

# Walter Sisulu University

**PROFESSORIAL INAUGURAL LECTURE**

**19 May 2009**

## “ Low-Valent Titanium Induced Carbonyl Coupling Reactions ”

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SCHOOL OF APPLIED AND ENVIRONMENTAL SCIENCES  
DEPARTMENT OF CHEMISTRY AND CHEMICAL  
TECHNOLOGY**

**TOPIC**

**LOW-VALENT TITANIUM-INDUCED CARBONYL COUPLING  
REACTIONS**

**BY**

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**DATE: 19 MAY 2009  
VENUE: WSU AUDITORIUM**





# LOW-VALENT TITANIUM-INDUCED CARBONYL COUPLING REACTIONS

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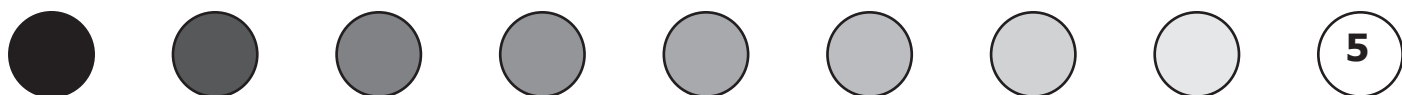
It is my pleasure to stand here before you to give this inaugural lecture on behalf of the Department of Chemistry and Chemical Technology in the New School of Applied and Environmental Sciences. I happen to be the founding Director of this new school which is located in the Faculty of Science, Engineering and Technology. I feel honoured to present the first inaugural lecture from my faculty.

My teaching and research interest lies principally in applied chemistry. In this field, I research and develop new processes as well as improving upon the efficacy of existing ones. I also have a vested interest in indigenous knowledge systems more particularly natural product chemistry. This is not surprising given my background in herbal medicine.

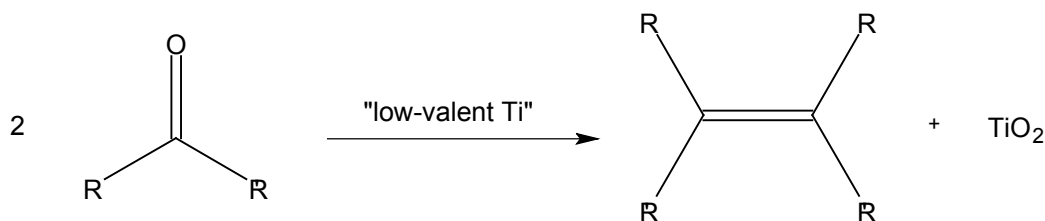
For many years I have worked on metal activated reactions in organic synthesis, where the chemistry of zinc- and silver on graphite was considerably extended. Today I am paying particular attention to titanium metal, its brief history and the role it has played and continue to play in carbonyl coupling reactions. I will give an overview of the literature on this, followed by contributions that I have made alongside other researchers.

## 1. INTRODUCTION

Interest in the use of low-valent titanium species as reagents in organic synthesis began with *Van Tamelen* and his research team in 1965, when they reported the first ever low-valent titanium-induced reductive dimerization of alcohols to give hydrocarbons [1]. In the early seventies shortly after the *Van Tamelen* report, the research teams of *Mukaiyama*, [2] *Tyrlik* [3] and *McMurry* [4] made the independent and simultaneous discovery that ketones and aldehydes undergo reductive dimerization to yield olefins on treatment with low-valent titanium reagents. Particularly *McMurry* and his co-workers [5,6,7] have extensively investigated this reaction,



therefore this process is now generally referred to as the “*McMurry reaction*” (scheme 1).



R, R' = H, alkyl or aryl

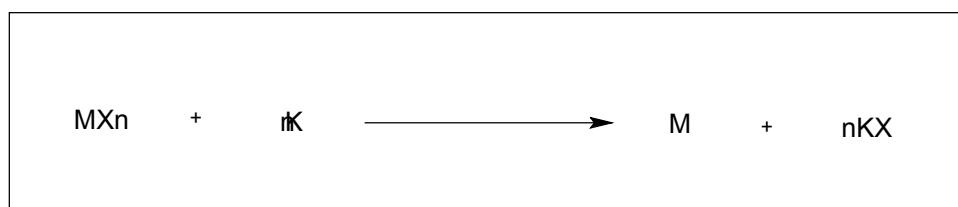
Scheme 1

Since its discovery, this reaction has served as an important carbon-carbon bond forming process and now finds wide applications in organic synthesis.

## 2. LOW-VALENT TITANIUM REAGENTS

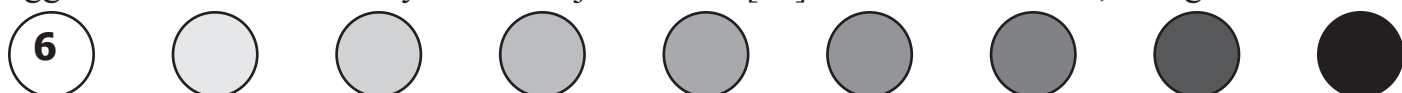
### Preparation

Within the area of metal-catalysed reactions, an increasing interest is addressed to the use of highly active zerovalent metals[8]. The efficiency of these reactions depends on the active surface area of the metal used, which is a direct function of their degree of dispersion. *Rieke* and co-workers[9,10] developed a method for generating metal suspensions by the reduction of the respective metal salts with an alkali metal in ethereal or hydrocarbon solvents (scheme 2).

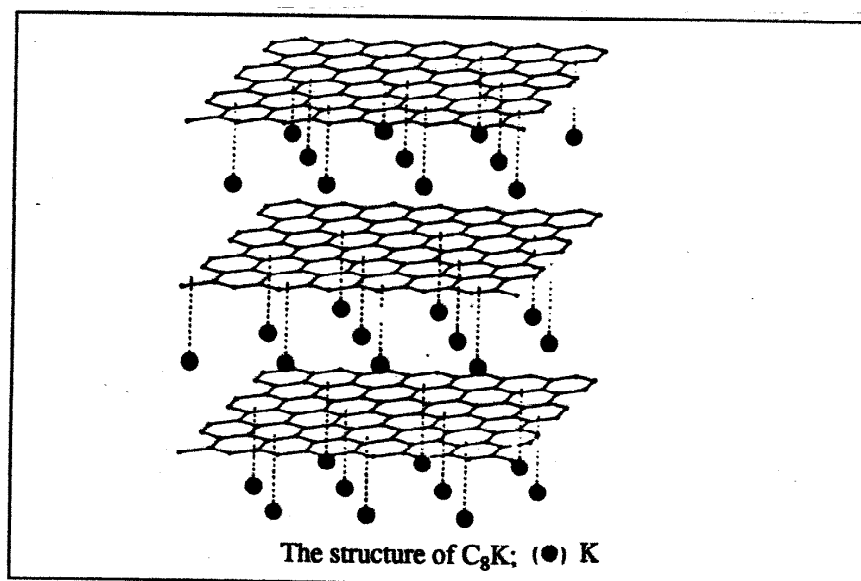


Scheme 2

For most of the reported cases, potassium was used as the reducing agent and THF as the solvent. Lumps of potassium metal and the respective metal salt were heated in dry THF under an atmosphere of argon. The reduction was said to be complete within a few hours and the fine black suspension of the respective metal was produced. In some cases, the alkali metal salt generated in the reduction was said to have a harmful effect on the desired reactions[9]. Metal suspensions obtained by the *Rieke* method represent an important breakthrough in the history of metal activation. It was this method that offered the possibility of preparing the relatively active *Rieke-titanium* by heating titanium trichloride and potassium in THF. One of the greatest disadvantages of this method is the highly exothermic nature of these reactions which are liable to run away especially when working with large quantities. Moreover, sintering and agglomeration of the catalyst is of major concern[11]. The *Rieke* method, though not without



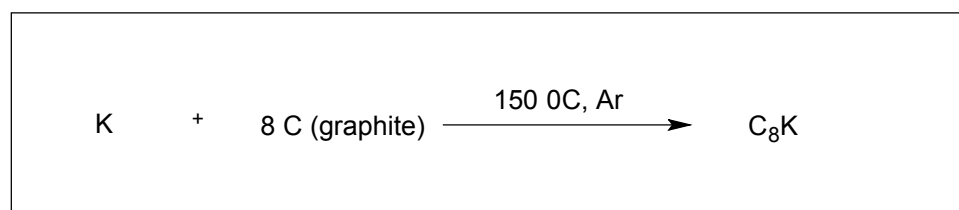
problems, thus opens up the way for the fine dispersion of metals on various supports. Graphite is one of the commonly used supports nowadays. It is capable of intercalating foreign atoms, molecules and even metals[12,13]. The most commonly used potassium-graphite intercalation reagent  $C_8K$  shows an interlayer distance of  $5.3\text{\AA}$ [12] and all carbon layers are separated by a layer of potassium (scheme 3)



Scheme 3

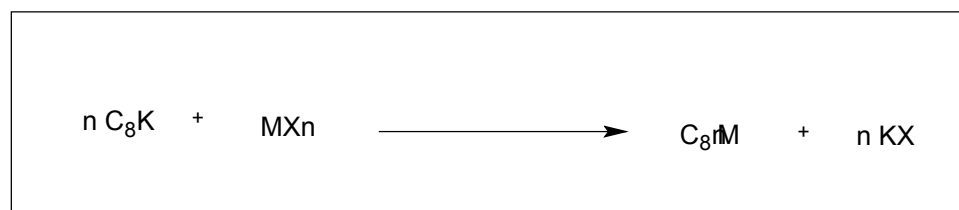
It is now generally accepted that the alkali metal atoms diffuse in the intercalation process from the periphery of the graphite layers into part or all of the interlayer spacing. The preparation of the metal-graphite reagents is carried out in two steps:

The generation of the bronze coloured  $C_8K$ [12,14] at  $150\text{ }^\circ\text{C}$  under a flow of argon (scheme 4):

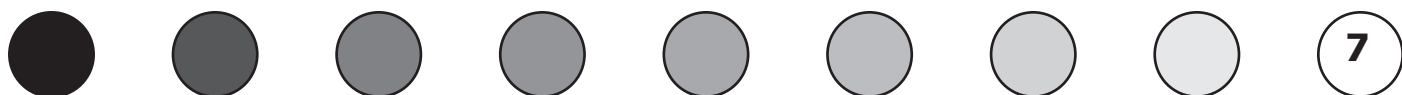


Scheme 4

The reduction of the respective metal salt by  $C_8K$  under an atmosphere of argon under reflux (scheme 5):



Scheme 5



In this way, the metal generated is finely dispersed on the graphite surface layer and is highly reactive. Thanks to this method, the chemistry of titanium[12] amongst other metals has been considerably extended.

Despite this progress, a full examination of the literature reveals many ambiguities, be it in the reaction mechanism, choice of solvent, different reducing agents for titanium salts, selectivity of product formation, substrate and reagent reactivity, just to name a few. At this stage, the following is noteworthy:

There is evidence that “*Rieke-titanium*”[9] suitable for the *McMurray* reactions, can only be obtained directly from  $\text{TiCl}_3$ . Its reduction is usually carried out by using metals such as Li[15,16,17], Na[15], K[5,6,15], Mg[3,15], Zn/Cu-couple[6]. The reduction of  $\text{TiCl}_3$  with  $\text{LiAlH}_4$ [4,18], or  $\text{TiCl}_4$  with any of the above mentioned reducing agents invariably affords “*low-valent titanium*” salts[15].

Considering the fact that in some cases the same McMurry procedure is applied to greatly differing coupling problems there is, in turn, no obvious reason for the various reagent preparations described for the same type of reduction. This discrepancy is exemplified by the cyclization procedures used for either diketones[6] or ketoesters[19] by two reagent combinations as far apart as  $\text{TiCl}_3/\text{Zn-Cu-couple}/\text{THF}$ [6] or  $\text{TiCl}_3/\text{LiAlH}_4/\text{TEA}/\text{DME}$ [19] are employed despite the completely analogous mechanisms of these reductions[19].

When *low-valent* titanium reagents are used for pinacolisation[20] reactions, they tend to form olefinic by-products.

In the reduction of titanium salts by Zn/Cu-couple or  $\text{LiAlH}_4$ , the presence of lewis acids had been found to have an adverse effect[21] on *McMurry* reactions. The use of triethyl amine (TEA)[9] in this reaction system might be to neutralize the acid.

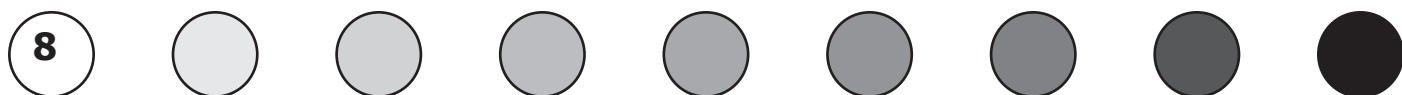
The use of  $\text{C}_8\text{K}$ [22] as the intermediate reducing agent for titanium salts completely avoids the introduction of the lewis acid species into the reaction system.

The use of sodium-naphthalene[21] as the intermediate reducing agent has been reported to be a good alternative. However, this method presents a major setback during workup since large quantities of naphthalene must be separated from the desired product. This can be tedious, time consuming and can cause reduced yields.

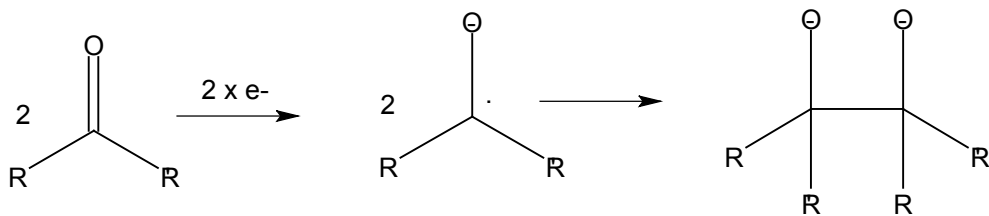
Mechanism of the Carbonyl Coupling Reactions

The carbonyl coupling reactions is a two step process viz:

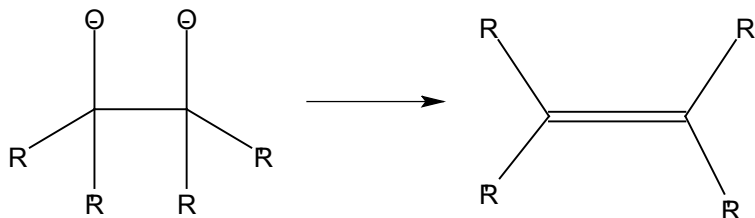
The reductive dimerization of the starting carbonyl compound with formation of the carbon-carbon bond.







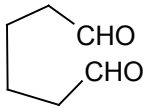
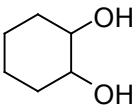
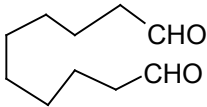
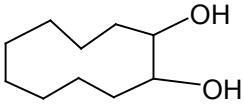
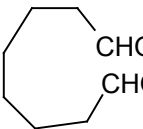
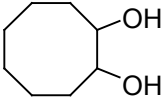
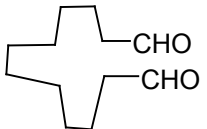
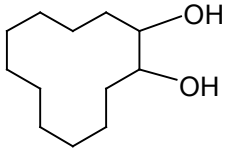
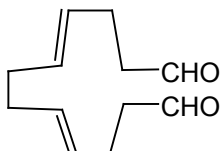
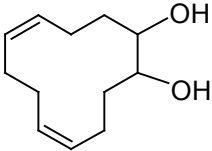
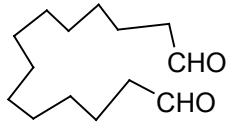
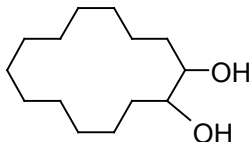
Deoxygenation of the titanium pinacolate intermediate to form the corresponding alkene.



The first step is simply a pinacol reaction and is not unique to low-valent titanium. It is known[23] as far back as 1859 that various metals are capable of adding an electron to a carbonyl carbon atom forming a “ketyl” which subsequently dimerizes. Evidence for this first step in the titanium-induced coupling reaction is straightforward, since the intermediate pinacols had been isolated by carrying out the reaction at 0 °C[24].



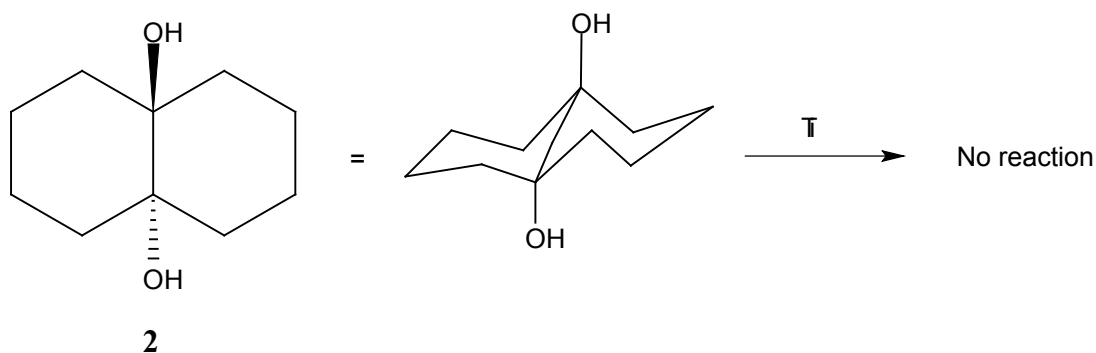
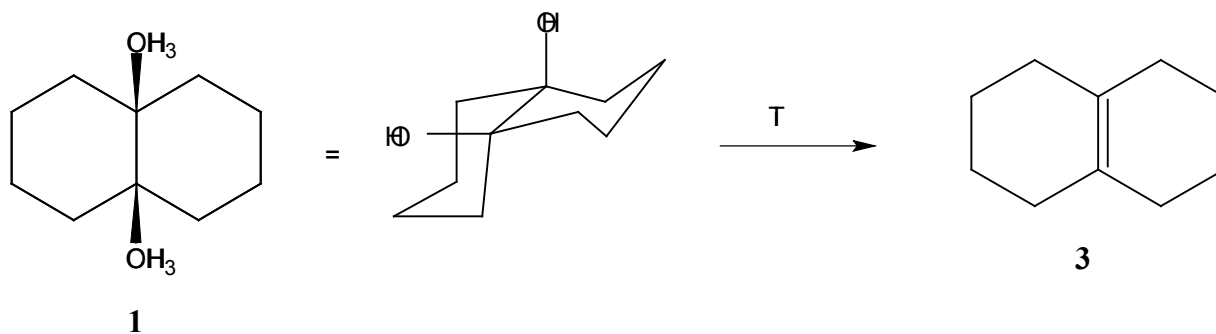
Table 1. Titanium-induced Intramolecular Pinacol Coupling Reactions[24]

| Entry | Dialdehyde  | Pinacol   | Cis/trans ratio | Yield (%) |
|-------|---|---|-----------------|-----------|
| 1     |    |    | 100 : 0         | 85        |
| 2     |    |    | 25 : 75         | 80        |
| 3     |    |    | 70 : 30         | 82        |
| 4     |    |    | 25 : 75         | 75        |
| 5     |   |   | 5 : 95          | 83        |
| 6     |  |  | 30 : 70         | 89        |

Upon treatment of pinacols with active titanium at solvent refluxing temperature, they are readily deoxygenated to yield the corresponding alkene. The reaction follows an **intermolecular** pathway on monocarbonyl compounds to yield acyclic alkenes and on high dilution an **intramolecular** pathway on dicarbonyl compounds to yield cycloalkenes[25]. As substrates, dialdehydes, diketones and ketoaldehydes can be used.

In the process of the alkene formation, the two C-O bonds do not appear to break at the same time and a mixture of *cis*- and *trans*-alkenes is produced starting from a diol of known stereochemistry[24]. Furthermore, the two oxygen atoms of the pinacol must be able to approach and bond to the titanium surface. Thus, the *cis* isomer of 9,10-decalindiol reacts smoothly with low-valent titanium to yield the anticipated olefin but the *trans* isomer does not react even on prolonged treatment. The two oxygens of the *cis* isomer are in close proximity while those of the *trans* are prevented by the steric hindrance from coming in contact with the titanium surface.

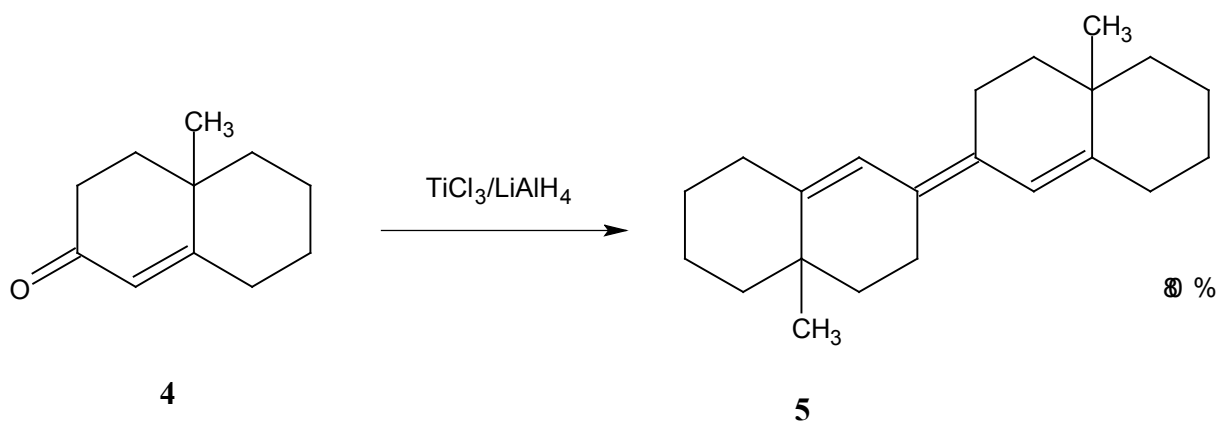




### 3. INTERMOLECULAR COUPLING OF ALDEHYDES AND KETONES

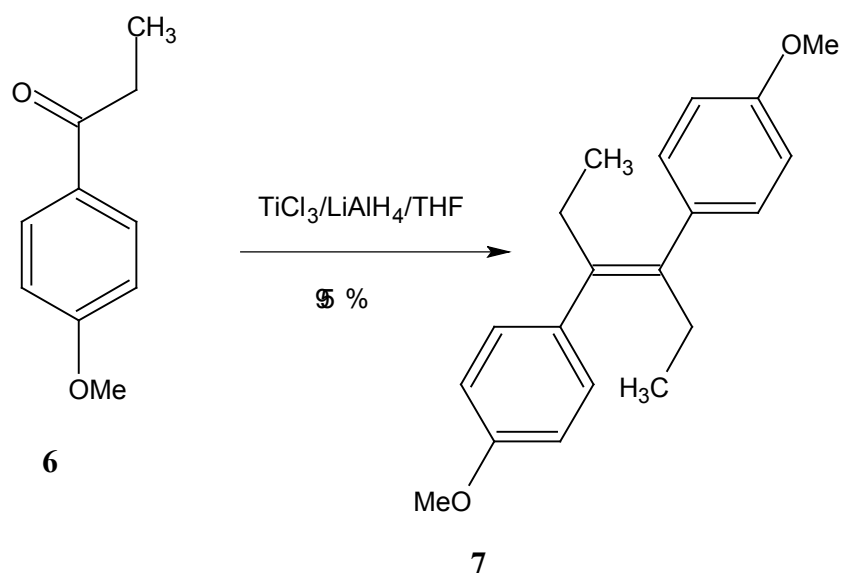
#### 3.1 Synthesis of Alkenes

In his effort to develop an alternative process to *Wolff-Kishner* reaction, *McMurry* and his team[7] subjected enone (**4**) to  $\text{TiCl}_3/\text{LiAlH}_4$  and to their surprise, obtained a hydrocarbon, not the one they anticipated but a reductively dimerized triene (**5**) in 80% yield.



While *McMurry* was not alone at the time in making this fundamental discovery[2,3], he was however, quick to ascertain the potential of his discovery and embarked on exploring the scope of the new reaction. He soon realised that the reductive coupling reaction was not limited to  $\alpha,\beta$ -unsaturated ketones but was general for all kinds of ketones and aldehydes and that the titanium reagent did not isomerize olefin geometry[7].

Dimestrole (**7**), a precursor of diethylstilbestrol is readily prepared from the ketone (**6**)[5,6]



### 3.1.1 Synthesis of Strained Alkenes

The coupling of ketones with *low-valent* titanium reagent to form alkenes is generally effective for simple ketones. In sterically hindered ketones, however, the yields are generally low (table 2) and alternative synthetic routes have been unsuccessful for some of these compounds.

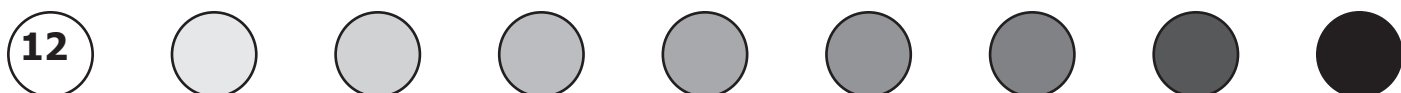
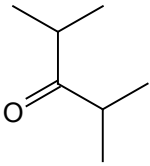
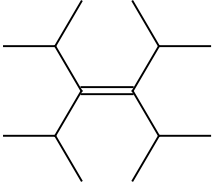
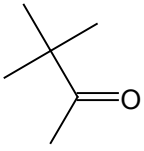
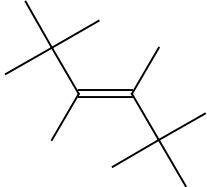
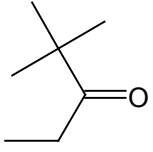
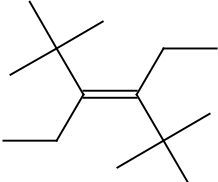
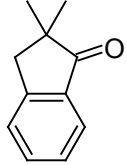
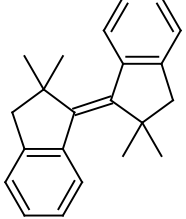
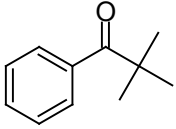
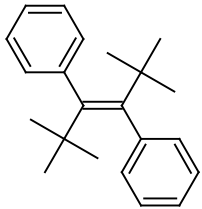
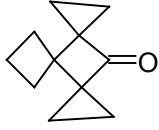
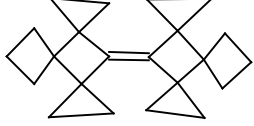
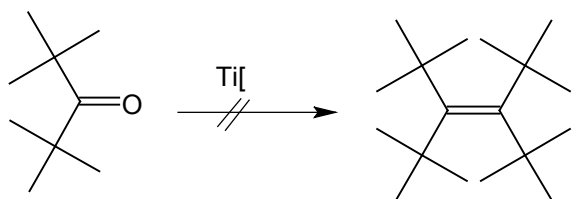


Table 2. Synthesis of Strained Olefins[24]

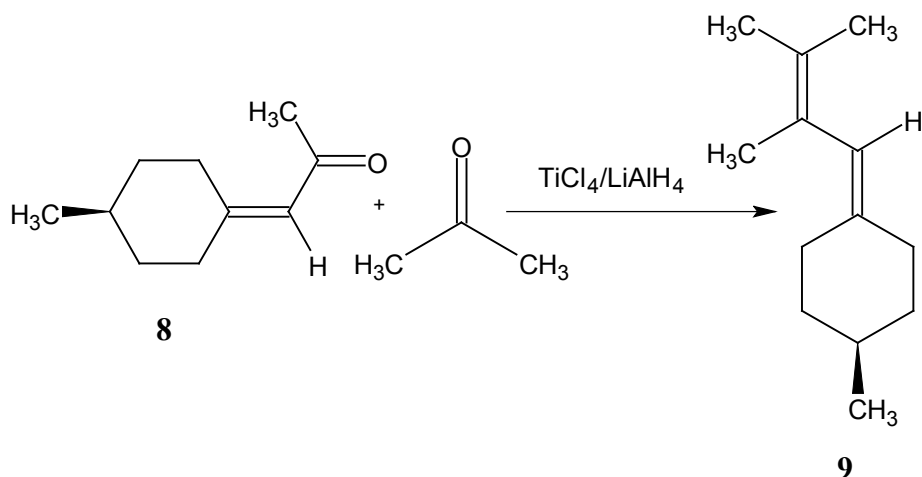
| Entry | Substrate   | Product   | Ref.   |
|-------|---|---|--------|
| 1     |    |    | 26, 27 |
| 2     |    |    | 28     |
| 3     |    |    | 29     |
| 4     |   |   | 30     |
| 5     |  |  | 31     |
| 6     |  |  | 32     |

To date the synthesis of tetra-*tert*-butylethylene remains elusive!

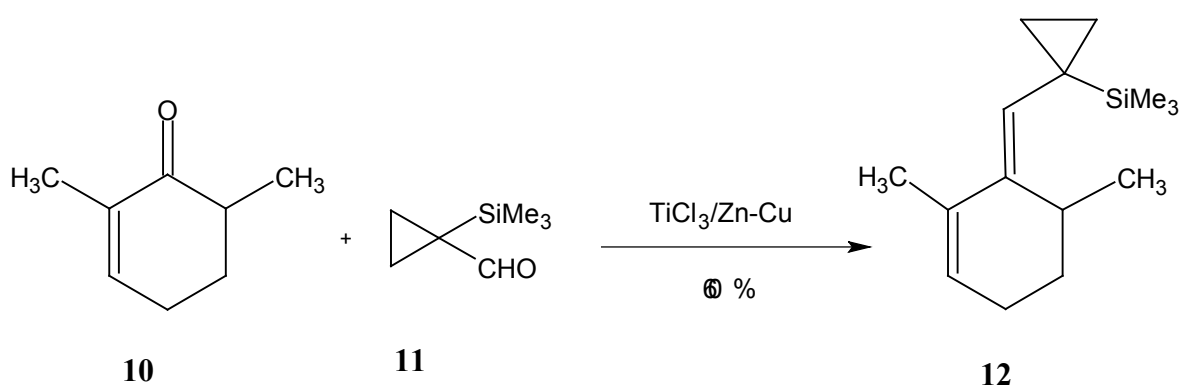


### 3.1.2 Mixed Carbonyl Coupling Reactions

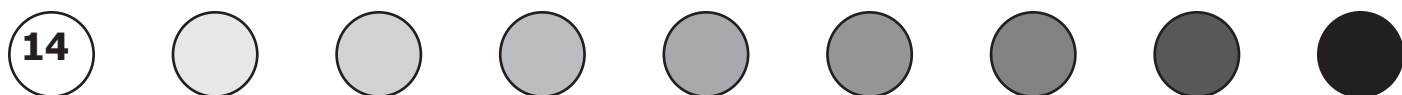
Intermolecular carbonyl coupling reactions are usually limited to the preparation of symmetrical olefins by the reductive dimerization of a ketone or an aldehyde. A mixture of two different carbonyl compounds will react generally to a nearly statistical mixture of olefins when subjected to *low-valent* titanium[33,34]. For the purposes of synthesis, such mixed couplings are only useful only if one component is used in excess and if the products are easily separable[24]. For example, mixed coupling of acetone with a chiral  $\alpha,\beta$ -unsaturated ketones like (R)-(-)-(4-methylcyclohexylidene)acetone affords a diene (**9**) initially prepared by Walborsky for chiroptical study[35].

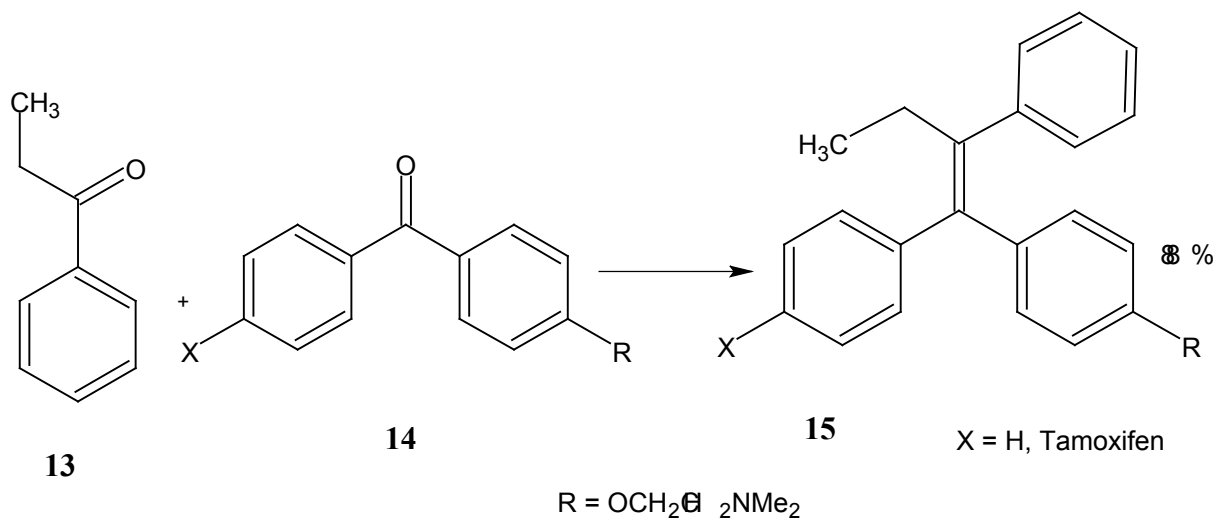


Another example of a mixed coupling reaction is the reaction of an equimolar amount of 2,6-dimethyl-2-cyclohexenone (**10**) and formyl(trimethylsilyl)cyclopropane (**11**) with low-valent titanium. *Paquette*[36] prepared sesquiterpene vetispiroene (**12**) by this method with a yield of 60%. There is however, no apparent justification why the mixed product should be so strongly favoured over the symmetrical products in this case.



Mixed carbonyl coupling reaction has paved the way for the synthesis of the antitumor agent tamoxifen (**15**) and several of its analogs[37,38].

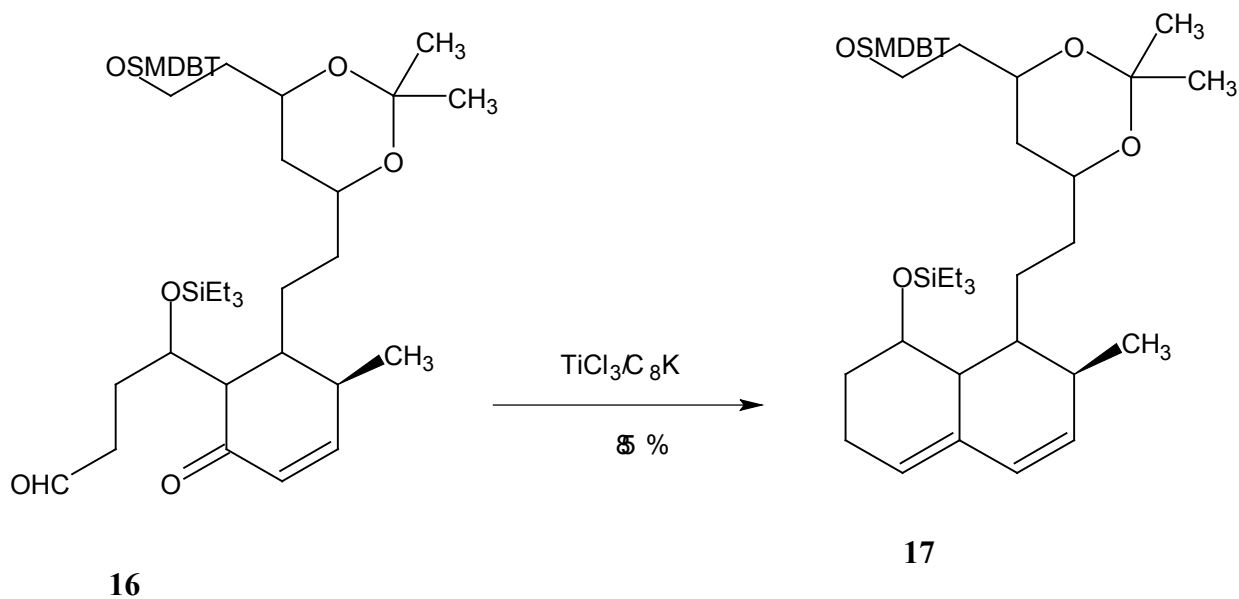




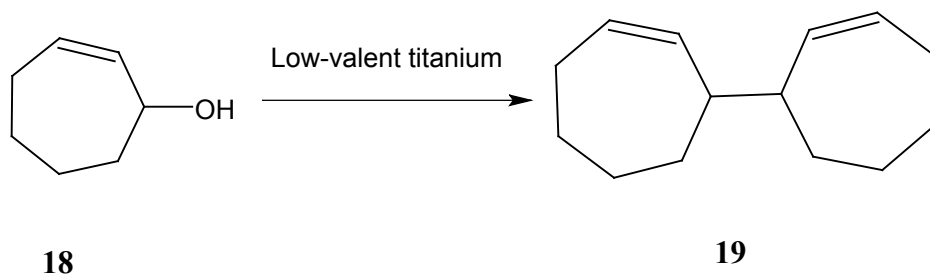
### 3.1.3 Functional Group Compatibility

Several easily reducible functional groups do not survive in the presence of low-valent titanium due to the strong reducing potential of this reagent.

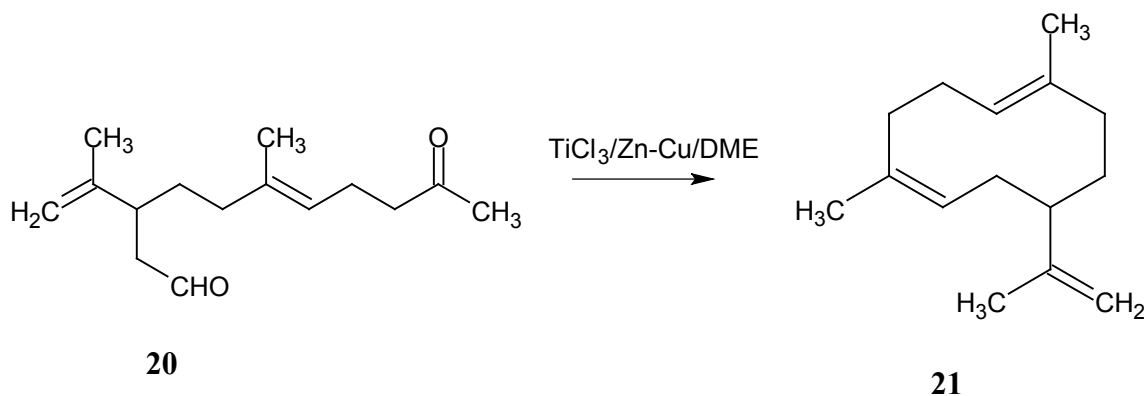
*Acetal.* Not many carbonyl coupling reactions are known to take place in the presence of acetal groups. Clive reported[39] the coupling of acetal (**16**) in the course of compactin (**17**) synthesis.



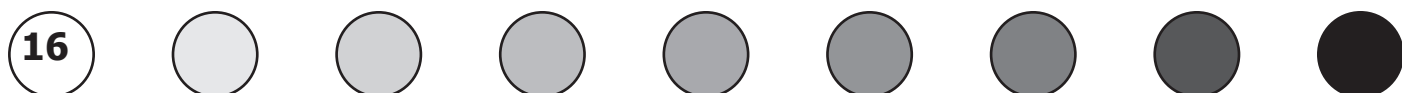
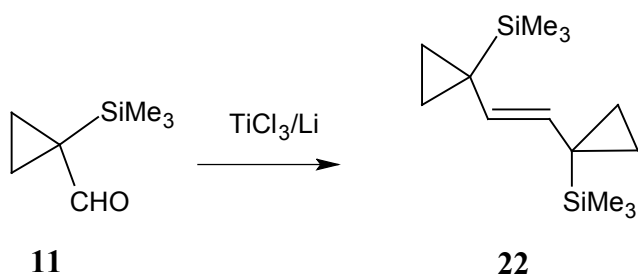
*Alcohol.* There are hardly any cases of carbonyl coupling reactions in the presence of free alcohols. While saturated alcohols like in cholesterol are unaffected by low-valent titanium, allylic alcohols however, undergo reductive coupling[40].



*Alkene.* Alkenes are unaffected by *low-valent* titanium, and an array of carbonyl coupling reactions have been carried out in the presence of carbon-carbon double bonds. Compound **(21)** a natural product was synthesized from the unsaturated keto-aldehyde **(20)** without any evidence of double bond isomerization[41]

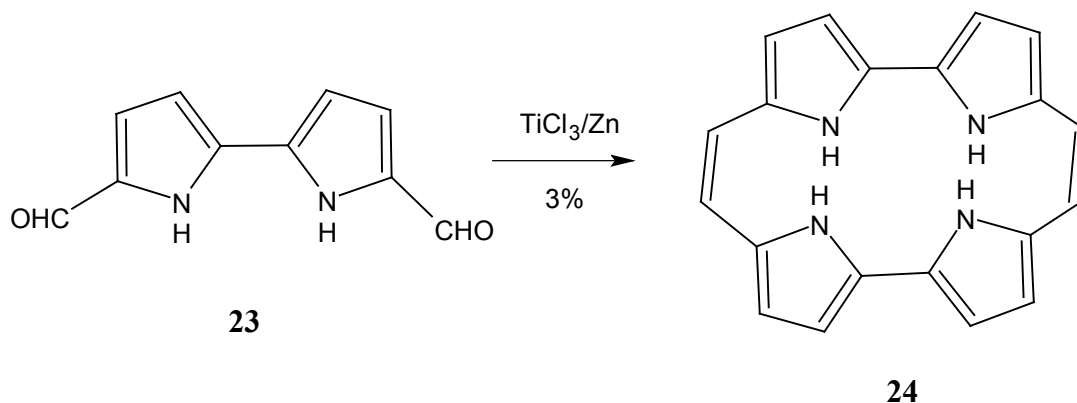


*Alkyl silane.* Paquette's successful coupling of formyl(trimethylsilyl)cyclopropane[42] indicates that tetraalkylsilanes appear to be inert towards *low-valent* titanium.



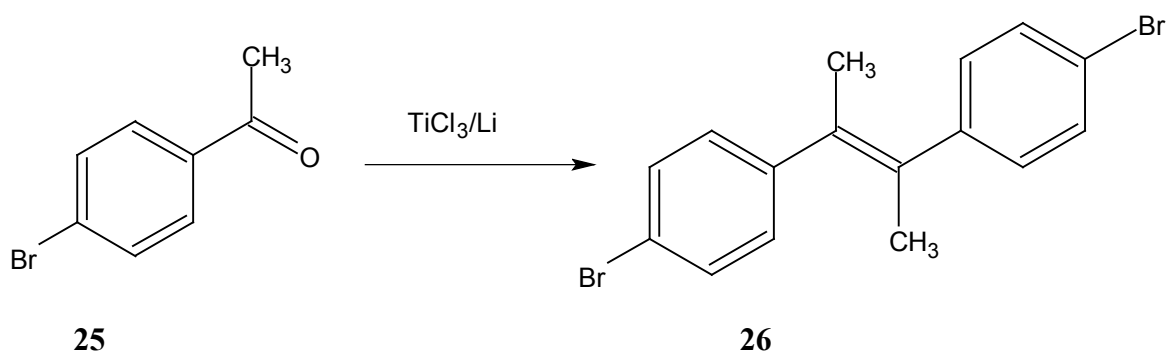


*Amines.* Amines are inert towards *low-valent* titanium and have been added in some reactions to improve yields[43].

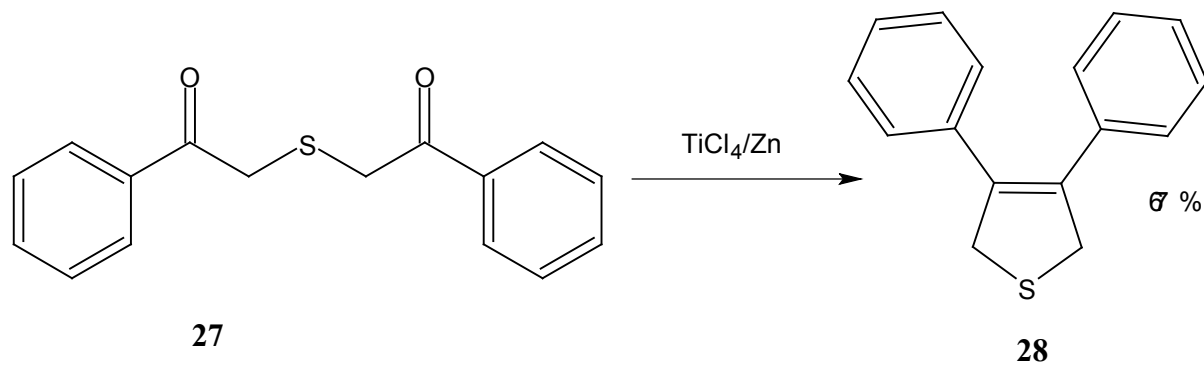


*Ether.* All types of ethers are compatible to *low-valent* titanium. THF, DME and benzyl ethers[44] are used as solvents in these reactions without any reported adverse effects. Even silyl ethers are compatible[45].

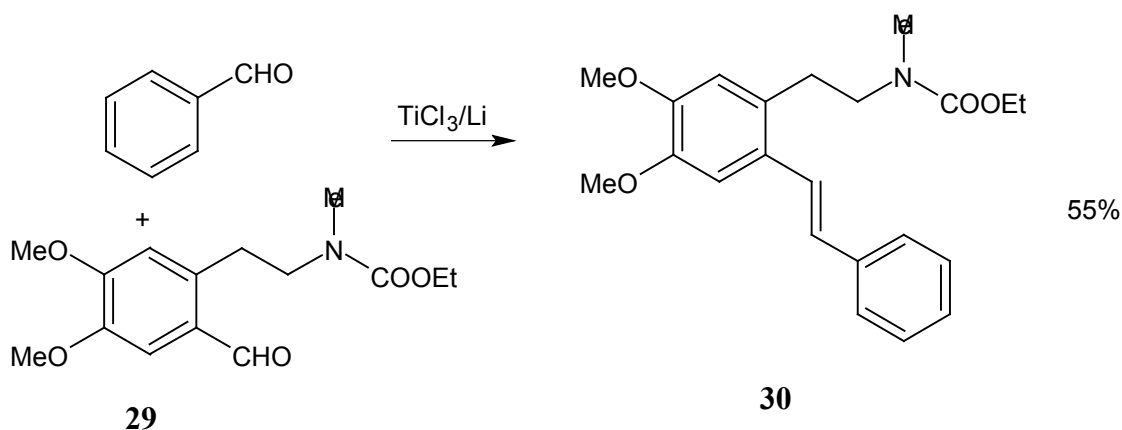
*Halides.* Halides substituted on aromatic nucleus appear to be compatible as illustrated by this example[46].



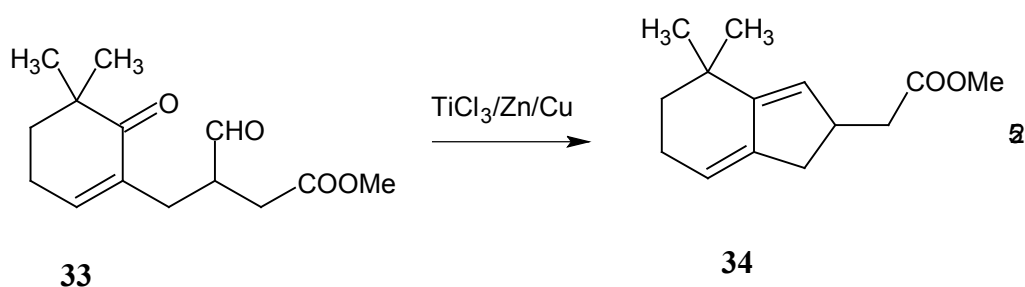
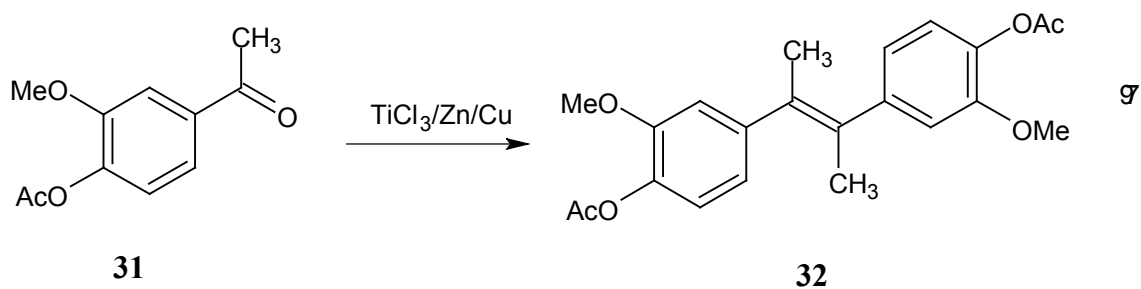
*Sulfide.* Not many cases have been reported and no problems were encountered with the following example[47].



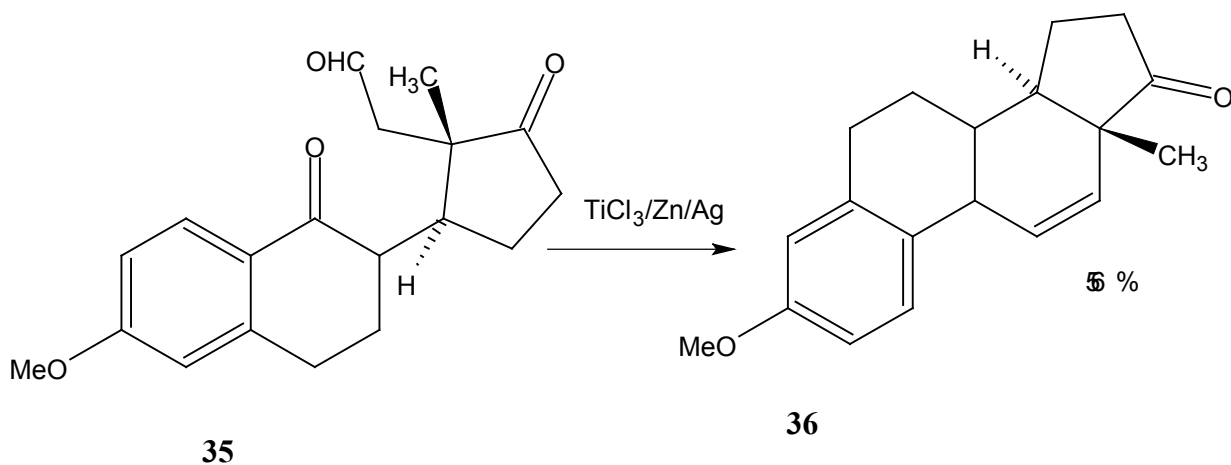
*Amide.* Although amides have been reported to react slowly with *low-valent* titanium reagents[24] *Castedo*[48] demonstrated a mixed coupling of an aldehydo urethane (**29**) with benzaldehyde.



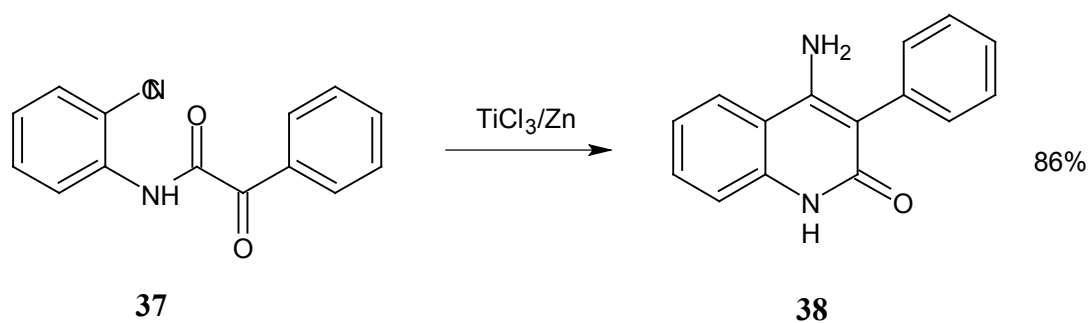
*Ester.* Various carbonyl coupling reactions have taken place in the presence of esters. **Intermolecular** coupling is usually the most successful[49] and **intramolecular** coupling is only successful when it involves the formation of five- or six-membered rings[50].



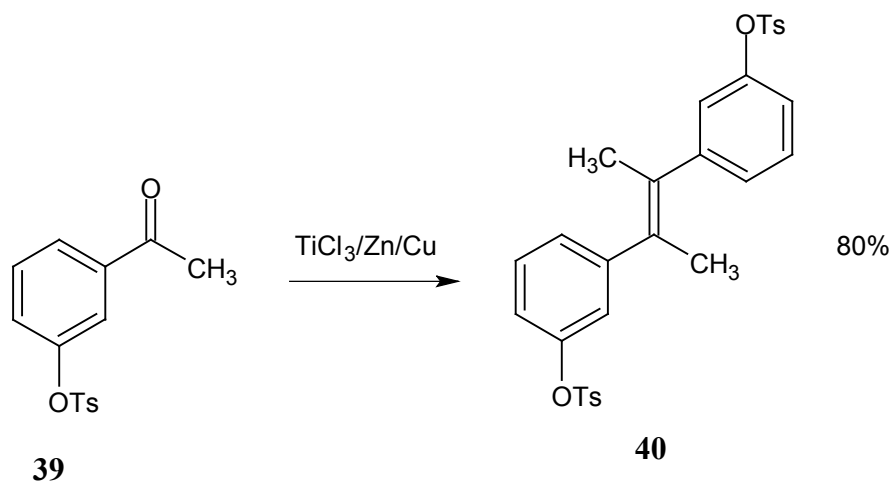
**Ketone.** Ketones do in fact survive ketone-coupling reaction if in an **intramolecular** cyclization leading to a five- or six-membered ring occurs rapidly enough so that the reaction can be quenched before competing intermolecular dimerization reaction sets in[24]. This is clearly demonstrated by Ziegler in the total synthesis of an estrone (**35**  $\rightarrow$  **36**)[51].



**Nitrile.** Although nitriles were predicted to react slowly with *low-valent* titanium[52], a recent report[53] demonstrates its participation in an **intramolecular** cyclization reaction



**Toluenesulfonate.** Unsuccessful attempts have been made to reduce sulfones with *low-valent* titanium[54]. There is only one reported case of an **intermolecular** carbonyl coupling reaction in the presence of a tosylate group[49].

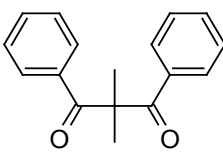
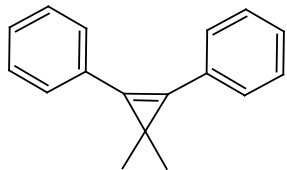
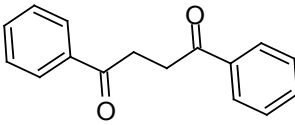
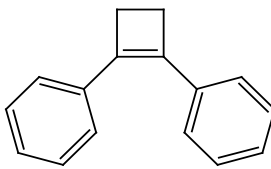
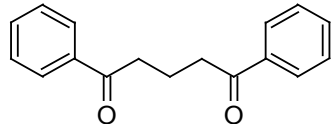
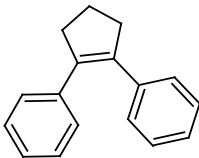
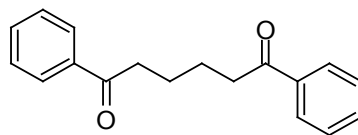
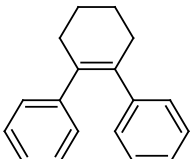
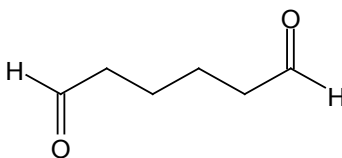
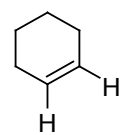
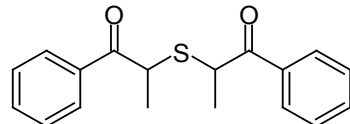
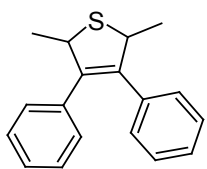
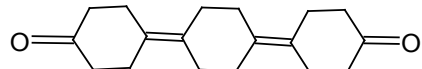
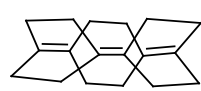
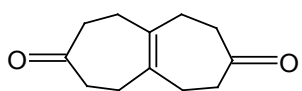
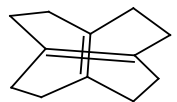


## 4. INTRAMOLECULAR CARBONYL COUPLING REACTIONS

The importance of titanium-induced carbonyl coupling reactions to synthetic organic chemists cannot be over emphasized. The formation in good yields of a plethora of rings of various sizes and shapes that otherwise would have been quite difficult to prepare is testimony thereof. Cycloalkanes and many natural products have been readily prepared. These reactions require high dilution in order to achieve **intramolecular** cyclization rather than **intermolecular** polymerization. Some examples of intramolecular coupling of diketones are shown in table 3.



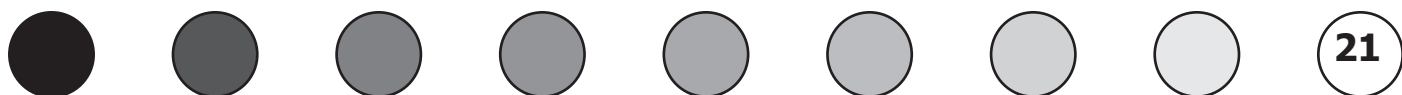
Table 3. Intramolecular Dicarbonyl Coupling

| Entry | Substrate   | Product  | Ref.   |
|-------|---|--|--------|
| 1     |    |     | 55, 56 |
| 2     |    |     | 55     |
| 3     |    |     | 55     |
| 4     |    |     | 55     |
| 5     |   |   | 57     |
| 6     |  |   | 47     |
| 7     |  |  | 58, 59 |
| 8     |  |   | 60     |

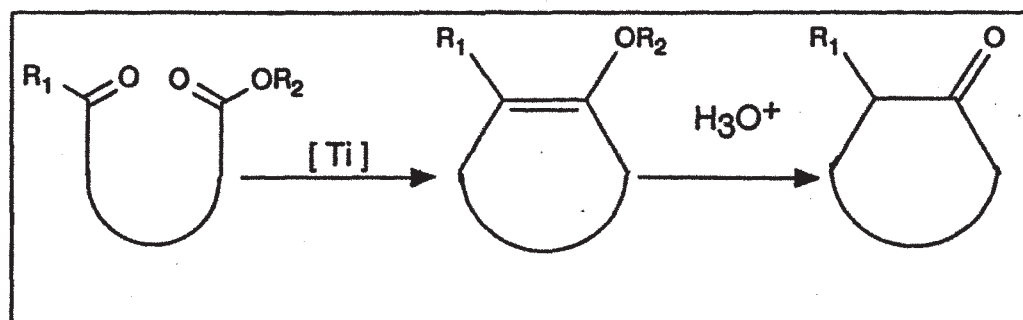
## 5. INTRAMOLECULAR KETO ESTER COUPLINGS

### 1.1 Synthesis of Cyclic Ketones

The examples described thus far have to do with either ketones or aldehydes or both. The carbonyl coupling reaction has found an interesting extension to ketoester cyclization[19,60]. The mechanism of this reaction is claimed to be the exact analogue of the dicarbonyl coupling

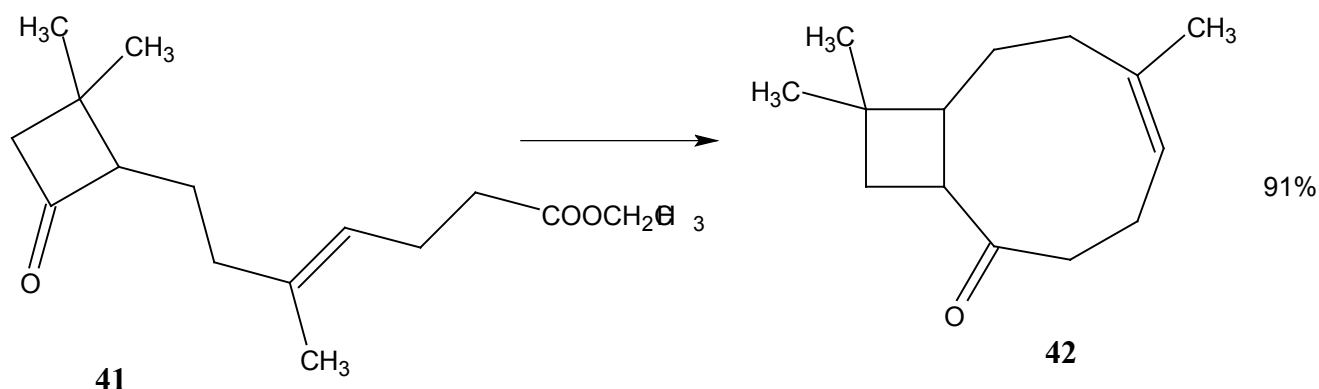


reaction[19]. Thus, an assumed initial pinacol-type reaction forms the carbon-carbon bond, followed by deoxygenation to yield an enol ether. Acid hydrolysis affords the final cyclanone product (scheme 6). Evidence for this proposed mechanism comes from the fact that the enol ether has been isolated[19], by excluding the acidic conditions during workup.



Scheme 6

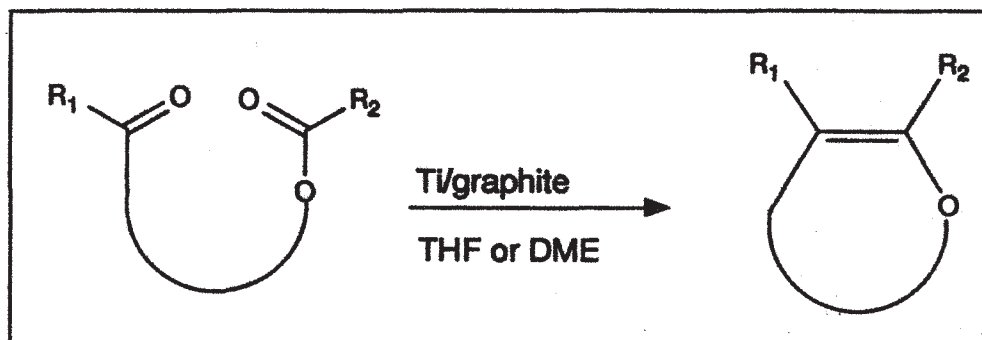
This reaction has paved the way for the synthesis of cycloalkanones of medium- to large-ring sizes which otherwise would be difficult to get. Titanium-induced synthesis of cyclononenone (**42**) illustrates the importance of this process[60].



## 6. SYNTHESIS OF HETEROCYCLIC COMPOUNDS

### 6.1 Preparation of Furans

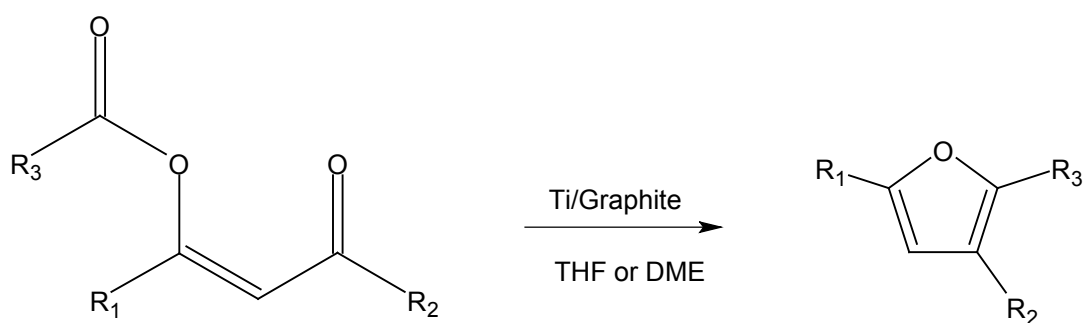
Further extension of the ketoester cyclization to the closely related acyloxycarbonyl compounds was envisaged to afford products with the enol ether forming part of the heterocyclic ring system (scheme 7).



Scheme 7

Keto-enol tautomerism[63] is common to carbonyl compounds containing an  $\alpha$ -hydrogen. Although the conversion of a carbonyl compound to its tautomer is not generally a preparative procedure, these reactions do have their preparative aspects. With a trace of acid or base, the tautomeric equilibrium state can be considerably influenced[64]. Thus 1,3-dicarbonyl compounds (43) and (44) were acylated under standard conditions to substrates (43a), (44a), and (44c) which on treatment with titanium/graphite in refluxing THF afforded the anticipated furans (table 4)[65]. The instability of 2-methyl-3,5-diphenylfuran (44b) already reported[66] appears to be characteristic of this compound. It decomposed immediately on attempted workup.

Table 4. Titanium Induced Synthesis of Furans

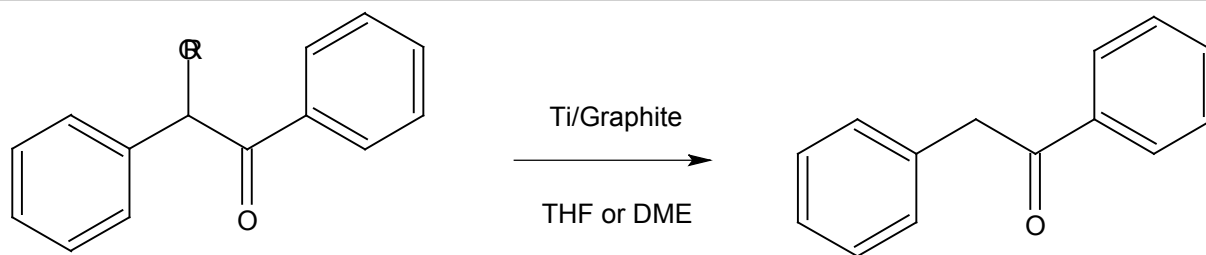


|     | R <sub>1</sub> | R <sub>2</sub> | R <sub>3</sub> |     | R <sub>1</sub> | R <sub>2</sub> | R <sub>3</sub> | Yield % |
|-----|----------------|----------------|----------------|-----|----------------|----------------|----------------|---------|
| 43a | Me             | Me             | Ph             | 43b | Me             | Me             | Ph             | 5       |
| 44a | Ph             | Ph             | Me             | 44b | Ph             | Ph             | Me             | a       |
| 44c | Ph             | Ph             | Ph             | 44d | Ph             | Ph             | Ph             | 2       |

<sup>a</sup>decomposed on attempted workup

On subjecting O-benzoylbenzoin (**45a**) and O-acetylbenzoin (**45b**) to *low-valent* titanium, instead of the anticipated oxeten derivatives, these compounds were spontaneously deoxygenated affording deoxybenzoin (**45d**) in good yields (table 5)[67].

Table 5. Deoxygenation of Benzoin and its Derivatives by Low-Valent Titanium



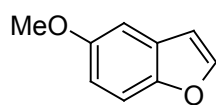
| Substrate  | R  |
|------------|----|
| <b>45a</b> | Ph |
| <b>45b</b> | Ac |
| <b>45c</b> | H  |

| Product    | % Yield |
|------------|---------|
| <b>45d</b> | 80      |
| <b>45d</b> | 92      |
| <b>45d</b> | 80      |

A closer look at the literature[18] revealed that  $\alpha$ -hydroxyketones and cyanohydrins were deoxygenated on treatment with low-valent titanium. To verify this information, benzoin (**45c**) was treated with titanium/graphite and it did deoxygenate forming the anticipated deoxybenzoin (**45d**).

## 1.2 Preparation of Benzofurans

Benzofuran ring systems are present in many natural and synthetic products which show pharmacodynamic properties[67]. Some fully unsaturated benzofurans occur naturally, such as the simple 5-methoxybenzofuran (**46**), which exhibits bactericidal properties[68].



**46**

The efficiency of the ketoester cyclization paved the way for the extension of the reaction to the synthesis of benzofurans[65,68,69,70]]. The results of varied types of benzofurans are listed on table 6.



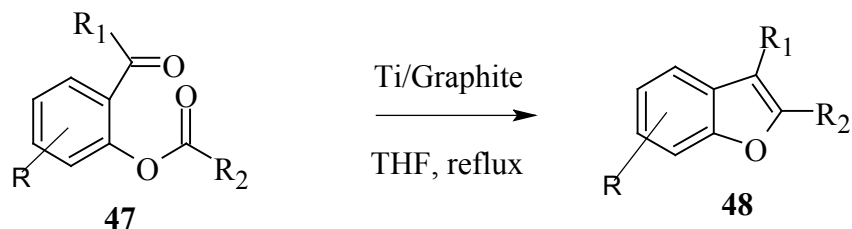


Table 6. Synthesis of benzofuran derivatives using low-valent titanium reagent [50]

| R <sub>1</sub> | R <sub>2</sub> | R                         | Method | Yield % |
|----------------|----------------|---------------------------|--------|---------|
| H              | H              | H                         | A      | 8       |
| H              | Me             | H                         | A      | 5       |
| Me             | H              | H                         | A      | 8       |
| Me             | H              | H                         | B      | 5       |
| Me             | 3-MeOPh        | H                         | B      | 6       |
| Me             | H              | 4-OMe                     | B      | 5       |
| Me             | H              | 5-OMe                     | B      | 5       |
| Me             | H              | 6-OMe                     | B      | 3       |
| Me             | H              | 4, 5 - (OMe) <sub>2</sub> | B      | 2       |
| Me             | Me             | H                         | A      | [d]     |
| H              | Me             | H                         | A      | [d]     |
| H              | H              | H                         | A      | 9       |
| H              | 3-MeOPh        | 4-OMe                     | A      | [d]     |

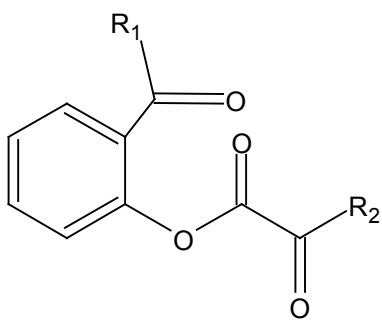
A = Ti-graphite, THF, reflux    B = TiCl<sub>4</sub>/Zn/dioxane, reflux    [d] = decomposed

### 1.3 Synthesis of Coumarins

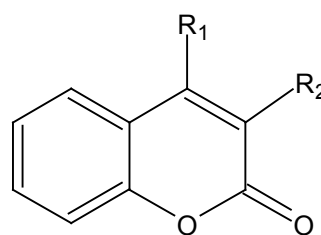
A set of suitable substrates **49a – c** was prepared by the acylation of commercially available  $\alpha$ -hydroxyaryl ketones or hydroxyaryl esters with different  $\alpha$ -ketoacid chlorides under standard conditions. However, only moderate yields were obtained due largely to the low nucleophilicity of the phenolic –OH and of partial hydrolysis of the esters **49a – c** during column chromatography.

On treatment of the esters **49a,b** with low-valent titanium generated by reducing TiCl<sub>3</sub> with zinc dust in refluxing THF, afforded the coumarins **50a** and **50b** in good yields (table 7)[53].

Table 7. Synthesis of Coumarins Mediated by Low-Valent Titanium



| Substrate  | R <sub>1</sub> | R <sub>2</sub> |
|------------|----------------|----------------|
| <b>49a</b> | H              | H              |
| <b>49b</b> | H              | Ph             |
| <b>49c</b> | OMe            | Ph             |

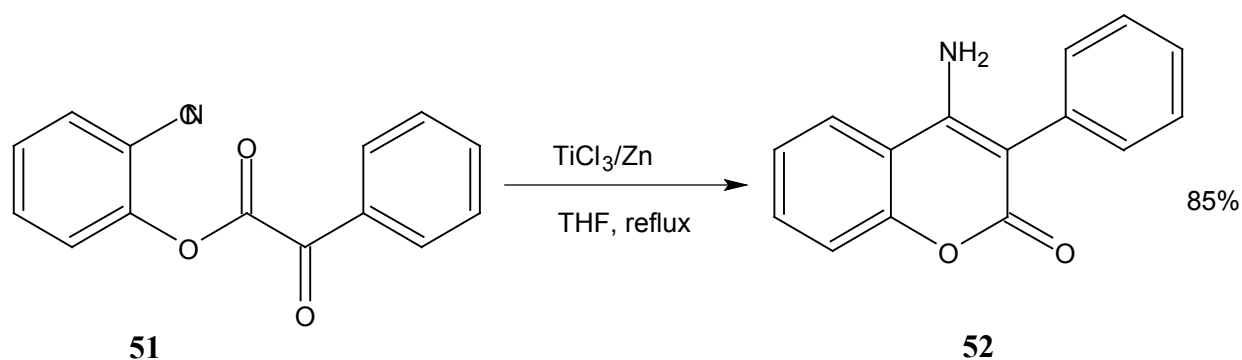


| Product    | R <sub>1</sub> | R <sub>2</sub> | Yield (%) |
|------------|----------------|----------------|-----------|
| <b>50a</b> | H              | H              | 8         |
| <b>50b</b> | H              | Ph             | 6         |
| <b>c</b>   |                |                |           |

**c** = methyl 2-hydroxybenzoate

The treatment of the ester **49c** resulted in hydrolysis of the ketoester and formation of the parent compound methyl 2-hydroxybenzoate.

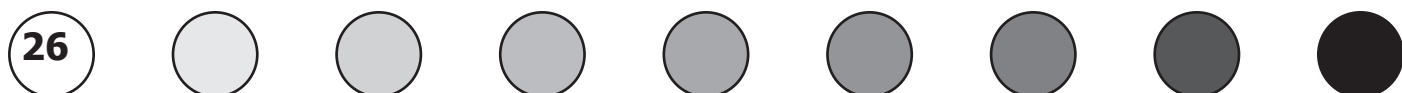
Furthermore, compound **51** on treatment with *low-valent* titanium afforded 4-amino-3-phenylcoumarin **52** without difficulty.



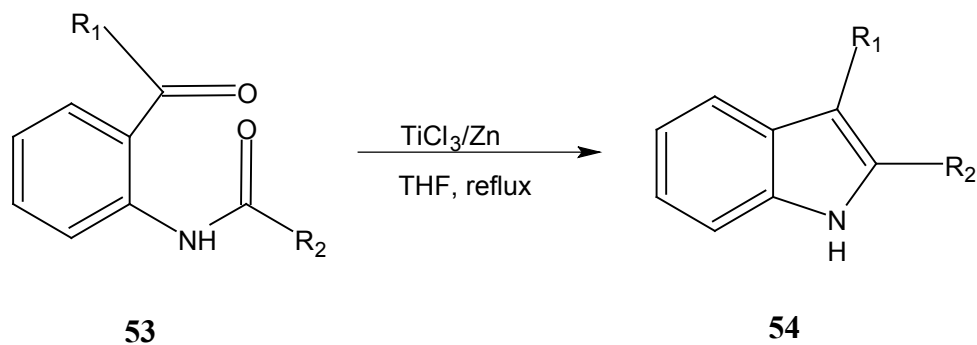
Although the examples listed for the synthesis of coumarins are few in number, they do however, indicate the potential of producing coumarins by this method and should be explored.

#### 6.4 Titanium-induced synthesis of Indoles

So far the titanium-induced ketoester cyclization paved the way for the extension of the reaction to encompass the synthesis of furans, benzofurans and coumarins. Although carboxylic acid amides were considered inert towards *low-valent* titanium reactions[24] a new entry into



the synthesis of indoles from acylamidocarbonyl compounds has proved remarkable for the synthesis of indoles[65,67,70]. For example, the high-dilution technique[24] commonly used in cyclization reactions is now unnecessary. The formation of indoles takes place readily, even at high concentrations without evidence of **intermolecular** coupling reactions competing. All amides ranging from formamide up to fatty acid amides, including aromatic and heteroaromatic ones, undergo comparatively rapid reactions affording anticipated indoles in good to excellent yields. The results of some of the titanium-induced indole formation are listed in table 8.

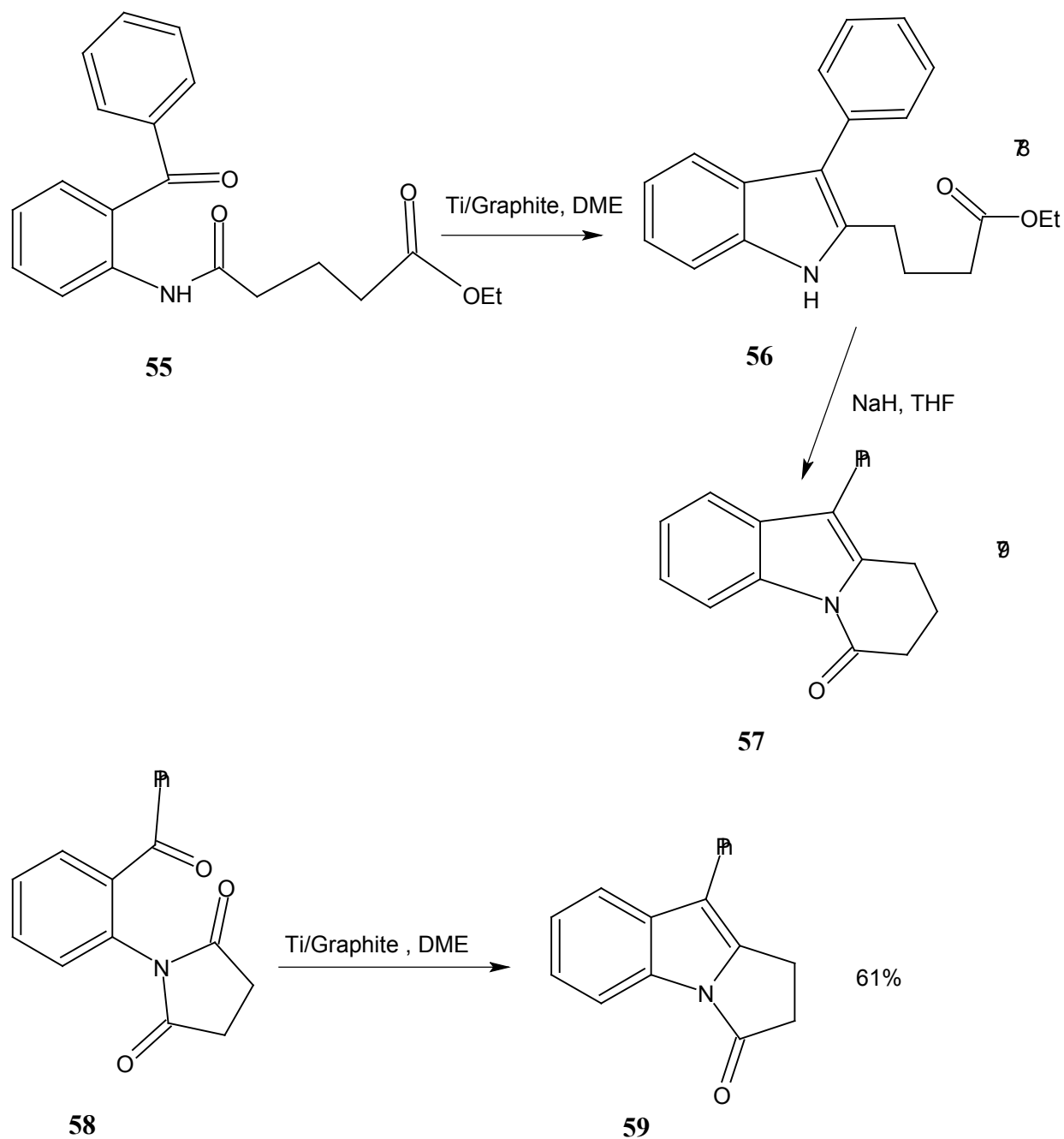


Table

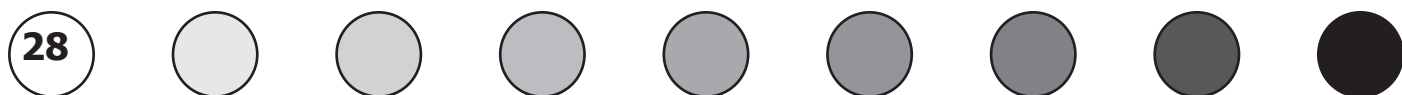
| R <sub>1</sub> | R <sub>2</sub>                                  | Yield (%) | R <sub>1</sub> | R <sub>2</sub>               | Yield (%) |
|----------------|---|-----------|----------------|------------------------------|-----------|
| Ph             | Ph  | 7         | Ph             | Thiophenyl -                 | 9         |
| Ph             | Ph  | 7         | Ph             | <i>m</i> -FPh                | 9         |
| Ph             | Ph  | 9         | Ph             | <i>p</i> -ClPh               | 6         |
| Ph             | Ph  | 8         | Ph             | <i>m</i> -BrPh               | 8         |
| Ph             | H   | 2         | Ph             | <i>p</i> -IPh                | 8         |
| Ph             | (CH <sub>2</sub> ) <sub>4</sub> Cl <sub>3</sub> | 2         | Ph             | <i>m</i> -MeOPh              | 6         |
| H              | Ph  | 9         | Ph             | <i>p</i> -F <sub>3</sub> CPh | 3         |
| Ph             | <i>t</i> -Bu                                    | 8         | Ph             | <i>p</i> -NCPH               | 7         |
| Ph             | H   | 6         | Ph             | HC = CHPh                    | 6         |

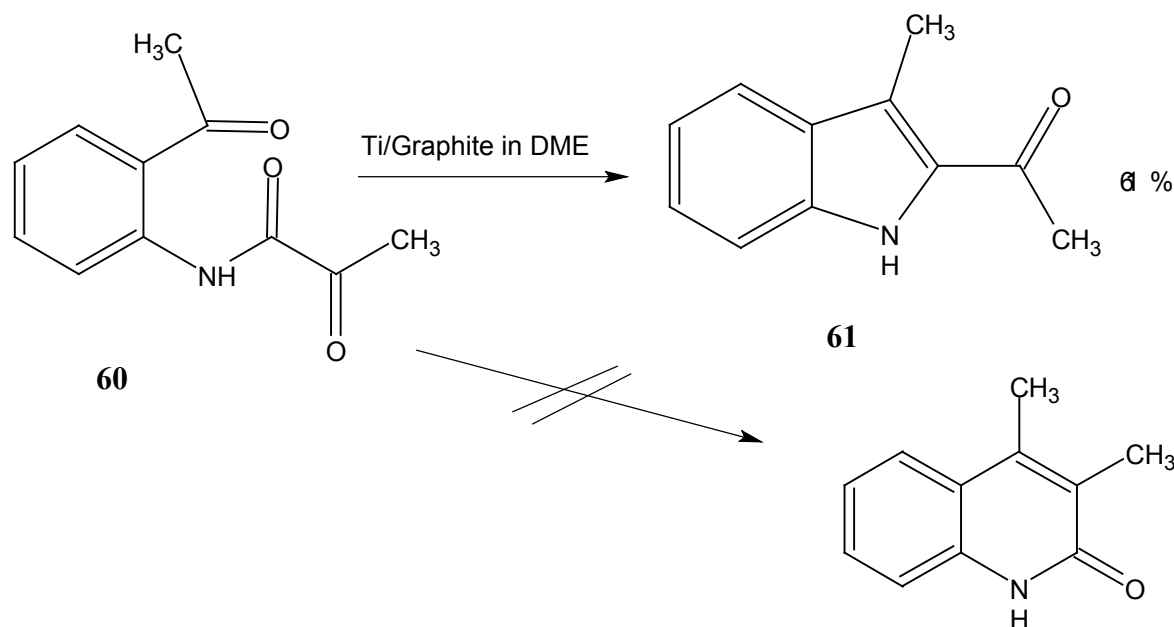
[b] together with 2,3-diphenylindole (< 10%)

The indole synthesis (table 8) illustrates not only the ease with which these products are formed but it also underscores the functional group compatibility in the presence of *low-valent* titanium. Furthermore, steric hinderance does not seem to feature prominently in this indole synthesis given the fact that substrate (cf. Table 8, R<sup>1</sup> = Ph, R<sup>2</sup> = *t*-Bu) is easily transformed to the desired product. The synthesis of tricyclic skeletal framework can be illustrated by the reactions (55) to (57) and (58) to (59)[67].



The indole synthesis also exhibits a striking chemoselectivity thereby putting into question the known bias of different carbonyl groups engaging readily in reductive coupling reactions. The chemoselectivity can best be illustrated by the synthesis of salvadoricine (**61**)<sup>[71]</sup> a simple indole isolated from *Savadora persica* and widely used in Pakistan as a drug.

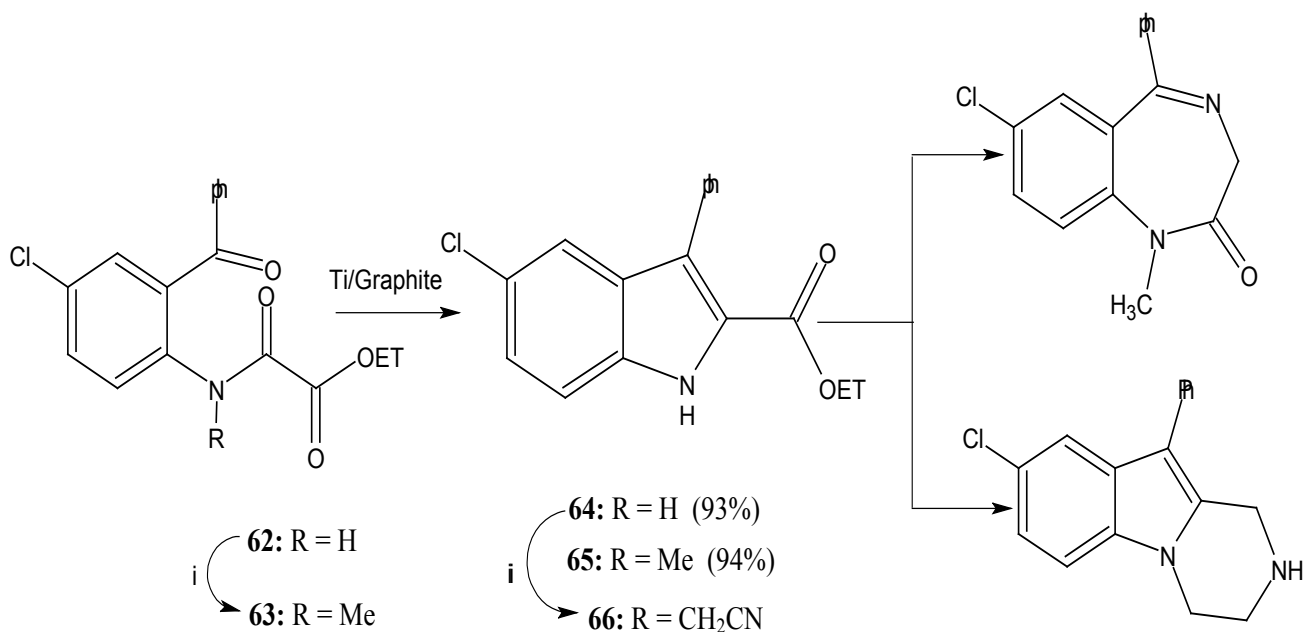




Several aspects of this chemoselective transformation are worth mentioning:

- The observation, that a keto-amide coupling completely overcomes both inter- as well as intra-molecular diketone coupling is in sharp contrast to earlier reports[24,34] on *low-valent* titanium coupling reactions;
- This reaction pathway is even more surprising given the fact that an *intramolecular* diketone coupling would have provided a well known and stable 3,4-dimethyl-2(1H)-quinolone;
- High dilution are unnecessary for the formation of indoles[65,67];
- Owing to the short reaction times the remaining ketone in (**61**) perfectly resists subsequent intermolecular coupling although an excess of the *low-valent* titanium reagent is present in the reaction system;

In accordance with this result, the trifunctional substrate (**62**) and (**63**), obtained from commercially available 5-chloro-2-aminobenzophenone and ethyl oxalyl chloride, formed indoles (**64**) and (**65**) in 93 and 94% isolated yield, respectively[71].



In this case, no inconveniences due to the adjacent ester group were encountered, although titanium-induced cyclization of oxoalkanoates are well established in the literature[19,61,72,73]. While indole (**65**) is a precursor for diazepam[74], alkylation of the nitrogen atom in compound (**64**) with chloroacetonitrile afforded indole (**66**) being structurally related to precursors for serotonin and histamine antagonists[75]. With this new approach to the indole nucleus by closure of the C2 – C3 bond, the synthesis of zindoxifen (**67a**), known to be strongly tumor-inhibiting, and a series of structural analogues (**67b – d**) of this pharmacologically important compound was made possible[76].

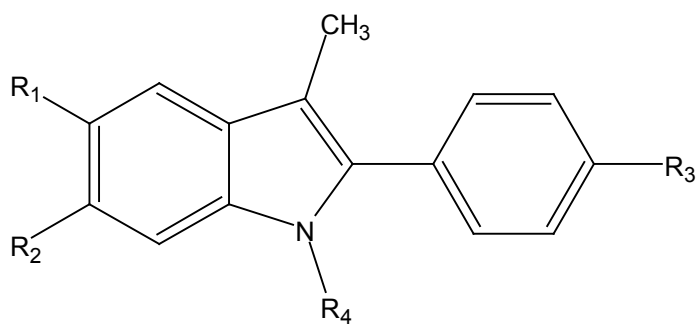


Table 9. Titanium induced synthesis of zindoxifen and analogues

|            | R <sub>1</sub> | R <sub>2</sub> | R <sub>3</sub> | R <sub>4</sub> |
|------------|----------------|----------------|----------------|----------------|
| <b>67a</b> | OAc            | H              | OAc            | E              |
| <b>67b</b> | OH             | H              | OH             | E              |
| <b>67c</b> | OH             | OH             | OH             | Me             |
| <b>67d</b> | OMe            | OMe            | OMe            | Me             |

### 1.5 Synthesis of 2-Quinolones

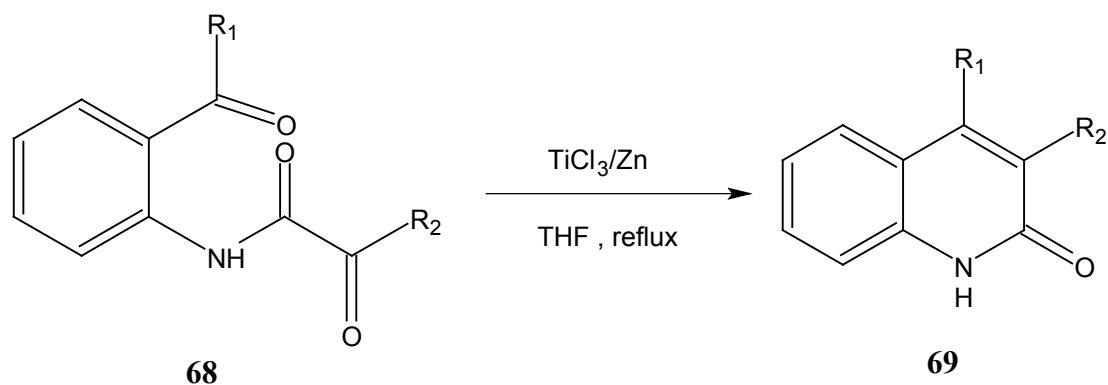
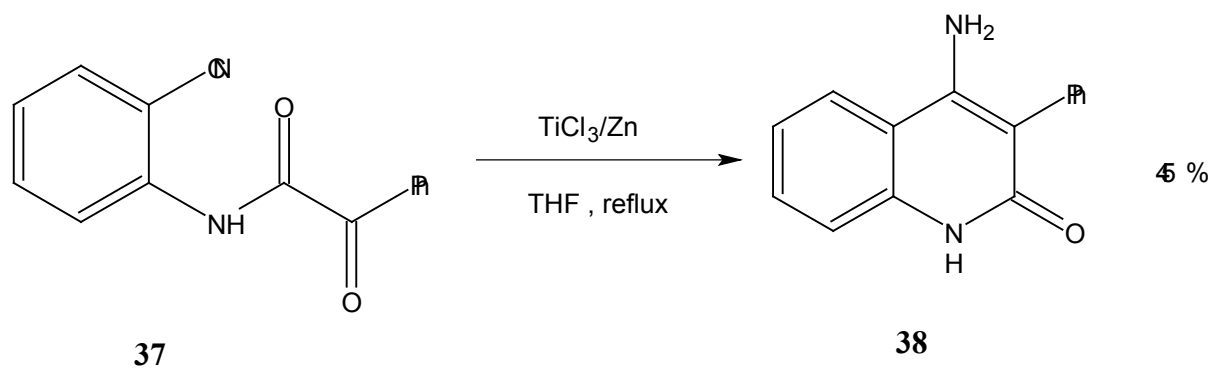


Table 10. Low-valent titanium induced 2-quinolone synthesis

| Entry | R <sub>1</sub> | R <sub>2</sub> | Yield (%) |
|-------|----------------|----------------|-----------|
| 1     | H              | H              | 6         |
| 2     | Me             | H              | 8         |
| 3     | H              | H              | 6         |
| 4     | H              | Me             | 6         |
| 5     | Me             | 2-Thienyl      | 5         |
| 6     | OMe            | OH             | 41        |



The acylation of 2-aminobenzonitrile with phenylglyoxylic acid chloride gave rise to the ester (37) which on treatment with *low-valent* titanium gave rise to 2-amino-3-phenyl-2-quinolone (38) in moderate yield[53].



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## 7. CONCLUSION

Almost any of the organic or organoelement compounds can be synthesized by a choice of several different methods, but for a given compound there usually will be a preferred reaction, depending on such factors as yield, convenience, economy and ease of purification of the product. In the field of metal-catalyzed reactions, the efficiency of the reactions depends on the active surface area of the metal used which is a direct function of their degree of dispersion. The high demand for efficiency, no longer met by the classical methods, has brought further impetus in the development of metal activation.

The primary aim of this work has been the development of a methodological strategy of using highly active metal reagents and in particular titanium. The progress achieved by the use of these reagents, shows how misleading the strange conviction often held, that certain reactions were “worked out”, in the sense of being complete and understood.

The carbonyl coupling reactions has evolved since its inception in the early seventies. The reaction now finds applications in the synthesis of an array of products ranging from strained olefins to all kinds of unusual molecules and natural products. Further expansion of the reaction to the synthesis of varied heterocyclic molecules (such as furans, benzofurans, coumarins, quinolones and indoles) as described herein, signify a major lip forward but by no means the end of the road for titanium in organic synthesis.



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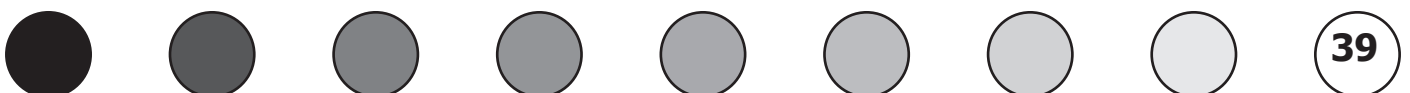
Many thanks go to my friends who have come from far away to be here and listen to me speak. I recognise the presence of Professor and Mrs Asrat Tegaye, Dr Phakiso Mokhahlane and Dr Demetrio Benetello. I thank you sincerely for your efforts and wish you a safe journey back to your families and loved ones.

I am always mesmerized by the WSU choir when and wherever I here them sing. Today is no different, and I thank you from the bottom of my heart.

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Mr Vice Chancellor Sir, Ladies and Gentlemen,

I Thank You.



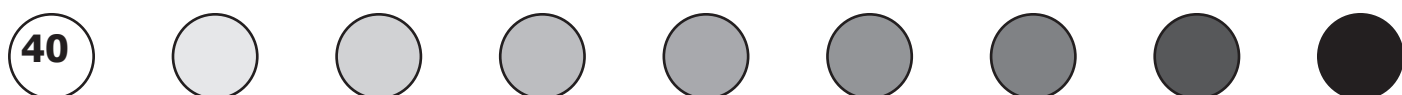
## CITATION FOR PROFESSOR N D JUMBAM

Professor Ndze Denis Jumbam was born in 1956 to Mr Mathias Jumbam and Lucella Labe Jumbam in Shisong-Nso, in the highlands of the interior of West Cameroon. He is the last born in a family of seven brothers and one sister. He trained as a Herbalist under the mentorship of his father and village traditional healers. He qualified and was licenced in 1976 by the Traditional Healers Association of Cameroon.

After completing high school in 1976 he left for Northern Nigeria where he worked for two years as a teacher in St. Peters Junior Seminary. He joined the University of Freiburg in 1978 in Switzerland where he learned German and started his academic career as a chemist. He left for Germany in 1985, where he trained at the Technical University of Leuna Merseburg as a Process Chemist. He did a postgraduate degree in Industrial Management at the Technical University of Berlin. He then moved to Austria where he did a Ph.D in Industrial Organic Chemistry at the Technical University of Graz. During this time, he also did a Postgraduate degree in Environmental Protection Technology.

He returned to Germany in 1991 where he worked as a research scientist in Max-Planck Insitute for Coal Research. He joined the University of Zimbabwe as a lecturer in 1994 and later the University of Transkei in March 1998 as a Senior Lecturer. He worked in this University as Deputy Dean of the Faculty of Science from 1999 to 2002 and as acting Head of Department of Chemistry from 2003 to 2006. He was promoted to Professor of Chemistry in 2007 and later appointed as Director of School of Applied and Environmental Sciences in January 2009, a position he holds to date. Professor Jumbam has a wealth of experience in supervising postgraduate students, has attended national and international conferences and published in peer reviewed journals.

Professor Jumbam is married and has three children.











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