

## CARBONYL OLEFINATION USING TITANIUM-CARBENE REAGENTS.

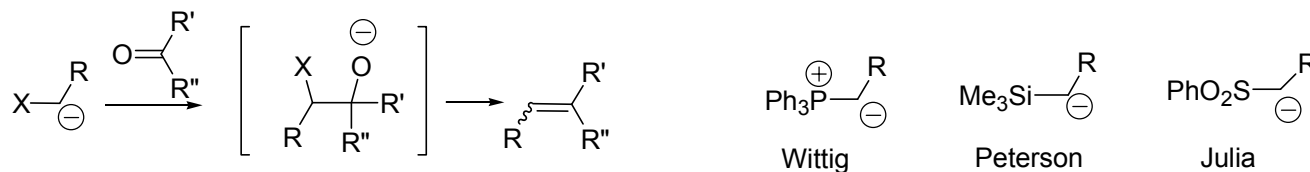
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### INTRODUCTION

Carbonyl olefination is one of the most important reactions in organic synthesis. Wittig-type reagents<sup>1</sup> are the most commonly used for this purpose, and *E/Z*-selective methods for carbon-carbon double bond construction have been developed using phosphorous-based olefinating reagents, which include Wittig-Schlosser,<sup>2</sup> Horner-Emmons-Wadsworth,<sup>3</sup> Horner-Wittig<sup>4</sup> and other reactions. Other procedures were introduced to overcome some drawbacks of phosphorous-based olefination, mostly to improve reactivity and selectivity. Among them are Peterson- and Julia-olefinations<sup>5,6</sup> (Scheme 1), as well as other protocols using S, Se, B and other heteroatom-stabilized anions. Selenium-based olefin synthesis<sup>7</sup> allows the construction of very sterically hindered tetrasubstituted alkenes.

#### Scheme 1.



However, major limitations of these methodologies still remain. The inherent basicity of the anions used leads to undesired side-reactions when applied to base-sensitive substrates. Another limitation is that typically only aldehydes and ketones can be used as the substrates in these reactions. Carboxylic acids, their esters, amides, thioesters and many other derivatives generally are either unreactive or do not react in the desired manner.

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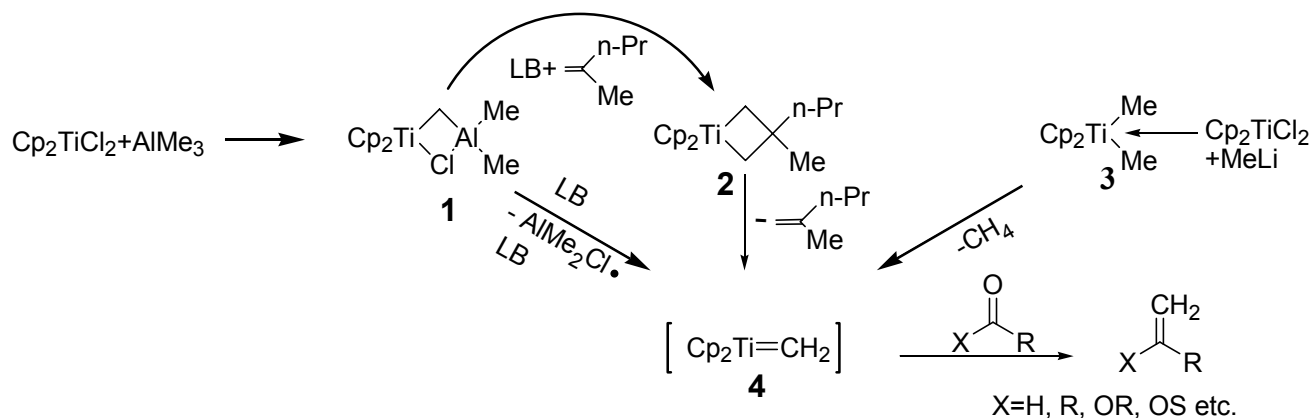
### Metallacarbenes

Carbenes are molecules containing divalent carbon atoms. Carbenoids have tetravalent carbons, but have some properties that resemble those of carbenes. The ability to transfer a divalent carbon to other molecules is one of these properties. Metallacarbenes are carbenoids that contain a transition metal and some of them are stable at room temperature. They can be considered divalent carbon species coordinated to a metal via a formal double bond. Several metallacarbenes have been demonstrated to function as alternatives to using anions for carbonyl olefination.<sup>8</sup> The metallocarbenes have the advantage of having only weakly basic or acidic properties, being reactive with carboxylic acid derivatives and being reactive enough to form tetrasubstituted alkenes.

## Titanocene-Carbenoids in Carbonyl Olefination

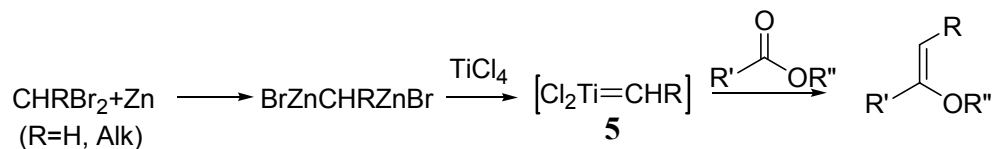
In 1978 Tebbe reported that reagent **1**, the product of reaction between titanocene dichloride and trimethylaluminum (Scheme 2), can convert carbonyl groups into methylenes in presence of Lewis bases.<sup>9</sup> Since then, many variations of this reaction have been developed. It was suggested that the reaction goes via titanocarbene species **4**, after Lewis base binding of the aluminum fragment. Grubbs<sup>10</sup> in 1980 introduced titanacyclobutanes **2**, which can be obtained by treatment of Tebbe reagents with an olefin in presence of a Lewis base to bind the aluminum species. Grubbs reagents also convert a carbonyl into a C=C-double bond, but unlike Tebbe reagents, they are less air sensitive and do not have Lewis acidic properties, which can be harmful for some applications. Finally, in 1990 Petasis<sup>11</sup> was able to show that dimethyltitanocene **3**, like the Grubbs reagents, can eliminate methane upon thermolysis to give the intermediate **4** possessing the same carbenoid properties as Tebbe and Grubbs reagents. Dimethyltitanocene is even less air and moisture sensitive and is much easier to prepare than the Grubbs or Tebbe reagents.

### Scheme 2.



Takai in 1978 reported that a reagent prepared from Zn, TiCl<sub>4</sub> and CH<sub>2</sub>Br<sub>2</sub> (Scheme 3) can also olefinate carbonyl in a manner similar to Tebbe-like reagents.<sup>12</sup> The mechanism of the reaction and the active species are still unknown. One of the suggested reactive intermediates (**5**) is similar to the species **4**.

### Scheme 3.

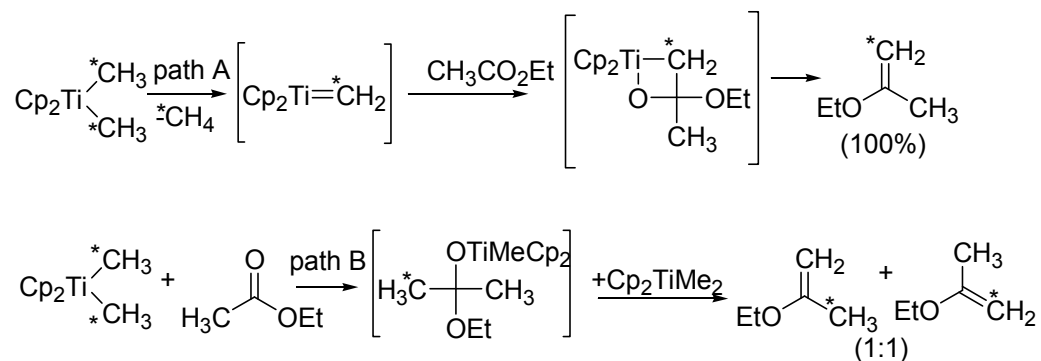


The above reagents can only perform methylenation, not alkyldination. In 1987; however, Takai and Oshima,<sup>13</sup> using TMEDA and 1,1-dibromoalkanes instead of dibromomethane, were able to accomplish alkyldination of carboxylic esters, drastically increasing the scope of Ti-based olefination.

## Mechanism of Olefination via Titanium-Carbenes

The most thorough mechanistic study on Ti-based olefination has been done using the Petasis reagent.<sup>14</sup> The mechanism of the reaction is assumed to be the one shown as path A, Scheme 4. According to this mechanism, the first step is a carbene formation. The carbene is formed via thermolysis with elimination of methane. The carbene then reacts with a carbonyl compound. An alternative suggested mechanism is represented as path B.

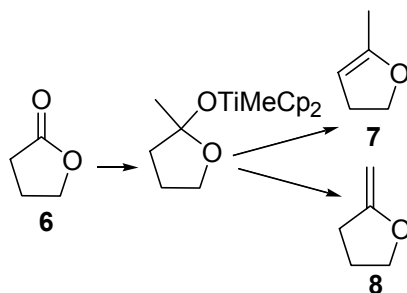
**Scheme 4.**



The following data favor the former mechanism and disprove the later one:

1. There is no D- or <sup>13</sup>C-scrambling observed in the course of the reaction. (Originally, mechanism via path B was suggested, since there was some scrambling observed; however, this was later shown to be caused by secondary reactions, like 1,3 H-shift.)
2. The reaction is first order in Ti and zero order in carbonyl compound. (This is consistent with the carbene formation as a slow, rate-determining step, followed by a fast addition to a carbonyl.)
3. There is a substantial kinetic isotope effect. (KIE=8-10 at 80°C. The magnitude of the KIE means that this is a primary KIE and that the rate-determining step involves a C-H bond rupture.)
4. The double bond is formed regioselectively, which would not be true for the mechanism B. (E.g., **6** on treatment with dimethyltitanocene would give a mixture of **7** and **8**, if the reaction followed path B, Scheme 5).

**Scheme 5.**



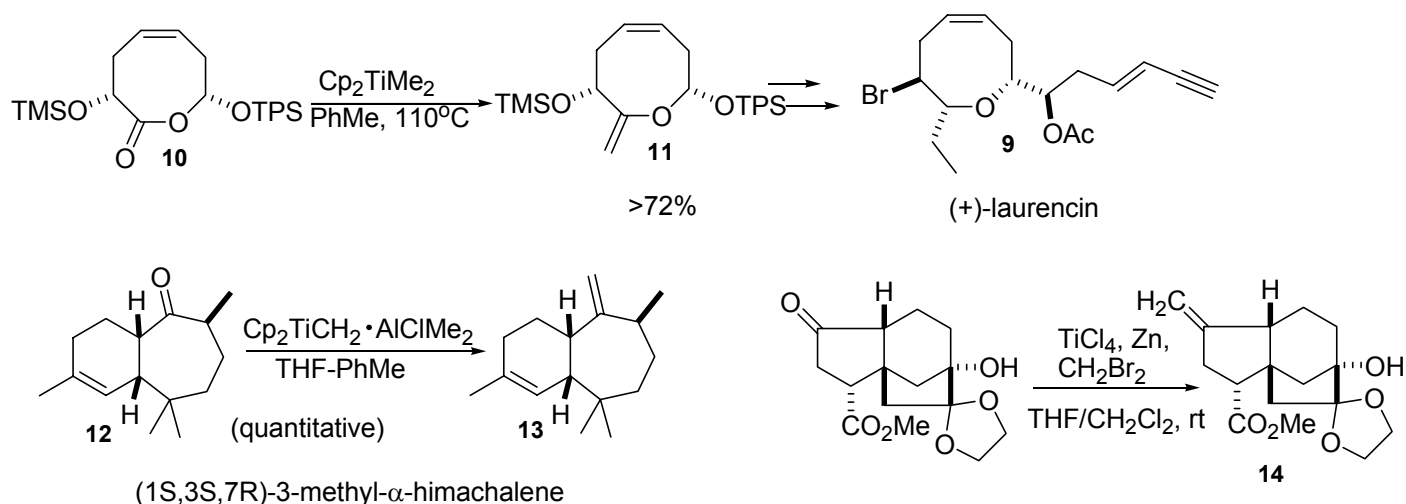
In addition to the Petasis methylenating reagent, some other<sup>15</sup> analogs can be prepared by alkylation of titanocene dichloride (e.g., benzyl,<sup>16</sup> trimethylsilylmethyl,<sup>17</sup> cyclopropyl<sup>18</sup> derivatives).

Higher homologs (for example, ethylenating agents) of Tebbe, Grubbs and Petasis reagents could not be prepared in the usual way, probably, due to  $\beta$ -elimination.<sup>15</sup> Methylenation does not proceed in the same manner with some substrates. For example, halo-anhydrides of carboxylic acids, due to the presence of a good leaving group, form methyl-ketone enolates, which can be used immediately in aldol or another reaction.<sup>19</sup> Alkenes can form cyclopropane structures when reacted with titanocarbenes; however, this reaction is typically slower compared to carbonyl olefination.<sup>20</sup>

### Titanium Olefination in Natural Product Total Synthesis

The olefination techniques discussed above have been used widely in organic synthesis. Scheme 6 shows portions of several representative examples.

#### Scheme 6.



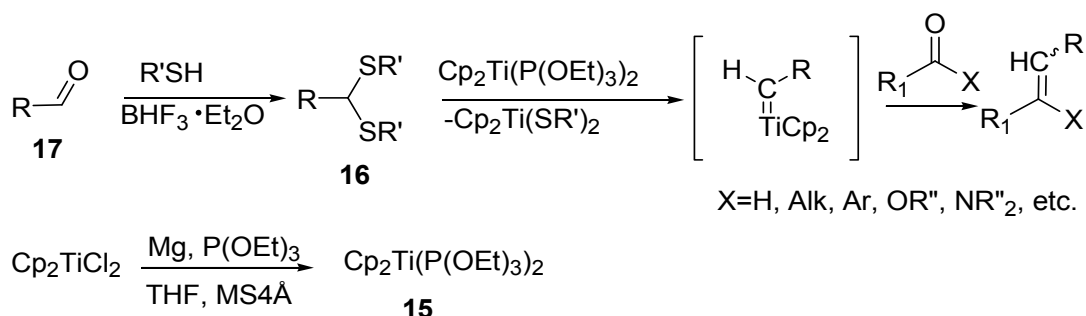
In the synthesis of (+)-laurencin **9**, the Petasis reagent was used to convert lactone **10** into exocyclic enol ether **11**.<sup>21</sup> No epimerization at the adjacent stereocenter was observed. Mori quantitatively methylenated a cyclic ketone **12**, to make (1*S*, 3*S*, 7*R*)-3-methyl- $\alpha$ -himachalene **13**.<sup>22</sup> Use of more basic reagents for such a crowded ketone could be expected to lead to considerable epimerization. Lombardo<sup>23</sup> used his reagent to install a methylene group at a cyclopentane ring to form **14** on the way to gibberellins. In this case, Wittig and some other reagents led to epimerization at the adjacent stereocenter, whereas by using  $\text{TiCl}_4/\text{Zn}/\text{CH}_2\text{Br}_2$ , a 90% yield was achieved without epimerization.

### Development of New Ways to Olefinate Carbonyl. Use of Dithioacetals.

The major limitation of the methodologies above is that generally, only methylenation can be accomplished. Takai's variation<sup>13</sup> ( $\text{TiCl}_4/\text{TMEDA}/\text{Zn}/\text{R}_2\text{HBr}_2$ , Scheme 3) can be used to construct trisubstituted alkenes, but it is not easy to make geminal dibromides in good yield. Takeda has reported that dithioacetals and titanocene-bis-triethylphosphite **15** can be used for alkylidenation (Scheme 7).<sup>24</sup>

Dithioacetals **16** and dithioketals can be easily formed from the corresponding aldehydes **17** or ketones by treatment with a thiol in presence of Lewis acids, Scheme 7. Alternatively, dithioacetals and dithioketals can be obtained by alkylation of dithiomethane. The low-valence titanium-species **15** can easily be prepared by stirring titanocene dichloride with magnesium, triethylphosphite and molecular sieves 4 Å (trace of moisture can have a dramatic effect on the yield) in THF at room temperature. The mechanism involving the same reactive species, alkylidenetitanocene, was suggested.

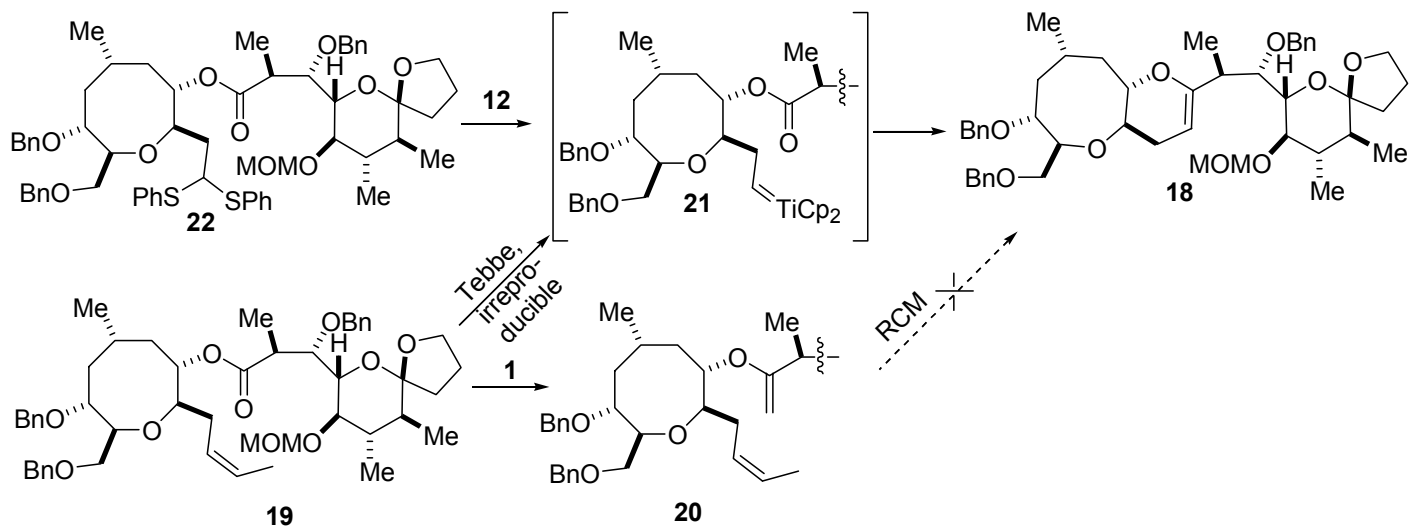
**Scheme 7.**



Aldehydes, ketones, carboxylic acid esters, amides, and many other derivatives can be easily transformed into substituted alkenes using this methodology. The more stable isomer is usually favored (*E*-, in case of disubstituted olefins or enamines, but esters afford mostly *Z*-enol ethers). Intramolecular variations of olefination have also been accomplished.<sup>25, 26</sup>

Hirama has applied this methodology in his total synthesis of ciguatoxin.<sup>27</sup> His initial attempts to form the cycle in **18** from **19** (Scheme 8) by Tebbe-olefination, followed by ring-closing metathesis, failed. Intermediate **20** (and others, similar to it) did not cyclize under usual metathesis conditions. He was able to observe **18** in this reaction (though in irreproducible yield, 0-60%). Thus, he concluded that the target product **18** was being formed via intramolecular carbonyl olefination (**19**→**21**→**18**). Using Takeda's approach, treatment of the corresponding dithioacetal **22** with  $\text{Cp}_2\text{Ti(P(OEt)}_3)_2$  gave reproducible yields (52-67%) of the intermediate **18**.

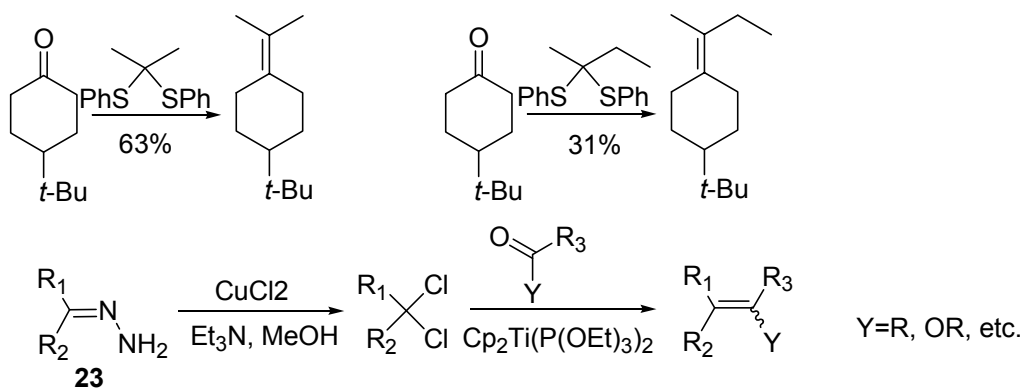
### Scheme 8.



### Use of Chlorides as Carbene-Precursor.

The dithioketal approach described above gives low yields as the steric bulk of the substrates increases. Scheme 9 demonstrates that a slight increase in the size of the dithioketal substituents leads to a dramatic decrease in the yield.

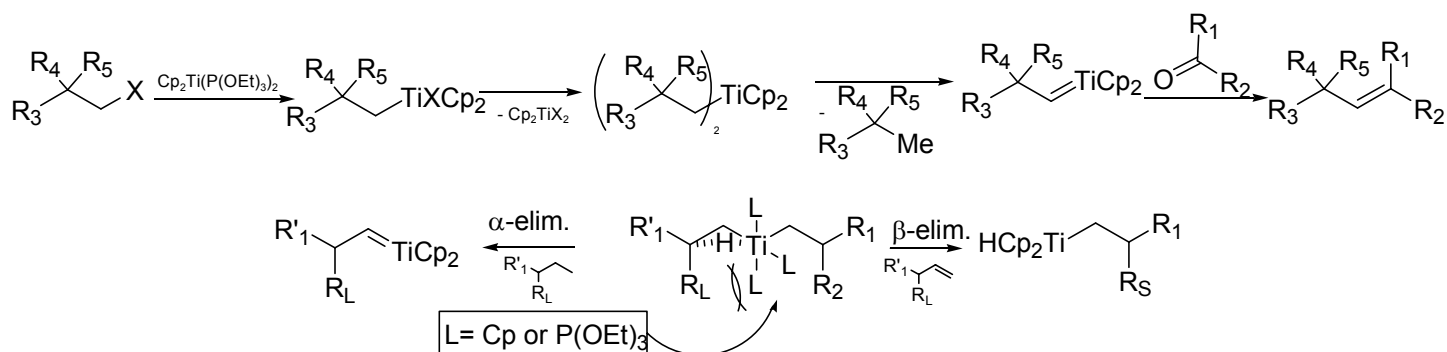
### Scheme 9.



Takeda suggested that the problem is caused by low reactivity of hindered dithioketals to form metallocarbene. Switching to a geminal dichloride allowed him to overcome this problem.<sup>28</sup> Unlike Takai's approach, this methodology allows also for the construction of tetrasubstituted alkenes, since the dihaloalkane substrate can have two substituents. The more stable double-bond configuration is usually favored; however, the selectivity, in general, is modest. Takeda also suggested a new, milder way to form *gem*-dihalides by oxidation of hydrazones **23** with copper-dihalide.<sup>29</sup> Use of carbon tetrachloride or chloroform as a *gem*-dichloride source leads to conversion of dialkylketones into 1,1-dichloroalkenes or monochloroalkenes.<sup>30</sup>

Monohalides can also be used as metallocarbene precursors (Scheme 10).<sup>31</sup> Since the oxidation state of the starting material is lower than that of the product, half of the chloride is lost as the alkane upon disproportionation. Through further exploration of the reaction, it was found that increasing the steric bulk at the  $\beta$ -position of the dialkyl-titanium species leads to improved yields. It was suggested that as a steric bulk at that position increases,  $\beta$ -hydrogen-elimination becomes less favored, and the desired  $\alpha$ -elimination predominates. The selectivity of this reaction has the same trends as other Ti-based procedures, e.g., *Z*-enol ethers are formed selectively.

**Scheme 10.**



## CONCLUSIONS

Metallocarbenes, exemplified by titanocene-derivatives, can be a useful alternative to classical ways of carbonyl group olefination. Easily enolizable carbonyl compounds can be converted to alkenes in high yield, and competing reactions that often make anionic-olefination impossible are not observed.

However, the major advantage of this class of reagents is that carboxylic acid derivatives can also be easily olefinated. Access to enol-ethers, enamines, thioenol-ethers and many other very sensitive compounds has thus become much easier since the discovery of these types of reagents. The original olefination techniques allowed only performing methylenation, but the use of dihaloalkanes has allowed the extension of this reaction to 1,2-di- and tri-substituted alkenes.

Further developments of titanocene-carbene chemistry by Takeda were directed at making 1,2-di- and tri-substituted olefins using dithioacetal/ titanocene-bis-triethylphosphite as the substrates. The products usually favor the more stable alkene isomers (e.g., *Z*-enol ethers or *E*-enamines and 1,2-disubstituted alkenes). However, the selectivity is often modest and improving the selectivity should be one of the goals of future studies. Intramolecular variations of this reaction have also been developed and applied in natural product total synthesis.

Use of *gem*-dihalides as precursors to titanocene-carbene active species, provides access to tetrasubstituted olefins with selectivity trends that resemble those of the dithioacetal approach. A

milder way to form geminal dihalides was developed to accompany this reaction. The use of monohalides as precursors makes building trisubstituted alkenes with a *tert*-butyl type of substituent possible. However, half of the halide is lost in a disproportionation process needed to adjust oxidation states.

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