ORGANOMETALLICS
Note

Organometallics **2010,** *29,* 3227–3230 3227
DOI: 10.1021/om100245r

Synthesis of Stable Functional Titanocene Enolates§

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Received March 30, 2010

Summary: A modular approach to bench-stable titanocene enolates is described. The reaction of titanocenes containing pendent acid chlorides with activated methylene compounds in the presence of excess base results in the formation of the pivotal enolates. In all cases, the enolates are coordinated to the titanocene, which acts as a stabilizing template in an intramolecular manner, as demonstrated by NMR spectroscopy and X-ray crystallography. Upon protonation with strong acids, the C−C bond formed during the acylation is cleaved. Hence, the template effect can be reversed by adjusting the acidity of the reaction medium.

Introduction

Due to their ability to bind and recognize other molecular entities, cationic and neutral titanocenes with pendent polar functional groups have attracted attention in a number of topical fields. These include the treatment of cancer in medicinal chemistry by titanocenes[1] and the assembly of supramolecular aggregates and nanostructures by organometallic gelators.[2] Moreover, cationic amide-substituted titanocenes have emerged as novel reagents in catalytic[3] electron transfer reactions[4] with epoxides. In this manner, thermodynamically and kinetically difficult radical 4-*exo* cyclizations[5] that are impossible to realize with traditional alkyl-substituted titanocenes[6] that operate via a passive occupation of space[7] could be accomplished. These particular catalysts are also highly attractive for other purposes in reagent-controlled radical chemistry, such as stereoselective radical generation[8] and the control of diastereoselectivity of C−C bond forming processes such as intermolecular additions[7,8c] to activated olefins or radical cyclizations.[9]

The common feature of the use of the functionalized titanocenes is the proper adjusting of the intermolecular interactions between the titanocene's functional groups, its metal center, and its binding partners, such as enzymes or receptors in medicinal chemistry,[1] the solvent and other molecules of the gelator in the formation of gels,[2] and organic substrates in catalysis.[5] Another interesting aspect of the chemistry of the functionalized titanocenes, which has, as yet, not been exploited, is constituted by the intramolecular stabilization of reaction products or reactive intermediates by intramolecular coordination of these species to

§ Dedicated to Prof. Uwe Rosenthal on the occasion of his 60th birthday.

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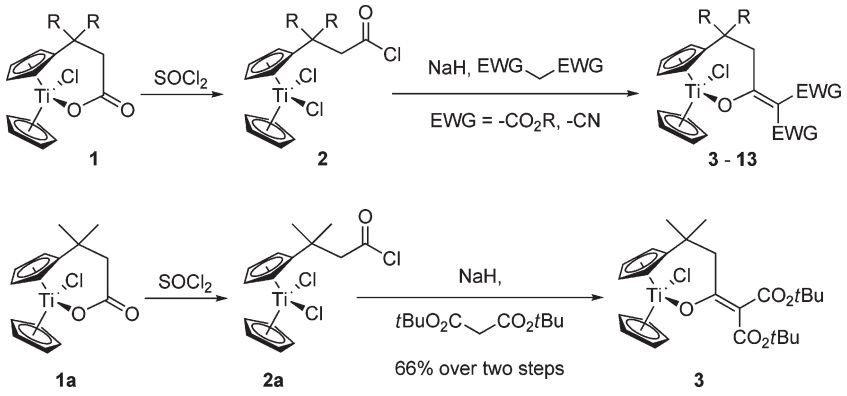
Published on Web 06/24/2010

Scheme 1. Synthetic Approach to the Synthesis of Enolates Templated by Titanocenes



the titanium in a template manner. To this end, enolates constitute an attractive class of intermediates because of their undisputed utility in synthetic applications and because of the well-documented influence of the counterion on their stability and reactivity. In this note, we describe our first results in this area.

Results and Discussion

Our synthetic approach to the synthesis of the titanocene-templated enolates is highlighted in Scheme 1. It is based on the use of the titanocene-containing acid chlorides **2** that are readily accessible in gram quantities from the titanocene carboxylates **1** via our recently developed modular titanocene synthesis.[10] Our approach of functionalizing the cyclopentadienyl ligands after metalation is especially attractive here because the ester and especially the ketone groups of the desired products are not stable to the strongly nucleophilic cyclopentadienyl anion. Therefore, they cannot be introduced to the ligand before metalation because of the high nucleophilicity of cyclopentadienyl anions.[11]

Our synthesis relies critically on the reactions of acid chlorides with C-nucleophiles to yield ketones. As enolate precursors, activated methylene compounds, such as malonates or malonodinitriles, are especially attractive for three reasons. First, enolate generation can simply be carried out with NaH as base. Thus, the only byproduct of the acylation will be NaCl, which is easy to remove by a simple filtration. Second, the two ester and the two nitrile groups can in principle be utilized for further functionalization such as complexation of other metal complexes. Third, upon *in situ* deprotonation of the acidic tricarbonyl compounds formed as intermediates, the desired titanocene-templated enolates can be obtained directly.

Gratifyingly, with **1a** and di-*tert*-butyl malonate as enolate precursor, the desired product **3** could be obtained in 66% yield. Choosing appropriate conditions for the purification are crucial. Gel permeation chromatography on BioBeads, as introduced for the purification of cationic titanocenes by Meléndez,[11] with CH_2Cl_2 as eluent proved to be the method of choice for the removal of residual **1a**. Crystallization of the crude reaction also provides clean **3**, albeit in substantially reduced yields. The ^1H and ^{13}C NMR spectra prove the complexation of the enolate oxygen to titanium. The CH_3 groups of the *gem*-dimethyl group are observed as two signals in the ^1H and ^{13}C NMR spectra. The two protons of the methylene group attached to the *gem*-dimethyl group are diastereotopic and hence appear as an AB system in the ^1H NMR spectrum. Further examples for the preparation of these enolates are summarized in Table 1.

The desired products were obtained in 54% to almost quantitative yields as red solids that are stable under ambient conditions for several days. The coordination of titanium by the enolate oxygen results in spectra similar to **3** for all titanocene enolates prepared here. For **9** this complexation was additionally confirmed by an X-ray structural analysis (Figure 1).

The Ti−O bond length (1.91 Å) is in the typical range of Ti−O bonds.[12] The length of the enolate double bond (1.35 Å) is also typical for a C−C double bond. It should be noted that only the ester group (*E*) to the enolate oxygen is in conjugation with the enolate (dihedral angle = 179°), whereas the second ester group is oriented almost perpendicular (97°) to the olefin and hence does not participate in the stabilization of the enolate. The almost perfect staggering of the substituents of the C(sp^3)−C(sp^3) bond of the tether in **9** and the dihedral angle (C13−C12−C6−C7) of 172.65°, which is close to 180°, suggest strongly that the titanium-containing ring is unstrained.

In principle, the two ester groups and especially the two nitrile groups are ideally positioned to interact with other metals or metal complexes to form bi- or even polymetallic complexes. This issue will be further pursued.

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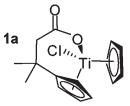
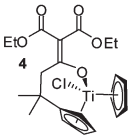
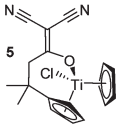
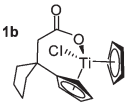
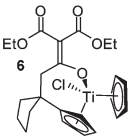
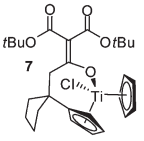
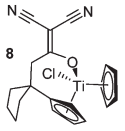
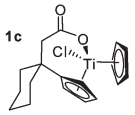
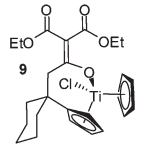
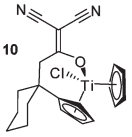
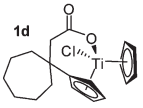
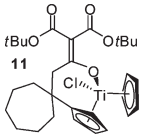
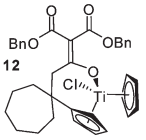
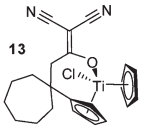
Table 1. Synthesis of the Enolates 4−13 (yield over two steps)

carboxylate	product	yield/ %
 **1a**	 **4**	55
1a	 **5**	60
 **1b**	 **6**	95
1b	 **7**	60
1b	 **8**	76
 **1c**	 **9**	78
1c	 **10**	98
 **1d**	 **11**	64
1d	 **12**	72
1d	 **13**	54

The intramolecular binding of the enolate by the titanium thus provides a unique stabilization of the reactive intermediate that even allows a chromatographic purification.

We decided to probe the relevance of this template effect by exposing the enolates to water and acid. Compound **6** was dissolved in D_8-THF and H_2O (0.5 −1.0 equiv) and compound **7** in CD_2Cl_2 and H_2O. The ^1H NMR spectra revealed no decomposition of **6** and **7** to **1b** over 72 h in these solvents.

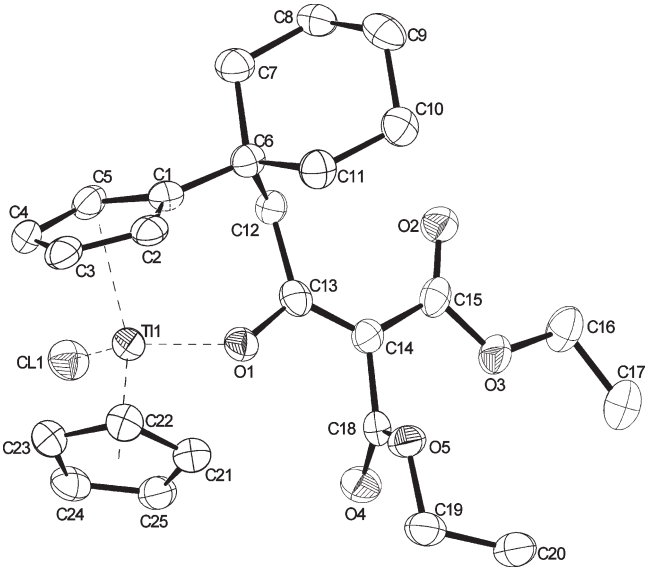
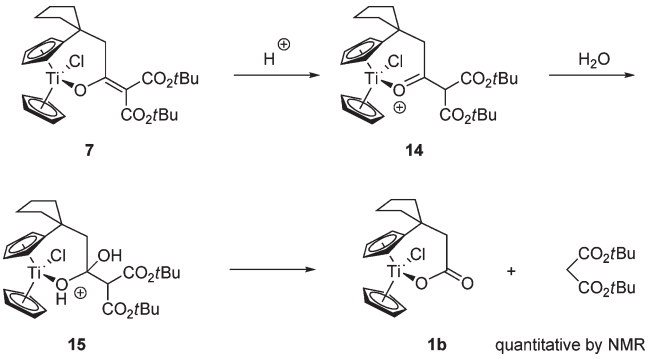


Figure 1. Molecular structure of **9**. Displacement parameters are drawn at the 50% probability level. Hydrogen atoms are omitted for reasons of clarity.

Scheme 2. Activation of 7 by the Titanocene Template under Protic Conditions



This changes upon addition of concentrated HCl to the NMR solvent. After 48 h the enolate **7** was consumed and the carboxylate **1b** had formed quantitatively. We attribute this C−C bond cleavage to a template activation of the ketone **14** formed upon protonation (Scheme 2). Complexation of the carbonyl group by the Lewis acidic cationic titanocene leads to a strong activation toward addition of the weakly nucleophilic H_2O. After formation of the hydrate **15**, di-*tert*-butyl malonate and carboxylate **1b** are formed by C−C bond cleavage and proton transfer. Thus, depending on the acidity or basicity of the reaction medium, the titanocene template can either activate the carbonyl group toward nucleophilic addition or stabilize its corresponding enolate by complexation.

Summary

In summary, we have devised a synthetic approach to bench-stable functionalized titanocene enolates that critically relies on a modification of the titanocenes after metalation. The enolate oxygen is complexed by a titanium template to achieve an arrangement of the substituents of the cyclopentadienyl ligands that displays minimal steric interactions. Upon protonation of the enolate to the ketone, the titanocene template strongly activates the carbonyl

group toward addition of H_2O, which results in the cleavage of the C−C bond formed under basic conditions.

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 distilled from sodium. Cyclopentadiene was freshly distilled before use.

Physical Measurements and Instrumentation. ^{1}H NMR and ^{13}C NMR spectra were recorded on a DPX 300 and a DPX 400 Bruker spectrometer; chemical shifts (in ppm) are reported relative to nondeuterated solvent residual as reference. EI mass spectra were recorded on a MS 50 spectrometer from Kratos as well as on a MAT 95 spectrometer from Thermoquest. IR spectra were recorded on a MAT 95 XL spectrometer from Thermo Finnigan, and ESI mass spectra were recorded on a micrOTOF-Q spectrometer from Bruker Daltonik. 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.

Synthesis of Titanocene Enolates 3, 5, and 9. Synthesis of **3**: **1a** (156 mg, 0.500 mmol) was reacted with $SOCl_2$ (1.5 mL) for 2 h at rt. Excess $SOCl_2$ was removed *in vacuo* for 2 h at 50 °C. The acid chloride was dissolved in THF (10 mL) and transferred via syringe to a suspension of NaH (60 mg, 1.5 mmol, 60% dispersion in mineral oil) and di-*tert*-butyl malonate (151.4 mg, 0.70 mmol, 1.40 equiv) in THF (10 mL). Stirring was continued for 16 h at rt. After filtration through Celite the solvent was removed under reduced pressure. The residue was chromatographed on Bio Beads S-X3 to yield enolate **3** (168.6 mg, 66%) as a red solid: mp 77−78 °C (dec); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.56 (ddd, $^3J_{HH}$ = 3.1 Hz, $^3J_{HH}$ = 3.0 Hz, $^4J_{HH}$ = 2.3 Hz, 1H), 6.45 (s, 5H), 6.38 (ddd, $^3J_{HH}$ = 3.0 Hz, $^4J_{HH}$ = 2.3 Hz, $^4J_{HH}$ = 2.3 Hz, 1H), 5.98 (ddd, $^3J_{HH}$ = 3.1 Hz, $^3J_{HH}$ = 3.1 Hz, $^4J_{HH}$ = 2.5 Hz, 1H), 5.94 (ddd, $^3J_{HH}$ = 2.5 Hz, $^4J_{HH}$ = 2.5 Hz, $^4J_{HH}$ = 2.5 Hz, 1H), 3.22 (d, $^2J_{HH}$ = 15.0 Hz, 1H), 2.87 (d, $^2J_{HH}$ = 15.0 Hz, 1H), 1.54 (s, 9H), 1.47 (s, 9H), 1.30 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.3, 166.9, 166.1, 146.3, 122.5, 118.7, 117.9, 114.4, 106.0, 105.9 80.3, 80.0, 44.7, 33.9, 29.1, 28.5, 28.5, 28.4; HRMS (ESI, 10 eV) *m*/*z* calcd for $C_{26}H_{35}ClNaO_5{}^{48}Ti^+$ 531.1592, found 531.1601 $[M + Na]^+$; IR ATR, ν [cm^{-1}] 2970, 1690, 1570, 1365, 1340, 1230, 1160, 1080, 1000, 820, 540.

Synthesis of **5**: **1a** (156 mg, 0.500 mmol) was reacted with $SOCl_2$ (2.5 mL) for 2 h at rt. Excess $SOCl_2$ was removed *in vacuo* for 2 h at 50 °C. The acid chloride was dissolved in THF (10 mL) and transferred via syringe to a suspension of NaH (100 mg, 2.5 mmol, 60% dispersion in mineral oil) and malononitrile (37.0 mg, 0.550 mmol, 1.10 equiv) in THF (10 mL). Stirring was continued for 16 h at rt. After filtration through Celite the solvent was removed under reduced pressure. The residue was chromatographed on Bio Beads S-X3 to yield enolate **5** (108 mg, 60%) as a red solid: mp 66−70 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (ddd, $^3J_{HH}$ = 3.0 Hz, $^3J_{HH}$ = 3.0 Hz, $^4J_{HH}$ = 2.1 Hz, 1H), 6.66−6.63 (m, 1H), 6.62 (s, 5H), 5.93−5.88 (m, 2H), 2.83 (d, $^2J_{H,H}$ = 14.9 Hz, 1H), 2.77 (d, $^2J_{H,H}$ = 14.9 Hz, 1H), 1.36 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.3, 146.7, 126.6, 120.7, 116.2, 116.2, 115.4, 114.2, 107.4, 62.3, 46.4, 34.3, 29.8, 27.0; HRMS (ESI, 10 eV) *m*/*z* calcd for $C_{18}H_{17}N_2O^{48}Ti^+$ 325.0816, found 325.0807 $[M - Cl]^+$; IR ATR, ν [cm^{-1}] 2920, 2850, 2220, 2205, 1505, 1430, 1385, 1235, 1025, 1015, 820, 615.

Synthesis of **9**: **1c** (177 mg, 0.500 mmol) was reacted with $SOCl_2$ (0.2 mL) in CH_2Cl_2 (5 mL) for 2.5 h at rt. Excess $SOCl_2$ was removed *in vacuo* for 2 h at 70 °C. The acid chloride was dissolved in THF (10 mL) and transferred via syringe to a suspension of NaH (50 mg, 1.25 mmol, 60% dispersion in mineral oil) and diethyl malonate (110 mg, 0.688 mmol, 1.38 equiv) in THF (10 mL). Stirring was continued for 16 h at rt. After filtration through Celite the solvent was removed under reduced pressure. Recrystallization (CH_2Cl_2/cyclohexane) yielded enolate **9** (192 mg, 78%) as a red solid: mp 220 °C (dec); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66 (td, $^3J_{H,H}$ = 3.0 Hz, $^4J_{H,H}$ = 2.1 Hz, 1H), 6.54−6.50 (m, 1H), 6.41 (s, 5H), 5.94 (td, $^3J_{H,H}$ = 3.1 Hz, $^4J_{H,H}$ = 2.3 Hz, 1H), 5.89 (dt, $^3J_{H,H}$ = 2.8 Hz, $^4J_{H,H}$ = 2.5 Hz, 1H), 4.32−4.09 (m, 4H), 3.16 (d, $^2J_{H,H}$ = 13.7 Hz, 1H), 3.07 (d, $^2J_{H,H}$ = 13.6 Hz, 1H), 1.97−1.36 (m, 10H), 1.33 (t, $^3J_{H,H}$ = 7.1 Hz, 3H), 1.25 (t, $^3J_{H,H}$ = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3, 167.6, 166.0, 145.5, 125.7, 118.7, 115.5, 114.7, 108.1, 103.9, 60.6, 59.8, 43.9, 38.1, 36.7, 26.9, 25.8, 22.1, 22.0, 14.3, 14.3; HRMS (ESI, 10 eV) *m*/*z* calcd. for $C_{25}H_{31}O_5{}^{48}Ti^+$ 459.1648, found 459.1646 $[M - HCl - C_2H_5]^+$; IR ATR, ν [cm^{-1}] 3105, 2930, 2855, 1650, 1555, 1445, 1315, 1270, 1200, 1170, 1090, 1045, 955, 825, 470. Anal. Calcd for $C_{25}H_{31}ClO_5Ti$ (494.83) C, 60.68; H, 6.31. Found: C, 60.60; H, 6.68.

Acknowledgment. We are indebted to the SFB 624 ("Template−Vom Design Chemischer Schablonen zur Reaktionssteuerung" for continuing financial support.

Supporting Information Available: This material is available free of charge via the Internet at http://pubs.acs.org.

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