DOI: 10.1002/ejoc.200((will be filled in by the editorial staff))

Cuprate addition to a 6-substituted pentafulvene: preparation of *sec*-alkyl substituted titanocene dichlorides and their biological activity

Melchior Cini,[a,b] Tracey D. Bradshaw,*[b] William Lewis[a] and Simon Woodward*[a]

Dedicated to the memory of Prof. Noel Zarb Adami

Keywords: Alkylation / Antitumor agents / Titanium / Fulvene / Grignard

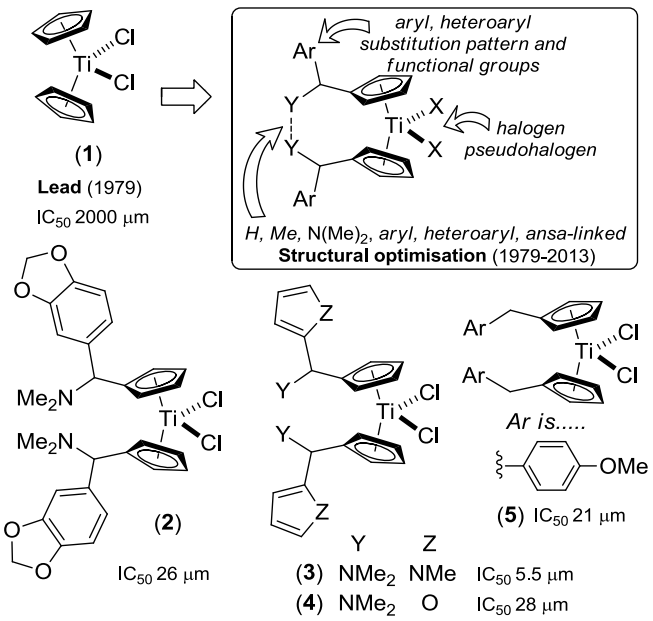
Copper-catalysed (10 mol-% CuBr•SMe_2, CuCN-LiCl, or CuI/PPh_3) addition of RMgBr to the pentafulvene 1-(cyclopenta-2,4-dien-1-ylidenemethyl)-2-methoxy-benzene allows the formation of cyclopentadienyl derivatives with α–CHR(2-MeOPh) sidechains (R = Me, Et, *n*Bu, *i*Bu, allyl, Ph) without H^- transfer. Deprotonation of these *sec*-alkyl substituted cyclopentadienyls followed by $TiCl_4$ addition allow the isolation of $TiCl_2$(η-C_5H_4CHR(2-OMePh)) as *rac*:*meso* mixtures that show (GI_{50} 2.3 – 42.4 μm) activity against human colon, breast and pancreatic cell lines.

[a] School of Chemistry, the University of Nottingham, University Park, Nottingham NG7 2RD, UK
Fax: +44-(0)115-9513564
E-mail: simon.woodward@nottingham.ac.uk
Homepage: www.nottingham.ac.uk/~pczsw/SWGroup
[b] School of Pharmacy, Centre for Biomolecular Sciences, the University of Nottingham, University Park, Nottingham NG7 2RD, UK
Fax: +44-(0)115- 9513412
E-mail: tracey.bradshaw@nottingham.ac.uk
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.xxxxxxxxx.

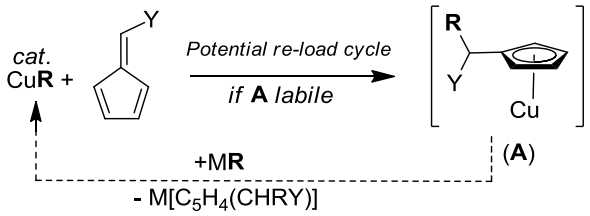
Introduction

Since the initial disclosure of its moderate cytoxicity to Ehrlich ascites tumour cells,[1] the complex Cp_2TiCl_2 (Cp = η-C_5H_5) (**1**) and its derivatives have attracted considerable attention, in part, due to their potential against tumour types resistant to existing treatments (especially cisplatin). As the biological activity of **1** has proved too low for clinical use,[2] numerous studies have targeted the structural modifications summarised in Scheme 1 in a quest for compounds with greater potency (lower IC_{50} or GI_{50} values).[3] These modifications, reported by Tacke and others, have resulted in the identification of the compounds **2**-**4** and **5** (so called 'Titanocene-Y') as the current 'optimal' structures - delivering IC_{50} values in the range 5.5-28 μm against an identical pig kidney tumour LLC-PK cell line (thus allowing direct comparison). The secondary centres in **2**-**3** and the proximal oxygen of **4** suggested to us that species containing (η-C_5H_4CHR(2-MeOPh)) units might be good candidates for therapeutic screening. However, these are notably absent in the current titanocene dichloride compound library. A closer look at the literature reveals that additions of RLi or RMgX to 6-substituted pentafulvenes (the normal optimal route) suffer badly from competing hydride transfer (unless R = Me or Ar).[3] This synthetic deficiency has left the –CHAlkylAr motif rather underrepresented in substituted cyclopentadienyl chemistry, where aside from any biological use, wide ranges of additional applications in organic synthesis and catalysis have also been identified.[4]

Based on our experiences,[5] we speculated that hydride transfer would be avoided if a 'Michael-like' organocopper addition giving **A** was employed (Scheme 2). Cyclopentadienyl groups are widely regarded as 'non transferable' from transition metals, but $CpCu^I$ complexes are some of the most labile known.[6] We reasoned that with a suitable nucleophilic terminal organometallic it should prove possible to close the catalytic cycle of Scheme 2.



Scheme 1. Lead and titanocene structural optimisation. Biological activities against identical pig kidney cancer LLC-PK cells; for which cisplatin gives an IC_{50} value of 3.3 μm. In this paper GI_{50} values are used – the concentration which inhibits cell proliferation by 50%.



Scheme 2. Proposed use of fulvenes substrates in copper-catalysed addition of terminal organometallics.

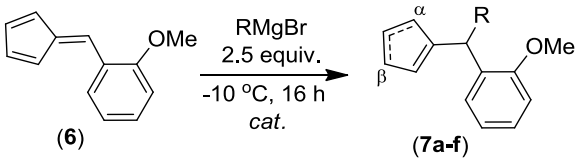
Thus, our targets became: (i) defining the new catalysis of Scheme 2; and (ii) carrying out screening for the derived titanocenes in human carcinoma cell lines.

Results and Discussion

Synthesis

1-(Cyclopenta-2,4-dien-1-ylidenemethyl)2-methoxybenzene (**6**) was selected for our trials and prepared by literature procedures from cyclopentadiene and 2-MeO(C_6H_4)CHO.[7] Initial addition of **6** to a 5-fold excess of a stoichiometric cuprate prepared from CuI/LiBr/EtMgBr in THF at -10 °C showed the ethyl addition product **7a** in modest yield (43%) after 16 h at -10 °C; but with no detectable hydride transfer by-products. In particular, two overlapping multiplets at δ_H 1.81-2.08 confirmed the presence of diastereotopic methylene groups from the ethyl addition. Additionally, two broadened signals at δ_H 2.85 and 3.00 in a 0.8 H:1.2 H ratio indicated the presence of two [1,5] hydrogen shift tautomers where the CH_2 is either α or β to the *ipso*-cyclopentadienyl carbon. Through 2D (COSY, HMQC and HMBC) near full assignment of the two sets of tautomeric signals could be made, however, they could not be independently distinguished. Next attention was focussed on attaining a viable catalytic system. Base reaction conditions of -10 °C and 16 h with 2.5 equivalents of RMgBr were selected and the other reaction components varied (Table 1).

Table 1. Development of catalytic procedure for RMgBr additions to fulvene (**6**).[a]



(**6**) (**7a-f**)

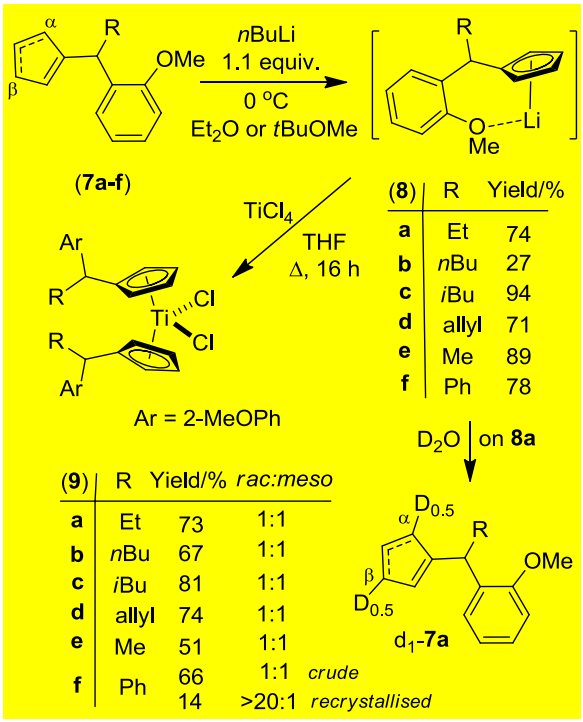
Run	Cu^I (mol-%)	Additive (mol-%)	R	Solvent	Yield/%
1	CuCN	LiCl	Et	THF	88
	(10)	(10)	(**7a**)		
2	CuBr•SMe_2	-	Et	THF	85
	(10)		(**7a**)		
3	CuBr•SMe_2	-	*n*Bu[b]	THF	87
	(10)		(**7b**)		
4	CuBr•SMe_2	-	*i*Bu	THF	92
	(10)		(**7c**)		
5	CuBr•SMe_2	-	allyl	THF	91
	(10)		(**7d**)		
6	CuBr•SMe_2	-	Me	THF	27[c]
	(10)		(**7e**)		
7	CuBr•SMe_2	-	Ph	THF	24[c]
	(10)		(**7f**)		
8	CuI	PPh_3	Me	*t*BuOMe	91[d]
	(8)	(10)	(**7e**)		
9	CuI	PPh_3	Ph	*t*BuOMe	66
	(8)	(10)	(**7f**)		

[a] Carried out from **6** on a 1-10 mmol scale, isolated yields except were noted. [b] *n*BuMgCl used. [c] Conversion of **6**. [d] Isolated yield from 77% conversion (10 mmol scale).

As copper(I) cynanide is known to result in highly reactive cuprates[8] it was selected for an initial trial and provided a high yield of **7a** at 10 mol-% (run 1). Either no reactions at all with EtMgBr (or slow and unclean transformations under other promotions) were observed in the absence of Cu^I under the conditions tried. Due to practical considerations (cyanide waste and the need to dry LiCl) we sought an alternative to CuCN and were delighted to find that, for a range of Grignards (runs 2-5), essentially quantitative conversion of **6** (>95%) could be attained and high yields of the cyclopentadiene products **7** isolated using simple commercial CuBr•SMe_2. These runs could be conducted on at least 2 g scale without diminuation of yields. One limitation of the CuBr•SMe_2 catalyst system was that it would not provide the methyl and phenyl derivatives (**7e-f**) in good yield – only partial conversions were attained (runs 6-7). These deficiencies could be overcome through the use of *t*BuOMe (MTBE) and PPh_3 (runs 8-9). Presumably the lower coordination ability of MTBE leads to a more Lewis acidic cuprate that can overcome slower transmetallation rates from these Grignard reagents from 'CpCu^I' (**A**) Scheme 2. Some support is given to this idea by the observation that MeMgBr (Mg-C 60 kcal mol^{-1})[9] is the slowest reacting system and the only one that does not give complete conversion (*ca.* 80±5% depending on the reaction scale). We were interested to probe if the crucial phosphine in these systems is able to deliver ligand accelerated catalysis – and thus, potentially an asymmetric synthesis. Screening of a small library of chiral phosphines provided no evidence of any induced stereoselectivity in the addition of EtMgBr to **6** under any of the conditions we tried. We conclude that while the added PPh_3 in runs 8-9 plays a cuprate stabilising role it is not critically involved in the addition transition state. All of the isolated cyclopentadiene products (**7**) are colourless oils and show the expected spectroscopic properties. All are isolated as close to a 1:1 mixture of α:β [1,5] hydrogen shift tautomers.

With an efficient route to **7** in hand attention was focused on the preparation of the derived titanocenes. Rapid quantatitive deprotonation of **7a** by *n*BuLi (1.1 equiv.) in THF, Et_2O or MTBE at 0 °C was confirmed by D_2O quench leading to d_1-**7a** as an α/β isomer mix (Scheme 2). Direct use of these reaction mixtures with either $TiCl_4$ or $TiCl_4(THF)_2$ led only to intractable mixtures. As has been found before[3] filtration and drying of the intermediate organolithium species **8** is required in order to attain chemoselective preparation of the titanocene dichlorides (**9**). Presently the nature of the impurity(ies) in the crude deprotonation mixture that causes these issues is unknown. The lower yield of **8b** is caused by its higher solubility in hydrocarbons containing trace *t*-BuOMe. Recrystallisation of the crude titanocene reaction mixtures containing **9** allowed the isolation of analytically pure red-orange/brown powders containing a 1:1 mixture of *rac*:*meso* diastereomers for **9a-e** from CH_2Cl_2-pentane. The ^{1}H NMR spectrum of the *rac* and *meso*-**9a** is representative of the class. A triplet at δ_H 0.76 is due to the methyl group of one diastereomer and shows a typical $^3J_{HH}$ of 7.5 Hz. This signal is overlapped by the equivalent methyl of the other diastereomer at δ_H 0.77. A

broad signal at δ_H 1.96 and an associated multiplet 2.08-2.23 (integrating to 4 H) are assigned to the overlapping diastereomeric signals of the CH_2 groups while the methoxy and α-CH groups of the two stereoisomers are coincident at δ_H 3.78 and 4.42 respectively. The broadness of the latter indicates restricted rotation within the molecule – most likely about the Cp-CHEtAr bond. The chemical shift region between 5.97 to 6.73 ppm contains two sets of diastereotopic cyclopentadienyl methine protons. The ^1H:^1H COSY spectrum of the aromatic region (see Supporting Data) allows assignment of two sets of four mangnetically inequivalent protons (δ_H 5.97, 6.06, 6.46, 6.73 and δ_H 6.01, 6.17, 6.40 and 6.71) for the C_5H_4R units of the two diastereomers. The phenylene signals are badly overlapped with only slight separation on the H-C(4) Ar (δ_H 7.22 and 7.23) and H-C(5) Ar (δ_H 6.90 and 6.91) signals of the diastereomers. The *rac*/*meso* signals of H-C(3) Ar at 6.91 ppm and H-C(6) Ar at 7.04 ppm are essentially coincident with the latter signal being appreciably broadened at ambient temperature.



(8)	R	Yield/%
a	Et	74
b	*n*Bu	27
c	*i*Bu	94
d	allyl	71
e	Me	89
f	Ph	78

(9)	R	Yield/%	*rac*:*meso*
a	Et	73	1:1
b	*n*Bu	67	1:1
c	*i*Bu	81	1:1
d	allyl	74	1:1
e	Me	51	1:1
f	Ph	66	1:1 *crude*
		14	>20:1 *recrystallised*

Scheme 3. Preparation of titanocene dichlorides (**9**).

In the case of **9f** only small initial crops of crystalline *rac*-**9f** were isolated from $CHCl_3$-hexane, and the *meso* form could not be isolated in a pure form from the mother liquors (which provided only sticky intractable *rac*/*meso* mixtures). The relative *rac* stereochemistry of **9f** could be confirmed by X-ray crystallography (Figure 1). The Ti-Cl and Ti-C(Cp_{ave}) distances in *rac*-(**9f**) at 2.335 and 2.392 Å respectively compare well with typical titanocene dichloride structures in the Cambridge Crystallographic Database bearing a Cp-CHAr unit.[10] These mono substituted titanocene dichlorides show Ti-Cl and Ti-C(Cp_{ave}) ranges of 2.31-2.37 and 2.39-2.45 Å respectively. Often the Ti-C distance associated with the point of substitution in such complexes is appreciably lengthened (2.40-2.49 Å) and this is the case in *rac*-(**9f**) which shows 2.442 Å for Ti-C(1). The exact mode of anti cancer therapeutic action of such complexes is not completely understood – but labilisation of both the Ti-Cl and Ti-Cp ligands has been postulated.[2] It is unknown if steric factors are involved in such processes, if they occur, but clearly such effects are present in **9f**. The origin of the restricted rotation in the complexes **9** is also clear from the structure of *rac*-(**9f**) were the C(2)-C(7) 3.28 Å and C(5)-C(15) 3.00 Å distances are close to the expected C…C van der Waals contact ranges.

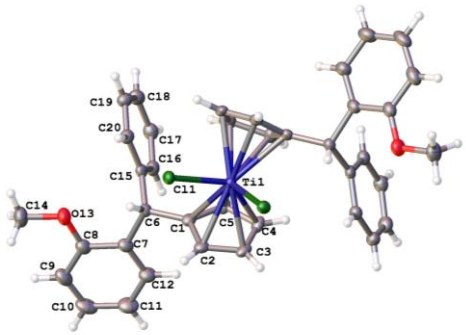
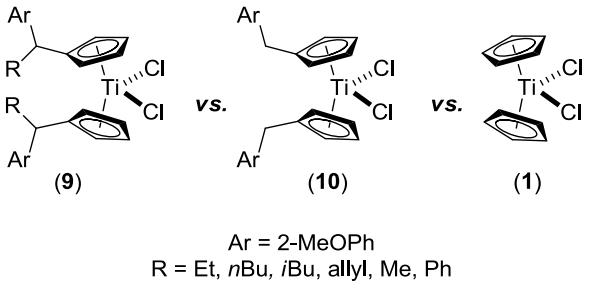


Figure 1. Molecular structure of *rac*-**9f**.

Growth inhibitory studies

The antiproliferative activities of the RCHAr-substituted titanocenes (**9**) in comparison to the simple benzyl-substituted titanocene analogue (**10**)[11], titanocene dichloride (**1**) (Scheme 4) and cisplatin, *cis*-$PtCl_2(NH_3)_2$, were evaluated *in vitro* against HCT-116 (colo-rectal), MiaPaCa-2 (pancreatic), and MDA-468 (triple negative breast) carcinoma cell lines, representing intractable cancers from three different organ sites. Breast cancer is the most common cancer among women (1.38 million new cases worldwide in 2008), and the second most commonly diagnosed cancer overall – 23% of all cancers dignosed in 2008 were breast cancer.[12a] Triple negative (basal-like) breast cancer i.e. those which do not express oestrogen receptor, progesterone receptor or human epidermal growth factor 2, tends to affect younger women, is aggressive, more resistant to therapy and associated with poor prognoses.[12b] Colo-rectal carcinoma is the third most common cancer and caused >600000 deaths globally in 2008.[12a] Pancreatic carcinoma is particularly resistant to chemotherapy, often diagnosed with metastatic disease, and an appalling 5 year survival rate (<5%). Thus, development of new therapies for such malignant diseases represents a currently severely unmet need.



Scheme 4. Species compared in growth inhibitory studies against cisplatin, *cis*-$Cl_2Pt(NH)_3$.

Compound concentrations which inhibit cell growth by 50% (GI_{50} values) after 72 h exposure of cells to agents **9**, **10** and **1**, were obtained by standard MTT [3-(4, 5-dimethyl-thiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay and are represented in Table 2. Compound stocks (10 mM) were prepared in DMSO and diluted in nutrient medium immediately prior to use. All of the complexes **9** were assayed as 1:1 *rac*/*meso* mixtures of stereoisomers except for **9f** which was a single *rac* diastereomer.

As can be deduced from Table 2, all chiral-substituted titanocenes (**9**) are active against all the studied cancer cell lines in the examined concentration range (0.01 µM - 100 µM). Dose-response relationships of (**9a**) and (**9e**) in HCT-116, MiaPaCa-2 and MDA-468 carcinoma cell lines are highlighted in Figure 3.

Table 2. Growth inhibitory assays. GI_{50} values are represented as mean ± SEM of three independent experiments (n = 4 per experiment).

	Mean GI_{50} (µM)		
Compound	HCT-116	MiaPaCa-2	MDA-468
(9a)	7.7 ± 1.4	5.8 ± 2.3	2.3 ± 0.8
(9b)	42.4 ± 4.8	34.7 ± 3.1	14.6 ± 4.2
(9c)	24.6 ± 3.5	22.4 ± 3.9	32.3 ± 1.7
(9d)	28.6 ± 2.9	24.8 ± 1.0	26.7 ± 0.5
(9e)	5.7 ± 2.8	6.6 ± 1.0	7.7± 2.6
rac-**(9f)**	25.0 ± 0.5	11.4 ± 2.6	27.5 ± 0.5
(10)	73.4 ± 3.9	22.7 ± 1.5	76.2 ± 2.6
(1)	>100	>100	>100
cisplatin	6.9 ± 0.1	6.8 ± 2.4	0.6 ± 0.1

Duplicate DMSO (vehicle) controls were carried out on all three cell lines representative of DMSO content over the whole range of concentrations; growth of cells was not significantly inhibited (DMSO ≤ 1%). On direct comparison of **9** with **1** and **10**, it can be deduced that all chiral complexes **9** are much more active than their titanocene reference counterparts. Of particular note are **9a**, and **9e** with GI_{50} values < 10 µM in all 3 cell lines – making them some of the most active titanocenes reported in this area, and directly comparable to cisplatin (particularly against HCT-116 and MiaPaCa-2 cells). This can be attributed to the presence of their -CHRAr substituents, which might lead to a significant increase in inhibitory activity – as has been seen before.[3]. MDA 468 demonstrates greater sensitivity towards **9a**, **9b** and cisplatin. MiaPaCa-2 is more (reltively) sensitive to the growth inhibitory properties of ***rac*-9f** and **10**. Titanocenes **9d** and **9e** demonstrate approximately equiactivity in all 3 cell lines. In an *in vitro* cytotoxicity study carried out on benzyl-substituted titanocenes such as **5** against 36 human tumour cell lines from 14 different organ sites it was found that the cytotoxicity of **5** relative to cisplatin was comparatively much lower in colon carcinoma cell lines whilst comparable in pancreas and breast carcinoma cell lines.[13]

Of particular note is the chain length effect on the cytoxicity of family (**9**), it can be seen in Table 2 and Figure 3 that the longer the chain length, the lower the cytoxicity values obtained. As the chain length increases the cytotoxicity diminishes by a faction of *ca*. 6 from a C_1-C_2 side chain to a *n*-butyl chain. Best results were obtained for titanocenes with ethyl side chain (**9a**) showing GI_{50} values of 7.7 µM for HCT-116, 5.8 µM for MiaPaCa-2 and 2.3µM for MDA-468 or methyl side chain (**9e**) with GI_{50} values of 5.7 µM for HCT-116, 6.6 µM for MiaPaCa-2 and 7.7 µM for MDA-468 These two titanocenes show almost identical activity with uniform growth inhibitory responses in all three cancer cell lines that are similar to standard cisplatin (which shows GI_{50} values of 6.9 µM for HCT-116, 6.8 µM for MiaPaCa-2 and 0.6 µM for MDA-468). Compounds **9a** and **9e** are are equiactive to cisplatin based on an unpaired t-test ($P < 0.01$),[14] except for **9e** vs. cisplatin in MDA-468 (where cisplatin is significantly more active).

The growth inhibitory range shown by the *n*- and *i*-butyl derivatives (**9c-d**) across HCT-116 and MDA-468 cell lines deserves comment. Complex **9c** is statistially (unpaired t-test – $P < 0.01$) less active towards HCT-116 than MDA-468, while for **9d**, the trend is reversed. It has been proposed[2] that the cyclopentadienyl ligands are removed in the cytotoxic events acssociated with Cp_2TiCl_2 theraputics; limiting the role of the cyclopentadienyl ligand to modulating drug uptake into the cell. The activity profile of **9c-d** is therefore somewhat unexpected in the light the rather close structural similarity of these complexes. This might hint at significant molecular recognition at some point in the mode of action rather than simple pharmokinetic affects. Finally, we note also significantly increased growth inhibition evoked by the class **9**, compared to titanocene-Y **5**, in colon carcinoma cell lines.[13]

Conclusion

Through use of copper-catalysis the additions or alkyl Grignard reagents to pentafulvene acceptors becomes a practical process without competing hydride transfer. The resultant cyclopentadienyl ligands are readily complexed to $TiCl_4$ and the resulting substituted $(\eta\text{-}C_5H_4CHRAr)_2TiCl_2$ (R = alkyl) (**9**) are some of the most cytotoxic agents that have been found in this area. As the cyclopentadienes **7** are prepared in racemic form the complexes **9** are attained as *rac*/*meso* mixtures of diastereomers. In principle, organometallic reagents in the presence of chiral additives (e.g. (-)-sparteine) offer the possibility to access enantioenriched samples of **7** and hence **9**. This approach is now being actively targeted in our laboratory as screening individual stereoisomeric forms of **9** is likely to be a useful tool in identifying the biological mode of action of these titanocene dichlorides.

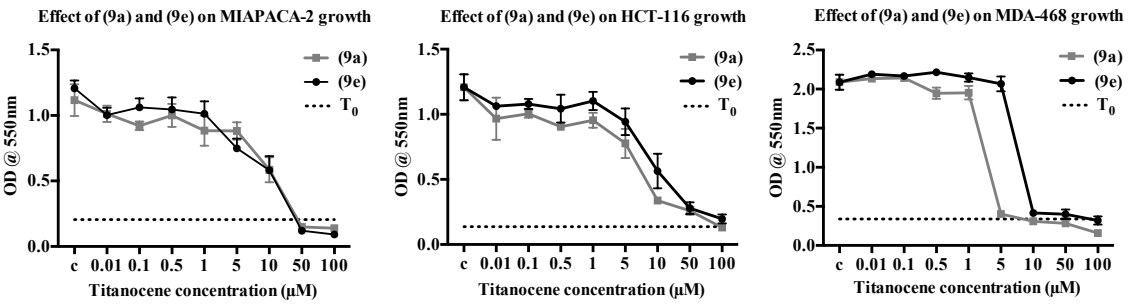


Figure 3. MTT assay profiles for (**9a**) and (**9e**) on MIAPACA-2, HCT-116 and MDA-468 growth.

Experimental Section

All reactions involving air sensitive reagents/intermediates were performed under an atmosphere of argon using standard Schlenk techniques. Reaction solvents were distilled from appropriate drying agents under argon. THF, ether and methyl *tert*-butyl ether were dried and distilled over sodium/benzophenone. Grignard reagents were purchased from Acros and Sigma-Aldrich. All organolithium and Grignard reagents were titrated using Gilman Double titration procedure before use. Saturated NH_4Cl/NH_3 solution pH 8 was prepared by mixing 8 mL of 35% v/v NH_3 in 500 mL saturated $NH_4Cl_{(aq)}$. All other solvents and reagents were used as received from commercial suppliers. Column chromatography was performed using Davisil silicagel 60 and TLC analysis carried out on Merck silicagel 60 F_{254nm}. Nuclear magnetic resonance (NMR) spectra (^1H, ^{13}C) were recorded on either Joel EX270 or Bruker AV400, DPX400, AV(III)400 or AV500 spectrometers, using $CDCl_3$ as the deuterated solvent. Chemical shift values are reported in ppm using solvent resonances as internal standards ($CHCl_3$: δ 7.27 for ^1H, δ 77.0 for ^{13}C). Coupling constants (*J*) are quoted in Hertz. Carbon NMR multiplicities and connectivities were assigned using DEPT and HMQC experiments. Infrared spectra were recorded on either Nicolet Avatar 320 FTIR using Nicolet Avatar 360 FT-IR reflecting probe (ATR diffuse reflectance) or Perkin Elmer 1600 FTIR (thin films). High resolution mass spectra (HRMS) were recorded on a Bruker ApexIV FT-ICRMS using electron-impact ionisation (EI) or Bruker MicroTOF LC-MS using electrospray ionisation (ESI). Mass spectra (MS) were recorded on MALDI-TOFMS using Bruker Ultraflex. Elemental analyses were performed using an Exeter Analytical CE-440 instrument. Melting points were determined using a Stuart Scientific SMP3 melting point apparatus and are uncorrected. X-ray data for: CCDC 931593 (*rac*-**9f**) are available from the Cambridge Crystallographic database (http://webcsd.ccdc.cam.ac.uk/) by quoting the appropriate CCDC number above. Compound **10** was prepared by a literature route.[11]

Synthesis of 6-substituted fulvene

1-(cyclopenta-2,4-dien-1-ylidenemethyl)-2-methoxybenzene (6): Prepared as described in the literature,[7] with minor modifications. 2-Methoxybenzaldehyde (16.3 g, 0.12 mol) and excess freshly fractionated cyclopentadiene (38-41 °C, 25.2 mL, 0.30 mol) were dissolved in methanol (120 mL) to give a colourless solution which on dropwise addition of pyrrolidine (15.0 mL, 0.18 mol), the solution changed colour from colourless through yellow through dark red. The reaction was left to stir at room temperature whilst being monitored by TLC (pentane: CH_2Cl_2 4:1). After 60 min, acetic acid (18.0 mL, 0.32 mol) was added. The mixture was diluted with ether (300 mL) and deionized water (50.0 mL). After extraction from the aqueous layer (2 x 100 mL diethyl ether), the combined organic portions were washed twice with brine (2 x 80 mL) and once with deionized water (50 mL) and dried over anhydrous $MgSO_4$. The volatiles were evaporated *in vacuo*. (CARE! **6** is highly malodorous). The crude product (21.1 g, 95%) obtained as a red oil, was used immediately to avoid Diels-Alder dimerization which was facile in the neat liquid (*ca*. 10% over 7 days at -20 °C as detected by NMR spectroscopy). Alternatively, a 3.00 g portion of such contaminated product was filtered through a 40 mm pad of silica gel, eluting first with pentane (2 x 100 mL), and then with pentane: CH_2Cl_2 4:1 (2 x 100 mL). The last two pentane-dichloromethane fractions were combined and evaporated *in vacuo* yielding a light red oil (2.44 g, 81%) which was stored at -20 °C. R_f = 0.34 (pentane:CH_2Cl_2 4:1) ^1H NMR (400.1 MHz, $CDCl_3$, 25 °C): δ = 3.91 (s, 3H, -OCH_3), 6.43 (dt, 1 H, *J* = 5.1, 1.8 Hz, *H*-C(4)), 6.58 (ddd, 1H, *J* = 5.1, 1.6 Hz, 0.6 Hz, *H*-C(1)), 6.69-6.72 (m, 2H, *H*-C(2) and *H*-C(3)), 6.95 (dd, 1H, *J* = 8.3, 0.6 Hz, *H*-C(3')), 7.06 (dddd, 1H, *J* = 7.6, 7.5, 1.0, 0.6 Hz, *H*-C(5')), 7.39 (ddd, 1H, *J* = 7.3, 1.6, 1.6 Hz, *H*-C(4')), 7.62 (br, s, unresolved long range couplings, 1H, *H*-C(6)), 7.66 (dd, 1H, *J* = 7.8 Hz & 1.8 Hz, *H*-C(6')). ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 °C): δ = 55.5 (OCH_3), 110.5 (*C*(3')), 120.5 (*C*(5')), 120.6 (*C*(2 or 3)), 125.9 (*C*(1')), 126.8 (C(4)), 130.5 (*C*(1 or 4')), 130.6 (*C*(1 or 4')), 132.4 (*C*(6')), 133.7 (*C*(6)), 134.7 (*C*(2 or 3)), 144.9 (*C*(5), 158.4 (*C*(2')). This previously uncorrelated data was obtained using HMQC, HMBC and DEPT 90/135. IR (thin film): $\tilde{\nu}$ = 3070, 3002, 2937, 2836, 1622, 1597, 1489, 1464, 1339, 1302, 1249, 1109, 1049, 1027, 903, 842, 753, 624 cm^{-1}. MS ($EI^{+\bullet}$) $[M+1]^{+\bullet}$ (13.7%) *m/z* = 185.1, $[M^{+\bullet}]$ (100%) m/z = 184.1, $[M-H]^{+\bullet}$ (38.7%) 183.1, $[M-CH_3]^{+\bullet}$ (77.6%) 169.1, $[M-OCH_3]^{+\bullet}$ (44.9%) 153.1. HRMS ($EI^{+\bullet}$) ($M^{+\bullet}$) Calcd. for $C_{13}H_{12}O$: 184.0888 g mol^{-1}, found: 184.0881 g mol^{-1}.

Synthesis of (±)-substituted cyclopentadienyl compounds 7

General Procedure for CuBr•SMe_2 catalysed additions 6

To a dry Schlenk tube, equipped with a magnetic stirrer and a septum, CuBr•SMe_2 (206 mg, 1.00 mmol, 10 mol-%) was added to dry THF (30.0 mL) and left to stir at room temperature (15 min). The solution was cooled to -10 °C and the appropriate Grignard reagent (25.0 mmol, 2.5 equiv. - from a typically 0.50–0.90 M THF solutions, 20 wt% THF-toluene solution or 1.00–3.00 M ether solutions) was added dropwise and the reaction was left to stir (15 min) at -10 °C. A colour change from yellow to purple was noted. Neat (**6**) (1.84 g, 10.0 mmol, 1.0 equiv.) was dissolved in dry THF (10.0 mL) and added to the Grignard-cuprate solution dropwise. The reaction was then stirred for 16 h at -10 °C. Saturated NH_4Cl/NH_3 solution pH 8 (25 mL) was added dropwise to quench the reaction, which was then allowed to warm to room temperature with rapid stirring. The reaction mixture was diluted with ether (60 mL) and the organic phase extracted, washed with NH_4Cl/NH_3 solution pH 8 (15 mL) and brine (2 x 40 mL). The organic layer was then dried over $MgSO_4$. All volatiles were removed under reduced pressure to yield the crude product, which was then purified by column chromatography (pentane-CH_2Cl_2) to yield the purified products.

General Procedure for CuI/PPh_3 catalysed additions to 6

To a dry Schlenk tube, equipped with a magnetic stirrer and a septum, CuI (152 mg, 0.80 mmol, 8.0 mol-%) and triphenylphosphine (262 mg, 1.00 mmol, 10 mol-%) were added to dry methyl *tert*-butyl ether (30 mL) and left to stir at room temperature (30 min). The solution was cooled to -10 °C and the appropriate Grignard reagent (25.0 mmol, 2.5 equiv. from a 2.80–3.00 M ether solution) was added dropwise and the reaction was left to stir (15 min) at -10 °C. Neat (**6**) (1.84 g, 10.0 mmol, 1.0 equiv.) was dissolved in dry methyl *tert*-butyl ether (10 mL) and added to the Grignard-cuprate solution dropwise. The reaction was then stirred for 16 h at -10°C. Quenching and work-up was carried out as above for the CuBr•SMe_2 promoted reactions.

General procedure for CuCN/LiCl catalysed additions to 6

To a dry Schlenk tube, equipped with a magnetic stirrer and a septum was added dried LiCl (63.6 mg, 1.50 mmol, 5.0 mol-%) and CuCN (134 mg, 1.50 mmol, 5.0 mol-%) (TOXIC!). The mixture was then heated under vacuum (5 min) using a hot air gun (>100 °C), cooled to room temperature, flushed with argon and dry THF (50 mL) was added. The solution was cooled to -10 °C and a solution of 0.83 M ethylmagnesium bromide in THF (45.0 mL, 37.5 mmol, 2.5 equiv.) was added dropwise. A colour change from colourless to grey then purple. Other Grignard reagents resulted in equivalent solutions. Neat (**6**) (2.76 g, 15.0 mmol, 1.0 equiv.) was dissolved in 25. mL dry THF. The latter solution was added to the complexed Grignard solution dropwise. A colour change from dark purple to yellow was noted. The reaction was then stirred for 16 h at -10 °C. Saturated NH_4C /NH_3 solution pH 8 (35 mL) was then added dropwise to quench the reaction, which was then allowed to warm to room temperature with rapid stirring. The reaction mixture was diluted with ether (90 mL) and the

organic phase extracted, washed with NH_4Cl/NH_3 solution pH 8 (15 mL) and brine (2 x 50 mL). The organic layer was then dried over $MgSO_4$. Aqueous cyanide residue were quenched with bleach. All volatiles were removed under reduced pressure to yield the crude product, which was then purified by column chromatography (pentane-CH_2Cl_2) to yield the purified product.

1-(1-(Cyclopenta-1,3-dien-1-yl)propyl)-2-methoxybenzene and 1-(1-(cyclopenta-1,4-dien-1-yl)propyl)-2-methoxy benzene (7a): Prepared by the CuBr•SMe_2 procedure using EtMgBr (8.7 mL of 2.90 M ether solution, 25.0 mmol, 2.5 equiv.). The crude product was purified by flash column chromatography on silica gel (pentane-CH_2Cl_2 8:1, R_f 0.32) to yield **7a** as a colourless oil (1.82 g, 85%). The individual α/β tautomer (0.8:1.2 ratio) signals could not be uniquely identified and are referred as tautomer 1 and tautomer 2 and integrated on this basis. ^{1}H NMR (400.2 MHz, $CDCl_3$, 25 ^{o}C): δ_H 0.92 (t, 1.2 H, *J* = 7.3 Hz, CH_2*Me* tautomer 1) *overlapped by* 0.93 (t, 1.8 H, *J* = 7.3 Hz, CH_2*Me* tautomer 2), 1.81-2.08 (m, 2 H, *CH*$_2$Me both tautomers), 2.82-2.87 (br, 0.8 H, C*H*$_2$ in Cp tautomer 1), 2.98-3.02 (br, 1.2 H, C*H*$_2$ in Cp tautomer 2), 3.85 (s, 1.2 H, O*Me* tautomer 1) *overlapped by* 3.86 (s, 1.8 H, O*Me* tautomer 2), 4.12-4.22 (m, 1.0 H, *CH*Et both tautomers), 6.10-6.15 (m, 0.6 H, Cp tautomer 2), 6.23-6.31 (m, 0.8 H, Cp tautomer 1), 6.36-6.45 (m, 1.2 H, Cp tautomer 2), 6.45-6.48 (m, 0.4 H, Cp tautomer 1), 6.87-6.96 (m, 2.0 H, Ar both tautomers), 7.11-7.23 (m, 2.0 H, Ar both tautomers). ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ^{o}C): δ_C 12.5 (CH_2*Me* both tautomers), 27.3 (Me*C*H$_2$ tautomer 2), 27.8 (Me*C*H$_2$ tautomer 1), 39.6 (*C*HEt tautomer 2), 40.4 (*C*HEt tautomer 1), 41.0 (*C*H$_2$ in Cp tautomer 2), 42.6 (*C*H$_2$ in Cp tautomer 1), 55.5 (O*Me* both tautomers), 110.6 (Ar both tautomers), 120.6 (Ar both tautomers), 125.8 (Cp tautomer 2), 126.3 (Cp tautomer 1), 126.8 (Ar tautomer 1), 126.9 (Ar tautomer 2), 127.9 (Ar tautomer 1), 128.0 (Ar tautomer 2), 130.7 (Cp tautomer 1), 132.1 (Cp tautomer 2), 132.9 (Cp tautomer 2), 133.1 (Cp tautomer 1), 133.6 (Cp tautomer 1), 134.6 (Cp tautomer 2), 149.9 (Cp-*C*-CHEt tautomer 2), 152.8 (Cp-*C*-CHEt tautomer 1), 157.1 (*C*-O-Me tautomer 1), 157.3 (*C*-O-Me tautomer 2). IR (thin film): $\tilde{\nu}$ = 3064, 2961, 2932, 2874, 2835, 1598, 1490, 1463, 1241, 1031, 899, 752 cm^{-1}. HRMS (EI$^{+\bullet}$) ($M^{+\bullet}$) Calcd. for $C_{15}H_{18}O$ – 214.1358, found: 214.1360. CHN Anal. calcd. for $C_{15}H_{18}O$: C, 84.07; H, 8.47; found: C, 84.01; H, 8.67. Also prepared according to the CuCN/LiCl procedure to yield 2.82 g, 88%.

1-(1-(Cyclopenta-1,3-dien-1-yl)pentyl)-2-methoxybenzene and 1-(1-(cyclopenta-1,4-dien-1-yl)pentyl)-2-methoxybenzene (7b): Prepared by the CuBr•SMe_2 procedure using *n*-BuMgCl (14.6 g of 20 wt% THF/toluene solution, 25.0 mmol, 2.5 equiv.). The crude product was purified by flash column chromatography on silica gel (pentane:CH_2Cl_2 6:1, R_f 0.34) to yield **7b** as a colourless oil (2.10 g, 87%). The individual α/β tautomer (0.8:1.2 ratio) signals could not be uniquely identified and are referred as tautomer 1 and tautomer 2 and integrated on this basis. ^{1}H NMR (400.1 MHz, $CDCl_3$, 25 ^{o}C): δ_H 0.88 (t, 3.0 H, *J* = 7.0 Hz, CH_2*Me* both tautomers), 1.17-1.39 (m, 4.0 H, C_2*H*$_4$Me both tautomers), 1.75-2.00 (m, 2.0 H, C*H*$_2$C$_3$H$_7$ both tautomers), 2.80-2.85 (m, 0.8 H, C*H*$_2$ in Cp tautomer 1), 2.95-3.01 (m, 1.2 H, C*H*$_2$ in Cp tautomer 2), 3.84 (s, 1.2 H, O*Me* tautomer 1) *overlapped by* 3.84 (s, 1.8 H, O*Me* tautomer 2), 4.18-4.27 (m, 1.0 H, C*H*-Bu both tautomers), 6.06-6.12 (m, 0.6 H, Cp tautomer 2), 6.21-6.27 (m, 0.8 H, Cp tautomer 1), 6.36-6.47 (m, 1.6 H, Cp both tautomers), 6.85-6.94 (m, 2.0 H, Ar both tautomers), 7.10-7.20 (m, 2.0 H, Ar both tautomers). ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ^{o}C): δ_C 14.0 (CH_2*Me* both tautomers), 22.7 (C_2H_4Me both tautomers), 30.0 (C_2H_4Me tautomer 2) *overlapped by* 30.1 (C_2H_4Me tautomer 1), 34.1 (*C*H$_2$C$_3$H$_7$ tautomer 2), 34.6 (*CH*$_2$C$_3$H$_7$ tautomer 1), 37.7 (*C*H-Bu tautomer 2), 38.5 (*C*H-Bu tautomer 1), 41.0 (*C*H$_2$ in Cp tautomer 2), 42.6 (*C*H$_2$ in Cp tautomer 1), 55.5 (O*Me* both tautomers), 110.6 (Ar both tautomers), 120.6 (Ar both tautomers) 125.7 (Cp tautomer 2), 126.2 (Cp tautomer 1), 126.7 (Ar both tautomers), 127.9 (Ar tautomer 1), 128.0 (Ar tautomer 2), 130.7 (Cp tautomer 2), 132.1 (Cp tautomer 1), 133.1 (Cp tautomer 2), 133.2 (Cp tautomer 2), 133.9 (tautomer 1), 134.6 (Cp tautomer 2), 150.1 (Cp-*C*-CH tautomer 2), 153.0 (Cp-*C*-CH tautomer 1), 157.0 (*C*-O-Me tautomer 1, 157.1 (*C*-O-Me tautomer 2). IR (thin film): $\tilde{\nu}$ = 3064, 3028, 2998, 2931, 2859, 1598, 1491, 1463, 1439, 1367, 1288, 1242, 1117, 1052, 1032, 931, 899, 752, 676 cm^{-1}. HRMS (EI$^{+\bullet}$) ($M^{+\bullet}$) Calcd. for $C_{17}H_{22}O$ – 242.1671, found 242.1670. CHN Anal. calcd. for $C_{17}H_{22}O$: C, 84.25; H, 9.15; found: C, 84.27; H, 9.10.

1-(1-(cyclopenta-1,3-dien-1-yl)-3-methylbutyl)-2-methoxybenzene and 1-(1-(cyclopenta-1,4-dien-1-yl)-3-methylbutyl)-2-methoxybenzene (7c): Prepared by the CuBr•SMe_2 procedure using using *i*BuMgCl (12.5 mL of 2.00 M ether solution, 25.0 mmol, 2.5 equiv.). The crude product was purified by flash column chromatography on silica gel (gradient pentane/CH_2Cl_2 initially 6:1, R_f 0.38) to yield **7d** as a colourless oil (2.23 g, 92%). The individual α/β tautomer (0.8 : 1.2 ratio) signals could not be uniquely identified and are referred as tautomer 1 and tautomer 2 and integrated on this basis. ^{1}H NMR (400.1 MHz, $CDCl_3$, 25 ^{o}C): δ_H 0.89-0.93 (m, 6 H, C*H*$_3$CHC*H*$_3$ both tautomers), 1.4-1.53 (m, 1.0 H, CH$_3$C*H*CH$_3$ both tautomers), 1.68-1.83 (m, 2.0 H, CHC*H*$_2$C$_3$H$_7$ both tautomers), 2.80-2.85 (m, 0.8 H, C*H*$_2$ in Cp tautomer 1), 2.95-2.99 (m, 1.2 H, C*H*$_2$ in Cp tautomer 2), 3.83 (s, 1.2 H, O*Me* tautomer 1) *overlapped by* 3.84 (s, 1.8 H, O*Me* tautomer 2), 4.30-4.40 (m, 1.0 H, C*H*-*i*Bu both tautomers), 6.05-6.10 (m, 0.6 H, Cp tautomer 2), 6.20-6.28 (m, 0.8 H, Cp tautomer 1), 6.33-6.47 (m, 1.5 H, Cp both tautomers), 6.85-6.93 (m, 2.0 H, Ar both tautomers), 7.09-7.19 (m, 2.0 H, Ar both tautomers). ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ^{o}C): δ_C 22.4 (*C*H$_3$CHCH$_3$ tautomer 1), 22.5 (*C*H$_3$CHCH$_3$ tautomer 2), 23.0 (CH$_3$CH*C*H$_3$ tautomer 2), 23.1 (CH$_3$CH*C*H$_3$ tautomer 1), 25.8 (CH$_3$*C*HCH$_3$ both tautomers), 35.5 (*C*H-*i*Bu tautomer 2), 36.3 (*C*H-*i*Bu tautomer 1), 41.0 (*C*H$_2$ in Cp tautomer 2), 42.6 (*C*H$_2$ in Cp tautomer 1), 43.8 (CH*C*H$_2$C$_3$H$_7$ tautomer 2), 44.2 (CH*C*H$_2$C$_3$H$_7$ tautomer 1), 55.5 (O*Me* both tautomers), 110.6 (Ar tautomer 2) *overlapped by* 110.7 (Ar tautomer 1), 120.6 (Ar both tautomers) 125.6 (Cp tautomer 2), 126.1 (Cp tautomer 1), 126.7 (Ar tautomer 1), 126.8 (Ar tautomer 2), 128.0 (Ar tautomer 1), 128.2 (Ar tautomer 2), 130.7 (Cp tautomer 2), 132.1 (Cp tautomer 1), 133.2 (Cp both tautomers), 133.8 (Cp tautomer 1), 134.7 (Cp tautomer 2), 150.3 (Cp-*C*-CH tautomer 2), 153.2 (Cp-*C*-CH tautomer 1), 157.0 (*C*-O-Me tautomer 1, 157.1 (*C*-O-Me tautomer 2). IR (thin film): $\tilde{\nu}$ = 3064, 2954, 2868, 2835, 1598, 1491, 1464, 1438, 1366, 1288, 1241, 1168, 1096, 1053, 1032, 899, 807, 752, 677, 622 cm^{-1}. HRMS (EI$^{+\bullet}$) ($M^{+\bullet}$) Calcd. for $C_{17}H_{22}O$ – 242.1671, found 242.1676. CHN Anal. calcd. for $C_{17}H_{22}O$: C, 84.25; H, 9.15; found: C, 83.85; H, 9.12.

1-(1-(Cyclopenta-1,3-dien-1-yl)but-3-en-1-yl)-2-methoxybenzene and 1-(1-(cyclopenta-1,4-dien-1-yl)but-3-en-1-yl)-2-methoxybenzene (7d): Prepared by the CuBr•SMe_2 procedure using using allylmagnesium bromide in (25.0 mL of 1.00 M ether solution, 25.0 mmol, 2.5 equiv.). The crude product was purified by flash column chromatography on silica gel (gradient pentane/CH_2Cl_2 initially 6:1, R_f 0.28) to yield **7c** as a colourless oil (2.06 g, 91%). The individual α/β tautomer (0.9:1.1 ratio) signals could not be uniquely identified and are referred as tautomer 1 and tautomer 2 and integrated on this basis. ^{1}H NMR (400.1 MHz, $CDCl_3$, 25 ^{o}C): δ_H 2.55-2.77 (m, 2.0 H, C*H*$_2$CH-Cp both tautomers), 2.82-2.86 (m, 0.9 H, C*H*$_2$ in Cp tautomer 1), 2.96-3.02 (m, 1.1 H, C*H*$_2$ in Cp tautomer 2), 3.83 (s, 1.3 H, O*Me* tautomer 1), 3.84 (s, 1.7 H, O*Me* tautomer 2), 4.26-4.37 (m, 1.0 H, CH$_2$C*H*-Cp both tautomers), 4.90-4.95 (m, 1.0H, C*H*$_2$C$_2$H$_3$-CH-Cp both tautomers), 4.98-5.05 (m, 1.0 H, C*H*$_2$C$_2$H$_3$-CH-Cp both tautomers), 5.72-5.85 (m, 1.0 H, C*H*CH$_2$CH-Cp both tautomers), 6.12-6.15 (m, 0.5 H, Cp tautomer 2), 6.22-6.30 (m, 0.9 H, Cp tautomer 1), 6.36-6.42 (m, 1.1 H, Cp tautomer 2), 6.42-6.45 (m, 0.4 H, Cp tautomer 1), 6.85-6.93 (m, 2.0 H, Ar both tautomers), 7.08-7.20 (m, 2.0 H, Ar both tautomers). ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ^{o}C): δ_C 38.0 (*C*H-allyl tautomer 1), 38.5 (*C*H-allyl tautomer 2), 38.8 (*C*H$_2$CH-Cp tautomer 2), 39.0 (*C*H$_2$CH-Cp tautomer 1), 41.0 (*C*H$_2$ in Cp tautomer 2), 42.7 (*C*H$_2$ in Cp tautomer 1), 55.5 (O*Me* both tautomers), 110.6 (Ar both tautomers), 115.4 (*C*H$_2$C$_2$H$_3$-CH-Cp tautomer 2) *overlapped by* 115.5 (*CH*$_2$C$_2$H$_3$-CH-Cp tautomer 1), 120.5 (Ar tautomer 2)

overlapped by 120.6 (Ar tautomer 1) 126.3 (Cp tautomer 2), 126.8 (Cp tautomer 1), 127.0 (Ar both tautomers), 128.1 (Ar tautomer 1), 128.3 (Ar tautomer 2), 131.0 (Cp tautomer 2), 132.1 (Cp tautomer 1), 132.3 (Cp tautomer 2), 133.1 (Cp tautomer 1), 133.3 (Cp tautomer 2), 134.6 (Cp tautomer 1), 137.5 (*C*HCH$_2$CH-Cp both tautomers), 149.2 (Cp-*C*-CH tautomer 2), 151.9 (Cp-*C*-CH tautomer 1), 156.9 (*C*-O-Me tautomer 1), 157.0 (*C*-O-Me tautomer 2). IR (thin film): $\tilde{\nu}$ = 3072, 3029, 3001, 2935, 2836, 1640, 1599, 1586, 1491, 1463, 1439, 1365, 1339, 1289, 1242, 1186, 1162, 1114, 1052, 1032, 995, 951, 911, 899, 808, 753, 678, 619, 572, 503, 478, 460 cm^{-1}. HRMS (EI$^{+\bullet}$) (M$^{+\bullet}$) Calcd. for $C_{16}H_{18}O$ – 226.1358, found 226.1360. CHN Anal. calcd. for $C_{16}H_{18}O$: C, 84.91; H, 8.02; found: C, 84.90; H, 8.02.

1-(1-(cyclopenta-1,3-dien-1-yl)ethyl)-2-methoxybenzene and 1-(1-(cyclopenta-1,4-dien-1-yl)ethyl)-2-methoxybenzene (7e): Prepared by the CuI/PPh$_3$ procedure using MeMgBr (8.3 mL of 3.00 M ether solution, 25.0 mmol, 2.5 equiv.). The crude product was purified by flash column chromatography on silica gel (gradient pentane/CH_2Cl_2 initially 10:1, R_f 0.30) to yield **7e** as a colourless oil (1.83 g, 91%). The individual α/β tautomer (1.2:0.8 ratio) signals could not be uniquely identified and are referred as tautomer 1 and tautomer 2 and integrated on this basis. ^{1}H NMR (400.2 MHz, $CDCl_3$, 2 5ºC): δ_H 1.46 (d, 3.0 H, *J* = 7.2 Hz, CH*Me* both tautomers), 2.81-2.86 (m, 1.2 H, C*H*$_2$ in Cp tautomer 1), 2.99-3.02 (m, 0.8 H, C*H*$_2$ in Cp tautomer 2), 3.85 (s, 1.8 H, O*Me* tautomer 1) *overlapped by* 3.86 (s, 1.2 H, O*Me* tautomer 2), 4.25-4.40 (m, 1.0 H, *CH*Me both tautomers), 6.08-6.13 (m, 0.4 H, Cp tautomer 2), 6.22-6.29 (m, 1.2 H, Cp tautomer 1), 6.33-6.41 (m, 0.8 H, Cp tautomer 2), 6.42-6.48 (m, 0.6 H, Cp tautomer 1), 6.85-6.93 (m, 2.0 H, Ar both tautomers), 7.03-7.08 (m, 1.0H, Ar both tautomers), 7.14-7.21 (m, 1.0 H, Ar both tautomers). ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ_C 19.9 (*Me*CH tautomer 2), 20.4 (*Me*CH tautomer 1), 32.4 (Me*C*H tautomer 2), 33.1 (Me*C*H tautomer 1), 41.0 (*C*H$_2$ in Cp tautomer 2), 42.7 (*C*H$_2$ in Cp tautomer 1), 55.5 (O*Me* both tautomers), 110.5 (Ar both tautomers), 120.6 (Ar both tautomers), 125.5 (Cp tautomer 2), 126.2 (Cp tautomer 1), 126.8 (Ar tautomer 1), 126.9 (Ar tautomer 2), 127.7 (Ar tautomer 1), 127.9 (Ar tautomer 2), 131.0 (Cp tautomer 1), 132.1 (Cp tautomer 1), 133.3 (Cp tautomer 2), 134.2 (Cp tautomer 2), 134.7 (Cp tautomer 2), 135.2 (Cp tautomer 1), 151.1 (Cp-*C*-CH tautomer 2), 153.9 (Cp-*C*-CHEt tautomer 1), 156.5 (*C*-O-Me tautomer 1), 156.8 (*C*-O-Me tautomer 2). IR (thin film): $\tilde{\nu}$ = 3061, 2962, 2835, 1599, 1491, 1463, 1438, 1367, 1289, 1241. 1163, 1111, 1030, 931, 899, 808, 753, 677, 573, 503 cm^{-1}. HRMS (EI$^{+\bullet}$) (M$^{+\bullet}$) Calcd. for $C_{14}H_{16}O$ – 200.1201, found: 200.1205.

1-(Cyclopenta-1,3-dien-1-yl(phenyl)methyl)-2-methoxybenzene and 1-(cyclopenta-1,4-dien-1-yl(phenyl)methyl)-2-methoxybenzene (7f): Prepared by the CuI/PPh$_3$ procedure using PhMgBr (9.0 mL of 2.80 M ether solution, 25.0 mmol, 2.5 equiv.). The crude product was purified by flash column chromatography on silica gel (gradient pentane/CH_2Cl_2 initially 10:1, R_f 0.20) to yield **7f** as a colourless oil (1.73 g, 66%). The individual α/β tautomer (0.9:1.1 ratio) signals could not be uniquely identified and are referred as tautomer 1 and tautomer 2 and integrated on this basis. ^{1}H NMR (400.2 MHz, $CDCl_3$, 25 ºC): δ_H: 2.99-3.04 (br, 0.9 H, C*H*$_2$ in Cp tautomer 1), 3.05-3.09 (br, 1.1 H, C*H*$_2$ in Cp tautomer 2), 3.81 (s, 3.0 H, O*Me* both tautomers), 5.63-5.67 (br, 0.5 H, *CH*Ph tautomer 2), 5.67-5.71 (br, 0.5 H, *CH*Ph tautomer 1), 5.81-5.84 (m, 0.5 H, Cp), 5.98-6.02 (br, m, 0.5 H, Cp), 6.37-6.41 (m, 0.5 H, Cp), 6.43-6.47 (m, 0.5 H, Cp), 6.47-6.52 (m, 1.0 H, Cp), 6.91-6.99 (m, 2.0 H, Ar both tautomers), 7.07-7.14 (m, 1.0 H, Ar both tautomers), 7.22-7.30 (m, 4.0 H, Ar & Ph both tautomers), 7.31-7.37 (m, 2.0 H, Ph both tautomers). ^{13}C NMR (100.6 MHz, $CDCl_3$, 25 ºC): δ_C 41.0 (*C*H$_2$ in Cp tautomer 2), 43.6 (*C*H$_2$ in Cp tautomer 1), 44.7 (*C*HPh tautomer 2), 45.4 (*C*HPh tautomer 1), 55.6 (O*Me* both tautomers), 110.6 (Ar tautomer 1), 110.7 (Ar tautomer 2), 120.3 (Ar both tautomers), 125.9 (Ph both tautomers), 127.3 (Ar tautomer 1), 127.4 (Ar tautomer 2), 128.0 (Ph x 2 both tautomers), 128.9 (Ph x 2 tautomer 1), 129.0 (Ph x 2 tautomer 2), 129.1 (Ar tautomer 2), 129.6 (Ar tautomer 1), 129.7 (Cp tautomer 2), 130.0 (Cp tautomer 1), 131.6 (Cp tautomer 2), 131.8 (Cp tautomer 2), 132.0 (Cp tautomer 2), 132.6 (Cp tautomer 1), 133.4 (Cp tautomer 1), 135.1 (Cp tautomer 2), 143.4 (Ph-*C*-CH tautomer 2), 143.9 (Ph-*C*-CH tautomer 1), 149.1 (Cp-*C*-CH tautomer 2), 151.6 (Cp-*C*-CH tautomer 1), 156.8 (*C*-O-Me tautomer 1), 157.0 (*C*-O-Me tautomer 2). IR (thin film): $\tilde{\nu}$ = 3061, 3026, 2935, 2835, 1598, 1450, 1462, 1438, 1361, 1289, 1243, 1162, 1105, 1051, 1030, 900, 755, 700, 634 cm^{-1}. HRMS (EI$^{+\bullet}$) (M$^{+\bullet}$) Calcd. for $C_{19}H_{18}O$ – 262.1358, found: 262.1361.

General Procedure for synthesis of *rac*/*meso*-substituted titanocenes 9

A flame dried Schlenk tube was left to cool under vacuum for 30 min and then weighed under vacuum. Under a stream of argon atmosphere, **7** (1.0 equiv.) was added, followed by dry ether or methyl *tert*-butyl ether (4.00 mL per 1.00 mmol of **7**). The mixture was cooled to 0 ºC, followed by the addition of *n*-BuLi 1.60 M in hexane (1.1 equiv.). The solution was left to stir for 30 min at 0 ºC yielding a white precipitate of the lithium substituted-cyclopentadienide **8** in a faint yellow solution. The solvent was removed from **8** by cannula filtration procedure, and the solid washed twice with dry ether (2 x 1.0 mL per 1.0 mmol of **7**) and re-filtered under argon. The precipitate was dried under vacuum at 0.1 mmHg for 1 h and weighed under vacuum. The lithium substituted-cyclopentadienide **8** (2.0 equiv.) was dissolved in dry THF (4.0 mL per 1.0 mmol of **8**) to give a colourless solution. In another Schlenk tube, titanium tetrachloride 1.00 M solution in toluene (1.0 equiv.) was dissolved in dry THF (8.0 mL per 1.0 mmol of titanium tetrachloride) to give a yellow solution. The solution of titanium tetrachloride was added to the solution of **8** via cannula at room temperature, to give a dark red solution and refluxed for 16 h at 85 ºC. The resultant solution was then cooled and the solvent was removed under reduced pressure. The remaining brown residue was extracted with chloroform and filtered through Celite to remove LiCl. The solvent removed *in vacuo* yielding the crude solid material. Purification was carried out by direct infusion of pentane on top of a saturated solution of **9** in CH_2Cl_2 (final mixture *ca.* 5:1 pentane: CH_2Cl_2).

***Rac*/*meso*-dichloridobis(1-propyl-1'-(2-methoxyphenyl)-η^5-cyclopentadienyl)titanium (9a):** Prepared using **7a** (535 mg, 2.50 mmol, 1.0 equiv.), dry ether (10 mL) and *n*-BuLi (1.7 mL, 2.75 mmol, 1.1 equiv.) yielding lithium substituted-cyclopentadienide **8a** (410 mg, 1.86 mmol, 74%). This intermediate (1.86 mmol, 2.0 equiv.) was dissolved in 7.5 mL dry THF to give a colourless solution. Titanium tetrachloride (0.93 mmol, 0.93 mL, 1.0 equiv.) was dissolved in 7.5 mL dry THF to give a yellow solution. After purification, a red solid was obtained (359 mg, 71% - based on titanium). The individual *rac* and *meso* diastereomers (1:1 ratio) signals could not be uniquely identified and are thus identified as isomer 1 or 2. M.p. 173-174 ºC. ^{1}H NMR (500.1 MHz, $CDCl_3$, 22 ºC): δ_H 0.76 (t, 3 H, *J* = 7.5 Hz, CH$_2$*Me* isomer 1 or 2) *overlapped by* 0.76 (t, 3 H, *J* = 7.5 Hz, CH$_2$*Me* isomer 1 or 2), 1.88-2.03 (br, 2 H, *CH*$_2$Me both isomers), 2.08-2.23 (m, 2 H, *CH*$_2$Me both isomers), 3.78 (s, 6 H, 2 x OMe, both isomers), 4.42 (br, 2 H, *CH*Et both isomers), 5.97 (AB, 1 H, J_{AB} = 2.0 Hz, Cp isomer 1), 6.01 (AB, 1 H, J_{AB} = 2.0 Hz, Cp isomer 2), 6.06 (AB, 1 H, J_{AB} = 2.5 Hz, Cp isomer 1), 6.17 (AB, 1 H, J_{AB} = 2.5 Hz, Cp isomer 2), 6.40 (AB, 1 H, J_{AB} = 2.5 Hz, Cp isomer 2), 6.46 (AB, 1 H, J_{AB} = 2.5 Hz, Cp isomer 1), 6.71 (AB, 1 H, J_{AB} = 2.5 Hz, Cp isomer 2), 6.73 (AB, 1 H, J_{AB} = 2.5 Hz, Cp isomer 1), 6.86-6.92 (m, 4 H, *H*-C(4) and *H*-C(6) Ar, both isomers), 7.03 (br d, 2H, J = 6.9 Hz, *H*-C(3) Ar, both isomers), 7.20 (ddd, 1 H, *J* = 7.5, 7.0, 1.0 Hz, *H*-C(5) Ar) *overlapped by* 7.25 (ddd, 1 H, *J* = 7.5, 7.0, 1.0 Hz, *H*-C(5) Ar) ^{13}C NMR (125.8 MHz, $CDCl_3$, 25 ºC): δ_C 11.9 (CH$_2$*Me* both isomers), 26.2 (*C*H$_2$Me isomer 1 or 2), 26.3 (*C*H$_2$Me isomer 1 or 2), 42.1 (*CH*Et both isomers), 55.4 (OMe both isomers), 111.1 (*C*(6) Ar both isomers), 115.4 (br, Cp isomer 1), 116.4 (br, Cp isomer 2), 117.4 (Cp isomer 2), 118.3 (Cp isomer 1), 118.8 (Cp isomer 1), 119.2 (Cp isomer 2), 120.7 (*C*(3) or *C*(4) Ar both isomers), 120.7 (*C*(3) or *C*(4) both isomers Ar), 121.9 (Cp isomer

2), 123.1 (Cp isomer 1), 127.6 (*C*(5) Ar both isomers), 129.9 (br, *ipso*-Cp isomer), 131.7 (br, *ipso*-Cp isomer), 142.2 (*C*(2) Ar isomer 1 or 2), 142.5 (*C*(2) Ar isomer 1 or 2), 157.6 (*C*(1) Ar both isomers). IR (ATR.): $\tilde{\nu}$ = 3118, 2962, 2933, 2875, 2835, 1597, 1583, 1490, 1459, 1434, 1379, 1334, 1290, 1242, 1183, 1157, 1117, 1080, 1048, 1025, 908, 838, 829, 797 775, 752, 740, 712 cm^{-1}. HRMS (ESI^+) ($M+Na^+$) Calcd. for $C_{30}H_{34}Cl_2NaO_2Ti^+$ – 567.1308, found: 567.1319. CHN Anal. calcd. for $C_{30}H_{34}Cl_2O_2Ti$: C, 66.07; H, 6.28; found: C, 65.94; H, 6.28.

***Rac*/*meso*-dichloridobis(1-pentyl-1'-(2-methoxyphenyl)-η^5-cyclopentadienyl)titanium (9b):** Prepared using **7b** (606 mg, 2.50 mmol, 1.0 equiv.), dry methyl *tert*-butyl ether (10 mL) and *n*-BuLi (1.7 mL, 2.75 mmol, 1.1 equiv.) yielding **8b** (170 mg, 27% yield). This intermediate (0.69 mmol, 2.0 equiv.) dissolved in 2.8 mL dry THF to give a colourless solution. Titanium tetrachloride (0.34 mmol, 0.34 mL, 1.0 equiv.) was dissolved in 2.8 mL dry THF to give a yellow solution. After purification, a red solid was obtained (143 mg, 69% - based on titanium). The individual *rac* and *meso* diastereomers (1:1 ratio) signals could not be uniquely identified and are thus identified as isomer 1 or 2. M.p. 121-123 °C. ^{1}H NMR (500.1 MHz, $CDCl_3$, 22 °C): δ_H 0.82 (t, 6 H, *J* = 7.5 Hz, CH_2*Me* both isomers) 0.95-1.08 (br, 2 H, C_2*H*$_4$Me both isomers), 1.10-1.40 (m, 6 H, C_2*H*$_4$Me both isomers), 1.85-2.16 (m, 2.0 H, C*H*$_2$C$_3$H$_7$ both isomers), 3.78 (s, 6 H, 2 x OMe, both isomers), 4.49 (br, 2 H, *CH*-Bu both isomers), 5.95 (s, 1 H, Cp isomer 1), 6.01 (s, 2 H, Cp both isomers), 6.16 (s, 1 H, Cp isomer 2), 6.39 (s, 1 H, Cp isomer 2), 6.48 (s, 1 H, Cp isomer 1), 6.69 (s, 1 H, Cp isomer 2), 6.74 (s, 1 H, Cp isomer 1), 6.82-6.95 (m, 4 H, *H*-C(4) and *H*-C(6) Ar, both isomers), 7.03 (br d, 2 H, *J* = 6.0 Hz, *H*-C(3) Ar, both isomers), 7.20 (br t, 2 H, *J* = 7.5 Hz, *H*-C(5) Ar both isomers) ^{13}C NMR (125.8 MHz, $CDCl_3$, 25 °C): δ_C 14.1 (CH_2*Me* both isomers) 22.6 (*C*H$_2$Me both isomers), 29.4 (*C*H$_2$CH$_2$Me both isomers), 33.0 (CH*C*H$_2$C$_3$H$_7$ isomer 1 or 2) overlapped by 33.1 (CH*C*H$_2$C$_3$H$_7$ isomer 1 or 2), ≈39.5-40.5 (*CH*Bu both isomers), 55.5 (OMe both isomers), 111.1 (*C*(6) Ar both isomers), 115.2 (br, Cp isomer 1 or 2), 116.8 (br, Cp isomer 2), 117.6 (Cp isomer 2), 118.1 (Cp isomer 1), 119.2 (Cp isomer 1 or 2), 119.6 (Cp isomer 1), 120.7 (*C*(3) or *C*(4) Ar isomer 1 or 2) overlapped by 120.8 (*C*(3) or *C*(4) Ar isomer 1 or 2), 121.3 (Cp isomer 2), 123.0 (Cp isomer 1), 127.6 (C(5) Ar both isomers), 129.9 (br, *ipso*-Cp isomer), 132.2 (br, *ipso*-Cp isomer), 142.3 (C(2) Ar isomer 1 or 2), 142.8 (C(2) Ar isomer 1 or 2), 157.5 (C(1) Ar both isomers). IR (ATR): $\tilde{\nu}$ = 3105, 2954, 2928, 2869, 1596, 1585, 1491, 1463, 1438, 1336, 1288, 1240, 1189, 1162, 1124, 1088, 1051, 1029, 949, 843, 826, 804, 782, 753, 735, 714, 702, 685, 675 cm^{-1}. MS (MALDI TOF – DCTB matrix, 10% laser): m/z 565.3 (M-Cl, 100%), 530.3 (M-2Cl, 3%). CHN Anal. calcd. for $C_{34}H_{42}Cl_2O_2Ti$: C, 67.89; H, 7.04; found: C, 67.80; H, 7.08.

R*ac*/*meso*)-dichloridobis(1-(3-methylbutyl)-1'-(2-methoxyphenyl)-η^5-cyclopentadienyl)titanium (9c): Prepared using **7c** (735 mg, 3.00 mmol, 1.0 equiv.), dry ether (12.1 mL) and *n*-BuLi (2.1 mL, 3.34 mmol, 1.1 equiv.) yielding **8d** (706 mg, 2.84 mmol, 94% yield). This intermediate (2.84 mmol, 2.0 equiv.) was dissolved in 11.5 mL dry THF to give a colourless solution. Titanium tetrachloride (1.42 mmol, 1.42 mL, 1.0 equiv.) was dissolved in 11.5 mL dry THF to give a yellow solution. After purification, a red solid was obtained (682 mg, 80% - based on titanium). The individual *rac* and *meso* diastereomers (1:1 ratio) signals could not be uniquely identified and are thus identified as isomer 1 or 2. M.p. 161-162 °C. ^{1}H NMR (500.1 MHz, $CDCl_3$, 50 °C): δ_H 0.84 (d, 6 H, *J* = 6.4 Hz, C*H*$_3$CHCH$_3$ both isomers), 0.93 (d, 6 H, *J* = 6.8 Hz, CH$_3$CHC*H*$_3$ both isomers), 1.4-1.53 (m, 2 H, CH$_3$C*H*CH$_3$ both isomers), 1.75-2.15 (m, 4 H, C*H*$_2$CHCp both isomers), 3.79 (s, 6 H, 2 x OMe, both isomers), 4.45-4.85 (br, 2 H, *CH*-*i*Bu both isomers), 5.94 (s, 1 H, Cp isomer 1), 6.00 (s, 2 H, Cp both isomers), 6.16 (s, 1 H, Cp isomer 2), 6.37 (s, 1 H, Cp isomer 2), 6.48 (s, 1 H, Cp isomer 1), 6.65 (s, 1 H, Cp isomer 2), 6.72 (s, 1 H, Cp isomer 1), 6.85-6.95 (m, 4 H, *H*-C(4) and *H*-C(6) Ar, both isomers), 7.00-7.15 (br, 2 H, *H*-C(3) Ar, both isomers), 7.20 (t, 2 H, *J* = 7.6 Hz, *H*-C(5) Ar both isomers) ^{13}C NMR (125.8 MHz, $CDCl_3$, 25 °C): δ_C 21.8 (C*H*$_3$CHCH$_3$ both isomers), 24.1 (CH$_3$CHC*H*$_3$ both isomers), 25.7 (CH$_3$C*H*CH$_3$ both isomers), 42.8 (C*H*$_2$CHCp both isomers), 55.5 (OMe both isomers), 111.3 (C(6) Ar both isomers), 117.5 (br, Cp isomer 1 or 2), 117.9 (br, Cp isomer 2), 119.2 (Cp isomer 2), 119.8 (Cp isomer 1), 120.7 (C(3) or C(4) Ar isomer 1 or 2), 120.9 (Cp both isomers), 122.7 (Cp isomer 1), 127.6 (C(5) Ar both isomers), 129.9 (br, *ipso*-Cp isomer 1 or 2), 132.4 (br, *ipso*-Cp isomer 1 or 2), 142.6 (C(2) Ar isomer 1 or 2), 143.0 (C(2) Ar isomer 1 or 2), 157.6 (C(1) Ar both isomers). IR (ATR): $\tilde{\nu}$ = 3105, 2953, 2868, 2838, 1653, 1596, 1586, 1491, 1464, 1438, 1384, 1364, 1327, 1287, 1242, 1187, 1168, 1119, 1097, 1051, 1043, 1028, 906, 848, 828, 806, 754, 717, 702 cm^{-1}. MS (MALDI TOF – DCTB matrix, 10% laser): m/z 565.3 (M-Cl, 100%), 530.3 (M-2Cl, 11%). CHN Anal. calcd. for $C_{34}H_{42}Cl_2O_2Ti$: C, 67.89; H, 7.04; found: C, 67.73; H, 7.10.

R*ac*/*meso*-dichloridobis(1-but-3-en-1-yl-1'-(2-methoxyphenyl)-η^5-cyclopentadienyl)titanium (9d): Prepared using **7d** (1.09 g, 4.8 mmol, 1.0 equiv.), dry methyl *tert*-butyl ether (19.2 mL) and *n*-BuLi (3.3 mL, 5.28 mmol, 1.1 equiv.) yielding **8c** (785 mg, 71% yield). This intermediate (3.38 mmol, 2.0 equiv) was dissolved in 13.5 mL dry THF to give a colourless solution. Titanium tetrachloride (1.70 mmol, 1.70 mL, 1.0 equiv.) was dissolved in 13.5 mL dry THF to give a yellow solution. After purification, a brown solid was obtained (713 mg, 74% - based on titanium). The individual *rac* and *meso* diastereomers (1:1 ratio) signals could not be uniquely identified and are thus identified as isomer 1 or 2. M.p. 139-140 °C. ^{1}H NMR (500.1 MHz, $CDCl_3$, 25 °C): δ_H 2.71-2.83 (m, 2 H, C*H*$_2$CH-Cp isomer 1 or 2), 2.87-2.97 (m, 2 H, C*H*$_2$CH-Cp isomer 1 or 2), 3.78 (s, 6 H, 2 x O*Me* both isomers), 4.55-4.70 (m, 2 H, CH$_2$C*H*-Cp both isomers), 4.80-4.85 (br s, 1 H, C*H*$_2$C$_2$H$_3$-CH isomer 1 or 2), 4 (br s, 1 H, C*H*$_2$C$_2$H$_3$-CH isomer 1 or 2), 4.92-4.95 (br m, 1 H, C*H*$_2$C$_2$H$_3$-CH isomer 1 or 2), 4.95-4.97 (br m, 1 H, C*H*$_2$C$_2$H$_3$-CH isomer 1 or 2), 5.58-5.67 (m, 2 H, CH$_2$C*H*CH$_2$ both isomers), 5.98 (AB, 1 H, J_{Aq} = 2.0 Hz, Cp isomer 1), 6.02 (AB, 1 H, J_{AB} = 2.5 Hz, Cp isomer 2), 6.08 (AB, 1 H, J_{AB} = 2.0 Hz, Cp isomer 1), 6.18 (AB, 1 H, J_{AB} = 2.0 Hz, Cp isomer 2), 6.41 (AB, 1 H, J_{AB} = 2.5 Hz, Cp isomer 2), 6.45 (AB, 1 H, J_{AB} = 2.5 Hz, Cp isomer 1), 6.71-6.73 (2 x AB, 2 H, J_{AB} = 2.5 Hz, C_5H_4 both isomers), 6.85-6.91 (m, 4 H, *H*-C(4) and *H*-C(6) Ar, both isomers), 6.99-7.05 (t, 2 H, *J* = 6.5 Hz, *H*-C(3) Ar, both isomers), 7.20 (ddd, 2 H, *J* = 8.0, 7.5, 1.5 Hz, *H*-C(5) Ar). ^{13}C NMR (125.8 MHz, $CDCl_3$, 25 °C): δ_C 37.5 (*C*H$_2$CH-Cp isomer 1 or 2) *overlapped by* 37.5 (*C*H$_2$CH-Cp isomer 1 or 2), 40.6 (Cp-*C*H-Ph both isomers), 55.4 (OMe both isomers), 111.0 (C(6) Ar both isomers), 115.2 (br, Cp isomer 1), 116.1 (*C*H$_2$C$_2$H$_3$-CH both isomers) *overlapped by* 116.1 (Cp isomer 2), 117.4 (Cp isomer 2), 118.4 (Cp isomer 1), 118.6 (Cp isomer 1), 119.3 (Cp isomer 2), 120.6 (C(3) or C(4) Ar both isomers), 121.8 (Cp isomer 2), 122.8 (Cp isomer 1), 127.8 (C(5) Ar both isomers), 130.1 (br, *ipso*-Cp isomer), 131.3 (br, *ipso*-Cp isomer), 136.4 (CH$_2$C*H*CH$_2$ both isomers), 141.5 (C(2) Ar isomer 1 or 2), 141.7 (C(2) Ar isomer 1 or 2), 157.2 (C(1) Ar both isomers). IR (ATR): $\tilde{\nu}$ = 3074, 2939, 2836, 1639, 1598, 1588, 1492, 1462, 1438, 1421, 1337, 1288, 1275, 1244, 1177, 1123, 1093, 1078, 1052, 1030, 995, 960, 907, 847, 816, 786, 753, 732, 718 cm^{-1}. MS (MALDI TOF – DCTB matrix, 10% laser): m/z 533.2 (M-Cl, 100%), 430.3 (M-2Cl, 6%). HRMS (ESI^+) ($M+Na^+$) Calcd. for $C_{32}H_{34}Cl_2O_2TiNa^+$ – 591.1308, found: 591.1313. CHN Anal. calcd. for $C_{32}H_{34}Cl_2O_2Ti$: C, 67.50; H, 6.02; found: C, 67.86; H, 6.02.

R*ac*/*meso*)-dichloridobis(1-ethyl-1'-(2-methoxyphenyl)-η^5-cyclopentadienyl)titanium (9e): Prepared using **7e** (802 mg, 4.00 mmol, 1.0 equiv.), dry ether (16.0 mL) and *n*-BuLi (2.70 mL, 4.40 mmol, 1.1 equiv.) yielding **8e** (738 mg, 89%). This intermediate (3.58 mmoles, 2.0 equiv.) was dissolved in 14.0 mL dry THF to give a colourless solution. Titanium tetrachloride (1.80 mmol, 1.80 mL, 1.0 equiv.) was dissolved in 14.0 mL dry THF to give a yellow solution. After purification, a red solid was obtained with a yield (based on titanium) of 51% (472 mg, 0.91 mmol). The individual *rac* and *meso* diastereomers (1:1 ratio) signals could not be

uniquely identified and are thus identified as isomer 1 or 2. M.p. 144-145 °C. ^{1}H NMR (500.1 MHz, $CDCl_3$, 25 °C): δ_H 1.54 (d, 3 H, *J* = 7.0 Hz, CH*Me* isomer 1 or 2) *overlapped by* 1.55 (d, 3 H, *J* = 7.0 Hz, CH*Me* isomer 1 or 2), 3.81 (s, 3 H, O*Me*, isomer 1 or 2) *overlapped by* 3.82 (s, 3 H, O*Me*, isomer 1 or 2), 4.67-4.75 (m, 2 H, *CH*Me both isomers), 6.06 (Ap, 1 H, J_{Aq} = 2.5 Hz, Cp isomer 1) *overlapped by* 6.08 (AB, 1 H, J_{AB} = 2.5 Hz, Cp isomer 2), 6.29 (AB, 1 H, J_{AB} = 2.5 Hz, Cp isomer 1) overlapped by 6.31 (AB, 1 H, J_{AB} = 2.5 Hz, Cp isomer 2), 6.43-6.46 (m, 2 H, Cp both isomers), 6.72-6.76 (m, 2 H, Cp both isomers), 6.84-6.90 (m, 4 H, *H*-C(4) and *H*-C(6) Ar, both isomers), 6.94 (dd, 1 H, *J* = 7.0 Hz, 1.5 Hz, *H*-C(3) Ar, isomer 1 or 2) *overlapped by* 6.95 (dd, 1 H, *J* = 7.0 Hz, 1.5 Hz, *H*-C(3) Ar, isomer 1 or 2), 7.19 (ddd, 1 H, *J* = 7.0, 6.5, 1.0 Hz, *H*-C(5) Ar) *overlapped by* 7.20 (ddd, 1 H, *J* = 7.0, 6.5, 1.0 Hz, *H*-C(5) Ar) ^{13}C NMR (125.8 MHz, $CDCl_3$, 25 °C): δ_C 19.3 (CH*Me* both isomers), 34.5 (*CH*Me both isomer 1 or 2) overlapped by 34.5 (*CH*Me both isomer 1 or 2), 55.4 (OMe both isomers), 110.9 (C(6) Ar both isomers), 116.3 (Cp isomer 1), 116.3 (Cp isomer 2), 117.2 (Cp isomer 1), 117.4 (Cp isomer 2), 119.0 (Cp isomer 1), 119.4 (Cp isomer 2), 120.7 (C(3) or C(4) Ar both isomers), 121.8 (Cp isomer 2), 122.0 (Cp isomer 1), 127.5 (C(5) Ar both isomers), 128.7 (C(3) or C(4) Ar both isomers), 134.6 (*ipso*-Cp both isomers), 142.2 (C(2) Ar isomer 1 or 2), 142.5 (C(2) Ar isomer 1 or 2), 156.6 (C(1) Ar both isomers). IR (ATR): $\tilde{\nu}$ = 3110, 2936, 2834, 1598, 1586, 1491, 1461, 1437, 1421, 1366, 1334, 1290, 1241, 1179, 1123, 1110, 1076, 1043, 1031, 986, 917, 861, 851, 827, 812, 753, 706 cm^{-1}. MS (MALDI TOF – DCTB matrix, 10% laser): m/z 481.1 (M-Cl, 100%), 446.1 (M-2Cl, 29%). HRMS (ESI$^+$) (M+Na$^+$) Calcd. for $C_{28}H_{30}Cl_2O_2TiNa^+$ – 539.0995, found: 539.1004. CHN Anal. calcd. for $C_{28}H_{30}Cl_2O_2Ti$: C, 65.01; H, 5.85; found: C, 65.33; H, 6.14.

***Rac*-dichloridobis(1-(phenyl)methyl-1'-(2-methoxyphenyl)-η^5-cyclopentadienyl)titanium (9f):** Prepared using **7f** (707 mg, 2.70 mmol, 1.0 equiv.), dry ether (10.8 mL) and *n*-BuLi (1.90 mL, 2.97 mmol, 1.1 equiv.) yielding **8f** (568 mg, 78% yield). This intermediate (2.12 mmol, 2.0 equiv), then dissolved in 8.5 mL dry THF to give a colourless solution. Titanium tetrachloride (1.05 mmol, 1.05 mL, 1.0 equiv.) was dissolved in 8.5 mL dry THF to give a yellow solution. Purification involved the dissolution of the crude red solid, 0.350 g (66%), in a saturated solution of chloroform (1 part) followed by layering of hexane (4 parts), giving red crystals of the *rac*-isomer of **9f** (confirmed by X-ray data) with a yield (based on titanium) of (93.0 mg, 14% - based on titanium). The mother liquors *ca*. 50% contained a *rac/meso* mixture of **9f** that could not be brought to a state of analytical purity despite repeted trials. M.p. 244-245 °C. ^{1}H NMR (500.1 MHz, $CDCl_3$, 25 °C): δ_H 3.67 (s, 6 H, 2 x O*Me*), 4.87 (AB, 2 H, J_{AB} = 2.5 Hz, Cp), 5.97 (br s, 2 H, C*H*Ph), 5.99 (AB, 2 H, J_{AB} = 2.5 Hz, Cp), 6.42 (AB, 2 H, J_{AB} = 2.5 Hz, Cp), 6.68 (dd, 2 H, *J* = 7.5, 1.5 Hz, Ph), 6.76 (AB, 2 H, J_{AB} = 2.5 Hz, Cp), 6.78-6.83 (m, 4 H, *H*-C(4) and *H*-C(6) Ar), 7.17 (dd, 1 H, *J* = 7.5 Hz, 1.5 Hz, *H*-C(3) Ar), 7.18-7.23 (m, 7 H, Ph and Ar), 7.25 (br s, 2 H, Ph), 7.26-7.27 (m, 2 H, Ph), 7.27-7.28 (m, 1 H, Ph). ^{13}C NMR (125.8 MHz, $CDCl_3$, 25 °C): δ_C 45.9 (*CH*Ph) 55.4 (OMe), 110.3 (Cp), 110.8 (C(6) Ar), 116.0 (Cp), 120.0 (Ar), 123.7 (Cp), 126.6 (Ar or Ph), 127.9 (Ar or Ph) *overlapped by* 127.9 (Ar or Ph), 128.8 (Ph), 129.6 (Ph or Ar), 131.8 (Cp), 132.7 (Ph), 140.5 (Ar or Ph), 141.5 (Ar or Ph), 158.7 (C(1) Ar). IR (ATR): $\tilde{\nu}$ = 3119, 2838, 1599, 1584, 1488, 1461, 1452, 1436, 1341, 1319, 1290, 1246, 1187, 1162, 1008, 1075, 1058, 1050, 1029, 953, 940, 898, 847, 837, 826, 794, 783, 765, 751, 735, 728, 700, 686 cm^{-1}. MS (MALDI TOF – DCTB/NaI matrix, 25% laser): m/z 605.2 (M-Cl, 100%), 570.2 (M-2Cl, 7%). HRMS (ESI$^+$) (M+Na$^+$) Calcd. for $C_{38}H_{34}Cl_2O_2TiNa^+$ – 663.1308, found: 663.1315. CHN Anal. calcd. for $C_{39}H_{36}Cl_4O_2Ti$ (**9f** dichloromethane monosolvate from CH_2Cl_2/hexanes): C, 64.49; H, 5.00; found: C, 64.61; H, 5.00.

Dichloridobis-1-(2-methoxyphenyl)-η^5-cyclopentadienyl) titanium (10): Procedure as in literature.[11] The compound had properties identical to those in the primary literature (^{13}C NMR, IR, MS, CHN analyses) but its ^{1}H NMR specrum showed differences in the multiplicities of the C_5H_4 'Cp' protons: ^{1}H NMR (500.1 MHz, $CDCl_3$, 22 °C): δ_H 3.84 (s, 6.0 H, 2 x O*Me*), 4.03 (s, 4 H, 2 x Cp-C*H*$_2$), 6.33 (t, 4 H, *J* = 5.5 Hz, 2 x Cp), 6.40 (t, 4 H, *J* = 5.0 Hz, 2 x Cp), 6.85-6.92 (m, 4 H, 2 x Ar), 7.16 (dd, 2 H, *J* = 7.5 Hz, 1.5Hz, *H*-C(6')), 7.23 (dt, 2 H, *J* = 7.5 Hz, 1.5 Hz, Ar).

Growth inhibitory studies *in vitro*

The antiproliferative activity was performed by MTT [3-(4, 5-dimethyl-thiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay on three different human carcinoma cell lines; colon (HCT-116), pancreas (MiaPaCa-2), and breast (MDA-468). The carcinoma cell lines were maintained in RPMI 1640 medium supplemented with 10% (v/v) FBS (foetal bovine serum). Cells were seeded into 96-well plates at a density of 3 x 10^3 per well (180 µL per well) and allowed to adhere for 24 h at 37 °C / 5% CO_2. A 10 mM top stock solution in DMSO was then freshly made. Serial dilutions were prepared in RMPI 1640 medium supplemented with 10% FBS. Control wells recieved vehicle alone (20 µL per well). The final concentrations in the wells were; 0.01 µM, 0.1 µM, 0.5 µM, 1 µM, 5 µM, 10 µM, 50 µM and 100 µM. The final concentration of DMSO in the wells never exceded 1%. Vehicle control assays were performed (0.0001 – 1% DMSO) Experimental plates were incubated for a further 72 h period at 37 °C / 5% CO_2. Cell viability was recorded at the time of agent addition (T_0) and following 72 h exposure: following addition of MTT solution (2 mg/mL in PBS - 50 µL per well), experimental plates were incubated for 3 h to allow reduction of MTT to insoluble dark purple formazan crystals. The supernatant in each well was then aspirated and cellular formazan solublised by addition of DMSO (150 µL per well). Absorbance was read at a wavelength of 550 nm using an Anthos Labtec systems plate reader. Measured intensity is proportional to metabolic activity which correlates to cellular viability. Agent GI_{50} values (the concentration of agent which inhibits growth by 50%) were calculated by performing MTT assays at time of drug addition as well as after 72 h exposure.

Supporting Information ^{1}H and ^{13}C NMR spectra for all compounds prepared in this study.

Acknowledgments

One of us (MC) is grateful to the Strategic Educational Pathways Scholarship (Malta) – Scholarship part-financed by the European Union – European Social Fund and the Schools of Chemistry and Pharmacy University of Nottingham and the Edith Johnson bequest for the provision of studentship support at M.Sc. and Ph.D. levels respectively.

References

[1] H. Köpf, P. Köpf-Maier, *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 477-478.

[2] Biology overviews: a) S. Gómez-Ruiz, D. Maksimović-Ivanić, S. Mijatović, G. N. Kaluđerović, *Bioinorg. Chem. and Appl.* **2012**, 140284 (esp. Sec. 2); b) U. Olszewski, G. Hamilton, *Anti-Cancer Agents in Medicinal Chemistry* **2010**, *10*, 302-311.

[3] Structure optimisation reviews: a) M. Hogan, M. Tacke in *Topics in Organometallic Chemistry* (Eds.: G. Jaouen, N. Metzler-Nolte) Springer, New York, **2010**, vol. 32, pp. 119-140; b) K. Strohfeldt, M. Tacke, *Chem. Soc. Rev.* **2008**, *37*, 1174-1187. Selected recent synthetic developments: c) J. Claffey, H. Müller-Bunz, M. Tacke, *J. Organomet. Chem.* **2010**, *695*, 2105-2117; d) M. Napoli, C. Saturnino, E. Sirignano, A. Popolo, A. Pinto, P. Longo, *Eur. J. Med. Chem.* **2010**, *46*, 122-128. e) L. M. Gao, J. L. Vera, J. Matta, E. Meléndez, *J Biol. Inorg. Chem.* **2010**, *15*, 851-859; f) J. Zagermann, A. Deally, N. Metzler-Nolte, H. Mueller-Bunz, D. Wallis, M. Tacke, *Polyhedron* **2011**, 30, 2387-2390; g) J. Ceballos-Torres, S. Gomez-Ruiz, G. N. Kaluderovic, M. Fajardo, R. Paschke, S. Prashar, *J.*

Organomet. Chem. **2012**, *700*, 188-193; h) M. L. Hlavinka, Q. Yang, M. M. Murph, *PCT Int. Appl.* WO 2012170384 A1 20121213, **2012** 91 pp; i) A. Deally, F. Hackenberg, G. Lally, H. Muller-Bunz, M. Tacke, *Organometallics* **2012**, *31*, 5782-5790.

[4] Overviews: a) R. L. Halterman, *Chem. Rev.* **1992**, *92*, 965-94. b) M. Hapke, C. C. Tzschucke, *Angew. Chem. Int. Ed.* **2013**, *52*, 3317-3319. Selected recent applications of substituted CpTi species: c) D. J. Cho, C. J. Wu, S. Sujith, W.-S. Han, S. O. Kang, B. Y. Lee, *Organometallics* **2006**, *25*, 2133-2134; d) A. Gansäuer, M. Otte, L. Shi, *J. Am. Chem. Soc*. **2011**, *133*, 416-417; e) A. Gansäuer, A. Okkel, D. Worgull, G. Schnakenburg, *Organometallics*, **2010**, *29*, 3227-3230; f) T. Janssen, R. Severin, M. Diekmann, M. Friedemann, D. Haase, W. Saak, S. Doye, R Beckhaus, *Organometallics* **2010**, *29*, 1806-1817.

[5] a) M. Welker, S. Woodward, A. Alexakis, *Org. Lett.* **2010**, *12*, 576-579; b) X. Tang, A. J. Blake, W. Lewis, William, S. Woodward, *Tetrahedron: Asym.* **2009**, *20*, 1881-1891; c) X. Tang, S. Woodward, N. Krause, *Eur. J. Org. Chem.* 2009, 2836-2844.

[6] Displacement of Cp from CpCu: a) A. L. Johnson, A. M. Willcocks, P. R. Raithby, M. R. Warren, A. J. Kingsley, R. Odedra, *Dalton Trans.* **2009**, 922-924. b) M. Swart, *Inorg. Chim. Acta* **2007**, *360*, 179-189; c) A. N. Shoshkin, L. N. Bochkarev, S. Ya. Khorshev, *Russ. J. Gen. Chem.* **2002**, *72*, 715-716; d) A. J. Edwards, M. A. Paver, P. R. Raithby, M.-A. Rennie, C. A. Russell, D. S. Wright, *Organometallics* **1994**, *13*, 4967-4972; e) H. K. Shin, M. J. Hampden-Smith, E. N. Duesler, T. T. Kodas, *Polyhedron* **1991**, *10*, 645–647; J. E. Maansson, T. Olsson, O. Wennerstroem, *Acta Chem. Scand., Ser. B* **1979**, *B33*, 307-308.

[7] J. Honzicek, I. Klepalova, J. Vinklarek, Z. Padelkova, I. Cisarova, P. Siman, M. Rezacova, *Inorg. Chim. Acta* **2011**, *373*, 1-7.

[8] B. H. Lipshutz, R. S. Wilhelm, D. M. Floyd, *J. Am. Chem. Soc.* **1981**, *103*, 7672-7674.

[9] S. Woodward *Tetrahedron* **2002**, *58*, 1017-1050.

[10] Cambridge Crystallographic Data Centre (CCDC, www.ccdc.cam.ac.uk). Structures used were: ECUHEQ, ECUJAO, KEDKEJ, MAJMAM and VATWAO.

[11] J. Claffey, M. Hogan, H. Müller-Bunz, C. Pampillón, M. Tacke, *J. Organomet. Chem.* **2008**, *693*, 526-536.

[12] Summaries of cancer therapy data: a) www.cancerresearchuk.org b) K. R. Bauer, M. Brown, R. D. Cress, C. A. Parise, V. Caggiano, *Cancer*, **2007**, *109*, 1721-1728.

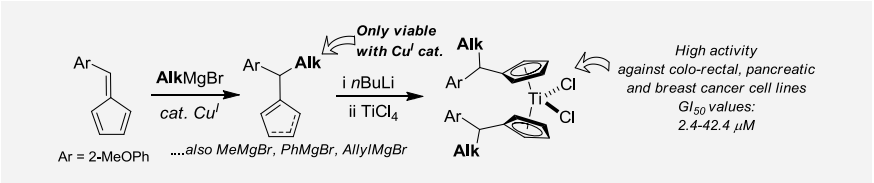
[13] G. Keltera, N. J. Sweeney, K. Strohfeldt, H.-H. Fiebig, M. Tacke, *Anti-Cancer Drugs* **2005**, *16*, 1091-1098.

[14] Unpaired t-tests were performed using GraphPad Prism version 6.00 for Windows, GraphPad Software, San Diego California USA, www.graphpad.com

Received: ((will be filled in by the editorial staff))
Published online: ((will be filled in by the editorial staff))

Entry for the Table of Contents

((Cyclopentadienes))



((Text for Table of Contents))

Direct addition of Alkyllithium and Grignard reagents with β-hydrogens to fulvenes has been dogged with problems of competing hydride transfer. Copper-catalysis overcomes this and allows access to titanocene dichlorides with high anti cancer activity.

((Melchior Cini, Tracy Bradshaw,* William Lewis and Simon Woodward*)) ……..... Page No. – Page No.

Cuprate addition to a 6-substituted pentafulvene: preparation of *sec*-alkyl substituted titanocene dichlorides and their biological activity

Keywords: ((**Alkylation** / **Antitumor agents** / **Titanium** / **Fulvene** / **Grignard**))