Development of New Organotitanium Intermediates for Applications in Organic Synthesis Using the $TiCl_4/R_3N$ Reagent System

A Thesis
Submitted For The Degree Of
DOCTOR OF PHILOSOPHY

By

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January 2000

To

my parents

K. Pandi
C. Pooranam Pandi

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Statement

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the School of Chemistry, University of Hyderabad, under the supervision of Professor M. Periasamy.

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators.

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Certificate

Certified that the work embodied **in** this thesis entitled '**Development of New Organotitanium Intermediates for Applications in Organic Synthesis Using the $TiCl_4/R_3N$ Reagent System' has** been carried out by Mr. P. Bharathi, under my supervision and the same has not been submitted elsewhere for a Degree.

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29/1/2000

PROFESSOR M. PERIASAMY
(THESIS SUPERVISOR)

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P. Bharathi

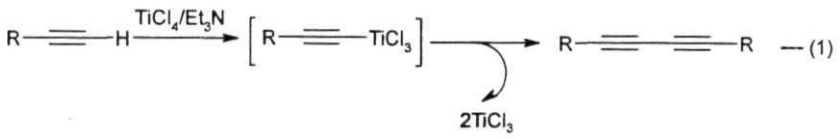
ABBREVIATIONS

aq.	aqueous
Ar	aryl
Bu	butyl
Cp	cyclopentadienyl
DCM	dichloromethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
Et	ethyl
EtOAc	ethyl acetate
EI	electron impact
eq	equation
equiv.	equivalent
HMPT	hexamethylphosphoric triamide
liq.	liquid
Me	methyl
M. p.	melting point
M	metal
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
n-	primary
OAc	acetyl
Ph	phenyl
Pr	propyl
rt	room temperature
THF	tetrahydrofuran
TMEDA	*N,N,N',N'*-tetramethylethylenediamine
TMS	tetramethylsilane

Abstract

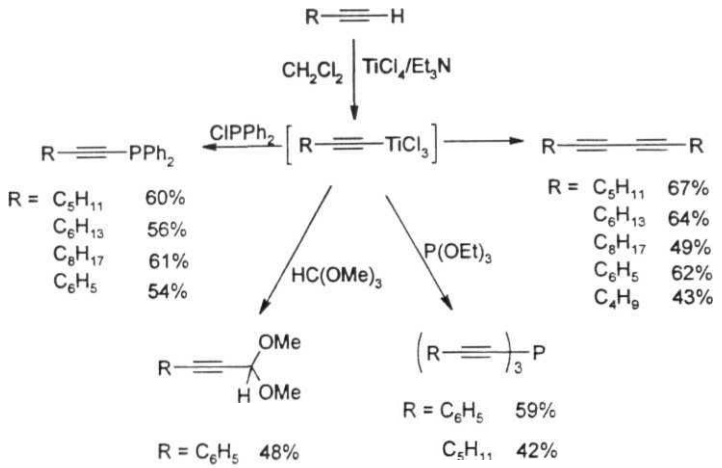
This thesis describes studies on the **"Development of New Organotitanium Intermediates for Applications in Organic Synthesis Using the $TiCl_4/R_3N$ Reagent System". It** comprises of three chapters. Each chapter is subdivided into four parts, namely **Introduction, Results and Discussion, Conclusions** and **Experimental Section** along with **References.** The work described in this thesis is exploratory in nature and the chapters are arranged in the order the investigations were executed.

The Chapter 1 deals with the applications of the alkynyltitanium reagents prepared using 1-alkyne/$TiCl_4/R_3N$ system. The alkynyltitanium reagents were prepared directly from 1-alkynes without using other organometallic reagents such as RLi or RMgX (eq 1).

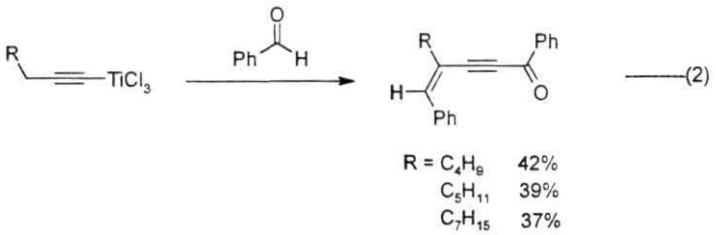


Whereas, the 1,3-diynes were isolated in 49-67% yield in runs without electrophiles, the corresponding addition/substitution products were obtained with electrophiles (Scheme 1).

Scheme 1

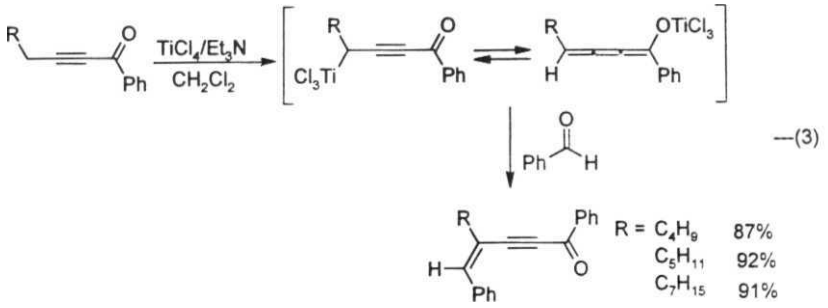


It has been observed that the alkynyltitanium reagent reacts with 2 equivalents of benzaldehyde to give the corresponding enynone (eq 2).



Most probably, the enynone formation involves an alkynyl ketone intermediate that undergoes further metalation and addition to another benzaldehyde. This was further confirmed by carrying out the reaction starting

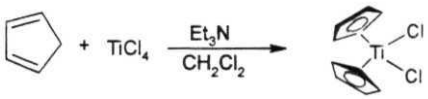
from the alkynyl ketone. The transformation was examined with various alkynyl phenyl ketones (eq 3).



—(3)

The mechanistic aspects of these transformations are discussed. Attempts towards the reaction with other electrophiles such as CO and CO_2, were not successful.

The metalation of cyclopentadiene with the $TiCl_4/Et_3N$ reagent was briefly examined. It was observed that the titanocenedichloride was obtained in 74% yield (eq 4).

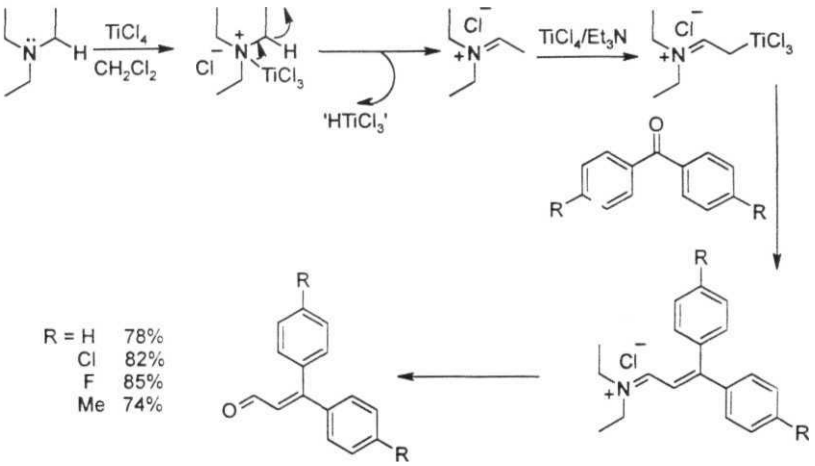


—(4)

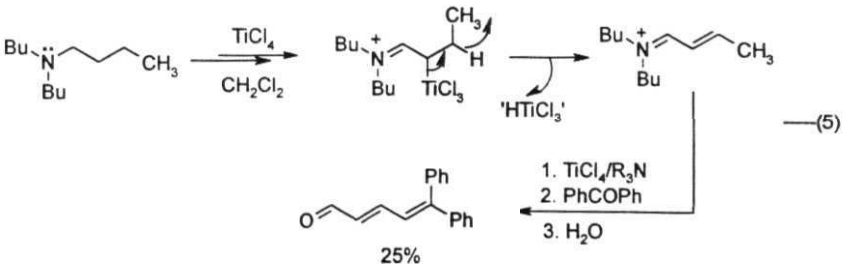
In Chapter 2, studies on the preparation of iminium ion intermediates by the reaction of trialkylamines with $TiCl_4$ and their applications in organic synthesis are described. The reaction of $TiCl_4$ with trialkylamines at 0-25 °C

leads to iminium ions that on metalation **followed by reaction with diaryl** ketones give a,p-unsaturated aldehydes (Scheme **2).**

Scheme 2.

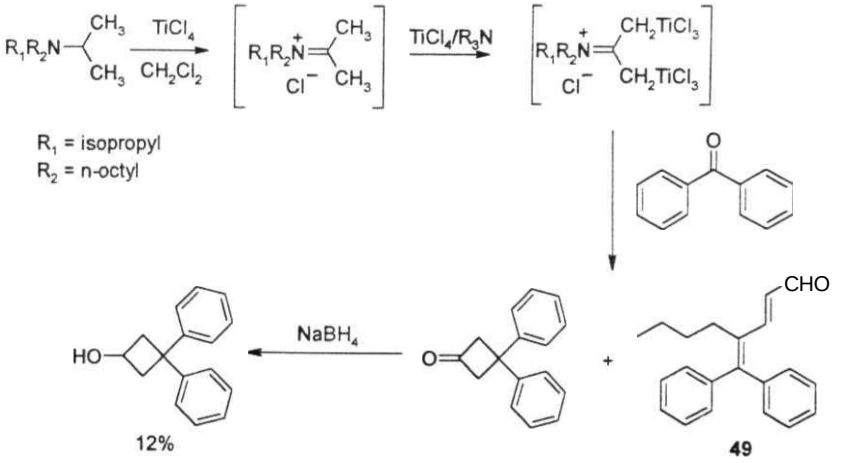


This transformation was also found to be general for various ketones. Reactions using several other amines were also examined. In the case of tributylamine, there is further dehydrogenation of the initially formed iminium ions (eq 5).



The use of cyclic *N*-alkylamines and *N,N*-diisopropyl-*N*-alkylamines for the preparation of the corresponding iminium ions was also examined. Interestingly, it was observed that the iminium ion derived from *N,N*-diisopropyl-*N*-octylamine reacts with benzophenone to give an inseparable mixture of the aldehyde 49 and 3,3-diphenylcyclobutanone. The 3,3-diphenyl-cyclobutanol (12%) was obtained by the reduction of the mixture of aldehyde 49 the corresponding cyclobutanone using $NaBH_4$ (Scheme 3).

Scheme 3.

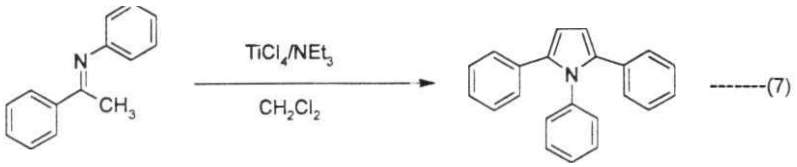


Reaction of tribenzylamine with $TiCl_4$ gave dibenzylamine and benzaldehyde (eq 6).

$$(PhCH_2)_3N: \xrightarrow[CH_2Cl_2]{TiCl_4} (PhCH_2)_2NH + PhCHO \qquad \text{---(6)}$$

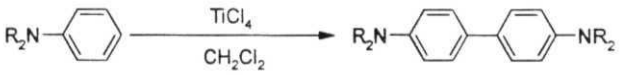
Abstract

In Chapter 3, studies on the use of the $TiCl_4$ and Et_3N for other synthetic applications are described. It was observed that the reaction of certain aryl methyl ketimines with $TiCl_4/Et_3N$ produces the 2,5-diarylpyrrole in good yields (eq 7).



-------(7)

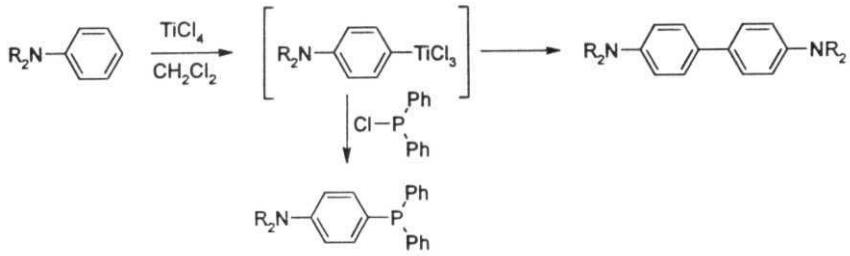
Reaction of *N,N*-dialkyl-*N*-arylamines, led to the formation of the corresponding benzidines (eq 8).



—(8)

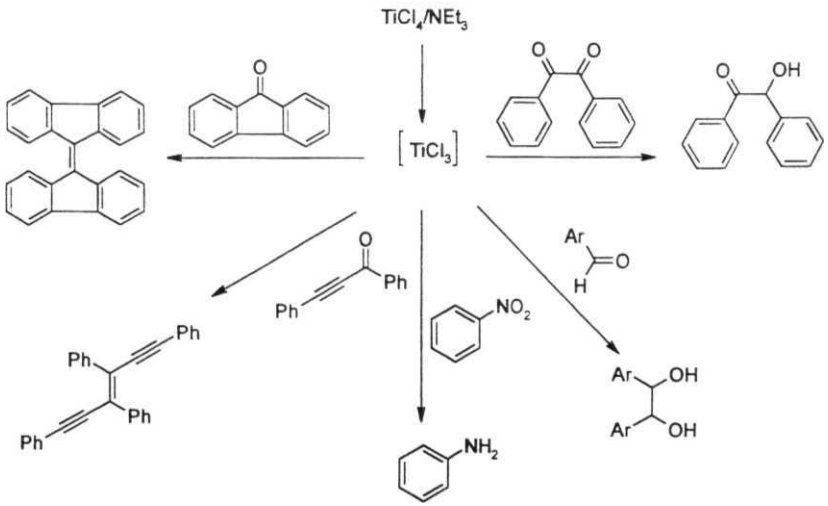
Several tertiary alkyl anilines were converted into the corresponding benzidine derivatives. Most probably, these reactions go through aryltitanium intermediates. The organometallic intermediate was trapped using chlorodiphenylphosphine as electrophile (Scheme 4). Mechanistic pathways of these interesting transformations were considered.

Scheme 4.



Synthetic applications of low valent titanium species formed in the reaction of $TiCl_4$ with Et_3N were also examined (Scheme 5).

Scheme 5.



The results are discussed in comparison with the literature reports on the use of low valent titanium reagents in organic synthesis.

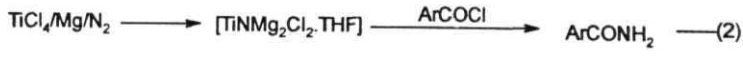
General Introduction

In recent years, the transition metal reagents are widely used in organic synthesis. Among the transition metal reagents that are used in their various oxidation states in organic synthesis, the titanium reagents are by far the most versatile. The applications of titanium reagents range from their use in achieving better selectivity of known organic transformations to the exploration of novel reactions.

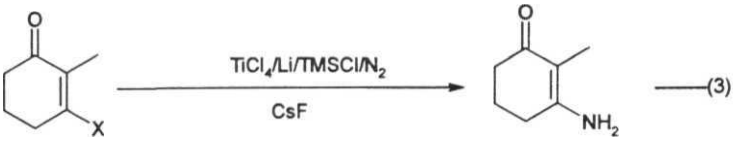
Several titanium reagents have become indispensable in organic transformations. The use of $TiCl_4$ as Lewis acid is well-established chemistry of wide scope.[1] The Zieglar-Natta catalysis using $TiCl_4$-$AlEt_3$, is an important polymerization process (eq 1).[2]

—(1)

Molecular nitrogen can be fixed under mild conditions using $TiCl_4$/RMgX or RLi, Cp_2TiCl_2/RMgX or RLi or $LiAlH_4$.[3] Later, KOBu-t and sodium naphthalenide along with TiCU was used for the reduction of N_2 to NH_3.[4] The titanium-nitrogen complex [$TiNMg_2Cl_2$.THF], prepared using TiCU-Mg under N_2, converts acid chlorides to primary amides (eq 2).[5] More recently, it has been reported that TiCU. in alliance with Li/TMSCl, mediates the nitrogen-fixation reactions (eq 3).[6]



—(2)



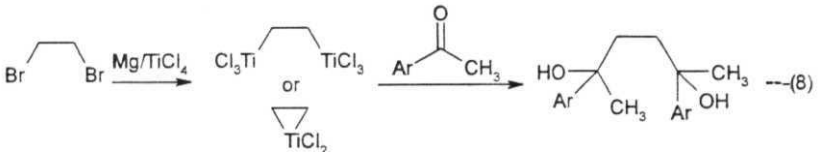
The low valent titanium species, generated by the reduction of $TiCl_4$ using metals and metal hydrides, have found numerous applications in deoxygenative reductive coupling of carbonyl compounds (e.g. McMurry reaction, eq 4).[7]

The Cp_2TiCl_2 is a reagent of choice for many catalytic and stoichiometric reactions.[8] In combination with $(CH_3)_3Al$ (Tebbe reagent), it has been used for olefination of carbonyl compounds (eq 5).

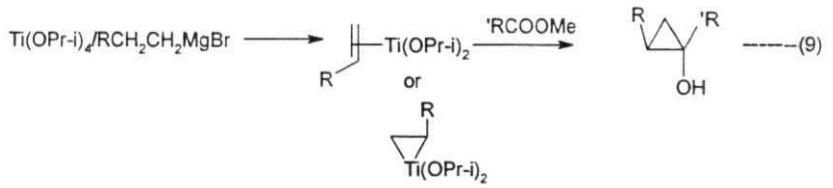
The $TiCl_4/CH_2Br_2/Zn$ reagent system is used in Wittig type olefination of carbonyl compounds (eq 6).[9]

The Me_2TiCl_2 reagent (Reetz reagent) has been employed in gem-dimethylation of carbonyl compounds (eq 7).[10]

Numerous reports indicate that the **transmetalation** of RLi or **RMgX** reagents with titanium reagents leads to better **chemo-**, **regio-**, and stereoselectivities.[11] In recent years, there have been sustained efforts on the preparation and use of 1,2-diorganometallic reagents **(eq 8)**.[12 13]



The Kulinkovich reaction involving organotitanium species is a useful reaction for the preparation of cyclopropyl derivatives (eq **9**).[14]



The Kulinkovich recipe **Ti(OPr-i)$_4$/i-PrMgX** has been widely used in many synthetic transformations.[15]

In continuation of our efforts on the preparation and use of **'Cp$_2$Ti'**[12] and **1,2-diorganometallics** prepared using **TiCl$_4$/Mg/BrCH$_2$CH$_2$Br**,[13] we have undertaken the present study, which deals with the development of reactive **organotitanium**

intermediates formed in the reaction of various organic substrates using the $TiCl_4/R_3N$ reagent system.

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Chapter 1

Studies on the alkynyltitanium reagent obtained using 1-alkyne/$TiCl_4$/Et_3N system

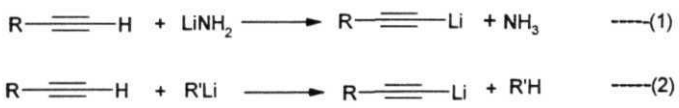
1. 1 Introduction

The $TiCl_4/Et_3N$ reagent system has been extensively used in the preparation of titanium enolates for synthetic applications.[1] It appeared desirable to undertake studies on the use of $TiCl_4/Et_3N$ with organic substrates that would result in the formation of organotitanium intermediates. Hence, we have examined the use of 1-alkynes to obtain the corresponding $RC{\equiv}CTiCl_3$ species. Accordingly, it may be of interest to briefly review the various ways of preparation of the alkynylmetallics and their synthetic applications here.

1.1.1 Preparation of various alkynylmetal reagents

a) Preparation of alkynyllithium reagents

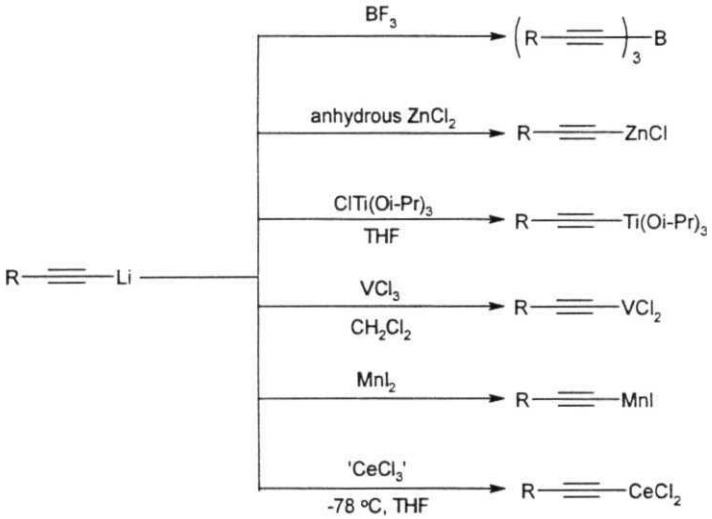
Alkali amides in liquid ammonia or alkyl lithium reagents are the most frequently used bases in the preparation of alkynyllithium reagents from 1-alkynes (eq 1 & 2).[2]



These alkynyllithium reagents are very much useful in the synthesis of other alkynyl metal reagents. For example, the alkynylcerium,[3] alkynylvana-

dium,[4] alkynylzinc,[5] alkynylmanganese[6] and alkynylborane[7] reagents are readily obtained by the reaction of alkynyllithium reagents with the corresponding metal salts or halides. Reaction of alkynyllithium with chlorotriisopropoxytitanium produces the corresponding alkynyltriisopropoxytitanium[8] (Scheme 1).

Scheme 1.

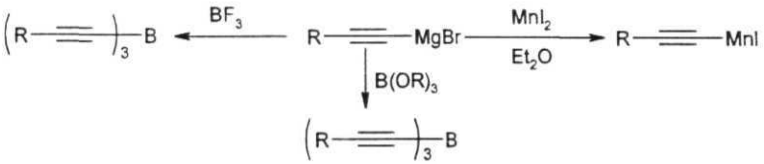


b) Preparation of alkynylmagnesiumhalides

The reaction of 1-alkynes with EtMgBr in THF gives the corresponding alkynylmagnesium bromide (eq 3).[2]

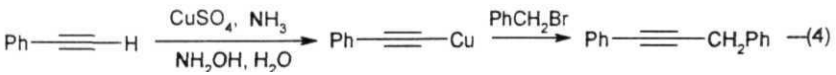
Similar to **alkynyllithium** reagents, alkynylmagnesium halides are also used in the preparation of other alkynyl metal reagents by transmetalation reactions (Scheme 2).[11,6]

Scheme 2.

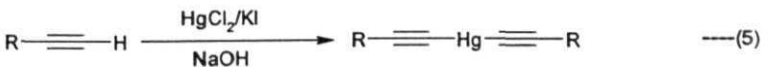


c) Direct formation of alkynylmetal reagents

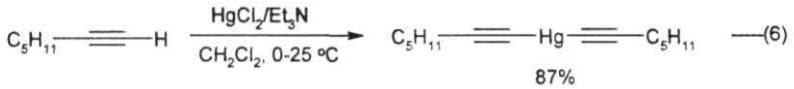
Some alkynylmetal reagents can be also directly prepared from 1 -alkynes without going through transmetalation reaction. Among them, the alkynylcopper reagents are the most versatile. Reaction of 1-alkynes with a mixture of copper(II)sulphate, concentrated aq. NH_3 and hydroxylamine produces the alkynylcopper reagent (eq 4).[9]



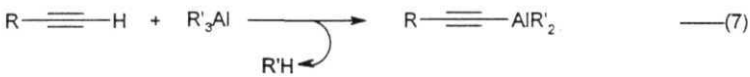
Alkynylmercury reagents are obtained in the reaction of HgI_2, prepared using $HgCl_2$, KI and NaOH, with 1-alkynes (eq 5).[10a]



We have observed that addition of Et_3N to a mixture of 1-alkyne and $HgCl_2$ in CH_2Cl_2 readily produces the corresponding dialkynyl mercury in good yield, 87% (eq 6).[10b]



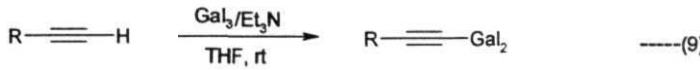
Alkynyl aluminum species are obtained in the reaction of 1-alkynes with trialkyl- or triarylaluminum compounds (eq 7).[11]



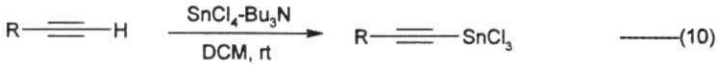
Coordination complexes of triethynylaluminum with THF, dioxane, trimethylamine and pyridine have been prepared. The tris-(propynyl)-, tris-(hexynyl)-, and tris-(phenylethynyl)- aluminum compounds are also known.[11]

Triethylgallium reacts with alkynes to give gallium acetylides (eq 8).[11]

Recently, it has been reported that 1-alkynes react with GaI_3 in the presence of R_3N to produce the corresponding alkynylgallium species (eq 9).[12]

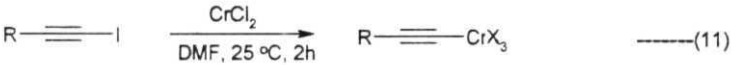


Yamaguchi **et.al.**, reported that the reaction of **1-alkynes** with $SnCl_4$-Bu_3N produces the **alkynyltin** reagents (eq **10**).[13]



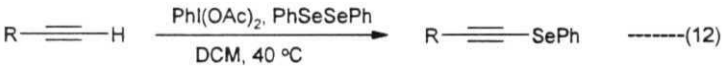
——(10)

Reduction of alkynyl halides by $CrCl_2$ gives the alkynylchromium reagents (eq **11**).[14]



——(11)

The alkynylselenides are **useful** intermediates in organic synthesis. Much attention has been devoted to their preparation and applications.[15] **1-Alkynes** react with iodobenzene diacetate and PhSeSePh at 40 °C to give the corresponding acetylenic selenides (eq **12**).[15]



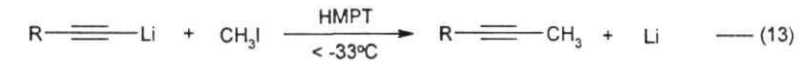
——(12)

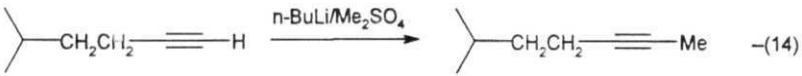
1.1.2 Synthetic applications of alkynylmetal reagents

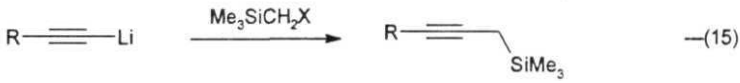
The alkynylmetal reagents exhibit the reactivity similar to other organometallic reagents. Alkylation, acylation and halogenation are some of the most often reported reactions.

a) Reactions of alkynyllithium reagents

Alkylation of alkynyllithium reagents are carried out using MeI in HMPT (eq 13).[2] Recently, Me_2SO_4[16] and trimethylsilylhalides[17] were used to obtain the corresponding derivatives (eq 14 & 15).







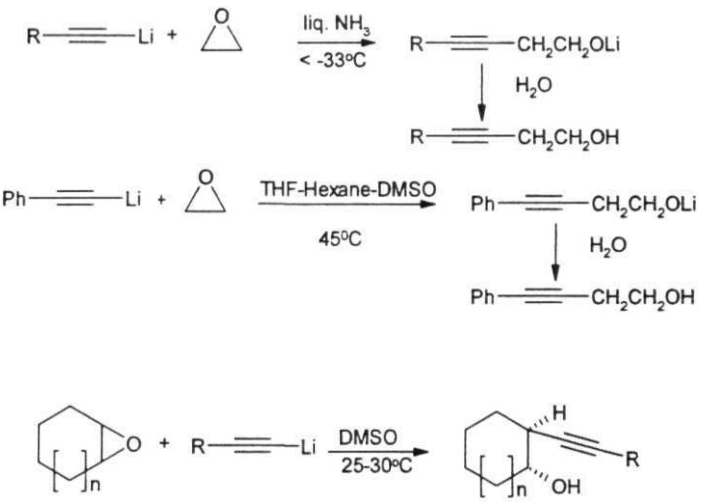
The addition of alkynyllithium reagents to carbonyl compounds leads to the formation of propargyl alcohols (eq 16).[2]

Similar reactivity was also observed with alkynylcerium,[3] alkynylgallium,[12] alkynyltin[13] and alkynylmagnesium reagents.[2]

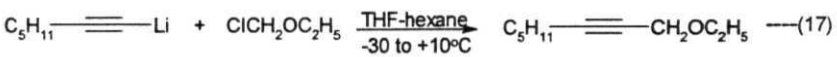
The 'homo-propargylic alcohols' are prepared conveniently in molar scale by the reaction of oxiranes with lithium acetylides in liquid ammonia.[2]

Bicyclicoxiranes are opened by alkynyllithium reagents to afford **stereochemically** pure **β-hydroxy** derivatives in good yields (Scheme 3).[18]

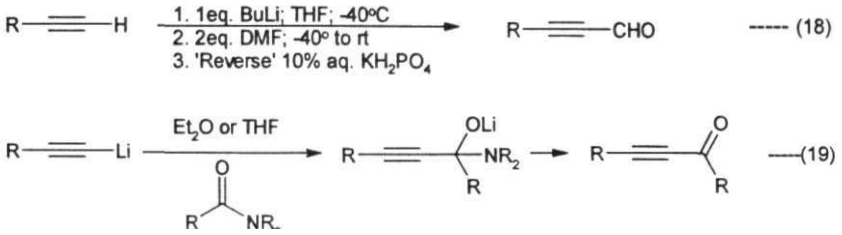
Scheme 3.



Alkynylethers are readily obtained by the reaction of alkynyllithium with **α-chloroethers** (eq 17).[2]

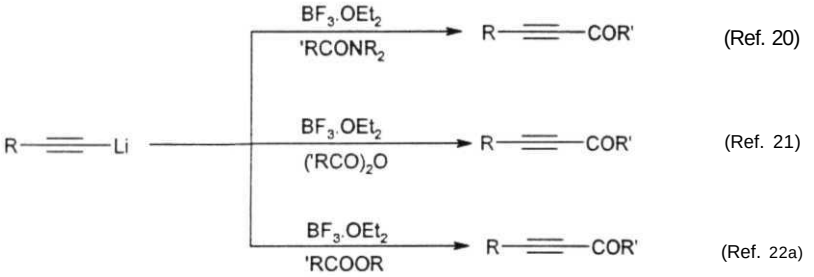


Reaction of alkynyllithium species with dimethylformamide gives the corresponding aldehyde in good yields (eq **18**).[19] The corresponding ketones are obtained using other **acyl** tertiary amides (eq 19).[2]

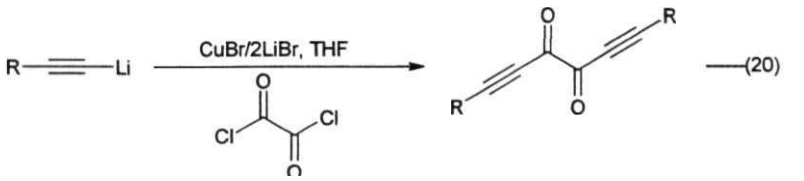


Alkynyl ketones are also conveniently synthesized by the reaction of alkynyllithium with tertiary amides, anhydrides and esters via alkynylborates (Scheme 4).

Scheme 4.



A convenient preparation of dialkynyl-l,2-diketones was reported using lithium acetylides and oxalyl chloride in the presence of CuBr/LiBr (eq 20).[22b]

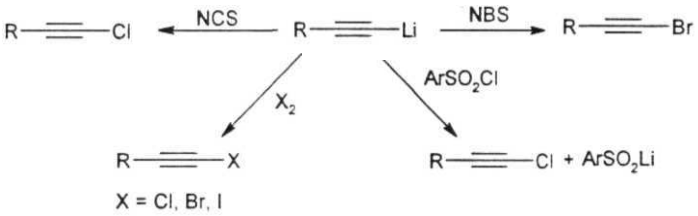


Pouring of the alkynyllithium on powdered dry-ice gives the corresponding propiolic acid. Yields are mostly excellent and often quantitative (eq 21).[2]

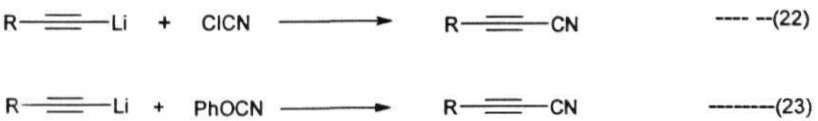
—(21)

Halogenation using Cl_2, Br_2, and I_2 are carried out most conveniently with the lithium acetylides. Arenesulfonyl chloride and TV-halo succinimides are also used for this purpose (Scheme 5).[2]

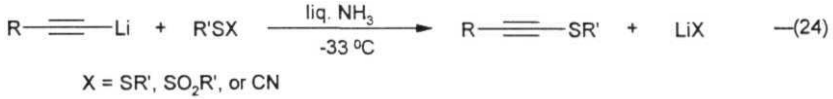
Scheme 5.



A number of alkynyl nitriles have been prepared from alkynyllithium and cyanogen chloride using Et_2O as solvent (eq 22).[2] Cyanogen bromide is unsuitable because the acetylide attacks on bromine. It was reported that phenyl isocyanate could be a very good variant for ClCN (eq 23).[23]

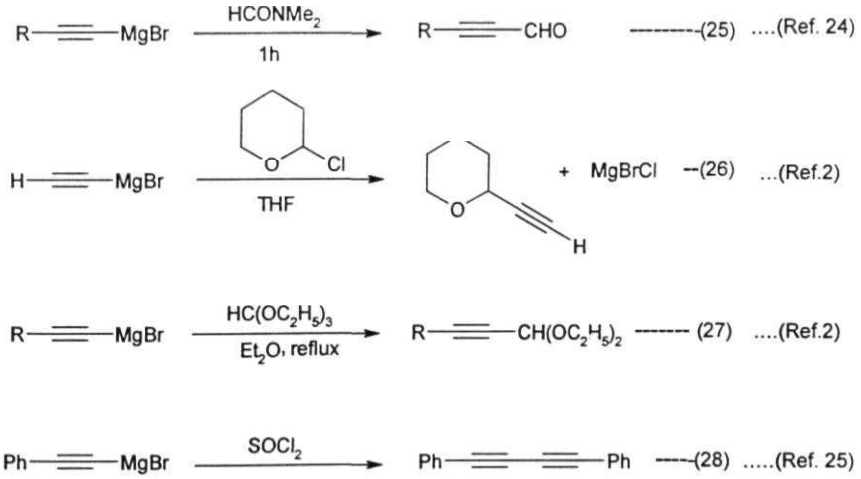


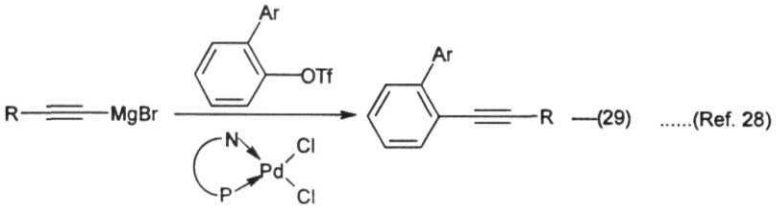
Alkynyllithium reagents react readily with **disulfides, R'SSR',** thiocyanates, **R'SCN,** and **thiosulfonates, $R'SSO_2R'$** (eq 24). The reactions can be carried out in liquid ammonia as well as in organic solvents and generally give excellent yields of the acetylenic **sulfides.**[2]



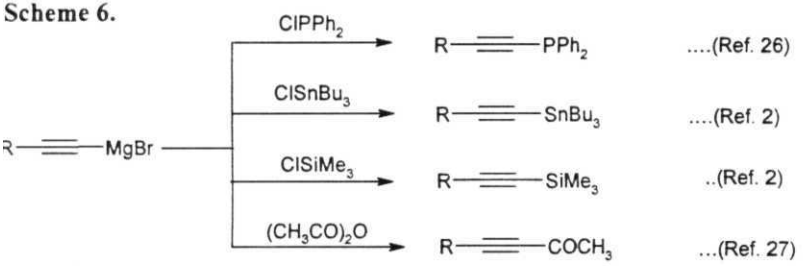
b) Reactions of alkynylmagnesiumhalides

Alkynylmagnesium reagents are relatively mild compared to the lithium reagents. Most of the reactivities shown by alkynyllithium reagents were also observed in the case of alkynylmagnesium reagents. These reactions are presented in the following equations and Scheme 6.





Scheme 6.

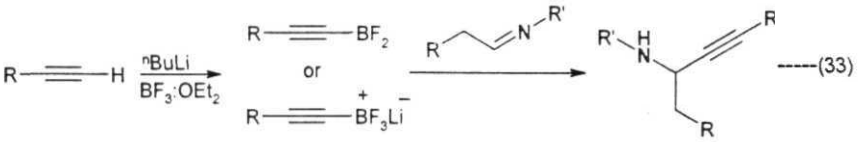


The synthesis of higher alkynes from ethynyl magnesium bromide has been reported under palladium catalysis. Sodium acetylide and lithium acetylide also exhibit the same reactivity (eq 32).[31]

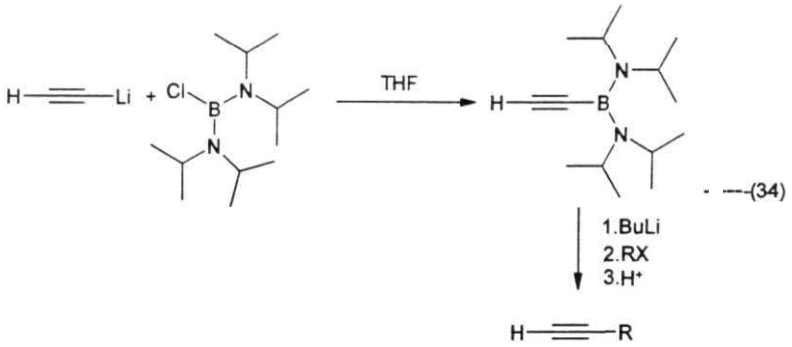
c) Reactions of other alkynylmetal reagents

Interesting unique reactivities and selectivities were also observed in the reaction of some other alkynyl organometallic species.

Generally, the imines exert poor reactivity in the nucleophilic addition of organometallic reagents.[32a,32b] However, the alkynylboranes, prepared using alkynyllithium and $BF_3.OEt_2$, add to aldimines to afford β-aminoalkynes in good yields (eq 33).[32c]



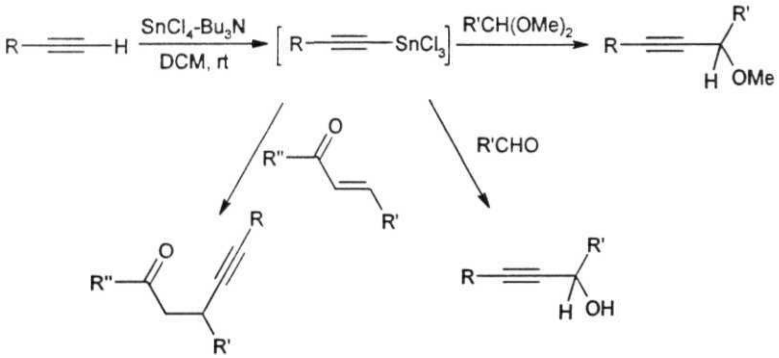
Preparation of higher terminal alkynes was reported using ethynyl boron derivatives (eq 34).[32d]



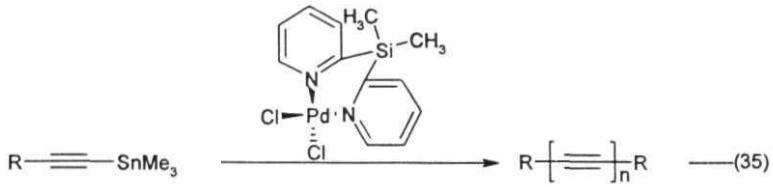
In the reaction with oxiranes, the classical acetylides, derived from alkali metals, give low yields and become inapplicable as the degree of substitution of oxiranes is increased.[32e] Alkynyl boranes, generated *in situ* from alkynyllithium reagents and BF_3:OEt_2, were found to react with oxiranes under mild reaction conditions to give P-hydroxy acetylenes in high yields.[32e] Carboxylic acid anhydrides give the corresponding a,P-acetylenic ketones.[32f]

The alkynyltin compounds react with aldehydes, acetals and enones (Scheme 7).[13] The $Sn(OTf)_2$/amine system is also effective for the synthesis of propargyl alcohols from 1-alkynes and carbonyl compounds.[33]

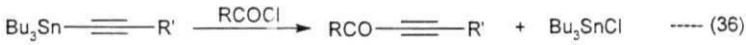
Scheme 7.



Recently, the alkynyltin reagents were used to prepare extended linear-carbon polymers under Pd catalysis (eq 35).[34]

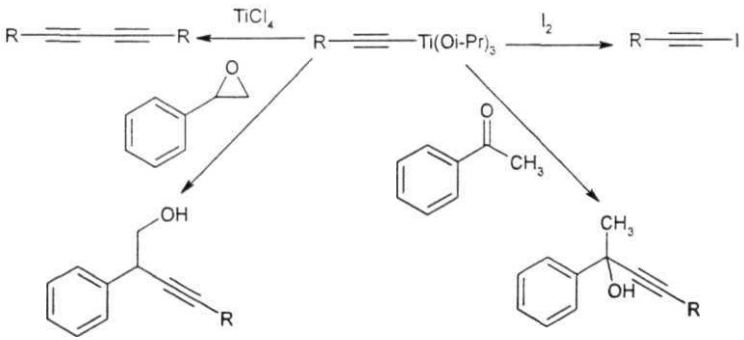


Acylation of alkynyltin was carried out using $Pd(PPh_3)_4$. The corresponding alkynyl ketone was obtained in good yields (eq 36).[35]

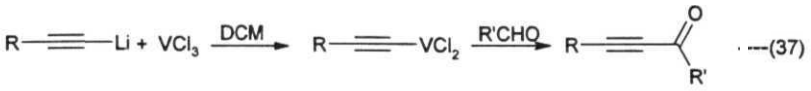


In 1987, Seebach et. al., reported the reactivity of chlorotriisopropoxytitanium with a few electrophiles (Scheme 8).[8]

Scheme 8.

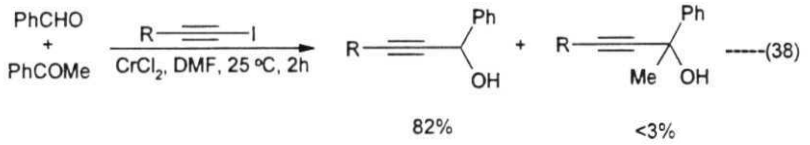


The alkynylvanadium reagents readily react with aldehydes leading to the corresponding α,β-acetylenic ketones in good to moderate yields through nucleophilic addition-oxidation mechanism (eq 37).



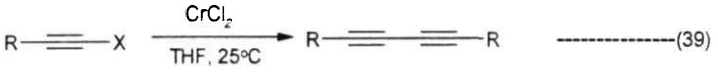
---(37)

Alkynylchromium reagents react selectively with aldehydes in the presence of a ketone (eq 38).[14]



-----(38)

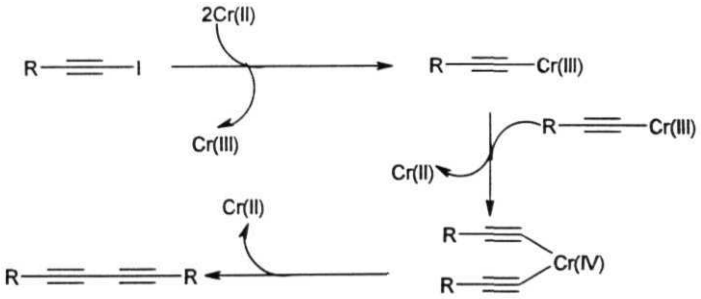
In the absence of electrophiles, alkynylchromium reagents give the corresponding symmetrical 1,3-diyne (eq 39).[14]



----------(39)

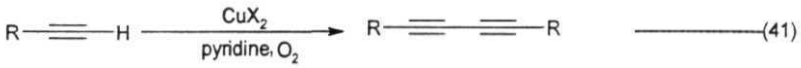
The reaction is believed to go through the reaction pathway shown in Scheme 9.

Scheme 9.



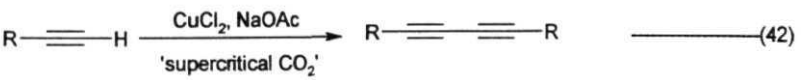
On reaction with acyl chlorides, alkynylmanganese reagents lead only to the ketone (eq 40). It is of interest to note that the corresponding organomagnesium or organolithium reagents lead to alcoholic side products.[6]

Eglinton coupling involves the use of cupric salts and pyridine in stoichiometric amounts (eq 41).[36]

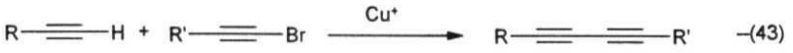


The Glaser coupling of 1-alkynes involves the use of catalytic amounts of copper halides in the presence of ammonia or ammonium chloride.[37a] It was found that alkynes can be coupled within minutes at room temperature with O_2 or air using a catalytic amount of an amine complex of a copper (II) salt in an organic solvent.[38]

Very recently, the Glaser coupling has been carried out in 'supercritical CO_2' (eq 42).[37b]

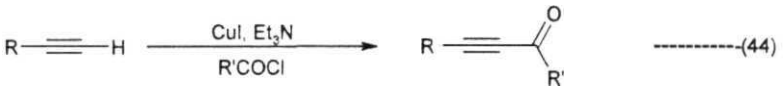


The unsymmetrical diynes can be obtained by Cadiot-Chodkiewicz coupling using a haloalkyne and a copper acetylide (eq 43).[39]



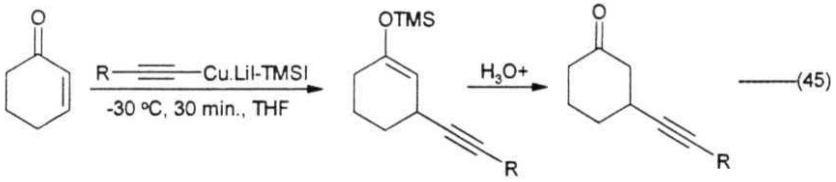
–(43)

The copper acetylides are readily acylated using acid chlorides to give a,p-acetylenic ketones (eq 44).[40]



----------(44)

In the presence of trimethylsilyl iodide and lithium iodide in THF, the otherwise unreactive copper acetylides add to enones to provide good yields of the silyl enol ethers of β-alkynyl carbonyl compounds (eq 45).[41]



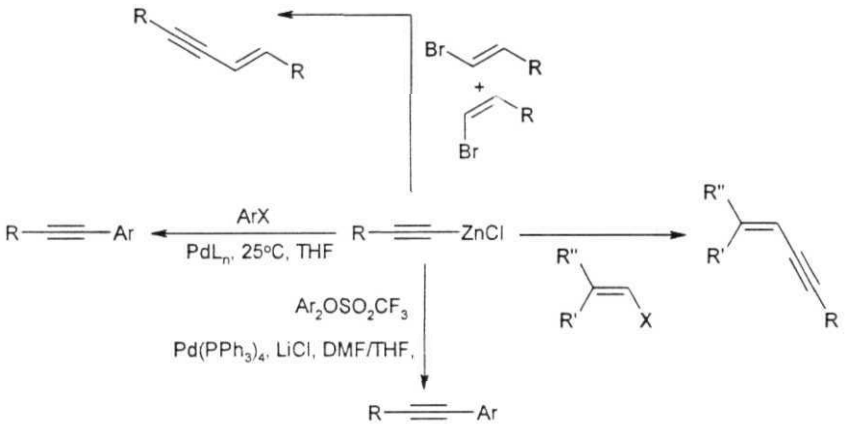
(45)

The palladium catalyzed reactions of alkynylzinc chlorides with alkenyl iodides or bromides provide the corresponding terminal or internal enynes in good yields with high stereospecificity (>97%).[5]

Palladium catalyzed cross-coupling reactions of 1-alkynylzinc chlorides with a diastereoisomeric mixture of alkenyl halides have been described.[5] The

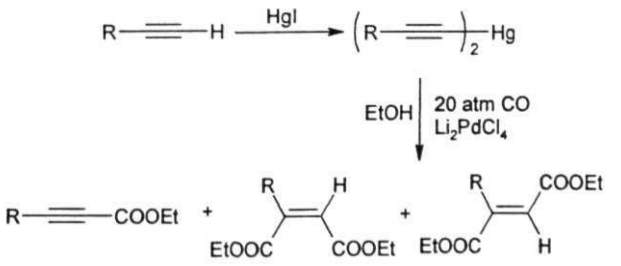
(*E*)-bromoalkene reacts preferentially in these reactions to afford good yields of (*E*)-enynes having high chemical purity.[42] Arylation of alkynylzinc chloride are conveniently carried out using $Ar_2OSO_2CF_3$[43] and ArX[44] (Scheme 10).

Scheme 10.



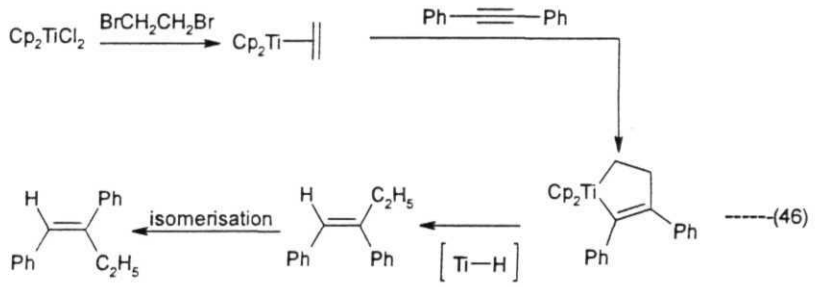
Alkynylmercurials undergo carbonylation reactions under 20 atm. of CO to give the propiolic ester besides olefinic dicarboxylic acid (Scheme 11).[45]

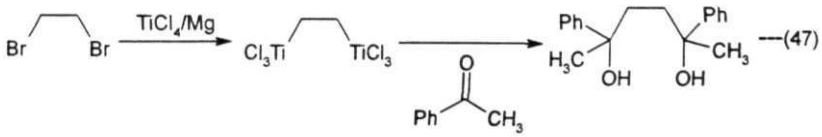
Scheme 11.



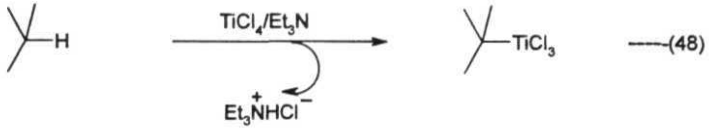
1. 2 Results and Discussion

Previously, efforts were made in this laboratory towards the preparation and applications of the titanocene **"Cp_2Ti"** species[46] (eq 46) and the use of **$BrCH_2CH_2Br/TiCl_4/Mg$** system for the preparation of **1,2-diorganometallic** species[47] for synthetic applications (eq 47).





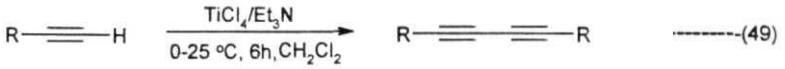
In continuation of these efforts, we have decided to examine the use of **$TiCl_4/Et_3N$** reagent system for the direct metalation of organic compounds (eq 48).



The $TiCl_4/Et_3N$ system has been widely used in organic synthesis for the preparation of titanium enolates through removal of acidic hydrogen from the corresponding carbonyl compounds.[1] The acidity of the inactivated hydrocarbon moieties is expected to be in the order: $sp > sp^2 > sp^3$.)bviously, we decided to examine the use of the 1-alkynes for this purpose.

1. 2. 1 The formation of alkynyltitanium reagent

We have observed that the reaction of $TiCl_4$ with a mixture of terminal alkynes and trialkylamines readily produces the symmetrical 1,3-diynes (eq 49).



The reaction was carried out with several 1-alkynes and the results are summarized in Table 1. The diynes were isolated in 49-67% yields. Phenyl acetylene and 1-heptyne gave 62% and 67% yields respectively (Table 1, entries 1 and 5). 1-Octyne, 1-dodecyne, 1-decyne and 1-hexyne gave 64%, 51%, 49% and 43% yields respectively (Table 1, entries 2-4 and 6).

Table 1. The reaction of 1-alkynes with $TiCl_4/R_3N$

No.	Substrate	Amine	Product	Yield (%)
1.	$C_6H_5-\equiv-H$	Et_3N	$C_6H_5-\equiv\equiv-C_6H_5$ (1)	62
2.	$C_6H_{13}-\equiv-H$	Et_3N	$C_6H_{13}-\equiv\equiv-C_6H_{13}$ (2)	64
3	$C_{10}H_{21}-\equiv-H$	Et_3N	$C_{10}H_{21}-\equiv\equiv-C_{10}H_{21}$ (3)	51
4	$C_8H_{17}-\equiv-H$	Et_3N	$C_8H_{17}-\equiv\equiv-C_8H_{17}$ (4)	49
5	$C_5H_{11}-\equiv-H$	Et_3N	$C_5H_{11}-\equiv\equiv-C_5H_{11}$ (5)	67
6	$C_4H_9-\equiv-H$	Et_3N	$C_4H_9-\equiv\equiv-C_4H_9$ (6)	43
7	$C_5H_{11}-\equiv-H$	$^nBu_3N$	$C_5H_{11}-\equiv\equiv-C_5H_{11}$ (5)	61
8	$C_5H_{11}-\equiv-H$	$EtN(Pr^i)_2$	$C_5H_{11}-\equiv\equiv-C_5H_{11}$ (5)	58
9	$C_5H_{11}-\equiv-H$	$^nPr_3N$	$C_5H_{11}-\equiv\equiv-C_5H_{11}$ (5)	59

[a] The products were identified by spectral (IR, ^{1}H-NMR and ^{13}C-NMR) and physical constant data and comparison with reported data.
[b] The yields are based on the alkynes used.

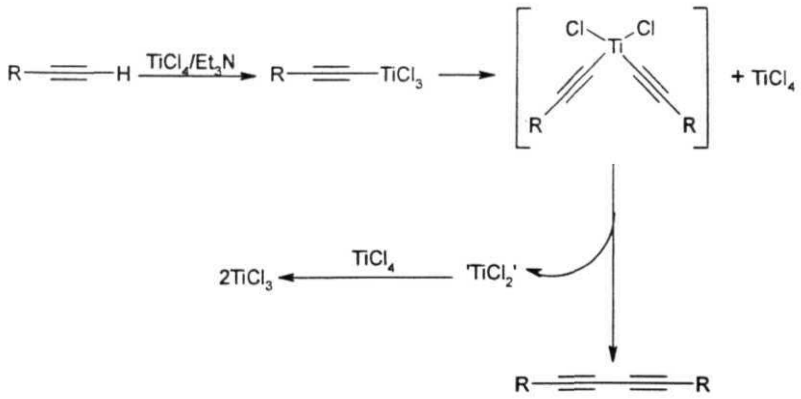
The present conversion of 1-alkynes to symmetrical 1,3-diynes is convenient and easy to carry out from a synthetic point of view.

The effect of various trialkylamines on the yields of diynes was also examined. The reactions using Bu_3N, $EtN(Pr^i)_2$ and Pr_3N, gave 61%, 58% and

59% yields of diyne when 1-heptyne was used (Table 1, entries 7-9). The reaction takes place at room temperature. However, the addition of $TiCl_4$ to the mixture of amine and alkyne was carried out at 0 °C. Chloroform can be used in the place of dichloromethane without significant change in the yields. Reactions using pyridine and diethylamine did not give the diyne and the alkyne remained unaffected.

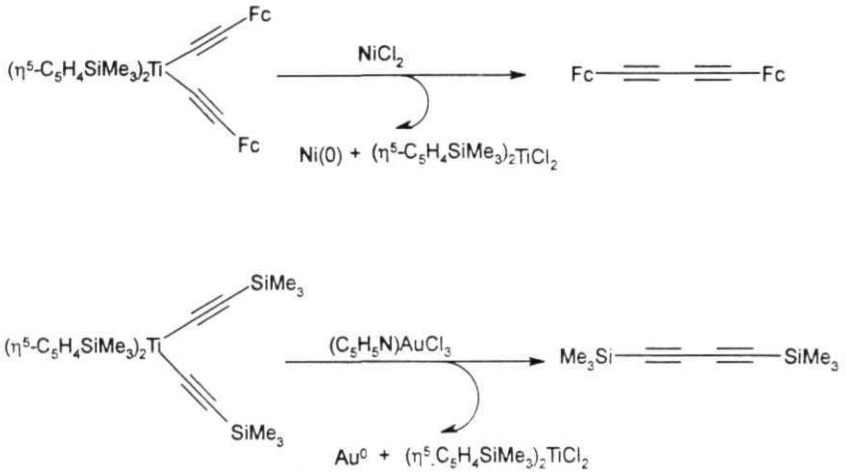
As described in the introductory section, alkynylcopper and alkynyl chromium reagents undergo such dimerization reactions to give the symmetrical 1,3-diynes. A similar mechanistic pathway can be considered to rationalize the present transformation (Scheme 12).

Scheme 12.



It has been previously reported that bis(alkynyl) titanocenes give the 1,3-diynes on reaction with $(C_5H_5N)AuCl_3$[48] and $NiCl_2$.[49] In these reactions, the substituted alkyne moieties are reductively coupled to give 1,3-diynes (Scheme 13).

Scheme 13.



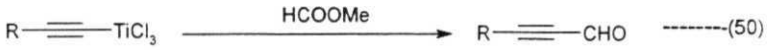
1. 2. 2 Reaction of alkynyltitanium with various electrophiles

The organotitanium reagents have a very rich reaction chemistry with electrophiles.[50] To examine the use of alkynyltitanium generated in *situ* using $TiCl_4/Et_3N$ system, the reactions with various electrophiles were carried out. Initial experiments using carbonyl compounds such as acetophenone indicated the predominant formation of products derived from aldol condensation.

Accordingly, we have examined the use of electrophiles which do not contain α-hydrogen.

1. 2. 2. 1 Reaction of alkynyltitanium with HCOOMe

As described in the introductory section, it was expected that alkynyltitanium reagent would undergo reaction with methyl formate to give the acetylenic aldehyde (eq 50).



--------(50)

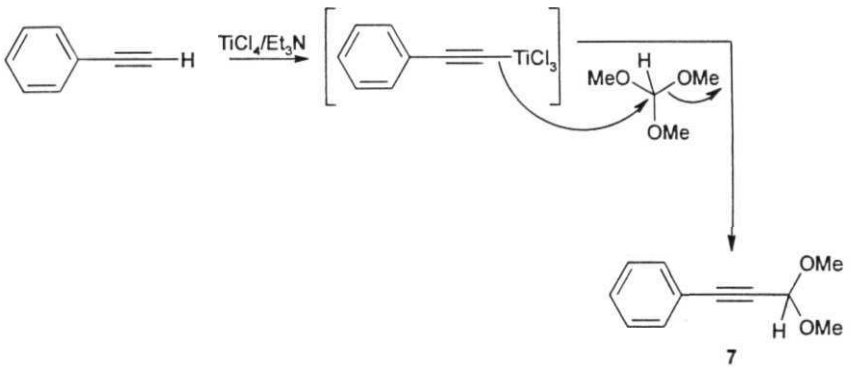
However, the reaction was not clean and a complex mixture of unidentified products was obtained. The unclean reaction may be attributed to further reaction of the expected aldehydic product. As it will be discussed later, such carbonyl compounds lead to further reaction with electrophiles through the corresponding allenic titanium enolates.

1. 2. 2. 2 Reaction of alkynyltitanium with trimethyl orthoformate

The metal acetylides are expected to react with trialkylformates to give the corresponding monoalkynylated acetals.[2] When phenylethynyl titanium reagent was prepared from phenyl acetylene using $TiCl_4/NEt_3$ in the presence of

trimethyl orthoformate the corresponding acetal 7, was isolated in 48% yield (Scheme 14).

Scheme 14.



7

In the case of aliphatic alkynes, (RC≡CH, R= C_5H_{11}, C_8H_{17}), the reaction gave a complex mixture of products. Presumably, the complications here may be due to further reactions of acetal formed.

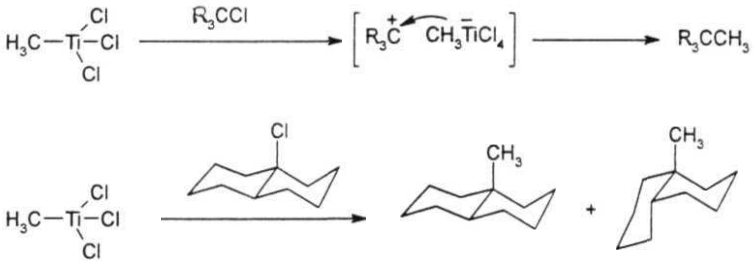
1. 2. 2. 3 Reactions of alkynyltitanium with CO and CO_2

The reaction of alkynyltitanium species was examined by carrying out the reaction of 1 -alkynes with $TiCl_4/Et_3N$ while bubbling of CO and CO_2 in separate runs. In addition to the corresponding diynes, unidentified mixture of products derived from CO or CO_2 were isolated.

1. 2. 2. 4 Reactions of alkynyltitanium with t-BuCl and $PhCH_2Cl$

The methyltitanium reagents exhibit exceptional reactivity with alkyl-halides that are good precursors for the formation of carbocations (Scheme 15).[50]

Scheme 15.

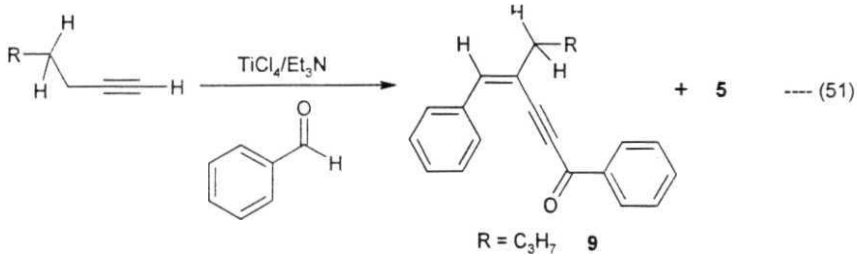


To examine whether such a reactivity can be realized using the $RC{\equiv}CTiCl_3$ species, we carried out the reaction of $RC{\equiv}CH$ with t-BuCl in the presence of $TiCl_4/Et_3N$. Unfortunately, again, a complex mixture of olefinic products (IR, ^{1}H-NMR and ^{13}C-NMR analysis) was obtained in addition to the corresponding diyne and the expected phenyl t-butyl acetylene was not present in the reaction mixture. Similar unclean reaction was also observed in the reaction of 1-heptyne with benzyl chloride and $TiCl_4/Et_3N$.

1. 2. 2. 5 Reaction of alkynyltitanium with benzaldehyde

As outlined in the introductory section, benzaldehyde reacts with the $RC{\equiv}CTi(O^{i}Pr)_3$ to give the corresponding secondary alcohol (Scheme 7).[8]

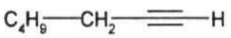
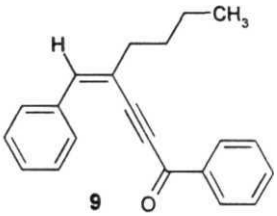
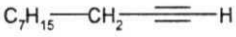
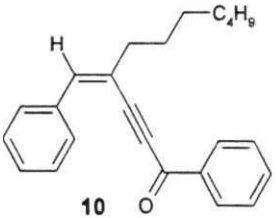
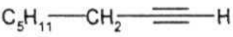
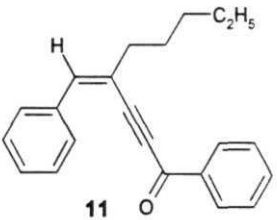
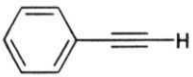
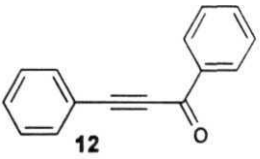
However, the reaction of 1-heptyne and $TiCl_4/Et_3N$ with benzaldehyde is somewhat complicated and the enynone 9 was isolated in 42% yield besides some unidentified polar compounds (eq 51).



The formation of the enynone 9, was found to be general for several other aliphatic alkynes. The results are summarized in Table 2.

In all reactions. the corresponding diyne was isolated as minor products. 1-Heptyne gave the ketone 9 in 42% yield besides the diyne (10%), (Table 2, entry 1). 1-Decyne and 1-octyne produced the ketones 10 and 11 in 37% and 39% respectively besides the corresponding diynes (8% and 11%), (Table 2, entries 2 & 3). In these reactions, some unidentified polar compounds were also formed.

Table 2. The reaction of alkynyltitanium with benzaldehyde

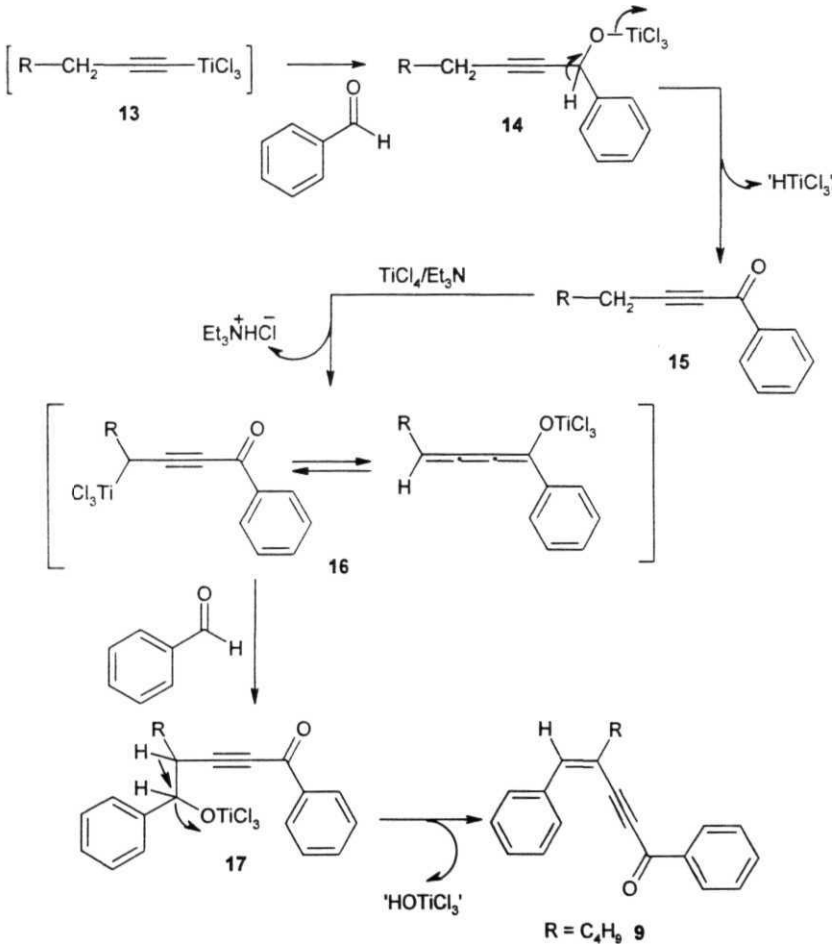
No.	Substrate	Product	Yield (%)
1.		 **9**	42
2.		 **10**	37
3.		 **11**	39
4.		 **12**	31

•The products were identified by spectral and physical constant data (IR, ^{1}H-NMR ^{13}C-NMR and Mass) and comparison with reported data.

[b]The yields are based on the alkynes used.

The formation of the enynone in the case of alkynyltitanium species may be explained by the tentative mechanism outlined in Scheme 16.

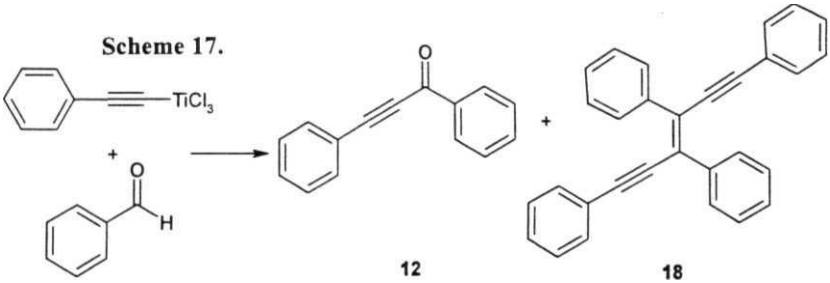
Scheme 16.



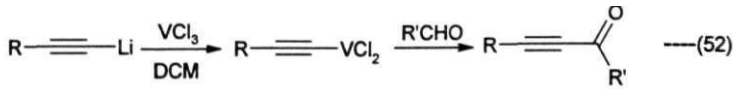
The alkynyltitanium 13 adds to the aldehyde to give the alkoxy intermediate 14 which loses '$HTiCl_3$' species giving the ketone 15. The propargylic carbon in the ketone 15 is further metalated by $TiCl_4/Et_3N$ giving the organometallic intermediate 16, which can give the enynone 9, on reaction with benzaldehyde through the intermediate 17.

It was of interest to examine the reaction with phenyl acetylene as it cannot lead to the enynone. It was observed that in this case the corresponding ketone 12 (31%) and the olefin 18 (12%) were obtained (Scheme 17). Presumably, the olefin 18 would have formed through the McMurry coupling of the ketone 12.

Scheme 17.



Previously, such a reactivity pattern was reported with alkynylvanadium reagents, which give alkynyl ketones on reaction with aldehydes (eq 52).[4] However, the vanadium reagents do not lead to any further reaction at the propargylic position as observed here with the alkynyltitanium intermediates.



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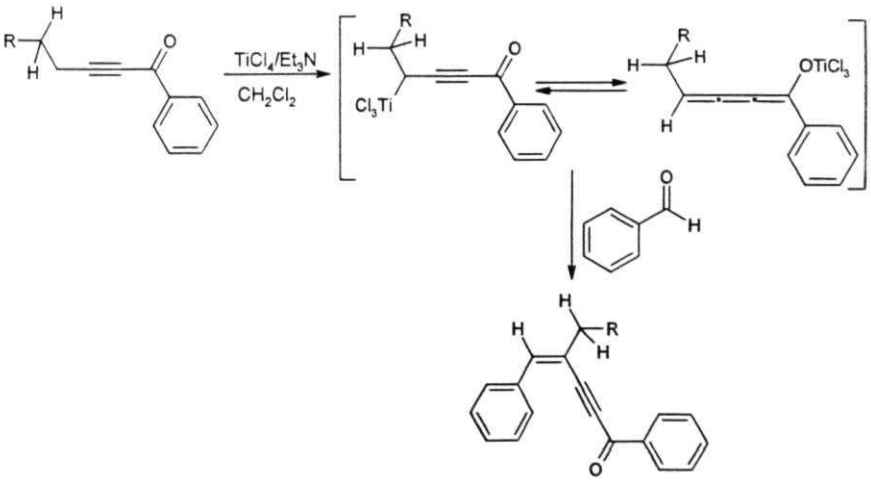
1.2.3 Allenic titanium enolates

It is visualized that the formation of the enynone in the reaction of alkynyltitanium with benzaldehyde involves the corresponding allenic titanium enolate intermediates (Scheme 16). Accordingly, it should be possible to obtain these derivatives starting from the alkynyl phenyl ketone. When the reaction was carried out using the alkynyl ketone and benzaldehyde, it was found that the corresponding enynone was isolated in very good yield (Scheme 18). The reaction was also examined with some other ketones. The results are summarized in Table 3.

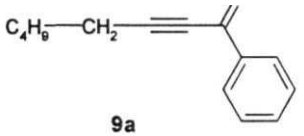
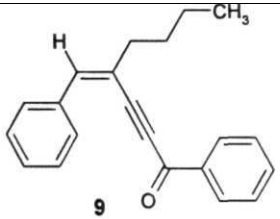
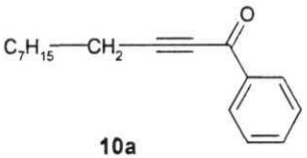
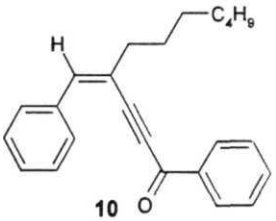
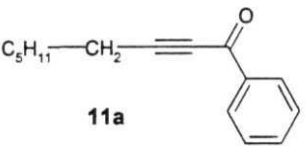
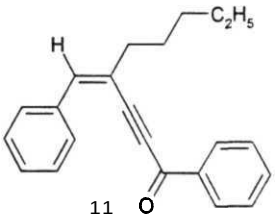
Since neither amine nor $TiCl_4$ alone mediates this transformation, the reaction should go through the allenic titanium enolates (Scheme 18).

Scheme 18.



9-11

Table 3. The reaction of allenic titanium enolates with benzaldehyde

No.	Substrate	Product	Yield (%)
1.	 **9a**	 **9**	87
2.	 **10a**	 **10**	91
3.	 **11a**	 **11**	92

[a]The products were identified using IR, ^{13}C-NMR, ^{1}H-NMR and mass spectral analysis.
[b]The yields are based on the ketones used.

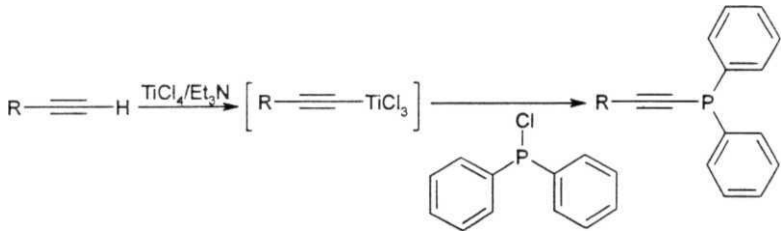
1. 2. 4 Reaction of aikynyltitanium with phosphorus derivatives

1. 2. **4. 1** Reaction with chlorodiphenylphosphine

Reactive organometallic species (e.g. RLi or RMgX) readily react with phosphorous halides.[51] The isolation of phosphorus derived compounds in

organometallic reactions would provide evidence for the existence of species containing C-M bonds.[51] We have examined the use of $ClPPh_2$ so as to examine the presence of $RC{\equiv}CTiCl_3$, in the reaction of $RC{\equiv}CH$ with $TiCl_4/Et_3N$. Indeed, the alkynyl diaryl phosphines were isolated when the reaction was carried out in the presence of $ClPPh_2$ (Scheme 19). The reaction was found to be general with various alkynes. The results are summarized in Table 4.

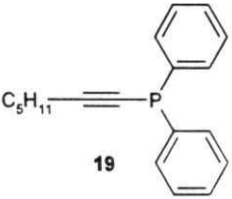
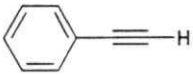
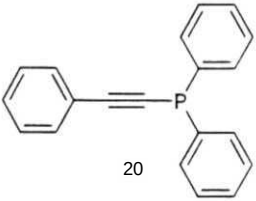
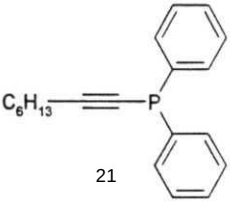
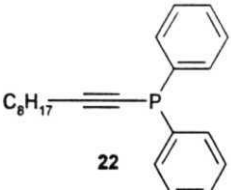
Scheme 19.



In a run with 1-heptyne, the alkynyl phosphine was isolated in 60% yield and the diyne was not formed (Table 4, entry 1). Phenyl acetylene gave the corresponding phosphine in 54% yield in addition to 2% of the 1,3-diyne (Table 4, entry 2). 1-Octyne and 1-decyne were found to react in the same way giving the corresponding phosphines in 56% and 61% yields respectively (Table 4, entries 3 and 4).

In this reaction, the nucleophilic alkynyltitanium reagent attacks the electrophilic phosphorus center leading to the formation of the corresponding

Table 4. The reaction of alkynyltitanium with ClPPh,

No.	Alkyne	Product	Yield (%)
1.		 **19**	60
2		 20	54
3		 21	56
4.		 **22**	61

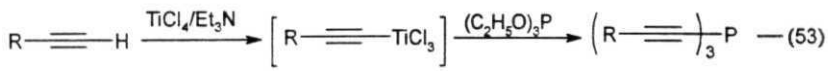
[a]The products were identified by spectral data (IR, ^{1}H-NMR, ^{13}C-NMR, and Mass) and comparison with data obtained for the authentic sample prepared using the reported procedure.[51]

[b]Yields are based on the alkynes used.

alkynyl phosphines. The starting '$TiCl_4$' is expected to be the by product according to the proposed mechanism. However, our attempts to make the reaction as the catalytic on $TiCl_4$ were not fruitful. The conversion was better when the reaction was carried out using stoichiometric amounts of $TiCl_4$. It may be of interest to note that alkynylmagnesium bromide reacts with $ClPPh_2$ to give the same compounds.[518]

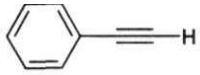
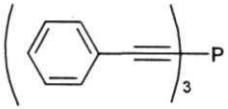
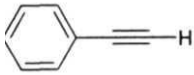
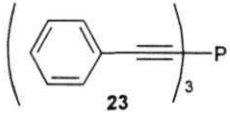
1. 2. 4. 2. Reaction with trialkyl phosphites

The reaction of titanium acetylide with trialkyl phosphites produces the trialkynyl phosphines in good yields. In this reaction, all the three alkoxy groups on phosphorus are substituted by the alkyne moieties in the alkynyltitanium reagent (eq 53).



Previously, the preparation of the trialkynyl phosphines was reported in the reaction of alkynyllithium with PCl_3.[52] The present method provides a simple, convenient procedure to prepare these compounds without starting from an organometallic compound.

Table 5. The reaction of alkynyltitanium with triethyl phosphite

No.	Alkyne	Amine	Product	Yield (%)
1.		Et_3N	 **23**	59
2	C_5H_{11}—≡—H	Et_3N	$(C_5H_{11}—≡—)_3P$ **24**	42
3		$EtN(i\text{-}Pr)_2$	 **23**	51
4.	C_5H_{11}—≡—H	Bu_3N	$(C_5H_{11}—≡—)_3P$ **24**	41

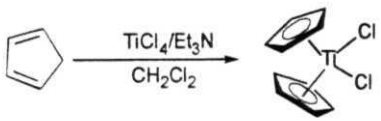
"The products were identified by spectral data (^{1}H-NMR,^{13}C-NMR, ^{31}P-NMR and Mass) and comparison with reported data.
[b]Yields are based on the alkynes used.

Unfortunately, the trialkynyl phosphines are formed in these reactions only in moderate yields. Whereas phenyl acetylene produced the corresponding phosphine in 59% yield, 1-heptyne gave 42% yield. It was also found that the use of other amines such as Bu_3N, $EtN(^iPr)_2$, did not have significant effect on the yields. Also, mono- or disubstituted products were not isolated in this

reaction. The yields are better with triethyl phosphite (59%) compared to the trimethyl derivative (51%).

1. 2. 5 Synthesis of Cp_2TiCl_2 from cyclopentadiene and $TiCl_4/Et_3N$

Cyclopentadiene is also a good carbon acid. Accordingly, we have briefly examined the reaction of $TiCl_4/Et_3N$ with cyclopentadiene. When $TiCl_4$ was added to cyclopentadiene in presence of triethylamine, the Cp_2TiCl_2 was isolated in 74% yield (eq 54). Previously, the Cp_2TiCl_2 was prepared in benzene solution using $TiCl_4/Et_3N$ in 3% yield.[53] Accordingly, the present method should be useful for such applications.



25

-----54

1. 3 Conclusions

Direct preparation of alkynyltitanium reagents has been achieved using 1-alkynes/$TiCl_4$/Et_3N reagent system for the first time. It has been found that these reagents readily react with various electrophiles. In the reaction with methyl formate, CO, CO_2, benzyl chloride and t-BuCl mixtures of unidentified products were obtained. The reaction of trimethyl orthoformate gave the corresponding alkynylated acetal in 42% yield. It was observed that the alkynyltitanium undergoes nucleophilic addition-oxidation with benzaldehyde. It also reacts with phosphorus compounds to give the corresponding electrophilic substitution products. Allenic titanium enolates are readily obtained in the reaction of alkynyl ketones with $TiCl_4$/Et_3N. These species react with benzaldehyde to give the corresponding enynones in good yields. A simple, convenient procedure for making Cp_2TiCl_2 has been developed using $TiCl_4$/Et_3N in CH_2Cl_2.

1. 4 Experimental Section

1. 4. 1 General Information

Melting points reported in this thesis are uncorrected and were determined using a Buchi-510 capillary point apparatus. Infrared spectra were recorded on Perkin-Elmer IR spectrophotometer Model 1310 and JASCO FT 5300 spectrophotometer with polystyrene as reference. ^{1}H-NMR (200 MHz), ^{13}C-NMR (50 MHz) and ^{31}P-NMR (80.96 MHz) were recorded on Bruker-AC-200 spectrometer with chloroform-d as a solvent and TMS as reference (δ=0 ppm). Elemental analyses were carried out using a Perkin-Elmer elemental analyzer model-240 C. Mass spectral analysis was carried out on VG 7070H mass spectrometer using El technique at 70eV. Analytical thin layer chromatographic tests were carried out on glass plates (3x10 cm) coated with 250mμ acme's silica gel-G and GF_{254} containing 13% calcium sulfate as binder. The spots were visualized by short exposure to iodine vapor or UV light. Column chromatography was carried out using acme's silica gel (100-200 mesh).

All the glassware were pre-dried at 140 °C in an air-oven for 4 h, assembled hot and cooled under a stream of dry nitrogen. Unless, otherwise mentioned, all the operations and transformations of reagents were carried out using standard syringe, septum technique recommended for handling air sensitive

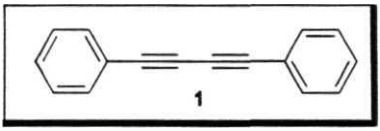
organometallic compounds. Reagents prepared *in situ* in solvents were transformed using a double-ended stainless (Aldrich) needle under a stream of nitrogen whenever required.

In all experiments, a round bottom flask of appropriate size with a side arm, a side septum, a magnetic stirring bar, a condenser and a connecting tube attached to a mercury bubbler were used. The outlet of the mercury bubbler was connected by a long tube to the atmosphere. All dry solvents and reagents (liquids) used were distilled from appropriate drying agents. As a routine practice, all organic extracts were concentrated on Buchi-EL-rotary evaporator. All yields reported are isolated yields of materials judged homogeneous by TLC, IR and NMR spectroscopy.

Titanium tetrachloride, supplied by Spectrochem Ind. Ltd., was used. It was used as 1:1 $TiCl_4$:CH_2Cl_2 stock solution. Triethylamine supplied by Ranbaxy (India) was used. It was distilled over CaH_2 and stored over KOH pellets. 1-Alkynes were purchased and some were prepared by the reported methods. 1-Heptyne was supplied by Lancaster (England). 1-Octyne and 1-hexyne were supplied by E. Merck (India). 1-Decyne and 1-dodecyne were prepared from 1-decene and 1-dodecene using standard bromination and dehydrobromination sequence. Chlorodiphenylphosphine and trimethyl ortho-formate were supplied by E. Merck (India). PhCHO was distilled before use. Triethyl phosphite was purchased from Fluka (Switzerland).

1.4.2 The reaction of 1-alkynes with $TiCl_4/Et_3N$

Dichloromethane (40 mL), Et_3N (15 mmol, 2.1 mL) and phenyl acetylene (5 mmol, 0.5 mL) were stirred under an atmosphere of nitrogen. $TiCl_4$ (10 mmol, 2.2 mL of 1:1 solution of $TiCl_4/CH_2Cl_2$) in CH_2Cl_2 (10 mL) was added dropwise under N_2 at 0 °C for 15 min. The reaction mixture was stirred for 0.5 h at 0 °C and stirred further for 5.5 h at 25 °C. It was quenched with a saturated NH_4Cl solution (20 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 X 25 mL). The combined organic extract was washed with brine solution (10 mL) and dried over anhydrous $MgSO_4$ The solvent was removed and the residue was chromatographed on a silica gel column. Hexane eluted the 1,4-diphenyl-1,3-butadiyne.



1

Yield 62%

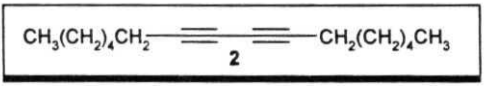
M. p. 87 °C (Lit.[38] 87-88 °C).

IR (KBr) (cm^{-1}) 3058, 740, 690.

^{1}H-NMR (δ ppm, $CDCl_3$) 7.4-7.1 (m, 10H).

^{13}C-NMR (δ ppm, $CDCl_3$) 74.0, 81.6, 121.9, 128.42, 129.15, 132.50, (Spectrum No. 1).

The above procedure was followed for the conversion of several other 1-alkynes to the corresponding 1,3-diynes.



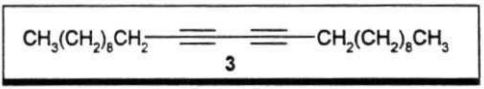
2

Yield 64%

IR (neat) (cm^{-1}) 2932, 2860, 2156, 1460.

^{1}H-NMR (8 ppm, $CDCl_3$) 2.3 (t, J=6.4 Hz, 4H, CH_2), 1.7-1.2 (m, 16H, CH_2), 0.9 (t, J=6.1 Hz, 6H, CH_3).

^{13}C-NMR (δ ppm, $CDCl_3$) 14.0, 19.2, 22.58, 28.39, 28.58, 31.35, 65.3 (OC), 77.4 (OC).



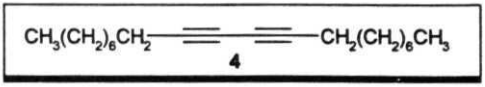
3

Yield 51%

IR (neat) (cm^{-1}) 2945, 2840, 2144, 1467.

^{1}H-NMR (8 ppm, $CDCl_3$) 2.23 (t, J=6.38 Hz, 4H, CH_2), 1.65-1.2 (m, 32H), 0.9 (t, J=6.4 Hz, 6H, CH_3).

^{13}C-NMR (8 ppm, $CDCl_3$) 14.00, 19.11, 22.52, 28.21, 28.88, 29.00, 29.18, 29.48, 29.59, 31.91, 65.34 (OC), 77.41(C≡C).



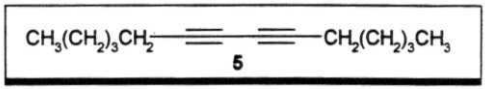
4

Yield 49%

IR (neat) (cm^{-1}) 2943, 2872, 2123, 1481.

^{1}H-NMR (8 ppm, $CDCl_3$) 2.1 (t, J=6.48 Hz, 4H, CH_2), 1.7-1.2 (m, 24H), 1.0 (t, J=6.49 Hz, 6H, CH_3).

^{3}C-NMR (8 ppm, $CDCl_3$) 14.02, 19.19, 22.62, 28.38, 28.86, 29.08, 29.68, 31.83, 65.34 (OC), 77.41(C≡C).



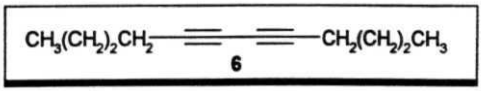
5

Yield 67%

IR (neat) (cm^{-1}) 2982, 2892, 2119, 1472.

^{1}H-NMR (8 ppm, $CDCl_3$) 2.25 (t, J=6.6 Hz, 4H, CH_2), 1.7-1.2 (m, 12H), 0.9 (t, J=6.71 Hz, 6H, CH_3), (Spectrum No. 2).

^{13}C-NMR (8 ppm, $CDCl_3$) 13.85, 19.15, 22.13, 28.05, 30.99, 65.31 (C≡C), 77.45 (OC), (Spectrum No. 3).



6

Yield 43%

IR (neat) **(cm^{-1}) 2971, 2868, 2112, 147**

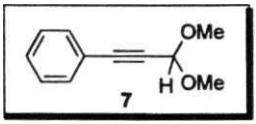
^{1}H-NMR (8 ppm, **$CDCl_3$**) 2.0 (t, **J=6.39** Hz 4H, **CH_2**), 1.6-1.25 **(m,** 8H), 0.9 **(t, J=6.83** Hz, 6H, **CH_3)**.

^{13}C-NMR **(δ ppm, $CDCl_3$)** 13.44, 18.84, 21.89, 30.42, 65.35 **(C≡C),** 77.32 **(C≡C).**

The spectral data of 6 showed 1:1 correspondence with the reported data.[54]

1. 4. 3 Reaction of alkynyltitanium with trimethyl orthoformate

Dichloromethane (40 mL), **Et_3N (15 mmol,** 2.1 mL), phenyl acetylene **(10 mmol,** 1.1 **mL)** and trimethyl orthoformate **(15** mmol, 1.6 **mL)** were stirred under an atmosphere of nitrogen. **$TiCl_4$** (10 mmol, 2.2 **mL** of 1:1 solution of **$TiCl_4/CH_2Cl_2$)** in **CH_2Cl_2** (10 mL) was added dropwise under **N_2** at 0 °C for 15 **min.** The reaction mixture was stirred for 0.5 h at 0 °C and stirred further for 5.5 h at 25 °C. It was quenched with a saturated **NH_4Cl** solution (20 **mL).** The organic layer was separated and the aqueous layer was extracted with **CH_2Cl_2** (2 X 25 mL). The combined organic extract was washed with brine solution **(10 mL)** and dried over anhydrous **$MgSO_4$.** The solvent was removed **and** the residue was chromatographed on a silica gel column. EtOAc/hexane (1:99) mixture eluted the acetal 7.



7

Yield 48%

IR (neat) (cm^{-1}) 3056, 3028, 2935, 2829, 2226, 2189, 758, 690.

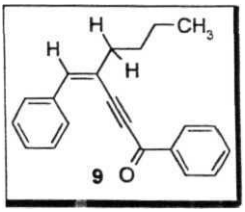
^{1}H-NMR (6 ppm, $CDCl_3$) 3.45 (s, 6H), 5,38 (s, 1H), 7.3-7.7 (m, 5H), (Spectrum No. 4).

^{13}C-NMR (8 ppm, $CDCl_3$) 52.51 (OCH_3), 83.62 (C≡C), 85.78 (C≡C), 93.63 ($CH(OCH_3)_2$), 121.77 (quaternary), 128.28 (CH), 128.87 (CH), 131.92 (CH), (Spectrum No. 5). (Signal assignments are based on DEPT experiments).

1. 4. 4 The reaction of alkynyltitanium with PhCHO

Dichloromethane (40 mL), Et_3N (15 mmol, 2.1 mL), 1-heptyne (5 mmol, 0.7 mL) and PhCHO (10 mmol, 1.0 mL) were stirred under an atmosphere of nitrogen. $TiCl_4$ (10 mmol, 2.2 mL of 1:1 solution of $TiCl_4/CH_2Cl_2$) in CH_2Cl_2 (10 mL) was added dropwise under N_2 at 0 °C for 15 min. The reaction mixture was stirred for 0.5 h at 0 °C and stirred further for 5.5 h at 25 °C. It was quenched with saturated NH_4Cl solution (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 X 25 mL). The combined organic extract was washed with brine solution (10 mL) and dried over

anhydrous $MgSO_4$. The solvent was removed and the residue was chromatographed on a silica gel column. Hexane eluted the 1,3-diyne. EtOAc/hexane (2:98) mixture eluted the enynone 9.



Yield 42%

IR (neat) (cm^{-1}) 3063, 2959, 2934, 2214, 1664, 1597, 720, 690.

^{1}H-NMR (8 ppm, $CDCl_3$) 1.0 (t, J=6.7 Hz, 3H, CH_3), 1.4-1.7 (m, 4H), 2.5 (t, J=6.88 Hz, 2H, CH_2), 7.4-8.2 (m, 11H).

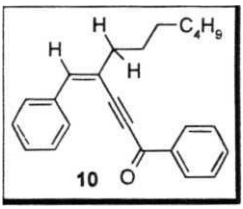
^{13}C-NMR (8 ppm, $CDCl_3$) 13.59 (CH_3), 19.75 (CH_2), 21.98 (CH_2), 30.28 (CH_2), 78.10 (C≡C), 103.19 (C≡C), 121.87 (CH), 128.02 (CH), 128.43 (CH), 129.72 (CH), 130.02 (CH), 130.21 (CH), 132.30 (CH), 134.97 (quaternary), 137.34 (quaternary), 143.91 (CH), 194.21 (CO), (Spectrum No. 6). (Signal assignments are based on DEPT experiments), (Spectrum No. 7).

MS (EI) m/z 288 (M^+, 15%), 246 [M^+-($CH_3CH=CH_2$), 86%].

The *E* and Z isomers are possible for the compounds 9, 10 and 11. However, ^{13}C-NMR data indicate the presence of only one isomer. The

configuration of this isomer is tentatively assigned as Z Since the alkynyl group is expected to have less steric requirement than the branched alkyl group, the Z isomer in which the alkynyl group is *cis* to the phenyl ring is expected to be more stable than the corresponding *E* isomer.[58,59] However, this structural assignment is only tentative and the *E* configuration cannot be ruled out based on the available spectral data.

The above procedure was followed for the conversion of several other 1· alkynes to the corresponding enynones.



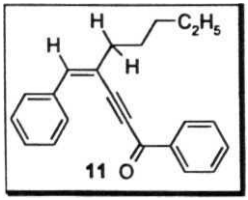
10

Yield 37%

IR (neat) (cm"[1]) 3063, 3028, 2928, 2856, 2216, 1664, 1597, 721, 692.

[1]H-NMR (6 ppm, $CDCl_3$) 0.85 (t, J=6.6 Hz, 3H, CH_3), 1.2-1.9 (m, 10H), 2.4 (t, J=6.75 Hz, 2H, CH_2), 7.4-8.2 (m, 11H).

[13]C-NMR (8 ppm, $CDCl_3$) 14.09, 20.09, 22.65, 28.27, 28.4, 28.91, 31.74, 78.16, 103.30, 130.18, 132.31, 135.02, 137.35, 143.85, 194.13.



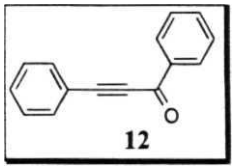
11

Yield 39%

IR (neat) (cm^{-1}) 3063, 3028, 2928, 2856, **2216,** 1664, **1597,** 721, 692.

^{1}H-NMR (6 ppm, $CDCl_3$) 1.0 (t, J=6.4 Hz, 3H), 1.1-1.8 (m, 6H), 2.4 (t, J=6.8 Hz, 2H), 7.3-8.1 (m, 11H).

^{13}C-NMR (6 ppm, $CDCl_3$) 194.14, 143.87, 137.35, 13.01, 139.33, 130.21-126.71, 121.90, 103.31, 31.09, 27.94, 22.58, 20.05, 13.95.



12

Yield 31%

IR (neat) (cm^{-1}) 3059, 3030, 2199, 1599, 758, 694.

^{1}H-NMR (6 ppm, $CDCl_3$) 7.5-7.2 (m, 10H).

^{13}C-NMR (5 ppm, $CDCl_3$) 173.50, 134.70, 134.46, 132.44, 133.36, 129.57,128.87,90.95,81.36.

The spectral data of 12 showed 1:1 correspondence with data

obtained for the authentic sample prepared using a reported procedure.[40]

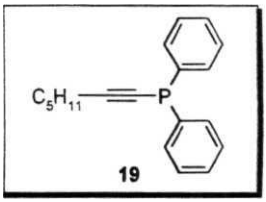
1.4.5 General procedure for the reaction of allenic titanium enolate with benzaldehyde

Dichloromethane (40 mL), Et_3N (15 mmol, 2.1 mL), alkynyl ketone (10 mmol) and benzaldehyde (10 mmol, 0.5 mL) were stirred under N_2. $TiCl_4$ (10 mmol, 2.2 mL of 1:1 solution of $TiCl_4/CH_2Cl_2$,) in CH_2Cl_2 (10 mL) was added dropwise under N_2 at 0 °C for 15 min. The reaction mixture was stirred for 0.5 h at 0 °C and stirred further for 5.5 h at 25 °C. It was quenched with a saturated NH_4Cl solution (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 X 25 mL). The combined organic extract was washed with brine solution (10 mL) and dried over anhydrous $MgSO_4$ The solvent was removed and the residue was chromatographed on a silica gel column. EtOAc/hexane (2:98) mixture eluted the enynone.

The products were identified by comparison with the enynones obtained in previous experiments.

1. 4. 6 The reaction of alkynyltitanium with chlorodiphenylphosphine

Dichloromethane (40 mL), Et_3N (15 mmol, 2.1 mL), 1-heptyne (5 mmol 0.7 mL) and $ClP(C_6H_5)_2$ (5 mmol, 0.9 mL) were stirred under N_2. $TiCl_4$ (10 mmol, 2.2 mL of 1:1 solution of $TiCl_4/CH_2Cl_2$) in CH_2Cl_2 (10 mL) was added dropwise under N_2 at 0 °C for 15 min. The reaction mixture was stirred for 0.5 h at 0 °C and stirred further for 5.5 h at 25 °C. It was quenched with ı saturated NH_4Cl solution (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 X 25 mL). The combined organic extract was washed with brine solution (10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed and the residue was chromatographed on a silica gel column. EtOAc/hexane (1:99) mixture eluted the alkynyl diaryl phosphine 19.



19

Yield 60%

IR (neat) (cm^{-1}) 3055, 2951, 2930, 2179, 740, 694.

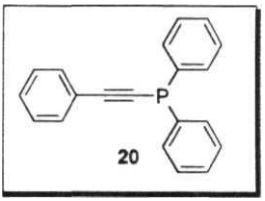
^{1}H-NMR (5 ppm, $CDCl_3$) 2.25 (t, J=5.8 Hz, 2H, CH_2), 1.7-12 (m, 6H), 0.9 (t, J=6.1 Hz, 3H, CH_3).

^{13}C-NMR (δ ppm, $CDCl_3$) 14.02, 20.42, 22.22, 28.31, **31.14,** 75.93, 110.61, 128.42, 128.57, 128.81, 130.83, 131.05, 132.25, 132.65, 137.16, 137.30.

The spectral data of 19 showed 1:1 correspondence with data obtained for the authentic sample prepared using the reported procedure,[51a] **(Spectrum** No. 8).

MS (EI) m/z 280 (M^+, 100%), 237 [(M^+-C_3H_7), 28%].

The above procedure was followed for the conversion of several other 1-alkynes to the corresponding alkynyl diaryl phosphines.



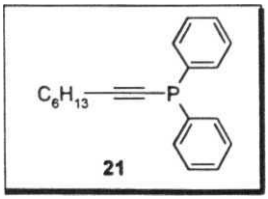
20

Yield 54%

IR (neat) (cm^{-1}) 3056, 3028, 2115, 741, 638.

^{1}H-NMR (8 ppm, $CDCl_3$) 7.1-8.3 (m, 15H).

^{13}C-NMR (8 ppm, $CDCl_3$) 86.08, 86.21, 107.99, 122.96, 128.51, 128.71, 128.86, 129.05, 129.19, 131.97, 132.52, 132.95, 136.45, 136.57, **(Spectrum No. 9).**



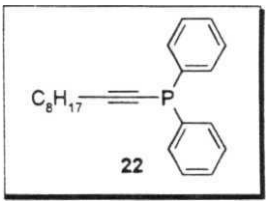
21

Yield 56%

IR (neat) (cm^{-1}) 3071, 3029, 2948, 2821, 2132, 721, 645.

^{1}H-NMR (6 ppm, $CDCl_3$) 7.8-7.1 (m, 10H), 2.4 (t, J=5.9 Hz, 2H, CH_2), 1.7-1.2 (m, 8H), 0.9 (t, J =6.18 Hz, 3H, CH_3).

^{13}C-NMR (8 ppm, $CDCl_3$) 13.99, 20.39, 22.55. 28.55, 31.15, 31.30, 75.88, 110.5, 128.38-135.61, 137.14, 137.26.



22

Yield 61%

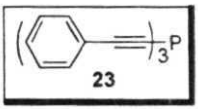
IR (neat) (cm^{-1}) 3055, 2928, 2179, 740, 694.

^{1}H-NMR (δ ppm, $CDCl_3$) 0.9 (t, J=6.01 Hz, 3H, CH_3), 1.3-1.8 (m, 12H), 2.3 (t, J=6.21 Hz, 2H, CH_2), 7.3-8.2 (m, 10H).

^{13}C-NMR (δ ppm, $CDCl_3$) 14.10, 20.42, 22.69, 28.62, 28.94, 29.11, 29.23, 31.85, 75.92, 110.57, 128.39, 128.54, 128.75, 130.81, 131.03, 132.02, 132.22, 132.64, 137.17, 137.32.

1. 4. 7 The reaction of alkynyltitanium with triethyi phosphite

Dichloromethane (40 mL), Et_3N (15 mmol, 2.1 mL), phenylacetylene (5 mmol, 0.5 mL) and $P(OEt)_3$ (5 mmol, 0.9 mL) were stirred under N_2. $TiCl_4$ (10 mmol , 2.2 mL of 1:1 solution of $TiCl_4/CH_2Cl_2$) in CH_2Cl_2 (10 mL) was added dropwise under N_2 at 0 °C for 15 min. The reaction mixture was stirred for 0.5 h at 0 °C and stirred further for 5.5 h at 25 °C. It was quenched with a saturated NH_4Cl solution (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 X 25 mL). The combined organic extract was washed with brine solution (10 mL) and dried over anhydrous $MgSO_4$ The solvent was removed and the residue was chromatographed on a silica gel column. EtOAc/hexane (1:99) mixture eluted the trialkynyl phosphine, 23.



23

Yield 59%

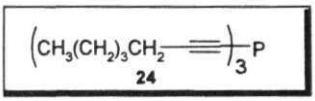
IR(neat) (cm^{-1}) 3059, 2164, 688.638.

^{1}H-NMR (8 ppm, $CDCl_3$) 7.2-8.1 (m, 15H).

^{13}C-NMR (8 ppm, $CDCl_3$) 79.85, 80.01, 106.04, 106.25, 122.50, 128.42, 129.51, 132.20, (Spectrum No. 10).

^{31}P-NMR (8 ppm, $CDCl_3$) -88.99. The spectral data of 23 showed 1:1 correspondence with the reported data.[58]

Mass **m/z** 334 **(M^+,** 68%), 333 (MM, 100%), **(Spectrum No. 11).**



24

Yield 42%

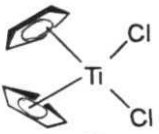
IR (neat) (cm-[1]) 2971, 2862, 2197, 1461.

^{1}H-NMR (8 ppm, $CDCl_3$) 2.2-2.4 (t, 2H), 1.2-1.8 (m 6H), 0.8 (t, 3H).

^{13}C-NMR (δ ppm, $CDCl_3$) 20.39, 22.55, 28-55, 31.15, 31.30, /5.88, 110.5, 128.38-135.61, 137.14, 137.26.

1. 4. 8 Synthesis of Cp_2TiCl_2

In CH_2Cl_2 (25 mL) cyclopentadiene (20 mmol, 1.6 mL) and Et_3N (20 mmol, 2.8 mL) were taken at -78 °C under N_2. $TiCl_4$ (10 mmol, 2.2 mL of 1:1 solution of $TiCl_4/CH_2Cl_2$) was added to this solution and stirred for lh at -78-25 °C. The reaction was quenched with a saturated NH_4Cl solution and the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2x25 mL). The combined organic extract was washed with brine solution (10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed and the residue was chromatographed on a silica gel column. Cp_2TiCl_2 was isolated using EtOAc/hexane (30:70) mixture as eluent.



25

Yield 64%

M. p 258 °C (Lit.[57] 260-280 °C).

^{13}C-NMR (8 ppm, $CDCl_3$) 120.17.

The spectral data of 25 showed 1:1 correspondence with the data of the authentic sample prepared using a reported procedure.[57]

1. 4. 9 Preparation of the alkynyl ketones 9a-11a[40]

To a mixture of alkyne (2.5 mmol) and CuI (5 mol%, 0.125 mmol) in Et_3N (20 mL), benzoyl chloride (3.12 mmol) was added. This reaction mixture was stirred at room temperature for 30 h under N_2 atmosphere. After removal of the solvent, methanol (25 mL) was added and the mixture was stirred for 5 minutes. The organic layer was separated and the aqueous layer was extracted with ether. The combined organic layer was dried over $MgSO_4$ and concentrated. The residue was chromatographed on a silica gel column. EtOAc/hexane (2:98) mixture eluted the alkynyl ketone.

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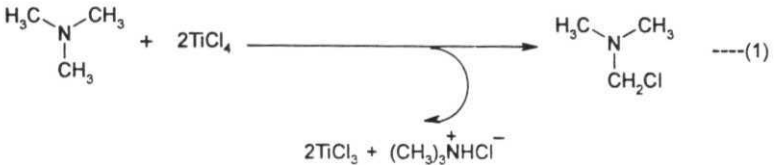
Chapter 2

Studies on the metalation of iminium ions formed in the reaction of trialkylamines with $TiCl_4$

2. 1 Introduction

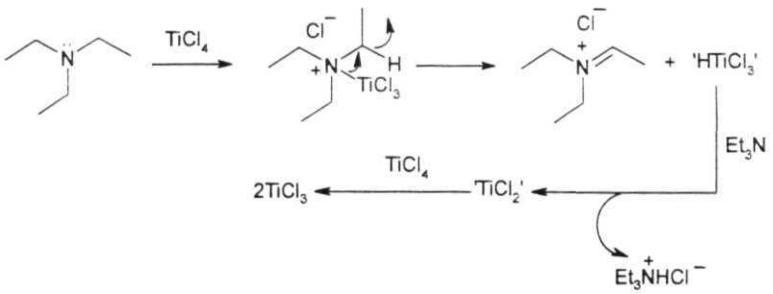
The investigations described in this chapter emerged from the observations made in the course of the studies discussed in Chapter 1. As outlined in Scheme 12 of Chapter 1, the formation of diyne in the reaction of $RC{\equiv}CH$ with $TiCl_4/Et_3N$ would lead to the concomitant production of $TiCl_3$ and other low valent titanium species. Indeed, this was noticed through the change in the color of the reaction mixture from light blue/green to violet to black. This color change is similar to that observed in the reduction of $TiCl_4$ using metals or metal hydrides.[1] The reaction mixture also became dark when the $TiCl_4$ was mixed with Et_3N without alkynes and the contents were stirred for 1 h at 0-25 °C. Clearly, the $TiCl_4$ is reduced to low valent titanium species even without oxidizable substrates. This reduction is possible only if the amine is oxidized in the course of the reaction.

In 1955, it was reported that the reaction of TiCL} with Me_3N produces '$TiCl_3$' and '$ClCH_2N(CH_3)_2$'[2]. However, the organic product was not characterized and the mechanism of the $TiCl_3$ formation was not clarified (eq 1).



The α-chloroamine formed here would exist as the corresponding iminium ion salt. Also, literature reports reveal that the tertiary amines on reaction with mercury(II)[3] and palladium(II)[4] salts result in iminium ions. Hence, we envisaged that $TiCl_4$ would oxidize the trialkylamines to give the iminium ions along with the $TiCl_2$ and/or $TiCl_3$ species (Scheme 1).

Scheme 1.

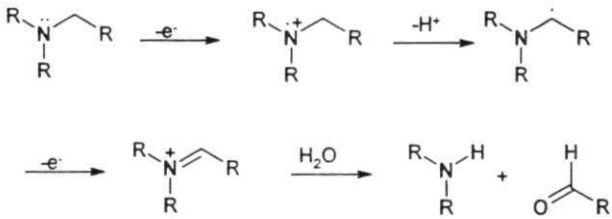


Such iminium ions are versatile synthetic intermediates. They react with various nucleophiles and also undergo dipolar cycloaddition reactions.[5,21] Any simple method for the preparation of these species deserves due attention because

of its rich synthetic value.[5,21] A brief review of the literature reports on the preparation of iminium ions would facilitate the discussion.

A direct route to prepare the iminium ions is through the oxidation of tertiary amines.[6] There are various oxidizing agents available for this purpose, both in aqueous as well as in non-aqueous conditions. These conversions are carried out using one-electron oxidants, electrochemical, photochemical and enzymatic oxidations. The electrochemical oxidation of tertiary amines is believed to occur by the mechanism shown in Scheme 2.[6]

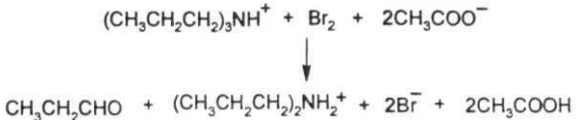
Scheme 2.



The iminium ion formed on hydrolysis yields the corresponding aldehyde and the secondary amine. For example, the electrochemical oxidation of tripropylamine gives propanal and dipropylamine (eq 2).[7]

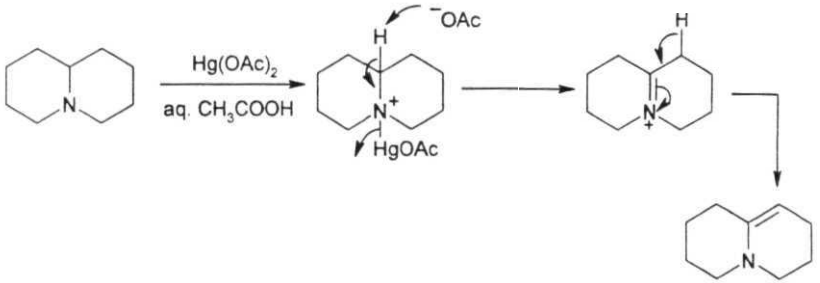
$$(CH_3CH_2CH_2)_3N: \xrightarrow[NaClO_4]{H_2O\text{-}CH_3CN} CH_3CH_2CHO + (CH_3CH_2CH_2)_2NH \qquad \text{—(2)}$$

Aqueous bromine also oxidizes the 1°, 2° and 3° amines to the corresponding carbonyl compounds and dealkylated amines (eq 3).[8]



—(3)

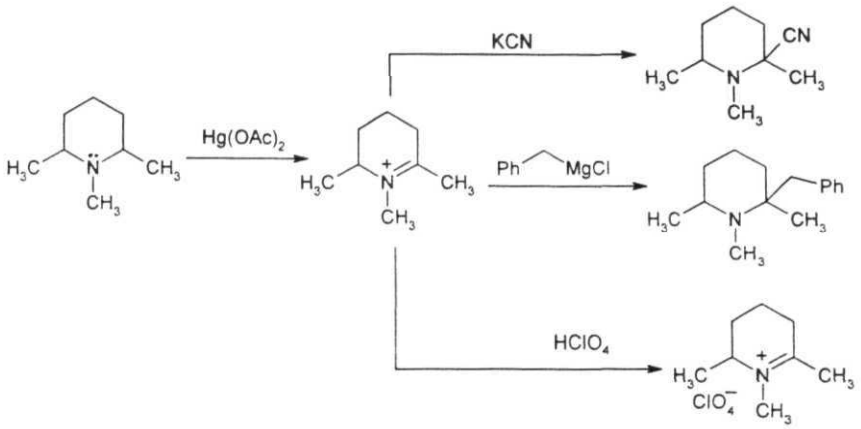
Bicyclic enamines can be prepared by the oxidation of bridge-head nitrogen in bicyclic tertiary amines using $Hg(OAc)_2$ (eq 4).



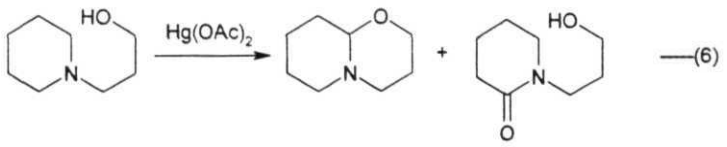
—(4)

The reactions of iminium ion derived from *N*-alkylpiperidine have been reported. The reactions with KCN and $PhCH_2MgCl$ give the corresponding nucleophilic addition products (Scheme 2a).[10]

Scheme 2a.



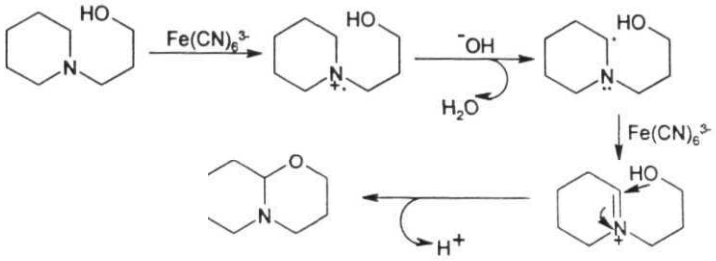
This method was extended to synthesize bicyclic oxazolidines and tetrahydro-1,3-oxazines from piperidino and pyrrolidino alcohols.[11] In this conversion, the tertiary amino alcohols are oxidized to iminium ions, which undergo intramolecular reaction with the tethered hydroxyl group to give the corresponding oxazolidines (eq 6).



—(6)

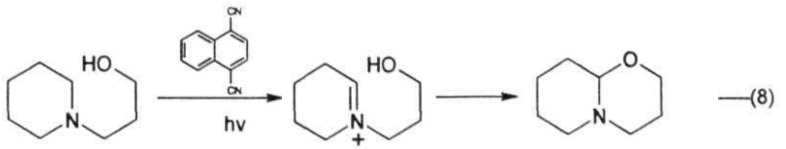
This transformation was also achieved using alkaline $K_3[Fe(CN)_6]$ as oxidizing agent (Scheme 3).[12]

Scheme 3.

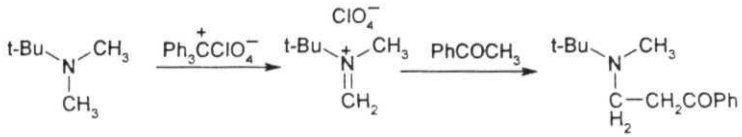


In this reaction, the corresponding secondary amines were also obtained from the competing oxidative *N*-dealkylation. Later, it was reported that ClO_2 also effected this transformation (eq 7).[13]

Irradiation of some amines in presence of 1,4-dicyanonaphthalene causes the formation of radical cations, which give iminium ions through loss of a proton. Intramolecular addition of a nucleophilic hydroxylic group yields the corresponding oxazolidines (eq 8).[14]



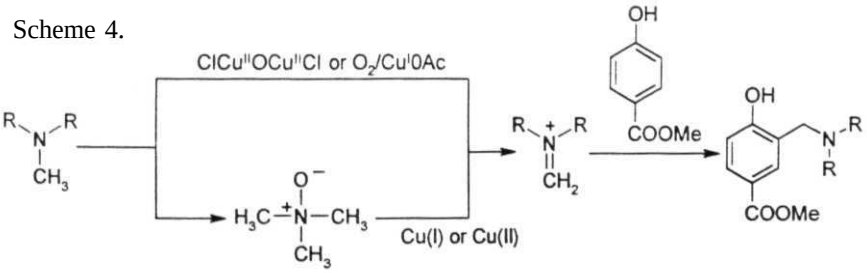
Hydride abstraction from tertiary amines by aryl methyl cations leads to iminium ions that can be hydrolyzed or trapped with nucleophiles (eq 9).[15]



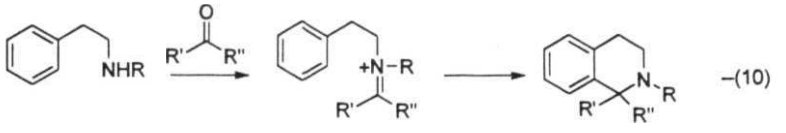
—(9)

The |i-oxo complex [$ClCu^{II}OCu^{II}Cl$], prepared *in situ* by the oxidation of $Cu^{I}Cl$ under O_2 in acetonitrile, oxidizes trimethylamine to provide the corresponding iminium ion, which on reaction with methyl ester of p-hydroxy benzoic acid gives the corresponding adduct (Scheme 4).[17a] It has also been reported that amine *N*-oxides on reaction with Cu^{I} or Cu^{II} salts lead to similar transformation (Scheme 4).[17a]

Scheme 4.

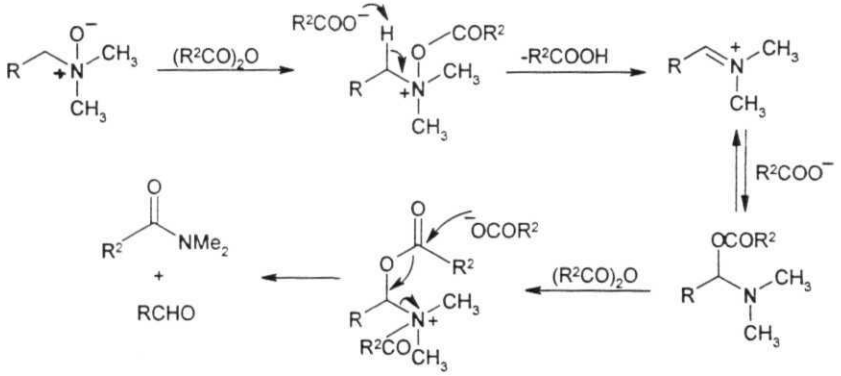


The Pictet-Spengler condensation of 2-phenylethylamines with reactive carbonyl compounds goes through the iminium ions (eq 10).[17b]

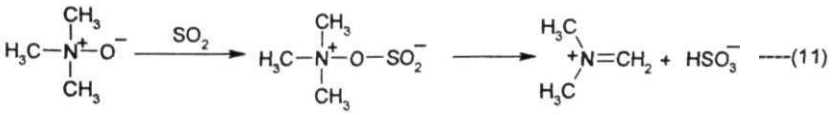


The Polonovski reaction involving tertiary amine *N*-oxides and acetic anhydride or acetyl chloride also goes through the corresponding iminium ion intermediate (Scheme 5).[18]

Scheme 5.



The reaction of amine oxides with SO_2, $(CH_3CO)_2O$, **and** $(CF_3CO)_2O$ results in the formation of the iminium ion intermediates (eq 11).[19]

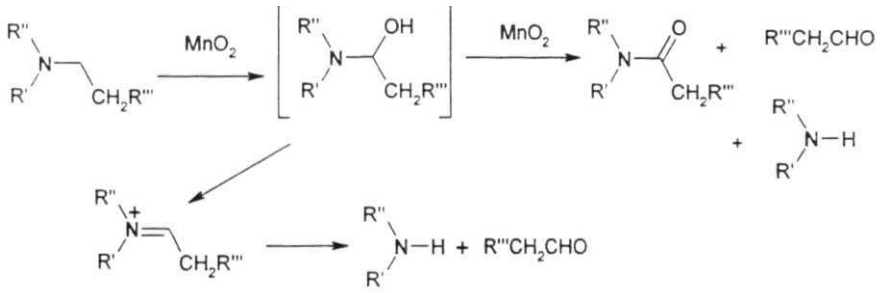


Chromium trioxide in combination with pyridine oxidizes tertiary amines to formamide (eq 12).[22]

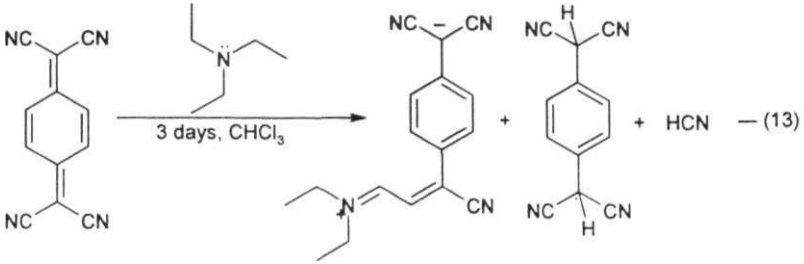
---- (12)

The oxidation products of tertiary amine with MnO_2 are formed through the iminium ion intermediates (Scheme 6).[2]

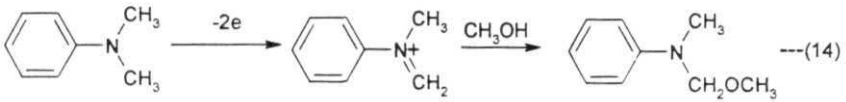
Scheme 6.



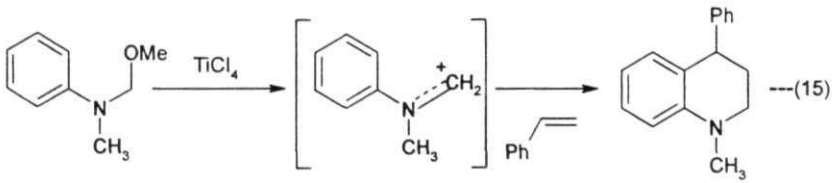
The TCNQ oxidation of tertiary amine has been reported to proceed via the formation of an enamine which subsequently attacks the TCNQ in a Stork-enamine type reaction (eq 13).[24]



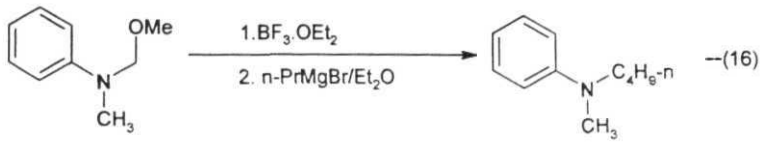
The anodic oxidation of *N,N*-dimethylaniline produces the corresponding iminium ion, which reacts with CH_3OH *in situ* to give a-methoxylated derivative in good yield (eq 14).[25]



It was also reported that the reaction of these α-methoxy-*N,N*-dimethylaniline with $TiCl_4$ afforded the corresponding iminium ion. Further reactions with styrene gives the corresponding tetrahydroquinoline derivative (eq 15).[26]



The reaction of Grignard reagents with these iminium ions formed in this way provides **the** corresponding tertiary amines (eq **16**).[27]



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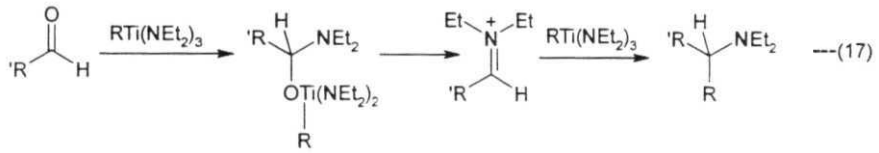
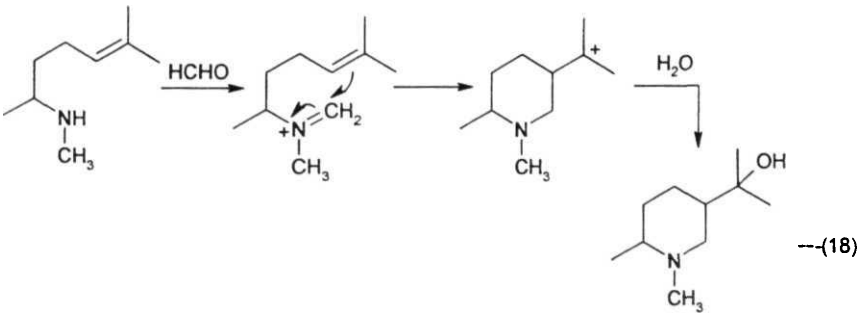
The reaction of tris-(diethylamino)-alkyltitanium reagents with aldehydes results in geminal amino-alkylation through the corresponding iminium ion intermediates (eq 17).[28]



---(17)

Olefinic amines are cyclized to give piperidine derivatives via iminium ion intermediates (eq 18).[20]



---(18)

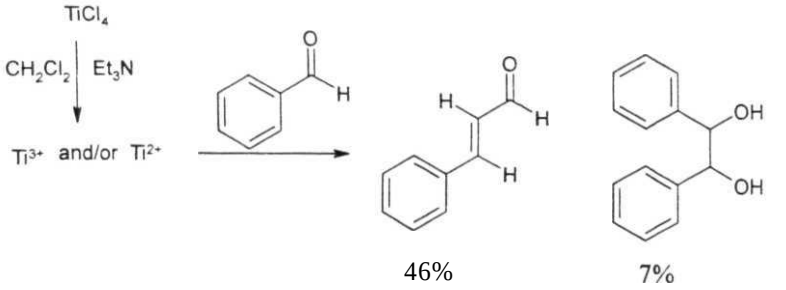
Since we have an easy access to the iminium ions in non-aqueous medium using $TiCl_4/Et_3N$, we have decided to investigate the reactivity of the iminium ions prepared in this way.

2. 2 Results and Discussion

2. 2. 1 The reaction of triethylamine with $TiCl_4$/diarylketones

As outlined in the introductory section, low valent titanium species and iminium ions are produced in the reaction of $TiCl_4$ with Et_3N. It appeared desirable to examine the synthetic applications of the low valent titanium species prepared in this way. We have observed that when benzaldehyde was added at -78 °C to this reaction mixture, cinnamaldehyde and the corresponding 1,2-diol were obtained in 46% and 7% yields respectively (Scheme 7).

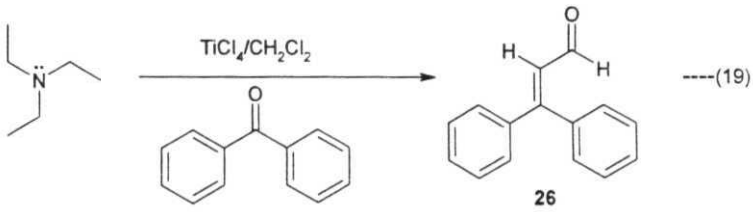
Scheme 7.



46% 7%

Fascinated by this surprising, unexpected result, we decided to investigate this new reactivity pattern of the $TiCl_4/R_3N$ reagent system further. It was observed that when the reaction was carried out using benzophenone at 0-25 °C,

only the α,β-unsaturated aldehyde, 26, was isolated in 72% yield and the corresponding diol was not formed (eq 19).

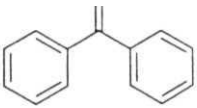
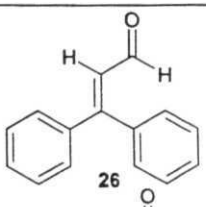
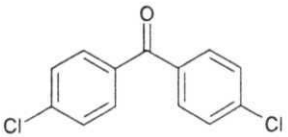
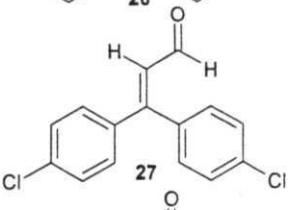
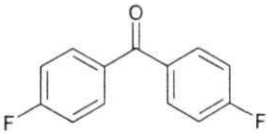
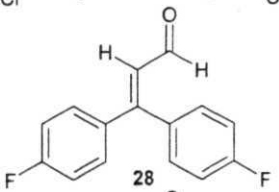
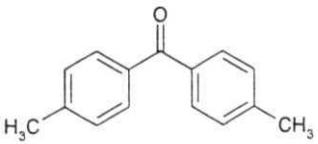
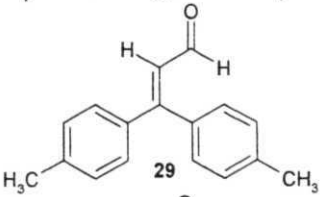
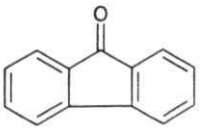
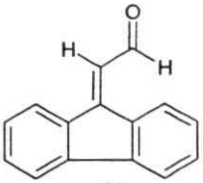


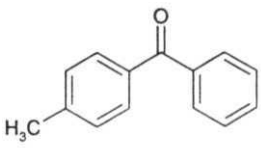
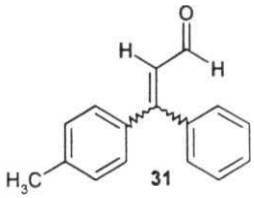
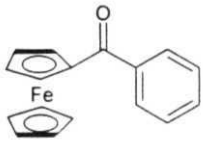
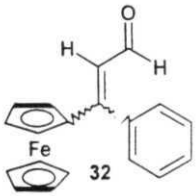
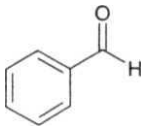
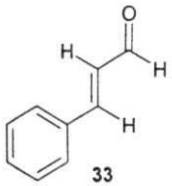
----(19)

The formation of the a,P-unsaturated aldehyde indicates the addition of 2 carbon atoms to the carbonyl compound. The possibility of the solvent, CH_2Cl_2, providing these two carbon atoms can be ruled out since the same reaction is also observed in solvents such as chlorobenzene and chloroform. Most probably, the two carbon atoms of the α,β-unsaturated aldehyde would have come from the ethyl group of the triethylamine. The mechanistic details of this transformation will be discussed later.

The reaction was examined with various ketones and benzaldehyde and the results are summarized in Table 1. The symmetric diaryl ketones produced the corresponding α,β-unsaturated aldehydes in good yields. The reaction of benzophenone with $TiCl_4/Et_3N$ gave 3,3-diphenyl-2-propenal, 26, in 72% yield (Table 1, entry 1). The substituted diaryl ketones, 4,4'-dichlorobenzophenone,

Table 1. The reaction of diarylketones with $TiCl_4/Et_3N$

No.	Substrate	Product	Yield (%)
1		 **26**	72
2		 **27**	82
3		 **28**	85
4.		 **29**	74
5		 **30**	58

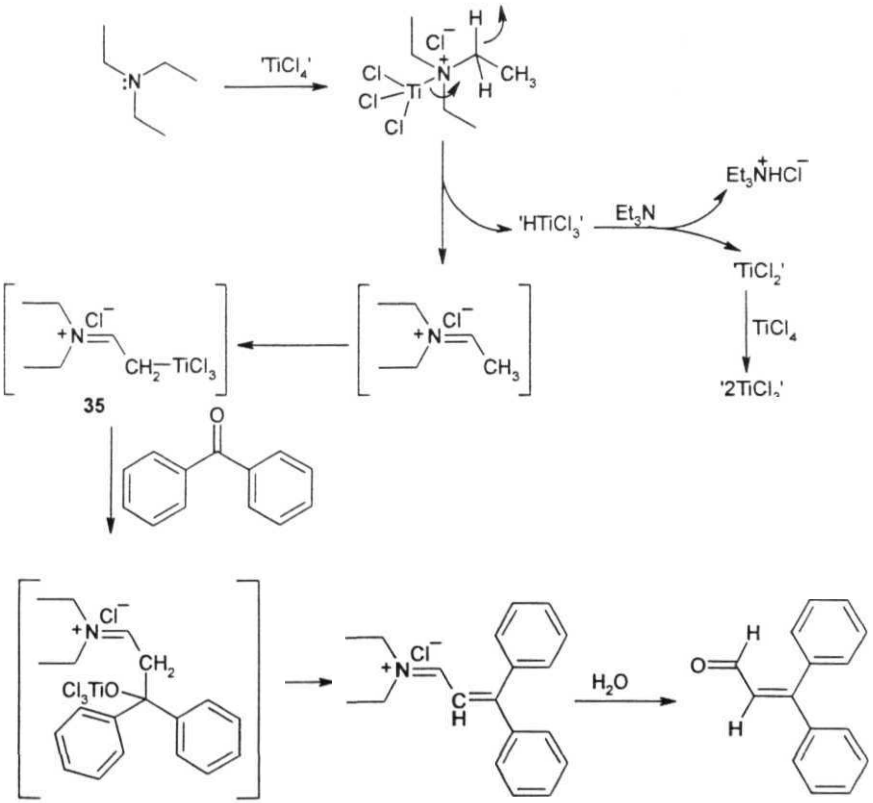
No	Substrate	Product	Yield (%)
6		 31	72
7.		 32	76
8		 33	46

[a]The products were identified using spectral data (IR, ^{1}H-NMR, ^{13}C-NMR and Mass) and comparison with reported data.
[b]Yields are based on ketones/aldehyde used.

4,4'-difluorobenzophenone, and 4,4'-dimethylbenzophenone. gave the corresponding aldehydes, 27, 28 and 29 in 82%, 85%, and 74% yields respectively (Table 1, entries 2, 3 and 4). In the case of fluorenone, the yield of the aldehyde, 30, was somewhat low, 58% (Table 1, entry 5). 4-Methylbenzophenone gave a 1:1 mixture of *E* and Z isomers, 31, (Table 1, entry 6). However, the ferrocenyl

phenyl ketone gave only one isomer, 32 (Table 1, entry 7) of unknown stereochemistry. In the case of benzaldehyde, cinnamaldehyde, 33, (46%) was obtained in addition to some unidentified polar compounds and a small amount of l,2-diphenylethane-l,2-diol (Table 1, entry 8). It is necessary to maintain the reaction temperature at 0 °C while adding the amine to the mixture of ketone and $TiCl_4$. However, addition of the ketone to the mixture of $TiCl_4$ and amine or

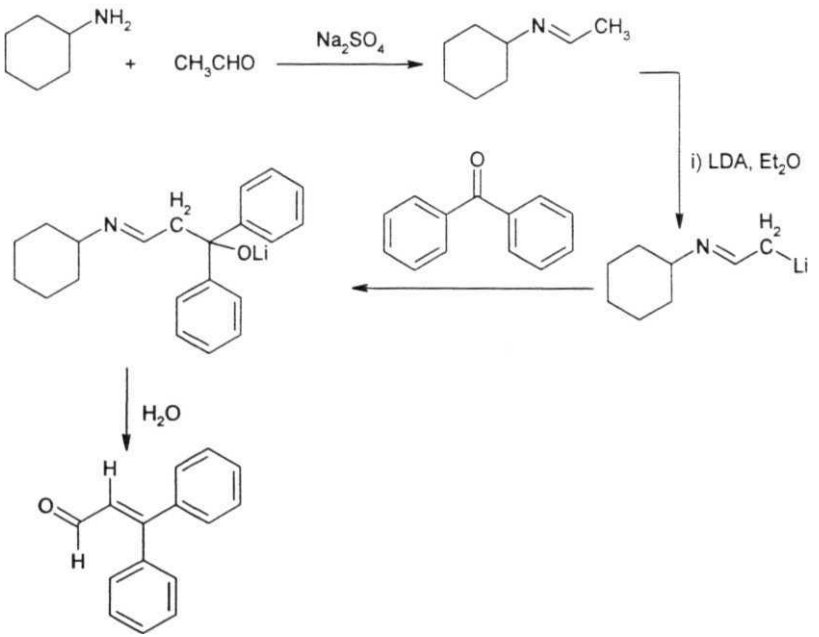
Scheme 8.



$TiCl_4$ to the mixture of amine and ketone did not have significant change in the course of the reaction.

The transformation may be explained by the tentative mechanistic pathway involving iminium ion intermediate as outlined in Scheme 8. The reaction of $TiCl_4$ with trialkylamine may proceed with the initial formation of an amine-$TiCl_4$ complex. The P-hydrogen of the amine moiety is expected to be more acidic and hence would lead to the elimination of P-hydrogen as '$HTiCl_3$' with the concomitant formation of the iminium ion intermediate 34 (Scheme 8).

Scheme 9.

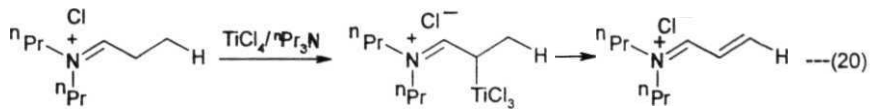


The iminium ion, on further reaction with $TiCl_4/Et_3N$, would give the metalated derivative 35 that on reaction with ketone could produce the nucleophilic addition product. Subsequently, the corresponding α,β-unsaturated aldehyde is produced on hydrolysis. Preparation of such a,P-unsaturated aldehydes require multistep operations.[29] For example, 3,3-diphenyl-2-propenal was synthesized from acetaldehyde imine as shown in Scheme 9.

Accordingly, the new synthesis of a,P-unsaturated aldehydes using $TiCl_4/Et_3N$ has considerable synthetic potential.

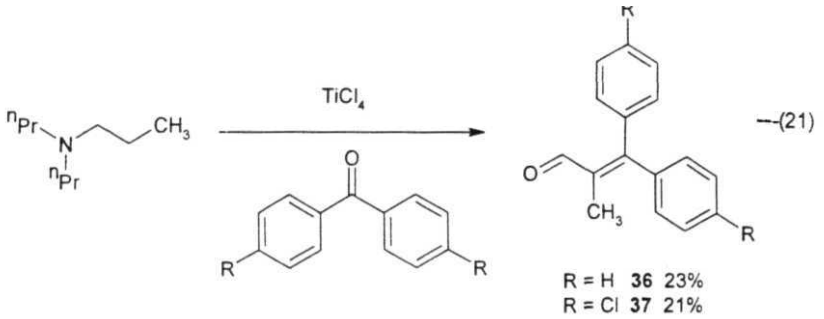
2. 2. 2 Reaction of tri-n-propylamine with $TiCl_4$/diarylketones

The formation of iminium ion from triethylamine and its subsequent metalation prompted us to investigate the reactivity of iminium ions derived from higher amines. It was of our interest to examine whether further P-hydride elimination is possible in the case of metalated iminium ion bearing β-hydrogen (eq 20).



---(20)

In the case of **tri-n-propylamine**, the reaction proceeded analogous to triethylamine to give the corresponding 3,3-diphenyl-2-methyl-2-propenal, 36, in 23% yield. **4,4'-Dichlorobenzophenone** also gave **21%** of the aldehyde, 37, (eq 21V

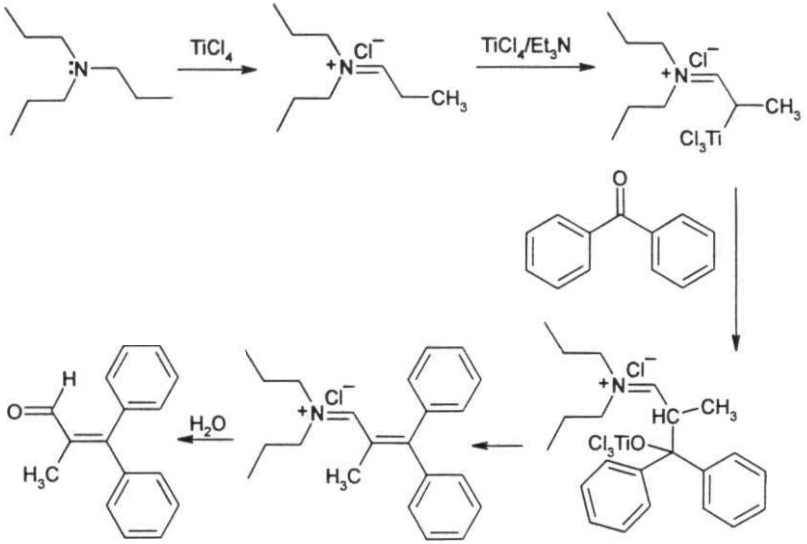


—(21)

The experiments were carried out under various conditions. However, unfortunately, the corresponding aldehydes were obtained in poor yields and the diaryl ketones were recovered in 55% and 58% yields. Presumably, α-metalated iminium ions may lead to some intractable water soluble products.

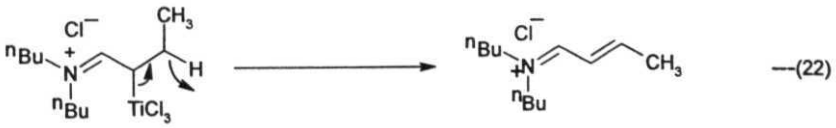
In this transformation, the propyl group acts as propanal equivalent (Scheme 10).

Scheme 10.



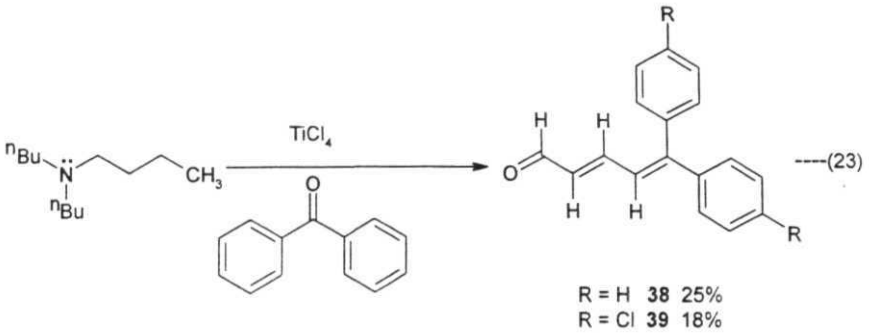
2. 2. 3 Reaction of tri-n-butylamine with $TiCl_4$/diarylketones

The reactivity of the iminium ion derived from tri-n-butylamine was investigated to examine whether there is any further p-hydride elimination (eq 22).



---(22)

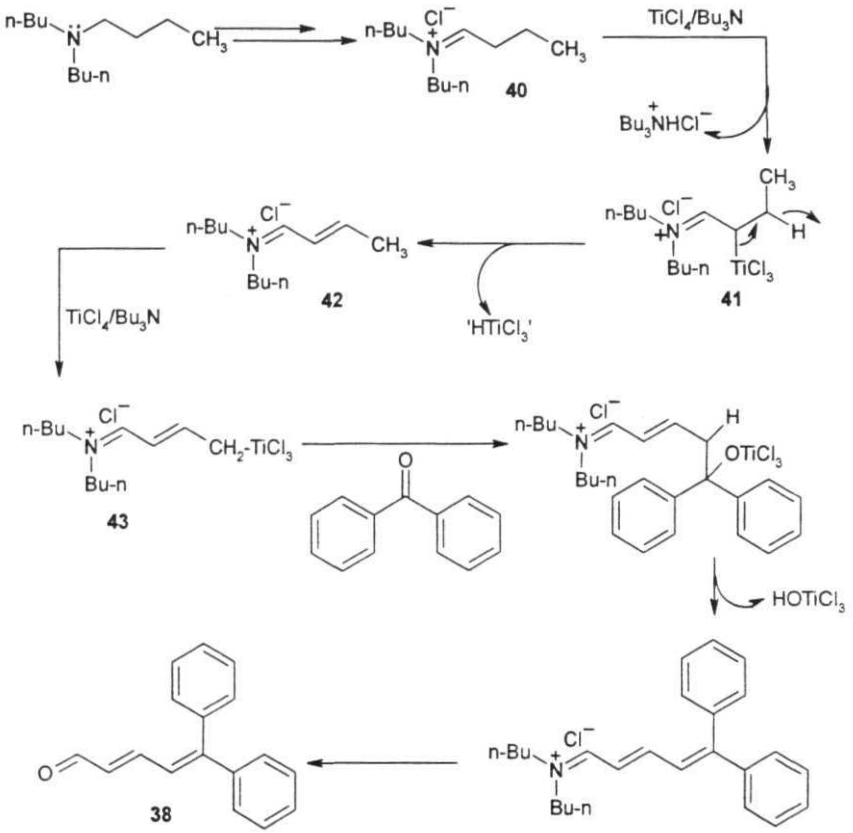
Indeed, when benzophenone was treated with $TiCl_4/NR_3$ (R = **n-butyl)** system, there was further dehydrogenation and the aldehyde 38 was obtained in 25% yield (eq 23).



This observation indicates that the initially formed iminium ion undergoes further metalation followed by P-hydride elimination to give the corresponding unsaturated iminium ion 42 (Scheme 11). This results in the introduction of another C-C double bond in the alkyl chain. This reaction was also carried out using 4,4'-dichlorobenzophenone. However, the yields of the aldehydes obtained were poor (25% and 18%) and the diary 1 ketones were recovered in 54% and 62% yields respectively.

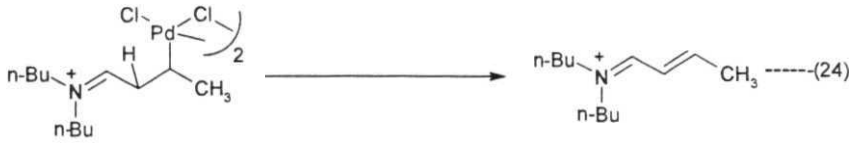
The reaction of tri-n-butylamine is interesting since there is further metalation. The transformation can be tentatively explained considering the sequence of reactions outlined in Scheme 11. As described in the reaction of

Scheme **11.**



triethylamine (Scheme 8), the first iminium ion 40 is formed from the oxidation of tri-n-butylamine by $TiCl_4$. This is further metalated by $TiCl_4/Bu_3N$ to give the corresponding organometallic intermediate 41 that undergoes β-hydride elimination leading to the second iminium ion 42, which on further metalation

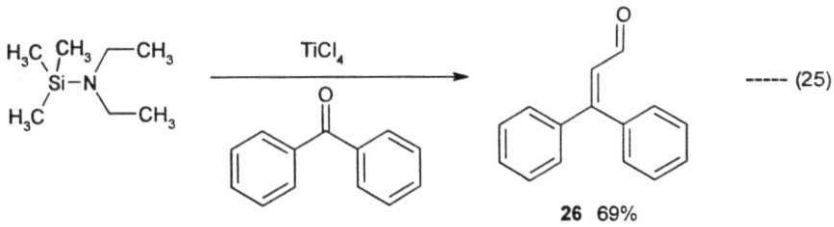
followed by the sequence of reactions shown in Scheme 11 to give the corresponding aldehyde, 38. It is of interest to note that similar P-hydride elimination of a metalated iminium ion has been previously reported in palladium chemistry (eq 24).[30]



------(24)

2. 2. 4 Reaction of $Me_3SiN(C_2H_5)_2$ with $TiCl_4$/benzophenone

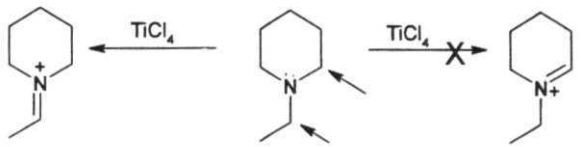
We have also examined the effect of trimethylsilyl group on the reactivity of the resulting iminium ion. It was of interest to examine whether the Me_3Si- group can be used as a 'dummy' non-transferable alkyl group in the transformation described above. There was no remarkable change when trimethylsilyldiethylamine was used in the reaction with benzophenone and the aldehyde 26 was isolated in 69% yield (eq 25).



----- (25)

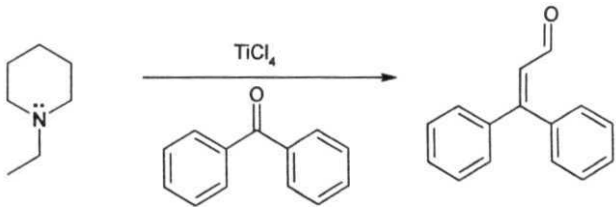
2. 2. 5 Reaction of *N*-alkylpiperidines with $TiCl_4$/benzophenone

In the case of *N*-alkylpiperidines, there are two possibilities in the formation of iminium ions. Oxidation can occur either at the ring or at the *N*-alkyl carbon atoms (eq 26). To examine these possibilities, the reaction with *N*-ethylpiperidine was examined.



—(26)

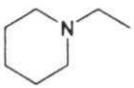
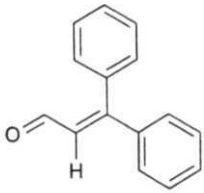
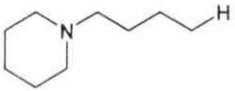
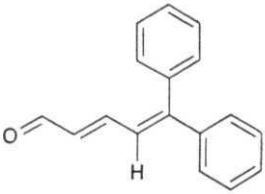
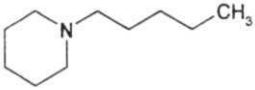
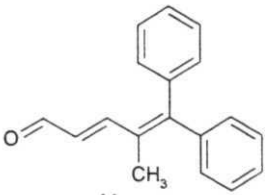
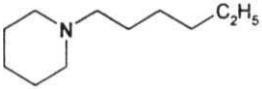
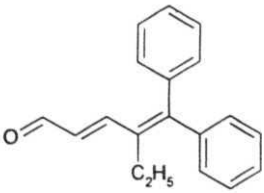
It was observed that the reaction of *N*-ethylpiperidine with $TiCl_4$ and benzophenone, gave 3,3-diphenyl-2-propenal in 48% yield (eq 27).

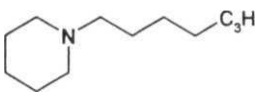
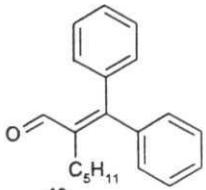
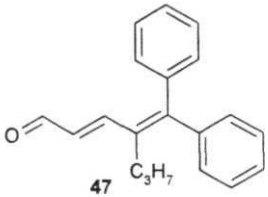
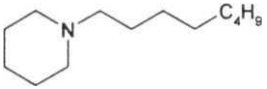
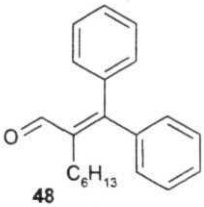
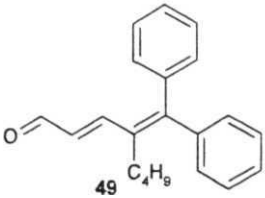


—(27)

Various *N*-alkylpiperidines were studied under different conditions to realize better yields. The results are summarized in Table 2. In the case of *N*-butylpiperidine, the butyl group was transferred. Whereas tri-n-butylamine gave 25% of the aldehyde 38, the *N*-butylpiperidine produced the product in only 18% yield. *N*-Pentylpiperidine and *N*-hexylpiperidine gave the products 44 and 45 in

Table 2. The reaction of benzophenone with $TiCl_4$/*N*-alkylpiperidines

No.	Amine	Aldehyde	Yield (%)
1,			48
2			18
3		 44	18
4.		 45	21

No	Amine	Aldehyde	Yield(%)
5		 **46** +  **47**	15 24
6		 **48** +  **49**	12 18

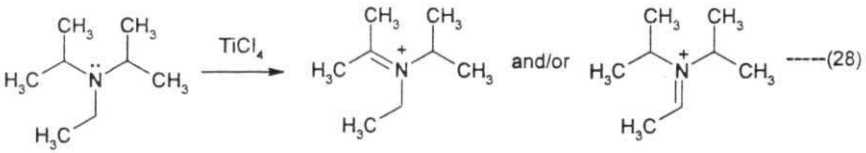
"The products were identified using spectral data (IR, ^{1}H-NMR, ^{13}C-NMR and Mass).
[b]Yields are based on the ketone used.

18% and 21% respectively. The *N*-heptylpiperidine, on reaction with $TiCl_4$ and benzophenone gave the aldehydes 46 and 47 in 15% and 24% yields respectively.

Also, the *N*-octylpiperidine produced the aldehydes 48 and 49 in 12% and 18% yields respectively.

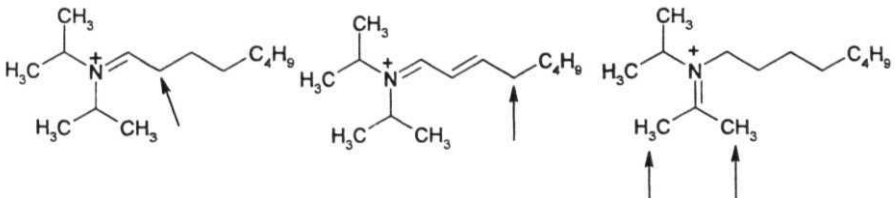
2. 2. 6 Reaction of *N,N*-diisopropyl-*N*-alkylamines with $TiCl_4$/-benzophenone

It was of interest to examine which of the iminium ion would form and transfer the alkyl group to benzophenone in the case of *N,N*-diisopropyl-*N*-ethylamine (eq 28).



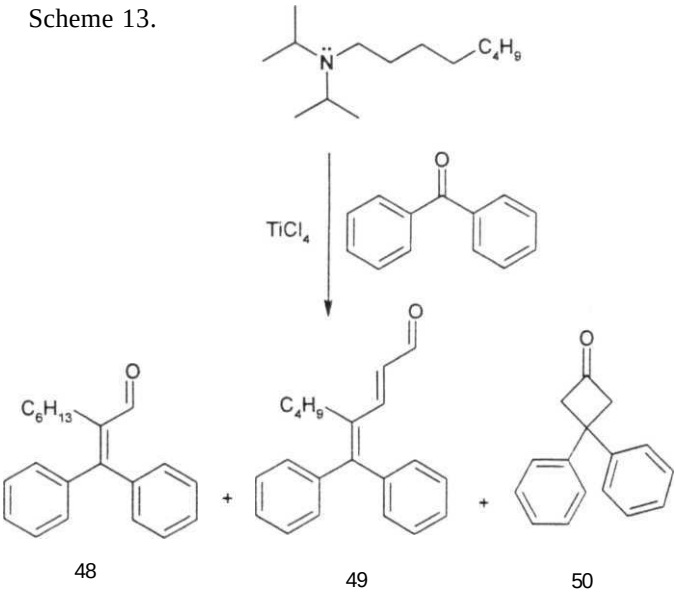
Surprisingly, in this case, the product mixture showed the presence of a cyclobutanone derivative (IR 1790 cm^{-1}) besides the aldehyde 26. However, the product mixture was obtained only in very small amounts. The use of *N,N*-diisopropyl-*N*-octylamine gave better results. In this case also, three types of iminium ions are expected (Scheme 12).

Scheme 12.

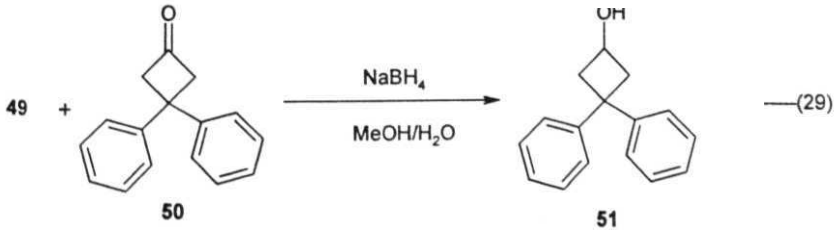


When the reaction was carried out using *N*,*N*-diisopropyl-*N*-octylamine, benzophenone and $TiCl_4$ aldehyde 48, and an inseparable mixture of aldehyde 49 and a cyclobutanone derivative were obtained (Scheme 13).

Scheme 13.

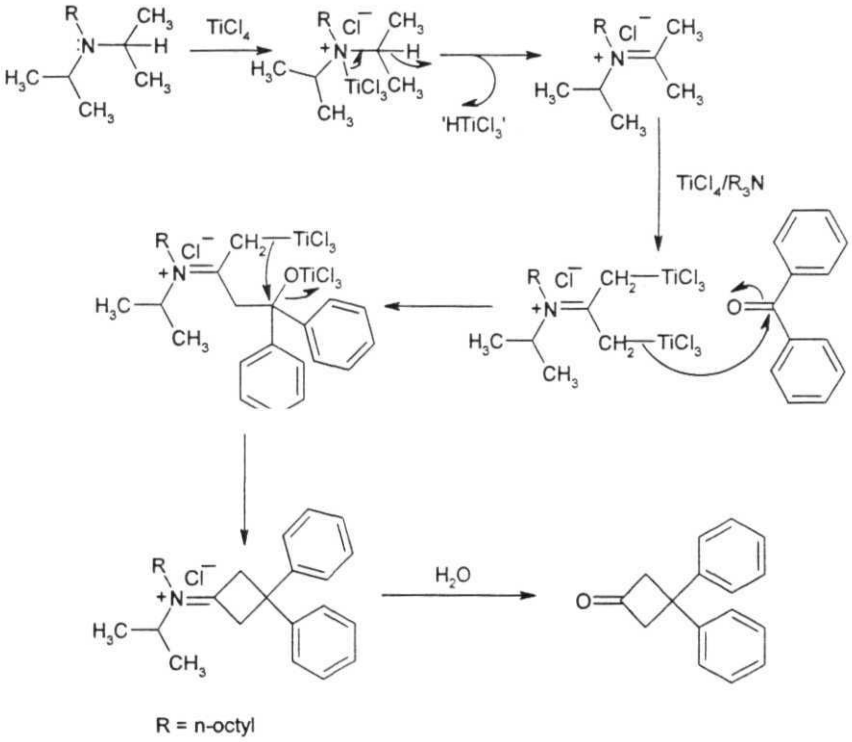


Fortunately, the corresponding cyclobutanol 51 can be readily separated after the reduction of the product mixture of 49 and the cyclobutanone 50 using $NaBH_4$ (eq 29).



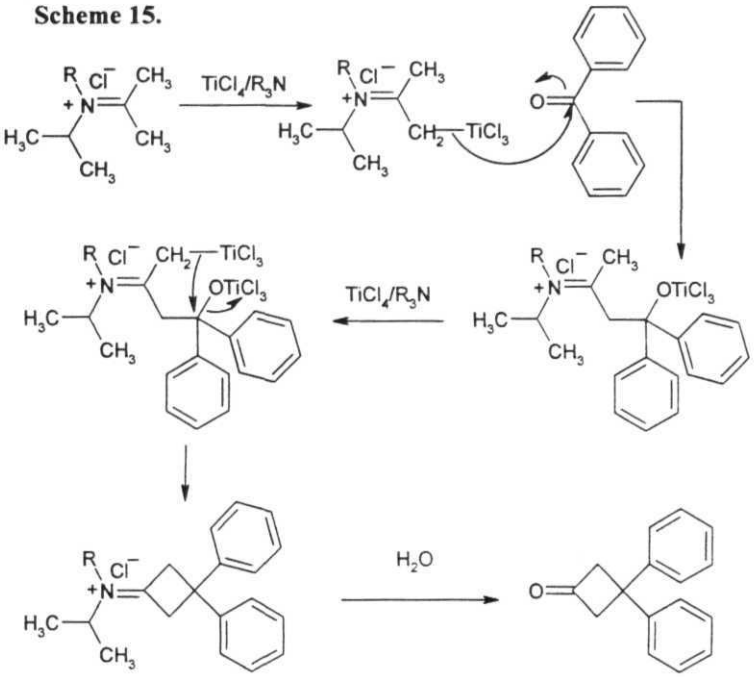
The formation of cyclobutanone derivative may be explained by the mechanism involving the dimetalated iminium ion intermediate (Scheme 14).

Scheme 14.



However, the possibility of sequential metalation-addition reactions cannot be ruled out (Scheme 15).

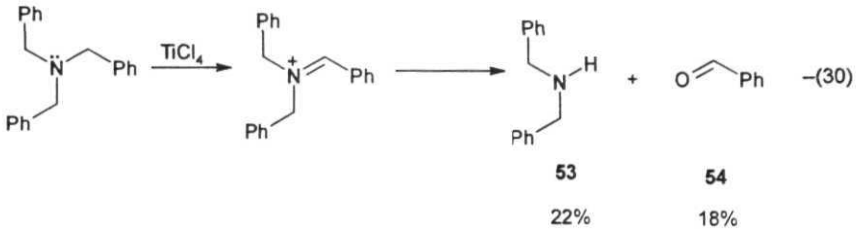
Scheme 15.



The present transformation is a simple alternate to hitherto known methods of synthesis of such cyclobutanone derivatives.[31] Clearly, a thorough systematic investigation is required to realize the synthetic potential of the intermediates involved in these transformations.

2. 2. 7 Reaction of tribenzylamine with $TiCl_4$

We have also examined the reaction of tribenzylamine with $TiCl_4$. In this case, benzaldehyde (18%) and dibenzylamine (22%) were isolated (eq 30).



–(30)

2. 2. 8 Attempted Grignard addition reaction

The iminium ions are electrophilic in nature and hence they are anticipated to react with nucleophilic reagents.[5] We have attempted to examine the reaction of iminium ions generated in this way with Grignard reagents. Unfortunately, when phenylmagnesium bromide, prepared from PhBr and Mg in THF, was added to the stirred solution of triethylamine and $TiCl_4$, a complex mixture of unidentified products was obtained (eq 31).

---(31)

2. 3 Conclusions

The reaction of $TiCl_4$ with trialkylamines readily produces the corresponding iminium ions that undergo further metalation by $TiCl_4/R_3N$. These organometallic intermediates react with diarylketones/benzaldehyde to give the corresponding α,β-unsaturated aldehydes. The reaction of tri-n-butylamine is interesting since there occurs further dehydrogenation in the alkyl chain. The iminium ion derived from isopropyl group results in the formation of the corresponding 3,3-diphenylcyclobutanone on reaction with benzophenone. Further systematic investigations on the synthetic applications of the iminium ion intermediates produced using $TiCl_4/R_3N$ should give fruitful results.

2. 4 Experimental Section

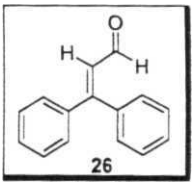
2. 4. 1 General information

Several informations given in the experimental section of Chapter 1 are also applicable for the experiments outlined here. Triethylamine, tri-n-propylamine and tri-n-butylamine were used after distillation over CaH_2 and stored in KOH pellets. *N*-Alkylpiperidines were prepared from the piperidines and the corresponding alkyl halides. Ferrocenyl phenyl ketone and *p*-tolyl phenyl ketones were prepared following reported procedures.[32] Tribenzylamine was prepared from benzylamine following a reported procedure.[33a] Benzophenone supplied by Loba (India) and, 4,4'-dichlorobenzophenone, 4,4'-difluorobenzophenone and 4,4'-dimethylbenzophenone supplied by Lancaster (Switzerland) were utilized.

2. 4. 2 The reaction of triethylamine with $TiCl_4$/benzophenone

In CH_2Cl_2 (25 mL), the benzophenone (2.5 mmol, 0.45 g) and $TiCl_4$ (10 mmol, 2.2 mL of 1:1 solution of $TiCl_4/CH_2Cl_2$) were taken at 0 °C under N_2. The Et_3N (10 mmol, 1.4 mL) was added to this solution and stirred for 0.5 h at 0 °C. It was stirred at 0-25 °C further for 8 h. A saturated NH_4Cl solution (20 mL) was added to the reaction mixture and stirred for 0.5 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). The

combined organic extract was washed with brine solution (10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed and the residue was chromatographed on a silica gel column. The unreacted ketone was eluted using EtOAc/hexane (2:98) mixture. The 3,3-diphenyl-2-propenal, 26, was separated using EtOAc/hexane (4:96) mixture as eluent, (0.374g, 72%).



26

Yield 72%.

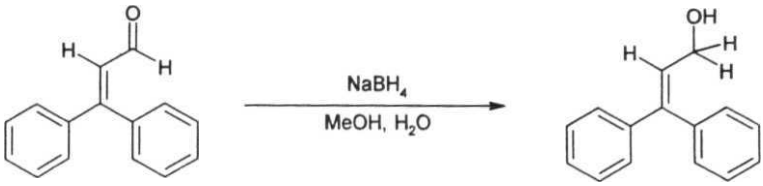
IR (neat) (cm^{-1}) 3057, 2843, 2752, 1666, 738, 700.

^{1}H-NMR (δ ppm, $CDCl_3$) 6.6 (d, J=7.79 Hz, 1H), 7.2-7.6 (m, 10H), 9.5 (d. J=7.88 Hz, 1H), (Spectrum No. 12).

^{13}C-NMR (δ ppm, $CDCl_3$) 193.02, 161.91, 139.77, 136.79, 130.68. 130.43, 129.40, 128.62, 128.36. 127.37, (Spectrum No. 13).

MS (EI) m/z 208 (M^+, 42%). 207 [(MM), (60%)], 178 [(M^+-1)-CHO, 66%], 102 [($C_6H_5C{\equiv}CH$), 100%].

This compound was further confirmed by converting it to the corresponding α,β-unsaturated alcohol using $NaBH_4$.



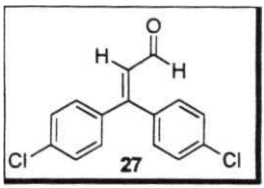
Yield 91%

IR(KBr) (cm^{-1}) 3452.

^{1}H-NMR (8 ppm, $CDCl_3$) 7.5-7.2 (m, 10H), 6.3 (t, 1H, olefinic proton), 4.25 (d, 2H, $-CH_2OH$), 1.6 (broad singlet, 1H, -OH).

^{13}C-NMR (δ ppm, $CDCl_3$) 144.09, 141.73, 139.24, 129.78, 128.24, 127.75, 127.64, 127.58, 60.63, (CH_2OH).

The above procedure was followed for the conversion of several other diaryl ketones to the corresponding a,P-unsaturated aldehydes.



27

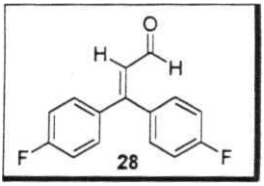
Yield 82%

IR (neat) (cm^{-1}) 3055, 2843, 2754, 1670.

^{1}H-NMR (6 ppm, $CDCl_3$) 6.6 (d, J=7.83 Hz, 1H), 7.25-7.6 (m, 8H), 9.55 (d, J=7.85 Hz, 1H).

^{13}C-NMR (8 ppm, $CDCl_3$) 192. 41, 159.18, 137.81, 136.94, 136.02, 134.66, 131.93, 129.80, 129.05, 128.88, 127.76, **(Spectrum No. 14).**

MS (EI) m/z 280 [(M^+-1)+4, 2.2%], 278 [(M^+-1)+2, 15.4%], 276 [(M^+-1), 20%].



28

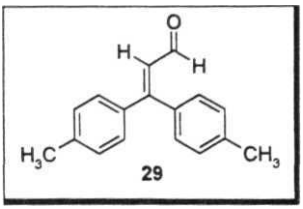
Yield 85%

IR (neat) (cm^{-1}) 3072, 2843, 2750, 1664.

^{1}H-NMR (δ ppm, $CDCl_3$) 6.5 (d, J=7.88 Hz, 1H). 7-7.4 (m, 8H), 9.45 (d, J=7.79 Hz, 1H).

^{13}C-NMR (δ ppm, $CDCl_3$) 192.42, 166.70, 166.01, 161.70, 161.02, 159.47, 135.77, 132.58, 132.41, 131.28, 130.64, 130.46, 129.83, 129.67, 127.41, 116.00, 115.85, 115.57, 115,42, 114.84, 114.29, 114.28.

MS (EI) m/z 244 (M^+, 100%).



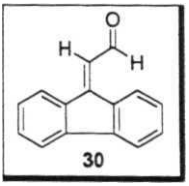
29

Yield 74%

IR (neat) (cm^{-1}) 3061, 2840, 2751, 1662.

^{1}H-NMR (δ ppm, $CDCl_3$) 2.35 (s, 3H), 2.45 (s, 3H), 6.65 (d, J=7.81 Hz, 1H), 7.2-7.4 (m, 8H), 9.6 (d, J=7.84 Hz, 1H).

^{13}C-NMR (δ ppm, $CDCl_3$) 193.30, 162.25, 140.84, 139.51, 137.20, 134.05, 130.78, 129.33, 128.98, 128.69, 126.53,21.28.



30

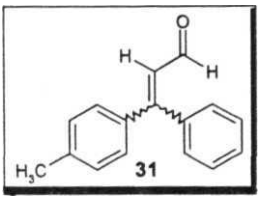
Yield 58%

IR (neat) (cm^{-1}) 2750, 1660.

^{1}H-NMR (δ ppm, $CDCl_3$) 6.8 (d, J=8.0 Hz, 1H), 7.2-7.4 (m, 8H), 10.8 (d, J=8.24 Hz, 1H).

^{13}C-NMR (δ ppm, $CDCl_3$) 190.08, 151.12, 142.68, 141.08, 138.50, 135.00, 131.48, 131.38, 127.94, 127.59, 122.93, 122.30, 120.47, 120.12.

MS (EI) m/z 206 (M^+, 100%), 178 (M^+-CHO, 80%).



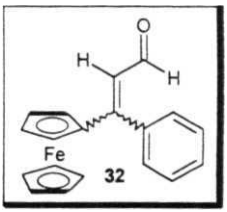
31

Yield 72%

IR (neat) (cm^{-1}) 3051, 3028, 2922, 2841, 2750, 1664.

^{1}H-NMR (6 ppm, $CDCl_3$) 2.39 (s, 3H), *2.44 (s, 3H)*, 6.57 (d, J=7.76 Hz, 1H), *6.61 (d, J=7.75 Hz, 1H)*, 7.20-7.46 (m, 18H), 9.7 (d, J=8.22 Hz, 1H) *(d, J=8.31 Hz, 1H)* (data in italic stand for isomer).

^{13}C-NMR (δ ppm, $CDCl_3$) 193.33, 162.29, 162.13, 140.99, 140.06, 139.68, 136.90, 133.85, 130.84-126.59,21.35.



32

Yield 76%

IR(KBr) (cm-^{1}) 3058, 3028, 2912, 2846, 2751, 1662.

^{1}H-NMR (δ ppm, $CDCl_3$) ^{1}H-NMR (δ ppm): 4.28-4.5 (m, 9H), 6.5 (d, J=8.11 Hz, 1H), 7.25-7.55 (m, 5H), 9.35 (d, J=7.98 Hz, 1H),

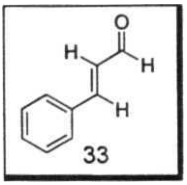
(Spectrum No. 15).

^{13}C-NMR (5 ppm, $CDCl_3$) 192.56, 165.28, 136.52, 129.38, 128.72, 128.02, 124.24, 81.99, 71.63, 70.23, 69.01, **(Spectrum No. 16).**

MS (EI) m/z 316 (M^+, 100%), 288 (M^+-CO, 61%), (Spectrum No. **17).**

2. 4. 3 The reaction of triethylamine with $TiCl_4$/benzaldehyde

In CH_2Cl_2 (25 mL), $TiCl_4$ (10 mmol. 2.2 mL of 1:1 solution of $TiCl_4/CH_2Cl_2$) was taken and the Et_3N (10 mmol, 1.4 mL) was added at -78 °C. This reaction mixture was stirred at -78 °C for 1 h. PhCHO (10 mmol, 1.0 mL) was added to this reaction mixture and allowed to stir further for 3 h at -78 °C to 25 °C. The reaction mixture was brought to room temperature. A saturated NH_4Cl solution (20 mL) was added to the reaction mixture and stirred for 0.5 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic extract was washed with brine solution (10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed and the residue was chromatographed on a silica gel column. The unreacted benzaldehyde was eluted using EtOAc/hexane (2:98) mixture. The cinnamaldehyde was separated using EtOAc/hexane (4:96) mixture as eluent (0.607g, 46%).



33

Yield 46%

IR (neat)` (cm^{-1}) 3061, 2816, 2743, 1678.

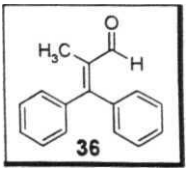
^{1}H-NMR (6 ppm, $CDCl_3$) 6.75 (dd, J=7.88 Hz, 1H), 7.3-7.7 (m, 6H), 9.75 (d, J=7.9 Hz, 1H). The spectral data of 33 showed 1:1 correspondence with the reported data.[34]

^{13}C-NMR (8 ppm, $CDCl_3$) 193.55, 152.65, 134.05, 131.23, 129.09, 128.51.

2. 4. 4 The reaction of $(CH_3CH_2CH_2)_3N$ with $TiCl_4$/diarylketones

In CH_2Cl_2 (25 mL), benzophenone (2.5 mmol, 0.45g) and $TiCl_4$ (10 mmol, 2.2 mL of 1:1 solution of $TiCl_4/CH_2Cl_2$) were taken at 0 °C under N_2. The n-Pr_3N (10 mmol, 1.9 mL) was added to this solution and stirred for 0.5 h at 0 °C. It was stirred at 0-25 °C further for 8 h. A saturated NH_4Cl solution (20 mL) was added to the reaction mixture and stirred for 0.5 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic extract was washed with brine solution (10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed and the residue was

chromatographed on a silica gel column. The unreacted ketone was eluted using EtOAc/hexane (2:98) mixture. The aldehyde, 3,3-diphenyl-2-methyl-2-propenal, 36, was separated using EtOAc/hexane (4:96) mixture as eluent.



36

Yield 23%

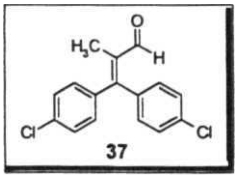
IR (neat) (cm^{-1}) 3059, 2851,2749, 1666.

^{1}H-NMR (8 ppm, $CDCl_3$) 2.0 (s, 3H), 7.2-7.5 (m, 10H), 9.6 (s, 1H), (Spectrum No. 18).

^{13}C-NMR (δ ppm, $CDCl_3$) 194.12 (CHO), 159.33 (quaternary), 140.87 (quaternary), 138.90 (quaternary'), 135.30 (quaternary), 131.17 (CH), 129.61 (CH), 128.92 (CH), 128.66 (CH), 128.26 (CH), 128.11 (CH), 14.26 (CH_3), (Spectrum No. 19).
(Signal assignments based on DEPT experiments).

MS (EI) m/z 222 (M^+,80%), 221 [(MM), 100%].

The above procedure was also adopted for the conversion of 4,4'-dichlorobenzophenone to the corresponding aldehyde.



37

Yield 21%

IR (neat) (cm^{-1}) 3056, 2834, 2715, 1661.

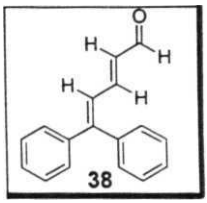
^{1}H-NMR (6 ppm, $CDCl_3$) 2.1 (s, 3H), 7.2-7.6 (m, 8H), 9.4 (s, 1H).

^{13}C-NMR (6 ppm, $CDCl_3$) 194.21, 159.33, 140.87, 138.90, 135.30, 131.17, 129.61, 128.92, 128.66, 128.26, 128.11, 14.26.

2. 4. 5 The reaction of $(CH_3CH_2CH_2CH_2)_3N$ with $TiCl_4$/diarylketones

In CH_2Cl_2 (25 mL), the benzophenone (2.5 mmol, 0.45g) and $TiCl_4$ (10 mmol, 2.2 mL of 1:1 solution of $TiCl_4/CH_2Cl_2$) were taken at 0 °C under N_2. The Bu_3N (10 mmol, 2.4 mL) was added to this solution and stirred for 0.5 h at 0 °C. It was stirred at 0-25 °C further for 8 h. A saturated NH_4Cl solution (20 mL) was added to the reaction mixture and stirred for 0.5 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic extract was washed with brine solution (10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed and the residue was chromatographed on a silica gel column. The unreacted ketone was eluted

using EtOAc/hexane (2:98) mixture. The aldehyde was separated using EtOAc/hexane (4:96) mixture as eluent.



38

Yield 25%

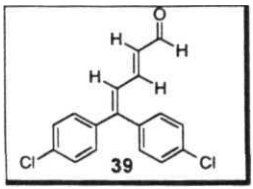
IR (neat) (cm^{-1}) 3059, 2957,2798, 1662.

^{1}H-NMR (8 ppm, $CDCl_3$) 6.25 (dd, J=8.01 Hz, 1H), 6.95 (d, J=7.9 Hz, 1H), 7.25 (dd, J=7.93 Hz, 1H), 7.35-7. 7 (m, 10H), 9.48 (d, J=7.89 Hz, 1H), (Spectrum No. 20).

^{13}C-NMR (8 ppm. $CDCl_3$) 193.70 (CHO), 153.07 (quaternary), 149.62, 140.85 (quaternary), 138.37 (quaternary). 132.50 (CH), 130.37 (CH). 129.24 (CH), 128.66 (CH), 128.50 (CH), 128.28 (CH), 125.27 (CH), (Spectrum No. 21).

(Signal assignments based on DEPT experiments).

MS (EI) m/z 234 (M^+, 69%), 205 [(M^+-CHO), 100%].



39

Yield	18%
IR (neat)	(cm^{-1}) 3054, 2926, 2757, 1661.
^{1}H-NMR	(5 ppm, $CDCl_3$) 6.32 (dd, J=7.88 Hz, 1H), 7.1 (d, J=8.1 Hz. 1H), 7.31 (dd. J=7.97 Hz, 1H), 7.32-7.9 (m, 8H), 9.41 (d, J=7.9 Hz, 1H).
^{13}C-NMR	(8 ppm, $CDCl_3$) 193.61, 153.07, 149.62, 140.85, 138.37, 132.50, 130.37, 129.24, 128.66, 128.50, 128.28, 125.27.

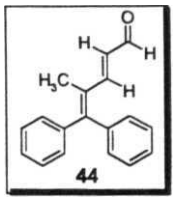
2. 4. 6 Reaction of $(CH_3CH_2)_2NSiMe_3$ with $TiCl_4$/benzophenone

In CH_2Cl_2 (25 mL), benzophenone (2.5 mmol, 0.45g) and $TiCl_4$ (10 mmol, 2.2 mL of 1:1 solution of $TiCl_4/CH_2Cl_2$) were taken at 0 °C under N_2. The $(CH_3CH_2)_2NSiMe_3$ (10 mmol, 1.9 mL) was added and stirred for 0.5 h at 0 °C. It was stirred at 0-25 °C further for 8 h. A saturated NH_4Cl solution (20 mL) was added to the reaction mixture and stirred for 0.5 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic extract was washed with brine solution (10 mL) and dried

over anhydrous $MgSO_4$. The solvent was removed and the residue was chromatographed on a silica gel column. The unreacted ketone was eluted using EtOAc/hexane (2:98) mixture. The 3,3-diphenyl-2-propenal 26, was separated using EtOAc/hexane (4:96) mixture as eluent.

2. 4. 7 The reaction of *N*-alkylpiperidines with $TiCl_4$/diaryl ketones

In CH_2Cl_2 (25 mL), benzophenone (2.5 mmol, 0.45g) and $TiCl_4$ (10 mmol, 2.2 mL of 1:1 solution of $TiCl_4/CH_2Cl_2$) were taken at 0 °C under N_2. The *N*-pentylpiperidine (10 mmol, 1.4 mL) was added to this solution and stirred for 0.5 h at 0 °C. It was stirred at 0-25 °C further for 8 h. A saturated NH_4Cl solution (20 mL) was added to the reaction mixture and stirred for 0.5 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic extract was washed with brine solution (10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed and the residue was chromatographed on a silica gel column. The unreacted ketone was eluted using EtOAc/hexane mixture (2:98). The aldehyde, 44, was separated using EtOAc/hexane mixture (4:96) as eluent.



44

Yield 18%

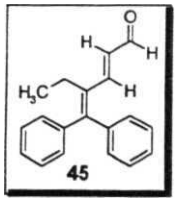
IR (neat) (cm^{-1}) 3042, 2926, 2825, 2749, 1663.

^{1}H-NMR (8 ppm, $CDCl_3$) 2.0 (s, 3H), 6.4 (dd, J=8.11 Hz, 1H), 7.2-7.6 (m, 11H), 9.55 (d, J=7.87 Hz, 1H), **(Spectrum No. 22).**

^{13}C-NMR (δ ppm, $CDCl_3$) 194.35, 153.77, 151.94, 141.82, 141.08, 130.63, 129.83, 129.17, 128.15, 127.87, 17.04, **(Spectrum No. 23).**

MS (El) m/z 248 (M^+, 100%), 220 [(M^+ -CO), 60%].

The above procedure was followed for the conversion of several other *N*-alkylpiperidines to the corresponding aldehydes.



45

Yield 21%

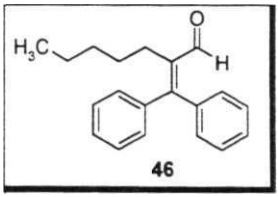
IR (neat) (cm^{-1}) 3062, 2926, 2841, 2747, 1664.

^{1}H-NMR (8 ppm, $CDCl_3$) 1.1 (t, J=7.48 Hz, 3H, CH_3), 2.45 (q, J=7.3 Hz, 2H), 6.4 (dd, J=7.81 Hz, 1H) 7.2-7.5 (m, 11H), 9.5 (d, J=7.84 Hz, 1H), (Spectrum No. 24).

^{3}C-NMR (δ ppm, $CDCl_3$) 194.52 (CHO), 152.49 (CH), 151.50 (quaternary), 141.96 (quaternary), 141.08 (quaternary), 136.89 (quaternary), 130.48 (CH), 129.11 (CH), 128.95 (CH), 128.27 (CH), 128.17 (CH), 127.75 (CH), 23.43 (CH_2), 14.08 (CH_3), (Spectrum No. 25).

(Signal assignments based on DEPT experiments).

MS (EI) m/z 262 (M^+, 56%), 233 [(M^+-CHO), 60%].



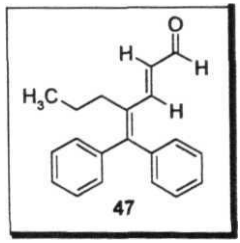
46

Yield 15%

IR (neat) (cm^{-1}) 3052, 2943, 2862, 2751, 1661.

'H-NMR (8 ppm, $CDCl_3$) 1.3 (t, J=7.2 Hz, 3H), 2.6-3.3 (m, 6H), 3. 6 (t, J=7.04 Hz, 2H), 7.3-7.8 (m, 10H), 9.8 (s, 1H).

^{13}C-NMR (δ ppm, $CDCl_3$) 194.50, 152.98, 151.72, 141.97, 141.14, 135.60, 130.43, 130.02, 129.06, 128.21, 32.41, 22.81, 14.17.



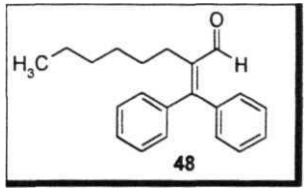
47

Yield 24%

IR (neat) (cm^{-1}) 3057, 2934, 2871, 2749, 1660.

^{1}H-NMR (8 ppm, $CDCl_3$) 1.2 (t, J=7.18 Hz, 3H), 2.3 (m, 2H), 3.1 (t, J=6.97 Hz, 2H), 6.4 (dd, J=7.88 Hz, 1H), 7.1-8.2 (m, 11H), 9.6 (d, J=7.91 Hz, 1H).

^{2}C-NMR (8 ppm, $CDCl_3$) 194.50, 152.98, 151.50, 141.96, 141.08, 135.60, 130.43, 130.02, 129.06, 128.21, 127.70, 32.41, 22.81, 14.17, (Spectrum No. 26).



48

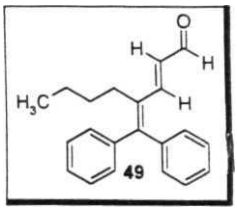
Yield 12%

IR (neat) (cm^{-1}) 3059, 3026, 2957, 2928, 2856, 2744, 1668.

^{1}H-NMR (8 ppm, $CDCl_3$) 9.6 (s, J=8.1 Hz, 1H), 7.0-7.55 (m, 10H), 2.45

(t, **J=7.17 Hz,** 2H), 1.7-1.1 **(m,** 8H), 0.8 (t, **J=6.99 Hz,** 3H).

^{3}**C-NMR** **(δ ppm, $CDCl_3$)** 194.11, 159.45, 141.06, 140.38, 139.04, 132.39, 130.97, 130.05, 128.89, 128.40, 128.29, 128.08, 31.42, 29.71, 29.37, 28.00, 22.54, 14.05, **(Spectrum No. 27).**



Yield 18%

IR **(cm^{-1})** 3059, 3026, 2957, 2928, 2856, 2744, 1668.

H-NMR **(δ ppm, $CDCl_3$)** 9.55 **(d,** J=7.8 **Hz, 1H),** 7.9 (d, 1H), 7.0-7.6 **(m, 10H),** 6.38 **(dd,** J=6.99 **Hz,** 1H), 2.45 (t, J=7.67 **Hz,** 2H), 1.7-1.1 **(m,** 4H), 0.8 (t, **J=7.13 Hz,** 3H), **(Spectrum** No. **28).**

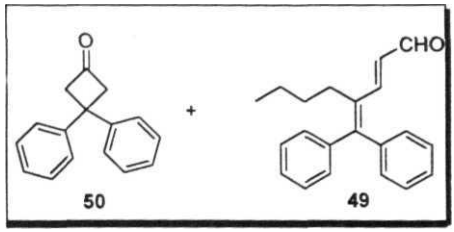
^{13}C-NMR (8 ppm, $CDCl_3$) 194.57, 153.06, 151.80, 141.98, 141.16, 135.74, 130.48, 129.09, 128.66, 128.20, 127.74, 31.69, 30.09, 22.85, 13.74, **(Spectrum** No. **29).**

The aldehydes 38, 39, 44, 45, 47 and 49 were tentatively assigned the stereochemistry as indicated since these isomers are expected to be more stable. Also, the reaction of benzaldehyde with **$TiCl_4/Et_3N$** gives only the more stable ***trans*-cinnamaldehyde (*E*-configuration).**

2. 4. 8 Reaction of *N,N*-diisopropyl-*N*-octylamine with $TiCl_4$/benzophenone

In CH_2Cl_2 (25 mL), benzophenone (2.5 mmol, 0.45 g) and $TiCl_4$ (10 mmol, 2.2 mL of 1:1 solution of $TiCl_4/CH_2Cl_2$) were taken at 0 °C under N_2. The *N,N*-diisopropyl-*N*-octylamine (10 mmol, 2.1 mL) was added to this solution and stirred for 0.5 h at 0 °C. It was stirred at 0-25 °C further for 8 h. A saturated NH_4Cl solution (20 mL) was added to the reaction mixture and stirred for 0.5 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic extract was washed with brine solution (10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed and the residue was chromatographed on a silica gel column. The aldehyde 48 was eluted using EtOAc/hexane (1:99) mixture and the unreacted benzophenone was eluted using EtOAc/hexane (2:98) mixture. The mixture of 3,3-diphenylcyclobutanone and the aldehyde 49, was isolated using EtOAc/hexane (4:96) mixture as eluent.

Spectral data indicated the presence of the aldehyde 49 and the 3,3-diphenylcyclobutanone, 50 in the mixture. The TLC analysis indicated that RF values for these compounds are very close (EtOAc/hexane mixture).



Yield 28% (collective yield based on the benzophenone used)

IR (neat) (cm^{-1}) 2731, 1674 (aldehyde 49).

(cm^{-1}) 1790(cyclobutanone).

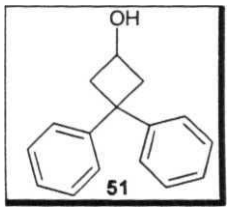
^{1}H-NMR (6 ppm, $CDCl_3$) 9.6 (d, J=7.8 Hz, 1H, CHO), 7.0-7.7 (m, aromatic for 49 and 50, 20H), 6.4 (dd, 1H), 2.4 (t, 2H), 1.7-1.1 (m, 4H), 0.8 (t. 3H) (aldehyde 49).

(8 ppm, $CDCl_3$), 3.8 (s, 4H) (3,3-diphenylcyclobutanone, 50). (reported data:[31] CCl_4, 7.2 (s, 10H), 3.67 (s, 4H), **(Spectrum** No. **30).**

^{13}C-NMR (δ ppm, $CDCl_3$) 194.57, 153.06, 151.80, 141.98, 141.16, 135.74, 130.48, 129.09, 128.66, 128.20, 127.74, 31.69, 30.09, 22.85, 13.74 (aldehyde 49). (δ ppm, $CDCl_3$) 205.36, 147.2, 130.06-126.47, 60.51, 42.08 (3,3-diphenylcyclobutanone, **50), (Spectrum No. 31).**

2. 4. 9 Reduction of 3,3-diphenylcyclobutanone to 3,3-diphenyl-cyclobutanol

The mixture of aldehyde and cyclobutanone obtained in the above reaction was taken in 15 mL of 1:1 mixture of MeOH:H_2O. To this was added $NaBH_4$ (10 mmol, 0.38 g) and the reaction mixture stirred for 4 h at 25 °C. The reaction was quenched with water and was neutralized with dil. HC1. The organic compounds were extracted with ether. The ether layer was washed with water. The solvent was evaporated and residue was column chromatographed on silica gel column. The 3,3-diphenylcylobutanol 51, was isolated using EtOAc/hexane (4:96) mixture as eluent.



Yield 12% (based on the benzophenone)

M.p. 105 °C (Lit.[31] 104-105 °C).

IR (KBr) (cm^{-1}) 3292, 2970, 2934.

^{13}C-NMR (5 ppm, $CDCl_3$) 150.69 (quaternary), 147.31 (quaternary), 128.49 (CH), 126.81 (CH), 125.94 (CH), 125.70 (CH),

63.03 (CHOH), 45.78 (CH_2), 42.96 (quaternary, $CC_6H_5)_2$), (Spectrum No. 32).

(Signal assignments based on DEPT experiments).

MS (EI) m/z 206 [(M^+-H_2O), 17%], 180 {[(M^+-H_2O)-HC≡CH)], 100%}.

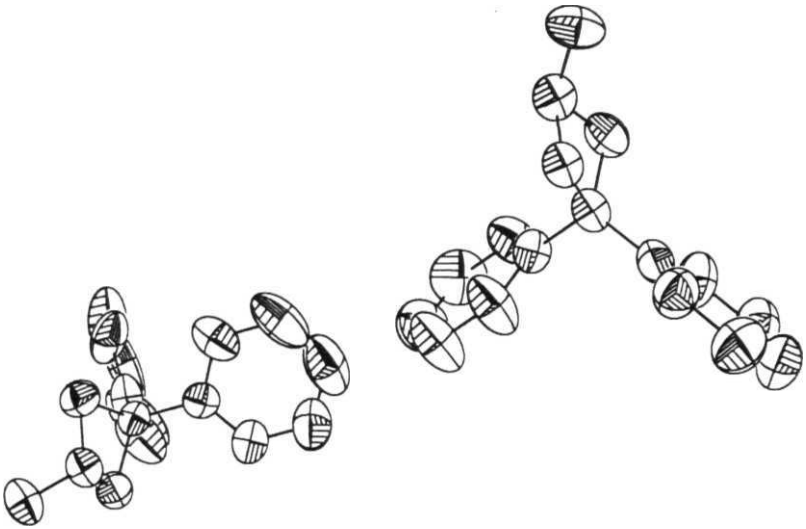
The **3,3-diphenylcyclobutanol** was further **confirmed** by X-ray crystal structural analysis.

The x-ray diffraction measurements were carried out at 293 K on an automated Enraf-Nonious MACH 3 diffractometer using graphite monochromated, Mo-Ka (λ=0.71073 A) radiation. Intensity data were collected by the ω–scan mode. The data were reduced using the XTAL programme. No absorption correction was applied.

Crystal Structure Data for **3,3-diphenylcyclobutanol** 51

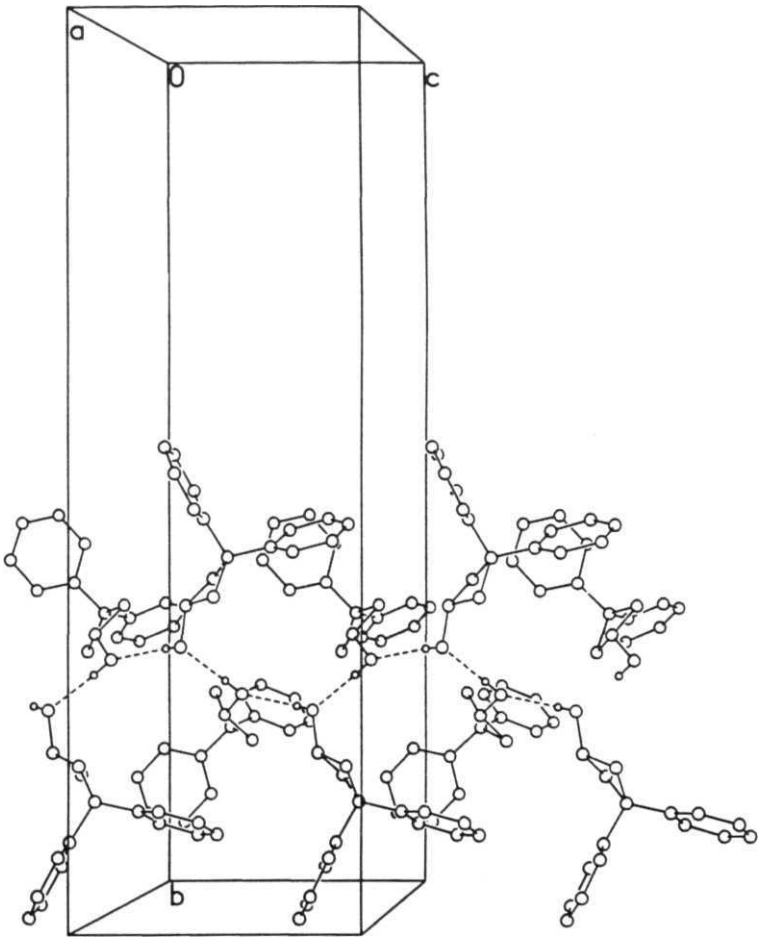
G range for data collection is 1.96 to 27.47°. Empirical formula $C_{16}H_{16}O$, colorless needles (0.72x0.76x0.72 mm), crystal system is monoclinic, space group P2]/C, unit cell dimensions: a= 10.566(2) A, 6=27.568(6) A, c=8.9747(18) A, β= 100.42(3) A.; Volume 2571.0(9) $Å^3$, Z=8 D_{calc}=1.159 Mg/m^3, absorption coefficient is 0.070 mm^{-1}, $F(000)$=960, index ranges $-13 \leq h \leq$

Figure 1. The ortep diagram of **3,3-diphenylcyclobutanol**



13, -35≤ *k*≤0, 0≤*l*≤ 11, total reflection collected were 6519 out of which 2113 were independent reflections with *R*(int)=0.0253 and *R*(sigma)=0.0671. The structure was solved by direct methods and refined by full-matrix least-squares procedure using the SHELX 86 and SHELX 97 program package, respectively. The refinement was carried out using 2113 observed [$F>4\sigma(F)$] reflections and converged to a final *R* 1=0.0724, *wR*2 = 0.1990 and goodness of fit is 1.113 with largest difference peak and hole 0.16 and -0.16 e $Å^{-3}$, respectively. Crystal suitable for X-ray diffraction was obtained through crystallization from hexane at room temperature.

Figure 2. Packing diagram of 3,3-diphenylcyclobutanol



The 3,3-diphenylcyclobutanol crystallizes in centrosymmetric monoclinic form. The structure is stabilized by two different O-H···O interactions. One O-H···O connects the inversion related molecules and the other O-H···O connects the glide related molecules and thus the molecule is forming a chain like structure along (001) as shown in the figure 2.

2. 4. 10 Reaction of tribenzylamine with $TiCl_4$

In CH_2Cl_2 (25 mL), tribenzylamine (10 mmol, 2.87 g) was taken and $TiCl_4$ (10 mmol, 2.2 mL of 1:1 solution of $TiCl_4/CH_2Cl_2$) was added to this at 0 °C under N_2. The reaction mixture was stirred for 0.5 h at 0 °C. It was stirred at 0-25 °C further for 8 h. A saturated NH_4Cl solution (20 mL) was added to the reaction mixture and stirred for 0.5 h. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic layer was extracted with conc. HC1 (2 x 20 mL). The remaining organic layer was washed with brine solution (10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed and the residue was chromatographed on a silica gel column. The benzaldehyde was isolated using EtOAc/hexane (4:96) mixture as eluent.

Yield 18%

IR (cm^{-1}) 3051, 2741, 1701.

^{1}H-NMR (8 ppm, $CDCl_3$) 9.1 (s, 1H), 7.3-. 1 (m, 5H). Spectral data showed 1:1 correspondence with reported data.[34]

The aqueous layer was neutralized with 30% NaOH solution and the organic compounds were extracted with CH_2Cl_2 (2 x 25 mL). The organic layer was washed with brine solution (10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed and the residue was chromatographed on a silica gel column. The dibenzylamine was isolated using EtOAc/hexane (4:96) mixture as eluent.

Yield 22%

IR (cm^1) 3441, 3051.

^{1}H-NMR (δ ppm, $CDCl_3$) 7.33 (s, 10H), 3.82 (s, 4H). 1.8 (s, 1H) (spectral data showed 1:1 correspondence with reported data).[34]

2. 4. 11 General procedure for the synthesis of *N*-alkylpiperidines

In acetonitrile (30 mL), anhydrous K_2CO_3 (200 mmol, 27.6 g) and piperidine (200 mmol, 19.7 mL) were taken. To this was added alkyl halide (200 mmol) and this reaction mixture was refluxed for 24 hrs. The reaction was brought to room temperature. K_2CO_3 was filtered off and the acetonitrile was distilled off. The residue was treated with water (20 mL) and organic layer was

separated and remaining aqueous layer was extracted with ether (2x30 mL). The combined organic extract was washed with brine solution (10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed and the amine was distilled out under reduced pressure.

N-Alkyl piperidines	Boiling point
N-Butylpiperidine	46 °C/20mm Hg (Lit.[35] 48 °C/20mm Hg)
N-Pentylpiperidine	79 °C/8mm Hg (Lit.[35] 80 °C/8mm Hg)
N-Hexylpiperidine	106 °C/20mm Hg (Lit.[35] 103-104 °C/20mm Hg)
N-Heptylpiperidine	102 °C/9mm Hg (Lit.[35] 100-103 °C/ 9mm Hg)
N-Octylpiperidine	134 °C/13mm Hg (Lit.[35] 136-138 °C /13mm Hg)
N, N-Diisopropyl-*N*-octylamine	110 °C/12 mm Hg

2. 4. 12 Preparation of tribenzylamine

A mixture of benzylamine (10.7 g, 100 mmol), KOH powder (69 g, 500 mmol), benzyl bromide (29.7 mL, 250 mmol) and NaI (3.0 g, 20 mmol) was refluxed for 20 h. The contents were brought to room temperature and extracted with ether (3 x 50 mL). The ether layer was treated with 5N HC1 (30 mL) to

precipitate the amine as hydrochloride salt which was found to be insoluble in water. The amine hydrochloride was once washed with ether (30 mL) and neutralized with 5N KOH (phenolphthalein indicator). The amine was extracted with ether (3 x 25 mL), dried over anhydrous $MgSO_4$ and the solvent was evaporated. The residue was recrystallised from benzene-hexane mixture to yield tribenzylamine, mp 93 °C (Lit.[33b] 91-94 °C) (Yield, 80%).

2. 4. 13 Preparation of ferrocenyl phenyl ketone

Into a 500-mL round-bottomed flask place 100 mL of CH_2Cl_2 , ferrocene (4.7 g, 25 mmol) and distilled benzoyl chloride (2.9 mL, 25 mmol). To this was added anhydrous aluminium chloride (3.7 g, 27 mmol) with intermittent shaking of the reaction mixture at 0 °C. The reaction mixture was refluxed for 3 h or until hydrogen chloride is no longer evolved. The contents of the reaction were poured into the mixture of ice and 100 mL of conc. HC1. The organic layer was separated and the aqueous layer was extracted with ether (3 x 25 mL). The combined organic layer was washed with 5 % NaOH solution, then water and brine solution and dried over anhydrous $MgSO_4$. The solvent was removed and residue was column chromatographed on a silica gel column. The ferrocenyl phenyl ketone was eluted using EtOAc/hexane (4:96) mixture.

2. 4. 14 Preparation of 4-methylbenzophenone

Into a 500-mL round-bottomed flask place 100 mL of toluene and distilled benzoyl chloride (2.9 mL, 25 mmol). To this was added anhydrous aluminium chloride (3.7 g, 27 mmol) with intermittent shaking of the reaction mixture at 0 °C. The reaction mixture was refluxed for 3 h or until hydrogen chloride is no longer evolved. The contents of the reaction were poured into the mixture of ice and 100 mL of conc. HC1. The organic layer was separated and the aqueous layer was extracted with ether (3 x 25 mL). The combined organic layer was washed with 5 % NaOH solution, then water (30 mL) and brine solution (30 mL) and dried over anhydrous $MgSO_4$. The solvent was removed and residue was column chromatographed on a silica gel column. The 4-methyl benzophenone was eluted using EtOAc/hexane (4:96) mixture.

2. 5 References

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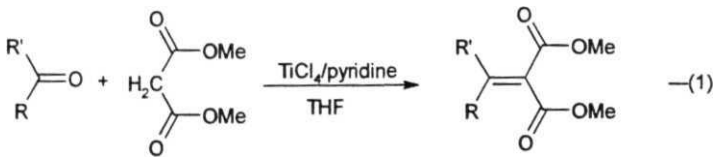
Chapter 3

Studies on other synthetic applications of the $TiCl_4/R_3N$ reagent system

3. 1 Introduction

In this chapter, we describe the results of the studies on several other synthetic applications of the $TiCl_4/R_3N$ reagent system. A brief review of the literature report on this topic will be helpful for the discussion. The major use of the $TiCl_4/R_3N$ reagent system is for the preparation of titanium enolates for applications in stereo- and enantioselective aldol condensation reactions. The aldol reaction of titanium enolates is one of the best studied reactions. In many cases, these enolates lead to higher stereoselectivity and chemoselectivity in their reactions than the lithium enolates.[1] Also, they are easily prepared using inexpensive reagents.

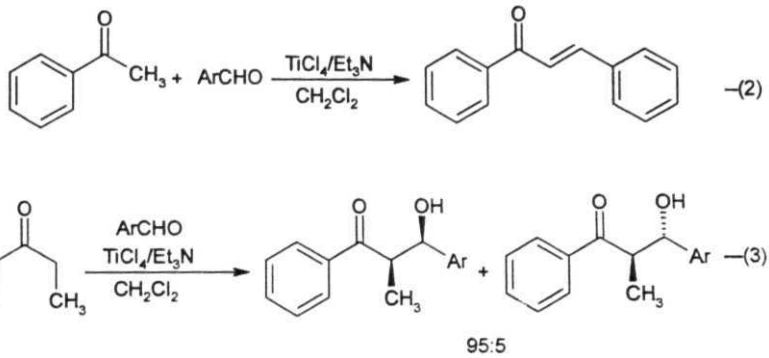
In 1970, it was reported that the $TiCl_4$/pyridine reagent in THF mediates the Knoevenagel condensation reaction (eq 1)[2]. It was postulated that the reaction goes through the corresponding titanium enolate intermediate.



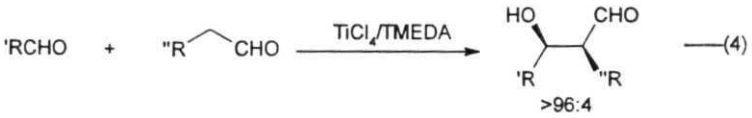
—(1)

Later, the reaction of titanium enolate of aryl alkyl ketone with aromatic aldehyde was reported (eq 2). In the case of propiophenone, P-hydroxy ketones

were isolated as 95:5 mixture of syn:anti stereoisomers (eq 3).[3]

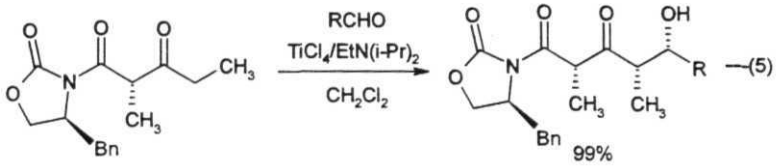


In the aldol addition of an enolizable aldehyde using $TiCl_4$/-TMEDA, a high syn- selectivity was observed at -40 °C (eq 4).[4]



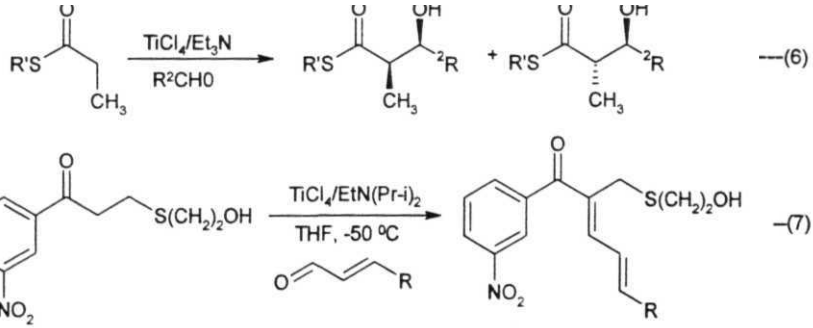
These reactions have some advantages over earlier methods of generating titanium enolates by transmetalation process.[1] The preparation and applications of titanium enolates prepared using $TiCl_4/R_3N$ were studied extensively by Evans et. al.[5] They have shown that, the titanium enolates prepared using $TiCl_4/R_3N$ react with various electrophiles, including acetals, alkylating agents and Michael acceptors.[6] Also, a diastereoselective aldol reaction using P-ketoimide derived

enolate has been used in the efficient construction of complex polypropionate-derived natural products (eq 5).[7]



—(5)

Titanium enolates of certain thioesters and α-thio substituted esters undergo aldol condensation reaction with achiral and chiral aldehydes. The diastereoselectivity realized in these reactions was 48:52 to 95:5 (syn:anti) depending on the substituents (eq 6 & 7).[8,9]

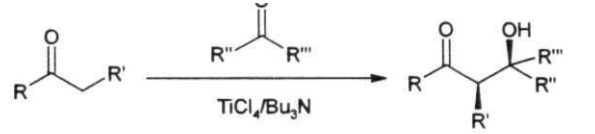


—(6)

—(7)

The stoichiometry and the nature of amine have significant effect on the stereochemical outcome in these reactions.[10]

Cross aldol reaction with high syn- stereoselectivity was also reported using $TiCl_4/Bu_3N$ (eq 8). This reagent system was also used for the Claisen condensation reactions of methyl esters in the presence of catalytic amounts of TMSOTf (eq 9).[11]



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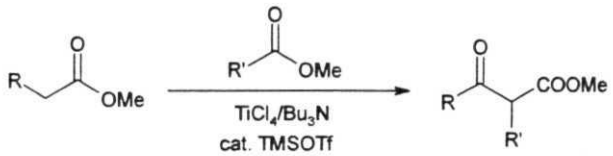

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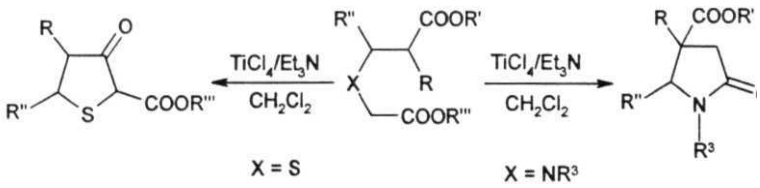
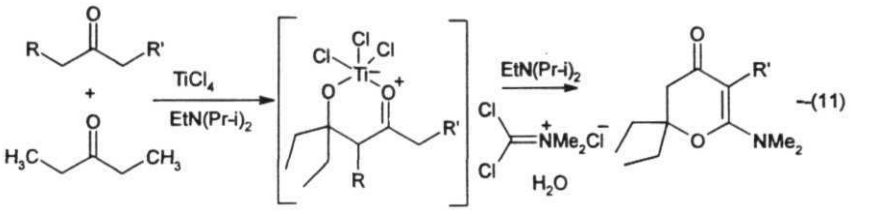
Dieckmann type cyclization to obtain 5 membered ring nitrogen and sulfur heterocycles was also reported using $TiCl_4/Et_3N$ system (eq 10).[12]

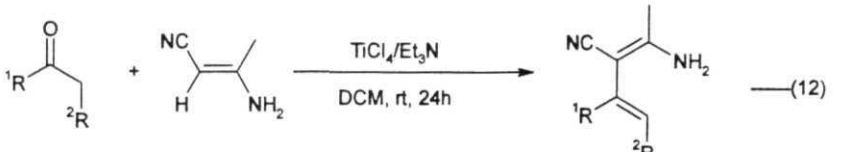


—(10)

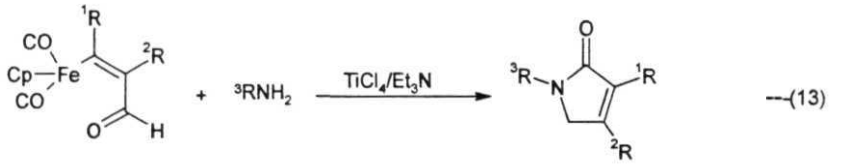
Apart from the use in the aldol type reactions, titanium enolates have been used to prepare 5,6-dihydro-4H-pyran-4-ones derivatives through reaction with phosgene iminium chloride (eq 11).[13]



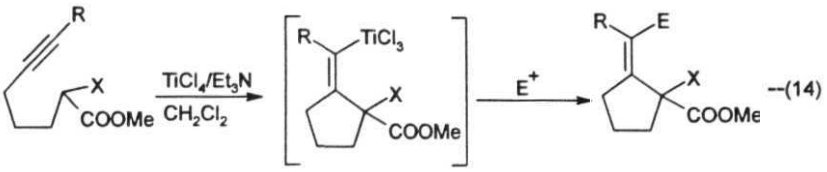
A straightforward synthesis of conjugated β-enaminonitriles from ketones and β-aminocrotononitrile mediated by $TiCl_4/Et_3N$ was reported (eq 12).[14]



A convenient synthesis of α,β-unsaturated γ-lactams was reported through the reaction of iron formyl complexes (eq 13).[15]



Intramolecular carbotitanation of inactivated alkynes was realized using $TiCl_4/Et_3N$ (eq 14).[16]



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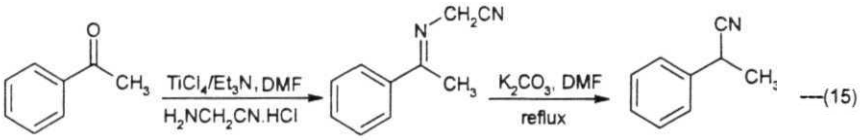
Aryl methyl ketones are converted to α-methylbenzyl cyanide via the imine intermediate (eq 15).



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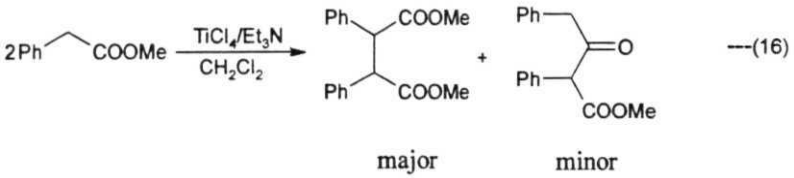
Recently, it was reported that certain ester titanium enolates undergo oxidative coupling reaction to give diphenyl succinic acid derivatives using $TiCl_4/Et_3N$ (eq 16).[18]



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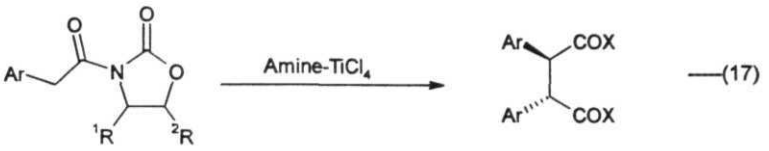
The $TiCl_4/Et_3N$ reagent system was also used for the homocoupling of chiral 3-(arylacetyl)-2-oxazolidones (eq 17).[19]



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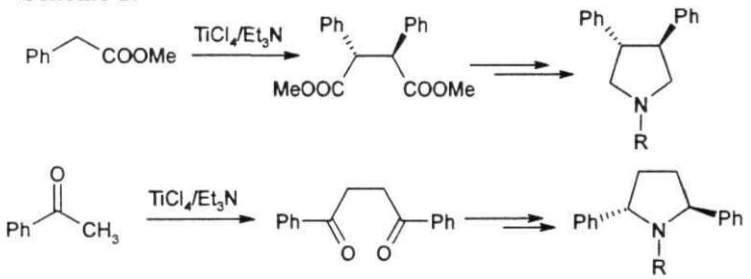
Very recently, efforts were made in this laboratory towards the synthesis of C_2 chiral pyrrolidine systems employing the $TiCl_4/Et_3N$ induced oxidative coupling methods (Scheme 1). [20]

Scheme 1.

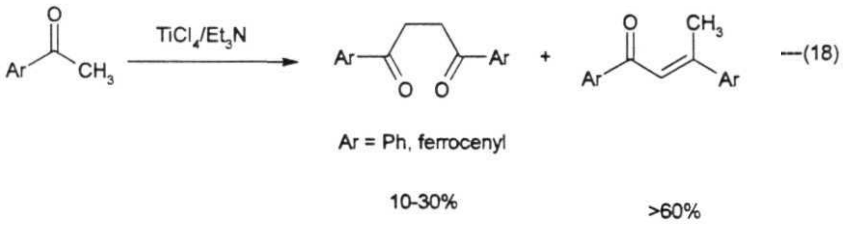


Accordingly, we investigated the synthetic applications of the $TiCl_4/Et_3N$ system further. The results are described in this chapter. Also, the results obtained on the application of low valent titanium species formed in the reaction of $TiCl_4/Et_3N$ are discussed.

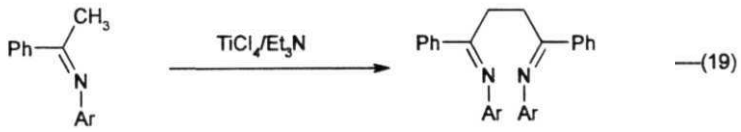
3. 2 Results and Discussion

3. 2. 1 Reaction of aryl methyl ketimines with $TiCl_4/Et_3N$

Preliminary studies in this laboratory revealed that the reaction of aryl methyl ketone to $TiCl_4/Et_3N$ reagent system results in the formation of the corresponding 1,4-diketone.[21] Unfortunately, however, the aldol condensation product was the major product in this reaction (eq 18).

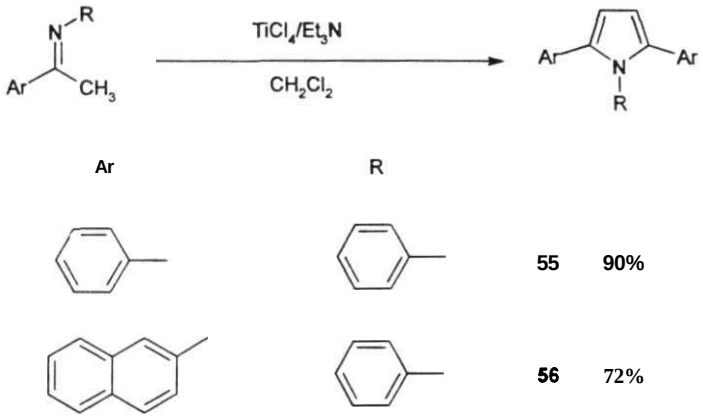


Since the corresponding ketimines are not expected to undergo such undesired condensation reactions readily, we decided to employ these substrates for this purpose to obtain the corresponding diimines (eq 19).



Surprisingly, it was observed that the reaction of the aryl methyl ketimines with $TiCl_4/Et_3N$ system gives the corresponding 2,5-diaryl pyrroles (Scheme 2).

Scheme 2.



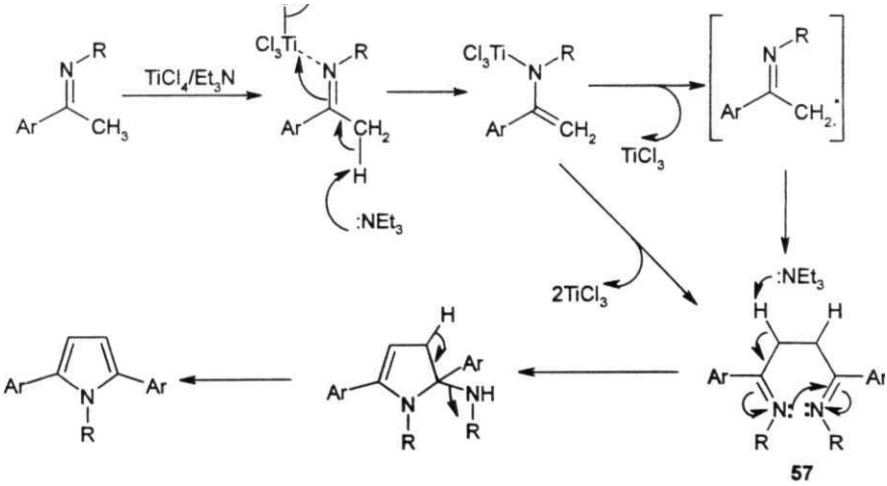
The scope of this transformation was further examined in this laboratory.[22] It was found that the l-methyl-2,5-diphenylpyrrole, 1 -phenyl-2,5-bis(p-tolyl)-pyrrole, 1 -phenyl-2,5-bis(p-chlorophenyl)-pyrrole, 1 -(p-methoxyphenyl)-2,5-diphenylpyrrole, and 1-(p-chlorophenyl)-2,5-diphenylpyrrole were obtained in moderate to good yields (63-90%) in the reaction of corresponding ketimines with $TiCl_4/Et_3N$.[22]

This interesting transformation has good synthetic potential since the pyrroles are obtained in a one pot operation in contrast to the hitherto known methods of preparations, which involve multistep synthetic sequences.[23] In a

classical **Paal-Knorr** synthesis, the **1,4-diketones** are heated with the amines to get the corresponding 2,5-disubstituted pyrroles.[24]

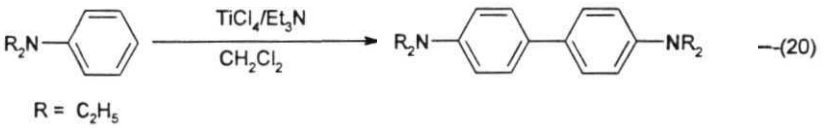
The conversion of **aryl alkyl** ketimines to the corresponding pyrroles (Scheme 2) can be rationalized through a tentative mechanistic pathway outlined in Scheme 3. Coordination of $TiCl_4$ to the **imine** nitrogen would make the methyl proton acidic enough to be pulled by Et_3N. The resulting complex could decompose to produce the radical, that can give the diimine, 57. Cyclization and aromatization would **give** the corresponding pyrrole (Scheme 3). Alternatively, the intermediate can dimerize to give two $TiCl_3$ and the diimine, 57. We have observed that neither $TiCl_4$ nor Et_3N alone effects this transformation.

Scheme 3.



3. 2. 2 Reaction of *N,N*-dialkyl-*N*-arylamines with $TiCl_4$

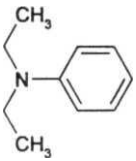
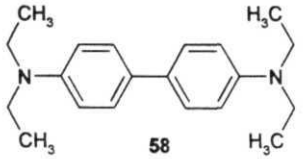
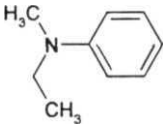
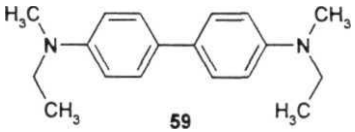
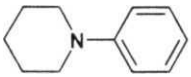
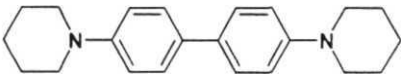
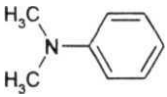
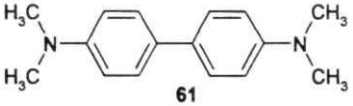
In continuation of the studies described in Chapter 2 on the preparation of iminium ions using trialkylamines and $TiCl_4$, we became interested in the reaction of aromatic tertiary amines with $TiCl_4$ There are two possibilities here. The side chain may undergo deprotonation leading to iminium ion as in the case of trialkylamines or the ring may undergo deprotonation leading to ring metalation. After extensive experimental studies, it was found that the reaction of *N,N*-diethylaniline with $TiCl_4$ produced the corresponding *N,N,N'N*-tetraethylbenzidine (eq 20).



—(20)

The results indicate the possibility of the formation of aryltitanium intermediates through ring metalation. This transformation was examined using several amines and the results are summarized in the Table 1. *N,N*-Diethylaniline, *N*-ethyl-*N*-methylaniline, *N*-phenylpiperidine and *N,N*-dimethylaniline gave the corresponding benzidines in 92%, 77%, 71% and 57% yields, respectively. When the reaction was carried out using *N*-ethyl-*N*-benzyl aniline, a complex mixture of products was isolated.

Table 1. The reaction of *N,N*-dialkylanilines with $TiCl_4$

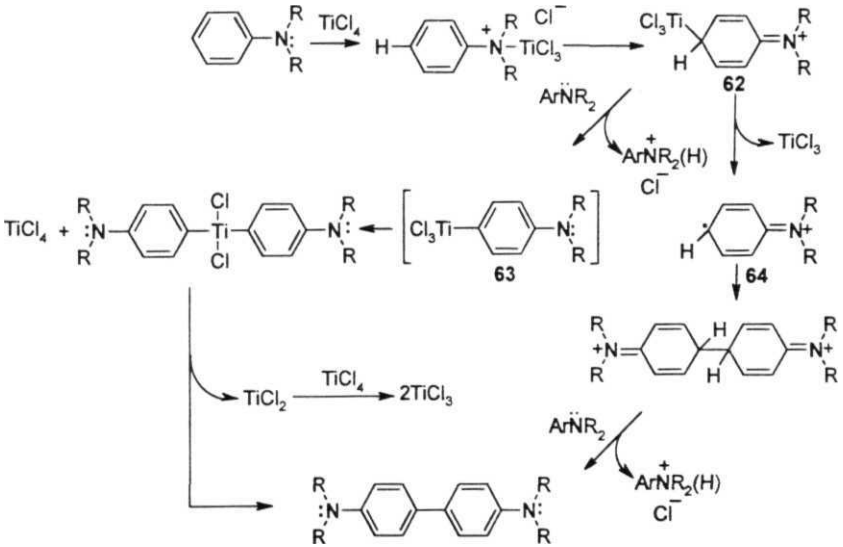
No	Amine	Benzidine	Yield (%)
1.		 58	92
2		 59	77
3		 60	71
4		 61	57

•The products were identified using the spectral data (IR, ^{1}H-NMR, ^{13}C-NMR and Mass), physical constant data and comparison with the reported data.
'Yields are based on the recovered starting material.

Previously, such oxidative coupling reactions were reported in electrochemical oxidation,[25] oxidation using cerium sulphate in aqueous acid solution,[26] peroxidase[27] and iodosobenzene acetate.

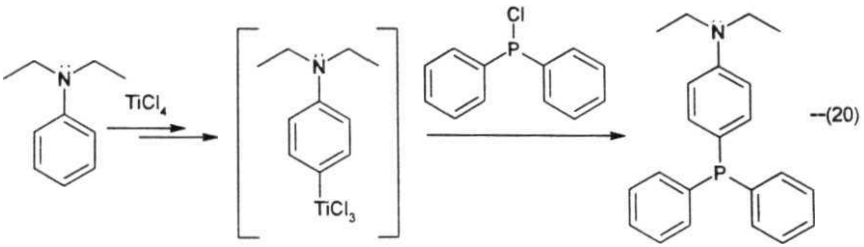
The oxidative dimerization reaction observed can be rationalized by a tentative mechanistic pathway outlined in Scheme 4, involving aryltitanium and/or radical cation intermediates. The initial reaction of $TiCl_4$ and $ArNR_2$ would give the titanium amine complex that could reorganize to form the intermediate 62, which on deprotonation leads to the aryltitanium intermediate 63. The corresponding benzidines could form via two reaction pathways as shown in Scheme 4.

Scheme 4.



It has been reported that the aryltitanium species decompose to give the corresponding radical species.[29] To examine the intermediacy of the aryltitanium species, we carried out the reaction in the presence of chlorodiphenylphosphine

as electrophile. Indeed, the corresponding substitution product was obtained This observation illustrates the presence of the aryltitanium intermediates in the reaction mixture (eq 20).



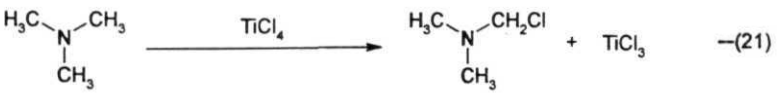
--(20)

65

3. 2. 3 Application of low valent titanium species produced in the reaction of $TiCl_4$ with R_3N

3. 2. 3. 1 Reductive coupling of aromatic aldehydes and ketones

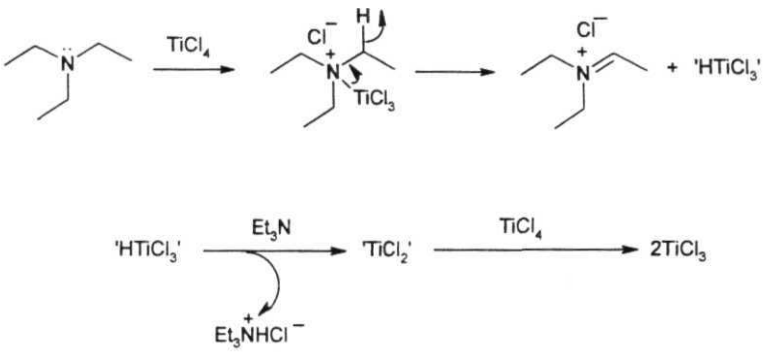
As discussed in Chapter 1, it was reported that the reaction of $TiCl_4$ with $(CH_3)_3N$ leads to the formation of chloroamines and '$TiCl_3$'.[30] However, the mechanism of this reaction was not clarified (eq 21).



--(21)

As described in Chapter 1 and 2 the formation of iminium ions in **the** reaction of trialkylamines with $TiCl_4$ should result in the concomitant production of $TiCl_3$ **and/or** $TiCl_2$ (Scheme 5).

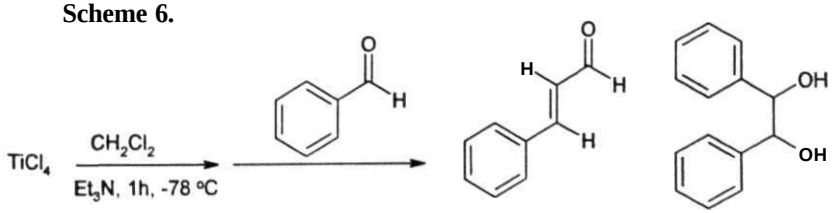
Scheme 5.



Et_3NHCl

As discussed in Chapter 2, the 1,2-diol 66 is formed in addition to cinnamaldehyde in the reaction of benzaldehyde with $TiCl_4/Et_3N$ reagent system (Scheme 6). Clearly, this observation further illustrates the presence of low valent titanium species in the reaction mixture.

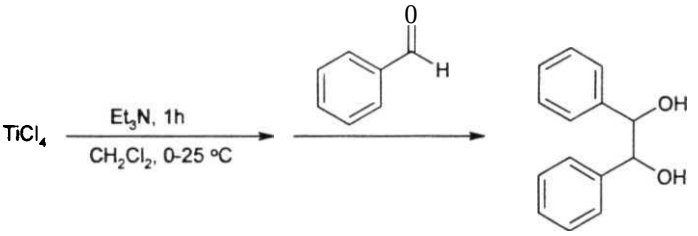
Scheme 6.



33 46%

66 **7%**

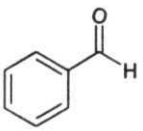
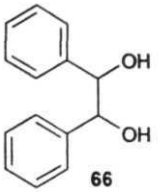
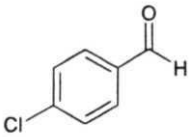
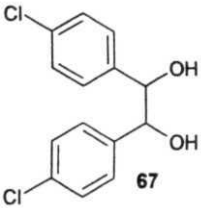
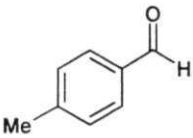
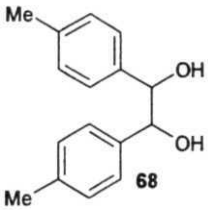
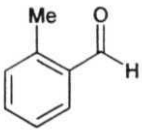
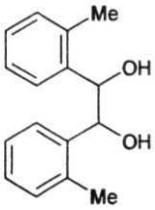
The low valent titanium reagents are generally prepared through reduction of $TiCl_4$ with metals or metal hydrides.[31] The $TiCl_4/R_3N$ gives low valent titanium species without metals or metal hydrides. Accordingly, we decided to investigate the use of the titanium species produced in this way for synthetic applications. It was found that the reductive coupling of aromatic aldehydes can be made as the major reaction pathway by slight modification of experimental conditions (eq 22).



66 71%

Whereas addition of benzaldehyde to a stirred solution of $TiCl_4/Et_3N$ at -78 °C followed by reaction at 0 °C gave the cinnamaldehyde (46%) and 1,2-diol, 66 (7%) (Scheme 6), the addition of benzaldehyde at 0-25 °C gave the 1,2-diol, 66 as the major product in 71% yield as 74/26 *dl/meso* mixture (eq 22). The generality of this process was examined using several other aldehydes and the results are summarized in Table 2.

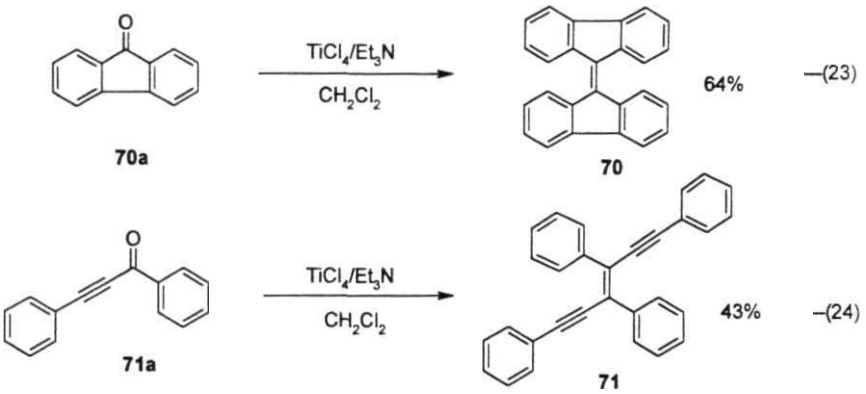
Table 1. The reaction of aromatic aldehydes with $TiCl_4/Et_3N$

No.	Aldehyde	Diol	Yield (%)	dl/meso
1.		 **66**	71	74/26
2		 **67**	**58**	**83/17**
3		 **68**	**61**	100/0
4		 **69**	63	75/25

[a]The products were identified using the spectral data (IR, ^{1}H-NMR) and comparison with the reported data. [43]

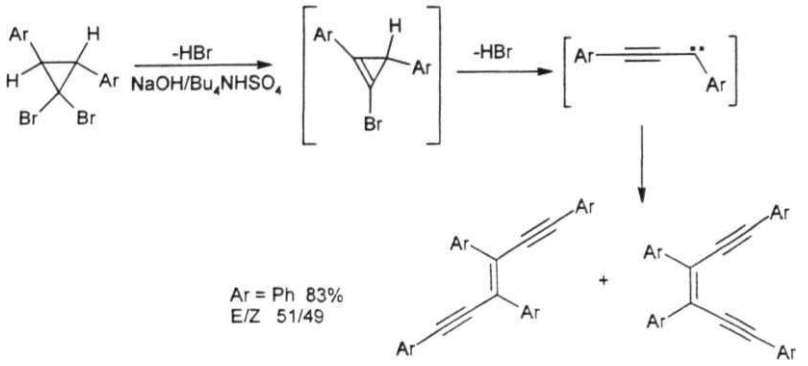
[b]Yields are based on the aldehydes used.

Whereas, ***p*-chloro** benzaldehyde and ***o*-methyl** benzaldehyde gave a mixture of *dl/meso* isomers (83/17 and 75/25 respectively) in 58% and 63% yields, the ***p*-methyl** benzaldehyde yielded the *dl* isomer only (61%). In the case of enolizable ketones, such as acetophenone, the anticipated **diol** was not obtained and the reaction was not clean. The fluorenone (70a) and phenylethynyl phenyl ketone (71a) were found to undergo classical McMurry coupling reactions to give the corresponding **olefins** (70 and 71) under these conditions (eq 23 & 24).



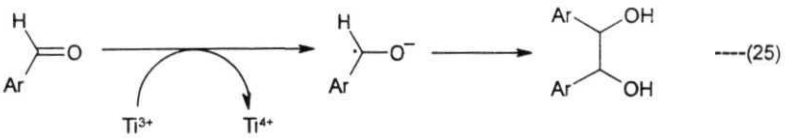
Recently, the mixture of **1,3,4,6-tetraphenyl-hex-3-ene-1,5-diyne** (71 and isomer), has been synthesized via the corresponding carbene intermediate (Scheme 7).[32] It should be noted that the present transformation produces only the *E* isomer.

Scheme 7.



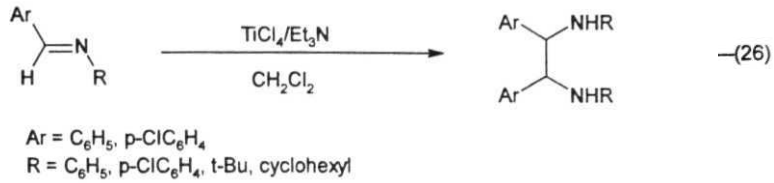
It is well known that the $TiCl_3$ in CH_2Cl_2 brings about the reductive coupling of aldehydes.[33] The present transformations can also be explained involving $TiCl_3$ intermediate as outlined in eq 25. In the case of fluorenone and the alkynyl ketone, the intermediate undergoes further deoxygenation (McMurry coupling) leading to the formation of the corresponding olefin (eq 23 & 24).

Previously, $TiCl_4$/metal reagent system has been reported to convert aromatic aldehydes to the corresponding 1,2-diols.[34]



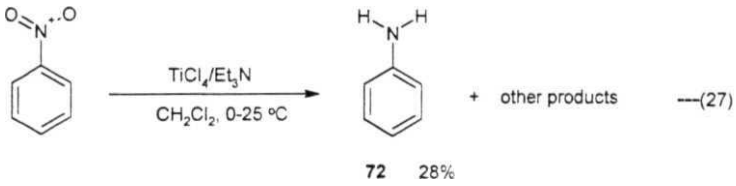
----(25)

It was also observed in this laboratory that the low valent titanium species produced in this way converts aldimines to the corresponding diamines (eq 26).[35]



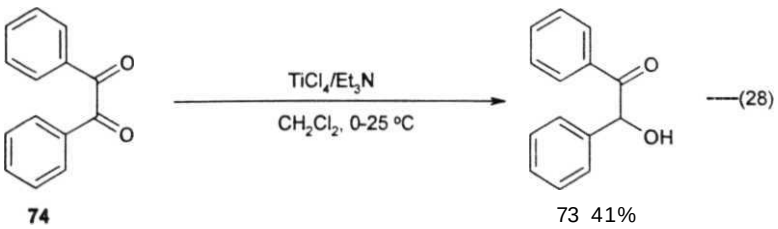
3. 2. 3. 2 Reduction of nitrobenzene to aniline

Aqueous '$TiCl_3$' has been reported to reduce the nitro to amino group.[36] The low valent titanium reagent prepared using $TiCl_4/Et_3N$ exhibits similar reactivity with nitrobenzene and the aniline is formed as one of the products albeit in low yield (28%) in addition to some unidentified polar compounds (eq 27).

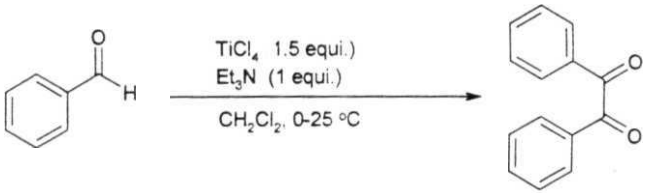


3. 2. 3. 3 Reaction of benzil with $TiCl_4/Et_3N$

The titanium species prepared using $TiCl_4$ and Et_3N also reduces benzil to benzoin in 41% yield (eq 28).



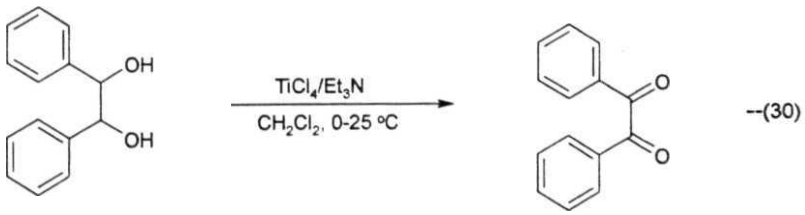
The reductive coupling of benzaldehyde to the 1,2-diol (eq 22) was carried out using 1 equivalent of $TiCl_4$ and 1.5 equivalent of Et_3N for the preparation of low valent titanium species. An interesting observation was made when the reaction of benzaldehyde was carried out in the presence of additional amounts of $TiCl_4$. It was observed that the benzil (42%) was produced besides 12% of 1,2-diol under these conditions (eq 29).



74

---(29)

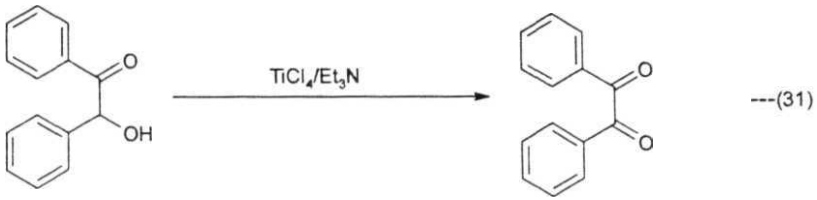
Presumably, the initially formed diol is oxidized to the diketone in the presence of excess $TiCl_4$. This was further confirmed by carrying out the reaction starting from the diol. When $TiCl_4$ and Et_3N were taken in 1:1 ratio and 1.2-diphenyl-1.2-ethanediol in 0.25 equivalent, benzil was isolated in 77% yield (eq 30).



77%

--(30)

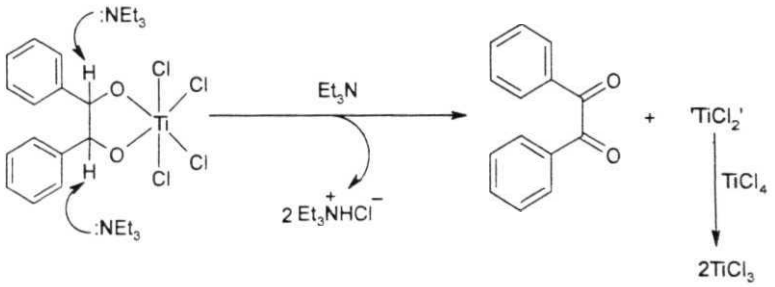
Under similar conditions, the benzoin was also converted to benzil in 48% yield (eq 31). This transformation was previously reported using $FeCl_3.6H_2O$.[37]



---(31)

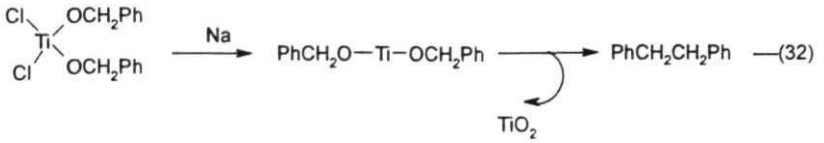
The oxidation of 1,2-diphenylethane diol to benzil using $TiCl_4/Et_3N$ can be explained by the tentative mechanism shown in Scheme 8.

Scheme 8.



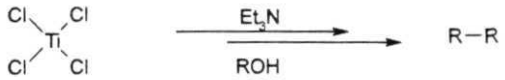
3. 2. 4 Reaction of alcohols with $TiCl_4/Et_3N$

Reductive coupling of an alcohol to the corresponding hydrocarbon is a process of wide interest.[38] It was reported that titanium(IV) dichloride-dialkoxide on reduction using sodium afforded bibenzyl besides diphenylmethane and benzyl alcohol (eq 32).[39]



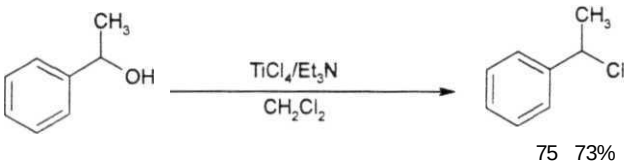
—(32)

It was envisaged that similar reactivity pattern could be realized using $TiCl_4/Et_3N$ (eq 33).



—(33)

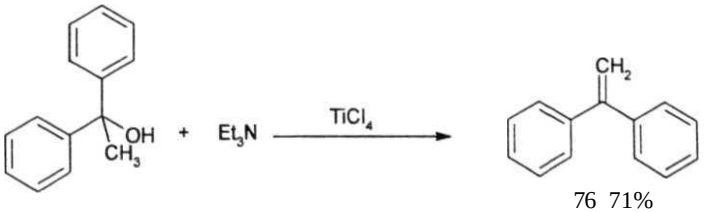
However, when the reaction was carried out using 1-phenylethanol the expected hydrocarbon was not formed and only the a-methylbenzyl chloride. 75. was obtained in 73% yield (eq 34).



75 73%

—(34)

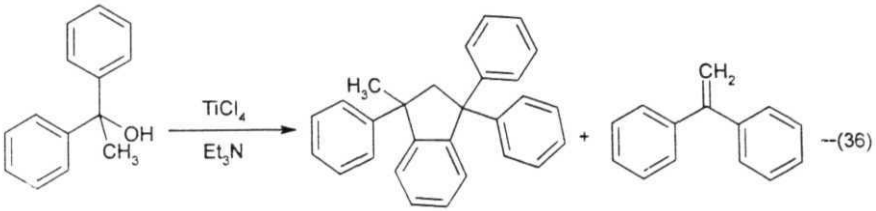
We have also observed that when the $TiCl_4$ was added to a mixture of triethylamine and 1,1-diphenylethanol, the 2,2-diphenyl ethylene, 76, was isolated in 71% yield (eq 35).



76 71%

—(35)

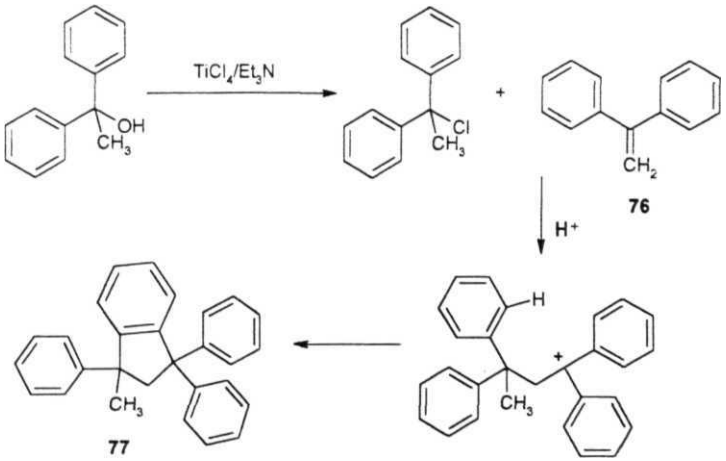
Also, when the Et_3N was added to a stirred solution of alcohol and $TiCl_4$ at 0 °C, the indalin derivative 77, was obtained in 73% yield in addition to the olefin (8%) (eq 36).



77 73% **76 8%**

This transformation may be rationalized by the tentative mechanism outlined in Scheme 9.

Scheme 9.



3. 3 Conclusions

The $TiCl_4/R_3N$ reagent system was found to be useful for many other synthetic transformations. The reaction of aryl methyl ketimines with $TiCl_4/Et_3N$ leads to the formation of the corresponding 2,5-diaryl pyrroles in good yields. The reaction of *N,N*-dialkylanilines with $TiCl_4$ gives the aryltitanium species which produce benzidines. In the presence of Ph_2PCl the corresponding aryl phosphine was obtained. The low valent titanium species generated using triethylamine and $TiCl_4$ has been used for the reductive coupling of aromatic aldehydes to the corresponding 1,2-diols.

3. 4 Experimental Section

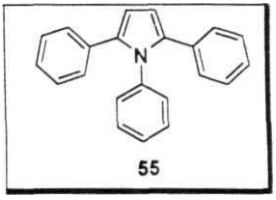
3. 4. 1 General Information

Several informations given in the experimental sections of Chapter 1 and Chapter 2 are also applicable for the experiments described here. The aryl alkyl ketimines were prepared following the method developed in this laboratory using the corresponding ketones and amines. The aryl alkyl ketones supplied by Sisco (Ind.) Ltd., were used. The amines were distilled over CaH_2 and stored on KOH pellets. The aldehydes used are commercially obtained and used after distillation. Fluorenone obtained from Merck (Ind.) Ltd., was used.

3. 4. 2 General procedure for the reaction of ketimines with $TiCl_4/Et_3N$

Dichloromethane (25 mL). Et_3N (15 mmol, 2.1 mL) and ketimine (10 mmol) were taken under N_2 atmosphere. $TiCl_4$ (10 mmol, 2.2 mL of 1:1 solution of $TiCl_4/CH_2Cl_2$) in CH_2Cl_2 (10 mL) was added dropwise under N_2 at 0 °C for 15 min. The reaction mixture was stirred for 0.5 h at 0 °C and stirred further for 7-8 h at 25 °C. It was quenched with a saturated K_2CO_3 solution (30 mL) and the reaction mixture was filtered through Buchner funnel. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 X 25 mL). The

combined organic extract was washed with brine solution (10 mL) and dried over anhydrous $MgSO_4$ The solvent was removed and the residue was chromatographed on a silica gel column. Hexane eluted the corresponding pyrrole.



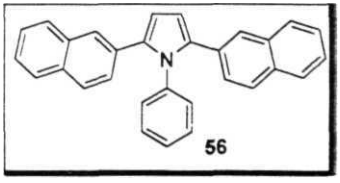
55

Yield 90%

M. p. 233-234 °C (Lit.[40] 234 - 236°C).

^{1}H-NMR (6 ppm, $CDCl_3$) 7.05-7.35 (m, 15H), 6.5 (s, 2H).

^{13}C-NMR (5 ppm, $CDCl_3$) 138.0. 135.0. 133.29, 128.93-126.20, 109.93; (Spectrum No. 33).



56

Yield 72%

M.p. 222-224 °C

^{1}H-NMR (6 ppm, $CDCl_3$) 7.8-7.1 (m, 19H), 6.65 (s, 2H).

^{13}C-NMR (8 ppm, $CDCl_3$) 139.5, 136.03, 133.2, 131.9, 130.7, 129.88-

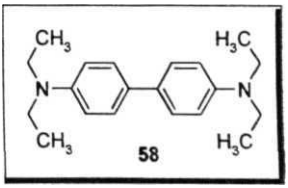
125.66,123.9,110.61.

Analysis: Calculated for $C_{30}H_{21}N$: C, 91.11; H, 5.35; N, 3.54. Found: C, 91.12; H, 5.36; N, 3.58.

MS (EI) m/z 395 (M^+, 62%).

3. 3. 3 The reaction of *N,N*-dialkylanilines with $TiCl_4$

In CH_2Cl_2 (25 mL), *N,N*-diethylaniline (10 mmol, 1.6 mL) was taken at 0 °C under N_2. The $TiCl_4$ (3.3 mL of 1:1 solution of $TiCl_4/CH_2Cl_2$, 15 mmol) in CH_2Cl_2 (10 mL) was added dropwise to this solution. It was stirred at 25 °C for 8 h. A saturated K_2CO_3 solution (20 mL) was added and stirred for 0.5 h. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic extract was washed with brine solution (10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed and the residue was chromatographed on a silica gel column. The unreacted amine was eluted using EtOAc:hexane (1:99) mixture. The benzidine 58, was separated using EtOAc/hexane (2:98) mixture as eluent.



58

Yield 92%

IR(KBr) (cm^{1})3058, 3028, 2966, 2878, 1608

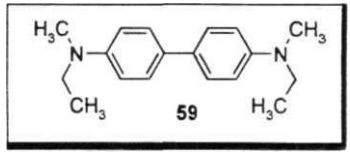
M.p. 85°C (Lit.[41] 85 °C)

^{1}H-NMR (8 ppm, $CDCl_3$) 7.5 (d, 4H), 6.8 (d, 4H), 3.5 (q, 8H), 1.3 (t, 12H).

^{13}C-NMR (δ ppm, $CDCl_3$) 146.40, 129.01, 127.19, 112.44, 44.59, 12.85.

MS (EI) m/z 297 (M^+, 95%), 282 [(M^+-CH_3), 77%].

The above procedure was followed for the conversion of several other *N,N*-dialkylanilines to the corresponding benzidines.



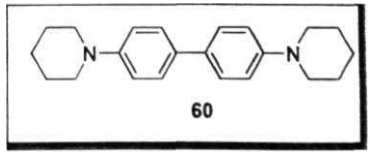
59

Yield 77%

IR (cm^{-1}) 3058, 3028, 2966, 2878, 1608.

^{1}H NMR (8 ppm, $CDCl_3$) 7.6 (d, 4H), 6.9 (d, 4H), 3.5 (q, 4H), 3.0 (s, 6H), 1.2 (t, 6H), (Spectrum No. 34).

^{13}C NMR (8 ppm, $CDCl_3$) 147.82, 129.49, 127.07, 112.95, 47.02, 37.61, 11.39), (Spectrum No. 35).



60

Yield 71%

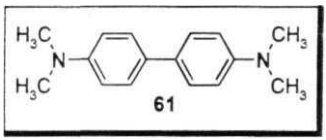
M. p. 208 °C

IR (cm-[1]) 3057, 2967, 2928, 740, 629.

^{1}H-NMR (6 ppm, $CDCl_3$) 7.5 (d, 4H), 7.1 (d, 4H), 3.2 (s, 8H), 1.6-1.8 (m, 12H).

^{13}C-NMR (6 ppm, $CDCl_3$) 150.78, 132.02, 127.02, 116.75, 50.79, 25.87, 24.36.

MS (EI) m/z 320 (M^+, 100%), 152 [$(C_6H_4)_2$),4%].



61

Yield 57%

M.p. 197-198 °C (Lit.[42] 198 °C)

IR (cm"[1]) 3058, 2947, 2931, 740, 629

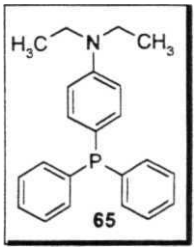
^{1}H-NMR (6 ppm, $CDCl_3$) 7.6 (d, 4H), 6.9 (d, 4H). 3.1 (s. 12H).

^{13}C-NMR (δ ppm, $CDCl_3$) 149.40, 130.02, 127.04, 113.26, 40.83.

3. 4. 4 Reaction of $TiCl_4$/*N,N*-diethylaniline in the presence of $ClPPh_2$

In CH_2Cl_2 (25 mL), tf,tf-diethylaniline (10 mmol, 1.6 mL) and $ClPPh_2$ (10 mmol, 1.8 mL) were taken at 0 °C under N_2. The $TiCl_4$ (15 mmol, 3.3 mL of 1:1

solution of $TiCl_4/CH_2Cl_2$) in CH_2Cl_2 (10 mL) was added dropwise to this solution. It was stirred at 25 °C for 8 h. A saturated K_2CO_3 solution (20 mL) was added and stirred for 0.5 h. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic extract was washed with brine solution (10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed and the residue was chromatographed on a silica gel colurrn. The unreacted amine was eluted using EtOAc/hexane (1:99) mixture. The triaryl phosphine 65 was isolated using EtOAc/hexane (2:98) mixture as eluent.



65

Yield 72%

IR (KBr) (cm^{-1}) 3067, 2928.

M.p. 110 °C.

^{1}H-NMR (5 ppm, $CDCl_3$) 7.1-7.8 (m, 14H), 3.4 (q, 4H), 12 (t, 6H).

^{13}C-NMR (5 ppm, $CDCl_3$) 148.46, 139.10, 138.90, 136.08, 135.64, 133.51, 133.13, 128.32, 128.09, 119.94, 111.73, 111.56, 44.25,

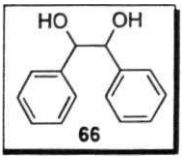
12.62, **(Spectrum No. 36).**

MS (El) m/z 333 (M^+, 100%), 318 [(M^+-CH_3), 63%], **(Spectrum No. 37).**

3. 4. 5 The reductive coupling of aromatic aldehydes to 1,2-diols

Dichloromethane (25 mL) and Et_3N (15 mmol, 2.1 mL) were taken under N_2 atmosphere. TiCl4 (10 mmol, 2.2 mL of 1:1 solution of $TiCl_4/CH_2Cl_2$) was added under N_2 at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and the benzaldehyde (5 mmol, 0.5 mL) was added to this reaction mixture and stirred further for 5 h at 0-25 °C. It was quenched with a saturated NH_4Cl solution (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 X 25 mL). The combined organic extract was washed with brine solution (10 mL) and dried over anhydrous $MgSO_4$ The solvent was removed and the residue was chromatographed on a silica gel column. The 1,2-diphenyl ethane diol was isolated using EtOAc/hexane (10:90) mixture as eluent.

All the diols reported here have been reported previously. They were identified by comparison with reported data.[43] The *dl/meso* ratio was determined through analysis of ^{1}H-NMR data. The melting points reported here are the observed melting points of the obtained *dl/meso* mixture.



66

Yield 71%

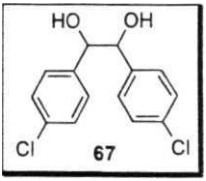
M.p. 118 °C (mp of *dl* form: 119 °C)[43]

IR(KBr) (cm^{-1}) 3416, 3053,3028,2916

^{1}H-NMR (δ ppm, $CDCl_3$) 2.91 (s, broad, 2H), 4.72 (s, 2H, *dl),* 4.8 (s, 2H, *meso*). 7.11-7.35 (m, 10H).[43]

dl/meso 74/26

The above procedure was followed for the conversion of several other aromatic aldehydes to the corresponding 1,2-diols.



67

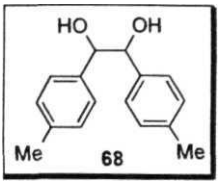
Yield 58%

M. p. 150-152 °C (mp of *dl* form: 157 °C)[43]

IR (KBr) (cm^{-1}) 3423, 3063. 3029, 2912.

^{1}H-NMR (δ ppm, $CDCl_3$) 3.05 (s, broad, 2H), 4.60 (s, 2H, *dl),* 4. 85 (s, 2H, *meso),* 7.12-7.32 (m, 8H).[43]

dl/meso 83/17



68

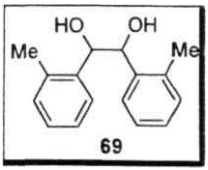
Yield 61%

M.p. 160-161 °C (mp of *dl* form: 160 °C[43])

IR(KBr) (cm^{-1}) 3423, 3049.

^{1}H-NMR (δ ppm, $CDCl_3$) 2.30 (s, 6H), 2.8 (s, 2H), 4.68 (s, 2H, *dl),* 7.10-7.25 (m 8H).[43]

dl/meso 100/0



69

Yield 63%

M. p. 114-116 °C (mp of *dl* form: 115 °C).[43]

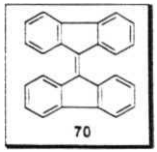
IR(KBr) (cm^{-1}) 3456, 3061.

^{1}H-NMR (δ ppm, $CDCl_3$) 1.71 (s, 6H), 2.92 (s, broad, 2H), 5.0 (s, 2H, *dl),* 5.15 (s, 2H, *meso*), 6.81-7.71 (m, 8H).[43]

dl/meso 75/25.

3. 4. 6 The reaction of aromatic ketones with TiC_4/Et_3N

Dichloromethane (25 mL) and Et_3N (15 mmol, 2.1 mL) were taken under N_2 atmosphere. $TiCl_4$ (10 mmol, 2.2 mL of 1:1 solution of $TiCl_4/CH_2Cl_2$) was added under N_2 at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and the fluorenone (5 mmol, 0.9 g) was added to this reaction mixture and stirred further for 5 h at 0-25 °C. It was quenched with a saturated NH_4Cl solution (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 X 25 mL). The combined organic extract was washed with brine solution (10 mL) and dried over anhydrous $MgSO_4$ The solvent was removed and the residue was chromatographed on a silica gel column. The olefin 70 was isolated using hexane as eluent.



70

Yield 64%

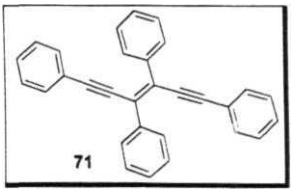
IR (cm^{-1}) 3049, 740, 620

M. p. 247 °C (Lit.[44] 244-247 °C)

^{1}H-NMR (6 ppm, $CDCl_3$) 7.15-7.7 (m, 16H).

^{13}C-NMR (8 ppm, $CDCl_3$) 141.35, 141.04, 138.32, 129.16, 126.85, 126.75, 119.89.

The above procedure was followed for the conversion of phenylethynyl phenyl ketone to the corresponding olefin 71.



71

Yield 43%

IR(KBr) (cm^{1}) 3080, 2199

^{1}H-NMR (8 ppm, $CDCl_3$) 7.1-7.8 (m, 20H).

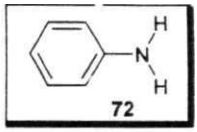
^{13}C-NMR (8 ppm, $CDCl_3$) 139.14, 131.44. 129.29, 128.71, 128.47, 128.32, 127.88, 123.33, 98.68. 90.9. (The stereochemistry was assigned by comparison with the reported ^{13}C-NMR data).[2-

MS (EI) m/z 380 (M^+, 28%), 302 [(M^+-$C_6H_5^{+\bullet}$), 100%]

3. 4. 7 Reduction of nitrobenzene to aniline

In CH_2Cl_2 (25 mL), nitrobenzene (5 mmol, 0.5 mL) and $TiCl_4$ (10 mmol, 2.2 mL of 1:1 solution of $TiCl_4/CH_2Cl_2$) were taken at 0 °C under N_2. Et_3N (15 mmol, 2.1 mL) was added to this solution. It was stirred at 0-25 °C for 2 h. Saturated K_2CO_3 solution (20 mL) was added and stirred for 0.5 h. The organic

layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL). The combined organic extract was washed with brine solution (10 mL) and dried over anhydrous $MgSO_4$. The solvent was removed and the residue was chromatographed on a silica gel column. An unidentified mixture of compounds was eluted using EtOAc/hexane (6:94) mixture. The aniline was separated using EtOAc/hexane (10:90) mixture as eluent, Yield 21%.



72

Yield 28%

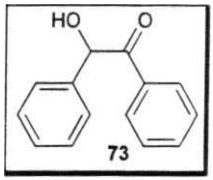
IR (neat) (cm^{-1}) 3479 and 3385 (doublet), 3072, 2972.

^{1}H-NMR (5 ppm, $CDCl_3$) 3.35 (s, 2H). 6.4-7.3 (m, 5H).[46] The product was identified by TLC analysis and comparison of the data with that obtained for the authentic sample.

3. 4. 8 Reduction of benzil to benzoin

Dichloromethane (25 mL) and Et_3N (15 mmol, 2.1 mL) were taken under N_2 atmosphere. $TiCl_4$ (10 mmol, 2.2 mL of 1:1 solution of $TiCl_4/CH_2Cl_2$) was added under N_2 at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and the benzil (5 mmol, 1.05 g) was added to this reaction mixture and stirred further for 5 h at 0-25 °C. It was quenched with a saturated NH_4Cl solution (20 mL). The

organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 X 25 mL). The combined organic extract was washed with brine solution (10 mL) and dried over anhydrous $MgSO_4$ The solvent was removed and the residue was chromatographed on a silica gel column. The product benzoin was isolated using EtOAc/hexane (8:92) mixture as eluent. The benzoin was identified by comparison of mp, IR and ^{1}H-NMR data with that of the authentic sample.



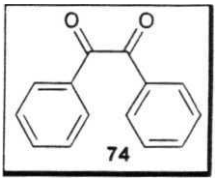
73

Yield	41%
M.p.	136-137 ^{0}C (Lit.[45] 137 °C)
IR	(cm^{-1}) 3421, 1683.
^{1}H-NMR	(8 ppm, $CDCl_3$) 7.93-7.47 (m, 10H), 5.95 (s, 1H), 4.52 (s. 1H).[46]

3. 4. 9 Oxidation of 1,2-diphenyl-1,2-ethanediol to benzii

In CH_2Cl_2 (25 mL), l,2-diphenyl-l,2-ethanediol (2.5 mmol, 0.535 g,) and $TiCl_4$ (10 mmol, 2.2 mL of 1:1 solution of $TiCl_4/CH_2Cl_2$) were taken together at

0 °C. To this stirred mixture, Et_3N (10 mmol, 1.4 mL) was added. The reaction mixture was stirred at 0-25 °C for 6 h. It was quenched with a saturated NH_4Cl solution (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 X 25 mL). The combined organic extract was washed with brine solution (10 mL) and dried over anhydrous $MgSO_4$ The solvent was removed and the residue was chromatographed on a silica gel column. The benzil was isolated using EtOAc/hexane (4:96) mixture as eluent.



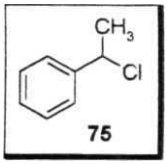
74

Yield	77%
M. p.	95 °C (Lit.[45] 95-96 °C).
IR(KBr)	(cm^{-1}) 3058. 1658.
^{1}H-NMR	(6 ppm, $CDCl_3$) 7.4-7.8 (m, 10H).
^{13}C-NMR	(δ ppm, $CDCl_3$) 196.53, 137.73, 132.35, 129.99, 128.97, 128.27.

3. 4. 10 The reaction of 1-phenylethanol with $TiCl_4/Et_3N$

In CH_2Cl_2 (25 mL), 1-phenylethanol (10 mmol, 1.2 mL) and $TiCl_4$ (10 mmol, 2.2 mL of 1:1 solution of $TiCl_4/CH_2Cl_2$) were taken at 0 °C under N_2. To this Et_3N (15 mmol, 2.1 mL) was added dropwise and stirred further for 6 h at 0-

25 °C. It was quenched with a saturated NH_4Cl solution (20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 X 25 mL). The combined organic extract was washed with brine solution (10 mL) and dried over anhydrous $MgSO_4$ The solvent was removed and the residue was chromatographed on a silica gel column. The α-methylbenzyl chloride was isolated using EtOAc/hexane (2:98) mixture as eluent.



75

Yield 73%

IR (neat) (cm^{-1}) 3065, 3032, 2978, 2928, 2866, 763, 696.

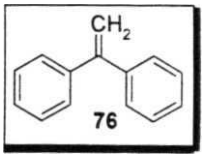
^{1}H-NMR (6 ppm, $CDCl_3$) 7.3-7.7 (m, 5H), 5.2 (q, 1H), 1.9 (d, 3H) (The spectral data showed 1:1 correspondence with reported data).[46]

^{13}C-NMR (6 ppm, $CDCl_3$) 143.02, 128.76, 128.35, 126.03, 58.85, 26.68.

3. 4. 11 Reaction of 1,1-diphenylethanol with $TiCl_4/Et_3N$

In CH_2Cl_2 (25 mL), 1,1-diphenylethanol (10 mmol, 2.0 g) and $TiCl_4$ (10 mmol, 2.2 mL of 1:1 solution of $TiCl_4/CH_2Cl_2$) were taken at 0 °C under N_2. To this Et_3N (10 mmol, 1.4 mL) was added and stirred further for 6h at 0-25 °C. It was quenched with a saturated NH_4Cl solution (20 mL). The organic layer was

separated and the aqueous layer was extracted with CH_2Cl_2 (2 X 25 mL). The combined organic extract was washed with brine solution (10 mL) and dried over anhydrous $MgSO_4$ The solvent was removed and the residue was chromatographed on a silica gel column. The 2,2-diphenylethylene was isolated using hexane as eluent and the l-methyl-l-phenyl-3,3-diphenyl indalin, 77, was isolated using EtOAc/hexane (2:98) mixture as eluent.

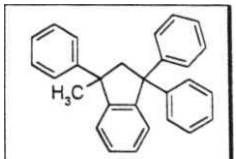


76

Yield 8%

1R (cm^{-1}) 3080, 3057, 3028, 773, 698.

^{1}H-NMR (δ ppm, $CDCl_3$) 7.3 (s, 10H), 5.4 (s, 2H)[4]



77

Yield 73%

IR (cm^{-1}) 3063, 2931

^{1}H-NMR (8 ppm, $CDCl_3$) 7.5-7.0 (m, 19H), 3.5 (d, 1H, CH_2), 3.3 (d, 1H, CH_2), 1.6 (s, 3H. CH_3), (Spectrum No. 38)

^{13}C-NMR (8 ppm, $CDCl_3$) 150.71 (quaternary), 149.50 (quaternary), 149.05(quaternary), 148.74 (quaternary), 147.66 (quaternary), 128.95 (CH), 128.85 (CH), 128.13 (CH), 128.05 (CH), 127.78 (CH), 127.63 (CH), 127.54 (CH), 127.04 (CH), 126.17 (CH), 125.84 (CH), 125.77 (CH), 125.21 (CH), 61.55 (CH_2), 61.15 (quaternary), 51.38 (quaternary), 29.09 (CH_3), (Spectrum No. 39), (Signal assignments are based on DEPT experiments), (Spectrum No. 40).

3. 5 References

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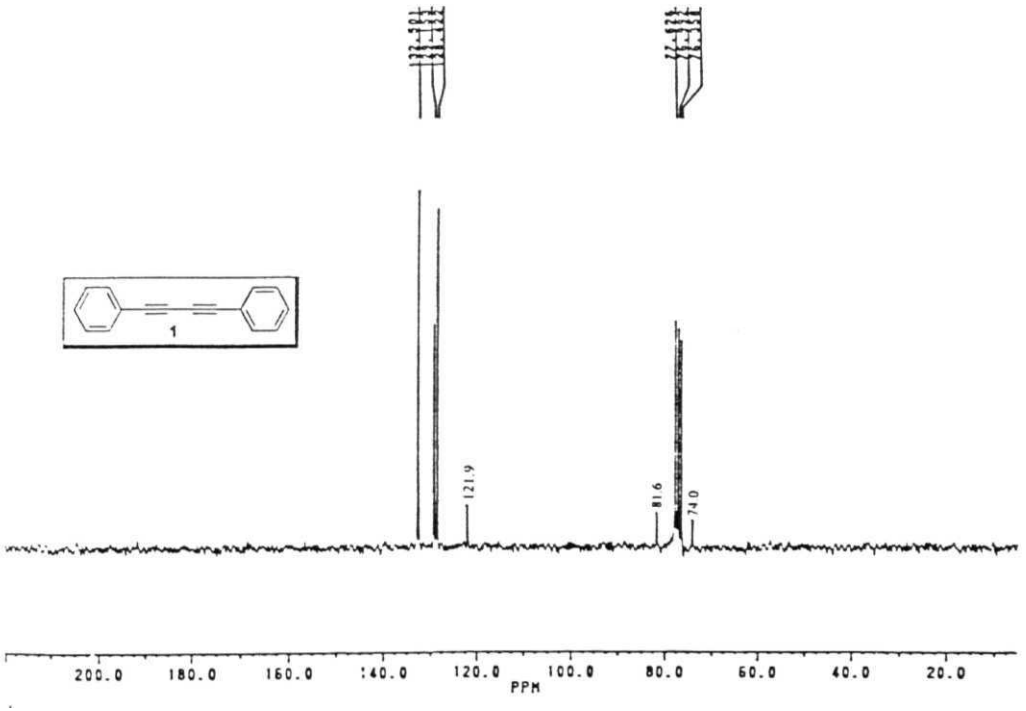
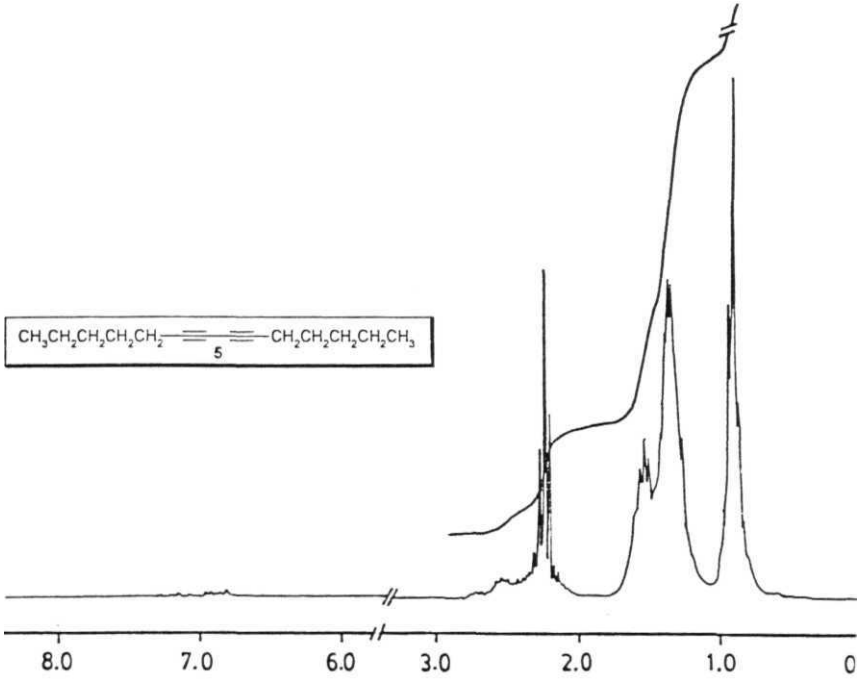
Representative Spectra

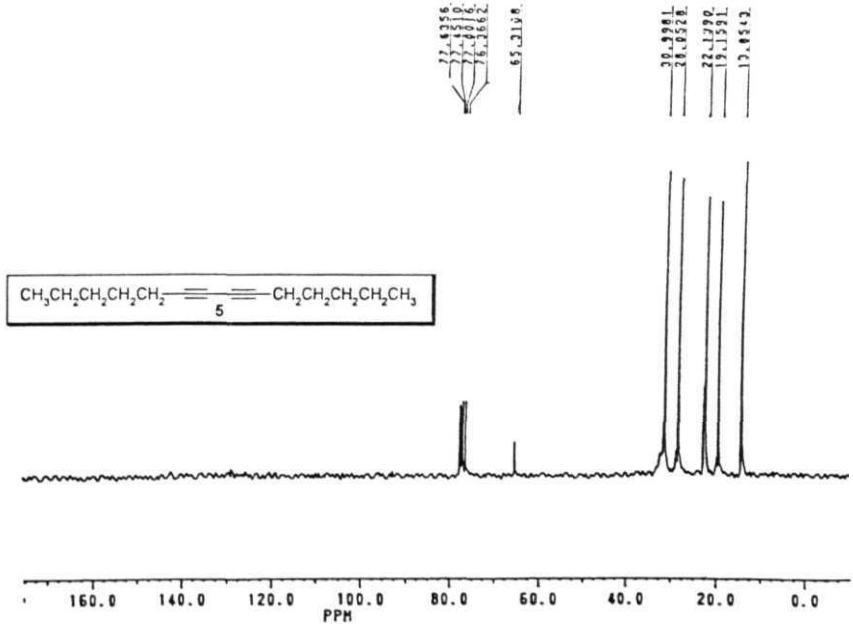
Spectrum No. 1 (Chapter!), ^{13}C-NMR Spectrum (50 MHz, $CDCl_3$)



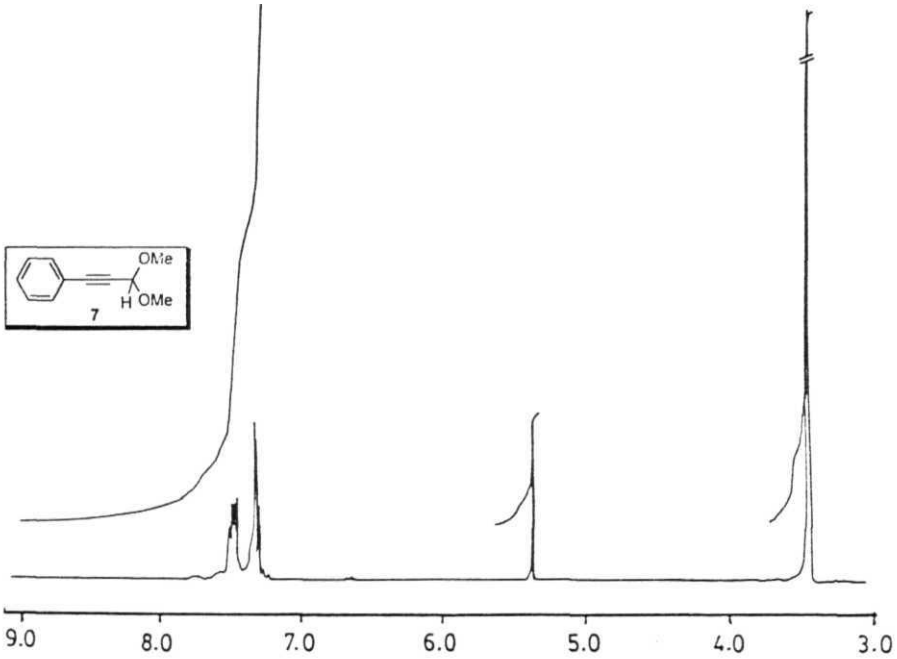
Spectrum No. 2 (Chapter 1), ^{1}H-NMR Spectrum (200 MHz, $CDCl_3$)



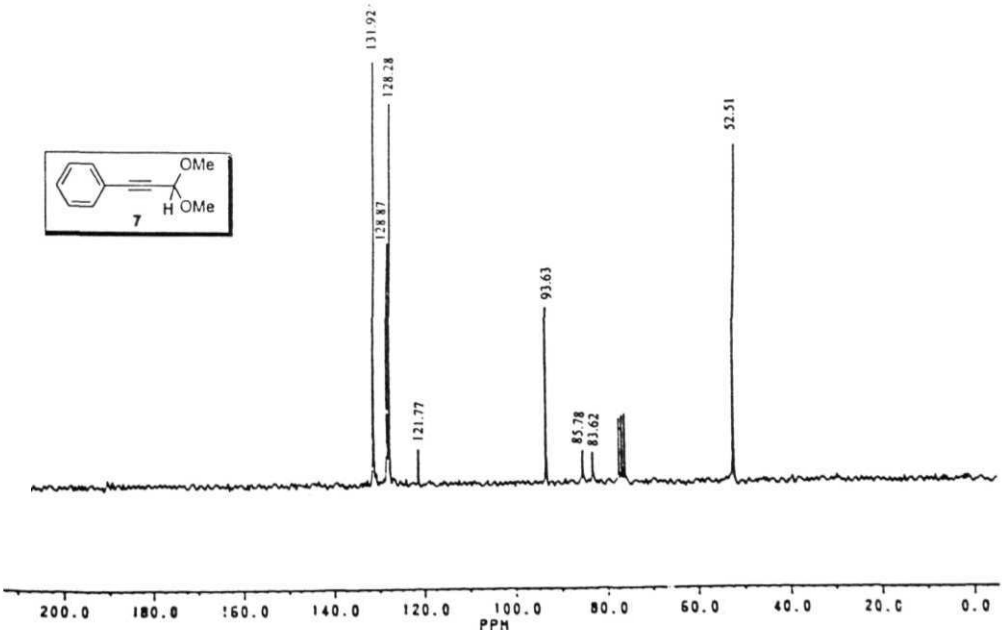
Spectrum No. 3 (Chapter 1), ^{13}C-NMR Spectrum (50 MHz, $CDCl_3$)



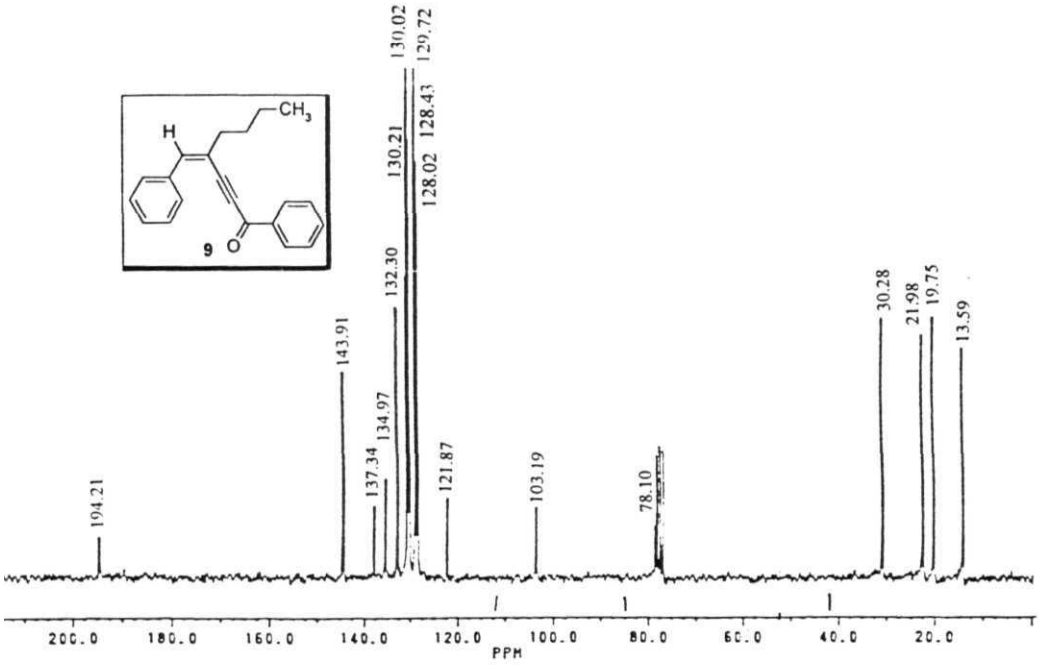
Spectrum No. 4 (Chapter 1), ^{1}H-NMR Spectrum (200 MHz, $CDCl_3$)



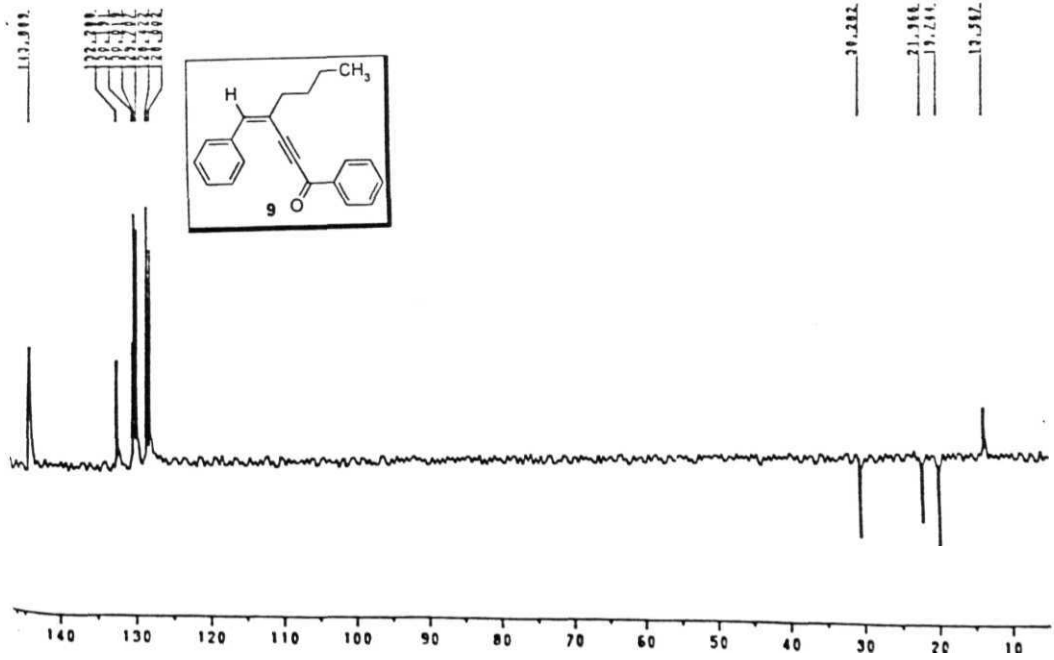
Spectrum No. 5 (Chapter 1), ^{13}C-NMR Spectrum (50 MHz, $CDCl_3$)



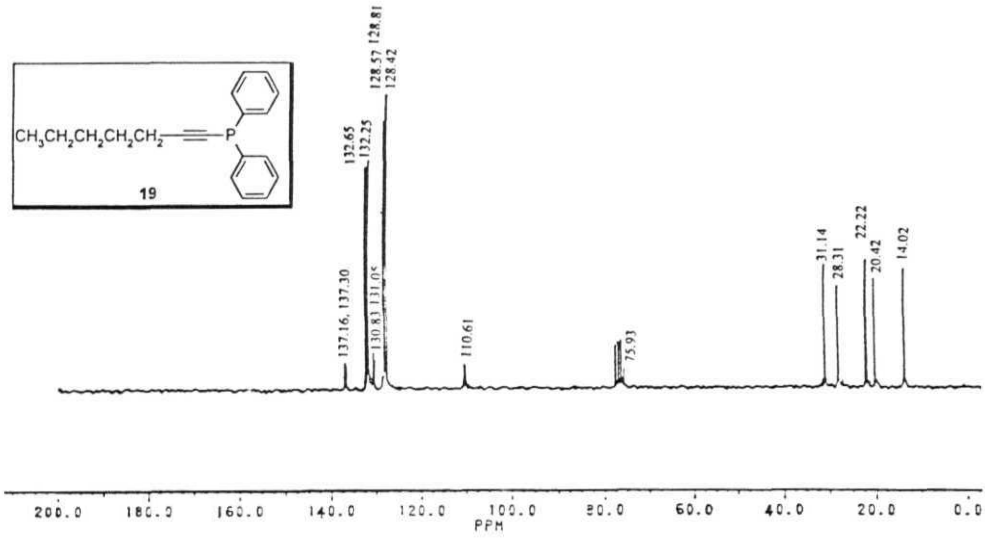
Spectrum No. 6 (Chapter 1), ^{13}C-NMR Spectrum (50 MHz, $CDCl_3$)



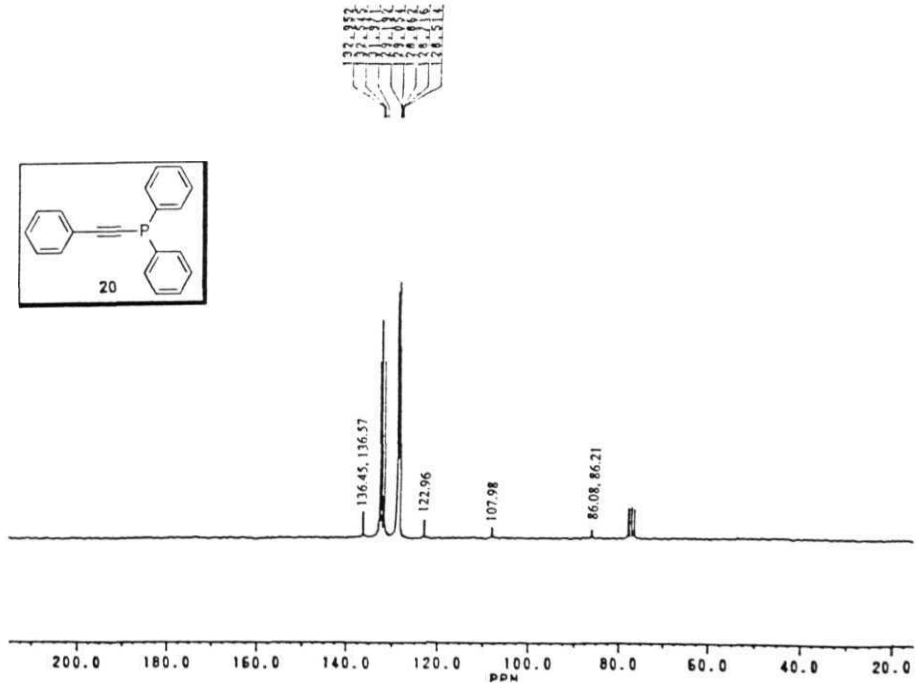
Spectrum No. 7 (Chapter 1), DEPT Experiments (CH_3 and CH up, CH_2 down)



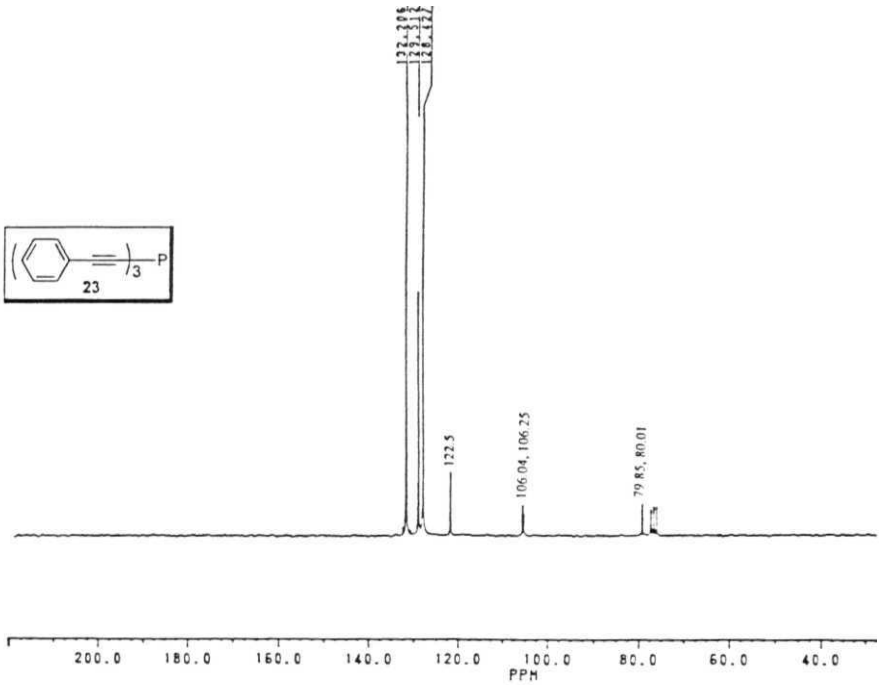
Spectrum No. 8 (Chapter 1), ^{13}C-NMR Spectrum (50 MHz, $CDCl_3$)



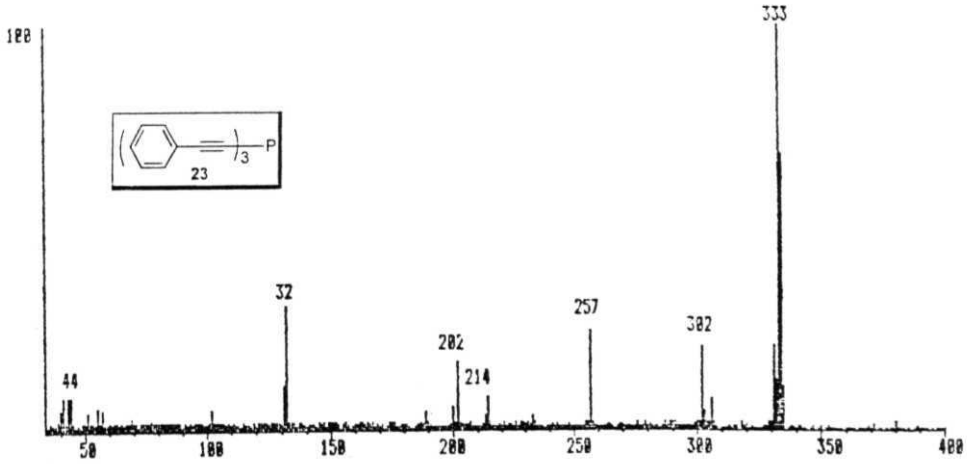
Spectrum No. 9 (Chapter 1), ^{13}C-NMR Spectrum (50 MHz, $CDCl_3$)



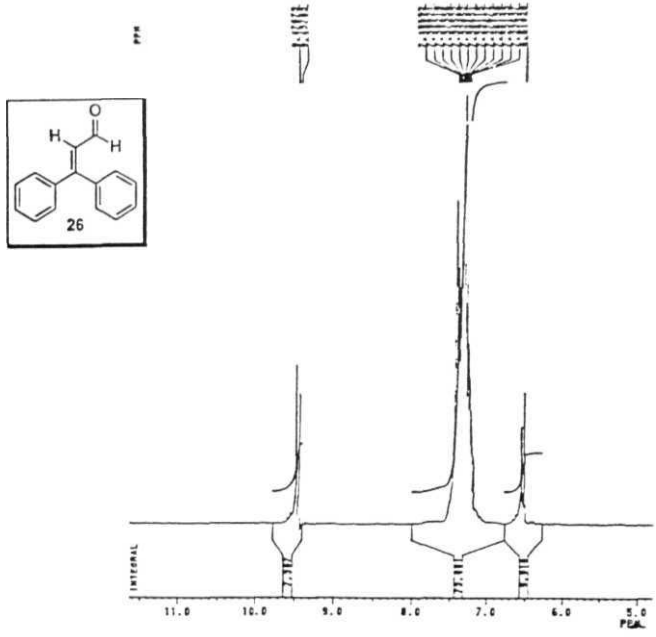
Spectrum No. 10 (Chapter 1), ^{13}C-NMR Spectrum (50 MHz, $CDCl_3$)



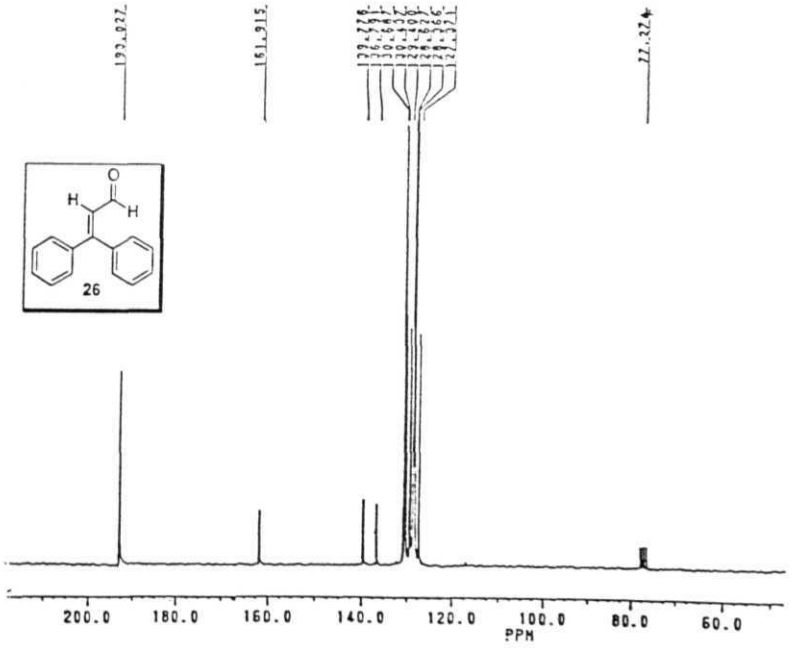
Spectrum No. **11** (Chapter 1). Mass Spectrum (ED



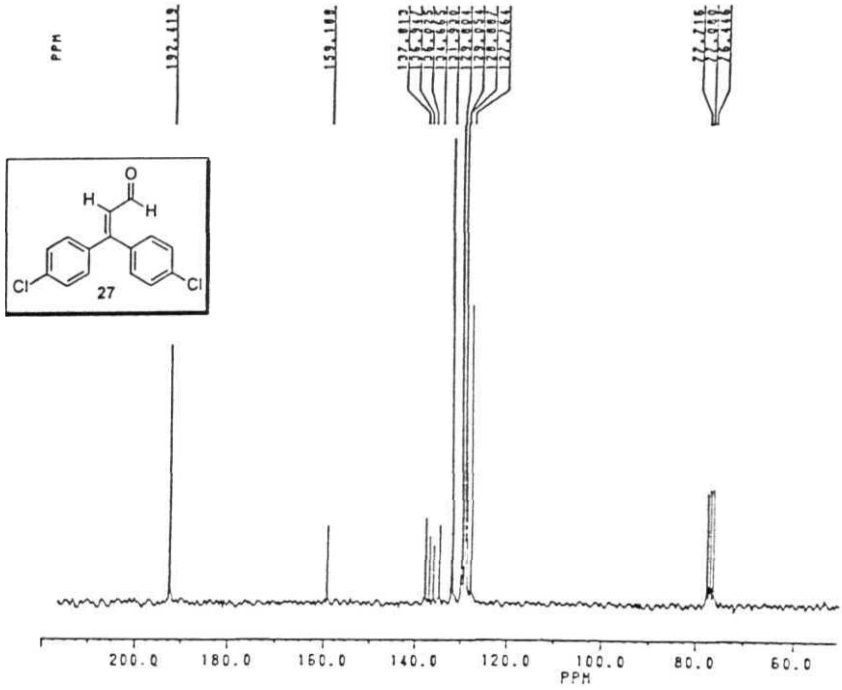
Spectrum No. 12 (Chapter 2), ^{1}H-NMR Spectrum (200 MHz, $CDCl_3$)



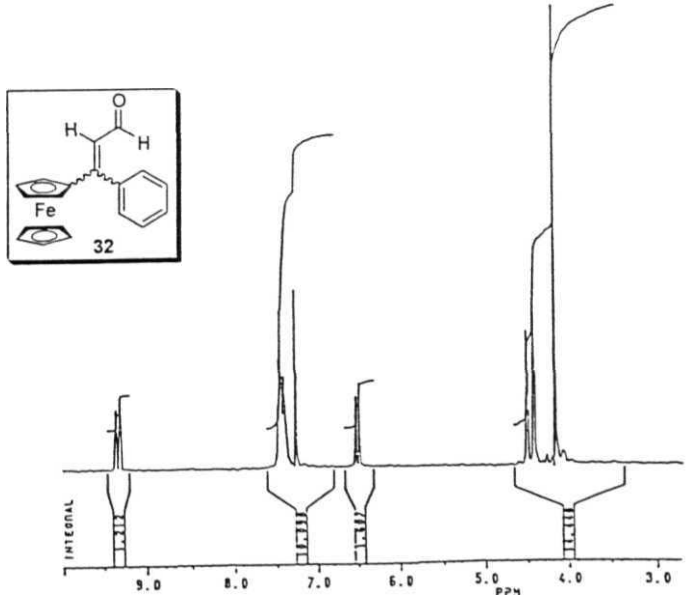
Spectrum No. 13 (Chapter 2). ^{13}C-NMR Spectrum (50 MHz, $CDCl_3$)



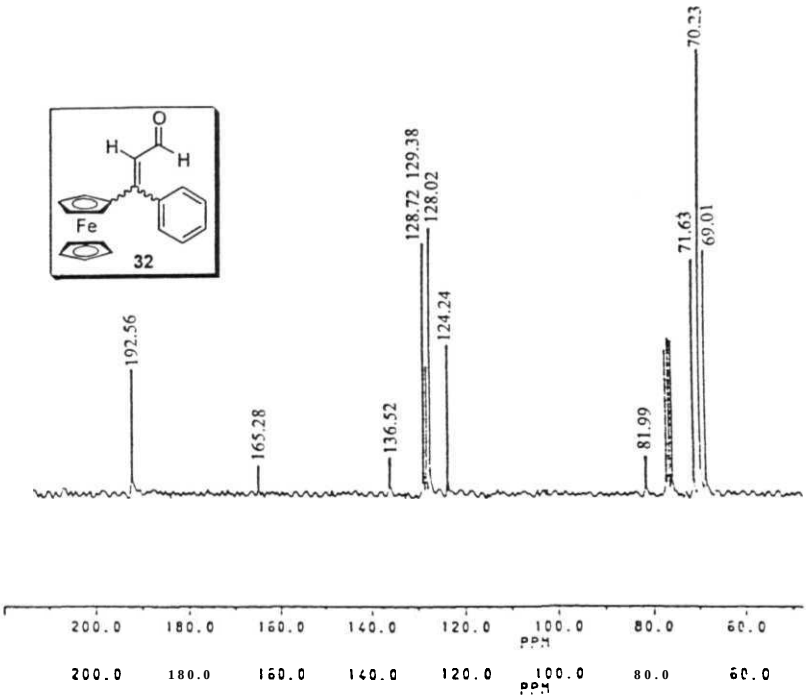
Spectrum No. 14 (Chapter 2), ^{13}C-NMR Spectrum (50 MHz, $CDCl_3$)



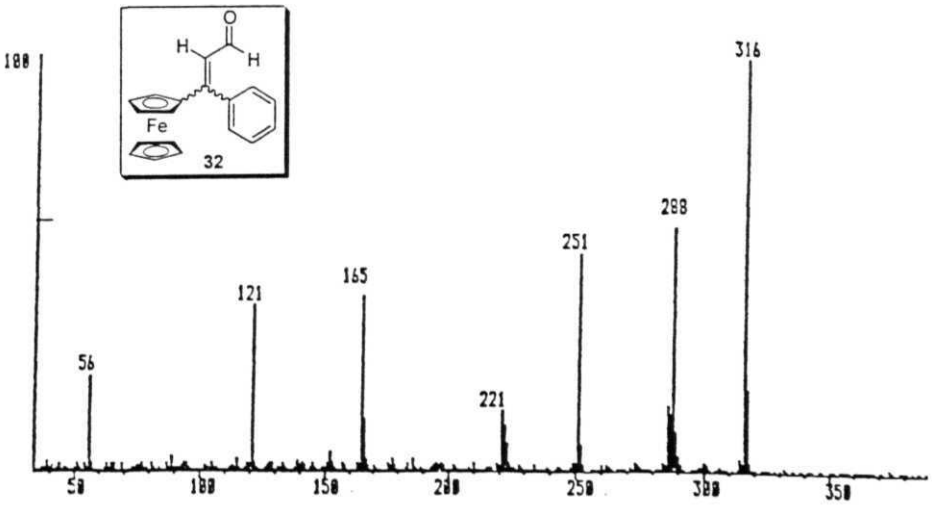
Spectrum No. 15 (Chapter 2). ^{1}H-NMR Spectrum (200 MHz. $CDCl_3$)



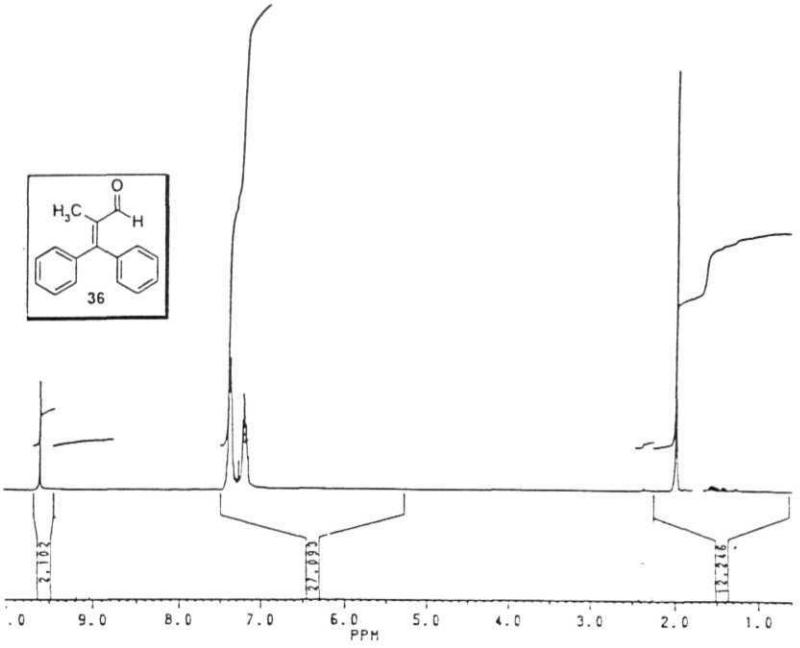
Spectrum No. 16 (Chapter 2). ^{13}C-NMR Spectrum (50 MHz, $CDCl_3$)



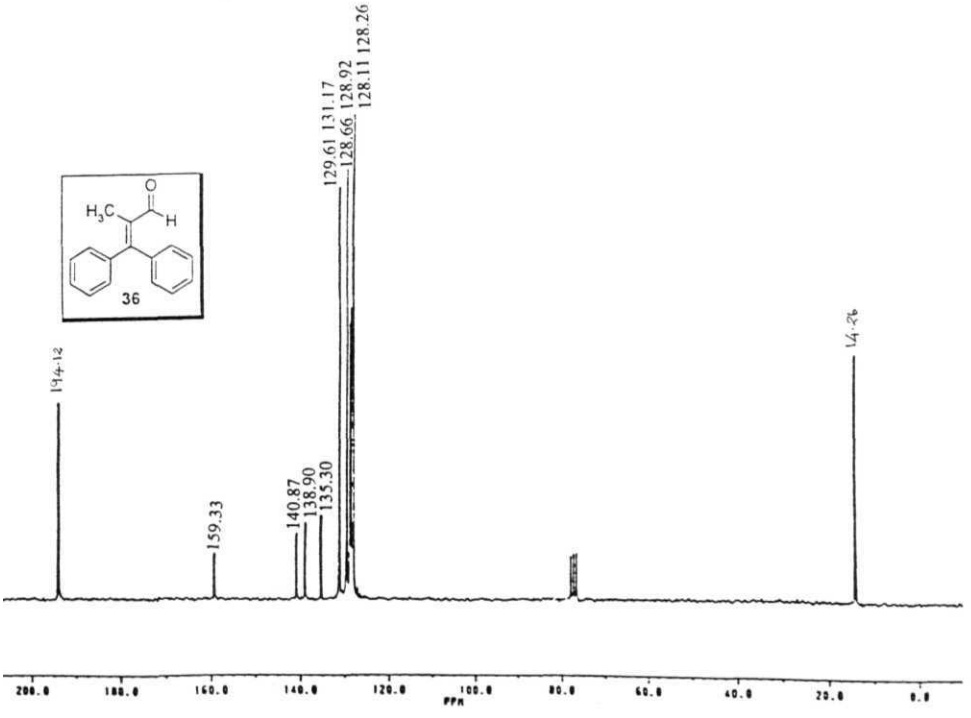
Spectrum No. 17 (Chapter 2). Mass Spectrum (ED



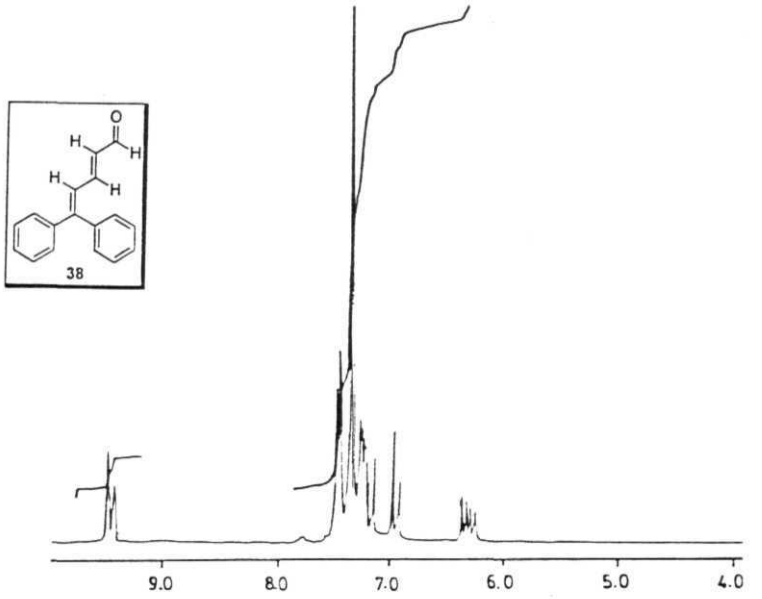
Spectrum No. 18 (Chapter 2), ^{1}H-NMR Spectrum (200 MHz, $CDCl_3$)



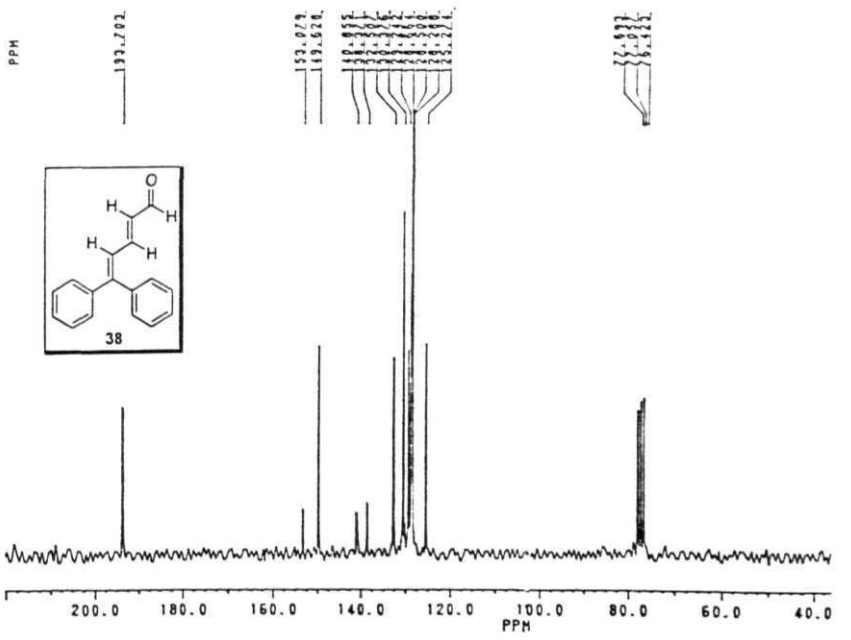
Spectrum No. 19 (Chapter 2), ^{13}C-NMR Spectrum (50 MHz, $CDCl_3$)



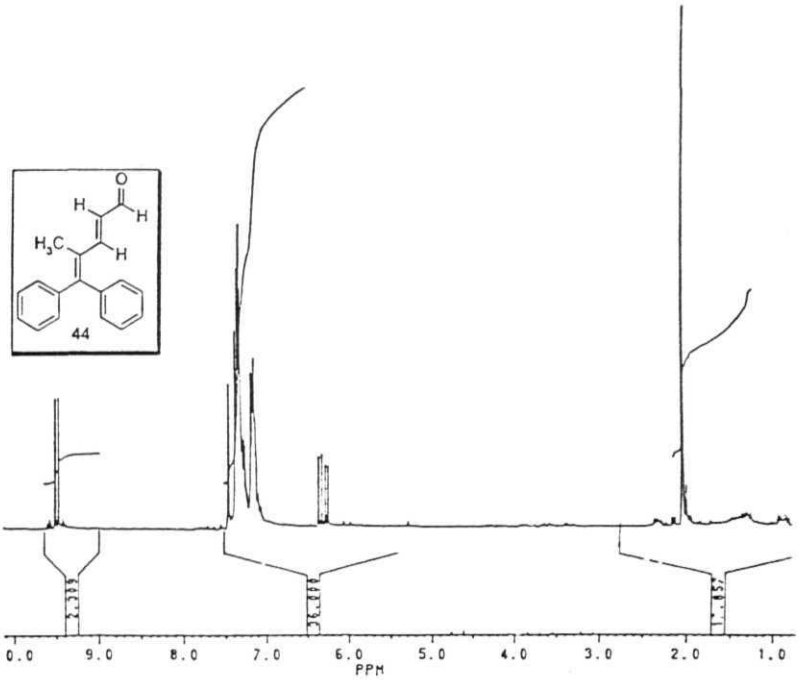
Spectrum No. 20 (Chapter 2), ^{1}H-NMR Spectrum (200 MHz, $CDCl_3$)



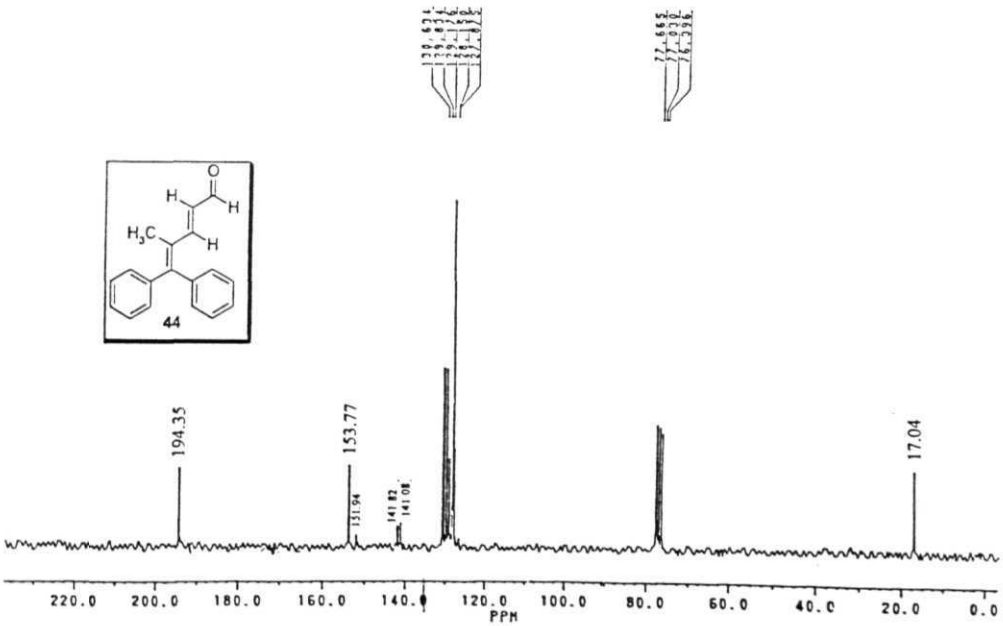
Spectrum No. 21 (Chapter 2), ^{13}C-NMR Spectrum (50 MHz, $CDCl_3$)



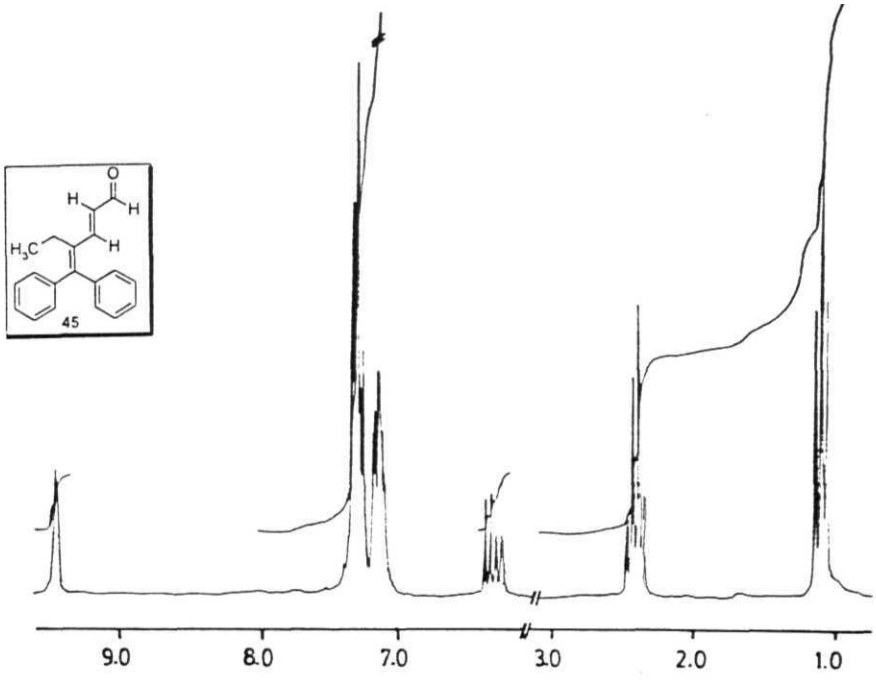
Spectrum No. 22 (Chapter 2), ^{1}H-NMR Spectrum (200 MHz, *CDCU)*



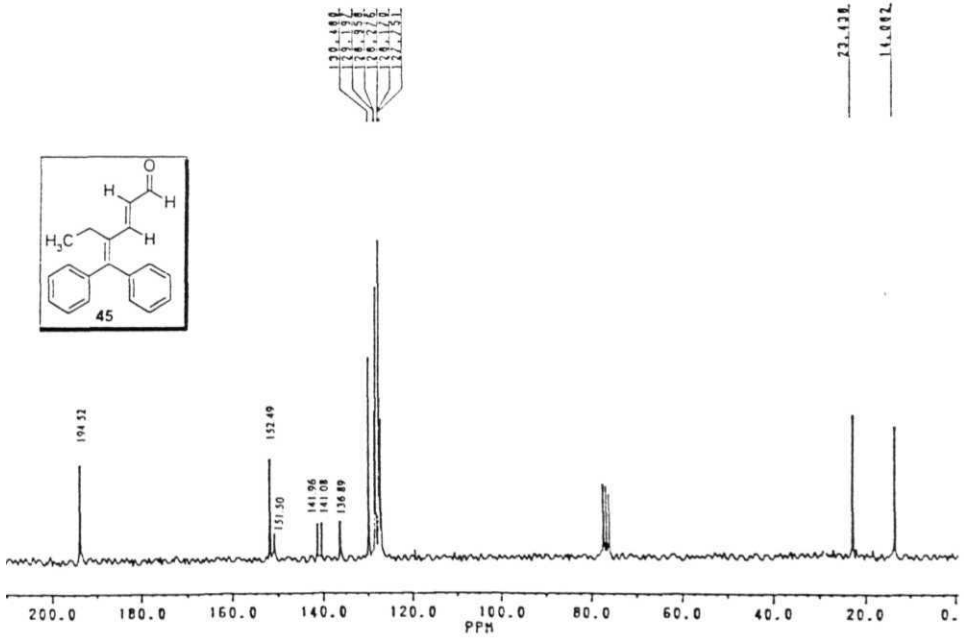
Spectrum No. 23 (Chapter 2), ^{13}C-NMR Spectrum (50 MHz, $CDCl_3$)



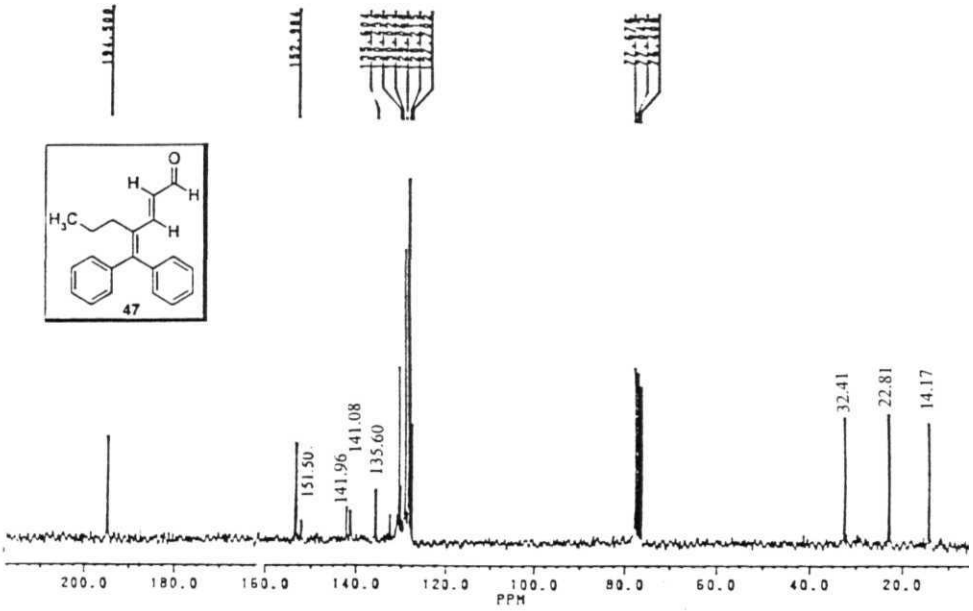
Spectrum No. 24 (Chapter 2), ^{1}H-NMR Spectrum (200 MHz, $CDCl_3$)



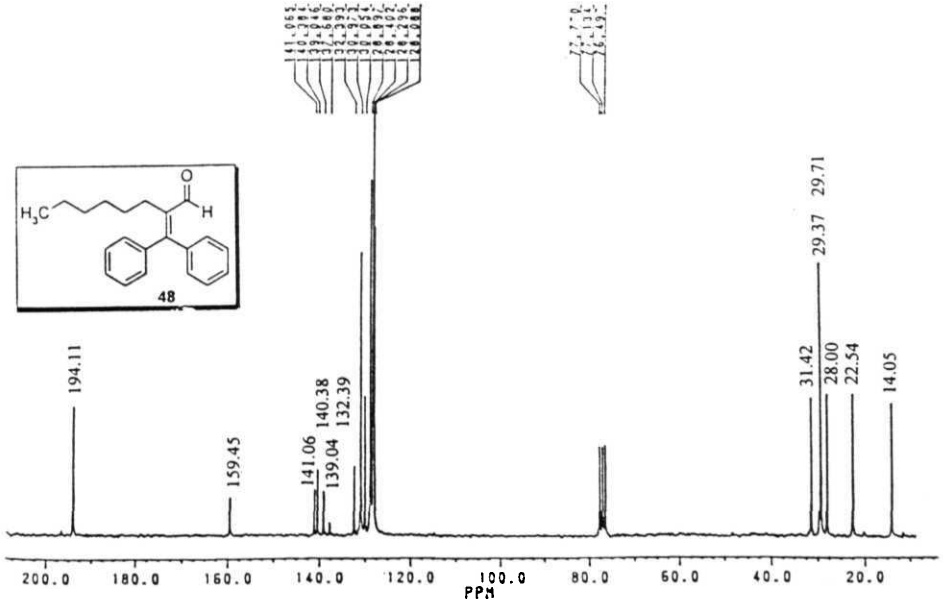
Spectrum No. 25 (Chapter 2), ^{13}C-NMR Spectrum (50 MHz, $CDCl_3$)



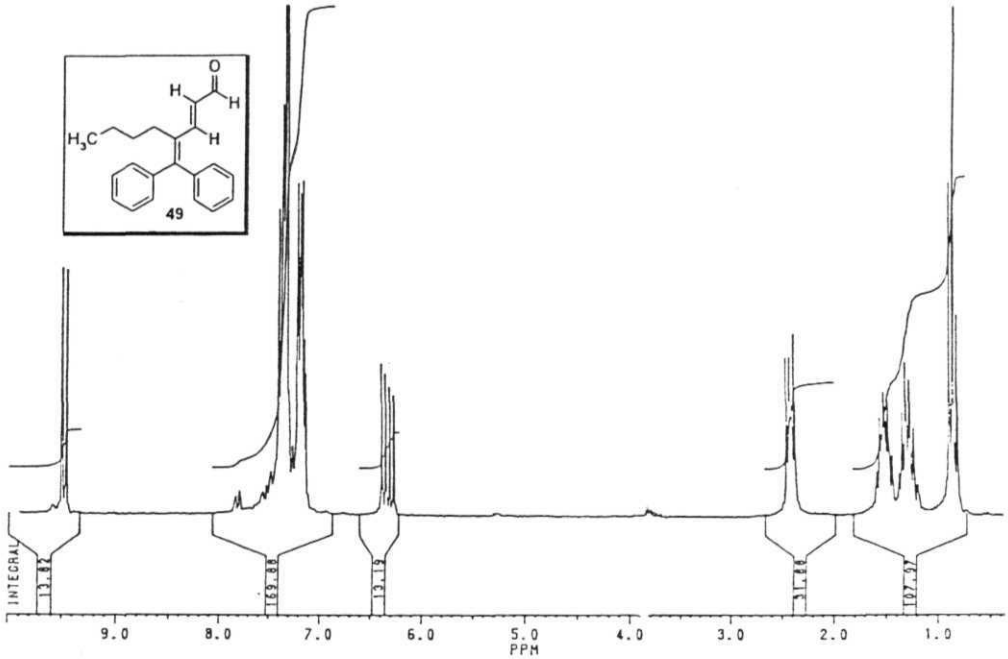
Spectrum No. 26 (Chapter 2), ^{13}C-NMR Spectrum (50 MHz, $CDCl_3$)



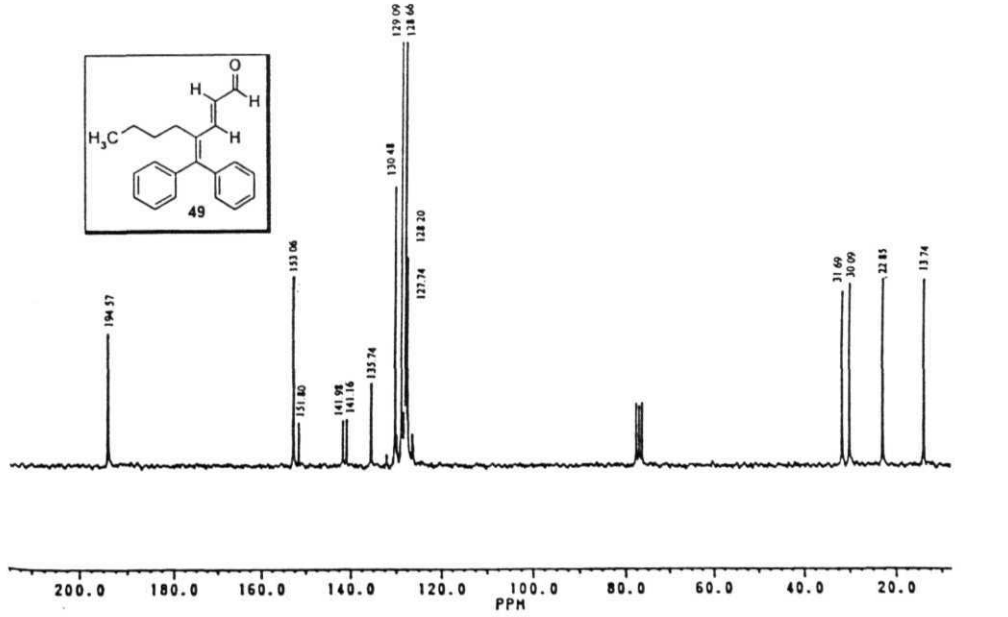
Spectrum No. 27 (Chapter 2), ^{13}C-NMR Spectrum (50 MHz, $CDCl_3$)



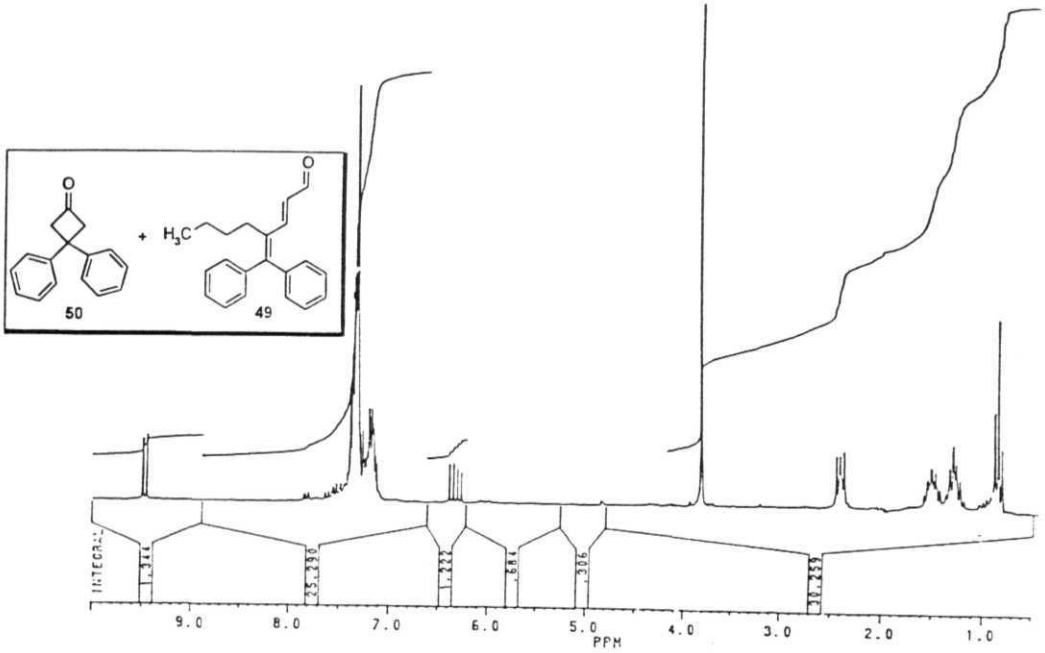
Spectrum No. 28 (Chapter 2), **^{1}H-NMR** Spectrum (200 MHz, **$CDCl_3$**)



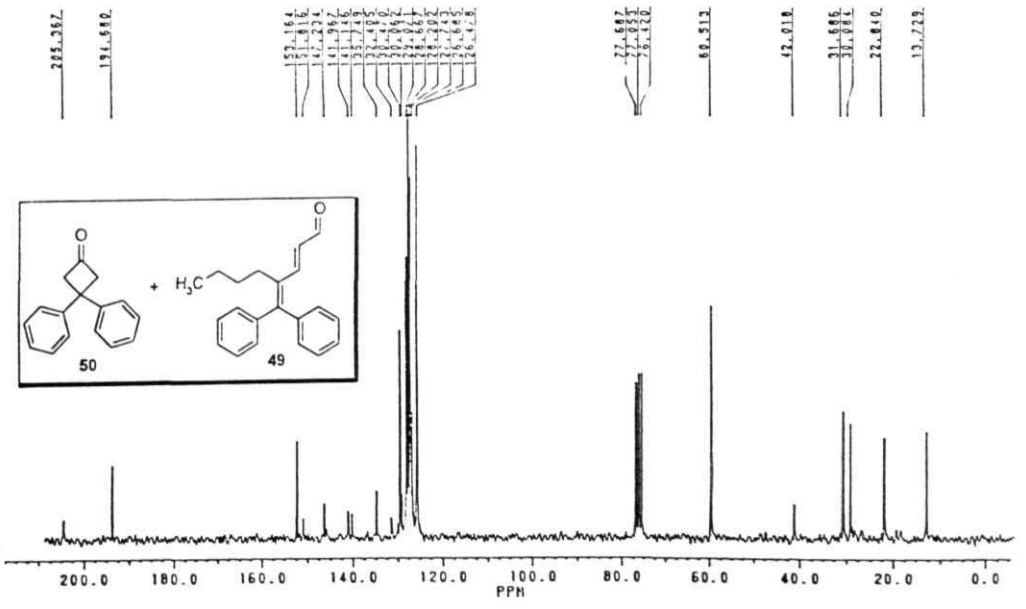
Spectrum No. 29 (Chapter 2), ^{13}C-NMR Spectrum (50 MHz, $CDCl_3$)



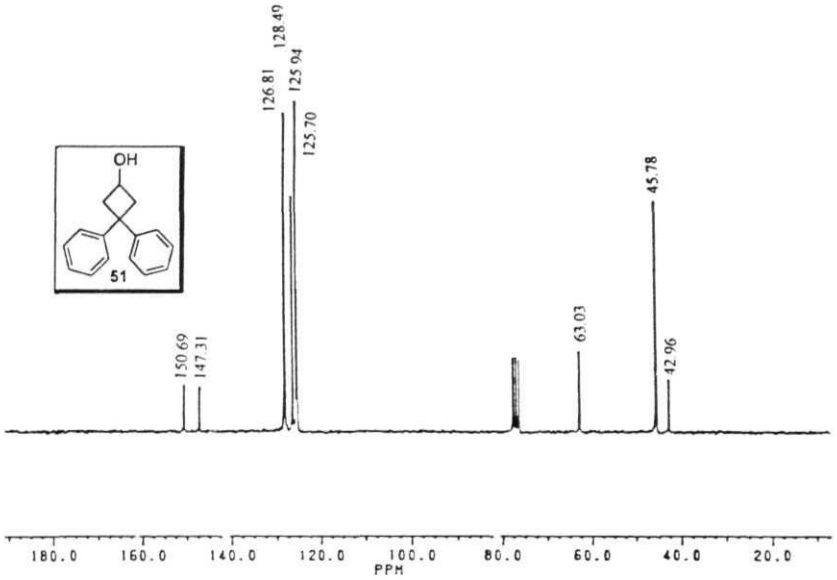
Spectrum No. 30 (Chapter 2), ^{1}H-NMR Spectrum (200 MHz. $CDCl_3$)



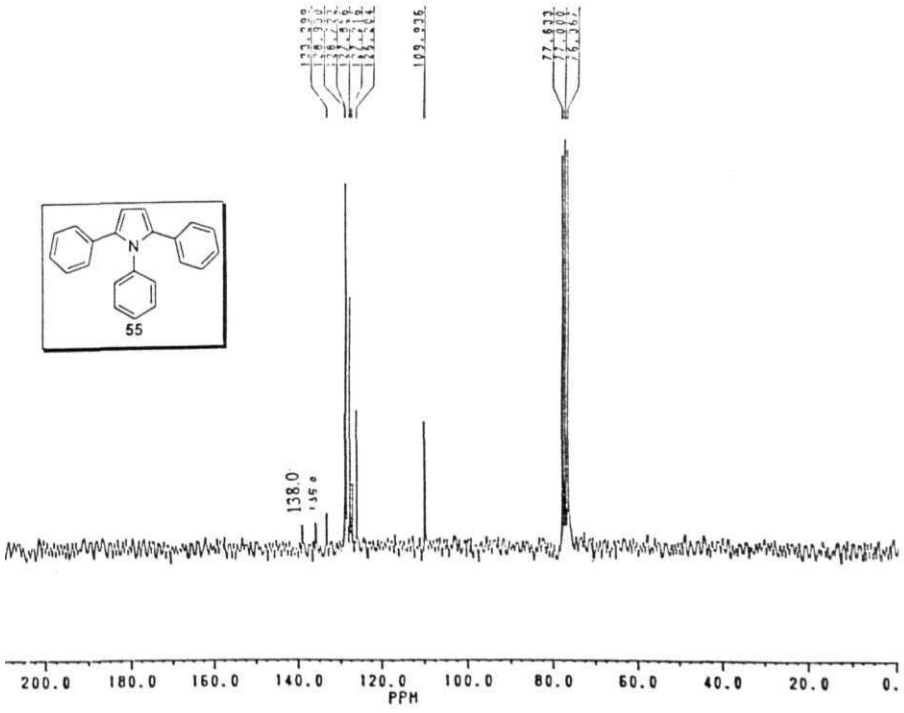
Spectrum No. 31 (Chapter 2), ^{13}C-NMR Spectrum (50 MHz, $CDCl_3$)



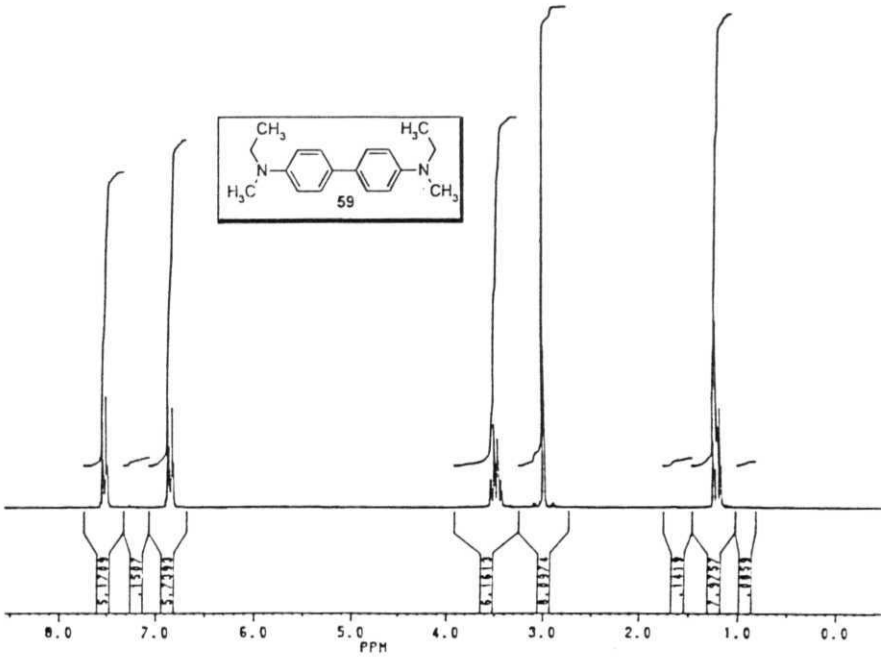
Spectrum No. 32 (Chapter 2), ^{13}C-NMR Spectrum (50 MHz, $CDCl_3$)



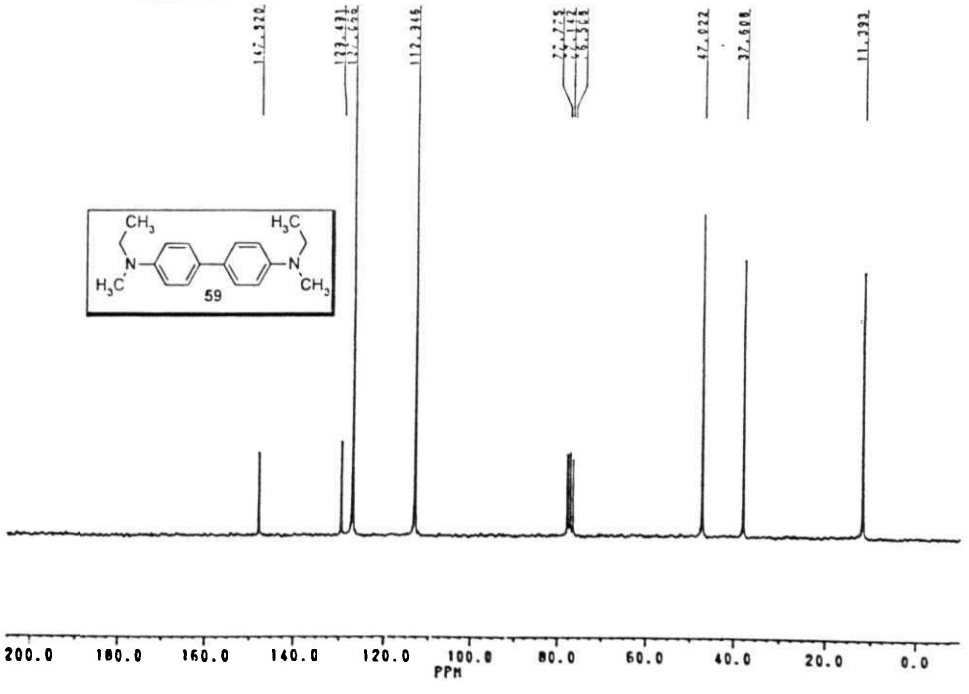
Spectrum No. 33 (Chapter 3), ^{13}C-NMR Spectrum (50 MHz, $CDCl_3$)



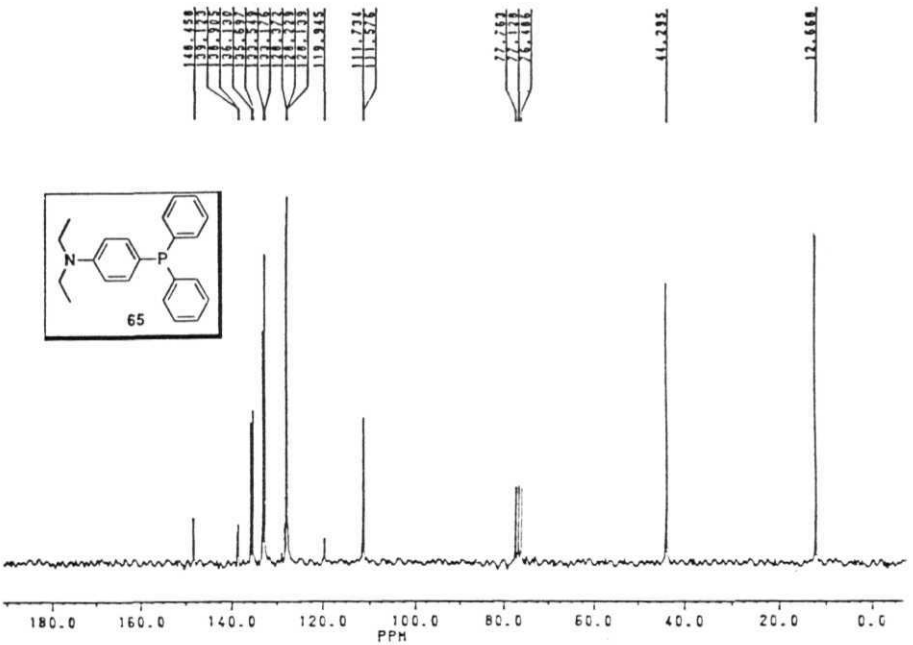
Spectrum No. 34 (Chapter 3), ^{1}H-NMR Spectrum (200 MHz, $CDCl_3$)



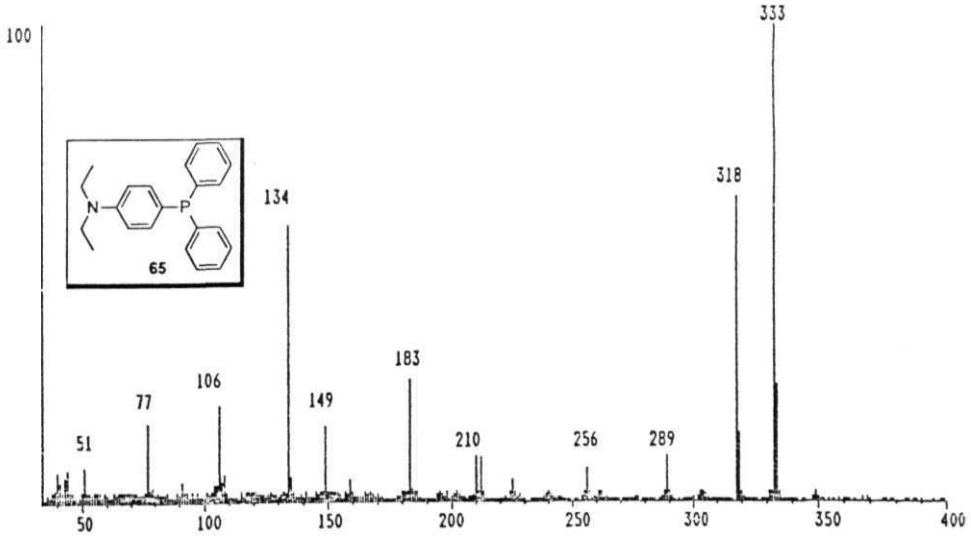
Spectrum No. 35 (Chapter 3), ^{13}C-NMR Spectrum (50 MHz, $CDCl_3$)



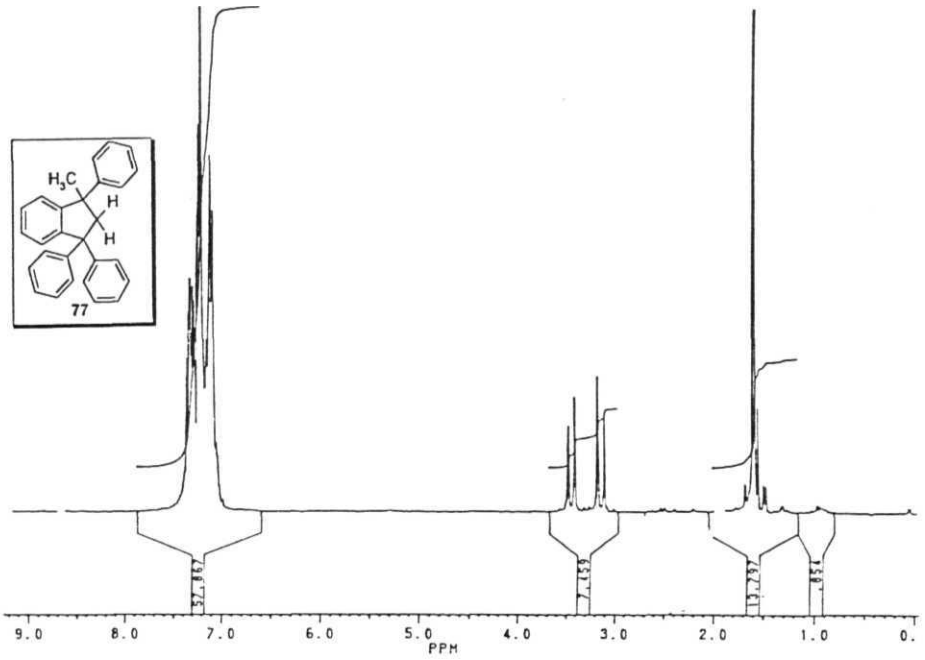
Spectrum No. 36 (Chapter 3), ^{13}C-NMR Spectrum (50 MHz, $CDCl_3$)



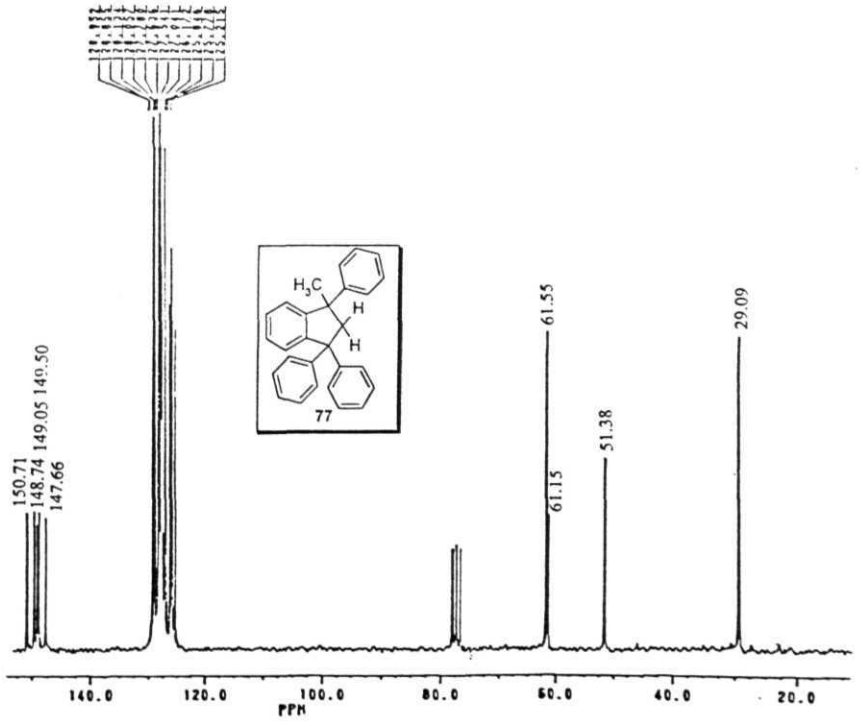
Spectrum No. 37 (Chapter 3), Mass Spectrum (EI)



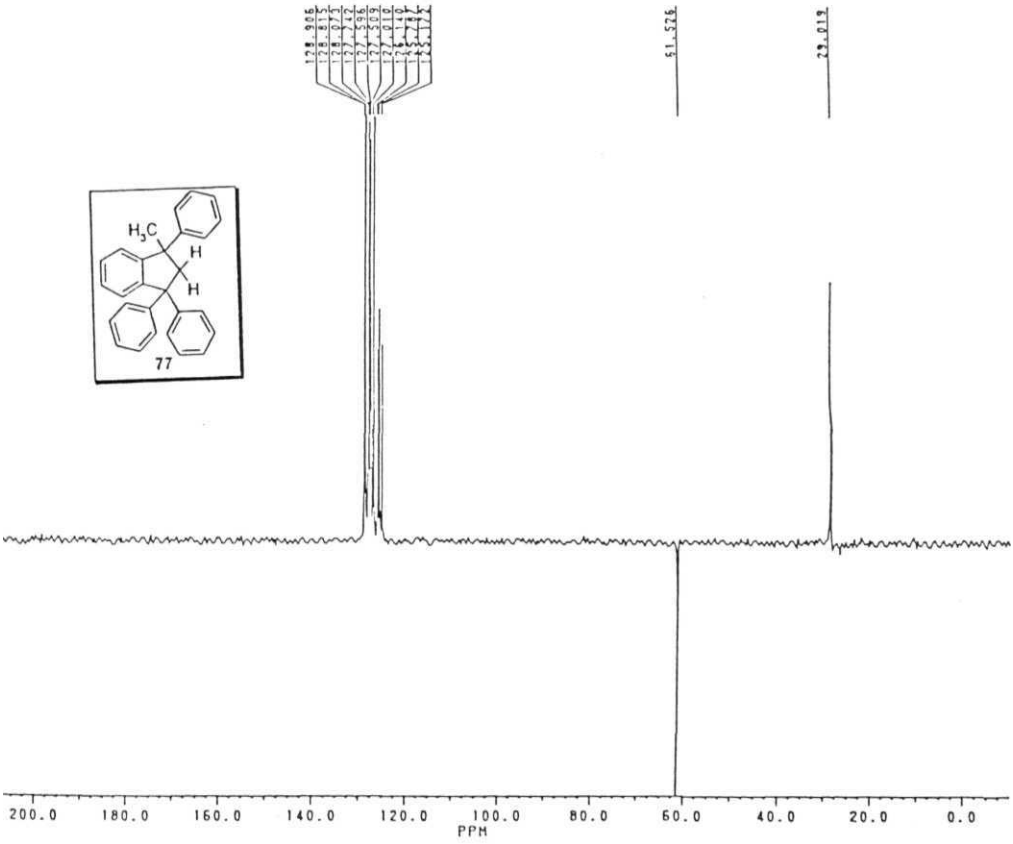
Spectrum No. 38 (Chapter 3), ^{1}H-NMR Spectrum (200 MHz, *CDCU)*



Spectrum No. 39 (Chapter 3), ^{13}C-NMR Spectrum (50 MHz, $CDCl_3$)



Spectrum No. 40 (Chapter 3), DEPT Experiments (CH_3 and CH up, CH_2 down)



LIST OF PUBLICATIONS

1. A new method of acylation and formylation of polycyclic aromatic hydrocarbons, M. Periasamy, M. Rama Reddy, **P. Bharathi,** *Synth. Commun.,* **1999**, *29*, 677.

2. Conversion of aryl methyl ketimines to 2,5-diaryl pyrroles using $TiCl_4/Et_3N$, M. Periasamy, G. Srinivas, **P. Bharathi,** *J. Org. Chem.,* **1999,** *64,* 4204.

3. Metalation of iminium ions formed in the reaction of tertiary amines with $TiCl_4$, **P. Bharathi,** M. Periasamy, *Organic Lett.,* **1999,** /, 857.

4. Reductive coupling of aromatic aldehydes and imines by the low valent titanium species generated in the reaction of $TiCl_4$ with Et_3N, M. Periasamy, G. Srinivas, G. V. Karunakar, **P. Bharathi,** *Tetrahedron Lett.,* **1999,** *40,* 7577.

5. Terminal alkynes/$TiCl_4/Et_3N$ and their reactions with electrophiles, **P. Bharathi,** M. Periasamy, *Communicated.*

6. Aryltitanium species through the reaction of *N,N*-dialkyl-*N*-arylamines with $TiCl_4$: Oxidative coupling, *N*-dealkylation and reaction with electrophiles. M. Periasamy, K. N. Jayakumar, **P. Bharathi,** *communicated.*

7. Reaction of alkynyltitanium with benzaldehyde: Stereoselective synthesis of trisubstitued olefins via allenic titanium enolates, M. Periasamy, P. **Bharathi,** G.V. Karunakar, *Manuscript under preparation.*

8. The reaction of *N,N*-diisopropyl-*N*-alkylamines with $TiCl_4$: **Formation of** 1,3-dianions and their use in the preparation of cyclobutanone derivatives, M. Periasamy, K. N. Jayakumar, **P. Bharathi,** *Manuscript under preparation.*

9. A convenient synthesis of metallocene-$TiCl_2$ complexes using $TiCl_4/Et_3N$, **P. Bharathi,** M. Periasamy, *Manuscript under preparation.*