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) determines the electronic and steric properties of the reagents. This is useful in predicting the stereochemical outcome in reactions with alkoxy carbonyl compounds. TiCl₄ 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 number 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, stereoselectivity 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).

Scheme 1

\[
\text{ORGANYL-Li} \xrightarrow{\text{CITiX}_3} \text{ORGANYL-TiX}_3
\]

X = Cl, OR, NR₂

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 RTiCl₃ are highly Lewis acidic, a property which is essential in chelation-controlled additions to chiral alkoxy carbonyl compounds or in alkylation reactions of S₅₁-active alkyl halides. Lewis acidity decreases drastically in going to RTi(OR')₃, RTi(NR')₃ or RTiX₂Cp, which means that they are ideal reagents for non-chelation-controlled additions. In all cases basicity and reactivity are considerably 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 TiCl₄ mediated α-tert-alkylation of enol silanes (which sometimes involve Cl,Ti-enolates) (ref. 6,9). They set the stage for testing organotitanium reagents on a broad scale (ref. 4).

Scheme 2

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 regarding the above principles. Included are also novel applications of TiCl₄ and SnCl₄ mediated C-C bond forming reactions (ref. 11).
2 CHEMOSELECTIVITY

The parent compound CH₃Ti(OCHMe₂)₃ ₂ is accessible in essentially quantitative yield from CH₃Li and ClTi(OCHMe₂)₃ ₁. It is a distillable compound, which shows some degree of aggregation in benzene, depending upon concentration and temperature (ref. 7-8).

\[
\begin{align*}
\text{CH₃Li} & \quad \text{ClTi(OCHMe₂)₃} \quad \text{CH₃Ti(OCHMe₂)₃ (}>95\%)
\end{align*}
\]

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 (0-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).

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 CH₃TiCl. Previously, we had shown that it is completely aldehyde-selective in the presence of ketones; in most cases it was prepared from (CH₃)₂Zn and TiCl₄ in CH₂Cl₂ (ref. 3). A new and highly useful procedure involves the reagent system CH₃Li/TiCl₄/ether or CH₃MgCl/TiCl₄/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
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Smoothly to ketones (-20°C → 0°C, 3 - 4 h). Enolizable ketones (e.g., 16) as well as those which contain additional functionality react chemoselectively (ref. 14).

\[
\begin{align*}
\text{12} & \quad \text{13} (76\%) \\
\text{CO}_2\text{Et} \quad & \quad \text{CO}_2\text{Et} \\
\text{16} & \quad \text{17} (86\%) \\
\end{align*}
\]

Many of the above reactions fail to proceed smoothly with \(\text{CH}_3\text{Li}, \text{CH}_3\text{MgX}\) or \(\text{CH}_3\text{Ti(OCHMe)}_3\), e.g., in case of 12 or 14; \(\text{CH}_3\text{MgX}\) adds to 14 solely at the aromatic ring (ref. 16). In summary, \(\text{CH}_3\text{Li/TiCl}_2/\text{ether}\) (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 \(\text{CH}_3\text{Ti(OCHMe)}_3\) (one part), an aldehyde (one part) and a ketone (one part), only the aldehyde adduct was observed (observed -3,8,10). However, this does not provide any information as to the actual relative rate. Precise kinetic studies at room temperature using various aldehyde/ketone pairs show that the \(k_{\text{rel}}\) values vary as follows (ref. 17):

\[
k_{\text{rel}} = \frac{k_{\text{aldehyde}}}{k_{\text{ketone}}} \approx 220 - 700
\]

For example:

\[
k_{\text{heptanal}}/k_{\text{3-heptanone}} \approx 223 \quad \text{and} \quad k_{\text{benzaldehyde}}/k_{\text{acetophenone}} \approx 550.
\]

At lower temperatures the \(k_{\text{rel}}\) values are likely to be considerably larger. In case of \(\text{CH}_3\text{Li}, \text{CH}_3\text{MgX}\) and even \(\text{CH}_3\text{Zr(OCHMe)}_2\) (ref. 7,8,10,18), discrimination is much lower (\(k_{\text{rel}} \approx 1\) for the Li and Mg reagents and \(\approx 30\) for the Zr analog).

Why are titanium reagents so selective? There are probably two factors involved: steric and electronic (ref. 7-8). \(\text{CH}_3\text{Ti(OCHMe)}_3\) is bulkier than \(\text{CH}_3\text{Li}\) or \(\text{CH}_3\text{MgX}\) in addition to the fact that the Ti=O bond is shorter (1.75 - 1.9 \(\text{Å}\)) than the C-Li, C-Mg and C-Zr (2.1 \(\text{Å}\)) analogs. Thus, in the transition state of carbonyl addition, the latter cases are not as congested (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 \(\text{CH}_3\text{Ti(OCHMe)}_3\) to heptanal 24 in \(\text{CH}_2\text{Cl}_2\) 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).

\[
\text{CH}_3\text{Ti(OCHMe)}_3 + \text{24} \quad \rightarrow \quad \text{25} \quad \text{26}
\]

The activation parameters turned out to be as follows:

<table>
<thead>
<tr>
<th>Solvent</th>
<th>(\Delta G^{\ddagger}) kcal/mol</th>
<th>(\Delta H^{\ddagger}) kcal/mol</th>
<th>(\Delta S^{\ddagger}) cal·K(^{-1})·mol(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{CH}_2\text{Cl}_2)</td>
<td>16.9 ± 1.3</td>
<td>12.4 ± 1.2</td>
<td>-19.3 ± 4</td>
</tr>
<tr>
<td>THF</td>
<td>16.5 ± 1.3</td>
<td>20.5 ± 1.2</td>
<td>17.2 ± 4</td>
</tr>
</tbody>
</table>

The rate of addition is essentially solvent-independent, but THF participation is nevertheless involved. Whereas \(\Delta S^{\ddagger}\) in case of \(\text{CH}_2\text{Cl}_2\) is negative as expected for this bimolecular reaction, it is positive 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 27 (two THF molecules arbitrarily assumed) must first kick off the THF to form free 2 before adding to heptanal. This simplified scheme neglects dimeric or aggregated forms of 2, which are in rapid equilibrium with the monomeric form as shown by low temperature $^1$C-NMR experiments (ref. 7,8,17).

\[
\begin{align*}
\text{THF} & \quad \text{34} \\
\text{CH}_3\text{Ti(OCHMe}_2)_3 & \xrightarrow{\text{THF}} \quad \text{2} \\
\text{THF} & \quad \text{27} \\
2 & + 24 \quad \longrightarrow \quad 25 \\
\text{27} + 24 & \quad \longrightarrow \quad 25 + 2 \text{THF}
\end{align*}
\]

4 STEREOSELECTIVITY

4.1 The Cram/anti-Cram problem

Early studies (ref. 3) regarding Cram-selectivity of the addition of \( \text{CH}_3\text{Ti(OCHMe}_2)_3 \) and \( \text{CH}_3\text{TiCl}_3 \) (from \( \text{CH}_2\text{Cl}_2 \)) to \( 2\)-phenylpropanal 28 have since been extended to other titanium reagents and to other aldehyde groups (ref. 7,8,14,20). Diastereoselectivities of 90-99% in favor of the Cram product are common:

\[
\begin{align*}
\text{28} & \rightarrow \text{29} \quad (93:7 \text{ (ref. 5,21)}) \\
\text{CH}_3\text{Li/TiCl}_4 & \rightarrow \text{30} \quad (90:10 \text{ (ref. 14)})
\end{align*}
\]

In spite 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 \( \beta \)-chiral \( \beta \)-alkoxy aldehydes was solved by using Lewis acidic titanium reagents such as \( \text{CH}_3\text{TiCl}_3 \), \( \text{TiCl}_4 \), \( \text{CH}_2\text{=CHCH}_2\text{SiMe}_3 \) or \( \text{TiCl}_4/\text{R}_2\text{Zn} \), 1,3 asymmetric induction being >90% (ref. 23). Iterative processes \( (34a \rightarrow 38 \rightarrow 40) \) pose no problems (ref. 22).

\[
\begin{align*}
\text{34} & \rightarrow \text{35} \rightarrow \text{36} >90 \quad \text{(ref. 23)} \\
a) \text{R} = \text{CH}_2\text{Ph; } \text{R}' = \text{Me} \\
b) \text{R} = \text{CH}_2\text{Ph; } \text{R}' = \text{n-Bu}
\end{align*}
\]

\[
\begin{align*}
\text{34a} & \rightarrow \text{38} \quad (99\% \text{ pure}) \rightarrow \text{39} \rightarrow \text{40} >98\% \text{ pure} \quad \text{(ref. 22)}
\end{align*}
\]

\[
\begin{align*}
\text{34} & \rightarrow \text{35} \rightarrow \text{36} >90 \quad \text{(ref. 23)} \\
a) \text{R} = \text{CH}_2\text{Ph; } \text{R}' = \text{Me} \\
b) \text{R} = \text{CH}_2\text{Ph; } \text{R}' = \text{n-Bu}
\end{align*}
\]

\[
\begin{align*}
\text{34a} & \rightarrow \text{38} \quad (99\% \text{ pure}) \rightarrow \text{39} \rightarrow \text{40} >98\% \text{ pure} \quad \text{(ref. 22)}
\end{align*}
\]
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 diastereoselectivity (generally syn) is excellent, so that essentially one of four possible diastereomers are formed (ref. 23).

\[
\begin{align*}
R Q & \text{OH} \\
& \text{R} Q \text{O} \text{H}
\end{align*}
\]

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

\[
\begin{align*}
\text{RCH} = \text{CH}_2 \text{CH}_2 \text{SH}_3 & \text{TiCl}_4 \\
\text{CH}_2 \text{=CH}_2 \text{SiMe}_3 & \text{TiCl}_4 \\
\text{R}_2 \text{CN} & \text{CN} \text{R}_2
\end{align*}
\]

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.:

\[
\begin{align*}
\text{R} & = \text{CH}_2 \text{Ph} \\
\text{RCH} \text{OH} & \text{TiCl}_4 \\
\text{TiCl}_4 & \text{Me}_3 \text{SiCN}
\end{align*}
\]

α-chiral α-alkoxy aldehydes such as 49 also undergo chelation-controlled additions with CH$_2$TiCl$_4$, 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).

\[
\begin{align*}
\text{R} & = \text{CH}_2 \text{Ph} \\
\text{RCH} \text{OH} & \text{TiCl}_4 \\
\text{TiCl}_4 & \text{Me}_3 \text{SiCN}
\end{align*}
\]

The TiCl$_4$ and SnCl$_4$ mediated reactions of 49 (and similar aldehydes) with enol silanes constitute 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 aldehydes proceeds stereorandomly (ref. 23), the observed excellent simple diastereoselectivity in case of alkoxy aldehydes seems surprising. It has been rationalized on the basis of different 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).
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 RTiX3 (X = OCHMe2, NET2); 2) BF3 mediated additions of allyl and enol silanes (ref. 25); 3) FN(H-Bu)4 induced additions of enol silanes (ref. 25), and 4) intramolecular allyl transfer processes (Section 4.4).

Titanium reagents of the type RTi(OCHMe2)3, RTi(NET2)3 or RTiCl2Cp 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, CH3Ti(OCHMe2)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 CH3Ti(OCHMe2)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-oxo-ketones was finally solved (ref. 34). For example, 68 leads to a single diastereomer 70.
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4.4 Intramolecular allyl-transfer reactions

In contrast to α-alkoxy aldehydes, β-chiral β-alkoxy analogs do not react stereoselectively with non-chelating organotitanium reagents such as CH₃Ti(OCHMe₂)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 intramolecular allylation. 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 TiCl₄ in CH₂Cl₂ 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

ACKNOWLEDGEMENT

We thank the DFG and VCI for financial support.
REFERENCES


11. The present review does not list new examples of the application of organotitanium reagents in organic synthesis described by other groups. The interested reader is referred to the reviews (ref. 6-8, 10).


15. We have previously added CH₃TiCl₃ (prepared from (CH₃)₄Ti and TiCl₄ in CH₂Cl₂) to donor molecules such as ether, THF or TEMED to form octahedral complexes, which react smoothly with aldehydes: M.T. Reetz and J. Westermann, Synth. Commun. 11, 647-654 (1981).


19. Prof. T. Kauffmann has proposed a similar explanation based on the different atomic volumes of Ti, Zr and other metals: private communication to M.T. Reetz (1985).


21. This reaction was performed at ~120°C; at ~78°C selectivity is slightly lower (ref. 5).


36. M.T. Reetz and T. Zierke in collaboration with D. Arlt and K.E. Piejko (Bayer AG, Leverkusen).