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Note

An improved synthesis of Kagan's menthyl substituted titanocene and zirconocene dichloride, comparison of their crystal structures, and preliminary catalyst evaluation

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Abstract

An improved synthesis of **1** and **2** is described that allows access to these complexes in multigram quantities necessary for catalytic applications. The crystal structures of **1** and **2** are compared and the conformational preferences of the ligands, that are important for catalytic applications, are discussed. Complex **2** was evaluated as a catalyst for carbomagnesation reactions.
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1. Introduction

Recently, titanocene and zirconocene complexes have emerged as powerful reagents in enantioselective catalysis in a number of highly useful reactions, e.g., zirconium catalyzed alkylation of alkenes with Grignard reagents and zirconium catalyzed alkylation of alkenes with alkyl-aluminum reagents, titanium catalyzed carbonylative enyne cyclizations, and hydrogenations [1]. We have introduced Kagan' s complex **1** [2a] and Vollhardt' s phenyl substituted analogue [2b] as catalysts for the highly enantioselective opening of *meso*-epoxides with ensuing C–H or C–C bond formation [3]. The method is based on Nugent's and RajanBabu's [4] stoichiometric reaction that we have developed into a catalytic process [5]. For **1** and **2** to be useful in practical applications it is essential that large amounts of the complex can be prepared in a

straightforward manner. However, the original procedure, shown in Fig. 1, is only applicable for the synthesis of relatively small amounts of **1** and its zirconium analogue **2**. This is due to the low yields during the formation and purification of cyclopentadiene **4** and moderate yields during the metallation.

2. Results

We have therefore developed a synthesis of **1** and **2** that increases the yields of the desired complexes by factors of 4 and almost 8, respectively, by carefully optimizing the reaction conditions. It is relying on the use of *neo*-menthyl mesylate **3** [6] that is substantially more reactive in S_N2 reactions than the originally employed tosylate. Cyclopentadiene **4** could indeed be isolated from the reactions of **3** in much higher yields. Gratifyingly, even the separation of **4** from menthene formed as by-products (ca. 15% of menthene are formed through elimination) was unnecessary and the mixture of hydrocarbons obtained

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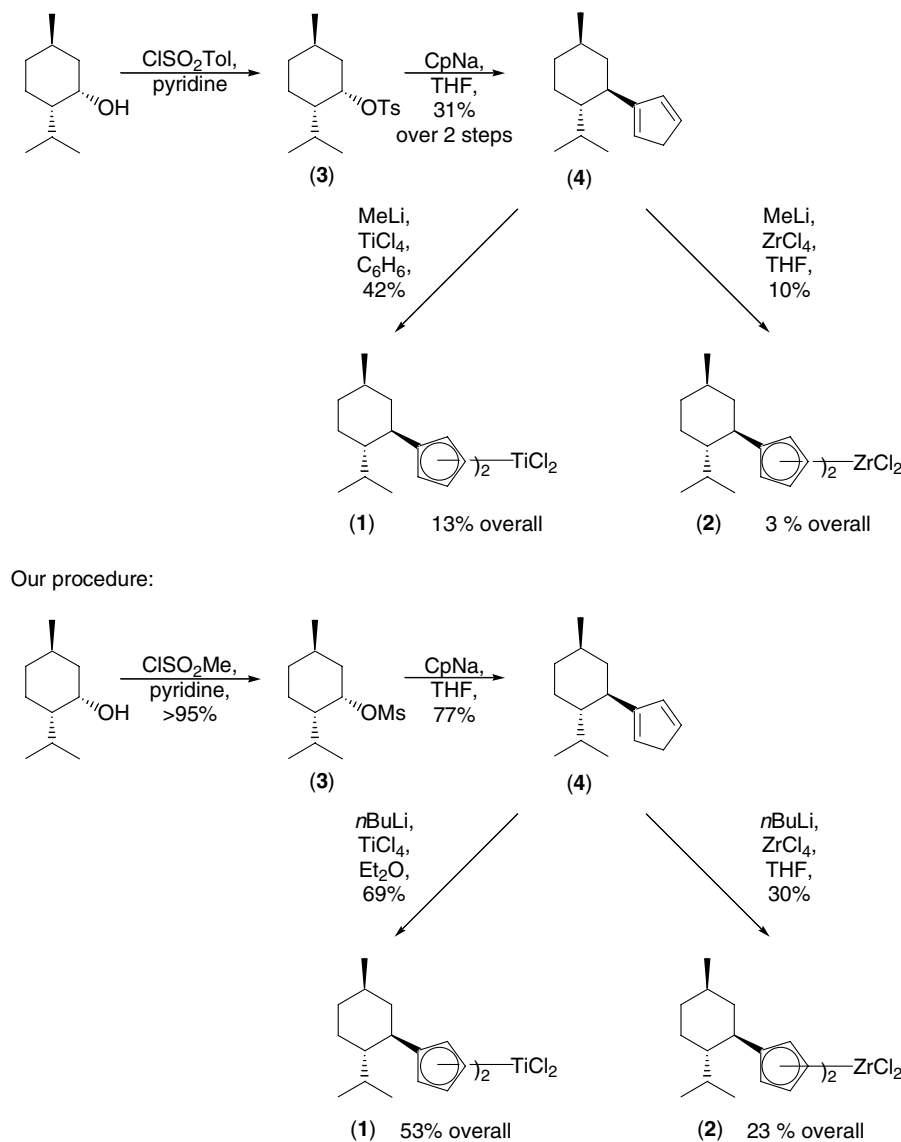
Fig. 1. Synthesis of **1** and **2**.

after a filtration through a plug of silica could be used directly in the ensuing metallation reaction. The overall yield of **4** was 77% which compares favorably with the 31% obtained in the original procedure [2a]. After deprotonation of **4** with *n*-BuLi the cyclopentadienyl ligand was obtained. Addition of the red solution to TiCl₄ in ether instead of toxic benzene gave a precipitate that was washed with *t*-butyl methyl ether and filtered through celite with CH₂Cl₂ to yield **1** in 69% yield as shown in Fig. 2. This orange powder was pure by ¹H- and ¹³C NMR spectroscopy. Using the original procedure **1** was isolated in 42% yield. Zirconocene **2** was synthesized by the same route. A yield of 30% yield (10% by the original method) was obtained after crystallization from dichloromethane. We believe that replacing carcinogenic benzene as the reaction solvent and the substantially simplified purification results in the higher yields during the metallation. For details see Fig. 1.

2.1. Comparison of the crystal structures

The knowledge of the structures of organometallic reagents is important for the understanding of their reactivities, especially in catalytic reactions. Crystal data of **2** are given in Table 1 and the molecular structure is shown in Fig. 2.

The differences follow the general trend for titanocenes and zirconocenes. The Cp–M distance, the Cp–M–Cp angle, and the M–Cl bond lengths are slightly larger for **2**. Moreover, only one side of the chlorine ligands is sterically shielded. Within the ligand framework the conformational preferences of the substituents are very similar and independant of the metal, however. This can, for example, be deduced from the dihedral angles C2′C1′C1C2 and C6′C1′C1C2 that give an indication of the canting of the cyclopentadienyl rings. The values were measured as 81.9(2) and −153.8(2) for **2** and
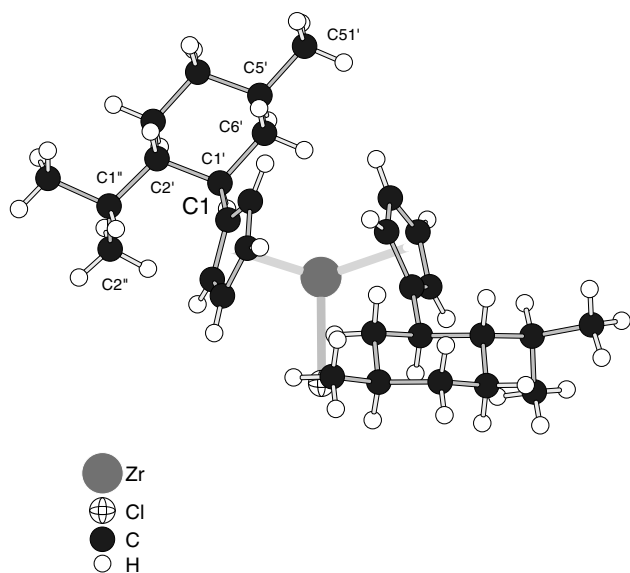
Fig. 2. X-ray structure of **2**.

Table 1
Crystal data and structure refinement of **2**

	2
Formula	$C_{30}H_{46}Cl_2Zr$
Formula weight	568.79
Dimensions (mm)	$0.40 \times 0.30 \times 0.20$
Crystal system	Tetragonal
Space group	$P4(2)$ (No. 77)
Unit cell dimensions	
a (Å)	15.3519(2)
b (Å)	15.3519(2)
c (Å)	6.4391(1)
α (°)	90
β (°)	90
γ (°)	90
V (Å^3)	1517.57(4)
Z	2
ρ_{calc} (g cm^{-3})	1.245
μ (mm^{-1})	0.553
$F(000)$	600
Diffractometer	Nonius Kappa CCD
Radiation	Mo Kα
λ (Å)	0.71073
T (K)	123(2)
Max 2θ (°)	55
Number of data	29430
Number of unique data	3475
Number of unique data [$I > 2(I)$]	3200
Number of variables	150
Number of restraints	1
$R(F)$[a]	0.0188
$wR_2(F^2)$[a]	0.0469
For all data $wR_2(F^2)$	0.0479

[a] For $I > 2(I)$.

83.1(5) and −153.9(4) for **1**, respectively. All other angles and bond distances are also essentially the same.

Thus, similar stereoselectivities can be expected for both **1** and **2** in related transformations. Due to the

popularity of Brintzinger' s complexes EBTHITiCl$_2$ and EBTHIZrCl$_2$ in metallocene catalysis it is of general interest to compare **1** and **2** to these complexes. We have already demonstrated that Brintzinger's titanocene is inferior to **1** in epoxide openings [4]. This was presumably due to a chiral pocket too tight for efficient electron transfer. In the field of zirconocenes arguably the most important application of Brintzinger's complex in organic synthesis is constituted by enantioselective carbomagnesation reactions [1a,1b,1c]. We therefore decided to investigate **2** in these transformations. Some preliminary results are summarized in Fig. 3.

While **2** displayed excellent catalytic activity in both reactions, the enantioselectivities were very low (ee < 5) in both cases. The yield of only 57% for **5** was obtained after distillation because alcohol **5** is very volatile. GC analysis of the crude mixture revealed complete conversion of substrate into product. Essentially the same scenario was observed in the second reaction. Almost quantitative conversion and high yields of the desired products were obtained, the enantioselectivity was virtually non-existent, however. Thus, the ligand arrangement in **2** is not well suited for the selectivity requirements of these transformations. The necessary tight arrangement as in Brintzinger's complexes [7] EBTHITiCl$_2$ and EBTHIZrCl$_2$ or the roof wall substitution (a vivid depiction introduced by Whitby [8]) is obviously not given here. We therefore conclude that **2** is much better suited for reactions requiring a more open arrangement of the ligands. This is the case in our enantioselective opening of *meso*-epoxides [4]. We are currently pursuing the search for these transformations.

3. Experimental

3.1. X-ray crystallographic studies of **2**

The structure was solved by Patterson methods (SHELXS97) [9]. The non-hydrogen atoms were refined anisotropically on F^2 (SHELXL-97) [9]. H atoms were refined using a riding model. The absolute configuration was determined by refinement of Flack's parameter ($x = -0.02(3)$). Further details are given in Table 1.

3.2. General procedures

All reactions were carried out using dry THF or diethylether (freshly distilled from K/Na) under an argon atmosphere. Pyridine was dried over CaH$_2$ and distilled prior to use. Flash chromatography was carried out according to the procedure of Still et al. [10].

3.3. (1S,2S,5R)-methane sulfonic acid-[(5-methyl-2-prop-2-yl)-cyclohexy-1-yl]-ester (**3**)

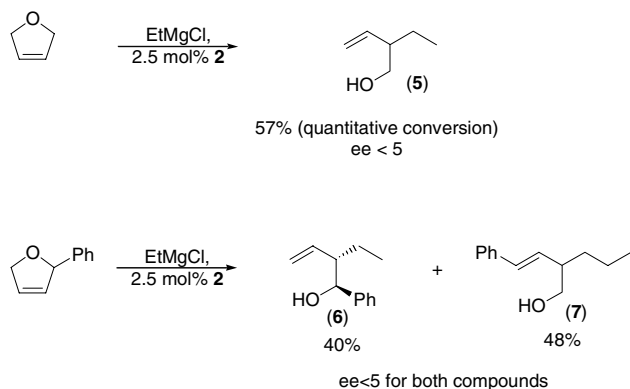To a solution of mesyl chloride (9.54 ml, 123 mmol) in dry pyridine at −10 °C was added *neo*-menthol (15.3 ml,

Fig. 3. Carbomagnesations catalyzed by **2**.

88.0 mmol) in pyridine (18 ml). Stirring was continued for 30 min at −10 °C and 15 h at 2 °C. After pouring on conc. HCl (82 ml) and crushed ice (295 g) the mixture was extracted with Et$_2$O (3 × 180 mL). The combined organic phases were dried (MgSO$_4$) and the volatiles evaporated in vacuum. Mesylate **3** was obtained in quantitative yield (20.6 g), and used without further purification.

3.4. Cyclopenta-1,3-dienyl-(1R,2S,5R)-4-methyl-1-(prop-2-yl)-cyclohexane (4)

To a suspension of NaH [4.86 g (95%), 202 mmol] in dry THF (120 ml) was added freshly cracked cyclopentadiene (17.4 ml, 211 mmol) at 0–5 °C. After stirring for 30 min **3** (20.6 g, 88.0 mmol) was added in THF (44 mL) and the mixture allowed to warm to room temperature over 24 h. After addition of H$_2$O (100 mL), the mixture is extracted with pentane (3 × 100 mL). The combined organic phases were washed with H$_2$O (100 mL), dried (MgSO$_4$) and the volatiles evaporated in vacuum (15 °C water bath). The crude product (17.8 g) was purified by filtration through a plug of silica with petrol ether. The product obtained (15.5 g) contained about 15% of menthene and was used without further purification. The yield of **4** is 77%.

3.5. Bis{η^5{(1R,2S,5R)-5-methyl-2-[prop-2-yl]-cyclohex-1-yl}cyclopentadienyl}-titanium dichloride (1)

To a solution of **4** [12.0 g (85%), 50.0 mmol] in THF (100 mL) was added nBuLi (21.0 mL of a 2.50 M solution in hexanes, 52.5 mmol) at 0–5 °C. This solution was added to a solution of TiCl$_4$ (2.69 mL, 24.5 mmol) in ether (100 mL) at 0 °C. After keeping at this temperature for 2 h stirring was continued at room temperature for 20 h. The volatiles were removed in vacuum and the residue purified by washing with tbutylmethyl ether (500 mL) and filtration through celite with dichloromethane to yield **1** (8.95 g, 69%) as an orange powder that was pure by ^{1}H- and ^{13}C NMR analysis.

3.6. Bis{η^5 {(1R,2S,5R)-5-methyl-2-[prop-2-yl]-cyclohex-1-yl}cyclopentadienyl}-zirconium dichloride (2)

To a solution of **4** [16.32 g (85%), 68 mmol] in THF (100 mL) was added nBuLi (50.5 mL of a 1.4 M solution in hexanes, 72 mmol) at 0–5 °C. This solution was added to a solution of ZrCl$_4$ (7.70 g, 33 mmol) in THF (100 mL) at 0 °C. After stirring at room temperature for 16 h H$_2$O is added (5 mL) and most of the volatiles are removed in vacuum. The crude product obtained after filtration is washed with pentane (3 × 100 mL). The remaining solid is crystallized from CH$_2$Cl$_2$ to yield **2** as colorless crystals (6.00 g, 30%).

3.7. Carbomagnesation of 2,5-dihydrofuran

Complex **2** (397 mg, 0.7 mmol) was dissolved in THF (40 mL) and ethylmagnesium chloride (50 mL of a 2.8 M solution in THF, 140 mmol) was added at room temperature. After stirring for 1 h a mixture of 2,5-dihydrofuran (2.16 mL, 28 mmol) and ethylmagnesium chloride (2 mL of a 2.8 M solution in THF, 5.6 mmol) was added and stirring was continued for 18 h. After cooling to 0 °C HCl (10 mL of a 2 M solution) was added. The mixture was diluted with water (100 mL) and extracted with CH$_2$Cl$_2$ (100 mL). After evaporation of most of the solvent (ca. 90 mL) the remaining mixture is distilled to give **5** (1.60 g, 57%) as a colorless liquid. The compound had an ee of less than 5% as judged by analysis of the ^{1}H NMR spectra of their Mosher esters.

3.8. Carbomagnesation of 2-phenyl-2,5-dihydrofuran

To a solution of 2-phenyl-2,5-dihydrofuran (146 mg, 1.0 mmol) in THF (2 mL) was added **2** (7.0 mg, 25 μmol), and ethylmagnesium chloride (1.7 mL of a 3.2 M solution in THF, 5.4 mmol) and the mixture was stirred for 16 h at room temperature. The reaction was quenched by addition of aq. HCl and the mixture extracted with CH$_2$Cl$_2$. After drying (MgSO4) and evaporation of the volatiles the crude product was purified by SiO$_2$ chromatography (CH:EE = 89:11) to yield **6** (70.2 mg, 40%) [11] and **7** (84.8 mg, 48%) [11]. Both compounds had ee's lower than 5% as judged by analysis of the ^{1}H NMR spectra of their Mosher esters.

4. Conclusion

In summary, we have demonstrated an improved modified approach to titanocene **1** and zirconocene **2** in multigram quantities from the readily available neo-menthyl mesylate **3** as starting material. Both complexes display similar conformational preferences that result in a wide chiral pocket. Thus, reactions that are efficiently catalyzed by Brintzinger's complexes [7] that possess a tighter arrangement of the ligands around the metal display very low selectivity with **2**.

5. Supplementary material

Crystallographic data for **2** as supplementary Publication No. CCDC-246956. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, fax.: (internat.) +44 1223 336 033; e-mail: deposit@ccdc.cam.ac.uk.

Acknowledgments

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