

Cp₂TiCH₂ COMPLEXES IN SYNTHETIC APPLICATIONS

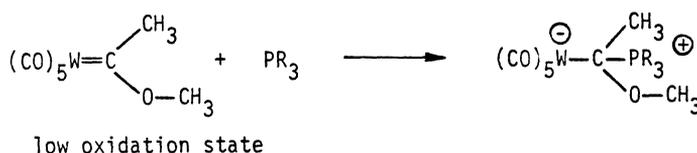
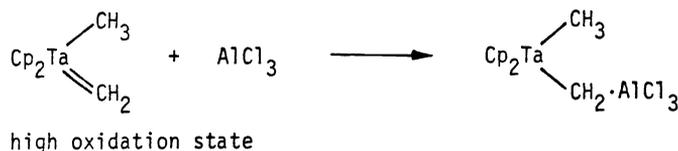
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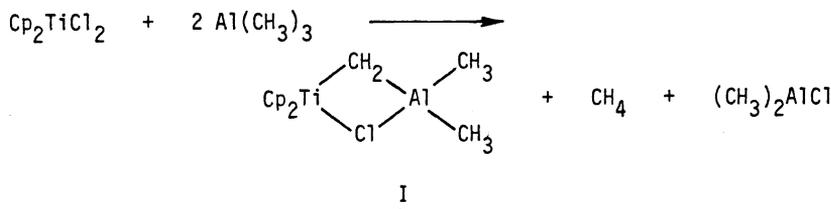
Abstract - The reactive 16e⁻ species Cp₂Ti=CH₂ can be generated in situ from either its aluminum alkyl adducts or olefin adducts (metallacyclobutanes). This complex reacts with a wide variety of unsaturated functionalities including >C=O, >C=C<, -C≡C- and -C≡N. In most instances the >C=O groups are methylenated. 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

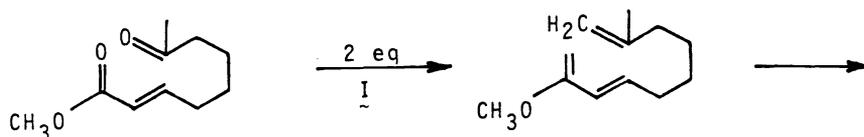
Alkylidene complexes of high oxidation state transition metals have been recognized for the past several years. They were first proposed as intermediates in numerous reactions (1), and have been isolated recently as tantalum (2), tungsten (3), and titanium (4) complexes. The low valent analogs prepared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



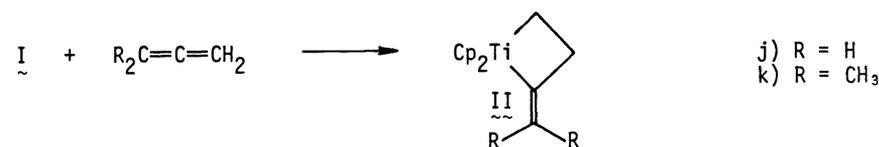
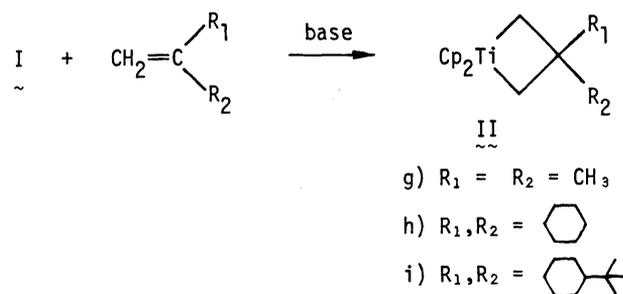
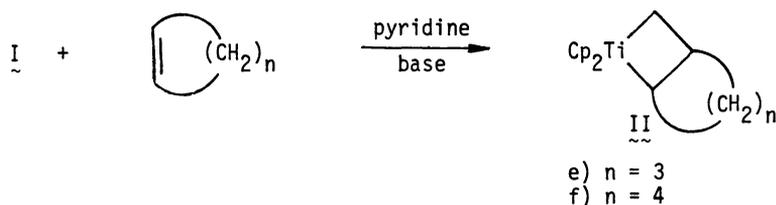
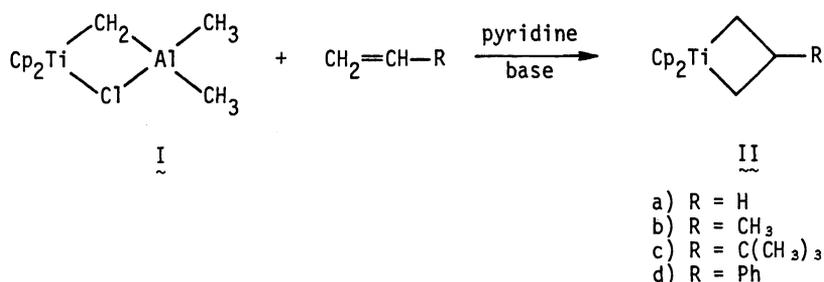
tend to be nucleophilic at carbon (5) while the low oxidation state systems are electrophilic (2-4). As a consequence of this polarization and the magnitude of the early metal to oxygen bond strengths, the high oxidation state systems act as powerful "Wittig" reagents. The most general reagent of this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

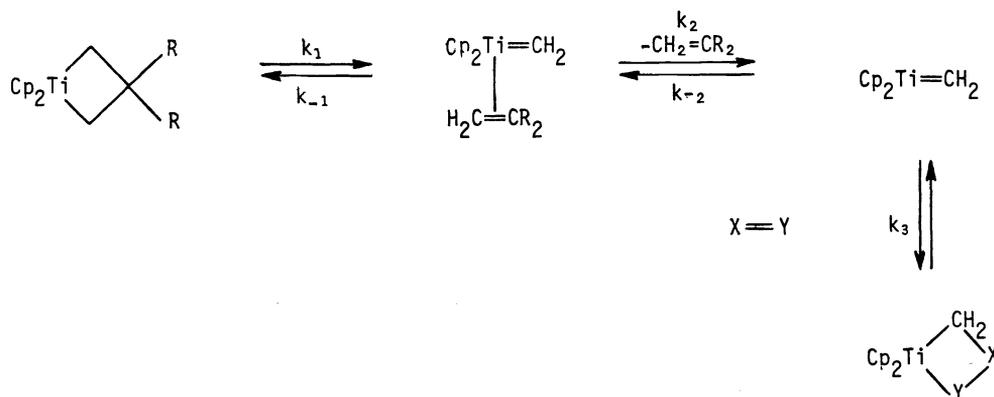


Reactions of I with olefins were studied as a part of our investigation of the mechanism of the olefin metathesis reaction (8). Unexpectedly, we found that a series of stable metallacycles (II) could be prepared from a wide range of olefins (9, 10).

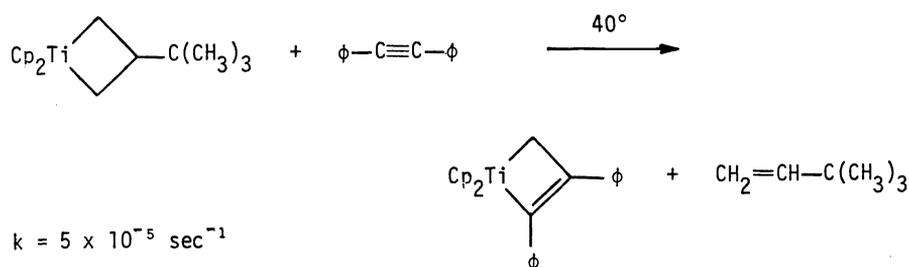


Early reactions carried out to define the reactivities of IIc and g have revealed that these metallacycles undergo three types of facile reactions with added reagents (9, 10): 1) X-Y reagents appear to replace the olefin in the cyclic structure; 2) Electrophiles cleave the Ti-C bonds; and 3) Oxidizing 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.



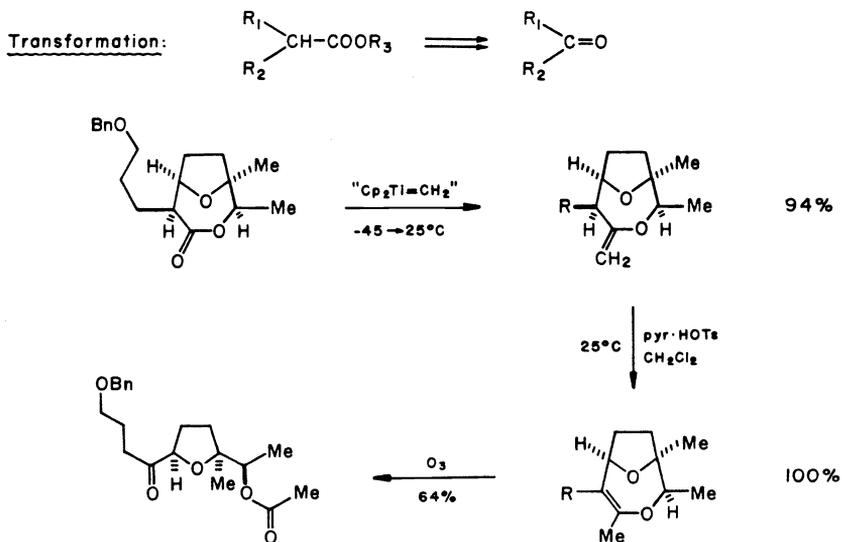
The rate at which the metallacycles undergo this reaction is determined by the substitution pattern. Thus, the Cp₂TiCH₂ species can be generated under a variety of conditions (10).

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.

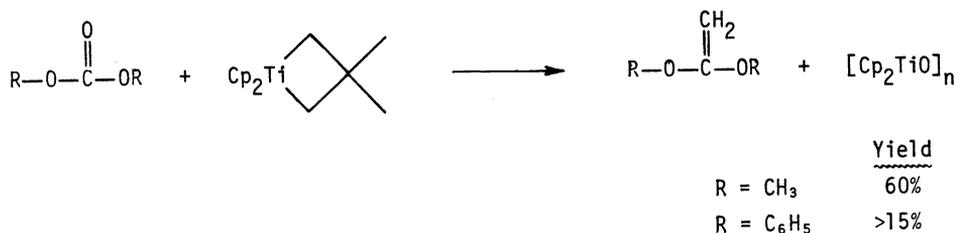
TABLE I.

<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

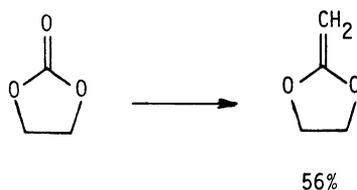


D. A. Evans, T. Shih

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.

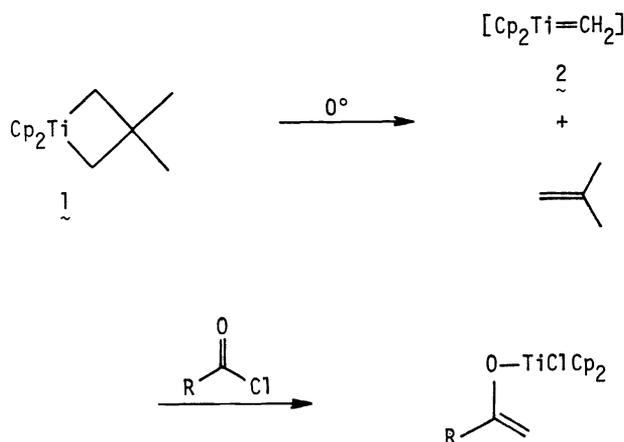


The products are isolated by distillation from the reaction mixture after filtration of the $(\text{Cp}_2\text{TiO})_n$ polymer.

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 Cp_2TiCH_2 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.

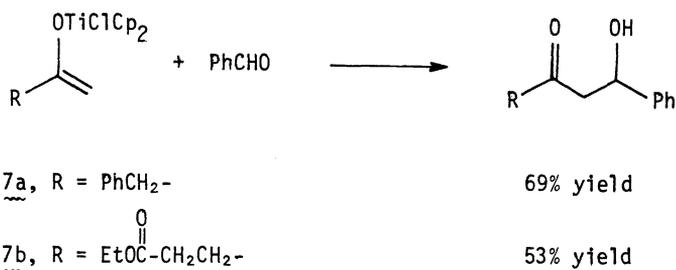


Yields of Methyl Ketones from Acid Chlorides

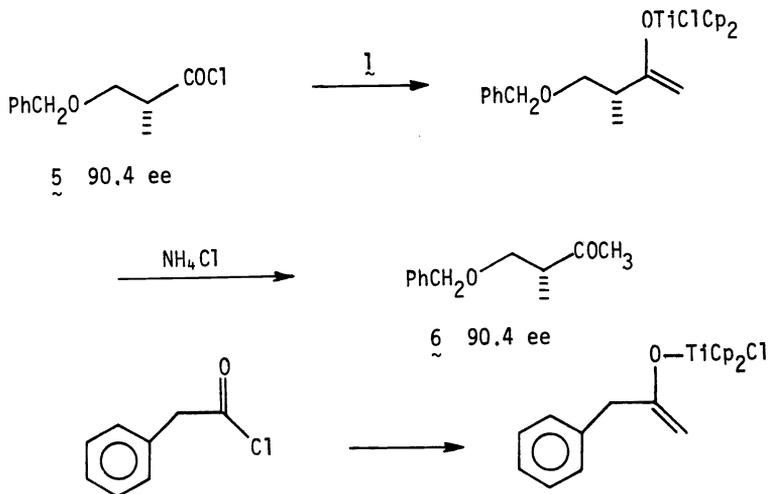
RC(O)Cl	RC(O)CH ₃ Yield, % ^a
benzoyl chloride	92 ^b
pivaloyl chloride	96 ^b
ethyl chloroformate	48 ^b
ethylsuccinyl chloride	89 ^b
phenylacetylchloride	97 ^b
3-phenylpropionylchloride	87 ^c
1-naphthoyl chloride	92 ^c
5	76 ^d

^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

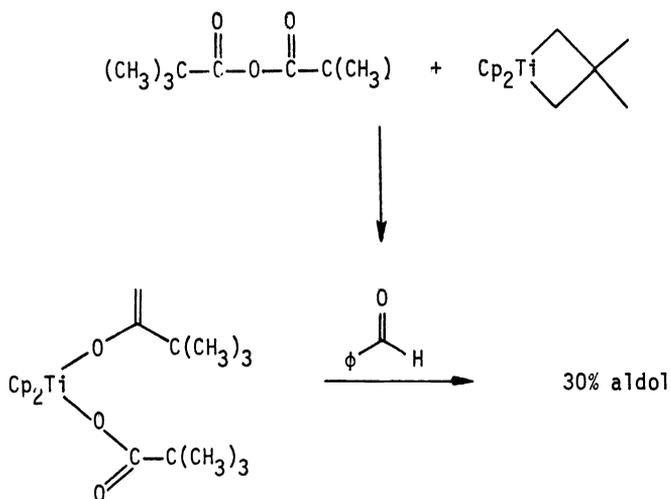
These can be used directly in aldol or other enolate reactions.



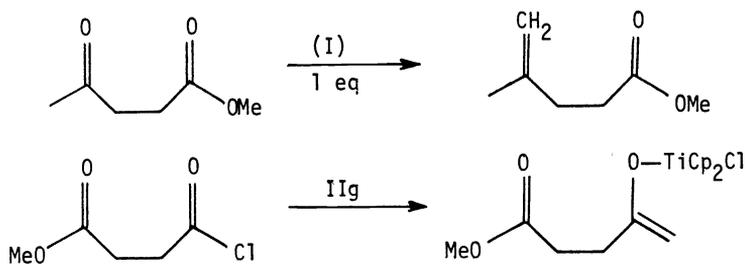
The enolates did not isomerize and could thus be used to generate enolates that were chiral at the α-center, and unstable regioisomers of enolates that are unavailable by other techniques.



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

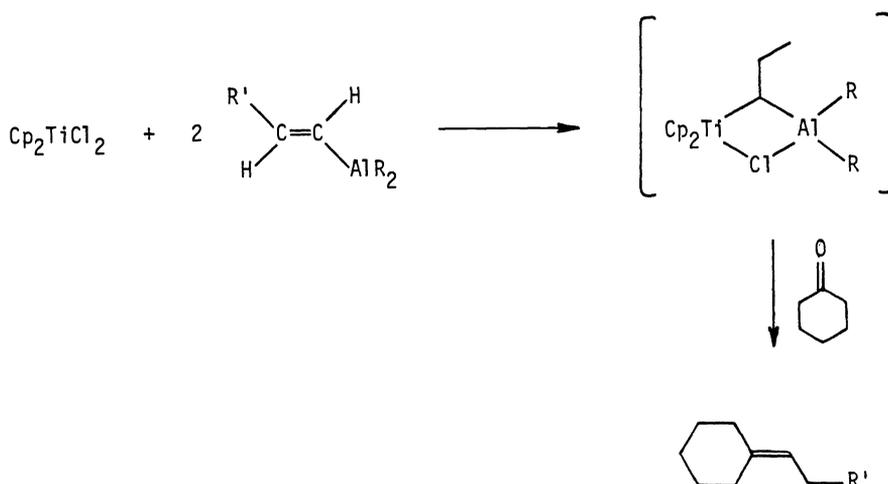
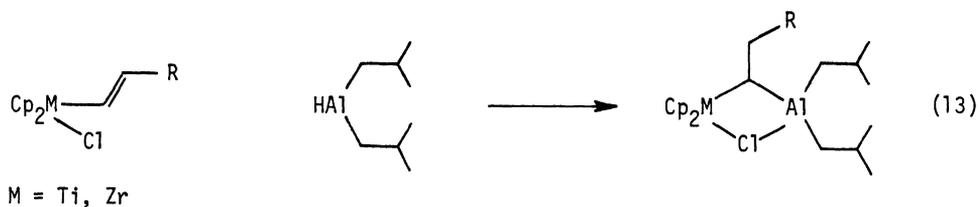
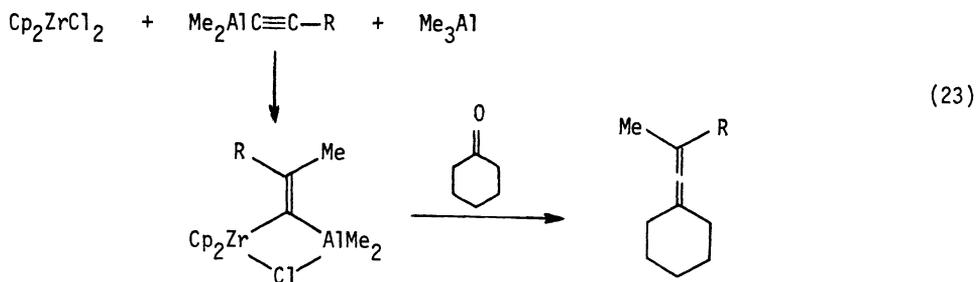


Other Functional Groups

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).

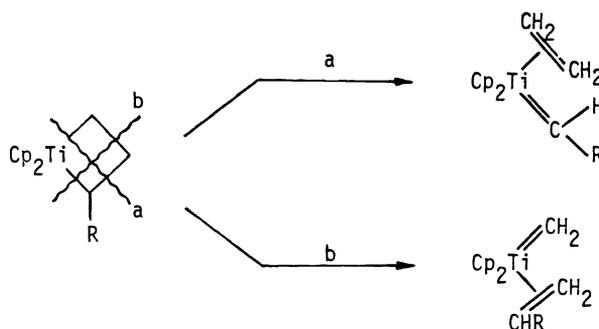
Substituted Reagents

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).

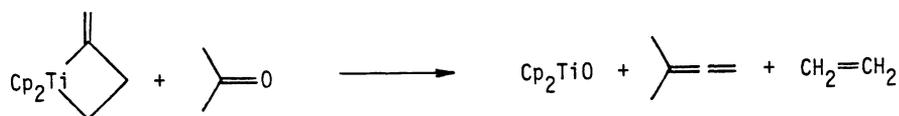


This last reaction, in which the reagent is poorly defined (24), will convert esters to vinyl ethers (25).

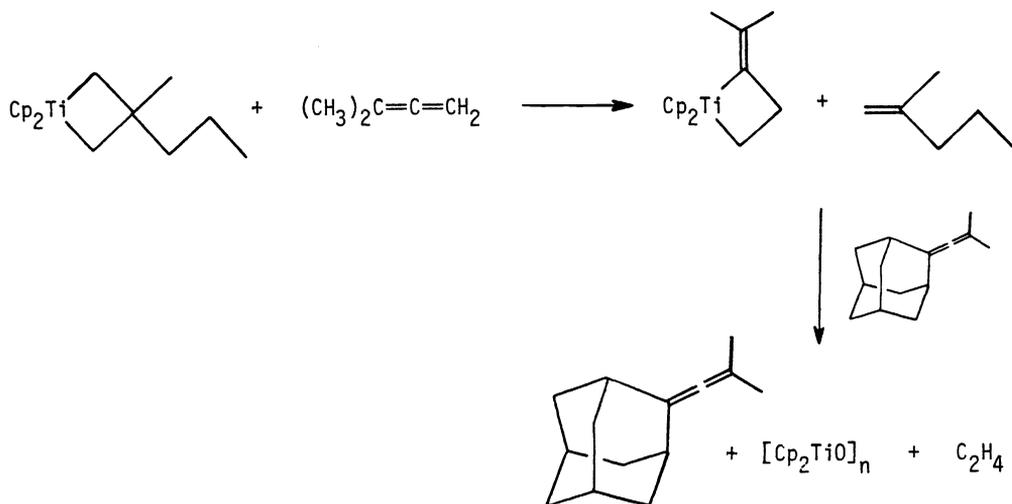
Metallacycle decomposition provides a very different route to such species. It has been demonstrated that the majority of the titanocene metallacycles produced to date decompose through a carbene-olefin complex (9, 10). These intermediates are excellent sources of the alkylidene fragment. Consequently,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



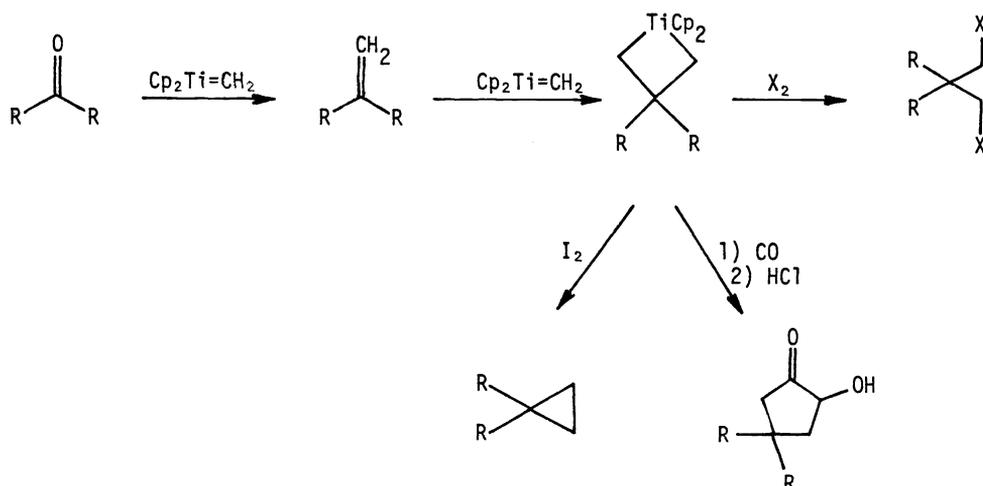
This reaction provides a facile one-pot synthesis of tetrasubstituted allenes.



These reactions are carried out by treating a source of Cp_2TiCH_2 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 $\text{Cp}_2\text{Ti}=\text{CH}_2$ 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.

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