Selective reactions of organotitanium reagents
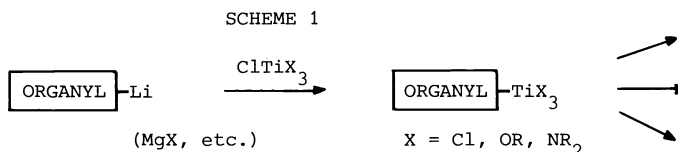
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Abstract - Classical "carbanions" can be titanated to form reagents which
behave chemo-, regio- and stereoselectively in reactions with alkyl
halides and carbonyl compounds. The nature of the ligands at Ti(IV) deter-
mines the electronic and steric properties of the reagents. This is useful
in predicting the stereochemical outcome in reactions with alkoxy carbonyl
compounds. $TiCl_4$ can also be used for stereoselective C-C bond formation.

1 INTRODUCTION

Alkyllithium and magnesium reagents as well as a host of deprotonated CH-acidic compounds
(esters, nitriles, sulfones, etc.) form an integral part of carbanion chemistry. Countless
examples of addition reactions of carbonyl compounds (Grignard- and aldol-type), Michael
additions and substitution processes involving alkyl halides are known. Nevertheless, a num-
ber of problems persist. The reagents are generally very basic and reactive, which means that
only a limited number of additional functional groups are tolerated. Furthermore, stereo-
selectivity is often low. Based on early experience with simple methyltitanium reagents
(ref. 1-4), we postulated that titanation of classical "carbanions" may increase chemo-,
regio- and stereoselectivity in reactions with carbonyl compounds, alkyl halides and other
electrophiles (ref. 5-8).

<div align="center">SCHEME 1</div>

$$\boxed{ORGANYL}\!-\!Li \xrightarrow{ClTiX_3} \boxed{ORGANYL}\!-\!TiX_3$$

(MgX, etc.)   X = Cl, OR, NR_2

The proper choice of the ligands X allows two parameters to be controlled in a predictable
way (ref. 5-8): 1) The electronic property of titanium, e.g., Lewis acidity, and 2) the
steric environment around the metal. For example, compounds $RTiCl_3$ are highly Lewis acidic,
a property which is essential in chelation-controlled additions to chiral alkoxy carbonyl
compounds or in alkylation reactions of S_N1-active alkyl halides. Lewis acidity decreases
drastically in going to $RTi(OR')_3$, $RTi(NR_2)_3$ or $RTiX_2Cp$, which means that they are ideal re-
agents for non-chelation-controlled additions. In all cases basicity and reactivity are con-
siderably lower than those of RMgX, RLi and resonance-stabilized "carbanions".

Early examples of chemoselectivity pertain to the methylation of tertiary alkylhalides having
additional functionality (ref. 2) and to the $TiCl_4$ mediated α-tert-alkylation of enol silanes
(which sometimes involve Cl_3Ti-enolates) (ref. 6,9). They set the stage for testing organo-
titanium reagents on a broad scale (ref. 4).
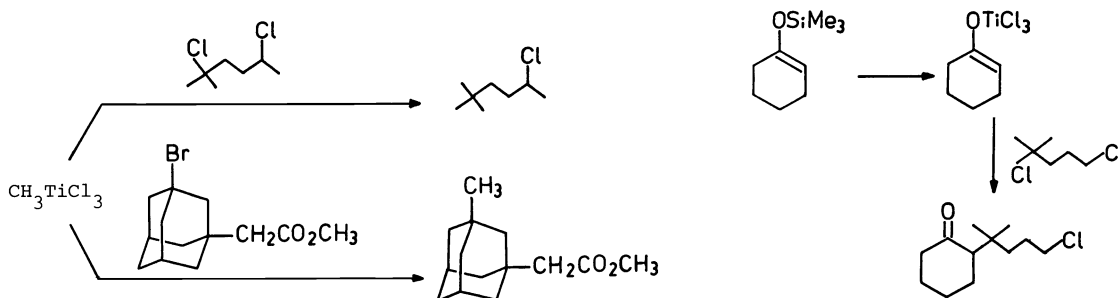
Since several reviews of these and other aspects (including limitations) of organotitanium
reagents have appeared (ref. 7,8,10), this lecture concentrates on new developments regar-
ding the above principles. Included are also novel applications of $TiCl_4$ and $SnCl_4$ mediated
C-C bond forming reactions (ref. 11).

2 CHEMOSELECTIVITY

The parent compound $CH_3Ti(OCHMe_2)_3$ **2** is accessible in essentially quantitative yield from CH_3Li and $ClTi(OCHMe_2)_3$ **1**. It is a distillable compound, which shows some degree of aggregation in benzene, depending upon concentration and temperature (ref. 7-8).
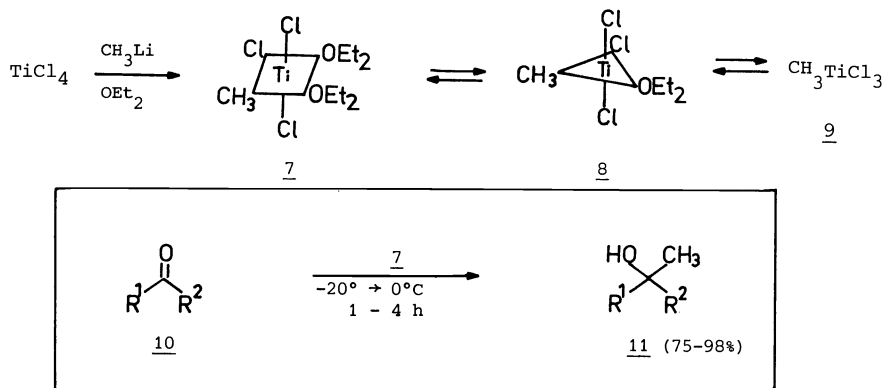
$$ClTi(OCHMe_2)_3 \xrightarrow{CH_3Li} CH_3Ti(OCHMe_2)_3 \quad (>95\%)$$

$$\underline{1} \qquad\qquad\qquad \underline{2}$$
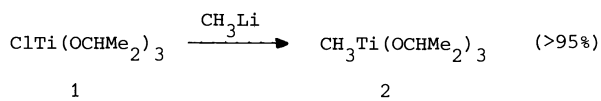
2 adds smoothly to a variety of aldehydes (-78°C → 22°C/1 - 5 h), including those which have additional sensitive functionality (ref. 3-8,10). Reactions with ketones are considerably slower; in fact, addition is sometimes too sluggish to be of synthetic value (ref. 7-8). However, this property is desirable in case of chemoselective additions to keto-aldehydes, e.g., **3a** → **4a** (ref. 12). Such aldehyde-selectivity can also be induced in case of other "aggressive" carbanions such as lithiated sulfones. Titanation to produce **5** (O-titanated form arbitrarily assumed) results in a well-behaved species (ref. 12). The lithium precursor reacts chemorandomly.

Titanium ate complexes, first introduced in 1981 (ref. 13), are also selective. For example, **6** reacts with **3** solely at the aldehyde function (ref. 12).

3   **4**

2:	a) R = CH_3	(80%)
5:	b) R = CH_2SO_2Ph	(91%)
6:	c) R = $CH_2CH=CH_2$	(85%)
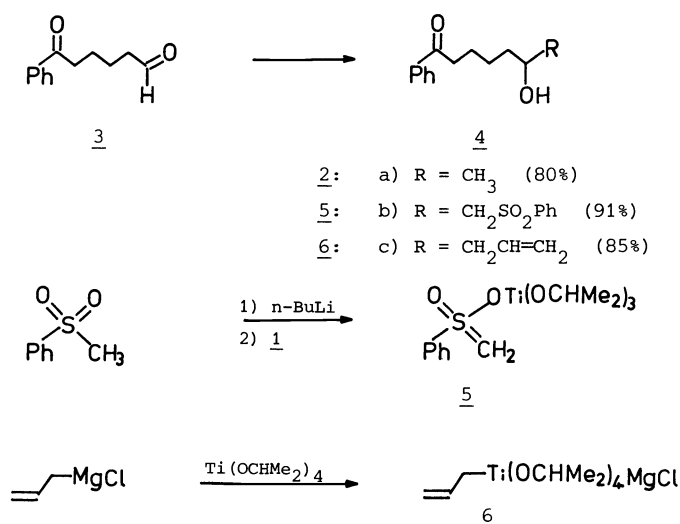
Inspite of the usefulness of the isopropoxy ligand system in controlling chemoselectivity, the parent compound **2** (which is much less reactive than **5**, **6** or other titanated "resonance-stabilized carbanions") is not a good reagent in case of ketones having additional functionality. Ketone addition is so slow that the other functionalities begin to compete in undesired reactions. For this reason we have recently tested the more reactive CH_3TiCl_3. Previously, we had shown that it is completely aldehyde-selective in the presence of ketones; in most cases it was prepared from $(CH_3)_2Zn$ and $TiCl_4$ in CH_2Cl_2 (ref. 3). A new and highly useful procedure involves the reagent system $CH_3Li/TiCl_4$/ether or $CH_3MgCl/TiCl_4$/ether (ref. 14). Currently, it is unclear whether **7**, **8** or **9** is the reacting species (ref. 15). In any case, it not only reacts completely aldehyde-selectively (e.g., with **3**), but also adds

7   **8**   **9**

10   **11** (75-98%)

smoothly to <u>ketones</u> (-20°C → 0°C, 3 - 4 h). Enolizable ketones (e.g., <u>18</u>) as well as those which contain additional functionality react chemoselectively (ref. 14).
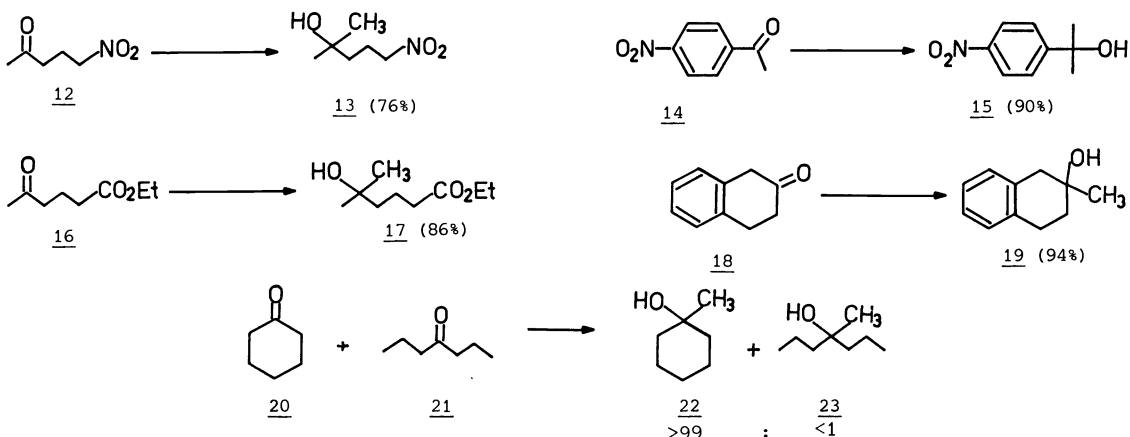
Many of the above reactions fail to proceed smoothly with CH_3Li, CH_3MgX or $CH_3Ti(OCHMe_2)_3$, e.g., in case of <u>12</u> or <u>14</u>; CH_3MgX adds to <u>14</u> solely at the aromatic ring (ref. 16). In summary, $CH_3Li/TiCl_4$/ether (or the Mg-analog) is a readily available, non-basic and chemoselective reagent. In relevant cases it is also stereoselective (see Section 4).

3 KINETICS

In competition experiments involving $CH_3Ti(OCHMe_2)_3$ (one part), an aldehyde (one part) and a ketone (one part), only the aldehyde adduct was observed (ref. 3-8,10). However, this does not provide any information as to the actual relative rate. Precise kinetic studies at <u>room temperature</u> using various aldehyde/ketone pairs show that the k_{rel} values vary as follows (ref. 17):

$$k_{rel} = k_{aldehyde}/k_{ketone} \cong 220 - 700$$

For example:

$$k_{heptanal}/k_{3-heptanone} \cong 223 \quad \text{and} \quad k_{benzaldehyde}/k_{acetophenone} \cong 550.$$

At lower temperatures the k_{rel} values are likely to be considerably larger. In case of CH_3Li, CH_3MgX and even $CH_3Zr(OR)_3$ (ref. 7,8,10,18), discrimination is much lower ($k_{rel} \cong 1$ for the Li and Mg reagents and $\sim 12 - 30$ for the Zr analog).

<u>Why are titanium reagents so selective?</u> There are probably two factors involved: steric and electronic (ref. 7-8). $CH_3Ti(OCHMe_2)_3$ is bulkier than CH_3Li or CH_3MgX in addition to the fact that the Ti-O bond is shorter (1.75 - 1.9 Å) than the C-Li, C-Mg and C-Zr (~ 2.1 Å) analogs. Thus, in the transition state of carbonyl addition, the latter cases are not as conjested (ref. 19). Electronically, the C-Ti bond is not as polar as the C-Mg or C-Li entities, again accounting for lower rate of addition and greater selectivity.

We have also determined the rate constants of the addition of $CH_3Ti(OCHMe_2)_3$ <u>2</u> to heptanal <u>24</u> in CH_2Cl_2 and THF in the temperature range -20°C to -65°C. In all cases good adherence to second-order rate law was observed (ref. 17).
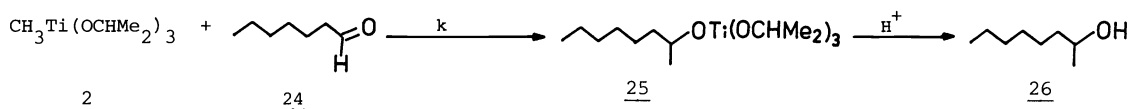
The activation parameters turned out to be as follows:

Solvent	$\Delta G^{\ddagger}$ (kcal/mol)	$\Delta H^{\ddagger}$ (kcal/mol)	$\Delta S^{\ddagger}$ (cal·K^{-1}·mol^{-1})
CH_2Cl_2	16.9 ± 1.3	12.4 ± 1.2	-19.3 ± 4
THF	16.5 ± 1.3	20.5 ± 1.2	17.2 ± 4

The rate of addition is essentially solvent-independent, but THF participation is nevertheless involved. Whereas $\Delta S^{\ddagger}$ in case of CH_2Cl_2 is negative as expected for this bimolecular reaction, it is <u>positive</u> when THF is the solvent. Although a final decision regarding the ex-

planation must await further experimentation, the following scheme is in line with the data. Solvated reagent as shown in <u>27</u> (two THF molecules arbitrarily assumed) must first kick off the THF to form free <u>2</u> before adding to heptanal. This simplified scheme neglects dimeric or aggregated forms of <u>2</u>, which are in rapid equilibrium with the monomeric form as shown by low temperature ^{13}C-NMR experiments (ref. 7,8,17).

$$
\begin{array}{c}
\text{THF} \\
\downarrow \\
CH_3Ti(OCHMe_2)_3 \\
\uparrow \\
\text{THF} \\
\underline{27}
\end{array}
\quad \underset{\xleftarrow{\hspace{1cm}}}{\xrightarrow{\text{THF}}} \quad
CH_3Ti(OCHMe_2)_3 \;+\; 2\ \text{THF} \\
\qquad\qquad\qquad\qquad\qquad \underline{2}
$$

$$\underline{2} \;+\; \underline{24} \longrightarrow \underline{25}$$

$$\underline{27} \;+\; \underline{24} \longrightarrow \underline{25} \;+\; 2\ \text{THF}$$
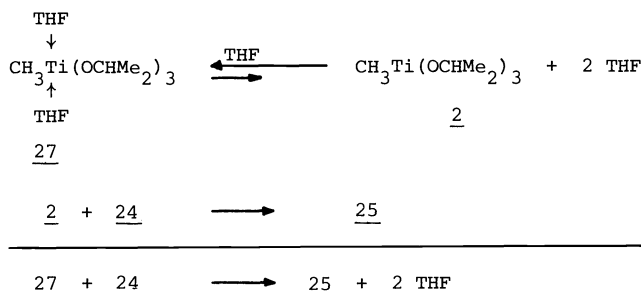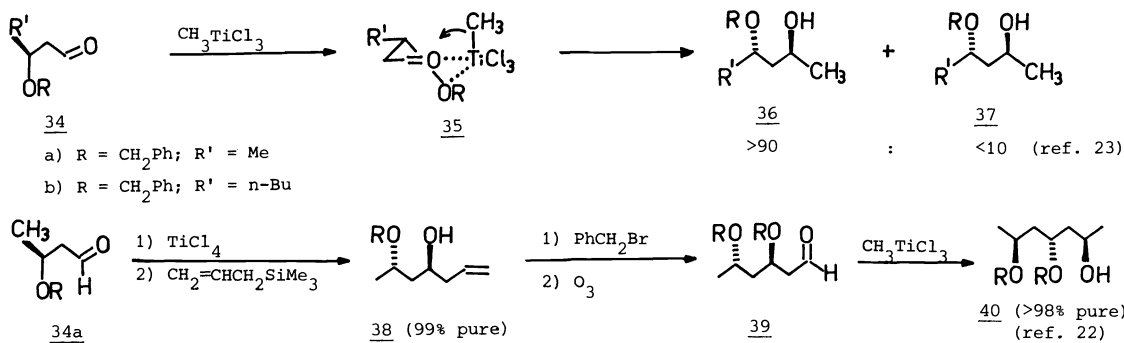
4   STEREOSELECTIVITY

4.1   The Cram/anti-Cram problem

Early studies (ref. 3) regarding Cram-selectivity of the addition of $CH_3Ti(OCHMe_2)_3$ and CH_3TiCl_3 (from $(CH_3)_2Zn/TiCl_4$ in CH_2Cl_2) to 2-phenylpropanal <u>28</u> have since been extended to other titanium reagents and to other chiral aldehydes (ref. 7,8,14,20). Diastereoselectivities of 90-99% in favor of the Cram product are common:

$CH_2=CHCH_2Ti(NEt_2)_3$	93	:	7 (ref. 5,21)
$CH_3Li/TiCl_4$	90	:	10 (ref. 14)

>99	:	<1 (ref. 8)
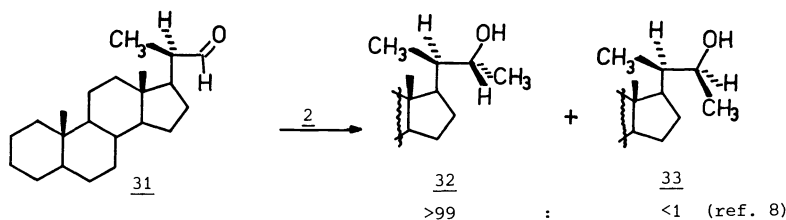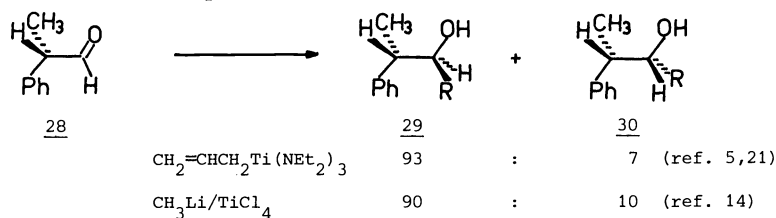
Inspite of the usefulness of titanium reagents in the above reactions, the problem of anti-Cram selectivity persists. It is likely to be solved using chirally modified "reagent specific" organometallics. Potent optically active titanium reagents are just beginning to be developed (ref. 8).

4.2   Chelation-controlled additions to chiral alkoxy carbonyl compounds

The long-pending problem of chelation-controlled addition (ref. 22) to β-chiral β-alkoxy aldehydes was solved by using Lewis acidic titanium reagents such as CH_3TiCl_3, $TiCl_4/$ $CH_2=CHCH_2SiMe_3$ or $TiCl_4/R_2Zn$, 1,3 asymmetric induction being >90% (ref. 23). Iterative processes $(\underline{34a} \rightarrow \underline{38} \rightarrow \underline{40})$ pose no problems (ref. 22).

<u>34</u>
a) R = CH_2Ph; R' = Me
b) R = CH_2Ph; R' = n-Bu

<u>36</u>		<u>37</u>
>90	:	<10 (ref. 23)

<u>34a</u>   <u>38</u> (99% pure)   <u>39</u>   <u>40</u> (>98% pure)
(ref. 22)

Importantly, chelation-controlled aldol additions in these systems are possible for the first time (ref. 23). In case of prochiral enol silanes, chelation-control and simple diastereo-selectivity (generally syn) is excellent, so that essentially one of four possible diastereo-mers are formed (ref. 23).

$$\underline{34a} \xrightarrow[\text{2) } R^1\text{-C(OSiMe}_3)\text{=C}R^1R^2]{\text{1) TiCl}_4} \quad \underline{41} \quad + \quad \underline{42}$$

41 : 42
>90 : <10

Recently, the methodology has been extended to acid nitriles (ref. 24):

43 → 44 →

$$CH_2=CHCH_2SiMe_3$$

45 : 46
>99 : <1   R' = CH$_2$CH=CH$_2$

$$\text{(}\overset{OSiMe_3}{\diagup}\text{)Ph}$$

>99 : <1   R' = CH$_2$CPh (C=O)

Many of the above processes have been applied to α-chiral β-alkoxy aldehydes, 1,2-asymmetric induction generally being >98% (ref. 25), e.g.:

$$\underline{47} \xrightarrow[\text{2) CH}_2\text{=C(OSiMe}_3)\text{OMe}]{\text{1) TiCl}_4} \underline{48} \text{ (>97% pure)}$$

R = CH$_2$Ph

α-chiral α-alkoxy aldehydes such as 49 also undergo chelation-controlled additions with CH$_3$TiCl$_3$, TiCl$_4$/allylsilanes and TiCl$_4$/R$_2$Zn (ref. 26). In case of allylsilane additions, SnCl$_4$ is sometimes more efficient (ref. 26-27). Recently, Me$_3$SiCN has been employed as a C-nucleophile (ref. 24).

$$\underline{49} \xrightarrow[\text{2) CH}_2\text{=CHCH}_2\text{SiMe}_3]{\text{1) TiCl}_4} \underline{50} + \underline{51}$$

R = CH$_2$Ph

50 : 51
>96 : <4

$$\underline{49} \xrightarrow[\text{2) Me}_3\text{SiCN}]{\text{1) TiCl}_4} \underline{52} + \underline{53}$$

52 : 53
80 : 20

The TiCl$_4$ and SnCl$_4$ mediated reactions of 49 (and similar aldehydes) with enol silanes con-stitute the first and presently only known method for chelation-controlled aldol additions, diastereomer ratios being >98 : 2 (ref. 26,28). In case of prochiral enol silanes, simple diastereoselectivity is usually syn. This behavior corresponds to that observed previously in case of β-alkoxy aldehydes 34 (ref. 23). Since the Mukaiyama aldol addition to normal alde-hydes proceeds stereorandomly (ref. 23), the observed excellent simple diastereoselectivity in case of alkoxy aldehydes seems surprising. It has been rationalized on the basis of dif-ferent aldehyde activation (ref. 22,28). Lewis acids complex with simple aldehydes RCHO anti to the R group (we have proven this for the first time by an X-ray analysis of PhCHO-BF$_3$), whereas syn complexation occurs in case of alkoxy aldehydes; an acyclic approach of the enol silane explains syn-selectivity (ref. 22,28).

$$\underline{49} \xrightarrow[\text{2) CH}_2\text{=C(OSiMe}_3)\text{Ph}]{\text{1) TiCl}_4} \underline{54} + \underline{55}$$

54 : 55
97 : 3
(no sign of the other two diastereomers)

Recently, the above methodologies have been applied to natural products chemistry (ref.29-31). We ourselves have made use of them in reactions of the aldehyde 56 (available from mannitol), which deliver essentially single diastereomers via α-chelation (ref. 32). 57 is the precursor of D-threo-desoxy-ribose.
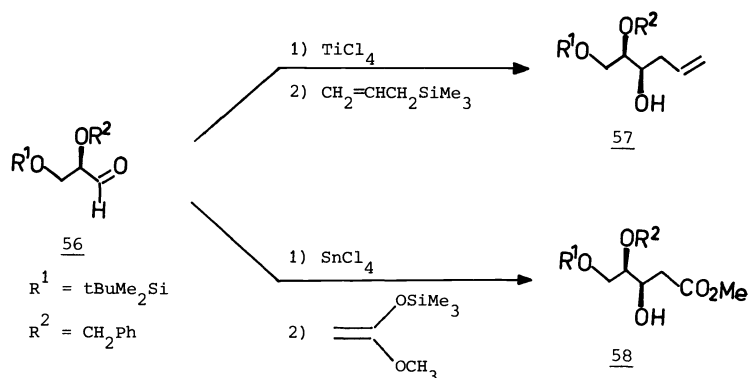

4.3 Non-chelation-controlled additions to chiral alkoxy carbonyl compounds

Non-chelation-control is more difficult because there are no general ways to reduce the number of degrees of freedom of non-complexed molecules (ref. 22). Reagents incapable of chelation must be used and electronic and/or steric factors relied upon, notably those defined by the Felkin-Anh or Cornforth models (ref. 33). We have developed four strategies (ref. 22): 1) Addition of non-chelating reagents $RTiX_3$ (X = $OCHMe_2$, NEt_2); 2) BF_3 mediated additions of allyl and enol silanes (ref. 25); 3) $FN(n-Bu)_4$ induced additions of enol silanes (ref. 25), and 4) intramolecular allyl transfer processes (Section 4.4).

Titanium reagents of the type $RTi(OCHMe_2)_3$, $RTi(NEt_2)_3$ or $RTiCl_2Cp$ are of low Lewis acidity and thus incapable of undergoing chelation in case of α- or β-alkoxy aldehydes (ref. 7,22, 26). For example, $CH_3Ti(OCHMe_2)_3$ reacts with α-alkoxy aldehydes of the type 49 to produce >92% of the non-chelation-controlled product (ref. 7,22,26). This has been applied to carbohydrate chemistry (ref. 7,8,32):
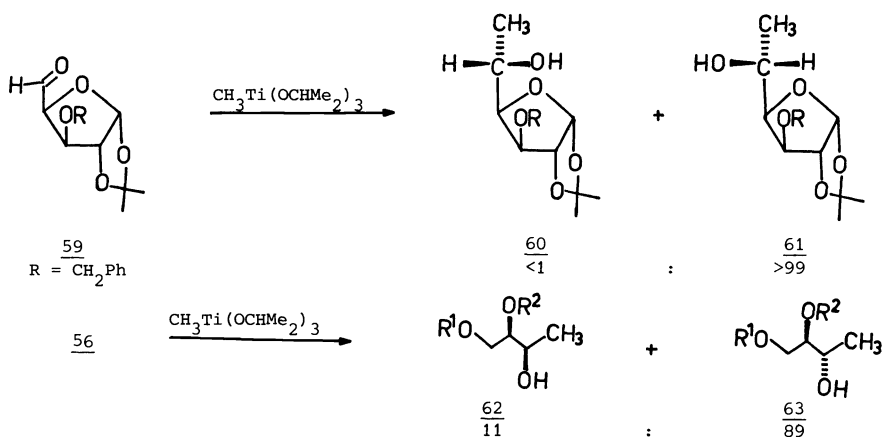
Non-chelation-controlled aldol additions are also possible (ref. 8,22,25,26):
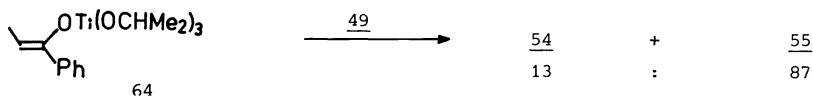
Surprisingly, ketones of the type 65 react with $CH_3Ti(OCHMe_2)_3$ to form the chelation-controlled adduct 66, presumably because the ketone moiety is more Lewis basic than aldehyde functions. By using silyl protective groups, the problem of non-chelation-controlled addition to α-oxy-ketones was finally solved (ref. 34). For example, 68 leads to a single diastereomer 70.

	66	67
CH₃MgCl	>99 :	<1
CH₃TiCl₃	>99 :	<1
CH₃Ti(OCHMe₂)₃	>99 :	<1
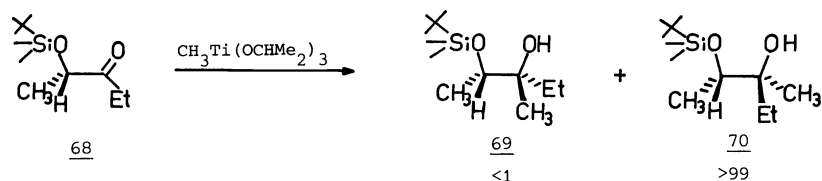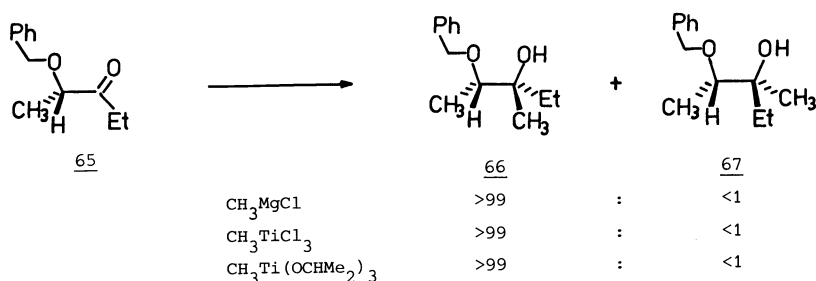
4.4 Intramolecular allyl-transfer reactions

In contrast to α-alkoxy aldehydes, ß-chiral ß-alkoxy analogs do not react stereoselectively with non-chelating organotitanium reagents such as $CH_3Ti(OCHMe_2)_3$ (ref.22). The chiral center is too far removed from the aldehyde function, and 1,3 asymmetric induction is almost nil. Although reagent specific organometallics having a chiral center are likely to solve such problems in the future, we have developed a different strategy, namely <u>intramolecular allylation</u>. Instead of using benzyl protective groups as in 34, the allyldimethylsilyl group is employed as in 71 (ref.34). We speculated that chelation according to 72 would trigger intramolecular allylation. Indeed, adding 71 to a solution of $TiCl_4$ in CH_2Cl_2 resulted in preferential formation of 74. This means reversal of diastereofacial selectivity relative to the reactions of 34 (cf.Section 4.2). It remains to be seen whether this template effect can be extended to other reactions, e.g., intramolecular enol silane additions.
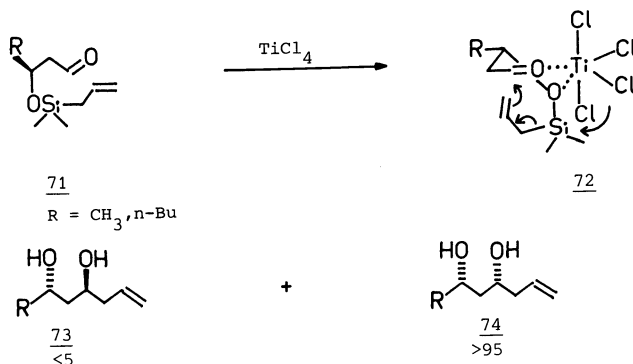
4.5 Polymerization of methyl methacrylate

Recently Webster et al at Dupont have described group transfer polymerization of methacrylate using O-silyl ketene ketals in the presence of catalysts (35).We have discovered a process which does not require any catalyst (36). Titanium ester enolates cause rapid oligomerization to produce living polymers in quantitative yield. The molecular weight distribution is fairly narrow (Scheme 2).

Scheme 2

$$\frac{\bar{M}_w}{\bar{M}_n} = 1.4$$
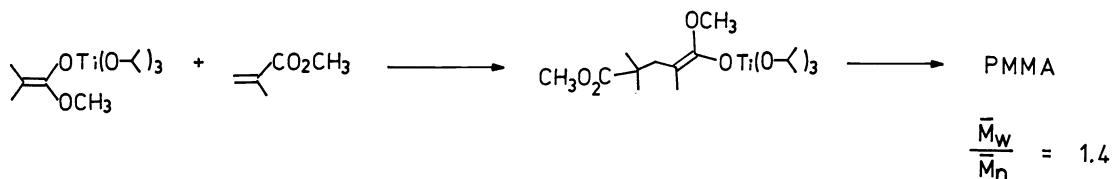
ACKNOWLEDGEMENT

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