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Chemoselective Addition of Organotitanium Reagents to Carbonyl Compounds

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The conversion of classical carbanions such as RMgX, RLi, or deprotonated nitriles, sulfones, and carboxylic esters into titanium analogs results in reagents which add chemoselectively to carbonyl compounds in the presence of other functional groups. The standard titanating agent is chlorotriisopropoxytitanium (**1**). Grignard-type reactions and aldol additions are aldehyde-selective in the presence of ketones. Other functional groups such as alkyl and aryl halides, esters, amides as well as nitro and cyano moieties are tolerated. Discrimination between two aldehydes or two ketones is also possible. Replacing alkoxy ligands by methyl groups at titanium increases reactivity dramatically, relative rates increasing in the series $CH_3Ti(OCHMe_2)_3 < (CH_3)_2Ti(OCHMe_2)_2 < (CH_3)_4Ti$. The latter reagent and its zirconium analog methylate sterically hindered and/or enolizable ketones which normally fail to undergo Grignard reactions. The ate complex $H_2C=CHCH_2Ti(OCHMe_2)_4MgCl$ (**63**) is aldehyde-selective, while the amino analog $H_2C=CHCH_2Ti(NMe_2)_4MgCl$ (**64**) adds selectively to ketones in the presence of aldehydes.

Chemoselektive Addition von Organotitan-Agenzien an Carbonyl-Verbindungen

Die Überführung von klassischen Carbanionen wie RMgX, RLi oder deprotonierten Nitrilen, Sulfonen oder Carbonsäureestern in Titan-Analoga ergibt Agenzien, die in Gegenwart von anderen funktionellen Gruppen chemoselektiv an Carbonylverbindungen addieren. Das Standard-Titanierungsagens ist Chlortriisopropoxytitan (**1**). Grignard-artige Reaktionen sowie Aldoladditionen sind aldehyd-selektiv in Gegenwart von Ketonen. Andere funktionelle Gruppen wie Alkyl- und Arylhalogenide, Ester, Amide sowie Nitro- und Cyanreste werden toleriert. Die Unterscheidung zwischen zwei Aldehyden oder zwei Ketonen ist ebenfalls möglich. Der Ersatz von Alkoxyliganden durch Methylgruppen hat eine drastische Erhöhung der Reaktivität zur Folge, d.h. die relativen Geschwindigkeiten nehmen in folgender Serie zu: $CH_3Ti(OCHMe_2)_3 < (CH_3)_2Ti(OCHMe_2)_2 < (CH_3)_4Ti$. Das letztere Agens sowie das Zirkon-Analogon methylieren sterisch gehinderte und/oder enolisierbare Ketone, die normalerweise keine Grignard-Reaktionen eingehen. Der At-Komplex $H_2C=CHCH_2Ti(OCHMe_2)_4MgCl$ (**63**) ist aldehyd-selektiv, während die entsprechende Aminoverbindung $H_2C=CHCH_2Ti(NMe_2)_4MgCl$ (**64**) selektiv mit Ketonen in Gegenwart von Aldehyden reagiert.

Although carbanions play an important role in synthetic organic chemistry, lack of chemo- and stereoselectivity is frequently observed[1]. For example, phenylmagnesium bromide hardly discriminates between aldehydes and ketones[2]. Similar lack of chemoselectivity has been observed for other Grignard reagents and their lithium counterparts[3] as well as for such resonance stabilized species as lithium ester enolates[4],

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deprotonated nitriles, and sulfones[5]. Furthermore, many of these classical reagents also attack other functional groups, so that synthetic organic chemists have traditionally avoided strategies in which polyfunctional molecules are treated with highly reactive carbanions. Concerning stereoselectivity, some of these classical reagents have been shown to be useful in certain C – C bond forming reactions, e.g., lithium enolates in aldol additions[6]. Nevertheless, a number of problems remain unsolved, e.g., 1,2-asymmetric induction in nucleophilic additions to chiral carbonyl compounds[6,7].

We have previously shown that certain organotitanium reagents react chemo- and diastereoselectively with S_N1-active alkyl halides[8] and carbonyl compounds[9]. These observations led to the working hypothesis that selectivity of classical carbanions increases by titanation using $ClTiX_3$[10]. It became clear that steric and electronic properties (e.g., Lewis acidity) of the reagents can be adjusted in a predictable way by choice of the ligand X at titanium[11a]:

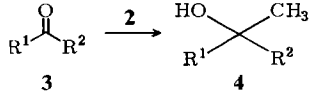
$$\boxed{\text{ORGANYL}}\text{–Li (MgX) (ZnX)} \xrightarrow{ClTiX_3} \boxed{\text{ORGANYL}}\text{–}TiX_3 \qquad X = Cl, OR, NR_2$$

Here we present an account of the scope and limitations of the above concept, particular emphasis being on chemoselectivity in nucleophilic additions to carbonyl compounds. In the following paper the results of stereochemical studies are described[12].

Exploratory Studies

Although some alkyltitanium compounds had been shown to give a positive Gilman test[13], synthetic implications did not become apparent until 1979/80. We noticed that several organotitanium reagents react chemoselectively with certain functional groups in the presence of others[8,9,14–17]. For example, triisopropoxymethyltitanium (**2**), prepared in high yield by reacting chlorotriisopropoxytitanium (**1**) with methylmagnesium chloride or methyllithium[13], adds to aldehydes **3** (R^2 = H) under mild conditions (–50 to +22 °C/2–3 h) to form Grignard-type adducts **4** (>90% conversion)[9]. In contrast, ketones **3** require room temperature and considerably longer reaction times (8–72 h). Even then conversion is sometimes meager. We later solved this problem by carrying out the addition reaction in the *absence of solvent* (Table 1).

$$\underset{\mathbf{1}}{ClTi(OCHMe_2)_3} \xrightarrow{CH_3Li} \underset{\mathbf{2}}{CH_3Ti(OCHMe_2)_3}$$



3 **4**

The quenching reagent **1** is readily available by mixing one part $TiCl_4$ and three parts $Ti(OCHMe_2)_4$. **2** is a distillable compound, miscible with most non-protic organic solvents, e.g., ether, THF, CH_2Cl_2, or toluene. In dilute solutions of benzene **2** is mainly monomeric as shown by cryoscopic measurements[18]. In more concentrated

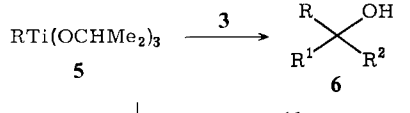
solutions some degree of aggregation is observed[18,19]. If alkoxy groups smaller than isopropoxy are chosen, as in $CH_3Ti(OEt)_3$, the reagents are dimeric or oligomeric *via* Ti – O bridging[11a]. For carbonyl addition reactions, isolation of **2** is not necessary. An *in situ* reaction mode involving treatment of **1** with methyllithium followed by addition of carbonyl compounds results in essentially the same yields of **4**[3,5].

Table 1. Addition Reactions of $CH_3Ti(OCHMe_2)_3$ (**2**) with Carbonyl Compounds **3**[a] to Give $R^1R^2C(OH)CH_3$ (**4a–i**)

R^1	R^2	Temp. (°C)	Reaction Time (h)	Product	Yield[b]
$(CH_3)_2CHCH_2$	H	0	0.25	**4a**	95 (83)
n-C_5H_{11}	H	0	0.5	**4b**	95 (76)
C_6H_5	H	0	0.25	**4c**	100 (92)
C_6H_5	H	0	0.25	**4c**	100[c]
C_6H_5	H	−40	2	**4c**	95
C_6H_5	H	−78	6	**4c**	70
C_6H_5	H	0	0.25	**4c**	100[d]
$C_6H_5CH_2$	H	−40→0	2	**4d**	90 (74)
c-C_6H_{11}	H	0	0.5	**4e**	90 (85)
4-pyridinyl	H	−20	1.5	**4f**	90 (75)[d]
2-thienyl	H	−20	1.5	**4g**	95 (87)[d]
n-C_5H_{11}	CH_3	+22	24	**4h**	47
n-C_5H_{11}	CH_3	+22	48	**4h**	67
n-C_5H_{11}	CH_3	+22	24	**4h**	90 (83)[e]
$-[CH_2]_5-$		+22	6	**4i**	90 (82)

[a] Reactions in ether using **2** prepared *in situ* from **1** and methyllithium unless otherwise stated. – [b] Conversion as determined by ^1H NMR spectroscopy or gaschromatography; the numbers in brackets refer to isolated yields. – [c] Reaction in ether using distilled **2**. – [d] Reaction in CH_2Cl_2 using distilled **2**. – [e] Reaction in the absence of solvent using distilled **2**.

Upon testing homologs of **2**, it became clear that *n*-alkyl- and allyltriisopropoxytitanium compounds cannot be distilled without extensive decomposition[16]. However, they can be handled and reacted in solution[20]. Thus, titanation of ethyllithium and *n*-butyllithium or allylmagnesium halide affords solutions of **5a–c** which undergo reactions with carbonyl compounds (Table 2). In contrast, similar experiments using isopropyl- or *tert*-butyllithium were less rewarding due to extensive β-hydride elimination, formation of low-valent titanium species and other side reactions[21]. Clearly, these observations point to synthetic limitations regarding branched reagents. An exception is cyclopropyllithium which can be converted to **5d**. Aryl- and (trimethylsilyl)methyl derivatives (**5e,f**) are readily accessible and add to aldehydes, although differences in reactivity are apparent (Table 2).



5 **6**

	R		R
5a	C_2H_5	**5d**	*c*-C_3H_5
b	*n*-C_4H_9	**e**	C_6H_5
c	$H_2C{=}CHCH_2$	**f**	Me_3SiCH_2

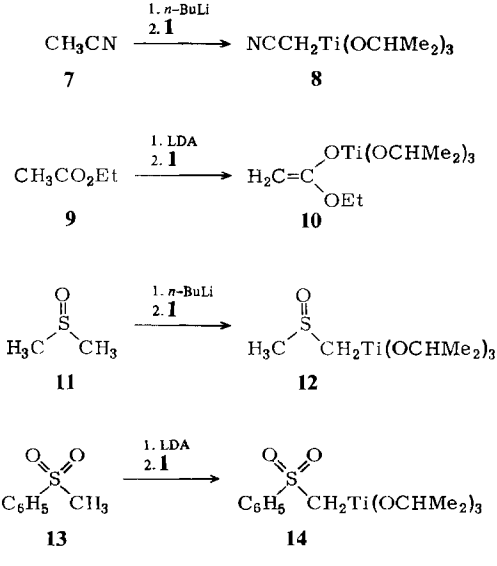
(**6a-r** see Table 2)

Table 2. Addition Reactions of Organotitanium Reagents with Carbonyl Compounds **3** to Give RR^1R^2COH (**6a–r**)

Reagent	Temp. (°C)	Reaction Time (h)	R	R^1	R^2	Product	Yield[a]
5a[b]	−30→+22	6	C_2H_5	C_6H_5	H	**6a**	≈80 (69)
5b[b]	−20→+22	6	n-C_4H_9	C_6H_5	H	**6b**	≈80 (72)
5c[c]	−30	0.5	$H_2C=CHCH_2$	$(CH_3)_2CHCH_2$	H	**6c**	>80 (60)
5c[c]	−30	0.5	$H_2C=CHCH_2$	C_6H_5	H	**6d**	>90 (84)
5c[c]	−30	0.5	$H_2C=CHCH_2$	n-C_6H_{13}	H	**6e**	>90 (88)
5c[c]	−10	1	$H_2C=CHCH_2$	n-C_5H_{11}	CH_3	**6f**	≈90 (81)
5d[b]	−20	1	c-C_3H_5	C_6H_5	H	**6g**	80 (71)
5e[c]	−10	1	C_6H_5	c-C_6H_{11}	H	**6h**	≈95 (84)
5e[c]	−10	1	C_6H_5	CH_3	H	**6i**	≈95 (86)
5f[c]	+22	48	$(CH_3)_3SiCH_2$	C_6H_5	H	**6j**	≈60 (41)
8[c]	−78→+22	3	$NCCH_2$	C_6H_5	H	**6k**	≈95 (81)
10[c]	−78	3	$CH_2CO_2C_2H_5$	n-C_6H_{13}	H	**6l**	≈95 (83)
10[c]	−78→0	4	$CH_2CO_2C_2H_5$	$-[CH_2]_5-$		**6m**	90 (78)
12[c]	−78→+10	12	$CH_3S(O)CH_2$	C_6H_5	H	**6n**	–[d]
12[c]	+22	12	$CH_3S(O)CH_2$	C_6H_5	H	**6n**	–[d]
14[c]	−78→+22	3	$CH_2SO_2C_6H_5$	C_6H_5	H	**6o**	≈100 (95)
14[c]	−78→+22	3	$CH_2SO_2C_6H_5$	n-C_3H_7	H	**6p**	>90 (82)
14[c]	−78→+22	3	$CH_2SO_2C_6H_5$	C_6H_5	CH_3	**6q**	90 (83)
14[c]	−78→+22	3	$CH_2SO_2C_6H_5$	$-[CH_2]_5-$		**6r**	≈85 (79)

[a] The numbers refer to approximate conversion as determined by ^1H NMR spectroscopy, those in brackets to isolated yields. – [b] Reaction performed in ether. – [c] Reaction performed in THF. – [d] No addition product observed.

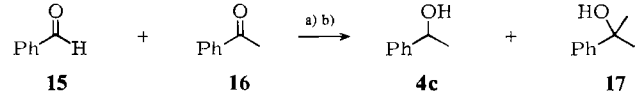
Besides **2** and **5**, several titanium reagents were prepared by deprotonation and titanation of CH-acidic compounds. The precise structure and aggregation state of **8**, **10**, **12**, and **14** remain to be established. In case of **9** → **10** we currently assume *O*-titanation as indicated, in analogy to titanium enolates of ketones[22].



Although detailed kinetic studies have not been completed*), Tables 1 and 2 point to several important trends regarding reactivity. *n*-Alkyltitanium reagents appear to react less efficiently with carbonyl compounds than the parent methyl compound **2**. Reagents having additional functional groups capable of resonance (**5c**, **8**, **10**, **14**) add very rapidly to aldehydes and ketones with excellent yields. Presently it is unclear why the titanated sulfoxide **12** fails to react with aldehydes; aqueous workup simply regenerates **11**. The (trimethylsilyl)methyl reagent **5f** is considerably less reactive than the parent compound **2**, very likely due to steric reasons.

Aldehyde-Selectivity

The above results suggest that chemoselective addition of carbon nucleophiles to aldehydes in the presence of ketones should be possible. Indeed, in a competition experiment involving the reaction of one part **2** with one part benzaldehyde (**15**) and one part acetophenone (**16**), only the aldehyde adduct **4c** was detected[9,10]. In a related study another group has reached similar results[23]. In sharp contrast, methyllithium reacts chemo-randomly and also leads to side products such as aldol adducts[3]. The highly selective behavior of **2** also applies to other aldehyde/ketone pairs[11a].

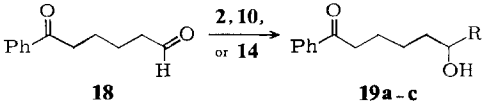


15 **16** **4c** **17**

a) $CH_3Ti(OCHMe_2)_3$ > 99 : <1
b) CH_3Li ≈ 1 : 1

Similar effects have been observed for **5**, **8**, **10**, and **14** and other titanated species[11]. However, the highly reactive allyltitanium reagent **5c** is *not* completely aldehyde-selective, the benzaldehyde/acetophenone adduct ratio being 86:14[5]. This problem has been solved using titanium ate complexes (see below). Finally, such reagents as **2** are capable of distinguishing between two ketones or two aldehydes[10,11a].

The conclusion derived from intermolecular competition experiments apply fully to keto-aldehydes. Thus, aldehyde-selectivity was observed in the reactions leading to **19a–c** (the numbers in brackets refer to isolated yield).



18 **19a–c**

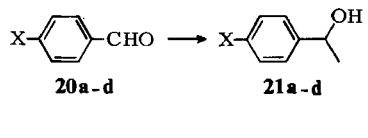
		R	
with **2**:	**19a**	CH_3	(80%)
with **10**:	**b**	CH_2CO_2Et	(74%)
with **14**:	**c**	CH_2SO_2Ph	(91%)

In contrast, the lithium precursors of **2**, **10**, and **14** lead to mixtures. For example, the Li-enolate of ethyl acetate reacts with **18** at −78°C to afford 32% of **19b** and 38% of the ketone adduct as well as the bis-adduct and unreacted **18**[4].

*) Careful kinetic investigations concerning the addition of **2** to several aldehydes and ketones show that aldehydes react faster than ketones by a factor of 220–450[11a]. Thus, the k_{rel} value of 10^5 (and $\Delta\Delta G^{\neq}$ = 7 kcal/mol) estimated by another group[11b] is a gross error.

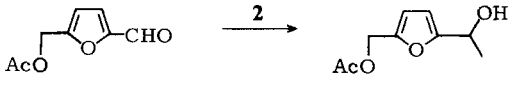
Other Functional Groups

Triisopropoxymethyltitanium (**2**) was reacted with a variety of di- and polyfunctional compounds[11], some of which are shown below. In case of **20d** two equivalents of **2** were used. **34** reacts selectively at the keto-function, but the initial adduct **35** lactonizes to **36** under the reaction conditions.

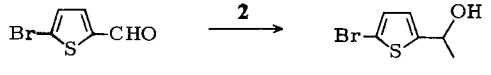


20a-d **21a-d**

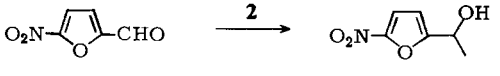
	X	%
20, 21a	CN	85
b	NO_2	95
c	Br	96
d	CO_2H	79



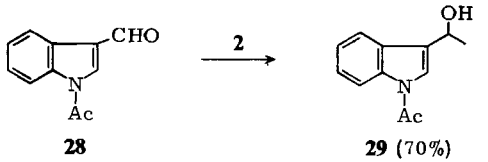
22 **23** (81%)



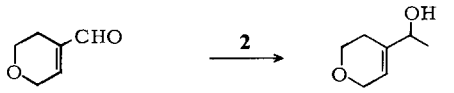
24 **25** (89%)



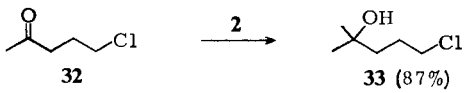
26 **27** (79%)



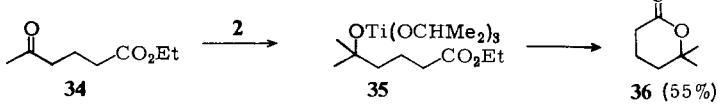
28 **29** (70%)



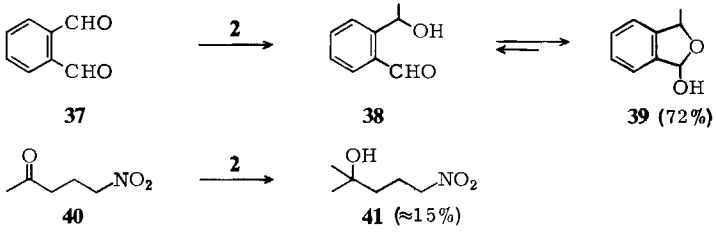
30 **31** (84%)



32 **33** (87%)



34 **35** **36** (55%)



Although some of the carbonyl compounds react smoothly with CH_3Li or CH_3MgCl, the experiments were necessary to test chemo- and regioselectivity in titanium chemistry. Thus, **2** reacts with α,β-unsaturated aldehydes solely in a 1, 2 manner (**28**, **30**).

In several cases titanation led to distinctly better yields. For example, CH_3Li fails to react chemoselectively with **22**, only 39% of **23** being formed[20]. CH_3MgI is even less effective (10% of **23** in a complex product mixture)[20]. Finally, CH_3Li and CH_3MgCl do not undergo clean mono-addition with the dialdehyde **37**, in each case a mixture of **39**, the bis-adduct as well as unreacted **37** being formed[20]. A limitation regarding titanium chemistry was observed upon reacting the aliphatic nitroketone **40**, since only ≈ 15% of the adduct **41** was formed after two days at room temperature[3]. In this case addition to the ketone is slow relative to reaction at the nitro group (possibly titanation at the CH-acidic methylene moiety). This restriction does not apply to aliphatic nitroaldehydes, which react smoothly with **2** at the carbonyl function[24]. Furthermore, the more reactive dialkyltitanium reagents add chemoselectively to **40** in the desired manner (see below). The rate of addition of **2** to aldehydes is comparable to that of protonation by alcohols: **2** reacts with a 1 : 1 mixture of **15** and 2-propanol at −25 °C to afford ≈ 55% of **4c**[26].

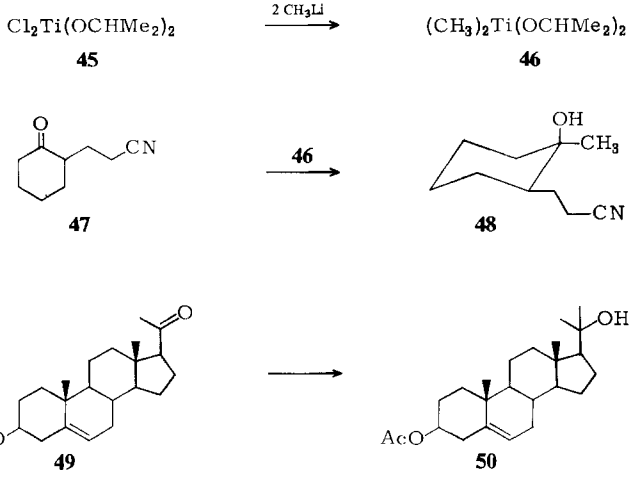
Variation of the Ligands at Titanium

Although titanium reagents **42**–**44** having chlorine ligands are also aldehyde-selective[9], they do not offer real advantages regarding preparation and handling. We initially prepared them by reacting dimethyl- or diphenylzinc with $TiCl_4$ in CH_2Cl_2[9,25]. Alternatively, **42** can be synthesized by adding methyllithium to $TiCl_4$ in ether[26]. However, titanation of other carbanions using $TiCl_4$ is not always as smooth[26]. Thus, in order to increase chemoselectivity, chlorotriisopropoxytitanium (**1**) should be viewed as the "universal" quenching reagent[11a]. This does not apply to stereoselectivity, since the nature of the ligands determines Lewis acidity of the metal which in turn influences such phenomena as chelation or non-chelation control[11a,27].

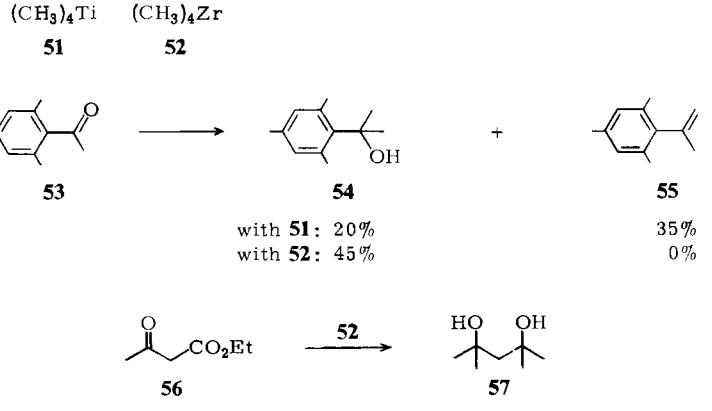
CH_3TiCl_3	$PhTiCl_3$	Ph_2TiCl_2
42	**43**	**44**

In spite of the usefulness of the triisopropoxy ligand system, further variations were tested. It was found that the replacement of alkoxy ligands by methyl groups increases reactivity considerably[11a]. In order to prepare the dimethyl derivative **46**, $TiCl_4$ and

$Ti(OCHMe_2)_4$ were mixed in a 1:1 ratio[28] and the resulting **45**[29] treated with two equivalents of methyllithium[3]. **46** adds to ketones (1:1 ratio) rapidly at 0 °C to 22 °C[3]. The transfer of the second methyl groups onto ketones is considerably slower, i.e., much like the reaction of **2**. Although a 1:1 ratio of reagent to carbonyl compound means utilization of only one active methyl group, **46** is nevertheless useful in certain cases. For example, it adds chemoselectively to the nitro-ketone **40** to form 78% of **41**, a result which is not possible using the monomethyl reagent **2**. Rapid chemoselective addition also occurs in case of **47** which leads to a single diastereomer. The difference between **2** and **46** is also apparent in the different rates of addition to the steroid **49**. Additional advantages of **46** have been observed in certain stereoselective reactions[11a].



with **2** (22 °C/2 d): 90–94% conversion
with **46** (22 °C/1 h): ≈50% conversion
with **46** (22 °C/4 h): 98% conversion

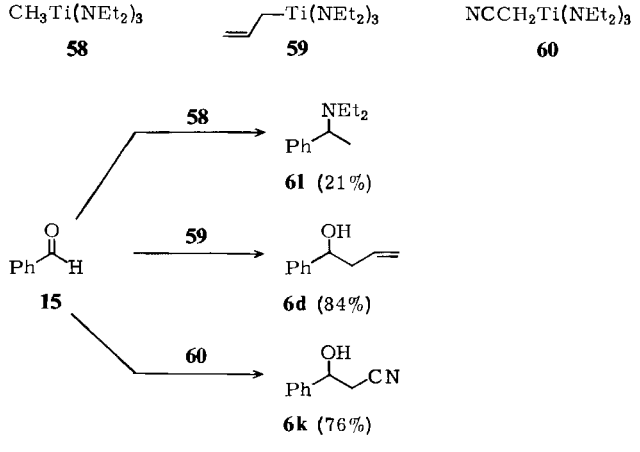


with **51**: 20% 35%
with **52**: 45% 0%

Further increase in reactivity was observed upon replacing all of the alkoxy ligands by methyl groups[10b]. The reaction of $TiCl_4$ with four equivalents of methyllithium in

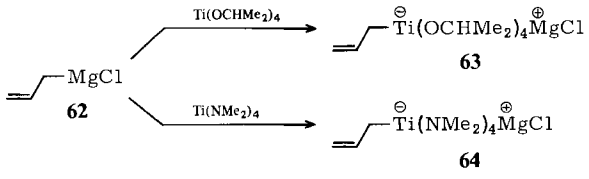
ether affords tetramethyltitanium (**51**), which is known to be stable below $-25\,^{\circ}C$[30]. Treatment of ketones with one part **51** leads to spontaneous Grignard-type addition. Of course, such reactions are meaningful only when CH_3Li, CH_3MgX, **2**, or **46** fail, e.g., in case of sterically hindered and/or enolizable ketones. For example, these reagents do not add to **53**, in contrast to **51**. Even more efficient is the zirconium analog **52**[31], which we found to be a *highly reactive reagent of low basicity*[10b]. This is also reflected by the ready conversion of acetoacetic ester **56** into the diol **57**.

Bürger has synthesized a variety of alkyltitanium triamides $RTi(NEt_2)_3$[32] by the reaction of RLi or RMgX with $ClTi(NEt_2)_3$[33]. They are thermally much more stable than the triisopropoxy analogs, i.e., *n*-alkyl and vinyl derivatives can be distilled without decomposition[32]. Unfortunately, the reagents are generally unsuitable for Grignard-type additions because amino-alkylations occur (e.g., **15** + **58** → **61**)[11a,20,34], a process of little value due to its low yield (20 – 50%). It is initiated by transfer of the amino group onto the aldehyde function followed by immonium ion formation and capture by methyltitanium species. This restriction is not observed in case of very reactive carbon nucleophiles which compete effectively with potential amino group transfer. Thus, titanated enolates and nitriles as well as allyl carbon derivatives having three amino groups at the metal behave as effective carbon nucleophiles. In competition experiments the allyl reagent **59** affords mixtures of aldehyde and ketone adducts, the latter dominating somewhat[11a].

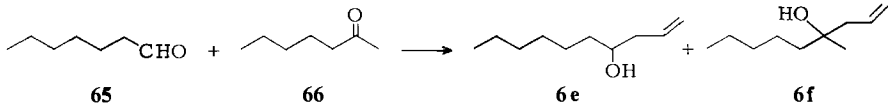


Control of Chemoselectivity using Allyltitanium Ate Complexes

Since the highly reactive allyltitanium reagents **5c** and **59** were the only exceptions regarding strict aldehyde-selectivity, additional optimization was necessary[5]. We speculated that the reaction of $Ti(OCHMe_2)_4$ with allylmagnesium chloride (**62**) might lead to the addition product **63**, and not to the substitution product $H_2C=CHCH_2Ti(OCHMe_2)_3$ (**5c**). Presently, formula **63** should be regarded as a formal description for an ate complex, since structural information is not available. The same applies to the amino analog **64**. They are related to titanium enolate ate complexes[22a].



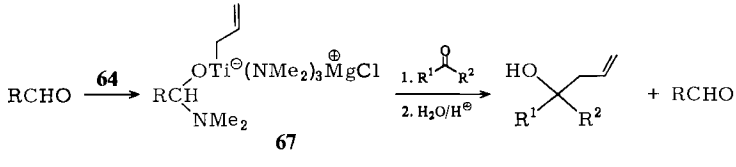
Upon reacting aldehyde/ketone pairs with **63**, essentially complete aldehyde-selectivity was observed[35]. This shows that whatever the precise structure of the reagent may be, the reacting species is neither $H_2C=CHCH_2MgCl$ nor $H_2C=CHCH_2Ti(OCHMe_2)_3$. Since the yields of addition products are ≈ 95%, **63** *may be regarded as a tempered and highly efficient Grignard-type reagent which is accessible from readily available reagents.*



65 **66** **6e** **6f**

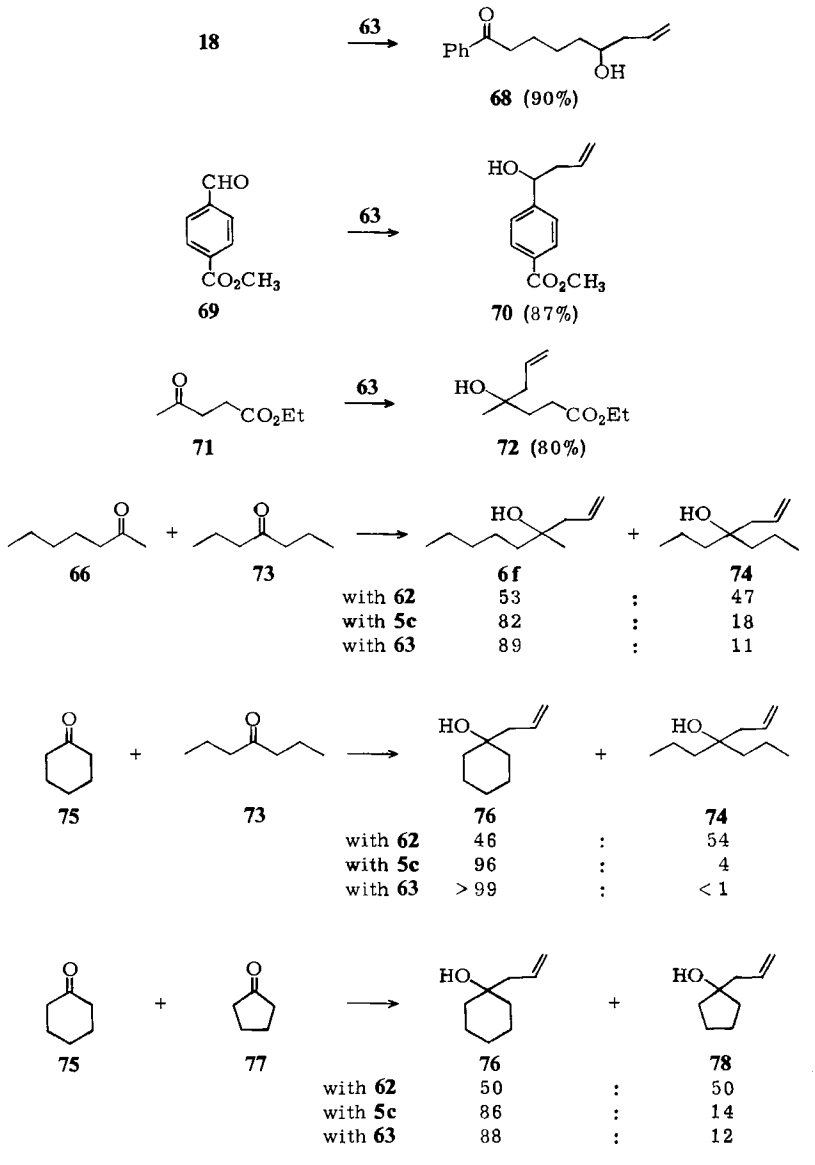
with **62**	29	:	71
with **63**	98	:	2
with **64**	2	:	98

The reaction of the amino ate complex **64** turned out to be a surprise, since essentially complete *reversal of chemoselectivity* was observed for **65**/**66** and other aldehyde/ketone pairs[35]. A reasonable explanation is the chemoselective transfer of an amino ligand onto the aldehyde, which is thus protected in the form of **67**. The allyl group then adds to the only available carbonyl function. Aqueous workup thus affords the ketone adduct and regenerates the aldehyde. This interesting behavior could not be extended to other alkyl ate complexes $RTi(NMe_2)_4MgX$[20]. However, a related and general procedure has been developed in which neutral titanium amides $Ti(NR_2)_4$ are used as *in situ* protecting reagents followed by the addition of conventional reagents such as RMgX, RLi, or enolates to the unprotected carbonyl function[36]. In a formal sense, this one-pot procedure allows for ketone-selectivity or addition at the more hindered site of diketones. In fact, even in case of allyl additions, it is sometimes more efficient than the use of **64**, e.g., in ketone/ketone discrimination. For this reason only a limited number of experiments employing **64** were performed.



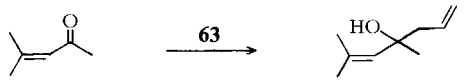
67

The results of the competition experiments using the alkoxy ate complex **63** suggested that it should behave chemoselectively in case of difunctional substrates. Indeed, this was observed for the keto-aldehyde **18** as well as for **69** and **71**. It should be noted that $H_2C=CHCH_2MgCl$ itself delivers mixtures[5]. Furthermore, even ketone/ketone discrimination is possible, as evidenced by several competition experiments.



Alkoxy ate complexes such as $CH_3Ti(OCHMe_2)_4MgCl$ or $CH_3Ti(OCHMe_2)_4Li$ are also aldehyde-selective[11a,20], but the yields of addition products are often lower than those observed for **2**. Thus, in these cases the usual titanation reagent **1** is to be preferred.

The question of 1,2- versus 1,4-addition in case of α,β-unsaturated carbonyl compounds was settled by reacting the alkoxy ate complex **63** with mesityl oxide (**79**). Only the 1,2-adduct **80** was detected (84% yield).



79 **80**

Comparison with other Metals

All presently available data show that titanation of numerous classical carbanions tempers reactivity and basicity considerably, producing "well behaved" reagents[11]. Further advantages pertain to the ready availability of the titanating agent **1** from cheap materials and to the non-toxic nature of the titanium species formed during aqueous workup (ultimately TiO_2). Previously, such indiscriminate reagents as RMgX and RLi had been converted into zinc or cadmium analogs in order to perform ketone syntheses from carboxylic acid chlorides[37]. However, RZnX and RCdX (or the dialkyl compounds) generally do not react smoothly with aldehydes or ketones, so that adjustment of chemoselectivity as described in this paper is not feasible using these metals. Manganese reagents likewise convert carboxylic acid chlorides into ketones[38]. They also react with aldehydes faster than with ketones, although the scope of this methodology remains to be established[39]. In competition experiments employing aldehyde/ketone pairs, the BF_3 mediated addition of allyltri-*n*-butyltin turned out to be only slightly aldehyde selective ($\approx$ 70 : 30 product mixtures)[40]. Recently, several methyl transition metal compounds (Cr, Mo, Ta, Nb) have been added chemoselectively to aldehydes, although a large excess is usually required[41]. Several alkylzirconium reagents have been added to carbonyl compounds[10b,42]; generally they appear to be somewhat less chemoselective than the titanium analogs[11a]. However, branched alkyl derivatives can be synthesized and reacted with aldehydes[42]. Allylboron reagents add readily to aldehydes, but sluggishly to ketones, a property which makes chemoselective transfer possible[43]. This cannot be generalized because alkyl- or arylboron compounds do not add to aldehydes. Although certain cuprates appear to react smoothly with aldehydes[44], competition experiments in other cases have shown that mixtures of aldehyde/ketone adducts are produced[45]. However, they react with α,β-unsaturated carbonyl compounds solely in a 1,4-manner, which underlines the complementary nature of the organometallic reagents in organic synthesis[46].

We thank the *Fonds der Chemischen Industrie* and the *Deutsche Forschungsgemeinschaft* for support of this work.

Experimental Part

All operations were carried out under dry nitrogen in flame-dried flasks. Melting and boiling points are uncorrected. Diethyl ether and tetrahydrofuran were dried by distillation from sodium hydride and kept over molecular sieves (4 Å). Dichloromethane was distilled from P_2O_5 and then passed through a column of basic Al_2O_3 (Woelm Super I). Pentane was also passed through a similar Al_2O_3 column. – ^1H NMR spectra: Varian T-60, Bruker WH 400. – ^{13}C NMR spectra: Varian CFT-20 and XL 100. – IR spectra: Perkin-Elmer 457. – MS: Varian CA 7. – GC: Perkin-Elmer EM 960 (capillary column, carbowax) coupled with an electronic integrator. –

Elemental analyses: Analytic Department of the Fachbereich Chemie (Marburg) and Mikroanalytische Laboratorium Beller (Göttingen).

Chlorotriisopropoxytitanium (**1**): The original procedure[10b,47] was modified slightly as follows: A 1 l three-necked flask equipped with a dropping funnel, magnetic stirrer and nitrogen inlet is charged with 213 g (0.75 mol) of tetraisopropoxytitanium. Titanium chloride (47.5 g, 0.25 mol) is then slowly added at about 0°C. After reaching room temp. the mixture is distilled (61 – 65°C/0.1 Torr) to afford 247 g (95%) of **1**. The syrupy liquid is >98% pure and slowly solidifies at room temperature. Gentle warming with a heat gun results in liquid formation. Thus, manipulation with a syringe and serum cap presents no problems. Alternatively, the product can be mixed with the proper solvent (e.g., pentane, toluene, ether, THF, CH_2Cl_2, etc.) to provide stock solutions. The reagent is hydroscopic, but can be stored in pure form or in solution under nitrogen for months. The actual synthesis can also be performed in solvents, as has already been described[47].

Triisopropoxymethyltitanium (**2**)

Method A: The procedure of *Clauss*[48] has been modified slightly as follows: A 2 l three-necked flask equipped with a dropping funnel and magnetic stirrer is charged with 250 ml of ether and 130.3 g (0.50 mol) of **1** and cooled to –40°C. The equivalent amount of methyllithium (e.g., 312.5 ml of a 1.6 M ether solution) is slowly added and the solution allowed to come to room temp. within 1.5 h. The solvent is removed *in vacuo* and the yellow product distilled directly from the precipitated lithium chloride at 48 – 53°C/0.01 Torr: 113 g (94%). – ^{1}H-NMR (CCl_4): δ = 0.5 (s, 3H), 1.3 (d, 18H), 4.5 (m, 3H). – The compound is air sensitive, but can be kept under nitrogen in a refrigerator for weeks or months. Upon standing slow crystallization begins, which can be reversed by gentle warming with a heat gun. Stock solutions can be prepared by mixing with the desired solvent.

Method B: The above procedure is applied on a smaller scale (10 – 100 mmol, as needed for immediate use), but the ether solution of **2** containing precipitated lithium chloride is used for carbonyl additions without any further treatment or purification.

Method C: In a 1 l three-necked flask (dropping funnel, magnetic stirrer) the solution of 85.2 g (0.30 mol) of tetraisopropoxytitanium in 200 ml of ether is treated with 18.9 g (0.10 mol) of titanium chloride at 0°C. The solution is stirred at room temp. for 1.5 h and is then cooled to about –30°C. Methyllithium (0.40 mol) is added and the solution stirred for 1 h, during which room temp. is allowed to be reached. Workup as in Method A affords 87 g (90%) of **2**.

General Procedure for the Addition of Triisopropoxymethyltitanium (**2**) *to Carbonyl Compounds:* In a 100 ml flask the solution of 10 mmol of an aldehyde or ketone in 30 ml of ether (or dichloromethane) is treated with 2.9 g (12 mmol) of **2**. The reaction temperatures and times are given in Table 1. Generally (as in case of the other aldehydes studied), the temp. of 0°C and a reaction time of about 1 h is sufficient; sometimes it is beneficial to let the flask reach room temperature. In case of ketones, room temp. and reaction times of 6 – 72 h are necessary, and an excess of **2** may be useful (e.g., 70% excess in case of sterically hindered **49**) or a reaction mode without any solvent. The mixture is poured onto 60 ml of a saturated NH_4F solution*), the aqueous phase extracted with ether, and the combined organic phases dried over $MgSO_4$. The solvent is removed and the residue distilled (e.g., with a Kugelrohr) or crystallized. Most of the alcohols are common compounds which were identified by comparison (e.g., ^{1}H-NMR spectroscopy) with authentic samples.

*) This type of workup generally prevents formation of thick, hard-to-handle TiO_2-containing precipitates. The organic phase may in fact be slightly cloudy and should not be shaken excessively long with the NH_4F/water phase. Often workup using dil. HCl works just as well.

The isolation method is specified for the less common compounds: **4f**[49] (Kugelrohr distillation 100°C/14 Torr), **4g**[50] (Kugelrohr distillation 105–110°C/20 Torr), **21a**[51] (Kugelrohr distillation 125–130°C/1 Torr), **21b**[52] (Kugelrohr distillation 115°C/1 Torr), **21c**[53] (Kugelrohr distillation 130–135°C/15 Torr), **21d**[54] (recrystallization from ethanol: m.p. 136–138°C; lit.[54] 138–139°C), **27**[50] (Kugelrohr distillation 125°C/20 Torr), **33**[55] (short path distillation 80–82°C/12 Torr), **36**[56] (short path distillation at 80°C/12 Torr directly from the reaction mixture without prior aqueous workup).

6-Hydroxy-1-phenyl-1-heptanone (**19a**): The solution of 1.9 g (10 mmol) of 6-oxo-6-phenylhexanal (**18**) in 40 ml of THF is treated with 2.4 g (10 mmol) of distilled **2** at −78°C. The cooling bath is removed and stirring continued for 6 h. The reaction mixture is poured on dil. HCl, ether is added and the aqueous phase extracted with ether. The combined organic phases are washed with water and dried over $MgSO_4$. The solvent is removed and the residue distilled in a Kugelrohr (220°C/0.02 Torr): 1.65 (80%). – ^{1}H-NMR (CCl_4): δ = 1.0 (d, 3H), 1.1–1.9 (m, 6H), 2.8 (t, 2H), 3.2–3.8 (m, 2H), 6.9–7.5 (m, 3H), 7.6–8.0 (m, 2H). – ^{13}C-NMR ($CDCl_3$): δ = 23.2, 23.9, 25.2, 38.2, 38.7, 67.3, 127.8, 128.3, 132.7, 136.7, 200.3. – MS: *m/e* = 206 (4%), 188 (57), 105 (100), 77 (42).

$C_{13}H_{18}O_2$ (206.3) Calcd. C 75.69 H 8.80 Found C 75.92 H 8.67

5-(Acetoxymethyl)-α-methyl-2-furanmethanol (**23**): Isolated by Kugelrohr distillation (135°C/0.1 Torr). – ^{1}H-NMR ($CDCl_3$): δ = 1.45 (d, 3H), 1.95 (s, 3H), 3.1 (broad s, 1H), 4.65 (q, 1H), 4.8 (s, 2H), 6.0 (d, 1H), 6.2 (d, 1H). – ^{13}C-NMR ($CDCl_3$): δ = 20.5, 21.0, 58.0, 63.1, 105.7, 111.1, 148.3, 158.5, 186.1. – IR (film): 3520–3250, 2960, 2930, 1700, 1670, 1220 cm^{-1}.

$C_9H_{12}O_4$ (184.2) Calcd. C 58.69 H 6.57 Found C 58.33 H 6.52

5-Bromo-α-methyl-2-thiophenemethanol (**25**): Isolated by Kugelrohr distillation (115°C/2 Torr). – ^{1}H-NMR ($CDCl_3$): δ = 1.6 (d, 3H), 3.8 (broad s, 1H), 5.1 (q, 1H), 6.9 (d, 1H), 7.1 (d, 1H). – ^{13}C-NMR ($CDCl_3$): δ = 24.7, 65.9, 110.8, 124.1, 129.1, 151.3. – IR (film): 3400–3300, 2980, 1430, 1370, 1060 cm^{-1}.

C_6H_7BrOS (207.1) Calcd. C 34.80 H 3.41 Found C 35.32 H 3.29

1-Acetyl-α-methyl-3-indolemethanol (**29**): Isolation by crystallization from CH_2Cl_2; m.p. 98°C. – ^{1}H-NMR ($CDCl_3$): δ = 1.6 (d, 3H), 2.3 (s, 3H), 3.0 (s, 1H), 5.0 (q, 1H), 7.2–7.6 (m, 3H), 7.9 (m, 1H), 8.7 (m, 1H). – ^{13}C-NMR ($CDCl_3$): δ = 23.5, 63.5, 116.5, 129.6, 120.9, 123.4, 125.1, 127.2, 128.5, 136.0, 168.8. – IR (KBr): 3500, 3120, 2980, 2930, 2870, 1810, 1680, 1600, 1590, 1450, 1390, 1370, 1350, 1230 cm^{-1}.

$C_{12}H_{13}NO_2$ (203.2) Calcd. C 70.62 H 6.45 N 6.89 Found C 70.34 H 6.30 N 6.61

5,6-Dihydro-α-methyl-2H-pyran-3-methanol (**31**): Isolated by Kugelrohr distillation (150°C/1.5 Torr). – ^{1}H-NMR ($CDCl_3$): δ = 1.3 (d, 3H), 2.0–2.4 (m, 2H), 3.5 (broad s, 1H), 3.7 (t, 2H), 4.1 (m, 3H), 5.7–5.9 (m, 1H). – ^{13}C-NMR ($CDCl_3$): δ = 21.4, 24.5, 64.0, 64.6, 68.5, 117.8, 140.5. – IR (film): 3460–3320, 2970–2850, 1650, 1110 cm^{-1}.

$C_7H_{12}O_2$ (128.2) Calcd. C 65.60 H 9.44 Found C 65.37 H 9.72

1,3-Dihydro-3-methyl-1-isobenzofuranol (**39**): Isolation by Kugelrohr distillation (150°C/1 Torr). – ^{1}H-NMR ($CDCl_3$): δ = 1.3 (s), 1.4 (s), 4.8–5.5 (m), 6.3 (broad s), 7.0–7.5 (m), integrals not specified because compound is mixture of diastereomers. – IR (film): 3550–3180, 2970, 2920–2860, 1420, 1345 cm^{-1}.

$C_9H_{10}O_2$ (150.2) Calcd. C 71.98 H 6.71 Found C 71.85 H 6.54

General Procedure for the Preparation and in situ Addition of Alkyltitanium Reagents: In a 100 ml flask a solution of 3.2 g (12 mmol) of **1** in 40 ml of ether is treated with 12 mmol of an

alkyllithium (e.g., ethyl-, *n*-butyl-, cyclopropyl-, or trimethylsilyllithium) at −30°C. The temp. is allowed to come to about −10°C (≈0.5 h) and the mixture treated with 10 mmol of an aldehyde. The reaction time and temp. are chosen as indicated in Table 2. In case of allyl addition, allylmagnesium chloride in THF is added to **1** at −30°C followed by treatment with an aldehyde or ketone as summarized in Table 2; workup as above. In case of phenyl addition, titanation is performed in THF using phenyllithium and **1**; during workup ether is added for better separation of the phases. The isolation method is specified for the less common compounds: **6g**[57] (Kugelrohr distillation 90°C/14 Torr), **6j**[58] (Kugelrohr distillation 85°C/0.2 Torr).

Titanation and Reaction of CH-Acidic Compounds: Standard techniques employing *n*-butyllithium or lithium diisopropylamide (LDA) are used to lithiate CH-acidic compounds[1]. For example, the solution of 0.82 g (20 mmol) of acetonitrile (**7**) in 50 ml of THF is treated with 11 ml of a 1.8 n *n*-butyllithium solution at −78°C. After 1 h, 0.52 g (20 mmol) of **1** is added and the mixture is stirred for about 45 min at the same temperature. In case of the sulfone **13**, *n*-butyllithium is added slowly at 0°C. Stirring is continued for 30 min, the solution cooled to −78°C followed by treatment with **1**; the temp. is then allowed to reach −40°C. Ethyl acetate (**9**) is lithiated in THF using LDA at −78°C; titanation with **1** occurs rapidly (0.5 h) at the same temperature. Carbonyl additions are performed under the conditions stated in Table 2. In all cases a 10% excess of titanium reagent is used. Standard workup employing aqueous NH_4F leads to the yields given in Table 2. The isolation method is specified for the less common compounds: **6k**[59] (Kugelrohr distillation 120−125°C/0.1 Torr), **6l**[60] (Kugelrohr distillation 130°C/0.1 Torr), **6m**[61] (Kugelrohr distillation 110°C/0.1 Torr), **6o**[62] (recrystallization from CCl_4; m.p. 90−92°C; lit.[62] 92−94°C).

2-Phenyl-1-(phenylsulfonyl)-2-propanol (**6q**): Recrystallization from CCl_4; m.p. 96°C. − ^{1}H-NMR ($CDCl_3$): δ = 1.7 (s, 3H), 3.7 (d, 2H), 3.9 (s, 1H), 7.2−7.6 (m, 10H). − IR (KBr): 3540, 3065, 2980, 1450, 1310, 1255, 1085 cm^{-1}.

$C_{15}H_{16}O_3S$ (276.4) Calcd. C 65.19 H 5.84 Found C 65.13 H 5.64

1-(Phenylsulfonyl)-2-pentanol (**6p**): Isolation by filtering through a short silica gel column (CCl_4). − ^{1}H-NMR ($CDCl_3$): δ = 0.7−1.4 (m, 7H), 3.1−3.2 (m, 2H), 3.3 (d, 1H), 4.1 (m, 1H), 7.5−7.9 (m, 5H). − IR (film): 3540, 3020, 2990, 2940, 1470, 1325, 1160, 1100 cm^{-1}.

$C_{11}H_{16}O_3S$ (228.3) Calcd. C 57.87 H 7.06 Found C 58.09 H 7.07

1-[(Phenylsulfonyl)methyl]cyclohexanol (**6r**): Isolation by filtering through a short silica gel column (CCl_4). − ^{1}H-NMR ($CDCl_3$): δ = 1.5−1.8 (m, 10H), 3.2 (s, 1H), 3.3 (s, 2H), 7.6−8.1 (m, 5H). − IR (film): 3570, 2980, 2900, 1460, 1320, 1160, 1095 cm^{-1}.

$C_{13}H_{18}O_3S$ (254.4) Calcd. C 61.39 H 7.13 Found C 61.05 H 7.37

Ethyl 3-Hydroxy-8-phenyl-8-oxooctanoate (**19b**): Ethyl acetate (**9**) (0.44 g, 5.0 mmol) is lithiated and titanated in 20 ml of THF as described above. The solution is added to 6-oxo-6-phenylhexanal (**18**) (1.1 g, 5.7 mmol) in 20 ml of THF at −78°C. After 1 h the mixture is poured on dil. HCl, ether is added and the phases are separated. The aqueous phase is extracted twice with ether and the combined organic phases dried over $MgSO_4$. After stripping off the solvent, the residue is distilled in a Kugelrohr (240°C/0.05 Torr) to afford 1.03 g (74%) **19b**. − ^{1}H-NMR ($CDCl_3$): δ = 1.3 (t, 3H), 1.4−1.9 (m, 6H), 2.4−2.47 (dd, 2H), 3.0 (t, 2H), 3.2 (broad s, 1H), 4.0 (m, 1H), 4.2 (q, 2H), 7.3−7.6 (m, 3H), 7.9−8.0 (m, 2H). − ^{13}C-NMR ($CDCl_3$): δ = 14.1, 23.9, 25.1, 36.2, 38.2, 41.3, 60.6, 67.7, 127.9, 128.5, 132.9, 136.9, 172.9, 200.2.

$C_{16}H_{22}O_4$ (278.4) Calcd. C 69.04 H 7.97 Found C 69.05 H 8.09

6-Hydroxy-1-phenyl-7-(phenylsulfonyl)heptanone (**19c**): The sulfone **13** (0.47 g, 3.0 mmol) is titanated in 20 ml of THF as described above. The solution is added to 0.57 g (3.0 mmol) of

6-oxo-6-phenylhexanal (**18**) in 20 ml of THF at −78 °C. After thawing and stirring at room temp. for 1 h, 100 ml of ether is added and the mixture poured on dil. HCl. The aqueous phase is extracted twice with ether, the combined organic phases washed with water and dried over Na_2SO_4. After removal of the solvent the residue is filtered through a short silica gel column (CCl_4) to afford 0.95 g (91%) of **19c**. – ^{1}H-NMR ($CDCl_3$): δ = 1.4 – 1.8 (m, 8H), 2.9 – 3.3 (m, 3H), 4.2 (m, 1H), 7.1 – 8.0 (m, 10H). – IR (film): 3550, 2980, 1700, 1465, 1320, 1160, 1090 cm^{-1}.

$C_{19}H_{22}O_4S$ (346.5) Calcd. C 65.87 H 6.40 Found C 65.20 H 6.35

Ketone Addition Reactions using Diisopropoxydimethyltitanium (**46**)

Dichlorodiisopropoxytitanium (**45**)[28,29,63]: The solution of 71 g (0.25 mol) of tetraisopropoxytitanium in 350 ml of ether is treated with 47.5 g (0.25 mol) of titanium chloride at 0 °C. After stirring for 1 h, ether is added to a total volume of 1 l. This solution of **45** is 1 M and is kept in the refrigerator under nitrogen.

Preparation and in situ Reaction of **46**[48]: 20 ml (20 mmol) of the above solution of **45** is treated with 40 mmol of methyllithium at −30 °C. After 10 min conversion to **46** is complete, and a ketone (20 mmol) is added. (**46** can be isolated[3], but this is not necessary for ketone additions.) After stirring at room temp. for 2 – 4 h, the usual workup using saturated NH_4F affords the Grignard-type adducts.

2-Methyl-5-nitro-2-pentanol (**41**)[64]: Isolation by Kugelrohr distillation 100 °C/0.1 Torr (78%). – ^{1}H-NMR (CCl_4): δ = 1.2 (s, 6H), 1.3 – 2.0 (m, 4H), 4.3 (t, 2H).

2-Hydroxy-2-methylcyclohexanepropanenitrile (**48**): Isolation by Kugelrohr distillation 100 °C/0.1 Torr (90%). – ^{1}H-NMR (CCl_4): δ = 1.3 (s, 3H), 1.5 (m, 12H), 2.3 (t, 2H). – ^{13}C-NMR ($CDCl_3$): δ = 15.0, 21.4, 24.9, 25.1, 26.1, 28.4, 39.9, 44.1, 70.7, 119.9. – IR (film): 3490, 2930, 2860, 2245 cm^{-1}.

$C_{10}H_{17}NO$ (167.2) Calcd. C 71.82 H 10.24 N 8.37 Found C 71.81 H 10.12 N 8.29

3-O-Acetyl-20-methyl-5-pregnene-3β,20-diol (**50**)[64]: Isolated by recrystallization from ethanol (82%); m.p. 148 – 149 °C (lit.[64] 142 – 151 °C).

Carbonyl Addition Reactions using Tetramethylzirconium (**52**): The suspension of 2.33 g (10 mmol) of dry zirconium chloride in 60 ml of ether is treated with 40 mmol of methyllithium (e.g., 25 ml of a 1.6 M solution) at −78 °C[65]. The stirred suspension is warmed to −30 °C during 2 h. 1.62 g (10 mmol) of the ketone **53** is added and the mixture stirred for 2 h at −20 °C. The same procedure is employed for **56** (0.88 g, 10 mmol; in this case three methyl groups of $ZrCl_4$ are utilized). The mixtures are poured on dilute HCl, the aqueous phase is extracted with ether and the combined organic phases washed with water and dried over $MgSO_4$. In case of **53**, ^{1}H NMR spectrum of the crude product shows the presence of 45% of **54**; crystallization from pet.-ether (60 – 90 °C) affords 516 mg (29%) of **54**. In case of **56**, the crude product is Kugelrohr distilled (85 – 90 °C/15 Torr) to yield 950 mg (72%) of **57**.

α,α,2,4,6-Pentamethylbenzenemethanol (2-Mesityl-2-propanol) (**54**)[66]: m.p. 109 – 111 °C (pet.-ether 60 – 90 °C). – ^{1}H-NMR ($CDCl_3$): δ = 1.6 (s, 6H), 1.7 (broad s, 1H), 2.1 (s, 3H), 2.4 (s, 6H), 6.7 (s, 2H).

2,4-Dimethyl-2,4-pentanediol (**57**)[67]: ^{1}H-NMR ($CDCl_3$): δ = 1.2 (s, 12H), 1.6 (s, 2H), 3.8 (broad s, 2H).

Reactions of Alkyltris(diethylamino)titanium Reagents

N,N-Diethyl-1-phenylethylamin (**61**): The solution of 1.06 g (10 mmol) of benzaldehyde (**15**) in 50 ml of ether is treated with 2.81 g (10 mmol) of tris(diethylamino)methyltitanium (**58**) at room

temperature. After 3 h the mixture is poured on dil. HCl, the aqueous phase extracted with ether and the combined organic phases are washed with water. The ^{1}H NMR spectrum of the crude product shows ≈45% of **61**. Kugelrohr distillation (70°C/0.1 Torr) yields 365 mg (21%) of **61**[68]. – ^{1}H-NMR ($CDCl_3$): δ = 0.9 (t, 6H), 1.2 (d, 3H), 2.5 (q, 4H), 3.4 (q, 1H), 7.0 (s, 5H).

1-Phenyl-3-buten-1-ol (**6d**): Chlorotris(diethylamino)titanium[33] (3.0 g, 10 mmol) in 30 ml of ether is treated with 10 mmol of allylmagnesium chloride in THF at 0°C. After 30 min at room temp., the solution is cooled to –40°C and 1.06 g (10 mmol) of benzaldehyde (**15**) added. After 1 h the mixture is poured on dil. HCl, the aqueous phase extracted twice with ether, and the combined organic phases washed with water and dried over $MgSO_4$. After stripping off the solvent the residue is Kugelrohr distilled (130°C/12 Torr) to afford 1.2 g (82%) of **6d**[69].

β-Hydroxybenzenepropanenitrile (**6k**): Acetonitrile (0.82 g, 20 mmol) is lithiated as described above. 6.0 g (20 mmol) of chlorotris(diethylamino)titanium is added at –78°C and the mixture stirred for 1 h. At –50°C benzaldehyde (2.1 g, 20 mmol) is added. After 2 h the mixture is worked up as in the synthesis of **6d** (see above). Kugelrohr distillation (120–125°C/0.1 Torr) affords 2.2 g (73%) of **6k**[59].

Formation and Reaction of the Allyltitanium Ate Complex **63**: The solution of 18 mmol of allylmagnesium chloride in about 40 ml of THF is treated with 5.68 g (20 mmol) of tetraisopropoxytitanium at –78°C. The formation of the orange ate complex **63** is complete after 30 min. Addition of aldehydes or ketones under the conditions used in reactions of **5c** (Table 2) results in 85–90% conversion[5]. The reaction mixtures are poured on dil. HCl, ether is added, and the aqueous phase extracted three times with ether. The combined organic phases are washed with water and dried over $MgSO_4$. In case di- or polyfunctional molecules, the solution containing **63** should be added to the substrate (reversed reaction mode).

6-Hydroxy-1-phenyl-8-nonen-1-one (**68**): The stirred solution of 1.9 g (10 mmol) of 6-oxo-6-phenylhexanal (**18**) in 20 ml of THF is treated slowly with 10 mmol of the ate complex **63** (see above) at –78°C. After 1 h the cold mixture is worked up as described above. Kugelrohr distillation (180°C/0.02 Torr) affords 2.1 g (90%) of **68**. – ^{1}H-NMR (CCl_4): δ = 1.0–1.9 (m, 6H), 2.0 (m, 2H), 2.8 (t, 2H), 3.0–3.7 (m, 2H), 4.8–5.0 (m, 2H), 5.3–6.0 (m, 1H), 7.0–7.5 (m, 3H), 7.7–8.1 (m, 2H). – ^{13}C-NMR ($CDCl_3$): δ = 24.0, 25.2, 36.3, 38.3, 41.8, 70.3, 117.6, 127.8, 128.4, 132.8, 134.7, 136.7, 200.3. – MS: *m/e* = 191 (23%), 105 (100), 77 (90).

$C_{15}H_{20}O_2$ (232.3) Calcd. C 77.55 H 8.68 Found C 77.28 H 8.55

Methyl 4-(1-Hydroxy-3-butenyl)benzoate (**70**): The same procedure as in the synthesis of **68** is used. Starting from 10 mmol of **63** and 1.64 g (10 mmol) of **69**, 1.8 g (87%) of **70**[70] are obtained (Kugelrohr distillation 180°C/0.01 Torr).

Ethyl 4-Hydroxy-4-methyl-6-heptenoate (**72**): The same procedure as in the synthesis of **68** is used. Employing 18 mmol of **63** and 2.6 g (18 mmol) of ethyl levulinate (**71**) results in 2.7 g (80%) of **72** (Kugelrohr distillation 60–65°C/0.1 Torr). – ^{1}H-NMR (CCl_4): δ = 1.0 (s, 3H), 1.1 (t, 3H), 1.6 (m, 2H), 2.0–2.5 (m, 5H), 3.1 (q, 2H), 4.0 (m, 2H), 4.4–5.0 (m, 1H). – ^{13}C-NMR ($CDCl_3$): δ = 14.1, 26.2, 28.9, 35.9, 46.6, 60.4, 71.2, 118.7, 133.6, 174.3. – IR (film): 3480, 3075, 2980, 1740 cm^{-1}.

$C_{10}H_{18}O_3$ (186.3) Calcd. C 64.49 H 9.74 Found C 64.29 H 9.56

4,6-Dimethyl-1,5-heptadien-4-ol (**80**): To a solution of 10 mmol of **63** in THF is added 0.98 g (10 mmol) of mesityl oxide (**79**) at –78°C. After 2 h the usual workup affords crude **80** which contains no trace of a 1,4-adduct as shown by GC. Kugelrohr distillation leads to 1.16 g (84%) of **80**[71].

Competition Experiments

Reactions using Triisopropoxymethyltitanium (**2**): The mixture of 1.06 g (10 mmol) of benzaldehyde (**15**) and 1.20 g (10 mmol) of acetophenone (**16**) in 50 ml of ether is treated with 2.4 g (10 mmol) of **2** at −50°C. After 5 h the mixture is worked up using NH_4F as in other reactions of **2** (see above) and the crude product analyzed by GC. The GC chromatogram shows essentially only **4c** and unreacted **16**. Similar experiments using other aldehyde/ketone pairs also point to complete aldehyde-selectivity[11a].

Reactions using Allyltitanium Ate Complexes: A 1:1 mixture of two carbonyl compounds (10 mmol, respectively) in 40 ml of THF is treated with 9.5 mmol of the ate complex **63** (preparation see above) at −78°C. After 1 h the mixture is poured on dil. HCl and worked up in the usual way. The ratio of the two Grignard-type adducts in the crude product is determined by GC; anthentic samples are used for identification. Reactions involving the amino ate complex **64**, prepared by adding allylmagnesium chloride to tetrakis(dimethylamino)titanium[72] at −78°C (0.5 h), are carried out analogously. In all cases conversion to the alcohols is >95% based on **63** or **64**, as determined by ^1H NMR spectroscopy and GC.

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