The Effect of Open and Closed Structures of Titanocenes on the Control of Diastereoselectivity of Radical Reactions

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*Summary: A comparison of the X-ray structures of dichlorobis{(1-methylcyclohexyl)-η⁵-cyclopentadienyl}-titanium (**1**) and dichlorobis{(1-butyl-1-methylbutyl)-η⁵-cyclopentadienyl}titanium (**2**), containing tertiary alkyl substituents, and the known complex dichlorobis(cyclohexyl-η⁵-cyclopentadienyl)titanium (**3**), with two cyclohexyl substituents, has been carried out. The structural features are of relevance for the understanding of activity and selectivity of these complexes in diastereoselective additions of acrylates to β-titanoxy radicals and for the design of novel catalysts.*

Introduction

The control of selectivity in both free radical reactions and metal-mediated or -catalyzed radical reactions by the action of external reagents has attracted considerable interest recently.[1] Our catalytic approach uses titanocene complexes as electron transfer reagents and collidine hydrochloride (Coll*HCl) as mediator for catalysis in reductive epoxide openings to yield β-titanoxy radicals.[2] In this manner the first enantioselective radical generation was realized[3] by the use of menthol-derived titanocene complexes.[4] The method is based on a reaction stoichiometric in Cp_2TiCl_2 that was introduced by Nugent and RajanBabu.[5]

In this note we describe our results employing the titanocenes **1** and **2** with extremely bulky tertiary alkyl substituents and with complex **3**[6] containing the secondary cyclohexyl group in diastereoselective radical additions and correlate the results to the structures obtained by X-ray crystallography. These structures can be used as models for catalyst conformation in solution, as we have demonstrated earlier for other titanocenes.[7]

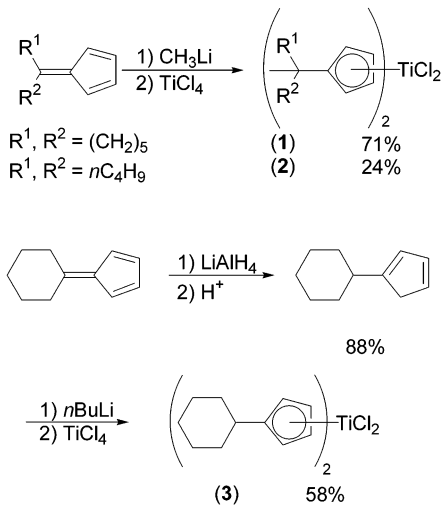

Figure 1. Synthesis of the novel titanocenes **1** and **2** and an improved synthesis of **3**.

Results and Discussion

Synthesis and Structures of the Titanocenes. Complexes **1** and **2** were synthesized by addition of MeLi to known fulvenes[8] and ensuing in situ metalation of the generated cyclopentadienyl anion with $TiCl_4$. The yield of **2** was lower because of its distinctly higher solubility in ethereal solvents caused by the long alkyl groups. For the preparation of **3**,[6] it proved to be advantageous to isolate the cyclopentadiene obtained by $LiAlH_4$ reduction of the fulvene. After deprotonation with *n*BuLi metalation with $TiCl_4$ proceeded eventlessly. The in situ method yielded **3** in only 23% yield. The preparations are summarized in Figure 1.

Crystals of **1** and **2** suitable for X-ray crystallography were obtained by slow evaporation of concentrated solutions in CH_2Cl_2. These structures and that of **3** are

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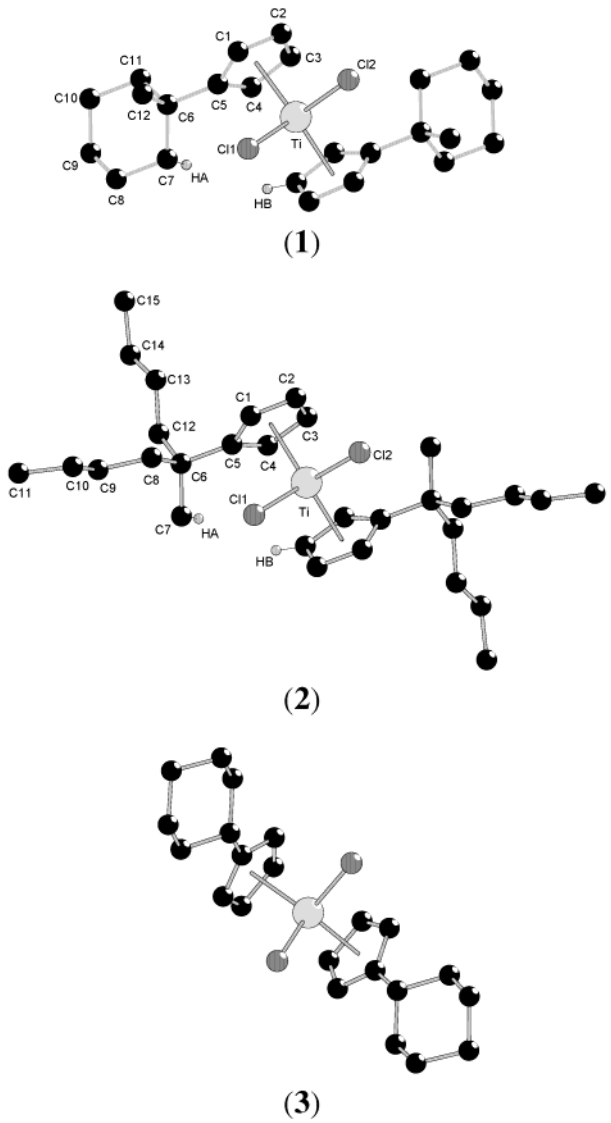


Figure 2. X-ray structures of **1**, **2**, and **3**.

Table 1. Selected Bond Lengths [Å] and Angles [deg] for 1 and 2 (esd's in parentheses)

dist. or angle	1	2
Ti−Cl	2.3724(4)	2.3742(4)
Cl−Ti−Cl	91.700(18)	92.092(19)
C_5−Ti	2.4843(12)	2.4867(12)
C_5−Ti−$C_5^{\#1}$	140.34(6)	137.78(6)
C_5−C_6	1.5247(17)	1.5251(18)
C_4−C_5−C_6	125.44(11)	124.20(12)
C_1−C_5−C_6−CH_3	−11.69(17)	−136.36(14)

shown in Figure 2. Selected data for **1** and **2** are presented in Table 1. Crystal data are presented in Table 2.

In both complexes **1** and **2** the bulky alkyl groups are positioned laterally behind the chlorine ligands and point away from each other. The backside of the complex is completely blocked by the cyclopentadienyl ligand and the alkyl groups in both cases. This is indicated by a close contact between the only hydrogens (H_A and H_B) in **1** and **2** shown in Figure 2 (235 and 236 pm, respectively). It should be noted that due to steric interactions the tertiary carbons are not, as one would expect, placed in the plane of the cyclopentadienes. The overall orientation of the ligands results in a fairly open front space around the chlorine ligands that is important for an unhindered binding of substrates. For the following discussion we introduce the expression "open structure" for this arrangement.

Table 2. Crystallographic Data and Summary of Data Collection and Refinement for 1 and 2

	1	2
formula	$C_{24}H_{34}Cl_2Ti$	$C_{30}H_{50}Cl_2Ti$
dimens,mm	0.60 × 0.30 × 0.10	0.50 × 0.30 × 0.15
cryst syst	monoclinic	monoclinic
space group	*C*2/*c* (No.15)	*C*2/*c* (No.15)
unit cell dimens	a = 23.7298(4) Å, α = 90°	a = 30.8243(7) Å, α = 90°
	b = 6.5506(1) Å, β = 93.429(2)°	b = 6.7389(1) Å, β = 93.001(1)°
	c = 13.7888(2) Å, γ = 90°	c = 13.9847(3) Å, γ = 90°
V, Å^3	2139.55(6)	2900.94(10)
Z	4	4
ρ_{cacl}, g cm^{-3}	1.370	1.212
μ (Mo Kα), mm^{-1}	0.657	0.495
F(000)	936	1144
diffractometer	Nonius KappaCCD	
radiation	Mo Kα	
λ, Å	0.71073	
T, K	123(2)	
max 2θ, deg	50	50
no. of data	20 419	7587
no. of unique data	1891	2539
no. of unique data [$I > 2\sigma(I)$]	1797	2238
no. of variables	123	150
R(F)[a]	0.0229	0.0254
wR2(F^2)	0.0653	0.0720

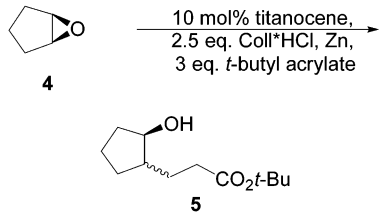
[a] For $I > 2\sigma(I)$.

In complex **3** the cyclohexyl groups are positioned between the chlorine ligands. Compared to **1** and **2** approach of substrates to the titanium center is thus hindered. We therefore call this alignment "closed structure".

Applications in Radical Addition Reactions. We investigated the use of the three titanocenes in the opening and addition reactions of cyclopentene, cyclohexene, cycloheptene, and norbornene oxide **4**, **6**, **8**, and **10**. Although the values for the diastereoselectivity given in the figures refer to the isolated material after chromatography, these values did not deviate significantly (±3%) from the ones obtained by analysis of the crude mixtures in several cases examined. The workup procedures also do not affect the isolated yields of the products as has already been established before.[2,3] Usually, in these reactions starting material is completely consumed within less than 6 h (TLC, GC analysis). The extended reaction times shown here have been used for the sake of convenience (overnight reactions) and do not affect the outcome of the transformations (yields, selectivities). The byproducts formed consist mainly of the chlorohydrins generated by Lewis acid- or acid-mediated ring opening via S_N reactions. This pathway is becoming more relevant when catalyst activity is reduced by bulky ligands.

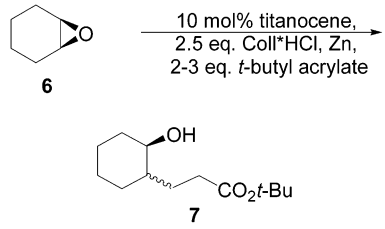
In the opening of **4** all complexes exhibited similar degrees of diastereoselectivity. The yields with **1** and **2** were essentially the same (61% and 63%), whereas **3** resulted in a better result (72%), as depicted in Figure 3.

It seems that complexes with an "open" and a "closed" structure are suitable for binding of the sterically undemanding **4** containing the essentially flat cyclo-



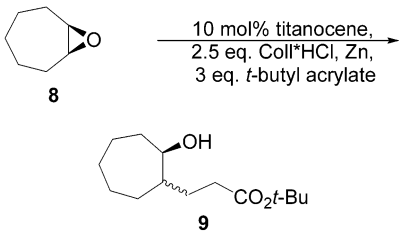
1 : 61%; *trans*:*cis* = 95:5
2 : 63%; *trans*:*cis* = 92:8
3 : 72%; *trans*:*cis* = 96:4

Figure 3. Titanocene-catalyzed opening of **4**.



1 : 67%; *trans*:*cis* = 70:30
2 : 52%; *trans*:*cis* = 74:26
3 : 51%; *trans*:*cis* = 70:30

Figure 4. Titanocene-catalyzed opening of **6**.



1 : 58%; *trans*:*cis* = 93:7
2 : 48%; *trans*:*cis* = 93:7
3 : 35%; *trans*:*cis* = 82:18

Figure 5. Titanocene-catalyzed opening of **8**.

pentane unit. Also, control of diastereoselectivity in the resulting β-titanoxy cyclopentyl radical addition to yield **5** is efficient in all cases.

As shown in Figure 4 the situation changes slightly for the opening of **6**. Here, only **1** gives an acceptable yield of the desired product **7**. Both the extremely bulky ligand in **2** and the "closed structure" in **3** prevent efficient binding of the substrate and result in decreased yields. Diastereoselectivity is in the usual range for β-substituted cyclohexyl radicals.[9]

This trend is becoming even more pronounced in the opening of **8** (Figure 5). In this case both **2** and **3** result in poor yields. Additionally control of diastereoselectivity is low for **3**. It seems that in the "closed structure" an efficient chirality transfer to more distant regions of the metal-bound radical necessary for high selectivity as observed for **1** and **2** is impossible.

In the case of norbornene oxide (**10**) the epoxide is in close proximity to one of the hydrogens of the methylene bridge. Thus, binding of catalysts to **10** must be considered as sterically difficult. This notion is borne out experimentally by the very low yield in the reaction with **3** as shown in Figure 6.

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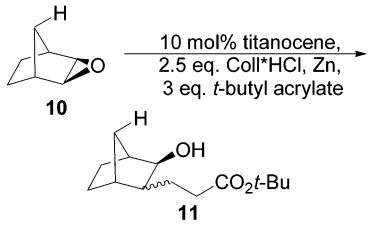

1 : 56%; *trans*:*cis* = 51:49
2 : 54%; *trans*:*cis* = 49:51
3 : 20%; *trans*:*cis* = 35:65

Figure 6. Titanocene-catalyzed opening of **10**.

The complexes with the "open structure" give much better yields of **11** than **3**. This constitutes a clear indication of a wider binding pocket resulting from the lateral positioning of the bulky substituents. Moreover, **3** is distinctly less able to override the high inherent *cis*-selectivity of the norbornene system than **1** and **2**. Thus, as in the case of **8**, the reagent control exercised by **3** is rather limited and essentially the same as for Cp_2TiCl_2.[2c]

Summary

In summary, we have demonstrated that an "open structure" of potential titanocene catalysts for epoxide opening via electron transfer and ensuing addition to an acrylate is to be preferred over a "closed structure" concerning both yield and diastereoselectivity of the overall process except for sterically unhindered cases.

For complexes possessing the "open structure" care has to be taken in avoiding substituents on the cyclopentadienyl ligand that are too bulky. In these cases substrate binding is retarded and accordingly low yields of the desired product will be obtained. However, control of diastereoselectivity in these cases is usually good to excellent.

Experimental Section

X-ray Crystallographic Studies of 1 and 2. The structures were solved by Patterson methods (SHELXS97).[10] The non hydrogen atoms were refined anisotropically on F^2 (SHELXL-97).[11] H atoms were refined using a riding model. An absorption correction was applied to **2**. Further details are given in Table 2.

General Procedures. The fulvenes were prepared according to literature procedures.[8] All reactions were carried out using dry THF (freshly distilled from K) under an argon atmosphere. Collidine hydrochloride was dried by gentle heating under vacuum prior to use. Flash chromatography was carried out according to the procedure of Still.[12]

Preparation of 1. Cyclopenta-2,4-dienylidenecyclohexane (5.84 g, 40 mmol) was dissolved in diethyl ether (40 mL) at 0 °C, and a solution of MeLi (1.5 M, 25.3 mL, 38 mmol) was added over 30 min. After stirring for 2 h the mixture was added to a solution of $TiCl_4$ (3.22 g, 17 mmol) in diethyl ether (40 mL). The suspension was stirred at 0 °C for 2 and 16 h at room temperature. The reaction was quenched by addition of HCl (1 M, 40 mL, containing NaCl, 4.00 g) and stirring for 30 min. After filtration through Celite the residue was washed with HCl (1 M, 100 mL). The red precipitate on top of the

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Celite was dissolved in CH_2Cl_2 (800 mL), the solution was dried ($MgSO_4$), and the volatiles were removed in a vacuum to yield **1** (5.36 g, 12 mmol) as a red solid (71%). Crystals suitable for crystallography were grown by slow evaporation of a concentrated solution in CH_2Cl_2. Mp: 223−225 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.57 (t, $^3J = {}^4J = 2.7$ Hz, 2H), 6.44 (t, $^3J = {}^4J = 2.7$ Hz, 2H), 1.18−1.76 (m, 10H), 1.34 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.5, 120.2, 117.2, 38.7, 37.6, 26.1, 23.8, 22.3. MS (70 eV, EI): *m*/*z* (%) 440 (16), 405 (38), 279 (100), 243 (5), 227 (18). HRMS (70 eV, EI): calcd for ($C_{24}H_{34}TiCl_2^{+\bullet} = M^{+\bullet}$) 438.1564, found 438.1560. IR (KBr): ν 3085, 2925, 1475, 1390, 1050, 910, 830 cm^{-1}. Anal. Calcd for $C_{24}H_{34}TiCl_2$ (441.31): C, 65.32; H, 7.77. Found: C, 65.06; H, 7.66.

Preparation of 2. The preparation was carried out as for **1** with 5-(1-butylpentylidene)cyclopenta-1,3-diene[13] (13.5 g, 71 mmol), MeLi (1.6 M, 50 mL, 80 mmol), and $TiCl_4$ (6.45 g, 34 mmol) to yield **3** (4.40 g, 8.3 mmol) as a red solid (24%). Mp: 157−159 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.53 (t, $^3J = {}^4J =$ 2.6 Hz, 2H), 6.45 (t, $^3J = {}^4J = 2.6$ Hz, 2H), AB signal (δ 1.68, δ 1.54, $^2J = 13.4$ Hz, additionally split by $^3J = 11.8$, 11.5, 5.2, 5.1 Hz, 4H), 1.31 (s, 3H), 0.90−1.29 (m, 8H), 0.85 (t, $^3J = 7.3$ Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.5, 120.3, 117.5, 40.4, 40.2, 26.2, 23.9, 23.5, 14.2. MS (70 eV, EI): *m*/*z* (%) 493 (100), 456 (4), 400 (15), 323 (19). IR (KBr): ν 3080, 2925, 1465, 1375, 1045, 905, 830 cm^{-1}. Anal. Calcd for $C_{30}H_{50}TiCl_2$ (529.50): C, 68.05; H, 9.52. Found: C, 68.00; H, 9.56.

Preparation of 3. Cyclohexylcyclopentadiene (13.5 g, 91 mmol) was dissolved in diethyl ether (500 mL), cooled to 0 °C, and deprotonated with *n*BuLi (2.45 M, 37.1 mL, 91 mmol) over a period of 30 min. After stirring for 2 h the mixture was added to $TiCl_4$ (4.9 mL, 44 mmol) dissolved in diethyl ether (200 mL) at 0 °C. After stirring for 16 h at reflux and cooling to 0 °C the reaction was quenched by the addition of aqueous HCl (1 M, 100 mL). The solid was filtered off and washed with pentane and combined with the solid obtained by reextracting the aqueous layer with CH_2Cl_2 (100 mL) to give **3**[6a] (10.5 g, 25 mmol) as a red solid (58%).

General Procedure (GP) for Titanocene-Catalyzed Epoxide Opening and Addition to Acrylates. To a suspension of collidine hydrochloride (394 mg, 2.50 mmol) in THF (10 mL) was added the titanocene (0.10 mmol, 10 mol %), zinc (131 mg, 2.00 mmol), acrylic acid *tert*-butyl ester (385 mg, 3.00 mmol), and the epoxide (1.00 mmol). After stirring at room temperature for 16 h *tert*-butyl methyl ether (30 mL) was added, and the mixture was filtered and washed with water (30 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with HCl (2 M, 20 mL), saturated $NaHCO_3$ (20 mL), brine (20 mL), and water (20 mL). After drying ($MgSO_4$) the volatiles were removed in a vacuum and the crude product was purified by chromatography over SiO_2.

Preparation of 5 (Figure 3):[3c] **Catalyst 1.** According to the GP, **1** (88.3 mg) and **4** (168 mg, 2.00 mmol) for 48 h gave **5** (262 mg, 1.22 mmol) as a 95:5 mixture of diastereoisomers (61%) by SiO_2 chromatography (cyclohexane (CH)/ethyl acetate (EE) = 84:16).

Catalyst 2. According to the GP, **2** (106 mg) and **4** (168 mg, 2.00 mmol) for 48 h gave **5** (270 mg, 1.26 mmol) as a 92:8 mixture of diastereoisomers (63%) by SiO_2 chromatography (CH/EE = 84:16).

Catalyst 3. According to the GP, **3** (82.7 mg) and **4** (168 mg, 2.00 mmol) for 48 h gave **5** (308 mg, 1.44 mmol) as a 96:4 mixture of diastereoisomers (72%) by SiO_2 chromatography (CH/EE = 84:16).

Preparation of 7 (Figure 4):[3c] **Catalyst 1.** According to the GP, **1** (88.3 mg), **6** (196 mg, 2.00 mmol), and *tert*-butyl acrylate (257 mg, 2.00 mmol) for 48 h gave **7** (308 mg, 1.34 mmol) as a 70:30 mixture of diastereoisomers (67%) by SiO_2 chromatography (CH/EE = 97:3−95:5).

Catalyst 2. According to the GP, **2** (106 mg), **6** (196 mg, 2.00 mmol), and *tert*-butyl acrylate (257 mg, 2.00 mmol) for 48 h gave **7** (238 mg, 1.04 mmol) as a 74:26 mixture of diastereoisomers (52%) by SiO_2 chromatography (CH/EE = 97:3−95:5).

Catalyst 3. According to the GP, **3** (82.7 mg) and **6** (168 mg, 2.00 mmol) for 48 h gave **7** (234 mg, 1.02 mmol) as a 70:30 mixture of diastereoisomers (51%) by SiO_2 chromatography (CH/EE = 97:3−95:5).

Preparation of 9 (Figure 5):[3c] **Catalyst 1.** According to the GP, **1** (44.1 mg, 0.10 mmol) and **8** (112 mg, 1.00 mmol) for 20 h gave **9** (140 mg, 0.58 mmol) as a 93:7 mixture of diastereoisomers (58%) by SiO_2 chromatography (CH/EE = 94:6−90:10).

Catalyst 2. According to the GP, **2** (53 mg, 0.10 mmol) and **8** (112 mg, 1.00 mmol) for 20 h gave **9** (117 mg, 0.48 mmol) as a 93:7 mixture of diastereoisomers (48%) by SiO_2 chromatography (CH/EE = 94:6−90:10).

Catalyst 3. According to the GP, **3** (88.3 mmol) and **8** (112 mg, 1.00 mmol) for 16 h gave **9** (85.4 mg, 0.35 mmol) as a 82:18 mixture of diastereoisomers (35%) by SiO_2 chromatography (CH/EE = 94:6−90:10).

Preparation of 11 (Figure 6):[3c] **Catalyst 1.** According to the GP, **1** (44.1 mg, 0.10 mmol) and **10** (110 mg, 1.00 mmol) for 60 h gave **11** (136 mg, 0.56 mmol) as a 49:51 mixture of diastereoisomers (56%) by SiO_2 chromatography (petrol ether (PE)/*tert*-butyl methyl ether (MTBE) = 80:20−75:25).

Catalyst 2. According to the GP, **2** (53 mg, 0.10 mmol) and **10** (110 mg, 1.00 mmol) for 48 h gave **11** (131 mg, 0.54 mmol) as a 51:49 mixture of diastereoisomers (54%) by SiO_2 chromatography (PE/MTBE = 80:20−75:25).

Catalyst 3. According to the GP, **3** (41.3 mg, 0.10 mmol) and **10** (110 mg, 1.00 mmol) for 60 h gave **11** (46 mg, 0.19 mmol) as a 65:35 mixture of diastereoisomers (20%) by SiO_2 chromatography (PE/MTBE = 80:20−75:25).

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Supporting Information Available: Crystallographic tables for **1** and **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

OM0342208

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