

Cp₂TiCH₂ COMPLEXES IN SYNTHETIC APPLICATIONS

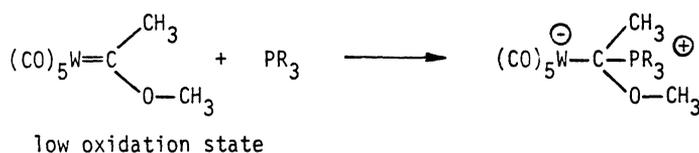
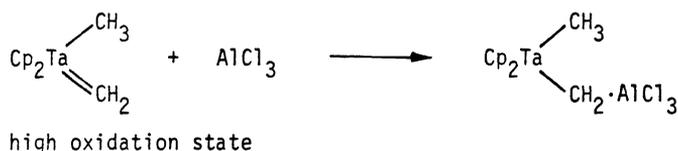
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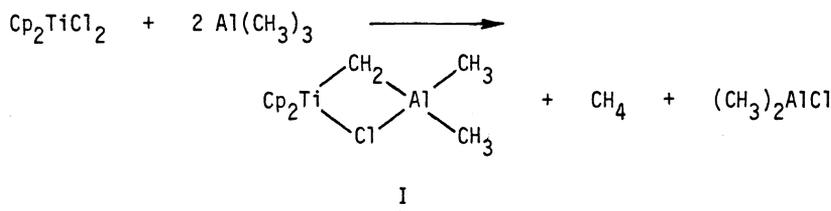
Abstract - The reactive 16e⁻ species Cp₂Ti=CH₂ can be generated in situ from either its aluminum alkyl adducts or olefin adducts (metallacyclobutanes). This complex reacts with a wide variety of unsaturated functionalities including >C=O, >C=C<, -C≡C- and -C≡N. In most instances the >C=O groups are methylenated. Key to the utility of these complexes is their lack of basic properties in contrast with phosphorous ylides; all of the normal "Wittig" side reactions are eliminated using these reagents. Acid chlorides and anhydrides are converted into enolate complexes, which can be used in aldol type chemistry. The combination of the reactivity toward C=O and C=C results in an efficient method for the conversion of unhindered carbonyl centers into quaternary carbon centers.

BACKGROUND

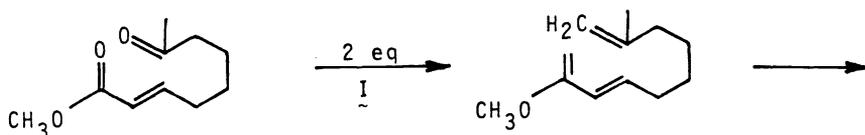
Alkylidene complexes of high oxidation state transition metals have been recognized for the past several years. They were first proposed as intermediates in numerous reactions (1), and have been isolated recently as tantalum (2), tungsten (3), and titanium (4) complexes. The low valent analogs prepared earlier show different types of reactions and trends in stability (5). The high oxidation state complexes



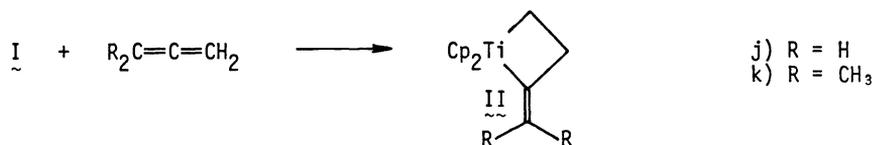
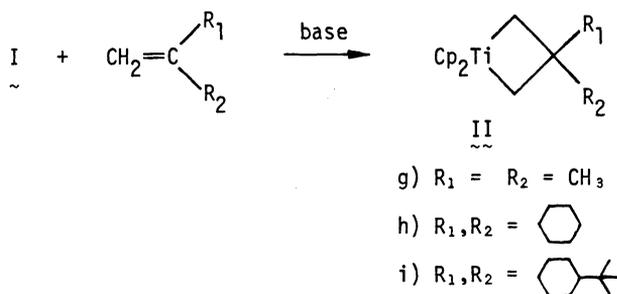
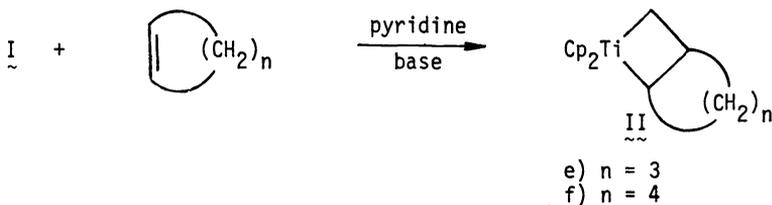
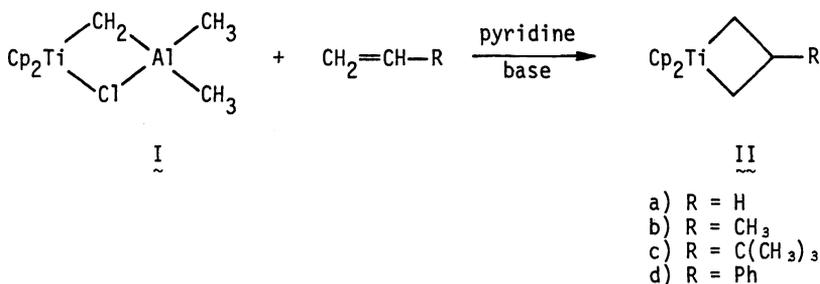
tend to be nucleophilic at carbon (5) while the low oxidation state systems are electrophilic (2-4). As a consequence of this polarization and the magnitude of the early metal to oxygen bond strengths, the high oxidation state systems act as powerful "Wittig" reagents. The most general reagent of this class is that prepared from titanocene dichloride and trimethyl aluminum, I (4).



This complex has been developed as a useful reagent for the conversion of esters into vinyl ethers (6). The reaction has been observed to be very general and is now being used in a number of complex syntheses by other groups (2). For example:

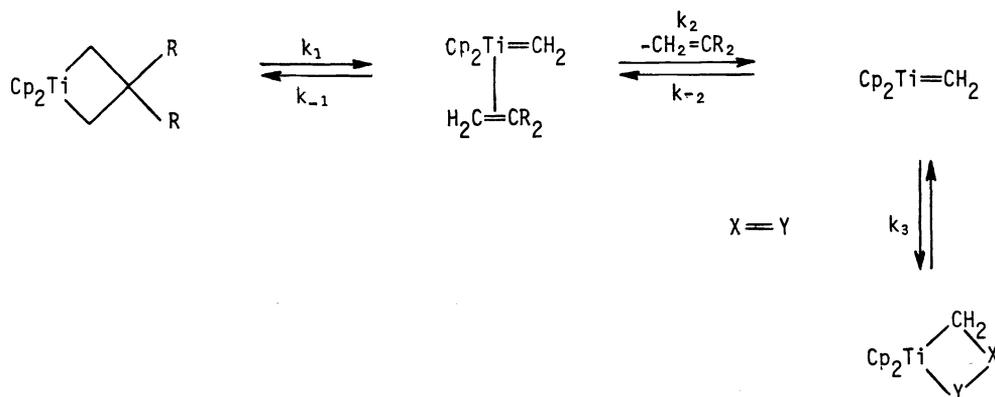


Reactions of I with olefins were studied as a part of our investigation of the mechanism of the olefin metathesis reaction (8). Unexpectedly, we found that a series of stable metallacycles (II) could be prepared from a wide range of olefins (9, 10).

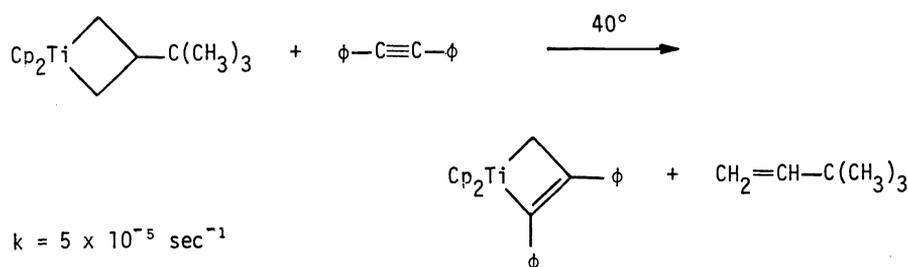


Early reactions carried out to define the reactivities of IIc and g have revealed that these metallacycles undergo three types of facile reactions with added reagents (9, 10): 1) X-Y reagents appear to replace the olefin in the cyclic structure; 2) Electrophiles cleave the Ti-C bonds; and 3) Oxidizing agents induce reductive elimination to form cyclopropanes. Most of these studies have been carried out with the metallacycle IIg derived from isobutylene. These are outlined in Scheme I.

Reactions of the first type have been studied in the most detail, since this is the key reaction in olefin metathesis (11). It also provides an aluminum-free source of the Cp₂TiCH₂ fragment for further synthetic reactions. Numerous labeling and kinetic studies suggest that these reactions proceed through the following basic steps (10, 11).



Most of the detailed studies have been carried out using the more stable (10) monosubstituted metallacycle. For example, the following reaction is 1st order in metallacycle and zeroth order in substrate. This suggests that k_1 is rate determining.



The rate at which the metallacycles undergo this reaction is determined by the substitution pattern. Thus, the Cp₂TiCH₂ species can be generated under a variety of conditions (10).

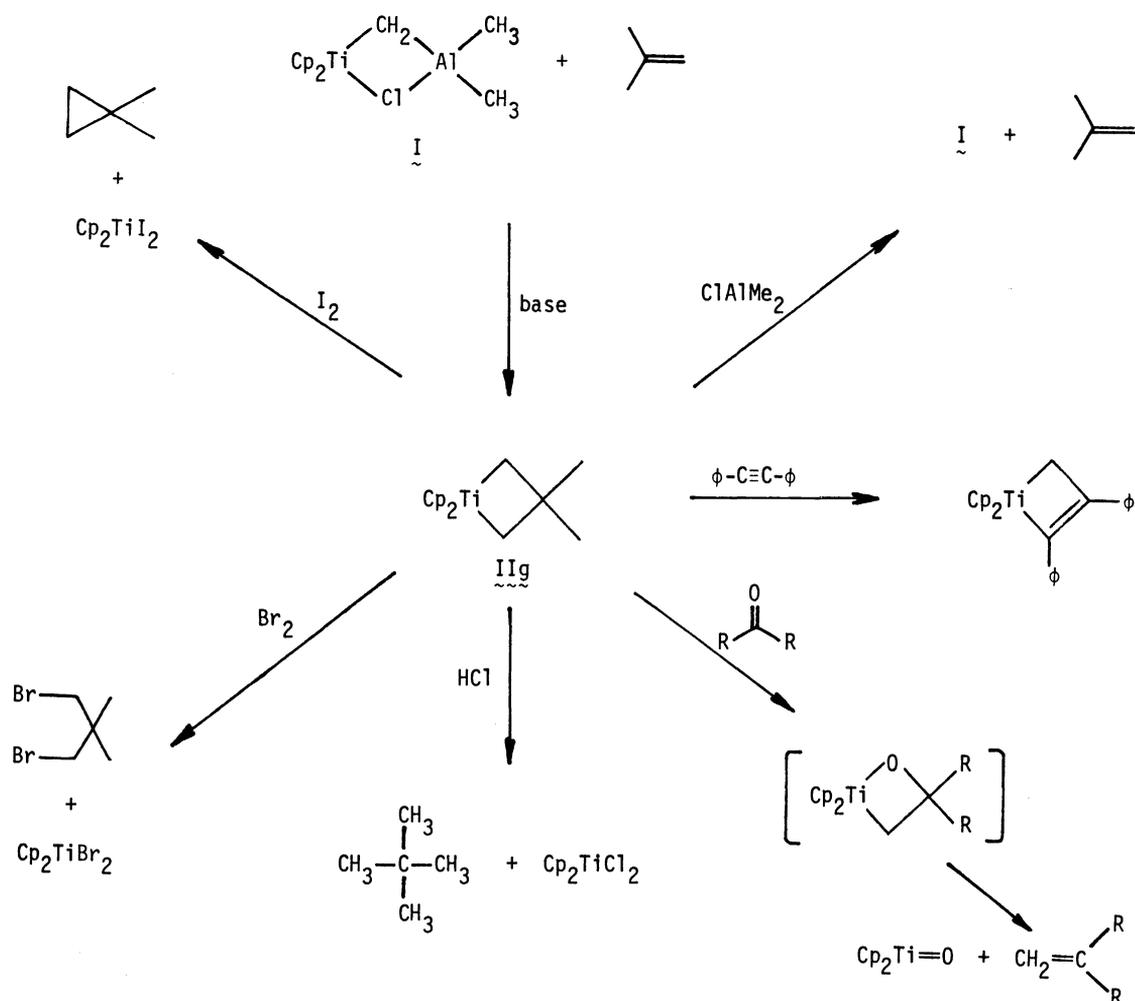
For most preparative applications, the metallacycle prepared from 2-methylpentene (12) is the reagent of choice. It is prepared readily as a crystalline solid by standard procedures using a liquid olefin.

An added virtue of the metallacycles is their stability to air. Crystalline samples of all of the metallacycles prepared to date can be handled in air for reasonable periods of time, a large improvement over the aluminum reagent.

TABLE I.

<u>Cp₂TiCH₂ Source</u>	<u>Temperature for Reaction</u>
$\text{Cp}_2\text{Ti}-\text{CH}_2-\text{AlClMe}_2 + \text{Base}$	-40°C
	5°C
	0°C
	45°C
	60°C

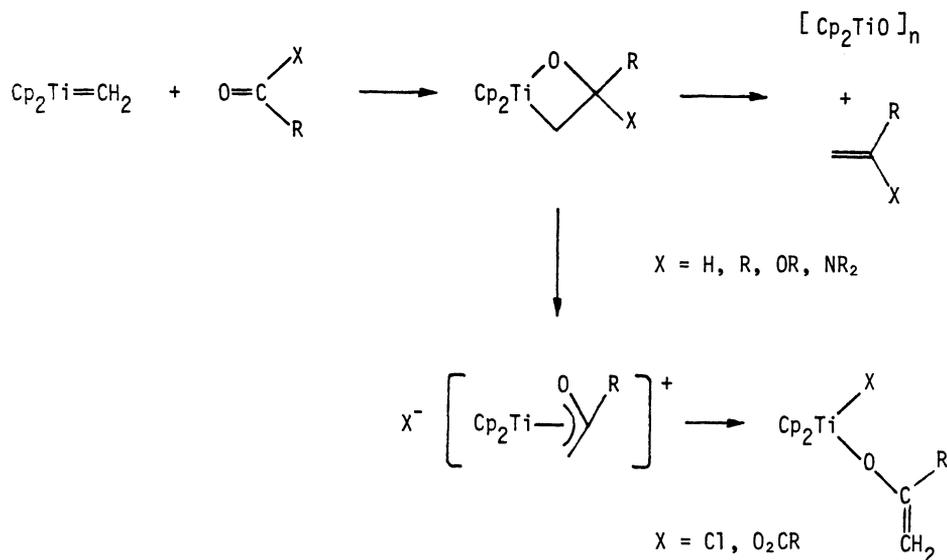
SCHEME I

REACTIONS OF FUNCTIONAL GROUPS WITH $\text{Ti}=\text{CH}_2$ Introduction

Two general classes of reactions of organic functional groups have been observed with the methylene reagents. With most carbonyl compounds, the carbonyl is converted to the corresponding methylene compound without a buildup of intermediates (13-15). At the other extreme, organometallic intermediates are generated when the " $\text{Ti}=\text{CH}_2$ " fragment reacts with olefins. These reactions show considerable potential in synthesis and are discussed below.

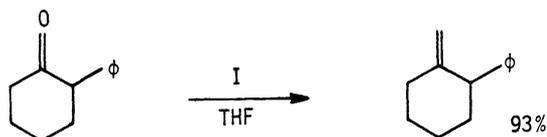
Carbonyl Reactions

Most functional groups containing a $\text{C}=\text{O}$ undergo clean $\text{C}=\text{C}$ forming reactions. There are two general types of products that have been observed with carboxylic acid derivatives: a) those in which the carbonyl oxygen is replaced by a methylene and b) those that replace the substituent on the carbonyl with methylene. The two best examples of these are esters which yield vinyl ethers (a reaction not possible using the Wittig synthesis) (6) and acid chlorides which are converted to enolates of methyl ketones (16). It is assumed that all of these reactions proceed through an oxy metallacycle intermediate. If one of the substituents on the β -carbon is a good leaving group, an enolate is produced. Otherwise, the oxy metallacycle cleaves to the "Wittig" product, driven by the generation of stable polymeric titanocene oxides. Those derivatives which have been found to fall in the "Wittig" class are ketones, aldehydes, esters and amides; whereas, acid chlorides and anhydrides yield enolates. Examples of these reactions for each carbonyl function and various Cp_2TiCH_2 sources are considered below.

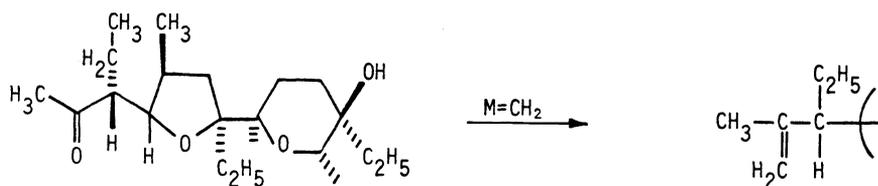


Ketones and Aldehydes. A number of phosphorous reagents are useful for methylenation of aldehydes and ketones (17). However, in many cases the reaction is of limited use. Since the reagents are basic, easily enolizable ketones often give poor yields of "Wittig" products and isotopic labels or asymmetric centers at the α -carbon are scrambled.

These "Cp₂TiCH₂" reagents do not appear to enolize ketones. Thus, optically active ketones and enolizable ketones can be converted to the corresponding methylene products in high yields. For example, 2-phenylcyclohexanone is methylenated with these reagents (18).



The retention of α -optical activity has been demonstrated by the Ireland group in one of their approaches to the right half of Lasalocid A (7b).

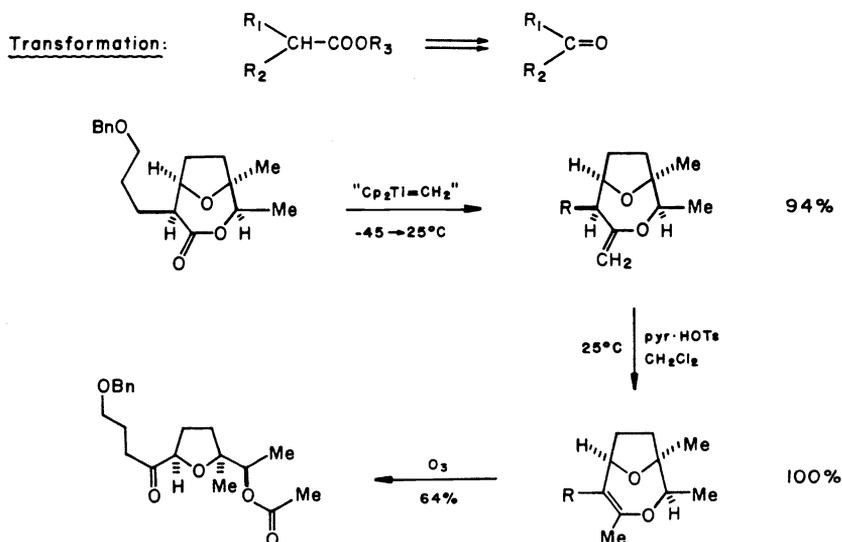


Cp₂Ti=CH₂ - 60-70% yield (rapid) - no isomerization of α center

$\phi_3\text{P}=\text{CH}_2$ - 20-30% yield (very slow) - mostly isomerized

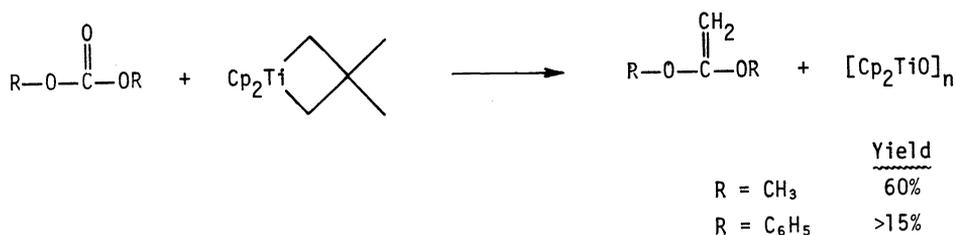
Esters and Lactones. This class of compounds has been studied in depth and provides most of the examples of methylenations of the "Wittig" type (phosphorous based reagents do not methylenate these compounds). Alkoxide (even phenoxide) is a sufficiently poor leaving group to afford high yields of vinyl ethers. A series of benzoic esters were investigated and little effect of the steric bulk of the alkoxy group was observed.

This reaction has been used in a variety of synthetic transformations (7). One of the more recent comes from the Evans group (7a). In this example, the reaction has been carried out on a multigram scale.

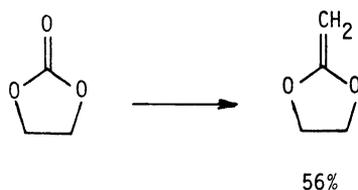


D. A. Evans, T. Shih

For some compounds the starting material and/or product are acid sensitive. In such cases the metallacycles are the reagents of choice. Valerolactone is rapidly polymerized by the Tebbe reagent (19). However, the expected methylenation product is obtained with the metallacycles (10, 12). Dimethyl carbonate gives methylenation products that are unstable in the presence of the aluminum reagent (19). Good yields of ketene ketals are obtained when a metallacycle is used (20).



The reaction is particularly effective with cyclic carbonates.

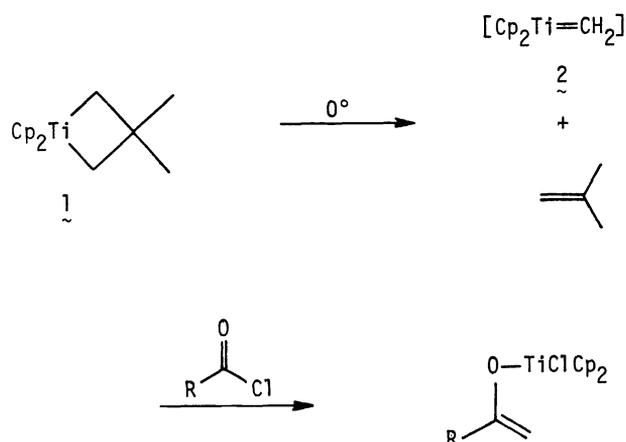


The products are isolated by distillation from the reaction mixture after filtration of the (Cp₂TiO)_n polymer.

Amides. Preliminary reactions of amides with the aluminum reagent appear to give enamines in high yields. However, difficulty is encountered in isolating the free base. Since aqueous workup is not required for the metallacycle reactions, these routes to enamines appear promising (10, 12).

Acid Chlorides and Anhydrides. These acid derivatives react with Cp₂TiCH₂ to produce enolates instead of the expected "Wittig" olefins (16, 21).

It has been demonstrated that a variety of acid chlorides can be converted into the enolates of the corresponding methyl ketone (16). Yields in these reactions as measured by protonolysis to the methyl ketone or by isolation of the enolates, are good to excellent in most cases.

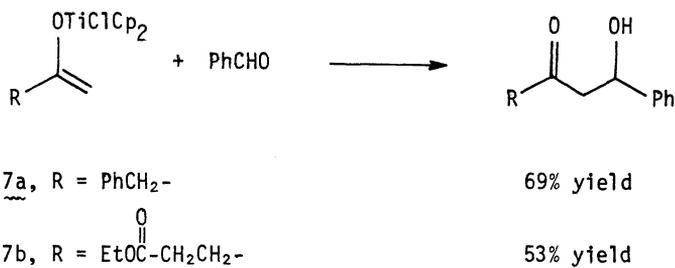


Yields of Methyl Ketones from Acid Chlorides

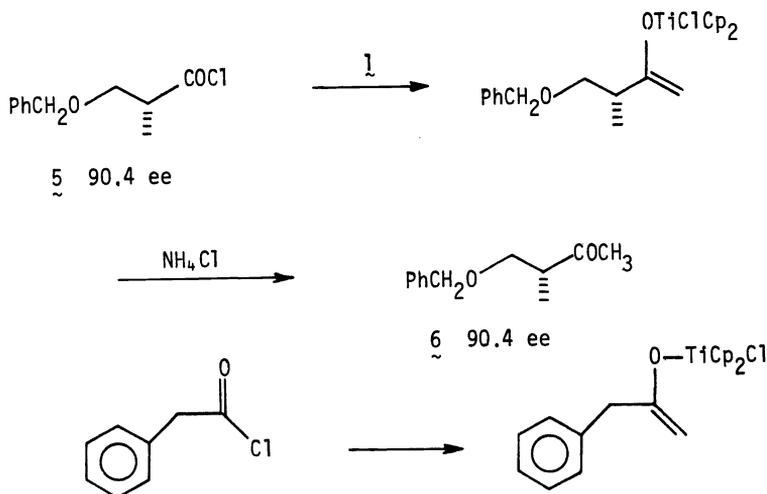
RC(O)Cl	RC(O)CH ₃ Yield, % ^a
benzoyl chloride	92 ^b
pivaloyl chloride	96 ^b
ethyl chloroformate	48 ^b
ethylsuccinyl chloride	89 ^b
phenylacetylchloride	97 ^b
3-phenylpropionylchloride	87 ^c
1-naphthoyl chloride	92 ^c
5	76 ^d

^aBased on the amount of acid chloride added.
^bYield was determined by quantitative VPC analysis. Product was characterized by VPC and ¹H NMR comparison with an authentic sample.
^cYield of isolated product from 1 mmol of acid chloride. Product was characterized by ¹H and ¹³C NMR comparison with an authentic sample.
^dYield of isolated product from 1 mmol of acid chloride. The reaction was quenched with saturated aqueous NH₄Cl. Product was characterized by ¹H NMR, ¹³C NMR, and IR spectroscopy in addition to comparison with an independently synthesized sample. The product produced satisfactory C,H analysis

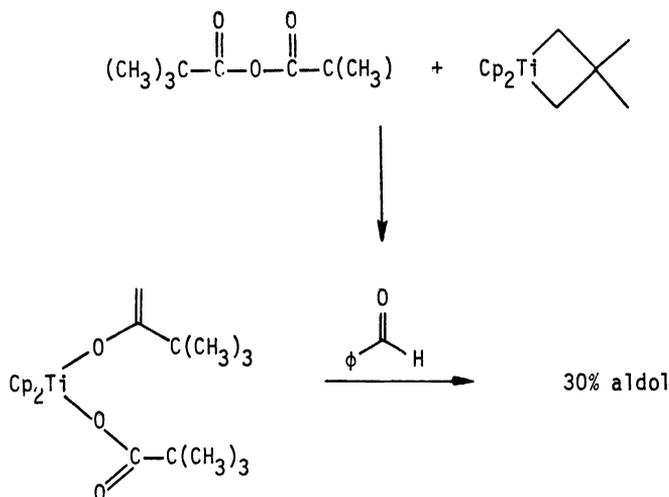
These can be used directly in aldol or other enolate reactions.



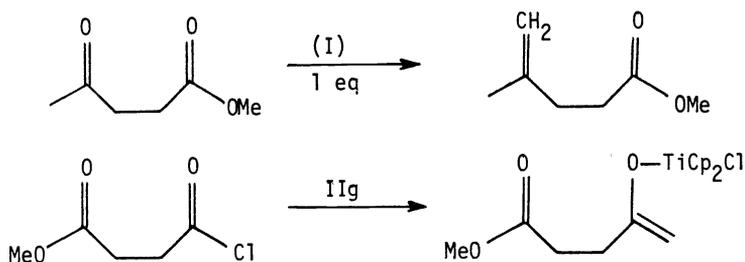
The enolates did not isomerize and could thus be used to generate enolates that were chiral at the α-center, and unstable regioisomers of enolates that are unavailable by other techniques.



Anhydrides produce enolates in lower yields than acid chlorides and the resulting carboxylate derivatives do not participate in normal aldol reactions (21).



Selectivity. In competition studies, the $\text{Cp}_2\text{Ti}=\text{CH}_2$ reagents show high selectivity in the cases studied to date. This selectivity is demonstrated in the following examples

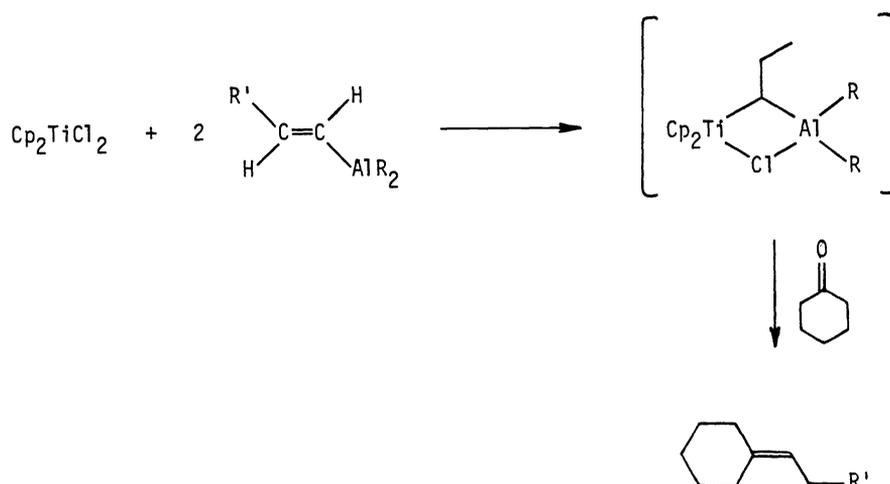
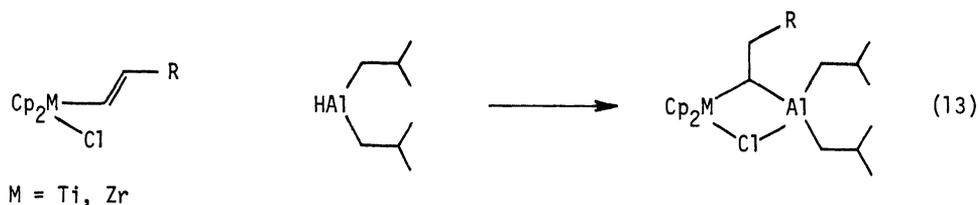
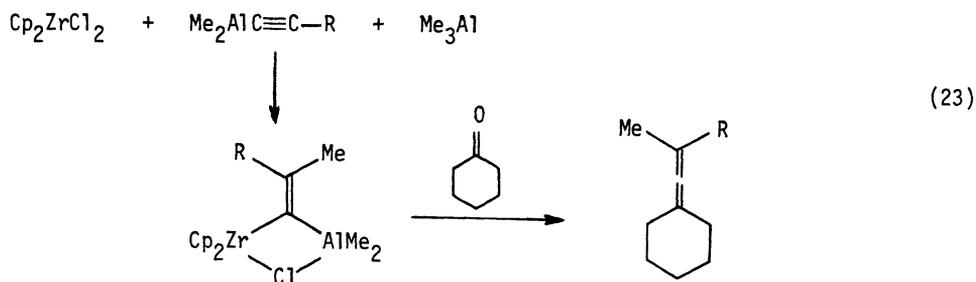


Other Functional Groups

Acetylenes, nitriles and imines undergo clean reactions with the $\text{Cp}_2\text{Ti}=\text{CH}_2$ reagents. The chemistry of these complexes has been described elsewhere (14, 22).

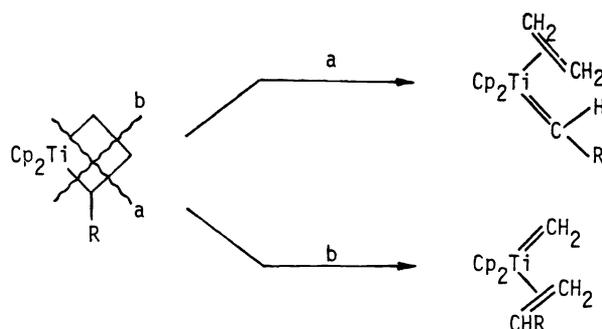
Substituted Reagents

The chemistry discussed earlier has all been carried out using the parent, unsubstituted complex. Sources of substituted analogs which would extend the usefulness of this chemistry are becoming available. In the group IV complexes, there are now three routes to substituted alkylidene complexes (13, 23).

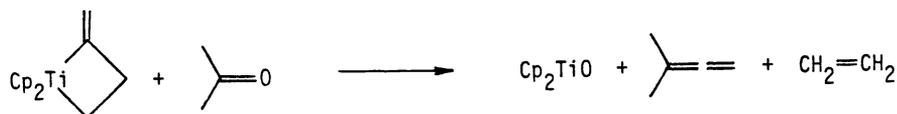


This last reaction, in which the reagent is poorly defined (24), will convert esters to vinyl ethers (25).

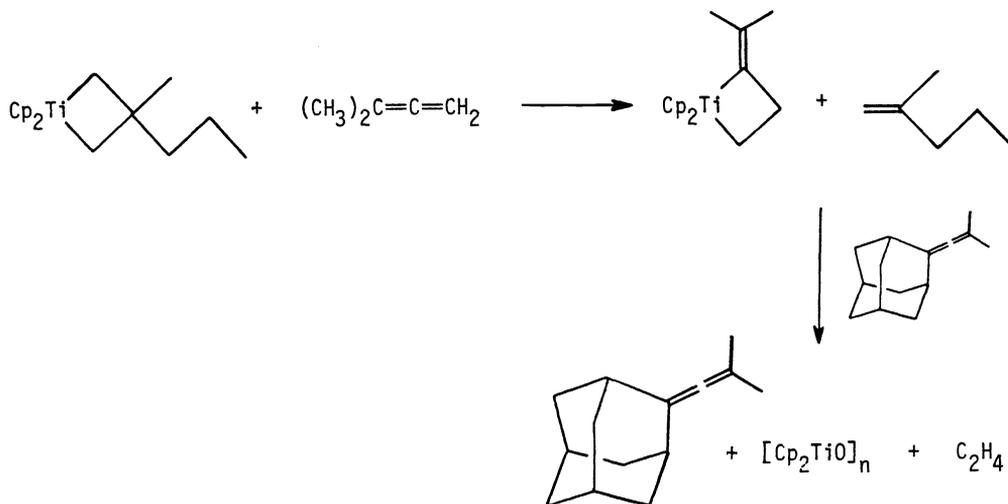
Metallacycle decomposition provides a very different route to such species. It has been demonstrated that the majority of the titanocene metallacycles produced to date decompose through a carbene-olefin complex (9, 10). These intermediates are excellent sources of the alkylidene fragment. Consequently, α -substituted metallacycles could be sources of substituted alkylidene fragments.



All, except one, of those α -substituted metallacycles available react mainly through path b. For steric and possibly electronic reasons, the less substituted alkylidene is usually favored. Only if the substituent is small and the functionalized olefin is destabilized, can path a dominate. This gives rise to reactive vinylidenes from the metallacycles derived from allenes, **IIj** and **k** (26),



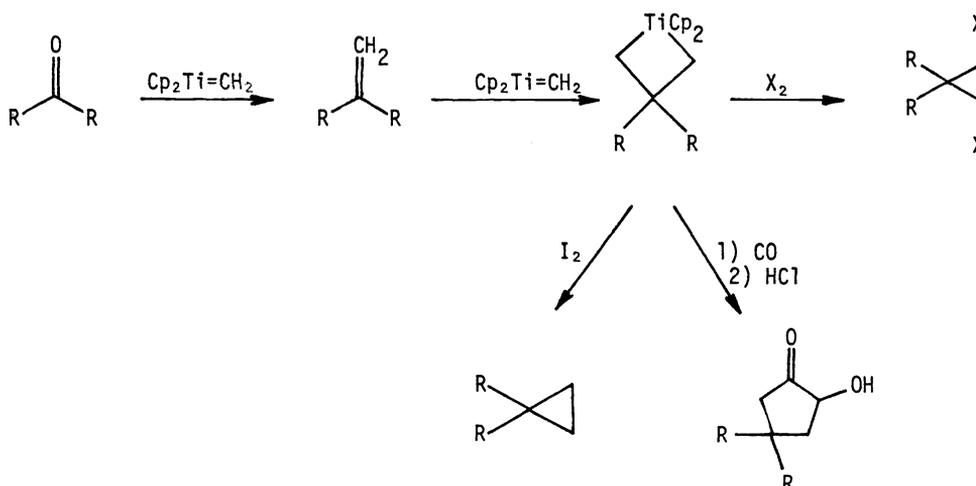
This reaction provides a facile one-pot synthesis of tetrasubstituted allenes.



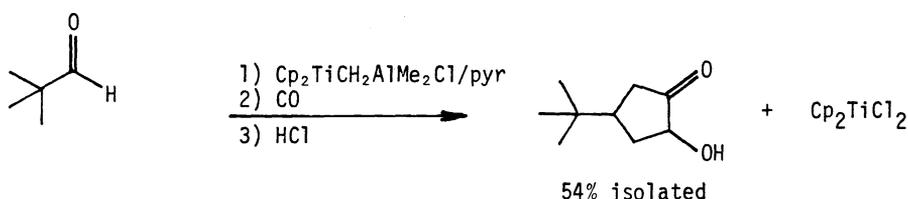
These reactions are carried out by treating a source of Cp₂TiCH₂ with the allene and adding this mixture to the ketone. After stirring overnight, filtration through silica and evaporation of the filtrate produces allenes of >95% purity in 60-80% yields.

Combined Carbonyl and Olefin Chemistry

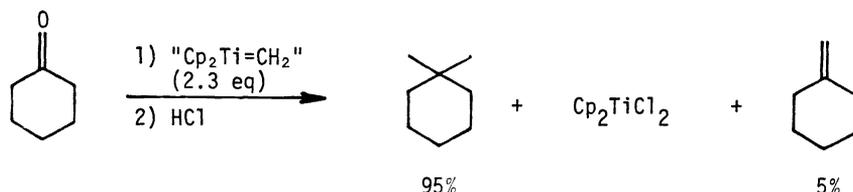
It has been demonstrated that the Cp₂Ti=CH₂ fragment will react with both olefins and carbonyl species. Thus the "Wittig" type olefin products can be converted *in situ* to a variety of functionalized products.



Combining these reactions results in a wide range of one-pot annelation procedures for ketones. In fact one cyclic acyloin synthesis has been carried out in overall 54% yield (27). This yield after minimum optimization suggests these reactions could provide extremely efficient routes to complex systems.



Protonolysis of the intermediate metallacycle results in the conversion of a ketone to a gem-dimethyl group. The use of the titanium methylene reagent is probably inferior in most cases to the route developed by Retz and coworkers (28). However, the Retz procedure appears to require the generation of carbonium ion intermediates and is most successful in highly alkylated systems. Since the methylene reagent is selective for less substituted olefins and can be generated under mild, almost neutral conditions it serves as a complementary reagent to the simple CH₃TiX₃ complexes used in the Retz transformation.



The major advantage of this reaction is the ability to convert a carbonyl into a quaternary center and retain functionality on the two added carbons. All of the chemistry of metallacycle transformations demonstrated with the olefins can be applied directly to ketones by the addition of a second equivalent of this reagent and base. Our present knowledge of metallacycle stability and the destabilization of metallacycles due to steric hindrance, suggests that these reactions will be limited to lightly substituted ketones (18).

CONCLUSIONS

The above examples provide abundant evidence that these reactions of alkylidenes and metallacycles will open some useful new approaches to C-C bond formation in organic synthesis.

Acknowledgment - The authors gratefully acknowledge the financial support of the National Science Foundation and the National Institutes of Health.

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