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Stereoselective Addition of Organotitanium Reagents to Carbonyl Compounds

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Titanation of alkyllithium or -magnesium compounds using $ClTi(OR)_3$ results in reagents which show markedly increased diastereofacial selectivity (80 – 90%) in reactions with α-chiral aldehydes or ketones. Titanation is also the method of choice in Grignard-type additions to substituted cyclohexanones; $CH_3Ti(OCHMe_2)_3$ (**6a**) adds predominantly from the equatorial direction, while allyltitanium reagents **11b** and **12** show axial preference. Crotyltitanium compounds react with carbonyl compounds to afford primarily adducts having *anti*-configuration, a process which is of particular value in case of ketones (*anti/syn* ratios up to 99 : 1). Titanation of (trimethylsilyl)allyllithium (**48**) with $Ti(OCHMe_2)_4$ reverses regioselectivity in reactions with aldehydes and ketones, β-hydroxy silanes **50** being the only observed products. These have *anti*-configuration and can be converted either into *Z*- or *E*-dienes using the Peterson elimination under basic or acidic conditions, respectively.

Stereoselektive Addition von Organotitan-Agenzien an Carbonyl-Verbindungen

Titanierung von Alkyllithium- oder -magnesium-Verbindungen mittels $ClTi(OR)_3$ ergibt Reagenzien, die eine deutlich erhöhte Diastereoselektivität (80 – 90%) bei Reaktionen mit α-chiralen Aldehyden oder Ketonen zeigen. Titanierung ist auch die Methode der Wahl im Falle von Grignard-artigen Additionen an substituierte Cyclohexanone; $CH_3Ti(OCHMe_2)_3$ (**6a**) greift bevorzugt von der äquatorialen Seite an, während die Allyltitan-Reagenzien **11b** und **12** hauptsächlich axialen Angriff eingehen. Crotyltitan-Agenzien reagieren mit Carbonyl-Verbindungen unter bevorzugter Bildung von Addukten mit der *anti*-Konfiguration, eine besonders wertvolle Reaktion im Falle von Ketonen (*anti/syn*-Verhältnisse bis zu 99 : 1). Titanierung von (Trimethylsilyl)allyllithium (**48**) mit $Ti(OCHMe_2)_4$ kehrt die Regioselektivität bei Additionen an Aldehyde und Ketone um, denn die einzigen Produkte sind β-Hydroxysilane **50**. Sie haben die *anti*-Konfiguration und können mit Hilfe der Peterson-Eliminierung unter basischen bzw. sauren Bedingungen in *Z*- oder *E*-Diene übergeführt werden.

In the preceding paper[1] we showed that titanation of carbanions provides a simple means to increase chemoselectivity in reactions with carbonyl compounds[2,3]. The present communication deals with the control of stereoselectivity[2]. In particular, three types of diastereodifferentiation are considered: 1) Diastereofacial selectivity involving α-chiral carbonyl compounds (1,2-asymmetric induction). 2) Equatorial *versus* axial addition to cyclohexanones. 3) Simple diastereoselectivity[4] in the addition of substitut-

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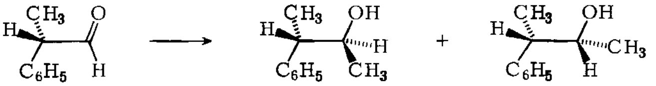
ed allyltitanium reagents to carbonyl compounds (union of two prochiral sp^2-hybridized carbon atoms).

Diastereofacial Selectivity

Since *Cram's* pioneering study concerning 1,2-asymmetric induction in the addition of Grignard and organolithium reagents to α-chiral carbonyl compounds[5], a number of additional reports have appeared[6]. In the absence of special effects such as steric conjestion or chelation, it is difficult to attain high levels of asymmetric induction. Thus, diastereomer ratios in the transfer of methyl, *n*-alkyl, or allyl groups to simple carbonyl compounds are generally not better than 3:1[6]. For example, CH_3MgX reacts with 2-phenylpropanal (**1**)*) to provide a 66:34 mixture of the *Cram* and anti-*Cram* products **2** and **3**, respectively[5,6]. Methyllithium (**4**) is slightly better (70:30 ratio)[7], but the use of more "mild" reagents such as CH_3CdX or CH_3ZnX fails to improve diastereoselectivity[8]. We were therefore pleased to discover that triisopropoxymethyltitanium (**6a**)[1] raises the **2**:**3** ratio to an unprecedented 89:11[9]. Solvent or temperature effects are not pronounced (Table 1). Reagents **7** and **8** having chlorine ligands are not quite as efficient[9] (Table 1). The highest degree of 1,2-asymmetric induction was observed in the reaction of methyltriphenoxytitanium (**6b**) (93:7 product ratio)[10]. It is less reactive than **6a**.



1 **2** **3**

$$CH_3Li + ClTi(OR)_3 \longrightarrow CH_3Ti(OR)_3 \qquad CH_3TiCl_3 \qquad (CH_3)_2TiCl_2$$

4   **5a** $R = CH(CH_3)_2$ **6a**   **7**   **8**

b $R = C_6H_5$ **b**

Table 1. 1,2-Asymmetric Induction in the Addition of Methyltitanium Reagents to **1**

Reagent	Solvent	Temp. (°C)	Reaction time (h)	Product ratio[a] **2**:**3**
6a[b]	ether	$-40 \rightarrow 0$	4	89:11
6a[c]	ether	$-40 \rightarrow 0$	4	89:11
6a[b]	THF	0	2	88:12
6b[d]	THF	$-50 \rightarrow 0$	8	$\boxed{93:\ 7}$
7[e]	CH_2Cl_2	−78	2	81:19
8[f]	CH_2Cl_2	−78	1	81:19
8[f]	CH_2Cl_2	−98	1	82:18

[a] Conversion in all cases >90%. – [b] Distilled reagent. – [c] Reagent prepared *in situ* from **5a** and methyllithium and used without separation from lithium salts. – [d] Reagent prepared *in situ* from **5b** and methyllithium and used without separation from lithium salts. – [e] Reagent prepared from $(CH_3)_2Zn$ and $TiCl_4$ (1:2 ratio) and used *in situ*. – [f] Reagent prepared from $(CH_3)_2Zn$ and $TiCl_4$ (1:1 ratio) and used *in situ*.

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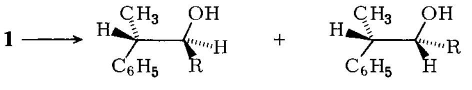
*) Here and in case of **13** one enantiomeric form is arbitrarily shown, although a racemate was used. The products are thus also racemates.

Aldehyde **1** was also reacted with *n*-butyl-[11], allyl-[12], and phenyltitanium[9] reagents **11**, **12**. Although systematic optimization involving variation of ligands was not carried out, titanation of RLi or RMgX increases 1,2-asymmetric induction, the phenyl reagent **11c** being the only exception (Table 2). In all cases the results are in line with the *Cram*[5,6] or *Felkin-Anh*[13] open-chain model.



9a-c **10a-c**

	R
a	n-C_4H_9
b	$H_2C{=}CHCH_2$
c	C_6H_5

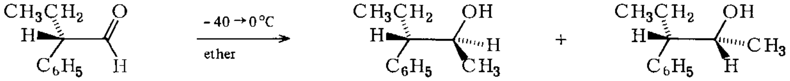
$RTi(OCHMe_2)_3$ **11a-c**

$H_2C{=}CHCH_2Ti(NEt_2)_3$ **12**

Table 2. 1,2-Asymmetric Induction in the Addition of Organotitanium Reagents to **1**

Reagent	Solvent	Temp. (°C)	Reaction time (h)	Product	Conversion (%)	Product ratio **9**:**10**
11a	ether	−30→ +22	8	**9a/10a**	≈75	88:12
11b	THF	−78	2	**9b/10b**	>95	68:32
11c	THF	−20	1	**9c/10c**	>95	75:25
12	THF	−78	2	**9b/10b**	>95	89:11
12	pentane	−78	2	**9b/10b**	>95	89:11
12	pentane	−120	3	**9b/10b**	>90	93: 7

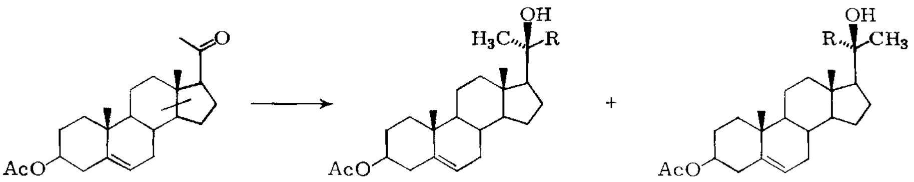
The reaction of triisopropoxymethyltitanium (**6a**) with 2-phenylbutanal (**13**) afforded a diastereomer ratio of **14**:**15** = 87:13, in contrast to CH_3MgI (70:30). Again, optimization was not attempted.



13 **14** **15**

	14		**15**
with **6a**	87	:	13
with CH_3MgI	70	:	30

Since the stereoselective introduction of steroidal side chains is of synthetic value, several reactions using pregnenolone acetate (**16**) as a model compound were carried out. Previously, **16** had been reacted with CD_3MgI to provide an 88:12 mixture of the (20*S*)- and (20*R*)-alcohol (**17a** and **18a**, respectively)[14]. Diastereofacial selectivity was increased considerably by the use of the deuterated titanium reagent **19**, since only a trace of the (20*R*)-alcohol **18a** was observed[11]. Improvement via titanation also resulted in case of allyl addition. The ^{13}C NMR spectrum of the reaction product **17b**/**18b** shows essentially only a single diastereomer. A clear limitation of organotitanium-chemistry has to do with the fact that the less reactive *n*-alkyl reagents do not add to such sterically hindered ketones as **16**[15].



16 **17a** **18a**

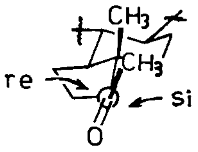
b **b**

R = CD_3

R = $H_2C{=}CHCH_2$

with CD_3MgI[14]	88	:	12
with $CD_3Ti(OCHMe_2)_3$ (**19**)	96	:	4
with  MgCl	83	:	17
with **11b**	>95	:	<5

The configurational assignment of the allyl adducts **17b**/**18b** is based on the comparison of their 400 MHz ^1H NMR spectra with those of the known CD_3-adducts **17a**/**18a**[14]. In both cases the methyl group at the carbinol function of the predominant (20*S*)-alcohol appears at lower field than that of the corresponding (20*R*)-alcohol. This assignment is also in line with the general preference for *si* attack at steroidal C^{20} ketones[6b,16]. Strict application of *Cram*'s model predicts a reacting conformation **20** in which the largest of the three groups at the α-chiral center occupies an *anti*-periplanar position relative to the carbonyl function. However, the generally accepted "D-ring conformation" **21** seems more likely[6b,14]. It corresponds to the *Felkin-Anh* model in which the largest α-substituent is perpendicular to the CO unit.



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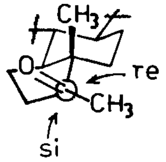

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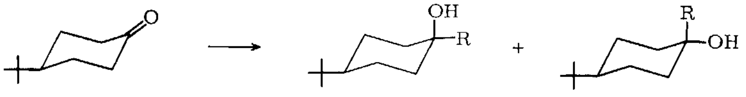
Diastereoselective Addition to Cyclohexanones

The question of axial or equatorial nucleophilic addition to cyclohexanones has been addressed in several hundred publications[17], conformationally locked 4-*tert*-butylcyclohexanone (**22**) traditionally serving as the standard substrate. Alkyl-organometallics such as RMgX or RLi generally undergo preferential equatorial attack because steric interaction of the incoming reagent with the 3,5-axial hydrogens is greater than torsional strain involving the 2,6-axial hydrogens[17]. Unfortunately, quite often the difference is not large enough, so that diastereoselectivity is low, e.g., CH_3MgI and CH_3Li deliver ≈2 : 1 ratios of **23a** and **24a**[17]. Dramatic improvements are observed if mixtures of two parts CH_3Li and one part $LiClO_4$ according to *Ashby*[18] or two parts CH_3Li and three parts $(CH_3)_2CuLi$ according to *Still*[19] are added to one part **22**. The **23a** : **24a** ratios then reach unprecedented values of 92 : 8 and 94 : 6, respectively. Nevertheless, it was of interest to test organotitanium reagents.



22

23a R = CH_3 **24a**

b R = $H_2C{=}CHCH_2$ **b**

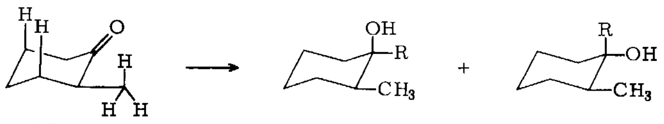
Whereas dichlorodimethyltitanium (**8**) affords an 82:18 ratio of **23a**:**24a**[9], $CH_3Ti(OCHMe_2)_3$ (**6a**) is better suited (Table 3). In ether at 0°C the diastereomer ratio is 89:11[20,21], and this can be improved to 94:6 by using hexane and slightly lower temperatures[22]. Thus, titanium chemistry is the cheapest and most efficient method currently known.

Table 3. Diastereoselective Addition to **22**

Reagent	Solvent	Temp. (°C)	Reaction time (h)	Product[a]	Product ratio 23:24
8[b]	CH_2Cl_2	−78	4	**23a**/**24a**	82:18
6a	CH_2Cl_2	+22	5	**23a**/**24a**	82:18
6a	ether	+22	5	**23a**/**24a**	86:14
6a	ether	0	24	**23a**/**24a**	89:11
6a	*n*-hexane	−15→+22	24	**23a**/**24a**[c]	94: 6
11b	THF	−78	2	**23b**/**24b**	43:57
12	pentane	−78	2	**23b**/**24b**	23:77
12	pentane	−120	3	**23b**/**24b**[d]	20:80

[a] Conversion >90% in all cases. – [b] Reagent prepared from $(CH_3)_2Zn$ and $TiCl_4$ (1:1 ratio) and used *in situ*. – [c] Yield of distilled product: 89%. – [d] Yield of distilled product: 85%.

The addition of allylmagnesium bromide to **22** is thought to proceed *via* six-membered cyclic transition states in which steric strain (axial attack) is slightly less than torsional strain (equatorial attack), the **23b**:**24b** ratio being 45:55[17]. Whereas **11b** is not much better (43:57 ratio at −78°C), the aminotitanium reagent **12** shows definite improvement (23:77 ratio at −78°C and 20:80 ratio at −120°C)[23].

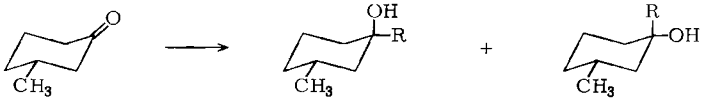


25 **26a-c** **27a-c**

	R
a	CH_3
b	C_6H_5
c	$H_2C{=}CHCH_2$

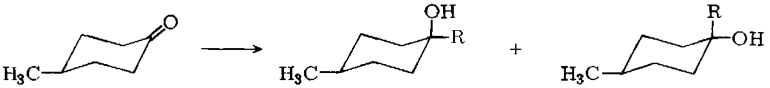
The pronounced tendency of organometallics to attack 2-methylcyclohexanone (**25**) (racemic **25** and **28** were used) from the equatorial direction has been ascribed to increased steric interaction of the pseudo-axial hydrogen of the methyl groups with the axially incoming nucleophiles[17]. Thus, CH_3Li, CH_3MgCl, and C_6H_5MgBr deliver **26**:**27** ratios of 88:12, 88:12, and 91:9, respectively[17]. This effect is even greater in case of the titanium reagents **6a** (**26a**:**27a** = 96:4) and **11c** (**26b**:**27b** = >99: <1). Here again, 2 $CH_3Li/LiClO_4$ and 2 $C_6H_5Li/LiClO_4$ are also highly diastereoselective (94:6 and 96:4 diastereomer ratios, respectively)[18], but require an excess of active methyl or phenyl groups in the reagents. Here, as before, the stereoselective introduction of allyl groups is more difficult. Allyltriisopropoxytitanium (**11b**) affords a 76:24 product ratio of **26c** and **27c**, respectively, which is identical to the performance of diallylmagnesium[24]. Salt-free diallylzinc, prepared from dimethylzinc and triallylboron, shows greater diastereoselectivity (89:11 ratio)[24].

In case of conformationally labile cyclohexanones **28** and **31**, the behavior of classical reagents is essentially stereo-random[17]. Therefore, the diastereoselectivities of 70 – 89% achieved by titanium reagents are indeed remarkable[15,23]. Optimization *via* variation of the ligands at titanium was not carried out, but could lead to further improvements.



28 **29a** R = CH_3 **30a**
b R = $H_2C{=}CHCH_2$ **b**

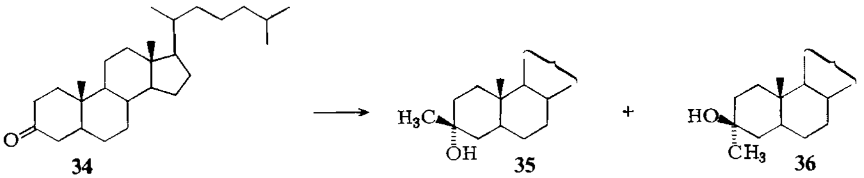
	29		30
with CH_3MgI[17]	54	:	46
with **6a**	89	:	11
with $(H_2C{=}CHCH_2)_2Mg$[24]	54	:	46
with **12**	31	:	69



31 **32a** R = CH_3 **33a**
b R = $H_2C{=}CHCH_2$ **b**

	32		33
with CH_3MgI[17]	52	:	48
with **6a**	88	:	12
with $(H_2C{=}CHCH_2)_2Mg$[24]	44	:	66
with **12**	27	:	73

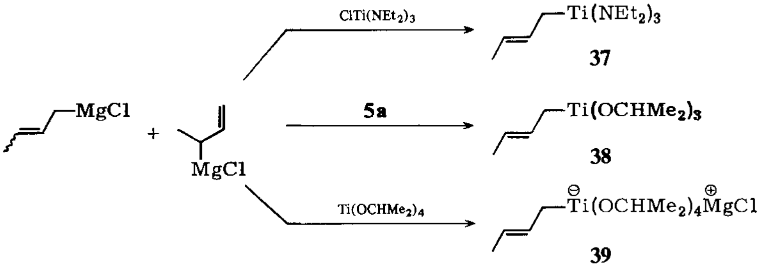
As a final example, we reacted cholestanone (**34**) with **6a**. The ratio of α- to β-alcohol (**35**:**36**) turned out to be 87:13, as determined by ^{13}C NMR spectroscopy. This is considerably better than the 56:44 product ratio obtained from the corresponding Grignard reaction[25].

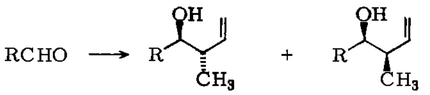


34 **35** **36**

Simple Diastereoselectivity

The idea that crotylmetal reagents can be used as enolate equivalents in the stereoselective construction of β-hydroxy-carbonyl compounds has been applied in numerous cases[26]. Generally, the stereochemical outcome (*anti*- or *syn*-adducts)*) depends upon the geometry of the crotylmetal reagent (*E*- or *Z*-configuration, respectively). High degrees of simple diastereoselectivity in reactions with aldehydes have been achieved, as in the reaction of *E*- and *Z*-crotylboron compounds[26,27]. Nevertheless, it was of interest to study substituted allylic titanium reagents, particularly in view of the fact that the problem of diastereoselective additon to *ketones* had not been solved. When we began our investigation, crotyltris(diethylamino)titanium (**37**) had already been described in the literature as a distillable compound, readily accessible from crotylmagnesium chloride (mixture of regio- and *Z*/*E*-isomers) and bromotris(diethylamino)titanium[28]. The product of this reaction was believed to be a mixture of regio- and *Z*/*E*-isomers. However, an analysis of the 400 MHz ^1H NMR spectrum shows the presence of essentially only one compound, either **37** or its *Z*-isomer[23]. Although the vicinal coupling constant of the olefinic protons (12.8 Hz) does not allow for an unambiguous assignment, the assumption of *E*-configuration seems plausible. Currently, no structural information is available concerning the non-distillable alkoxytitanium compounds **38** and **39**.





40a-f **41a-f** **42a-f**

	R
a	C_6H_5
b	n-C_6H_{13}
c	$(CH_3)_2CH$
d	C_2H_5
e	CH_3
f	c-C_6H_{11}

The addition of **37**–**39** to aldehydes proceeds almost quantitatively and with complete regioselectivity to afford *anti*- and *syn*-adducts **41** and **42**, respectively. (One enantiomeric form is shown arbitrarily; racemates are formed.) As shown in Table 4, simple diastereoselectivity varies somewhat according to the type of ligands at titanium, but *anti*-adducts predominate in all cases[23,29]. A general conclusion regarding the optimum ligand system cannot be made. For example, in case of an aromatic aldehyde such as benzaldehyde, the ate complex **39** is the reagent of choice, but in the aliphatic series the aminotitanium compound **37** is more selective. An independent study has

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*) Several other types of nomenclature have been suggested for these and for the related aldol adducts, but there seems to be a trend to accept the *anti*/*syn*-system[26].

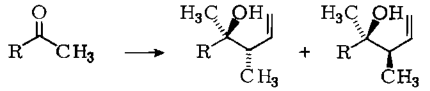
shown that crotyltriphenoxytitanium reacts with benzaldehyde to afford an 85:15 *anti/syn* ratio[30a]. Thus, in this case the more easily accessible ate complex **39** is certainly to be preferred; however, in other cases the triphenoxy ligand system is more selective. We have also observed that the *nature of the N-alkyl groups of aminotitanium reagents affects stereoselectivity.* Thus, the less bulky tris(di*methyl*amino) analog of **37** is less diastereoselective (**41b**:**42b** = 66:34)[23]. In conclusion, the readily available crotyltitanium reagents discussed here may be useful in certain cases, but a number of other crotylmetal reagents show distinctly higher degrees of diastereoselectivity[26], including halobis(cyclopentadienyl)titanium derivatives[31].

Table 4. Diastereoselective Addition of Crotyltitanium Reagents to Aldehydes

Reagent	Solvent	Temp. (°C)	Reaction time (h)	Product[a]	Product ratio
37	pentane	−120	3	**41a/42a**	69:31
38	THF	−78	2	**41a/42a**	80:20
39	THF	−78	2	**41a/42a**	84:16
37	pentane	−120	3	**41b/42b**	82:18
38	THF	−78	2	**41b/42b**	75:25
39	THF	−78	2	**41b/42b**	71:29
37	ether	−78	2	**41c/42c**	85:15
38	THF	−78	2	**41c/42c**	84:16
39	THF	−78	2	**41c/42c**	80:20
37	pentane	−120	3	**41d/42d**	85:15
37	pentane	−120	3	**41e/42e**	67:33
37	pentane	−120	3	**41f/42f**	88:12

[a] Conversion in all cases >90%.

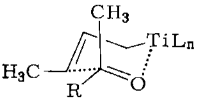
Real benefits of crotyltitanium reagents became apparent in reactions with *ketones.* Upon adding **37** to 3-methyl-2-butanone (**43a**), a 97:3 ratio of **44a**:**45a** was registered (>95% conversion)[32]. Several other ketones were also tested with **37**–**39** (Table 5). In case of acetophenone (**43d**), the ate complex **39** is best suited, but purely aliphatic ketones react most selectively with **37**. This is analogous to the trend observed in case of aromatic and aliphatic aldehydes. Crotyltriphenoxytitanium also adds stereoselectively to ketones, but offers no advantages regarding accessibility or degree of diastereoselectivity[30b]. It should be noted that the Grignard reagent is non-selective and that allylboron compounds react sluggishly or not at all with ketones[26].



43a-d **44a-d** **45a-d**

	R
a	$(CH_3)_2CH$
b	n-C_6H_{13}
c	$(CH_3)_3C$
d	C_6H_5

Since **44** and **45** lack vicinal hydrogens at the two chiral centers, the usual method of *anti/syn* assignment using ^1H NMR coupling constants cannot be applied here. In case of **44a** and **44d**, our assignments are made by comparison with authentic samples[30b, 33]. The tentative assignments of the other adducts are based on the assumption of analogous topology in the transition state. The traditional six-membered chair transition state[26] in which the smaller of the two groups of the carbonyl function (in our case methyl) occupies the pseudo-axial position, as in **46**, leads to the observed *anti*-adducts **44**[23]. The alternative chair transition state **47** has the more bulky group in the energetically unfavorable axial position and affords the minor *syn*-adduct **45**. Inspite of the plausibility of this interpretation, the high degree of simple diastereoselectivity is remarkable. The difference in size between the two groups of the ketone is not as large as that between the hydrogen atom and the alkyl (aryl) group in case of aldehydes, which react *less* selectively.



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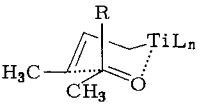

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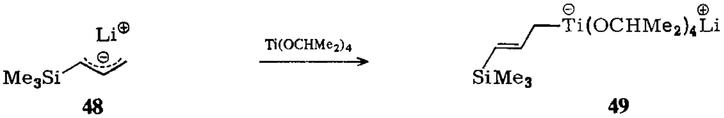
Table 5. Diastereoselective Addition of Crotyltitanium Reagents to Ketones

Reagent[a]	Temp. (°C)	Reaction time (h)	Product[b]	Product ratio
37	−78	2	**44a/45a**[c]	$\boxed{97:\ 3}$
38	−78	2	**44a/45a**	88:12
39	−78	2	**44a/45a**	78:12
37	−78	2	**44b/45b**[d]	$\boxed{72:28}$
38	−78	2	**44b/45b**	67:33
39	−78	2	**44b/45b**	56:44
37	−50	6	**44c/45c**[e]	$\boxed{99:\ 1}$
38	−50	6	**44c/45c**	90:10
39	−50	6	**44c/45c**	92: 8
37	−78	2	**44d/45d**	85:15
38	−78	2	**44d/45d**	83:17
39	−78	2	**44d/45d**	91: 9
39	−120	5	**44d/45d**[f]	$\boxed{94:\ 6}$

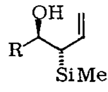
[a] All reactions in THF except addition of **39** to acetophenone at −120°C (mixture of THF and pentane). – [b] Conversion in all cases >90%. – [c] Isolated yield 90%. – [d] Isolated yield 85%. – [e] Isolated yield 73%. – [f] Isolated yield 85%.

Finally, we studied a system which poses problems relating to regio- and stereoselectivity, namely (trimethylsilyl)allyllithium (**48**). This ambident reagent is known to react with aldehydes and ketones regioselectively at the γ-position to afford δ-hydroxy vinylsilanes[34]. In order to reverse regioselectivity, the counter ion has been varied. Whereas MgX_2, ZnX_2, and CdX_2 have no appreciable effect, the presence of hexamethylphosphoramide in combination with $MgBr_2$ favors α-attack, although mixtures are obtained[35]. The first method to control clean α-attack is due to ***Matteson,*** who converted **48** into a boron compound (53% distilled yield)[36a]; addition to aldehydes provided *anti*-adducts **50** stereoselectively (≧97 : ≦3 diastereomer ratios). Later *Yamamoto* treated **48** with chlorodicyclopentylboron and also obtained **50** upon reaction with aldehydes[36b)]. We speculated that a simple one-pot procedure involving treatment of **48** with $Ti(OCHMe_2)_4$ followed by aldehyde addition could result in complete regio- and stereoselectivity. Indeed, this turned out to be the case[37)]. Only **50** is formed, which can be converted stereospecifically either into *Z*- or *E*-dienes using the *Peterson* elimination under basic or acidic conditions, respectively[36)]. Thus, the present methodology is more efficient than previous reactions starting from **48**. Titanation of **48** using **5a**[23)], $ClTi(NEt_2)_3$[23)], or $(\eta^5\text{-}C_5H_5)_2TiCl$[38)] results in species which also provide *anti*-adducts **50**; however, the cheap $Ti(OCHMe_2)_4$ is clearly the titanating agent of choice. Finally, **49** reacts chemoselectively with aldehydes in the presence of ketones, esters, or alkyl halides.



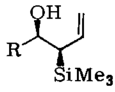
48

49



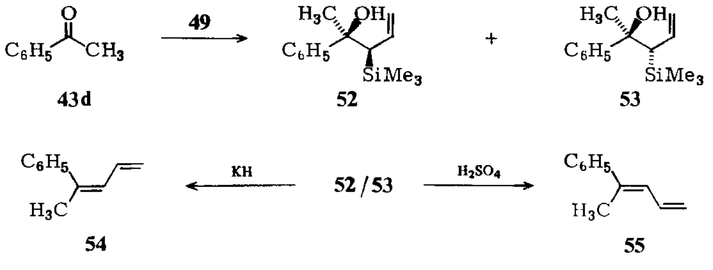
50

	R
a	C_6H_5
b	$n\text{-}C_6H_{13}$
c	$(CH_3)_2CH$



51

We also tested the reaction of **49** with acetophenone (**43d**). In this case a 91 : 9 ratio of *anti*- and *syn*-adducts (**52** and **53**, respectively) was observed[37)]. Treatment of the mixture **52**/**53** with KH or H_2SO_4 afforded **54** and **55**, respectively, the isomeric purity being > 90% in each case.



Conclusions

The present study shows that stereo- and regioselectivity of classical carbanions in reactions with carbonyl compounds can often be adjusted by prior titanation[2)]. Although isopropoxy ligands are cheap and have been used most often, other ligands such as amino or phenoxy groups are sometimes beneficial. Titanation using $Ti(OCHMe_2)_4$ affords ate complexes which are also synthetically useful, provided the carbanionic precursor is resonance stabilized; normal alkyl ate complexes are generally less efficient than the corresponding neutral triisopropoxy derivatives[39)]. Other than these comments, no general rules as to the optimum choice of ligands can be set up currently. This does not apply to diastereoselective addition to chiral α- or β-alkoxy carbonyl compounds which are capable of chelation. In these cases chloro ligands impart pronounced Lewis acidity upon titanium, which consequently allows for high degrees of chelation control[40]; in contrast, alkoxy or amino ligands reduce Lewis acidity drastically, making non-chelation control possible, i.e., the reversal of diastereofacial selectivity[40].

We have also applied the principle of variable adjustment of carbanion-selectivity via titanation[2,12] in other situations, e.g., in stereoselective aldol-type of additions involving *O*-titanated ketones[41], esters[2], and heterocycles[2] as well as *N*-titanated hydrazones and imines[42]. Recently, other authors have reported further examples[43].

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Experimental Part

The same general comments apply here as stated in the preceding publication[1]. Reagents **6a**, **11a–c**, and **12** were prepared as described[1]. **37** was synthesized by *Bürger*'s method[28] using chlorotris(diethylamino)titanium[44] (in place of the bromide). **38** and **39** were synthesized in complete analogy to the allyl analogs[1].

In all cases involving organotitanium reagents having isopropoxy, phenoxy, or diethylamino ligands, addition reactions were performed in the same manner as described in the preceding publication[1]. Chlorotriphenoxytitanium (**5b**) was prepared according to a known procedure[30a,c] and treated with methyllithium to produce **6b**, which was used *in situ*. Generally, a 5–10% excess of reagent was used (in case of steroids **16** and **34** a 70–100% excess). The diastereomer ratios were determined by capillary GC or ^{13}C NMR spectroscopy. Authentic samples described in the literature were used for identification where possible (**2/3**[5], **9a/10a**[45], **9c/10c**[5], **14/15**[5], **17a/18a**[14], **23a/24a**[17], **23b/24b**[17], **26a/27a**[17], **26b/27b**[17], **26c/27c**[24], **29a/30a**[17] **29b/30b**[24], **32a/33a**[17], **32b/33b**[24], **35/36**[25], **41a–e/42a–e**[27], **44a/45a**[33], **44d/45d**[30b], **50a–c**[36].

Addition Reactions using Trichloromethyltitanium (**7**) *and Dichlorodimethyltitanium* (**8**) *to Aldehyde* **1**: Solutions of **7** and **8** are prepared by mixing $(CH_3)_2Zn$ and $TiCl_4$ in dichloromethane as previously described[46]. In each case 10 mmol are treated with 1.34 g (10 mmol) of the aldehyde **1** under the conditions specified in Table 1. The reaction mixture is poured on dil. HCl, the aqueous phase extracted with CH_2Cl_2 and the combined organic phases are washed with water. After drying over $MgSO_4$, the solvent is stripped off and the crude product identified by ^{1}H NMR spectroscopy and GC using an authentic sample[5a] (Table 1).

2-Phenyl-5-hexen-3-ol (**9b/10b**): Isolated by short path distillation (115–116°C/12 Torr); yield 85%. – ^{1}H-NMR (CCl_4): δ = 1.1 (d), 1.2 (d), 1.9 (m), 2.5 (m), 2.6 (s), 3.5 (m), 4.5–5.0 (m), 5.3–6.0 (m), 7.2 (s). – ^{13}C-NMR ($CDCl_3$) of major isomer **9b**: δ = 16.3, 39.3, 45.3, 75.0, 117.8, 126.9, 127.7, 128.4, 135.0, 144.4. – MS: *m/e* = 176 (1%), 135 (13), 106 (100), 91 (46), 43 (11).

$C_{12}H_{16}O$ (176.3) Calcd. C 81.77 H 9.15 Found C 81.84 H 9.37

The configurational assignment is made by assuming *Cram*'s rule[5] and by hydrogenation of **9b/10b** to form the formal *n*-propyl adduct of **1**, which was compared to a sample made by reaction of *n*-propylmagnesium bromide with **1**[23].

3β-Acetoxy-20-[D$_3$]methyl-5-pregnen-20-ol (**17a/18a**): The solution of 1.09 g (4.2 mmol) of chlorotriisopropoxytitanium (**5a**) in 10 ml of ether is treated with 4.1 mmol of [D$_3$]methyllithium at −30°C. After stirring for 30 min, 1.0 g (2.8 mmol) of pregnenolone acetate (**16**) in 10 ml of ether is added. The mixture is stirred at room temp. for 48 h and poured on saturated NH_4F/water. The aqueous phase is extracted three times with ether, the combined organic phases are washed with water and dried over $MgSO_4$. Upon removing the ether, 0.95 g (91%) of white crystals are obtained having a m.p. of 142−143°C (lit.[14] 141−145°C). The 400 MHz ^1H NMR spectrum (CCl_4) shows the carbinol methyl group of **17a** to absorb at $\delta = 1.3$, in accord with the literature value[14]. At $\delta = 1.2$ the carbinol methyl peak of **18a** is known to appear, but in the crude product obtained here there is only a minute peak as part of the underground; integration leads to a **17a**: **18a** ratio of $>96:<4$.

3β-Acetoxy-20-allyl-5-pregnen-20-ol (**17b/18b**): The solution of 0.52 g (2.0 mmol) of **5a** in 10 ml of THF is treated with 2.0 mmol of allylmagnesium chloride in THF at −78°C. After 30 min pregnenolone acetate (**16**) (358 mg, 1.00 mmol) is added and the mixture stirred for 5 h at −78°C. The solution is poured on dil. HCl, ether is added and the aqueous phase extracted three times with ether. The combined organic phases are dried over $MgSO_4$ and the solvent evaporated. The ^{13}C NMR spectrum of the crude product shows essentially only one ($\geq 95\%$) diastereomer **17b**. The ^1H NMR spectrum shows the carbinol methyl group of **17b** to appear at $\delta = 1.28$; at $\delta = 1.14$ there is a minute peak which may be described to the methyl group at C-20 of **18b**. Integration (i.e., determination of isomer ratio) is not meaningful due to overlap with noise and other signals. Recrystallization from ethanol affords 240 mg (60%) of a white solid having a m.p. of 180−185°C. − ^{13}C-NMR ($CDCl_3$): δ = 13.5, 19.2, 20.8, 21.4, 22.3, 23.8, 26.6, 27.7, 31.2, 31.7, 36.5, 36.9, 38.0, 40.0, 42.6, 48.2, 49.9, 56.7, 57.9, 78.6, 118.1, 122.5, 134.4, 139.6, 170.5. − MS: *m/e* = 359 (19%), 340 (37), 299 (89), 43 (100). − IR (KBr): 3560, 2930, 1720, 1250 cm^{-1}.

$C_{26}H_{40}O_3$ (400.6) Calcd. C 77.95 H 10.06 Found C 78.00 H 10.20

1-Cyclohexyl-2-methyl-3-buten-1-ol (**41f/42f**): Isolated by Kugelrohr distillation (130°C/12 Torr): 77% of a colorless liquid consisting of 88% of **41f** and 12% of **42f**. The NMR data given here refer to the major component **41f**: ^1H-NMR ($CDCl_3$): δ = 1.0 (d, 3H), 1.0−2.5 (m, 13H), 3.0 (s, 1H), 4.8−5.0 (m, 2H), 5.2−6.0 (m, 1H). − ^{13}C-NMR ($CDCl_3$): δ = 17.0, 26.1, 26.5, 27.0, 30.0, 40.3, 40.5, 78.8, 116.1, 140.4. − MS: *m/e* = 113 (24%), 95 (100), 83 (11), 56 (31).

$C_{11}H_{20}O$ (168.3) Calcd. C 78.51 H 11.98 Found C 78.52 H 12.14

General Procedure for the Preparation and Reaction of the Ate Complex **49**: The mixture of 1.26 g (11 mmol) of allyltrimethylsilane and 1.16 g (10 mmol) of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) in 40 ml of THF is treated with 10 mmol of *tert*-butyllithium at −78°C[34]. The mixture is stirred at −30°C for 2 h. Upon re-cooling to −78°C, tetraisopropoxytitanium (3.12 g, 11 mmol) is added. After 1 h, 9.0 mmol of an aldehyde or ketone are added. Following a reaction time of 2 h (for aldehydes) or 6 h (for ketones), the 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 stripped off and the residue Kugelrohr distilled: **50a**[36] (120°C/0.01 Torr; 81%), **50c**[36] (50°C/0.01 Torr; 66%), **52/53**[35] (120°C/0.01 Torr; 75% yield).

3-(Trimethylsilyl)-1-decen-4-ol (**50b**): Isolated by Kugelrohr distillation (110°C/0.01 Torr); 78% yield. − ^1H-NMR ($CDCl_3$): δ = 0.04 (s, 9H), 0.87 (t, 3H), 1.2−1.5 (m, 11H), 1.66 (m, 1H), 3.8 (m, 1H), 4.89−5.04 (m, 2H), 5.73−5.83 (m, 1H). − ^{13}C-NMR ($CDCl_3$): δ = 2.0, 14.0, 22.6, 25.8, 29.3, 31.8, 37.3, 42.54, 71.54, 114.9, 135.9. − IR (film): 3440, 3070, 2940, 1625, 1245 cm^{-1}. − MS: *m/e* = 213 (1%), 143 (13), 138 (17), 73 (100), 54 (79).

$C_{13}H_{28}OS$ (228.5) Calcd. C 68.35 H 12.35 Found C 68.65 H 12.11

Peterson Elimination of **52/53**

cis-Elimination: To the suspension of 0.24 g (6.0 mmol) of potassium hydride[47] in 20 ml of THF is added the carbinol pair **52/53** (91 : 9 mixture; 1.17 g, 5.0 mmol) at room temperature. After 1 h the mixture is poured on ice water, ether is added and the aqueous phase extracted with ether. The combined organic phases are washed with water and dried over $MgSO_4$. After stripping off the solvent, the product is distilled in a Kugelrohr (130°C/12 Torr) to yield 580 mg (81%) of **54/55**[35]. GC and ^{13}C NMR spectroscopy show a **54** : **55** ratio of $>90 : <10$. – ^{13}C-NMR ($CDCl_3$) of the major isomer **54**: δ = 25.4, 115.9, 126.9, 127.9, 128.1, 128.2, 134.5, 139.2, 141.4.

trans-Elimination: To the mixture of 1.17 g (5.0 mmol) of the carbinol pair **52/53** (91 : 9 mixture) in 20 ml of THF are added 3–4 drops of conc. H_2SO_4[47]. After stirring for 1 h, the mixture is poured on saturated NH_4Cl solution, ether is added, and the aqueous phase extracted with ether. The combined organic phases are washed with water and dried over $MgSO_4$. Kugelrohr distillation (130°C/12 Torr) affords 590 mg (82%) of **54/55**[35]. GC and ^{13}C NMR spectroscopy show a **54** : **55** ratio of $<10 : >90$. – ^{13}C-NMR ($CDCl_3$) of the major isomer **55**: δ = 15.9, 117.5, 125.6, 127.1, 127.7, 128.7, 133.5, 136.6, 142.9.

Chemoselective Studies Involving the Ate Complex **49**: The ate complex **49**, prepared in THF as described above, is added to a 1 : 1 mixture of benzaldehyde and acetophenone at –78°C. After 1 h the mixture is worked up and the crude product analyzed by GC. Complete aldehyde-selectivity is observed (i.e., <1% of the ketone adduct **52/53** is present). Similar experiments utilizing 1 : 1 mixtures of benzaldehyde and ethyl acetate or benzaldehyde and 1-bromohexane also lead solely to the aldehyde adduct **50a**.

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