The Application of Low-Valent Titanium Reagents in Organic Synthesis

Dieter Lenoir

Lehrstuhl für Ökologische Chemie und Geochemie der Universität Bayreuth, Postfach 101251, D-8580 Bayreuth, Federal Republic of Germany

The number and variety of applications of low-valent titanium reagents has expanded greatly since their initial use in 1973. This review examines the preparation of low-valent titanium reagents and their development as reagents for inter- and intramolecular coupling, reductive elimination and allylkulation, with reference to aspects of the mechanism and stereoselectivity.

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1. Introduction

The reductive coupling of aldehydes and ketones to give alkenes by low-valent titanium species, generated in situ, was first reported independently between 1973 and 1974 by Tyrlik et al.\(^1\) Mukaiyama et al.\(^2\) and McMurry et al.\(^3\) The latter used titanium trichloride and lithium aluminum hydride to generate the low-valent titanium species; this has been further elaborated by McMurry and co-workers.\(^4,5\) and is now generally referred to as, “the McMurry reaction”. The reaction conditions have also been modified, for instance titanium tetrachloride/zinc has been developed as a reagent and is now widely used.\(^6\) The reaction has also been reviewed, the applications of the reaction were covered some years ago.\(^5,7,8,9\) A detailed study of the mechanism of the reaction has also been published by Geise and co-workers.\(^10\)

\[
\begin{align*}
\text{R}^1 & \equiv \text{O} \\
\text{R}^1 & \equiv \text{O} \\
\text{R}^2 & + \text{H}, \text{alkyl}, \text{aryl}
\end{align*}
\]

After a short introduction into the mechanistic aspects, the scope and applications of low-valent titanium species in synthetic organic chemistry will be covered in depth. Recent advances in the allylation of carbonyl compounds using titanium carbene complexes will also be discussed.

2. Low-Valent Titanium Reagents

2.1. Preparation

The yield and stereoselectivity of low-valent titanium coupling reactions are dependent upon; the choice of titanium reagent, its preparation, and the applied experimental conditions.\(^11\) The reagents and solvents must be pure and absolutely dry, since traces of oxidation and hydrolysis products can interfere with the reaction and reduce the yield. The reaction should therefore be performed under a dry argon atmosphere.

A Ti(0) or a Ti(I) species can be prepared depending on the reducing conditions applied.\(^10\) Titanium trichloride is reduced by lithium aluminum hydride\(^6,5\) according to the stoichiometric equation:

\[
5\text{TiCl}_3 + 3\text{LiAlH}_4 \rightarrow 5\text{Ti}(0) + 3\text{Al}(0) + 12\text{HCl} + 3\text{LiCl}
\]

The following reducing agents have also been applied to titanium trichloride; lithium,\(^10,11\) sodium,\(^10\) potassium,\(^4,10\) potassium-graphite intercalate \((\text{K}_x\text{C}_6\text{K})\),\(^12\) magnesium,\(^1,10\) zinc-copper couple,\(^13\) and Rieke-titanium.\(^14\) It has been found that a slight excess of reducing agent is usually necessary to obtain an optimum yield of the desired product.\(^10\) Titanium trichloride and lithium aluminum hydride can produce a Ti(0) or a Ti(I) species depending on the mole ratio of TiCl\(_3\)/LiAlH\(_4\), a ratio of 1:0.6 produces a Ti(0) species and 1:0.5 a Ti(I) species. Both of these reagents are commercially available.

Starting from titanium tetrachloride, the reduction to low-valent titanium can be performed by zinc,\(^2,5\) zinc-copper couple,\(^15\) magnesium/mercury,\(^10\) aluminum/aluminum trichloride,\(^10\) or
lithium aluminum hydride. Dicyclopentadienyltitanium dichloride and trimethylaluminum, or with Grignard reagents, has also been used.

Tetrahydrofuran is usually the solvent of choice for the reaction but dioxane and dimethoxyethane are also applied. The reaction conditions have also been carefully elaborated to obtain optimum yields by the preparation of a crystalline titanium tri-chloride dimethoxyethane complex which is reduced by zinc-copper couple.

2.2. Mechanism and Stereoselectivity

A black slurry of low-valent titanium species is freshly prepared, the carbonyl compound is added and the reaction is allowed to proceed for a fixed time. The sequence of events is depicted mechanistically, both in solution and on the surface of the titanium, in Scheme A.

In the initial step (a), an electron is transferred from titanium to the carbonyl group generating a radical anion, which has been detected by ESR-spectroscopy. The ketyl radical then dimerizes to the corresponding pinacol (b), which can be isolated as the primary reaction product when low temperatures are used. Deoxygenation by a cis-type concerted mechanism of the pinacol occurs readily (c and d) leading to alkenes, due to the large affinity of titanium for oxygen. These reactions all occur on the surface of the titanium.

Stereoselectivity is observed in diol formation (ratio of meso to d,l-isomers) as well as in olefin formation (ratio of E/Z-isomers); these effects will be described below. The stereoselectivity of the olefin formation depends on the choice of the titanium reagent. The E/Z-ratio in coupling of aliphatic methyl alkyl ketones depends strongly on the steric bulk of the alkyl groups.

The observed E/Z ratios are different when the low-valent titanium species is generated from TiCl₃/LiAlH₄; for example the ratio of E/Z is close to unity in alkene formation from pinacolone. The stereoselectivity of stilbene formation from benzaldehyde is also dependent on the reagents used to generate the titanium species.

A complete rationale for these results has still to be found. The deoxygenation step also shows stereoselective behavior; meso- and d,l-isomers of the same glycols give different mixtures of E/Z isomeric alkenes. More examples of this behavior will be given later.

3. Intermolecular Coupling Aldehydes and Ketones

3.1. Preparation of Alkenes

Low-valent titanium reagents have been widely used for the preparation of symmetrical alkenes, starting from the corresponding aldehyde or ketone. There are many examples, for a selection refer to previous reviews.
Some synthetically useful examples will be discussed in this section. Beta-carotene (2), a food coloring compound and precursor of vitamin A, can be prepared in high yield from retinal (1). The titanium reagent for the coupling can either be TiCl₄/LiAlH₄ or TiCl₄/LiAlH₄ in the presence of a proton sponge. Dimestrole (4), precursor of diethylstilbestrol, can be prepared from the ketone 3. Worthy of note are the synthesis of mini-carotene, a lower homologue of beta-carotene (2), and the C₄₀-saturated terpenoid used as a crude oil marker.

Reductive Coupling of Aldehydes and Ketones; General Procedure
Method A: K metal (1.92 g, 49 mmol) is washed with hexane to remove oil and is added to a stirred slurry of TiCl₄ (2.15 g, 14 mmol) in dry THF (75 mL) at r.t. under an inert atmosphere. After refluxing for 40 min, the black mixture is cooled and a solution of ketone or aldehyde (3.5 mmol) in THF (5 mL) is added. After a further 16 h at reflux, the reaction mixture is cooled to r.t. and transferred by syringe to a glass filtration tube (medium fri) under an inert atmosphere. The mixture is vacuum filtered, and the filtrate is then concentrated by solvent removal on a rotary evaporator to yield the crude product. In this manner tetrasopropylethylene and 10-iceose are isolated by chromatography in 37% and 60% yield, respectively.

Method B: Zn dust (10 g, 130 mg-atom) is added in small portions to TiCl₄ (14.2 g, 82 mL, 75 mmol) in THF (200 mL) with ice cooling under an N₂ atmosphere. Pyridine (5 mL) and ketone (70 mmol) in THF (200 mL) are added. The mixture is heated at reflux for 20 h. After being cooled to r.t., the reaction is quenched with 10% aq. KOH (150 mL). The mixture is extracted with Et₂O or pentane (5 x 50 mL). The extract is washed with water twice, dried (MgSO₄), filtered, and concentrated under vacuum. The residue is isolated by chromatography on silica (Merck 60, 0.2-0.6 mm, 60 g) using pentane or hexane as an eluent. The alkene is obtained after evaporation of the solvent and further purified by standard procedures.

We have developed the latter procedure (Method B) and used it for the coupling of a wide variety of ketones. Although yields are sometimes a little lower compared to other procedures, the method is easy to perform and the reagents are less expensive. The addition of pyridine is not essential in most cases.

In general most monocyclic ketones of varying ring size, as well as polycyclic ketones, can be coupled to give the corresponding alkenes. The following alkenes have thus been obtained: cyclohexylidenecyclohexane (5a), and the alkyl derivative 5b, adamantylidenedecamantane (6a) and the alkyl derivatives 6b, 6c (4-protopadamantyliden) hydroxprotopadamantane 7, 4, 4'-homoadamantylidenhomoadamantane (8), tetracyclopropylethylene (9) and its derivatives, and finally the highly nucleophilic olefin 10, 10'-bisspiro[2.0.2.0.2.2]decyldiene (10).
1-Ethyladamantanone couples to give the strained ethylene 6c, 23 but neither tert-butyl isopropyl ketone, 35 nor di-tert-butyl ketone 36, 37 could be coupled to give the corresponding alkene by any of the low-valent titanium species. The reaction of di-tert-butyl ketone with TiCl₄/LiAlH₄ in refluxing dioxane yields exclusively di-tert-butyl carbinol, 36 no C-C-coupling is observed. tert-Butyl cyclopropyl ketone reacts with low-valent titanium to give a complex mixture of products. 35 A small amount of C-C-coupled saturated material can be isolated, demonstrating the limitations of the reaction due to severe steric hindrance. For comparison with alternative alkenes synthesis see Section 3.1.4.

### 3.1.2. Preparation of Aromatic Olefins

Sterically uncrowded and crowded stilbene derivatives 12 have been prepared from ketones 11 by a low-valent titanium coupling reaction (Table 2).

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>Reagent</th>
<th>Yield (%)</th>
<th>E/Z ratio</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>TiCl₄/Zn/THF</td>
<td>88</td>
<td>1:4</td>
<td>1</td>
</tr>
<tr>
<td>H</td>
<td>CH₃</td>
<td>TiCl₄/Zn/dioxane</td>
<td>98</td>
<td>99:1</td>
<td>2</td>
</tr>
<tr>
<td>H</td>
<td>CH₃</td>
<td>TiCl₄/LiAlH₄</td>
<td>97</td>
<td>85:15</td>
<td>3</td>
</tr>
<tr>
<td>H</td>
<td>CH₂CH₃</td>
<td>THF</td>
<td>81</td>
<td>26:74</td>
<td>38</td>
</tr>
<tr>
<td>H</td>
<td>CH₂CH₂</td>
<td>TiCl₄/Zn/THF</td>
<td>59</td>
<td>27:73</td>
<td>38</td>
</tr>
<tr>
<td>H</td>
<td>CH₂CH₂</td>
<td>TiCl₄/Zn/THF</td>
<td>25</td>
<td>88:12</td>
<td>38</td>
</tr>
<tr>
<td>CH₃</td>
<td>CH₃</td>
<td>TiCl₄/Zn/THF</td>
<td>45</td>
<td>100:1</td>
<td>36</td>
</tr>
<tr>
<td>CH₃</td>
<td>CH₂CH₂</td>
<td>TiCl₄/Zn/THF</td>
<td>82</td>
<td>100:1</td>
<td>39</td>
</tr>
<tr>
<td>CH₃</td>
<td>CH₃</td>
<td>TiCl₄/LiAlH₄</td>
<td>22</td>
<td>1:12</td>
<td>40</td>
</tr>
<tr>
<td>H</td>
<td>CH₂CH₂</td>
<td>TiCl₄/LiAlH₄</td>
<td>42</td>
<td>1:18</td>
<td>40</td>
</tr>
</tbody>
</table>

The preference for formation of Z-products of uncrowded stilbenes 12a, 12f, has been attributed to complexation and stabilization of the two aromatic moieties by titanium possible only in the meso-diol form, which further yields the Z-stilbene on deoxynation. 38 Whilst TiCl₄/Zn yields Z-products preferentially (12a-e), E-stilbene 12a is formed in the coupling reaction when TiCl₄/LiAlH₄ is the reagent. 3

tert-Butyl phenyl ketone (11e) yields exclusively the crowded E-stilbene 12e, regardless of the reagent used to generate low-valent titanium; a detailed study of this chemistry has recently been published. 39 In the coupling of the highly crowded ketones 11g, h, formation of ethane derivatives is observed and reduced methylene compounds are isolated as side-products. 40 Supermesityl aldehyde (11: R¹ = C(CH₃)₃, R² = H) when reacted with TiCl₄/LiAlH₄ couples to give exclusively the ethane derivative 1,2-disupermesitylene in 52% yield. 42 Mesityl tert-butyl ketone and dimesityl ketone 35 do not give C,C-coupling products when reacted with low-valent titanium reagents. 40-43 This shows the limitation of the reaction, as severe steric crowding would be present in the hypothetical coupled products.

Diaromatic ketones, for example, benzenophene, 4 9-fluorenone, 1 and 1,1'-dinaphthyl ketone, 44 on treatment with low-valent titanium give the corresponding aryl ethylenes in excellent yields. Phenyl 3-pyridyl ketone gives the corresponding ethylene in 31% yield. 45 Di-o-tolyl ketone yields the 'tetra-o-tolyl ethylene along with small amounts of the ethane derivative. 44 Surprisingly, coupling of the dibenzo-cycloheptanone 13 using TiCl₄/Zn does not yield the expected product 14, but results in the formation of the chiral bridged diphenylanthracene 15 and the ethane derivative 16. 45

Benzylated cyclic ketones 17 can be coupled to give cyclic stilbene derivatives 18 (Table 3).

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Yield (%)</th>
<th>E/Z ratio</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>TiCl₄/LiAlH₄/THF</td>
<td>62</td>
<td>9:1</td>
<td>46</td>
</tr>
<tr>
<td>TiCl₄/Zn/THF</td>
<td>76</td>
<td>9:1</td>
<td>46</td>
</tr>
<tr>
<td>TiCl₄/Zn/THF</td>
<td>78</td>
<td>7:3</td>
<td>46</td>
</tr>
<tr>
<td>TiCl₄/Zn/THF</td>
<td>38</td>
<td>8:2</td>
<td>39</td>
</tr>
</tbody>
</table>

Several alkyl and methoxy derivatives of ketones 17 have been coupled successfully using low-valent titanium reagents. 46 Derivatives of 18 (n = 3) are useful starting materials in the preparation of perylene compounds. 42 (E)-1,3,4-Dihydro-2,2-dimethyl-1,2-dihydropyrene-1,3,4,4-tetrahydro-2,2-dimethyl napthalene (19) and its Z-isomer have also been prepared and studied; due to severe crowding of the stilbene system only the E-isomer can be isolated in crystalline form because of the very low Z:E barrier of 21 kcal/mol observed in solution since Z:19 rearranges instantaneously to E:19. 47
3.1.3. Mixed Coupling of Carbonyl Groups

The intermolecular coupling of identical aldehydes and ketones yields symmetrical olefins. A mixture of two different carbonyl compounds will react generally to a nearly statistical mixture of olefins when subjected to low-valent titanium. Some new olefins have been prepared by this method, e.g., crowded ethylenes 20 from the reaction of pivalaldehyde/corresponding ketone in a 4:1 mole ratio. The crowded ethylenes 20a,b have been used for the determination of thermal barriers to Z/E isomerization; 1,2-dimethyl- and 1,2-diethyl-di-tert-butyl-ethylenes (Table 1) have also been used for this purpose.

1-(2-[2.2]-Paracyclophano)-2-ferrocenylethylene (21) can be prepared by mixed coupling of either aldehyde in 33% yield. By applying an excess of one carbonyl compound mixed coupling can be synthetically useful, for example, in the isopropylidenation of carbonyl groups using an excess of acetone. Cholestaneone (22) gives the mixed coupled product 23 in 54% yield; cholestanyldenecholestane is only formed in 29% yield. Adamantaneone gives the isopropylidene derivative with a yield of 63% under the same conditions.

It is also possible to couple mixtures of dialkyl- and diaryl ketones (Scheme B). The mixed coupling of equimolecular amounts of benzophenone and cyclohexanone gives 1,1-diethylnaphthalene in 78% yield, with the self-condensation products tetraphenylethane and cyclohexyldieneoctafluorocyclohexane in 19% and 6% yield, respectively.

Mechanistically this can be explained in terms of the different reduction potentials of the ketones. As the second reduction potential of diaryl ketones is less negative than the first reduction potential of dialkyl ketones, the initial step is one-electron transfer from low-valent titanium to the diaryl ketone. The diion thus formed then adds to the dialkyl ketone to give a mixed product, which is further deoxygenated to yield the alkene.

Mixed coupling has also been applied in synthesis of the antitumor agent tamoxifen (31, R = H) by the coupling of ketones 29 and 30. Several derivatives of tamoxifen (31) have also been prepared starting from the substituted benzophenone 30.

3.1.4. Scope and Limitation of the Coupling Reaction

The coupling reaction can be compared with two more recent alkyne preparations. The Barton-Kellogg method (thiadiazoline method), makes use of the cycloaddition of thiocarbonylketenes 32 to diazoalkanes 33 yielding the five-membered heterocycles 34, which are subjected to a double extrusion process to give alkenes 35.
developed by Olah.\textsuperscript{54} Ketone 39 react with isopropyllithium to give the carbinal 40, which is dehydrated to the alkene 41 without isolation.

\[ \text{30Cl}_2 \]

3.1.5. Selective Coupling of Ketones and Aldehydes

3.1.5.1. Groups with Large Reduction Potentials

Low-valent titanium coupling methods can tolerate the presence of various functional groups in the molecules to be coupled. Carbon-carbon double bonds are generally inert to all low-valent titanium species, and no isomerization is observed. Reports of coupling in the presence of carbon-carbon triple bonds are rare, and a partial hydrogenation tends to occur. Ethers and alcohols are generally stable under coupling conditions; however, 2-alkyl-3-ethoxyacroleins 42 react to give 2,5-dialkyl-2,4-hexadienals 43 in moderate yields.\textsuperscript{65} Benzyl-\textsuperscript{66} and silyl ethers generally pose no problems under these reaction conditions. Acetals have also been shown to be stable (see examples given below), as well as alkylvinylsilanes.\textsuperscript{48} Special care must be taken in the workup conditions for acetals.

\[ \text{EIOH} \xrightarrow{\text{TiCl}_4/\text{LiAIH}_4/TlF} \]

These are also several examples of the stability of secondary and tertiary amines under low-valent titanium coupling conditions. Aromatizable halides do not interfere with the coupling reaction if the correct conditions are used, for example; the coupling of 44 to give 45,\textsuperscript{68} and 46 to give 47.\textsuperscript{69}

\[ \text{Scheme C} \]

An alternative method (Scheme C) allows the preparation of a variety of symmetrical and unsymmetrical alkenes from carboxylic acid derivatives. Tri-tert-butylethylene and tetracyclopropylethylene have been prepared by this route.\textsuperscript{62} However, the reaction is limited in its initial step by the steric crowding of the starting carboxylic acid, for example, 1,2,2-trimethylbutyric acid and its methyl ester do not react with tert-butyllithium.\textsuperscript{53} Thus attempted synthesis of tri-tert-butylmethylcyclohexene failed as the initial step was unsuccessful. However, this alkene has been successfully prepared by another strategy by Krebs et al.\textsuperscript{57} A modified version of this method has recently been
Under normal conditions (TiCl₃/LiAlH₄) aromatic iodides, bromides and chlorides can also be reduced to arenes. A trifluoromethyl group present in the aryl system does not interfere with the coupling reaction. Sulfides and selenides are also stable towards the reductive power of low-valent titanium. Amides are only stable under special conditions. Ferrocene units are stable towards titanium tetrachloride and zinc, for example, acetyl ferrocene can be coupled to the isomeric 2-butene derivatives.

3.1.5.2. Groups with Low Reduction Potentials

Aromatic aldehydes and ketones have been coupled in the presence of adjacent acyloxy, methoxy, methoxycarbonyl and tosylxoy groups using titanium trichloride/zinc-copper in dimethoxyethane. Selected examples for the coupling of aromatic carbonyl compounds to give stilbenes are shown in Table 4.

### Table 4. Reductive Coupling of Aromatic Carbonyl Compound 48

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>Solvent</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>Ac</td>
<td>Me</td>
<td>DME</td>
<td>87</td>
</tr>
<tr>
<td>H</td>
<td>H</td>
<td>Ac</td>
<td>Ac</td>
<td>THF</td>
<td>87</td>
</tr>
<tr>
<td>CH₃</td>
<td>H</td>
<td>Ac</td>
<td>Ac</td>
<td>DME</td>
<td>64</td>
</tr>
<tr>
<td>CH₃</td>
<td>H</td>
<td>Ts</td>
<td>H</td>
<td>THF</td>
<td>80</td>
</tr>
<tr>
<td>CH₃</td>
<td>Ts</td>
<td>H</td>
<td>H</td>
<td>THF</td>
<td>92</td>
</tr>
</tbody>
</table>

- **DME** = dimethoxyethane.
- **OTs** = 4-CH₃C₆H₄SO₃.

Noteworthy is the coupling of methyl benzoate using titanium trichloride/magnesium to give benzil (46%) and 1,2-dibenzoyl-1,2-diphenylethylene (20%). Further examples of intramolecular coupling in the presence of ester groups are given later in this review.

It is also possible to perform a selective coupling reaction in the presence of two different keto groups, if one group can cyclize intramolecularly; this interesting selectivity will be further discussed. Carboxylic acids do react with low-valent titanium. Benzoyl chloride (50) reacted in a one-pot reaction with titanium trichloride/lithium aluminum hydride to give tetraphenyluran (51) in 80% yield. The intermediates in this reaction have been shown to be benzil and 1,2-dibenzylstilbene.

### 3.2. Preparation of Glycols

Aldehydes and ketones can be coupled to give pinacols with low-valent titanium (see Scheme D) using mild and special reaction conditions; in general, the reaction is performed at 0 °C.

![Scheme D](image)

Diols cannot always be isolated, since deoxygenation can occur very quickly to give the alkene. In general mixtures of meso- and d,l-isomers are formed by coupling of unsymmetrical carbonyl compounds. Three-Selectivity has been obtained in the formation of symmetrical glycols using a cyclopentadienyl-bound titanium(III)-reagent, which is prepared from reaction of cyclopentadienyltitanium(IV) with Grignard reagents. Some examples of glycol formation using low-valent titanium are shown in Table 5. In all cases tetrahydrofuran was used as the solvent.

### Table 5. Intermolecular Coupling of Ketones and Aldehydes

<table>
<thead>
<tr>
<th>Starting Material</th>
<th>Product</th>
<th>Reagent</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TiCl₃/Mg·Hg</td>
<td>93</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>TiCl₃/Mg</td>
<td>45</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>TiCl₃/C₆H₆K (1:2)</td>
<td>64</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>TiCl₃/Mg·Hg</td>
<td>95</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>TiCl₃/C₆H₆K (1:1)</td>
<td>65</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>TiCl₃/Zn</td>
<td>98</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>TiCl₃/Mg·Hg</td>
<td>84</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Cp₂TiCl₂·P₂MgCl</td>
<td>(80:1)</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>Cp₂TiCl₂</td>
<td>50</td>
<td>68</td>
<td></td>
</tr>
<tr>
<td>TiCl₃/Zn</td>
<td>91</td>
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</tr>
<tr>
<td>Cp₂TiCl₂</td>
<td>57</td>
<td>68</td>
<td></td>
</tr>
</tbody>
</table>

- **Threo/erythro**.

### 1,2-Diphenylethane-1,2-diol: Typical Procedure:

A suspension of zinc powder (0.59 g, 9 mmol) in THF (10 mL) is added slowly to a mixture of benzaldehyde (0.318 g, 3 mmol) and titanium tetrachloride (0.86 g, 4.5 mmol) in THF (20 mL) at -10 under Ar. The yellow solution immediately changes to purple and then turns dark brown. The mixture is stirred for 2 h at 0 °C, then 10% aq. K₂CO₃ solution (10 mL) added and the solution extracted with Et₂O (50 mL). The solvent is evaporated in vacuo to give the diol; yield: 0.310 g (98%).

### 3.2.2. Mixed Coupling of Carbonyl Compounds

Corey et al. have successfully coupled carbonyl compounds to give unsymmetrical or mixed diols. Mixed coupling takes place when a cyclic ketone and a 3 mole excess of a carbonyl compound, such as acetone or acetaldehyde, are reacted with TiCl₃/Mg·Hg. The unsymmetrical diol can be easily separated from the product mixture by chromatography. For example, an equimolecular mixture of cyclohexanone and acetone gives the mixed diol in 76% yield.
A variation of the pinacol coupling, the reaction of aromatic aldehydes 52 with secondary amines and with titanium tetrachloride/magnesium gives \(N,N,N',N'\)-tetraalkyl-1,2-diaryl-1,2-ethanediamines 53 in good yield. The 1:1 mixture of meso- and \(d,l\)-isomers can be separated by crystallization or chromatography.\(^{76}\) Various substituted aromatic aldehydes have been coupled in this way.

\[
\begin{align*}
R & = \text{CN, Cl} \\
R & = \text{CN, Cl} \\
R & = \text{CN, Cl}
\end{align*}
\]

4. Intramolecular Coupling of Carboxyl Groups

4.1. Preparation of Cycloalkenes and Cyclic Ketones

Intramolecular coupling of \(\alpha,\alpha\)-dicarbonyl compounds has been applied to the synthesis of cycloalkenes,\(^{82}\) intramolecular coupling of keto esters gives cyclic ketones.\(^{77}\)

Some typical examples of intramolecular coupling of \(\alpha,\alpha\)-dicarbonyl compounds are shown in Table 6. In general, tetrahydrofuran is the solvent, and high dilution conditions are used to avoid intermolecular reactions.\(^{8}\)

Intramolecular coupling of dicarbonyl compounds has recently been optimized using titanium trichloride/dimethyloxide solution as the titanium source and zinc copper as the reducing agent.\(^{20}\) Yields for cyclic alkenes for medium-sized rings are much higher compared to those from the corresponding acyloins, Thorpe, and Dieckmann condensations.\(^{23}\)

<table>
<thead>
<tr>
<th>Macro cyclic Di alcohol Coupling:</th>
<th>1,2 Dimethylecyletetradecene.(^{70}) Typical Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dimethylexide (DME) was distilled twice from K under an Ar atmosphere; pentane was distilled from CaH(_2) and deoxygenated prior to use by purging with Ar for 10 min. All manipulations were carried out under an atmosphere of Ar and all transfers were done using Schlenk apparatus.</td>
<td></td>
</tr>
<tr>
<td>Preparation of TiCl(_4) (DME):</td>
<td></td>
</tr>
<tr>
<td>TiCl(_4) (25.0 g, 0.162 mol) is suspended in dry DME (350 mL), and the mixture refluxed for 2 d under Ar. After cooling to r.t., the solid is filtered under Ar, washed with pentane (50 mL), dried under vacuum to give fluffy, blue crystalline TiCl(_4) (DME), yield: 32.0 g (80%) that is used in the coupling reaction. The solvate is air sensitive but can be stored indefinitely under Ar at r.t.</td>
<td></td>
</tr>
<tr>
<td>Preparation of Zinc-Copper Couple:</td>
<td></td>
</tr>
<tr>
<td>Zn-Cu couple is prepared by addition of Zn dust (9.8 g, 150 mmol) to N(_2)-purged water (40 mL), the slurry is purged with N(_2) for 15 min, and addition of CuSO(_4) (0.75 g, 4.7 mmol). The black slurry is filtered under N(_2), washed with deoxygenated (nitrogen-purged) water (10 mL), acetone (10 mL), and Et(_2)O (10 mL), and dried under vacuum. The couple can be stored indefinitely in a Schlenk tube under N(_2).</td>
<td></td>
</tr>
</tbody>
</table>

Table 6. Intramolecular Dicarbonyl Coupling

<table>
<thead>
<tr>
<th>Starting Material</th>
<th>Product</th>
<th>Reagent</th>
<th>Yield (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>TiCl(_4)/LiAlH(_4)</td>
<td>50</td>
<td>79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TiCl(_4)/Zn–Cu</td>
<td>87</td>
<td>79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TiCl(_4)/LiAlH(_4)</td>
<td>40</td>
<td>61–78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TiCl(_4)/LiAlH(_4)</td>
<td>78</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TiCl(_4)/Zn–Cu</td>
<td>50</td>
<td>79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TiCl(_4)/LiAlH(_4)</td>
<td>61</td>
<td>78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TiCl(_4)/Zn–Cu</td>
<td>76</td>
<td>79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TiCl(_4)/LiAlH(_4)</td>
<td>61</td>
<td>77</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TiCl(_4)/Zn–Cu</td>
<td>85</td>
<td>79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TiCl(_4)/Zn–Cu</td>
<td>30</td>
<td>72</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TiCl(_4)/Zn–Cu</td>
<td>73</td>
<td>71</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cycloalkenes can be prepared in all ring sizes up to 22 carbon atoms, the low-valent titanium reagent is usually titanium trichloride/zinc-copper.\(^{5}\) Intramolecular keto ester coupling works only well with five-, six-, and seven-membered rings.\(^{77}\)

Intramolecular coupling of 2,0-dicarbonyl compounds has recently been optimized using titanium trichloride/dimethyloxide solution as the titanium source and zinc copper as the reducing agent.\(^{20}\) Yields for cyclic alkenes for medium-sized rings are much higher compared to those from the corresponding acyloins, Thorpe, and Dieckmann condensations.\(^{23}\)

Intramolecular coupling has been widely used for the synthesis of compounds with unusual new structures (Table 7) and natural products (Table 8). Low-valent titanium coupling of the 4,10-dioxobicyclo[5.5.0]dodeca-1,7-ene (54) failed to give the novel compound 55, since further rearrangement is too fast.\(^{80}\)

In the synthesis of natural products, low-valent titanium coupling has also been successfully used for the synthesis of the following compounds: hirsutene (TiCl\(_4\)/K, THF);\(^{81}\) bicyclo[5.5.0]dodeca-1,7-ene (TiCl\(_4\)/K, THF);\(^{82}\) lipoic acid (TiCl\(_4\)/Zn–Cu, DME);\(^{83}\) compactin (TiCl\(_4\)/Ca, THF);\(^{84}\) cannabidiol II (TiCl\(_4\)/Zn–Cu, THF);\(^{85}\) the taxane skeleton (TiCl\(_4\)/Zn–Cu, DME);\(^{86}\) isomajol;\(^{87}\) ceroplasin (TiCl\(_4\)/Zn–Cu, DME);\(^{88}\) and strigol (TiCl\(_4\)/Zn–Cu, DME).\(^{89}\) Selective coupling has also been
Table 7. Synthesis of Unusually Structured Compounds.

<table>
<thead>
<tr>
<th>Starting Material</th>
<th>Product</th>
<th>Reagent</th>
<th>Yield (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Chemical Structure" /></td>
<td><img src="image2" alt="Chemical Structure" /></td>
<td>TiCl₄/K/DME</td>
<td>13</td>
<td>90</td>
</tr>
<tr>
<td><img src="image3" alt="Chemical Structure" /></td>
<td><img src="image4" alt="Chemical Structure" /></td>
<td>TiCl₄/Zn/pyridine/THF</td>
<td>40</td>
<td>91</td>
</tr>
<tr>
<td><img src="image5" alt="Chemical Structure" /></td>
<td><img src="image6" alt="Chemical Structure" /></td>
<td>TiCl₄/Zn/THF</td>
<td>95</td>
<td>92</td>
</tr>
<tr>
<td><img src="image7" alt="Chemical Structure" /></td>
<td><img src="image8" alt="Chemical Structure" /></td>
<td>TiCl₄/Zn/dioxane</td>
<td>90</td>
<td>93</td>
</tr>
<tr>
<td><img src="image9" alt="Chemical Structure" /></td>
<td><img src="image10" alt="Chemical Structure" /></td>
<td>TiCl₄/Li/DME</td>
<td>56</td>
<td>94</td>
</tr>
<tr>
<td><img src="image11" alt="Chemical Structure" /></td>
<td><img src="image12" alt="Chemical Structure" /></td>
<td>TiCl₄/LiAlH₄/DME</td>
<td>35</td>
<td>95</td>
</tr>
<tr>
<td><img src="image13" alt="Chemical Structure" /></td>
<td><img src="image14" alt="Chemical Structure" /></td>
<td>TiCl₄/LiAlH₄/THF</td>
<td>77</td>
<td>96</td>
</tr>
<tr>
<td><img src="image15" alt="Chemical Structure" /></td>
<td><img src="image16" alt="Chemical Structure" /></td>
<td>TiCl₄/LiAlH₄/THF</td>
<td>35</td>
<td>97</td>
</tr>
<tr>
<td><img src="image17" alt="Chemical Structure" /></td>
<td><img src="image18" alt="Chemical Structure" /></td>
<td>TiCl₄/Zn/THF</td>
<td>32</td>
<td>98</td>
</tr>
<tr>
<td><img src="image19" alt="Chemical Structure" /></td>
<td><img src="image20" alt="Chemical Structure" /></td>
<td>TiCl₄/LiAlH₄/THF</td>
<td>14</td>
<td>99</td>
</tr>
<tr>
<td><img src="image21" alt="Chemical Structure" /></td>
<td><img src="image22" alt="Chemical Structure" /></td>
<td>TiCl₄/LiAlH₄/THF</td>
<td>32</td>
<td>99</td>
</tr>
<tr>
<td><img src="image23" alt="Chemical Structure" /></td>
<td><img src="image24" alt="Chemical Structure" /></td>
<td>TiCl₄/Zn/Cu/DME</td>
<td>24</td>
<td>100</td>
</tr>
<tr>
<td><img src="image25" alt="Chemical Structure" /></td>
<td><img src="image26" alt="Chemical Structure" /></td>
<td>TiCl₄/Zn/Cu/DME</td>
<td>90</td>
<td>101</td>
</tr>
<tr>
<td><img src="image27" alt="Chemical Structure" /></td>
<td><img src="image28" alt="Chemical Structure" /></td>
<td>TiCl₄/Zn/Cu/DME</td>
<td>82</td>
<td>102</td>
</tr>
<tr>
<td><img src="image29" alt="Chemical Structure" /></td>
<td><img src="image30" alt="Chemical Structure" /></td>
<td>TiCl₄/Zn/pyridine/THF</td>
<td>2</td>
<td>103</td>
</tr>
<tr>
<td><img src="image31" alt="Chemical Structure" /></td>
<td><img src="image32" alt="Chemical Structure" /></td>
<td>TiCl₄/Zn/pyridine/THF</td>
<td>16</td>
<td>104</td>
</tr>
</tbody>
</table>
applied to the synthesis of estrone, intramolecular coupling of the aldehyde group in the intermediate 56 occurs faster at the ketone group in the tetralone moiety, than with the cyclopentanone moiety, to give 57.

Intramolecular coupling of keto esters to give cyclic ketones has not been frequently applied compared to dicarbonyl coupling of aldehydes or ketones. Cyclic coupling of keto esters 58 yields cyclic ketones 59 (n = 3–8), whilst bicyclic ketones 61 can be synthesized from the cyclohexanone derivatives 60 (R = H, n = 2–6, 11; R = t-C₄H₉, n = 1).

The key step in the total synthesis of γ-caryophyllene is the intramolecular coupling of the keto ester 62 to give the ketone 63, which is further methylated. This is the only example of a double bond E/Z isomerization by low-valent titanium.

4.2. Preparation of Cyclic Diols

The reaction of ω,ω-dialdehydes 64 (n = 1, 3, 5, 7, 9) with low-valent titanium can be used for synthesis of cyclic di-α,β-diols 64 in good yields. The cis/trans ratio of the cyclic glycols is dependent upon the ring size.

Two further intramolecular coupling reactions should be mentioned. The formation of the tricyclic diols 6715 and 6913 from 66 and 63, respectively.

* Reagent: TiCl₃/Zn–Cu/DME.
* Reagent: TiCl₃/Zn/THF.
5. Reductive Eliminations

5.1. Deoxygenation of Glycols

Glycols can be deoxygenated by low-valent titanium species, some stereoselectivity is observed; for example, in the deoxygenation of meso- and 1,5,6-decadiois (70) to isomeric 5-decenes 71.4

Polycyclic 1,2-diols can only be deoxygenated if the hydroxy groups are as cis-oriented, binding together to a common titanium metal surface (see Scheme E). cis-9,10-Decalindiol (72) is deoxygenated to 9,10-decalene (73), the trans-isomer is completely inert to deoxygenation by low-valent titanium.4

1,2-Adamantandiol is not deoxygenated by low-valent titanium, even though both hydroxy groups can bind to a common metal surface.442 Deoxygenation would yield the highly strained adamantene, which would be energetically unfavorable. Both isomeric 2,3-hydroxyboranes 74 are deoxygenated to the olefin norborne (75) with low-valent titanium.4

5.2. Reductive Elimination of Other Groups

Several functional groups can be successfully subjected to reductive elimination by low-valent titanium species. Oxiranes, for example stilbene oxide (76)118 and 1,2-epoxycyclohexane (77), are reduced to the corresponding alkenes with moderate yields. Low-valent titanium species generated from titanocene dichloride/magnesium can be used for the deoxygenation of oxiranes with high selectivity (in the presence of ester groups) and stereoselectivity (with retention of configuration) in high yield (~ 90%).115 The bromohybin trans-2-bromo-1-hydroxy-cyclooctane (78) is converted to cyclooctene in 96% yield by low-valent titanium.25 This reaction has been applied to a number of bromohyrdrins, which were converted to the corresponding alkenes.25

Cyclic endo-peroxides, for example 79, give 1,3-dienes on treatment with low-valent titanium.116

1,3-Alkanediols, such as 80 yield the 1,3-coupled product 81 with inverted configuration.117 Diallylic 1,4-diol, for example 82 (and its cis-isomer), yield 1,3-dienes on treatment with low-valent titanium.117

\[
\text{82} \xrightarrow{\text{TiCl}_3/\text{LiAlH}_4/\text{THF}} \text{83}
\]

N-Hydroxyamines 84 are deoxygenated with low-valent titanium to give enamines 85.119 Aromatic nitro compounds give the corresponding coupled aza compounds in good yield.44

Synthesis of novel benzenoid molecules by low-valent titanium deoxygenation should be mentioned.119

6. Alkylidenation of Carbonyl Groups

6.1. Methylenations

Carbonyl groups of aldehydes, ketones, esters, amides, and acyl amides 86 can be efficiently methylated to compounds 87 with dicyclopentadienyl titanium methylene complex (Tebbe reagent).120,121 This is prepared from the reaction of two equivalents of trimethylaluminum with dicyclopentadienyltitanium(IV) dichloride.122 An alternative more convenient method developed by Grubbs122 uses TiCl3, Zn/CH2Cl2.

The reaction is synthetically useful for the methylation of hindered or base sensitive ketones and offers advantages over the classical Wittig reaction. Keto esters can be selectively methylated at the keto group.
The dicyclopentadienyltitanium-methylene complex can be regarded as the Lewis acid part of the Lewis acid–base complex first formed from the reagents (Scheme F).  

\[ \text{Cp}_2\text{TiCl}_2 + 2 \text{Al(CH}_3)_3 \rightarrow \text{Cp}_2\text{Ti} \quad \text{Al} \quad \text{Cp}_2\text{Ti} = \text{CH}_2 \]

Scheme F

The complex is a Schrock-type, with a 16e configuration. Its polarization results in an electrophilic metallic centre and a nucleophilic carbon centre. The same complex can also be formed from titanacyclobutanes (Scheme F).

\[ \text{Cp}_2\text{Ti} \quad \text{R} \quad \text{R} \quad \text{Cp}_2\text{Ti} = \text{CH}_2 \quad \text{Cp}_2\text{Ti} = \text{CH}_2 \]

Scheme G

The reaction proceeds by a mechanism analogous to that of the Wittig reaction leading to an oxatitanacyclobutane derivative, which undergoes cycloreversion to give the methylene compound (Scheme H).

\[ \text{Cp}_2\text{Ti} \quad \text{R} \quad \text{X} \quad \text{Cp}_2\text{Ti} = \text{O} \quad \text{R} \quad \text{X} \]

Scheme H

Five typical examples of the methylation of esters and lactones are summarized in Table 9. Entries 1–4 were performed with Tebbe’s reagent, the methylation of the cyclic carbonate leading to the ketone acetals (entry 5) with Grubbs’ reagent (dicyclopentadienyltitanacynaclobutane). The use of the latter is strongly recommended if Lewis acid labile starting materials or products are used. No racemization of chiral products is observed with this reagent.

**Table 9. Methylation of Esters and Lactones**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Starting Material</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Ester 1" /></td>
<td><img src="image" alt="Product 1" /></td>
<td>89</td>
<td>121</td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Ester 2" /></td>
<td><img src="image" alt="Product 2" /></td>
<td>96</td>
<td>121</td>
</tr>
<tr>
<td>3</td>
<td><img src="image" alt="Ester 3" /></td>
<td><img src="image" alt="Product 3" /></td>
<td>87</td>
<td>121</td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="Ester 4" /></td>
<td><img src="image" alt="Product 4" /></td>
<td>81</td>
<td>121</td>
</tr>
<tr>
<td>5</td>
<td><img src="image" alt="Ester 5" /></td>
<td><img src="image" alt="Product 5" /></td>
<td>56</td>
<td>122</td>
</tr>
</tbody>
</table>

**Preparation of Tebbe’s Reagent:** Neat AlMe3 (42 mL, 0.2 mol) is added via cannula to a suspension of dicyclopentadienyltitanium dichloride (50 g, 0.2 mol) in toluene (200 mL) under a dry N2-atmosphere with exclusion of moisture. Evolution of CH4 starts immediately. The red solution is stirred for 48 h, while all volatiles are removed by vacuum distillation into a cold trap (Cautions: all aluminum alkyls react violently with protons and pad.

To the red precipitate is added an equimolecular amount of AlMe3 (42 mL) in toluene (100 mL). The resulting solution is filtered through a pad of Celite supported on a coarse frit and concentrated to the point of saturation (~ 160 mL total volume). The saturated solution is carefully layered with an equal volume of hexane and allowed to stand undisturbed at ~ 20°C for 2–3 days. The supernatant is removed via cannula and the red crystalline mass is washed with petroleum ether (bp 60–90°C) at ~ 20°C (~3 × 10 mL). The solids are dried under high vacuum. Yields are in the range of 30–35 g (53–61%).

**Methylation of Carbonyl Compounds; General Procedure:** To a solution of the carbonyl compound (1 mmol) in THF (3 mL) is added Tebbe complex (0.5 M) in toluene (2 mL). After 30 min Et3O (ca. 10 mL) is added, and then 0.1 M aq. NaOH (10 drops) is slowly added to destroy the active aluminum compounds. The deep red reaction mixture is dried (Na2SO4) filtered, through Celite and concentrated in vacuo. The crude product is purified by chromatography on basic alumina eluting with 2:5% Et3O in pentane.

Vinyl ethers can be prepared from esters, amides are converted to enamines. Acid chlorides and anhydrides are converted into titanium enolate complexes which react further by aldol-type chemistry. The reaction of phenacyl chloride (88) with the Tebbe reagent forms the titanium enolate 89 which reacts with benzaldehyde to give the β-hydroxy ketone 90.

![Reaction Scheme](image)

This reaction has found a broad application in organic synthesis, including synthesis of natural products, which cannot be covered here in detail. A typical example is the synthesis of (+)-4,12-camphellene (96) via the adducts 91, 92.
The preparation of substituted allenes 99 by reaction of an allene 97 with a ketone 98 in the presence of Grubbs' reagent has proved to be a very useful synthetic method (Table 10).127

Table 10. Synthesis of Substituted Allenes 99 with Grubbs' Reagent

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td></td>
<td>58</td>
</tr>
<tr>
<td>CH₃</td>
<td></td>
<td>75</td>
</tr>
<tr>
<td>CH₃</td>
<td>2-adamantanone</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>cyclopentanone</td>
<td>72</td>
</tr>
</tbody>
</table>

6.2. Alkylidenations

The low-valent titanium species prepared from the reaction of titanium tetrachloride and zinc does not only couple carbonyl compounds to allenes and 1,2-diois; in the presence of 1,2-dihalo-1-allenes, alkylideneation of the carbonyl group is observed.126 Various esters 100 have been converted by this reagent into the corresponding alkenyl ethers 101 with high Z-selectivity Table 11.128

5-Methoxyundecene; Typical Procedure:126

A solution of TiCl₄ (1.0 M, 4.0 mmol) in CH₂Cl₂ is added at 0 °C to THF (10 ml) under Ar. To the yellow solution at 25 °C is added TMEDA (1.2 ml, 8.0 mmol) and the mixture is stirred at 25 for 10 min. Zn dust (0.59 g, 9.0 mmol) is added to the mixture. The color of the suspension turns from brownish-yellow to dark greenish-blue in a slightly exothermic process. The mixture is stirred at 25 for 30 min, a solution of methyl pentanoate (0.12 g, 1.0 mmol) and 1,1-dibromohexane (0.54 g, 2.2 mmol) in THF (2 mL) is added to the mixture. The color of the resulting mixture gradually turns dark brown while being stirred at 25 °C for 2 h. The mixture is cooled to 0 °C and sat. aq. K₂CO₃ (1.3 ml) is added. The mixture is stirred at 0 °C for another 15 min, then flushed with Et₂O and passed rapidly through a short column of basic alumina (activity III) eluting with Et₂O/Et₂N (200:1, 100 ml). The resulting clear solution is concentrated and the residue is purified by column chromatography on basic alumina (activity III) eluting with pentane to give the desired 5-methoxy-undecene; yield: 0.18 g (96% ), Z/E = 91:9.

7. Conclusions and Summary

The reductive coupling of aldehydes and ketones by low-valent titanium species (McMurry reaction) has greatly extended the standard potential of the olefin synthesis. In general, symmetrical 1,2-dialkyl-, trialkyl-, and tetraalkylenes are obtained in good to excellent yields. Synthesis of some unsymmetrical olefins has been achieved by mixed coupling. Mostly stereoselectivity cannot be controlled, similar to other olefin syntheses. The preparation of many new highly crowded ethenes and stilbenes has been accomplished by this method. But neither di-tert-butyl nor tert-butyl isopropyl ketone can be coupled showing the steric limitation of the reaction.

Intramolecular coupling is also possible, allowing the preparation of several new unusually structured cyclic compounds as well as a great variety of natural products. The reaction can also be performed in the presence of some other reducible moieties like halogen, methoxycarbonyl and sulfonyle groups. Using special conditions glycos, which are formed as primary products of the coupling reaction, can be prepared. The titanium methylcyclopentane complexes discovered recently by Tebbe and by Grubbs are synthetically useful for methylation of various carbonyl groups, including esters and other carboxylic acid derivatives, extending the potential of the Wittig reaction.

Low-valent titanium species are also very versatile reagents for syntheses of glycos; the alternate reagents like low-valent vanadium,7,120 samarium131 and zinc-copper in the presence of ultrasonic treatment132 have only been applied in more special cases.

Addendum. I would like to thank Prof. J. E. McMurry for valuable discussions and an exchange of information. A review written by Prof. J. E. McMurry about the same topic will appear shortly in Chem. Rev.

Received: 29 March 1989; revised: 29 August 1989

Table 11. Alkylidenation of Esters 100 to Etoh Ethers 101

<table>
<thead>
<tr>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Ratio Z/E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ph</td>
<td>Me</td>
<td>CH₁₂</td>
<td>2</td>
<td>86</td>
<td>92:8</td>
</tr>
<tr>
<td>Ph</td>
<td>Me</td>
<td>CH₂(CH₂)₂</td>
<td>2</td>
<td>79</td>
<td>96:4</td>
</tr>
<tr>
<td>CH₃</td>
<td>Me</td>
<td>CH₁₂</td>
<td>3</td>
<td>68</td>
<td>94:6</td>
</tr>
<tr>
<td>(CH₂)₂CH₂</td>
<td>Me</td>
<td>CH₁</td>
<td>3</td>
<td>53</td>
<td>89:11</td>
</tr>
<tr>
<td>(CH₂)₂CH₂</td>
<td>CH₃</td>
<td>CH₃</td>
<td>3</td>
<td>85</td>
<td>94:6</td>
</tr>
<tr>
<td>(CH₂)₂CH₂</td>
<td>Me</td>
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<td>88</td>
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</tr>
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December 1989


(110) McMurry, J. E., Rico, J. G., personal communication.


