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Titanocene Dihalides and Ferrocenes Bearing a Pendant α-D-Xylofuranos-5-yl or α-D-Ribofuranos-5-yl Moiety. Synthesis, Characterization, and Cytotoxic Activity

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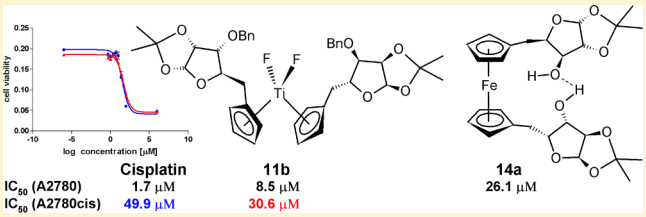
Supporting Information

ABSTRACT: Titanocene dichlorides of general formula $[(\eta^5\text{-}C_5H_5)(\eta^5\text{-}C_5H_4R)TiCl_2]$ (where R = 5-deoxy-1,2-di-*O*-isopropylidene-3-*O*-benzyl-α-D-xylofuranos-5-yl (Xylf) (**8a**); R = 5-deoxy-1,2-di-*O*-isopropylidene-3-*O*-benzyl-α-D-ribofuranos-5-yl (Ribf) (**8b**)) and $[(\eta^5\text{-}C_5H_4R)_2TiCl_2]$ (R = Xylf (**9a**); R = Ribf (**9b**)) were prepared by reaction of the corresponding lithium cyclopentadienides **7a**,**b** with an equimolar amount of $[(\eta^5\text{-}C_5H_5)TiCl_3]$ or a 0.5 mol amount of $[TiCl_4(THF)_2]$. Titanocene difluorides of the general formula $[(\eta^5\text{-}C_5H_4R^1)(\eta^5\text{-}C_5H_4R^2)TiF_2]$ (R^1 = H and R^2 = Ribf (**10**); $R^1 = R^2$ = Xylf (**11a**); $R^1 = R^2$ = Ribf (**11b**)) were obtained by fluorination of the corresponding titanocene dichlorides **8b** and **9** with the fluorinating agent $\{2\text{-}(CH_2NMe_2)C_6H_4\text{-}\kappa C,N\}(n\text{-}Bu)_2SnF$ in high yields. Alternatively, complexes **11** were prepared in a straightforward way by direct reaction of $[TiF_4(THF)_2]$ with 2 equiv of the corresponding lithium cyclopentadienide **7a**,**b**. Ferrocene complexes $[(\eta^5\text{-}C_5H_4R)_2Fe]$ (R = Xylf (**12a**); R = Ribf (**12b**)) were synthesized by metathesis of 2 equiv of lithium cyclopentadienide **7a**,**b** and 1 equiv of anhydrous $FeCl_2$. Deprotection of the benzyl group in ferrocenes **12** proceeded cleanly by a catalytic hydrogenation on Pd/C and afforded the ferrocene diols $[(\eta^5\text{-}C_5H_4R)_2Fe]$ (R = 5-deoxy-1,2-di-*O*-isopropylidene-α-D-xylofuranos-5-yl (Xylf-OH) (**14a**); R = 5-deoxy-1,2-di-*O*-isopropylidene-α-D-ribofuranos-5-yl (Ribf-OH) (**14b**)). A scaled up benzyl deprotection with Et_3SiH as a hydrogen source led to the replacement of only one benzyl group, which gave the ferrocene alcohol $[(\eta^5\text{-}C_5H_4R^1)(\eta^5\text{-}C_5H_4R^2)Fe]$ (R^1 = Xylf and R^2 = Xylf-OH (**13**)). The prepared complexes were characterized by elemental analysis, melting point determination, NMR, IR, and ESI-MS, and the molecular structure of **9b** was determined by X-ray diffraction analysis. The cytotoxic activity of complexes **8**−**14** against A2780 and A2780cis cancer cells was evaluated by MTT tests. Titanocene difluorides **10** and **11** and ferrocene diol **14a** showed cytotoxicity against A2780 cells in the medium to low micromolar range, while the most active species, **11b**, displayed about 40% higher cytotoxicity against A2780cis in comparison to a cisplatin standard.



INTRODUCTION

The discovery of the cytotoxic properties of cisplatin[1] initiated the search for other transition-metal antitumor complexes. Despite steady effort, only a few nonplatinum complexes have entered clinical trials,[2] the first among them being titanocene dichloride.[3,4] However, the clinical trials of titanocene dichloride were discontinued due to nephrotoxicity and other side effects together with low efficacy.[5] The last two decades have seen a renewed research interest in titanium anticancer compounds, as documented by several reviews in recent years.[6−10] The substitution of the cyclopentadienyl moiety was found to be a useful tool to modulate biological properties, giving rise to a structure−activity concept similar to that used in tailoring active catalysts for polymerization or organic synthesis.[11] In this respect, titanocene dichlorides bearing cyclopentadienyl rings substituted by alkyl and alkenyl,[12−14] methoxyalkyl,[15] substituted aryl,[16] silyl,[17] and carboxylic acid esters[18] were prepared and evaluated. Similarly, the effect of the bridge between cyclopentadienyl rings on the biological performance of *ansa*-titanocene dichlorides was recently elucidated.[12,13,19,20] The Baird[21−24] and McGowan groups[25−27]

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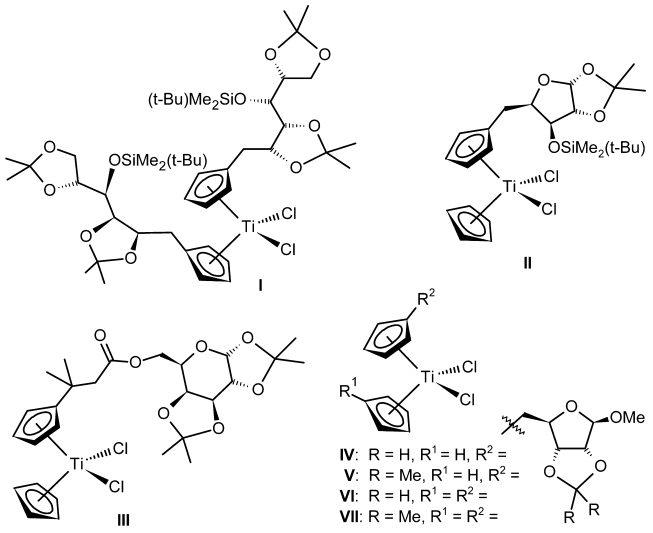
have synthesized a family of water-soluble titanocene dichlorides bearing ionic alkyl and arylammonium substituents. These ionic complexes showed a remarkable cytotoxic activity against human ovarian cancer cell lines A2780, which was retained even against the cisplatin-resistant cell line A2780cis. Tacke and co-workers introduced a modular synthesis of titanocene dichlorides bearing a modified benzyl[28−31] or methyleneheteroaryl group[32,33] starting from substituted fulvenes. Among these series, titanocene Y, $[\{\eta^5\text{-}C_5H_4CH_2C_6H_4\text{-}(p\text{-OMe})\}_2TiCl_2)]$, was found to be a promising drug candidate toward a wide range of human tumor cells.[34] A recent study showed that the increased cytotoxity of titanocene Y toward HT-29 colon carcinoma cells in comparison to titanocene dichloride is directly related to a higher cellular uptake of the former species,[35] where human serum albumin acts as an active transporter for titanocene Y.[36] Transferrin, another serum protein, has been implicated in the delivery of Ti(IV) compounds into the cell.[37−39] The aforementioned examples indicate that the efficient transport of titanocene into a carcinogenic cell is a crucial parameter for its biological performance.

Various tumors show increased D-glucose uptake *in vivo* (known as the Warburg effect)[40] in comparison to that of the normal tissue by 1 order of magnitude.[41] This leads to an overexpression of the D-glucose transporters (GLUTs) in cancer cells, which makes GLUT receptors another prospective target for the transport of anticancer drugs selectively into cancerous cells.[42] It should be noted that the transport via GLUT receptors is not restricted to D-glucose; other simple monosacharides are transported as well. Among others, D-xylose and D-ribose were found to be transported into the cell by means of GLUT, a slightly higher affinity to the transporter being found for the former species.[43] Generally, conjugation of a transition-metal complex to a carbohydrate moiety leads to its reduced toxicity, better biocompatibility, and increased solubility in aqueous media. Several reviews dealing with carbohydrate−metal conjugates published in the last 14 years show an increasing interest in the field.[44−48] Whereas numerous ferrocene−carbohydrate conjugates have been described,[49−58] there are very few examples of carbohydrate-modified cyclopentadienyl ligands in titanocene dichlorides. Titanocene dichlorides (see Chart 1) bearing cyclopentadienyl rings modified with D-mannitol (**I**),[59] α-D-xylofuranose (**II**),[60] and α-D-galactopyranose (**III**)[61,62] have been reported, although no cytotoxicity data were presented. A family of titanocene dichlorides bearing one (**IV** and **V**) or two (**VI** and **VII**) modified ribofuranose moieties was recently patented.[63] Complexes **IV**−**VII** were tested against L929, KB 3.1, A-431, and A-498 cell lines with the cytotoxicity increasing in the order **VII** < **IV** < **V** < **VI**, the last one having a cytotoxicity (IC_{50} = 5.5 μM for L929 and 5.3 μM for KB 3.1) comparable with that of cisplatin (IC_{50} = 2.2 μM for L929 and 1.2 μM for KB 3.1).

Herein we present the preparation of titanocene dichlorides, titanocene difluorides, and ferrocenes bearing a cyclopentadienyl ring modified with a substituent derived from protected α-D-xylofuranose or α-D-ribofuranose (epimers differing in stereochemistry at the C(3) stereogenic center in the furanose ring). The cytotoxic activity of the prepared complexes against A2780 and A2780cis cell lines was determined with the aim of evaluating the effect of the carbohydrate configuration (α-D-xylofuranose vs α-D-ribofuranose), the number of carbohydrate units in the complex (one vs two), carbohydrate protection (benzyl protected vs deprotected), and σ ligand (chlorido vs fluorido) on the antiproliferative activity of the complexes.

Chart 1



RESULTS AND DISCUSSION

Synthesis of Cyclopentadienyl Ligands 6. The starting material for the preparation of protected 5-deoxypentofuranos-5-yl cyclopentadienes **6a**,**b** was the readily available diacetone glucose **1**,[64] which was converted into tosylates **4** and **5** using a reaction sequence based mostly on literature procedures (Scheme 1). Reaction of tosylates **5** and **4** with sodium cyclopentadienide in dimethylformamide provided pentofuranosyl cyclopentadienes **6a**/**6a**′ and **6b**/**6b**′, which were obtained as inseparable mixtures of 1,3- and 1,4-cyclopentadienes in yields 65% and 68%, respectively.

Synthesis and Characterization of Titanocene Dihalides 8−11. Deprotonation of cyclopentadienes **6a**/**6a**′ and **6b**/**6b**′ with *n*-BuLi in Et_2O (Scheme 2) cleanly afforded corresponding lithium cyclopentadienides **7a**,**b** as white or slightly pink solids in 92% and 75% yields, respectively. The proposed structures of the lithium cyclopentadienides **7a**,**b** were supported by their ^1H and ^{13}C NMR spectra in THF-d_8.

Reaction of $[(\eta^5\text{-}C_5H_5)TiCl_3]$ with an equimolar amount of lithium cyclopentadienides **7a**,**b** in THF (Scheme 2) afforded the corresponding heterosubstituted titanocene dichlorides **8a**,**b** in 64% and 75% yields, respectively. Reaction of $[TiCl_4(THF)_2]$ with 2 equiv of lithium cyclopentadienides **7a**,**b** in THF (Scheme 2) led after workup to the homosubstituted titanocene dichlorides **9a**,**b** in 40 and 72% yields, respectively. Complexes **8** and **9** were obtained as red or red-orange solids, stable in air and moderately stable to humidity.

The replacement of σ-bonded chloride ligands with fluoride ligands in the titanocene moiety resulted in specific cases in an increased cytostatic efficiency against cancer cells.[70] To date, the preparation of titanocene difluorides has been based solely on fluorination of the respective dichloro- or dimethyltitanocenes with one of the following fluorinating agents: NaF,[71] Me_3SnF,[70,72] $BF_3{\cdot}OEt_2$,[73] AgF,[74] and $\{2\text{-}(CH_2NMe_2)C_6H_4\text{-}\kappa C,N\}(n\text{-}Bu)_2SnF$.[75−77]

We have explored the reaction of titanocene dichloride **8b** with 2 equiv of $\{2\text{-}(CH_2NMe_2)C_6H_4\text{-}\kappa C,N\}(n\text{-}Bu)_2SnF$ in CH_2Cl_2 at room temperature (Scheme 3, top). The reaction

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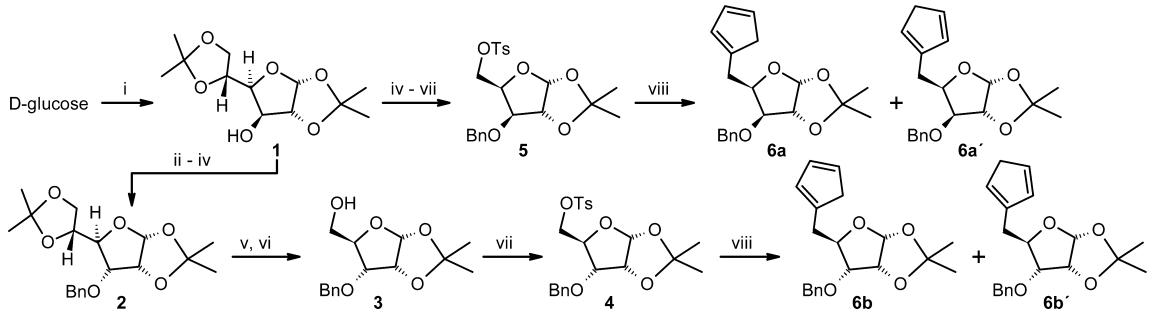
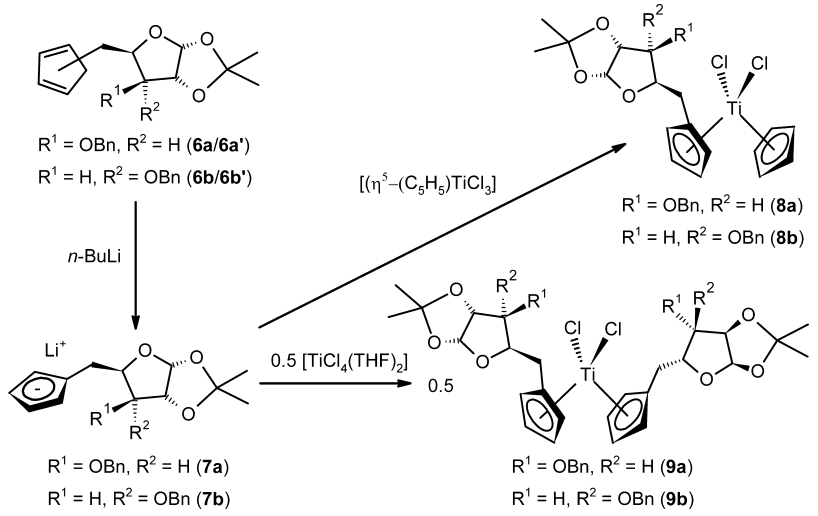
Scheme 1. Preparation of Protected 5-Deoxypentofuranos-5-ylcyclopentadienes 6a,b[a]

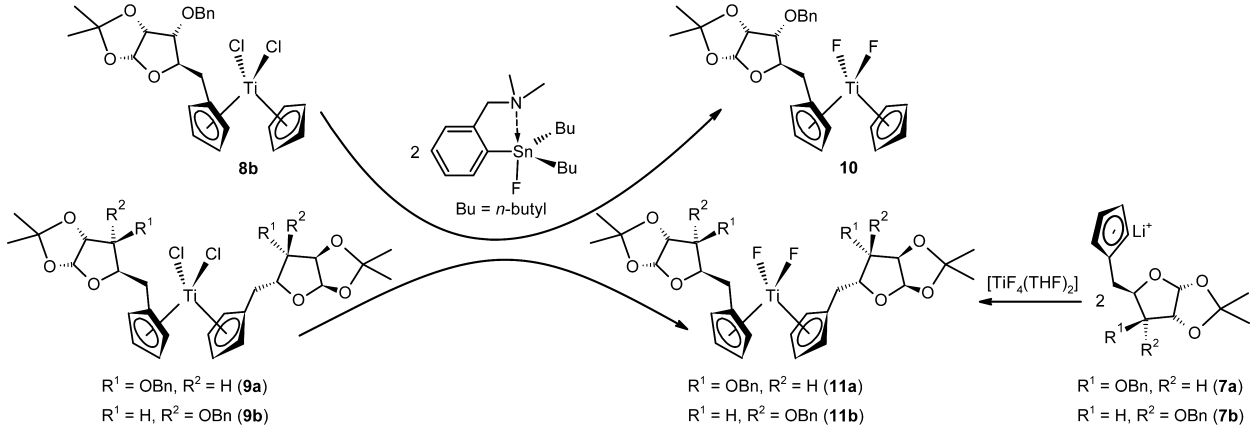


[a]Reagents: (i) acetone, $ZnCl_2$;[64] (ii) CrO_3, acetic anhydride, pyridine;[65] (iii) $NaBH_4$, EtOH, H_2O;[66] (iv) BnBr, NaH, THF;[67] (v) AcOH, H_2O;[67,68] (vi) $NaIO_4$, MeOH, H_2O, then $NaBH_4$, MeOH, H_2O;[67,68] (vii) TsCl, pyridine, for **5** see ref 69 and for **4** see the Supporting Information; (viii) C_5H_5Na, DMF.

Scheme 2. Preparation of Titanocene Dichlorides 8 and 9



Scheme 3. Preparation of Titanocene Difluorides 10 and 11



proceeded smoothly within 3 days, and the progress of the reaction could be monitored by a color change of the solution from red to orange. The formed byproduct {2-(CH_2NMe_2)-C_6H_4-$\kappa C,N$}(n-Bu)$_2$SnCl was removed by repeated washing with pentane, and titanocene difluoride **10** was obtained in high yield (86 and 93% in two independent experiments) as a yellow solid. The fluorination method was extended to symmetrically substituted titanocenes **9**. The reaction of titanocene dichlorides **9a,b** with 2 equiv of {2-(CH_2NMe_2)C_6H_4-$\kappa C,N$}-(n-Bu)$_2$SnF (Scheme 3, left side) in CH_2Cl_2 at room temperature afforded titanocene difluorides **11a,b** in 88% and 94% yields, respectively. In an alternative approach, we have tested the fluorination of **9a** with NaF in water,[71,78] which could be advantageous because it is a cheap, commercially available reagent. However, the reaction of titanocene dichloride **9a** with an excess of NaF (see the Supporting Information) in water for 3 h led only to ca. 10% conversion to titanocene difluoride **11a** (unreacted starting **9a** and several

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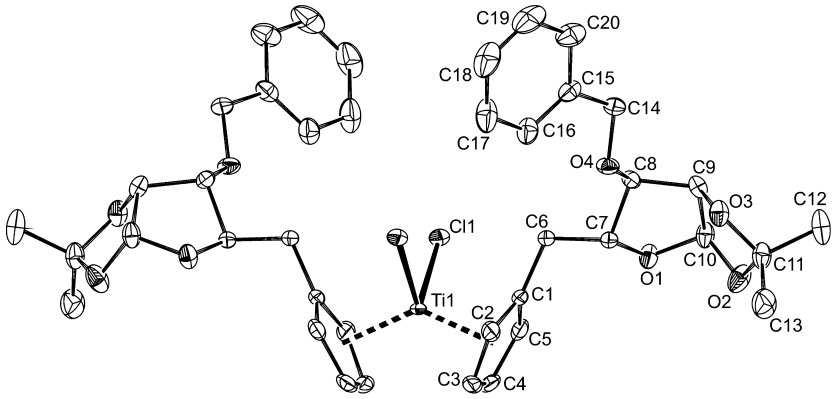
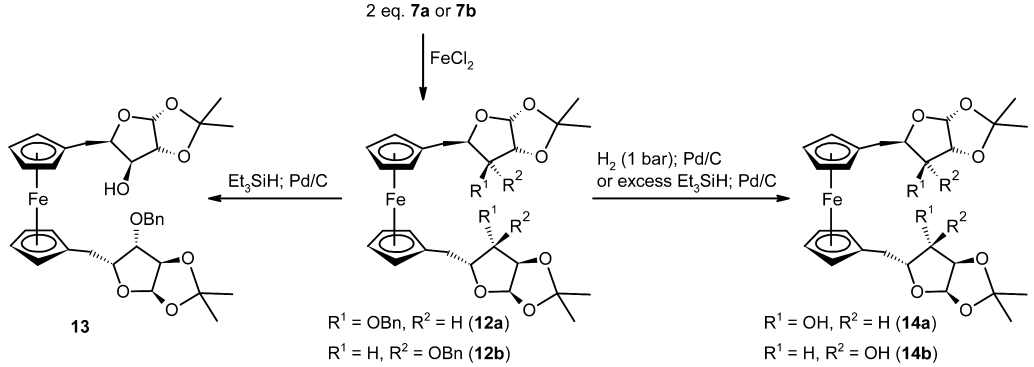


Figure 1. Molecular structure of **9b** at the 40% probability level with atom-labeling scheme. Hydrogen atoms are omitted for clarity.

Scheme 4. Preparation of Ferrocenes 12−14



unidentified titanium species were also present, as determined with ^{1}H and ^{19}F NMR spectroscopy). Unfortunately, a prolonged reaction time led to hydrolytic decomposition of **9a** rather than to an increased yield of **11a**.

Although the fluorinating agent {2-(CH_2NMe_2)C_6H_4-$\kappa C,N$}-(n-Bu)$_2$SnF gave satisfactory results, we were looking for an alternative route, which would afford titanocene difluorides in a single step without the necessity of corresponding titanocene dichloride preparation. Complex [$TiF_4(THF)_2$] was proposed as a convenient precursor for titanocene difluorides.[79] Surprisingly, its use for cyclopentadienyllithium to titanium transmetalation (widely applied for the preparation of titanocene dichlorides from [$TiCl_4(THF)_2$]) has not been reported in the literature so far. The reaction of 2 equiv of lithium cyclopentadienides **7a**,**b** with [$TiF_4(THF)_2$] (Scheme 3, right side) in THF proceeded at room temperature and afforded titanocene difluorides **11a**,**b** in 84% and 68% yields, respectively.

The prepared titanocene dihalides **8**−**11** were characterized by elemental analysis, melting points, NMR, IR, and ESI-MS. The presence of four chiral centers in the furanose moiety gave rise to an ABCD spin system for the methine signals *CH* in monosubstituted cyclopentadienyl ring(s) in both ^{1}H and ^{13}C NMR (see the Experimental Section and Supporting Information) spectra of all complexes, while the methine signal of the unsubstituted cyclopentadienyl ring in complexes **8** and **10** appears as a singlet in both ^{1}H and ^{13}C NMR spectra. The carbohydrate part displays qualitatively the same spectral pattern for both furanose rings in all complexes, except for the multiplicity of the vicinal proton signals of C(3)*H* and C(2)*H*. While a dihedral angle between these two protons in ribofuranose moiety led to their mutual splitting with a coupling constant $^{3}J_{HH}$ in the range 4.3−4.5 Hz, the inversion of configuration at the C(3) stereogenic center (giving rise to a xylofuranose moiety) resulted in no measurable coupling. Signals of the ribofuranose moiety (in complexes **8b**, **9b**, **10**, and **11b**) were shifted to a higher field in comparison to the corresponding methine groups in the xylofuranose moiety (in complexes **8a**, **9a**, and **11a**) in both ^{1}H and ^{13}C NMR spectra. Chemical shifts of the furanose methine groups (C(1)H−C(4)H) are not sensitive to coordination of the cyclopentadienylfuranose ligand to titanium in titanocene dichlorides and difluorides, which indicates only negligible mutual interaction between the titanocene and the carbohydrate fragment in solution. The signals of fluoride ligands in ^{19}F NMR spectra were found as singlets at 64.18 ppm for **11a** and 63.57 ppm for **11b** and as two closely positioned doublets centered at 64.10 and 64.23 ppm for **10**. These values are close to the value found for titanocene difluoride (64.2 ppm),[72] which also points to negligible interaction between the Ti−F bond and the carbohydrate moiety.

ESI-MS spectra of all studied titanocene dihalides corroborated the proposed structure, showing $[M + K]^+$, $[M + Na]^+$, and $[M - halide]^+$ ions as the characteristic species. Generally, the $[M - Cl]^+$ ion in titanocene dichlorides **8** and **9** possesses higher relative abundance in comparison to the $[M - F]^+$ ion in titanocene difluorides **10** and **11**, which roughly reflects the greater stability of the Ti−F bond. The IR spectra of titanocene difluorides **10** and **11** show characteristic medium to strong bands at 549−582 cm^{-1} due to Ti−F stretching vibrations.

Molecular Structure of Titanocene Dichloride 9b. Titanocene dichloride **9b** crystallized in orthorhombic space group $P2_12_12$ (No. 18) with one chiral molecule in the asymmetric unit. Selected geometric parameters are given in the

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Supporting Information, and the molecular structure is depicted in Figure 1. The molecule has C_2 symmetry with a 2-fold rotation axis passing through the titanium atom and bisecting the Cl−Ti−Cl′ angle. The metallocene complex possesses a bent structure (the dihedral angle between Cp planes is 51.4(1)°), where the Cp rings are close to an eclipsed conformation (torsion angle φ = 3.1(4)°). The pendant carbohydrate moieties are oriented toward the opened side of the metallocene wedge, and they are pointing away from the metal center, showing no intramolecular interaction with the titanium atom. The molecular packing (see the Supporting Information) further supports the absence of any intermolecular interactions, as the carbohydrate and titanocene domains are separated from each other. The furanose ring adopts a conformation close to the twist $^3T_4$ conformation (ring puckering parameter Φ = 311.8(3)°)[80] and retains the α-D-*ribo* absolute configuration, which proves that no racemization at stereogenic centers occurred during the whole synthesis.

Synthesis and Characterization of Ferrocenes 12−14. The transmetalation from lithium to iron was used for the preparation of homoleptically substituted ferrocenes. The reaction of 2 equiv of lithium cyclopentadienides **7a**,**b** with anhydrous $FeCl_2$ in THF (Scheme 4, middle) afforded substituted ferrocenes **12a**,**b** in 68% and 64% yields, respectively. The ferrocenes could be easily purified by column chromatography on silica gel with a hexane−ethyl acetate mixture as an eluent. The products were obtained as yellow-orange oils or waxes, stable to air and humidity. They were soluble in most organic solvents (toluene, ethyl acetate, THF, dichloromethane, chloroform) but only sparingly soluble in water. In an alternative route to **12a**, we have tested the reaction of the in situ prepared 1,1′-dilithioferrocene with 2 equiv of tosylate **5** in boiling THF (for details see the Supporting Information). However, the reaction did not proceed, probably due to the low nucleophilicity of 1,1′-dilithioferrocene.

The poor solubility of ferrocenes **12** in water is undesirable for their use in biological assays. In order to improve their solubility in protic solvents (mainly water), deprotection of the benzyl group at the C(3) carbon was attempted. In an initial effort, a hydrogenation catalyzed by Pd/C with triethylsilane as a hydrogen source was carried out according to a literature procedure.[81] The screening experiment utilizing **12a** on a ca. 1 mmol scale with an excess of triethylsilane (Scheme 4, right side) in methanol led to complete removal of benzyl groups in 1 h, affording diol **14a** in 86% yield.

However, scaling up the reaction 4 times led to only partial deprotection and formation of ferrocenyl alcohol **13** (Scheme 4, left side) in 78% yield. We assume that the Pd/C catalytic dehydrogenation of triethylsilane (i.e., hydrogen evolution) is considerably faster than the Pd/C catalytic debenzylation; therefore, an excess of triethylsilane should be occasionally added to achieve a sufficient concentration of hydrogen in the reaction mixture to complete the debenzylation (for details see the Experimental Section). While this was rather impractical, molecular hydrogen was further used for debenzylation of ferrocenes **12**. The Pd/C-catalyzed hydrogenation of **12a**,**b** under atmospheric pressure of molecular hydrogen in THF or methanol afforded the corresponding diols **14a**,**b** in 82% and 70% yields (Scheme 4, right side). The diols **14** were obtained as yellow solids stable in air and soluble in most organic solvents. Repeated recrystallizations of **14a** from methanol, acetone, or THF afforded a crystalline material; however, it was not suitable for X-ray analysis.

All prepared ferrocenes **12**−**14** were characterized by elemental analysis, NMR, IR, and ESI-MS, and in addition, melting points were determined for diols **14**. The ^1H and ^{13}C NMR spectra (see the Experimental Section and Supporting Information) of ferrocenes **12**−**14** corroborated the proposed structures. The signal of the hydroxyl group(s) appeared as a doublet spanning the region 5.10−5.23 ppm (5.21 ppm, $^3J_{HH}$ = 5.1 Hz for **13**; 5.23 ppm, $^3J_{HH}$ = 5.1 Hz for **14a**; 5.10 ppm, $^3J_{HH}$ = 6.9 Hz for **14b**) in ^1H NMR spectra of DMSO-d_6 solutions of the ferrocenyl alcohols **13** and **14**. The equivalence of both hydroxyl protons in diols **14** indicates that both substituted cyclopentadienyl rings freely rotate in solution and formation of intramolecular hydrogen bonds is suppressed.

The situation is more complex in the solid state, as was indicated by IR spectroscopy (see the Supporting Information). A unique absorption band for valence −OH vibration was found at 3467 cm^{-1} for **13** and at 3459 cm^{-1} for **14b**, which is consistent with the presence of only terminal hydroxyl groups in the structure. In contrast to that, two absorption bands at 3457 and 2565 cm^{-1} were found for two distinct hydroxyl groups in **14a**. We suggest that the former could be attributed to a terminal hydroxyl group and the latter to a hydrogen-bonded hydroxyl group, constituting an intramolecular bridge between both carbohydrate moieties (see the Supporting Information).

Cytotoxicity Studies. The cytotoxic properties of complexes **8**−**14** against A2780 and A2780cis cells were evaluated by MTT tests. IC_{50} values of 24 h and 72 h treatments for A2780 and 24h treatment for A2780cis are summarized in Table 1. A 24 h assay for the A2780 cell line shows no cytostatic effect (IC_{50} > 100 μM) for titanocene dichlorides **8** and **9** or for fully protected ferrocenes **12** and ferrocene diol **14b**. On the other hand, the titanocene difluoride complexes **10** and **11a** possessed cytotoxicity in a moderate micromolar range (36.4 ± 1.1 μM for **10**; 60 ± 9 μM for **11a**), and the most active complex **11b** showed a cytotoxicity value of the same order of magnitude as Cisplatin (19.6 ± 1.3 μM for **11b**; 12.9 ± 1.5 μM for cisplatin). In the prolonged 72 h assay, titanocene difluoride **11b** attained the highest cytotoxicity among the tested complexes (IC_{50} = 8.5 ± 1.5 μM), the value being ca. 4-fold lower in comparison to that of its chlorido analogue **9b** (38

Table 1. Cytotoxic Activity (IC_{50} Values (μM)) of Carbohydrate-Modified Titanocene Dihalides 8−11 and Ferrocenes 12 and 14 against A2780 and A2780cis

compd	A2780 (24 h)	A2780 (72 h)	A2780cis (24 h)
8a	>100	NT[a]	NT
8b	>100	NT	NT
9a	55[b]	NT	NT
9b	>100	38 ± 5	65 ± 12
10	36.4 ± 1.1	17 ± 4	48 ± 12
11a	60 ± 9	30 ± 3	>100
11b	19.6 ± 1.3	8.5 ± 1.5	31 ± 6
12a	>100	NT	NT
12b	>100	NT	NT
14a	38.3 ± 1.1	26 ± 12	NT
14b	>100	NT[a]	NT
cisplatin[c]	12.9 ± 1.5	1.74 ± 0.27	50 ± 9

[a]Not tested. [b]Performed only once. [c]*cis*-$[PtCl_2(NH_3)_2]$.

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± 5 μM). Generally, the prolonged assay for the A2780 cell line led to a decrease in IC_{50} values by about half for titanocene difluorides **10** and **11** (36.4 ± 1.1 μM (24 h) vs 17 ± 4 μM (72 h) for **10**; 60 ± 9 μM (24 h) vs 30 ± 3 μM (72 h) for **11a**; 19.6 ± 1.3 μM (24 h) vs 8.5 ± 1.5 μM (72 h) for **11b**) and by about one-third for ferrocene diol **14a** (38.3 ± 1.1 μM (24 h) vs 26 ± 12 μM (72 h)), which indicates their capability of prolonged residing in cells during the assay. The titanocene complexes active against the A2780 cell line (**9b**, **10**, and **11**) were further evaluated against the A2780cis cell line in a 24 h assay. Complexes **9b** and **10** showed cytotoxicity comparable to that of cisplatin, while the most active **11b** has about 40% higher cytotoxicity than cisplatin (31 ± 6 μM for **11b** and 50 ± 9 μM for cisplatin).

The function of fluoride σ ligands is not clear from the literature. Köpf-Maier et al. proposed only a negligible effect of halide ligands in Cp_2TiX_2 (X = F, Cl, Br, I) against EAT tumors, although a slightly higher activity was found for the fluoro analogue (LD_{50} = 60 mg/kg for Cp_2TiF_2 vs LD_{50} = 100 mg/kg for Cp_2TiCl_2).[4] On the other hand, a 3−5-fold decrease in activity against several cell lines going from fluorido to chlorido titanocenes Cp'_2TiX_2 (X = F, Cl; Cp′ = $C_4H_4CH_{3-n}\{C_6H_4(p\text{-OMe})\}_n$, n = 1, 2) was reported by Tacke et al.[70] A greater bond strength of the Ti−F bond (569 ± 34 kJ mol^{-1}) in comparison to the Ti−Cl bond (494 kJ mol^{-1}) would lead to a slower solvolysis of the fluoride, while not completely preventing the solvolysis (the Ti−O bond strength is 666.5 ± 6.3 kJ mol^{-1}).[82] Therefore, we tentatively suggest that a slower decay of titanocene difluorides into biologically inactive insoluble species with multiple Ti−O−Ti bonds takes place in an aqueous environment. It should be mentioned that the cytotoxicity of titanocene difluorides does not arise from the toxicity of the fluoride anion itself, as fluoride anions (e.g., in NaF solutions) revealed significant cytotoxicity only at relatively high concentrations above milimolar values.[83]

The effect of the configuration of the carbohydrate substituent on the metallocene biological performance is not obvious, as the ribofuranose moiety enhanced the activity of titanocene difluorides **11** (A2780(72 h), 30 ± 3 μM for **11a**, 8.5 ± 1.5 μM for **11b**; A2780cis, >100 μM for **11a**, 31 ± 6 μM for **11b**) while it decreased the activity of ferrocene diols **14** (A2780(24 h), 38.3 ± 1.1 μM for **14a**, >100 μM for **14b**) in comparison to the xylofuranose analogues in both studied cell lines. Nevertheless, a roughly 2-fold higher cytotoxicity of titanocene difluoride **11b** (A2780(72 h), 8.5 ± 1.5 μM; A2780cis, 31 ± 6 μM) bearing two ribofuranose moieties in comparison to the titanocene difluoride **10** bearing only one ribofuranose moiety (A2780(72 h), 17 ± 4 μM; A2780cis, 48 ± 12 μM) implies a strengthening effect of two carbohydrate substituents attached to a metallocene moiety on the cytostatic activity.

CONCLUSIONS

A synthetic protocol for the preparation of titanocenene dichlorides and ferrocenes bearing a fully protected 5-deoxyxylofuranose or 5-deoxyribofuranose moiety has been developed. The synthesis started from D-glucose, and the cyclopentadiene moiety was attached to the 5-position of 5-deoxyxylofuranose or 5-deoxyribofuranose in eight steps. Deprotonation of the corresponding cyclopentadienes **6** followed by a metathesis reaction between lithium cyclopentadienide-carbohydrate **7** and $[(\eta^5\text{-}C_5H_5)TiCl_3]$, $[TiCl_4(THF)_2]$, and $FeCl_2$ gave the corresponding titanocene dichlorides **8** and **9** or ferrocenes **12**, respectively. Ferrocene diols **14** were obtained from ferrocenes **12** by deprotection of the benzyl group at the C(3) carbon of the furanose ring. Nevertheless, a scaled up benzyl deprotection with Et_3SiH as a hydrogen source led to the removal of only one benzyl group to give ferrocene alcohol **13**. Fluorination using the fluorinating agent $\{2\text{-}(CH_2NMe_2)C_6H_4\text{-}\kappa C,N\}(n\text{-}Bu)_2SnF$ was found to be an easy and clean procedure for the generation of titanocene difluorides **10** and **11** from the corresponding dichlorides **8b** and **9** in excellent yields. However, a direct reaction of lithium cylopentadienides **7** with $[TiF_4(THF)_2]$ was found to be a straightforward way for the preparation of symmetrically substituted titanocene difluorides **11** in a single step in yields comparable to those achieved for the analogous titanocene dichlorides from $[TiCl_4(THF)_2]$. As titanocene difluorides are important catalytic precursors in many catalytic processes (e.g., defluorination, hydrosilylation; for a complete listing see a recent review article),[84] we suggest that the described metathesis method of their preparation may find a widespread use.

An evaluation of the cytotoxic activity of the prepared complexes against A2780 and A2780cis cell lines revealed an increased activity of titanocene difluorides in comparison to the corresponding dichlorides. Furthermore, an increase in cytotoxicity has been achieved by the incorporation of two carbohydrate moieties into the titanocene framework, in comparison to the titanocene complexes bearing only a single carbohydrate moiety. Therefore, titanocene difluorides bearing two carbohydrate molecules seem to be the most promising species for future investigations. The most cytotoxic complex, **11b**, reached about 5-fold lower activity against A2780 cell line in comparison to cisplatin, while about 40% higher activity was reached against the cisplatin-resistant A2780cis cell line. This seems to imply a different mechanism of action of the species in comparison to cisplatin, which would be advantageous in the treatment of cisplatin-resistant cancers. Studies on the mechanism of action of active compounds (mainly **11b**) and elucidation of function of the carbohydrate moiety in the cellular uptake are currently under way.

EXPERIMENTAL SECTION

General Considerations. All manipulations with air-sensitive compounds were carried out under an argon atmosphere using standard Schlenk techniques. ^1H (299.98 or 499.87 MHz), ^{13}C (75.44 or 125.71 MHz), and ^{19}F (282.22 or 470.37 MHz) NMR spectra were measured on a Varian Mercury 300 or Varian Innova 500 spectrometer at 25 °C. ^1H and ^{13}C chemical shifts (δ/ppm) are given relative to solvent signals (δ_H/δ_C: $CDCl_3$, 7.26/77.16; THF-d_8, 3.58/67.21; DMSO-d_6, 2.50/39.52). The ^{19}F NMR spectra were referenced to external $CFCl_3$. EI-MS spectra were measured using an Agilent 6890 gas chromatograph coupled to an Agilent 5973 mass spectrometer operating in 70 eV ionization mode. Electrospray mass spectra (ESI-MS) were measured with a Bruker Esquire 3000 instrument on dichloromethane/acetonitrile solutions. IR spectra of samples in KBr pellets were measured on a Nicolet Avatar FTIR spectrometer in the range 400−4000 cm^{-1}. Melting points were determined on a Kofler block and were uncorrected. Elemental analyses were carried out on a FLASH EA1112 CHN-O Automatic Elemental Analyzer (Thermo Scientific).

Chemicals. Solvents were appropriately dried (THF, diethyl ether, toluene by refluxing with Na/benzophenone; dichloromethane by refluxing with CaH_2) distilled, and stored over 4Å molecular sieves. MeLi (1.6 M solution in diethyl ether), $[(\eta^5\text{-}C_5H_5)TiCl_3]$, $[TiCl_4(THF)_2]$, and Pd/C (palladium on carbon, 10 wt % Pd) were purchased from Aldrich and used as received. Et_3SiH was dried by

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refluxing over $LiAlH_4$ and distilled prior to use. $[TiF_4(THF)_2]$[79] and {2-$(CH_2NMe_2)C_6H_4$-$\kappa C,N$}$(n\text{-Bu})_2SnF$[75] were prepared by literature methods.

Preparation of Cyclopentadienes 6a/6a′. A solution of sodium cyclopentadienide in tetrahydrofuran (6 mL, 2 M, 12 mmol) was added dropwise with cooling (−50 °C) and stirring to a solution of 3-*O*-benzyl-1,2-di-*O*-isopropylidene-5-*O*-(*p*-toluenesulfonyl)-α-D-xylofuranose (**5**;[69] 2.945 g, 6.78 mmol) in anhydrous dimethylformamide (10 mL). The mixture was warmed to room temperature, and stirring was continued for 2 h while a fine precipitate formed. The reaction mixture was then kept at 5 °C overnight. TLC in ethyl acetate/light petroleum (1/5) indicated the absence of the starting compound. The unreacted cyclopentadienide was decomposed by addition of 5 mL of water, and after 10 min the reaction mixture was poured onto ice. The water phase was extracted three times with ethyl acetate/diethyl ether (1/1) and then once with diethyl ether. The organic extracts were combined, dried over sodium sulfate, and concentrated to afford 2.4 g of the crude product. Chromatography on silica gel in ethyl acetate/light petroleum (1/5) afforded the crystalline product as an inseparable mixture of **6a** and **6a**′ in a 5/4 molar ratio. Yield 1.454 g (65%). Mp: 68 °C. ^{1}H NMR (500 MHz, $CDCl_3$) for **6a**: 1.31, 1.49 (2 × s, 2 × 3H, CMe_2); 2.84 (m, 2H, $CH_2C_5H_5$); 2.87, 2.97 (2 × m, 2 × 1H, CH_2, C_5H_5); 3.83 (dd, $^3J_{H4H3}$ = 3.1 Hz, 1H, C(3)*H*); 4.36 (pseudo td, $^3J_{H4H3}$ = 3.1 Hz, $^3J_{H4H5}$ = 7.0 Hz and $^3J_{H4H5'}$ = 7.1 Hz, 1H, C(4)*H*); 4.48 (d, $^2J_{HH}$ = 11.8 Hz, 1H, CH_2Ph); 4.62 (d, $^3J_{H1H2}$ = 3.9 Hz, 1H, C(2)*H*); 4.68 (d, $^2J_{HH}$ = 11.8 Hz, 1H, CH_2Ph); 5.93 (d, $^3J_{H1H2}$ = 3.9 Hz, 1H, C(1)*H*); 6.22, 6.27, 6.41 (3 × m, 3 × 1H, =*CH*, C_5H_5); 7.28−7.37 (m, 5H, *Ph*). ^{1}H NMR (500 MHz, $CDCl_3$) for **6a**′: 1.31, 1.49 (2 × s, 2 × 3H, CMe_2); 2.56, 2.84 (2 × m, 2 × 1H, $CH_2C_5H_5$); 2.93 (m, 2H, CH_2, C_5H_5); 3.81 (d, $^3J_{H4H3}$ = 3.1 Hz, 1H, C(3)*H*); 4.40 (pseudo td, $^3J_{H4H3}$ = 3.1 Hz, $^3J_{H4H5}$ = 7.2 Hz and $^3J_{H4H5'}$ = 7.1 Hz, 1H, C(4)*H*); 4.48 (d, $^2J_{HH}$ = 11.8 Hz, 1H, CH_2Ph); 4.62 (d, $^3J_{H1H2}$ = 3.9 Hz, 1H, C(2)*H*); 4.67 (d, $^2J_{HH}$ = 11.8 Hz, 1H, CH_2Ph); 5.94 (d, $^3J_{H1H2}$ = 3.9 Hz, 1H, C(1)*H*); 6.07, 6.42, 6.45 (3 × m, 3 × 1H, =*CH*, C_5H_5); 7.28−7.37 (m, 5H, *Ph*). ^{13}C NMR (126 MHz, $CDCl_3$) for **6a**: 25.89, 26.40 (CMe_2); 28.84 ($CH_2C_5H_5$); 43.72 (CH_2, C_5H_5); 71.71 (CH_2Ph); 79.79 (*C*(4)); 82.00 (*C*(3)); 82.10 (*C*(2)); 104.87 or 104.89 (*C*(1)); 111.44 (CMe_2); 127.85, 128.05 or 128.09, 128.52 or 128.69 (*CH*, *Ph*); 128.65, 131.50, 132.63 (*CH*, C_5H_5); 137.86 or 137.89 (C_{ipso}, *Ph*); 145.31 (C_{ipso}, C_5H_5). ^{13}C NMR (126 MHz, $CDCl_3$) for **6a**′: 25.89, 26.40 (CMe_2), 28.00 ($CH_2C_5H_5$); 41.23 (CH_2, C_5H_5); 71.65 (CH_2Ph); 79.79 (*C*(4)); 81.84 (*C*(3)); 82.10 (*C*(2)); 104.87 or 104.89 (*C*(1)); 111.44 (CMe_2); 127.85, 128.05 or 128.09, 128.52 or 128.69 (*CH*, *Ph*); 128.20, 134.14, 135.02 (*CH*, C_5H_5); 137.86 or 137.89 (C_{ipso}, *Ph*); 143.09 (C_{ipso}, C_5H_5). EI-MS (*m*/*z* (%)): 328 ($M^{\bullet+}$, 3), 249 (7), 211 (6), 164 (8), 91 (100), 79 (10). Anal. Calcd for $C_{20}H_{24}O_4$ (328.39): C, 73.15; H, 7.37. Found: C, 73.07; H, 7.42.

Preparation of Cyclopentadienes 6b/6b′. A solution of sodium cyclopentadienide in tetrahydrofuran (3.8 mL, 2 M, 7.6 mmol) was added dropwise with cooling (−50 °C) and stirring to a solution of 3-*O*-benzyl-1,2-di-*O*-isopropylidene-5-*O*-(*p*-toluenesulfonyl)-α-D-ribofuranose (**4**; 1.939 g, 4.46 mmol) in anhydrous dimethylformamide (9 mL). The mixture was warmed to room temperature, and stirring was continued for 2 h while a fine precipitate formed. The reaction mixture was then kept at 5 °C overnight. TLC in ethyl acetate/light petroleum (1/2 and 1/5) indicated the absence of the starting compound. The unreacted cyclopentadienide was decomposed by addition of 4 mL of water, and after 10 min the reaction mixture was poured onto ice. The water phase was extracted three times with ethyl acetate. The organic extracts were combined, washed with brine, dried over sodium sulfate, and concentrated to afford 1.7 g of the crude product. Chromatography on silica gel in ethyl acetate/light petroleum (1/5) yielded a syrupy product as an inseparable mixture of **6b** and **6b**′ in an equimolar ratio, which crystallized spontaneously upon storing overnight at room temperature. Yield: 0.993 g (68%). Mp: 58−65 °C. ^{1}H NMR (500 MHz, $CDCl_3$) for **6b**: 1.35, 1.59 (2 × s, 2 × 3H, CMe_2); 2.60, 2.82 (2 × m, 2 × 1H, $CH_2C_5H_5$); 2.93 (m, 2H, CH_2, C_5H_5); 3.43 (dd, $^3J_{H2H3}$ = 8.8 Hz and $^3J_{H3H4}$ = 8.8 Hz, 1H, C(3)*H*); 4.21 (ddd, $^3J_{H4H5}$ = 3.6 Hz, $^3J_{H4H5'}$ = 7.1 Hz and $^3J_{H4H3}$ = 8.8 Hz, 1H, C(4)*H*); 4.53 (dd, $^3J_{H1H2}$= 3.8 Hz and $^3J_{H2H3}$ = 8.8 Hz, 1H, C(2)*H*); 4.53 or 4.54 (d, $^2J_{HH}$ = 12.0 Hz, 1H, CH_2Ph); 4.76 or 4.77 (d, $^2J_{HH}$ = 12.0 Hz, 1H, CH_2Ph); 5.71 (d, $^3J_{H1H2}$ = 3.8 Hz, 1H, C(1)*H*); 6.18, 6.27, 6.40 (3 × m, 3 × 1H, =*CH*, C_5H_5); 7.30−7.37 (m, 5H, *Ph*). ^{1}H NMR (500 MHz, $CDCl_3$) for **6b**′: 1.35, 1.59 (2 × s, 2 × 3H, CMe_2); 2.56, 2.80 (2 × m, 2 × 1H, $CH_2C_5H_5$); 2.91 (m, 2H, CH_2, C_5H_5); 3.43 (dd, $^3J_{H4H3}$ = 8.8 Hz and $^3J_{H2H3}$ = 8.8 Hz, 1H, C(3)*H*); 4.28 (ddd, $^3J_{H4H5}$ = 3.6 Hz, $^3J_{H4H5'}$ = 7.1 Hz and $^3J_{H4H3}$ = 8.8 Hz, 1H, C(4)*H*); 4.53 (dd, $^3J_{H1H2}$ = 3.8 Hz and $^3J_{H2H3}$ = 8.8 Hz, 1H, C(2)*H*); 4.53 or 4.54 (d, $^2J_{HH}$ = 12.0 Hz, 1H, CH_2Ph); 4.76 or 4.77 (d, $^2J_{HH}$ = 12.0 Hz, 1H, CH_2Ph); 5.71 (d, $^3J_{H1H2}$ = 3.8 Hz, 1H, C(1)*H*); 6.05, 6.37, 6.45 (3 × m, 3 × 1H, =*CH*, C_5H_5); 7.30−7.37 (m, 5H, *Ph*). ^{13}C NMR (126 MHz, $CDCl_3$) for **6b**: 26.57, 26.74 (CMe_2); 32.81 ($CH_2C_5H_5$); 44.26 (CH_2, C_5H_5); 72.02 or 72.04 (CH_2Ph); 77.04 or 77.06 (*C*(2)); 77.74 (*C*(4)); 80.92 (*C*(3)); 103.88 or 103.91 (*C*(1)); 112.70 (CMe_2); 127.94 or 127.98, 128.02 or 128.07, 128.40 or 128.42 (*CH*, *Ph*); 129.02, 131.73, 132.15 (*CH*, C_5H_5); 137.57 or 137.64 (C_{ipso}, *Ph*); 144.62 (C_{ipso}, C_5H_5). ^{13}C NMR (126 MHz, $CDCl_3$) for **6b**′: 26.57, 26.74 (CMe_2), 31.78 ($CH_2C_5H_5$); 41.28 (CH_2, C_5H_5); 72.02 or 72.04 (CH_2Ph); 77.04 or 77.06 (*C*(2)); 77.32 (*C*(4)); 80.69 (*C*(3)); 103.88 or 103.91 (*C*(1)); 112.70 (CMe_2);); 127.94 or 127.98, 128.02 or 128.07, 128.40 or 128.42 (*CH*, *Ph*); 128.87, 133.41, 135.18 (*CH*, C_5H_5); 137.57 or 137.64 (C_{ipso}, *Ph*); 142.42 (C_{ipso}, C_5H_5). EI-MS (*m*/*z* (%)): 313 (1), 270 (8), 269 (7), 248 (3), 179 (7), 91 (100). Anal. Calcd for $C_{20}H_{24}O_4$ (328.39): C, 73.15; H, 7.37. Found: C, 72.94; H, 7.43.

Preparation of Lithium Cyclopentadienide 7a. To a mixture of cyclopentadienes **6a**/**6a**′ (1.429 g, 4.36 mmol) in Et_2O (50 mL) was slowly added dropwise a solution of *n*-BuLi in hexane (2.00 mL, 2.5 M, 5.00 mmol), which caused immediate precipitation of a white solid. The suspension was stirred for 12 h and then filtered. The obtained white solid was washed with Et_2O (2 × 10 mL) and dried under vacuum to constant weight. Yield: 1.338 g (92%). ^{1}H NMR (300 MHz, THF-d_8): 1.23 (s, 3H, CMe_2); 1.39 (s, 3H, CMe_2); 2.85 (dd, $^2J_{HH}$ = 13.6 Hz, $^3J_{HH}$ = 7.5 Hz, 1H, $CH_2C_5H_4$); 2.94 (dd, $^2J_{HH}$ = 13.6 Hz, $^3J_{HH}$ = 7.5 Hz, 1H, $CH_2C_5H_4$); 3.78 (d, $^3J_{HH}$ = 3.0 Hz, 1H, C(3)*H*); 4.39 (td, $^3J_{HH}$ = 7.5 Hz, $^3J_{HH}$ = 3.0 Hz, 1H, C(4)*H*); 4.55 (d, $^2J_{HH}$ = 11.8 Hz, 1H, CH_2Ph); 4.61 (d, $^3J_{HH}$ = 3.9 Hz, 1H, C(2)*H*); 4.64 (d, $^2J_{HH}$ = 11.8 Hz, 1H, CH_2Ph); 5.53 − 5.63 (m, 4H, C_5H_4); 5.72 (d, $^3J_{HH}$ = 3.9 Hz, 1H, C(1)*H*), 7.18 − 7.39 (m, 5H, *Ph*). ^{13}C NMR (75 MHz, THF-D_8): 26.64, 27.27 (CMe_2); 29.55 ($CH_2C_5H_4$); 72.38 (CH_2Ph); 83.09 (*C*(3)); 83.92 (*C*(2)); 84.27 (*C*(4)); 103.26, 103.45 (*CH*, C_5H_4); 105.59 (*C*(1)); 111.55 (CMe_2); 114.54 (C_{ipso}, C_5H_4); 128.16, 128.36, 129.03, (*CH*, *Ph*); 140.00 (C_{ipso}, *Ph*).

Preparation of Lithium Cyclopentadienide 7b. To a mixture of cyclopentadienes **6b**/**6b**′ (1.848 g, 5.63 mmol) in Et_2O (60 mL) cooled to 0 °C was slowly added dropwise a solution of *n*-BuLi in hexane (2.40 mL, 2.5 M, 6.00 mmol), which caused precipitation of a slightly pink waxy solid within several minutes. The resulting suspension was stirred for 12 h. The solution was removed by reverse filtration, and the obtained slightly pink gel was washed with Et_2O (2 × 15 mL) and dried under vacuum to constant weight. Yield: 1.403 g (75%). ^{1}H NMR (300 MHz, THF-d_8): 1.28 (s, 3H, CMe_2); 1.47 (s, 3H, CMe_2); 2.67 (dd, $^2J_{HH}$ = 13.8 Hz, $^3J_{HH}$ = 7.2 Hz, 1H, $CH_2C_5H_4$); 2.88 (dd, $^2J_{HH}$ = 13.8 Hz, $^3J_{HH}$ = 5.7 Hz, 1H, $CH_2C_5H_4$); 3.52 (dd, $^3J_{HH}$ = 8.7 Hz, $^3J_{HH}$ = 4.5 Hz, 1H, C(3)*H*); 4.06−4.16 (m, 1H, C(4)*H*); 4.49 (d, $^2J_{HH}$ = 11.4 Hz, 1H, CH_2Ph); 4.61 (pseudo t, $^3J_{HH}$ = 4.5 Hz, $^3J_{HH}$ = 3.9 Hz, 1H, C(2)*H*); 4.66 (d, $^2J_{HH}$ = 11.4 Hz, 1H, CH_2Ph); 5.52 − 5.56 (m, 2H, C_5H_4); 5.56−5.61 (m, 2H, C_5H_4); 5.60 partially overlapped (d, $^3J_{HH}$ = 3.9 Hz, 1H, C(1)*H*); 7.20−7.40 (m, 5H, *Ph*). ^{13}C NMR (75 MHz, THF-d_8): 27.09, 27.14 (CMe_2); 34.64 ($CH_2C_5H_4$); 72.46 (CH_2Ph); 78.80 (*C*(2)); 81.37 (*C*(4)); 83.70 (*C*(3)); 103.54, 103.81 (*CH*, C_5H_4); 104.99 (*C*(1)); 112.86 (CMe_2); 113.44 (C_{ipso}, C_5H_4); 128.59, 129.09, 129.13 (*CH*, *Ph*); 139.08 (C_{ipso}, *Ph*).

Preparation of Titanocene Dichloride 8a. A solution of lithium cyclopentadienide **7a** (0.210 g, 0.63 mmol) in THF (10 mL) was dropped into a solution of $[(\eta^5\text{-}C_5H_5)TiCl_3]$ (0.137 g, 0.63 mmol) in THF (10 mL) cooled to −20 °C. The reaction mixture was warmed to room temperature and stirred for 1 h. Volatiles were evaporated under

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vacuum, and the residue was extracted with chloroform (6 mL). The chloroform extract was layered with heptane (20 mL), which afforded a red oil after several days in the refrigerator (4 °C). The oil was isolated, and crystallization was attempted from a toluene/heptane mixture (4 mL/2 mL) at low temperature (4 °C). Nevertheless, the product again appeared as a red oil after several days. The oil was separated and dried under vacuum for several hours, which caused its solidification to a red solid. Yield: 0.205 g (64%). Mp: 48 °C. ^{1}H NMR (300 MHz, $(CD_3)_2SO$): 1.24, 1.37 (2 × s, 2 × 3H, CMe_2); 2.95−3.00 (m, 2H, $CH_2C_5H_4$); 3.73 (d, $^3J_{HH}$ = 3.3 Hz, 1H, C(3)*H*); 4.21−4.26 (m, 1H, C(4)*H*); 4.47, 4.69 (2 × d, 2 × $^2J_{HH}$ = 11.7 Hz, 2 × 1H, CH_2Ph); 4.74 (d, $^3J_{HH}$ = 3.9 Hz, 1H, C(2)*H*); 5.85 (d, $^3J_{HH}$ = 3.9 Hz, 1H, C(1)*H*); 6.33−6.42 (m, 2H, C_5H_4); 6.65 (s, 5H, C_5H_5); 6.67−6.75 (m, 2H, C_5H_4); 7.30−7.38 (m, 5H, *Ph*). ^{1}H NMR (300 MHz, $CDCl_3$): 1.31, 1.47 (2 × s, 2 × 3H, CMe_2); 3.07 (dd, $^2J_{HH}$ = 15.6 Hz, $^3J_{HH}$ = 5.4 Hz, 1H, $CH_2C_5H_4$); 3.12 (dd, $^2J_{HH}$ = 15.6 Hz, $^3J_{HH}$ = 8.3 Hz, 1H, $CH_2C_5H_4$); 3.82 (d, $^3J_{HH}$ = 3.0 Hz, 1H, C(3)*H*); 4.28 (ddd, $^3J_{HH}$ = 8.3 Hz, $^3J_{HH}$ = 5.4 Hz, $^3J_{HH}$ = 3.0 Hz, 1H, C(4)*H*); 4.51 (d, $^2J_{HH}$ = 11.9 Hz, 1H, CH_2Ph); 4.62 (d, $^3J_{HH}$ = 4.0 Hz, 1H, C(2)*H*); 4.71 (d, $^2J_{HH}$ = 11.9 Hz, 1H, CH_2Ph); 5.96 (d, $^3J_{HH}$ = 4.0 Hz, 1H, C(1)*H*); 6.34−6.38 (m, 1H, C_5H_4); 6.43−6.47 (m, 1H, C_5H_4); 6.48−6.52 (m, 2H, C_5H_4); 6.55 (s, 5H, C_5H_5); 7.29−7.41 (m, 5H, *Ph*). ^{13}C NMR (75 MHz, $CDCl_3$): 26.28, 26.82 (CMe_2); 30.19 ($CH_2C_5H_4$); 72.04 (CH_2Ph); 79.96 (*C*(4)); 82.18 (*C*(2)); 82.65 (*C*(3)); 105.09 (*C*(1)); 111.54 (CMe_2); 115.75, 119.07 (*CH*, C_5H_4); 120.03 (C_5H_5); 122.30, 123.36 (*CH*, C_5H_4); 127.94, 128.18, 128.74 (*CH*, *Ph*); 135.11 (C_{ipso}, C_5H_4); 137.46 (C_{ipso}, *Ph*). ESI-MS (*m*/*z*; ESI$^+$, relative abundance): 549 ([M + K]$^+$, 93); 533 ([M + Na]$^+$, 90); 475 ([M − Cl]$^+$, 100). IR (KBr, cm^{-1}): 3110 (w), 3063 (w), 3029 (w), 2984 (m), 2931 (m), 2873 (w), 1603 (vw), 1496 (w), 1454 (sh, m), 1382 (m), 1374 (m), 1350 (w), 1300 (sh, w), 1248 (s), 1214 (s), 1164 (s), 1076 (vs), 1027 (s), 961 (w), 887 (w), 851 (m), 822 (vs), 737 (m), 698 (m), 669 (vw), 635 (vw), 603 (vw), 512 (vw), 466 (vw). Anal. Calcd for $C_{25}H_{28}Cl_2O_4Ti$ (511.27): C, 58.73; H, 5.52. Found: C, 58.95; H, 5.68.

Preparation of Titanocene Dichloride 8b. To a solid mixture of lithium cyclopentadienide **7b** (0.262 g, 0.78 mmol) and [(η^5-C_5H_5)$TiCl_3$] (0.155 g, 0.71 mmol) cooled to −78 °C was added THF (10 mL). The mixture was warmed to room temperature and stirred for an additional 12 h. Volatiles were removed under vacuum, and the residue was extracted with dichloromethane (15 mL). Evaporation of dichloromethane afforded the crude product as an orange-red fluffy solid, which was recrystallized from a dichloromethane/heptane mixture at low temperature (4 °C). The precipitated red-orange solid was isolated, washed with heptane (2 × 2 mL), and dried under vacuum. Yield: 0.297 g (75%). Mp: 172 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 1.34, 1.56 (2 × s, 2 × 3H, CMe_2); 2.79 (dd, $^2J_{HH}$ = 15.1 Hz, $^3J_{HH}$ = 8.1 Hz, 1H, $CH_2C_5H_4$); 3.17 (dd, $^2J_{HH}$ = 15.1 Hz, $^3J_{HH}$ = 3.1 Hz, 1H, $CH_2C_5H_4$); 3.40 (dd, $^3J_{HH}$ = 8.9 Hz, $^3J_{HH}$ = 4.4 Hz, 1H, C(3)*H*); 4.15 (pseudo td, $^3J_{HH}$ = 8.9 Hz, $^3J_{HH}$ = 8.1 Hz, $^3J_{HH}$ = 3.1 Hz, 1H, C(4)*H*); 4.53 (d, $^2J_{HH}$ = 11.9 Hz, 1H, CH_2Ph); 4.55 (pseudo t, $^3J_{HH}$ = 4.4 Hz, $^3J_{HH}$ = 3.8 Hz, 1H, C(2)*H*); 4.79 (d, $^2J_{HH}$ = 11.9 Hz, 1H, CH_2Ph); 5.70 (d, $^3J_{HH}$ = 3.8 Hz, 1H, C(1)*H*); 6.25−6.28, 6.34−6.37, 6.39−6.42, 6.42−6.45 (4 × m, 4 × 1H, C_5H_4); 6.54 (s, 5H, C_5H_5); 7.32−7.40 (m, 5H, *Ph*). ^{13}C NMR (75 MHz, $CDCl_3$): 26.60, 26.82 (CMe_2); 33.48 ($CH_2C_5H_4$); 72.29 (CH_2Ph); 77.00 (*C*(2)); 77.78 (*C*(4)); 81.00 (*C*(3)); 104.05 (*C*(1)); 112.96 (CMe_2); 116.27, 116.36 (*CH*, C_5H_4); 119.93 (*CH*, C_5H_5); 124.07, 124.42 (*CH*, C_5H_4); 128.28, 128.40, 128.70 (*CH*, *Ph*); 133.53 (C_{ipso}, C_5H_4); 137.45 (C_{ipso}, *Ph*). ESI-MS (*m*/*z*; ESI$^+$, relative abundance): 549 ([M + K]$^+$, 95); 533 ([M + Na]$^+$, 100); 475 ([M − Cl]$^+$, 97). IR (KBr, cm^{-1}): 3114 (w), 3107 (w), 3064 (vw), 3034 (vw), 2986 (w), 2976 (w), 2950 (w), 2931 (w), 2895 (w), 2885 (w), 1627 (vw), 1498 (w), 1453 (m), 1434 (m), 1384 (m), 1372 (m), 1329 (w), 1307 (w), 1263 (m), 1240 (m), 1224 (s), 1207 (m), 1169 (m), 1132 (s), 1102 (s), 1072 (s), 1061 (m), 1041 (s), 1010 (s), 974 (w), 962 (m), 923 (vw), 891 (w), 874 (s), 858 (s), 838 (s), 822 (vs), 786 (vw), 760 (m), 741 (w), 706 (vs), 688 (w), 618 (w), 608 (m), 588 (vw), 559 (w), 514 (w), 495 (vw), 436 (vw), 415 (w). Anal. Calcd for $C_{25}H_{28}Cl_2O_4Ti$ (511.27): C, 58.73; H, 5.52. Found: C, 59.12; H, 5.81.

Preparation of Titanocene Dichloride 9a. A solution of lithium cyclopentadienide **7a** (0.600 g, 1.79 mmol) in THF (15 mL) was dropped into a solution of $TiCl_4(THF)_2$ (0.270 g, 0.81 mmol) in THF (15 mL) cooled to −78 °C. The resulting red solution was stirred for 1 h and then allowed warmed to room temperature and stirred for an additional 14 h. After evaporation of THF under vacuum, the crude product was extracted with dichloromethane (8 mL and 2 × 2 mL). The volume of the collected dichloromethane fraction was reduced to half, and the obtained dark red solution was layered with hexane (20 mL). A dark red-brown oil separated after several days at 4 °C. The oil was isolated, washed with 4 × 2 mL of pentane, and dried under vacuum for several hours, which caused its solidification to a brown powder. The mother liquor and collected washings gave an additional crop of the product. Overall yield: 0.252 g (40%). Mp: 110 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 1.31, 1.46 (2 × s, 2 × 6H, CMe_2); 3.05 (dd, $^2J_{HH}$ = 15.4 Hz, $^3J_{HH}$ = 5.4 Hz, 2H, $CH_2C_5H_4$); 3.12 (dd, $^2J_{HH}$ = 15.4 Hz, $^3J_{HH}$ = 8.0 Hz, 2H, $CH_2C_5H_4$); 3.81 (d, $^3J_{HH}$ = 3.1 Hz, 2H, C(3)*H*); 4.30 (ddd, $^3J_{HH}$ = 8.0 Hz, $^3J_{HH}$ = 5.4 Hz, $^3J_{HH}$ = 3.1 Hz, 2H, C(4)*H*); 4.51 (d, $^2J_{HH}$ = 11.9 Hz, 2H, CH_2Ph); 4.61 (d, $^3J_{HH}$ = 4.0 Hz, 2H, C(2)*H*); 4.70 (d, $^2J_{HH}$ = 11.9 Hz, 2H, CH_2Ph); 5.94 (d, $^3J_{HH}$ = 4.0 Hz, 2H, C(1)*H*); 6.31−6.36 (m, 2H, C_5H_4); 6.37−6.44 (m, 4H, C_5H_4); 6.44−6.49 (m, 2H, C_5H_4); 7.27−7.38 (m, 10H, *Ph*). ^{13}C NMR (75 MHz, $CDCl_3$): 26.32 (CMe_2); 30.17 ($CH_2C_5H_4$); 72.05 (CH_2Ph); 80.06 (*C*(4)); 82.24 (*C*(2)); 82.66 (*C*(3)); 105.09 (*C*(1)); 111.53 (CMe_2); 115.21, 118.63, 121.98, 123.33 (*CH*, C_5H_4); 127.92, 128.13, 128.72 (*CH*, *Ph*); 134.46 (C_{ipso}, C_5H_4); 137.53 (C_{ipso}, *Ph*). ESI-MS (*m*/*z*; ESI$^+$, relative abundance): 811 ([M + K]$^+$, 6); 795 ([M + Na]$^+$, 12); 737 ([M − Cl]$^+$, 100). IR (KBr, cm^{-1}): 3107 (vw), 3089 (vw), 3062 (vw), 3031 (w), 2985 (m), 2932 (m), 1689 (vw), 1581 (vw), 1497 (m), 1454 (m), 1374 (sh, s), 1350 (w), 1298 (vw), 1255 (m), 1214 (s), 1164 (s), 1076 (vs), 1027 (vs), 960 (w), 887 (m), 856 (s), 827 (m), 738 (s), 699 (s), 634 (w), 514 (vw). Anal. Calcd for $C_{40}H_{46}Cl_2O_8Ti$ (773.57): C, 62.10; 5.99 H, . Found: C, 62.23; H, 6.08.

Preparation of Titanocene Dichloride 9b. To a solid mixture of lithium cyclopentadienide **7b** (0.508 g, 1.52 mmol) and $TiCl_4(THF)_2$ (0.241 g, 0.72 mmol) cooled to −78 °C was added THF (15 mL). The mixture was warmed to room temperature and stirred for 12 h. Volatiles were evaporated under vacuum, and the solid residue was extracted with dichloromethane (14 mL). The resulting dark red-brown solution was evaporated to dryness, and the residue was redissolved in a minimal amount of dichloromethane (4 mL) and layered with heptane (14 mL). After the mixture was stored for several days in the refrigerator (4 °C), a red crystalline solid appeared (suitable crystals for X-ray analysis were chosen). The material was isolated, washed consecutively with a dichloromethane−heptane mixture and heptane, and dried under vacuum. The combined mother liquid and washings gave another crop of the product after several days in the freezer (−28 °C). Overall yield: 0.401 g (72%). Mp: 168 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 1.34, 1.56 (2 × s, 2 × 6H, CMe_2); 2.77 (dd, $^2J_{HH}$ = 15.0 Hz, $^3J_{HH}$ = 8.0 Hz, 2H, $CH_2C_5H_4$); 3.14 (dd, $^2J_{HH}$ = 15.0 Hz, $^3J_{HH}$ = 3.1 Hz, 2H, $CH_2C_5H_4$); 3.39 (dd, $^3J_{HH}$ = 8.9 Hz, $^3J_{HH}$ = 4.4 Hz, 2H, C(3)*H*); 4.15 (pseudo td, $^3J_{HH}$ = 8.9 Hz, $^3J_{HH}$ = 8.0 Hz, $^3J_{HH}$ = 3.1 Hz, 2H, C(4)*H*); 4.53 (d, $^2J_{HH}$ = 11.9 Hz, 2H, CH_2Ph); 4.53 (pseudo t, $^3J_{HH}$ = 4.4 Hz, $^3J_{HH}$ = 3.8 Hz, 2H, C(2)*H*); 4.78 (d, $^2J_{HH}$ = 11.9 Hz, 2H, CH_2Ph); 5.69 (d, $^3J_{HH}$ = 3.8 Hz, 2H, C(1)*H*); 6.19−6.23, 6.29−6.32 (2 × m, 2 × 2H, C_5H_4); 6.35−6.40 (m, 4H, C_5H_4); 7.31−7.40 (m, 5H, *Ph*). ^{13}C NMR (75 MHz, $CDCl_3$): 26.63, 26.86 (CMe_2); 33.47 ($CH_2C_5H_4$); 72.32 (CH_2Ph); 77.06 (*C*(2)); 77.88 (*C*(4)); 80.99 (*C*(3)); 104.07 (*C*(1)); 112.96 (CMe_2); 115.96, 116.20, 123.72, 124.03 (*CH*, C_5H_4); 128.30, 128.43, 128.72 (*CH*, *Ph*); 132.94 (C_{ipso}, C_5H_4); 137.50 (C_{ipso}, *Ph*). ESI-MS (*m*/*z*; ESI$^+$, relative abundance): 811 ([M + K]$^+$, 100); 795 ([M + Na]$^+$, 27); 737 ([M − Cl]$^+$, 17). ESI-MS (*m*/*z*; ESI$^-$, relative abundance): 809 ([M + Cl]$^-$, 100); 482 ([M + Cl − Cṕ]$^-$, 20). IR (KBr, cm^{-1}): 3116 (sh, w), 3089 (vw), 3065 (vw), 3027 (vw), 2988 (w), 2974 (w), 2957 (vw), 2924 (m), 2898 (w), 2865 (vw), 1627 (vw), 1608 (vw), 1498 (m), 1454 (m), 1432 (m), 1373 (sh, s), 1350 (w), 1307 (m), 1252 (m), 1209 (s), 1167 (s), 1141 (s), 1093 (vs), 1027 (vs), 997 (s), 943 (vw), 926 (vw), 907 (w),

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871 (s), 854 (s), 830 (m), 734 (s), 698 (m), 658 (vw), 611 (w), 547 (vw), 513 (w), 460 (vw), 433 (vw). Anal. Calcd. for $C_{40}H_{46}Cl_2O_8Ti$ (773.57): C, 62.10; 5.99 H, . Found: C, 62.15; H, 5.96.

Preparation of Titanocene Difluoride 10. A solution of **8b** (0.120 g, 0.24 mmol) and {2-(CH_2NMe_2)C_6H_4-$\kappa C,N$}(*n*-Bu)$_2$SnF (0.188 g, 0.48 mmol) in dichloromethane (10 mL) was stirred for 3 days, whereupon the mixture gradually changed color from red to orange and finally to yellow. All volatiles were removed under vacuum, and a sticky yellow residue was triturated five times with pentane (5 × 10 mL) in an ultrasonic bath for 10 min. The resulting yellow solid was dried under vacuum. Yield: 0.105 g (93%). Mp: 122−125 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 1.34, 1.56 (2 × s, 2 × 3H, CMe_2); 2.60 (dd, $^2J_{HH}$ = 15.3 Hz, $^3J_{HH}$ = 8.1 Hz, 1H, CH_2C$_5$H$_4$); 2.94 (dd, $^2J_{HH}$ = 15.3 Hz, $^3J_{HH}$ = 3.1 Hz, 1H, CH_2C$_5$H$_4$); 3.36 (dd, $^3J_{HH}$ = 8.9 Hz, $^3J_{HH}$ = 4.3 Hz, 1H, C(3)*H*); 4.15 (pseudo td, $^3J_{HH}$ = 8.9 Hz, $^3J_{HH}$ = 8.1 Hz, $^3J_{HH}$ = 3.1 Hz, 1H, C(4)*H*); 4.52 (d, $^2J_{HH}$ = 11.9 Hz, 1H, CH_2Ph); 4.52 (pseudo t, $^3J_{HH}$ = 4.3 Hz, $^3J_{HH}$ = 3.8 Hz, 1H, C(2)*H*); 4.76 (d, $^2J_{HH}$ = 11.9 Hz, 1H, CH_2Ph); 5.68 (d, $^3J_{HH}$ = 3.8 Hz, 1H, C(1)*H*); 5.98−6.02, 6.10−6.14 (2 × m, 2 × 1H, C$_5H_4$); 6.33−6.37 (m, 2H, C$_5H_4$); 6.40 (br s, 5H, C$_5H_5$); 7.32−7.39 (m, 5H, *Ph*). ^{13}C NMR (75 MHz, $CDCl_3$): 26.66, 26.86 (CMe_2); 31.82 (CH_2C$_5$H$_4$); 72.29 (CH_2Ph); 77.00 (*C*(2)); 77.78 (*C*(4)); 81.07 (*C*(3)); 104.11 (*C*(1)); 112.93 (CMe_2); 115.75, 116.60 (CH, C$_5$H$_4$); 118.53 (CH, C$_5$H$_5$); 118.64, 118.85, (CH, C$_5$H$_4$); 128.26, 128.38, 128.69 (CH, *Ph*); 137.40 (C_{ipso}, C$_5$H$_4$); 137.56 (C_{ipso}, *Ph*). ^{19}F NMR (282 MHz, $CDCl_3$): 64.10, 64.23 (2 × d, $^2J_{FF}$ = 23.6 Hz, 2 × 1F, TiF_2). ESI-MS (*m*/*z*; ESI$^+$, relative abundance): 517 ([M + K]$^+$, 100); 501 ([M + Na]$^+$, 51); 459 ([M − F]$^+$, 6). IR (KBr, cm^{-1}): 3109 (w), 3030 (vw), 2989 (w), 2886 (w), 1633 (vw), 1498 (w), 1454 (sh, w), 1373 (sh, w), 1349 (vw), 1302 (vw), 1252 (w), 1215 (m), 1167 (m), 1135 (m), 1091 (m), 1025 (m), 914 (vw), 872 (m), 816 (m), 750 (m), 701 (m), 655 (w), 610 (m), 581 (s), 567 (vs), 549 (vs), 513 (w), 457 (vw), 417 (m). Anal. Calcd for $C_{25}H_{28}F_2O_4Ti$ (478.37): C, 62.76; H, 5.90. Found: C, 62.91; H, 6.07.

Preparation of Titanocene Difluoride 11a. *Route 1*. A solution of **9a** (0.031 g, 40 μmol) and {2-(CH_2NMe_2)C_6H_4-$\kappa C,N$}(*n*-Bu)$_2$SnF (0.035 g, 90 μmol) in dichloromethane (4 mL) was stirred for 12 h at room temperature and then refluxed for 2 h. The ^{1}H NMR of the sample taken from the reaction mixture showed an accomplished reaction. Volatiles were removed under vacuum, and the residual yellow wax was triturated three times with hexane (3 × 5 mL) under sonification for 10 min and finally dried under vacuum. The yield of a yellow powder was 0.026 g (88%).

Route 2. A mixture of **7a** (0.285 g, 0.85 mmol) and [TiF_4(THF)$_2$] (0.109 g, 0.41 mmol) was cooled to −78 °C, and THF (15 mL) was added. The mixture was warmed to room temperature and stirred for an additional 15 h. After this time the ^{1}H NMR of the sample showed that the reaction proceeded to completion. Volatiles were removed under vacuum, and the residue was extracted with toluene (10 mL). The volume of the yellow-orange toluene solution was reduced to ca. 4 mL, and the product was precipitated with heptane (10 mL), washed with heptane (2 × 5 mL), and dried under vacuum. The yield of an ocher powder was 0.257 g (84%).

Mp: 125−130 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 1.30, 1.46 (2 × s, 2 × 6H, CMe_2); 2.84 (dd, $^2J_{HH}$ = 15.4 Hz, $^3J_{HH}$ = 5.1 Hz, 2H, CH_2C$_5$H$_4$); 2.96 (dd, $^2J_{HH}$ = 15.4 Hz, $^3J_{HH}$ = 8.6 Hz, 2H, CH_2C$_5$H$_4$); 3.79 (d, $^3J_{HH}$ = 3.1 Hz, 2H, C(3)*H*); 4.31 (ddd, $^3J_{HH}$ = 8.6 Hz, $^3J_{HH}$ = 5.1 Hz, $^3J_{HH}$ = 3.1 Hz, 2H, C(4)*H*); 4.48 (d, $^2J_{HH}$ = 11.9 Hz, 2H, CH_2Ph); 4.60 (d, $^3J_{HH}$ = 4.0 Hz, 2H, C(2)*H*); 4.67 (d, $^2J_{HH}$ = 11.9 Hz, 2H, CH_2Ph); 5.92 (d, $^3J_{HH}$ = 4.0 Hz, 2H, C(1)*H*); 6.06−6.10 (m, 2H, C$_5H_4$); 6.10−6.14 (m, 2H, C$_5H_4$); 6.30−6.36 (m, 4H, C$_5H_4$); 7.29−7.37 (m, 10H, *Ph*). ^{13}C NMR (75 MHz, $CDCl_3$): 26.34, 26.89 (CMe_2); 28.55 (CH_2C$_5$H$_4$); 71.94 (CH_2Ph); 79.73 (*C*(4)); 82.20 (*C*(2)); 82.65 (*C*(3)); 105.07 (*C*(1)); 111.47 (CMe_2); 114.84, 116.96, 117.32, 118.20 (CH, C$_5$H$_4$); 127.83, 128.08, 128.68 (CH, *Ph*); 137.61, 137.68 (2 × C_{ipso}, C$_5$H$_4$ and *Ph*). ^{19}F NMR (282 MHz, $CDCl_3$): 64.18 (s, 2F, TiF_2). ESI-MS (*m*/*z*; ESI$^+$, relative abundance): 779 ([M + K]$^+$, 100); 763 ([M + Na]$^+$, 41); 721 ([M − F]$^+$, 10). IR (KBr, cm^{-1}): 3113 (vw), 3090 (vw), 3063 (vw), 3031 (vw), 2986 (m), 2933 (m), 1497 (w), 1455 (m), 1382 (m), 1374 (m), 1350 (w), 1299 (vw), 1257 (m), 1215 (s), 1165 (s), 1076 (vs), 1028 (vs), 960 (vw), 888 (m), 857 (m), 832 (m), 739 (m), 699 (m), 582 (sh, m). Anal. Calcd for $C_{40}H_{46}F_2O_8Ti$ (740.67): C, 64.86; H, 6.26. Found: C, 65.03; H, 6.41.

Preparation of Titanocene Difluoride 11b. *Route 1*. A solution of **9b** (0.080 g, 103 μmol) and {2-(CH_2NMe_2)C_6H_4-$\kappa C,N$}(*n*-Bu)$_2$SnF (0.081 g, 210 μmol) in dichloromethane (15 mL) was stirred for 2 days. Volatiles were removed under vacuum, and the residual yellow wax was triturated five times with pentane (5 × 10 mL) under sonification and finally dried under vacuum. The yield of a yellow solid was 0.072 g (94%).

Route 2. A solution of **7b** (0.260 g, 0.78 mmol) in THF (15 mL) was gradually dropped into a cold (−78 °C) solution of [TiF_4(THF)$_2$] (0.094 g, 0.35 mmol) in THF (20 mL). The mixture was warmed to room temperature and stirred for an additional 12 h. Volatiles were removed under vacuum, and the residue was extracted with dichloromethane (in total 18 mL). Evaporation of the solvent gave **11b** as a yellow-brown solid. Yield: 0.176 g (68%).

Mp: 153 °C. ^{1}H NMR (300 MHz, $CDCl_3$): 1.33, 1.55 (2 × s, 2 × 6H, CMe_2); 2.59 (dd, $^2J_{HH}$ = 15.3 Hz, $^3J_{HH}$ = 8.4 Hz, 2H, CH_2C$_5$H$_4$); 2.93 (dd, $^2J_{HH}$ = 15.3 Hz, $^3J_{HH}$ = 3.0 Hz, 2H, CH_2C$_5$H$_4$); 3.34 (dd, $^3J_{HH}$ = 8.7 Hz, $^3J_{HH}$ = 4.5 Hz, 2H, C(3)*H*); 4.14 (pseudo td, $^3J_{HH}$ = 8.7 Hz, $^3J_{HH}$ = 8.4 Hz, $^3J_{HH}$ = 3.0 Hz, 2H, C(4)*H*); 4.49 (pseudo t, $^3J_{HH}$ = 4.5 Hz, $^3J_{HH}$ = 3.6 Hz, 2H, C(2)*H*); 4.50 (d, $^2J_{HH}$ = 12.0 Hz, 2H, CH_2Ph); 4.74 (d, $^2J_{HH}$ = 12.0 Hz, 2H, CH_2Ph); 5.67 (d, $^3J_{HH}$ = 3.6 Hz, 2H, C(1)*H*); 5.94−5.99, 6.05−6.10 (2 × m, 2 × 2H, C$_5H_4$); 6.26−6.34 (m, 4H, C$_5H_4$); 7.20−7.40 (m, 10H, *Ph*). ^{13}C NMR (75 MHz, $CDCl_3$): 26.66, 26.85 (CMe_2); 31.80 (CH_2C$_5$H$_4$); 72.26 (CH_2Ph); 77.03 (*C*(2)); 77.48 (*C*(4)); 81.07 (*C*(3)); 104.08 (*C*(1)); 112.87 (CMe_2); 115.24, 116.14, 118.39, 118.44 (CH, C$_5$H$_4$); 128.22, 128.35, 128.66 (CH, *Ph*); 136.68 (C_{ipso}, C$_5$H$_4$); 137.58 (C_{ipso}, *Ph*). ^{19}F NMR (282 MHz, $CDCl_3$): 63.57 (s, 2F, TiF_2). ESI-MS (*m*/*z*; ESI$^+$, relative abundance): 779 ([M + K]$^+$, 100); 763 ([M + Na]$^+$, 68); 721 ([M − F]$^+$, 5). IR (KBr, cm^{-1}): 3089 (vw), 3064 (vw), 3031(vw), 2986 (m), 2934 (m), 1497 (w), 1455 (m), 1435 (vw), 1373 (sh, m), 1350 (vw), 1306 (w), 1249 (m), 1215 (s), 1168 (s), 1136 (s), 1092 (sh, s), 1023 (vs), 872 (m), 831 (m), 741 (m), 700 (m), 655 (vw), 609 (w), 581 (m), 559 (m), 513 (vw), 418 (w). Anal. Calcd for $C_{40}H_{46}F_2O_8Ti$ (740.67): C, 64.86; H, 6.26. Found: C, 65.09; H, 6.39.

Preparation of Ferrocene 12a. Solid $FeCl_2$ (0.127 g, 1.00 mmol) was added to a solution of lithium cyclopentadienide **7a** (0.701 g, 2.10 mmol) in THF (100 mL). The mixture was stirred for 20 h and then refluxed for 5 h. After the mixture was cooled to room temperature, volatiles were evaporated under vacuum. The orange-brown oily residue was purified by column chromatography on silica gel using a hexane/ethyl acetate mixture (from 10/1 to 10/4, v/v) to obtain the desired compound as a yellow-orange oil. Yield 0.480 g (68%). R_f = 0.2 (hexane/ethyl acetate, 10/1). ^{1}H NMR (300 MHz, $CDCl_3$): 1.30, 1.47 (2 × s, 2 × 6H, CMe_2); 2.75 (dd, $^2J_{HH}$ = 14.1 Hz, $^3J_{HH}$ = 6.3 Hz, 2H, CH_2C$_5$H$_4$); 2.80 (dd, $^2J_{HH}$ = 14.1 Hz, $^3J_{HH}$ = 7.8 Hz, 2H, CH_2C$_5$H$_4$); 3.74 (d, $^3J_{HH}$ = 3.3 Hz, 2H, C(3)*H*); 3.93−3.95, 3.95−3.98, 3.98−4.02, 4.04−4.07 (4 × m, 4 × 2H, C$_5H_4$); 4.16−4.23 (m, 2H, C(4)*H*); 4.50 (d, $^2J_{HH}$ = 11.9 Hz, 2H, CH_2Ph); 4.59 (d, $^3J_{HH}$ = 3.9 Hz, 2H, C(2)*H*); 4.68 (d, $^2J_{HH}$ = 11.9 Hz, 2H, CH_2Ph); 5.92 (d, $^3J_{HH}$ = 3.9 Hz, 2H, C(1)*H*); 7.28−7.42 (m, 10H, *Ph*). ^{13}C NMR (75 MHz, $CDCl_3$): 26.24, 26.76 (CMe_2); 28.02 (CH_2C$_5$H$_4$); 68.46, 68.54, 69.57, 69.76 (CH, C$_5$H$_4$); 71.64 (CH_2Ph); 81.53 (*C*(4)); 81.92 (*C*(2)); 82.00 (*C*(3)); 84.41 (C_{ipso}, C$_5$H$_4$); 104.87 (*C*(1)); 111.29 (CMe_2); 127.65, 127.95, 128.61 (CH, *Ph*); 137.74 (C_{ipso}, *Ph*). ESI-MS (*m*/*z*; ESI$^+$): 733 ([M + Na]$^+$); 710 ([M]$^+$). IR (KBr, cm^{-1}): 3088 (w), 3066 (vw), 3031 (w), 2987 (m), 2958 (m), 2932 (s), 2884 (w), 1735 (m), 1497 (m), 1454 (s), 1440 (w), 1382 (s), 1374 (s), 1349 (m), 1332 (w), 1311 (vw), 1298 (w), 1245 (s), 1214 (s), 1165 (s), 1070 (vs), 1020 (vs), 959 (m), 924 (m), 887 (s), 860 (s), 827 (m), 809 (m), 737 (s), 697 (s), 636 (vw), 603 (vw), 504 (sh, m). Anal. Calcd for $C_{40}H_{46}O_8Fe$ (710.62): C, 67.60; H, 6.53. Found: C, 67.43; H, 6.45.

Preparation of Ferrocene 12b. To a mixture of $FeCl_2$ (30 mg, 237 μmol) and lithium cyclopentadienide **7b** (171 mg, 512 μmol) was added THF (8 mL), and the mixture was stirred overnight. Volatiles were removed under vacuum, and the residue was chromatographed on silica gel using hexane/ethyl acetate (5/1, v/v). The title compound was obtained as an orange wax. Yield: 0.118 g (64%). R_f

= 0.2 (hexane/ethyl acetate, 5/1). ^{1}H NMR (300 MHz, $CDCl_3$): 1.33, 1.58 (2 × s, 2 × 6H, CMe_2); 2.46 (dd, $^2J_{HH}$ = 15.0 Hz, $^3J_{HH}$ = 6.3 Hz, 2H, $CH_2C_5H_4$); 2.77 (dd, $^2J_{HH}$ = 15.0 Hz, $^3J_{HH}$ = 3.3 Hz, 2H, $CH_2C_5H_4$); 3.34 (dd, $^3J_{HH}$ = 9.0 Hz, $^3J_{HH}$ = 4.3 Hz, 2H, C(3)*H*); 3.80−3.84, 3.91−3.95, 3.95−3.98, 4.06−4.10 (4 × m, 4 × 2H, C_5H_4); 4.14 (ddd, $^3J_{HH}$ = 9.0 Hz, $^3J_{HH}$ = 6.3 Hz, $^3J_{HH}$ = 3.3 Hz, 2H, C(4)*H*); 4.45 (d, $^3J_{HH}$ = 3.9 Hz, 2H, C(2)*H*); 4.50 (d, $^2J_{HH}$ = 12.0 Hz, 2H, CH_2Ph); 4.76 (d, $^2J_{HH}$ = 11.9 Hz, 2H, CH_2Ph); 5.64 (d, $^3J_{HH}$ = 3.9 Hz, 2H, C(1)*H*); 7.28−7.42 (m, 10H, *Ph*). ^{13}C NMR (75 MHz, $CDCl_3$): 26.72, 26.92 (CMe_2); 31.53 ($CH_2C_5H_4$); 68.34, 68.62, 70.27, 70.44 (*C*H, C_5H_4); 72.21 (CH_2Ph); 77.14 (*C*(2)); 78.21 (*C*(4)); 80.37 (*C*(3)); 83.67 (C_{ipso}, C_5H_4); 104.02 (*C*(1)); 112.76 (CMe_2); 128.13, 128.29, 128.59 (*C*H, *Ph*); 137.85 (C_{ipso}, *Ph*). ESI-MS (*m*/*z*; ESI$^+$): 710 (M^+). IR (KBr, cm^{-1}): 3085 (vw), 3064 (vw), 3028 (vw), 2986 (m), 2933 (m), 2889 (w), 1634 (vw), 1496 (w), 1454 (m), 1427 (vw), 1382 (m), 1371 (s), 1350 (w), 1304 (m), 1248 (m), 1215 (s), 1167 (s), 1133 (s), 1103 (s), 1095 (s), 1026 (vs), 911 (w), 888 (w), 871 (m), 812 (w), 740 (m), 699 (m), 644 (vw), 611 (vw), 546 (vw), 523 (w), 498 (w), 451 (vw). Anal. Calcd for $C_{40}H_{46}O_8Fe$ (710.62): C, 67.60; H, 6.53. Found: C, 67.74; H, 6.59.

Preparation of Ferrocene Alcohol 13. A catalytic amount of Pd/C (10 wt % Pd, 0.045 g) was added to a solution of **12a** (0.250 g, 0.35 mmol) in methanol (5 mL). Neat Et_3SiH (3.5 mL, 22.0 mmol) was dropped into the mixture, which caused an immediate hydrogen evolution. The formed hydrogen overpressure was compensated by attaching a latex balloon to the reaction flask. The mixture was stirred for 5 h and then monitored with TLC. As the TLC analysis still showed the presence of the starting ferrocene **12a**, an additional portion of Et_3SiH (1.0 mL, 6.3 mmol) was added and the mixture was stirred for a further 12 h. The mixture was filtered and the residue washed with MeOH (5 mL). Combined methanol fractions were evaporated to dryness, and the resulting orange-brown wax was purified by column chromatography on silica gel (eluted with pure chloroform followed by a chloroform/methanol mixture 10/1, v/v). The ^{1}H NMR showed **13** as the major product in addition to a small amount of **14a**. Further purification by column chromatography using a hexane/ethyl acetate mixture (2/1, v/v) gave pure **13** as a brown wax. Yield: 0.170 g (78%). Moreover, pure **14a** (0.015 g, 8% yield) was obtained by further column elution. R_f = 0.2 (hexane/ethyl acetate, 2/1). ^{1}H NMR (500 MHz, DMSO-d_6): 1.21, 1.24, 1.34, 1.37 (4 × s, 4 × 3H, CMe_2); 2.45−2.52 obscured by solvent signal (m, 1H, $CH_2C_5H_4$); 2.55−2.71 (m, 3H, $CH_2C_5H_4$); 3.71 (d, $^3J_{HH}$ = 2.9 Hz, 1H, C(3′)*H*); 3.79 (dd, $^3J_{HH}$ = 5.1 Hz, $^3J_{HH}$ = 2.6 Hz, 2H, C(3)*H*); 3.96−4.02 (m, 6H, C_5H_4 and C(4)*H*); 4.03−4.05 (m, 1H, C_5H_4); 4.05−4.12 (m, 3H, C_5H_4 and C(4′)*H*); 4.38 (d, $^3J_{HH}$ = 3.8 Hz, 1H, C(2)*H*); 4.48, 4.71 (2 × d, 2 × $^2J_{HH}$ = 11.7 Hz, 2 × 1H; CH_2Ph); 4.72 (d, $^3J_{HH}$ = 3.8 Hz, 1H, C(2′)*H*); 5.21 (d, $^3J_{HH}$ = 5.1 Hz, 1H, O*H*); 5.79 (d, $^3J_{HH}$ = 3.8 Hz, 1H, C(1)*H*); 5.83 (d, $^3J_{HH}$ = 3.8 Hz, 1H, C(1′)*H*); 7.30−7.35 (m, 1H, *Ph*); 7.36−7.43 (m, 4H, *Ph*). ^{13}C NMR (125 MHz, DMSO-d_6): 25.97, 26.00, 26.47, 26.56 (CMe_2); 27.51 ($CH_2C_5H_4$); 67.72, 67.75, 67.79, 67.81, 68.94, 69.15, 69.46, 69.47 (CH, C_5H_4); 70.63 (CH_2Ph); 73.76 (*C*(3)); 80.83 (*C*(4′)); 81.11 (*C*(2′); 81.38 (*C*(4)); 81.60 (*C*(3′)); 84.55 (C_{ipso}, C_5H_4); 84.98 (*C*(2)); 85.01 (C_{ipso}, C_5H_4); 104.02 (*C*(1)); 104.16 (*C*(1′)); 110.05, 110.25 (CMe_2); 127.61, 127.63, 128.32 (*C*H, *Ph*); 137.92 (C_{ipso}, *Ph*). ESI-MS (*m*/*z*; ESI$^+$): 643 ([M + Na]$^+$); 620 ([M]$^+$). IR (KBr, cm^{-1}): 3467 (w), 3088 (vw), 3031 (vw), 2987 (s), 2958 (m), 2933 (s), 2888 (w), 1735 (w), 1497 (vw), 1455 (m), 1441 (vw), 1374 (sh, s), 1350 (vw), 1332 (w), 1296 (w), 1254 (s), 1216 (s), 1165 (s), 1070 (vs), 1024 (vs), 957 (m), 926 (w), 886 (s), 861 (s), 826 (sh, m), 739 (m), 698 (m), 668 (vw), 635 (w), 604 (vw), 527 (vw), 504 (sh, m), 444 (vw). Anal. Calcd. for $C_{33}H_{40}O_8Fe$ (620.50): C, 63.87; H, 6.50. Found: C, 64.15; H, 6.77.

Preparation of Ferrocene Diol 14a. *Route 1.* A catalytic amount of Pd/C (10 wt % Pd, 0.015 g) was added to a solution of **12a** (0.070 g, 0.99 mmol) in methanol (4 mL). Neat Et_3SiH (1.0 mL, 6.3 mmol) was dropped into the mixture, which caused an immediate hydrogen evolution. The formed hydrogen overpressure was compensated by attaching a latex balloon to the reaction flask. The mixture was stirred for 1 h, while TLC analysis showed complete consumption of the starting material. The mixture was filtered, the solid residue was washed with methanol (5 mL), and volatiles were removed from the collected methanol fractions. The solid residue was purified by column chromatography on a silica gel with a chloroform/methanol mixture (10/1, v/v) as an eluent. The crystallization of the obtained solid from methanol gave **14a** as a yellow crystalline solid. Yield: 0.045 g (86%).

Route 2. To a solution of **12a** (0.060 g, 0.085 mmol) in THF (4 mL) was added a catalytic amount of Pd/C (10 wt % Pd, 0.015 g). The reaction flask was attached to a latex balloon filled with hydrogen gas, and the hydrogen was continuously refilled until the reaction proceeded to completion (ca. 40 h) as detected by TLC. The following workup was identical with that in the above experiment and afforded 0.037 g (82%) of **14a**.

R_f = 0.6 (chloroform/methanol, 10/1). Mp: 200 °C. ^{1}H NMR (300 MHz, DMSO-d_6): 1.21, 1.34 (2 × s, 2 × 6H, CMe_2); 2.49 partially obscured by solvent signal (dd, $^2J_{HH}$ = 14.2 Hz, $^3J_{HH}$ = 7.1 Hz, 2H, $CH_2C_5H_4$); 2.62 (dd, $^2J_{HH}$ = 14.2 Hz, $^3J_{HH}$ = 6.6 Hz, 2H, $CH_2C_5H_4$); 3.78 (dd, $^3J_{HH}$ = 5.1 Hz, $^3J_{HH}$ = 2.7 Hz, 2H, C(3)*H*); 3.97 partially overlapped (pseudo td, $^3J_{HH}$ = 7.1 Hz, $^3J_{HH}$ = 6.6 Hz, $^3J_{HH}$ = 2.7 Hz, 2H, C(4)*H*); 3.99−4.02 (m, 4H, C_5H_4); 4.03−4.06 (m, 2H, C_5H_4); 4.09−4.12 (m, 2H, C_5H_4); 4.37 (d, $^3J_{HH}$ = 3.8 Hz, 2H, C(2)*H*); 5.23 (d, $^3J_{HH}$ = 5.1 Hz, 2H, O*H*); 5.78 (d, $^3J_{HH}$ = 3.8 Hz, 2H, C(1)*H*). ^{13}C NMR (75 MHz, DMSO-d_6): 26.03, 26.60 (CMe_2); 27.59 ($CH_2C_5H_4$); 67.74, 67.77, 69.17, 69.54 (*C*H, C_5H_4); 73.78 (*C*(3)); 81.44 (*C*(4)); 84.97 (C_{ipso}, C_5H_4); 85.00 (*C*(2)); 104.04 (*C*(1)); 110.09 (CMe_2). ESI-MS, (*m*/*z*; ESI$^+$): 553 ([M + Na]$^+$); 530 ([M]$^+$). ESI-MS (*m*/*z*; ESI$^-$): 529 ([M − H]$^-$). IR (KBr, cm^{-1}): 3457 (br w), 3103 (vw), 3090 (vw), 2992 (m), 2980 (m), 2965 (w), 2934 (m), 2888 (w), 2565 (br m), 1453 (vw),1442 (vw), 1385 (m), 1376 (s), 1332 (vw), 1291 (vw), 1251 (m), 1216 (s), 1164 (s), 1074 (vs), 1018 (vs), 955 (m), 927 (m), 884 (m), 859 (m), 823 (m), 751 (w), 634 (vw), 529 (vw), 509 (m), 499 (m). Anal. Calcd for $C_{26}H_{34}O_8Fe$ (530.38): C, 58.87; H, 6.46. Found: C, 58.82; H, 6.49.

Preparation of Ferrocene Diol 14b. The procedure described above for **14a** (Route 2) was used. Thus, **12b** (0.139 g, 0.195 mmol) was catalytically (0.030 g Pd/C) hydrogenated within 44 h to give **14b** as a yellow solid. Yield: 0.074 g (70%). R_f = 0.7 (chloroform/methanol, 10/1). Mp: 175 °C. ^{1}H NMR (300 MHz, DMSO-d_6): 1.25, 1.43 (2 × s, 2 × 6H, CMe_2); 2.33 (dd, $^2J_{HH}$ = 15.0 Hz, $^3J_{HH}$ = 8.4 Hz, 2H, $CH_2C_5H_4$); 2.72 (dd, $^2J_{HH}$ = 15.0 Hz, $^3J_{HH}$ = 2.1 Hz, 2H, $CH_2C_5H_4$); 3.38−3.49 (m, 2H, C(3)*H*); 3.79 (pseudo td, $^3J_{HH}$ = 8.4 Hz, $^3J_{HH}$ = 8.7 Hz, $^3J_{HH}$ = 2.1 Hz, 2H, C(4)*H*); 4.00 (br s, 4H, C_5H_4); 4.04 (br s, 2H, C_5H_4); 4.06 (br s, 2H, C_5H_4); 4.41 (pseudo t, $^3J_{HH}$ = 3.9 Hz, $^3J_{HH}$ = 4.2 Hz, 2H, C(2)*H*); 5.10 (d, $^3J_{HH}$ = 6.9 Hz, 2H, O*H*); 5.62 (d, $^3J_{HH}$ = 3.9 Hz, 2H, C(1)*H*). ^{13}C NMR (75 MHz, DMSO-d_6): 26.34, 26.51 (CMe_2); 31.33 ($CH_2C_5H_4$); 67.73, 67.81, 69.05, 69.93 (*C*H, C_5H_4); 74.45 (*C*(3)); 78.71 (*C*(2)); 79.28 (*C*(4)); 85.02 (C_{ipso}, C_5H_4); 103.12 (*C*(1)); 110.99 (CMe_2). ESI-MS (*m*/*z*; ESI$^+$): 562 ([M − H + Na]$^+$); 530 ($M^{+\cdot}$). IR (KBr, cm^{-1}): 3459 (s), 3106 (vw), 3095 (vw), 3086 (vw), 2991 (m), 2937 (m), 2888 (w), 1733 (vw), 1454 (w), 1395 (m), 1388 (m), 1376 (m), 1318 (w), 1254 (m), 1216 (s), 1167 (m), 1121 (vs), 1099 (m), 1062 (vs), 1016 (vs), 926 (vw), 871 (s), 813 (w), 758 (vw), 689 (vw), 641 (vw), 620 (w), 585 (vw), 553 (vw), 505 (w), 494 (w), 450 (vw). Anal. Calcd for $C_{26}H_{34}O_8Fe$ (530.38): C, 58.87; H, 6.46. Found: C, 59.01; H, 6.55.

X-ray Crystallography. Single-crystal X-ray diffraction data for **9b** were obtained using a Nonius KappaCCD difractometer equipped with a Bruker ApexII detector by monochromatized Mo Kα radiation (λ = 0.71073 Å) at 150(2) K. The structure was solved by direct methods (SHELXS)[85] and refined by full-matrix least squares based on F^2 (SHELXL97).[86] The hydrogen atoms were fixed into idealized positions (riding model) and assigned temperature factors either $H_{iso}(H)$ = 1.2[U_{eq}(pivot atom)] or 1.5U_{eq} for the methyl moiety. The determination of the absolute configuration was based on an anomalous dispersion of heavy atoms. The graphic depiction of the molecular structure was created using the PLATON program.[87]

Crystal data for ***9b****:* $C_{40}H_{46}Cl_2O_8Ti$, M = 773.57, orthorhombic, $P2_12_12$ (No. 18), a = 10.5322(11) Å, b = 27.861(2) Å, c = 6.5319(6) Å, V = 1916.7(3) Å^3, Z = 2, D_x = 1.340 g mL^{-1}, dark red crystal of dimensions 0.38 × 0.33 × 0.32 mm, multiscan absorption correction (μ = 0.41 mm^{-1}), T_{min} = 0.859, T_{max} = 0.878. A total of 29069

reflections were measured (θ_{max}= 27.5°), 4401 of which were unique (R_{int} = 0.033) and 4181 were observed according to the $I > 2\sigma(I)$ criterion. The refinement converged (Δ/σ_{max}< 0.002) to R = 0.029 for observed reflections and $R_w(F^2)$ = 0.073; GOF = 1.06 for 233 parameters and all 4401 reflections. The final difference map displayed no peaks of chemical significance ($\Delta\rho_{max}$ = 0.32 e Å^{-3}, $\Delta\rho_{min}$ −0.19 e Å^{-3}). The chirality parameter was −0.01(2). Crystallographic data (excluding structure factors) for the structure of **9b** have been deposited with the Cambridge Crystallographic Data Centre with CCDC number 961600. Copies of the data can be obtained, free of charge, on application to the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax, +44-(0)1223-336033; e-mail, deposit@ccdc.cam.ac.uk).

MTT Cytotoxicity Tests. *Reagents.* All tested compounds were prepared as 65 mM stock solutions in DMSO and stored at −20 °C. Cisplatin (*cis*-diamminedichloroplatinum(II)) was obtained from Ebewe Pharma GmbH, Unterach, Austria.

Cell Line and Culture Condition. The A2780 and A2780cis ovarian carcinoma cell lines were obtained from the American Type Culture Collection (ATCC) and grown in RPMI 1640 medium supplemented with 10% heat-inactivated fetal bovine serum (BIOCHROM AG; Berlin, Germany), 100 U/mL of penicillin, and 0.1 mg/mL of streptomycin (Hyclone Laboratories, Logan, UT, USA) and L-glutamine 2 mM (Gibco) in a humidified incubator at 37 °C under a 5% CO_2 atmosphere and subcultured twice a week.

MTT Assay. Cells were seeded in 96-well plates at a density of 10000 cells per well and incubated overnight. Subsequently cells were treated with the respective titanocene and ferrocene derivatives for 24 and 72 h. Then 20 μL per well of MTT (thiazolyl blue tetrazolium bromide, 2.5 mg/mL; Sigma-Aldrich Co., St. Louis, MO, USA) was added and incubated for 3 h under culture conditions. After 3 h the medium was removed, the formazan product was dissolved in 50 μL of DMSO (SERVA Electrophoresis GmbH, Heidelberg, Germany), and optical densities were measured at 595 nm using a microplate spectrophotometer reader (Tecan GENios, TECAN Austria GmbH). Absorbance values were used to count IC_{50} values of each tested compound in GraphPad Prism 5 software.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Text, figures, tables, and a CIF file giving details for the preparation of ligand precursors and their characterization, ^{1}H NMR spectra of the described metallocene compounds **8a**−**14b**, tables of characteristic ^{1}H chemical shifts for compounds **8a**−**14b** and tables of characteristic ^{13}C chemical shifts for compounds **8a**−**11b**, numbering of atoms in compound **13**, crystallographic data for the structure of **9b**, selected structural parameters for **9b**, a view of the crystal packing in **9b**, IR spectra of compounds **13**−**14b**, and dose−response curves for compounds having IC_{50} values below 100 μM against A2780 and A2780cis cell lines. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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