Organic Reactions

VOLUME 43

Organic Reactions

VOLUME 43

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PREFACE TO THE SERIES

In the course of nearly every program of research in organic chemistry the investigator finds it necessary to use several of the better-known synthetic reactions. To discover the optimum conditions for the application of even the most familiar one to a compound not previously subjected to the reaction often requires an extensive search of the literature; even then a series of experiments may be necessary. When the results of the investigation are published, the synthesis, which may have required months of work, is usually described without comment. The background of knowledge and experience gained in the literature search and experimentation is thus lost to those who subsequently have occasion to apply the general method. The student of preparative organic chemistry faces similar difficulties. The textbooks and laboratory manuals furnish numerous examples of the application of various syntheses, but only rarely do they convey an accurate conception of the scope and usefulness of the processes.

For many years American organic chemists have discussed these problems. The plan of compiling critical discussions of the more important reactions thus was evolved. The volumes of *Organic Reactions* are collections of chapters each devoted to a single reaction, or a definite phase of a reaction, of wide applicability. The authors have had experience with the processes surveyed. The subjects are presented from the preparative viewpoint, and particular attention is given to limitations, interfering influences, effects of structure, and the selection of experimental techniques. Each chapter includes several detailed procedures illustrating the significant modifications of the method. Most of these procedures have been found satisfactory by the author or one of the editors, but unlike those in *Organic Syntheses* they have not been subjected to careful testing in two or more laboratories.

Each chapter contains tables that include all the examples of the reaction under consideration that the author has been able to find. It is inevitable, however, that in the search of the literature some examples will be missed, especially when the reaction is used as one step in an extended synthesis. Nevertheless, the investigator will be able to use the tables and their accompanying bibliographies in place of most or all of the literature search so often required.

Because of the systematic arrangement of the material in the chapters and the entries in the tables, users of the books will be able to find information desired by reference to the table of contents of the appropriate chapter. In the interest of economy the entries in the indices have been kept to a minimum, and, in particular, the compounds listed in the tables are not repeated in the indices.

The success of this publication, which will appear periodically, depends upon the cooperation of organic chemists and their willingness to devote time and effort to the preparation of the chapters. They have manifested their interest already by the almost unanimous acceptance of invitations to contribute to the work. The editors will welcome their continued interest and their suggestions for improvements in *Organic Reactions.*

Chemists who are considering the preparation of a manuscript for submission to *Organic Reactions* are urged to write either secretary before they begin work.

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CONTENTS

CHAPTER PAGE

1. Carbonyl Methylenation and Alkylidenation Using Titanium-Based Reagents
Stanley H. Pine 1

2. Anion-Assisted Sigmatropic Rearrangements
Stephen R. Wilson 93

3. The Baeyer–Villiger Oxidation of Ketones and Aldehydes
Grant R. Krow 251

Cumulative Chapter Titles by Volume 799

Author Index, Volumes 1–43 811

Chapter and Topic Index, Volumes 1–43 815

CHAPTER 1

CARBONYL METHYLENATION AND ALKYLIDENATION USING TITANIUM-BASED REAGENTS

STANLEY H. PINE

Department of Chemistry and Biochemistry, California State University, Los Angeles, California

CONTENTS

	PAGE
INTRODUCTION	2
MECHANISM AND STEREOCHEMISTRY	3
SCOPE AND LIMITATIONS	4
Methylenation of Esters	4
Alkylidenation of Esters	5
Reactions with Other Carboxylic Acid Derivatives	6
Methylenation of Ketones and Aldehydes	7
Alkylidenation of Ketones	9
Functional Group Selectivity	9
OTHER ALKYLIDENATION METHODS	10
REACTION CONDITIONS	10
EXPERIMENTAL PROCEDURES	11
(5′-*tert*-Butyl-1′-cyclohexenyl)methyl 2-(1-Butenyl) Ether (Methylenation of an Ester Using the Tebbe Reagent **1**)	11
3-Benzyloxy-1-phenyl-1,3-butadiene (Methylenation of a Conjugated Ester Using the Tebbe Reagent **1**)	12
1-Phenoxy-1-phenylethene (Methylenation of an Ester Using the in situ Tebbe Reagent **1**)	12
5-(3′-Benzyloxypropyl)-1,2-dimethyl-4-methylene-3,9-dioxabicyclo[4.2.1]nonane (Methylenation of a Lactone Using the Tebbe Reagent **1**)	12
3,4-Dihydro-2-methylene-2*H*-1-benzopyran (Methylenation of a Lactone Using the in situ Tebbe Reagent **1**)	13
2-Methoxy-1-trimethylsilyl-1-tridecane (Alkylidenation of an Ester Using a Modified Takai Reagent **5**)	13
4-Phenyl-1-methylidenecyclohexane (Methylenation of a Ketone Using the in situ Tebbe Reagent **1**)	14
2,6-Dimethylmethylidenecyclohexane (Methylenation of a Hindered Ketone Using the Tebbe Reagent **1**)	14
3-Methylene-*p*-menthane (Methylenation of a Ketone Using the Lombardo Modification **3**)	14

Organic Reactions, Vol. 43, Edited by Leo A. Paquette et al.
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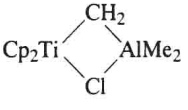
2-(*tert*-Butyldimethylsiloxy)-4a-methyl-3-(1-methylethylidene)-5-methylene-3,4,4a,5,6,7,8,8a-octahydronaphthalene (Methylenation of a Hindered Ketone Using the Lombardo Modification **3**) 15
8-*tert*-Butyldimethylsilyloxy-1-[(2-methoxyethoxy)methoxy]-4-methylene-1α,2,3,3aα,4,5,8β,8aα-octahydroazulene (Methylenation of an Enolizable Ketone Using the Lombardo Modification **3**) 15
trans-3,4-Diphenyl-1-methylidenecyclopentane (Methylenation of a Ketone Using Takai Reagent **3** Prepared from Diiodomethane) 16
3,3-Dimethyl-1,1-diphenyl-1,4-pentadiene (Alkylidenation of a Ketone with a Metallacycle **2**) 16
TABULAR SURVEY 16
Table I. Methylenation of Esters 18
Table II. Methylenation of Ketones 35
Table III. Methylenation of Aldehydes 68
Table IV. Methylenation of Amides 72
Table V. Alkylidenation of Esters 75
Table VI. Alkylidenation of Ketones and Aldehydes 83
Table VII. Alkylidenation of Amides 86
REFERENCES 87

INTRODUCTION

Alkylidenation of the carbonyl group of ketones and aldehydes is among the most useful reactions of organic synthesis. The Wittig reaction of phosphoranes is probably the most widely used method of alkylidenation,[1-4] although a variety of other approaches have been developed to accomplish this transformation.[5-8]

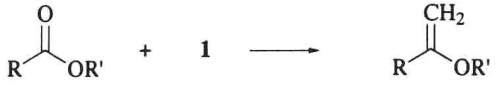
The observation that titanium-based reagents can accomplish such a transformation[9-11] has provided a new approach to alkylidenation. Not only do these reagents accomplish alkylidenation of the carbonyl group of aldehydes and ketones, but they are also effective with esters,[10,12-14] lactones,[10,15,16] amides,[12,17] thioesters,[18] and certain other carboxylic acid derivatives.[19,20] Alkylidenation of the carbonyl group of carboxylic acid derivatives cannot normally be accomplished by the Wittig reaction.[21,22]

Initial interest in the reaction focused on methylenation using the titanium–aluminum complex known as the Tebbe reagent **1**.[9]

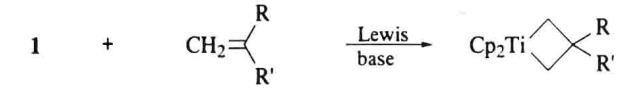


1

Pine, Grubbs, Evans, and co-workers explored the reactions of **1** with carboxylic esters and observed their conversion to enol ethers in high yield.[9,10,12]



Furthermore, **1** was also found to methylenate aldehydes and ketones, sometimes more effectively than the Wittig method.[23,24] The related titanium metallacycles **2**, which are prepared from **1** and an alkene in the presence of a Lewis base,[25] accomplish similar alkylidenations.[15]



2

During the same period Takai and co-workers reported a still undefined reagent **3** prepared from zinc, a dihalomethane, and titanium tetrachloride that was shown to methylenate aldehydes and ketones.[11] Modification of this mixture provides a reagent that accomplishes methylenation and alkylidenation of carboxylic acid derivatives.[14,18,19,26] An alternative preparation of **3** by Lombardo[27,28] has also received wide use.

$$Zn—CH_2X_2—TiCl_4$$

3

Reagents for carbonyl alkylidenation involving titanium–magnesium,[29] zirconium,[30,31] tantalum,[32] tungsten,[33,33a] molybdenum,[34–37] boron,[38] and chromium[39] have also been studied, but none has found such broad use in synthesis as **1** and **3**.

MECHANISM AND STEREOCHEMISTRY

The structure of the Tebbe reagent (**1**) is well established as a titanium–aluminum metallacycle. It is the bridging methylene that is transferred to the carbonyl.[9] The reactive species is believed to be the titanium methylidene **4** generated when a Lewis base (LB) complexes with the aluminum atom of **1**.[9,15,40]

$$1 + LB \longrightarrow [Cp_2Ti = CH_2] + (CH_3)_2ClAl \cdots LB$$

4

The titanium methylidene **4** and some homologs have also been generated thermally from the titanium metallacycles **2**.[15]

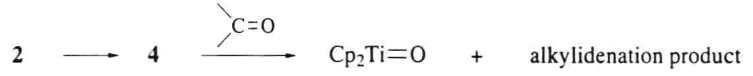
Intermediate **4** is very reactive and has never been isolated or observed spectroscopically.[41,42] However, **4** has been observed as a tetrahydrofuran complex[43] and isolated as its phosphine complex[40,44–46] Homologous phosphine complexes are known,[47] although their use in alkylidenation has not been reported. Intermediate **4** is generally classified as a nucleophilic carbene in an operational description of its reactivity.[32,48]

In contrast to **1** and **2**, there appears to be little information about the species involved in the reagent mixture **3**. It is generally considered to be a *gem*-dimetal-

lamethane.[11,49-53] Here, functional group specificity seems to depend on reaction conditions,[18,19] and even on the mode of preparation of the reagent.[27,28]

In the absence of an added Lewis base, reaction of **1** with an ester such as methyl benzoate proceeds slowly ($t_{1/2} \approx 1$ hour) to produce the enol ether. The reaction is first order in reagent and first order in ester. The large negative entropy value for this reaction suggests that a complex intermediate forms which then leads to product.[54] When a Lewis base is added to the reaction mixture, methylenation is quite rapid and is usually complete in minutes. In this case the Lewis base presumably complexes with the aluminum portion of **1** to free **4** for reaction with the carbonyl group. Ketones and amides react rapidly even in the absence of added Lewis base.

The metallacycles **2** react by a thermal process in which an alkene is eliminated to provide **4**.[40,55] It has been suggested that a driving force for alkylidenation of a carbonyl by **2** is the formation of titanocene oxide.[56]



Alkylidenation of a carbonyl group can give either *E* or *Z* stereoisomers. Within a limited number of experimental examples, the *Z* isomer generally predominates. This result has been observed for esters,[14,50] ketones,[14] thioesters,[18] and silyl esters.[19] By contrast, amides lead predominately to *E* enamines.[18] In all of these classes of compounds the degree of stereoselectivity is variable and appears to be related to the size of the groups surrounding the carbonyl.[18]

SCOPE AND LIMITATIONS

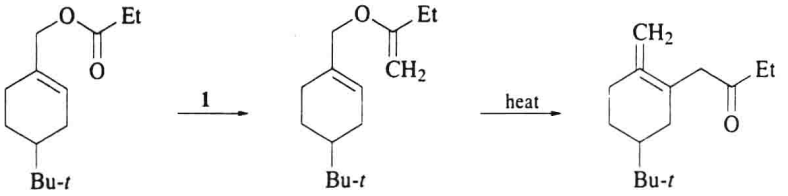
These titanium-based reagents were initially explored to supplement the Wittig alkylidenation. The Wittig reaction has some synthetic limitations. Wittig reagents do not alkylidenate the carbonyl group of esters and other carboxylic acid derivatives; the reaction rate is low because of steric hindrance at the carbonyl, and there is a tendency for enolization to occur with certain substrates.

Methylenation of Esters

Reagent **1** converts esters to enol esters in high yield.[9,10,12] Metallacycles **2**, though not widely used, also acomplish the same transformation.[15] Reagent **1** provides the only one-step synthesis of a vinyl ether from an ester. It reacts with a large variety of substrates including aromatic, aliphatic, and cyclic esters (lactones) as well as formates, carbonates, silyl esters, and thioesters.

In addition to the isolation and use of enol ethers as synthetic products, one useful application associated with **1** is the ability to convert esters with an appropriately po-

sitioned double bond to products derived from a subsequent electrocyclic rearrangement.[13,57–63] In some reactions Claisen rearrangement occurs without isolation of the enol ether intermediate.[57,61,63] It has been suggested that the aluminum- or titanium-containing byproducts function as Lewis acid catalysts for the rearrangement.



The $Zn–CH_2X_2–TiCl_4$ mixture **3** has had very limited use for ester methylenation.[13,57,64]

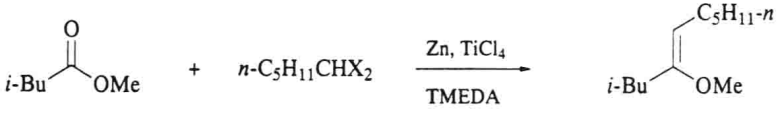
Alkylidenation of Esters

Reagents **1** and **2** only accomplish methylenation of the ester carbonyl group. However, the use of 1,1-dihaloalkanes instead of dihalomethanes in the preparation of **3** leads to a new reagent **5** that accomplishes general alkylidenation of esters.[14] Tetramethylethylenediamine (TMEDA) is required, and the reagents are mixed in a different order than that used for **3**.

$$Zn—RCHX_2—TiCl_4—TMEDA$$

5

One may speculate that TMEDA complexes with the metal of the mixture to enhance reactivity toward an ester carbonyl group. The process produces mixtures of geometrical isomers in which the *Z* stereoisomer predominates.[14,50] The difficulty in forming the requisite dihaloalkanes can be the limiting step in such an application.



An intramolecular ester alkylidenation was used in a synthesis of capnellene.[65,66] A titanium metallacycle **2** was formed from a norbornene derivative containing an ester by using **1** in the presence of *p*-dimethylaminopyridine (DMAP). The strained alkene of norbornene formed a particularly stable metallacycle,[66] while the hindered *endo-tert*-butyl ester did not react with **1**. Subsequent heating of the metallacycle

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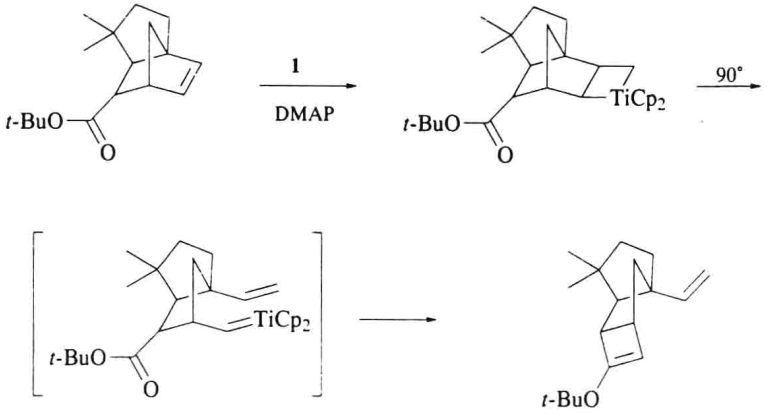
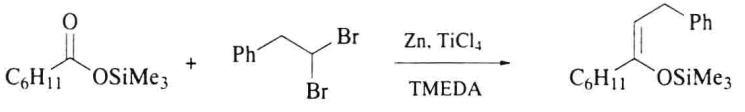
derivative generated the titanium alkylidene which then accomplished an intramolecular alkylidenation of the ester.

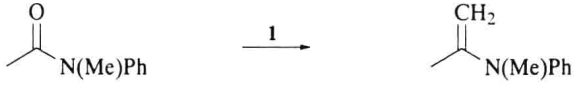


Reactions with Other Carboxylic Acid Derivatives

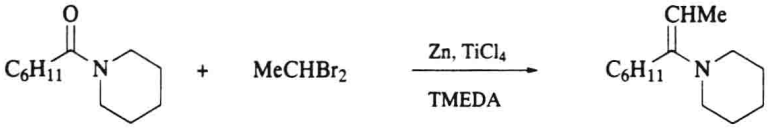
Silyl esters and thioesters react with **1**[67] and **5**[18,19] to produce the corresponding enol ethers by a process similar to that discussed above for esters.



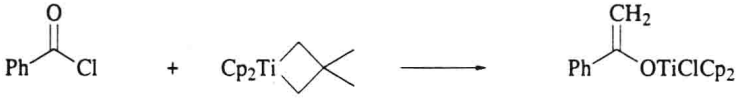
Amides react with **1** to give methylenenamines.[12]



The method provides an attractive alternative to established methods of enamine formation.[68-70] Difficulty in recovery of unstable enamines is often a limitation of the procedure. However, alkylation of the enamine formed with **1** can, in principle, provide the product of amide alkylidenation. There is one report of an amide alkylidenation using **5**.[18]



Acyl halides react with **1** or **2** to give titanium enolates rather than the chlorovinyl products expected from carbonyl methylenation.[71-73] The alternative sequence has been attributed to the lability of the halide in an initially formed titanium oxametallacycle. This route to titanium enolates and their subsequent alkylation does have synthetic utility.[73]

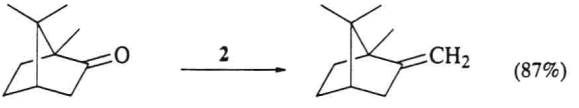


2

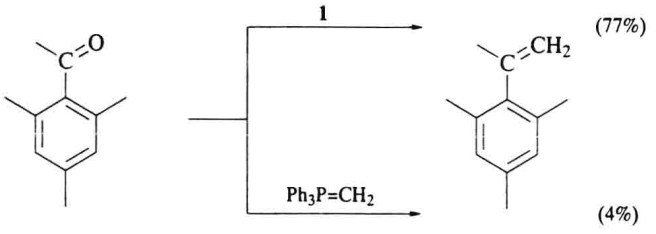
Anhydrides and imides follow pathways similar to that of an acyl halide in their reaction with **1** or **2**,[20] although the synthetic utility of this chemistry has not been explored.

Methylenation of Ketones and Aldehydes

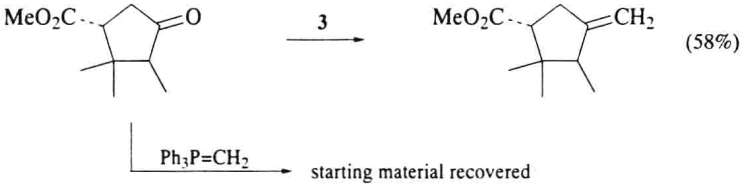
The principal use of these titanium reagents has been for the methylenation of ketones and aldehydes, a process that duplicates the classical Wittig procedure with methylenetriphenylphosphorane. Reagents **1**, **2**, and **3** have shown general utility with a large variety of structures. Reagent **3** has had the broadest range of applications with ketones and aldehydes since it does not react with esters and appears to be more tolerant than **1** or **2** toward the presence of other functional groups. The reagents generally react more rapidly than the analogous Wittig reagent and have proven particularly useful for transformations that cannot be accomplished satisfactorily by the Wittig reaction.



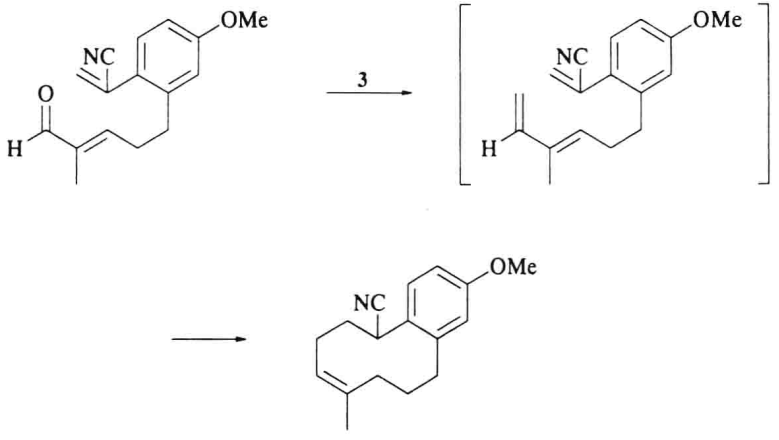
Steric hindrance is one of the factors that severely limits the Wittig methylenation.[7,74,75] In a study that compared the effectiveness of **1** with methylenetriphenylphosphorane for ketone methylenation, it was found that the titanium reagent is markedly superior to the Wittig reagent when the carbonyl group is hindered.[23]



The basic nature of Wittig reagents and most of the processes that involve an elimination step to accomplish alkylidenation[5,7,76] can limit effective reaction with enolizable ketones. This problem is commonly associated with the acidity of the substrate or with steric hindrance that inhibits reaction at the carbonyl.[57] By contrast the titanium reagents have proven particularly effective for the methylenation of enolizable ketones.[24,27,77-82]



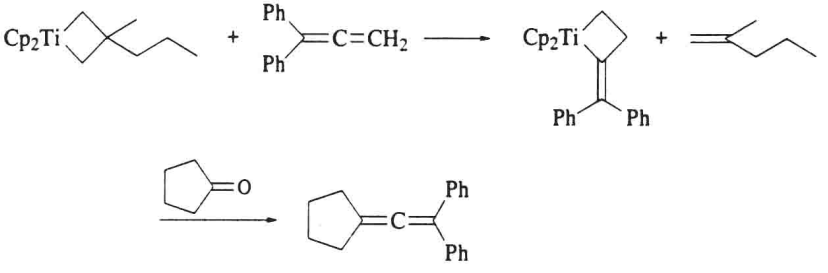
Methylenation of aldehydes has been carried out using all of the titanium reagents discussed above. In one example, reaction of **3** with an unsaturated aldehyde proceeded through a diene that underwent a Diels–Alder cyclization.[62]



Alkylidenation of Ketones

A significant limitation to the use of the titanium reagents **1**, **2**, and **3** is that they only accomplish methylenation of a ketone. Attempts to form higher homologs of the titanium–aluminum metallacycle following the synthesis model for **1** are not successful. This has been attributed to decomposition by β-hydride elimination.[30,83] Homologs of **1** have been prepared by hydroalumination of an alkenyltitanium,[30] hydrotitanation of an alkenylalane,[84] methyltitanation of an alkynylalane,[85] and from a divinyltitanocene.[86] These potential reagents for carbonyl alkylidenation have not yet been used in synthesis.

A clever approach to alkylidenation involves exchange of one alkylidene group of the titanium metallacycle for another using an allene, and then allowing the new metallacycle to alkylidenate a ketone.[87] A new allene is formed.

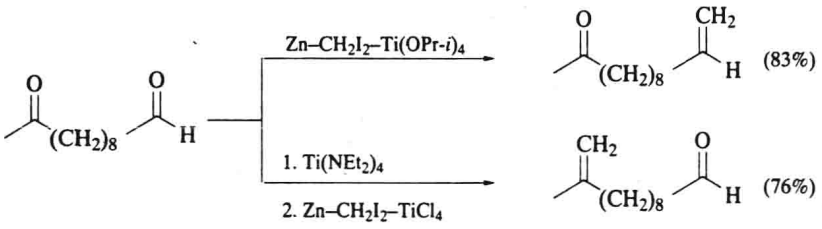


Although alkylidenation of esters and amides has been accomplished through the modified reagent **5** generated from a 1,1-dihalo compound, there are no published reports of similar alkylidenation being carried out with aldehydes or ketones.[88]

Functional Group Selectivity

Reagents **1** and **2** methylenate the carbonyl group of aldehydes, ketones, esters, and amides. Ketones and amides react with **1** more rapidly than esters so that it is often possible to selectively methylenate only one functional group.[12,89] However, the reactivity differences are not great, and unless a functional group is hindered,[66,89] it may be advisable to protect one of the groups while the other undergoes reaction. Reagent **1** reacts with acidic hydrogens such as those on alcohols or carboxylic acids, and those functional groups usually should be protected.

Reagent mixture **3** is selective for ketones and aldehydes, hence methylenation is effective in the presence of esters[77,90–95] and hydroxy groups.[96–99] An interesting modification of **3** allows selective reaction of an aldehyde in the presence of a ketone by using $Ti(OPr\text{-}i)_4$ instead of $TiCl_4$.[51] Furthermore, reaction of a ketone in the presence of an aldehyde can be accomplished by first complexing the aldehyde carbonyl with $Ti(NEt_2)_4$, then using reagent **3**.[51]



Reagent **1** reacts with carbon–carbon double bonds to form metallacycles,[25] but at a rate that is slower than its reaction with a carbonyl group. Although there is the potential for interaction of **1** with a double bond in the substrate that could lead to *E-Z* or positional isomerization, this has generally not been a problem.[10,12] A few examples of positional isomerization have been reported[100–102] but appear to be due to residual metals or the presence of a proton source.

OTHER ALKYLIDENATION METHODS

Direct alkylidenation of the carbonyl group of carboxylic acid derivatives was not a viable synthetic operation prior to the availability of **1**.[21,22,103] However, many methods had been developed for alkylidenation of aldehydes and ketones. The most widely used is the Wittig reaction using phosphoranes[1] and related phosphonates.[104,105] The Wittig method is often unsuccessful when the carbonyl group is sterically crowded,[7,74,75,106] and its basic condition can lead to enolization or epimerization of the substrate.[57,78,80] Modifications to the preparation of the phosphorus ylides have minimized some of these problems.[107–110]

A variety of methods have been developed which involve addition of an anionic reagent to the carbonyl carbon, then elimination of the alcohol intermediate. Like the Wittig reaction, most of these involve basic reaction conditions and can result in enolization. These anionic reagents include trimethylsilylmethylmagnesium chloride,[5] trimethylsilylmethyllithium,[111] trimethylsilylmethyllithium–cerium trichloride,[112] trimethylsilylbenzyllithium,[113] phenylthiomethyllithium,[7] triphenylstannylmethyllithium,[6] sodium phenylselenide,[114] 1-lithioalkyldimethylphosphonothionates,[76] lithioalkylphenylphosphinothioic amides,[8] and methylphenylsulfonimidoylmethyllithium.[115]

REACTION CONDITIONS

The Tebbe reagent **1**, a deep red moisture-sensitive solid, can be prepared in advance of its use[9] since it is stable indefinitely as a dry solid or as a homogeneous solution in toluene or benzene. It it available commercially and is usually used in stoichiometric quantities.

In situ methods for preparation of the reagent have also been developed to simplify its use,[72,100,116,117] although yields of the methylenation product are generally lower than those obtained by using the pure reagent. The metallacyclic analogs **2** of **1** are prepared from **1**[25] and are reported to be more air stable than **1**. They usually

must be heated to provide the active alkylidene. Their use in synthesis has been rather limited.

Because of its sensitivity to moisture, **1** is handled by common inert atmosphere techniques.[118] Solvents and apparatus should be dry. Solvents are usually dried and freed of oxygen by distillation from sodium–benzophenone ketyl.[119] In some reactions, base washing of apparatus to remove acid residues has led to enhanced yields.[100]

Reagent mixture **3** (and **5**) is normally prepared in situ as needed for use. It is a dark viscous material that is only partially soluble in the solvents usually used for reaction (tetrahydrofuran and dichloromethane). Methods involving a three-day preparation[28] or a 15 to 30-minute preparation[11] are both in general use, although the longer period is reported to provide better results.[28] The methylene reagent **3** slowly decomposes at room temperature but can be stored for up to one year at $-20°$.[28] Reactions are usually carried out using stoichiometric amounts of titanium tetrachloride relative to the carbonyl compound with excess zinc and dihalomethane.[28] In some cases large excesses of all reagents relative to the carbonyl are needed to provide good yields.[82,120,121] The zinc is usually activated by washing with hydrochloric acid[28,122] and in some cases purity of the zinc[16] and titanium tetrachloride[92] has proven important for good yields of product. Dry solvents and an inert atmosphere are used.

Purification of most of the products of these reactions involves chromatography to separate the inorganic residues from the organic product. Enol ethers may undergo hydrolysis or isomerization during chromatography by an acid-catalyzed mechanism. In this case, product stability is often enhanced by using basic alumina, and in some examples the eluent is saturated with trimethylamine.[12]

All of the titanium reagents mentioned above react with moisture. Residues from the reaction procedures can usually be destroyed by careful quenching with acetone. Aluminum-containing residues react more vigorously and are better destroyed with butanol.

EXPERIMENTAL PROCEDURES

(5′-*tert*-Butyl-1′-cyclohexenyl)methyl 2-(1-Butenyl) Ether (Methylenation of an Ester Using the Tebbe Reagent 1).[60] To a solution of 0.303 g (1.34 mmol) of 5-*tert*-butyl-1-cyclohexenylmethyl propanoate in 3 mL of THF cooled to $-40°$ was added 4.5 mL of a 0.33 M solution (1.48 mmol) of Tebbe reagent in toluene over a period of 3 minutes. After 1 hour at $-40°$, the reaction mixture was allowed to warm to room temperature and stirred further for 1.5 hours. The reaction was quenched with 0.5 mL of 10% aqueous sodium hydroxide, then diluted with 100 mL of diethyl ether. After drying with anhydrous sodium sulfate and filtering through Celite, the solvent was removed under vacuum. The product was purified by chromatography using alumina (activity III) with hexane as eluent. The enol ether, 0.257 g (86%), was recovered as a colorless oil (bp 60°, 0.1 torr). ^{1}H NMR ($CDCl_3$) δ 0.88 (s, 9H, $C(CH_3)_3$), 1.0–2.35 (m, 12H), 3.82 (br s, 2H, CH_2O), 4.05 (br s, 2H $C{=}CH_2$), 5.72 (br s, 1H, $C{=}CHC$).

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