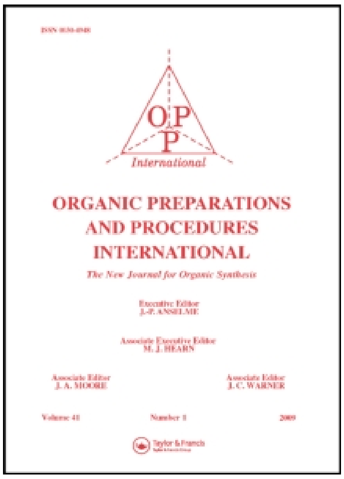

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ORGANIC REDUCTIVE COUPLING WITH TITANIUM AND VANADIUM CHLORIDES. A REVIEW

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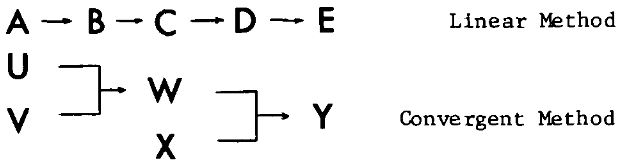
INTRODUCTION

Reduction[1,2] is perhaps one of the more common and synthetically useful reactions which has been extensively studied and reviewed. In recent years, transition metals or derivatives of these metals have become increasingly important in organic synthesis. Reagents derived from at least 20 of the 27 transition metals in the first, second and third transition series (Group IIB being excluded) have been found useful in different important organic synthetic reactions.[3-8] Studies on the utility of low valent titanium[9,10] and vanadium[11,12] and of zirconium complexes (hydrozirconation)[13] in organic reduction reactions, in particular, have been actively pursued. Reactions of these reagents with almost all common reducible organic functional groups have been investigated and have become very useful in functional group transformations.

Of the two major ways -- "linear" and "convergent" -- of assembling multiatomic molecules,[14] the linear method (involves mainly functional group transformation) is usually a long sequence of reactions, requires a large amount of a single starting material (A), and yields very little end product (E). The convergent method (usually involves a coupling reaction or dimerization), though requiring several starting materials (U, V, X), involves fewer reactions and produces a good yield of the final product (Y). The latter method is thus generally preferred.

Particularly useful reagents for the convergent sequence depicted in Scheme 1 are the chlorides[15] of titanium and vanadium which effect the



SCHEME 1

successful reductive coupling of organic halides, carbonyl compounds (hereafter called carbonyls) and alcohols. These reagents may be used under a wide variety of conditions,[8-12] and this review attempts to provide a clear comparison of these reagents in their respective reductive coupling reactions.

I. ORGANIC HALIDES

A. Reductive Coupling of Benzylic and Allylic Halides

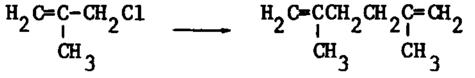
In 1973, the chloro-complex of vanadium(II), $VCl_2(py)_4$, was reported to be rapidly oxidized by active (benzylic) halides to V(III), with simultaneous production of the coupled products (R-R).[16] No products of the type R-H from hydrodehalogenation are observed. Benzotrichlorides such as $PhCCl_3$ behave similarly to benzyl chlorides, with retention of four chloro atoms during coupling (Eq. 3).

$$PhCY_2X \xrightarrow[rt]{VCl_2(py)_4} PCY_2CY_2Ph \qquad \begin{array}{lr} X = Br,\ Y = H,\ 78\text{-}88\% & (1) \\ X = Cl,\ Y = H,\ 91\% & (2) \\ X = Y = Cl,\ 80\% & (3) \end{array}$$

The $TiCl_3$-$LiAlH_4$ or $TiCl_4$-$LiAlH_4$ system[21] provides a superior method for reductive coupling of allylic and benzylic halides.[17-20] The intermediate is believed to involve a Ti(II) species, and a radical mechanism is suggested for the coupling reactions (Scheme 2).

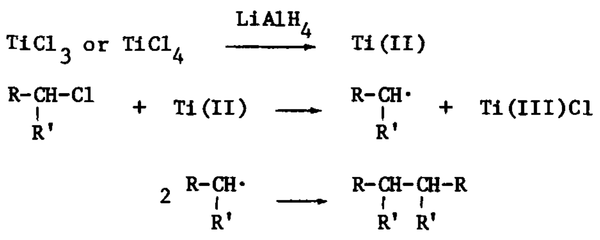
More recent studies have shown that the V(II) species[22] derived from VCl_3 and $LiAlH_4$ has an even higher reducing power than the Ti(II) reagent

$Ph_2CHCl \longrightarrow Ph_2CHCHPh_2$ 85% (4)



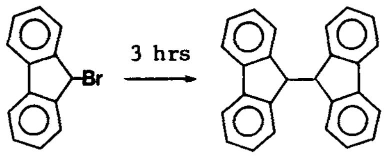
$H_2C{=}\underset{CH_3}{C}{-}CH_2Cl \longrightarrow H_2C{=}\underset{CH_3}{C}CH_2CH_2\underset{CH_3}{C}{=}CH_2$ 76% (5)

CONDITIONS : $TiCl_3$- or $TiCl_4$-$LiAlH_4$, THF, reflux, 10 hrs.

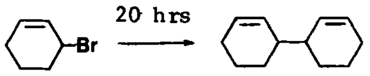


SCHEME 2

in the reductive coupling of benzylic and allylic halides. We believe this system is also experimentally the most convenient, since VCl_3 is stable in air, whereas $TiCl_3$ and $TiCl_4$ are sensitive to oxygen and moisture.



96% (6)



80% (7)

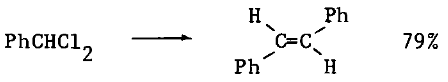
CONDITIONS : VCl_3-$LiAlH_4$, THF, reflux

B. Reductive Coupling of Aryl gem-Dihalides to Olefins

The Ti(II) species described above[21,23,24] also causes reductive coupling of aryl *gem*-dihalides to the corresponding aryl-substituted ethylenes[21] in high yields. Aliphatic *gem*-dihalides, however, fail to react under the same conditions.

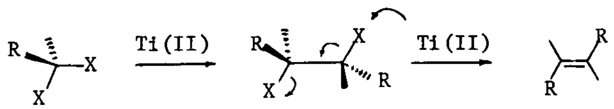
trans-Stilbene is the sole product obtained from benzylidene dichloride and thus a vicinal dihalide is presumed[21] to be an intermediate which subsequently gives the product through *trans*-elimination in the presence

$$Ph_2CCl_2 \longrightarrow Ph_2C{=}CPh_2 \quad 96\% \qquad (8)$$



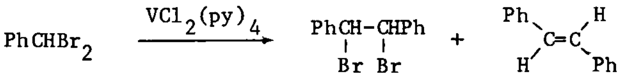
$$PhCHCl_2 \longrightarrow \overset{H}{\underset{Ph}{}}C{=}C\overset{Ph}{\underset{H}{}} \quad 79\% \qquad (9)$$

REAGENT : $TiCl_3$-$LiAlH_4$



of excess Ti(II).

Benzylidene dibromide is also known to be reductively coupled by $VCl_2(py)_4$.[16] However, it is less effective than $TiCl_3$- or $TiCl_4$-$LiAlH_4$ and gives a mixture of stilbene dibromide and trans-stilbene. The isolation of the vicinal dibromide supports the preceding argument that the stilbene stems from the intermediate vicinal dihalide.



$$PhCHBr_2 \xrightarrow{VCl_2(py)_4} \underset{Br\quad Br}{PhCH{-}CHPh} + \overset{Ph}{\underset{H}{}}C{=}C\overset{H}{\underset{Ph}{}} \qquad (10)$$

3 : 1

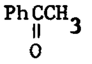
II. ALDEHYDES AND KETONES

A. Reductive Coupling of Carbonyls to Olefins

Even though the reduction of carbonyls to methylenes[25-27] is well documented, no general and direct method was available to achieve reductive coupling of carbonyls to olefins prior to the use of low-valent titanium.

The reducing system $TiCl_3$-3THF-Mg produces a low-valent titanium species which reductively couples carbonyls to olefins.[28] Surprisingly, an ester is reduced to give a mixture of benzil and an enedione (Eq. 13). Acids and amides, however, are unreactive.

This reducing system is, in general, only useful for aromatic carbonyls; moderate to good yields are obtained in most cases, and the olefinic



$$PhC(=O)CH_3 \longrightarrow Ph(CH_3)C{=}C(CH_3)Ph \quad (\underline{trans}:\underline{cis} = 4:3) \quad 71\% \qquad (11)$$

$$PhCHO \longrightarrow Ph(H)C{=}C(H)Ph \quad (\underline{trans}:\underline{cis} = 1:1) \quad 60\% \qquad (12)$$

$$PhCOOCH_3 \longrightarrow \underset{46\%}{PhCOCOPh} + \underset{20\%}{Ph(PhCO)C{=}C(PhCO)Ph} \qquad (13)$$

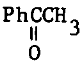
REAGENT : $TiCl_3$-3THF-Mg

product is a mixture of isomers if aldehydes or unsymmetrical ketones are used (Eq. 11 and 12). Since nitrogen reacts with $TiCl_3$-3THF-Mg to form a complex (Eq. 14), the reduction is only achieved if the reactions are conducted under an argon atmosphere.[28]

$$N_2 + TiCl_3\text{-}3THF\text{-}Mg \longrightarrow NTiMg_2Cl_2.THF \qquad (14)$$

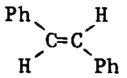
An experimentally preferable reducing system -- one using low-valent titanium compound from $TiCl_4$ and Zn -- has been reported.[29] However, the reduction is applicable only to aromatic carbonyls.

$$Ph_2C{=}O \xrightarrow[5\text{ hrs}]{THF} Ph_2C{=}CPh_2 \quad 97\% \qquad (15)$$



$$PhC(=O)CH_3 \xrightarrow[4\text{ hrs}]{dioxane} Ph(CH_3)C{=}C(CH_3)Ph \quad (\underline{trans}:\underline{cis} = 1:4) \quad 92\% \qquad (16)$$

$$PhCHO \xrightarrow[4\text{ hrs}]{dioxane}$$



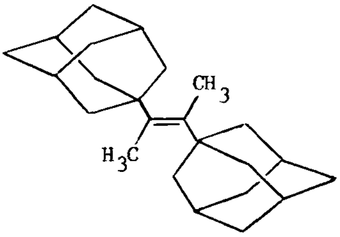
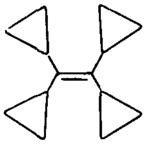
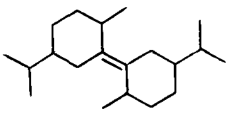
98% (17)

CONDITIONS : $TiCl_4$-Zn, reflux

Symmetrical tetrasubstituted olefins have also been prepared readily (Table 1) by the reductive coupling of the corresponding ketones (aromatic or aliphatic) in tetrahydrofuran or p-dioxane by a $TiCl_2$-py system.[30] The $TiCl_2$ is prepared in situ by treatment of $TiCl_4$ with Zn powder, a procedure similar to that of the system discussed previously. Though only moderate yields are obtained with most aliphatic ketones, some hindered olefins have been prepared readily by this method.

TABLE 1. Reductive Coupling of Ketones with $TiCl_2$-py:[30]

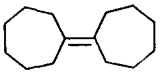
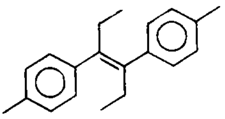
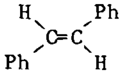
$$RR'C{=}O \longrightarrow RR'C{=}CRR'$$

RR'C=CRR'		RR'C=CRR'	
	15%		25%
$(C_2H_5)_2C=C(C_2H_5)_2$	62%		51%

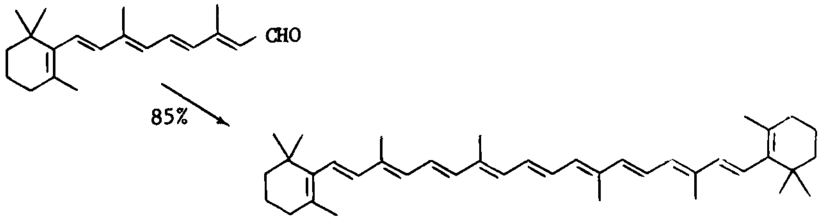
The $TiCl_3$-$LiAlH_4$ system[31] appears to work equally well for both saturated and conjugated carbonyls and is most useful for the synthesis of symmetrical olefins (Table 2).

TABLE 2. Reductive Coupling of Ketones with $TiCl_3$-$LiAlH_4$:[31]

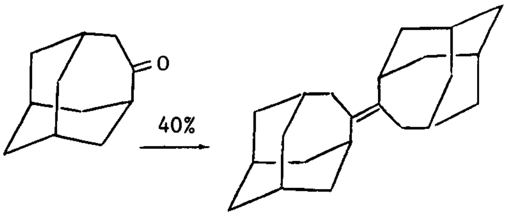
$$RR'C{=}O \longrightarrow RR'C{=}CRR'$$

RR'C=CRR'		RR'C=CRR'	
	95%		85%
 $H(Ph)C=C(Ph)H$	85%	$Ph_2C=CPh_2$	95%

Multiple unsaturation in the structure is compatible with this reagent; indeed β-carotene, a polyolefin of commercial importance, can be prepared in 85% yield from the coupling of retinal (Eq. 18).[31,32] The same reducing system has also been used successfully in the preparation of the novel, highly hindered olefin 4,4'-homoadamantylidene-homoadamantane[33] (Eq. 19). Though the yield is only 40%, it is interesting to note that only the



(18)

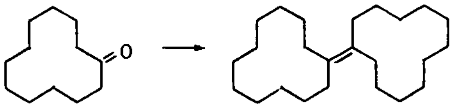


(19)

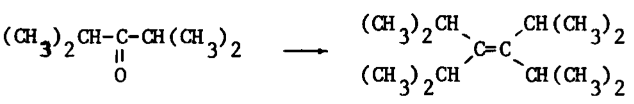
REAGENT : $TiCl_3$-$LiAlH_4$

trans-isomer is formed.

However, even with this more effective reagent, coupling of saturated aliphatic carbonyls to produce olefins can sometimes be erratic. The more difficult to prepare, but more active, Ti(0) metal powder produced from $TiCl_3$-K smoothly couples saturated ketones and aldehydes to the corresponding olefins in high yields.[34] Diisopropyl ketone gives tetraisopropylethylene in 40% yield (Eq. 21), and thus even hindered ketones can



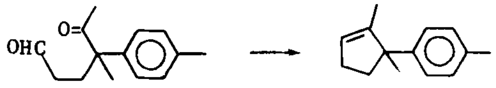
90% (20)



$$(CH_3)_2CH-\underset{\underset{O}{\|}}{C}-CH(CH_3)_2 \longrightarrow \begin{matrix}(CH_3)_2CH & & CH(CH_3)_2\\ & C=C & \\ (CH_3)_2CH & & CH(CH_3)_2\end{matrix}$$

40% (21)

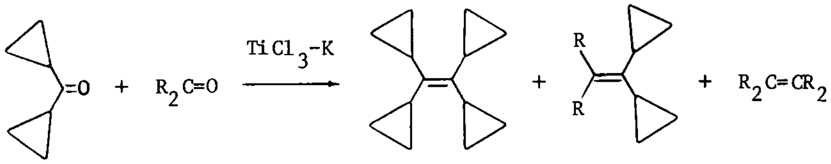
$CH_3(CH_2)_3CHO \longrightarrow CH_3(CH_2)_3CH=CH(CH_2)_3CH_3$ (trans:cis = 7:3) 77% (22)



55% (23)

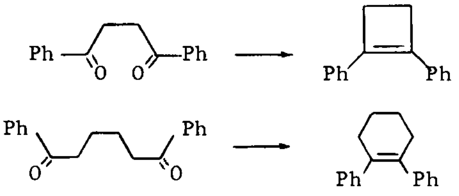
REAGENT : $TiCl_3$-K

be coupled in acceptable yield using this system. Aldehydes also couple in good yields (Eq. 22), but a mixture of isomers is formed. Intramolecular dicarbonyl coupling to form rings also proceeds in moderate yield (Eq. 23). The same reducing system has also been applied successfully in the preparation of heavily substituted cyclopropylethylenes via mixed carbonyl coupling[35] (Eq. 24 and 25).



R = $(CH_3)_2CH$- : 7.3% 17.4% 4.4% (24)
R = CH_3CH_2- : 3.1% 20.2% 7.8% (25)

The $TiCl_3$-$LiAlH_4$ system has also been found to effect intramolecular coupling of 1,4- and 1,5-diketones to the corresponding cycloalkenes in moderate yields.[36] The ease of preparation of these cycloalkenes thus increases the utility of the $TiCl_3$-$LiAlH_4$ reagent.



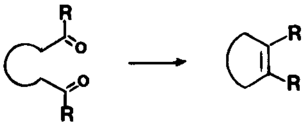
40-61% (26)

35% (27)

REAGENT : $TiCl_3$-$LiAlH_4$

Cycloalkenes of ring size 4-16 have also been prepared in good yields[37] (50-95%) by intramolecular coupling of dicarbonyl compounds induced by a reagent prepared from $TiCl_3$-Zn-Cu (Table 3). Though Ti(0) from $TiCl_3$-K (or from $TiCl_3$-Li) also effects the intramolecular coupling reaction, the $TiCl_3$-Zn-Cu system has been shown to be a safer and even more effective coupling reagent.[37] The cyclization reaction appears general for both aldehydes and ketones (Table 3), and the yields of medium-ring olefins

TABLE 3. Intramolecular Reductive Coupling of Dicarbonyl Compounds with $TiCl_3$-Zn-Cu :[37]



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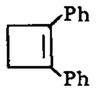
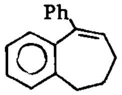
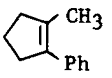
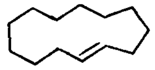
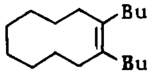
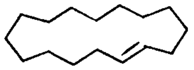
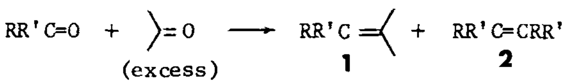
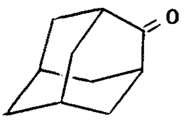
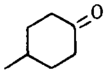
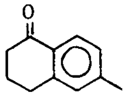
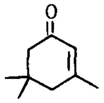
	87%		80%
	70%		52%
	75%		85%

(ring size 7-11) are higher than those of other known methods.[38] This Ti-induced dicarbonyl coupling also appears equally effective for all ring sizes. Its generality and high product yield have contributed to a significant improvement in medium- to large-ring carbocyclic synthesis.

It has also been reported that unsymmetrical olefins can be prepared in useful yields by Ti(0)-induced mixed-ketone coupling if one of the components is used in excess.[39] The Ti(0) species is produced from the reducing system $TiCl_3$-Li. This method is general for alkyl and conjugated carbonyls, though in most cases the self-coupled product is formed as a minor product (Table 4). Acetone is used as the component in excess, since it is inexpensive, and its self-coupled product, tetramethylethylene, is volatile and thus can be easily removed. Although the reaction is limited to the synthesis of olefins containing the isopropylidene group, the isopropylidene products can be isolated in synthetically useful yields. In view of the fact that the isopropylidene group is a common structural unit of many sesquiterpenes,[40] this one-step mixed coupling may prove of value. When one of the reactants is a diaryl ketone,[39] no excess of either

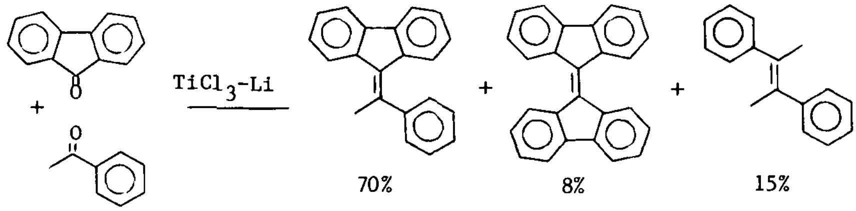
TABLE 4. Mixed-Ketone Reductive Coupling with TiCl$_3$-Li:[39]



RR'C=O	Yield 1	Yield 2
	63%	12%
	55%	22%
	85%	9%
	63%	0%

component is needed. Despite the 1:1 use of carbonyl compounds, the formation of self-coupled products remains minor, and the desired cross-coupled products can be isolated in high yields (Eq. 28 and 29).

$$\begin{array}{ccl} \mathrm{Ph_2C{=}O} & & \mathrm{Ph_2C{=}CH(CH_2)_4CH_3} \quad + \quad \mathrm{Ph_2C{=}CPh_2} \\ + & \xrightarrow{\mathrm{TiCl_3\text{-}Li}} & \quad \sim 84\% \qquad\qquad\qquad\quad \sim 9\% \\ \mathrm{CH_3(CH_2)_4CHO} & & + \quad \mathrm{CH_3(CH_2)_4CH{=}CH(CH_2)_4CH_3} \quad \sim 8\% \end{array} \qquad (28)$$

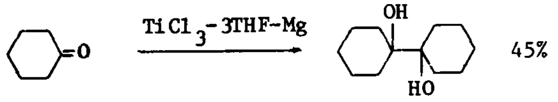


(29)

B. Reductive Coupling of Carbonyls to Pinacols

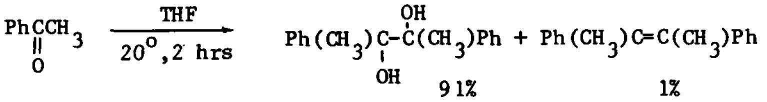
Pinacol formation from the reaction of carbonyl compounds with active metals[41] is well known; the same reaction may also be achieved photochemically.[42] However, the yields of products obtained from both of these reactions are usually low, especially with aliphatic ketones. Low-valent titanium derived from TiCl$_3$ and TiCl$_4$ has again been found to be superior in these reactions.

The $TiCl_3$-3THF-Mg system, which with aryl carbonyls gives the corresponding olefins (Eq. 11-13), gives only the pinacol with cyclohexanone.[28]

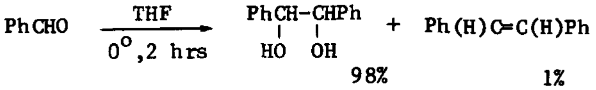


(30)

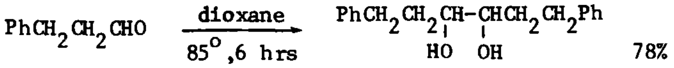
The $TiCl_4$-Zn system, which with aryl carbonyls gives olefins under refluxing conditions (Eq. 15-17), gives the corresponding pinacols under milder conditions.[29] With unconjugated carbonyls, pinacols are usually obtained as main products even at refluxing temperature (Eq. 33).



$$\underset{\underset{\mathrm{O}}{\|}}{\mathrm{PhC}}\mathrm{CH_3} \xrightarrow[20^{\circ},2\ \mathrm{hrs}]{\mathrm{THF}} \underset{91\%}{\mathrm{Ph(CH_3)}\underset{\mathrm{OH}}{\mathrm{C}}\text{-}\overset{\mathrm{OH}}{\mathrm{C}}\mathrm{(CH_3)Ph}} + \underset{1\%}{\mathrm{Ph(CH_3)C{=}C(CH_3)Ph}} \qquad (31)$$



$$\mathrm{PhCHO} \xrightarrow[0^{\circ},2\ \mathrm{hrs}]{\mathrm{THF}} \underset{98\%}{\mathrm{Ph}\underset{\mathrm{HO}}{\mathrm{CH}}\text{-}\underset{\mathrm{OH}}{\mathrm{CH}}\mathrm{Ph}} + \underset{1\%}{\mathrm{Ph(H)C{=}C(H)Ph}} \qquad (32)$$

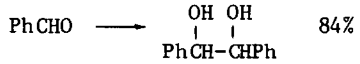


$$\mathrm{PhCH_2CH_2CHO} \xrightarrow[85^{\circ},6\ \mathrm{hrs}]{\mathrm{dioxane}} \mathrm{PhCH_2CH_2}\underset{\mathrm{HO}}{\mathrm{CH}}\text{-}\underset{\mathrm{OH}}{\mathrm{CH}}\mathrm{CH_2CH_2Ph} \quad 78\% \qquad (33)$$

REAGENT : $TiCl_4$-Zn

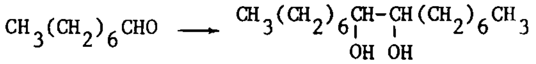
Recently, it has also been reported that ketones and aldehydes, either aromatic or aliphatic, are satisfactorily and consistently coupled in good yields to the corresponding pinacols by the Ti(II) species generated from titanium tetrachloride and amalgamated 70-80 mesh magnesium, $TiCl_4$-Mg(Hg).[43] Since pinacols instead of olefins are isolated in this reduction, the potential pinacolic rearrangement of these reductive coupling products greatly extends their synthetic utility.

The same reductive coupling method has been extended to the synthesis of unsymmetrical pinacols (Eq. 37 and 38), with acetone being used in excess.[43] The $TiCl_4$-Mg(Hg) system fails when a low molecular weight aldehyde is used instead of acetone as the excess component. However, in



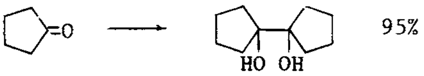
$$\mathrm{PhCHO} \longrightarrow \mathrm{PhCH(OH){-}CH(OH)Ph} \quad 84\%$$

(34)



$$\mathrm{CH_3(CH_2)_6CHO} \longrightarrow \mathrm{CH_3(CH_2)_6CH(OH){-}CH(OH)(CH_2)_6CH_3} \quad 80\%$$

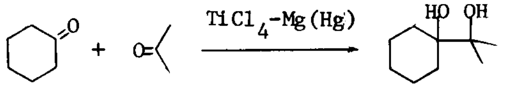
(35)



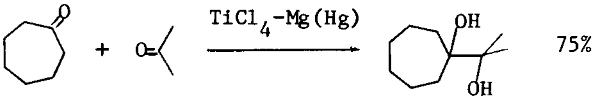
(36)

REAGENT : $TiCl_4$-Mg(Hg)

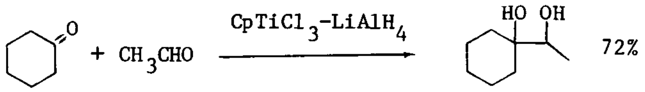
this case, the reaction can be effected by cyclopentadienyl-titanium trichloride and lithium aluminium hydride, $CpTiCl_3$-$LiAlH_4$[43] (Eq. 39).



(37)



(38)

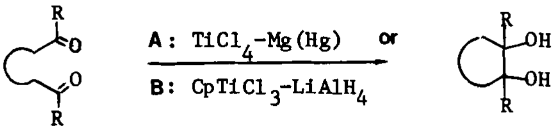


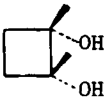
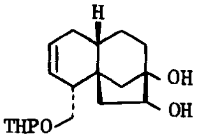
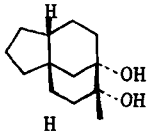
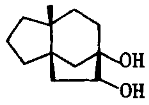
(39)

The reducing systems $TiCl_4$-Mg(Hg) and $CpTiCl_3$-$LiAlH_4$ also provides new reagents for inducing the intramolecular reductive coupling of dicarbonyl compounds to pinacols with four-, five- and six-membered ring structures in fair to good yields (Table 5).[43] Of special note is the synthesis of a four-membered ring in high yield, since classical methods give cyclobutanediols in only low yields.[44] Also noteworthy is that in many reactions, one isomer (usually the cis-isomer) predominates.

Good yields of pinacols are also obtained from the reductive coupling of carbonyls by the $TiCl_3$-hexamethylbenzene-Al-$AlCl_3$ system.[43] However, this reagent is inferior to $TiCl_4$-Mg(Hg) and $CpTiCl_3$-$LiAlH_4$ for preparative reactions, as the large amount of hexamethylbenzene involved compli-

TABLE 5. Intramolecular Reductive Coupling of Dicarbonyl Compounds with $TiCl_4$-Mg(Hg) or $CpTiCl_3$-$LiAlH_4$:[43]



Product	Reagent	Yield
	A	81%
 cis:trans = 8:3	B	55%
	A	43%
 cis:trans = 4:1	A	90%

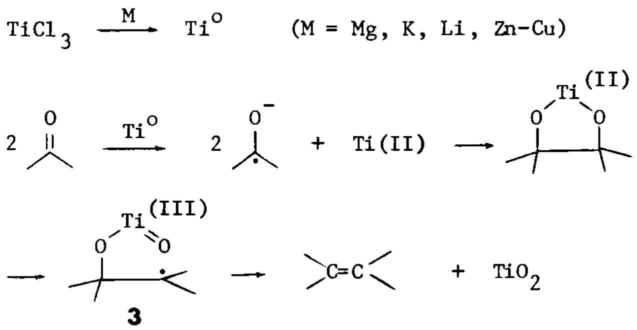
cates the isolation of the desired product.

C. Mechanism of the Reductive Coupling of Carbonyls

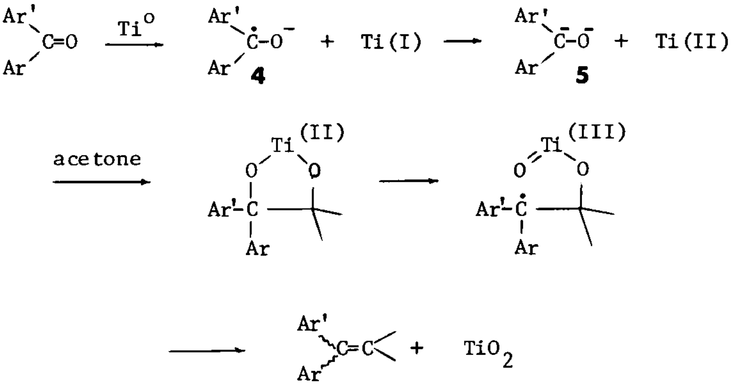
Although several mechanisms have been proposed[10b,29,31,33,36,38,42] to account for the reductive coupling of carbonyls to olefins and/or pinacols, all are rather similar and can be summarized as a family of plausible mechanisms if it is assumed that either Ti(0) or Ti(II) is the reactive species in these reactions.

The reducing systems $TiCl_3$-3THF-Mg, $TiCl_3$-K, $TiCl_3$-Li and $TiCl_3$-Zn-Cu are believed to produce a Ti(0) species which performs the overall reduction (Scheme 3), the product being mainly the olefin. Due to the formation of **3**, where free rotation of the carbon-carbon bond is possible, the coupling of aldehydes or unsymmetrical ketones will give a mixture of isomers.

For diaryl ketone-acetone mixed coupling, an alternative mechanistic path is possible. The route would involve the further reduction of the stabilized radical anion **4** to the dianion **5**[45] followed by nucleophilic



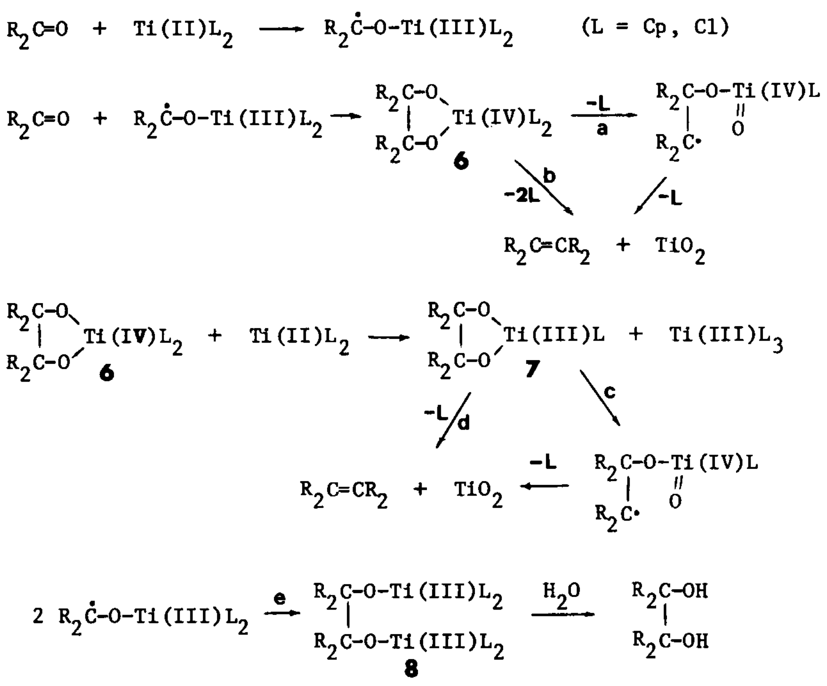
SCHEME 3



SCHEME 4

addition to acetone (Scheme 4).

On the other hand, the reducing systems $TiCl_4$-Zn, $TiCl_3$-$LiAlH_4$, $TiCl_4$-Mg(Hg), $CpTiCl_3$-$LiAlH_4$ and $TiCl_3$-HMB-Al-$AlCl_3$ are believed to produce a Ti(II) species which promotes a pinacol reduction of a carbonyl to an intermediate coupled complex (**6** or **7** or **8**). Further reduction of the cyclic titanium complexes (**6** or **7**) by concerted loss of TiO_2 (paths **b**,**d**) or by stepwise loss of the oxygens (paths **a**, **c**) then gives the olefin. Pinacols are believed to be produced through path **e** from **8** (Scheme 5).



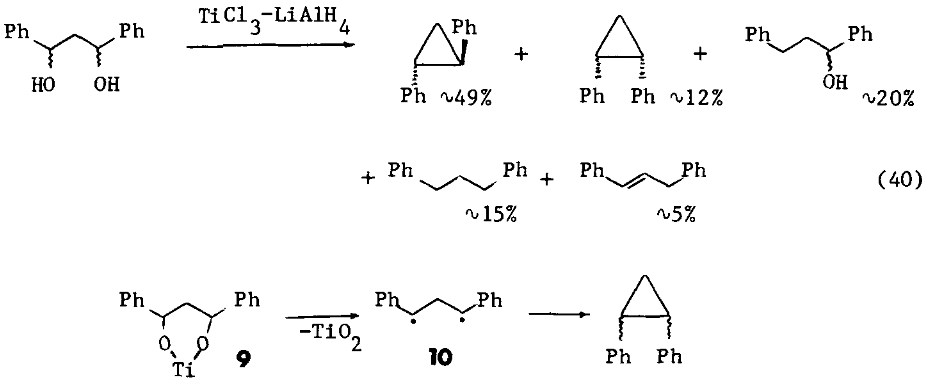
SCHEME 5

IV. ALCOHOLS

A. Reductive Coupling of 1,3-Diols

Since pinacol dianions are plausible intermediates in the reductive coupling of carbonyls to olefins by Ti(0) (Schemes 3 and 4), one would expect Ti(0) to reduce other 1,2-diols to olefins as well. This has in fact been proven to be the case.[43] The successful reduction of 1,2-diols to olefins by Ti(0) powder has also prompted investigation[46] into the intramolecular reductive coupling of 1,3-diols to cyclopropanes, since both olefins and cyclopropanes have identical double-bond equivalents. It has been found that reaction of 1,3-diols with $TiCl_3$-$LiAlH_4$ gives mainly the cyclopropanes.

A mechanism based on earlier work[47,48] has been proposed which assumes the titanium(II) species **9** to be the intermediate. Thermal decomposition



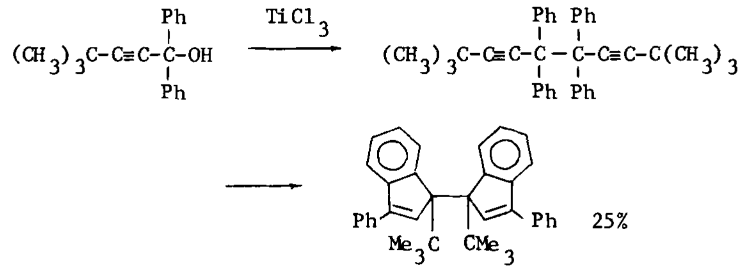
(40)

SCHEME 6

of **9** produces TiO_2 and the diradical **10** which closes to give the <u>cis</u>- and <u>trans</u>-cyclopropanes.[49]

B. Reductive Coupling of Acetylenic Carbinols

It is interesting to note that acetylenic diphenyl carbinols are reductively coupled by $TiCl_3$ to tetraphenyldialkyl- or tetraphenyldiarylethynyl ethanes,[50] some of which undergo rearrangement in solution at room temperature to give compounds with a di-indene structure (Eq. 41). Though the reaction may not be very useful synthetically, it is sufficiently interesting to warrant mention here.

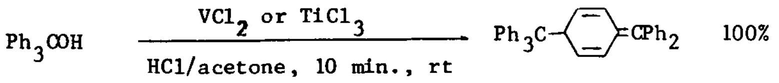


$$(CH_3)_3C\text{-}C{\equiv}C\text{-}C(Ph)_2\text{-}OH \xrightarrow{TiCl_3} (CH_3)_3C\text{-}C{\equiv}C\text{-}C(Ph)_2\text{-}C(Ph)_2\text{-}C{\equiv}C\text{-}C(CH_3)_3$$

(41)

C. Reductive Coupling of Benzylic and Allylic Alcohols

Coupling of benzylic and allylic alcohols to bibenzyls and 1,5-dienes is not very well-known when compared to the coupling of the corresponding organic halides. However, direct coupling of allylic alcohols, in particular, would be quite useful. The reaction -- which is practical because allylic alcohols are usually more readily available than the corresponding halides -- can generate a 1,5-diene structure, which is present in many naturally occurring compounds.[40]



(42)

$$Ph_2CHOH \xrightarrow[\text{HCl/acetone, rt}]{VCl_2} Ph_2CH\text{-}CHPh_2 \quad 31\text{-}89\% \qquad (43)$$

Triphenylcarbinol and diphenylcarbinol are reductively coupled[51] by VCl_2 or $TiCl_3$. The products are "hexaphenylethane"[52] and tetraphenylethane respectively (Eq. 42 and 43). Even though the reaction has not been studied for other alcohols, metal ion reduction of carbonium ions to free radicals[53] is postulated as a mechanistic pathway (Scheme 7).

$$Ph_2CHOH + H_3O^+ \longrightarrow Ph_2CH^+ + 2H_2O$$

$$Ph_2CH^+ + V(II) \text{ or } Ti(III) \longrightarrow Ph_2CH\cdot + V(III) \text{ or } Ti(IV)$$

$$2\ Ph_2CH\cdot \longrightarrow Ph_2CH\text{-}CHPh_2$$

SCHEME 7

Reductive coupling of alcohols to hydrocarbons has also been effected by the $TiCl_4$-K system[47] (preformation of the alkoxide is required). A valence change of II to III for titanium is presumed to be involved. However, the reduction is only moderately effective for benzylic and allylic alcohols. Attempts to produce coupled hydrocarbons from aliphatic (n-amyl, cyclohexyl) alcohols and phenols were also unsatisfactory.

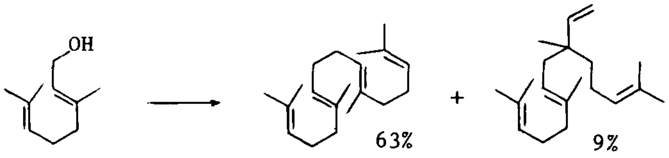
$$PhCH_2OH \longrightarrow PhCH_2\text{-}CH_2Ph \quad 51\% \qquad (44)$$

$$CH_2{=}CHCH_2OH \longrightarrow CH_2{=}CHCH_2\text{-}CH_2CH{=}CH_2 \quad 38\% \qquad (45)$$

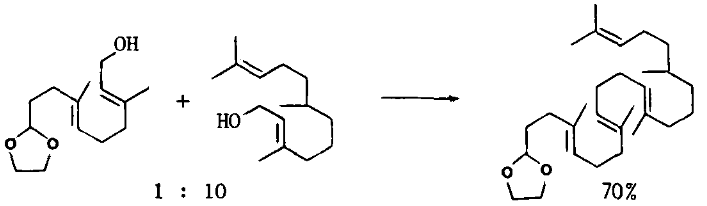
REAGENTS : 1) NaH; 2) $TiCl_4$-K

A system which has proved to be effective for a one-step synthesis of 1,5-dienes via reductive coupling of allylic alcohols involves the combined action of $TiCl_3$ and alkyl- or aryllithium.[48] Mixed coupling between different alcohols can also be achieved by this reagent; a good yield of the cross-coupled product results from an excess of one of the two allylic alcohols (Eq. 48).

$$PhCH_2OH \longrightarrow PhCH_2\text{-}CH_2Ph \quad 68\% \tag{46}$$



(47)



(48)

REAGENT : $TiCl_3$-RLi

Evidence from different studies[54] shows that the mechanism for the reductive coupling of these benzylic and allylic alcohols by $TiCl_4$-K and

$TiCl_4$-K : $ROH + NaH \longrightarrow RO^-Na^+ + H_2$

$$2RO^- + TiCl_4 \longrightarrow (RO)_2TiCl_2 \xrightarrow{K} (RO)_2Ti$$

$TiCl_3$-RLi : $TiCl_3 + 2ROH \xrightarrow{2R'Li} (RO)_2TiCl$

$$\xrightarrow{R'Li} (RO)_2TiR' \xrightarrow{-R'} (RO)_2Ti$$

$$Ti(OR)_2 \xrightarrow{a} R\cdot + TiO(OR)$$

$$\downarrow$$

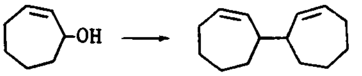
$$Ti(OR)_2 \xrightarrow{b} TiO_2 + 2R\cdot \longrightarrow R\text{-}R$$

SCHEME 8

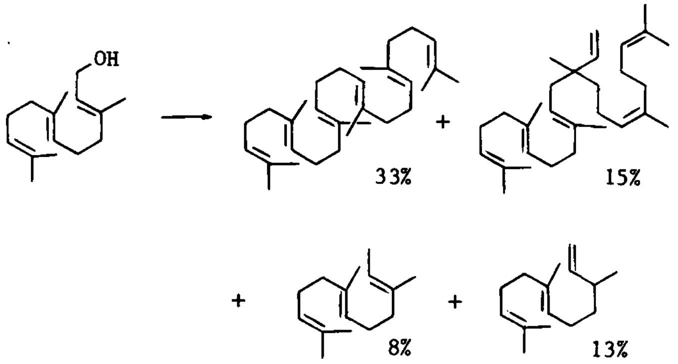
$TiCl_3$-RLi may follow the steps shown in Scheme 8. Though the concerted expulsion of carbon radicals (path b) is more favored, the stepwise expulsion (path a) is also very likely.

The $TiCl_3$-$LiAlH_4$ system is also effective and convenient in the alcohol reductive coupling reaction.[55] Again, mainly benzylic and allylic alcohols have been found to couple well. Steric bulk of the alcohol seems to have no deleterious effect, since 2-phenyl-2-propanol couples in 95% yield (Eq. 49). High unsaturation in the alcohol leads to some uncoupled reduced by-products (Eq. 51). The mechanism is probably similar to that involving free radical formation as proposed in Scheme 8.

$$PhC(OH)(CH_3)_2 \longrightarrow PhC(CH_3)_2C(CH_3)_2Ph \qquad 95\% \qquad (49)$$



87% (50)



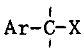
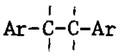
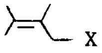
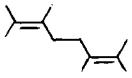
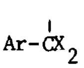
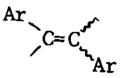
(51)

REAGENT : $TiCl_3$-$LiAlH_4$

IV. CONCLUSION

The versatility of VCl_2, $TiCl_3$ and $TiCl_4$ in effecting several reductive coupling reactions is quite obvious, since good product yields are obtained under different conditions and with different accompanying reagents. In the reductive coupling of organic halides (Table 6), VCl_3-$LiAlH_4$ is the system of choice due to its greater stability in air and to the ease of

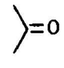
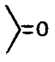
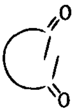
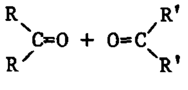
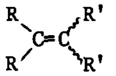
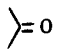
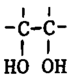
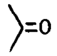
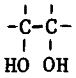
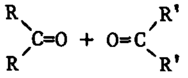
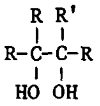
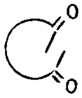
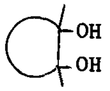
TABLE 6. Reductive Coupling of Organic Halides.[56,57]

Reactant	Product	Reagent	General Procedure	Reference
 $\text{Ar-}\overset{|}{\underset{|}{\text{C}}}\text{-X}$	 $\text{Ar-}\overset{|}{\underset{|}{\text{C}}}\text{-}\overset{|}{\underset{|}{\text{C}}}\text{-Ar}$	VCl_3-$LiAlH_4$	1	22
		$TiCl_3$-$LiAlH_4$	2	21
		$TiCl_4$-$LiAlH_4$	2	21
		$VCl_2(py)_4$	-	16
		VCl_3-$LiAlH_4$	1	22
		$TiCl_3$-$LiAlH_4$	2	21
		$TiCl_4$-$LiAlH_4$	2	21
 $\text{Ar-}\overset{|}{\text{C}}X_2$		$TiCl_3$-$LiAlH_4$	2	21
		$TiCl_4$-$LiAlH_4$	2	21
		$VCl_2(py)_4$	-	16

carrying out the reaction. The yields of products obtained are also excellent. $TiCl_3$ (solid powder) is slightly more sensitive to air and moisture than $TiCl_4$ (liquid), but this problem has practically been solved,[58] and $TiCl_3$-$LiAlH_4$ has become an increasingly important reagent.

Seven reagents from $TiCl_3$ and $TiCl_4$ are available for the reductive coupling of carbonyls to olefins (Table 7). $TiCl_3$-$LiAlH_4$ is by far the most widely used reagent in these reactions. However, it is only superior in the coupling of aliphatic carbonyls, giving good yields of the olefins, but it is not equally effective in the other reductions. $TiCl_3$-K gives the most consistent results, being equally successful in the coupling of aliphatic carbonyls as well as in the intramolecular and mixed coupling reactions. $TiCl_4$-Zn, a reagent easiest to prepare for the coupling of aromatic carbonyls, gives almost quantitative yields of the olefins. The safest and most effective reagent for intramolecular coupling of dicarbonyls is $TiCl_3$-Zn-Cu, which is capable of producing cycloalkenes of ring size 4-16. For mixed coupling of two carbonyl compounds, $TiCl_3$-Li is the

TABLE 7. Reductive Coupling of Aldehydes and Ketones.[56,57]

Reactant	Product	Reagent	General Procedure	Reference
 aryl		$TiCl_4$-Zn	3	29
		$TiCl_3$-$LiAlH_4$	8	31
		$TiCl_3$-3THF-Mg	9	28
 aliphatic		$TiCl_3$-$LiAlH_4$	8	31
		$TiCl_3$-K	10	34
		$TiCl_2$-py	11	30
		$TiCl_3$-Zn-Cu	4	37
		$TiCl_3$-K	10	34
		$TiCl_3$-$LiAlH_4$	12	36
 R,R'=alkyl,aryl		$TiCl_3$-Li	5	39
		$TiCl_3$-K	13	35
 aryl		$TiCl_4$-Zn	14	29
		$TiCl_4$-Mg(Hg)	6	43
 aliphatic		$TiCl_4$-Zn	14	29
		$TiCl_4$-Mg(Hg)	6	43
		$TiCl_3$-3THF-Mg	9	28
		$TiCl_3$-HMB-Al-$AlCl_3$	-	43
 R' = alkyl, H		$TiCl_4$-Mg(Hg)	6	43
		$CpTiCl_3$-$LiAlH_4$	15	43
		$TiCl_4$-Mg(Hg)	6	43
		$CpTiCl_3$-$LiAlH_4$	15	43

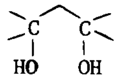
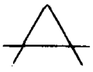
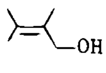
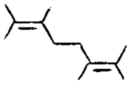
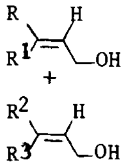
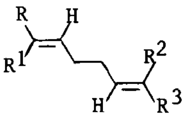
best choice, giving good yields of the products and, in some cases, without requiring an excess of one component.

The two best reagents for coupling of carbonyls to pinacols are

$TiCl_4$-Zn and $TiCl_4$-Mg(Hg) (Table 7). Both of them give the desired products in high yields under mild conditions. Experimentally, the $TiCl_4$-Zn method might be slightly simpler, since the preparation of the amalgam is required in the other case. However, $TiCl_4$-Mg(Hg) is the main reagent for intramolecular and mixed coupling of carbonyls to the respective pinacols. $CpTiCl_3$-$LiAlH_4$ acts as a good supplemental reagent to $TiCl_4$-Mg(Hg) and is a better reagent when, in particular, low molecular weight aldehydes are used.

In the reductive coupling of alcohols (Table 8), $TiCl_3$-$LiAlH_4$ is again the most generally employed reagent. It couples 1,3-diols to cyclopropanes and is very successful in the coupling of benzylic and allylic alcohols. $TiCl_3$-RLi, in most cases, is as effective as $TiCl_3$-$LiAlH_4$, and induces

TABLE 8. Reductive Coupling of Alcohols.[56,57]

Reactant	Product	Reagent	General Procedure	Reference
		$TiCl_3$-$LiAlH_4$	16	46
$-\overset{\vert}{\underset{\vert}{C}}-OH$ benzylic	$-\overset{\vert}{\underset{\vert}{C}}-\overset{\vert}{\underset{\vert}{C}}-$	$TiCl_3$-$LiAlH_4$ $TiCl_3$-RLi $TiCl_4$-K VCl_2/HCl $TiCl_3$/HCl	17 7 18 - -	55 48 47 51 51
		$TiCl_3$-$LiAlH_4$ $TiCl_3$-RLi $TiCl_4$-K	17 7 18	55 48 47
		$TiCl_3$-RLi	7	48

mixed coupling of allylic alcohols to give good yields of 1,5-dienes. Coupling involving $TiCl_4$-K requires more drastic conditions and usually gives lower yield of the desired product.

A series of carbon-carbon bond formation reactions promoted by $TiCl_4$ have also been reviewed.[59] Moreover, carboxylic acids have been found to undergo $TiCl_3$-RLi-induced coupling to pinacols,[60] and tropylium salts are coupled cleanly in high yields with aqueous solutions of V(II) or Ti(III) chlorides.[61]

Thus, the reagents derived from the chlorides of vanadium and titanium have undoubtedly become very useful synthetic tools in organic chemistry.

V. GENERAL PROCEDURES[57]

General Procedure 1.[22] $LiAlH_4$ (1 mole) was added slowly to a suspension of VCl_3(3 moles) in dry THF. After 5 min, the halide (1 mole) was added as a THF solution and the mixture refluxed for 3-20 hrs. The reaction mixture was then quenched with water and extracted with benzene [Yield : 82-96%(benzylic halides); ∿80%(allylic halides)].

General Procedure 2.[21] $LiAlH_4$ (1 mole) was added slowly to a stirred slurry of $TiCl_3$ or $TiCl_4$ (2 moles) in THF under nitrogen. The resultant mixture was stirred for 30 min, and a solution of the halide (1 mole) in THF was then added dropwise with stirring. The mixture was refluxed for 10 hrs, decomposed with aqueous NH_4Cl solution, and extracted with ether [Yield : 36-85%(benzylic halides); ∿75%(allylic halides); 79-96%(aryl gem-dihalides)].

General Procedure 3.[29] A suspension of Zn powder (3 moles) in THF was added slowly to a stirred mixture of the carbonyl (1 mole) and $TiCl_4$ (1.5 moles) in THF at refluxing temperature. After 4-5 hrs, the reaction mixture was hydrolyzed with 10% NaOH solution and the product obtained by usual work-up [Yield : 92-98%].

General Procedure 4.[37] The Zn-Cu couple was prepared by adding Zn dust (150 mmol) to deoxygenated H_2O (40 ml), purging the slurry with N_2 for 15 min, and then adding $CuSO_4$ (4.7 mmol). The black slurry was filtered under N_2, washed with deoxygenated H_2O, acetone, and ether and then dried in vacuo. $TiCl_3$ (6.68 mmol) and Zn-Cu couple (15.4 mmol) were placed in a flask via a Schlenk tube under argon. Anhydrous DME (20 ml) was added, and the mixture was refluxed for 1 hr. The dicarbonyl (0.61 mmol) in DME (40 ml) was added to the refluxing slurry via a motor-driven syringe pump over 30 hrs. After an additional 14 hrs reflux, the mixture was cooled to room temperature, passed through a small Florisil pad, concentrated, and chromatographed on alumina [Yield : 50-95%].

General Procedure 5.[39] $TiCl_3$ (8 moles) was slurried in dry DME under argon, and Li pieces (28 moles) were added. After 1 hr reflux, the mixture was cooled, and a solution of acetone (4 moles) and the other carbonyl (1 mole) in DME was added. The mixture was then stirred for 2 hrs at room temperature and then refluxed for 20 hrs. The mixture was cooled to room temperature, and petroleum ether was added slowly. The organic layer was then decanted from the black residue and purified by the usual work-up [Yield : 50-94%].

General Procedure 6.[43] A solution of $HgCl_2$ (0.08 mole) in dry THF was added to 70-80 mesh Mg (3 moles) and stirred at room temperature under argon for 15 min. The thick amalgam was taken up in THF, cooled to -10^o, and treated dropwise with $TiCl_4$ (1.5 moles). A solution of the carbonyl (1 mole) in THF was added, followed by stirring at 0^o for 0.5-13 hrs. The mixture was quenched with saturated K_2CO_3 solution, diluted with ether, filtered through Celite, and the product isolated after usual work-up [Yield : $\sim$85%(aryl ketones); 80-95%(aliphatic ketones); 65-76%(mixed coupling); 32-90%(intramolecular coupling)].

General Procedure 7.[48] RLi (3 moles; greater proportions of this reagent substantially lower the yield) and $TiCl_3$ (1 mole) were mixed under nitrogen at -78° in glyme. After a few min, the alcohol (2 moles) was added while maintaining the temperature at -78°. The mixture was then allowed to warm to room temperature and subsequently refluxed for 15 min. The product was then extracted into ether [Yield : ∿70% in all reductions].

TABLE 9. General Procedures 8-18.[57]

General Procedure	Ratio[a]	Solvent	Reaction Time	Reaction Temperature	Hydrolyzing Agent	Extraction Solvent	Yield	Reference
8	1:2.5:1	THF	12h	65°	-[b]	-[b]	85-95%[c] 80-95%[d]	31
9	2:1[e]:2.5	THF	1.5h	40°	dil. HCl	ether	67-80%[f] ∿45%[g]	28
10	(1:4:12)[h]	THF	12-24h	65°	EtOH	-[b]	40-91%[d] ∿55%[i]	34
11	(1:1:2)[j]	THF or dioxane	20h-3d	$65-100^{\circ}$	10% $CaCO_3$ solution	ether or pentane	15-80%	30
12	(1:5:2)[h]	THF	24h-5d	65°	H_2O	ether or pet ether	35-61%	36
13	(1:6:18)[h]	THF	12h	65°	EtOH	hexane	∿30%[k]	35
14	1:1.5:3	THF or dioxane	2-6h	$0-100^{\circ}$	10% NaOH solution	-[b]	91-98%[c] ∿80%[d]	29
15	1:6:4.5[h]	THF	2.5h	rt	sat. K_2CO_3 solution	ether	∿70%[d] 49-55%[i]	43
16	(1:13:4)[h]	THF or glyme	2-8d	$65-85^{\circ}$	MeOH	pet ether	∿40%[k]	46
17	1:3:1	glyme	16h	85°	dil. HCl	ether	68-95%[l] 48-87%[m]	55
18	2:1:2	benzene	20h	$(80^{\circ})^{n}$	$EtOH/H_2O$	ether	∿50%[l] ∿40%[m]	47

NOTES FOR TABLE 9

(a) Ratio of reactant : metal halide : reducing agent; (b) No specific hydrolyzing agent and/or extraction solvent were reported; (c) For aryl ketones; (d) For aliphatic ketones; (e) $TiCl_3.3THF$ was prepared by stirring $TiCl_3$(0.13 mole) in THF(250 ml) for 24h under argon. The blue complex was filtered and dried under vacuum; (f) Formation of olefins; (g) Formation of pinacols; (h) The mixture of metal halide and reducing agent was heated at reflux for 15-60 min before the reactant was added; (i) For intramolecular coupling; (j) After the addition of Zn to $TiCl_4$, pyridine was added to form the $TiCl_2$.py complex; (k) A mixture of products; (l) For benzylic alcohols; (m) For aliphatic alcohols; (n) After refluxing for 20h, the solvent was removed by distillation, and the residue was heated at 100-140° until a light gray color was observed.

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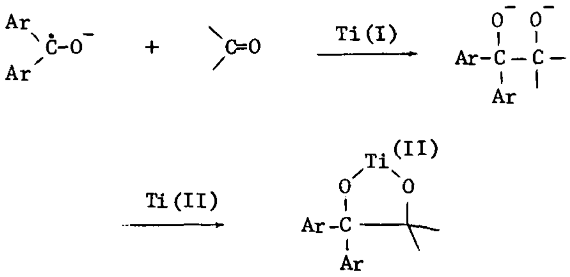

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