MODERN SYNTHETIC METHODS 1983

Transition Metals in Organic Synthesis
Editor: R. Scheffold

J. K. Stille · Principles and Rules
L. S. Hegedus · Group VIII Transition Metals
J. F. Normant · Copper and Manganese
D. Seebach · Titanium and Zirconium
R. Scheffold · B_{12} and related Co-Complexes

Salle + Sauerländer

TITANIUM AND ZIRCONIUM DERIVATES IN ORGANIC SYNTHESIS

A Review with Procedures

by Professor Dieter Seebach, Dr. Beat Weidmann and Leo Widler

Laboratorium für Organische Chemie der Eidgenössischen
Technischen Hochschule, ETH-Zentrum, Universitätstrasse 16,
CH - 8092 Zürich (Switzerland)

List of Contents

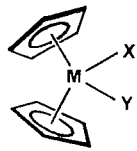
I INTRODUCTION

Derivatives of titanium and zirconium have become increasingly important in organic synthesis during the past decade. This is documented in several review articles covering different facets. These reviews will be referred to in the appropriate sections of the present treatise, which emphasizes the practical and experimental aspects. With few exceptions, we also restrict the discussion to non-catalytic uses of derivatives of these metals. Thus, their industrially important role as components of the catalytic mixtures used for *Ziegler-Natta* polymerization [1], for metathesis [2], and for nitrogen fixation [3] will not be covered here.

The laboratory use of titanium and zirconium derivatives has focused on selectivity of known transformations rather than on novel reactivity. The applications can be divided into two big groups; one includes carbon carbon bond forming processes, the other one functional group transformations. After some comments on the availability, with procedures describing the preparation and purification of starting materials, section II, these two groups of applications will be the main subject, sections III and IV.

II REAGENTS AND STARTING MATERIALS

In almost all applications simple, readily available derivatives of tetravalent titanium and zirconium are employed. The actual reagent is often generated *in situ* and may be derived from lower-valent titanium or zirconium. The original reagents are either titanocene or zirconocene derivatives 1-3 or they are halo-, alkoxy-, dialkylamino- and organometallic compounds of type MX_4 (4-13) or $XM(Y)_3$ (14-21) without π-ligands on the central atom. Many of these compounds are commercially available, see Table 1; all of them are easily prepared on large scale, see the procedures below. Unlike most other transition metal reagents, the titanium and zirconium derivatives can be employed stoichiometrically, not only because they are cheap, but also because they are non-toxic. This is especially true of the second group of reagents 4-21: on contact with water they hydrolyze to give oxide-hydrates and eventually TiO_2 or ZrO_2, highly insoluble and, if desired, readily recovered materials. In contrast, the Cp_2-derivatives are very stable to hydrolysis to the inorganic oxides. After aqueous workup, Cp_2MCl_2



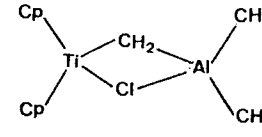
a: X = Y = Cl

b: X = Y = Br

c: X = Cl, Y = H

1: M = Ti

2: M = Zr



3

$M(Halogen)_4$:	4:	$TiCl_4$	6:	$ZrCl_4$
	5:	$TiBr_4$		
$M(OR)_4$:	7:	$Ti(OEt)_4$	9:	$Zr(OProp)_4$
	8:	$Ti(OCHMe_2)_4$	10:	$Zr(OBut)_4$
			11:	$Zr(OC_6H_5)_4 \cdot THF$
$M(NR_2)_4$:	12:	$Ti(NMe_2)_4$		
	13:	$Ti(NEt_2)_4$		
$ClM(OR)_3$:	14:	$ClTi(OCHMe_2)_3$	16:	$ClZr(OBut)_3$
	15:	$ClTi(OC_6H_5)_3$	17:	$ClZr(OC_6H_5)_3$
$XTi(NR_2)_3$:	18:	$ClTi(NMe_2)_3$		
	19:	$BrTi(NEt_2)_3$		
$RTi(OCHMe_2)_3$:	20a:	$H_3C\text{-}Ti(OCHMe_2)_3$		
	20g:	$H_5C_6Ti(OCHMe_2)_3$		

Table 1. Approximate prices of some commercially available titanium and zirconium derivatives [January 1983; see fine chemical catalogs and offers by Dynamit Nobel (Germany), DuPont (USA), Titanium Intermediates Ltd. (England); 1 $ ∿ 2 Sfr. ∿ 2.3 DM]

Compound	Mol. Wt.	Prices in $	
1a	249	15/10 g; 60/50 g	300.--/mol
2a	292	70/25 g; 200/100 g	580.--/mol
2c	258	50/5 g; 180/25 g	1,850.--/mol
4	190	15/liter	1.60/mol
5	367	65/100 g	240.--/mol
6	233	10/250 g; 30/kg	7.--/mol
7	228	30/500 ml	14.--/mol
8	284	25/500 g; 10/kg (50 kg order)	2.80/mol
9	328	10/kg	3.30/mol
10	458	50/kg; 20/kg (50 kg order)	9.20/mol
12	224	70/5 g; 260/25 g	2,330.--/mol

can be regenerated with hydrochloric acid. Otherwise, the hydrated titanocene or zirconocene can be separated from products by chromatography (see section III, F).

Some representative procedures are given on the following pages. These can also be used for the preparation of analogous starting materials.

Dicyclopentadienyl titanium and zirconium dichlorides 1a and 2a [4]

Cl_4M (4 or 6) + 2 C_5H_5Na → Cp_2MCl_2 + NaCl

A suspension of 1 mol of sodium cyclopentadienide in 1 L of dimethoxyethane is added under argon from a pressure equalized dropping funnel to a mechanically stirred mixture of 200 ml benzene and 0.5 mol MCl_4 (2 L three-necked flask, reflux condenser) at such a rate that the reaction does not become too vigorous. After the reaction mixture has cooled to room temperature, stirring is continued for 1 hour and the solvents are removed evaporatively

(water aspirator vacuum). The residue is quickly transferred into a Soxhlet thimble and extracted with ca. 500 ml $CHCl_3$, from which the product crystallizes and is filtered after cooling. Yield at least 50%. 1a: red crystals of m.p. 290°C; 2a: colorless crystals of m.p. 248°C (dec.).

Chloro-bis(cyclopentadienyl)-hydrido-zirconium (2c) [5]

$$2\ Cp_2ZrCl_2 + NaAlH_2(OCH_2CH_2OCH_3)_2 \rightarrow 2\ Cp_2ZrClH$$

To a ca. 0.2 M solution of the dichloride 2a in THF is added under argon a 0.5 mol equivalent of the reducing reagent (Vitride; as a benzene solution). The hydride 2c precipitates and is always contaminated with some NaCl, which does not interfere with subsequent reactions.

As reducing reagents, $LiAlH_4$ and $LiAl(O\text{-}t\text{-}C_4H_9)_3H$ have been recommended. The latter reagent produces analytically pure 2c after filtration and washing with THF.

Tebbe-Reagent (3) [6,7]

$$Cp_2TiCl_2 + 2\ Al(CH_3)_2 \rightarrow Cp_2Ti\begin{matrix}CH_2\\Cl\end{matrix}Al(CH_3)_2$$

A solution of 62 g of Cp_2TiCl_2 and 48 ml of Me_3Al in 250 ml of toluene is allowed to stand 60 hours at room temperature. The nonvolatile products are recrystallized from toluene to produce 35 g of crude 3 (80-90% pure). Pure samples can be obtained by recrystallization from a solution of Me_3Al in toluene and from pentane.

Purification of tetrabutoxy-zirconium (10) [8]

The commercial material contains ca. 1 equivalent of butanol per mol of 10. For many purposes, pure 10 is necessary as a starting material. Removal of the alcohol is accomplished in the following way: ca. 350 g of alcohol-containing material is heated in a 1 L flask (Aldrich Kugelrohr, Cat. No. Z 10,46-3) at 100°C/oil pump vacuum. After removal of most of the butanol, the gelatinous residue is distilled under high vacuum (200-250°C air bath temperature/0.001 Torr). The distillate has the consistency of melting glass and is dissolved in twice the volume of ether to give a stock solution for further use.

The tetrapropoxy derivative 9 is purified similarly.

Tetrakis(diethylamino)titanium (13) [9,10]

$$TiCl_4 + 4\ LiNEt_2 \rightarrow Ti(NEt_2)_4 + 4\ LiCl$$

A 2 L three necked flask equipped with a pressure equalized dropping funnel, a thermometer, and a mechanical stirrer and immersed in an ice/NaCl cooling mixture is charged under argon with 530 ml 1.55 N butyllithium in hexane

(0.82 mol). Anhydrous diethyl amine (60 g, 0.82 mol) is added at such a rate that the internal temperature is kept at -10°C. The cooling bath is removed and stirring continued at room temperature for 30 min. In the dropping funnel, a solution of 32.4 g 4 (0.17 mol) in 200 ml toluene is prepared. This red solution is added with cooling and stirring to the white $LiNEt_2$ suspension at such a rate that the temperature of the reaction mixture is maintained at ca. 10°C. The black-brown mixture is stirred at room temperature for 12 hours. The precipitate is allowed to settle, and the supernatant solution is decanted by suction through a sintered funnel under argon, using teflon tubing. The filtrate is freed of solvent under exclusion of air, and the residue distilled *in vacuo*. Yield of 13 37.5 g (66%), yellow-red liquid, b.p. 115°C/0.15 Torr, stable under an inert atmosphere.

The dimethylamino-derivative 12 is prepared similarly; a ca. 4 M, cold solution of dimethylamine in hexane is used instead of the neat diethylamine.

Chloro-triisopropoxy-titanium (14) [11,12,13]

$$3\ Ti(OCHMe_2)_4 + TiCl_4 \rightarrow 4\ ClTi(OCHMe_2)_3$$

Neat 4 (47.5 g, 0.25 mol) is added dropwise to a stirred solution of 213 g (0.75 mol) 8 in 250 ml hexane at 0°C. After warming to room temperature, the solvent is removed *in vacuo*, and the residue is distilled. Yield 245 g (94%), b.p. 60-61°C/0.2 Torr. All operations must be carried out with exclusion of moisture. The chloride 14 is highly viscous and may crystallize. With pure starting materials and accurate stoichiometry, undistilled 14 can be employed equally well for reactions. The components 4 and 8 can even be combined neat to give 14. For titanations it is useful to keep stock solutions of 14, for instance in hexane (250 g 14 diluted to 500 ml). These can easily be handled with syringes and added to organolithium or *Grignard* solutions for transmetallations.

Other halo-trialkoxy-titanium and -zirconium derivatives can be prepared in the same way. - Cf. also preparation of 19 below.

Chloro-triphenoxy-titanium (15) [14]

$$ClTi(OCHMe_2)_3 + 3\ C_6H_5OH \rightarrow ClTi(OC_6H_5)_3 + 3\ Me_2CHOH$$

To a solution of 14 (71.9 g, 276 mmol) in 500 ml toluene is added 77.9 g (828 mmol) phenol. The deep red solution is concentrated by distillation through a 10 cm *Vigreux* column which removes most of the isopropanol azeotropically. The residue is distilled in a Kugelrohr (see purification of 10, above) at 250°C/0.001 Torr to give 95.8 g (96%) 15 which crystallizes upon cooling. A 0.26 M stock solution in THF can be kept under exclusion of air.

This method of exchanging OR-groups is generally useful, for instance also for *in situ* preparation of derivatives with chiral OR-groups (see below).

Bromo-tris(diethylamino)titanium (19) [10,15]

$$TiBr_4 + 3\ Ti(NEt_2)_4 \rightarrow 4\ BrTi(NEt_2)_3$$

A 250 ml three-necked flask equipped with dropping funnel, thermometer, reflux condenser, and magnetic stirring bar (mechanical stirring in larger scale preparations!) is charged with 100 ml absol. hexane and 24.4 g (0.073 mol) 13. The yellow-red solution is cooled to -30°C under argon with stirring, and combined dropwise with a solution of 8.9 g (0.024 mol) 5 in 60 ml hexane. A dark suspension is formed which is allowed to warm to room temperature and then heated at reflux for 2.5 hours, whereupon most of the precipitate dissolves. The reflux condenser is quickly replaced by a *Liebig* condenser, and the hexane distilled off at normal pressure. The liquid residue is purified by short path distillation (b.p. 101-102°C/2x10^{-5} Torr) to give an orange-red viscous liquid which crystallizes occasionally (m.p. ca. 50°C), yield 29.6 g (89%).

Other halo-tris(dialkylamino)titanium derivatives can be prepared likewise.

Methyl-triisopropoxy-titanium (20a) [16]

$$CH_3Li + ClTi(OCHMe_2)_3 \rightarrow H_3C\text{-}Ti(OCHMe_2)_3 + LiCl$$

In a 2 L three-necked flask (dropping funnel, thermometer, Ar-inlet, magnetic stirrer) a solution of 635 ml 0.84 M CH_3Li in ether is added at -50°C within ca. 1.5 hour to a stirred solution of 125 ml (0.53 mol) 14 in 400 ml of the same solvent. After 2 hours stirring is stopped, and the cold supernatant solution is decanted from the LiCl precipitate. This is done by forcing the solution with argon pressure through teflon tubing into another flask. The solvent is removed by condensing the solvent from the magnetically stirred solution under reduced pressure into a cold trap. The residue is distilled *in vacuo* through a short path distillation apparatus. Yield of 20a 122 g (95%), bright yellow liquid of b.p. 50°C/0.01 Torr, m.p. 10°C. Samples of 20a have been kept without decomposition under an inert atmosphere in a refrigerator (ca. +5°C) for many months.

The solid phenyl derivative 20g [17] is prepared similarly. The crude product containing some LiCl is purified by extraction with pentane, rather than by distillation; 20g can be recrystallized by cooling pentane solutions to -80°C. It is a nearly colorless substance which can be stored under an inert atmosphere.

Other triisopropoxy organotitanium compounds are prepared *in situ* from 14 and the corresponding Li- or Mg-derivatives by the same type of reaction as the two derivatives described here.

III C,C-BOND-FORMING PROCESSES

There are certain selectivity problems with all classical C,C bond-forming reactions, see Scheme 1. Thus, the simple additions of nucleophilic organometallic reagents to carbonyl groups is complicated by the fact that aldehydes, ketones and esters are not well differentiated, that other electrophilic functional groups such as cyano, nitro, halo, trialkylstannyl may interfere, and that proton abstraction rather than addition occurs, see A, B, and C in Scheme 1. With α.β-unsaturated carbonyl substrates 1.2- and 1.4-additions compete and carbonyl derivatives with asymmetric carbon atoms may lead to diastereomeric mixtures, see D and E, respectively. In alkylations with halides or sulfonates β-elimination is often competing, see F. Finally, ambident nucleophiles such as metal enolates and unsymmetrically substituted allylic organometallic compounds can give rise to two constitutional isomers non-selectively, see G and H, respectively.

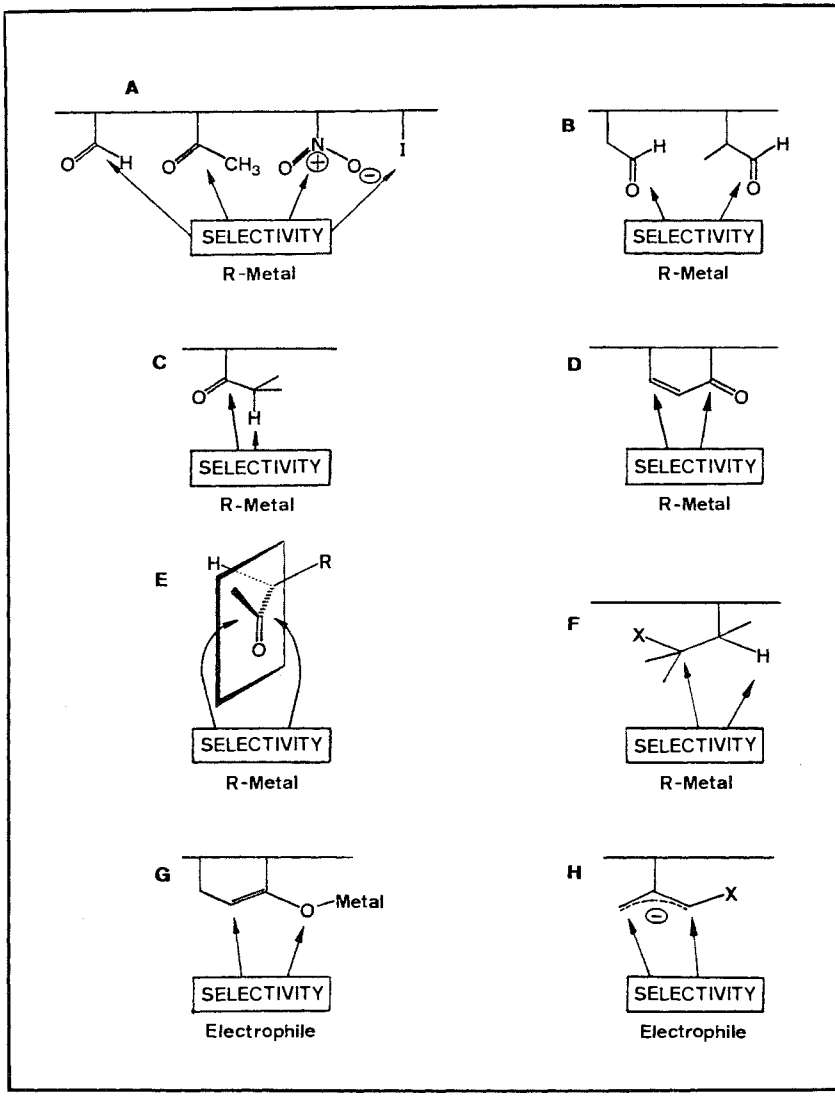
A) Nucleophilic Additions to Carbonyl Groups

We have covered the general aspects of this subject in a recent *Angewandte Chemie* review article entitled "Organometallic Compounds of Titanium and Zirconium as Selective Nucleophilic Reagents in Organic Synthesis" [18], and another survey has appeared last year [19]. We can therefore just briefly summarize the results here.

The different types of reagents which have thus far been employed for simple nucleophilic additions are shown in the Formulae 20-27, with the R-groups being specified in Table 2; for derivatives with chiral OR*-groups see section III A4, for allyl-metal reagents III F2. The titanocene and zirconocene derivatives (see 1 and 2) with alkyl and aryl groups attached to the metal are not useful for carbonyl additions. Cp_2MXR-Derivatives are used for carbonylations, for olefinations and for transfer of allylic groups, see below.

By far, most of the reagents 20-27 have been generated *in situ* by simply adding the corresponding transition metal derivatives 7, 8, 12, 13, 14-19 to the conventionally prepared organolithium or *Grignard* reagents. This trans-

Scheme 1


A
SELECTIVITY
R-Metal
B
SELECTIVITY
R-Metal
C
SELECTIVITY
R-Metal
D
SELECTIVITY
R-Metal
E
SELECTIVITY
R-Metal
F
SELECTIVITY
R-Metal
G
Metal
SELECTIVITY
Electrophile
H
SELECTIVITY
Electrophile

$R^1Ti(OR^2)_3$	$R^1Zr(OR^2)_3$	$R^1Ti(NR^2_2)_3$
20	21	22
$R^1_2Ti(X)_2$	R^1TiCl_3	R^1_4M
23	24	25 (M = Ti,Zr)
$[R^1Ti(OR^2)_4]^{\ominus}M^{\oplus}$		$[R^1Ti(NR^2_2)_4]^{\ominus}M^{\oplus}$
26	(M = Li or MgX)	27

metallation reaction is essentially instantaneous with titanium, even at low temperatures; with zirconium longer reaction times and higher temperatures up to 0°C may be required [8]. The reagents 20-27 are surprisingly stable. The R^1-groups attached to the metal may be varied widely (Table 2): primary, secondary and even tertiary alkyl, allyl, propargyl, vinyl, aryl, α- and β-heterosubstituted alkyl and aryl. Some simple rules about stability and reactivity are:

(a) The reactivity of the Ti-derivatives has been found to increase in the order $(R'_2N)_3TiR < (R'O)_3TiR < Cl_3TiR \ll (RO)_2TiR_2$, Cl_2TiR_2.

(b) The stability decreases in the same order: the aminoderivatives 22 with β-hydrogens on the R^1-groups can be distilled at temperatures up to 100°C, while the trichloro-analogues are unstable even in solution at low temperatures.

(c) The zirconium derivatives $(R'O)_3ZrR$ are more stable with respect to all processes which occur with reduction of the metal, such as β-hydrogen elimination, reductive elimination and one-electron transfer to electrophiles.

Table 2. List of organotitanium and -zirconium reagents of types 20-27 which have been used for C,C bond forming reactions. Allylic derivatives of this type are collected separately (Table 5), see section F3.

No.	R^1	R^2 (X, M)	Ref.
20a	CH_3	$CHMe_2$	20,21)
20b	CH_3	C_6H_5	19)
20c	C_2H_5	$CHMe_2$	19)
20d	n-C_4H_9	$CHMe_2$	22)
20e	$CH(CH_3)_2$	$CHMe_2$	12)
20f		$CHMe_2$	23)
20g	C_6H_5	$CHMe_2$	17,20,21)
20h		$CHMe_2$	23)
20i		$CHMe_2$	22)
20j	C_6F_5	$CHMe_2$	19,24)
20k	C_6H_5-S-CH_2	$CHMe_2$	22)
20l		$CHMe_2$	22)
20m	$(Me_3Si)_3C$	$CHMe_2$	22)
20n		$CHMe_2$	23)
20o	$(C_6H_5)_2AsCH_2$	$CHMe_2$	25)
20p	$(C_6H_5)_2SbCH_2$	$CHMe_2$	25)
21a	CH_3	C_4H_9	8)
21b	CH_3	C_3H_7	26)

No.	R^1	R^2 (X, M)	Ref.
21c	CH_3	C_6H_5	27)
21d	C_4H_9	C_4H_9	8)
21e	t-C_4H_9	C_4H_9	8)
21f		C_4H_9	8)
21g	C_6H_5	C_4H_9	8)
21h	C_6H_5	C_6H_5	27)
21i		C_4H_9	8)
22a	CH_3	C_2H_5	19,28)
22b	CH_3	$-(CH_2)_5^-$	28)
22c	C_4H_9	C_2H_5	28)
23a	CH_3	(X = $OCHMe_2$)	29)
23b	CH_3	(X = Cl)	21,30,31,32)
23c	C_2H_5	(X = Cl)	32)
23d	C_4H_9	(X = Cl)	32)
23e	C_6H_5	(X = Cl)	21)
24a	CH_3	---	21,30,32,33)
24b	C_6H_5	---	21)
24c	$(H_3C)_3Si-CH_2$	---	34)
25a	CH_3	(M = Ti)	26)
25b	CH_3	(M = Zr)	26)
26a	CH_3	$CHMe_2$ (M = Li)	10,19)
26b	CH_3	$CHMe_2$ (M = MgI)	19)
27	CH_3	C_2H_5 (M = Li)	10)

1) Selectivity of Addition

The most characteristic difference between the reagents $(R'O)_3MR$ (20, 21) and the classical nucleophilic reagents RLi and RMgX is the selectivity of the transition metal derivatives. Thus, $CH_3Ti(OCHMe_2)_3$ (20a) adds to benzaldehyde within a few hours at -60°C, while acetophenone requires room

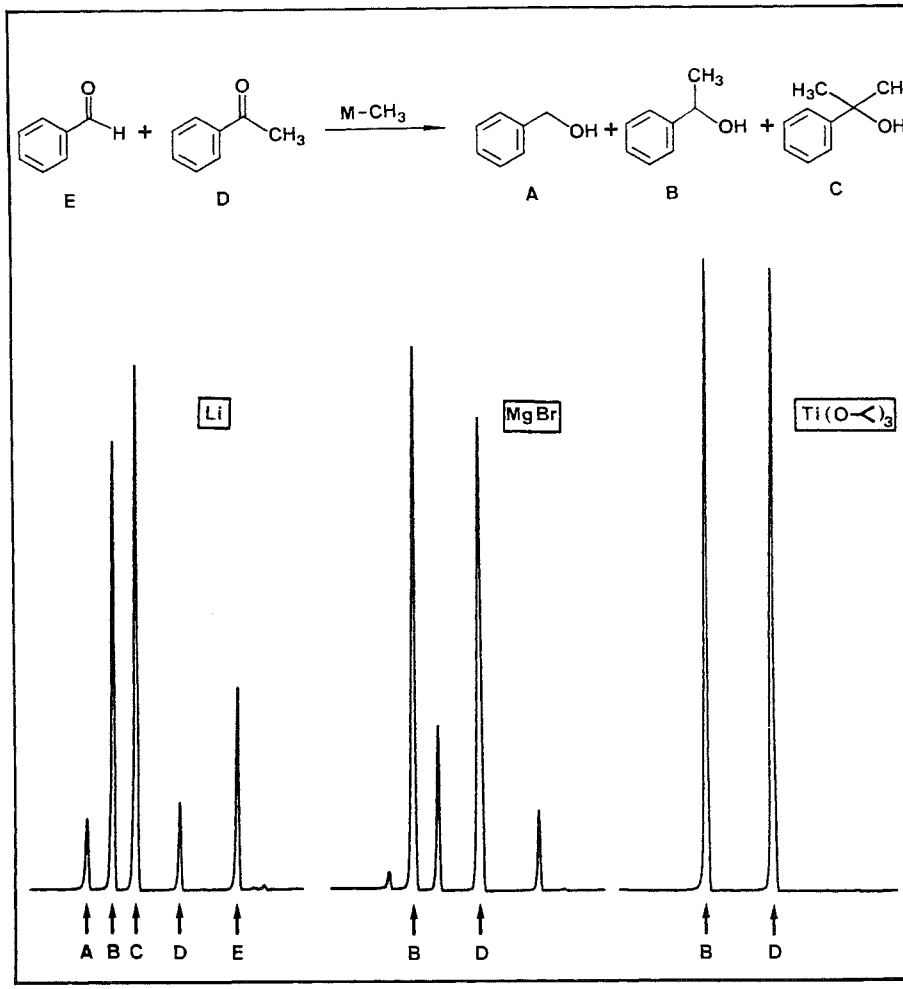


Fig. 1. Comparison of the 1:1:1 reactions of methyl-metal derivatives with benzaldehyde and acetophenone in ether at room temperature. The titanium reagent distinguishes perfectly between aldehyde and ketone! (The reactions with CH_3Li and CH_3MgBr are further complicated by the occurence of aldol reactions between the carbonyl compounds.)

temperature to give the adduct within a similar period of time. Addition of 20a to a 1:1 mixture of benzaldehyde and acetophenone in THF at room temperature produces only the adduct to the aldehyde, see Figure 1 and Figure 2 [20]. As is evident from Table 3, branched and unbranched aldehydes, cyclic and acyclic ketones, terminal and non-terminal ketones, and saturated and α.β-unsaturated ketones can also be distinguished with excellent selectivity. The examples in Scheme 2 show that other functional groups, such as COOR, $CONR_2$, CN, $C\text{-}NO_2$, C-halogen, and C-O-C do also not interfere with the addition to aldehyde groups.

Epoxides are also inert. The functional group selectivity of these new nucleophilic reagents $(R^2O)_3MR^1$ allows their use in solvents, such as acetonitrile, carbon tetrachloride, chloroform, and methylene chloride, which are not compatible with Li- and MgX-derivatives. To avoid hazardous ether solvents is attractive for industrial applications; for this purpose, the organotitanium compounds can even be generated directly in these solvents, using dialkylzinc or trialkylaluminium instead of RLi or RMgX [35].

The halogeno-titaniumorganic compounds (23,24), the tris(dialkylamino)-(22) and the ate-complexes (26,27) do not appear to be suitable for simple nucleophilic additions of alkyl and aryl groups to aldehydes or ketones; for their applications see later sections.

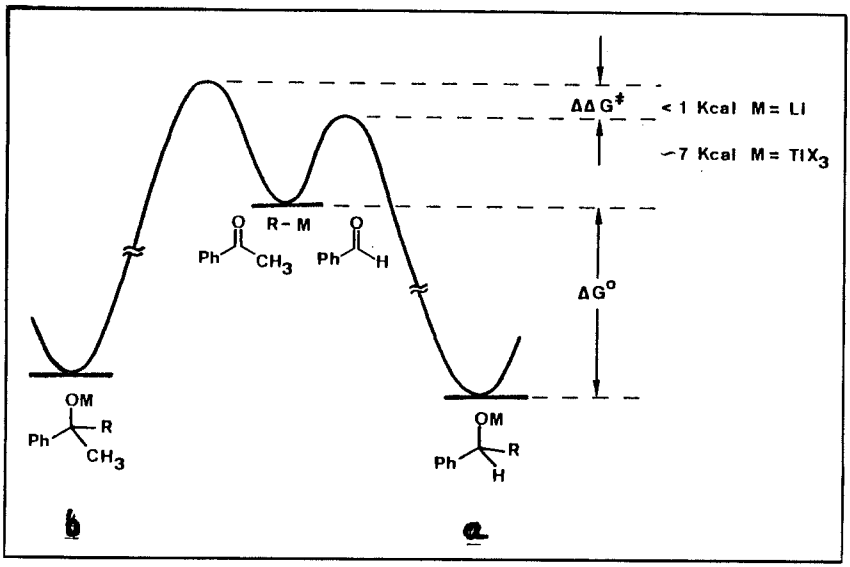


Fig. 2. Selectivity of organolithium and organotitanium reagents in reactions with 1:1 mixture of benzaldehyde and acetophenone. Reaction energy profile and examples.

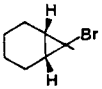
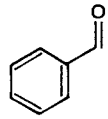
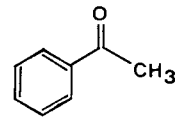
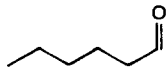
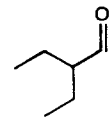
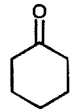
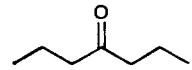
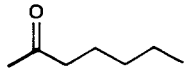
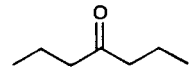
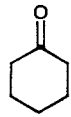
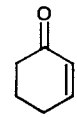
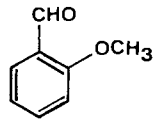
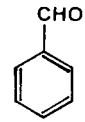
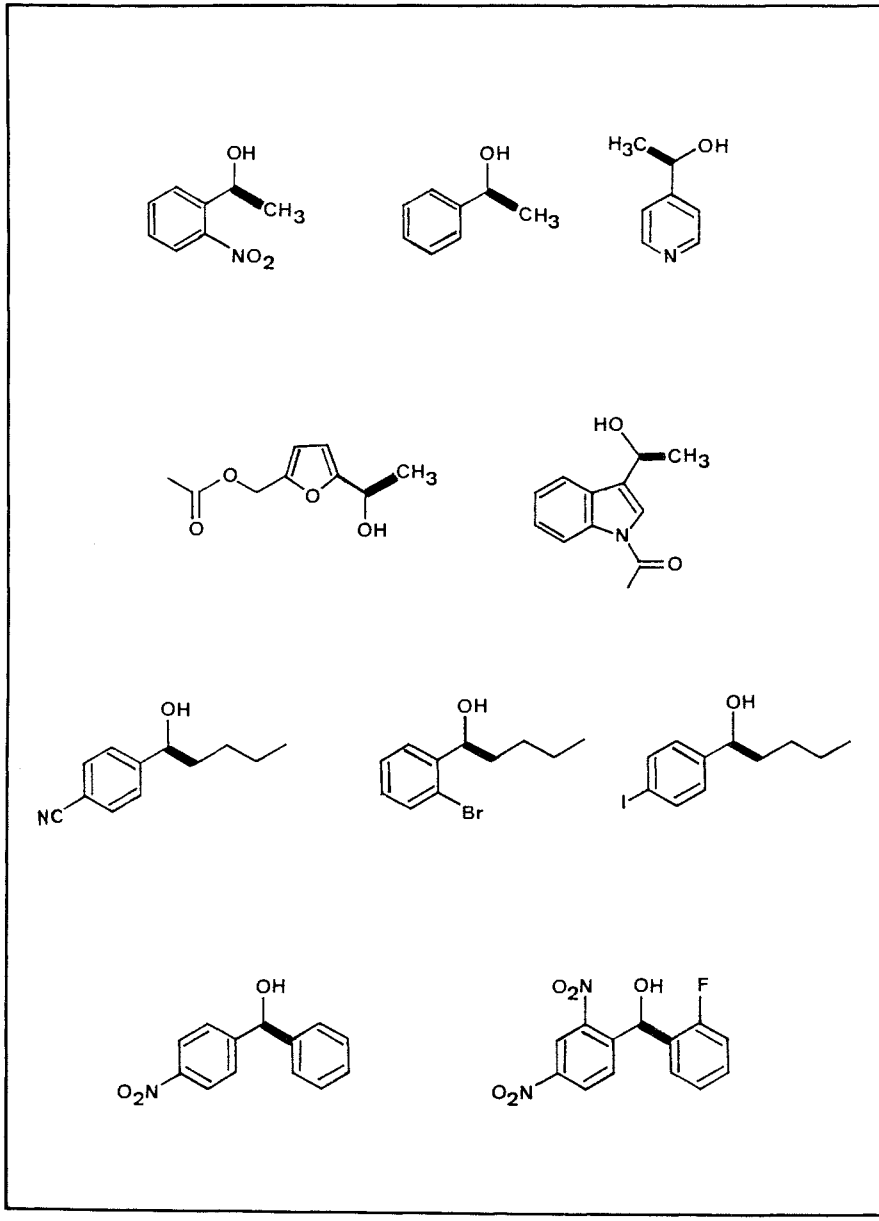
R- in R-Li and R-Ti($OiPr$)$_3$	Li-Reagent [°C]	a / b	Ti-Reagent [°C]	a / b
H_3C-	20	40 / 60	20	>98 / 2
H_5C_6-	0	40 / 60	0	>98 / 2
		--	-95 → r.t.	>98 / 2
		--	-80 → r.t.	>98 / 2
	-80	33 / 67	-80 → r.t.	>95 / 5
$H_5C_6SCH_2$-	-50	67 / 33	20	>98 / 2
	-70	67 / 33	20	>98 / 2
		--	-95 → r.t.	>98 / 2

Table 3. Selectivities in intermolecular competitions of CH_3-addition with $CH_3Ti(OCHMe_2)_3$ (20a) to pairs of carbonyl compounds in THF [19,20].

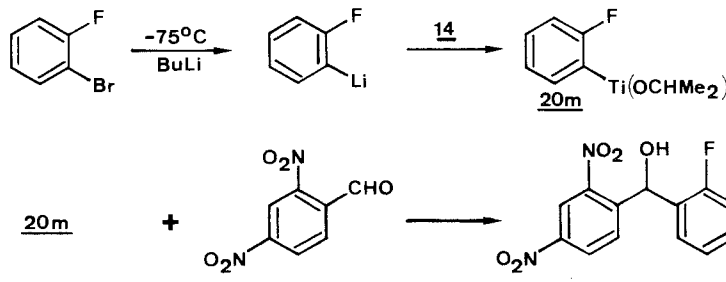
substrate pair		% selectivity
more reactive	less reactive	
		>99.9
		92
		>97
		85
		94
		87

Of the following two typical procedures, the first one demonstrates the stability and the small tendency of trialkoxy-organotitanium compounds to do one-electron transfer. In the second procedure, the butyltitanium 20d is added to iodo-benzaldehyde to give the carbonyl adduct, which is not formed with butyllithium because of attack at iodine.

Scheme 2. Adducts of organotitanium reagents of type R-Ti($OCHMe_2$)$_3$ to multifunctional aromatic aldehydes. The newly formed bonds are indicated by heavy lines. All yields are high [19,20].

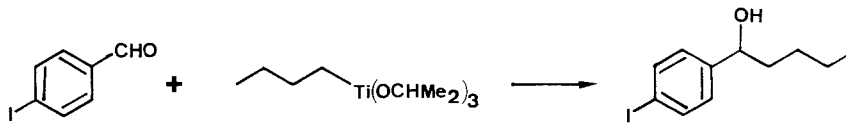


(o-Fluorophenyl)-triisopropoxy-titanium (20i) and its addition to 2.4-dinitrobenzaldehyde to give 2-fluoro-2'.4'-dinitro-benzhydrol [22]



A solution of 1.08 ml (10 mmol) 2-fluoro-brombenzene in 20 ml THF is treated with butyllithium in hexane (6.3 ml, 10 mmol) at -100°C. After 10 min. $ClTi(OCHMe_2)_3$ (14) (4.4 ml, 2.27 M in hexane) is added dropwise and the solution allowed to reach room temperature. (20i may be isolated similarly to 20g). After the addition of 2.4-dinitrobenzaldehyde (1.57 g, 8 mmol, in 5 ml THF) stirring is continued for 1 hour. Extractive workup (1 M HCl/ether) provides 2.28 g (98% yield) of the desired carbinol, m.p. 94-95 C°(ether/pentane).

1-p-Iodophenyl-1-pentanol [22]

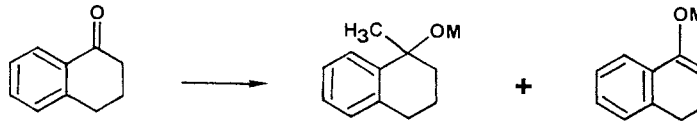


At -15°C butyllithium in hexane (6.33 ml, 10 mmol) is added to 2.2 ml (5 mmol) of 14 (2.27 M in hexane), diluted with 10 ml anhydrous ether. After the solution has been stirred for 1 hour at that temperature, p-iodobenzaldehyde dissolved in 10 ml THF is added and stirring is continued for 15 hours at room temperature. Extractive workup (1 M HCl/ether) affords 1.19 g (82%) spectroscopically pure 1-p-iodophenyl-1-pentanol.

2) Nucleophilicity vs. Basicity

The problem of enolate instead of adduct formation from certain ketones can not always be avoided with $(RO)_3Ti$-derivatives. The nucleophilicity can, however, be enhanced by two modifications, see Scheme 3 and Scheme 4. One is to switch for instance to the dimethyl-titanium [19] derivative 23a,

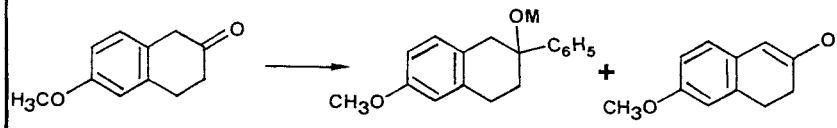
Scheme 3



CH_3-Ti$(OCHMe_2)_3$ (20a) 50 : 50

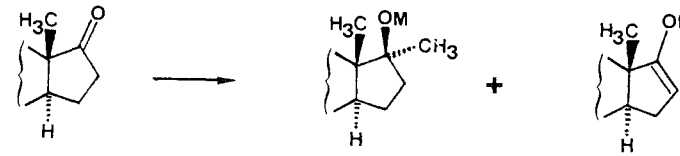
$(CH_3)_2$Ti$(OCHMe_2)_2$ (23a) 90 : 10

CH_3Zr$(OBut)_3$ (21a) 90 : 10



C_6H_5Ti$(OCHMe_2)_3$ (20g) 25 : 75

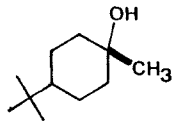
C_6H_5Zr$(OBut)_3$ (21g) 90 : 10



(pregnenolone) 20a 5 : 95

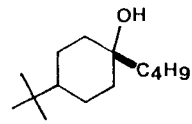
21a 80 : 20

Scheme 4. Adducts obtained from ketones and $RZr(OBut)_3$ (21). The newly formed bonds are indicated by heavy lines. % ds gives the diastereoselectivity [37] of addition [8,12].



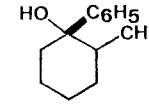
95%

(80% ds)



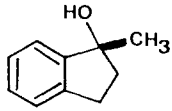
78%

(85% ds)

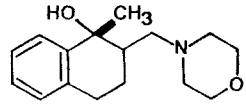


90%

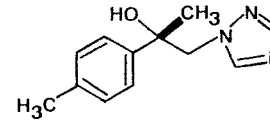
(>95% ds)



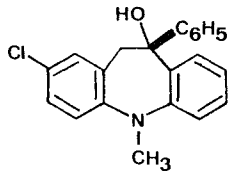
84%



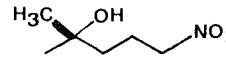
80%



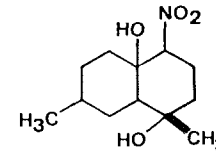
60%



78%



72%



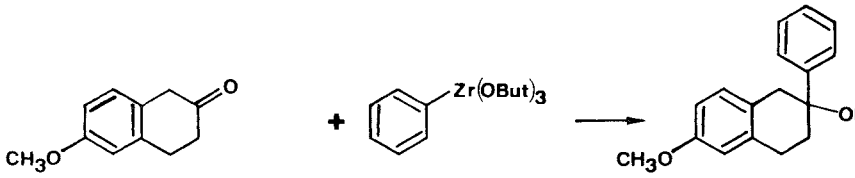
74%

(one Diastereomer)

with the obvious disadvantage that only half of the CH_3-groups of the reagent are transferred. The other, more general and more useful method is the employment of zirconium derivatives of type 21 which are much more nucleophilic than the titanium analogues. Their drawback is that they may transfer hydride from the α-OCH-position, see section IV 1. For two applications of organozirconium reagents see the accompanying procedures, one of which also demonstrates the functional-group selectivity and diastereoselectivity.

The ate-complexes 26 appear to be especially basic: Upon addition of acetophenone to $[CH_3Ti(OCHMe_2)_4]Li$, vigorous methane gas evolution ensues, and the ketone is recovered after workup [10].

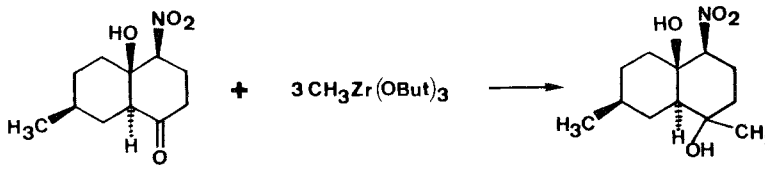
6-Methoxy-2-phenyl-1.2.3.4-tetrahydro-2-naphthol [12]



(21g)

At -20°C, 1.25 ml (2.5 mmol) phenylmagnesiumbromide (2 M in THF) and 1.25 ml (2.55 mmol) $ClZr(OBu)_3$ (16) (2.04 M in hexane) are combined to yield after stirring for 1 hour at -10°C the reagent 21g. The resulting solution is then treated with 300 mg (1.7 mmol) 6-methoxy-2-tetralone [38]. After one day at room temperature, 330 mg of the title compound (together with ca. 10% of starting material) is isolated by pouring into neutral 20% KF-solution and extracting with ether. Recrystallization from CH_2Cl_2/pentane affords colorless crystals of m.p. 88-89°C.

5,8-Dimethyl-2-nitro-bicyclo[4.4.0]decan-1,5-diol [8]



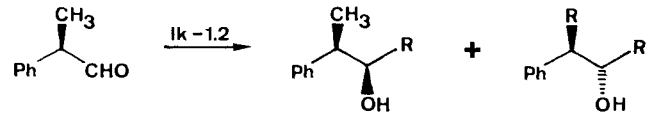
(21a)

A solution of 1.5 ml (3.1 mmol) $ClZr(OBu)_3$ (2.04 M in hexane) is diluted with 6 ml dry ether and treated with 1.75 ml (3 mmol) methyllithium (1.71 M in ether) at -20°C. After stirring 1 hour at -10°C, 223 mg (1 mmol) of 1-hydroxy-2-methyl-2-nitro-bicyclo[4.4.0]decan-5-on [39] dissolved in 2 ml CH_2Cl_2 is added. Progress of the reaction is followed by TLC. After 15 hours, the reaction mixture is hydrolyzed with 20% neutral KF-solution and the product extracted with ether. Removal of the solvent is followed by purification with prep. TLC (silicagel, CH_2Cl/EtOAc 10:1). The product obtained (178 mg, 74%) is a highly viscous, slightly yellow oil, which was found to consist of a single diastereomer (^{13}C-NMR), the configuration of which was not determined.

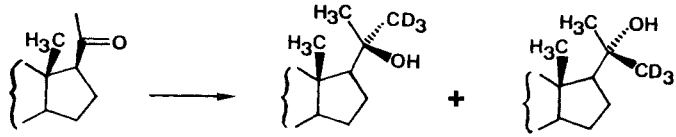
3) Diastereoselectivity

As might be expected, the $(RO)_3M$-derivatives are also more diastereoselective than their Li- and XMg-counterparts. An example is the addition of the methylzirconium 21a to a decalone in the preceding procedure, which furnishes a single diastereomer of as yet unknown configuration, cf. also some of the products from organozirconium derivatives listed in Scheme 3, above. For 1.2-, 1.3-, and 1.4-asymmetric inductions [40] observed in additions of organotitanium compounds, see the reactions in Scheme 5 and Scheme 6. Diastereoselective additions of crotyl and other allylic and also of propargylic Ti- and Zr-reagents are dicussed in section III F.

Scheme 5. Asymmetric inductions in the additions of methyl- and butyl-titanium derivatives to aldehydes and ketones containing asymmetric centers [19,26]. The relative topicities are specified *lk* (*Cram*'s rule), except in the last case.

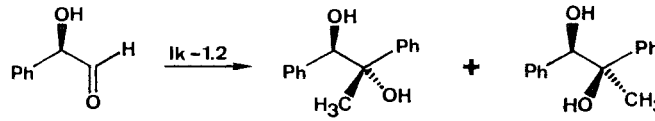


CH_3Li or CH_3MgCl		66 : 34
$CH_3Ti(OC_6H_5)_3$	(20b)	93 : 7
$n\text{-}C_4H_9Ti(OCHMe_2)_3$	(20d)	89 : 11

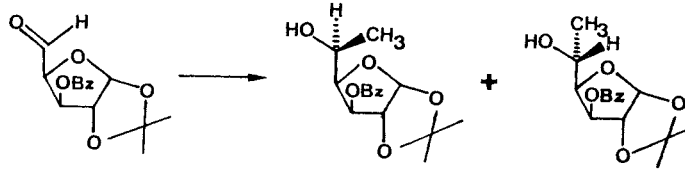


pregnenolone

$D_3CTi(OCHMe_2)_3$	96 : 4

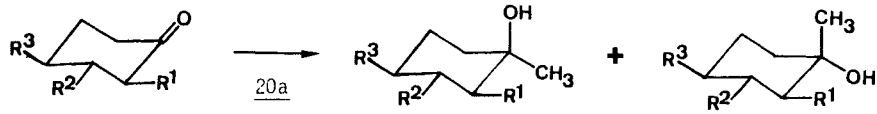


CH_3MgI		96 : 4
$CH_3Ti(OCHMe_2)_3$	(20a)	>99 : 1



CH_3MgX	(*lk* -1.2)	88 : 12
20a	(*ul*-1.2)	<2 : >98

Scheme 6 [19,20]

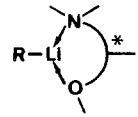


$CH_3Ti(OCHMe_2)_3$ (20a)

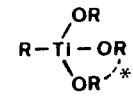
$R^1 = CH_3$, $R^2 = R^3 = H$	94 : 6
$R^2 = CH_3$, $R^1 = R^3 = H$	89 : 11
$R^3 = CH_3$, $R^1 = R^2 = H$	88 : 12
$R^3 = t\text{-}C_4H_9$, $R^1 = R^2 = H$	94 : 6

4) Enantioselectivity

There have been numerous attempts [41-44] to render organolithium and -magnesium compounds enantioselective by complexation with chiral amines, ethers, and aminoethers, see 28. Only special combinations of RLi and R'CHO gave inductions which are high enough for practical purposes. The organotitanium derivatives of type 29 are expected to give higher enantioface-differentiations because their chiral OR*-groups are bonded less loosly to



28

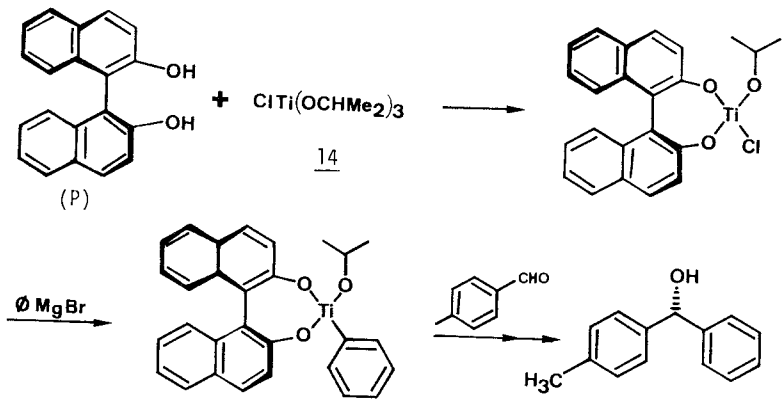


29

(see Scheme 7 for specification of R*)

the metal. Furthermore, a rational design of ligands for titanium appears to be easier. Scheme 7 contains all the chiral reagents tested so far, and in Table 4 the results of the inductions are listed. A more detailed discussion is given in the review article [18] mentioned above. It suffices to point out here, that the hitherto highest degrees of asymmetric inductions of the addition of phenyl groups and of methyl groups to aldehydes have been achieved with this new method; enantiomeric excesses above 50% are not rare (Table 4). Two procedures describe the method of attaching the chiral OR*-groups to titanium and of carrying out the additions.

(S)-(-)-p-Methyl-benzhydrol of 88% e.e. [12]



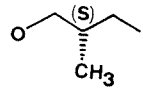
m (see Scheme 7)

To a solution of (S)-(-)-binaphthol (750 mg; 2.62 mmol) in 100 ml benzene is added an equimolar amount of 14. The solvent is carefully removed by fractionating through a 10 cm *Vigreux* column. The gradually rising boiling temperature indicates the change from benzene/2-propanol azeotrope (b.p. 71°C) to pure benzene. The residue which may retain some benzene is dissolved in 30 ml THF and treated at -20°C with 1.3 ml (2.60 mmol) phenylmagnesiumbromide (2 M in THF). After stirring for 1 hour at -20°C, p-tolylaldehyde (203 mg, 1.7 mmol) is added. The solution is allowed to reach room temperature overnight and is hydrolyzed with 20% neutral KF-solution. The combined ethereal extracts are washed three times with 1 N NaOH to remove the freed chiral ligand (which can be recovered in 70-80% yield by acidification of the aqueous layer with conc. phosphoric acid). After distillation (b.p. 120°C/0.05 Torr) (S)-(-)-p-methyl-benzhydrol (250 mg) is obtained in 74% yield and 88% e.e. $[\alpha]^{25}_{D} = -8.84^{o}$ (c = 4.8 in benzene).

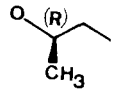
Scheme 7. Different types of chiral, non-racemic Ti-derivatives which have been tested so far in asymmetric additions to aldehydes and a ketone. For applications see Table 4.

R-Ti(OR*)$_3$

a CH_3



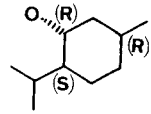
b CH_3



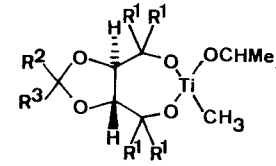
c CH_3

d C_6H_5

e 1-naphthyl

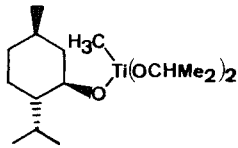


R-Ti(O')(OR*)$_2$

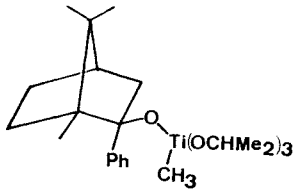


	R^1	R^2	R^3
f	CH_3	CH_3	CH_3
g	C_6H_5	CH_3	CH_3
h	CH_3	H	$C(CH_3)_3$

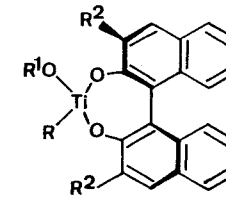
R-Ti(COR')$_2$OR*



n

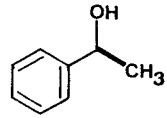


o

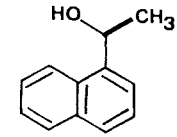


	R	R^1	R^2
i	CH_3	CH_2CH_3	H
j	CH_3	$CHMe_2$	H
k	CH_3	CMe_3	H
l	CH_3	$CHMe_2$	CH_3
m	C_6H_5	$CHMe_2$	H

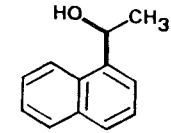
Table 4. Asymmetric additions of chiral organotitanium derivatives a - o (specification see in Scheme 7) to aldehydes.



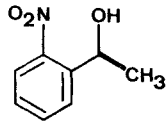
8% e.e.	(S)	with	a
12%	(S)		b
23%	(S)		c
20%	(R)		f
70%	(S)		g
32%	(R)		h
28%	(S)		i
59%	(S)		j
66%	(S)		k
54%	(S)		l
13%	(S)		n



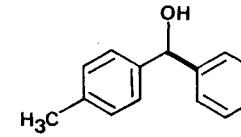
58% e.e.	(S)	with	c
25%	(R)		f
33%	(S)		g
46%	(S)		j
40%	(S)		l



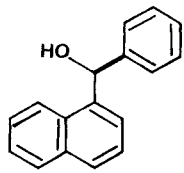
5% e.e. (R) with e



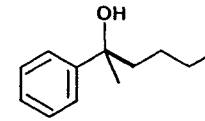
76% e.e. (S) with c



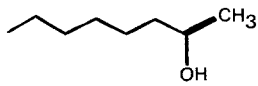
29% e.e.	(R)	with	d
88%	(S)		m
67%	(R)		h



>80% e.e. with m

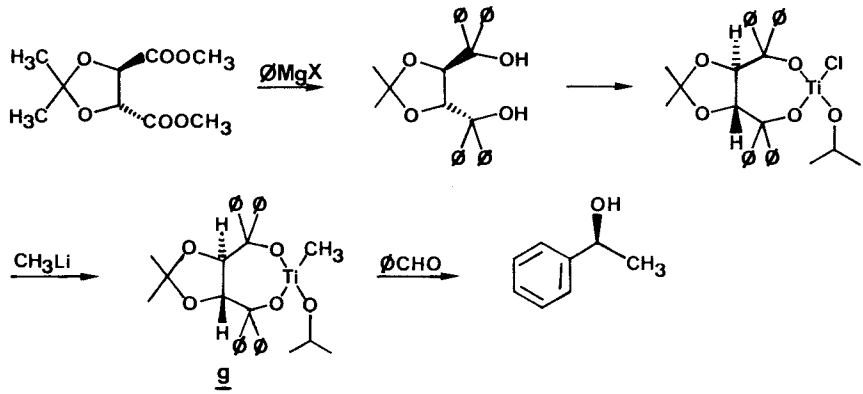


~40% e.e. with j



52% e.e. (S) with g

(S)-(-)-1-Phenyl-ethanol of 70% e.e. [45]



g

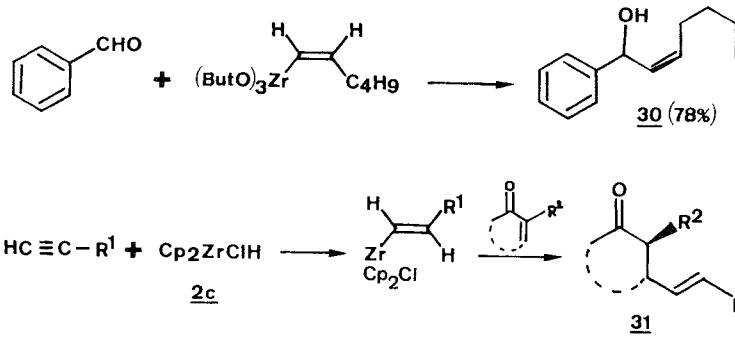
In a 1 L three-necked flask, equipped with a reflux condenser and a dropping funnel, is placed 9.72 g (0.40 g atoms) of magnesium turnings in an argon atmosphere. Ether (40 ml) is added to cover the magnesium and the reaction started through addition of ca. 2 ml bromobenzene and heating to reflux. The remaining bromobenzene (42 ml, 0.40 mol, total) dissolved in 80 ml of ether is added at such a rate that a moderate reflux is maintained. After the addition has been completed (ca. 1.5 hours), the solution is refluxed for 1 hour. The brown *Grignard* solution is then cooled to room temperature and diluted with 200 ml of ether. To this mixture the tartaric ester derivative[46] (dissolved in 100 ml of ether) is added from the dropping funnel. A vigorous reaction is observed and a yellow solid precipitates. After the addition is complete (ca. 90 min.), the reaction mixture is refluxed for 2 hours and then stirred for an additional 4 hours at room temperature. The flask is then placed in an ice-bath and the mixture hydrolyzed by the slow addition of 300 ml of a saturated NH_4Cl solution. The two layers are separated and the aqueous phase is extracted four times with ether. The combined etheral extract is washed twice with saturated aqueous NaCl-solution, dried and concentrated. The crude product is suspended in 100 ml of pentane and stirred for 1 hour at room temperature. The product is collected on a *Büchner* funnel and washed with 100 ml of pentane. Repeating this purification procedure yields 17.15 g (74% yield) of (2R,3R)-1.1.4.4-tetraphenyl--2.3-(2-propylidenedioxy)-butan-1.4-diol; m.p. 190-192°C. $[\alpha]_D$ = -59.2° (c = 1, $CHCl_3$).

A solution of 2.80 g (6.00 mmol) of the diol in 160 ml of anhydrous toluene is treated with 4.8 ml (6.00 mmol) of 14 (1.25 M in hexane). Through azeotropic distillation, 2-propanol is removed from the mixture. The residue, a brown oily liquid, is dissolved in 50 ml of ether and cooled to -15°C. After addition of 4 ml (5.92 mmol) of MeLi (1.48 M in ether), stirring is continued for 1 hour. The brown suspension is cooled to ca. -20°C and 0.5 ml (4.95 mmol) of benzaldehyde added. The reaction mixture is allowed to come

to room temperature overnight, is hydrolyzed with 20% neutral KF-solution and extracted with ether. The crude product is purified by flash-chromatography, employing ether/pentane 1:2 as eluant. The chiral auxiliary, which is eluted first, is recovered in nearly quantitative yield. 0.58 g (4.75 mmol) of methyl-phenyl-carbinol is obtained corresponding to a yield of 96%; $[\alpha]_D = -31.8^o$ (c = 5.1 in ethanol); e.e. = 70%.

B) *Michael* Additions

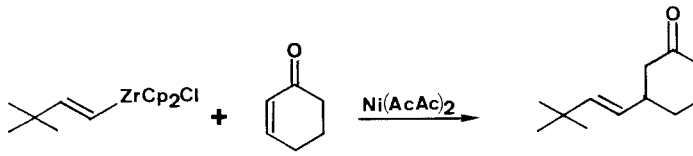
In the previous section, it was shown that the reagents of type $R^1M(OR^2)_3$ (20,21) are most useful for simple, highly selective additions to aldehydes and ketones. These same reagents show no tendency to add in a 1.4-fashion to α.β-unsaturated aldehydes and ketones [20,47]. Together with the fact that E/Z isomeric vinylzirconium derivatives react without loss of configurational purity, see formation of 30 [12], this may be taken as evidence [48] that no one-electron transfer is involved in their reactions. In



contrast, the vinyl Cp_2ZrCl-derivatives can be caused to add to the 3-position of enones exclusively in a nickel-catalyzed process [49]. The reactive species is probably an organonickel compound. The reaction furnishes *trans*-2.3-disubstituted ketones 31 from α-substitued cyclic enones. No *Michael* addition occurs with the alkyl analogues under these conditions. Since the vinylic reagents are made by hydrozirconation of acetylenes [50] (section IV D), an overall stereoselective reductive *Michael* addition of acetylenes to enones can be achieved.

Titanium mediated *Michael* additions of silyl enolethers will be mentioned in section III E3.

3-((E)-3.3-Dimethyl-1-butenyl)-cyclohexanone [51]

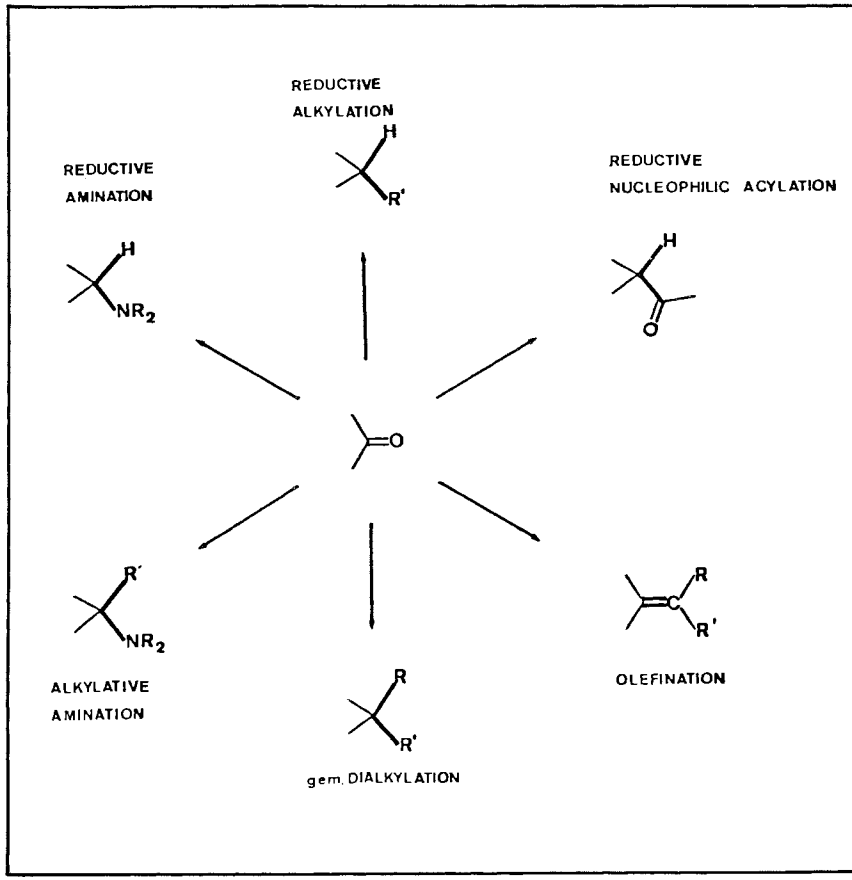


A solution of the vinylzirconium complex (1.92 g, 5.67 mmol, from 2c and *t*-butylacetylene) and 2-cyclohexenone (0.62 g, 6.48 mmol) in 30 ml THF is stirred under argon at $0^{\circ}C$. After addition of 0.15 g (0.59 mmol) $Ni(AcAc)_2$ stirring is continued in an ice-bath for 6.5 hours. Workup after quenching with saturated NH_4Cl by extraction with ether, washing of the ether solution with $NaHCO_3$ and brine, drying and evaporation of solvents gives after column chromatography 0.744 g (73%) of the $\gamma.\delta$-unsaturated ketone.

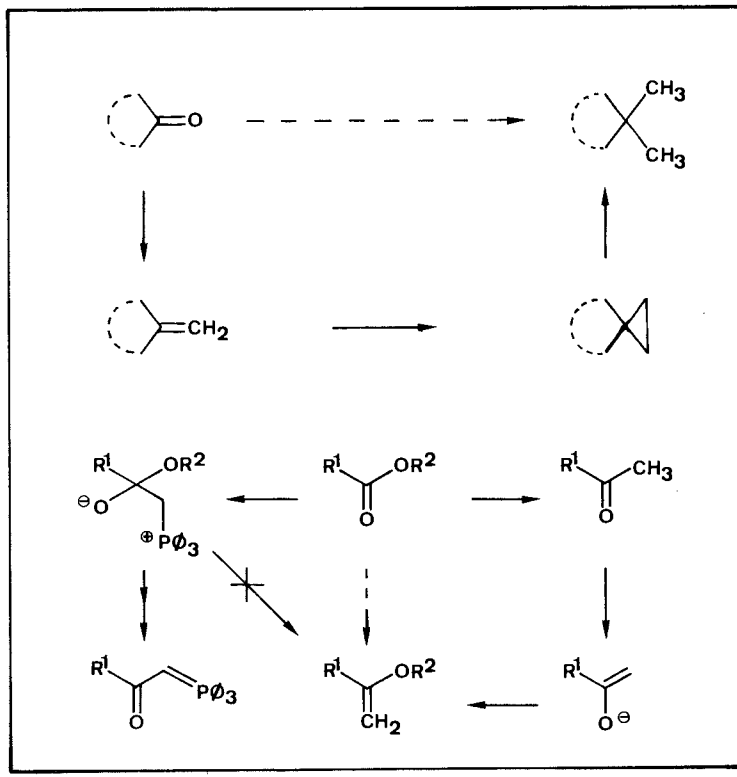
C) Olefination and Other Transformations of Carbonyl Derivatives with Removal of the Carbonyl Oxygen

There is a family of transformations by which the oxygen atom of carbonyl derivatives is replaced, Scheme 8. The methods of achieving such transformations are often elaborate, require several steps or are not applicable to certain types of carbonyl substrates. Thus, the geminal dimethylation is normally carried out by the three-step sequence olefination, cyclopropanation, hydrogenolysis, Scheme 9 (top). Another example is the conversion of carboxylic acid derivatives to heterosubstituted olefins, formally a *Wittig* reacton; since acylation of the *Wittig* reagents occurs instead of olefination, a conversion to a methylketone and its subsequent regioselective transformation are necessary, Scheme 8 (bottom part). Again, there are recent titanium-based methods by which this and other processes such as aminative alkylation can be achieved in one-pot reactions.

Scheme 8.


REDUCTIVE
ALKYLATION
REDUCTIVE
AMINATION
REDUCTIVE
NUCLEOPHILIC ACYLATION
ALKYLATIVE
AMINATION
OLEFINATION
gem. DIALKYLATION

Scheme 9. Multistep conversion of a ketone to a gem. dimethyl derivative and of an ester to an enol ether by conventional methods.

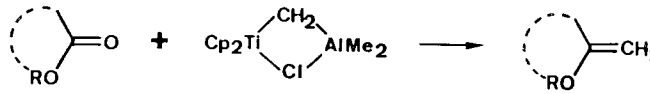


1) Olefinations with the *Tebbe* Reagent (3)

The methylene complex 3 was first prepared and characterized by *Tebbe* [6] who noticed that it smoothly converts cyclohexanone to methylene-cyclohexane, a reaction which can be carried out with *Wittig's* less fancy phosphorous ylid reagent. In the meantime, simple procedures for the preparation of 3 have been elaborated, and it is likely that 3 will be commercially available, shortly. Substituted methylene complexes of this type, with CHR instead of CH_2, have become accessible just recently [52]. The increased interest is not only due to numerous reports about the use of 3 in meta-

theses [53] but especially because it was found [54] that esters and lactones are directly converted to enol ethers by this reagent. The process is shown in Scheme 10, together with a number of examples. The reaction is not ester-selective, i.e. aldehyde and keto groups in the same molecule also undergo olefination. On the other hand, ether, thioether, and conjugated and non-conjugated olefinic double bonds are compatible with this new method of olefination. A new strategy of preparing intermediates for intramolecular *Diels-Alder* additions and for *Claisen* rearrangements is thus practicable, see bottom part of Scheme 10.

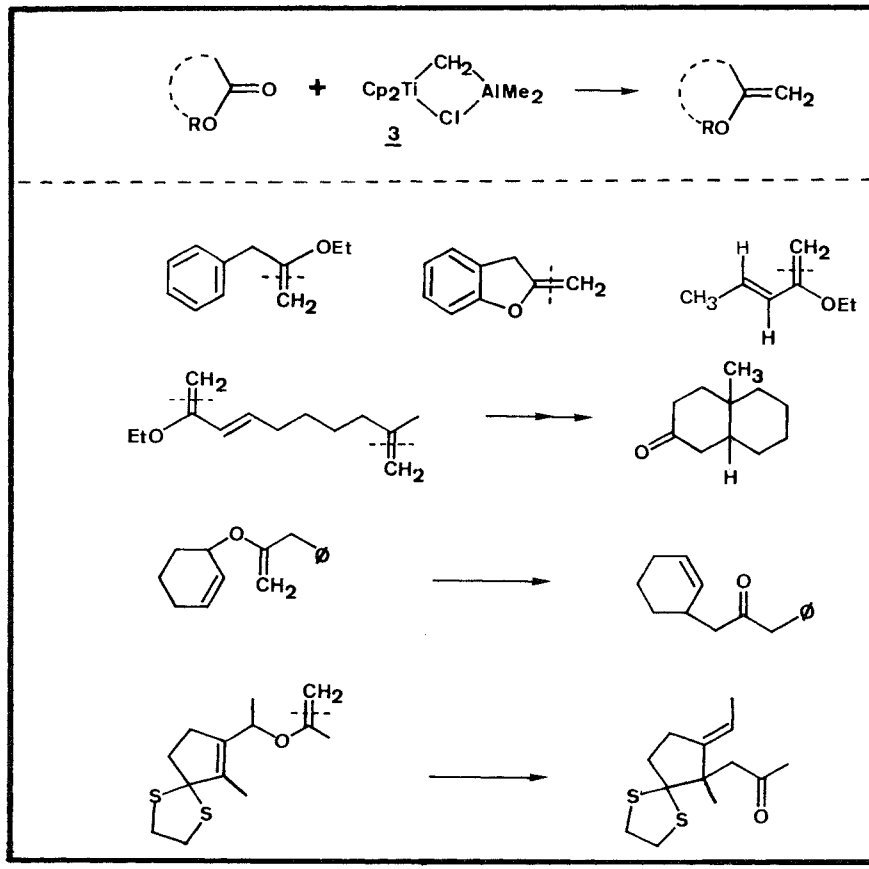
General procedure for transformation of esters into vinyl ethers [54]



A solution of 1 mmol of ester in 2 ml of toluene/THF (3:1) and 10 µl of pyridine is cooled to -40°C. 1.1 mmol of 3 (0.55 M in toluene) is added dropwise and the reaction is kept at -40°C for 30 min. and then allowed to warm to ambient temperature within 1.5 hours. The reaction is quenched by dropwise addition of 0.3 ml of 15% aqueous NaOH to the cooled (-10°C) reaction mixture and allowed to reach room temperature. After gas evolution has ceased, the dark green solution is diluted with ether, dried (Na_2SO_4) nd filtered through Celite. Upon solvent removal *in vacuo* the crude vinyl ether may be purified by filtration through a short column of alumina (neutral, activity III), using hexane as eluent to give the pure methylenation product in high yield.

Aldehyde-selective *Peterson* olefinations can be achieved with $Me_3SiCH_2TiCl_3$ (24c) [34]. This reaction also demonstrates the great influence of the X-groups in $RTiX_3$-reagents: the corresponding triisopropoxy-derivative does not react similarly [23] (see also next section). For further examples of olefinations, with allylic silylated nucleophiles, see section III F4; compare also olefinations with low-valent Ti-species/CH_2Br_2 in section III C1.

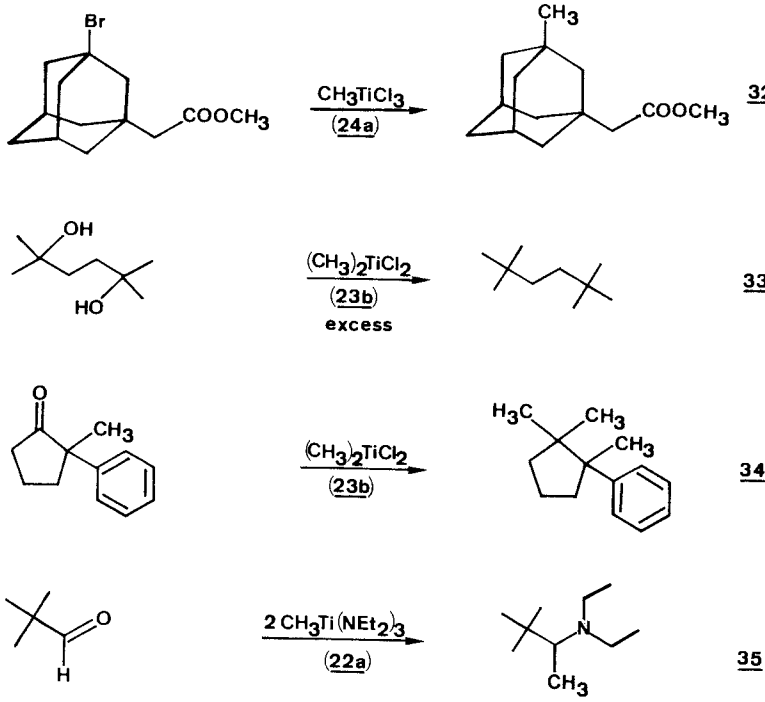
Scheme 10. Olefinations of esters and lactones with the *Tebbe* reagent. The dotted line shown in the olefins indicates the site of the CO double bond in the substrate [54,55].



2) Geminal Dimethylation and Amination/Alkylation of Carbonyl Derivatives

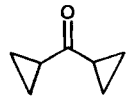
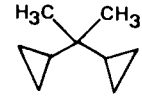
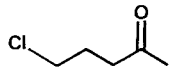
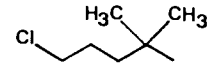
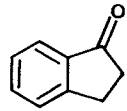
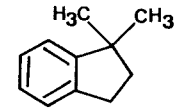
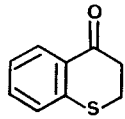
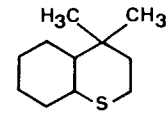
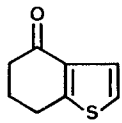
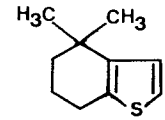
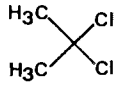
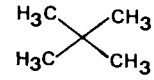
The stability of $RTiX_3$ derivatives increases with increasing donor ability of the X-groups, i.e. in the order X = CH_3, Cl, OR, NR_2. In the same order, the *Lewis* acidity and the reactivity decrease. Thus, CH_3TiCl_3 (24a) and $(CH_3)_2Ti(OCHMe_2)_2$ (23a) are both more reactive than methyl-triisopropoxy--titanium. It is likely, that the higher homologues of CH_3TiCl_3, of $(CH_3)_2TiCl_2$, and of $(CH_3)_2Ti(OR)_2$ are not stable enough to become syntheti-

cally useful. However, the CH_3-derivatives can be used for unique one step carbon-carbon bond-forming reactions, the detailed mechanisms of which are by no means clear. Thus, trichloro-methyl-titanium causes Br/CH_3 exchange at a bridgehead position (→32) [30], while tertiary alcohols undergo an overall OH/CH_3 exchange with dichloro-dimethyl-titanium (→33) [31]. Not surprisingly, the same reagent effects a geminal dimethylation of ketones (→34). In this last mentioned reaction, the substrate structure is such that intermediate carbocations would rearrange.



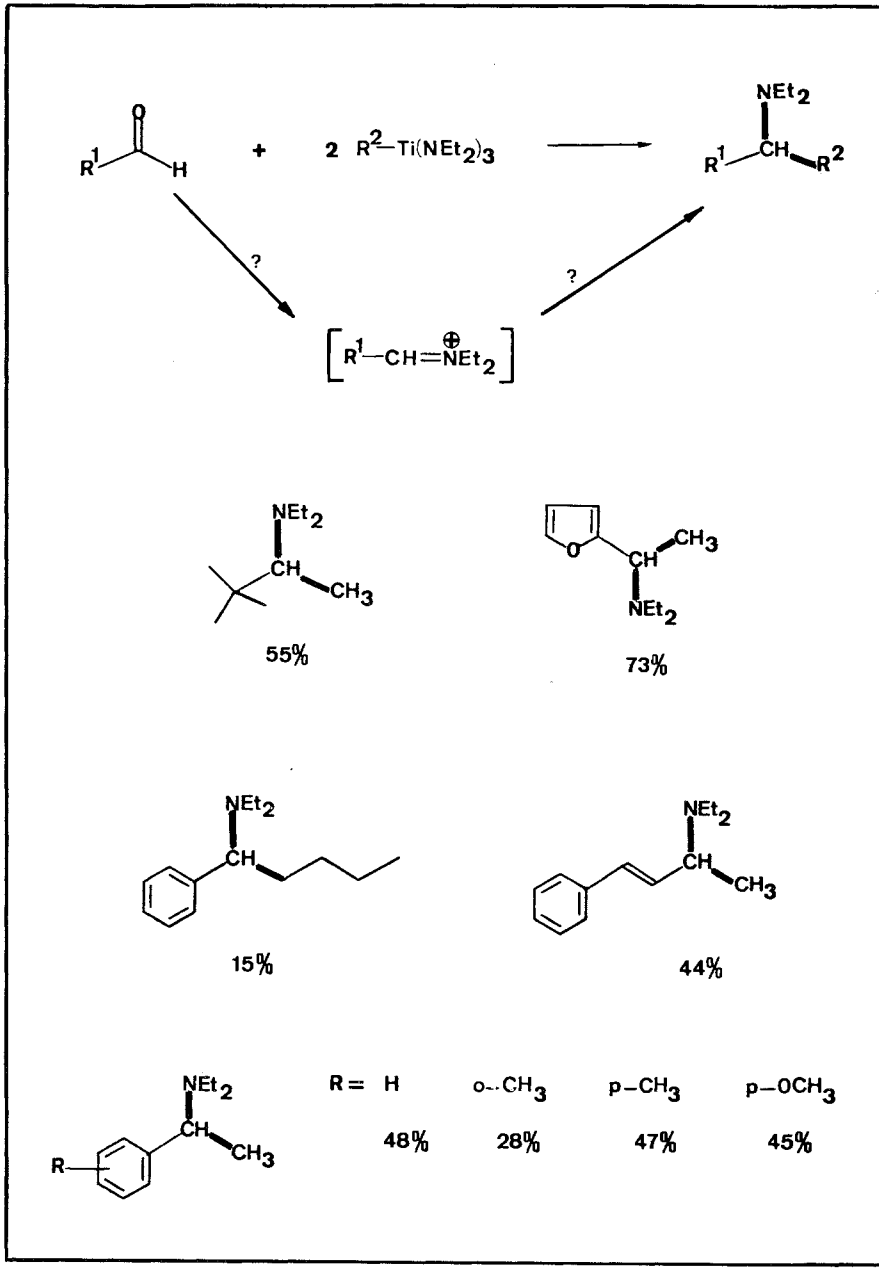
On the other end of the reactivity scale, the dialkylamino derivative 22 converts non-enolizable aldehydes to tertiary amines (→35) [28]. This new method for the one-step alkylative amination has been described in full detail. The yields are not as yet satisfactory; improvements seem possible. The accompanying Table 5 and Scheme 11 contain lists of examples of tertiary alkylations and of conversions of aldehydes to tertiary amines with simultaneous alkylation, respectively. Two typical procedures follow.

Table 5. Some further examples of the preparation of compounds with quaternary carbon atoms produced with methyl titanium reagents [31,32].

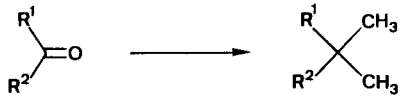
Starting material	Product	Method [a] or Reagent	Yield [%]
		B	84
		B	82
		A	86
		A	77
		B	74
		$MeTiCl_3$	95

a) See experimental details below.

Scheme 11. Products from aldehydes and alkyl-tris(dialkylamino)titanium derivatives [28]. The newly formed C.C and C.N bonds are indicated by heavy lines.



Procedures for direct geminal dimethylation of carbonyl compounds [31]



Method A: At -30°C the ketone (1 mol-equiv.) is treated with dimethyltitanium dichloride (23b) (2 mol-equiv.) in CH_2Cl_2 and the reaction mixture allowed to reach room temperature.

Method B: The ketone is combined with Me_2TiCl_2 (23b) at -30°C and after ca. 20 min. titaniumtetrachloride and dimethylzinc (1 mol-equiv. each) are added in rapid succession. The mixture is then allowed to warm to room temperature. This two-step procedure yields the desired products in a comparable yield to the method A; in some cases it proves to be even more successful.

Methylation of tertiary alcohols [31]

Titaniumtetrachloride (4) (1 mol-equiv.) is combined with the alcohol (1 mol-equiv.) in CH_2Cl_2 at ca. -30°C. After 5-10 min. the reaction mixture is treated with Me_2Zn (1 mol-equiv.) and the temperature maintained for 1 hour before workup. Alternatively Me_2TiCl_2 can be used equally well.

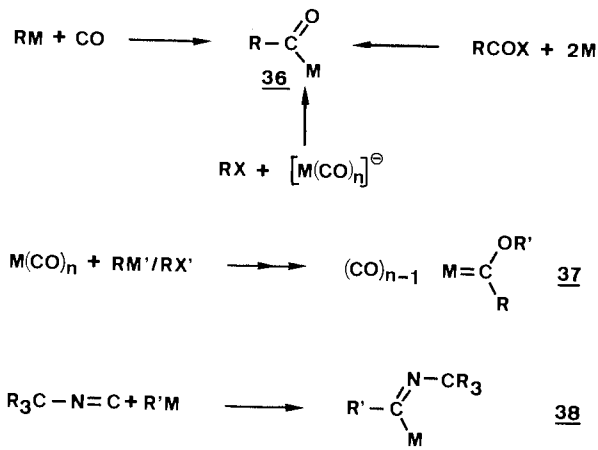
Diethyl-[1-(2'-furyl)ethyl]amine [28]

Methyllithium (3.2 mmol, 1.78 M in ether) is added slowly to a stirred solu-

tion of 1.116 g (3.2 mmol) of $BrTi(NEt_2)_3$ in 30 ml of ether at -30°C. After 30 min. at that temperature and 1 hour at room temperature, the yellow solution of 22a is combined at -60°C with 124 µl (1.49 mmol) of furfural and then stirred at room temperature for 18 hours. The reaction mixture, containing a white precipitate, is quenched with H_2O and the aqueous phase extracted three times with ether. After washing the combined etheral extracts with 2 N aqueous HCl the pH is adjusted to ca. 9 by addition of Na_2CO_3. The amine is extracted into ether, the ether solution washed with H_2O, dried (Na_2SO_4) and concentrated to give 174 mg (73% yield) of diethyl-[1-(2'-furyllethyl)amine as a yellow oil which is very sensitive to air.

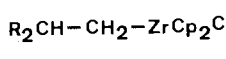
D) Carbonylation and Reactions of Isonitriles

A special case of addition to C,X multiple bonds is carbonylation, i.e. reactions with carbon monoxide and additions to isonitriles. These can also be considered as additions to carbene carbon atoms. A process of great practical importance involving carbon monoxide and transition metals is the hydroformylation [56]. Isonitriles are also important industrial starting materials [57]. Carbonylation leads to acyl metal complexes 36 which are also formed by alkylation of anionic metal carbonyl complexes (cf. of iron [58]), less often by direct metalation of acid halides [58,59] (cf. also the formation of carbene complexes 37).

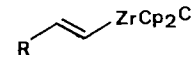


In contrast to acyl alkali and earth alkali derivatives of type 36, which are rather unstable [60], the imino analogues 38 are stable at least in solution with M = Li or MgX [61] and are useful nucleophilic acylating reagents (d^1-reactivity [62]). These can be alkylated (→ ketones) and hydroxylalkylated (→ α-hydroxyketones).

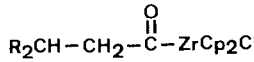
There are two interesting applications of titanium and zirconium compounds with carbonylation and additions to isonitriles: the hydrozirconation products (see section IV D) of olefins (39) and of acetylenes (40) react smoothly with CO to give acylzirconocene derivatives 41 and 42, respectively. These in turn can be converted (→ 43,44 [63]) to aldehydes, carboxylic acids or acyl halides, but they do not combine with carbon electrophiles such as aldehydes, ketones, and alkyl halides.



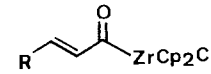
39



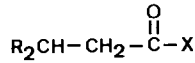
40



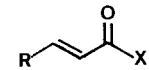
41



42

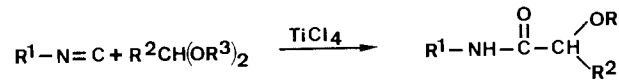


43

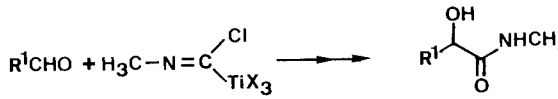


44

X = H, OH, OR, Br



45

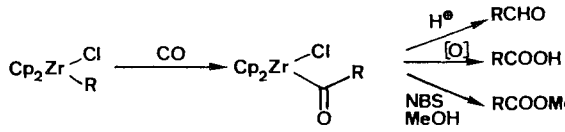


46

47

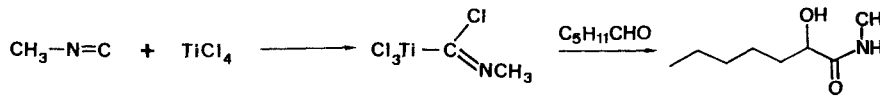
Two new titanium-mediated versions of the *Passerini* reaction [64] lead to α-alkoxyamides 45 and to amides 46 of aliphatic amines. In the first case, it is not clear whether an intermediate with a Ti-C bond is involved or whether $TiCl_4$ merely acts as a *Lewis* acid [65]. In the other reaction, one of the known adducts of $TiCl_4$ to isonitriles, for which structure 46 has been proposed [66], adds to aldehydes [10]. If structure 46 is correct, it is a case in which an organotitanium reagent is formed directly from an organic compound and TiX_4 rather than by transmetalation (see Table 2).

Carbonylation of organozirconium derivatives [63]



A solution of 2 mmol of the organozirconium compound 39 (cf. section IV, D) in 5 ml of benzene is stirred under 1.4 atm. of CO at room temperature. Carbonyl insertion to yield the acyl complex 41 is complete within some hours. 41 may be converted to aldehydes by addition of aqueous HCl in benzene solution at room temperature. Carboxylic acids are produced on treatment with aqueous NaOH followed by 30% H_2O_2 and acidification, whereas slow addition of NBS solution in methanol at room temperature results in formation of methyl esters.

2-Hydroxy-N-methyl-heptanoic amide [10]

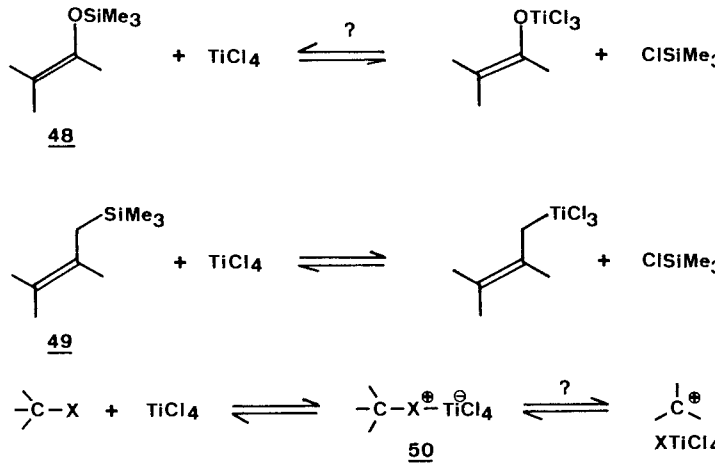


A solution of 1.1 ml (10 mmol) of titaniumtetrachloride in 40 ml CH_2Cl_2 is

cooled to ca. -5°C. After slow addition of 0.57 ml (10 mmol) of methylisocyanide the reaction mixture is warmed to room temperature. From the yellow solution a white solid precipitates. Stirring is continued for ca. 2.5 hours. Cooling to -60°C is followed by the addition of 1.17 ml (9.5 mmol) of hexanal. The mixture is warmed slowly to ca. -5°C. The precipitate begins to dissolve at -15°C and a clear yellow solution is obtained. Hydrolysis is achieved by treatment first with 25 ml 2 N aqueous HCl, and after the initially formed white solid is completely dissolved, an additional 20 ml of water is added. The green-yellow colour disappears during vigorous stirring for 1.5 hours. The layers are separated and the aqueous phase is extracted twice with CH_2Cl_2. After washing the combined organic extracts with saturated NaCl solution and drying ($MgSO_4$), the product, a white powder, is obtained on concentration in vacuo. Yield: 1.45 g (9.10 mmol; 96%).
m.p. 109.5-110°C (CH_2Cl_2).

E) α- and γ-Alkylations of Carbonyl Derivatives

Replacement of hydrogen by trialkyl silyl groups has led to a "new generation" of carbon nucleophiles for carbon-carbon bond formations. Although vinylsilanes and arylsilanes have also gained considerable importance, the most useful representatives of this class of compounds are undoubtedly the silyl enol ethers 48 [67-71] and the allylic silanes 49 [71,72]. The reactions of these species with electrophiles require catalytic or stoichiometric



"activation". For many purposes, the most powerful activation is provided by

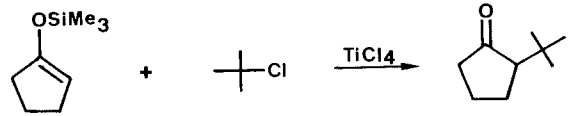
a stoichiometric amount of $TiCl_4$; with sensitive substrates this activation can be modulated [73] by using mixtures of $TiCl_4$ and $Ti(OR)_4$, i.e. $Cl_2Ti(OR)_2$ in the case of a 1:1 ratio. Although the mechanism is still subject to discussions, it is conceivable [74] that with silyl enol ethers 48 the actual reagent is a titanium enolate, and that likewise an allylic organotitanium derivative is formed from allylsilanes 49. Titanium derivatives of this kind have been generated deliberately from lithium enolates [75] and allylic *Grignard* reagents [14,76,77], respectively, and have been shown to be extremely reactive even at temperatures as low as -110°C, see next section (F). Of course, the titanium tetrachloride will also activate the electrophiles such as halogen and oxygen derivatives (→50), but many applications suggest that no free carbenium ions are formed. Maybe a simultaneous activation of the nucleophiles (→45, 49) and of the electrophiles (→50) is accomplished by Ti(IV) species. For extensive discussions, the reader is referred to some excellent recent review articles [67-72].

Whatever the detailed mechanism might be, the following most useful transformations can be achieved under these conditions. In the presence of $TiCl_4$ silyl enol ethers are converted to α-alkylated carbonyl derivatives with high regioselectivity and in good yields when treated with *t*-alkyl halides, *t*-alkyl ethers or *t*-alkyl esters, with benzylic halides, with α-chloro-thioethers, and with acetals of aldehydes and ketones. O-Alkylation and poor yields because of competing elimination and other side reactions are typical when lithium enolates are treated with the same "S_N1-type electrophiles". Also, aldol additions even to ketones occur with $TiCl_4$/silyl enol ethers. Thus, this kind of silyl enol ether chemistry is not alternative, but complementary to classical enolate chemistry.

It is remarkable that silyl enol derivatives can also undergo remote reactions, i.e. *Michael* additions with enones and d^4-reactions [62] when silyl dienol ethers are employed.

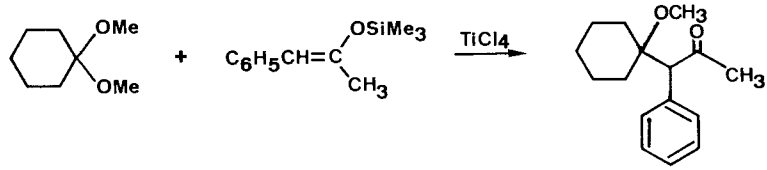
Same characteristic examples of $TiCl_4$-mediated transformations of silyl enol ethers are collected in Table 6, and several procedures follow.

2-*t*-Butyl-cyclopentanone [78]



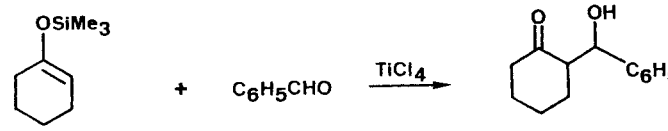
Under inert atmosphere a solution of 15.6 g (100 mmol) of 1-trimethylsilyloxy cyclopentene and 10.0 g (108 mmol) of *tert*-butylchloride is treated at -45°C with 20 g (105 mmol) of titanium tetrachloride dissolved in 30 ml of cold (-45°C) CH_2Cl_2. The reaction mixture is stirred for 30 min. and then diluted with 100 ml of CH_2Cl_2. After aqueous workup the crude product is purified by fractional distillation to yield 9.2 g (66% yield) of 2-*t*-butyl-cyclopentanone. b.p. 95°C/45 Torr.

α-(1-Methoxy-cyclohexyl)-α-phenyl-aceton [79]



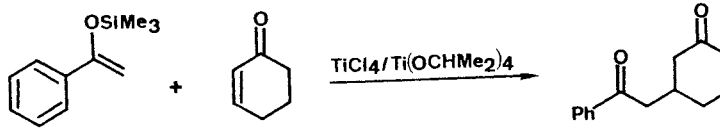
To a solution of 2.6 mmol $TiCl_4$ in 5 ml CH_2Cl_2 stirred under argon at -78°C is first added a methylene chloride solution of the dimethyl acetal of cyclohexanone (2.5 mmol), immediately followed by a solution of 1-phenyl-(2-trimethylsilyloxy)-1-propene in the same solvent. After stirring for 3 hours at -78 C the mixture is hydrolyzed and the aqueous layer extracted with ether. After drying, the solvents are evaporated and the residue is chromatographed on silicagel to give a 91% yield of the β-methoxy-ketone.

2-(Hydroxy-phenyl-methyl)-cyclohexanone [80]



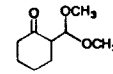
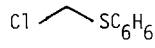
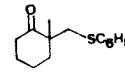
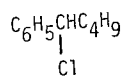
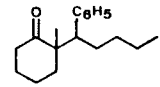
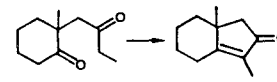
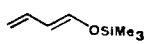
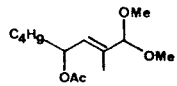
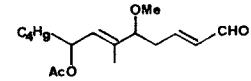
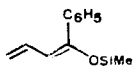
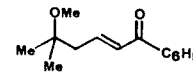
A methylene chloride solution (10 ml) of the silyl enol ether (0.43 g, 2.5 mmol) is added dropwise to a mixture obtained from 20 ml CH_2Cl_2, 0.29 g (2.75 mmol) benzaldehyde and 0.55 g (2.75 mmol) $TiCl_4$ and stirred at -78°C under argon. After 1 hour, hydrolysis at low temperature, extraction of the inorganic layer with ether, washing of the organic layers with water, drying (Na_2SO_4), and evaporating the solvents furnishes a residue which is chromatographed on silicagel with CH_2Cl_2 as eluant. First, 115 g (23%) of the *l*-diastereomer (m.p. 103°C), and then 346 mg (69%) of the *u*-diastereomer (m.p. 74°C) is eluted.

3-(2-Phenyl-2-oxoethyl)-cyclohexanone [81]



To a methylene chloride solution (4 ml) of $TiCl_4$ (1 mmol) and $Ti(OCHMe_2)_4$ (0.4 mmol) is added a mixture of α-trimethylsilyloxystyrene (1 mmol) and 2-cyclohexen-1-one (1 mmol) in methylenechloride (6 ml) at -78°C. After being stirred for 30 min., the mixture is hydrolyzed with 12 ml aqueous K_2CO_3 (0.75 g) and extracted with ether. The extract is washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure. The residue is chromatographed on silica gel, yielding 70% product of m.p. 75-76°C.

Table 6. Examples of $TiCl_4$-mediated reactions of silyl enol ethers with "S_N1--type" electrophiles. Equimolar amounts of $TiCl_4$ are usually employed, see procedures.

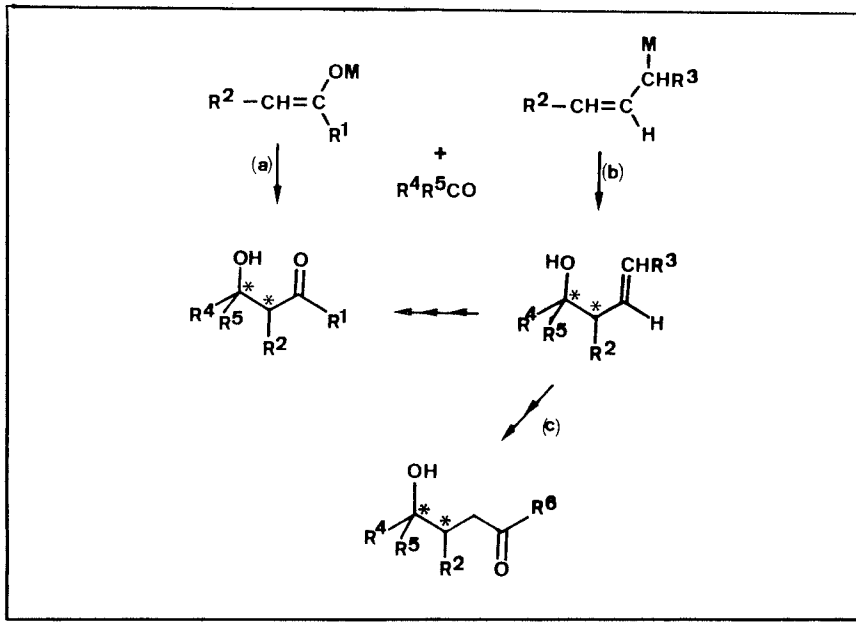
Silyl enol ethers	Electrophile	Product	Yield %	[ref.]
	t-C_4H_9-Cl		90	78)
	t-C_4H_9-OMe t-C_4H_9-OAc		30-55	67)
	$HC(OCH_3)_3$		71	79)
			71	82)
	t-C_4H_9Cl		86	78)
			82	67,83)
				84)
		82% 87%		
			85	85)
	$Me_2C(OMe)_2$		78	86)

F) Aldol Additions and Related Processes

There is no synthetic reaction about which so many papers and review articles appeared within a few years as about the diastereoselective aldol addition. The most comprehensive, competent and up-to-date survey is that by *C.H. Heathcock* and is entitled "The Aldol Addition Reaction", to be published in the forthcoming edition of *J.D. Morrison*'s book "Asymmetric Synthesis, Vol. 2". A complete list of the reviews with titles is given in references [87-97]. The interest in acyclic stereoselection arose when macrocyclic and open chain ionophores, antibiotics and other highly functionalized, physiologically active compounds became the target molecules of natural product synthesis; see for instance the most recent efforts towards the total synthesis of palitoxin [104].

Like other processes [101,102] in which two trigonal, two-dimensionally chiral centers combine to give two new asymmetric carbon atoms, the aldol addition can furnish two diastereomeric products. It is shown in Scheme 12

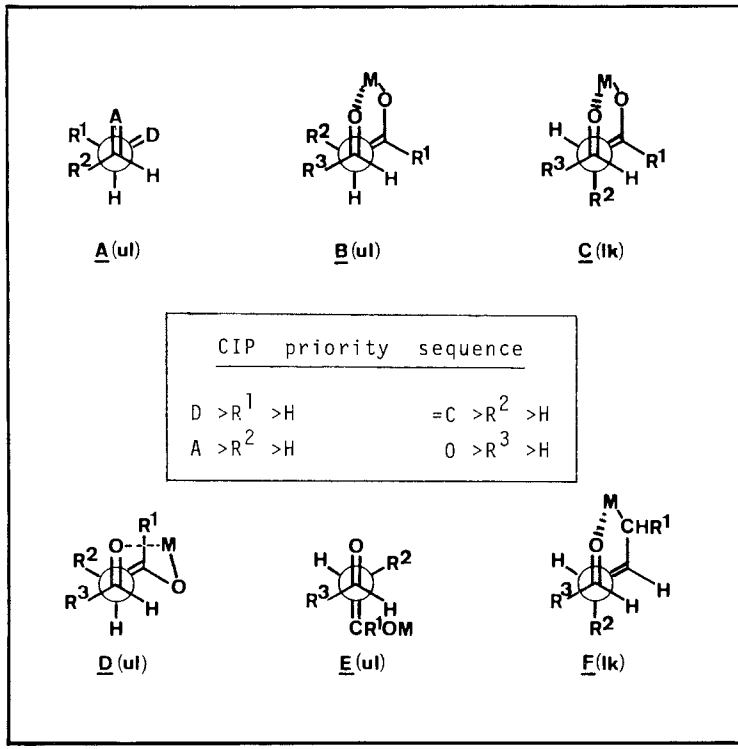
Scheme 12



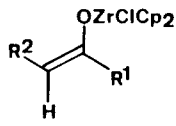
that the same β-hydroxy-carbonyl compounds, which are formed by aldol addition, route (a), can also be obtained from allylic organometallic compounds through homoallylic alcohols, route (b). This latter route requires more steps to the aldol-type products, but it is at the same time more flexible, because conversions of the olefinic double bond other than oxidative cleavage can produce a variety of structures, cf. the γ-hydroxy-carbonyl derivatives, route (c) in Scheme 12. If R^3 of the allylic metal derivative is a heteroatom, step (c) consists of a simple hydrolysis. For these reasons, it is not surprising that the generation and the regio- as well as diastereoselective carbonyl additions of allylic nucleophiles has also attracted much recent interest, as demonstrated by several review articles [96-100].

The stereochemical course of diastereoselective C,C bond formation by combination of two trigonal centers can be discussed with the *Newman* projec-

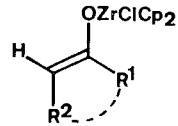
Scheme 13



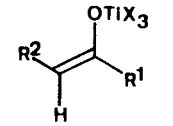
tions in Scheme 13. The relative topicities of approach of the donor and acceptor trigonal centers are specified [40] assuming the "normal" order of priority [105] of the groups as indicated in the center of Scheme 13. As a general rule, the *ul*-approach A is preferred [102]: (i) if no geometrical isomers exist of either the donor or the acceptor component, they combine as shown in A; (ii) the rate of reaction and the degree of selectivity are higher with *Z*-donors, B, than with *E*-donors, C; (iii) under many conditions, the aldol process occurs with *ul*-preference, independant of enolate configuration; whether this is due to a switch from the chair-like arrangement C to a boat-like arrangement D or to a so-called open approach E, and why this is so, is still subject to discussion [87,102,106]. The present authors think [102] that the open model E is highly unfavorable in aprotic solvents and in the absence of ions, when the temporary partial charge separation which must develop along the reaction coordinate is neither stabilized by solvation nor by chelation, nor by counterions.



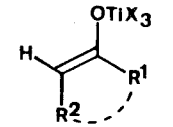
Z-51



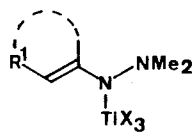
E-51



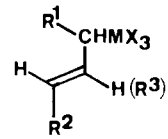
Z-52



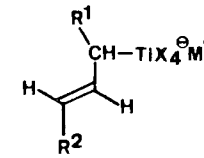
E-52



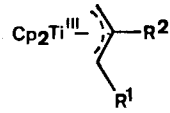
53



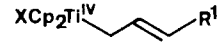
54



55



56



57

Returning to the subject matter, it is a fact that the metal enolates 51 and 52 and the enhydrazinolates 53 of titanium and zirconium are among the reagents with *ul*-preference, independant of the enolate geometry. In contrast, both titanocene and titanate derivatives with crotyl or higher or heterosubstituted allylic ligands (54, 55) show a strong *lk*-preference, see F in Scheme 13.

A collection of nucleophiles of type 51 - 57 is specified in Table 7.

Table 7. List of enolates, enhydrazinolates and allylic derivatives ot titanium and zirconium which were used for regio- and diastereoselective C,C bond formation.

	R^1	R^2	X (M)	Ref.
51a	C_2H_5	CH_3		107)
51b	C_6H_5	CH_3		108)
51c	$-(CH_2)_3-$			107)
51d	$-(CH_2)_4-$			107)
51e	$N(CHMe_2)_3$	CH_3		108)
51f	$N(CH_2)_3CH_2$	CH_3		108)
51g 51h	A (see Scheme 14)	CH_3		109)
51i	OCH_3	CH_3		108)
51j	t-C_4H_9O	CH_3		108)
51k	t-C_4H_9S	CH_3		108)
52a	C_2H_5	CH_3	$OCHMe_2$	75)
52b	C_2H_5	CH_3	$N(C_2H_5)_2$	75)
52c	t-C_4H_9	CH_3	$OCHMe_2$	75)
52d	C_6H_5	CH_3	$OCHMe_2$	75)

(Table 7 continued)

	R^1	R^2	X (M)	Ref.
52e	$C_6H_2(CH_3)_3$	CH_3	$OCHMe_2$	75)
52f	$-(CH_2)_3-$		$N(C_2H_5)_2$	75)
52g	$-(CH_2)_4-$		$OCHMe_2$	75)
52h	$-(CH_2)_4-$		$N(C_2H_5)_2$	75)
52i	$-(CH_2)_5-$		$OCHMe_2$	75)
52j	$-(CH_2)_5-$		$N(C_2H_5)_2$	75)
52k	OC_2H_5	CH_3	$OCHMe_2$	19)
52l	$-O-(CH_2)_2-$		$N(C_2H_5)_2$	19)
52m	$CH_3N-(CH_2)_2-$		$N(C_2H_5)_2$	19)
52n	$CH_3N-(CH_2)_4-$		$N(C_2H_5)_2$	19)
53a	CH_3		$N(C_2H_5)_2$	110)
53b	CH_3		$OCHMe_2$	110)
53c	$CH(CH_3)_2$		$OCHMe_2$	110)
53d	C_6H_5		$OCHMe_2$	110)
53e	C_6H_5		$N(C_2H_5)_2$	110)
54a	H	H	$OCHMe_2$ (Ti)	21)
54b	H	CH_3	OC_6H_5 [a] (Ti)	14)
54c	H	CH_3	OC_6H_5 (Zr)	111)
54d	H	C_4H_9	OC_6H_5 (Ti)	77)
54e	H	$CH(CH_3)_2$	OC_6H_5 (Ti)	77)
54f	LiS	H	$OCHMe_2$ (Ti)	22,112)
54g	LiS	H ($R^3 = CH_3$)	$OCHMe_2$ (Ti)	112,113)
54h	H	SCH_3	$OCHMe_2$ (Ti)	76,112,113)
54i	H	SC_6H_5	$OCHMe_2$ (Ti)	76,112,113)
54j	H	H	NEt_2 (Ti)	19)

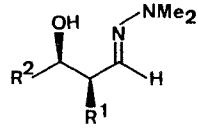
(Table 7 continued)

	R^1	R^2	X (M)	Ref.
54k	H	CH_3	NEt_2 (Ti)	19)
54l	$OCON^iPr$	CH_3	NEt_2 (Ti)	114)
55a	H	H	$OCHMe_2$ (MgCl)	19,115)
55b	H	CH_3	$OCHMe_2$ (MgCl)	19,115)
55c	H	CH_3	OC_6H_5 (MgCl)	19,115)
55d	H	$Si(CH_3)_3$	$OCHMe_2$ (Li)	19,115)
55e	H	H	NMe_2 (MgCl)	19,115)
55f	H	H	NMe_2 (Li)	19,115)
55g	H	H	NEt_2 (Li)	19,115)
55h	H	CH_3	NEt_2 (MgCl)	19,115)
56a	H	H		116)
56b	CH_3	H		116,117)
56c	CH_3	CH_3		117)
56d	C_2H_5	H		117)
56e	$(CH_3)_3Si$	H		99)
57a	CH_3		X = Cl	118)
57b			X = Br	118)
57c			X = I	118)

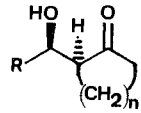
a) The crotyl titanium reagents were also tested with other OR-groups. The phenoxy derivatives gave the best diastereoselectivities in the standard reaction, i.e. addition to benzaldehyde. Therefore, all other experiments were conducted with the triphenoxy compounds.

1) Ti- and Zr-Enolates for Aldol Additions

The trialkoxytitanium and tris(diethylamino)titanium enolates 52 and analogous derivatives 53 of aldehyde dimethylhydrazones have been shown to combine with aldehydes with relative topicity *ul* [75,110]. The selectivity was found to be highest with the hydrazone derivatives (53b-53d) when X = $OCHMe_2$, yielding aldol-type products 58 of two different aldehydes with



58 R^1: Me, $CHMe_2$, C_6H_5
R^2: Me, $CHMe_2$, CMe_3, C_6H_5



59 n = 2,3,4
R = $CHMe_2$, C_6H_5

diastereoselectivities of up to and above 98:2; with $R^1 = R^2 = CH_3$ the *ul*-ratio [40] (R*,S*/R*,R*) is 95:5. This is in contrast to direct aldol reactions of aldehyde enolates, which are poor reactions with respect to both chemical yields and diastereoselectivities [87]. On the other hand, hydrazones of type 58 are not easy to hydrolyze, and oxidative methods of cleavage have the additional disadvantage of producing hazardous dimethylnitrosamine [119]. The titanium enolates 52f-52j derived from cyclic ketones give aldols 59 (>90% ds) with best selectivities, while the open chain counterparts give poorer diastereoselectivities [75].

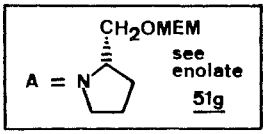
Most spectacular results are obtained with Cp_2ZrCl-enolates 51, which are not so selective when derived from ketones [107] and esters and more selective from thiolesters and amides [108], but which show a very high enantioselectivity when derived from certain chiral amides [91,109], see 51g and 51h in Table 7. The results of addition of these two Zr-enolates to pentanal, 2-methylpropanal and benzaldehyde are shown in Scheme 14. The proline-derived amide enolate produces almost exclusively the (2S,3R)-β-hydroxy

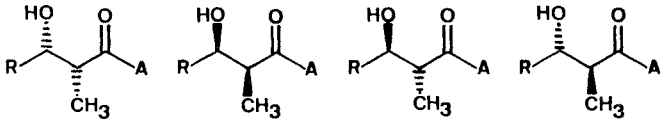
amide, while the valine-derived analogue yields, again with "almost perfect" selectivity, the (2R,3S)-diastereomer. Hydrolytic cleavage of the amides gives practically enantiomerically pure samples of the free acids of opposite chirality [109].

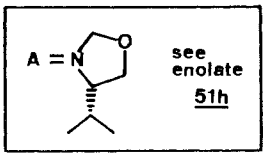
All the enolates 51 - 53 of titanium or zirconium are best generated *in situ* from the corresponding Li-enolates. It is not necessary to start from configurationally pure enolates. Some comments on the practical execution of the reaction of chiral Cp_2ClZr-enolates follow.

Scheme 14

C_4H_9	1	:	97	:	1	:	1
$CHMe_2$	0,5	:	98,3	:	0,8	:	0,4
C_6H_5	1,5	:	94,5	:	2	:	2

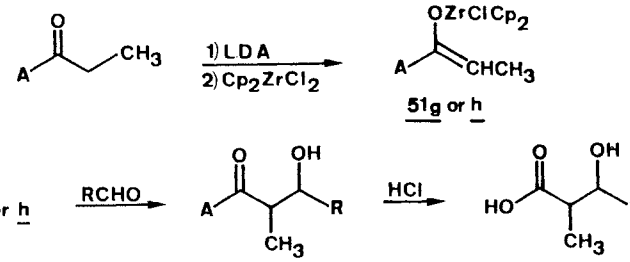






C_4H_9	96	:	2	:	1	:	1
$CHMe_2$	96	:	2	:	1,5	:	0,5
C_6H_5	96	:	1	:	2	:	1

Enantioselective Aldol Additions of Zirconium Enolates. General Procedure [108,109]



The lithium enolates 51 (Li instead of $ZrCp_2Cl$), which are generated from the respective propionamides and LDA (THF, 0°C, 30 min.), are transformed into the corresponding zirconium enolates 51g or 51h by treatment with 1.1 equiv. of Cp_2ZrCl_2 (0.16 M in THF). After cooling to -78°C, 0.9 to 1.1 equiv. of aldehyde is added, stirring is continued for 1 hour, and the reaction is quenched with saturated aqueous ammonium chloride. After filtration, the product is extracted into methylene chloride, dried (Na_2SO_4) and concentrated *in vacuo*.

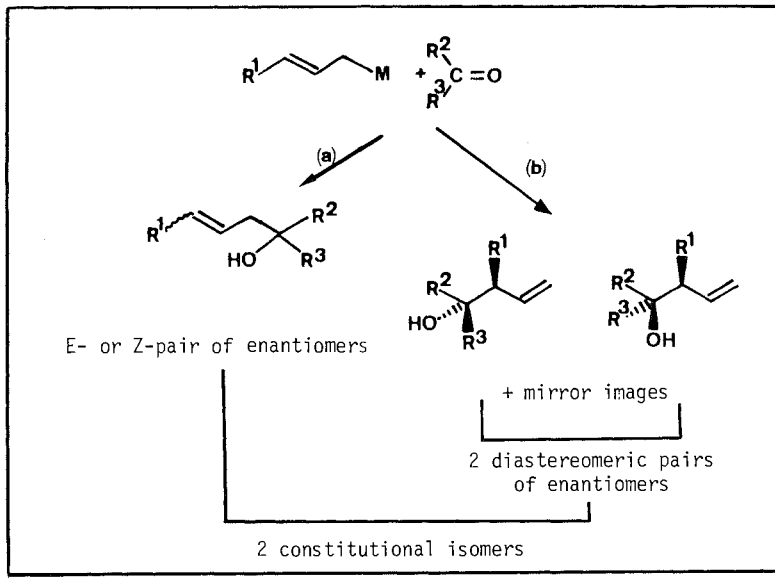
Treatment of the aldol adducts with 5% HCl (10 equiv. $H^{\oplus}$, 100°C, 2 hours) followed by neutralization with aqueous sodium bicarbonate and stirring for 5 min. at 25°C liberates the desired carboxylic acids.

2) 2-Alken-1-yl Titanium and Zirconium Derivatives

The synthetic importance of organometallic crotyl compounds has been thoroughly discussed in a recent review article [98]. The advances in this field become evident from the fact that no account on the use of allylic $RMX_4^{\ominus}$-, $(RO)_3M$- or $(R_2N)_3M$-derivatives of titanium or zirconium (see 54, 55) for synthetic purposes had been published a year ago, while now well over 50 reactions of a variety of species of this type are known [14,19,40,77,114,120,121]. The titanocene crotyl derivatives with Ti(III) and Ti(IV) valence state have been used longer [98,99]. Usually, all the allylic Ti(IV) derivatives are drawn as σ-bonded η^1-structures, the Cp_2Ti(III) derivatives as π-complexes with allyl as an η^3-ligand. We follow this custom here (see Scheme 12, Scheme 13, Table 7, and *Formulae* 54 - 57), although the struc-

tures of the species which are generated in solution or which actually react with electrophiles are not known. The structures of some products, and with it the relative topicity of their formation have, however, been proved by comparison with compounds of known configuration. In most cases, the configuration was tentatively proposed by analogy. The parent Ti- and Zr-allyl reagents [18,19] are only interesting for functional group selective transformations. Two types of constitutional isomers can be formed with

Scheme 15



substituted allylic organometallics of this type, see Scheme 15. As with other metals, 2-alken-1-yl titanium or zirconium compounds give rise to branched products exclusively, which result from attack of the electrophile at the higher substitued carbon atom, route (b) in Scheme 15; with hetero-substituted systems, R_1 = X, route (a) may be followed (see section F3).

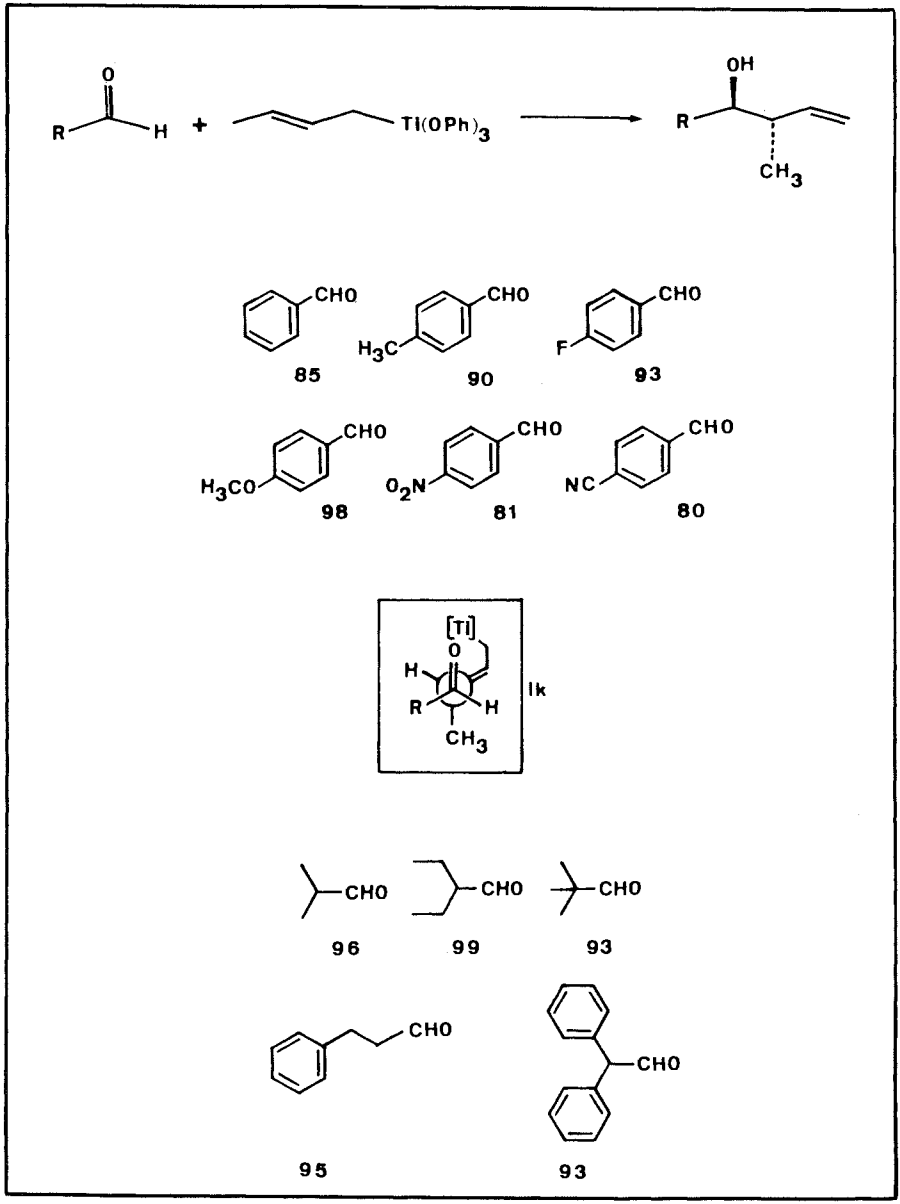
In contrast to alkenyl *Grignard* reagents, the corresponding titanium, but not so much the zirconium analogues (see 54b-54e) add to aldehydes [14,111] with high diastereoselectivity. Even ketones, with the naturally smaller size differences between the two groups bonded to the carbonyl carbon as compaired to aldehydes, give products with surprisingly high preference of one diastereomer [77]: the optimized selectivity of the crotyltitanium 54b

with benzaldehyde is 85% ds, with acetophenone 88% ds. Possibly, the smaller difference in size is counterbalanced by the lower reactivity of the ketone (later transition state?).(For aldehyde/ketone selectivity reversal see section IV, B2, below). With chiral, non-racemic OR*-groups on titanium or zirconium, no great enantiomeric excesses could be detected in aldehyde adducts of these supposedly S_E1-type reactions [111].

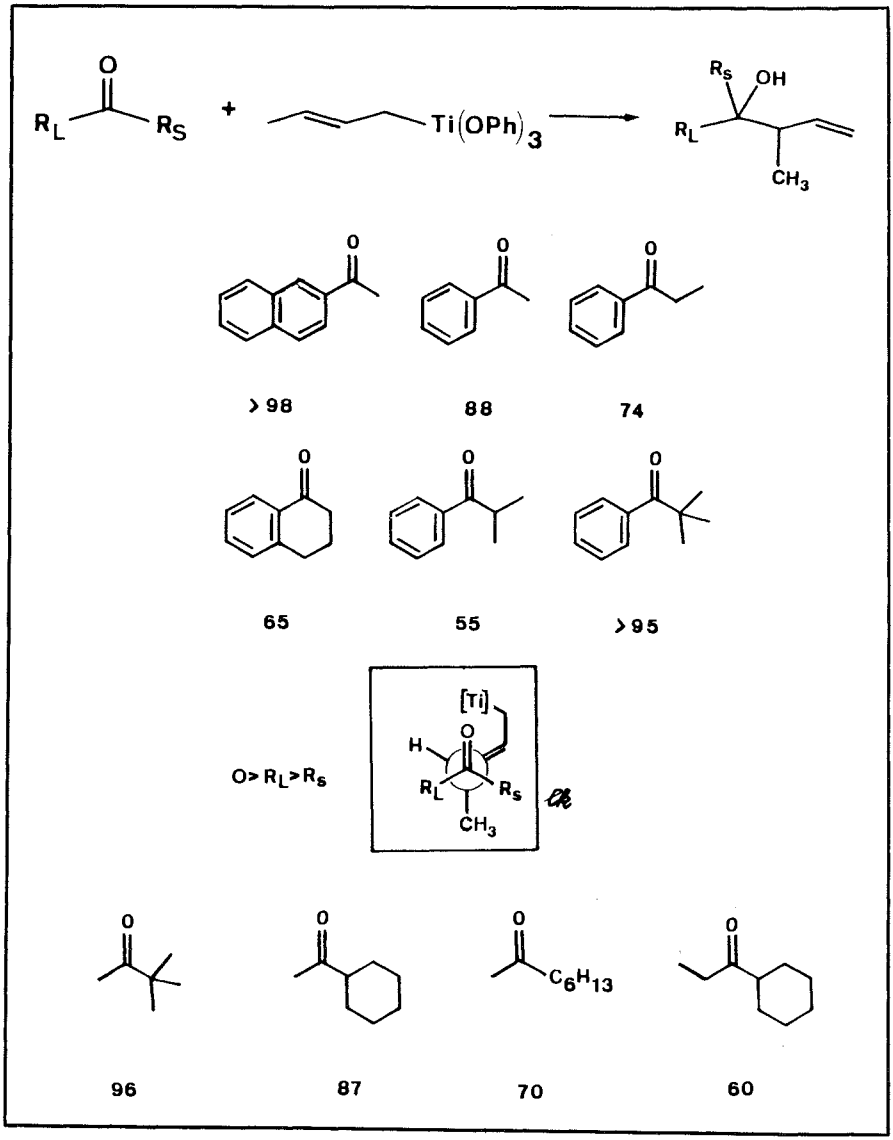
After numerous RO-groups in crotyl-Ti$(OR)_3$ were examined with benzaldehyde as a substrate [14], the "best" derivative with R = phenyl was used for all other investigations [14,-7]. Allylic *Grignard* reagents, prepared from the corresponding halide and *Rieke* magnesium [122], were combined with an equiv. amount of the triphenoxytitanium chloride (see section II above) and then at -100°C with carbonyl compounds. The results of α-methallylations of aldehydes are outlined in Scheme 16, those of additions of unsymmetrical ketones in Scheme 17. Finally, Scheme 18 contains a comparison of crotyl with other alkenyl titanium reagents in additions to aldehydes and ketones. The following points are noteworthy: (i) α-Branched and unbranched aliphatic aldehydes react most selectively. (ii) Benzaldehydes give >90% ds if substituted with donating groups, while the selectivity drops below 90% with acceptors. (iii) Ketones give useful selectivities (>80%) only when the difference in size of the groups attached to the carbonyl carbon is large enough. (iv) In three cases, the diastereoselectivity is equally good or even better with acetophenone (C_6H_5 *vs.* CH_3) than with benzaldehyde (C_6H_5 *vs.* H). (v) Increasing the size of the R-group on the allylic moiety, i.e. of the steric crowding of R between R_L and R_S in the transition state as indicated by the *Newman* projection in Scheme 18, hardly alters the diastereoselectivity of addition.

Further investigations are necessary in order to understand the reasons for the facts described above under (i), (ii), (iv), and (v), while the effect mentioned under (iii) is expected from simple steric considerations.

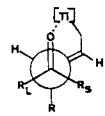
Scheme 16. Diastereoselectivities (% ds) of additions of crotyl-triphenoxy-titanium to aldehydes [14]. The numbers given underneath each aldehyde *formula* are the diastereoselectivities, i.e. the preference of relative topicity *lk* over *ul* [40] in percent.

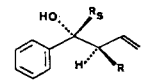


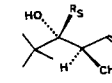
Scheme 17. Diastereoselectivities (% ds) of additions of crotyl-triphenoxytitanium to ketones [77]. The relative topicity of combination of the two trigonal centers is probably as indicated in the *Newman* projection of the approach projectory. However, proof by correlation was supplied only for the acetophenone and pivalophenone adducts. R_L = larger substituent; R_S = smaller substituent.



Scheme 18. Comparison of 2-buten-1-yl-, 2-hepten-1-yl-, and 4-methyl-2-penten-1-yl-triphenoxy-titanium in additions to ketones and aldehydes.



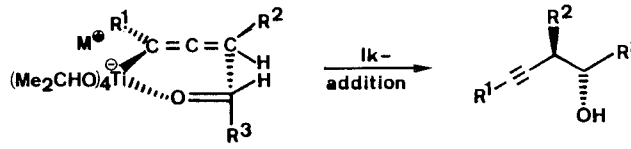




lk (RL>Rs)
ul (Rs>RL)

RL	Rs	% ds WITH R		
		CH_3	C_4H_9	$CH(CH_3)_2$
Ø	H	85	93	98
Ø	CH_3	88	87	87
Ø	$C\equiv C\text{-}CH_3$	72	77	77
Me_3C	H	>98		
Me_3C	CH_3	>98		
Me_3C	Ø	96		

A drastic increase in selectivity was observed when going from Li, Mg, or Zn to titanium ate-complexes in the addition of propargyl metal derivatives to aldehydes. The results can be explained by assuming a chelated transition state with relative topicity *lk*, see 60 → 61 [123].



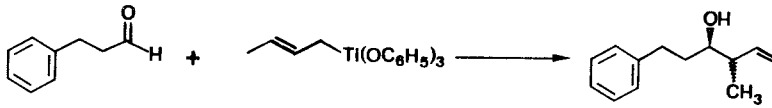
60 61

Preparation of (2-butenyl)magnesiumhalogenide [14]

Preparation of *Rieke* magnesium: Under Ar-atmosphere 2.12 g (87.2 g atoms) of magnesium turnings are covered with 20 ml THF, and 7.5 ml (87.0 mmol) of 1.2-dibromo ethane (in 30 ml THF) are added at such a rate, that reflux is maintained without heating. After complete addition, the reaction mixture is refluxed for an additional 30 min. and diluted with 50 ml THF. 6.4 g (164 g atoms) of freshly cut potassium is added to the hot solution of magnesiumbromide. Reduction commences on warming up cautiously to reflux temperature and is indicated by heavy foaming. After stirring at reflux for 2 - 3 hours, a dark grey mixture of finely powdered magnesium results.

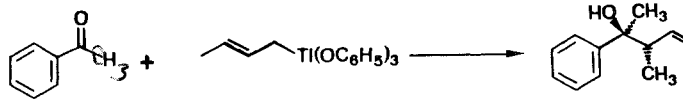
Preparation of the crotyl *Grignard* reagent: To the cold suspension 4.2 ml (431 mmol) of 2-butenylchloride is slowly added (over 5 - 10 min.) with vigorous stirring. After sedimentation overnight of the excess of magnesium an aliquot of the supernatant yellow (2-butenyl)magnesiumhalide solution is titrated, using N-phenyl-1-naphthylamine as indicator [124].

(*α*)-4-Methyl-1-phenyl-5-hexen-3-ol [14]



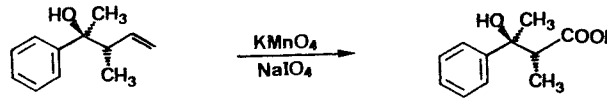
A solution of 18 ml (4.77 mmol) chloro-triphenoxy-titanium (0.265 M in THF, see section II) is cooled to -80°C. Ten ml (4.50 mmol) 2-butenyl-magnesium-chloride (0.45 M in THF) is slowly added by syringe. On addition of the first few drops the color changes from red to dark brown-red. After warming up to ca. -20°C within 1 - 2 hours, 3-phenyl-propanal (450 µl, 3.40 mmol) is added and the reaction mixture allowed to reach room temperature overnight. Hydrolysis with saturated aqueous KF-solution and extractive workup with ether furnishes the crude product, which is purified by flash-chromatography (light petroleum ether / diethyl ether 5:1) to give analytically pure 4-methyl-1-phenyl-5-hexen-3-ol. Yield: 450 mg (2.36 mmol; 70%); diastereomeric ratio 95:5 (determined by capillary gas-chromatography prior to any purification).

(ℓ)-3-Methyl-2-phenyl-4-penten-2-ol [77]



Under argon atmosphere 16 ml (4.24 mmol) chlorotriphenoxy titanium (0.265 M in THF, see section II) is cooled to -80°C. The red solution is treated with 10 ml (4.10 mmol) 2-butenyl-1-magnesiumhalogenide (0.41 M in THF). The color changes immediately to dark brown-red. After warming up slowly to -30°C within 1 - 2 hours, acetophenone (400 µl, 3.42 mmol) is added at -100°C. The solution is allowed to reach room temperature overnight. After hydrolysis with saturated neutral aqueous KF-solution, the reaction mixture is extracted three times with ether. The organic layer is washed thrice with 2 N NaOH and twice with saturated aqueous NaCl-solution, dried (Na_2SO_4) and concentrated to give the crude tertiary alcohol which is purified by flash-crhomatography (light petroleum ether / diethylether 4:1) to yield 469 mg (2.66 mmol, 78%) analytically pure 3-methyl-2-phenyl-4-penten-2-ol; diastereomeric ratio 85:15.

(ℓ)-3-Hydroxy-2-methyl-3-phenylbutanoic acid [77]

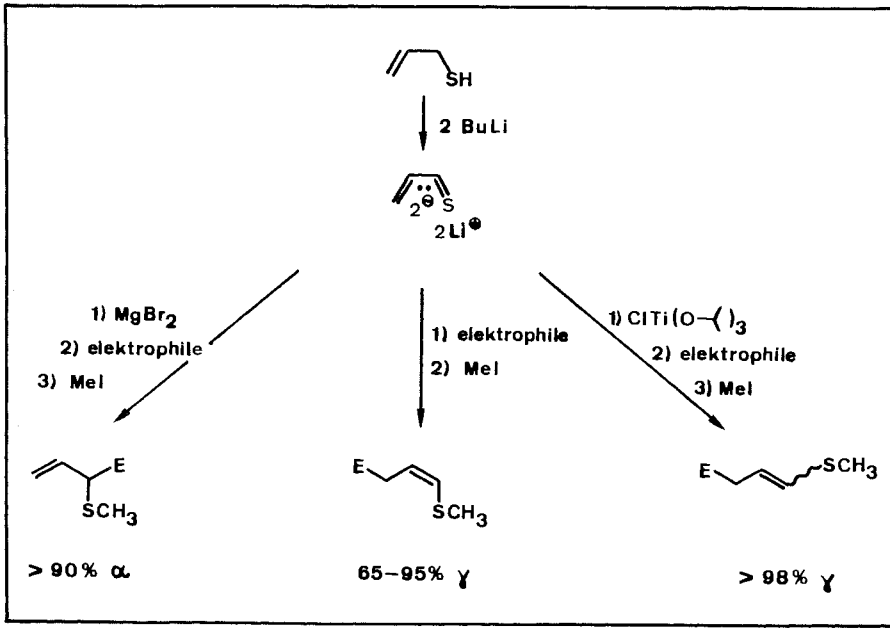


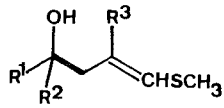
To a solution of 931 mg (5.28 mmol) of 3-methyl-2-phenyl-4-penten-2-ol in 75 ml dioxane and 225 ml H_2O, is added 350 mg $NaHCO_3$, 8.95 g (418 mmol) $NaIO_4$ and 112 mg (0.71 mmol) $KMnO_4$. The purple solution is stirred for 1 hour. Because the $KMnO_4$ is consumed after ca. 1 hour as indicated by a change of the color from purple to red, another 100 mg $KMnO_4$ is added. Stirring is continued for 3 hours. The reaction mixture is worked up with ether. The acid could be separated by extraction with saturated K_2CO_3 solution, careful acidification of the aqueous layer and reextraction with ether. Yield: 616 mg (3.17 mmol, 60%).

3) Heterosubstituted Allylic Organotitanium Reagents

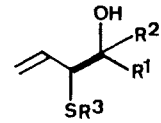
A case in which the regioselectivity of heterosubstituted allylic nucleophiles [125,126] depends strongly upon the metal, is the doubly deprotonated allyl mercaptan, Scheme 19. The dilithio derivative is only moderately

Scheme 19

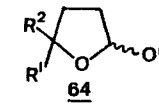




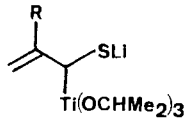
62 a: R^3 = H
b: R^3 = CH_3



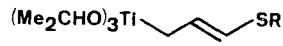
63 a: R^3 = CH_3
b: R^3 = C_6H_5



64



54 f,g (see table 7)
assumed structure



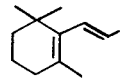
54 h,i (see table 7)
assumed structure

γ-selective [127], addition of an equiv. $MgBr_2$ causes good α-selectivity[128], and with one equiv. of triisopropoxy titanium chloride a complete (for practical purposes) γ-selectivity of reactions with aldehydes and ketones results [112], see Scheme 19 and *formula* 62a. The 2-methyl-substituted allylmercaptan reacts in the γ-position with a somewhat smaller preference (→ 62b). The α-products 63 are produced in almost as high selectivity as the γ-products 62a, and an equiv. of metalating reagent is saved, if instead of the allylmercaptan the allyl methyl or the allyl phenyl thioethers are lithiated and the resulting allyl lithium reagent transmetallated with $ClTi(OCHMe_2)_3$. The adducts 62 and 63 from aldehydes and ketones assembled in Table 8 demonstrate the generality of the method. Subsequent

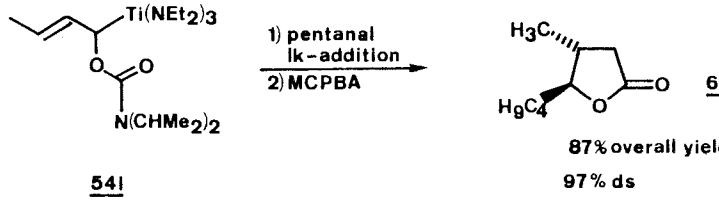
Table 8. γ-Adducts 62 and α-adducts 63 from aldehydes or ketones and reagents obtained by adding 14 to CH_2=CH-CHSLi$_2$, CH=C(CH_3)CHSLi or CH_2=CH-CHLiSR (see 54f, 54g, and 54h, 54i [112]). The γ-adducts are E/Z mixtures. Ratios of isomers were determined by ^{1}H-NMR. spectroscopy.

Prod. type	R^1	R^2	yield %	α / γ	% ds of 63
62a	CH_3	H	57	<5/95	
	C_2H_5	H	68	<5/95	
	H_2C=CH	H	39	<5/95	
	C_6H_5CH=CH	H	57	<5/95	
	C_6H_5	H	64	<5/95	
	p-I-C_6H_4	H	57	<5/95	
	p-CN-C_6H_4	H	50	<5/95	
	CH_3	CH_3	60		
	-$(CH_2)_4$-		85		
	H_2C=CH	CH_3	15		
	$(CH_3)_2C$=CH	CH_3	71		
	$H_3CO(H)C$=CH	CH_3	43		
	-CH=CH-$(CH_2)_3$-		74		

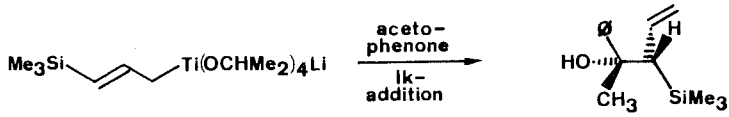
(Table 8 continued)

Prod. type	R^1	R^2	yield %	α / γ	% ds of 63
62a		CH_3	74		
	$C_6H_5CH=CH-$	CH_3	77		
	C_6H_5	CH_3	77		
	C_6H_5	C_6H_5	54		
62b	$C_6H_5-CH=CH$	H	42	2/98	
	C_6H_5	H	63	2/98	
	$p\text{-}CN\text{-}C_6H_4$	H	28	10/90	
	CH_3	CH_3	43	20/80	
	$-(CH_2)_4-$		51	10/90	
	$-CH=CH-(CH_2)_3-$		40	10/90	
	C_6H_5	CH_3	55	2/98	
63a	C_2H_5	H	89	98/2	3 : 1
	$C_6H_5CH=CH$	H	85	98/2	3 : 1
	C_6H_5	H	90	90/10	1 : 1
	$p\text{-}NO_2\text{-}C_6H_4$	H	70	98/2	2 : 1
	C_6H_5	CH_3	75	90/10	9 : 1
	C_6H_5	C_6H_5	98	90/10	
63b	C_2H_5	H	88	98/2	7 : 1
	$C_6H_5CH=CH-$	H	88	98/2	
	C_6H_6	H	82	98/2	3 : 1
	CH_3	CH_3	85	98/2	
	$-CH=CH-(CH_2)_3-$		75	98/2	6 : 1
	C_6H_5	C_6H_5	86	73/2	

synthetic conversions of the α- and γ-products [127-130], for instance alcoholysis of 62a to acetals 64 [112,127], become more interesting by the titanium-mediated improvement of selectivity of their formation. The structures responsible for γ- and α-selectivity of the two sulfur-substituted allylic titanium reagents are tentatively assigned as 54f, 54g, 54h and 54i, respectively (see *formulas* underneath 62, 63 and 64), assuming that the metal is σ-bonded in an allylic position with respect to the site of reaction. This same assumption is also made by other authors who studied RO- and Me_3Si-substituted analogues, see the preparation of 65 [114,121] and 66 [19].

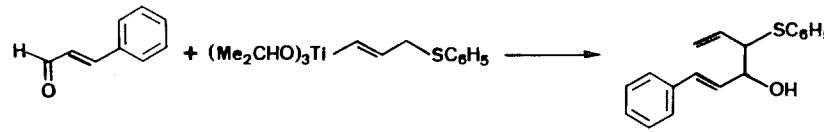


54l



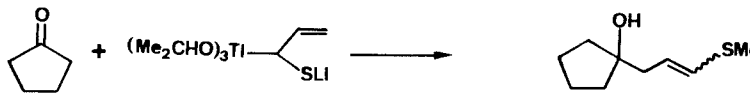
55d 66

1-Phenyl-4-thiophenyl-1.5-pentadien-3-ol [113]



A solution of 0.75 ml (5.11 mmol) of allyl phenyl sulfide in 30 ml dry ether is combined with 0.80 ml (5.34 mmol) TMEDA and treated at -80°C with 3.3 ml (5.21 mmol) of butyllithium (1.58 M in hexane). After stirring for ca. 2 hours at temperatures between -50°C and -20°C, the yellow reaction mixture is cooled to -70°C, 2.5 ml (5.23 mmol) triisopropoxy chlorotitanium is added and the brown-red solution slowly warmed up to ca. -30°C. At -90°C 0.5 ml (3.97 mmol) of cinnamic aldehyde is injected by syringe and the temperature raised to room temperature overnight. The crude product is chromatographed (petroleum ether / ether 4:1) to furnish 980 mg (3.50 mmol, 88%) of analytically pure α-adduct; diastereomeric ratio >6:1 (by ^{13}C-NMR).

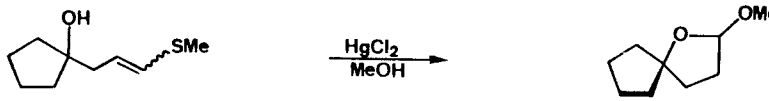
1-(3-Thiomethyl-2-propenyl)-cyclopentanol [112]



Purification of allyl mercaptan Allyl mercaptan is placed into a one-necked flask which is connected with a trap immersed into liquid nitrogen. The flask with the mercaptan is cooled to -50°C and the system is put under oil pump vacuum. The mercaptan is allowed to warm and condense into the liquid nitrogen trap. The mercaptan thus obtained should be used immediately. On storage and on contact with metal needles of syringes it polymerizes. It is best handled by pressing it through teflon tubes - also for avoiding annoyance by its bad odor.

Metallation of allyl mercaptan and reaction with cyclopentanone: Freshly purified allylmercaptan (1.90 g, 25.6 mmol) is dissolved in 160 ml anhydrous ether and 7.7 ml (51.4 mmol) of TMEDA. The solution is treated with 33 ml (51.2 mmol) of butyllithium (1.55 M in hexane) at 0°C. After stirring for ca. 5 hours, 12 ml (26 mmol) of triisopropoxy chlorotitanium is added to the yellow reaction mixture at -80°C. The color changes immediately to dark brown-red. The solution is allowed to reach ca. -30°C, cooled to -80°C and 1.8 ml (20.3 mmol) of cyclopentanone is added. After warming up to room temperature overnight, methyl iodide (2 ml, 32.1 mmol) is added and stirring continued for 3 - 4 hours. Workup consists of hydrolysis with saturated neutral aqueous KF-solution, extraction with ether and washing the combined organic layers with brine. Removal of the solvent affords crude product which is subjected to purification by flash-chromatography (pentane / ether 5:2). Yield: 2.61 g (15.2 mmol, 85%). In the ^{1}H-NMR only γ-adduct can be detected.

2-Methoxy-2-oxaspiro[4.4]nonan [112]



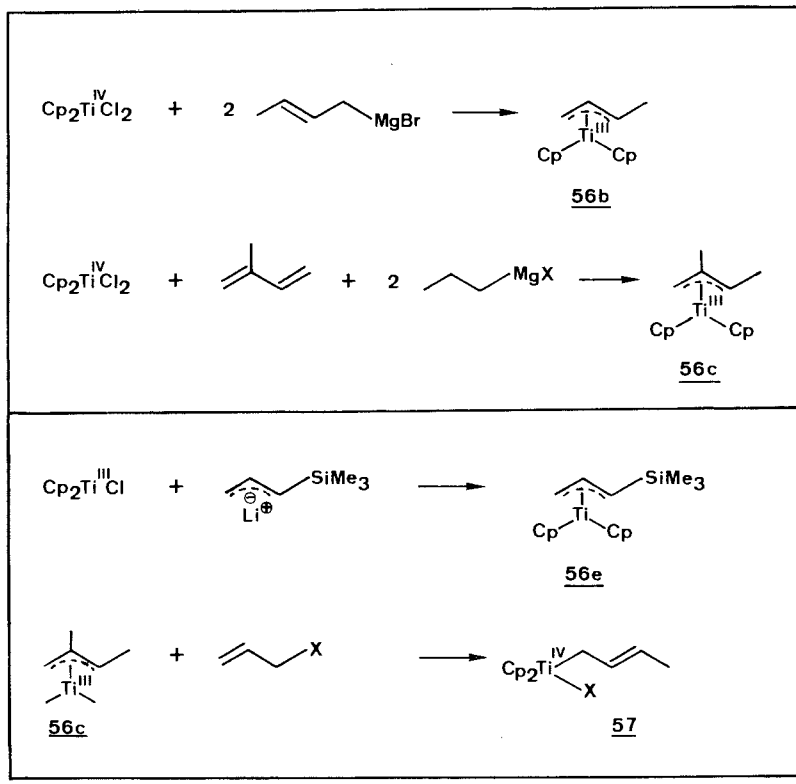
At room temperature, 525 mg (3.05 mmol) of 1-(3-thiomethyl-2-propenyl)cyclopentanol is combined with 14.9 g (10.7 mmol) $HgCl_2$ (20% in anhydrous MeOH).

After stirring for ca. 20 hours, the reaction mixture is poured on light petroleum ether / water (1:2) and the organic layer is extracted twice with petroleum ether. The solvent is removed and the residue purified by flash-chromatography (petroleum ether / ether 19:1). Yield: 0.33 g (70%).

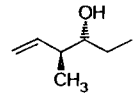
4) Allyl-titanocene Derivatives

There are titanocenes bearing allylic groups with either Ti(III) (π-allyl, η^3, see 56) or Ti(IV) (σ-allyl, η^1, see 57). Their use in organic synthesis has been reviewed just recently [99]. The Ti(III) derivatives are formed from dichloro-titanocene (1a) and two equiv. of allylic *Grignard* reagents, first equation in Scheme 20, or from 1a, a conjugated diene, such as isoprene, and

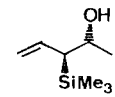
Scheme 20



propyl *Grignard* reagent, second equation in Scheme 20. In both cases, the organomagnesium compound acts as a reducing reagent. As shown in the third equation of Scheme 20, one can also start from monochloro-titanocene [Ti(III)] and an allylic lithium compound. This appears to be more economical with respect to the organic part of the reagent. Finally, allyl halides can directly be converted to halo-allyl-titanocenes [Ti(IV)] by the "oxidative trans-allylation", see the fourth equation of Scheme 20. The regioselective reactions of these titanocene derivatives with aldehydes occur with excellent diastereoselectivity with relative topicity *lk* [40], see the product 67 obtained with propanal.



67



68

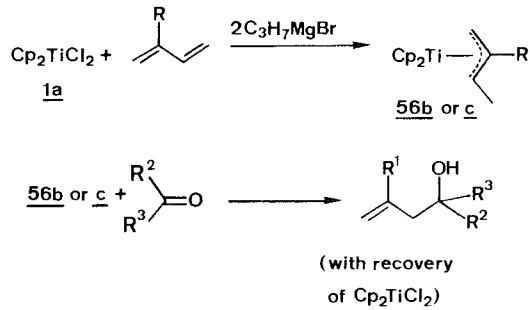
93 % ds with 56b

64 % ds with 57a, X = Cl

96 % ds with 57b, X = Br

The formation of the trimethylsilylated homoallylic alcohol 68 follows the same steric course [19], although its relative topicity is specified *ul*, due to change in the priority order. *Peterson* olefination, i.e. elimination of silanol from 68 gives either the *cis*-1.3-pentadiene (base treatment) or the *trans*-isomer (acidic conditions). The following general procedure demonstrates the preparation of allylic titanocenes directly from butadiene or isoprene, and gives instructions about the addition to an aldehyde or ketone. The recovery of titanocene after the reaction is also described.

Homoallylic alcohols from butadienes and aldehydes through titanocene derivatives [117]

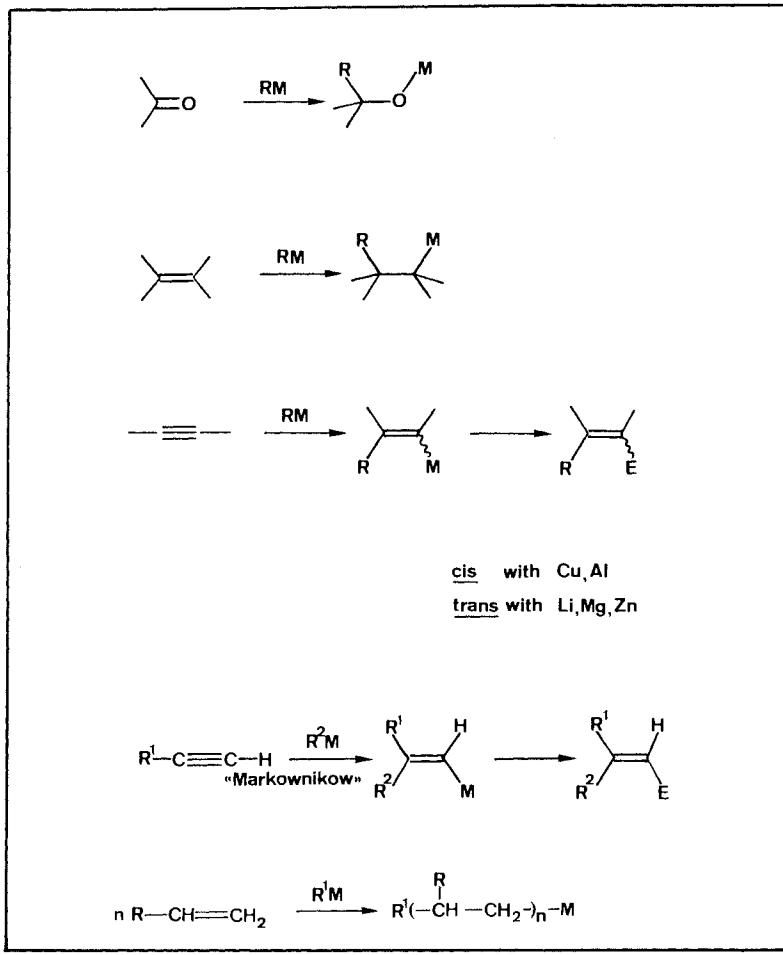


Propylmagnesiumbromide(16.6 ml, 1 M in ether) is added under argon to a stirred solution of 1a (2.1 g, 8.4 mmol) and butadiene (0.86 g, 15.9 mmol) or isoprene (0.60 g, 8.8 mmol) in ether (40 ml). After 30 min. at 20°C, 0.9 to 1.0 equiv. of an aldehyde or ketone is added by syringe, and the solution is stirred for 1 hour at room temperature. The mixture is quenched with 4 N HCl (40 ml), stirred for 30 min. under argon, and with stirring air is passed through the resulting two layers of ether (pale red color) and water (green) for 15 min. During this operation the green color fades out and 1.7 g of red crystals of 1a precipitate and are collected by filtration. The layers are separated, and the aqueous layer is extracted with ether. The combined ether layers are dried ($MgSO_4$), and the solvent is evaporated under reduced pressure to afford a mixture of 1a and an oil. Pentane is added to the mixture and an additional 100 mg 1a is isolated by filtration. Chromatography of the pentane solution on silica gel affords the product as an oil.

G) Carbometallations of C,C-Multiple Bonds

Carbometallation is the process in which an organometallic compound adds to a C,C double or triple bond. It is thus analogous to the more familiar addition of RM to the polar C,O or C,N double or triple bond, see the first three equations of Scheme 21. With unsymmetrically substituted multiple bonds, the addition is called "*Markownikow* addition" if the metal becomes bonded to the less substituted carbon, cf. fourth equation. Of course, the carbometallation which is applied on the largest scale is polymerization of

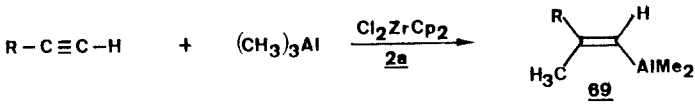
Scheme 21

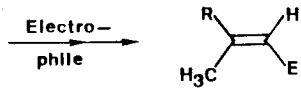


olefins by organometallic catalysts, including the *Ziegler-Natta* process, see fifth equation of Scheme 21. Attempts to cleanly perform mono-carbometallations are thus sometimes hampered by competing polymerization.

The most useful laboratoy applications appear to be the additions to acetylenes, because they can be used for the stereospecific synthesis of alkenyl derivatives. A recent review article on this topic [131] and the chapter by *J.F. Normant* in the present volume give all the relevant references and a competent discussion of the various modifications. Although carbometalla-

tions can be done with a large number of different metals, the copper derivatives are the most versatile ones and have been studied most extensively [131] for additions to acetylenes. Ironically, one of the most useful components for natural product synthesis, the methyl group, can not be added to these substrates satisfactorily [131]. Once again, titanium and zirconium derivatives come to the rescue: regioselective and *cis*-diastereoselective titanium- and especially zirconium-catalyzed carboaluminations are applicable to "methyl-metallations" (see reference [132] for an extensive survey). The vinyl alanes 69 thus obtained, usually with >95%, often with >98% E-preference, can be converted to many useful products by reaction with



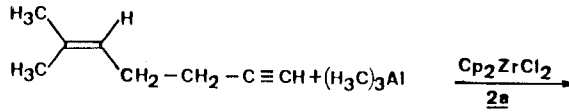


70, E = H, D, I, HgCl, BR_2, COOH, COOEt, CH_2OH, CH_2OMe, CH(OH)Et, CH_2CH_2OH, $CH_2CH_2COCH_3$.

various electrophiles, see the list underneath *formula* 70. A procedure for the *cis*-addition of CH_3 and I to a terminal triple bond follows.

Detailed procedures describing safe techniques of handling alkyl aluminum derivatives may be obtained from the Schering AG (Bergkamen) [133].

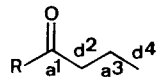
(E)-1-Iodo-2.6-dimethyl-1.5-heptadiene [131]



Dichloro-bis(η^5-cyclopentadienyl)zirconium (2.92 g, 10 mmol) (2a) is suspended in 1.2-dichloroethane (25 ml) and trimethylalane (1.44 g, 1.92 ml, 20 mmol) (pyrophoric!) [133] added under nitrogen at room temperature. The dichloro-bis(η-cyclopentadienyl)zirconium dissolves within 10 - 15 min. to produce a yellow solution, to which is added 6-methyl-5-hepten-1-yne (1.08 g, 10 mmol). After stirring for 24 hours at room temperature, iodine (3.04 g, 12 mmol), dissolved in THF (15 ml), is added dropwise at 0°C. After the iodine color has disappeared, the reaction mixture is quenched with water, and ether is added. The organic layer is separated, dried, and distilled to give the title compound; yield: 1.80 g, 72%; b.p. 54 - 55°C/0.55 Torr.

H) Oxidative and Reductive Coupling of Carbonyl Compounds - Redox Umpolung with Titanium Derivatives

With the exception of some allylic Ti-reagents corresponding to d^3-synthons (see 54f, 54g, and 54e, Scheme 19 and Table 8), the conversions of carbonyl



71

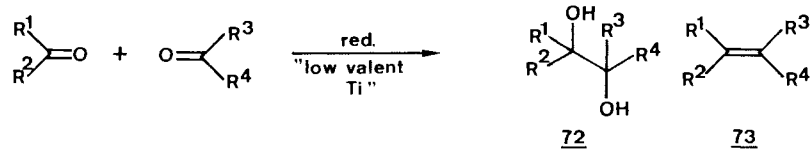
acceptor reactivity (a)
- a^1: carbonyl additions
- a^3: *Michael* additions

donor reactivity (d)
- d^2: enolates as nucleophiles
- d^4: dienolates with ω-reactivity

derivatives discussed in the previous sections all used normal reactivity, see 71.

The oxidation potential of Ti(IV) and the reducing properties of lower-valent titanium have been used for coupling of carbonyl compounds. Couplings between atoms of the same reactivity such as the pinacolization [134] and the acyloin condensation [135] or oxidation of enolate derivatives [136-139] furnish products with 1.2n-distances between functional groups, see 72, 73, and 74 in Scheme 22.

Scheme 22



72 73

preparation of low-valent titanium reagents

$TiCl_3$/LAH [140-145]

$TiCl_3$/K,Li [146-149]

$TiCl_3$/Mg [150]

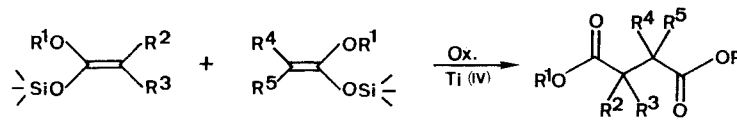
$TiCl_3$/Zn/Cu [151,152]

$TiCl_4$/Zn [153-155]

$TiCl_4$/Mg/Hg [156]

$CpTiCl_3$/LAH [156]

Al/$AlCl_3$/$TiCl_4$/hexamethylbenzene [148,156]



74

Especially useful is the coupling of ketones and aldehydes directly to olefins 73. Reviews on this topic by two of the discoverers [68,157] have appeared. This coupling is feasible even with formation of highly hindered olefins [154,155]. If two carbonyl compounds of sufficiently different redox potential are used [158], or if one component is cheap and can be used in excess [156], cross-coupling is possible. Intramolecular couplings with formation of one [156,159] or two [149] rings have been described. Some representative and/or especially impressive examples are listed in Table 9, together with references. It is of course possible to do the two steps, i.e. pinacol coupling to 72 and reductive deoxygenation to 73 separately. This means that glycols from sources other than the "Ti(0)"-coupling can be converted to olefins [140] with "low-valent" titanium.

The preparation of these so-called low-valent Ti-reducing reagents is crucial for the success of the reaction. The quality of these reagents is decisive with respect to reaction times, selectivity diol/olefin and yield. Numerous recipes have been recommended by the different authors in the field, see Scheme 22. Probably, zero-valent titanium [160] is the actual reagent with which the reaction begins; depending on the reducing reagents with which this mostly black, pyrophoric (!) material is made, other metals and/or metal salts are present. The driving force is the high affinity of titanium for oxygen, which eventually leads to TiO_2.

There are recent applications of the method in which stereoselectivity was observed, see 75 [152,161] and 76 [162]. Finally, vinylogous extensions of the

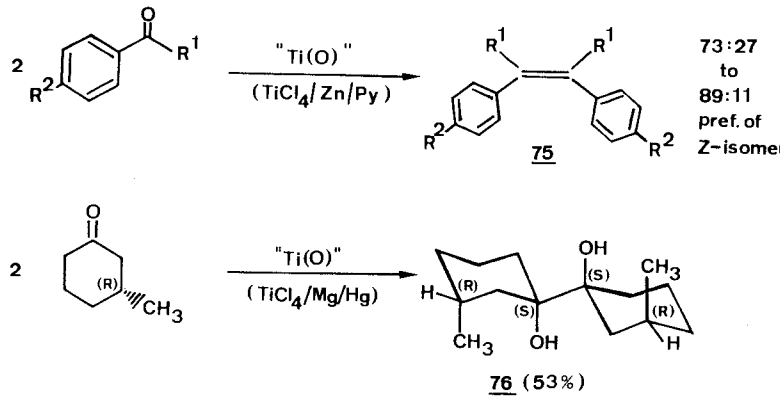
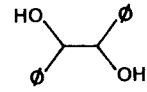
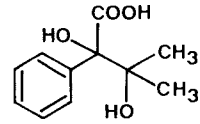
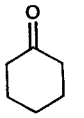
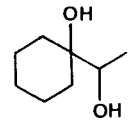
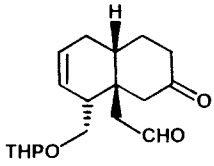
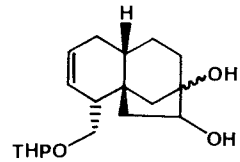
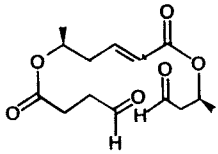
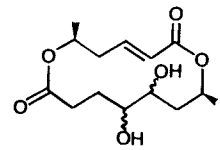
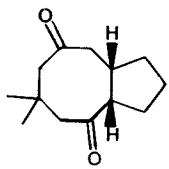
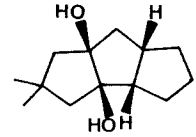
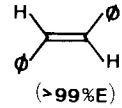
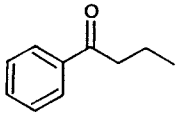
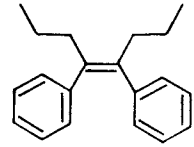
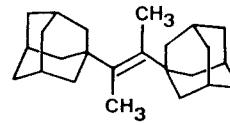
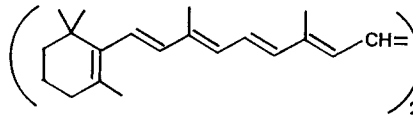
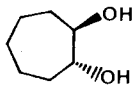
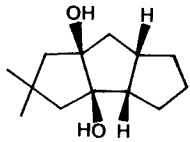
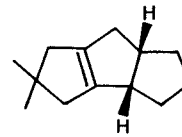


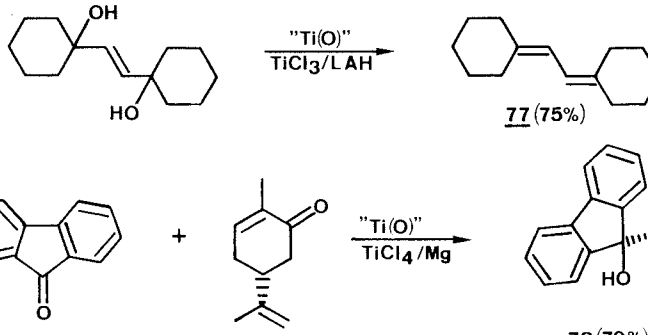
Table 9. Coupling of carbonyl compounds with "low-valent titanium" to 1.2-diols or to olefins. Two examples of deoxygenation of glycols to olefins are also given.

starting material	product	yield	conditions	ref.
2 Benzaldehyde		98%	$TiCl_4/Zn$ THF, 0°C	153)
$C_6H_5-CO-COOH$ + acetone		85%	$2\,TiCl_3$	158)
 + CH_3CHO		72%	$CpTiCl_3$/ LAH	156)
		55%	$CpTiCl_3$/ LAH	156)
 (→ (S,S)-(+)-Grahamimycin A1)		35%	$TiCl_4$ / Zn-Cu THF 5h reflux	159)
		—	$TiCl_3/K$ 5min THF,reflux	149)

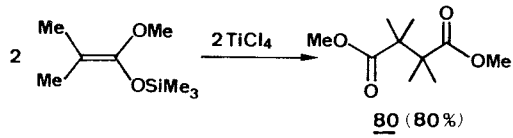
(Table 9 continued)

starting material	product	yield	conditions	ref.
2 Benzaldehyde	 (>99%E)	98%	$TiCl_4$/ Zn dioxane, reflux	153)
		50 %	$TiCl_4$/Zn/ Py THF, reflux	161)
1 – Adamantyl – methyl ketone		15%	$TiCl_4$/Zn/Py 3d,THF reflux	154)
retinal		85%	$TiCl_3$/LAH THF, reflux	140)
		55%	$TiCl_3$/K THF,reflux	146)
		—	$TiCl_3$/K 6 days reflux THF	149)

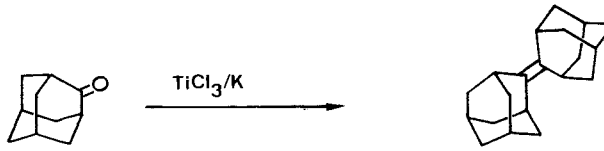
method are known, see 77 [163] and 78 [164], and similar conditions have been used for a modification of the *Wittig* reaction, see 79, employing dibromomethane as methylene source [165].



The oxidation of enolates with coupling by $TiCl_4$ was discovered as an accident during attempted titanium tetrachloride catalyzed reactions with silyl enol ethers of α-branched esters (ketene acetal derivatives). So far, there are only few examples reported in the literature [67,166,167], see for instance the formation of 80 [166] and the procedure below.

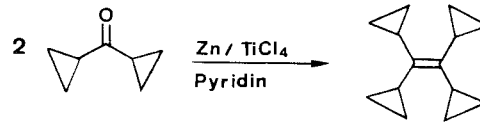


Adamantylidene-adamantane [147]



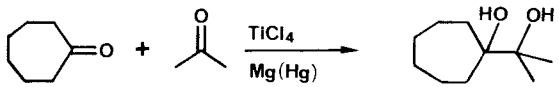
To a suspension of $TiCl_3$ (2.15 g, 14 mmol) in 75 ml of dry THF, 1.92 g (49 mmol) of potassium metal (washed with hexane to remove oil) is added under an inert atmosphere at room temperature. After refluxing for 40 min. and cooling, a solution of 525 mg (3.5 mmol) adamantanone in 5 ml THF is added. The reaction is complete after refluxing for 16 hours. The black slurry is vacuum filtered (medium frit) under an inert atmosphere and the filter cake is washed with hexane. The filtrate is concentrated in a rotatory evaporator to yield the crude product which is purified by column chromatography to yield 91% adamantylidene-adamantane of m.p. 183-185°C. Caution: The black filter cake is pyrophoric when exposed to air and has to be quenched carefully by dropwise addition of methanol under an inert atmosphere.

Tetracyclopropyl-ethylene [154]



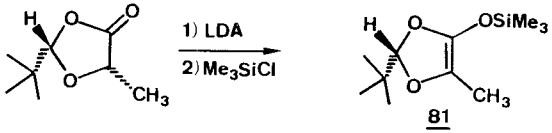
Under an inert atmosphere, neat titaniumtetrachloride (8.2 ml, 75 mmol) is added dropwise to 200 ml anhydrous THF with stirring and cooling in an ice-bath. Zinc powder (10 g, 150 mg-atom) is then added in small portions. After addition of pyridine (5 ml) and dicyclopropyl ketone (7.7 g, 70 mmol), the reaction mixture is heated under reflux for 20 hours. The suspension is cooled to room temperature and treated with 150 ml 10% aqueous K_2CO_3 solution. The aqueous phase is extracted with ether or pentane, the combined organic layers washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo*. The residue is chromatographed on silica gel with pentane. Yield: 25%, b.p. 70-72°C (0.5 mm Hg).

1-(2-Hydroxy-2-propyl)-cycloheptanol [156]

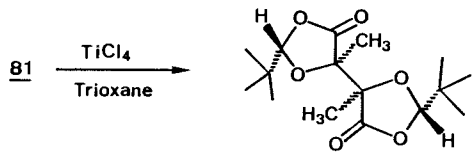


A slurry of 70-80 mesh magnesium (1.92 g, 80 mg-atom) and mercuric chloride (0.60 g, 2.21 mmol) in 10 ml THF is stirred under argon for 15 min. at room temperature. The turbid supernatant liquid is removed and the residue is washed with three portions of THF. After addition of 30 ml THF to the dull grey amalgam, the suspension is cooled to -10°C and treated dropwise with titanium tetrachloride (4.4 ml, 40 mmol). A solution of 2.24 g (20 mmol) cycloheptanone and 4.64 g (80 mmol) acetone diluted with 10 ml THF is then added to the yellow-green mixture. The color changes to purple and stirring is continued for 1.5 hours at 0°C. The reaction is quenched with 2 ml saturated aqueous K_2CO_3 solution and stirred for another 15 min. After addition of 100 ml ether and filtration through celite, the filtrate is washed with saturated NaCl solution, dried ($MgSO_4$) and concentrated to afford 5.61 g of a viscous oil. Column chromatography on silica gel (elution with ether/petroleum ether 2:3) gives 2.57 g (75% yield) of 1-(2-hydroxy-2-propyl)-cycloheptanol as colorless crystals; m.p. 51-52°C.

Oxidative dimerization of the O-(trimethylsilyl)ketene-acetal 81 [167]



81



82

Lithium diisopropyl amide (11.5 ml, 0.913 M in THF) is cooled to -78°C under

argon atmosphere and (2S,5S)-5-methyl-2-(*t*-butyl)-1.3-dioxolan-4-one [37] (1.6 g, 10 mmol) is slowly added. After stirring for 30 min., the solution is quenched by the addition of trimethyl chlorosilane. Within ca. 1 hour the temperature is raised to room temperature and stirring is continued for an additional hour. The solvent is removed evaporatively. The residue, which is fairly pure apart from the admixture of lithiumchloride, is directly used without further purification, owing to the high sensitivity of 81 to hydrolysis as well as to thermolysis.

To a solution of 5.7 g (30 mmol) titanium tetrachloride in 50 ml CH_2Cl_2 and 2.7 g (30 mmol) trioxane (which proved to be essential for the dimerisation, although originally meant to achieve hydroxymethylation of the ketene acetal) is added at -78°C the crude trimethylsilyl ketene acetal (ca. 10 mmol, cf. above) dissolved in 10 ml CH_2Cl_2. The resulting deep green reaction mixture is stirred for 3 hours at -78°C and then hydrolyzed by the addition of 100 ml H_2O. Extraction of the purple solution with ether, washing of the combined organic layers with H_2O, drying ($MgSO_4$) and removal of the solvent affords after distillation (120°C, 0.03 mm Hg) 1.2 g (3.8 mmol, 76%) of the dimer in form of colorless crystals; m.p. 123-125°C (from ether / pentane 1:1), $[\alpha]^{25}_D$ = +25.9° (1.95, $CHCl_3$). For the *tert*-butyl and also for the methyl group of compound 82 only one signal is observed in the ^{1}H-NMR, which proves the existence of a C_2-axis.

IV FUNCTIONALIZATIONS AND FUNCTIONAL GROUP INTERCONVERSIONS

The largest part of the present review deals with carbon carbon bond forming reactions which are mediated by titanium or zirconium derivatives. It was demonstrated in the previous chapter III that many classical processes can be made highly selective by turning from derivatives of the main-group metals to those of the early transition metals titanium and zirconium.

This somewhat shorter chapter will now highlight applications of the same elements which commence without elaboration of the carbon skeleton, but which rather change its functionality. It will become evident, that again great improvements in selectivity are possible with derivatives of these two metals. Also, this chapter will demonstrate again the great potential of the simple inexpensive and non-toxic titanates, zirconates and amide analogues in synthesis.

A) Reductions and Oxidations Involving Carbonyl Derivatives

1) *Meerwein-Ponndorf-Verley* Reductions and *Oppenauer* Oxidations with Zirconates

It is surprising, how few applications of these reactions are found in modern synthetic sequences. The complex hydrides of boron [168] and of aluminum [169] with all their modifications, and aluminum hydrides such as DIBAH have become the predominant reagents for carbonyl reduction. For oxidations, the various modifications of chromium(VI) reagents and, more recently, of the *Kornblum* reagent [170] prevail [*Pfitzer-Moffat* [171], *Corey-Kim* [172], *Swern* [173], etc.]

If applied catalytically, the *Meerwein-Ponndorf*-type reductions, for which a secondary alcohol such as isopropanol is used, or the *Oppenauer* oxidations, which can be carried out with acetone or chloral as oxidants, appear to be more economical, see the accompanying Table 10. Furthermore,

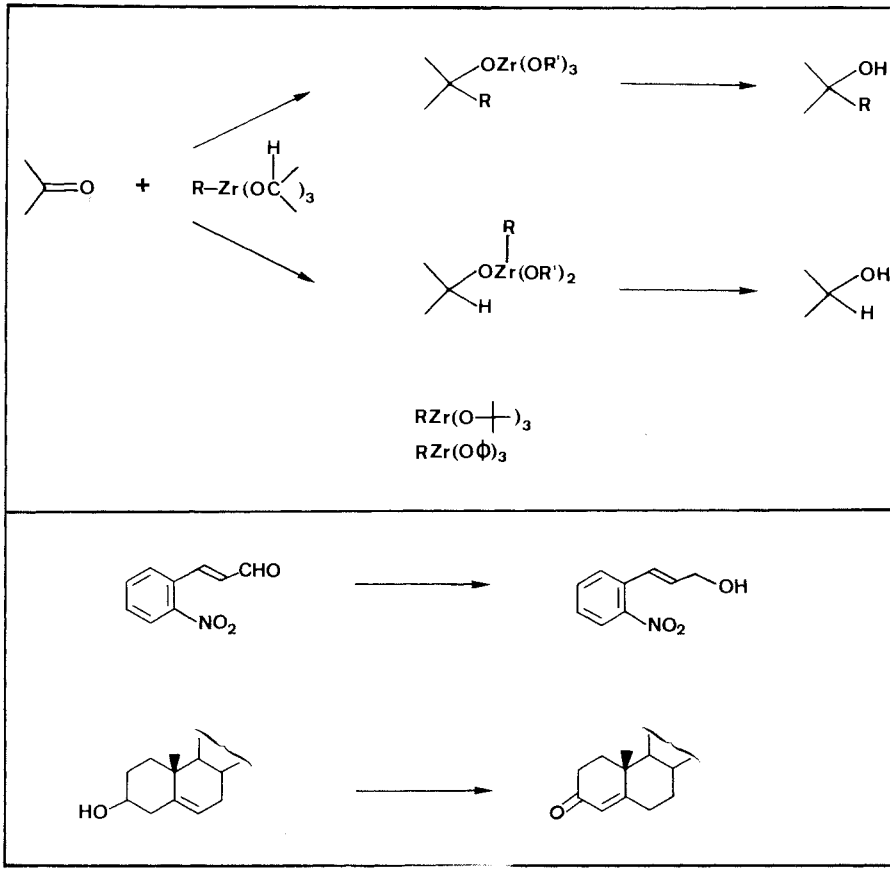
Table 10. Prices per equiv. of hydride or per reduction or oxidation equiv. for some common reducing and oxidizing reagents (from a 1983 catalogue).

Reagent	Mol.Wt.	Price in US $ (largest packing size)	
$LiAlH_4$	38	4.--/$H^{\ominus}$	
$NaBH_4$	38	2.--/$H^{\ominus}$	
DIBAH	142	23.--/$H^{\ominus}$	
$LiBHEt_3$	106	100.--/$H^{\ominus}$	(Superhydride®)
$NaBHEt_3$	122	400.--/$H^{\ominus}$	
$LiBH(i\text{But})_3$	190	100.--/$H^{\ominus}$	(Li-Selectride®)
$NaCNBH_3$	63	10.--/$H^{\ominus}$	
$LiAlH(O\text{-}t\text{-}C_4H_9)_3$	254	170.--/$H^{\ominus}$	
$NaAlH_2(OCH_2CH_2OCH_3)_2$	202	10.--/$H^{\ominus}$ equiv.	(Vitrid®)
$(CH_3)_2CHOH$	60	--.15/$H^{\ominus}$ equiv.	
$(CH_3)_2CO$	58	--.15/oxid. equiv.	
CCl_3CHO	147	4.50/oxid. equiv.	

for many purposes, these alcohol/carbonyl hydride donors and acceptors are extremely selective in the presence of further functional groups in the substrate. Thus, imino, nitro, cyano, ester, halo, sulfoxide and sulfone groups do not normally interfere with these reactions.

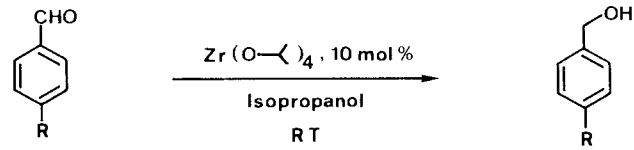
When *Meerwein et al.* first published their experiences with reductions of carbonyl groups by secondary alcohols in the presence of metal alkoxides, they strongly recommended [174] the use of aluminum alkoxides as catalysts, but they stated that zirconium and tin alkoxides are almost as good. In the course of investigations of organozirconium derivatives as nucleophiles it was found [8,27,175] that hydride can be transferred from the alkoxide group on the zirconium with a rate comparable to that of the R-group from zirconium, see Scheme 23. This can be avoided by using

Scheme 23



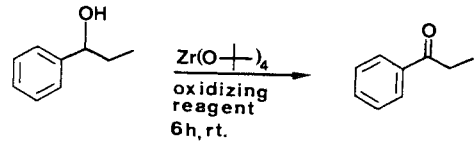
t-butoxy [23,111] or phenoxy groups on the zirconium [27]. These observations led to a reinvestigation [175] of zirconates as catalysts in reduction/oxidations through hydride transfer from and to carbon. Some results of reductions of aldehydes and ketones are given in Table 11, for oxidations see Table 12, Scheme 23, and the procedures below. It appears that the zirconate-catalyzed reactions may show high functional group selectivity; in contrast to aluminum alkoxides, which are often employed in stoichiometric amounts, the zirconates catalyze rapid conversions at lower concentrations.

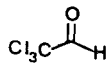
Table 11. Reactivities in the zirconate-catalyzed *Meerwein-Ponndorf-Verley* reduction as a function of the p-substituents of benzaldehyde.

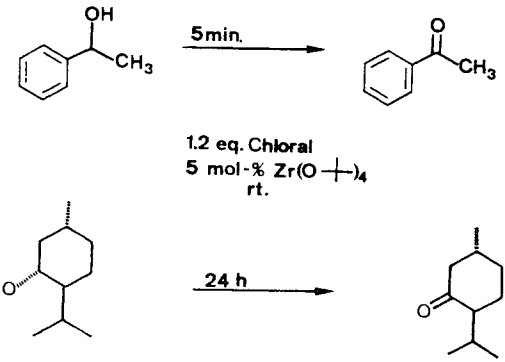


R	time (h)	benzyl alcohol (%)
NO_2	8	~100
C≡N	24	> 90
Cl	24	> 90
H	24	~ 60
OCH_3	24	~ 10
$N(CH_3)_2$	24	<1

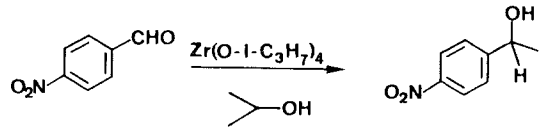
Table 12. Reactivities in the zirconate-catalyzed *Oppenauer* oxidation as a function of the oxidizing reagent (top part) and the substrate (lower part).



reagent	% conversion
	12
	64
	92

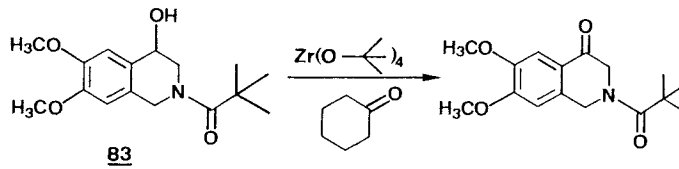


4-Nitrobenzyl alcohol [175]



In a dry flask 390 mg (1 mmol) of $Zr(O\text{-}i\text{-}C_3H_7)_4$ dissolved in 70 ml of anhydrous 2-propanol is combined with 1.5 g (9.93 mmol) of 4-nitro-benzaldehyde. After stirring for 24 hours, gas chromatographic analysis showed 94% conversion. The reaction mixture is then hydrolyzed with 50 ml 2 M aqueous HCl. Extraction with ether yields on evaporation of the solvent 1.25 g (8.16 mmol, 82%) of 4-nitro-benzyl alcohol.

Zirconate-catalyzed *Oppenauer* oxidation [175,177]



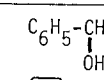
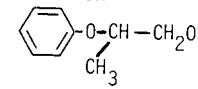
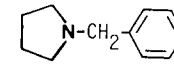
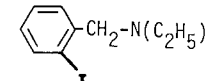
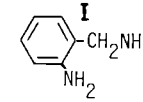
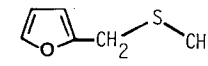
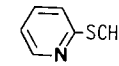
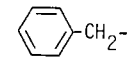
Tetrahydroisoquinoline derivative 83 (1.00 g, 3.41 mmol) is dissolved in 10 ml of cyclohexanone and a catalytic amount of $Zr(O\text{-}t\text{-}C_4H_9)_4$ (ca. 0.5 ml, 1.25 mmol) is added. After stirring at 80°C for 2 hours, the reaction is hydrolyzed with diluted HCl and extracted with ether. Cyclohexanone is removed under oil pump vacuum and the residue is purified by flash-chromatography (CH_2Cl_2/EtOAc 1:1). 450 mg (1.53 mmol, 45%) of the oxidation product is obtained, which can be crystallized from CH_2Cl_2/EtOAc 1:1 to furnish slightly yellow crystals. m.p. 129 - 130°C.

2) Titanium-mediated Reductions

There are some remarcably selective reductions of carbonyl derivatives and analogues by low-valent titanium which are worth mentioning here. Thus, addition of carboxylic acids, acid chlorides, carboxamides, oximes, nitro compounds and sulfoxides to a mixture obtained from $TiCl_4$ and

$NaBH_4$ causes smooth reduction to primary alcohols, amines, and thioethers, respectively [178], see the upper part of Table 13. Also, the Ti(III) derivative from dichloro-titanocene and isopropyl *Grignard* reagent catalyzes the reduction of carboxylic acids to aldehydes by the same magnesium derivative [179], bottom part of Table 13. A catalytic

Table 13. Reductions of carboxylic acids, amides, oximes, nitro groups (see procedure) and of sulfoxides (reverse addition) by a reagent from 1 equiv. $TiCl_4$ and 2 equiv. $NaBH_4$ in dimethoxyethane [178], entries 1 - 7. Reduction of carboxylic acids to aldehydes by $(CH_3)_2CHMgBr$ and cat. amounts of Cp_2TiCl_2 [179], entries 8 - 10.

Entry	Starting material	Product	Yield [%]
1	mandelic acid		60
2	α-phenoxy-propanoic acid		95
3	N-benzyl-pyrrolidone		93
4	o-iodo-diethylbenzamide		95
5	oxime of o-nitrobenzaldehyde		82
6	methyl-(2-furylmethyl)sulfoxide		91
7	methyl-(2-pyridyl)sulfoxide		89
8	$n\text{-}C_6H_{13}COOH$	$n\text{-}C_6H_{13}CHO$	73
9	$C_6H_5CH_2COOH$		48
10	benzoic acid	benzaldehyde	55

cycle was proposed [179], in which Cp_2TiH is the actual reducing reagent, and the aldehyde is thought to be protected as $RCH(OMgX)_2$ from further reduction.

General Procedures for Reductions with $TiCl_4/NaBH_4$ [178]; (cf. entries 1 - 7 of Table 13).

Stoichiometry: 1 RCOOH / 1.1 $TiCl_4$ / 3.3 $NaBH_4$; 1 RCOCl / 1.1 $TiCl_4$ / 2.2 $NaBH_4$; 1 $RCONR_2$ / 1.5 $TiCl_4$ / 3 $NaBH_4$; 1 R_2CNOH / 2.1 $TiCl_4$ / 4.2 $NaBH_4$; 1 RSOR' / 1.1 $TiCl_4$ / 2.2 $NaBH_4$.

For the reduction of 10 mmol substrate, a mixture from $TiCl_4$ and $NaBH_4$ in 40 ml dimethoxyethane (glyme) is prepared and stirred in an ice-bath. A solution of the substrate in 10 ml anhydrous glyme is added, and the reaction is quenched with cooling after 14 hours at room temperature by addition of 100 ml H_2O. Extraction with benzene(2x60 ml), in the case of amine products after basification with 28% aqueous ammonia, is followed by drying over Na_2SO_4, evaporation of the solvent and distillation or recrystallization.

General procedure for Reduction of Acids to Aldehydes [179]

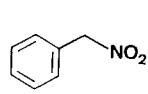
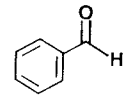
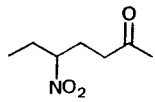
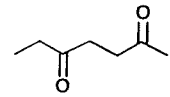
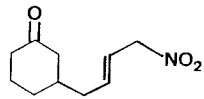
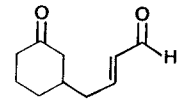
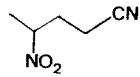
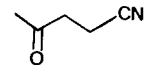
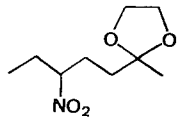
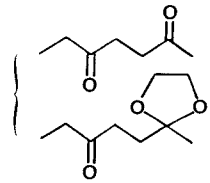
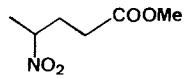
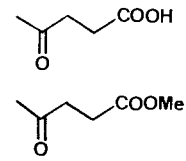
$$RCOOH + 2\ Me_2CHMgBr \xrightarrow{Cp_2TiCl_2} RCHO$$

To stirred 1 M $Me_2CHMgBr$ in ether (63 mmol) is first added Cp_2TiCl_2 (75 mg, 0.3 mmol), and 5 min. later a carboxylic acid (30 mmol), under an argon atmosphere and with ice cooling. After 4 hours at room temperature, 20 ml of 4 N HCl is added, the layers are separated, the aqueous layer extracted (30 ml ether), and the combined organic layers dried ($MgSO_4$) and distilled.

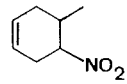
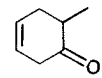
3) *Nef*-Reactions with $TiCl_3$

With the advent of numerous new carbon carbon bond-forming reactions of nitroalkanes [180-182] the importance of the *Nef*-reaction, which converts nitroalkanes to aldehydes or ketones, has grown. As with many other classical reactions, there are literally dozens of procedures for this conversion. One is the treatment of nitroalkanes with titanium trichloride [157,183]. In some cases, this method works when all the others fail. Representative procedures are given along with a list of examples in Table 14.

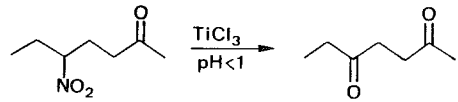
Table 14. Conversion of nitroalkanes to ketones and aldehydes by treatment of the nitrocompounds with $TiCl_3$ at pH <1 (A) or in a buffered solution at pH ca. 6 (B) [183]

starting material	product	method/% yield
		A 80
		A 85
		A 60 [184]
		A 55 B 90
		A 40 B 70
		A 40 B 90

(Table 14 continued)

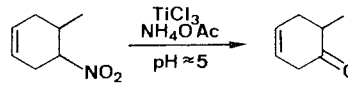
starting material	product	method/% yield
		A 35
		B 60

Heptan-2,5-dione [183] (Method A)



A 0.2 M solution of 5-nitroheptan-2-one is combined with four mol-equiv. of $TiCl_3$ (20% aqueous solution) and stirred under nitrogen at room temperature for 24 hours. The reaction mixture is then poured into ether. After separation of the two phases, the aqueous layer is extracted several times with ether. The combined organic extracts are washed with 5% $NaHCO_3$ and with brine, dried (Na_2SO_4) and concentrated. Distillation of the crude product affords heptan-2.5-dione in 85% yield.

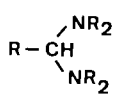
2-Methyl-4-cyclohexenone [183] (Method B)



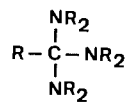
A 0.5 M solution of 4-nitro-5-methylcyclohexene in methanol is treated with 1 mol-equiv. of $NaOCH_3$ to form the corresponding sodium nitronate. An aqueous solution of $TiCl_3$ and NH_4OAc 1:6 is prepared (ca. 0.4 M with respect to $TiCl_3$). At room temperature 4 mol-equiv. of this buffered $TiCl_3$ solution is added in one portion to the nitronate under a nitrgen atmosphere. After 45 min. the reaction is worked up (cf. procedure above) and 6-methylcyclohex-3-en-1-one is isolated in 66% yield.

B) Reactions of Carbonyl Compounds Involving Dialkylamido-titanium Derivatives

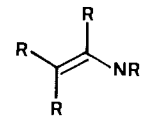
The early work on dialkylamido-derivatives of titanium has been described in an excellent review article [185]. The use of reagents of type $RTi(NR_2)_3$ 22 and $RTi(NR_2)_4M$ 27 as nucleophiles for carbonyl additions has been mentioned occasionally in chapter III (see amination/alkylation of carbonyl derivatives III C2; aldol additions and related processes III F). A procedure describing the preparation of the tetrakis(dimethyl- and diethylamino)-titanium (12, 13) is given in section II. The titanium(IV)dialkylamides, $Ti(NR_2)_4$, react rapidly with various carbonyl derivatives. Depending upon the particular structure of the carbonyl compound, different amino-derivatives can be formed with removal of the oxygen: aminals 84 with non-enolizable aldehydes such as benzaldehyde and pivalaldehyde, but also with acetal-



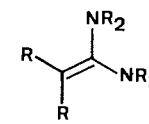
84



85

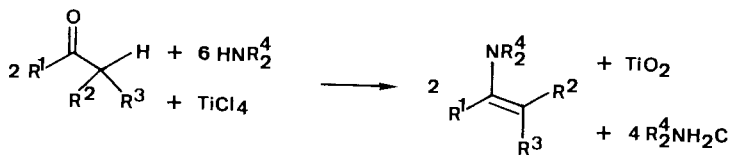


86



87

dehyde; *ortho*-amides 85 with non-enolizabel carboxylic acid derivatives; enamines 86 with most enolizable aldehydes and ketones; and ketene aminals 87 with enolizable carboxylic esters and amides [186]. This formation of enamines is one of the most efficient methods of preparing this class of substances, and the modification using $TiCl_4$ and secondary amines directly is generally referred to as the *Weingarten* method [187]. Its stoichiometry requires three moles of secondary amine per mole of enolizable carbonyl compound 88. It is especially effective with hindered ketones. Its disad-



88

86

vantage is obviously the necessity of using excess amine, if the amine is valuable. A typical procedure follows.

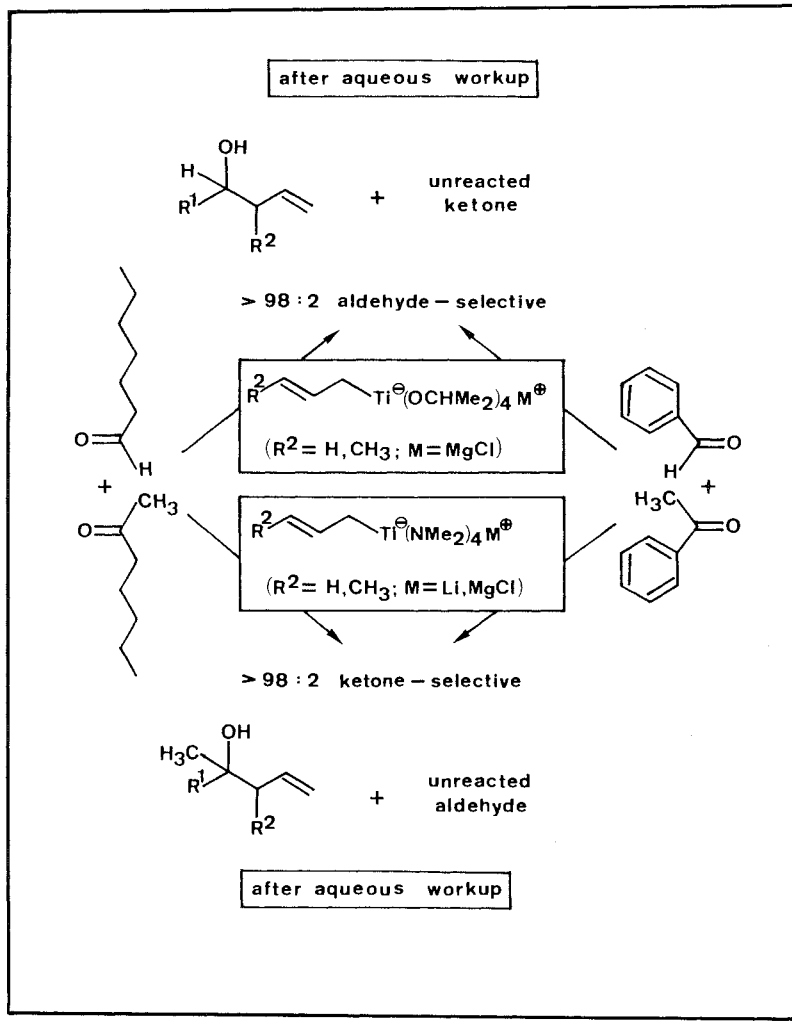
General Procedure for the Synthesis of Enamines with $TiCl_4$ [187]

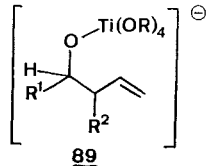
(see 88 → 86)

A two-liter four-necked flask is fitted with a mechanical overhead stirrer, a reflux condenser, an N_2 gas line, a thermometer, and a dropping funnel. Under an atmosphere of dry nitrogen, the flask is charged in this order with 500 ml solvent (benzene, pentane, or ether), 0.1 mole of ketone, and a solution of excess amine (4 - 5 equiv.) in 100 ml of the same solvent. To the resulting solution is added over a period of 20 - 60 min. 0.055 mole $TiCl_4$, dissolved in an additional 100 ml of solvent (benzene or pentane), while the temperature is kept between 0^o and 10^oC. The resulting mixture is stirred for several hours at 20^oC. The more hindered ketones (pinacolone, 2.5-dimethylcyclohexanone) require longer reaction times. The progress of the reaction is followed by NMR. analysis of aliquots. After the reaction is complete, the reaction mixture is filtered, the solvent is evaporated from the filtrate and the residue is distilled *in vacuo*. All these workup operations must be carried out quickly, under exclusion of moisture.

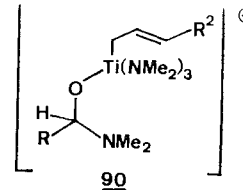
The rate at which dialkylamido-titanium derivatives transfer an amino group to a carbonyl carbon appears to be faster than that of alkyl transfer from titanium. Thus, the methylating amination (see section III C2) could only be explained with the assumption that the amino group is transferred faster than the methyl group [28]. In Scheme 24, a surprising reversed selectivity of additions to aldehydes and ketones is demonstrated, which becomes reasonable only if the above assumption is made. Addition of the ate-complex from tetraisopropoxy-titanium and allyl or crotyl *Grignard* reagent to a 1:1-mixture of an aldehyde and a ketone leads to the isolation of the adduct to the aldehyde, with the expected (see section III A1) selectivity. This is true both with aliphatic (left part of Scheme 24) and aromatic carbonyl derivatives (right top part of Scheme 24). On the other hand, as demonstrated in the bottom half of Scheme 24, the ate-complexes from tetrakis(dimethylamino)titanium are perfectly ketone selective, giving rise, after aqueous workup, to the ketone adduct and unreacted aldehyde. These findings [19,115] are explicable if the primary product from the alkoxy-ate-complex is 89, the result of allylic group transfer, while that with the amino-derivative is 90, i.e. the product of amino-group transfer. The adduct 90 is now a protected form of the aldehyde, and it acts as an allylic group transfer reagent towards the ketone!

Scheme 24. Aldehyde-selective additions of allylic groups from $[(Me_2CHO)_4Ti\text{-}CH_2\text{-}CH{=}CH\text{-}R]^-$ate-complexes and ketone-selective additions of allylic groups from $[(Me_2N)_4Ti\text{-}CH_2\text{-}CH{=}CHR]^-$ate-complexes [19,115].



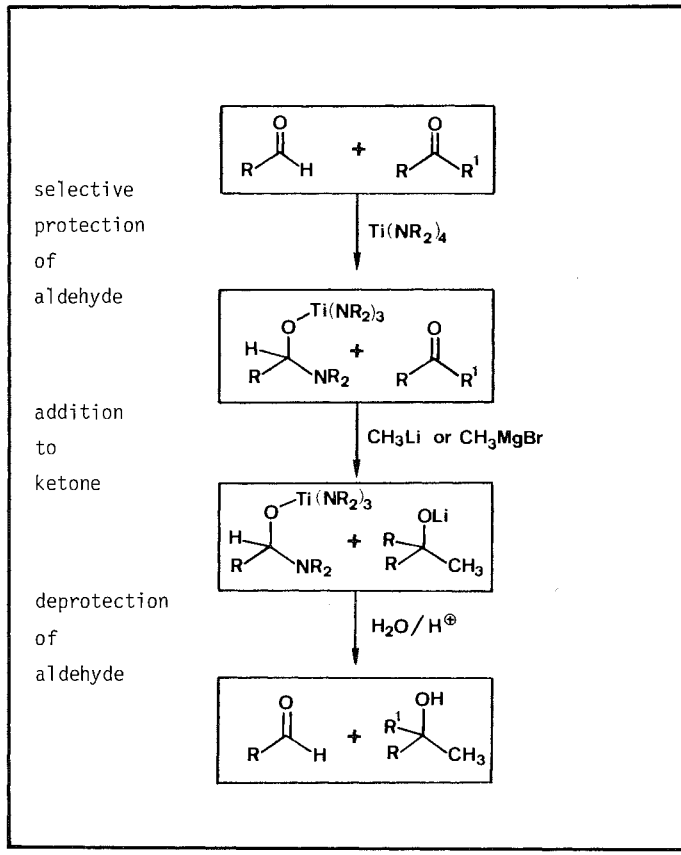


89



90

Scheme 25



No ate-complex needs to be generated in order to achieve ketone-selective additions of this type [188]. If tetrakis(dialkylamino)titanium is added at -78°C to an aldehyde/ketone mixture prior to methyllithium, again ketone-selective addition of the nucleophile is observed, see Scheme 25. Obviously, $Ti(NR_2)_4$ adds selectively to the aldehyde, leaving behind unchanged ketone, which is trapped by the "second" nucleophile MeLi.

Thus, the expected fast, selective, and irreversible (at low enough temperature) transfer of the amino group to the aldehyde is responsible for the reversal of the normal aldehyde vs. ketone selectivity, which seems surprising at first sight.

C) $Ti(OR)_4$-Catalyzed Transesterifications

The chemical industry offers (see Figures 3 - 5) and uses titanates as cheap bulk chemicals for various applications. Among other transformations, esterifications are catalyzed by titanates. A literature search, inspection of

Fig. 3

Fig. 4

"Call 800-441-9475 to get all the organic titanates you need, fast."

Ollie Yeaton, Sales Manager

Seven versatile DuPont TYZOR® organic titanates can improve your product properties.

To get all the DuPont organic titanates you need, when and where you need them, just call. We're the largest domestic manufacturer of titanates, fully integrated forward from our own titanium ore mines. So you can bet on reliable supply and delivery, whether you need tank trucks, drums or 40-lb. pails.

When TYZOR organic titanates are used to crosslink resins via active hydrogens, the cured resins display improved hardness, electrical properties and solvent resistance. Common applications for crosslinking with TYZOR include printing inks, paints, coatings and gels.

TYZOR is also being used more and more as an esterification catalyst for carboxylic esters.

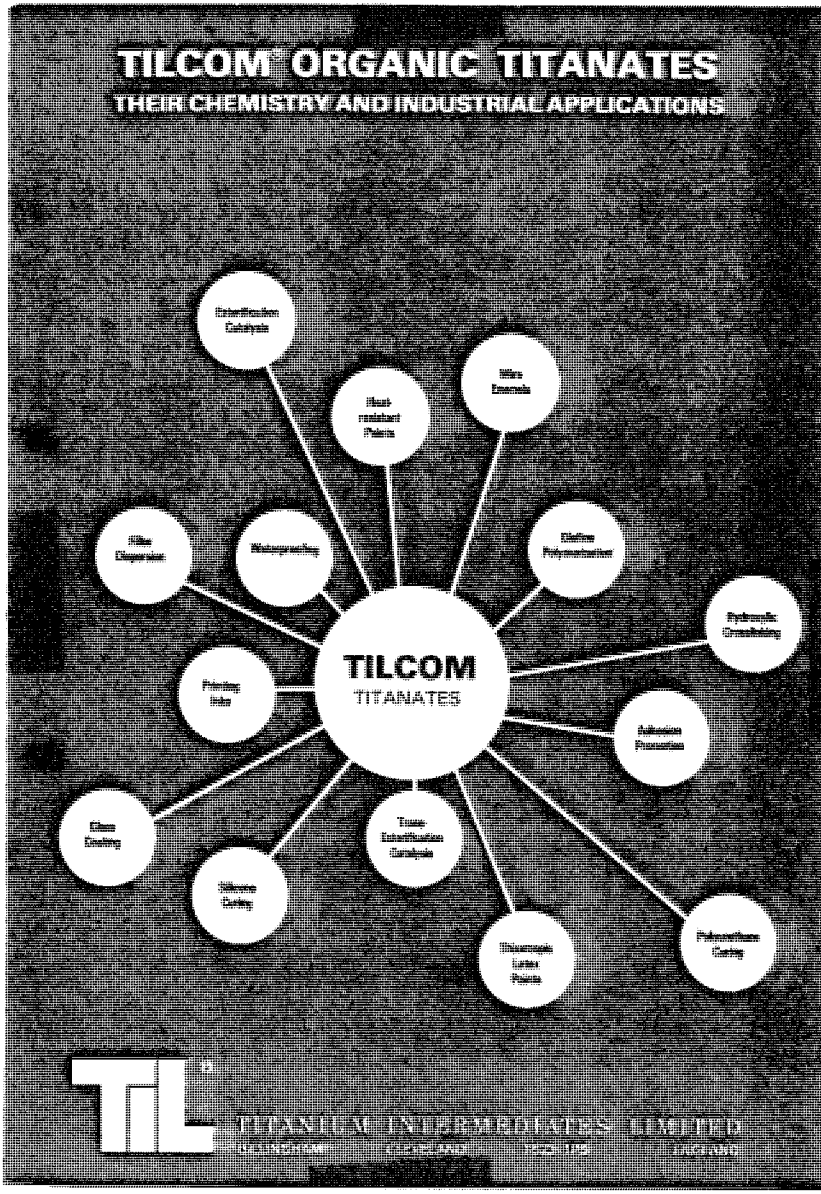
TYZOR organic titanates have a broad range of reactivity. Water-stable chelates are also available.

40% increase in TYZOR capacity.

In March, 1982, DuPont's already sizeable production capacity for TYZOR will expand by 40%. But right now, for all the organic titanates you need, call 800-441-9475. Or write: Ollie Yeaton, DuPont Company, Room G39404J1, Wilmington, DE 19898, to find out more about how you can use TYZOR organic titanates.

DU PONT

Fig. 5


TILCOM® ORGANIC TITANATES
THEIR CHEMISTRY AND INDUSTRIAL APPLICATIONS
TILCOM
TITANATES
TITANIUM INTERMEDIATES LIMITED

the eight volumes of *Fieser's* Reagents, and discussions with many colleagues revealed that titanate-mediated esterifications, deacylations, and transesterifications are well known to industrial chemists, but essentially unknown in research laboratories, especially at universities. Accordingly, almost all applications are described in the patent literature and involve rather simple, monofunctional substrates, see the discussion and the references in a recent article [189].

As demonstrated in Scheme 26, the equilibria between esters (RCOOR') and alcohols (R''OH) can be established with titanate catalysis. If an alcohol is used in large excess, as a solvent, a substrate ester is transesterified, a substrate acyl-protected alcohol is deprotected (top arrow in Scheme 26). If, however, an ester is used as a solvent, a substrate ester is also transesterified, but a substrate alcohol is esterified (arrow on the bottom of Scheme 26). These equilibrations can be exploited for selective transesterifications or deprotections of polyfunctional substrates, even in the presence of groups which are very sensitive to acid or base, such as C,C and C,N triple bonds, acetals, β-hydroxy- and β-acyloxy-esters, β-lactams, *t*-butyl-dimethylsilyloxy groups, BOC- [190] and other urethane protecting groups, etc. The titanates may be considered as "neutral *Lewis* acids" with a preference for carbonyl oxygen (C=$\underline{\bar{O}}$) over acetal, ether or alcohol oxygen (R-$\underline{\bar{O}}$-R).

The titanate catalyst used in most cases is tetraethoxytitanium; the small amounts of ethanol introduced into the equilibria do not influence the results if other than ethyl esters are to be made. For preparing methyl esters in methanol as the solvent, simple titanates can not be used, because the very insoluble tetramethoxytitanate precipitates. This can be avoided by using a catalyst obtained from $Ti(OEt)_4$ and one-half equiv. of glycol [191]. Another possibility of preparing methyl esters is to transfer the CH_3O-group from another ester, for instance methyl propionate which is employed as the solvent (bottom part of Scheme 26). Strangely, under these conditions no $Ti(OCH_3)_4$ precipitates [191].

Four characteristic examples are described below in full experimental detail; a list of recent applications is found in Table 15.

Scheme 26

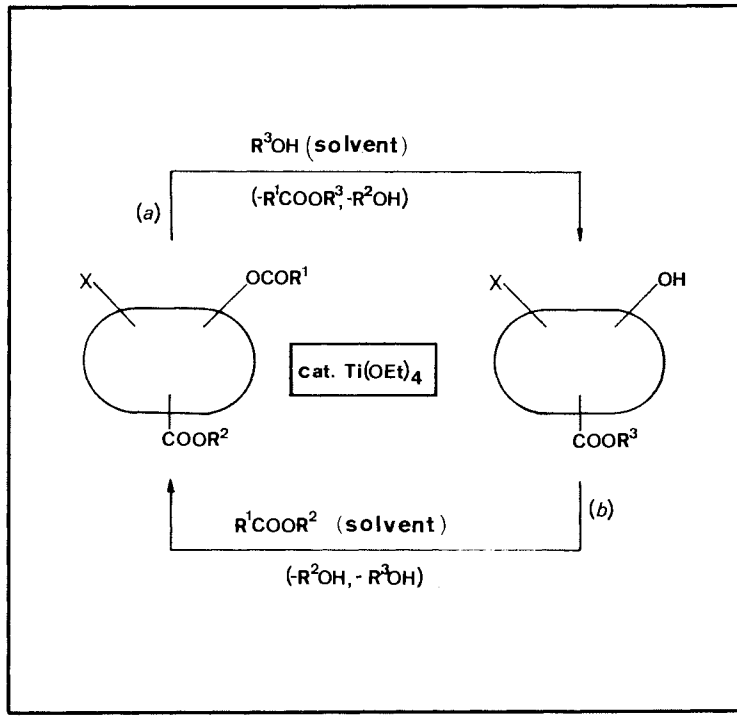
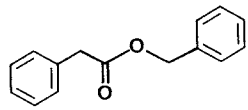
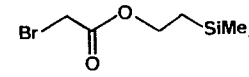


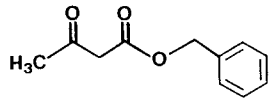
Table 15. Examples of esterification, transesterification, deprotection, and polyester depolymerization to give acid and/or base-sensitive products. The solvent for transesterifications is the alcohol of which the ester is formed; acetylations of alcohols are performed in ethyl acetate. The catalyst is indicated by A [$Ti(OEt)_4$], B [$Ti(O\text{-}i\text{-}C_3H_7)_4$] or C [$(EtO)_3Ti\text{-}OCH_2CH_2O\text{-}Ti(OEt)_3$]. D refers to the alternative method of forming methyl esters in methyl propionate with $Ti(OEt)_4$.



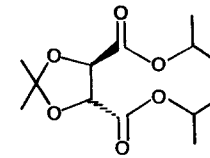
A 85% from ethyl ester [189]



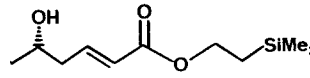
A 71% from ethyl ester [189]



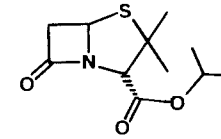
A 56% from t-butyl ester [189]



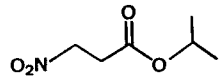
B 91% from methyl ester [189]



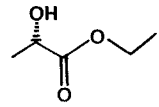
A 74% from methyl ester [189]



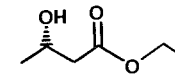
B 91% from methyl ester [189]



A 50% from methyl ester [189]

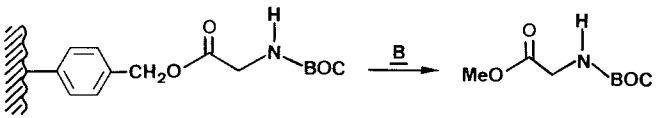


A 60% from propionate [189]

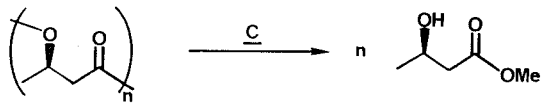


A 90% from 3.5-dinitrobenzoate [189]

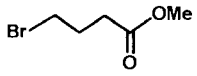
190)



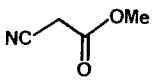
190)



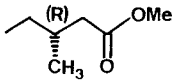
191)



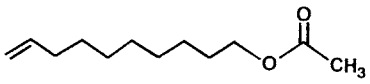
D 83% from ethyl ester 191)



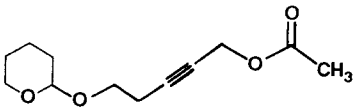
C 88% from ethyl ester 191)



C 77% from ethyl ester 191)

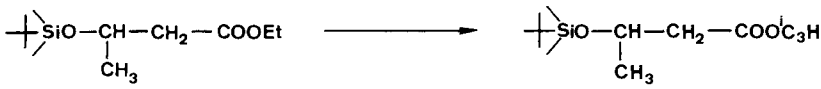


A 94% from alcohol 191)



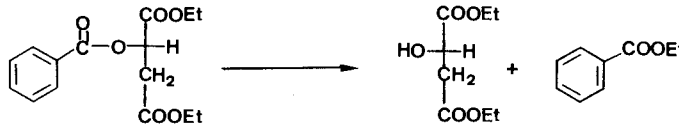
A 70% from alcohol 191)

Isopropyl-2-(*t*-butyl-dimethyl-silyloxy)-butyrate [189]



Ethyl 3-(*t*-butyldimethylsiloxy)-butanoate (2 g, 8.1 mmol) is dissolved in 2-propanol (30 ml), $Ti(O\text{-}i\text{-}C_3H_7)_4$ (1.00 g, 3.5 mmol) is added and the mixture is heated to reflux temperature for 6 hours. It is then cooled to ca. 45°C, quenched with 1 M aqueous HCl (temporary turbidity is observed), and extracted with pentane. The organic extract is washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and evaporated at 60°C under reduced pressure to remove the solvent and the residual 2-propanol. 1.76 g (6.76 mmol, 83%) of the transesterified product is obtained, which is pure according to ^{1}H-NMR.

Diethyl malate [189]



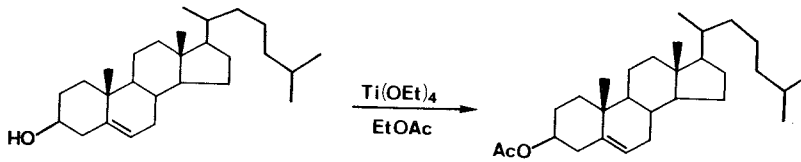
Optically pure (S)-(-)-O-benzoylmalate (2.00 g, 6.79 mmol) is dissolved in absolute ethanol (50 ml) and combined with $Ti(OEt)_4$ (1.00 g, 4.40 mmol). The mixture is heated under reflux for 6.5 hours. It is then cooled to ca. 40°C, hydrolyzed with 1 M aqueous HCl (temporary turbidity is observed) and extracted with ether. After removal of solvent and ethanol, the residue is distilled to yield 0.98 g (6.53 mmol, 96%) ethyl benzoate (b.p. 55°C/0.01 Torr) and 0.81 g (4.26 mmol, 64%) of diethyl (S)-(-)-malate (b.p. 90°C/0.01 Torr). $[\alpha]^{25}_D = -9.3^o$ (neat).

Methyl phenylacetate [190]

Method i): A solution of 2.0 g (12.2 mmol) of ethyl phenylacetate and ca. 0.5 g (ca. 2 mmol) of $Ti(OEt)_4$ in 50 ml of methyl propionate is refluxed for 110 hours. After cooling to ca. 40°C, the reaction mixture is treated with 30 ml 1 M aqueous HCl and extracted with ether. The combined organic layers are washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and concentrated on the rotatory evaporator. Kugelrohr distillation affords 1.70 g (11.3 mmol, 93%) of methyl phenylacetate, b.p. 155°C/9 Torr.

Method ii): A modified titanium catalyst (gly-Ti) is prepared by mixing one mol-equiv. of ethylene glycol with two mol-equiv. of $Ti(OEt)_4$. 1.0 g of this catalyst and 2.0g (12.2 mmol) of ethyl phenylacetate are dissolved in 50 ml of absolute methanol and heated at reflux temperature for 72 hours. The clear solution is then concentrated at the rotatory evaporator at reduced pressure to ca. 5 ml. After addition of 5 ml 1 M HCl solution, the reaction mixture is extracted four times with ether. The combined organic extract is washed with 1 N HCl, saturated $NaHCO_3$ and twice with brine, dried over $MgSO_4$, filtered and evaporated. The residue is purified by Kugelrohr distillation to yield 1.66 g (11.1 mmol, 91%) of the methyl ester.

3 β-Acetoxy-cholest-5-ene [190]



Cholest-5-en-3-ol (2.0 g, 5.17 mmol) and a catalytic amount of $Ti(OEt)_4$ (ca. 0.5 g), dissolved in 50 ml of ethyl acetate, is heated to reflux for 24 hours. After cooling to ca. 40°C and hydrolysis with dilute 1 M aqueous HCl, the reaction mixture is worked up with ether. After recrystallization from ethanol, 1.81 g (4.22 mmol, 82%) of 3 β-acetoxy-cholest-5-ene is obtained, m.p. 110-114°C, $[\alpha]^{25}D = -41^{0}$ (c = 2.23, $CHCl_3$).

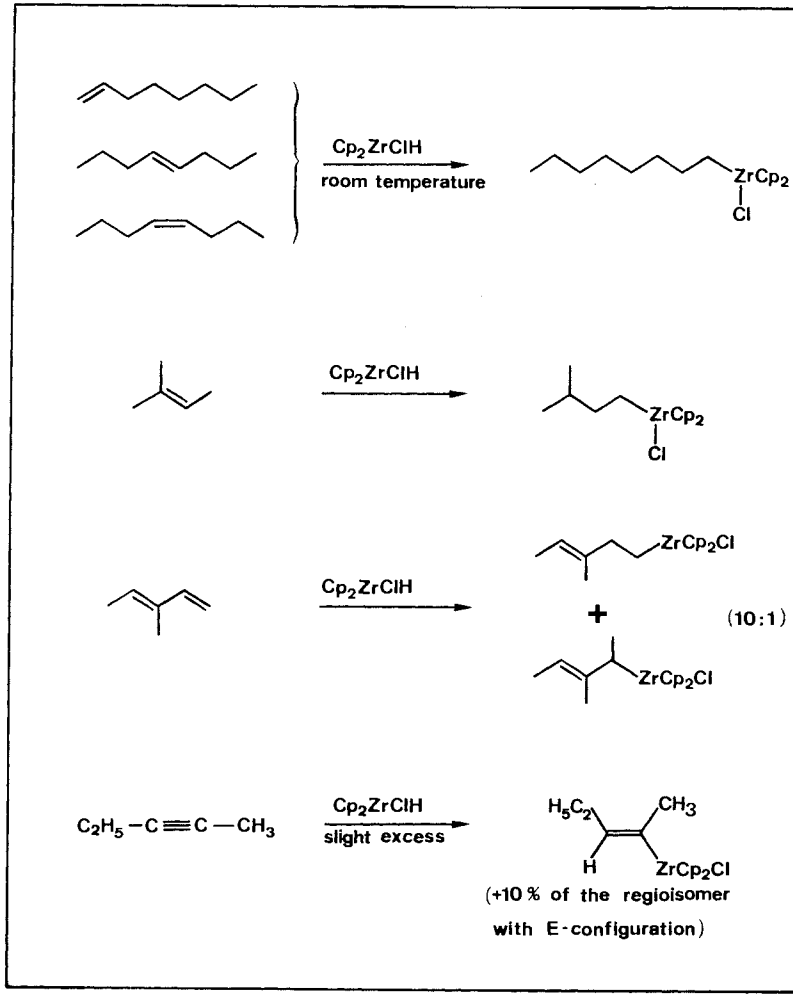
D) Additions to C,C Multiple Bonds and Eliminations - the Hydrozirconation

One of the earliest synthetic applications of zirconium derivatives as reagents was the hydrozirconation, which was reviewed [192] in 1976. In many respects, the hydrozirconation duplicates the hydroboration [193], in others it is complementary to it. An example is provided by the hydrometallation of isomeric octenes, see Scheme 27 [193]. While the hydroboration is reversible only at elevated temperatures, addition/elimination of the zirconocene hydride Cp_2ZrClH (2c, preparation see section II) to double bonds is so facile, that all three octenes furnish the same 1-octyl-zirconium derivative at room temperature. As is also evident from the examples given in Scheme 27, the hydrozirconation is strictly directed by steric factors [193]: its thermodynamically-controlled additions lead to primary organo-zirconocenes, tetrasubstituted and cyclic trisubstituted olefinic double bonds do

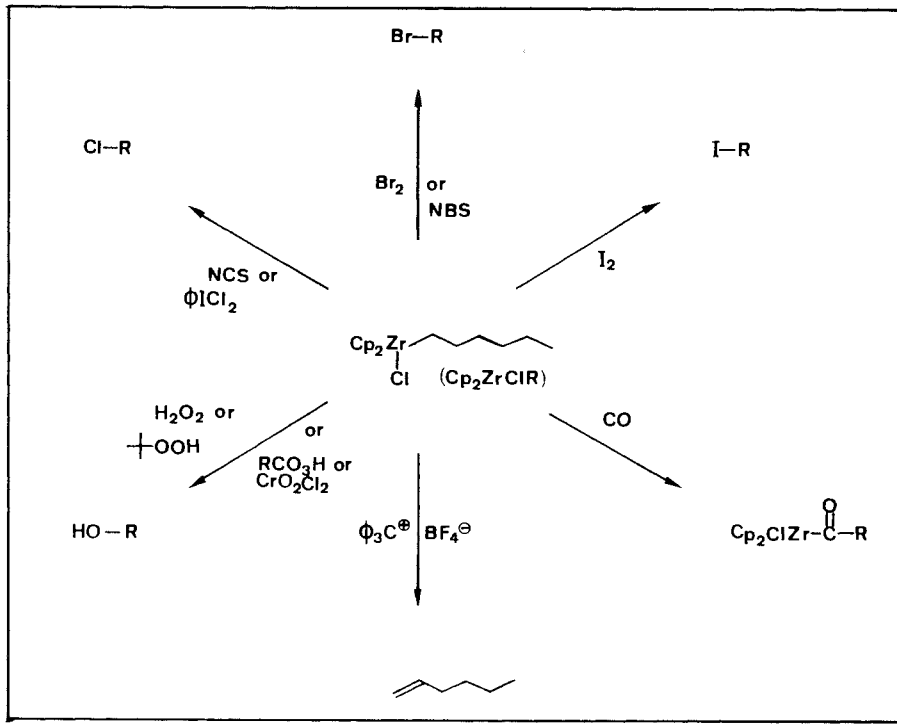
not react, and the addition to acetylenes produces that vinylzirconium compound in which the zirconium is bonded to the carbon with the smaller substituent, with hydrogen in the *cis*-position [193].

The hydrozirconation products are subjected to further transformations with replacement of the zirconium from the organic group. Two such transformations have been discussed in previous sections, the carbonylation (III D)

Scheme 27



Scheme 28



and the nickel-catalyzed *Michael* additions of vinyl-zirconocenes to α.β-unsaturated carbonyl compounds (III B). A carbozirconation step is also most likely to be involved in the Cp_2ZrCl_2-catalyzed carboaluminations (III G). Some reactions of hydrozirconation intermediates with formation of heterosubstituted carbon skeletons are shown in Scheme 28, and a typical procedure demonstrates the reversibility of hydrozirconations.

1-Triacontanol from 15-triacontene [194]

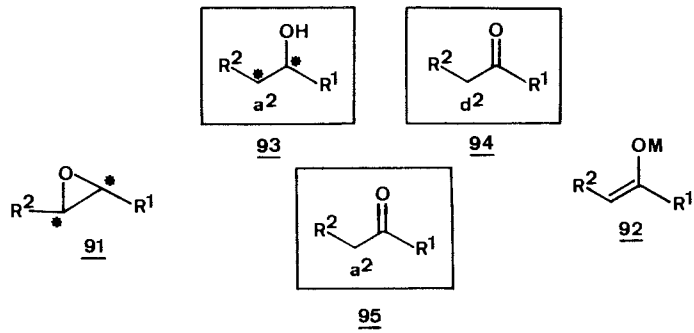
$$C_{14}H_{29}\text{-}CH{=}CH\text{-}C_{14}H_{29} \xrightarrow[2)\ t\text{-}C_4H_9OOH]{1)\ Cp_2ZrClH} H_{59}C_{29}\text{-}CH_2OH$$

The hydrozirconation reagent 2c is prepared *in situ* in the following way: A solution of 2.92 g (10 mmol) of Cp_2ZrCl_2 (2a) in 30 ml THF is combined within 10 min. at 23°C under inert atmosphere with an equiv. amount of Vitriole® (70% toluene solution, see section II).

After 2 hours, 2.1 g (5 mmol) of neat 15-triacontene is added by syringe through a serum capped side arm of the reaction flask. A suspension results which is kept under argon at 40°C for 4 days. After cooling to room temperature, the mixture is heated with 2.75 ml of 3.7 M t-C4H9OOH in 1.2-dichloro-ethane for 1 hour. For workup, 3 ml of H_2O are added, the mixture is filtered, and the filtrate is concentrated under reduced pressure to ca. 50 ml. Dilution with acetone (300 ml) gives 2 g of crude 1-triacontanol, which is recrystallized from 1.2-dichloroethane to give 1.5 g (68%) of 97% pure triacontanol, m.p. 89-90°C.

E) Stereoselective Epoxidations with Titanium and Vanadium Catalysts

Epoxides (91) are useful reagents in general organic synthesis, and versatile building blocks for natural product synthesis in particular. They are



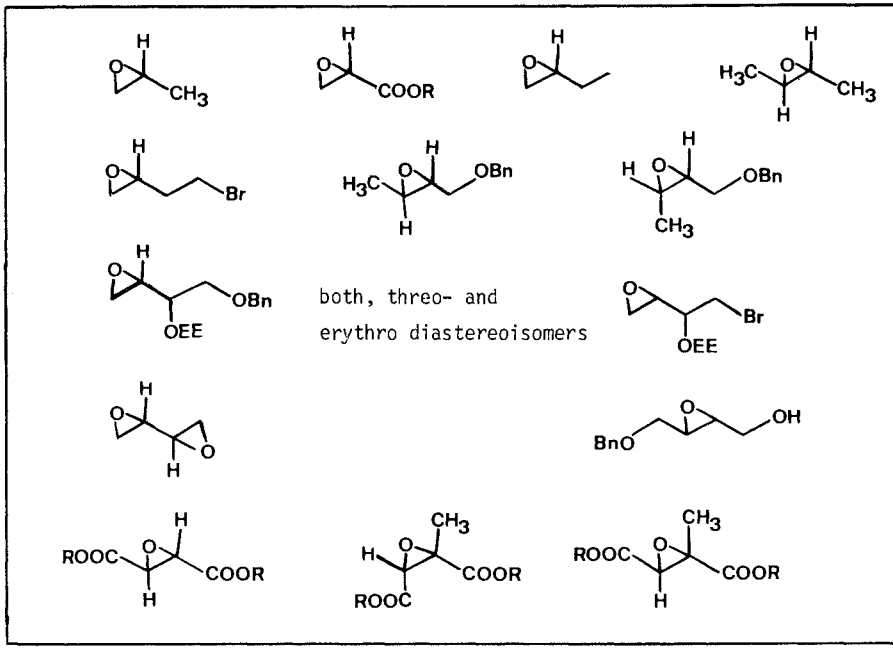
a^2-reagents [62], i.e. electrophiles in the β-position of an oxygen functionality. The 1.2-bifunctionality pattern makes epoxides the counterparts of enol derivatives 92, which are d^2-reagents, cf. the synthon boxes 93 and 94. Since the alcohols resulting from nucleophilic opening of epoxides can be oxidized to carbonyl derivatives, epoxides also correspond to aldehyde, ketone, acid, or ester d^2-synthons 95, depending on the nature of the R^1-group and of the particular transformation. But epoxides do not only provide an umpolung of carbonyl d^2-reactivity, they also can supply products with a given configuration: where enol derivatives 92 have two sp^2-carbon atoms, epoxides 91 have two asymmetric centers which may have a certain relative configuration *and* a certain sense of chirality. Enol derivatives may only react diastereoselectively under special circumstances, see section on aldol additions above, while epoxides are building blocks with centers of chirality [126]. Thus, if carbonyl compounds have been said to be "virtually the backbone of organic synthesis" [195], the epoxides correspond to at least "one of the main muscles".

"Stereochemical Aspects of the Synthesis of Epoxides" [196] and "Stereoselectivity in Reactions of Epoxides" [197] have been reviewed ten years ago. In continuation of his earlier studies on transition metal catalyzed oxidations, and especially on vanadium(V) and molybdenum(VI) mediated epoxidations by *t*-butyl hydroperoxide, which were reviewed with "practical considerations" in Aldrichimica Acta [198,199], *K.B. Sharpless* has now discovered a titanate/tartrate-catalyzed enantioselective epoxidation [200]. This has received the deserved attention by synthetic organic chemists and will be reviewed here briefly, together with some recent advances in diastereoselective epoxidations of homoallylic alcohols with vanadium(V)/*t*-butyl hydroperoxide.

1) Asymmetric Epoxidations of Allylic Alcohols with *t*-Butyl Hydroperoxide (TBHP) / Diethyl or Diisopropyl Tartrate (DET, DIPT) / Tetrakis-isopropoxy-titanium

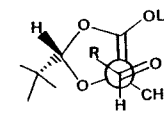
Our previous review in volume no. 2 of this series, *Modern Synthetic Methods 1980* [126], ended with a list of epoxides, see Scheme 29. These are all available in both enantiomeric and, where applicable, diastereomeric forms from simple precursors such as lactic acid, malic acid, and tartaric acid. With the new methodology [37,201] outlined in Scheme 30,

Scheme 29 from ref. [126]



Scheme 30

R^1	R^2	% Ausb.	% ds			
CH_3	C_2H_5	82	97	■		
	$(CH_2)_2CH_3$	72	97	■		■
	$(CH_2)_3CH_3$	68	97	■		
	$(CH_2)_6CH_3$	82	95	■		■
	$CH_2-CH=CH_2$	77	98			
	$CH_2C_6H_5$	81	96			
$CH_2C_6H_5$	C_2H_5	40	>95			
	$(CH_2)_2CH_3$	42	>95			
	$CH_2-CH=CH_2$	40	>95			
C_6H_5	$(CH_2)_2CH_3$	84	95			



R=C_2H_5

the list could now be extended by a number of enantiomerically pure 1.1-disubstituted oxiranes [167].

Since the 1980 Interlaken meeting, *Sharpless* and *Katsuki* [200] discovered an alternative way of preparing enantiomerically pure epoxyalcohols by a spectacularly effective asymmetric epoxidation (AE) of allylic alcohols with tartrate esters / $Ti(OAlkyl)_4$ / *t*-butyl hydroperoxide (TBHP). The mechanism of the process and the practical experimental details which facilitate execution of the process in the laboratory will be covered extensively in a review by *Sharpless* scheduled to appear during August of 1983 in Volume 16 (Issue no. 3) of Aldrichimica Acta. Another review on "Stereo- and Regioselective Openings of Chiral 2.3-Epoxy Alcohols. Versatile Routes to Optically Pure Natural Products and Drugs. Unusual Kinetic Resolutions", the manuscript of a lecture held at the Eleventh International Carbohydrate Symposium, August 1982, in Vancouver, Canada, will be published shortly [202]. We thank Professor *K. Barry Sharpless* for providing a manuscript copy of this last-mentioned article to us prior to publication; we are also grateful for copies of the dissertations of *B.E. Rossiter* [203] and *S.S. Woodard* [204].

The steric course of the asymmetric epoxidation is described in Scheme 31. With "normal" CIP-priority sequence [105], the relative topicity [40] of transfer of the epoxide oxygen under the influence of the tartrate ester is specified *lk*, i.e. the Si-face of the sp^2-center bonded to CH_2OH reacts if the tartrate has (S.S)-, the Re-face if it has (R.R)-configuration. Without quoting examples - there must be more than 100 by now, including ca. 40 applications in natural product syntheses [202] - the reasons for rapid adoption of the method are obvious [202]: 1) *simplicity* (all ingredients are inexpensive and commercially available), 2) *reliability* (it succeeds with most allylic alcohols), 3) *high enantiomeric purity* (generally >90% ee, usually >95% ee (i.e. ratio of enantiomers or enantioselectivity 97.5/2.5), 4) *absolute configuration of products predictable* (see Scheme 31), 5) *relatively insensitive to sense of chirality of centers in the substrate* (see discussion in next paragraph), 6) *versatility of 2.3-epoxy alcohols as intermediates* (see above, introduction to section E).

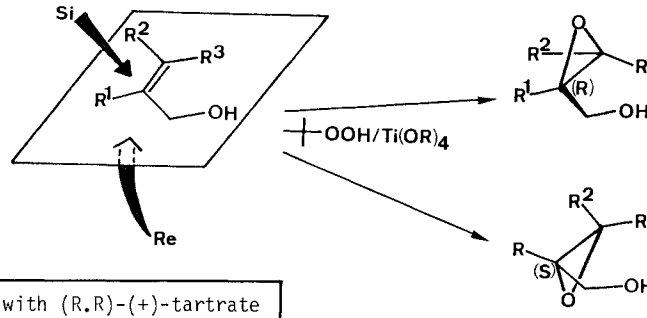
Thus, all positions R^1, R^2, and R^3 in the achiral allylic alcohol shown

Scheme 31

ASYMMETRIC EPOXIDATION WITH

RELATIVE TOPICITY *lk*

preferred with (S.S)-(-)-tartrate



preferred with (R.R)-(+)-tartrate

(i) Topicities and configurations for priority sequence in allylic alcohol: C-O > C=C > R^1; in product, epoxide: O > epoxy-C > CH_2OH; in dozens of published examples, we found only two exceptions to the priority sequence given for the allylic alcohol: $R^1 = R^2 = C_6H_5$, $R^3 = H$ and $R^1 = c\text{-}C_6H_{11}$, $R^2 = R^3 = H$ [200].

(ii) Reactivity increases with degree of substitution of the double bond; E-propenyl reacts for instance 70-100 times faster than vinyl [202,204].

(iii) Rate of reaction is larger with E- ($R^3 = H$) than with Z-allylic alcohol ($R^2 = H$).

(iv) Increasing size of R^3 decreases selectivity, thus with $R^3 = CH_2R$ the selectivity is still high - albeit in a slow reaction, while with $R^3 = C_6H_5$ or $CH(CH_3)_2$, the selectivity drops [202].

in Scheme 31 may be varied, except that with $R^3 \neq H$ the reaction is rather slow. Since (R.R)-(+)- and (S.S)-(-)-tartaric acids [126] are equally readily available in the amounts necessary for this asymmetric synthesis, both enantiomeric epoxides can be obtained. Tartrate ester employed in stoichiometirc amounts can be recovered in the workup procedure (see below).

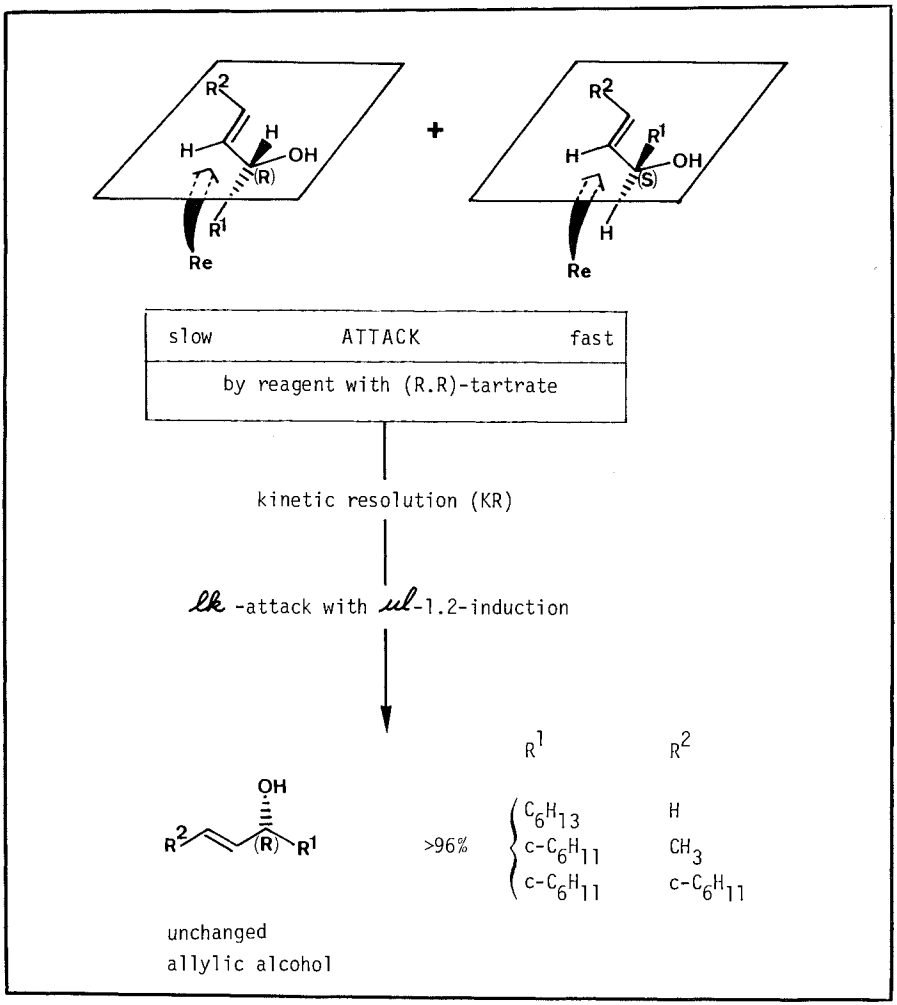
The reactions of allylic alcohols with centers of chirality are still subject to stereochemical control with relative topicity *lk*. Two cases have been studied more thoroughly: allylic alcohols with a center of chirality at the carbinol carbon and at the other allylic position (C-4).

As shown in Scheme 32, the *lk*-attack is controlled by *ul*-1.2-induction, if the hydroxylated center is substituted. With (S)-configuration on the asymmetric carbon atom, the Re-face of the neighbouring trigonal center reacts faster, if the (R.R)-(+)-tartrate-modified reagent is employed. Depending on the substrate structure, the relative rates range from ca. 15:1 to ca. 150:1 [205] which allows the preparation of allylic alcohols of this type with >99% ee by kinetic resolution [205]. Routinely, the reaction is run to a conversion of ca. 55%, and the unchanged enantiomer is recovered. On the other hand, of two enantiomeric allylic alcohols of the type shown in Scheme 32, one can selectively be epoxidized by (S.S)-tartrate-derived reagent (R in Scheme 32), the other one by (R.R)-tartrate-derived reagent (S in Scheme 32), producing enantiomeric epoxyalcohols of the same relative configuration (Re-attack on the S-enantiomer by R.R-reagent and Si-attack on the R-enantiomer by S.S.-reagent are preferred). The *ul*-1.2-induction observed here is also the preferred relative topicity in V($\bar{V}$)-catalyzed epoxyalcohol syntheses, see next section.

In contrast to the situation in Scheme 32, a center of chirality on the other side of the double bond, see Scheme 33, does not have enough influence to override the intrinsic *lk*-preference of the reagent. The other enantiomer of the alcohol can also be attacked from the diastereotopic Re-face by the (R.R)-reagent or from the diastereotopic Si-face by the (S.S)-reagent. Thus, if both enantiomeric alcohols are available, all four possible stereoisomers with *trans*-configuration on the oxirane ring can be prepared, see bottom of Scheme 33 (cf. ref. [218]).

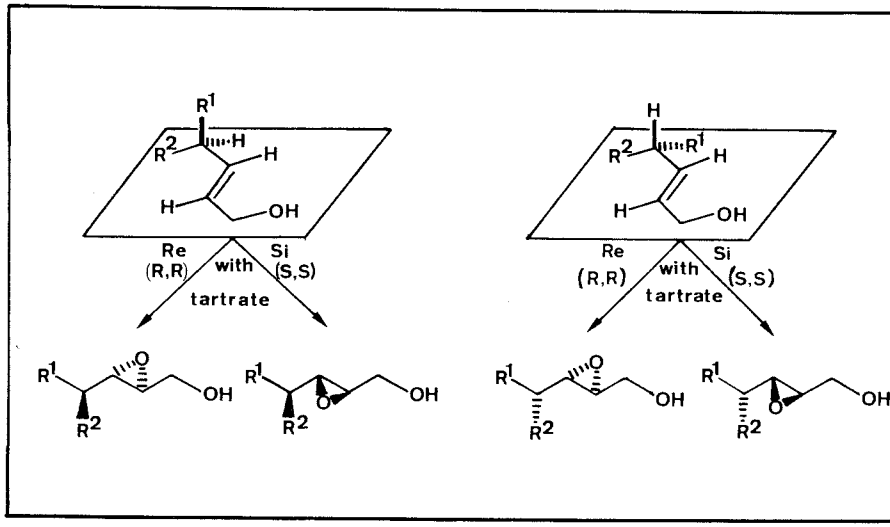
Scheme 32

Topicity and chirality specified with CHR(OH) > C= > H and O > C= > R^1



The asymmetric epoxidations of allylic alcohols described seems to be a case in which a non-enzymatic conversion reaches levels of selectivity which are usually considered typical of enzymic transformations. Furthermore, the substrate selectivity, i.e. the sensitivity to changes of substrate structure, is very low in this process. It is hard to imagine that

Scheme 33



an enzyme can convert substrates of such different structures equally selectively!

The mechanism of the reaction is still under investigation.

Practical considerations are of foremost importance in the titanate/tartrate-mediated asymmetric epoxidations with TBHP. Even with consideration of the limiting factors discussed above, "complaints" have become known about the reproducibility of the process. In all cases which we are aware of, the problems were due to non-optimal conditions. There are numerous, partially conflicting hints as to the practical execution of the reaction. The following procedures are typical.

Solutions of *t*-Butyl-hydroperoxide (TBHP) [198,203]

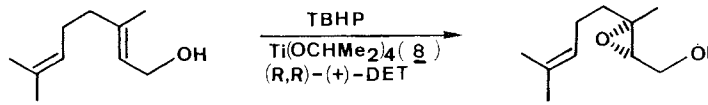
General Remarks: Absolutely anhydrous TBHP is explosive and should not be prepared without experience with peroxides and without extreme precautions [206,207]. Although handled on industrial scale, absolute TBHP is not commercially available and is excluded from conventional shipment. The 90% aqueous TBHP is less dangerous, but is also not recommended here. The best grade to start with is 70% aqueous TBHP, which should contain as little as possible hydrogen peroxide, di-*t*-butyl peroxide, and

t-butanol. For the asymmetric epoxidations, the preparation of anhydrous solutions of TBHP is necessary. The preferred solvent is 1.2-dichloroethane. Solutions of anhydrous TBHP are safe to handle and can be stored in a refrigerator, but must not be concentrated.

Preparation of a Dichloroethane Solution: In a 2-L separatory funnel, 500 ml (3.6 mol) 70% aqueous TBHP and 850 ml 1.2-dichloroethane are combined, and the upper aqueous layer of ca. 125 ml is removed. The 1225 ml organic layer containing 3.5 mol TBHP is placed into a 2-L flask, SiC boiling chips are added, and the flask is equipped with a water separator for heavier than water solvents. The flask is heated (steam or oil bath!) and the azeotrope containing ca. 20% water distilled off. After water ceases collecting in the trap, the solution is allowed to cool, the water separator is replaced by a short path distillation head, and heat is reapplied. Ca. 225 ml solvent are removed by distillation, leaving ca. 1 L of 3.5 M TBHP. Solutions in CH_2Cl_2 and other solvents can be prepared similarly. Store in a refrigerator.

Determination of TBHP Concentration: By iodometric titration [207]: the peroxide content is determined with an aliquot of the solution. - By NMR spectroscopy: a TBHP solution in $C_2H_4Cl_2$ is measured in $CDCl_3$ (TMS as internal standard). The *t*-C_4H_9 signal (ca. 1.25 δ) integration A and the dichloroethane signal (ca. 3.70 δ) integration B give the molarity of the solution as $M = A\,[0.10\,A + 0.18\,B]^{-1}$.

(2S,3S)-Epoxy-geraniol [200]



A dry 500 ml flask is charged (-23°C cooling bath; argon atmosphere; magnetic stirring) with 200 ml dry CH_2Cl_2, 5.94 ml (5.68 g, 20 mmol) 8 and 3.7 ml (4.5 g, 22 mmol) diethyl (+)-tartrate (10% excess). After stirring for 5 min., 3.47 ml (3.08 g, 20 mmol) geraniol and ca. 11 ml of ca. 3.5 M TBHP (40 mmol, 2 equiv.) as anhydrous solution in $C_2H_4Cl_2$, CH_2Cl_2 or CCl_4 are added. The homogeneous solution is sealed and kept in a freezer (ca. -20°C) overnight (ca. 18 hours). The reaction can be monitored by TLC. The flask is returned to the CCl_4 / dry ice bath (-23°C) and its stirred contents quenched with 50 ml 10% aqueous tartaric acid. The aqueous layer solidifies, the bath is removed after 30 min., after stirring at room temperature for one hour the layers are separated. The organic layer is washed with water, dried (Na_2SO_4) and concentrated.

The residue contains diethyltartrate or other tartrate esters which

may have been used, and TBHP. The peroxide content is so small in the present case that it does not have to be removed [198]. For hydrolysis of the ester, the crude product is dissolved in 150 ml ether and combined (stirring, ice bath) with 60 ml of 1 N NaOH. The two-phase system is stirred for no longer than 30 min., the organic phase is dried (Na_2SO_4), concentrated, and the residue (ca. 4.3 g) chromatographed on silica gel to give 2.6 g (77%) epoxide of $[\alpha]_D$ -6.36° (1.5, $CHCl_3$), corresponding to ca. 95% ee.

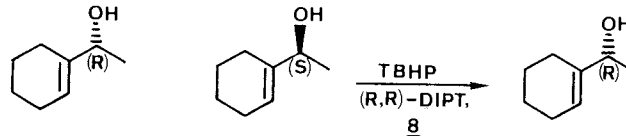
For water soluble epoxyalcohols, a modified procedure is recommended (see below). With more reactive allylic alcohols (without substituent *cis* to CH_2OH) catalytic amounts (0.1 equiv.) of both the titanate and the tartrate suffice. Diisopropyl tartrate is often preferable, but is more difficult to hydrolyze without destroying epoxide product.

Workup for water-soluble product epoxyalcohols [208]

At the end of the reaction period (see previous procedure), 4 equiv. of CH_3SCH_3 are added at -20°C, and after 40 min. the cold reaction mixture is slowly added to twice its volume of a vigorously stirred, saturated (ca. 5%) aqueous NaF solution at room temperature. After stirring for 5 - 20 hours, NaCl is added to saturate the aqueous phase. Filtration of the gel-like mixture through Celite®, separation of the phases, three extractions of the aqueous phase with CH_2Cl_2, drying of the combined organic layers over Na_2SO_4 and concentrating yields the epoxyalcohol mixed with the tartrate ester which are separated by chromatography on silica gel or, depending on the sensitivity of the epoxide and the relative boiling points, by fractional distillation.

Kinetic Resolution of Allylic Alcohols (Scheme 32) [205]

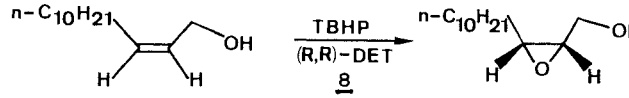
For instance:



A solution of 1 equiv. 8, 1.2 - 1.5 equiv. (R.R)-(+)-DIPT, 1 equiv. d,l-allylic alcohol in dry CH_2Cl_2 (10 ml/mmol of alcohol) is stirred at -20°C under inert atmosphere. Anhydrous TBHP (4 - 6 M in CH_2Cl_2, 0.6 equiv.) is added, and the homogeneous mixture is stored in a freezer (-20°C) for 15 hours to 12 days. The reaction must be monitored and should not be stopped before 55% conversion. The cold reaction mixture is poured into twice its volume of acetone containing 0.3 ml H_2O/mmol of the titanate 8. The mixture is allowed to warm to room temperature with stirring. Filtration, concentration, tartrate hydrolysis as described above and chromatography yields the product.

For the cyclohexenyl methyl carbinol 15 hours reaction time furnishes (R)-alcohol of >96% ee.

(+)-(2S,3R)-2.3-Epoxy-1-tridecanol [203]

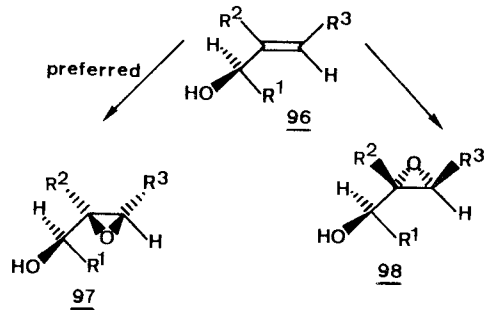


Under inert argon atmosphere, L-(+)-diethyl tartrate (11.3 g, 55 mmol) and *cis*-2-tridecen-1-ol (10.5 g, 50 mmol) are dissolved in 250 ml CH_2Cl_2 and cooled to -78°C. After adding $Ti(O\text{-}i\text{-}C_3H_7)_4$ (15 ml, 50 mmol) by syringe and stirring for several min., 26 ml (83 mmol) of anhydrous TBHP (3.2 M in CH_2Cl_2) is slowly added. The reaction mixture is warmed to -35°C and stirred for 3 days. It is quenched by combining with 150 ml of 10% tartaric acid and shaking vigorously. This is repeated followed by washing the organic layer with H_2O and brine. On concentration *in vacuo* a wet white solid is obtained, which is dissolved in 200 ml ether, combined with 100 ml of 1 M aqueous LiOH and stirred for 30 min. at 0°C. The ether solution is washed with brine, dried and concentrated to give a white mass. This is chromatographed on a Waters prep. 500 (petroleum ether / ether 1:1) to give 8.3 g (38.7 mmol, 77%) of fluffy white crystals.

2) Epoxidations of Allylic and Homoallylic Alcohols by TBHP/Vanadium(V)

Diastereoselective epoxidations of olefins containing alcohol functions with various distances between the two functional groups have been found to be more or less diastereoselective, both with peracids and with transition metal (V^{5+}, Mo^{6+} etc.) catalyzed *t*-butyl hydroperoxide as reagents, see a recent review on metal-catalyzed oxidations of olefins and acetylenes [198]. The preferred relative topicity *ul* of the 1.2-induction in titanate-induced epoxidations of α-branched *trans*-allylic alcohols was discussed in the previous section, see Scheme 32. A somewhat smaller *ul*-preference had also been found in $VO(acac)_2$-catalyzed TBHP epoxidations of the same allylic alcohol [198,209,210], while with a trimethylsilyl substituent in the 2-positon, the selectivities are much larger [211], see Table 16. *cis*-Substituents on the double bond of open-chain systems somehow direct the vanadium-catalyzed oxidation to the other diastereotopic face of the olefinic double bond, compare Table 16 with Table 17. Finally, with cyclic allylic alcohols, the result is a *cis*-

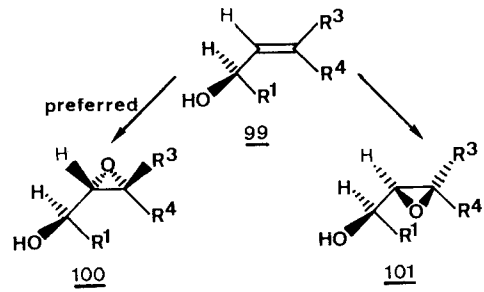
Table 16. Epoxidations of allylic alcohols without substituents in the *cis*-position of the carbinol center by TBHP/V^{5+} reagent.



R^1	R^2	R^3	preferred rel.topicity	97/98	ref.
CH_3	H	H	*ul*	80:20	198,209)
CH_3	CH_3	H	*ul*	95:5	198,209)
CH_3	H	CH_3	*ul*	71:29	198,209)
				60:40	210)
n-C_3H_7	H	C_2H_5	*ul*	63:37	210)
i-C_3H_7	H	H	*ul*	85:15	210)
t-C_4H_9	H	CH_3	*lk*	81:19	210)
CH_3	Me_3Si	H	*ul*	>99:1	211)
$CHMe_2$	Me_3Si	H	*ul*	>99:1	211)
CH_3	Me_3Si	CH_3	*ul*	>99:1	211)
$CHMe_2$	Me_3Si	CH_3	*ul*	>99:1	211)

epoxidation, see Scheme 34. Except with some cyclic substrates and with the bulky trimethylsilyl substitution, the selectivities are not as high as those which were encountered with the titanate/tartrate-mediated epoxidations, dealt with in the preceding section.

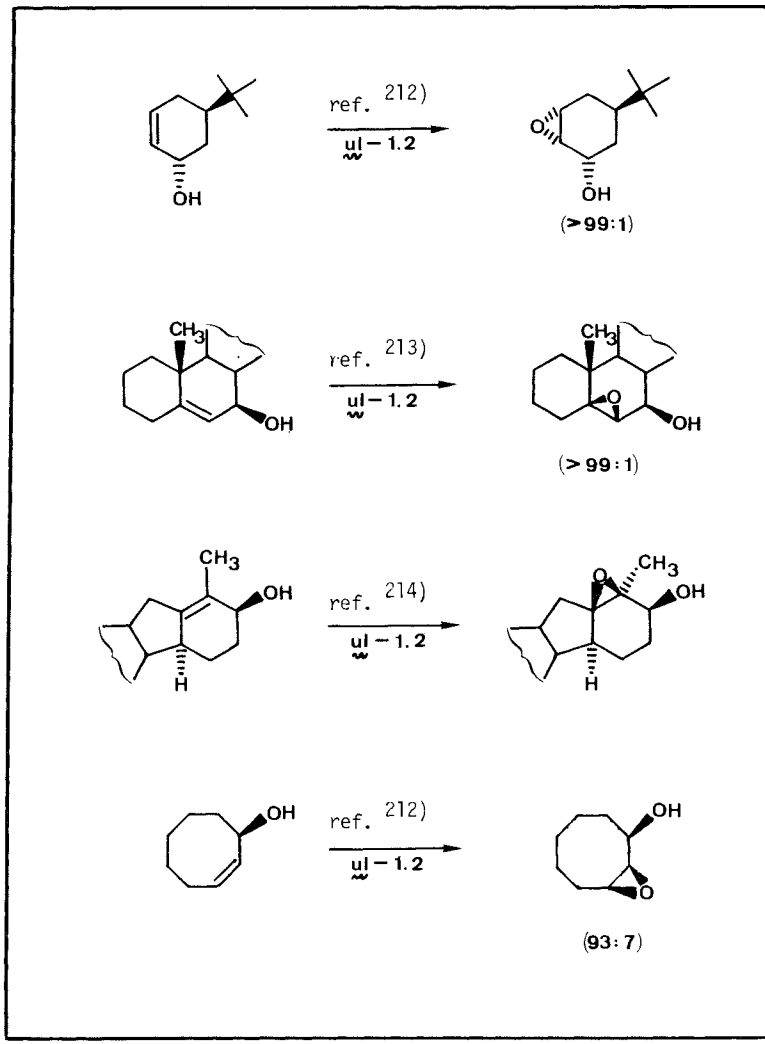
Table 17. Epoxidations of acyclic allylic alcohols with substituents in the *cis*-position of the carbinol center by TBHP/V^{5+} reagent.



R^1	R^3	R^4	preferred rel.topicity	100/101	ref.
CH_3	H	CH_3	*lk*	71:29	198,209)
CH_3	CH_3	CH_3	*lk*	86:14	209)
CH_3	H	$SiMe_3$	*ul*	96:4	211)
CH_3	CH_3	$SiMe_3$	*ul*	>99:1	211)
i-C_3H_7	H	$SiMe_3$	*ul*	>99:1	211)
C_6H_5	H	$SiMe_3$	*lk*	>99:1	211)

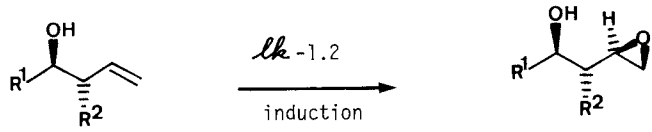
This is not so when we turn to the homoallylic alcohols [215]. Their epoxidation by the V^{5+}/TBHP-reagent is highly selective in most cases, see Table 18. Only bulky substitution at the carbinol center and *trans*-configuration of the double bond [215] causes the diastereoselectivity to fall below 80%; usually it is above 95%. The R^2-group (see Table 18) on the carbon atom between the carbinol center and the proximate olefin sp^2-center appears to be responsible for the stereochemical course of the reaction.

Scheme 34. $VO(acac)_2$-catalyzed *syn*-epoxidations of cyclic allylic alcohols by TBHP.



More convincing than for the simple allylic alcohols, see models 102 [198,209] and 103 [210], is the mechanistic picture 104 proposed [215] for this homoallylic case. A tetrahedral coordination of the vanadium is assumed, with a pseudo-axial and a pseudo-equatorial ligand on the metal. The better fit with Z- than with E-configuration on the double bond is thought to arise from repulsive interaction with the O-*t*-butyl group, see arrow ① in 104. The group located in *cis*-position on the remote olefinic

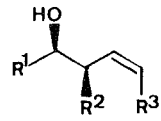
Table 18. Epoxidations of homoallylic [215] and of bis-homoallylic [216] alcohols by TBHP/V^{5+} reagent leading to products with up to four consecutive asymmetric centers in high diastereoselectivity.

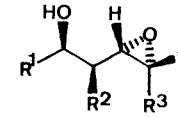


R^1	CH_3	C_6H_5	$CHMe_2$	CH_3
R^2	CH_3	CH_3	CH_3	$CHMe_2$
% ds	82	83	75	83

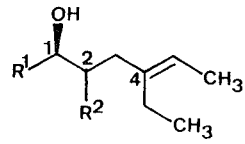
R^1	H	CH_3	C_6H_{13}	CH_3	$CHMe_2$
R^2	CH_3	H	H	CH_3	CH_3
R^3	CH_3	C_2H_5	$(CH_2)_7COOR$	C_6H_{13}	CH_3
% ds	>99.5	92	96	99	>99.5
1.2 rel.topicity	*lk*	--	--	*lk*	*lk*
1.3	--	*lk*	*lk*	*ul*	*ul*

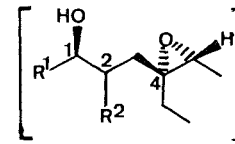
(Table 18 continued)





R^1	CH_3	CH_3	$CHMe_2$	C_5H_{11}	CH_3
R^2	CH_3	CH_3	CH_3	CH_3	C_5H_{11}
R^3	CH_3	C_6H_{13}	CH_3	CH_3	CH_3
% ds	99	98	67	94	>99.5
1.2 rel.topicity	*lk*	*lk*	*lk*	*lk*	*lk*
1.3	*lk*	*lk*	*lk*	*lk*	*lk*





l- or *u*-diastereomer

product cyclizes to a tetrahydrofuran

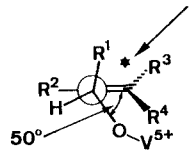
R^1	$CHMe_2$	$CHMe_2$	anisyl	anisyl
R^2	H	CH_3	H	CH_3

>88% Re attack of oxygen on C(4)

independant of configuration at C(2)

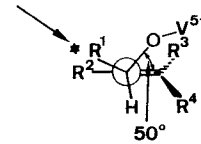
carbon forces a substituent in the allylic position into a quasi-equatorial position, arrow ② in 104. This in turn fixes the position of a substituent on the carbinol center as being either pseudo-axial or -equatorial, depending upon the relative configuration along the C(1), C(2) bond of the homoallylic system. If the substituent is larger than CH_2R and is forced into an axial position, the 1.3-repulsion indicated by arrow ③ in 104 becomes responsible for lower selectivity.

Similar considerations may be used [215] to discuss the still appreciable diastereoselectivity observed with bis-homoallylic alcohols, with which



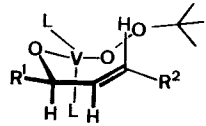
102 a

addition from below

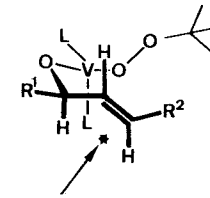


102 b

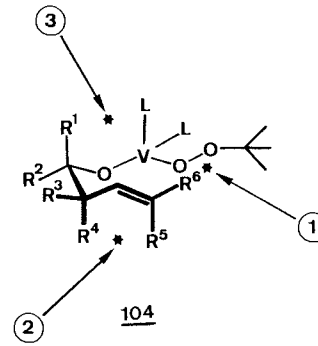
addition from above



103 a



103 b



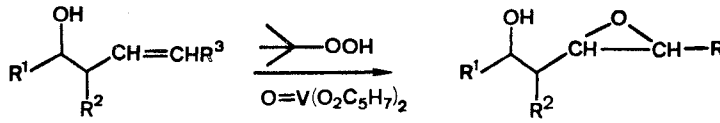
104

only the configuration at the carbinol center seems to matter for the stereochemical course of reaction [216], see bottom of Table 12.

These results are the more important, because there are hardly any other methods which allow remote stereocontrol of this type and quality.

O-Silylated allylic and homoallylic alcohols have just recently [217] been shown to be also epoxidized reasonably selectively by TBHP/V^{5+}.

General procedure for V^{5+}-catalyzed epoxidation of homoallylic alcohols [203,215]



To a ca. 0.1 M solution of the homoallylic alcohol in anhydrous CH_2Cl_2 is added ca. 1-2% of vanadium (IV) oxide bis(2.4-pentadionate) and 1.5 mol-equiv. of anhydrous 1 M *tert.*-butyl hydroperoxide (TBHP) at ice-bath temperature. The solution is stirred for 16 hours at room temperature. The remaining TBHP is best hydrolyzed by the addition of 1 mol-equiv. of freshly prepared 10% Na_2SO_3 at 0°C. Stirring is continued for an additional 2 - 3 hours with gradual warming to room temperature. The layers are separated and the organic phase is washed twice with water, once with brine, dried ($MgSO_4$) and concentrated. The crude products are purified by distillation or column chromatography.

V ACKNOWLEDGMENTS

We thank *Anneliese Hungerbühler, Martin Schiess, Peter Schnurrenberger, Albert K. Beck,* and *Silvia Sigrist* for preparing the manuscript, Professor *Walter L. Meyer* (on leave from the University of Arkansas) for his help with the correction of the typed version, and the *Dynamit Nobel AG* (D-Troisdorf) for generous supplies of titanates and zirconates used in our own investigations. We were fortunate to attract able and enthusiastic collaborators to join us part of the way through our continuing search for applications of transition metal derivatives in organic synthesis; their names are given in the list of references. Financial support and supply of starting materials *(Dr. H. Braunschweiger, F. Seemann)* by the *Sandoz AG* (Basel) is gratefully acknowledged.

LIST OF REFERENCES

1) See e.g. A. Segnitz in Houben-Weyl-Müller, "Methoden der organischen Chemie", 13/7, p. 326 (1975).

2) R.H. Grubbs, Prog. Inorg. Chem. 24, 1 (1978); N. Calderon, J.P. Lawrence & E.A. Ofstead, Adv. Organomet. Chem. 17, 449 (1979).

3) J. Chatt, L.M. da Câmara Pina & R.L. Richards, "New Trends in the Chemistry of Nitrogen Fixation", Academic Press, London 1980.

4) J.J. Eisch & R.B. King, "Organometallic synthesis", Vol. 1, Academic Press, London 1965, and ref. cited therein.

5) B. Kautzner, P.C. Wailes & H. Weigold, J. Chem. Soc. Chem. Commun. 1969, 1105; P.C. Wailes & H. Weigold, J. Organomet. Chem. 24, 405 (1970); D.B. Carr & J. Schwartz, J. Am. Chem. Soc. 101, 3521 (1979).

6) F.N. Tebbe, G.W. Parshall & G.S. Reddy, J. Am. Chem. Soc. 100, 3611 (1978).

7) S.H. Pine, R. Zahler, D.A. Evans & R.H. Grubbs, J. Am. Chem. Soc. 102, 3270 (1980).

8) B. Weidmann, Ch.D. Maycock & D. Seebach, Helv. Chim. Acta 64, 1552 (1981).

9) D.C. Bradley & I.M. Thomas, J. Chem. Soc. 1960, 3857.

10) M. Schiess, unpublished results, ETH Zürich 1982/83.

11) C.Dijkgraaf & J.P.G. Rousseau, Spectrochim. Acta A 24, 1213 (1968).

12) B. Weidmann, Dissertation ETH Zürich No. 7203 (1982).

13) M.T. Reetz, R. Steinbach & K. Kesseler, Angew. Chem. Suppl. 1982, 1899.

14) L. Widler & D. Seebach, Helv. Chim. Acta 65, 1085 (1982).

15) H. Bürger & H.J. Neese, Z. Anorg. Allg. Chem. 370, 275 (1969).

16) K. Clauss, Liebigs Ann. Chem. 711, 19 (1968).

17) H. Holloway, Chem. and Ind. 1962, 214.

18) B. Weidmann & D. Seebach, Angew. Chem. 95, 12 (1983); ibid. Int. Ed. Engl. 22, 31 (1983).

19) M.T. Reetz, Top. Curr. Chem. 106, 1 (1982).

20) B. Weidmann & D. Seebach, Helv. Chim. Acta 63, 2451 (1980).

21) M.T. Reetz, R. Steinbach, J. Westermann & R. Peter, Angew. Chem. 92, 1044 (1980); ibid. Int. Ed. Engl. 19, 1011 (1980).

22) B. Weidmann, L. Widler, A.G. Olivero, Ch.D. Maycock & D. Seebach, Helv. Chim. Acta 64, 357 (1981).

23) Ch.D. Maycock, unpublished results, ETH Zürich 1981.

24) B. Weidmann, unpublished results, ETH Zürich 1981.

25) Th. Kauffmann, E. Antfang, B. Ennen & N. Klas, Tetrahedron Lett. 23, 2301 (1982).

26) M.T. Reetz, R. Steinbach, J. Westermann, R. Urz, B. Wenderoth & R. Peter, Angew. Chem. 94, 133 (1982); ibid. Int. Ed. Engl. 21, 135 (1982); ibid. Suppl. 1982, 257.

27) Ch. Papaspyrou, unpublished results, ETH Zürich 1982.

28) M. Schiess & D. Seebach, Helv. Chim. Acta 65, 2598 (1982).

29) M.T. Reetz, R. Steinbach, B. Wenderoth & J. Westermann, Chem. and Ind. 1981, 541.

30) M.T. Reetz, J. Westermann & R. Steinbach, Angew. Chem. 92, 931 and 933 (1980); ibid. Int. Ed. 19, 900 and 901 (1980).

31) M.T. Reetz, J. Westermann & R. Steinbach, J. Chem. Soc. Chem. Commun. 1981, 237.

32) M.T. Reetz, R. Steinbach & B. Wenderoth, Synth. Commun. 11, 261 (1981).

33) M.T. Reetz, B. Wenderoth, R. Peter, R. Steinbach & J. Westermann, J. Chem. Soc. Chem. Commun. 1980, 1202.

34) T. Kauffmann, R. König, C. Pahde & A. Tannert, Tetrahedron Lett. 22, 5031 (1981).

35) J.G. Dillard, Inorg. Chem. 8, 2148 (1969); J.F. Hanlan & J.D. McCowan, Can. J. Chem. 50, 747 (1972).

36) T.S. Patterson, J. Chem. Soc. 69, 1002 (1896).

37) D. Seebach & R. Naef, Helv. Chim. Acta 64, 2704 (1981).

38) J.J. Sims, L.H. Selman & M. Cadogan, Org. Synth. 51, 109 (1971).

39) D. Seebach, T. Weller, G. Protschuk, A.K. Beck & M.S. Hoekstra, Helv. Chim. Acta 64, 716 (1981).

40) D. Seebach & V. Prelog, Angew. Chem. 94, 696 (1982); ibid.Int. Ed. Engl. 21, 654 (1982).

41) D. Seebach, H. Dörr, B. Astani & V. Ehrig, Angew. Chem. 81, 1002 (1969); ibid. Int. Ed. Engl. 8, 982 (1969).

42) D. Seebach, G. Crass, E.M. Wilka, D. Hilvert & E. Brunner, Helv. Chim. Acta 62, 2695 (1979).

43) T. Mukaiyama, K. Soai, T. Sato, H. Shimizu & K. Suzuki, J. Am. Chem. Soc. 101, 1455 (1979).

44) J.P. Mazaleyrat & D.J. Cram, J. Am. Chem. Soc. 103, 4585 (1981).

45) A.K. Beck, unpublished results, ETH Zürich 1982/83.

46) M. Carmack, C.J. Kelly, J. Org. Chem. 33, 2171 (1968).

47) C. Blandy & D. Gervais, Inorg. Chim. Acta 52, 79 (1981).

48) G.M. Whitesides, C.P. Casey & J.K. Krieger, J. Am. Chem. Soc. 93, 1379 (1971).

49) J. Schwartz, M.J. Loots & H. Kosugi, J. Am. Chem. Soc. 102, 1333 (1980); F.M. Dayrit & J. Schwartz, J. Am. Chem. Soc. 103, 4466 (1981), and ref. cited therein.

50) D.W. Hart, T.F. Blackburn & J. Schwartz, J. Am. Chem. Soc. 97, 679 (1975).

51) M.J. Loots & J. Schwartz, J. Am. Chem. Soc. 99, 8045 (1977).

52) F.W. Hartner & J. Schwartz, J. Am. Chem. Soc. 103, 4979 (1981).

53) E. Thorn-Csányi, Nachr. Chem. Tech. Lab. 29, 700 (1981).

54) S.H. Pine, R. Zahler, D.A. Evans, & R.H. Grubbs, J. Am. Chem. Soc. 102, 3270 (1980).

55) J.W. Sam Stevenson & T.A. Breyson, Tetrahedron Lett. 23, 3143 (1982).

56) S. Murai & N. Sonoda, Angew. Chem. 91, 896 (1979); ibid. Int. Ed. Engl. 18, 837 (1979); P. Pino, F. Piacenti & M Bianchi in "Organic Synthesis via Metal Carbonyls", Vol. 2, p. 43, Wiley-Interscience, 1977.

57) I. Ugi, Angew. Chem. 94, 826 (1982); ibid. Int. Ed. Engl. 21, 810 (1982).

58) J.P. Collman, Acc. Chem. Res. 8, 342 (1975).

59) I.I. Lapkin & T.N. Povarnitsyna, Zh. Obshch. Khim. 38, 99 (1968).

60) L.S. Trzupek, T.L. Newirth, E.G. Kelly, N.E. Sbarbati & G.M. Whitesides, J. Am. Chem. Soc. 95, 8118 (1973).

61) Reviews: M.P. Periasamy & H.M. Walborsky, Org. Prep. Proc. Int. 11, 293 (1979), and ref. cited therein.

62) D. Seebach, Angew. Chem. 91, 259 (1979); ibid. Int. Ed. Engl. 18, 239 (1979).

63) C.A. Bertelo & J. Schwartz, J. Am. Chem. Soc. 97, 228 (1975).

64) M. Passerini, Gazz. Chim. Ital. 51, 126 and 181 (1921). See also [57] and ref. cited therein.

65) T. Mukaiyama, K. Watanabe & M. Shiono, Chem. Lett. 1974, 1457.

66) B. Crociani, M. Nicolini & R.L. Richards, J. Organomet. Chem. 101, C 1 (1975).

67) M.T. Reetz, Angew. Chem. 94, 97 (1982); ibid. Int. Ed. Engl. 21, 96 (1982).

68) T. Mukaiyama, "Titanium Tetrachloride in Organic Synthesis", Angew. Chem. 89, 858 (1977); ibid. Int. Ed. Engl. 16, 817 (1977).

69) I. Fleming, "The Alkylation of Enolates and Enole Derivatives: The Use of Silyl Enole Ethers", Chimia 34, 265 (1980).

70) J.K. Rasmussen, "O-Silylated Enolates - Versatile Intermediates for Organic Synthesis", Synthesis 1977, 91.

71) E.W. Colvin, "Silicone in Organic Synthesis", Butterworths, London 1981.

72) T.H. Chan & I. Fleming, "Electrophilic Substitution of Organosilicone Compounds - Applications ot Organic Synthesis", Synthesis 1979, 761.

73) T. Mukaiyama & A. Ishida, Chem. Lett. 1975, 319.

74) M.T. Reetz, in "30 Jahre Fonds der Chemischen Industrie 1950-1980", p. 29, Verband der Chemischen Industrie e.V. 1980.

75) M.T. Reetz & R. Peter, Tetrahedron Lett. 22, 4691 (1981).

76) L. Widler, projected Ph.D. thesis, ETH Zürich 1983.

77) L. Widler & D. Seebach, Helv. Chim. Acta 65, 1972 (1982).

78) M.T. Reetz & W.F. Maier, Angew. Chem. 90, 50 (1978); ibid. Int. Ed. Engl. 17, 48 (1978).

79) T. Mukaiyama & M. Hayashi, Chem. Lett. 1974, 15.

80) T. Mukaiyama, K. Banno & K. Narasaka, J. Am. Chem. Soc. 96, 7503 (1974).

81) K. Narasaka, K. Soai, Y. Aikawa & T. Mukaiyama, Bull. Chem. Soc. Jpn. 49, 779 (1976).

82) I. Paterson & I. Fleming, Tetrahedron Lett. 1979, 995.

83) M.T. Reetz, S. Hüttenhain, P. Walz & U. Löwe, Tetrahedron Lett. 1979, 4971.

84) M. Miyashita, T. Yanami & A. Yoshikoshi, J. Am. Chem. Soc. 98, 4679 (1976).

85) A. Ishida & T. Mukaiyama, Bull. Chem. Soc. Jpn. 51, 2077 (1978).

86) I. Fleming & T.V. Lee, Tetrahedron Lett. 22, 705 (1981).

87) C.H. Heathcock, "The Aldol Addition Reaction" in "Asymmetric Synthesis", Vol. 2, chapter 2, Ed. J.D. Morrison, Academic Press Inc., New York 1983.

88) C.H. Heathcock, in "Comprehensive Carbanion Chemistry", Vol. II, Ed. T. Durst & E. Buncel, Elsevier, in preparation.

89) C.H. Heathcock, "The Aldol Condensation as a Tool for Stereoselective Organic Synthesis", Pure Appl. Chem. (1983), in press.

90) C.H. Heathcock, "Acyclic Stereoselection via the Aldol Condensation" in "Asymmetric Reactions and Processes in Chemistry", p. 55, Ed. E.L. Eliel & S. Otsuka, ACS-Symposium Series No. 185, 1982.

91) D.A. Evans, J.V. Nelson & T.R. Taber, "Stereoselective Aldol Condensations" in "Topics in Stereochemistry", Vol. 13, p. 1, Wiley-Interscience, New York 1982.

92) C.H. Heathcock, "Acyclic Stereocontrol Through the Aldol Condensation", Science 214, 395 (1981).

93) S. Masamune in "Organic Synthesis Totday and Tomorrow", p. 197, Ed. B.M. Trost & R. Hutchinson, Pergamon Press, New York 1981.

94) D.A. Evans, J.M. Takacs, L.R. McGee, M.D. Ennis, D.J. Mathre & J. Bartroli, "Chiral Enolate Design", Pure & Appl. Chem. 53, 1109 (1981).

95) G. Solladié, "Asymmetric Synthesis Using Nucleophilic Reagents Containing a Chiral Sulfoxide Group", Synthesis 1981, 185.

96) Y. Yamamoto & K. Maruyama, "The Metal Effect on the Stereoselection in Acyclic Systems - The Reaction of Allylic Organometallic Compounds and

of Metal Enolates", J. Synth. Org. Chem. Jpn. 40, 332 (1982).

97) M. Shibasaki & S. Ikegami, "Chelation-Controlled Stereo and Regioselective Reactions: Application to Natural Product Synthesis", J. Synth. Org. Chem. Jpn. 40, 602 (1982).

98) R.W. Hoffmann, "Diastereogenic Addition of Crotylmetal Compounds to Aldehydes", Angew. Chem. 94, 569 (1982); ibid. Int. Ed. Engl. 21, 555 (1982).

99) F. Sato, "Applications of Bis(η-cyclopentadienyl)titanium Compounds in Organic Synthesis", J. Synth. Org. Chem. Jpn. 40, 744 (1982).

100) T. Hiyama, "Chromium Reagents for Selective C-C Bond Formation", J. Synth. Org. Chem. Jpn. 39, 81 (1981).

101) D. Seebach, A.K. Beck, T. Mukhopadhyay & E. Thomas, "Diastereoselective Synthesis of Nitroaldol Derivatives", Helv. Chim. Acta 65, 1101 (1982).

102) D. Seebach & J. Goliński, "Diastereoselective *Michael* Additions", Helv. Chim. Acta 64, 1413 (1981).

103) S. Blarer, W.B. Schweizer & D. Seebach, "Diastereo- and Enantioselective *Michael* Additions", Helv. Chim. Acta 65, 1637 (1982).

104) Y. Kishi *et al.* , J. Am. Chem. Soc. 104, 7362, 7364, 7367 and 7369 (1982).

105) V. Prelog & G. Helmchen, Angew. Chem. 94, 614 (1982); ibid. Int. Ed. Engl. 21, 567 (1982).

106) M. Schlosser & B. Schaub, J. Am. Chem. Soc. 104, 5821 (1982).

107) Y. Yamamoto & K. Maruyama, Tetrahedron Lett. 21, 4607 (1980).

108) D.A. Evans & L.R. McGee, Tetrahedron Lett. 21, 3975 (1980).

109) D.A. Evans & L.R. McGee, J. Am. Chem. Soc. 103, 2876 (1981).

110) M.T. Reetz, R. Steinbach & K. Kesseler, Angew. Chem. 94, 872 (1982); ibid. Int. Ed. Engl. 21, 864 (1982); ibid. Suppl. 1982, 1899.

111) R. Imwinkelried, Master's thesis, ETH Zürich 1982/83.

112) L. Widler, Th. Weber & D. Seebach, Chem. Ber., 116 (1983) in preparation.

113) Th. Weber, Master's thesis, ETH Zürich 1982.

114) R. Hanko & D. Hoppe, Angew. Chem. 94, 378 (1982); ibid. Int. Ed. Engl. 21, 372 (1982); ibid. Suppl. 1982, 961.

115) M.T. Reetz & B. Wenderoth, Tetrahedron Lett. 23, 5259 (1982).

116) E. Klei, J.H. Teuben, H.J. de Liefde Meijer, E.J. Kwak & A.P. Bruins, J. Organomet. Chem. 224, 327 (1982).

117) F. Sato, S. Iijima & M. Sato, Tetrahedron Lett. 22, 243 (1981).

118) F. Sato, K. Iida, S. Iijima, H. Moriya & M. Sato, J. Chem. Soc. Chem. Commun. 1981, 1140.

119) E.J. Corey & D. Enders, Chem. Ber. 111, 1337 and 1362 (1978); D. Enders, H. Eichenauer & R. Pieter, Chem. Ber. 112, 3703 (1979); K.G. Davenport, H. Eichenauer, D. Enders, M. Newcomb & D.E. Bergbreiter, J. Am. Chem. Soc. 101, 5654 (1979).

120) D. Hoppe & A. Brönneke, Tetrahedron Lett. 24 (1983), in press.

121) D. Hoppe, Nachr. Chem. Tech. Lab. 30, 1030 (1982)

122) R.D. Rieke & S. Bales, J. Am. Chem. Soc. 96, 1775 (1974).

123) M. Ishiguro, N. Ikeda & H. Yamamoto, J. Org. Chem. 47, 2225 (1982).

124) D.E. Bergbreiter & E. Pendergrass, J. Org. Chem. 46, 219 (1981).

125) Review: D. Seebach & K.H. Geiss, J. Organomet. Chem. Library 1, 1 (1976).

126) D. Seebach & E. Hungerbühler, in "Modern Synthetic Methods 1980", Ed.: R. Scheffold, Salle + Sauerländer, Aarau 1980.

127) K.H. Geiss, B. Seuring, R. Pieter & D. Seebach, Angew. Chem. 86, (484 (1974); ibid. Int. Ed. Engl. 13, 479 (1974); K.H. Geiss, D. Seebach & B. Seuring, Chem. Ber. 110, 1833 (1977).

128) D. Seebach, K.H. Geiss & M. Pohmakotr, Angew. Chem. 88, 449 (1976); ibid. Int. Ed. Engl. 15, 437 (1976); M. Pohmakotr, K.H. Geiss & D. Seebach, Chem. Ber. 112, 1420 (1979).

129) K.H. Geiss, Dissertation, Giessen 1975.

130) P. Pohmakotr, Dissertation, Giessen 1978.

131) J.F. Normant & A. Alexakis, Synthesis 1981, 841.

132) E. Negishi, Pure & Appl. Chem. 53, 2333 (1981).

133) "Aluminiumalkyle, Hinweise zur sicheren Handhabung", Schering, Industrie-Chemikalien, D-4619 Bergkamen.

134) H.O. House, "Modern Synthetic Reactions", 2nd Edition, Benjamin, Menlo Park 1972.

135) J.J. Bloomfield, D.C. Owsley & J.M. Nelke, Org. React. 23, 259 (1976).

136) Y. Ito, T. Konoike & T. Saegusa, J. Am. Chem. Soc. 97, 649 (1975).

137) Y. Kobayashi, T. Taguchi & E. Tokuno, Tetrahedron Lett. 1977, 3741; Y. Ito, T. Konoike & T. Saegusa, J. Am. Chem. Soc. 97, 2912 (1975).

138) Y. Ito, T. Konoike, T. Harada & T. Saegusa, J. Am. Chem. Soc. 99, 1487 (1977).

139) R.M. Dessau & E.I. Heiba, J. Org. Chem. 39, 3457 (1974).

140) J.E. McMurry & M.P. Fleming, J. Am. Chem. Soc. 96, 4708 (1974).

141) H. Wynberg, K. Lammertsma & L.A. Hulshof, Tetrahedron Lett. 1975, 3749.

142) R.F. Langler & T.T. Tidwell, Tetrahedron Lett. 1975, 777.

143) D.S. Bomse & T.H. Morton, Tetrahedron Lett. 1975, 781.

144) A.L. Baumstark, E.J.H. Bechara & M.J. Semigran, Tetrahedron Lett. 1976, 3265.

145) P.D. Mollere, K.N. Houk, D.S. Bomse & T.H. Morton, J. Am. Chem. Soc. 98, 4732 (1976).

146) J.E. McMurry & M.P. Fleming, J. Org. Chem. 41, 896 (1976).

147) J.E. McMurry, M.P. Fleming, K.L. Kees & L.R. Krepski, J. Org. Chem. 43, 3255 (1978).

148) S.C. Welch & M. Walters, J. Org. Chem. 43, 4797 (1978).

149) J.E. Pauw & A.C. Weedon, Tetrahedron Lett. 23, 5485 (1982).

150) S. Tyrlik & I. Wolochowicz, Bull. Soc. Chim. Fr. 1973, 2147.

151) J.A. Marshall, R.E. Bierenbaum & K.H. Chung, Tetrahedron Lett. 1979, 2081.

152) L. Castedo, J.M. Saá, R. Suau & G. Tojo, J. Org. Chem. 46, 4292 (1981).

153) T. Mukaiyama, T. Sato & J. Hanna, Chem. Lett. 1973, 1041.

154) D. Lenoir, Synthesis 1977, 553.

155) D. Lenoir & P. Lemmen, Chem. Ber. 113, 3112 (1980).

156) E.J. Corey, R.L. Danheiser & S. Chandrasekaran, J. Org. Chem. 41, 260 (1976).

157) J.E. McMurry, Acc. Chem. Res. 7, 281 (1974).

158) A. Clerici & O. Porta, J. Org. Chem. 47, 2852 (1982).

159) D. Ghiringhelli, Tetrahedron Lett. 24, 287 (1983).

160) R.D. Rieke, Acc. Chem. Res. 10, 301 (1977).

161) J. Leimner & P. Weyerstahl, Chem. Ber. 115, 3697 (1982).

162) B.P. Mundy, R. Srinivasa, Y. Kim & T. Dolph, J. Org. Chem. 47, 1657 (1982).

163) H.M. Walborsky & H.H. Wüst, J. Am. Chem. Soc. 104, 5807 (1982).

164) J.M. Pons & M. Santelli, Tetrahedron Lett. 23, 4937 (1982).

165) K. Takai, Y. Hotta, K. Oshima & H. Nozaki, Tetrahedron Lett. 1978, 2417.

166) S. Inaba & I. Ojima, Tetrahedron Lett. 1977, 2009.

167) G. Calderari, Master's thesis, ETH Zürich 1982.

168) H.C. Brown & S. Krishnamurthy, Tetrahedron 35, 567 (1979). See also [169].

169) A. Hajós, "Complex Hydrides", Elsevier, Amsterdam 1979.

170) N. Kornblum, J.W. Powers, G.J. Anderson, W.J. Jones, H.O. Larson, O. Levand & W.M. Weaver, J. Am. Chem. Soc. 79, 6562 (1957).

171) K.E. Pfitzner & J.G. Moffatt, J. Am. Chem. Soc. 87, 5661 (1965). For a review see: J.G. Moffatt, "Sulfoxide - Carbodiimid and Related Oxidations" in "Oxidationen", Vol. 2, p. 1, Ed. R.L. Augustine & D.J. Tredor, Marcel Dekker, New York 1971.

172) E.J. Corey & C.U. Kim, J. Am. Chem. Soc. 94, 7586 (1972); E.J. Corey & C.U. Kim, Tetrahedron Lett. 1973, 919; E.J. Corey & J.W. Suggs, Tetrahedron Lett. 2647 (1975).

173) A.J. Mancuso, S.L. Huang & D. Swern, J. Org. Chem. 43, 2480 (1978).

174) H. Meerwein, B.v. Bock, Br. Kirschnick, W. Lenz & A. Migge, J. prakt. Chem. N.F. 147, 211 (1937).

175) A. Planta, Master's thesis, ETH Zürich 1982.

176) J.F. Eastham & R. Teranishi, Org. Synth. Coll. Vol. IV, 192 (1963).

177) M. Bös, unpublished results, ETH Zürich 1982.

178) S. Kano, Y. Tanaka, E. Sugino & S. Hibino, Synthesis 1980, 695.

179) F. Sato, T. Jinbo & M. Sato, Synthesis, 1981, 871.

180) Review: D. Seebach, E.W. Colvin, F. Lehr & T. Weller, Chimia 33, 1 (1979).

181) P. Knochel & D. Seebach, Nouv. J. Chim. 5, 75 (1981); P. Knochel & D. Seebach, Tetrahedron Lett. 22, 3223 (1981); ibid. 23, 3897 (1982); P. Knochel & D. Seebach, Synthesis 1982, 1017.

182) D. Seebach, A.K. Beck, F. Lehr, T. Weller & E.W. Colvin, Angew. Chem. 93, 422 (1981); ibid. Int. Ed. Engl. 20, 397 (1981); F. Lehr, J. Gonnermann & D. Seebach, Helv. Chim. Acta 62, 2258 (1979). See also [101].

183) J.E. McMurry & J. Melton, J. Org. Chem. 38, 4367 (1973); see also [157].

184) R. Henning, Dissertation, Giessen 1978; D. Seebach, R. Henning & F. Lehr, Angew. Chem. 90, 479 (1978); ibid. Int. Ed. Engl. 17, 458 (1978).

185) H. Bürger & H.J. Neese, Chimia 24, 209 (1970).

186) H. Weingarten & W.A. White, J. Am. Chem. Soc. 88, 850 (1966). H. Weingarten & W.A. White, J. Org. Chem. 31, 2874 (1966).

187) W.A. White & H. Weingarten, J. Org. Chem. 32, 213 (1967).

188) M.T. Reetz, Lecture presented at the University of Zurich, Dec. 17, 1982.

189) D. Seebach, E. Hungerbühler, R. Naef, P. Schnurrenberger, B. Weidmann & M. Züger, Synthesis 1982, 138.

190) H. Rehwinkel & W. Steglich, Synthesis 1982, 826.

191) P. Schnurrenberger, M.F. Züger & D. Seebach, Helv. Chim. Acta 65, 1197 (1982). See also D. Seebach & M.F. Züger, Helv. Chim. Acta 65, 495 (1982).

192) J. Schwartz & J. Labinger, Angew. Chem. 88, 402 (1976); ibid. Int. Ed. Engl. 15, 333 (1976).

193) H.C. Brown, "Organic Syntheses via Boranes", John Wiley & Sons, New York 1975.

194) T. Gibson, Tetrahedron Lett. 23, 157 (1982).

195) J.D. Roberts & M.C. Caserio, "Basic Principles of Organic Chemistry",

p. 426, Benjamin, New York 1965.

196) G. Berti, in "Topics in Stereochemistry", Vol. 7, p. 93, Ed.: N.L. Allinger & E.L. Eliel, John Wiley & Sons, New York 1973.

197) D.N. Kirk, Chem. and Ind. 1973, 109.

198) K.B. Sharpless & T.R. Verhoeven, Aldrichimica Acta 12, 63 (1979).

199) See also the review on "The Catalytic Epoxidation of Olefins with Organic Hydroperoxides", J. Sobczak & J.J. Ziolkowski, J. Mol. Catalysis 13, 11 (1981).

200) T. Katsuki & K.B. Sharpless, J. Am. Chem. Soc. 102, 5974 (1980).

201) D. Seebach, M. Bös & R. Naef, J. Am. Chem. Soc. 105 (1983), in press.

202) Eleventh International Carbohydrate Symposium, 1982, Vancouver: K.B. Sharpless, C.H. Behrens, T. Katsuki, A.W.M. Lee, V.S. Martin, M. Takatani, S.M. Viti, F.J. Walker & S.S. Woodard, Pure & Appl. Chem., (1983), in press.

203) B.E. Rossiter, "Selective Epoxidation of Olefins, Allylic Alcohols, and Homoallylic Alcohols with *tert*-Butyl Hydroperoxide and Molybdenum, Vanadium, and Titanium Catalysts. Application to Asymmetric Synthesis of (+)-Disparture and (-)-γ-Amino-β-(R)-Hydroxybutyric Acid", Dissertation, Stanford University 1981.

204) S.S. Woodard, "A Mechanistic Inverstigation of Asymmetric Epoxidation Catalyzed by Chiral Titanium-Tartrate Complexes, Dissertation, Stanford University 1981.

205) V.S. Martin, S.S. Woodard, T. Katsuki, Y. Yamada, M. Ideda & K.B. Sharpless, J. Am. Chem. Soc. 103, 6237 (1981).

206) W. Weigert, "Wasserstoffperoxid und seine Anwendung", Hüthig-Verlag, Heidelberg 1978.

207) R. Criegee, in Houben-Weyl, "Methoden der Organischen Chemie", Vol. VIII, p. 1 (1952).

208) B.E. Rossiter, T. Katsuki & K.B. Sharpless, J. Am. Chem. Soc. 103, 464 (1981).

209) B.E. Rossiter, T.R. Verhoeven & K.B. Sharpless, Tetrahedron Lett. 1979, 4733.

210) E.D. Mihelich, Tetrahedron Lett. 1979, 4729.

211) A.S. Narula, Tetrahedron Lett. 23, 5579 (1982).

212) T. Itoh, K. Jitsukawa, K. Kaneda & S. Teranishi, J. Am. Chem. Soc. 101, 159 (1979).

213) D. Baldwin & J.R. Hanson, J. Chem. Soc. Perkin Trans. 1, 1941 (1975).

214) A. Murai, N. Iwasa & T. Masamune, Chem. Lett. 1977, 235.

215) E.D. Mihelich, K. Daniels & D.J. Eickhoff, J. Am. Chem. Soc. 103, 7690 (1981).

216) T. Fukuyama, B. Vranesic, D.P. Negri & Y. Kishi, Tetrahedron Lett. 1978, 2741.

217) T. Hiyama & M. Obayashi, Tetrahedron Lett. 24, 395 (1983).

218) T. Katsuki, A.W.M. Lee, P. Ma, V.S. Martin, S. Masamune, K.B. Sharpless, D. Tuddenham, F.J. Walker & S.M. Viti, J. Org. Chem. 47, 1373 and 1378 (1982); A.W.M. Lee, V.S. Martin, S. Masamune, K.B. Sharpless & F.J. Walker, J. Am. Chem. Soc. 104, 3515 (1982).