



166166

12 MAY 2004

WO 01/42260

PCT/GB00/04760

PREPARATION OF METALLOCENES CARRYING A CYCLOPENTADIENE COMPRISING A BASIC
DONOR GROUP

FIELD OF THE INVENTION

This invention relates to methods for the synthesis of metallocenes.

5

BACKGROUND OF THE INVENTION

Amino-functionalised titanocenes are of increasing interest because of their potential to act as highly active and selective olefin polymerisation catalyst precursors [1,2,3,4]. The neutral amino function can reversibly co-ordinate to the metal centre, potentially stabilising highly reactive intermediates formed during homogeneous catalytic processors. High catalytic activity has been found with group IV metallocenes as well as with metallocenes involving other metals. For instance, half-sandwich complexes of chromium in which the pendant amino function is co-ordinated to the metal centre have been shown to be highly active olefin polymerisation catalysts [5]. Furthermore, the pendant amino function can interact with inorganic support materials, thereby incorporating traditional metallocene catalysts into heterogeneous catalysts.

10

15

Quaternisation of the pendant amino group can result in water stable and soluble species [1,2,4]. Such species may not only provide water soluble catalytic compounds but are also useful as anti-tumour drugs having advantages over the known anti-tumour drug titanocene dichloride. Although titanocene dichloride is an efficient anti tumour agent [6,7], it has low solubility and is unstable in aqueous solution. The greater stability and solubility of amino-functionalised titanocenes renders these materials, and their dihydrochloride derivatives, potentially more suitable as anti-tumour agents as well as providing more suitable models for studying the mechanism of action of titanocene dichloride as an anti tumour agent.

20

25

Known synthetic methods for the preparation of the dihydrochloride salts of amino-functionalised titanocenes involve the deprotonation of the neutral cyclopentadiene to give lithium, sodium or thallium salts [2,3,4]. *In situ* deprotonation can be achieved

30



G00002

by the addition of an external base [8]. The reaction of the metal salt with TiCl_4 results from the formation of the neutral metallocene which is then reacted with HCl to give the dihydrochloride salt. Accordingly such a process involves 3 steps from the cyclopentadiene to the dihydrochloride salt. There is a need for an improved process involving fewer steps and producing the dihydrochloride salt in relatively high yield.

STATEMENTS OF INVENTION

According to the present invention there is provided a method for the preparation of a metallocene halide salt having at least one cyclopentadiene group substituted by a basic group, said method comprising reacting together a metal halide with a cyclopentadiene substituted by said basic group.

Accordingly the present invention provides a single step process for the preparation of an amino-functionalised metallocene which can be produced in high yield. It is believed that this single step process is possible because the method utilises the presence of an "internal base" rather than by making use of an external base in the known 3 step process.

The method of the present invention may be applied to the preparation of metallocenes of both early and late transition metals including the group IV metals Ti, Zr and Hf.

Preferably the metal halide is a homoleptic halide, more preferably a homoleptic chloride, an example being TiCl_4 .

Preferably the substituted cyclopentadienyl carries a pendant Lewis base. More preferably the Lewis base is provided by an amino group, for instance, a tertiary amino group, examples being $-\text{CH}_2\text{CH}_2\text{N}(\text{CHCH}_3)_2$ and $-\text{CH}_2\text{CH}_2\text{N}(\text{CH}_2)_5$.

Preferably the cyclopentadienyl is contacted with the metal halide in the presence of an inert solvent such as toluene.

5 Preferably the substituted cyclopentadiene and the metal halide are reacted together at ambient temperature or below. One reactant may be added to the other in a dropwise fashion. The addition may be carried out more quickly the lower the temperature.

10 The metallocene halide salt prepared by the method of the present invention may be converted to the neutral metallocene by contacting the salt with a base. Furthermore the metallocene halide salt may be converted to other species. For example, contacting the metallocene halide salt with an alkylating agent results in the formation of an alkyl substituted metallocene.

15 The method of the present invention represents a new and facile route to metallocene halide salts in high yield. The method is therefore highly advantageous over the known three steps synthetic routes.

DETAILED DESCRIPTION OF THE INVENTION

20 The present invention will now be described in greater detail and with reference to Figures 1 and 2 of the accompanying drawings which illustrate the synthetic routes which will be described.

25 By way of example, Figure 1 illustrates the known synthetic route and the method of the present invention for the preparation of an amino-functionalised titanocene; the method of the invention is shown as step (v).

30 The titanocene dihydrochloride salt 2 can be synthesised either by direct reaction of two equivalents of the neutral cyclopentadiene 1 and TiCl_4 in toluene or by reaction of the sodium salt 3 with TiCl_4 followed by reaction with HCl. The substituted cyclopentadiene 1 can be synthesised as previously described by Herrmann and co-

workers [9]. The dihydrochloride salt is isolated as a dark orange solid which is soluble in a polar solvent such as methanol, water and acetonitrile.

5 The neutral titanocene 4 can be obtained by reaction of the dihydrochloride 2 with two equivalents of MeLi and by reaction by the sodium salt 3 with TiCl_4 in ether. The highly air and moisture sensitive titanocene 4 can be isolated as a crystalline, deep orange solid and is soluble in aprotic, polar and non-polar solvents such as ether and toluene. An analytically pure sample can be obtained by recrystallisation from ether.

10

Reaction of the dihydrochloride 2 with four equivalents of MeLi results in the formation of the thermally stable dimethylated species 5, as illustrated in Figure 2. Species 5 is a highly air sensitive red oil.

15 Accordingly the present invention provides a synthetic route for a titanocene dihydrochloride which is both air stable and water soluble and avoids a number of synthetic steps in which the reagents are air and water sensitive. The resultant "protected" titanocene can be stored indefinitely and the neutral titanocene can be generated by reaction with a base. Deprotonation can be carried out *in situ* by a
20 cocatalyst such as MAO (methylaluminoxane) to give the neutral metallocene dichloride as the catalyst precursor. Furthermore, reaction with four equivalents of an alkylating agent generates the dialkyl substituted titanocene.

SPECIFIC EXAMPLES

25 Examples of the preparation of titanocene compounds will now be described.

Synthesis of $(\text{CpCH}_2\text{CH}_2\text{N}(\text{CH}_2)_2)_2\text{TiCl}_2(1)$

Method 1: From $\text{NaCpCH}_2\text{CH}_2\text{N}(\text{CH}_2)_2(\text{CH}_2)_2$ and TiCl_4

30 1.37g (0.0069 mol) of $\text{NaCpCH}_2\text{CH}_2\text{N}(\text{CH}_2)_2(\text{CH}_2)_2$ was added as a slurry in 100 ml of THF to 0.38 ml (0.66 g, 0.0034 mol) TiCl_4 in 75 ml of THF. On addition an orange colour developed in the toluene and a colourless precipitate formed. The

reaction mixture was left to stir for 1 h after which the solvent was removed in vacuo. The product was extracted in 100 ml of toluene. Recrystallisation from toluene affords the product as dark orange crystals.

5 **Method 2: From $(\text{CpCH}_2\text{CH}_2\text{N}(\text{CH}_2)_2(\text{CH}_2)_2)_2\text{TiCl}_2 \cdot 2\text{HCl}$**

Two equivalents of MeLi (0.0018 mol, 1.26 ml, 1.4M solution in Et₂O) were added dropwise to a suspension 0.48 g of $(\text{CpCH}_2\text{CH}_2\text{N}(\text{CH}_2)_2(\text{CH}_2)_2)_2\text{TiCl}_2 \cdot 2\text{HCl}$ (0.00088 mol) in 100 ml of toluene. The mixture was stirred for 2 h after which an orange colour had developed in the toluene. The solution was filtered and the solvent removed in vacuo. The residue was extracted in 50 ml of toluene and the solvent was removed in vacuo leaving 1 as a dark orange solid. ¹H NMR (C₆D₆): δ 2.54 (t, 4H, CpCH₂), δ 2.07 (t, 4H, CpCH₂CH₂), δ 2.3689 (m, 8H, N(CH₂)₂) δ 1.55 (m, 8H, N(CH₂)₂(CH₂)₂), δ 1.37 (M, 4H, N(CH₂)₂(CH₂)₂(CH₂), 6.26, 5.89 (pt, 8H, CpH). ¹³C NMR (C₆D₆): δ 29.16 (CpCH₂), δ 59.6 (CpCH₂CH₂), δ 55.10 (N(CH₂)₂), δ 26.74 (N(CH₂)₂(CH₂)₂), δ 25.16 (N(CH₂)₂(CH₂)₂(CH₂), δ 114.98, 123.31 (Cp ring C, δ 136.65 (Cp ring quaternary). Anal. Calcd for $(\text{CpCH}_2\text{CH}_2\text{N}(\text{CH}_2)_2(\text{CH}_2)_2)_2\text{TiCl}_2$ (449.32); C, 61.16; H, 7.70; N, 5.94. Found: C, 61.4; H, 7.85; N, 6.10.

Synthesis of $(\text{CpCH}_2\text{CH}_2\text{N}(\text{CH}_2)_2(\text{CH}_2)_2)_2\text{TiCl}_2 \cdot 2\text{HCl}$ (2)

20 **Method 1 (illustrative of the method of the invention): from TiCl₄ and HCpCH₂CH₂N(CH₂)₂(CH₂)₂**

Two equivalents of freshly distilled HCpCH₂CH₂N(CH₂)₂(CH₂)₂ (3.0 g, 0.0169 mol) in toluene (50 ml) were added dropwise to a solution of TiCl₄ (1.6g, 0.0085 mol) in toluene (150 ml) at -78 °C. The solution was stirred for 30 minutes during which time a dark orange solid had precipitated. The mixture was warmed to room temperature and stirred for an additional 4 h. The toluene was removed in vacuo and the solid was washed with ether and dried in vacuo leaving 2 as a dark orange solid. Yield = 4.1 g, 89%.

Method 2: from $(\text{CpCH}_2\text{CH}_2\text{N}(\text{CH}_2)_2\text{N}(\text{CH}_2)_2)_2\text{TiCl}_2$ and HCl

To a solution of 0.10 g of 1 (in deuterated benzene in an NMR tube) was added an excess of HCl (40% solution). Immediately a dark orange solid precipitated. The benzene was removed in vacuo and the solid was dissolved in CD_3N .

- 5 ^1H NMR (MeOD): ^1H NMR (C_6D_6): δ 3.31 (t, 4H, CpCH_2), δ 3.45 (t, 4H, CpCH_2CH_2), δ 3.61, 3.00 (m, 8H, $\text{N}(\text{CH}_2)_2$) δ 1.95, 1.87 (m, 8H, $\text{N}(\text{CH}_2)_2(\text{CH}_2)_2$), δ 1.54 (m, 4H, $\text{N}(\text{CH}_2)_2(\text{CH}_2)_2\text{CH}_2$), 6.72, 6.48 (pt, 8H, CpH). ^{13}C NMR (C_6D_6): δ 26.43 (CpCH_2), δ 57.10 (CpCH_2CH_2), δ 54.39 ($\text{N}(\text{CH}_2)_2$) δ 24.23 ($\text{N}(\text{CH}_2)_2(\text{CH}_2)_2$), δ 22.64 ($\text{N}(\text{CH}_2)_2(\text{CH}_2)_2\text{CH}_2$), δ 124.64, 116.95 (Cp ring C), δ 133.33 (Cp ring quaternary). MS (FAB; m/z (relative intensity, %): 472 ($[\text{CpCH}_2\text{CH}_2\text{NH}(\text{CH}_2)_2(\text{CH}_2)_2)_2\text{TiCl}_2]^+$, 7.43).
- 10

Synthesis of $(\text{Cp}(\text{CH}_2)_2\text{N}(\text{CH}_2)_5)_2\text{TiMe}_2$ (3)

- 15 To a suspension of 2 in Et_2O (0.5 g, 0.92 mmol, 50 ml Et_2O) was added two equivalents of MeLi (1.4 M, 1.3 ml, 1.84 mmol) in Et_2O with vigorous stirring. Evolution of a gas was immediately apparent. The mixture was left to stir at room temperature for 2 h, during which a deep orange solution had formed and a colourless solid precipitated. The Et_2O was removed in vacuo and the product was extracted in
- 20 toluene to leave the product as a dark red-brown oil.

Synthesis of $[(\text{CpCH}_2\text{CH}_2\text{N}(\text{Me})(\text{CH}_2)_2(\text{CH}_2)_2)_2\text{TiCl}_2]\text{Cl}_2$ (4)

- Two equivalents (0.19 g, 0.0013 mol) of methyl iodide were added to 0.30 g (0.00067 mol) of $\text{CpCH}_2\text{CH}_2\text{N}(\text{CH}_2)_2(\text{CH}_2)_2)_2\text{TiCl}_2$ in 50 ml of toluene. The reaction mixture was stirred for 30 minutes after which a bright orange precipitate had formed and no colour remained in the toluene. The toluene was filtered from the product which was washed with diethyl ether to leave 4 as a powder red solid.
- 25

WO 01/42260

PCT/GB00/04760

Synthesis of $(\text{CpCH}(\text{CH}_2)_2(\text{CH}_2)_2\text{NCH}_3)_2\text{TiCl}_2$ (5)

5 Analogous to the preparation of $(\text{CpCH}_2\text{CH}_2\text{N}(\text{CH}_2)_2(\text{CH}_2)_2)_2\text{TiCl}_2$, the sodium salt $\text{NaCpCH}(\text{CH}_2)_2(\text{CH}_2)_2\text{NCH}_3$ (0.73 g, 3.92 mmol in 50 ml of THF) was added to a solution of TiCl_4 (0.38 g, 1.96 mmol in 100 ml of THF). The mixture was stirred for 2 hours after which a brown precipitate had formed and the solution had turned a deep red colour. The solution was filtered and solvent removed under vacuum to leave a dark orange solid.

10 Synthesis of $(\text{CpCH}(\text{CH}_2)_2(\text{CH}_2)_2\text{NCH}_3)_2\text{TiCl}_2 \cdot 2\text{HCl}$ (6)

Analogous to the preparation of $(\text{CpCH}_2\text{CH}_2\text{N}(\text{CH}_2)_2(\text{CH}_2)_2)_2\text{TiCl}_2 \cdot 2\text{HCl}$, the product can be synthesised by the direct reaction of $\text{NaCpCH}(\text{CH}_2)_2(\text{CH}_2)_2\text{NCH}_3$ and TiCl_4 in toluene and by reaction of $(\text{CpCH}(\text{CH}_2)_2(\text{CH}_2)_2\text{NCH}_3)_2\text{TiCl}_2$ with HCl .

WO 01/42260

PCT/GB00/04760

Selected NMR Data

Compound	Chemical Shifts of Cyclopentadienyl Protons (δ , ppm)	Solvent
1	6.26, 5.88	C ₆ D ₆
2	6.68, 6.56 6.72, 6.48 6.57, 6.47	CD ₃ CN CD ₃ OD D ₂ O
3	5.53, 5.87	C ₆ D ₆
4	6.75, 6.59	CD ₃ CN
5	6.37, 6.25	CDCl ₃
6	6.75, 6.70	CD ₃ OD

WO 01/42260

PCT/GB00/04760

REFERENCES:

- (1) Jutzi, P.; Redeker, T. *Eur. J. Inorg. Chem.* **1998**, 663-674.
- (2) Jutzi, P.; Redeker, T.; Neumann, B.; Stammeler, H.-G. *Organometallics* **1996**, *15*, 4153-4161.
- 5 (3) Blais, M. S.; Chien, J. C. W.; Rausch, M. D. *Organometallics* **1998**, *17*, 3775-3783.
- (4) Jutzi, P.; Kleimeier, J. *J. Organomet. Chem.* **1995**, *486*, 287-289.
- (5) Jolly, P.; Ionas, K.; Verkovnic, G. P. I. German Patent 19630580 A1, **1998**
- (6) Kopf-Maier, P. In *Complexes in Cancer Chemotherapy*; Keppler, B. K., Kd.;
10 VCH: Weinheim, New York, 1993; pp 259.
- (7) Toney, J. H.; Marks, T.J.J. *Am. Chem. Soc.* **1885**, *107*, 947-953.
- (8) Sinnema, P.-J.; van der Veen, L.; Spek, A. L.; Veldman, N.; Tauben, J.H. *Organometallics* **1997**, *16*, 4245-4247.
- (9) Herrmann, W.A., Morawietz, T. P.; Mashima, K. *J. Organomet. Chem.* **1995**,
15 *486*, 291-295.

CLAIMS

1. A method for the preparation of a metallocene halide salt having at least one cyclopentadiene group substituted by a basic group, said method comprising
5 reacting together a metal halide with a cyclopentadiene substituted by said basic group.
2. A method as claimed in claim 1 wherein said metal halide is a halide of an early or a late transition metal.
10
3. A method as claimed in claim 2 wherein said metal comprises titanium, zirconium or hafnium.
4. A method as claimed in any one of claims 1 to 3 wherein said metal halide
15 comprises a homoleptic halide.
5. A method as claimed in claim 4 wherein said homoleptic halide comprises a homoleptic chloride.
- 20 6. A method as claimed in claim 5 wherein said homoleptic chloride comprises titanium tetrachloride.
7. A method as claimed in any one of claims 1 to 6 wherein said substituted cyclopentadiene carries a pendant Lewis base.
25
8. A method as claimed in claim 7 wherein said Lewis base is provided by an amino group.
9. A method as claimed in claim 8 wherein said amino group comprises a
30 tertiary amino group.

WO 01/42260

PCT/GB00/04760

10. A method as claimed in claim 9 wherein said tertiary amino group comprises
-CH₂CH₂N(CHCH₃)₂ or -CH₂CH₂N(CH₂)₅.
- 5 11. A method as claimed in any one of claims 1 to 10 wherein said substituted
cyclopentadiene is contacted with said metal halide in the presence of an inert
solvent.
12. A method as claimed in claim 11 wherein said inert solvent comprises
toluene.
- 10 13. A method as claimed in any one of claims 1 to 12 wherein said substituted
cyclopentadiene and said metal halide are reacted together at ambient
temperature or below.

15

20