. Sarish, P. K. Ghorai, H. Ott, D. Stalke and H. W. Roesky, *Angew. Chem., Int. Ed.*, 2011, **50**, 3968-3972; (*f*) J. F. Dunne, D. B. Fulton, A. Ellern and A. D. Sadow, *J. Am. Chem. Soc.*, 2010, **132**, 17680-17683; (g) M. R. Maurya, A. Arya, U. Kumar, A. Kumar, F. Avecilla and J. C. Pessoa, *Dalton Trans.*, 2009, 9555-9566; (*h*) K. D. Hesp, S. Tobisch and M. Stradiotto, *J. Am. Chem. Soc.*, 2010, **132**, 413; (*i*) K. D. Hesp and M. Stradiotto, *J. Am. Chem. Soc.*, 2010, **132**, 18026-18029; (*j*) S. R. Mothe, M. L. Novianti, B. J. Ayers and P. W. H. Chan, *Org. Lett.*, 2014, **16**, 4110-4113; (*k*) Z. Liu, H. Yamamichi, S. T. Madrahimov and J. F. Hartwig, *J. Am. Chem. Soc.*, 2011, **133**, 2772-2782; (*l*) I. Nakamura, T. Onuma, R. Kanazawa, Y. Nishigai and M. Terada, *Org. Lett.*, 2014, **16**, 4198-4200; (*m*) N. Sakai, N. Takahashi and Y. Ogiwara, *Eur. J. Org. Chem.*, 2014, **2014**, 5078-5082; (*n*) C. B. Huehls, A. J. Lin and J. Yang, *Org. Lett.*, 2014, **16**, 3620-3623; (*o*) M. J. Gainer, N. R. Bennett, Y. Takahashi and R. E. Looper, *Angew. Chem., Int. Ed.*, 2011, **50**, 684-687; (*p*) S. Germain, E. Schulz and J. Hannedouche, *ChemCatChem*, 2014, **6**, 2065-2073; (*q*) G. Zi, *Dalton Trans.*, 2009, 9101-9109; (*r*) J. C. Bernhammer, N. X. Chong, R. Jothibasu, B. B. Zhou and H. V. Huynh, *Organometallics*, 2014, **33**, 3607-3617. (*s*) A. L. Reznichenko, H. N. Nguyen and K. C. Hultzsch, *Angew. Chem., Int. Ed.*, 2010, **49**, 8984-8987; (*t*) M. Zille, A. Stolle, A. Wild and U. S. Schubert, *RSC Advances*, 2014, 4, 13126-13133; (*u*) S. B. Amin and T. J. Marks, *J. Am. Chem. Soc.*, 2007, **129**, 10102-10103; (*v*) E. Kumaran, W. Y. Fan and W. K. Leong, *Org. Lett.*, 2014, **16**, 1342-1345; (w) T. Andrea and M. S. Eisen, *Chem. Soc. Rev.*, 2008, **37**, 550-567; (*x*) B. D. Stubbert and T. J. Marks, *J. Am. Chem. Soc.*, 2007, **129**, 4253-4271.

7 (*a*) R. Kubiak, I. Prochnow and S. Doye, *Angew. Chem., Int. Ed.*, 2010, **49**, 2626-2629; (*b*) E. Haak, I. Bytschkov and S. Doye, *Angew. Chem., Int. Ed.*, 1999, **38**, 3389-3391.

8 (*a*) F. Y. Zhou, M. S. Lin, L. Li, X. Q. Zhang, Z. Chen, Y. H. Li, Y. Zhao, J. Wu, G. M. Qian and B. Hu and W. Li, *Organometallics*, 2011, **30**, 1283-1286; (*b*) Z. Chen, L. Li, Y. M. Chen, B. Hu, J. Wu, X. F. Wang and T. Lei, Y. H. Li, *J. Chem. Res.*, 2012, **36**, 249-253; (*c*) D. L. Swartz, R. J. Staples and A. L. Odom, *Dalton Trans.*, 2011, **40**, 7762-7768; (*d*) S. Majumder and A. L. Odom, *Organometallics*, 2008, **27**, 1174-1177; (*e*) D. L. Swartz and A. L. Odom, *Organometallics*, 2007, **26**, 6684-6684.

9 J. C. H. Yim, J. A. Bexrud, R. O. Ayinla, D. C. Leitch and L. L. Schafer, *J. Org. Chem.*, 2014, **79**, 2015-2028; (*b*) P. R. Payne, R. K. Thomson, D. M. Medeiros, G. Wan and L. L. Schafer, *Dalton Trans.*, 2013, **42**, 15670-15677.

10 Y. Zhao, M. S. Lin, Z. Chen, H. Pei, Y. H. Li, Y. M. Chen, X. F. Wang, L. Li, Y. Y. Cao, Y. Zhang and W. Li, *RSC Adv.*, 2012, **2**, 144-150.

11 (*a*) I. A. Tonks, J. C. Meier and J. E. Bercaw, *Organometallics*, 2013, **32**, 3451-3457; (*b*) B. Lian, T. P. Spaniol, P. Horrillo-Martinez and K. C. Hultzsch, J. Okuda, *Eur. J. Inorg. Chem.*, 2009, 429-434.

12 (*a*) P. L. McGrane and T. Livinghouse, *J. Am. Chem. Soc.*,1993, **115**, 11485-11589; (*b*) E. Haak, I. Bytschkov and S. Doye, *Angew. Chem., Int. Ed.*,1999, **38**, 3389-3391.

13 (*a*) Y. M. Yao, X. P. Xu, B. Liu, Y. Zhang, Q. Shen and W. T. Wong, *Inorg. Chem.*, 2005, **44**, 5133-5140; (*b*) Y. M. Yao, M. T. Ma, X. P. Xu, B. Liu, Y. Zhang, Q. Shen and W. T. Wong, *Organometallics*, 2005, **24**, 4014-4020; (*c*) T. J. Woodman, M. Schormann, D. L. Hughes and M. Bochmann, *Organometallics*, 2004, **23**, 2972-2979.

14 (*a*) H. Wang, H. Chan, J. Okuda and Z. Xie, *Organometallics*, 2005, **24**, 3118-3124; (*b*) X. Wang, A. Thevenon, J. L. Brosmer, I. Yu, S. I. Khan, P. Mehrkhodavandi and P. L. Diaconescu, *J. Am. Chem. Soc.*, 2014, **136**, 11264–11267.

15 (*a*) C. Li, C. Yu and B. T. Ko, *Organometallics*, 2013, **32**, 172-180; (*b*)M. G. Davidson, M. D. Jones, M. D. Lunn and M. F. Mahon, *Inorg. Chem.*, 2006, **45**, 2282-2287.

16 A. Kowalski, A. Duda and S. Penczek, *Macromolecules*, 1998, **31**, 2114-2122.

17 K. M. Buettner and A. M. Valentine, *Chem. Rev.*, 2012, **112**, 1863-1881.

18 (*a*) C. M. Manna, O. Braitbard, E. Weiss, J. Hochman and E. Y. Tshuva, *Chem. Med. Chem.*, 2012, **7**, 703-708; (*b*) S. Meker, C. M. Manna, D. Peri and E. Y. Tshuva, *Dalton Trans.*, 2011, **40**, 9802-9809; (*c*) M. Shavit, D. Peri, C. M. Manna, J. S. Alexander and E. Y. Tshuva, *J. Am. Chem. Soc.,* 2007, **129**, 12098-12099; (*d*) D. Peri, S. Meker, C. M. Manna and E. Y. Tshuva, *Inorg. Chem.*, 2011, **50**, 1030-1038; (*e*) D. Peri, S. Meker, M. Shavit and E. Y. Tshuva, *Chem. -Eur. J.*, 2009, **15**, 2403-2415; (*f*) E. Y. Tshuva and D. Peri, *Coord. Chem. Rev.*, 2009, **253**, 2098-2115; (*g*) C. M. Manna, G. Armony and E. Y. Tshuva, *Inorg. Chem.*, 2011, **50**, 10284-10291; (*h*) C. M. Manna, G. Armony and E. Y. Tshuva, *Chem.-Eur. J.*, 2011,**17**, 14094-14103; (*i*) S. Meker, K. Margulis-Goshen, E. Weiss, S. Magdassi and E. Y. Tshuva, *Angew. Chem.,* 2012, **124**, 10667 – 10669.

19 M. Lin, Y. Cao, H. Pei, Y. Chen, J. Wu, Y. Li and W. Liu, *RSC Adv.*, 2014, **4**, 9255-9260.

20 G. Kelter, N. J. Sweeney, K. Strohfeldt, H. Fiebig and M. Tacke, *Anticancer Drugs*, 2005, **16**, 1091-1098.

21 G. M. Sheldrick, SHELXS-97, *Program for solution of crystalstructures*, University of Göttingen, Germany, 1997.