Titanium and Zirconium Complexes with Helical Bis(phenolato) Ligands as Hydroamination Catalysts

Klaudia Marcseková,[a] Christian Loos,[a] Frank Rominger,[a] Sven Doye*[b]

[a] Organisch-Chemisches Institut, Universität Heidelberg, Im Neuenheimer Feld 270, 69120 Heidelberg, Germany

[b] Institut für Reine und Angewandte Chemie, Universität Oldenburg, Carl-von-Ossietzky-Str. 9–11, 26111 Oldenburg, Germany
Fax +49(441)7983329; E-mail: doye@uni-oldenburg.de

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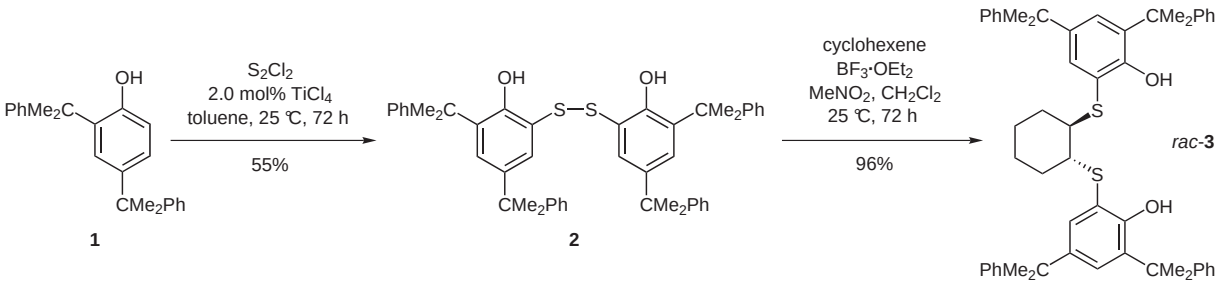
Abstract: A racemic bisphenolato (OSSO)-type ligand that contains a *trans*-1,2-cyclohexanediyl backbone can be obtained in two steps from commercially available starting materials. In situ combination of this ligand with $Ti(NMe_2)_4$ or $Zr(NMe_2)_4$ results in the formation of bis(phenolato) complexes that catalyze hydroaminations of alkynes and alkenes.

Key words: alkynes, aminations, amines, homogenous catalysis, titanium

During the last few years, many metal complexes that catalyze the addition of N–H across carbon–carbon multiple bonds have been identified.[1] In particular, neutral Ti- and Zr-complexes have been shown to catalyze the hydroamination of alkynes[2] and alkenes[3] with primary amines. Recently, corresponding cyclizations of aminoalkenes have been achieved in an enantioselective fashion[4] with ee values up to 93% in the presence of a chiral zirconium amidate complex.[4b] Inspired by a report from the Okuda group[5] that described the use of scandium complexes with dithiaalkanediyl-bridged bisphenolato (OSSO)-type ligands for the ring-opening polymerization of lactide we decided to investigate Ti- and Zr-complexes with corresponding chiral bisphenolato ligands as potential catalysts for enantioselective hydroamination reactions. However, in this context, it must be mentioned that during the course of our study, the Okuda group reported the synthesis of an enantiomerically pure chiral Ti-complex with an (OSSO)-ligand that contains a *trans*-1,2-cyclohexanediyl backbone and its use for the polymerization of styrene.[6] In this letter we describe a short racemic synthesis of a closely related but sterically more demanding chiral bisphenolato (OSSO)-ligand and its use for initial Ti- and Zr-catalyzed hydroamination reactions.

The synthesis of the desired ligand *rac*-**3** (Scheme 1) started with the reaction of commercially available phenol **1** with S_2Cl_2 in the presence of $TiCl_4$ which gave the disulfide **2** in 55% yield on a 50-gram scale.[7,8] Subsequently, **2** was directly reacted with cyclohexene in the presence of $BF_3{\cdot}OEt_2$ to give *rac*-**3** in 96% yield as a crystalline compound.[9,10] Interestingly, the 500 MHz ^{1}H NMR spectrum of *rac*-**3** in CD_2Cl_2 showed only two broad singlets for the two pairs of diastereotopic methyl groups at δ = 1.64 (12 H) and 1.70 (12 H) ppm. The desired *trans* configuration of the ligand *rac*-**3** was confirmed by X-ray crystallographic analysis (Figure 1).[11]

Since our original idea was to use a dimethyl titanium complex as the catalyst for the planned hydroamination reactions ligand *rac*-**3** was initially treated with $TiCl_4$ to give the bis(phenolato)titanium dichloro complex *rac*-**4** as a dark red crystalline compound (Scheme 2).[12] In contrast to the free ligand, the 500 MHz ^{1}H NMR spectrum of *rac*-**4** in CD_2Cl_2 showed four sharp singlets for the two pairs of diastereotopic methyl groups at δ = 1.65 (6 H), 1.70 (6 H), 1.73 (6 H) and 1.85 (6 H) ppm. To confirm the monomeric structure of complex *rac*-**4** an X-ray crystallographic analysis was carried out (Figure 2).[13] As observed before,[5,6] the helical arrangement of the ligand around the metal center causes an additional stereogenic unit. However, *rac*-**4** was obtained as a single diastereomer with distorted octahedral geometry around the titanium center.



Scheme 1 Two-step synthesis of bis(phenolato) ligand *rac*-**3**

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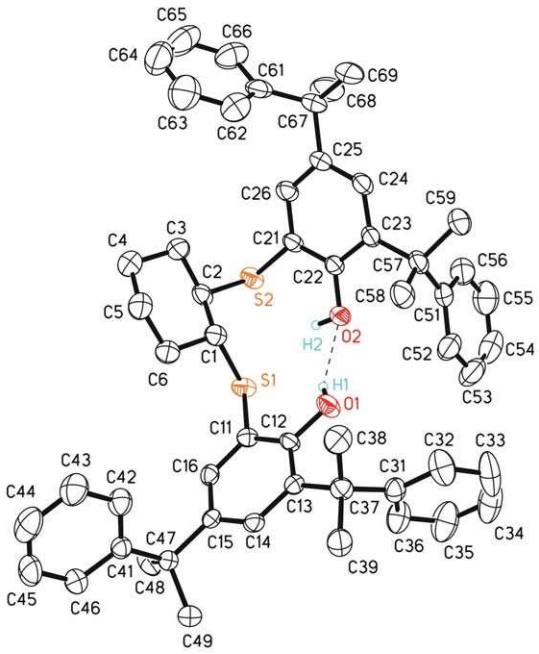
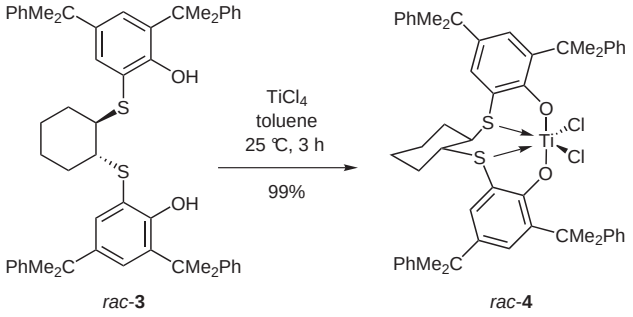


Figure 1 X-ray crystal structure of *rac*-**3**[11]



Scheme 2 Synthesis of titanium complex *rac*-**4**

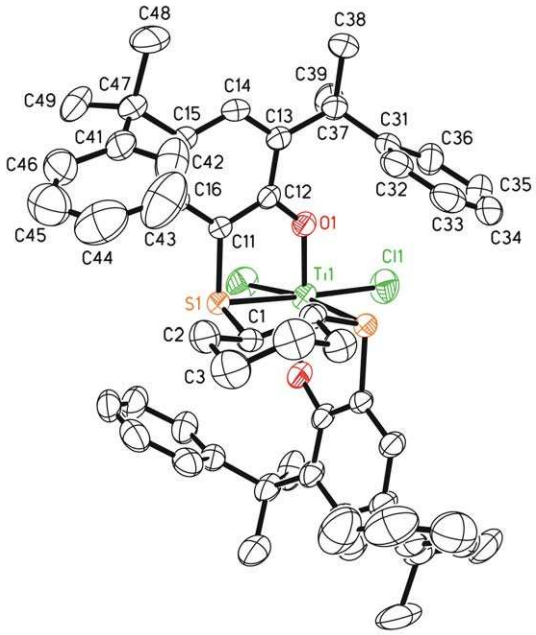


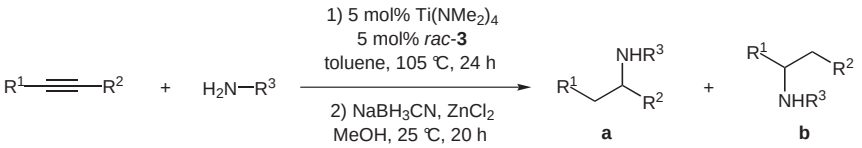
Figure 2 X-ray crystal structure of *rac*-**4**[13]

Due to the relatively strong binding chloro ligands *rac*-**4** showed only poor activity as a hydroamination catalyst. For example, in the presence of 5 mol% of *rac*-**4**, the reaction between 1-phenylpropyne and 4-methylaniline gave only trace amounts of hydroamination products after 48 hours at 105 °C. Consequently, we tried to exchange the chloro ligands with more labile methyl groups. However, our attempts to convert *rac*-**4** into the corresponding dimethyl complex using methyllithium in diethyl ether at temperatures between –20 °C and –80 °C failed. For that reason, we turned our attention to an in situ generation of the hydroamination catalyst from the combination of equimolar amounts of the ligand *rac*-**3** and $Ti(NMe_2)_4$.[4a,14] First of all, we tried to observe the involved amine elimination reaction by ^1H NMR spectroscopy. Upon mixing $Ti(NMe_2)_4$ and an equimolar amount of *rac*-**3** in CD_2Cl_2 at 25 °C the singlet for the methyl groups of $Ti(NMe_2)_4$ at δ = 3.04 ppm as well as the broad signals for the phenolic H-atoms (δ = 6.83 ppm) and the methyl groups of *rac*-**3** (vide supra) disappeared completely. On the other hand, four new sharp singlets for the diastereotopic methyl groups of the in situ formed Ti-complex appeared at δ = 1.66 (6 H), 1.68 (6 H), 1.70 (6 H) and 1.83 (6 H) ppm (compare with *rac*-**4**). Furthermore, a new dimethylamide signal at δ = 2.80 ppm (12 H) proved that a monomeric Ti-species comparable to the dichloro complex *rac*-**4** was present in solution. Additionally, a doublet at δ = 2.37 ppm caused by free dimethylamine was observed.

With this result in hand, we turned our attention to some intermolecular hydroaminations of alkynes (Table 1). The in situ formation of the catalyst was always carried out by stirring 5 mol% of the ligand *rac*-**3** and an equimolar amount of $Ti(NMe_2)_4$ in toluene for 30 minutes at room temperature. Subsequently, the alkyne and amine substrates were added and all resulting mixtures were heated to 105 °C for 24 hours (reaction times have not been minimized). After subsequent reduction with $NaBH_3CN$ in the presence of $ZnCl_2$, secondary amines were obtained from most of the test reaction sequences.[15]

As can be seen from Table 1, 4-methylaniline and cyclopentylamine underwent smooth addition reactions with 1-phenylpropyne (entries 1 and 2) to give the corresponding anti-Markovnikov products with excellent regioselectivity. Interestingly, sterically more demanding *tert*-butylamine did not undergo a hydroamination reaction with 1-phenylpropyne (entry 3). A similar behavior was observed with the terminal alkyne 1-dodecyne (entries 7–9). Again, no conversion was observed with *tert*-butylamine while 4-methylaniline and cyclopentylamine underwent a hydroamination reaction. Interestingly, 1-dodecyne and cyclopentylamine were selectively converted into the Markovnikov product (entry 8). Formation of the Markovnikov product was also favored with 4-methylaniline (entry 7) but in this case, the selectivity was only 6:1. anti-Markovnikov-selective additions to 4-methoxyphenylacetylene could be realized with 4-methylaniline,

Table 1 Intermolecular Hydroamination of Alkynes[15]

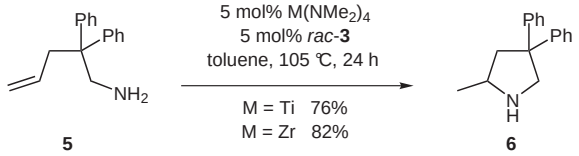


Entry	R^1	R^2	R^3	Yield **a** + **b** (%)[a]	Ratio **a**/**b**[b]
1	Ph	Me	tolyl	79	>99:1
2	Ph	Me	cyclopentyl	62	98:2
3	Ph	Me	*t*-Bu	–	
4	4-$MeOC_6H_4$	H	tolyl	51	2.4:1
5	4-$MeOC_6H_4$	H	cyclopentyl	64	7:1
6	4-$MeOC_6H_4$	H	*t*-Bu	28	>99:1
7	*n*-$C_{10}H_{21}$	H	tolyl	99	1:6
8	*n*-$C_{10}H_{21}$	H	cyclopentyl	58	< 1:99
9	*n*-$C_{10}H_{21}$	H	*t*-Bu	–	

[a] Reaction conditions: (1) alkyne (2.40 mmol), amine (2.64 mmol), $Ti(NMe_2)_4$ (0.12 mmol, 5 mol%), *rac*-**3** (0.12 mmol, 5 mol%), toluene (1.0 mL), 105 °C, 24 h; (2) $NaBH_3CN$ (4.80 mmol), $ZnCl_2$ (2.40 mmol), MeOH (10 mL), 25 °C, 20 h. Yields refer to isolated compounds.
[b] Determined by GC–MS.

cyclopentylamine and *tert*-butylamine (entries 4–6). Although the best regioselectivity was achieved with *tert*-butylamine the yield was only 28%. Increased yields (51% and 64%) but decreased regioselectivities (2.4:1 and 7:1) were observed with 4-methylaniline and cyclopentylamine. Additionally, it must be mentioned that reactions of 3-hexyne with various amines did not result in the formation of any hydroamination products. However, the results summarized in Table 1 clearly indicate that an in situ generated Ti-complex with an (OSSO)-type ligand that contains a *trans*-1,2-cyclohexanediyl backbone can principally be used as a catalyst for the intermolecular hydroamination of alkynes.

Finally, we performed two initial hydroamination experiments with aminoalkene **5** using an in situ generated Ti- or Zr-catalyst (Scheme 3). In both cases, formation of the catalyst was carried out by stirring 5 mol% of the ligand *rac*-**3** and an equimolar amount of either $Ti(NMe_2)_4$ or $Zr(NMe_2)_4$ in toluene for 30 minutes at room temperature. Subsequent addition of aminoalkene **5** and heating to 105 °C for 24 hours resulted in the formation of the desired cyclization product **6** in 76% and 82% yields, respectively.



Scheme 3 Intramolecular hydroamination of alkenes

In summary, we have shown for the first time that a dithiaalkanediyl-bridged bisphenolato (OSSO)-type ligand that contains a *trans*-1,2-cyclohexanediyl backbone can be used for various group IV metal-catalyzed hydroamination reactions. The helical arrangement of the chiral ligand around the metal center suggests that corresponding optically pure ligands[6] can be used for enantioselective hydroamination reactions. Further studies in this area are currently underway in our laboratories.

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(8) **Experimental Procedure**: S_2Cl_2 (16.88 g, 125 mmol) was added dropwise to a solution of 2,4-bis(α,α-dimethylbenzyl)phenol (**1**, 82.62 g, 250 mmol) and $TiCl_4$ (0.474 g, 2.5 mmol, 2.0 mol%) in toluene (180 mL) at –5 °C. The resulting mixture was stirred at –5 °C for 30 min and at r.t. for 72 h. Then, the mixture was washed with aq HCl (2 × 250 mL, *c* = 19%), sat. aq Na_2CO_3 solution and H_2O. The organic layer was dried with $MgSO_4$ and concentrated under vacuum. Crystallization from MeCN (1800 mL) gave analytically pure disulfide **2** (49.88 g, 69 mmol, 55%). ^{1}H NMR (300 MHz, CD_2Cl_2): δ = 0.97 (s, 12 H), 1.04 (s, 12 H), 6.49–6.62 (m, 24 H). Anal. Calcd for $C_{48}H_{50}O_2S_2$ (723.0): C, 79.73; H, 6.97; S, 8.87. Found: C, 79.70; H, 6.93; S, 8.96.

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(10) **Experimental Procedure**: Cyclohexene (4.6 g, 56 mmol) and $BF_3{\cdot}OEt_2$ (0.5 mL) were added to a solution of disulfide **2** (20 g, 28 mmol) in a mixture of nitromethane (15 mL) and CH_2Cl_2 (15 mL) at –10 °C. The resulting mixture was stirred at –10 °C for 3 h and at r.t. for 72 h. Then, the mixture was washed with sat. aq $NaHCO_3$ solution. The organic layer was dried with $MgSO_4$ and concentrated under vacuum. Crystallization from a 4:1-mixture of MeCN and acetone (200 mL) gave analytically pure bis(phenolato) ligand *rac*-**3** (21.68 g, 27 mmol, 96%). ^{1}H NMR (500 MHz, CD_2Cl_2): δ = 1.02–1.06 (m, 4 H), 1.54–1.58 (m, 2 H), 1.64 (s, 12 H), 1.70 (s, 12 H), 1.70–1.74 (m, 2 H), 2.47–2.51 (m, 2 H), 6.83 (s, 2 H), 7.10–7.14 (m, 6 H), 7.15–7.22 (m, 8 H), 7.25–7.30 (m, 8 H), 7.37 (d, *J* = 2.1 Hz, 2 H). Anal. Calcd for $C_{54}H_{60}O_2S_2$ (805.2): C, 80.55; H, 7.51; S, 7.96. Found: C, 80.38; H, 7.51; S, 7.97.

(11) Colorless crystal(polyhedron), dimensions 0.42 × 0.18 × 0.10 mm^3, crystal system triclinic, space group $P\bar{1}$, Z = 2, *a* = 8.5820(2) Å, *b* = 16.3662(4) Å, *c* = 18.3078(5) Å, *α* = 73.1710(10)°, *β* = 83.3570(10)°, *γ* = 77.9890(10)°, *V* = 2403.18(10) Å^3, *ρ* = 1.169 g/cm^3, *T* = 200(2) K, Θ_{max} = 25.42°, radiation Mo–K_α, λ = 0.71073 Å, 0.3° ω-scans with CCD area detector, covering a whole sphere in reciprocal space, 21011 reflections measured, 8802 unique [*R*(int) = 0.0883], 4564 observed [I >2σ(I)], intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied using SADABS[16] based on the Laue symmetry of the reciprocal space, *μ* = 0.15 mm^{-1}, T_{min} = 0.94, T_{max} = 0.98, structure solved by direct methods and refined against F^2 with a full-matrix least-squares algorithm using the SHELXTL-PLUS[16] software package, 577 parameters refined, hydrogen atoms were treated using appropriate riding models, except for H1 and H2 at the oxygen atoms, which were refined isotropically, goodness of fit 0.98 for observed reflections, final residual values *R*1(F) = 0.062, *wR*(F2) = 0.115 for observed reflections, residual electron density –0.30 eÅ^{-3} to 0.24 eÅ^{-3}. CCDC number 652550 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

(12) **Experimental Procedure**: $TiCl_4$ (95 mg, 0.5 mmol) was added to a solution of *rac*-**3** (402 mg, 0.5 mmol) in toluene (3 mL) at r.t. After the mixture had been stirred for 3 h at r.t., all volatiles (toluene, HCl) were removed under reduced pressure. The residue was washed with hexane. Crystallization from toluene gave complex *rac*-**4** (456 mg, 0.49 mmol, 99%) as red-brown crystals. ^{1}H NMR (500 MHz, CD_2Cl_2): δ = 0.64–0.72 (m, 2 H), 0.87–0.93 (m, 2 H), 1.46–1.48 (m, 2 H), 1.65 (s, 6 H), 1.68–1.69 (m, 2 H), 1.70 (s, 6 H), 1.73 (s, 6 H), 1.79–1.81 (m, 2 H), 1.85 (s, 6 H), 6.80 (d, *J* = 2.2 Hz, 2 H), 7.12–7.32 (m, 20 H), 7.56 (d, *J* = 2.1 Hz, 2 H). In order to avoid the formation of solid byproducts the reaction was performed in the absence of a base.

(13) Red-brown crystal(polyhedron), dimensions 0.20 × 0.16 × 0.05 mm^3, crystal system monoclinic, space group *C*2/*c*, Z = 4, *a* = 28.177(3) Å, *b* = 11.1949(13) Å, *c* = 19.892(2) Å, *β* = 105.392(3)°, *V* = 6049.5(12) Å^3, *ρ* = 1.215 g/cm^3, *T* = 200(2) K, Θ_{max} = 28.40°, radiation Mo–K_α, λ = 0.71073 Å, 0.3° ω-scans with CCD area detector, covering a whole sphere in reciprocal space, 31295 reflections measured, 7545 unique [*R*(int) = 0.0531], 5283 observed [I >2σ(I)], intensities were corrected for Lorentz and polarization effects, an empirical absorption correction was applied using SADABS[16] based on the Laue symmetry of the reciprocal space, *μ* = 0.34 mm^{-1}, T_{min} = 0.93, T_{max} = 0.98, structure solved by direct methods and refined against F^2 with a full-matrix least-squares algorithm using the SHELXTL-PLUS[16] software package, 488 parameters refined, hydrogen atoms were treated using appropriate riding models, goodness of fit 1.03 for observed reflections, final residual values *R1(*F) = 0.057, *wR*(F^2) = 0.117 for observed reflections, residual electron density –0.20 eÅ^{-3} to 0.38 eÅ^{-3}. CCDC number 652551 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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(15) **General Procedure**: A Schlenk tube equipped with a Teflon stopcock and a magnetic stirring bar was charged with $Ti(NMe_2)_4$ (27 mg, 0.12 mmol, 5.0 mol%), *rac*-**3** (97 mg, 0.12 mmol, 5.0 mol%) and toluene (1.0 mL). After this mixture had been stirred for 30 min at r.t., the alkyne (2.40 mmol) and the amine (2.64 mmol) were added and the resulting mixture was heated to 105 °C for 24 h. Then the

mixture was cooled to r.t. and a mixture of $NaBH_3CN$ (302 mg, 4.80 mmol) and $ZnCl_2$ (326 mg, 2.40 mmol) in MeOH (10 mL) was added. After this mixture had been stirred at 25 °C for 20 h, CH_2Cl_2 (50 mL) and sat. Na_2CO_3 solution (20 mL) were added. The resulting mixture was filtered and the solid residue was washed with CH_2Cl_2 (50 mL). After extraction, the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (6×50 mL). The combined organic layers were dried with Na_2SO_4. After concentration under vacuum, the residue was purified by flash chromatography (SiO_2). All compounds were identified by comparison of the obtained ^1H and ^{13}C NMR spectra with those reported in the literature.[17]

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