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# $Ti^{IV}$ Complexes of Branched Diamine Bis(phenolato) Ligands: Hydrolysis and Cytotoxicity

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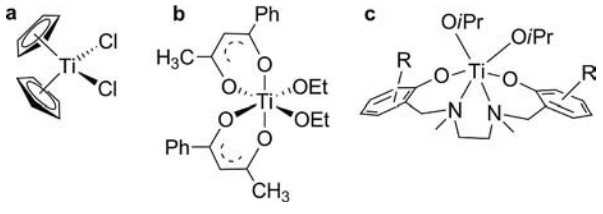
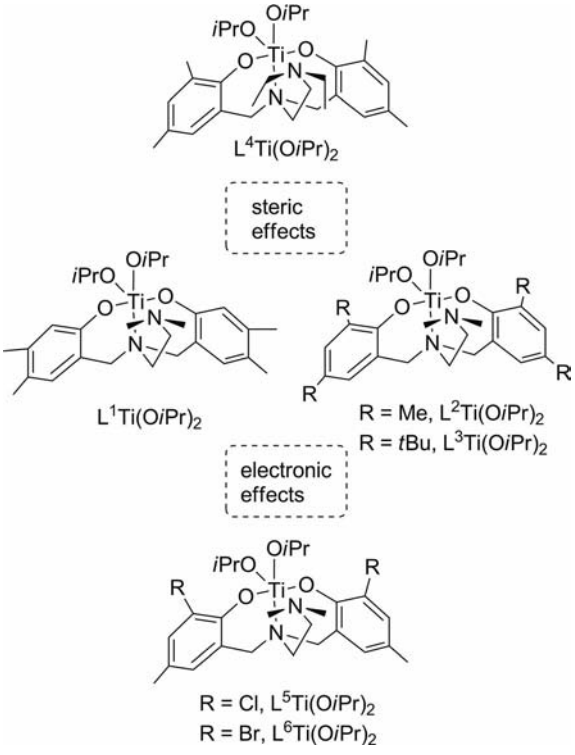
Six $Ti^{IV}$ complexes of branched diamine bis(phenolato) ligands that feature a pendant donor side arm with different aromatic and N-substitutions were synthesized and their hydrolytic stability and cytotoxicity were investigated as closely related analogues to the highly active and stable salan $Ti^{IV}$ complexes [salan = *N*,*N*′-bis(*o*-hydroxybenzyl)-1,2-diaminoethane]. Although the $C_s$-symmetrical complexes include binding of the side-arm N donor to the metal as analyzed crystallographically, thus making them highly similar in coordination features to the $C_2$-symmetrical salan complexes, they exhibit poor hydrolytic stability, presumably due to higher flexibility in binding of the side arm in solution. Complexes of alkyl aromatic substituents, both *N*-methylated and *N*-ethylated, with varying steric constraints demonstrated poor cytotoxicity. In contrast, *ortho*-halogenation, although it does not affect hydrolytic stability, substantially enhances the cytotoxicity towards colon HT-29 and ovarian OVCAR-1 cells.

## Introduction

Interesting cytotoxic activities have been recently reported for complexes of transition metals other than platinum.[1] One such metal is $Ti^{IV}$, complexes of which – namely, titanocene dichloride ([$Cp_2TiCl_2$], Scheme 1a), budotitane {[$(bzac)_2Ti(OEt)_2$], Scheme 1, b}, and their derivatives – have shown promising activity towards cisplatin-sensitive and resistant tumor cells with limited toxicity.[2] The main drawback in $Ti^{IV}$ complexes, however, is in their hydrolytic instability.[2d,2f,3] We have recently introduced a new family of $C_2$-symmetrical $Ti^{IV}$ complexes of [ONNO]-type diamine bis(phenolato) salan [salan = *N*,*N*′-bis(*o*-hydroxybenzyl)-1,2-diaminoethane] ligands (Scheme 1, c) that generally demonstrate higher activity towards ovarian OVCAR-1 and colon HT-29 cells than those of [$Cp_2TiCl_2$], [$(bzac)_2Ti(OiPr)_2$], and cisplatin, and substantially higher hydrolytic stability relative to that of known $Ti^{IV}$ complexes.[4] Herein we describe a new highly related family of complexes with similar donor atoms, coordination number, and general geometry (Scheme 2), but which differ in connectivity, in which one of the N donors is located on a side arm rather than being a part of the central ligand skeleton, thus leading to [ONON]-type complexes of $C_s$-symmetry rather than $C_2$. Such group IV metal complexes are known and have been previously investigated mainly in the field of




Scheme 1.




Scheme 2.

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catalysis.[5] The steric and electronic effects on hydrolysis and cytotoxic activity of $Ti^{IV}$ complexes of the [ONON]-type ligands is hereby discussed.

## Results and Discussion

Complexes [$\mathbf{L}^{1-6}$Ti(O*i*Pr)$_2$] **1**–**6** (Scheme 2), were cleanly synthesized from the corresponding ligands $H_2\mathbf{L}^{1-6}$, **1a**–**6a**, and titanium tetra(isopropoxide) similarly to known procedures[5b,5c] at room temperature and in THF solvent. The ligands were prepared by a convenient Mannich condensation between the substituted phenol, formaldehyde, and *N*,*N*-dimethylethylenediamine based on published procedures.[5] The complexes feature a $C_s$ symmetry due to binding of the phenolato O donors in a *trans* configuration, where the side-arm binding forces a *cis* configuration of the isopropoxo groups. This was evident by the NMR spectra of the complexes, which feature a single set of aromatic signals and an AB system for the benzylic methylene protons. Additional structural support was provided by the crystallographic analysis of **4** and **6**, for which an ORTEP drawing is provided in Figures 1 and 2, respectively, with lists of selected bond lengths and angles summarized in Tables 1 and 2, respectively. For the structure of **6**, one $CH_2$ unit of the diaminoethylene bridge and the two methyl groups are disordered, with 85% occupancy for the main set of C(18)–C(20), and full occupancy of the two depicted N atoms.

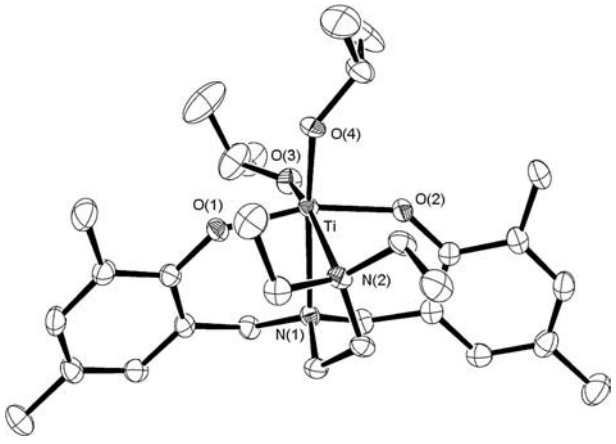


Figure 1. ORTEP drawing of [$\mathbf{L}^4$Ti(O*i*Pr)$_2$] (**4**) in 50% probability ellipsoids. Hydrogen atoms were omitted for clarity.

The X-ray structures of **4** and **6** reveal an approximate $C_s$ symmetry of the complexes in the solid state with two *cis* isopropoxo groups, in which the phenolato ligands are in a *trans* configuration, in accordance with the NMR spectroscopic features (which indicate a $C_s$ symmetry in solution) and similar to other known compounds of this class.[5b,5c] Binding of the side-arm donor to the metal is obvious in both structures, although for **6** the Ti–N bond to the side arm of 2.37 Å is rather similar to that to the central N donor of 2.34 Å, whereas for [$\mathbf{L}^4$Ti(O*i*Pr)$_2$], the metal bond to the side donor is substantially longer: 2.46 Å relative to 2.33 Å for the central N donor. This might be a result of the steric effects induced by the *N*-ethyl groups in **4**, as one methyl group points up with a 3.4 Å distance to O(4) (Figure 1).

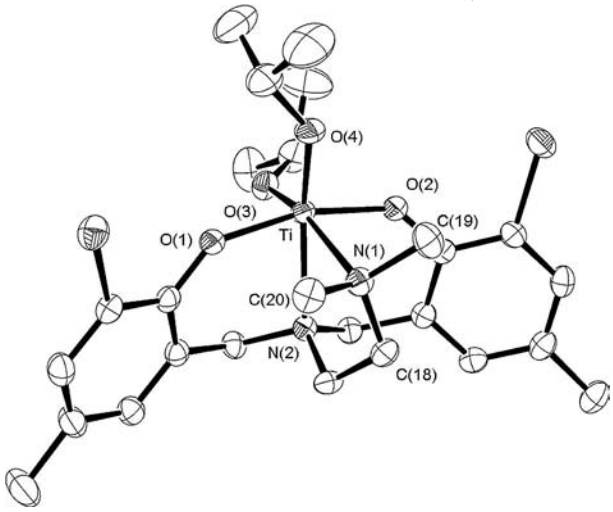


Figure 2. ORTEP drawing of [$\mathbf{L}^6$Ti(O*i*Pr)$_2$] (**6**) in 50% probability ellipsoids. Hydrogen atoms and disorder in the dimethylethylenediamine moiety were omitted for clarity to include only the C(18)–C(20) of 85% occupancy.

Table 1. Selected bond lengths [Å] and angles [°] for **4**.

| | | | |
|---|---|---|---|
| O(1)–Ti | 1.912(2) | N(1)–Ti | 2.327(2) |
| O(2)–Ti | 1.884(2) | N(2)–Ti | 2.464(2) |
| O(3)–Ti | 1.830(2) | | |
| O(4)–Ti | 1.809(2) | | |
| O(1)–Ti–O(2) | 163.69(9) | O(1)–Ti–N(1) | 84.20(8) |
| O(3)–Ti–O(1) | 93.98(9) | O(2)–Ti–N(1) | 82.16(8) |
| O(4)–Ti–O(1) | 94.06(9) | O(3)–Ti–N(1) | 88.65(8) |
| O(3)–Ti–O(2) | 94.60(9) | O(4)–Ti–N(1) | 166.49(9) |
| O(4)–Ti–O(2) | 97.11(9) | O(1)–Ti–N(2) | 83.23(8) |
| O(4)–Ti–O(3) | 104.84(9) | O(2)–Ti–N(2) | 84.75(8) |
| N(1)–Ti–N(2) | 75.60(8) | O(3)–Ti–N(2) | 164.19(9) |
| | | O(4)–Ti–N(2) | 90.89(8) |

Table 2. Selected bond lengths [Å] and angles [°] for **6**.

| | | | |
|---|---|---|---|
| O(1)–Ti | 1.905(1) | N(1)–Ti | 2.340(1) |
| O(2)–Ti | 1.916(1) | N(2)–Ti | 2.384(2) |
| O(3)–Ti | 1.796(1) | | |
| O(4)–Ti | 1.833(1) | | |
| O(1)–Ti–O(2) | 163.35(5) | O(1)–Ti–N(1) | 84.35(5) |
| O(3)–Ti–O(1) | 97.17(6) | O(2)–Ti–N(1) | 82.29(5) |
| O(4)–Ti–O(1) | 91.73(6) | O(3)–Ti–N(1) | 163.21(6) |
| O(3)–Ti–O(2) | 93.94(6) | O(4)–Ti–N(1) | 89.89(5) |
| O(4)–Ti–O(2) | 94.18(6) | O(1)–Ti–N(2) | 85.09(5) |
| O(4)–Ti–O(3) | 106.74(6) | O(2)–Ti–N(2) | 85.62(5) |
| N(1)–Ti–N(2) | 74.57(5) | O(3)–Ti–N(2) | 88.86(6) |
| | | O(4)–Ti–N(2) | 164.37(2) |

Cytotoxicity of the complexes was measured on colon HT-29 and ovarian OVCAR-1 human tumor cells according to the methylthiazolyldiphenyltetrazolium bromide (MTT) assay as described previously.[4a] The relative $IC_{50}$ values obtained after 3 d incubation of the complexes with the cells are summarized in Table 3. Additionally, the hydrolytic stability of the complexes was assessed by NMR

  

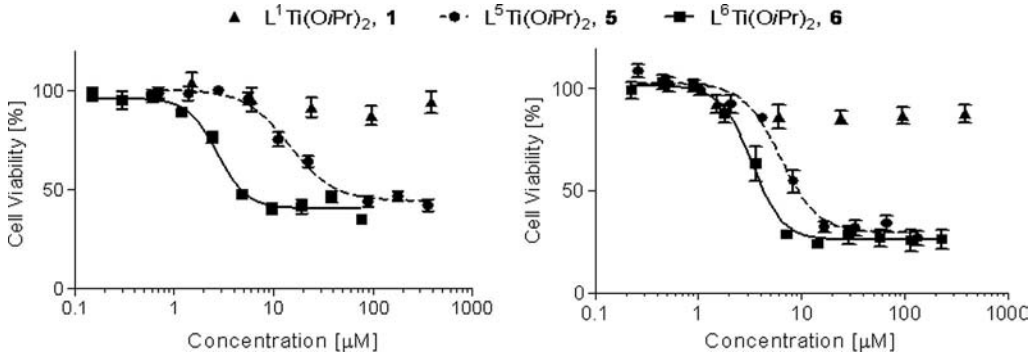


Figure 3. Dependence of HT-29 (left) and OVCAR-1 (right) cell viability after 3 d incubation period on administered concentration of **1**, **5**, and **6**.

spectroscopy as described previously[4a,4b] by adding 10% $D_2O$ to a solution of the complexes in [$D_8$]THF and monitoring changes in the spectra.

Table 3. Relative $IC_{50}$ and maximal inhibition values for the complexes **1**–**6**, cisplatin, [$Cp_2TiCl_2$], and [$(bzac)_2Ti(OiPr)_2$] towards HT-29 and OVCAR-1 cell lines.

| | HT-29 [μM] (maximum inhibition, %) | OVCAR-1 [μM] (maximum inhibition, %) |
|---|---|---|
| [$L^{1–4}Ti(OiPr)_2$] (**1**–**4**) | negligible activity | negligible activity |
| [$L^5Ti(OiPr)_2$] (**5**) | 14 ± 1 (56) | 6.3 ± 0.3 (71) |
| [$L^6Ti(OiPr)_2$] (**6**) | 2.7 ± 0.3 (60) | 3.3 ± 0.3 (74) |
| [$Cp_2TiCl_2$] | 609 ± 4 (90) | 701 ± 4 (90) |
| [$(bzac)_2Ti(OiPr)_2$] | 15.2 ± 0.3 (90) | 14.9 ± 0.4 (90) |
| cisplatin | 11.1 ± 0.4 (88) | 8.6 ± 0.2 (90) |

Complexes **1**–**4** vary in the steric effects caused by the alkyl substituents on the aromatic rings and on the side N donor. All four complexes demonstrate negligible cytotoxic activity towards both cell lines analyzed, as well as poor hydrolytic stability, as complete dissociation of the isopropoxo groups to give 2-propanol was observed within a few minutes following $D_2O$ addition. These observations are different than those of the analogous salan complexes, especially those with identical aromatic substitutions to **1** and **2**, which demonstrate high cytotoxicity and high hydrolytic stability with $t_{1/2}$ of 5–31 h for isopropoxo dissociation under similar conditions.[4b] As the coordination features of the two families of complexes – that is, the [ONNO]- and the [ONON]-type – are highly similar, we attribute the reduced hydrolytic stability of the latter, which might relate to the resulting diminished cytotoxicity, to the flexibility of the pending arm. The side-arm donor is probably able to detach from the metal more easily upon interaction with water, thus giving more rapidly inactive oxo-bridged cluster as also evidenced by the $^1H$ NMR spectra of the hydrolysis products.

*ortho*-Halogenation on the analogous salan [ONNO]-type complexes has previously been reported to increase both their hydrolytic stability and the cytotoxicity.[4a] Therefore, **5** and **6**, which feature *ortho*-Cl and *ortho*-Br substitutions, were analyzed. Interestingly, although the hydrolytic stability of these complexes remained poor, the cytotoxicity was markedly enhanced and gave relative $IC_{50}$ values that are mostly lower than those obtained for cisplatin and the known $Ti^{IV}$ complexes analyzed (Figure 3, Table 1). This implies that the pending donor arm is more important in destabilizing the complexes in water environment, in which the effect of halogenation on stability is less pronounced. Nevertheless, it is clear that cytotoxicity may be improved in an unrelated manner, even for unstable complexes.

## Conclusion

Herein we report a new family of potentially cytotoxic $Ti^{IV}$ complexes based on branched [ONON]-type tetradentate diamine bis(phenolato) ligands. The alkyl-substituted complexes are less hydrolytically stable than the analogous salan complexes with ligands of the diamine bis(phenolato) [ONNO]-type, presumably due to the different coordination sphere that includes a pendant donor side arm, which is probably related to their inactivity towards tumor colon and ovarian cells. Nevertheless, the cytotoxicity of complexes with pending donor arm, even relatively unstable ones, may be restored by *ortho* substitution with Cl or Br, an effect of cytotoxicity enhancement similar to the one observed for the salan analogues.[4a] Thus, the halogenation increased the cytotoxicity but not the hydrolytic stability. An advantage of these complexes emerges from their $C_s$ symmetry, which offers evidence that chirality is not a prerequisite for cytotoxic activity of such complexes and abolishes the need for chiral separation required for medicinal utility.[6] Additional investigations to include halogenated, methoxylated, and aminated derivatives are essential to further identify structural parameters that may enhance both the hydrolytic stability and cytotoxicity of these complexes, and to make them of potential applicability.

## Experimental Section

**General:** Ligands $H_2L^{1–4}$ (**1a**–**4a**) and $Ti^{IV}$ complexes [$L^{1–3}Ti(OiPr)_2$] (**1**–**3**) were synthesized as described previously.[5] Paraformaldehyde (ca. 95%), *N*,*N*-dimethylethylenediamine (95%), and substituted phenol compounds (> 95%) were purchased from Aldrich Chemical Company Inc. or Fluka Riedel-de Haën. Titanium tetra(isopropoxide) (97%) was purchased from Aldrich Chemical

  

Company, Inc. All solvents for complexes manipulation were distilled from K or K/benzophenone under nitrogen, or dried with aluminum column with an M. Braun SPS-800 drying system. All experiments that required a dry atmosphere were performed in an M. Braun dry box or under nitrogen atmosphere using Schlenk line techniques. NMR spectroscopic data were recorded with an AMX-400 or 500 MHz Bruker spectrometer. X-ray diffraction data were obtained with a Bruker Smart Apex diffractometer. Elemental analyses were performed in the microanalytical laboratory of our institute. Cytotoxicity was measured on HT-29 colon and OVCAR-1 ovarian cells obtained from ATCC Inc. using the methylthiazolyldiphenyltetrazolium bromide (MTT) assay as described previously.[4a] Relative $IC_{50}$ values were determined by a nonlinear regression of a variable slope (four parameters) model. Kinetic studies by NMR spectroscopy were performed as described previously,[4a,4b] using 6 mM of the complex solution in [$D_8$]THF and adding $>$ 1000 equiv. of $D_2O$ to give a final solution of 1:9 $D_2O$/[$D_8$]THF.

**Ligand $H_2L^5$ (5a):** This compound was synthesized by heating of the following mixture to reflux (for about 10 h): 2-chloro-4-methylphenol (0.47 mL, 4.0 mmol), *N*,*N*-dimethylethylenediamine (0.22 mL, 2.0 mmol), and paraformaldehyde (0.150 g, 5.0 mmol) in methanol (20 mL). The crude product was cooled, filtered, and washed with cold methanol (0.50 g, 63%). $^1$H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.14 (d, $J$ = 1.4 Hz, 2 H, Ar–H), 6.71 (d, $J$ = 1.4 Hz, 2 H, Ar–H), 3.64 (s, 4 H, $CH_2$), 2.67 (m, 4 H, $CH_2$), 2.31 (s, 6 H, $CH_3$), 2.22 (s, 6 H, $CH_3$) ppm. $^{13}$C NMR (500 MHz, $CDCl_3$, 30 °C): $\delta$ = 150.4, 130.2, 129.3, 128.8, 123.4, 121.3, 56.4, 55.9, 49.1, 45.1, 20.2 ppm. $C_{20}H_{26}Cl_2N_2O_2$ (397.34): calcd. C 60.46, H 6.60, N 7.05; found C 60.52, H 6.64, N 6.86.

**Ligand $H_2L^6$ (6a):** This compound was synthesized similar to **5a** from 2-bromo-4-methylphenol (0.48 mL, 4.0 mmol), *N*,*N*-dimethylethylenediamine (0.22 mL, 2.0 mmol) and paraformaldehyde (0.18 g, 6.0 mmol) (0.76 g, 78%). $^1$H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.33 (d, $J$ = 1.7 Hz, 2 H, Ar–H), 6.79 (d, $J$ = 1.7 Hz, 2 H, Ar–H), 3.66 (s, 4 H, $CH_2$), 2.64 (m, 4 H, $CH_2$), 2.43 (s, 6 H, $CH_3$), 2.22 (s, 6 H, $CH_3$) ppm. $^{13}$C NMR (500 MHz, $CDCl_3$, 30 °C): $\delta$ = 151.3, 133.2, 130.0, 129.4, 123.2, 110.8, 56.4, 56.1, 49.1, 45.1, 20.1 ppm. $C_{20}H_{26}Br_2N_2O_2$ (486.25): calcd. C 49.40, H 5.39, N 5.76; found C 49.46, H 5.39, N 5.66.

**Complex [$L^4$Ti(O*i*Pr)$_2$] (4):** This compound was synthesized in quantitative yield by treating Ti(O*i*Pr)$_4$ (0.18 g, 0.65 mmol) with $H_2L^4$[5a] (0.23 g, 0.60 mmol) in dry THF and could be recrystallized from hexane (0.060 g, 18%). $^1$H NMR (400 MHz, $CDCl_3$, 25 °C): $\delta$ = 6.93 (d, $J$ = 2.4 Hz, 2 H, Ar–H), 6.72 (d, $J$ = 2.4 Hz, 2 H, Ar–H), 5.07 (sept, $J$ = 6.1 Hz, 1 H, C*H*CH$_3$), 4.72 (sept, $J$ = 6.1 Hz, 1 H, C*H*CH$_3$), 4.54 (d, $J$ = 13.1 Hz, 2 H, $CH_2$), 3.19 (d, $J$ = 13.1 Hz, 2 H, $CH_2$), 2.59 (t, $J$ = 5.6 Hz, 2 H, $CH_2$), 2.27 (s, 3 H, $CH_3$), 2.26 (s, 3 H, $CH_3$), 2.05 (t, $J$ = 5.6 Hz, 2 H, $CH_2$), 1.41 (d, $J$ = 6.1 Hz, 6 H, CHC*H*$_3$), 1.13 (d, $J$ = 6.1 Hz, 6 H, CHC*H*$_3$), 0.99 (t, $J$ = 7.2 Hz, 6 H, $CH_3$) ppm. $^{13}$C NMR (400 MHz, $CDCl_3$, 30 °C): $\delta$ = 158.9, 131.3, 127.4, 125.7, 124.5, 124.1, 65.2, 55.1, 46.8, 26.1, 25.9, 20.5, 16.5, 8.9 ppm. $C_{30}H_{48}N_2O_4Ti$ (548.62): calcd. C 65.68, H 8.82, N 5.11; found C 65.61, H 8.78, N 5.61.

**Crystal Data for 4:** $C_{30}H_{48}N_2O_4Ti$, $M_r$ = 548.60, monoclinic, $a$ = 26.914(3) Å, $b$ = 12.721(1) Å, $c$ = 118.317(2) Å, $\beta$ = 103.816(2)°, $V$ = 6090.1(10) Å$^3$, $T$ = 173(1) K, space group $C2/c$, $Z$ = 8, $\mu$(Mo-$K_\alpha$) = 0.316 mm$^{-1}$, 32996 reflections measured, 6645 unique ($R_{int}$ = 0.0424). $R(F_o^2)$ for [$I > 2\sigma(I)$] = 0.0758, $R_w$ for [$I > 2\sigma(I)$] = 0.1562.

**Complex [$L^5$Ti(O*i*Pr)$_2$] (5):** This compound was synthesized in quantitative yield by treating Ti(O*i*Pr)$_4$ (0.050 g, 0.18 mmol) with $H_2L^5$ (0.072 g, 0.18 mmol) in dry THF and could be recrystallized from ethyl ether (0.075 g, 74%). $^1$H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.13 (s, 2 H, Ar–H), 6.76 (s, 2 H, Ar–H), 5.17 (sept, $J$ = 6.1 Hz, 1 H, C*H*CH$_3$), 4.72 (m, $J$ = 6.3 Hz, 1 H, C*H*CH$_3$), 4.52 (d, $J$ = 13.0 Hz, 2 H, $CH_2$), 3.21 (d, $J$ = 13.0 Hz, 2 H, $CH_2$), 2.50 (t, $J$ = 5.8 Hz, 2 H, $CH_2$), 2.25 (s, 6 H, $CH_3$), 2.23 (s, 6 H,$CH_3$), 1.93 (t, $J$ = 5.8 Hz, 2 H, $CH_2$), 1.43 (d, $J$ = 6.0 Hz, 2 H, CHC*H*$_3$), 1.13 (d, $J$ = 6.5 Hz, 2 H, CHC*H*$_3$) ppm. $^{13}$C NMR (500 MHz, $CDCl_3$, 30 °C): $\delta$ = 156.3, 130.4, 128.6, 126.7, 125.5, 121.1, 78.9, 77.7, 64.6, 58.6, 50.9, 48.6, 25.9, 25.8, 20.3 ppm. $C_{26}H_{38}Cl_2N_2O_4Ti$ (561.40): calcd. C 55.63, H 6.82, N 4.99; found C 55.80, H 6.57, N 4.69.

**Complex [$L^6$Ti(O*i*Pr)$_2$] (6):** This compound was synthesized in quantitative yield by treating Ti(O*i*Pr)$_4$ (0.050 g, 0.18 mmol) with $H_2L^6$ (0.088 g, 0.18 mmol) in dry THF and could be recrystallized from ethyl ether (0.055 g, 47%). $^1$H NMR (500 MHz, $CDCl_3$, 25 °C): $\delta$ = 7.32 (s, 2 H, Ar–H), 6.88 (s, 2 H, Ar–H), 5.20 (sept, $J$ = 5.9 Hz, 1 H, C*H*CH$_3$), 4.72 (sept, $J$ = 6.1 Hz, 1 H, C*H*CH$_3$), 4.52 (d, $J$ = 13.0 Hz, 2 H, $CH_2$), 3.21 (d, $J$ = 13.0 Hz, 2 H, $CH_2$), 2.52 (t, $J$ = 5.8 Hz, 2 H, $CH_2$), 2.29 (s, 6 H, $CH_3$), 2.25 (s, 6 H, $CH_3$), 1.96 (t, $J$ = 6.0 Hz, 2 H, $CH_2$), 1.46 (d, $J$ = 6.2 Hz, 2 H, CHC*H*$_3$), 1.14 (d, $J$ = 6.3 Hz, 2 H, CHC*H*$_3$) ppm. $^{13}$C NMR (500 MHz, $CDCl_3$, 30 °C): $\delta$ = 157.3, 133.3, 129.4, 127.2, 125.2, 111.5, 78.9, 77.7, 64.7, 58.5, 50.9, 48.9, 26.0, 25.4, 20.1 ppm. $C_{26}H_{38}Br_2N_2O_4Ti$ (650.31): calcd. C 48.02, H 5.89, N 4.31; found C 48.19, H 5.67, N 4.04.

**Crystal Data for 6:** $C_{26}H_{38}Br_2N_2O_4Ti$, $M_r$ = 650.30, monoclinic, $a$ = 9.2692(6) Å, $b$ = 13.2687(9) Å, $c$ = 23.550(2) Å, $\beta$ = 98.926(1)°, $V$ = 2861.3(3) Å$^3$, $T$ = 173(1) K, space group $P2_1/c$, $Z$ = 4, $\mu$(Mo-$K_\alpha$) = 0.717 mm$^{-1}$, 30973 reflections measured, 6232 unique ($R_{int}$ = 0.0214). $R(F_o^2)$ for [$I > 2\sigma(I)$] = 0.0262, $R_w$ for [$I > 2\sigma(I)$] = 0.0698.

CCDC-833128 (for **4**) and -833129 (for **6**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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