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A Practical and Inexpensive One-Pot Synthesis of Bis(indenyl)dimethyltitanium with Aqueous Workup Procedure

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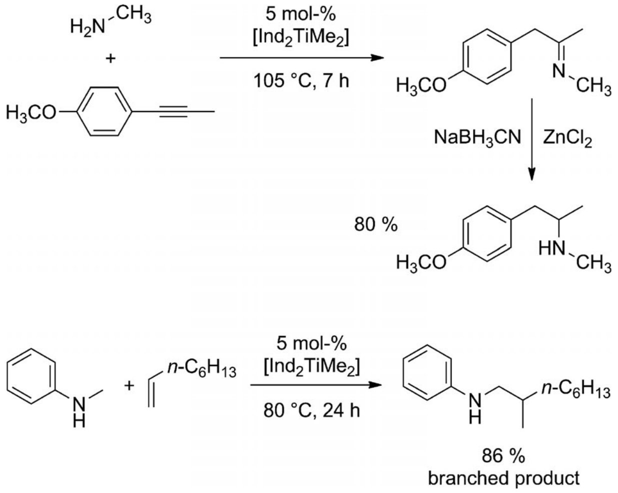
Abstract. A simple, reliable, and reproducible procedure for the multigram synthesis of highly pure bis(indenyl)dimethyltitanium is presented. The procedure relies on a one-pot conversion of inexpensive indene, methyllithium, and titanium tetrachloride to [Ind$_2$TiMe$_2$] and a convenient and quick aqueous workup protocol. Overall, quantities of several grams of [Ind$_2$TiMe$_2$] can be synthesized within a few hours. The procedure can also be used for the synthesis of [Cp$_2$TiMe$_2$] from cyclopentadiene, methyllithium, and titanium tetrachloride.

Introduction

During the past few years bis(indenyl)dimethyltitanium became an increasingly important catalyst precursor for polymerization,[1] hydroamination,[2] and hydroaminoalkylation[3] reactions. For example, [Ind$_2$TiMe$_2$] (Ind = η^5-indenyl) was found to be a highly active and general catalyst for the intermolecular hydroamination of alkynes.[2a] It catalyzes the reaction of primary aryl- and alkylamines with internal and terminal alkynes giving access to imines, which can subsequently be reduced to secondary amines. In the case of unsymmetrically substituted 1-phenyl-2-alkylalkynes, the hydroamination reactions occur with high regioselectivities, whereby formation of the anti-Markovnikov regioisomer is always favored. Correspondingly, it is possible to synthesize biologically interesting 2-phenylethylamine derivatives from 1-phenyl-2-alkylalkynes and methylamine by a simple hydroamination/reduction sequence (Scheme 1).[2c] In addition, [Ind$_2$TiMe$_2$] represents a versatile catalyst for hydroaminoalkylation reactions, which allow the 100 % atom-efficient addition of α-C–H bonds of primary or secondary amines to C–C double bonds of alkenes,[3a,3b] styrenes,[3b] or 1,3-butadienes.[3c] With this catalyst, 1-alkenes react with *N*-methylanilines to give the corresponding branched hydroaminomethylation products with very high regioselectivity (usually > 99:1) and catalysis can be achieved at temperatures as low as 80 °C (Scheme 1). Interestingly, significantly diminished regioselectivities in favor of the branched product (≈ 85:15) are observed when styrenes or 1,3-butadienes are used as substrates. However, due to the wide applicability of [Ind$_2$TiMe$_2$] in amine synthesis and our plan to use this catalyst for a number of future synthetic applications, we recently focused the problem to synthesize multigram amounts of highly pure [Ind$_2$TiMe$_2$] in a most cost-efficient and convenient way.



Scheme 1. [Ind$_2$TiMe$_2$]-catalyzed intermolecular hydroamination and hydroaminoalkylation reactions.

Results and Discussion

In the literature, different procedures for the synthesis of [Ind$_2$TiMe$_2$] can be found.[2b,4] For example, *Resconi* et al. described a one-pot synthesis starting from inexpensive indene, methyllithium, and titanium tetrachloride involving a final soxhlet-extraction, which delivers the catalyst as a yellow-brown powder.[4] In contrast, we described a synthesis of [Ind$_2$TiMe$_2$] from commercially available bis(indenyl)dichlorotitanium, which can easily be methylated with methyllithium in diethyl ether.[2b] In this case, purification of the catalyst was accomplished by a classical aqueous workup procedure, which gave [Ind$_2$TiMe$_2$] as a yellow crystalline compound of high

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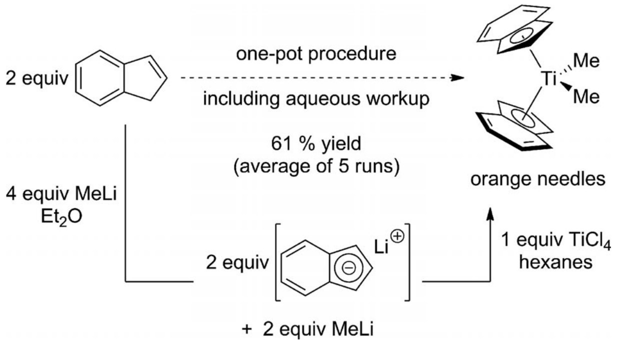
purity. In this context, it must be noted that [Ind_2TiMe_2] is a surprisingly water stable compound with only limited stability in the solid state and in solution at room temperature. Unfortunately, both synthetic approaches combine advantages and disadvantages. While the first synthetic approach starting from indene, methyllithium, and titanium tetrachloride is the most inexpensive option, the final purification procedure, the soxhlet-extraction, is a time-consuming method that also leads to decomposition of the temperature labile product [Ind_2TiMe_2]. The presence of thermally formed impurities in the finally isolated material is strongly indicated by the reported yellow-brown color[5] of the product and the inaccurate elemental analysis in the mentioned publication.[4] In contrast, our quick aqueous workup procedure, which is usually performed at room temperature (or below) offers the advantage that thermal decomposition of [Ind_2TiMe_2] is minimized. In addition, [Ind_2TiMe_2] is efficiently separated from all other water labile lithium or titanium species present in the reaction mixture. Unfortunately, bis(indenyl)dichlorotitanium is an expensive starting material, which represents a severe drawback especially when [Ind_2TiMe_2] needs to be synthesized on a multi-gram scale.

In order to provide the synthetic community with a simple, inexpensive, reliable, and reproducible procedure for a multigram synthesis of bis(indenyl)dimethyltitanium of high purity, we now combined the one-pot approach starting from inexpensive indene, methyllithium and titanium tetrachloride with a quick aqueous workup procedure (Scheme 2).



Scheme 2. One-pot synthesis of bis(indenyl)dimethyltitanium.

Initial preparation of an equimolar mixture of methyllithium and the indenyllithium salt was achieved by combining four equivalents of methyllithium with two equivalents of indene in diethyl ether at 0–25 °C. Rapid treatment of the obtained orange solution with one equivalent of titanium tetrachloride dissolved in hexanes at 0 °C gave a dark brown suspension. For the addition of titanium tetrachloride, a dropping funnel without a pressure equalizing tube equipped with a separate argon inlet was used to obtain an ether-free atmosphere in the funnel. This avoids the formation of any titanium tetrachloro ether complexes, which could disturb rapid addition of the titanium tetrachloride solution. Subsequent hydrolysis with ice-cold water and extraction of the aqueous layer with diethyl ether[6] afforded an ether solution of [Ind_2TiMe_2], from which the desired complex could be isolated by concentration under vacuum at 35 °C (rotary evaporator). After washing of the residue with hexanes at –50 °C,[7] [Ind_2TiMe_2] was obtained as orange needles in pure form as gauged by ^{1}H and ^{13}C NMR (see Supporting Information) and it was possible to obtain an accurate elemental analysis. Five runs of the described procedure were carried out by three different persons on a 20 or 40 mmol scale (based on $TiCl_4$) and the average yield was determined to be 61 %. In single experiments, the yields varied from 56 to 64 % proving the very good reproducibility of the procedure, which can entirely be carried out within a few hours. Due to its facile decomposition at room temperature, [Ind_2TiMe_2] was stored at –30 °C in the freezer. Although no loss of its catalytic activity (e.g. in hydroaminoalkylation reactions) could be determined over a period of several months, the color of the solid material slowly changed from orange to yellow. In general, storage of [Ind_2TiMe_2] at room temperature or in solution leads to rapid decomposition, which is always accompanied by a color change from yellow-orange to brown and finally to dark brown. In an inert atmosphere of nitrogen, the thermal decomposition point was determined to be 79–80 °C. This facile thermal decomposition could additionally be confirmed by NMR and ESR spectroscopy. Heating a sample of diamagnetic [Ind_2TiMe_2] in [D_6]benzene to a temperature of 80 °C for 3 h resulted in the total disappearance of all NMR signals of the titanium complex. On the other hand, the appearance of an ESR signal strongly indicates the formation of paramagnetic titanium species under these conditions. Interestingly, no corresponding ESR signal could be detected after storing [Ind_2TiMe_2] for six months at –30 °C in an inert atmosphere proving the good storability of the complex under these conditions.

Finally, it must be noted that the optimized procedure can also be used for the synthesis of the closely related metallocene bis(cyclopentadienyl)dimethyltitanium[8] from cyclopentadiene, methyllithium, and titanium tetrachloride. Due to the fact that in the solid state [Cp_2TiMe_2] (Cp = η^5-cyclopentadienyl) is not stable at room temperature, the compound was isolated as a 0.22 M solution in toluene (53 % yield; for details, see the Experimental Section).

Conclusions

A simple, reliable, and reproducible one-pot procedure for the multi-gram synthesis of highly pure bis(indenyl)dimethyltitanium was developed, which relies on the use of indene, methyllithium, and titanium tetrachloride as inexpensive starting materials. The isolation of the product is achieved by a convenient and quick aqueous workup procedure. Overall, quantities of several grams of [Ind_2TiMe_2] can easily be synthesized within a few hours. The successful application of the same procedure towards the synthesis of bis(cyclopentadienyl)dimethyltitanium shows that the new protocol might also be useful for the synthesis of other related metallocene derivatives.

Experimental Section

General Remarks: The reactions were carried out in an atmosphere of argon using standard Schlenk line techniques. Unless otherwise noted, all reagents were purchased from Acros Organics. Indene (90 %, stabilized) was purified by distillation (25 cm Vigreux column) at 3.00 Torr and stored in an argon atmosphere over molecular sieves (4 Å) at –30 °C prior to use. Cyclopentadiene was freshly distilled from dicyclopentadiene (93 %, stabilized, purchased from Merck Chemicals) and iron powder in an atmosphere of argon. Methyllithium (1.6 mol·L^{-1} in diethyl ether), titanium tetrachloride (99.9 %) and toluene (99.85 %, toluene extra dry with molecular sieves) were used as received. Diethyl ether, hexanes and [D$_6$]benzene were distilled from sodium in an argon atmosphere. NMR spectra were recorded with a Bruker Avance III spectrometer (^{1}H, 500 MHz; ^{13}C, 126 MHz) at 305 K. Chemical shifts (δ) are reported in ppm relative to the solvent residual peak of [D$_6$]benzene (^{1}H, 7.16 ppm; ^{13}C, 128.00 ppm). The IR spectrum was recorded with a Bruker Tensor 27 spectrometer using an attenuated total reflection method (ATR). The decomposition point was determined in a sealed capillary with a Schorpp-Gerätetechnik melting point MPM-H2 apparatus. Elemental analysis was performed with a HEKAtech Euro EA-CHNS Analyzer. The ESR experiments were carried out with a magnet tech MiniScope MS 300 spectrometer.

Preparation of Bis(indenyl)dimethyltitanium: A flame-dried 500 mL three-necked round-bottom flask, equipped with a Teflon®-coated oval stirring bar (2.5 cm), a septum, an argon inlet, and a dropping funnel[9] was charged with indene (4.65 g, 40.0 mmol) and diethyl ether (50 mL) and cooled to 0 °C. A solution of methyllithium (35.00 g, c = 1.6 mol·L^{-1} in diethyl ether, 80.0 mmol) was slowly added via syringe and the resulting mixture was stirred at 25 °C for 30 min to give an orange solution. The dropping funnel was charged with titanium tetrachloride (3.79 g, 20.0 mmol) and hexanes (50 mL). After the reaction vessel had been cooled to 0 °C, the solution of titanium tetrachloride in hexanes was added rapidly to form a dark brown suspension, which was stirred at 25 °C for 2.5 h. The mixture was poured into ice-cold water (300 mL) and the layers were separated.[6] The aqueous layer was extracted with diethyl ether (2 × 100 mL) and the combined organic layers were dried with MgSO$_4$ and filtered into a 500 mL round-bottom Schlenk flask. After concentration under vacuum (rotary evaporator, 35 °C) the flask was flushed with argon and cooled to –50 °C. Finally, the orange residue was washed with dry hexanes (50 mL) at –50 °C and dried under vacuum to give the title compound [Ind$_2$TiMe$_2$] as orange needles (3.91 g, 12.7 mmol, 64 %). The product was stored in an inert atmosphere (argon or nitrogen) at –30 °C. Mp. 79–80 °C (dec.). $C_{20}H_{20}Ti$ (308.24): C 77.66 (calcd. 77.93), H 6.63 (6.54) %. **^{1}H NMR** (500 MHz, C$_6$D$_6$, 305 K): δ = 7.18–7.22 (m, 4 H, CH), 6.92–6.96 (m, 4 H, CH), 5.80 (d, $^3J_{H,H}$ = 3.3 Hz, 4 H, CH), 5.38 (t, $^3J_{H,H}$ = 3.3 Hz, 2 H, CH), –0.50 (s, 6 H, CH$_3$) ppm. **^{13}C{^{1}H} NMR** (126 MHz, C$_6$D$_6$, DEPT, 305 K): δ = 125.6 (CH), 125.5 (C), 125.4 (CH), 117.5 (CH), 105.3 (CH), 51.5 (CH$_3$) ppm. **IR** (neat): $\tilde{\nu}$ = 3103 (vw), 3036 (w), 2951 (m), 2882 (m), 2792 (w), 1949 (vw), 1920 (w), 1896 (vw), 1818 (w), 1791 (w), 1721 (vw), 1698 (w), 1622 (w), 1595 (w), 1530 (w), 1483 (w), 1448 (w), 1410 (m), 1346 (s), 1338 (s), 1259 (w), 1214 (m), 1192 (w), 1151 (w), 1119 (w), 1104 (w), 1090 (w), 1046 (m), 994 (w), 976 (vw), 950 (w), 914 (m), 873 (w), 847 (w), 834 (w), 806 (vs), 748 (vs), 689 (m) cm^{-1}.

Preparation of Bis(cyclopentadienyl)dimethyltitanium: A flame-dried 500 mL three-necked round-bottom flask, equipped with a Teflon®-coated oval stirring bar (2.5 cm), a septum, an argon inlet, and a dropping funnel[9] was charged with freshly distilled cyclopentadiene (2.64 g, 40.0 mmol) and diethyl ether (50 mL) and cooled to 0 °C. A solution of methyllithium (35.00 g, c = 1.6 mol·L^{-1} in diethyl ether, 80.0 mmol) was slowly added via syringe and the resulting mixture was stirred at 25 °C for 30 min to give a white suspension. The dropping funnel was charged with titanium tetrachloride (3.79 g, 20.0 mmol) and hexanes (50 mL). After the reaction vessel had been cooled to 0 °C, the solution of titanium tetrachloride in hexanes was added rapidly to form a yellow-brown suspension, which was stirred at 25 °C for 2.5 h in the absence of light. The mixture was poured into ice-cold water (300 mL) and the layers were separated.[6] The aqueous layer was extracted with diethyl ether (100 mL) and the combined organic layers were dried with MgSO$_4$ and filtered into a 500 mL round-bottom Schlenk flask. After concentration under vacuum (rotary evaporator, 35 °C) to a volume of approximately 10 mL[10] the flask was flushed with argon and cooled to 0 °C. The orange solution was diluted with dry toluene (30 mL) and concentrated under vacuum at 0 °C to a volume of approximately 10 mL[10] to remove remaining diethyl ether and hexanes. Finally, the residue was diluted with dry toluene (40 mL) to give an orange solution of the title compound [Cp$_2$TiMe$_2$] (48 mL, c = 0.22 mol·L^{-1} in toluene, 10.6 mmol, 53 %). This solution was stored in an inert atmosphere (argon or nitrogen) in the dark at –30 °C. The concentration of the [Cp$_2$TiMe$_2$] solution was determined by ^{1}H NMR spectroscopy. **^{1}H NMR** (500 MHz, C$_6$D$_6$, 305 K): δ = 5.69 (s, 10 H, C$_5$H$_5$), 0.06 (s, 6 H, CH$_3$) ppm. **^{13}C{^{1}H} NMR** (126 MHz, C$_6$D$_6$, DEPT, 305 K): δ = 113.2 (CH), 46.1 (CH$_3$) ppm.

Supporting Information (see footnote on the first page of this article): Copies of the ^{1}H and ^{13}C NMR spectra of bis(indenyl)dimethyltitanium and dimethyltitanocene, pictures of the experimental setup.

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[5] Heating of [Ind$_2$TiMe$_2$] generally causes decomposition of the complex and a color change from yellow-orange to dark brown.

[6] During the aqueous workup procedure, occasionally, formation of an emulsion is observed. In this case, swirling of the separation funnel leads to a better phase separation.

[7] Washing with hexanes results in a significantly improved purity of the product due to removal of unreacted indene.

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[9] To obtain an ether-free atmosphere in the dropping funnel, a funnel without a pressure equalizing tube equipped with a separate argon inlet was used.

[10] **CAUTION:** Due to the fact that solid [Cp_2TiMe_2] can undergo spontaneous explosive decomposition, removal of the entire solvent must be avoided.

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