# Modular Synthesis of Functional Titanocenes

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A modular approach to carbonyl-functionalized titanocenes is described. Through the introduction of highly electrophilic acid chlorides to the complexes, reactions with nucleophiles can be realized that are incompatible with classical methods of titanocene synthesis. The first amino acid functionalized titanocenes were synthesized. The amide- and ketone-functionalized titanocenes are cationic, due to the complexation of the carbonyl groups that results in the formation of unstrained rings.

## Introduction

Organometallic complexes, and in particular metallocenes containing additional organic groups, have recently attracted considerable interest.[1] This has been especially so when both the metal and the organic fragment are able to bind and recognize other molecular entities or to mediate reactivity. Such bifunctional molecules are highly attractive as catalysts, for the generation of supramolecular aggregates, and for the selective binding of biological targets in medicinal chemistry.

Due to the Lewis acidity of their metals, group 4 metallocenes are of special interest in this respect. With appropriate substitution they can interact with both (Lewis) acidic and basic sites. Therefore, they have been employed successfully in the topical and interdisciplinary fields of organometallic antitumor agents[2] and organometallic gelators.[3]

Additionally, such complexes are also very interesting as electron transfer catalysts in reductive epoxide openings[4] for two reasons. First, in the same manner as for the addition of potent donor solvents,[5] the redox potential and Lewis acidity of titanocene(III) complexes can be tailored by interactions with appended donor ligands. In this way, the lifetime of the epoxide -derived radicals can be increased to enable kinetically and thermodynamically unfavorable transformations.[6,7] Second, the regioselectivity of epoxide opening, e.g. in enantioselective reactions,[8] can be controlled by fine tuning of the catalyst's steric demand.[9] This constitutes an approach more general and flexible than the introduction of bulky alkyl groups.[10]

Unfortunately, access to these functional complexes has, until recently, been rather difficult.[11] Because the [$TiCl_2$] fragment is rather electrophilic, titanocenes have been considered to be incompatible with most of the nucleophilic reagents typically used in organic synthesis. Introduction of functional groups is thus usually carried out early in the synthetic sequence before the metalation with titanium. In this manner a large variety of ether-, amine-, and thiol-substituted cyclopentadienes and the corresponding metallocenes have been prepared.[11]

However, this straightforward approach employing functionalized cyclopentadienyl anions has distinct disadvantages.[12]

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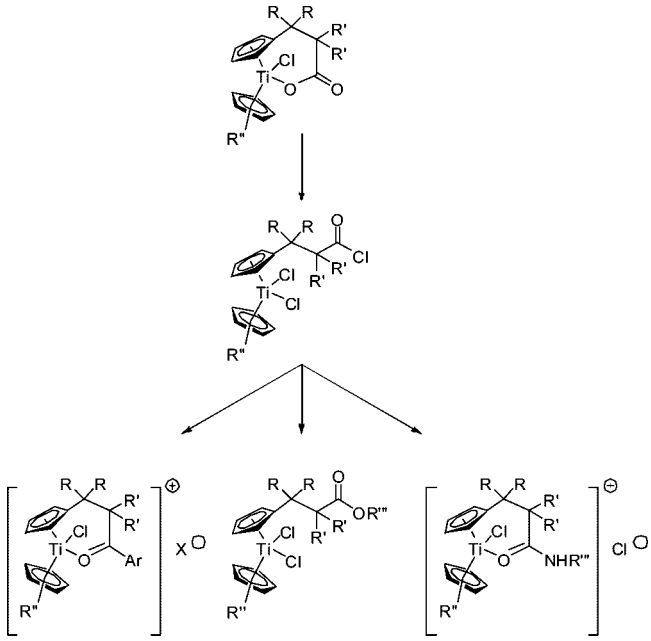
**Scheme 1. Modular Synthesis of Functionalized Titanocenes**



First, both the generation and use of these basic and strongly nucleophilic anions precludes the simple introduction of protic functional groups and synthetically useful carbonyl groups such as aldehydes and ketones. To the best of our knowledge, only unreactive alkyl-substituted amide groups have been successfully attached to titanocenes in this manner.[13] Second, the linear sequences usually employed do not allow the rapid preparation of large numbers of structurally and functionally diverse complexes due to the absence of synthetic branching points. Such an efficient approach is, however, essential for investigations in catalysis or medicinal chemistry, where screening of large parts of chemical space[14] is mandatory.

A modular route employing functional building blocks already containing the $[TiCl_2]$ fragment would circumvent these problems and, moreover, allow rapid and efficient access to titanocene complexes with novel properties. Here, we report exactly such a modular titanocene synthesis.[15]

## Results and Discussion

**Synthetic Strategy.** The key to using the building blocks as synthetic branching points is the incorporation of functional groups that are more electrophilic than the $[TiCl_2]$ moiety. We chose carboxylic acid chlorides as our target because they are highly reactive, can be prepared from carboxylic acid derivatives, and are among the most useful functional groups for the preparation of a wide variety of compounds by classical organic reactions. These transformations include the acylation of hetero nucleophiles and Friedel−Crafts acylation.[16] Thus, from a single building block large numbers of structurally and functionally diverse complexes become readily available (Scheme 1). All complexes described in this paper with a carbonyl group coordinated by titanium are chiral and have been obtained in racemic form.

**Scheme 2. Synthetic Approach to the Titanocene Carboxylates 4**

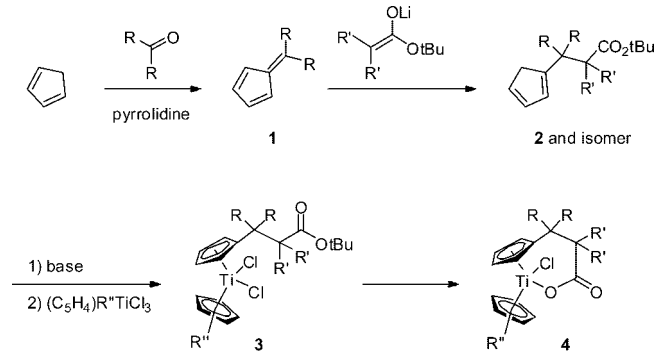


**Table 1. Synthesis of the Titanocene Carboxylates 4a−k**

| compd | R, R | R′, R′ | R″ | **2**[a]/% | **4**[b]/% |
|---|---|---|---|---|---|
| **a** | $CH_3$, $CH_3$ | H, H | H | 81 | 66 |
| **b** | $CH_3$, $CH_3$ | H, H | $CH_3$ | 81 | 40 |
| **c** | $CH_3$, $CH_3$ | H, H | $C(CH_3)_3$ | 81 | 50 |
| **d** | $CH_3$, $CH_3$ | H, H | 5 $CH_3$[c] | 81 | 47 |
| **e** | $CH_3$, $CH_3$ | $CH_3$, $CH_3$ | H | 16 | 67 |
| **f** | $(CH_2)_4$ | H, H | H | 57 | 58 |
| **g** | $(CH_2)_5$ | H, H | H | 50 | 61 |
| **h** | $(CH_2)_5$ | H, H | $C(CH_3)_3$ | 50 | 52 |
| **i**[d] | $(CH_2CH_2)_2CH$*t*Bu | H, H | H | 61 | 63 |
| **j** | $(CH_2CH_2)_2CH$*t*Bu | H, H | $C(CH_3)_3$ | 61 | 35 |
| **k** | *n*Bu, *n*Bu | H, H | H | 76 | 52 |

[a] From **1**. [b] From **2**. [c] Cp* as ligand. [d] See Figure2 for the structure of **4i**.

**Preparation of the Carboxylates.** For the flexibility of the synthesis, it is essential that the carboxylates themselves can be prepared in a general and modular manner. To realize this goal, we chose the synthetic sequence shown in Scheme 2.

It features two key steps. First, the introduction of the pivotal ester group is realized through an enolate addition to the fulvene **1**[17] to generate the functionalized cyclopentadienyl ligand **2**. This demonstrates that *tert*-butyl esters are compatible with the nucleophilic cyclopentadienyl anion. Second, after metalation with the (substituted) half-titanocenes, **3** is generated. The *tert*-butyl ester in **3** was chosen with the intention of an acid-induced ester cleavage that could even be promoted by the $[TiCl_2]$ fragment. Indeed, in most cases it turned out to be impossible to isolate **3** and in many cases pure **4** was obtained directly. When mixtures of **3** and **4** were obtained, the formation of **4** could be completed either by simple heating in toluene or by reaction with $ZnCl_2$. These results are summarized in Table 1.

The yields of cyclopentadiene formation are good to high, with the exception of **2e**, and are typically in the range of 40−70% for the metalation and ester cleavage that leads to the preparation of **4**. The molecular structures of **4a**,**e**, which demonstrate the intramolecular carboxylate formation, are shown in Figure 1. The Ti−O bond lengths of 1.95 and 1.91 Å are close to the value observed for the titanocene bis(benzoate) (1.92 Å).[18] The almost perfect staggering of the substituents of the $C(sp^3)-C(sp^3)$ bond of the tether in **4a**,**e** suggests strongly that the titanium-containing ring formed during ester cleavage is unstrained.

It should be noted that in the preparation of **4i** the issue of diastereoselectivity of the enolate addition to **1i** arises. We have

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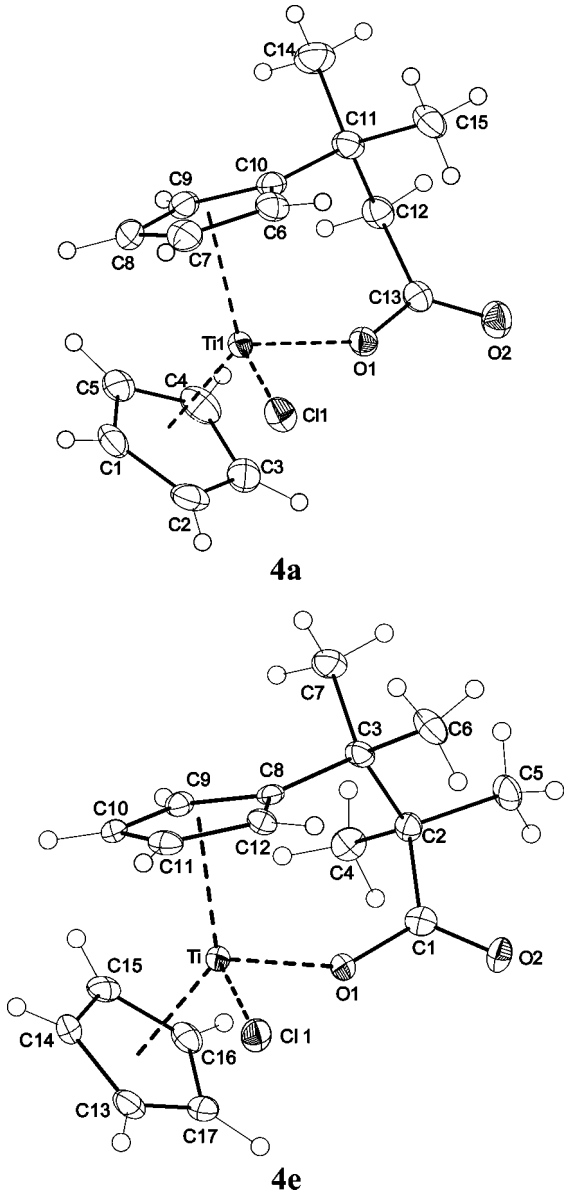


**Figure 1.** Molecular structures of **4a**,**e**. Displacement parameters are drawn at the 50% probability level. In **4a** the solvent toluene is not shown for reasons of clarity.

not yet been able to grow single crystals suitable for analysis by X-ray crystallography. The substitution pattern of the cyclohexane shown in Figure 2 is, however, strongly supported by the structure of the closely related **5**. It was prepared as a single isomer by addition of MeLi to **1i** followed by metalation with $TiCl_4$ and subsequent reaction of the half-titanocene obtained in this way with NaCp. The titanocene moiety is positioned axially and the *tert*-butyl equatorially. The Supporting Information gives details of the synthesis and characterization. The mechanistically analogous equatorial addition of nucleophiles to 4-*tert*-butylcyclohexanone lends further support to our assignment.[19]

Because all reactions employed are general with respect to substitution of the substrates, the carboxylate substitution pattern

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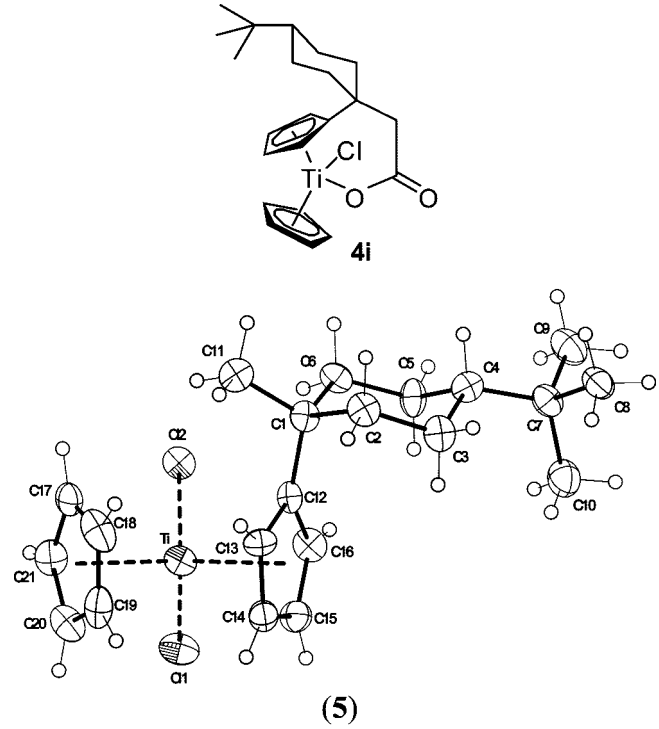
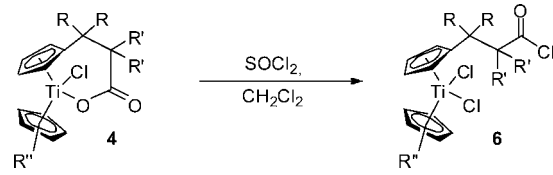



**Figure 2.** Proposed Structure of **4i** and molecular structure of **5**. Displacement parameters are drawn at the 50% probability level.

**Scheme 3. Preparation of the Acid Chlorides 6**




can be easily varied. Thus, our highly modular synthesis allows a straightforward access to large numbers of derivatives of **4**.

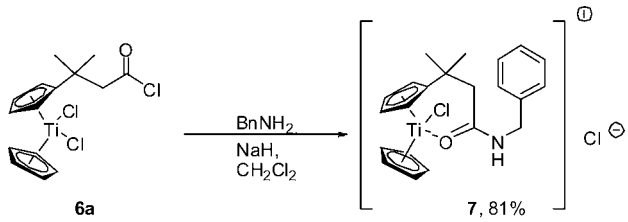
**Synthesis of Carbonyl-Substituted Titanocenes.** We turned our attention toward the use of the carboxylates as building blocks in acylation reactions of heteronucleophiles and Friedel−Crafts acylations. To this end, the corresponding acid chlorides **6** had to be prepared. We exploited the high stability of titanocenes toward acidic reaction conditions by treating the complexes **4** with $SOCl_2$, as shown in Scheme 3.

We assumed that the acid chlorides **6** were obtained in quantitative yield and used them without further purification. For the success of the ensuing reactions, it is essential that excess $SOCl_2$ is completely removed. This was routinely achieved by heating of the samples of **6** to 50 °C under vacuum for 2−3 h.

**Preparation of the Amide-Functionalized Titanocenes.** With the acid chlorides in hand, we investigated the preparation of the amides via acylation of amines. The optimized conditions for the reaction of benzylamine with **6a** are depicted in Scheme 4.

The use of NaH as base is essential for the success of the transformation. The byproducts of the reaction are either volatile ($H_2$) or can be removed by simple filtration (NaCl). It is indispensable that high-quality NaH be used. In the presence of NaOH, which is present in old or not properly handled samples of NaH, extensive decomposition of the titanocenes occurs, presumably through attack of the oxygen nucleophile at the titanium center. This is readily apparent from the color change from dark red (titanocenes intact) to light yellow. Amine

**Scheme 4. Optimized Preparation of 7 by Acylation of Benzylamine with 6a**




bases can be used to obtain the desired amides. However, we found it very hard to remove the amine hydrochlorides formed from the highly polar **7**. Polymer-bound pyridines also gave no satisfactory results.

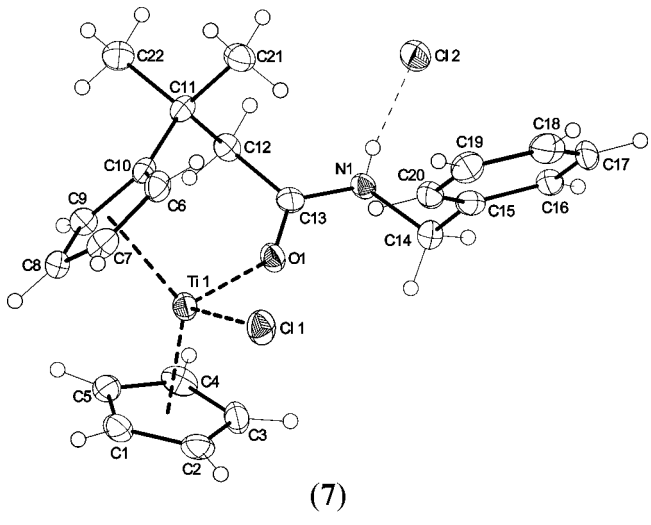
The cationic structure of **7** in the solid state is shown in Figure 3 and was proven by X-ray crystallography. The Ti−O distance (1.98 Å) is only slightly longer than in the carboxylate **4a** (1.95 Å). This indicates a rather strong interaction between the amide and the metal center. The almost perfect staggering of the substituents of the $C(sp^3)-C(sp^3)$ bond of the tether suggests an unstrained complexation for the amides, also. This is in sharp contrast to Erker's cationic complex[13] containing an additional $CH_2$ group in the tether that leads to 1,3-diaxial interactions. The shortened amide C−N bond (1.31 Å) reflects the mesomeric stabilization of the positive charge by the +M effect of N.

The higher stability of our cationic complexes is also reflected by their spontaneous formation. No activation by chloride abstraction with Meerwein's salt is necessary, as in Erker's case.[13] The ease of generation of our cationic titanocenes may well be essential for applications in catalysis.

In solution complexation is apparent from the NMR spectra. The protons of the methylene group α to the amide are diastereotopic and appear as an AB system. The same pattern is observed for the signal of the benzylic protons. Moreover, the methyl groups are diastereotopic in the $^1H$ NMR spectrum and the $^{13}C$ NMR spectrum. Without coordination of the amide by titanium, this could not be the case.

Our reaction conditions are quite general with respect to the alkyl groups derived from the pentafulvene, as summarized in Table 2. Only in the case of the highly substituted **9** was a relatively low yield of the amide observed.

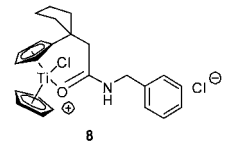
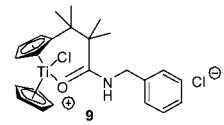
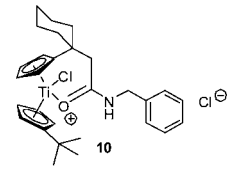
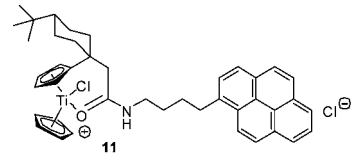
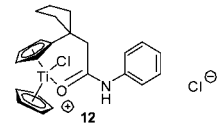
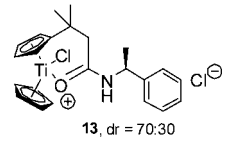
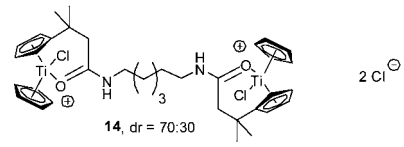
Recently, organometallic compounds that contain amino acids and peptides have attracted considerable interest as potential drugs and for the specific labeling of functional groups.[17c,20] However, titanocene-labeled amino acids and esters have remained elusive as of yet. To the best of our knowledge, the only related compound has been obtained by Beck via addition of the lithiated Schöllkopf auxiliary to dimethylfulvene and ensuing metalation of the cyclopentadienyllithium with $Cp^*TiCl_3$. However, no attempts for demasking the amino acid have been reported.[17c]




(7)

**Figure 3.** Structure of **7** in the solid state. Displacement parameters are drawn at the 50% probability level.

**Table 2. Synthesis of Amide-Functionalized Titanocenes**

| product | yield/ % |
|---|---|
|  **8** | 74 |
|  **9** | 34 |
|  **10** | 81 |
|  **11** | 53 |
|  **12** | 76 |
|  **13**, dr = 70:30 | 68 |
|  **14**, dr = 70:30 | 82 |

We therefore employed the titanocene-modified acid chlorides **5** in acylation reactions of amino acid esters. It turned out that using the amino ester hydrochlorides with NaH directly did not yield satisfactory results. Instead, the hydrochlorides were first treated with a suspension of $K_2CO_3$ in $CH_2Cl_2$ to yield the free amines. These relatively unstable compounds were readily acylated by **6a** in the presence of NaH. For the success of these reactions, it is essential to ensure that the amino acid hydrochlorides are dry. Otherwise, lower yields and extensive decomposition are observed. The conditions for the preparation of **15**−**18** are shown in Scheme 5.

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**Scheme 5. Conditions for the Acylation of Amino Acid Ester Hydrochlorides**

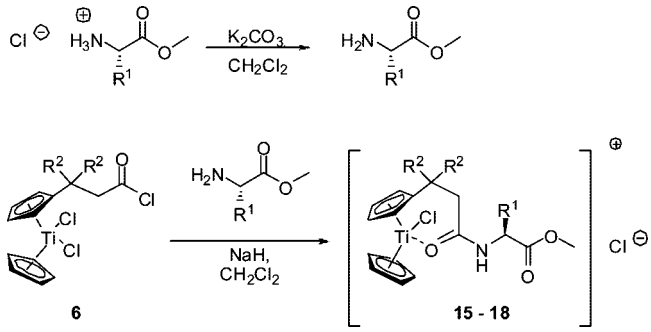
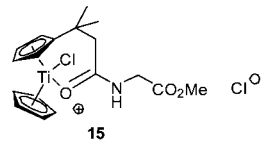
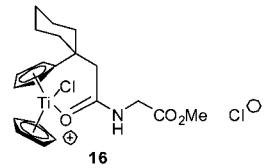
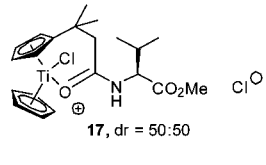
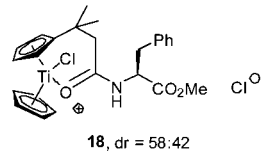



**Table 3. Synthesis of Amino Acid Functionalized Titanocenes**

| product | yield/ % |
|---|---|
|  **15** | 84 |
|  **16** | 68 |
|  **17**, dr = 50:50 | 60 |
|  **18**, dr = 58:42 | 31 |

Under these conditions we have been able to obtain the first examples of titanocene-functionalized amino acids, as summarized in Table 3.

The molecular structure of **15** in the solid state is depicted in Figure 4. As for the other amides, the carbonyl oxygen is coordinated by titanium, resulting in the formation of a cationic complex. The Ti−O distance (2.01 Å) and the staggering of the substituents are very similar to the situation observed for **7**.

As with **13**, the diastereoselectivity of the complexation of titanium is low for amino acids other than glycine.

**Preparation of the Ester-Functionalized Titanocenes.** The optimized conditions for the preparation of the amides also worked well for the acylation of alcohols. Some of the examples of the synthesis of ester-substituted titanocenes are summarized in Table 4.

As before, functional nucleophiles can be readily employed and varying the titanocene building block did not significantly affect the isolated yields of the products in most cases. In this manner, the cholesterol-substituted titanocenes **22** and **23**, complex **24** (containing a fluorescence label), and the dinuclear **25** could be obtained in high yields.

As exemplified for **26**, the ester group is not nucleophilic enough to coordinate to titanium, as shown in Figure 5. The

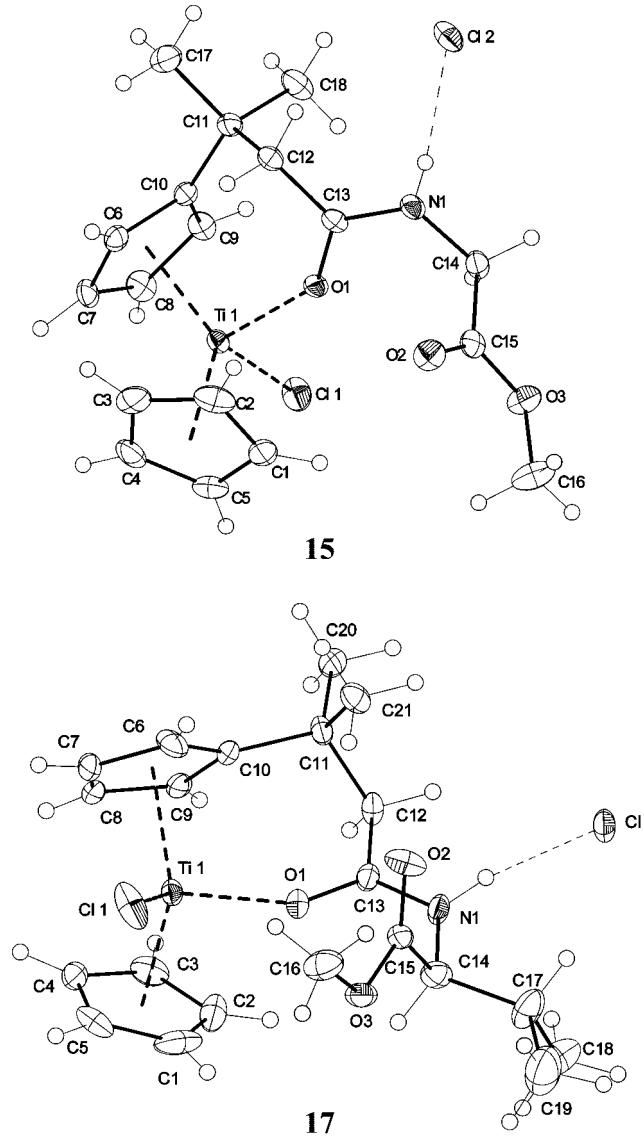
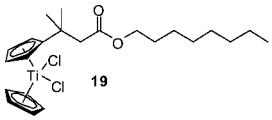
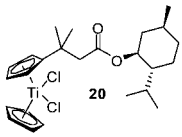
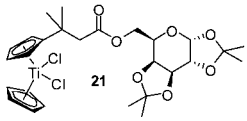
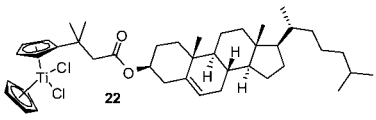
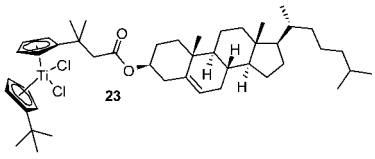
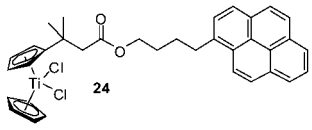
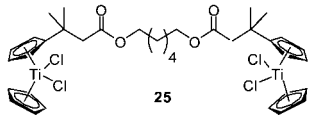
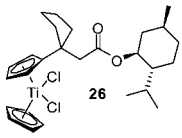



**Figure 4.** Molecular structures of **15** and **17**. Displacement parameters are drawn at the 50% probability level for **15** and the 30% level for **17**. In **17** the solvent $CH_2Cl_2$ is not shown for reasons of clarity.

spectroscopic data also suggest that in the ester-functionalized titanocene complexes the carbonyl group is not complexed by titanium, as opposed to the case for the amides. For the complexes **19**, **24**, and **25** without asymmetric carbon, the $^1$H NMR signal of the $CH_2$ group α to the ester is a singlet and in both the $^1$H NMR and $^{13}$C NMR spectra only one signal for the $CH_3$ groups is observed at the substituents on the "upper" Cp ligand. This is not possible with a chelation of the ester. In this case both the methylene protons and the methyl groups are diastereotopic and, hence, two signals should be detected, as is indeed observed for the amides. Moreover, for **20**−**23** and **26** with enantiomerically pure substituents only one set of signals is obtained in both $^1$H NMR and $^{13}$C NMR spectra. In the case of the cationic amide complexes **12**, **13**, **16**, and **17** two sets of signals were recorded, due to the relatively unselective chelation of the carbonyl group.

**Preparation of the Ketone-Functionalized Titanocenes.** Due to the high nucleophilicity of cyclopentadienyl anions, ketone-substituted titanocenes could not be prepared by the usual linear sequences for ligand preparation prior to metalation.

**Table 4. Synthesis of Ester-Functionalized Titanocenes**

| product | yield/ % |
|---|---|
|  **19** | 83 |
|  **20** | 72 |
|  **21** | 92 |
|  **22** | 74 |
|  **23** | 93 |
|  **24** | 79 |
|  **25** | 98 |
|  **26** | 55 |

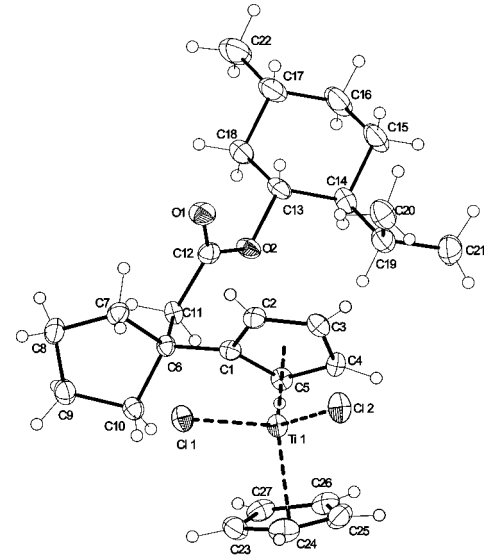
Therefore, such compounds have as yet not been described in the literature.[12]

We decided to exploit the stability of titanocenes under acidic conditions by employing the classical Friedel−Crafts acylation for the preparation of the desired ketones.[16]

The acidic reaction medium offers perspectives not available under the basic acylation conditions used above. The Lewis acid can abstract a chloride ligand from titanium and enforce the formation of a cationic complex, even in the presence of poor ketone donor ligands.

After screening of a number of reagents, it turned out that $ZnCl_2$ consistently gave the best yields of the desired ketone-functionalized titanocenes. The optimized conditions for the reactions of the acid chlorides **6** with methoxy-substituted arenes are shown in Scheme 6, and some examples are summarized in Table 5.

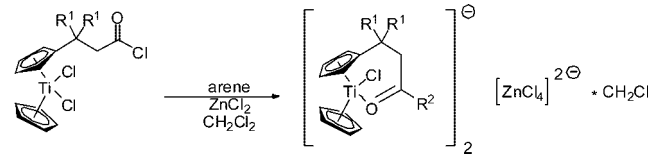
The ketone complexes were obtained in good to high yields as the cationic tetrachlorozincates containing one molecule of




**26**

**Figure 5.** Molecular structure of **26**. Displacement parameters are drawn at the 50% probability level.

**Scheme 6. Conditions for the Friedel-Crafts Acylation of 6**




$CH_2Cl_2$, as demonstrated by the molecular structure of **29** that is shown in Figure 6. The Ti−O distance (1.98 Å) is very similar to those of the carboxylates and amides. Also, the same staggering of the substituents of the tether was observed. This suggests a complexation of the ketone that is unstrained, as in the case of the carboxylates and amides.

The coordination of the keto group was proven spectroscopically for all complexes. The two protons of the $CH_2$ group α to the ketone are diastereotopic and hence appear as an AB system in the $^1H$ NMR spectrum. The same holds true for the $CH_3$ or $CH_2$ groups at the substituents on the "upper" Cp ligand.

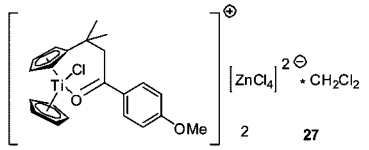
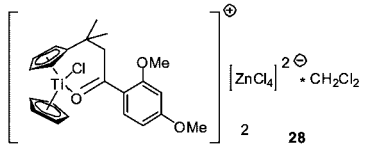
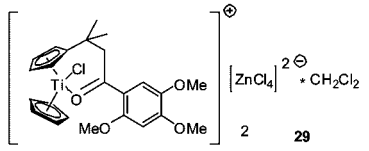
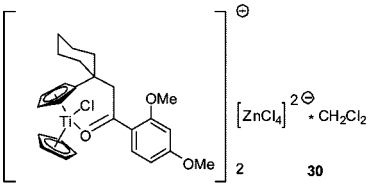
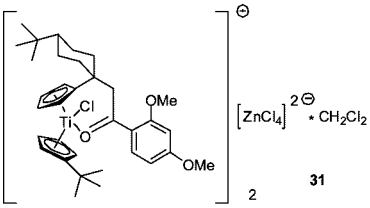
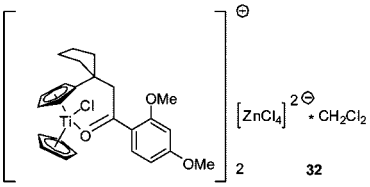
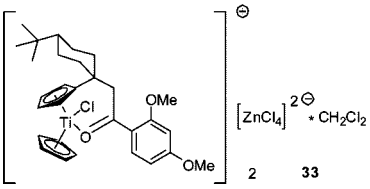
Our reaction conditions are relatively insensitive to the substitution pattern of both the upper and the lower cyclopentadienyl ligand. The ketones were obtained in good to high yields.

## Conclusion

In summary, we have developed a highly modular approach to the synthesis of carbonyl-substituted titanocenes that allows the rapid preparation of large numbers of structurally and functionally diverse complexes. The key intermediates of our sequences are titanocenes with appended acid chlorides. The high electrophilicity of the organic group allows reactions with nucleophiles that are incompatible with traditional methods of titanocene synthesis. In this manner the first examples of amino acid functionalized titanocenes were prepared.

The amide- and ketone-functionalized titanocenes spontaneously form cationic complexes that are highly attractive for applications in catalysis. The ease of this process is explained by our crystallographic investigations, which demonstrate that the coordination of the carbonyl groups results in the formation of an unstrained ring without diaxial interactions.

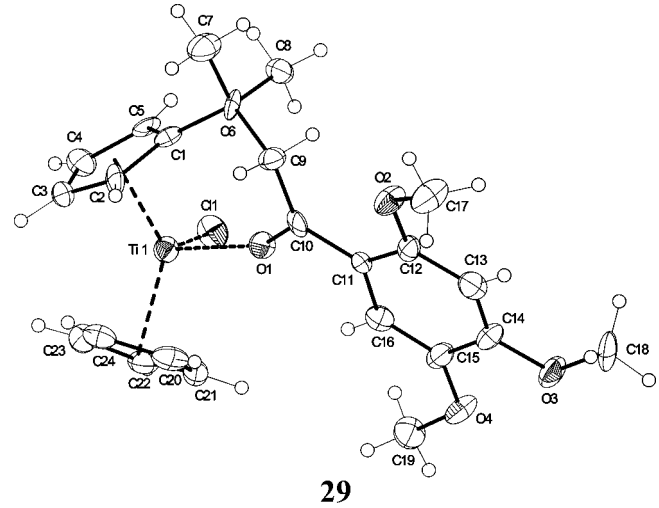
**Table 5. Synthesis of Ketone-Functionalized Titanocenes**

| product | yield/ % |
|---|---|
|  2 **27** | 97 |
|  2 **28** | 90 |
|  2 **29** | 49 |
|  2 **30** | 78 |
|  2 **31** | 58 |
|  2 **32** | 64 |
|  2 **33** | 86 |

## Experimental Section

**General Procedures.** All starting materials were purchased from commercial sources and used as received unless stated otherwise. Dichloromethane was dried prior to use over $CaH_2$; THF was destilled from sodium. Cyclopentadiene was freshly distilled before use.

**Physical Measurements and Instrumentation.** $^1$H NMR (400 MHz) and $^{13}$C NMR (100 MHz) spectra were recorded on Bruker DPX 300 and DPX 400 spectrometers; the chemical shifts (in ppm) are reported relative to residual nondeuterated solvent as reference. EI mass spectra were recorded on an MS 50 spectrometer from Kratos as well as on a MAT 95 spectrometer from Thermoquest. IR spectra were recorded on an ATR Nicolet 380 spectrometer from Thermo Electron. Melting points were measured on a Büchi 530 melting point apparatus and are uncorrected. Elemental analysis (EA) was performed on an Elmer Vario EL instrument from Vario.




**29**

**Figure 6.** Structure of one cationic titanocene unit of **29**. The second titanocene unit, $[ZnCl_4]^{2-}$, and $CH_2Cl_2$ are not shown for purposes of clarity. See the Supporting Information for a complete picture. Displacement parameters are drawn at the 50% probability level.

**Crystal Structure Studies for 4a (GA20) and 17 (GA23).** Single-crystal X-ray diffraction studies were carried out an a Nonius KappaCCD diffractometer at 123(2) K using Mo Kα radiation ($\lambda$ = 0.710 73 Å). The structures were solved by Patterson methods (**4a**) and direct methods (**17**) (SHELXS-97[21]), respectively, and refinement were carried out using SHELXL-97[21] (full-matrix least-squares refinement on $F^2$). The hydrogen atoms were localized by difference electron density determination and refined using a "riding" model (in **17** H(N) free). The absolute structure of **17** was determined by refinement of Flack's $x$ parameter ($x = -0.02(5)$[22]). Important details of the data collection and structure solution and refinement are given in Table 6. Crystallographic data (excluding structure factors) for the structures reported in this work have been deposited with the Cambridge Crystallographic Data Centre as Supplementary Publication Nos. CCDC 690363 (**4a**), CCDC 691963 (**4e**), CCDC 691965 (**5**), CCDC 690364 (**17**), CCDC 691964 (**26**), and CCDC 691962 (**29**). Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge DB2 1EZ, U.K. (fax, int.code+(1223)336-033; e-mail, deposit@ccdc.cam.ac.uk).

**General Procedures for the Preparation of Titanocene Carboxylates (GP1). Synthesis of Fulvene 1h.** Pyrrolidine (5.33 g, 75 mmol) was slowly added to a cooled solution (0 °C) of 4-*tert*-butylcyclohexanone (7.71 g, 50 mmol) and cyclopentadiene (6.61 g 100 mmol) in methanol (100 mL). The solution was stirred for 4 h and then neutralized with glacial acetic acid (5 mL), poured into brine (50 mL), extracted with cyclohexane (3 × 50 mL), and dried over $MgSO_4$. Removal of the solvent yielded **1h** (9.91 g (49 mmol; 98%) as a yellow solid. Mp: 83−84 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 6.56−6.59 (m, 2 H), 6.30−6.34 (m, 2 H), 3.08−3.16 (m, 2 H), 2.24 (td, $^3J$(H,H) = 13.0 Hz, $^2J$(H,H) = 4.2 Hz, 2 H), 2.00−2.10 (m, 2 H), 1.21−1.41 (m, 3 H), 0.87 (s, 9 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 158.5, 139.2, 130.9, 120.1, 48.2, 33.7, 32.7, 29.5, 27.7. HRMS (EI/70 eV): $m/z$ calcd for $C_{15}H_{22}^+$ 202.1721, found 202.1722 $[M]^+$. IR (KBr): $\nu$ 3070, 2950, 2860, 1640, 1620, 1465, 1440, 1360, 1085, 855, 690 cm$^{-1}$. Anal. Calcd for $C_{15}H_{22}$ (202.2): C, 89.04; H, 10.96. Found: C, 88.83; H, 11.02.

**Synthesis of Ligand 2h.** To diisopropylamine (4.63 g, 46 mmol) in THF (13 mL) was added at −60 °C *n*-BuLi (15.2 mL, 38 mmol,

(21) Sheldrick, G. M. *Acta Crystallogr.* **2008**, *A64*, 112–122.
(22) Flack, H. D. *Acta Crystallogr.* **1983**, *A39*, 876–881.

**Table 6. Crystallographic Data and Structure Solution and Refinement Details for 4a and 17**

| | 4a | 17 |
|---|---|---|
| empirical formula | $C_{15}H_{17}ClO_2Ti \cdot 0.5$(toluene) | $[C_{21}H_{29}ClNO_3Ti]^+[Cl]^- \cdot CH_2Cl_2$ |
| formula wt | 358.70 | 547.18 |
| temp (K) | 123(2) | 123(2) |
| cryst syst | monoclinic | orthorhombic |
| space group | $P2_1/n$ (No. 14) | $P2_12_12_1$ (No. 19) |
| $a$ (Å) | 6.3068(1) | 11.1976(3) |
| $b$ (Å) | 14.3906(2) | 11.3228(3) |
| $c$ (Å) | 18.1641(4) | 21.4285(7) |
| α (deg) | 90 | 90 |
| $\beta$ (deg) | 90.662(1) | 90 |
| $\gamma$ (deg) | 90 | 90 |
| $V$ (Å$^3$) | 1648.44(5) | 2716.88(14) |
| $Z$ | 4 | 4 |
| $D_{calcd}$ (g cm$^{-3}$) | 1.445 | 1.338 |
| abs coeff (mm$^{-1}$) | 0.69 | 0.73 |
| $F$(000) | 748 | 1136 |
| cryst size (mm) | 0.35 × 0.25 × 0.20 | 0.40 × 0.25 × 0.10 |
| $2\theta_{max}$ (deg) | 55 | 50 |
| limiting indices | $-6 \le h \le 8$, $-18 \le k \le 18$, $-23 \le l \le 23$ | $-10 \le h \le 13$, $-13 \le k \le 11$, $-25 \le l \le 24$ |
| no. of rflns collected | 16 446 | 12 377 |
| unique reflections | 3687 | 4736 |
| Rint | 0.044 | 0.025 |
| no. of data/restraints/params | 3687/27/189 | 4736/1/284 |
| GOF on $F^2$ | 1.05 | 1.08 |
| R1 ($I > 2\sigma(I)$) | 0.040 | 0.062 |
| wR2 (all data) | 0.106 | 0.185 |
| largest diff map peak/hole (e Å$^{-3}$) | 1.03/−0.60 | 1.19/−0.57 |

2.5 M in hexane). After the mixture was stirred for 1 h, *tert*-butyl acetate (5.32 g, 46 mmol) was added and the mixture was stirred for 1 h. After addition of **1h** (9.26 g, 46 mmol) the mixture was stirred at −60 °C for 16 h. The solution was washed with saturated $NH_4Cl$ solution (2 × 10 mL) and brine (3 mL). It was dried over $MgSO_4$ and purified by flash chromatography ($SiO_2$) to yield **2h** (8.94 g, 28 mmol; 61%) as a mixture of isomers forming a yellow solid. $R_f = 0.20$ (cyclohexane). Mp: 48−50 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 6.52 (dd, $^3J$(H,H) = 5.3 Hz, $^3J$(H,H) = 1.5 Hz, 1 H), 6.41 (ddd, $^3J$(H,H) = 5.2 Hz, $^3J$(H,H) = 1.8 Hz, $^3J$(H,H) = 1.8 Hz, 1 H), 6.29 (dd, $^3J$(H,H) = 5.4 Hz, $^3J$(H,H) = 1.3 Hz, 1 H), 6.22 (dd, $^3J$(H,H) = 2.0 Hz, $^3J$(H,H) = 1.1 Hz, 1H), 6.08 (dd, $^3J$(H,H) = 1.8 Hz, $^3J$(H,H) = 1.8 Hz, 1H), 2.97 (d, $^3J$(H,H) = 1.5 Hz, 2 H), 2.88 (d, $^3J$(H,H) = 1.4 Hz, 2H), 2.19−2.28 (m, 2 H), 2.22 (s, 2 H), 2.21 (s, 2H), 1.52−1.58 (m, 2 H), 1.37−1.48 (m, 2 H), 1.31 (s, 9 H), 1.29 (s, 9H), 1.03−1.16 (m, 2H), 1.00 (t, $^3J$(H,H) = 2.8 Hz, 1 H), 0.97 (t, $^3J$(H,H) = 2.7 Hz, 1H), 0.77 (s, 9H), 0.76 (s, 9 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 171.0, 170.9, 151.6, 149.7, 133.2, 132.0, 132.9, 131.2, 129.1, 127.8, 79.8, 52.3, 50.7, 48.5, 48.4, 40.2, 38.9, 37.5, 36.6, 32.5, 28.1, 27.7, 23.6. HRMS (EI/70 eV): *m*/*z* calcd for $C_{21}H_{34}O_2$ 318.2559, found 318.2557 [M]$^+$. IR (KBr): $\nu$ 2965, 1715, 1475, 1390, 1360, 1250, 1110, 985, 860, 680 cm$^{-1}$. Anal. Calcd for $C_{21}H_{34}O_2$ (318.5): C, 79.19; H, 10.76. Found: C, 78.80; H, 10.52.

**Synthesis of Carboxylate 4h.** To a solution of **2h** (4.37 g, 15 mmol) in THF (24 mL) was added at −78 °C *n*-BuLi (8.8 mL, 13 mmol, 2.5 M in hexane), and the mixture was stirred for 2 h. Then $CpTiCl_3$ (2.75 g, 13 mmol) in THF (62 mL) at −40 °C was added and the mixture was stirred 16 h at room temperature. Washing with MTBE yields **4h** (3.85 g, 9 mmol) as a red solid. Mp: >235 °C. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 6.74 (dd, $^3J$(H,H) = 5.0 Hz, $^3J$(H,H) = 3.1 Hz, 1 H), 6.66 (dd, $^3J$(H,H) = 5.0 Hz, $^3J$(H,H) = 2.6 Hz, 1 H), 6.51 (s, 5 H), 6.05 (dd, $^3J$(H,H) = 3.0 Hz, $^3J$(H,H) = 2.8 Hz, 2H, H-4), 2.65 (d, $^3J$(H,H) = 12.2 Hz, 1H), 2.26 (ddd, $^3J$(H,H) = 13.8 Hz, $^3J$(H,H) = 5.6 Hz, $^3J$(H,H) = 2.8 Hz, 1H), 2.12 (d, $^3J$(H,H) = 12.2 Hz, 1 H), 2.02 (ddd,$^3J$(H,H) = 13.8 Hz, $^3J$(H,H) = 6.1 Hz, $^3J$(H,H) = 2.9 Hz, 1 H), 1.44−1.66 (m, 3 H), 0.87−1.05 (m, 4 H), 0.75 (s, 9 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 175.6, 145.0, 127.8, 119.5, 116.8, 114.5, 109.5, 53.2, 47.6, 38.7, 38.4, 37.4, 32.4, 27.5, 23.4, 23.3. HRMS (EI/70 eV): *m*/*z* calcd for $C_{22}H_{29}{}^{48}TiO_2Cl$ 408.1336, found 408.1345 [M$^+$] IR (KBr pellet): $\nu$ 3100, 2940, 2860, 1650, 1445, 1320, 1280, 1165, 1115, 820, 690 cm$^{-1}$.

**General Procedure for the Preparation of Amide-Functionalized Titanocenes (GP2). 4f** (339 mg, 1.0 mmol) was reacted with $SOCl_2$ (1.0 mL) for 1 h at room temperature. Excess $SOCl_2$ was removed in vacuo for 2 h at 50 °C. The residue was dissolved in $CH_2Cl_2$ (5 mL) and the solution transferred via syringe to a suspension of NaH (192 mg, 8.0 mmol) and aniline (186 mg, 2.0 mmol) in $CH_2Cl_2$ (5 mL). Stirring was continued for 16 h at room temperature. Filtration through Celite and crystallization from $CH_2Cl_2$/pentane afforded **12** (343 mg, 76%) as red crystals. Mp: 221 °C. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta$ 13.15 (m, 1 H), 7.56 (d, $^3J$(H,H) = 7.9 Hz, 2 H), 7.47 (dd, $^3J$(H,H) = 7.9 Hz, $^3J$(H,H) = 7.9 Hz, 2 H), 7.45 (m, 1 H), 7.33 (t, $^3J$(H,H) = 7.4 Hz, 1 H), 7.13 (m, 1 H), 6.78 (s, 5 H), 6.73 (m, 1 H), 6.20 (m, 1 H), 3.34 (d, $^2J$(H,H) = 14.2 Hz, 1 H), 2.63 (d, $^2J$(H,H) = 14.2 Hz, 1 H), 1.49−1.92 (m, 8 H). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta$ 175.1, 149.5, 135.2, 129.2, 127.1, 123.6, 123.5, 121.7, 121.6, 116.8, 111.0, 45.4, 45.2, 35.3, 22.8. HRMS (EI, 70 eV): *m*/*z* calcd for $C_{23}H_{24}ClNO^{46}Ti$ 411.1067, found 411.1066 [M − HCl]$^+$. IR (ATR): $\nu$ 2725, 1625, 1605, 1570, 1495, 1440, 1375, 990, 825, 765, 690 cm$^{-1}$.

**General Procedure for the Preparation of Amino Acid Functionalized Titanocenes (GP3).** A suspension of glycine methyl ester hydrochloride (315 mg, 2.5 mmol) and $K_2CO_3$ (483 mg, 3.5 mmol) in $CH_2Cl_2$ (10 mL) was stirred for 16 h at room temperature. NaH (300 mg, 12.5 mmol) was added, and stirring was continued at room temperature for 1 h. **4g** (883 mg, 2.5 mmol) was reacted with $SOCl_2$ (3 mL) for 1 h at room temperature. Excess of $SOCl_2$ was removed in vacuo for 2 h at 50 °C. The residue was dissolved in $CH_2Cl_2$ (10 mL) and transferred via syringe to the reaction mixture. Stirring was continued for 16 h at room temperature. Filtration through Celite and recyrstallization from $CH_2Cl_2$/toluene afforded **16** (779 mg, 68%) as red crystals. Mp: 228 °C dec. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 12.42 (dd, $^3J$(H,H) = 5.1 Hz, 1 H), 7.21 7.17 (m, 1 H), 7.08 (br s, 1 H), 6.66 (s, 5 H), 6.57 (br s, 1 H), 6.10 (br s, 1 H), 3.96 (d, $^3J$(H,H) = 5.7 Hz, 2 H), 3.72 (s, 3 H), 3.39 (d, $^2J$(H,H) = 13.5 Hz, 1 H), 2.82 (d, $^2J$(H,H) = 13.5 Hz, 1 H), 1.98−1.85 (m, 2 H), 1.80−1.63 (m, 3 H), 1.60−1.49

(m, 1 H), 1.44−1.31 (br s, 3 H), 1.20−1.07 (br s, 1 H). $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ 178.3, 167.9, 150.3, 125.6, 121.9, 121.4, 115.8, 111.4, 52.8, 46.6, 42.4, 38.7, 38.5, 34.1, 25.3, 22.2, 21.8. HRMS (ESI, MeOH, 10 eV): *m*/*z* calcd for $C_{22}H_{30}NO_4{}^{48}Ti$ 420.1651, found 420.1651 $[M - 2Cl + OMe]^+$. IR (ATR): $\nu$ 2925, 2850, 1740, 1605, 1555, 1440, 1410, 1365, 1200, 825 $cm^{-1}$.

**General Procedure for the Preparation of Ester-Functionalized Titanocenes (GP4). 4a** (313 mg, 1.0 mmol) was reacted with $SOCl_2$ (1.0 mL) for 1 h at room temperature. Excess $SOCl_2$ was removed in vacuo for 2 h at 50 °C. The residue was dissolved in $CH_2Cl_2$ (5 mL) and the solution transferred via syringe to a suspension of NaH (120 mg, 5.0 mmol) and 1-octanol (130 mg, 1.0 mmol) in $CH_2Cl_2$ (5 mL). Stirring was continued for 16 h at room temperature. Filtration through Celite and recrystallization from $CH_2Cl_2$/pentane afforded **19** (382 mg, 83%) as red crystals. Mp: 119 °C. $^1$H NMR (500 MHz, $CD_2Cl_2$): $\delta$ 6.60 (dd, $^3J$(H,H) = 2.7, $^4J$(H,H) = 2.7 Hz, 2 H), 6.56 (s, 5 H), 6.48 (dd, $^3J$(H,H) = 2.7, $^4J$(H,H) = 2.7 Hz, 2 H), 3.95 (t, $^3J$(H,H) = 6.9 Hz, 2 H), 2.59 (s, 2 H), 1.55 (tt, $^3J$(H,H) = 6.9, $^3J$(H,H) = 6.9 Hz, 2 H), 1.25−1.34 (m, 10 H), 1.46 (s, 6 H), 0.90 (t, $^3J$(H,H) = 6.9 Hz, 3 H). $^{13}$C NMR (125 MHz, $CD_2Cl_2$): $\delta$ 171.5, 147.0, 120.8, 120.7, 117.7, 64.7, 49.1, 37.0, 32.2, 29.6, 29.0, 27.9, 26.3, 23.0, 14.3. HRMS (EI, 70 eV): *m*/*z* calcd for $C_{23}H_{34}ClO_2{}^{46}Ti$ 423.1774, found 423.1758 $[M - Cl]^+$. IR (film): $\nu$ 3100, 2960, 1710, 1450, 1330, 1220, 1110, 860 $cm^{-1}$.

**General Procedure for the Preparation of Ketone-Functionalized Titanocenes (GP5). 4a** (313 mg, 1.0 mmol) was reacted with $SOCl_2$ (1.0 mL) for 1 h at room temperature. Excess $SOCl_2$ was removed in vacuo for 2 h at 50 °C. The residue was dissolved in $CH_2Cl_2$ (5 mL) and the solution transferred via syringe to a suspension of $ZnCl_2$ (680 mg, 5 mmol) and 1,2,4-trimethoxybenzene (840 mg, 5 mmol). After the mixture was stirred overnight, the solvent was evaporated and **29** (1.44 g, 2.1 mmol) was isolated by crystallization from $CH_2Cl_2$/c-$C_6H_{12}$ as a red solid (49%). Mp: 165 °C dec. $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 6.89−6.92 (m, 2H), 6.47−6.49 (m, 1H), 6.37 (s, 5H), 6.18−6.21 (m, 1H), 6.15−6.17 (m, 1H), 5.71−5.74 (m, 1H), 4.07−4.09 (m, 1H), 4.04−4.06 (m, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 3.83 (s, 3H), 1.38 (s, 3H), 1.29 (s, 3H). $^{13}$C NMR (100 MHz, DMSO): $\delta$ 207.6, 162.7, 161.5, 157.9, 150.3, 148.5, 121.9, 119.8, 117.1, 113.0, 111.8, 109.7, 98.1, 57.8, 57.5, 56.3, 55.3, 35.3, 34.1, 33.1. MS (ESI/10 eV/MeOH): *m*/*z* (%) 459 ($M^+ - Cl + OMe$, 100), 445 (2), 427 (9), 353 (2). HRMS (ESI/10 eV/MeOH): *m*/*z* calcd for $C_{25}H_{31}O_5{}^{48}Ti^{+\cdot}$ 459.1648, found 459.1645 [$M^+ - Cl^- + OMe$]. IR (KBr pellet): $\nu$ 3080, 2960, 1620, 1560, 1485, 1380, 1265, 1220, 1015, 840, 730 $cm^{-1}$.

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**Supporting Information Available:** Text and figures giving details of the syntheses and characterization data for all compounds prepared in this paper. This material is available free of charge via the Internet at http://pubs.acs.org.

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