New synthetic methods using the $TiCl_4$-NR_3 reagent system

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Dedicated to Professor S. V. Kessar on the occasion of his 70th birthday

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Abstract

The $TiCl_4$-NR_3 reagent system is useful for carbon-carbon bond forming reactions such as the aldol and related condensation reactions, the diastereoselective coupling of phenyl acetic acid derivatives, the conversion of aryl alkyl ketimines and ketoximes to pyrroles, ketazines to dihydrodiazines, enamines to aromatic amines, *N,N*-dialkylanilines to the corresponding benzidine derivatives, trialkylamines to unsaturated aldehydes, diarylcyclobutanones, diarylcyclobutylamine derivatives via iminium ion intermediates and for the reductive coupling of aromatic aldehydes, aldimines and intramolecular reductive coupling of chiral diimine derivatives. In all cases, the organic products are obtained in moderate to good yields, in single-pot operations under ambient reaction conditions. Hence, these synthetic methods have considerable synthetic potential.

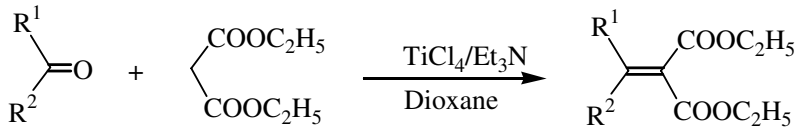
Keywords: Titanium enolates, alkynyltitanium, metalated iminium ions, stereoselective, coupling

Introduction

Titanium reagents are widely used in organic synthesis.[1] Whereas the organotitanium reagents are useful in C-C bond forming reactions, the simple TiX_4[1a-c] and TiX_3[1d,e] (X = Cl, OR) are frequently used in both stoichiometric and catalytic quantities in C-C bond forming reactions and functional group transformations. Among various titanium reagents, $TiCl_4$ has vast applications in organic synthesis. It has been used as such or in combination with an additive. In the last 20 years, several useful synthetic transformations involving the use of $TiCl_4$ along with a tertiary amine NR_3 were uncovered. These results are presented in this account.

Discussion

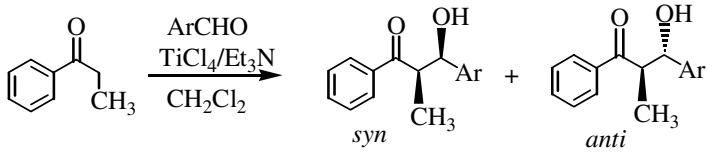
The $TiCl_4$-NR_3 reagent system has been widely used for the preparation of titanium enolates for applications in aldol and related reactions in organic synthesis. It was first used in Knoevenagel condensation reactions (Scheme 1).[2]



$R^1 = CH_3$, $R^2 = H$, 86%
$R^1 = n\text{-}C_4H_9$, $R^2 = H$, 81%
$R^1 = Ph$, $R^2 = H$, 97%

Scheme 1

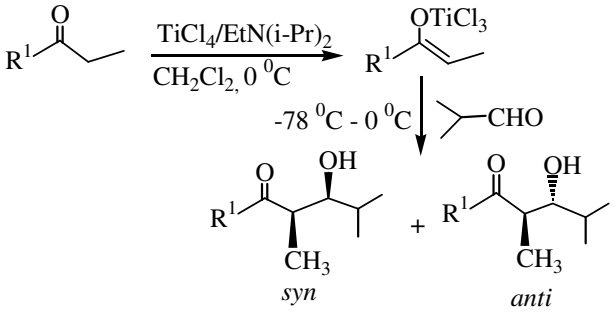
In 1986, it was discovered that the titanium enolate prepared using propiophenone reacts with arylaldehydes to give the corresponding aldols with very high *syn* selectivity (Scheme 2).[3]



	Yield	*syn* : *anti*
Ar = Ph	91%	95:5
Ar = *p*-OCH_3Ph	95%	89:11
Ar = *p*-CH_3Ph	94%	96:4
Ar = *p*-NO_2Ph	98%	87:13

Scheme 2

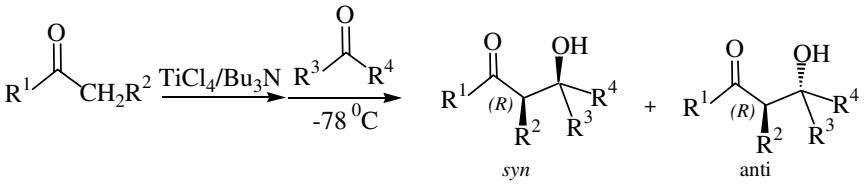
Similar reactivity pattern has been also observed in reactions using aliphatic ketones (Scheme 3).[4]



$R^1 = C_2H_5$, 95%, *syn* : *anti* = 92:8
$R^1 = i\text{-}C_3H_7$, 95%, *syn* : *anti* = 93:7

Scheme 3

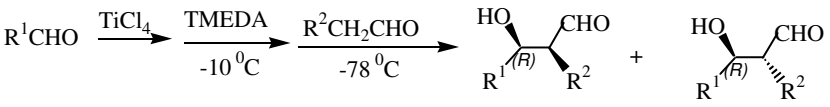
Stereoselective aldol reaction has been also observed in the reaction a titanium enolate prepared using a ketone and $TiCl_4/Bu_3N$ reagent system with another ketone (Scheme 4).[5]



	Yield	*syn:anti*
R^1 = Ph, R^2 = CH_3, R^3 = Ph, R^4 = CH_3	95%	>99:<1
R^1 = Ph, R^2 = CH_3, R^3 = Ph, R^4 = CH_2Cl	91%	>99:<1
R^1 = CH_3CH_2, R^2 = CH_3, R^3 = Ph, R^4 = CH_3	84%	84:16
R^1 = CH_3CH_2, R^2 = CH_3, R^3 = Ph, R^4 = CH_3CH_2	92%	72:28
R^1 = $CH_3CH_2CH_2$, R^2 = CH_3CH_2, R^3 = Ph, R^4 = CH_3	72%	>99:<1
R^1 = $CH_3CH_2CH_2$, R^2 = CH_3CH_2, R^3 = *n*-C_7H_{15}, R^4 = CH_3	60%	60:40

Scheme 4

Aldehyde complexes of $TiCl_4$ reacts with another aldehyde in the presence of TMEDA to give the corresponding aldol with very high *syn* selectivity (Scheme 5).[6]



syn : anti = >96 : <4

R^1 = Ph, R^2 =CH_3, 72%

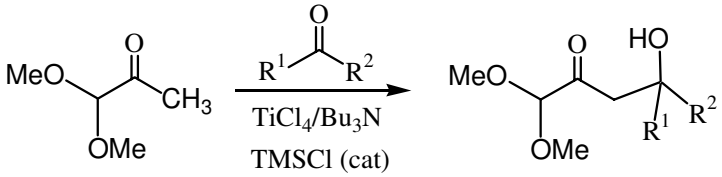
R^1 = Ph, R^2 =CH_3CH_2, 78%

R^1 = *i*-C_3H_7, R^2 = $CH_2$3, 49%

R^1 = CH_3CH_2, R^2 =CH_3, 84%

Scheme 5

Titanium enolate of an α-dialkoxyketone gives the corresponding aldol adduct in the presence of TMSCl catalyst (Scheme 6).[7]



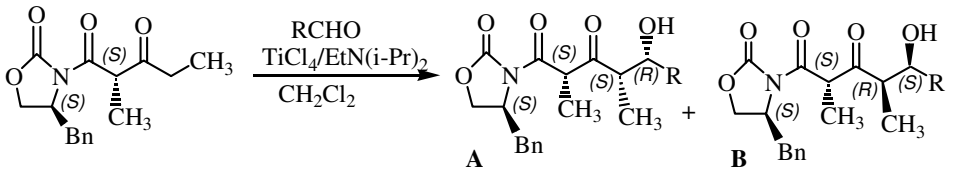
R^1 = Ph, R^2 = H, 80%

R^1 = n-C_4H_9, R^2 = H, 71%

R^1 = Ph, R^2 = CH_2Cl, 63%

Scheme 6

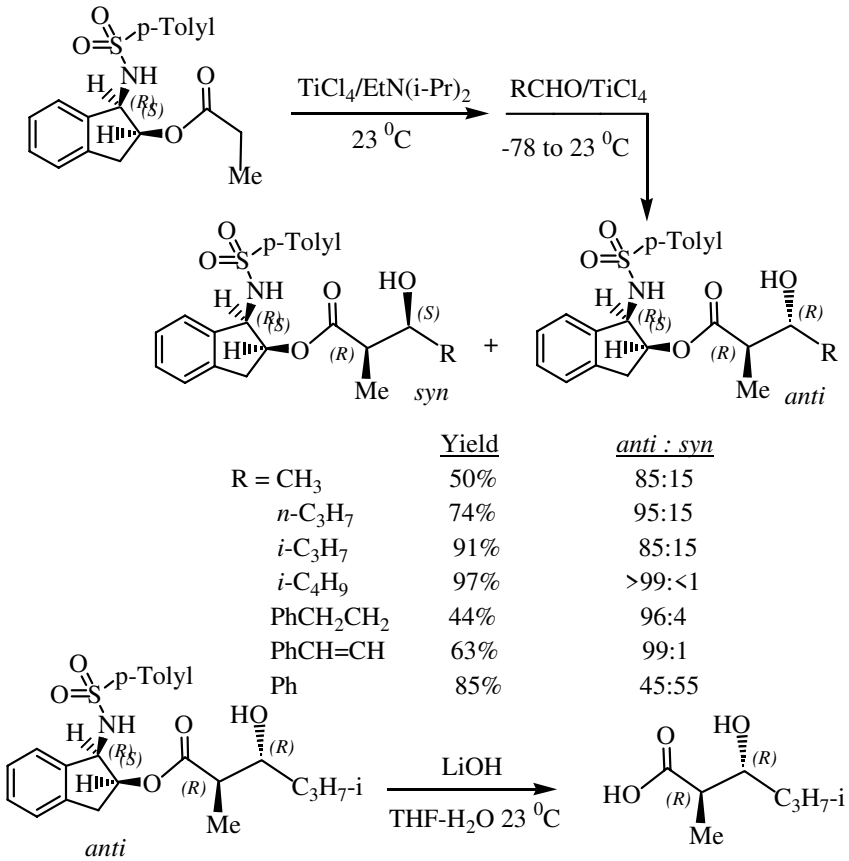
Preparation of titanium enolate using $TiCl_4/EtN(i\text{-}Pr)_2$ reagent system followed by aldol reaction with aldehydes leads to very high diastereoselectivity (Scheme 7).[8]



R =	Yield	A : B
H_3C, H_3C	86%	>99:<1
H_3C, H_2C	64%	98:2
CH_3CH_2	86%	>99:<1
Ph	81%	96:4

Scheme 7

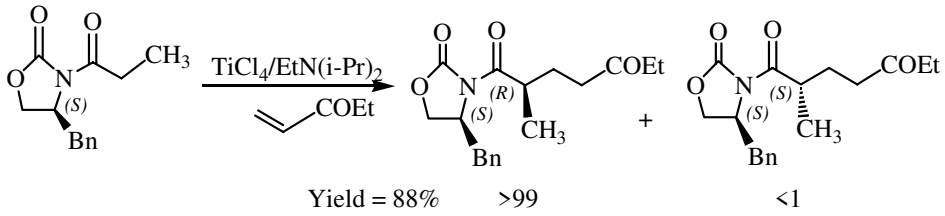
In these transformations, *syn* selectivity was realized. In contrast, high *anti* selectivity was realized in the reaction of a chiral amino indanol derived titanium enolate (Scheme 8).[9] Enantiomerically pure *anti*-aldols can be readily obtained upon hydrolysis of the *anti* adduct (Scheme 8).[9]



R =	Yield	*anti* : *syn*
CH_3	50%	85:15
n-C_3H_7	74%	95:15
i-C_3H_7	91%	85:15
i-C_4H_9	97%	>99:<1
$PhCH_2CH_2$	44%	96:4
PhCH=CH	63%	99:1
Ph	85%	45:55

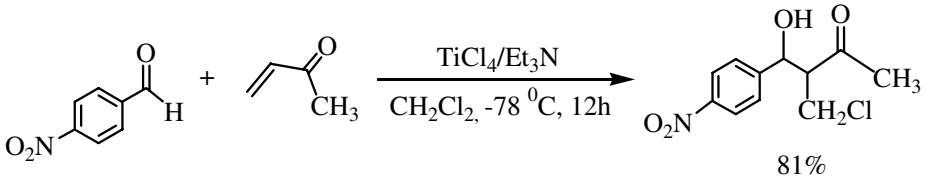
Scheme 8

The titanium enolates can be readily captured using a Michael acceptor. For example, the titanium enolate generated using *N*-propionyloxazolidone reacts with Michael acceptors to give the corresponding adducts with high diatereoselectivity (Scheme 9).[10]



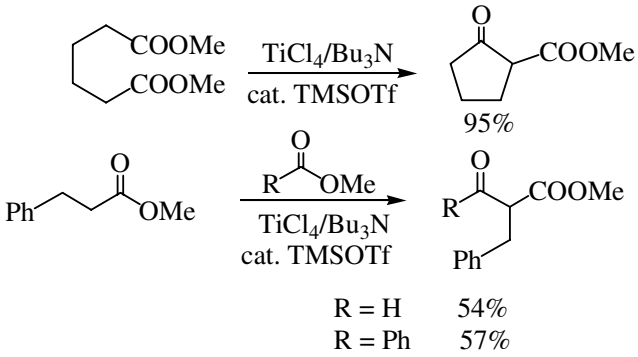
Scheme 9

Reaction of non-enolizable aldehydes with certain α,β-unsaturated carbonyl compounds in the presence of $TiCl_4/Et_3N$ reagent system leads to Baiylis-Hilman type reaction (Scheme 10).[11]



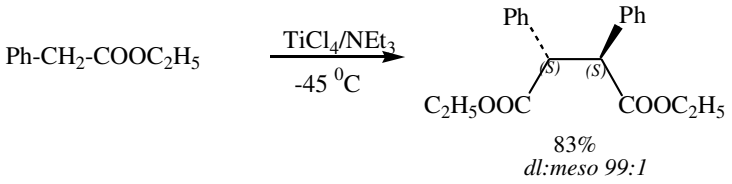
Scheme 10

Claisen condesation of esters is readily achieved using the $TiCl_4/Bu_3N$ reagent system (Scheme 11).[7,8]



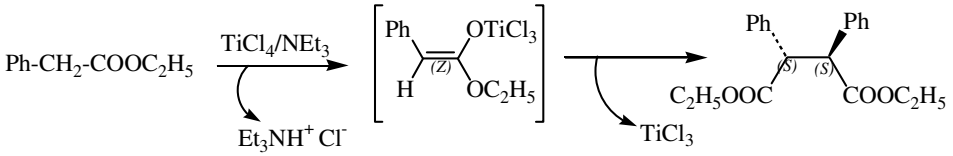
Scheme 11

In all these transformations the titanium species remains as Ti(IV) species. In recent years, several new organic transformations have been uncovered using the $TiCl_4/R_3N$ reagent system in which the $TiCl_4$ species becomes Ti(III). For example, in 1996, it was reported that the $TiCl_4$-NR_3 reagent system is useful in the preparation of the (*dl*)-C_2 symmetric 2,3-diphenylsuccinic acid esters (Scheme 12).[12] The reaction is highly chemo and diastereoselective.



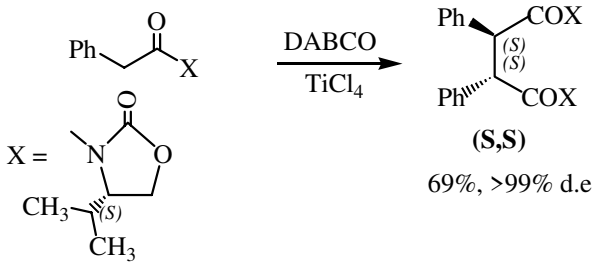
Scheme 12

The reaction proceeds through the formation of the corresponding titanium enolates, followed by oxidative coupling with concomitant formation of the titanium (III) species (Scheme 13).[12]



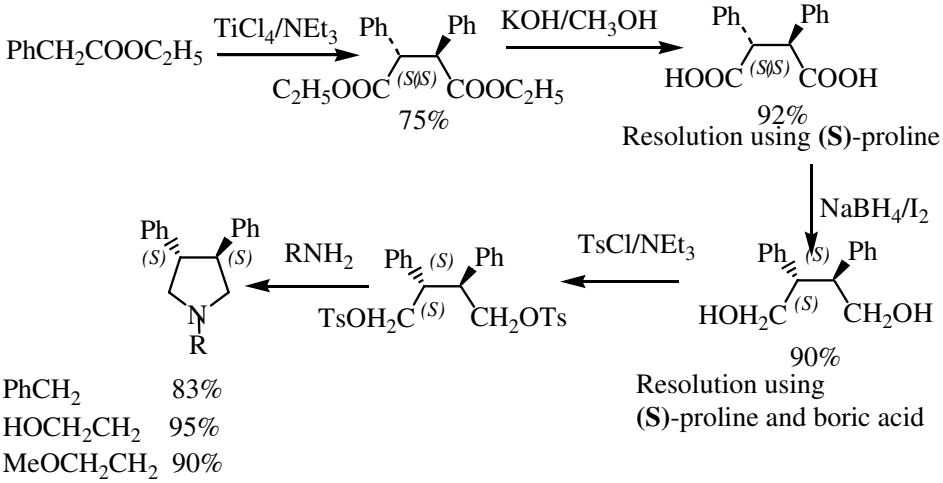
Scheme 13

Asymmetric versions of such oxidative coupling reactions have been reported (Scheme 14).[13]



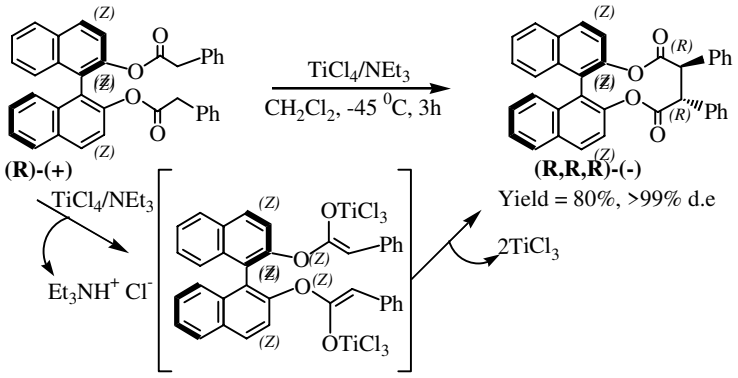
Scheme 14

Methods have been developed for the resolution of the corresponding racemic dicarboxylic acid for applications in the synthesis of chiral 3,4-diphenylpyrrolidine system (Scheme 15).[14]



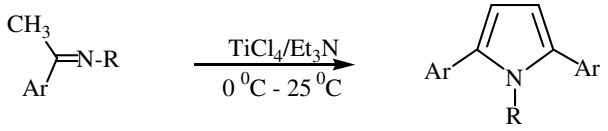
Scheme 15

During these research efforts, it was observed that the oxidative coupling of the chiral binaphthyl esters leads to diastereoselective formation of the corresponding cyclic compound (Scheme 16).[15]



Scheme 16

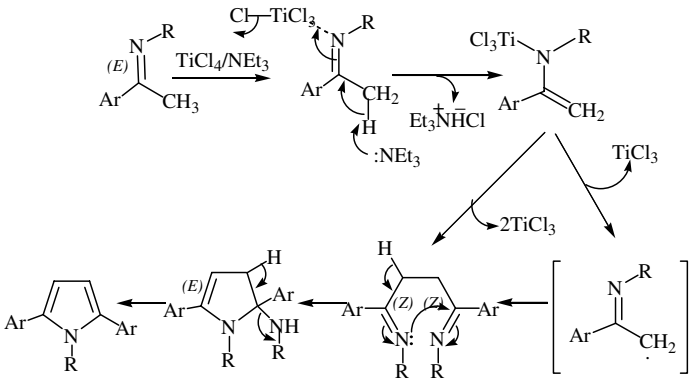
The reactivity pattern of the $TiCl_4/Et_3N$ reagent system with organic substrates containing acidic hydrogens were further examined. It was observed that the reaction of acetophenone with $TiCl_4/Et_3N$ reagent gave the corresponding 1,4-diketone in low yields (10-20%) along with the corresponding aldol condensation product.[16] However, the reaction of aromatic ketimines produced the corresponding 2,5-disubstituted pyrroles in good yields, through oxidative coupling and aromatisation reactions (Scheme 17).[17]



Ar = Ph, R = Ph	90%
Ar = Ph, R = *p*-OMePh	75%
Ar = Ph, R = *p*-ClPh	68%
Ar = Ph, R = CH_3	63%
Ar = 2-Naph, R = Ph	72%

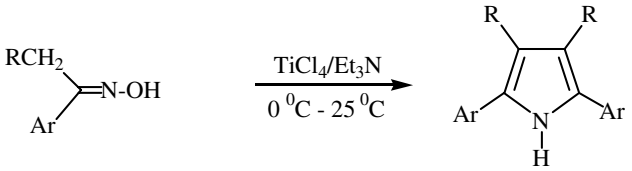
Scheme 17

The results can be rationalised by the mechanism shown in Scheme 18.[17]



Scheme 18

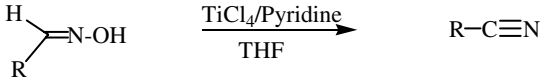
Also, it was found that certain ketoximes react with the $TiCl_4/NEt_3$ system to give the corresponding tetrasubstituted pyrroles (Scheme 19).[18]



Ar = Ph, R = Ph	81%
Ar = CH_2Ph, R = Ph	62%
Ar = *p*-CH_3Ph, R = CH_3	55%
Ar = Ph, R = CH_3CH_2	58%

Scheme 19

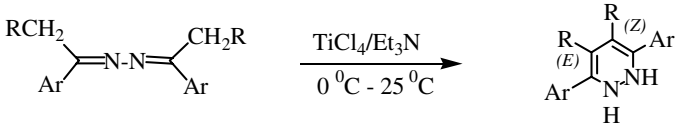
However, aldoximes give the corresponding nitriles on reaction with the $TiCl_4/R_3N$ reagent (Scheme 20).[19]



R = $CH_3CH_2CH_2$	80%
R = Ph	97%

Scheme 20

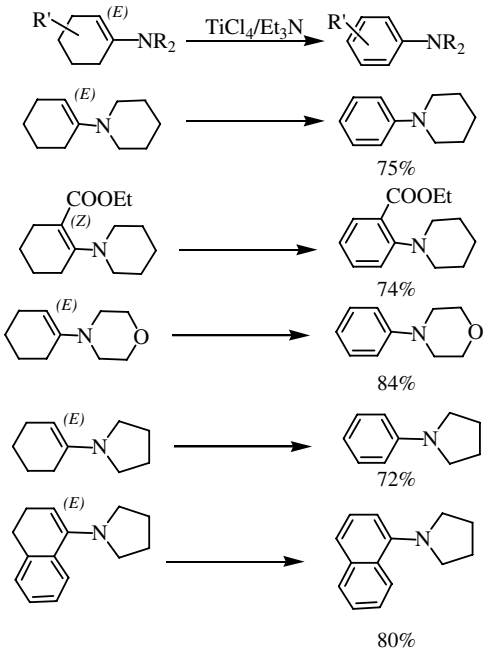
The reactions of hydrazones derived from ketones are expected to form the corresponding 1,2-diazines. However, in this case, the reaction gave the corresponding dihydro derivative (Scheme 21).[18]



Ar = Ph, R = H	50%
Ar = Ph, R = CH_3	55%

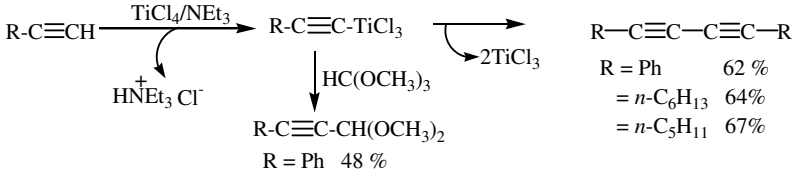
Scheme 21

Aromatisation takes place when certain enamines are used in the reaction with the $TiCl_4/NEt_3$ system (Scheme 22).[20] The results can be rationalized considering initial deprotonation similar to that outlined in Scheme 18.



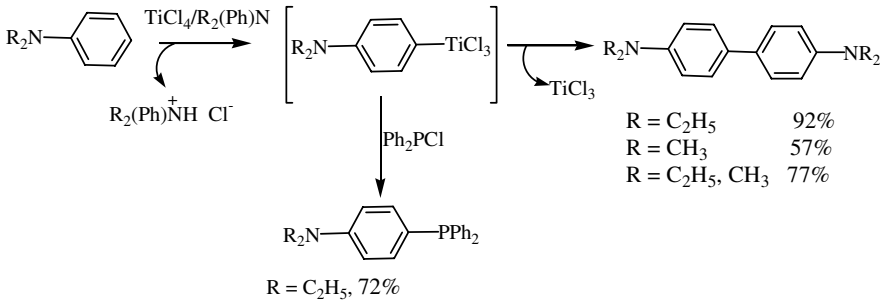
Scheme 22

It has been observed that the $TiCl_4$-NR_3 system reacts with 1-alkynes to give the corresponding diynes, through the intermediacy of the alkynyltitanium species.[21] Also, the alkynyltitanium species can be readily functionalised using certain electrophiles (Scheme 23).[21] Such direct metalation is an interesting observation, as previously alkynyl titanium reagents were prepared via metalation of 1-alkynes with alkyllithium reagents followed by exchange reaction with titanium complexes.[22]



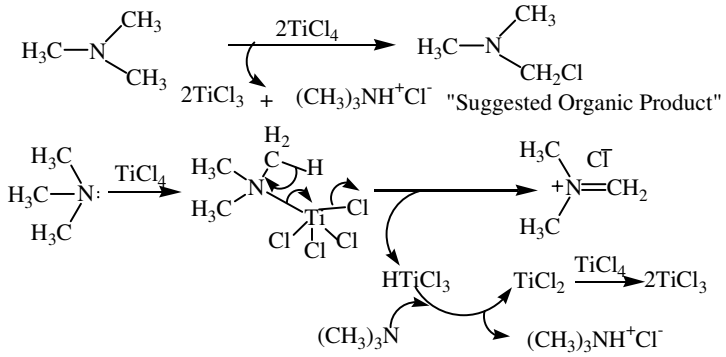
Scheme 23

Interesting oxidative coupling reactions have been observed using *N,N*-dialkylaniline derivatives.[23] The corresponding benzidine derivatives are the products. Again, this transformation can be rationalised considering the intermediacy of the corresponding aryltitanium species.[23] The aryltitanium species prepared in this way can be readily functionalized using certain electrophiles (Scheme 24).[23]



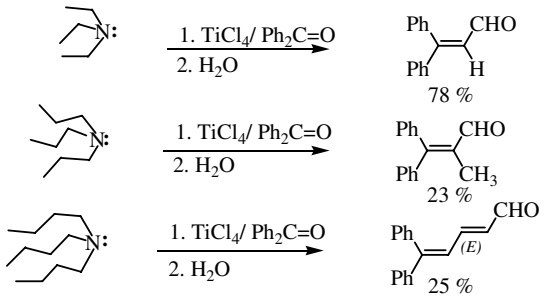
Scheme 24

In 1955, it was reported that the $TiCl_4$ oxidises tertiary amines. Presumably, the corresponding iminium ions would be the organic product and the reaction can be rationalised by the intermediates shown in Scheme 25.[24]



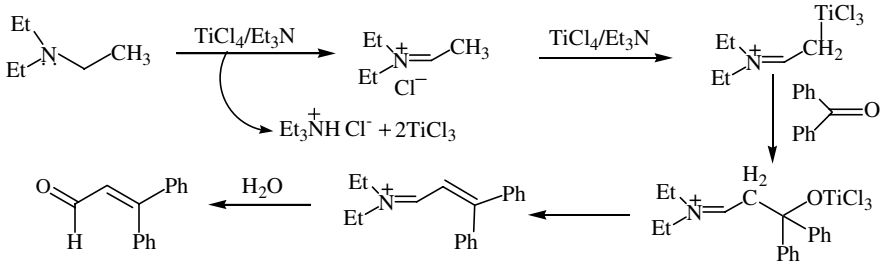
Scheme 25

Clearly, the tertiary amine can be oxidised by $TiCl_4$ in the absence of organic substrates containing acidic hydrogen. Accordingly, we have examined the reaction of organic substrates that could trap such iminium ion intermediates formed *in situ* from the amines. It was found that the reaction in the presence of benzophenone gives the corresponding unsaturated aldehydes via condensation with the iminium ions (Scheme 26).[25]



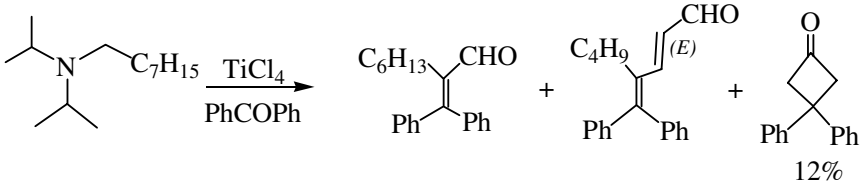
Scheme 26

The results can be rationalized considering the mechanism outlined in Scheme 27.[25]



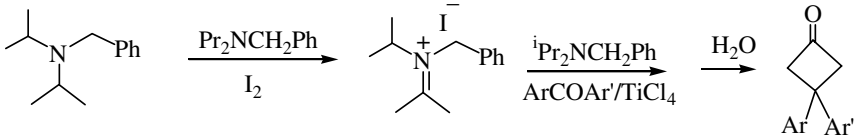
Scheme 27

Interestingly, the reaction of an *N,N*-diisopropylalkylamine leads to the formation of the corresponding cyclobutanone in low yields in addition to the aldehydic products Scheme 28.[26]



Scheme 28

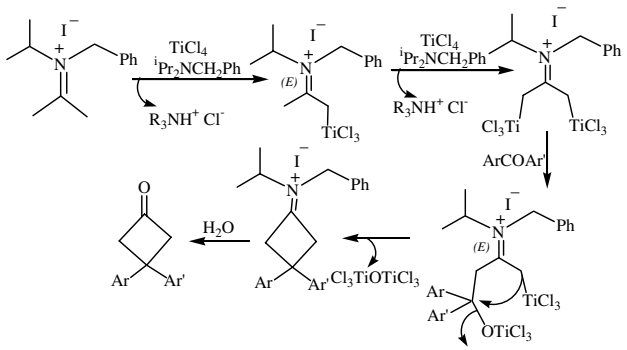
Fortunately, iminium ions prepared from *N,N*-diisopropylbenzylamine using I_2 react with $TiCl_4/NR_3$ reagent system to give the corresponding cyclobutanones in good yields (Scheme 29).[26]



Ar = Ar' = Ph	76%
Ar = Ar' = *p*-MePh	71%
Ar = Ar' = *p*-ClPh	86%
Ar = Ph, Ar' = *p*-MePh	73%
Ar = Ph. Ar' = α–Ferrocenyl	51%

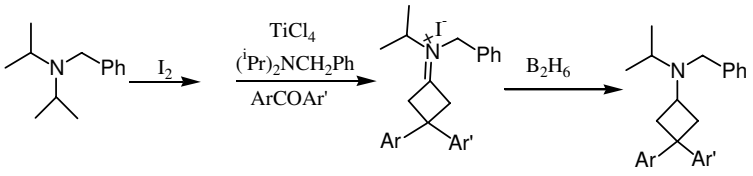
Scheme 29

The results can be rationalized by the mechanism and intermediates outlined in Scheme 30.[26]



Scheme 30

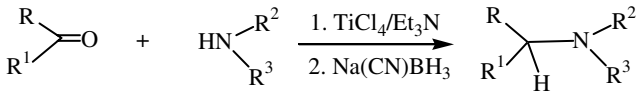
It has been reported certain diarylcyclobutylamine derivatives are biologically active.[27] Accordingly, we have examined the synthesis of the cyclobutylamine derivatives by carrying out the reduction of the iminium ion intermediates containing cyclobutyl moiety. It was observed that the corresponding cyclobutylamines are isolated in 60-70% yields under these conditions (Scheme 31).[28]

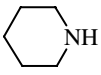
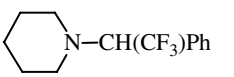


Ar = Ar' = Ph	73%
Ar = Ar' = *p*-OMePh	61%
Ar = Ar' = *p*-ClPh	79%
Ar = Ar' = *p*-FPh	76%
Ar = Ph. Ar' = *p*-MePh	51%

Scheme 31

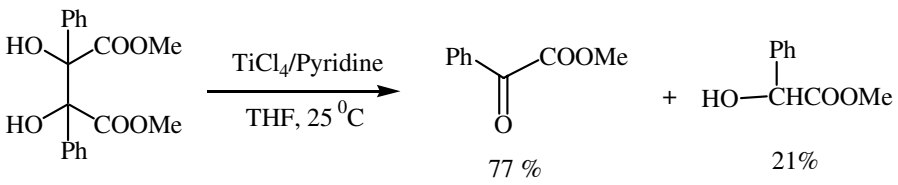
Reductive amination of carbonyl compounds with secondary amines is achieved via the reaction using $TiCl_4/NEt_3$ followed by $Na(CN)BH_3$ reduction (Scheme 32).[29]



Ketone	Amine	Product	Yield
Ph-CO-CH_3	$PhNH_2$	Ph$(CH_3)_3$CH-NHPh	94%
Ph-CO-$CH(CH_3)_2$	$(CH_3)_2NH$	Ph-CH(N$(CH_3)_2$)-$CH(CH_3)_2$	54%
Ph-CO-CF_3			60%

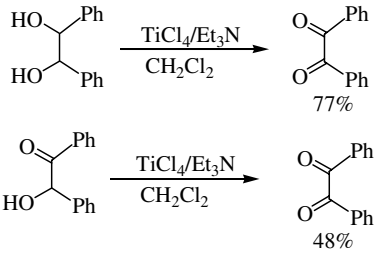
Scheme 32

The $TiCl_4$/amine system has been also used in the oxidation of certain alcohols. For example, the $TiCl_4$/pyridine reagent combination is useful for the oxidative cleavage of methyl diphenyltartrate to methyl phenylglyoxalate (Scheme 33).[30]



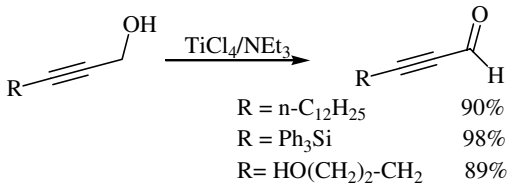
Scheme 33

The $TiCl_4/Et_3N$ combination oxidizes dihydrobenzoin and benzoin to benzil (Scheme 34).[31]



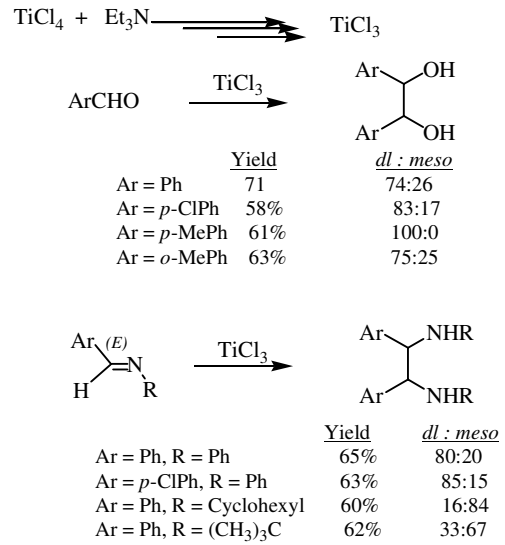
Scheme 34

Propargyl alcohols are oxidized to the corresponding aldehydes under similar conditions (Scheme 35).[32]



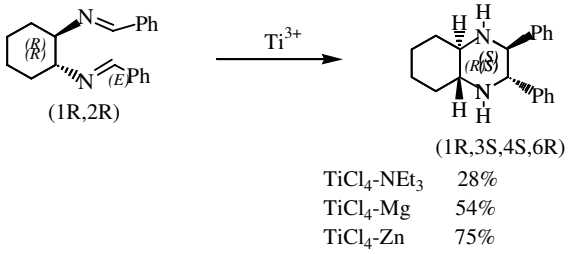
Scheme 35

As discussed previously (Scheme 25), the $TiCl_3$ species are produced in the reaction of $TiCl_4$ with NR_3. We have observed that the $TiCl_3$ produced *in situ* in this way can be readily exploited to achieve reductive coupling of aromatic aldehydes and aldimines (Scheme 36).[33]



Scheme 36

Also, the reaction of $TiCl_3$ prepared in this way is useful for the diastereoselective intramolecular reductive coupling reaction of aromatic aldimines containing chiral 1,2-cyclohexyldiamine moiety, albeit in low yields (Scheme 37).[34] However, the yields are better when the reaction is carried out with the $TiCl_3$ species prepared using the $TiCl_4$/Zn reagent system.



Scheme 37

In conclusion, the $TiCl_4/R_3N$ has been shown to be useful for the diastereoselective aldol and related reactions, oxidative coupling of phenylacetic acid derivatives, for the conversion of aryl alkyl ketimines and ketoximes to pyrroles, ketazines to dihydrodiazines, enamines to aromatic amines, *N,N*-dialkylanilines to the corresponding benzidine derivatives, trialkyl amines to unsaturated aldehydes, diarylcyclobutanones and diarylcyclobutylamine derivatives via metalation of iminium ion intermediates and for the reductive coupling of aromatic aldehydes, aldimines and intramolecular reductive coupling of certain chiral imine derivatives. Several of these transformations were previously carried out via multi-step syntheses. Since the transformations using the $TiCl_4/R_3N$ reagent system described here are carried out in essentially single pot operations starting from readily accessible organic substrates under

ambient conditions, these synthetic methods have considerable potential for further exploitation in organic synthesis.

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