First Synthesis of Metallated Titanacyclopropenes

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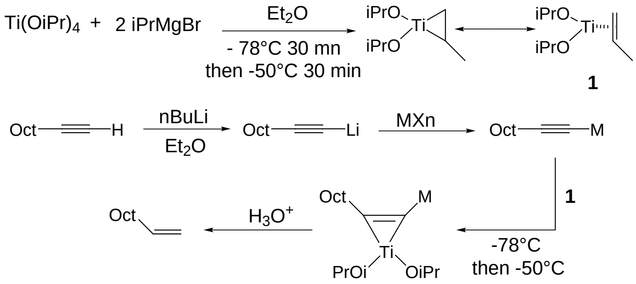
Dedicated fondly to Professor L. Ghosez on the occasion of his 65th birthday.

Abstract A novel and efficient one-pot synthesis of *tris*metallated olefins is described by using the di*iso*propyloxy(η^2-propene)titanium derivative.

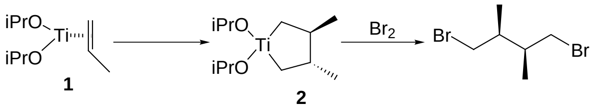
Key words: metallated titanacyclopropenes, titanium(II), bismetallic, alkynes, alkenes

The synthesis of polysubstituted olefins in a single-pot operation from common starting material is still the object of continuing vigorous research[1]. Among several strategies, the synthesis and reactivity of 1,1-dimetalloalkenes with a large variety of metals (dilithium[2], aluminum and titanium[3], aluminum and zirconium[3], zinc and zirconium[4], zinc and boron[5], copper and boron[5], copper and zirconium[4], lithium and boron[6], zinc and zinc[7] and finally boron and zirconium[8]) were used as a source of tri- and tetra-substituted olefins. In this context, we have already reported the allylmetallation of alkynyl metals[9] leading to sp^2 1,1-bismetallic derivatives in good overall yield[10]. These geminate bis-anions react selectively with two different electrophiles[10] and can be a source of chiral α,α'-disubstituted alkynes[10c]. However, in the course of our studies on the synthesis and reactivity of polymetallated alkenes, we needed a more general preparation of these reagents allowing the access to a variety of carbon skeletons. Our attention was drawn by the pioneering work of Sato *et al* who demonstrated that various disubstituted alkynes react with di*iso*propyloxy(η^2-propene)titanium **1**[11], readily generated by the reaction of $Ti(OiPr)_4$ with 2 equiv. of *i*PrMgX, to give the corresponding titanacyclopropene derivatives. Although terminal alkynes failed to participate in the present reaction, the use of this low-valent titanium alkoxide reagent was successfully applied to several systems[12]. The same type of intermediate as **1** had previously been used for the synthesis of cyclopropanols[13,14] and cyclopropylamines[15]. Inspired by this work, we were pleased to find that the ligand exchange of the low-valent titanium alkoxide can be performed with a metallated alkyne[16] to give the corresponding *metallated titanacyclopropene*. Our initial attempts consisted in adding alkynyl metal derivatives to the preformed Ti^{II} complex **1** (Scheme 1).



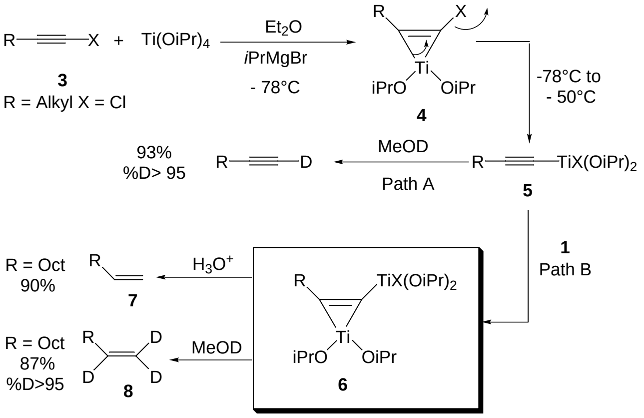
Scheme 1

However, this new strategy was only moderately successful since the overall chemical yield of the polymetallated olefin was strongly dependent on the nature of the alkynyl metal and on the experimental conditions. Indeed, starting from alkynyllithium (M = Li) or alkynylmagnesium bromide (M = MgBr), the desired product was not obtained in the former case and only in 20% yield in the latter one. The best cases were the alkynyltitanium *tri*isopropoxide (M = $Ti(OiPr)_3$, 41% yield) and either the alkynylzinc bromide (M = ZnBr, 65% yield) or alkynyl-alkylzinc (M = ZnBu, 68% yield). Unfortunately, even in these last three cases, it was very difficult in our hands to get reproducible results (i.e. for the alkynylzinc bromide the yield was varying from 25% to 70%). These fluctuations were attributed to the possible instability of the preformed low-valent titanium alkoxide **1** under these Grignard-type experimental conditions[17], and also to the rearrangement of **1** into the corresponding cyclic product **2**[18]. These results strongly suggest that we have a competing reaction of **1**; formation of the desired product or formation of **2**. Indeed, bromination of the reaction mixture instead of hydrolysis gave (D,L)-1,4-dibromo-2,3-dimethylbutane selectively in variable chemical yields (the balance being the product of the reaction of the metallated titanacyclopropene with Br_2).



Equation 1

In order to overcome these chemical yield variations as well as to avoid the formation of **2** it was necessary to find new experimental conditions in which the di*iso*propyloxy(η^2-propene)titanium **1** would be generated in the presence of the electrophile (Barbier Conditions)[17]. For this purpose, we found after several experiments[19] that treatment of chloroalkyne **3** (Scheme 2, R = alkyl, X = Cl) with 2.5 equivalents of the combination $Ti(OiPr)_4$/iPrMgBr (in a 1:2.5 ratio) gives, in a single-pot operation at –50 °C in 2 hours, the desired titano-titanacyclopropene **6** in high chemical yield (Scheme 2).



Scheme 2

A plausible mechanism for this reaction is shown in Scheme 2. The in situ formed di*iso*propyloxy(η^2–propene) titanium **1** (generated as described in Scheme 1) reacts with chloroalkyne **3**, via a ligand exchange[11], to give as an unstable intermediate[20] the chloro-titanacyclopropene **4** (R = alkyl, X = Cl). Then, **4** undergoes a very fast β-elimination[21] at low temperature to give the alkynyltitanium derivative **5**[22]. Quenching the reaction with MeOD at –78 °C proved the presence of the metallated alkyne **5** since the deuteroalkyne (Scheme 2, path A) was quantitatively obtained. When the reaction mixture is warmed to –50 °C and stirred for 2 hours, the second equiv. of **1** can react with **5** to give quantitatively the titano-titanacyclopropene **6** (Scheme 2, path B). After hydrolysis, **7** is isolated in high yield. The presence of 3 carbon-metal bonds was proven by reaction with MeOD to give **8** (>95%D in 87% yield). Results for a variety of alkynes are shown in the Table. In all cases, only the polymetallated species was obtained, whatever the nature of the R group.

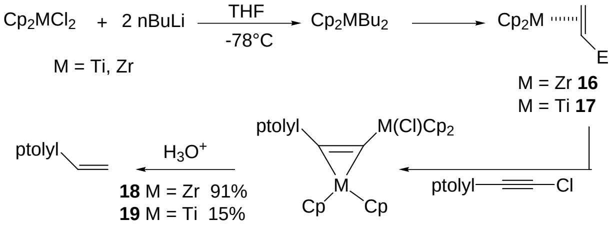
Table 1 Generalization for the synthesis of metallated titanacyclopropenes.

Entries	R	X	Compounds	Yield(%)[a]
1	Oct	Cl	**7**	90
2	Hex	Br	**10**	75
3	Hex	I	**11**	65
4	Hex	SPh	**12**	70
5	pTolyl	Cl	**14**	95
6	*tert*-AmylO$(CH)_2$	Cl	**15**	93

[a] Isolated yields after hydrolysis.

Indeed, several chloroalkynes with an alkyl, phenyl or homopropargylic ether group lead to the products in good to high yields (entries 1, 5 and 6). Interestingly, according to the nature of the leaving group, minor variations in the chemical yields are observed (compare entries 1, 2 and 3). Whereas the first step is still quantitative (formation of the metallated alkyne **5**), the second one is dependent on the nature of the halogen X on alkynyltitanium **5**. Even in the case of the alkynyl thiophenyl ether (entry 4), a good chemical yield was obtained.

On the other hand, further investigations revealed interesting reactivities of zirconocene-(1-butene) **16** and titanocene-(1-butene) **17** derivatives with a chloroalkyne. Indeed, whereas the reaction of **16**[23] with *p*tolylchloroacetylene (see Scheme 3) afforded the corresponding trismetallated olefin **18** in high yield (91% after hydrolysis), the same reaction with Cp_2Ti-(1-butene) **17**[24] lead only to 15% of **19**[25]. When the same strategy is applied to **3** (R = alkyl) either with **16** or **17** only low conversions to trimetallated olefins are obtained[26].



Scheme 3

In conclusion, the use of di*iso*propyloxy(η^2-propene)titanium **1** provides an efficient one-pot method for synthesizing trimetallated olefins from common starting materials[27]. It should be noted that whereas terminal alkynes failed in the present reaction[11], it occurs very nicely with a metallated alkyne and then *the alkynyl organometallic behaves like a carbon center*. Synthetic applications of the present methodology and investigations to confirm the mechanistic rationale of the reaction[28] are now in progress in our laboratory.

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(17) Grignard Conditions (formation of the organometallic derivative *and then introduction* of the electrophile) as compared to Barbier Conditions (formation of the organometallic derivative *in the presence* of the electrophile).

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(19) The addition of iPrMgBr to the mixture of alkynylzinc bromide and Ti(OiPr)$_4$ in Et$_2$O at –78 °C did not give the expected product but more probably the zincate. The transmetallation between iPrMgBr and the alkynylzinc bromide is faster than the reaction between the same Grignard reagent and Ti(OiPr)$_4$.

(20) All attempts to trap the intermediate **4** at low temperature were unsuccessful.

(21) Equivalent reactions were described in the literature for the formation of vinylzirconium derivatives from zirconocenes and vinyl halides see T. Takahashi, M. Kotora, R. Fischer, Y. Nishihara, K. Nakajima *J. Am. Chem. Soc.* **1995**, *117*, 11039.

(22) An alternative mechanism to obtain **5** can also be formulated via an oxidative addition of the Ti^{II} into the chloroalkyne.

(23) For the use of dialkylzirconocenes in synthesis, see the last review: E.I. Neghishi, T. Takahashi *Bull. Chem. Soc. Jpn.* **1998**, *71*, 755.

(24) For the use of dialkyltitanocenes in synthesis, see S.L. Buchwald, R.B. Nielsen *Chem. Rev.* **1988**, *88*, 1047.

(25) The balance being the starting material (21%) and the metallo-alkyne (65%)

(26) Whereas with **16** 40% of the polymetallated olefin can be obtained (accompanied by the formation of high molecular weight products), the use of **17** gave only 10% of the desired metallated double bond (the major product being the starting material)

(27) Representative experimental procedure: To a stirred solution of 1-chloro-1-decyne (300 mg, 1.7 mmol) and Ti(*O*-iPr)$_4$ (1.3 mL, 4.3 mmol) in 20 mL of Et$_2$O was added a 1.1 M solution of iPrMgBr in ether (7.8 mL, 8.58 mmol) at –78 °C under argon to give a yellow homogeneous solution. The solution was warmed to –50 °C over 30 min, during which period its color turned brown. After stirring at –50 °C for an additional 2h, a 1M solution of HCl was added. The organic phases were extracted twice with a 1M aqueous solution of HCl and the aqueous phases were washed with ether. The combined organic phases were dried over MgSO$_4$ and concentrated in vacuo to give a crude oil. Purification by chromatography (silica gel, hexane) afforded decene in 90% yield.

(28) Until now, all our attempts to get crystals for X-Ray structure determination failed.

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