

Dimethyltitanocene Cp_2TiMe_2 : A Useful Reagent for C–C and C–N Bond Formation

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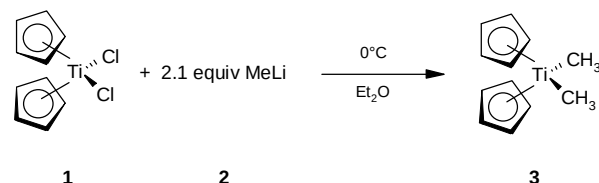
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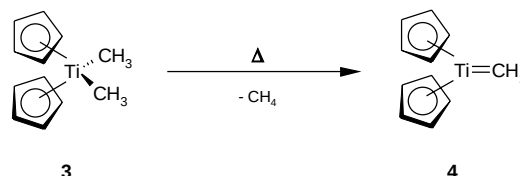
1. Introduction

Dimethyltitanocene Cp_2TiMe_2 (**3**) was first synthesized in 1956 by Clauss and Bestian (Hoechst AG). They found that titanocene dichloride Cp_2TiCl_2 (**1**) easily reacts with 2.1 equivalents of methyltitanium (**2**) in diethylether to form Cp_2TiMe_2 (**3**) (Scheme 1) [1].



Scheme 1 Synthesis of dimethyltitanocene, Cp_2TiMe_2 (**3**)

Cp_2TiMe_2 (**3**) is an orange solid (decomposition at 97 °C) which is sensitive to light and oxygen. It is soluble in most organic aprotic solvents like THF, toluene, Et_2O , CH_2Cl_2 or hexanes. However, in the solid state it is not stable for more than a few hours at room temperature but it can be stored for month in the dark in THF or toluene solution [2]. Surprisingly, both the solid as well as the solution can be briefly exposed to air and water without significant decomposition. Therefore, Cp_2TiMe_2 (**3**) is a reagent which can be conveniently handled under Schlenk conditions and does not require the use of a glove box [3]. It has been extensively used as a reagent for stoichiometric transformations and more recently as a catalyst for some modern applications. In this review several examples are given for the application of Cp_2TiMe_2 (**3**) as a reagent and as a catalyst. Extensive mechanistical studies suggest that the very reactive Schrock-type titanium carbene complex $\text{Cp}_2\text{Ti}=\text{CH}_2$ (**4**) which is formed from Cp_2TiMe_2 (**3**) via thermal α -elimination of methane (Scheme 2) represents the general reactive intermediate for most of these examples [4].



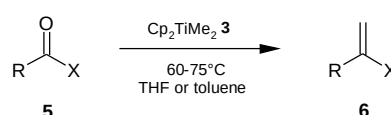
Scheme 2 Formation of carbene complex $\text{Cp}_2\text{Ti}=\text{CH}_2$ (**4**) via thermal α -elimination of methane from Cp_2TiMe_2 (**3**)

Although compound **4** has not yet been observed in its pure form, its phosphine complexes have been isolated and characterized [5]. Further mechanistical details for the following examples can be found in each chapter and in the references.

2. Stoichiometric Reactions

2.1. Methylenation of Carbonyl Compounds

The probably most important application of Cp_2TiMe_2 (**3**) as a reagent is the methylenation of carbonyl compounds **5** such as aldehydes, ketones, esters, lactones, anhydrides, carbonates, amides, imides, silyl esters, thioesters, selenoesters and acylsilanes yielding a wide variety of heteroatom substituted alkenes **6** (Scheme 3) [6–10].

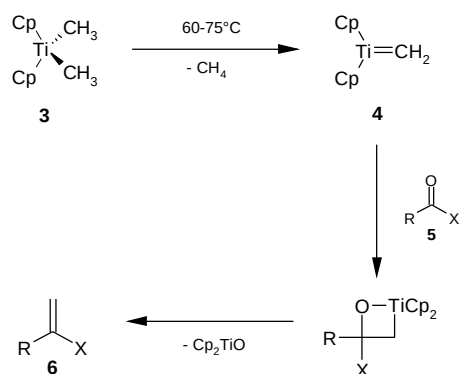


R = Alkyl, Aryl
X = H, Alkyl, Aryl, OR', OSi^t-BuMe₂, OCOR'
NR₂', N(R')COR'', SR', SeR', SiMe₃

Scheme 3 Methylenation of various carbonyl compounds

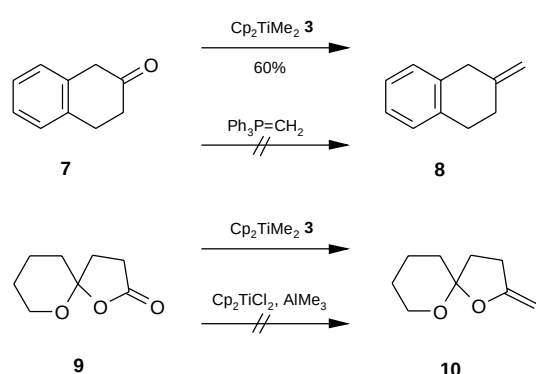
The procedure is particularly important for the synthesis of alkene derivatives which are difficult to synthesize using other synthetic approaches. The methylenation reaction proceeds simply by heating the carbonyl compound **5** in the presence of a stoichiometric amount of **3** in THF or toluene to 60–75 °C. The mechanism of the reaction, which is supported by deuterium and ¹³C-labeling experiments [4], includes the thermal formation of the carbene complex **4**, a subsequent [2+2]-cycloaddition between **4** and the carbonyl compound **5** and a final loss of Cp_2TiO (Scheme 4).

One big advantage of the described methylenation method is the fact that the isolation of the product does not require an aqueous workup procedure. This can be very important for



Scheme 4 Proposed mechanism for the methylenation of carbonyl compounds

the synthesis of sensitive compounds. Cp₂TiO, the single side product of the reaction, can be precipitated by adding pentane to the reaction mixture and easily separated from the product by filtration. Compared to other methylenation reagents like the Wittig-reagent (Ph₃P=CH₂), the Tebbe-reagent (Cp₂TiCl₂, AlMe₃) or titanacyclobutanes developed by Grubbs the use of Cp₂TiMe₂ (**3**) offers some further advantages. First of all and in contrast to the Tebbe-reagent **3** is only modestly sensitive to air and moisture. This makes the handling of **3** much more convenient. Furthermore **3** is less basic than the Wittig-reagent and less acidic than the Tebbe-reagent. Therefore, compared to the Wittig-reagent base labile or highly enolizable carbonyl compounds can be methylenated much easier using **3** as the methylenation reagent. In comparison with the Tebbe-reagent acid sensitive substrates can be used more successfully. Impressive examples are the synthesis of *exo*-methylene compound **8** from ketone **7** as well as the synthesis of spiroketal **10** from the corresponding lactone **9** (Scheme 5) [7].

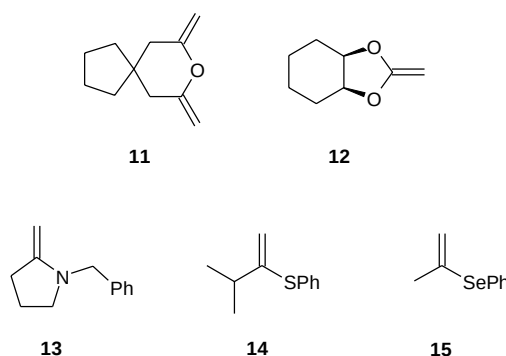


Scheme 5 Methylenation of sensitive compounds using Cp₂TiMe₂ (**3**)

Both reactions can be successfully performed using **3** as the methylenation reagent. In contrast, in the first example, the Wittig-reagent acts as a base exclusively while in the second example the Tebbe-reagent causes complete decomposition of the highly acid sensitive spiroketal lactone.

Further compounds (**11**–**15**) which are easily accessible from the corresponding carbonyl compounds (carbonates,

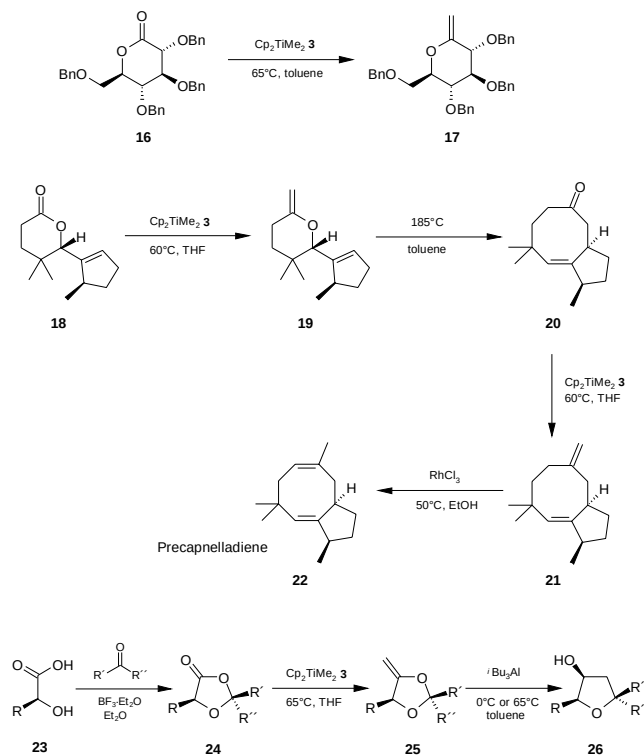
amides, thioesters, selenoesters) using **3** as a reagent are shown in Scheme 6.



Scheme 6 Various methylenation products

Due to the good leaving group quality of thiolates and selenolates the results obtained with thioesters and selenoesters are particularly impressive.

The advantages mentioned above combined with the smooth reaction conditions led to some interesting applications in the synthesis of natural products (Scheme 7). Aldonolactones **16** can be efficiently methylenated at the former anomeric center of the corresponding carbohydrates giving access to *C*-Glycoside congener **17** in high yields [8]. Precapnelladiene **22** was successfully synthesized via a methylenation-Claisen rearrangement-methylenation sequence starting from lactone **18** [9]. Methylenation of the diastereomeri-

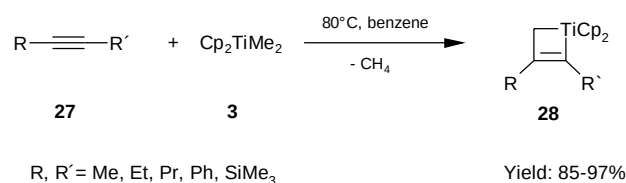


Scheme 7 Methylenation reactions in the synthesis of natural product derivatives

cally pure lactone **24** afforded the highly acid labile intermediate **25** which was easily converted to the corresponding tetrahydrofuran derivative **26** [10].

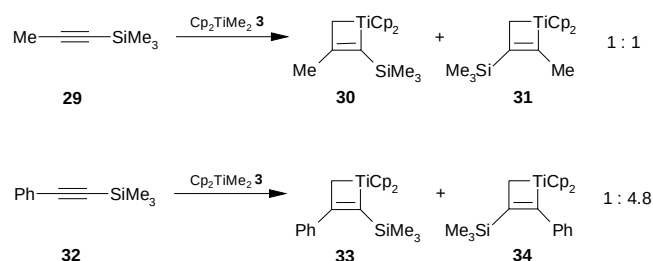
2.2. Reactions with Alkynes

Thermolysis of Cp_2TiMe_2 (**3**) at 80 °C in benzene (7–9 h) in the presence of internal alkynes **27** forms the corresponding titanacyclobutenes **28** cleanly and efficiently (Scheme 8) [11].

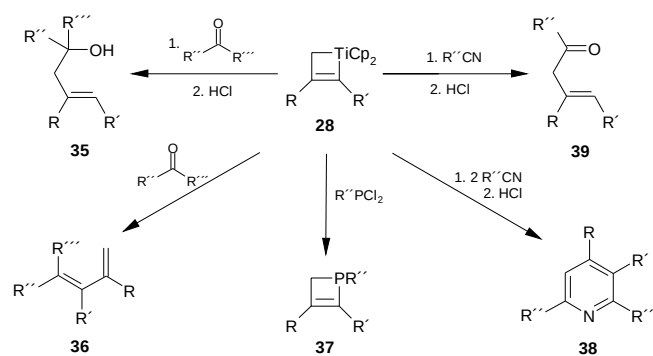


Scheme 8 Formation of titanacyclobutenes

Most likely, this reaction also involves a loss of methane to generate the very reactive titanium carbene complex $\text{Cp}_2\text{Ti}=\text{CH}_2$ (**4**) which undergoes a subsequent [2+2]-cycloaddition with the alkyne yielding the titanacyclobutene. For unsymmetrically substituted alkynes the regioselectivity of the [2+2]-cycloaddition is low. Therefore, reactions employing trimethylsilyl-methyl-acetylene (**29**) or trimethylsilyl-phenyl-acetylene (**32**) give mixtures of regioisomers (Scheme 9).



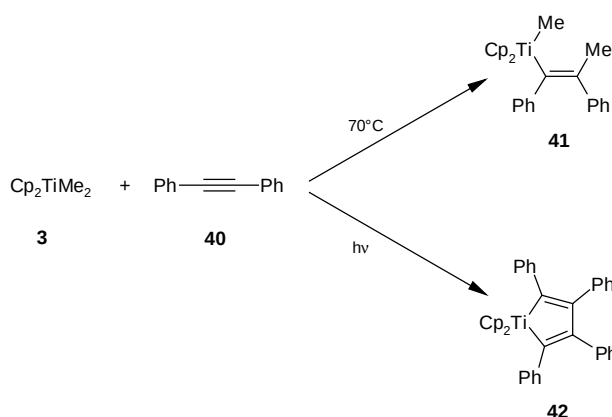
Scheme 9 Reaction of unsymmetrical alkynes with Cp_2TiMe_2



Scheme 10 Titanacyclobutenes as intermediates for organic synthesis

The generated titanacyclobutenes **28** are useful intermediates for organic synthesis [12]. They easily react with aldehydes or ketones, phosphorous dichlorides, and nitriles yielding homoallylic alcohols **35** [13], dienes **36** [14], phosphacyclobutenes **37** [15], pyridines **38** [16] or β,γ -unsaturated ketones **39** [13, 16] (Scheme 10).

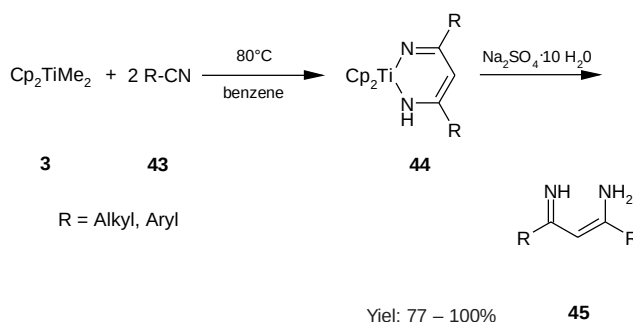
Interestingly, the reaction of Cp_2TiMe_2 (**3**) with diphenylacetylene **40** at temperatures < 80 °C forms the vinyl derivative **41** [11, 17] while under photolytic conditions titanacyclopentadiene **42** is mainly formed, presumably via a titanocene (Cp_2Ti) intermediate (Scheme 11) [18].



Scheme 11 Reaction between Cp_2TiMe_2 **3** and diphenylacetylene **40** at lower temperatures and under photolytic conditions

2.3. Reactions with Nitriles

Thermolysis of Cp_2TiMe_2 (**3**) at 80 °C in benzene in the presence of nitriles **43** (2 equiv.) forms the corresponding 1,3-diaza-2-titana-1,4-cyclohexadiene derivatives **44** in quantitative yield (Scheme 12) [11].



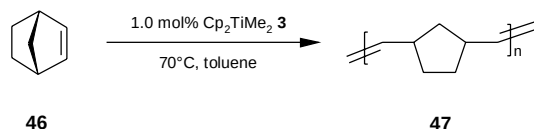
Scheme 12 Reaction between Cp_2TiMe_2 **3** and nitriles **43**

The reaction seems to occur via a [2+2]-cycloaddition between **4** and the nitrile forming an azatitanacyclobutene followed by an insertion of the second equivalent of nitrile into the titanium–carbon-bond. The obtained metallacycles **44** can be easily hydrolyzed to 4-amino-1-azadienes **45**, which are useful intermediates for the synthesis of a great variety of heterocyclic systems and open chain 1,3-difunctionalized compounds [19].

3. Catalytic Reactions

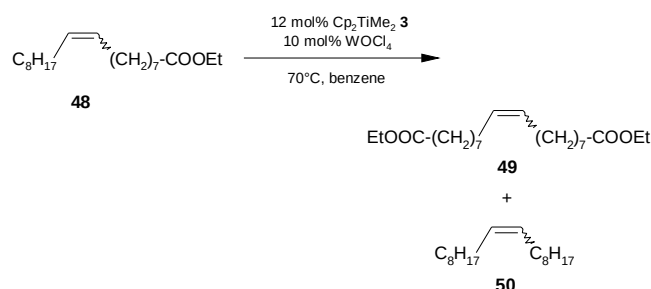
3.1. Metathesis

Heating of norbornene **46** in the presence of 1 mol% Cp₂TiMe₂ (**3**) results in ring-opening metathesis polymerisation (ROMP) of norbornene (Scheme 13) [20]. It is proposed that Cp₂Ti=CH₂ (**4**) is the active metathesis catalyst.



Scheme 13 Cp₂TiMe₂-catalyzed ring-opening metathesis polymerisation (ROMP) of norbornene **46**

Interestingly, the reaction proceeds smoothly at 70 °C in toluene while a THF solution under identical conditions did not show any polymerization. This significant inhibitory effect of THF can be explained by the tendency of THF to complex with titanium carbene intermediates. This results in a stabilization of these intermediates and a slower propagation process. In combination with tungsten compounds (WOCl₄, WCl₆) Cp₂TiMe₂ (**3**) further acts as a catalyst for olefin metathesis (Scheme 14) [21]. However, the reported results can not compete with results reported with catalysts based on ruthenium or molybdenum.

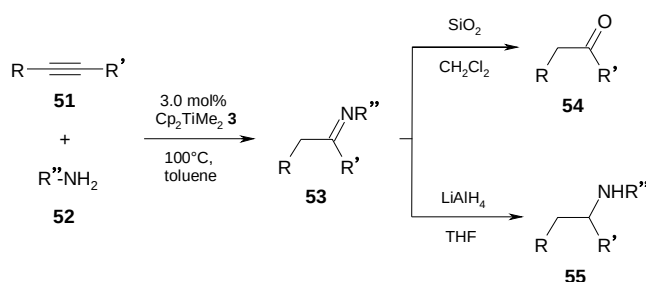


Scheme 14 Olefin metathesis

3.2. Hydroamination of Alkynes

The recently developed dimethyltitanocene-catalyzed intermolecular hydroamination of alkynes represents another important application for Cp₂TiMe₂ (**3**) as a catalyst [22]. At 100 °C in the presence of 1.0–3.0 mol% Cp₂TiMe₂ (**3**) primary amines **52** easily react with symmetrically and unsymmetrically substituted alkynes **51** to the corresponding imines **53**. The obtained imines can be subsequently reduced to amines **55** (LiAlH₄ or H₂, Pd/C) or hydrolyzed to ketones **54** (SiO₂). The procedure can be successfully used for the coupling of primary arylamines as well as primary *t*- and *s*-alkylamines while primary *n*-alkylamines are poor substrates. In the case of unsymmetrically substituted alkynes, the reaction occurs with high regioselectivity, forming the *anti*-Markownikow-products exclusively (Scheme 15, Table 1).

It is assumed that Cp₂TiMe₂ (**3**) reacts with an amine under loss of methane to form a catalytically active titanium-imido



Scheme 15 Cp₂TiMe₂-catalyzed intermolecular hydroamination of alkynes followed by hydrolysis or reduction

Table 1 Cp₂TiMe₂-catalyzed intermolecular hydroamination of alkynes with various amines

R	R'	R''	Ketone	Amine
Ph	Ph	Ph	92%	62%
Ph	Ph	<i>t</i> -Bu	91%	86% ^{a)}
Ph	Ph	Cy	65%	86% ^{a)}
Ph	Me	Ph	99%	
Ph	Et	Ph	73%	
Et	Et	Ph	30%	

^{a)} Reduction with 1 bar of H₂ and 5 mol-% Pd/C instead of LiAlH₄.

complex which undergoes a [2+2]-cycloaddition with the alkyne. The resulting azatitanacyclobutene is then irreversibly protonated by further amine to form a titanocene bis-amide, which is thermally cleaved into an enamine and the catalytically active titanium-imido complex. Finally, the enamine is converted into the imine under the reaction conditions.

3.3. Hydrogenation of Alkenes

Cp₂TiMe₂ (**3**) can also be used as a catalyst for the hydrogenation of alkenes. However, other titanocene bisalkyl derivatives show a much higher activity [23]. Furthermore, the active catalyst species (Cp₂Ti-H) can be better generated directly from Cp₂TiCl₂ (**1**). These disadvantages are responsible for the fact that **3** has not been used extensively as a catalyst for the hydrogenation of alkenes.

3.4. Miscellaneous Reactions

Since Cp₂TiMe₂ (**3**) forms cationic titanocene complexes in the presence of acids it has been successfully used as a catalyst for the Ziegler–Natta polymerisation of alkenes [24]. Organosilanes undergo dehydrogenative coupling in the presence of catalytic amounts of Cp₂TiMe₂ (**3**) forming oligomers or polymers [25]. This reaction is suppressed in the presence of alkenes. Instead, the olefin undergoes hydrogenation or hydrosilylation [26]. Furthermore, **3** catalyzes the formation of disilazanes from silanes and ammonia [27].

4. Conclusion

In conclusion, Cp₂TiMe₂ (**3**) represents an experimentally convenient reagent which can be used for a wide variety of transformations. As a reagent for the methylenation of carbonyl

compounds it is an alternative to the Wittig- and the Tebbe-reagent that offers some important advantages. It can also be used for the synthesis of titanacyclobutenes and 1,3-diaza-2-titana-1,4-cyclohexadienes from alkynes and nitriles. These metallacycles can be transformed into various interesting, titanium-free compounds. As a catalyst, Cp_2TiMe_2 (**3**) catalyzes the ring-opening metathesis of norbornene, the olefin metathesis of simple alkenes, the Ziegler–Natta-polymerisation of alkenes, the hydrogenation of alkenes, the oligomerisation of silanes and the intermolecular hydroamination of alkynes. In particular the recently obtained and promising results with **3** as a hydroamination catalyst lead to the conclusion that the catalytic properties of Cp_2TiMe_2 (**3**) are not totally exhausted yet.

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