

## Organotitanium compounds in organic synthesis

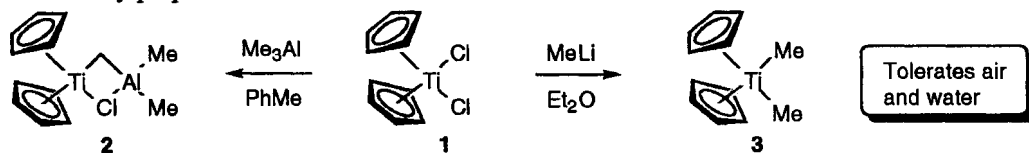
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**Abstract:** Mild thermolysis of dialkyltitanocenes can generate a reactive titanocene alkylidene species which in situ convert a variety of carbonyl compounds to the corresponding olefins. They also react with nitriles and alkynes and can serve as initiators of ring-opening metathesis polymerization. The olefination process mediated by these compounds is mild, experimentally convenient and works with many types of carbonyls, including: aldehydes, ketones, esters, lactones, silyl esters, anhydrides, carbonates, amides, lactams, imides, thioesters, selenoesters and acyl silanes. This olefination can be combined with subsequent transformations to produce carbocycles and heterocycles. Olefination of 1,3-dioxolan-4-ones followed by an aluminum-mediated rearrangement gives tetrahydrofurans, while a similar sequence with 1,3-dioxan-4-ones gives tetrahydropyrans in a highly stereocontrolled manner.

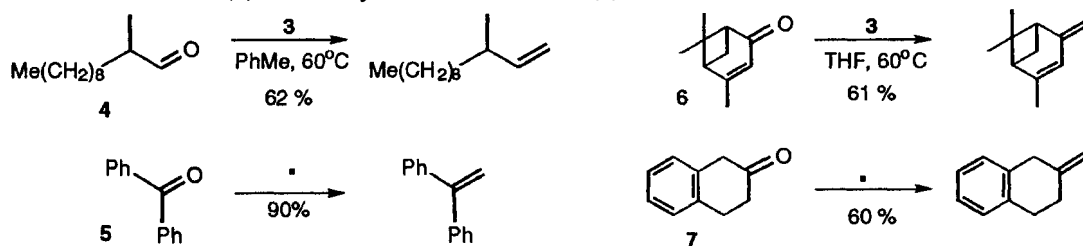
### Introduction

Considering its diverse chemical behavior, titanium, a very abundant, relatively inexpensive and generally nontoxic element, has been rather underutilized in organic synthesis. Although numerous compounds of titanium are known, only a handful of these (e.g.  $\text{TiCl}_4$ ,  $\text{TiCl}_3$ ,  $\text{Ti}(\text{OR})_4$ ,  $\text{TiCl}(\text{OR})_3$ ,  $\text{TiCl}_2(\text{OR})_2$ ,  $\text{Cp}_2\text{TiCl}_2$ , etc.) are widely used.[1] Despite the high reactivity of some titanium compounds, many organotitanium derivatives are very well behaved, particularly those with cyclopentadienyl (Cp) ligands.[2] In fact, compounds of this type show unique reactivity, including the formation of transient titanium alkylidene species ( $\text{Ti}=\text{C}$ ). One such compound, the Tebbe reagent[3] (2), prepared from titanocene dichloride (1) and  $\text{Me}_3\text{Al}$ , has been used extensively as a methylenating agent, despite some experimental drawbacks arising from the presence of the highly acidic aluminum moiety. Given the ability of Ti-based reagents to olefinate almost all types of carbonyls,[3] including those that are not olefinated with the basic Wittig-type methods, we have recently been searching for practical and experimentally convenient methods for Ti-mediated carbonyl olefinations. We have found that dialkyl titanocenes, such as dimethyl titanocene (3), which is easily prepared from 1 and  $\text{MeLi}$ , can indeed behave in this manner.

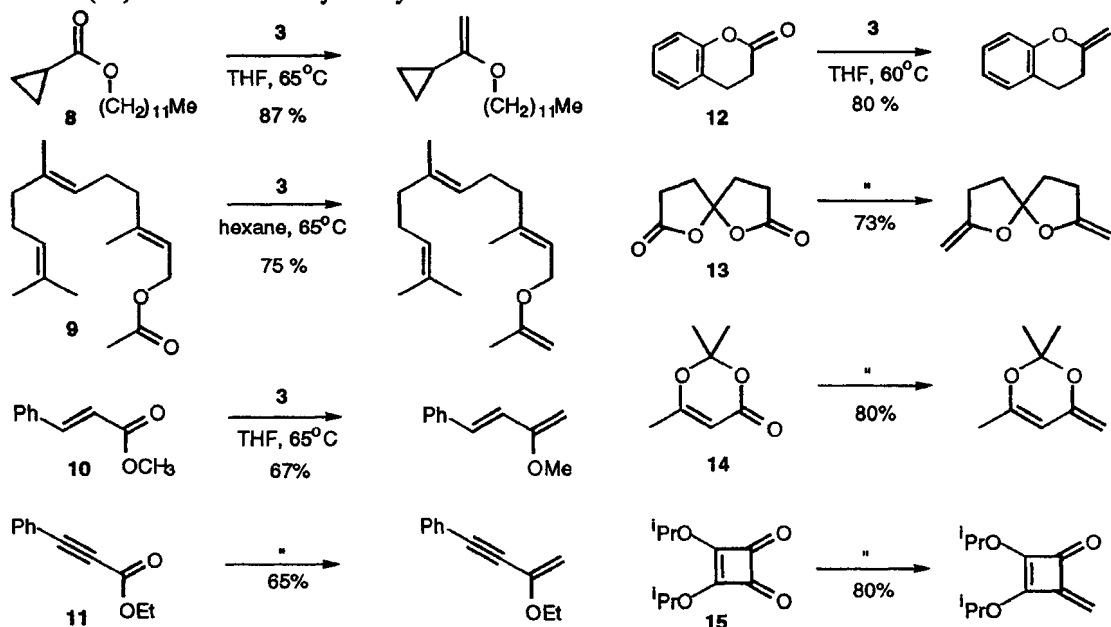


### Carbonyl methylenations with dimethyl titanocene

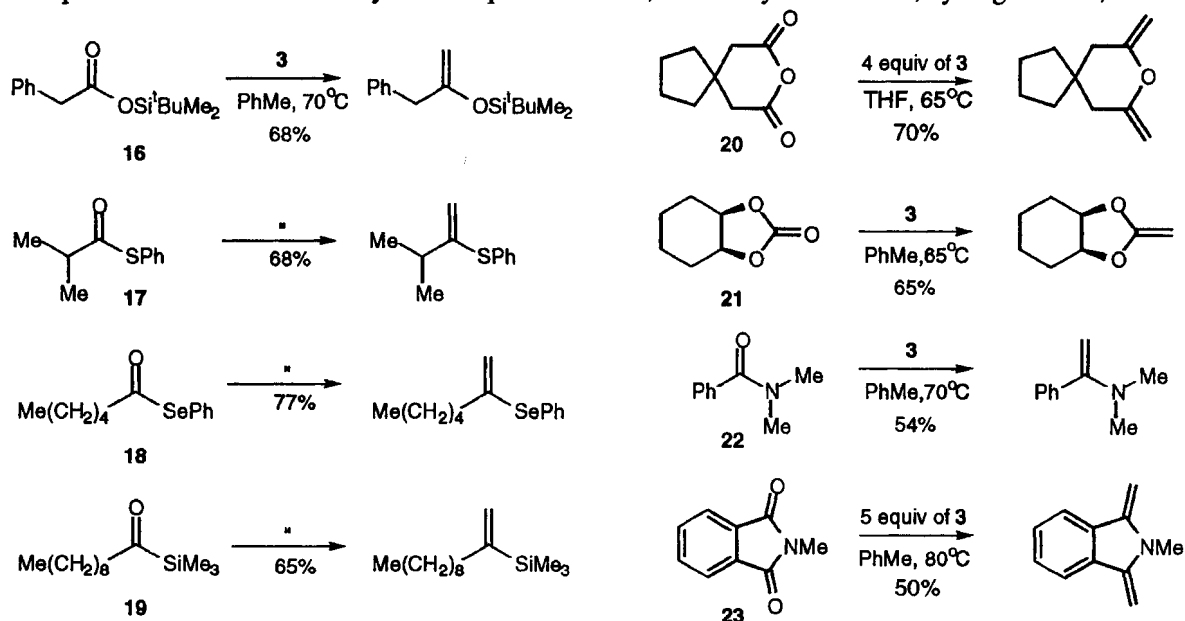
Although dimethyl titanocene (3) has been known for over 40 years,[2] its ability to methylenate carbonyl compounds has been discovered only recently.[4] Thus we have found that upon thermolysis at 60-75°C 3 can methylenate aldehydes (4) and ketones, including aryl ketones (5), cyclic ketones,  $\alpha,\beta$ -unsaturated ketones (6) and easily enolizable ketones (7).



The reagent also cleanly methylenates carboxylic esters (**8, 9**) and lactones (**12, 13**) to give the corresponding enol ethers, which can be isolated without an aqueous work-up. For this reason, even highly labile enol ethers can be synthesized with this method. More functionalized derivatives, such as  $\alpha,\beta$ -unsaturated esters (**10, 11**) and lactones (**14**), as well as vinylogous esters and cyclobutenedione derivatives (**15**) are also smoothly methylenated.

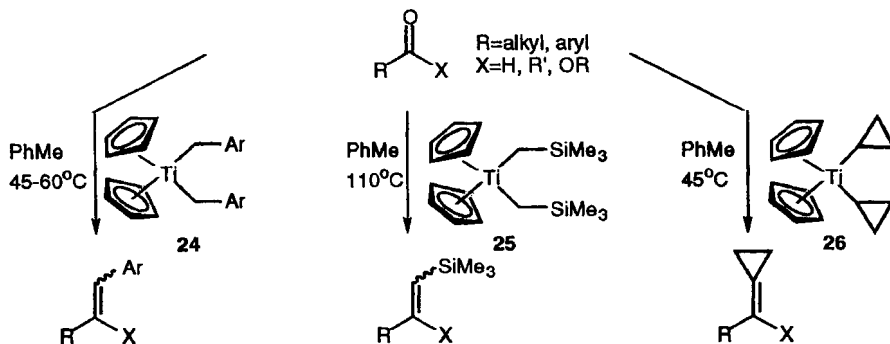


A variety of other heteroatom-substituted olefins are also converted to synthetically useful olefinic products. These include: silyl esters (**16**), thioesters (**17**), selenoesters (**18**) and acylsilanes (**19**). Similarly, anhydrides (**20**), carbonates (**21**), amides (**22**) and imides (**23**) give the corresponding enol ethers or enamines. In the case of anhydrides and imides excess of the reagent gives the bis-methylenation products, while smaller amounts give primarily the monomethylenation product. Some compounds prepared in this manner are highly labile and extra precautions to avoid hydrolysis have to be employed. Alternatively, the crude products can be used directly in subsequent reactions, such as hydroborations, hydrogenations, etc.

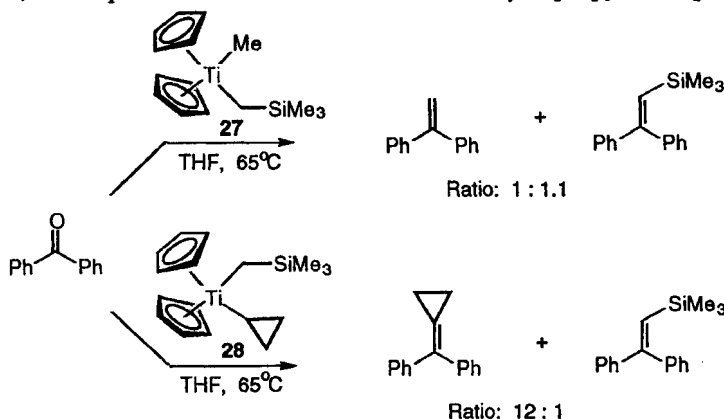


### Carbonyl olefinations with other titanocene derivatives

Several other dialkyltitanocenes were also shown to exhibit similar olefinating ability. Thus, dibenzyl titanocenes (**24**) give phenyl-substituted olefins,[5] bistrimethylsilyltitanocene (**25**) gives vinylsilanes,[6] while the biscyclopropyltitanocene (**26**) gives cyclopropylidenes.[7]

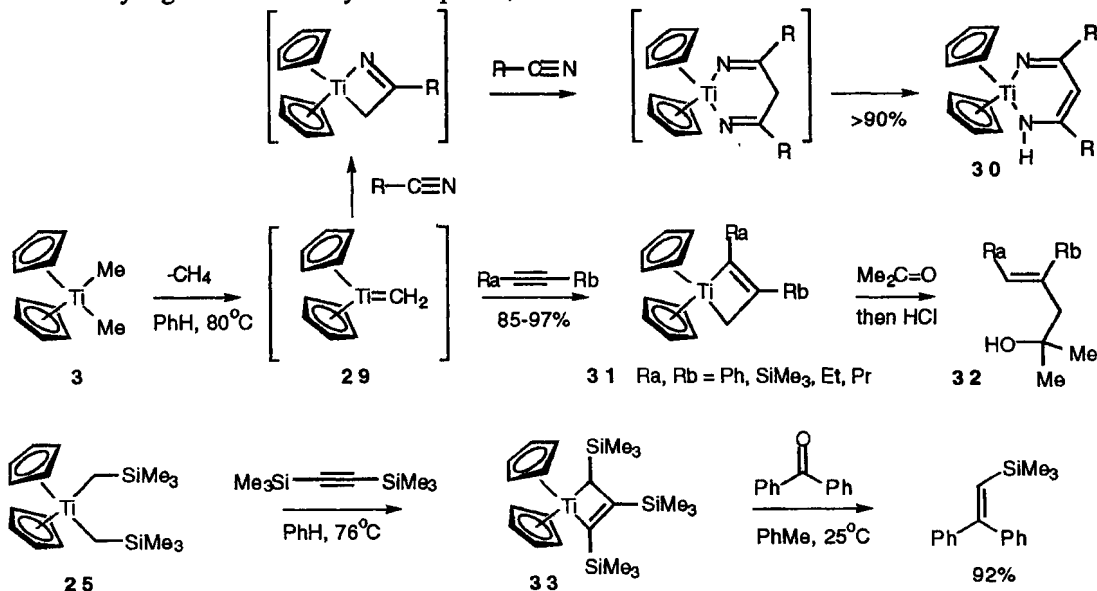


Surprisingly, the mixed titanocene **27** does not olefinate in a selective manner, despite an apparent electronic and steric difference among the methyl and trimethylsilylmethyl groups. The mixed cyclopropyl titanocene **28**, however, shows preference for the formation of the cyclopropylidene products.



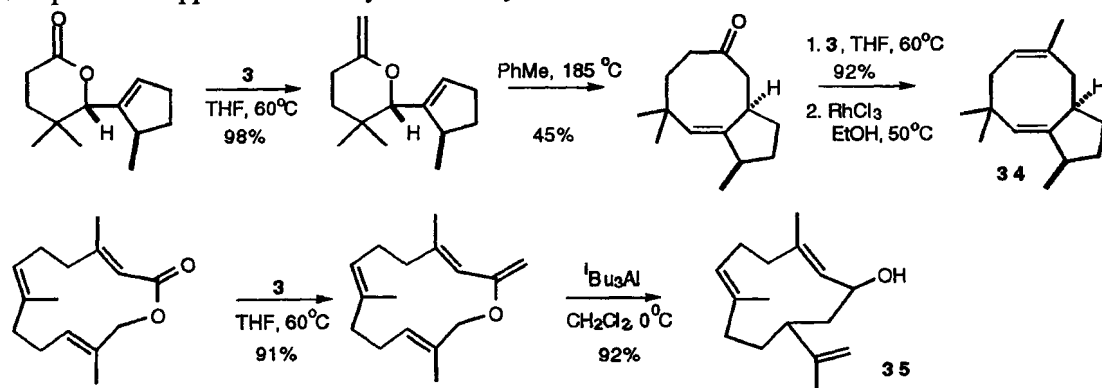
### Reactions with alkynes, nitriles and strained alkenes

While other mechanisms can be postulated, the methylenation process most likely proceeds via the titanocene methylenide intermediate (**29**) generated during the thermolysis of **3**. The coordination of the substrate to the titanium prior to the loss of methane is also possible. Although the formation of **29** has not been confirmed, this species can also explain the formation of adducts **30** during the reaction of **3** and nitriles,[8] the clean conversion to titanacyclobutenes (**31**) during the reaction with alkynes,[8] and the ability of **3** to serve as an initiator of ring-opening metathesis polymerization of strained alkenes.[9] Interestingly, while **31** undergo insertion processes with carbonyls forming homoallylic alcohols (**32**), the similar adducts **33**, derived from **25**, are efficient olefinating agents even at room temperature. Presumably loss of the acetylene moiety regenerates the alkylidene species, which carries out the olefination.

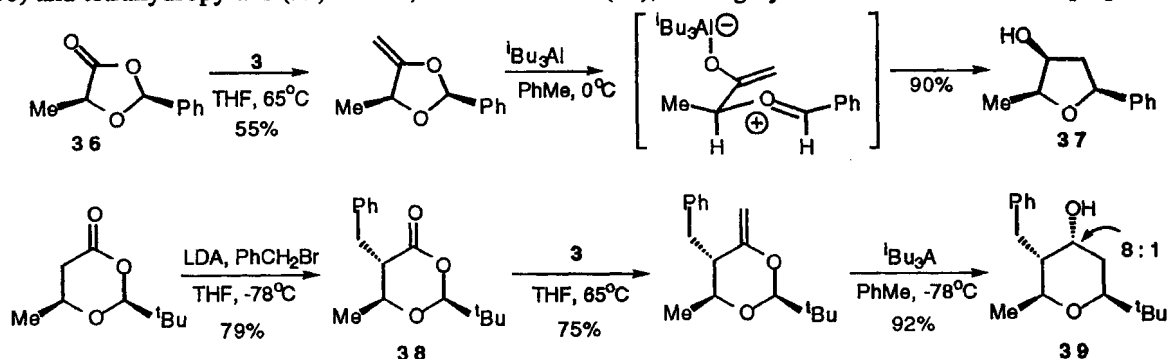


## Synthetic applications

Following our initial disclosure of methylenations with **3**, several synthetic applications have appeared in the literature by us [10, 11] and others [12]. Thus, in combination with a [3,3]-sigmatropic rearrangement, this process is applicable to the synthesis of cyclooctanoids (**34**) [10] and cembranoids (**35**) [11].



We have also developed a novel synthesis of heterocycles involving carbonyl olefination followed by aluminum-mediated [1,3]-rearrangement. This process gives tetrahydrofurans (**37**) from 1,3-dioxolan-4-ones (**36**) and tetrahydropyrans (**39**) from 1,3-dioxan-4-ones (**38**), in a highly stereocontrolled manner [13].



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