

A New Method for the Generation of Titanium(III) Complexes and its Application in Pinacol Coupling Reactions

Christoph Alexander Knoop, Armido Studer*

Organisch-Chemisches Institut, Fachbereich Chemie, Corrensstrasse 40, 48149 Münster, Germany
Fax: (+49)-251-833-6523, e-mail: studer@uni-muenster.de

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Abstract: A new method for the *in situ* generation of various Ti(III) complexes is presented. Cyclohexadienyl-Ti(IV) derivatives, which are readily prepared from the corresponding lithiated cyclohexadienes, afford the corresponding Ti(III) complexes upon thermal C–Ti bond homolysis. The Ti(III) compounds generated using this novel method have successfully been used in the reductive dimerization of benzaldehyde. In particular, TiBr₃, TiCp₂Cl and Ti(O-*i*-Pr)₃ have been generated *via* this approach. Moreover, the method also offers an entry to new chiral Ti(III) complexes as documented by the preparation of Ti(III)CpTADDOLate.

Keywords: radical chemistry; reductive cyclization; stereoselective reductions; synthetic methods; titanium

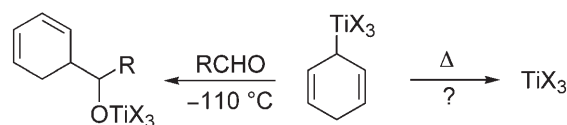
Radical chemistry has gained increasing importance during the last 30 years.^[1] In contrast to ionic chemistry, many functional groups are tolerated under radical conditions. Several methods for the clean generation of radicals have been reported to date. However, most of the radical reactions are conducted using toxic trialkyltin hydrides. To circumvent the use of toxic tin compounds, many research groups are currently looking at environmentally benign radical processes.^[2] Electron-transfer reagents have successfully been used in this context. In particular, samarium diiodide (SmI₂) has been found to be a highly efficient electron-transfer reagent for conducting various radical processes.^[3] However, SmI₂ is rather expensive and is readily oxidized on air.

As an alternative to SmI₂, Ti(III) complexes have been studied by various groups.^[4–11] Nugent and Rajan-Babu showed that titanocene(III) chloride can be applied to reductively open epoxides.^[5] The β-titanoxo radicals thus generated can be used in radical cyclizations and intermolecular addition reactions. Gansäuer^[6,7] later showed that the epoxide openings can be performed using catalytic^[8] amounts of titanocene(III) chloride.

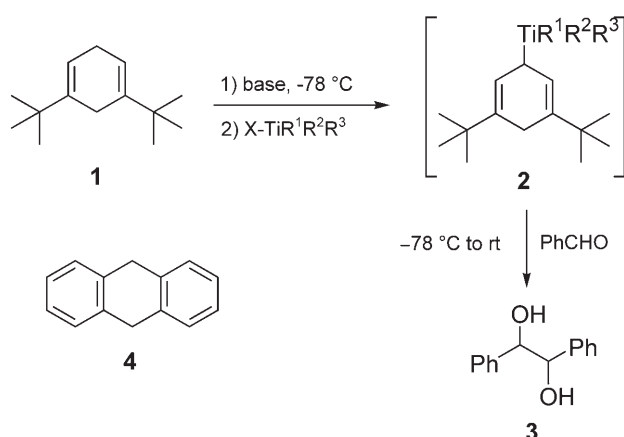
Reduction of activated alkyl halides have been achieved using Ti(III).^[9] Moreover, Ti(III) complexes have successfully been used in pinacol reactions.^[10,11] Even enantioselective couplings have recently been reported.^[12] Most of the Ti(III) complexes studied have been generated from the corresponding Ti(IV) compounds and a coreducing reagent.^[13]

Recently, we published our results on the use of cyclohexadienyl-Ti compounds in ionic allylations (Scheme 1).^[14] We assumed that these compounds may also offer a clean entry to Ti(III) complexes upon simple thermal Ti-carbon bond homolysis. In contrast to established methods for the generation of Ti(III) derivatives, a coreducing reagent is not necessary in our approach.^[15] Since the starting cyclohexadienyl-Ti(IV) compounds are readily prepared by transmetalation using the appropriate Ti(IV) complex, new unexplored Ti(III) reagents should be available *via* this route. In this communication we report first results on the use of cyclohexadienyl-Ti(IV) derivatives as precursors for Ti(III) complexes. Moreover, these reducing reagents will be applied in pinacol coupling reactions.

In order to suppress the ionic-type chemistry of cyclohexadienyl-Ti compounds (Scheme 1, on the left) we decided to block the allylic positions with bulky *tert*-butyl groups. In addition, the bulky substituents should allow a highly regioselective metalation for steric reasons. Birch reduction of readily available 1,3-di-*tert*-butylbenzene^[16] afforded cyclohexadiene **1** in 42% yield. Along with **1**, the isomeric 1,4-cyclohexadiene, which was separated by chromatography, was formed in < 5% yield. The metalation of diene **1** was studied first. As a test reaction to prove our concept the pinacol reaction of benzaldehyde was investigated. To this end, diene **1** was deprotonated with various strong bases at –78 °C in ethe-



Scheme 1. Cyclohexadienyl-Ti(IV) compounds in ionic allylations and as sources for Ti(III) complexes.



Scheme 2. Reductive coupling of benzaldehyde.

real solvents (Scheme 2). Transmetalation with a Ti(IV) complex furnished the cyclohexadienyl-Ti-derivative **2**. After addition of benzaldehyde, the reaction mixture was allowed to warm to room temperature.

The first experiment was conducted with *s*-BuLi/tetramethylethylenediamine (TMEDA) as base (1 equiv., 60 min, -78°C , Table 1, entry 1). Transmetalation was performed with $\text{Ti}(\text{O-}i\text{-Pr})_4$ (1 equiv., -78°C , 60 min) and benzaldehyde (1 equiv.) was added. We were pleased to observe that the desired reductive coupling of benzaldehyde to give diol **3** occurred. Moreover, ionic Ti(IV)-mediated allylation of benzaldehyde was completely suppressed by the bulky *tert*-butyl groups. However, the yield was not satisfactory (15%).^[17] The diastereoisomeric ratio was determined by $^1\text{H-NMR}$ spectroscopy (4:1). Incomplete deprotonation may be a reason for the moderate yield. Therefore, reaction was repeated using Schlosser base,^[18] however, a similar result was obtained (entry 2). Increasing the reaction time for deprotonation and transmetalation did not provide better

results. Reactions in dimethoxyethane and diethyl ether did not work (entries 3 and 4). Importantly, without transmetalation the pinacol coupling product was not formed, clearly showing that the coupling reaction occurs *via* the suggested intermediate **2** (entry 5).^[19] Using titanocene dichloride as transmetalation reagent, diol **3** was formed in 32% yield ($\text{dr}=2.5:1$, entry 6). A higher selectivity was obtained if the reaction mixture was allowed to warm to -15°C ($\text{dr}=6.3:1$, entry 7). Transmetalation at lower temperature (-100°C) did not provide a better result (entry 8). The selectivities obtained using *in situ* generated Cp_2TiCl are disappointingly low. Based on literature reports, far higher selectivities were expected for these reactions (97:3).^[13] We assumed that the strongly coordinating TMEDA may disrupt well-ordered rigid transition states for the coupling reaction. In fact, amine-free generation of Cp_2TiCl provided diol **3** in excellent selectivity ($>95:5$, entry 9). The yield could be improved upon increasing the amount of Ti(III) precursor (2 equivs., 56%, entry 10).

Coupling product **3** was not identified with $\text{Ti}(\text{NEt}_3)_4$ as Ti(III) precursor (entry 11). Probably, transmetalation did not proceed because the typical color change occurring after Li-Ti exchange was not observed. Reaction with TiCpCl_3 did not provide diol **3** (entry 12). *In situ* generated TiBr_3 provided the pinacol product in 37% yield ($\text{dr}=1.7:1$, entry 13).

Currently it is not clear why only moderate yields are obtained in pinacolizations using reagents of type **2**. Competing reduction of intermediately formed ketyl radical anion is not a problem since only trace amounts of benzyl alcohol were identified as side product. The cyclohexadienyl radical generated as by-product during Ti-C bond homolysis probably undergoes dimerization or disproportionation. Indeed, the disproportionation products 1,3-di-*tert*-butylbenzene and cyclohexadiene **1** were identified after the reactions. We assume that re-

Table 1. Reductive coupling under various conditions.

Entry	Base	Ti(IV) derivative	Solvent	Yield [%]	dr [<i>rac:meso</i>]
1	<i>s</i> -BuLi/TMEDA	$\text{Ti}(\text{O-}i\text{-Pr})_4$	THF	15	4:1
2	<i>s</i> -BuLi/ $\text{KO-}t\text{-Bu}$	$\text{Ti}(\text{O-}i\text{-Pr})_4$	THF	15	1.5:1
3	<i>s</i> -BuLi/ $\text{KO-}t\text{-Bu}$	$\text{Ti}(\text{O-}i\text{-Pr})_4$	DME	–	–
4	<i>s</i> -BuLi/ $\text{KO-}t\text{-Bu}$	$\text{Ti}(\text{O-}i\text{-Pr})_4$	Et_2O	–	–
5	<i>s</i> -BuLi/TMEDA	–	THF	–	–
6	<i>s</i> -BuLi/TMEDA	TiCp_2Cl_2	THF	32	2.5:1
7 ^[a]	<i>s</i> -BuLi/TMEDA	TiCp_2Cl_2	THF	24	6.3:1
8	<i>s</i> -BuLi/TMEDA	TiCp_2Cl_2 ^[b]	THF	22	2.0:1
9	<i>s</i> -BuLi/ $\text{KO-}t\text{-Bu}$	TiCp_2Cl_2	THF	32	$>95:5$
10 ^[c]	<i>s</i> -BuLi/ $\text{KO-}t\text{-Bu}$	TiCp_2Cl_2	THF	56	$>95:5$
11	<i>s</i> -BuLi/TMEDA	$\text{Ti}(\text{NMe}_2)_4$	THF	–	–
12	<i>s</i> -BuLi/TMEDA	TiCpCl_3	THF	–	–
13	<i>s</i> -BuLi/TMEDA	TiBr_4	THF	37	1.7:1

^[a] Reaction mixture was allowed to warm to -15°C .

^[b] Transmetalation at -100°C .

^[c] 2 equivalents of the Ti(III) precursor were used.

action of TiX_3 with the cyclohexadienyl radical to form HTiX_3 is not occurring since benzyl alcohol expected as product in that case^[20] was formed in only trace amounts, as already mentioned. We also tested dihydroanthracene (**4**) in the lithiation, transmetalation coupling sequence. However, diol **3** was not formed.

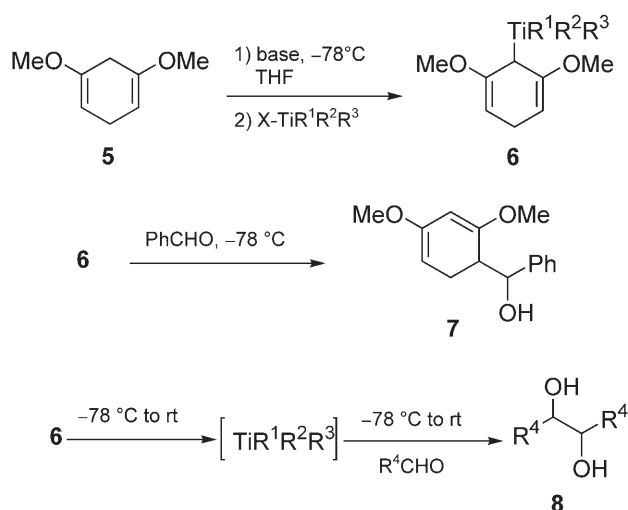
We then decided to use cyclohexadiene **5**, which is readily prepared from commercially available resorcin dimethyl ether, as precursor for Ti(III) compounds. Assisted by the methoxy substituents lithiation can readily be achieved.^[21] Transmetalation of the lithiated cyclohexadiene derived from **5** will afford the desired Ti(IV) derivative **6** which can be used in ionic allylations. Indeed, treatment of **6** ($\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{O-}i\text{-Pr}$) with benzaldehyde at -78°C provided alcohol **7**.^[22] However, we assumed that Ti(III) complexes can be liberated from **6** upon warming to room temperature. To this end, **Li-6** readily generated by deprotonation using *s*-BuLi/TMEDA, was transmetalated with $\text{Ti}(\text{O-}i\text{-Pr})_4$. The reaction mixture was subsequently allowed to warm to room temperature. Renewed cooling to

-78°C provided a solution containing titanium(III) triisopropoxide which was successfully used for the reductive dimerization of benzaldehyde. Diol **3** was isolated in 40% yield (Scheme 3, Table 2, entry 1). Using the same protocol TiCp_2Cl (entry 2) and TiBr_3 (entry 3) were generated and used in the pinacolization of benzaldehyde. Switching to Schlosser base provided similar results (compare entry 1 with 4 and entry 2 with 5). The yield could be increased upon using two equivalents of the Ti(III) precursor, however, selectivity decreased (entry 6). With the *s*-BuLi/KO-*t*-Bu/ $\text{Ti}(\text{O-}i\text{-Pr})_4$ -system other aldehydes were tested. Hence, reaction with tolyl-aldehyde provided the corresponding diol **8** ($\text{R}^4 = p\text{-MeC}_6\text{H}_4$) in 65% yield with moderate selectivity (entry 8). A lower yield was observed for the reaction with *p*-methoxybenzaldehyde (entry 9). 2-Naphthaldehyde provided a slightly better selectivity (entry 10).

Except for the TiBr_3 case, all the other Ti(III) complexes generated *via* cyclohexadiene **5** provided lower selectivities than using Ti(III) compounds deriving from metalated dienes of type **2**. We assume that the chelating methoxy substituents may still coordinate to the Ti(III) complex after Ti–C bond homolysis and this in turn may lead to decreased selectivities. Therefore, enantioselective coupling was studied using a chiral Ti(IV) derivative derived from cyclohexadiene **1**.

The TADDOL-derived^[23] Ti(IV) compound **9** was readily prepared from **1** as described above using CpTiCITADDOLate in the transmetalation.^[14] Addition of benzaldehyde and warming to room temperature provided diol **3** with 48% yield in a moderate diastereoselectivity (*dl:meso* = 3:1, Scheme 4). The enantiomeric excess of *dl-3* was determined by chiral HPLC (*ee* = 56%). To the best of our knowledge this is the first report on a chiral Ti(III)-TADDOLate.^[24] Although the selectivity is not high in the present case, we could show that our approach is useful for the study of new chiral Ti(III) compounds. Work along this line is underway.

We showed that cyclohexadienyl-Ti(IV) compounds, which are readily prepared from the corresponding lithiated cyclohexadienes by transmetalation using estab-

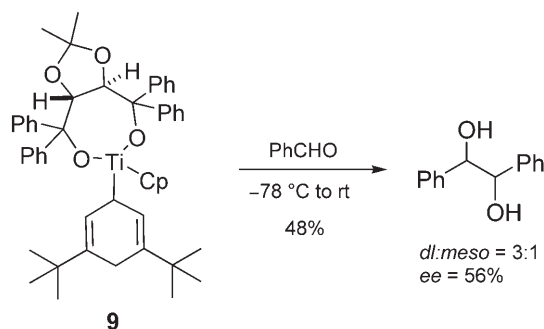


Scheme 3. An alternative approach to Ti(III) complexes.

Table 2. Reductive dimerization of various aldehydes using cyclohexadienes of type **6**.

Entry	Base	Ti(IV) derivative	R^4	Yield [%]	dr [<i>rac</i> : <i>meso</i>]
1	<i>s</i> -BuLi/TMEDA	$\text{Ti}(\text{O-}i\text{-Pr})_4$	Ph	40	1.8:1
2	<i>s</i> -BuLi/TMEDA	TiCp_2Cl_2	Ph	41	13:1
3	<i>s</i> -BuLi/TMEDA	TiBr_4	Ph	20	> 95:5
4	<i>s</i> -BuLi/KO- <i>t</i> -Bu	$\text{Ti}(\text{O-}i\text{-Pr})_4$	Ph	36	1:1
5	<i>s</i> -BuLi/KO- <i>t</i> -Bu	TiCp_2Cl_2	Ph	42	12:1
6 ^[a]	<i>s</i> -BuLi/KO- <i>t</i> -Bu	TiCp_2Cl_2	Ph	60	1:1.4
7	<i>s</i> -BuLi/KO- <i>t</i> -Bu	TiBr_4	Ph	18	> 95:5
8	<i>s</i> -BuLi/KO- <i>t</i> -Bu	$\text{Ti}(\text{O-}i\text{-Pr})_4$	<i>p</i> -MePh	65	1.9:1
9	<i>s</i> -BuLi/KO- <i>t</i> -Bu	$\text{Ti}(\text{O-}i\text{-Pr})_4$	<i>p</i> -MeOPh	19	2.6:1
10	<i>s</i> -BuLi/KO- <i>t</i> -Bu	$\text{Ti}(\text{O-}i\text{-Pr})_4$	2-naphthyl	31	5.6:1

^[a] 2 equivalents of the Ti(III) precursor was used.



Scheme 4. Coupling using a chiral Ti(III) complex.

lished Ti(IV) chemistry, undergo thermal Ti–C bond homolysis to generate the corresponding Ti(III) complexes. These Ti(III) compounds can be used in the reductive dimerization of benzaldehyde. Since many Ti(IV) compounds can be used in the transmetalation process, this new approach offers an entry to Ti(III) complexes which have not been prepared to date. For example, Ti(III)CpTADDOLate was successfully prepared by this method. Variation of the ligands in the precursor Ti(IV) complexes will allow one to tune the reactivity of the corresponding Ti(III) complexes. Moreover, our approach will open the door to new chiral Ti(III) complexes.

Experimental Section

General Remarks

All reactions were carried out in dried glassware under an argon atmosphere. Tetrahydrofuran (THF) was freshly distilled from potassium under argon. Diethyl ether (Et₂O) was freshly distilled from K/Na under argon. All other solvents and reagents were purified according to standard procedures or were used as received from Aldrich or Fluka. ¹H NMR spectra were recorded on a Bruker AMX 400, AC 300, ARX 300 or an ARX 200. Chemical shifts δ are given in ppm relative to CHCl₃ at 7.26 ppm as external standard. Diastereomeric ratios were determined using ¹H NMR spectroscopy or HPLC. Enantiomeric excess was measured by HPLC analysis using a Bakerbond Standard (DNBPG, covalent, 5- μ m, 4.6 $\times$ 250 mm) column (eluent: hexane/*i*-PrOH, 98/2 with addition of 0.1% acetic acid, flow rate 1 mL min⁻¹). TLC was performed using Merck silica gel 60 F254 plates; detection with UV or dipping into a solution of KMnO₄ (1.5 g in 400 mL H₂O, 5 g NaHCO₃), followed by heating. Flash column chromatography (FC) was performed using Merck or Fluka silica gel 60 (40–63 μ m) applying a pressure of about 0.4 bar.

Typical Procedure

Cyclohexadiene **1** (180 mg, 0.94 mmol) was dissolved in THF. The solution was cooled to -78°C and KO-*t*-Bu (16 mg, 1.03 mmol) followed by *s*-BuLi (817 μ L, 1.26 M in hexane,

1.03 mmol) were added. The solution was stirred at this temperature for 45 min. TiCp₂Cl₂ (257 mg, 1.03 mmol) was added. Stirring was continued for another 60 min at -78°C . After addition of benzaldehyde the reaction mixture was allowed to warm to room temperature over 0.5 h and was stirred for additional 15 h. The reaction was stopped upon addition of NH₄Cl (aqueous saturated) and HCl (1 M). The aqueous layer was extracted with *tert*-butyl methyl ether (MTBE, 3 times). The combined organic layers were dried over MgSO₄ and the solvents were removed under vacuum. Purification by FC (pentane/MTBE, 3/2) afforded diol **3**; yield: 56%.

Acknowledgements

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