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SOME RECENT ADVANCES IN THE USE OF TITANIUM REAGENTS FOR ORGANIC SYNTHESIS

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Abstract A large variety of allylic triphenoxy-titanium reagents, generated by trans-metallation from the corresponding lithium or magnesium derivatives, add to aldehydes and unsymmetrical ketones at the more highly substituted allylic carbon atom to give two diastereomers, generally in a ratio of 3:1 to more than 50:1. Thus, tertiary homoallylic alcohols, and from them β-hydroxy-carboxylic acids of a given configuration are readily accessible (Table 1). - The products from titanium tetrachloride and methyl- or phenyl-isocyanide, which have the structure of trichlorotitanio-imidchlorides (9), add to aldehydes and ketones to give - after hydrolysis - α-hydroxy-carboxamides in high yields (Scheme 3). - A building block approach is described for the alkylative amination of aldehydes to chain-elongated amines (12). With non-enolizable aldehydes, a Li-amide is first added to the carbonyl group, followed by Li/$TiCl_3$ exchange with titanium tetrachloride and addition of two equivalents of an organolithium compound (Scheme 4). With enolizable aldehydes, dialkylamino-trichloro-titanium is first added to the carbonyl group, followed by replacement of Cl_3TiO by an R-group with alkyllithium (Scheme 5). - With the chiral organotitanium compounds bearing binaphtholate (25, 26) or tartaric acid-derived diolates (27, 28), phenyl groups can be transferred to aromatic aldehydes, and methyl groups to aromatic or aliphatic aldehydes with high enantioselectivity (Scheme 6 and Table 2).

A) Introduction

Since we have published two extensive review articles dealing very generally with this subject,[1,2] we will describe here only a few new results which were obtained most recently. Also, only investigations done in our own laboratory will be mentioned in the present paper.[3-5] The material may be divided into four groups: allylic triphenoxy-titanium reagents, trichlorotitanio imidchlorides (from isocyanides and tetrachlorotitanium) as reagents for Passerini-type reactions, alkylative aminations (Mannich-type reactions) with titanium derivatives, and asymmetric additions of chiral organotitanium derivatives to aliphatic and aromatic aldehydes.

B) Selective Allylations with Titanium Reagents

One of our first observations concerning organotitanium reagents was their selectivity in differentiating between functional groups. This is evident from Fig. 1, in which capillary gas chromatograms (CGC) are shown of the mixtures obtained upon addition of methyllithium, methylmagnesium bromide, and methyl-triisopropoxy-titanium to a 1:1-mixture of benzaldehyde and acetophenone. The addition of a crotyl-metal derivative to the same mixture of carbonyl

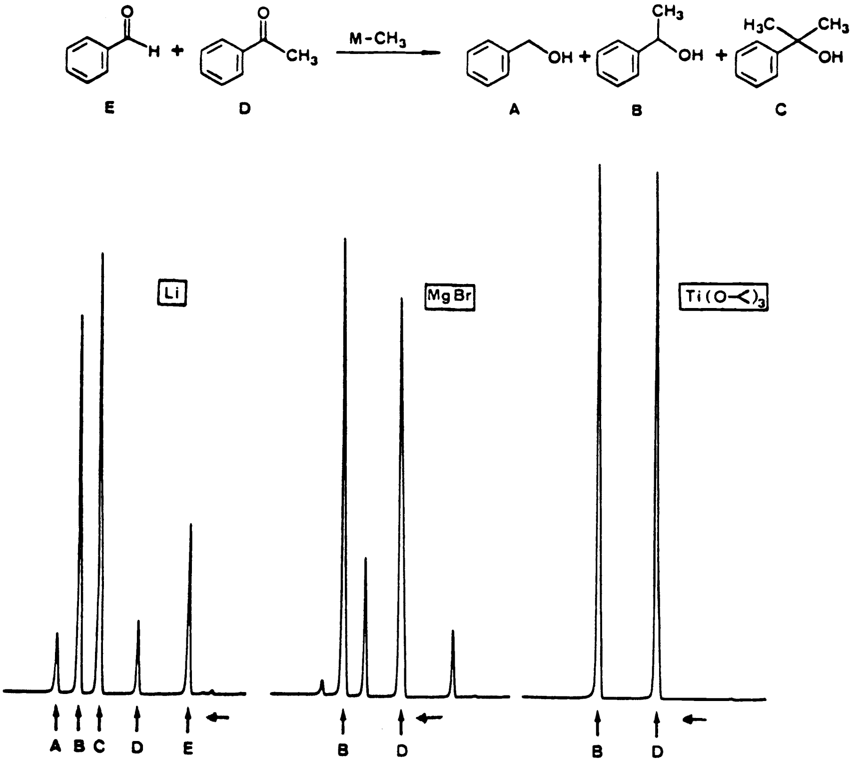


Fig. 1: Mixtures obtained from methyl-metal derivatives and a 1:1-mixture of C_6H_5CHO and $C_6H_5COCH_3$ at room temperature (see also ref.[1,2] and accompanying text).

compounds can, in principle, lead to three isomeric aldehyde-adducts and to three isomeric ketone adducts. With the Grignard-compound, the reaction is regioselective, but neither functional-group- nor diastereo-selective. With the triphenoxy-titanium analogue,[6] again a high selectivity is observed, see Fig. 2.

Not only crotyl but also other allylic triphenoxy-titanium reagents add diastereoselectively to aldehydes,[1,2,7,8] see Scheme 1, upper part.

Thus, the addition of (phenylallyl)-triphenoxy-titanium[9] gave adducts 1a and 1b with acetaldehyde and benzaldehyde, respectively, with the major diastereomer 1 predominating to the extent[10] (% ds) given on the bottom part of Scheme 1. While cyclohexenyl-triphenoxy-titanium[11,12] does not react diastereoselectively with aldehydes or ketones, the corresponding cyclopentenyl-[13] and cyclohexenyl-methyl-triphenoxy-titanium[14] derivatives add to aldehydes with preferential formation of one diastereomer, see Scheme 2, in addition, regioisomers are formed with these particular reagents. The main-product is thought to result from *lk*-approach of the aldehyde and the allylic titanium reagent (see box in Scheme 2, product formula 2). As with the analogous open-chain derivatives,[1,2,7,8] higher selectivities are observed upon addition to aliphatic aldehydes as compared with aromatic aldehydes.

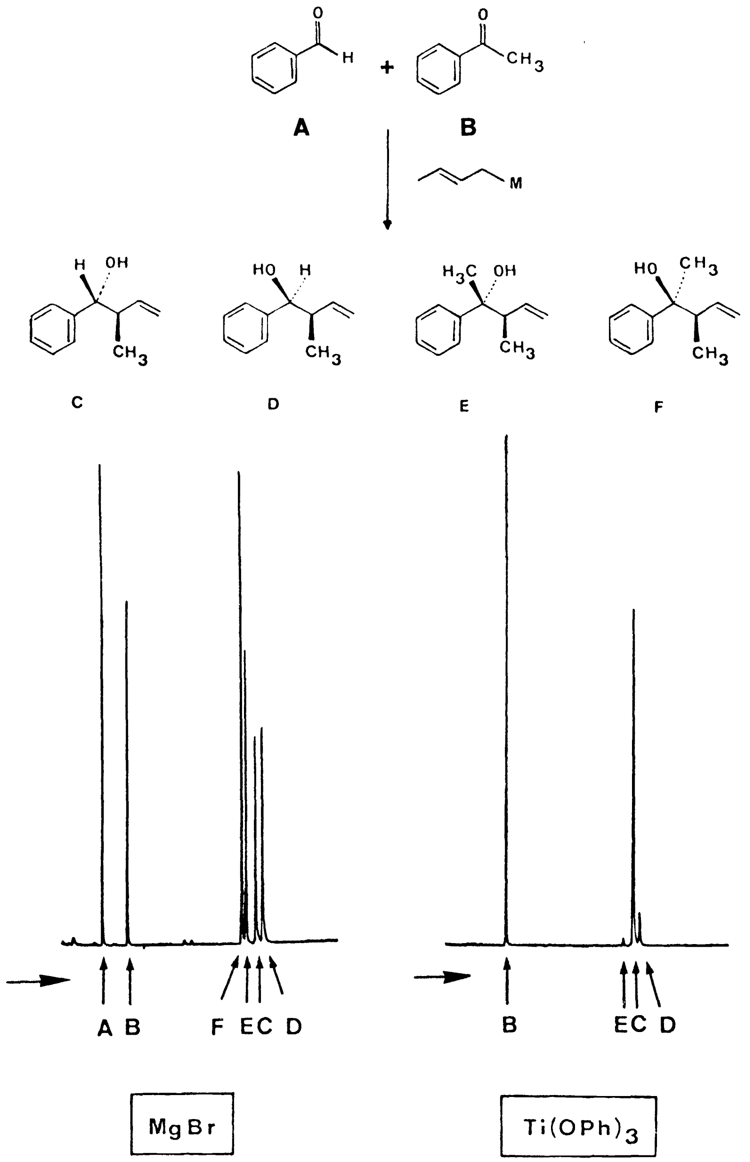
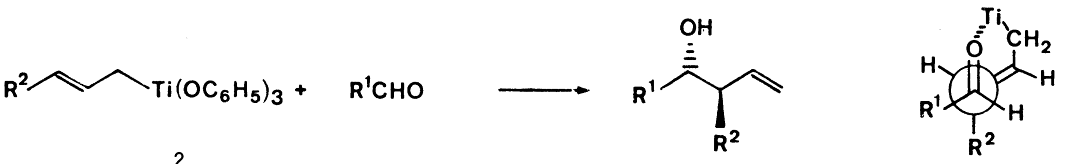


Fig. 2: CGC-chromatograms obtained after reaction of crotyl-magnesium bromide and of crotyl-triphenoxy-titanium with a 1:1-mixture of benzaldehyde and acetophenone.[10]

At the present time, and to the best of our knowledge, the various allylic organotitanium reagents[1-4] also provide the most diastereoselective additions to ketones. For the triphenoxy-titanium derivatives used in our investigations the results are assembled in Table 1. It can be seen, that open-chain and cyclic allylic organotitanium compounds show useful preferences if the two groups R^1 and R^2 on the keto-carbonyl group are not too similar in size. From the fact that the diastereoselectivities observed with ketones are often comparable to those obtained with aldehydes, we conclude that the less reactive ketones have transition states which lie closer to the products than those of aldehydes, so that smaller steric differences become significant. The product configurations have been determined by chemical

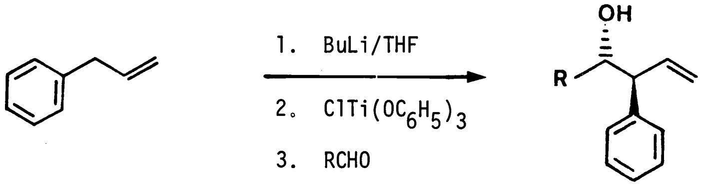
Scheme 1



$R^2 = CH_3$, $CH(CH_3)_2$, C_4H_9, C_6H_5

lk-addition with priority sequence $O > R^1 > H$ and $=CH > R^2 > H$

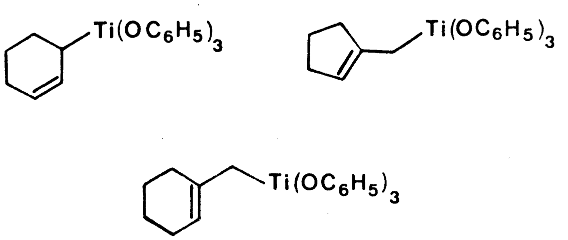
ul-addition with priority sequence $O > R^1 > H$ and $R^2 > =CH > H$

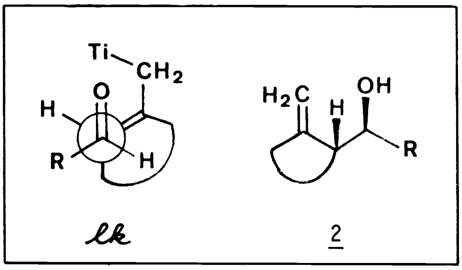


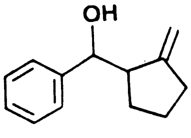
1a: R = CH_3 (> 97% ds)

1b: R = C_6H_5 (92% ds)

Scheme 2

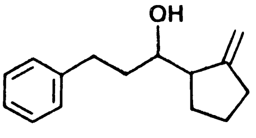






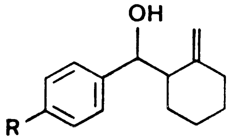
64% y / 85% ds

(+ 23% regioisomer)



60% y / 96% ds

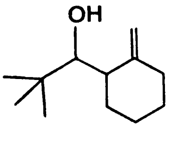
(+ 11% regioisomer)



R = H: 74% y / 87% ds (+ 6% regioisomer)

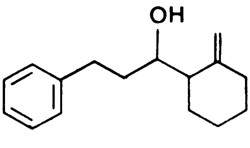
R = OCH_3: 87% y / 85% ds (no regioisomer)

R = NO_2: 78% y / 65% ds (+ 20% regioisomer)



64% y / >98% ds

(no regioisomer)



72% y / 98% ds

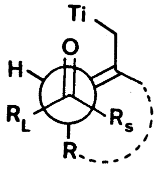
(ca. 6% regioisomer)

% y = chemical yield, not optimized, after conversion of allylic bromide to allylic Grignard-reagent with Rieke-magnesium, the content of organomagnesium derivative was determined by titration.

% ds = percentage of the major diastereomer formed.

regioisomer = product of C,C-bond formation at the CH_2-group.

correlation only in two cases,[7b] but we assume that the approach of the two trigonal centres is in all cases as shown in formula 3, thus all products ought to have the configuration indicated in formula 4. The significance of these results is that the homoallylic alcohols 4 can be oxidatively cleaved to β-hydroxy-carboxylic acids,[7b,15] see for instance 5 and 6, and these in turn are at present not available diastereoselectively by aldol-addition of propionate or other ester enolates to ketones.



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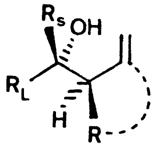

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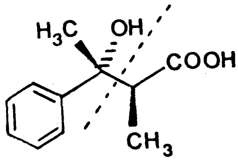

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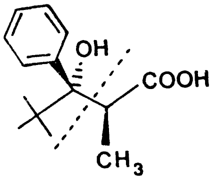

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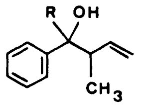
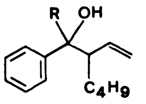
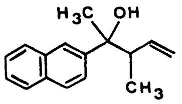
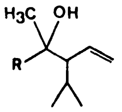
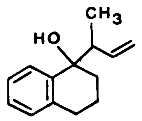
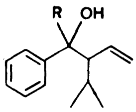
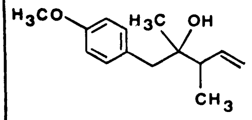
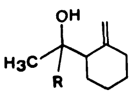
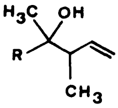
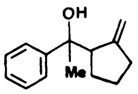
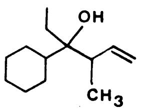
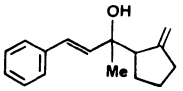
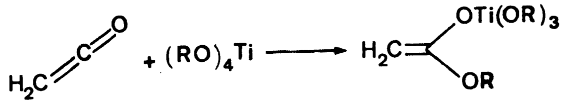
Table 1. Products 4 of diastereoselective addition of allylic titanium derivatives to unsymmetrical ketones.

Product	% Yield of 4	% of major diastereomer [% ds]	Product	% Yield of 4	% of major diastereomer [% ds]
 R = CH_3 R = CH_2CH_3 R = $CH(CH_3)_2$ R = $C(CH_3)_3$ R = $C{\equiv}C\text{-}CH_3$	85 - 96 87 79 74 99	84 - 88 74 55 > 98 72	 R = CH_3 R = $C{\equiv}C\text{-}CH_3$	89 87	87 77
	92	> 98	 R = C_6H_{13} (hexyl) R = C_6H_{11} (cyclohexyl)	89 73	75 96
	86	68	 R = CH_3 R = C_2H_5 R = $C{\equiv}C\text{-}CH_3$	90 85 88	87 65 77
	71	67	 R = $^iC_3H_7$ R = C_6H_{13} (cyclohexyl) R = C_6H_5 R = $C_{10}H_7$ (2-naphthyl)	79 87 83 90	> 97 93 70 90
 R = C_6H_{13} (hexyl) R = C_6H_{11} (cyclohexyl) R = $C(CH_3)_3$	98 93 63	70 87 96		73	ca. 80
	76	60		49	76

C) Nucleophilic Carbamoylation of Aldehydes and Ketones with the Adducts of Titanium Tetrachloride to Isocyanides

So far, the recent stoichiometric applications of organotitanium reagents have required a transmetallation of an organolithium, -magnesium or -zinc precursor, with two exceptions: The addition of tetraalkoxy-titanium to a ketene[16] to give the titanium enolate 7 and the ring opening of cyclopropanone acetals with titanium tetrachloride which leads[5] to propionic ester d^3-reagents[17] 8. Both reagents have been used for carbon carbon bond formations to yield aldol-Reformatzky-type products[18] and γ-hydroxy- or γ-chloro-esters or γ-lactones. Another type of compound containing a carbon-titanium bond was identified[19] as trichlorotitanio-imidchlorides 9. They were reported to be formed from methyl and t-butyl isocyanide and titanium tetrachloride. We have now found[20] that these adducts are extremely reactive carbonylophiles: Upon addition of an aldehyde or ketone to the suspension of reagents of the type 9 in methylene chloride, a clear solution is formed which - according to NMR analysis - contains the adducts 10. These are hydrolyzed by aqueous hydrochloric acid to give α-hydroxy-amides of the general formula 11. Some products obtained by us with methyl-isocyanide and with phenylisocyanide are given in the accompanying Scheme 3, together with the yields of



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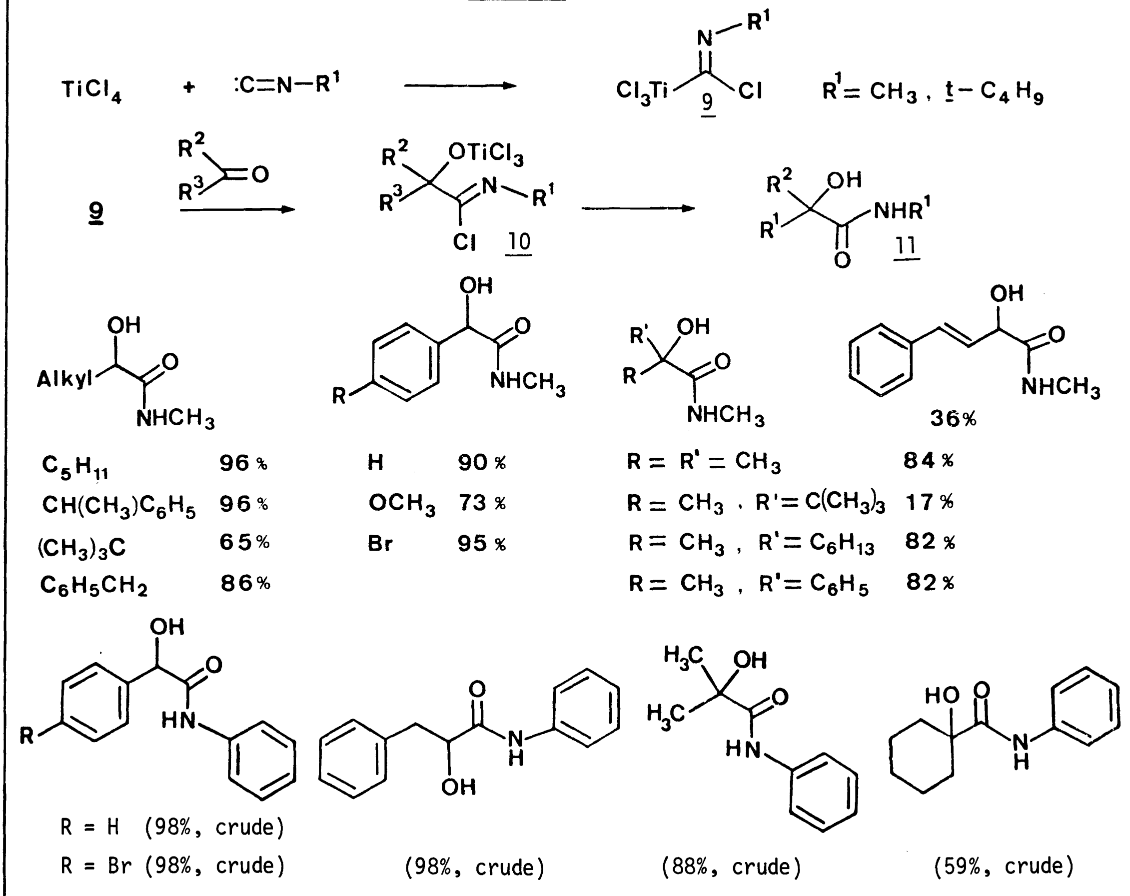
Scheme 3

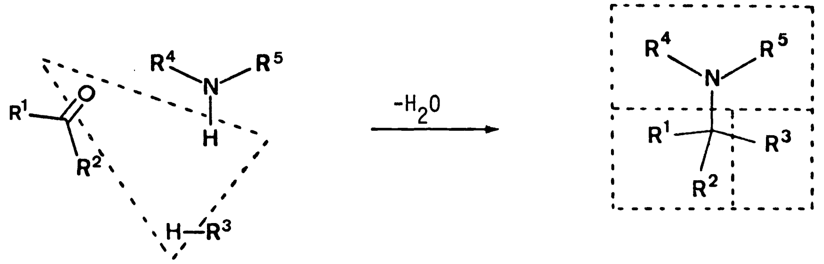


crude or purified products, most of which are nicely crystalline.[20] The present version of the classical Passerini-reaction[21] appears to be especially mild and versatile, producing directly the free α-hydroxyamides[22].

D) Alkylative Amination - a Building-Block Approach to the Mannich Reaction

In a general sense, the Mannich reaction can be defined as the combination of an electrophilic aldehyde or ketone carbonyl carbon with the nitrogen atom of an amine and a carbon nucleophile, with replacement of the C=O double bond by a C-N and a C-C single bond, see 12. There are numerous modifications of this reaction which can only be referred to here.[23] We have found and reported[24] earlier that the reaction of methyl-tris(diethylamino)-titanium (13) with aldehydes can lead to products 14 of alkylative amination. This at first sight very attractive method of preparing tertiary amines from aldehydes has a number of more or less serious disadvantages:

(i) the reagent 13 is made from methyllithium and chloro- or bromo-tris(diethylamino)titanium, which in turn must be prepared from titanium tetrachloride or bromide and the lithium amide; (ii) it is necessary to use two equivalents of the reagent 13 to effect a conversion of the aldehyde to the amine of ca. 50%; (iii) the reaction gives up to 50% yields



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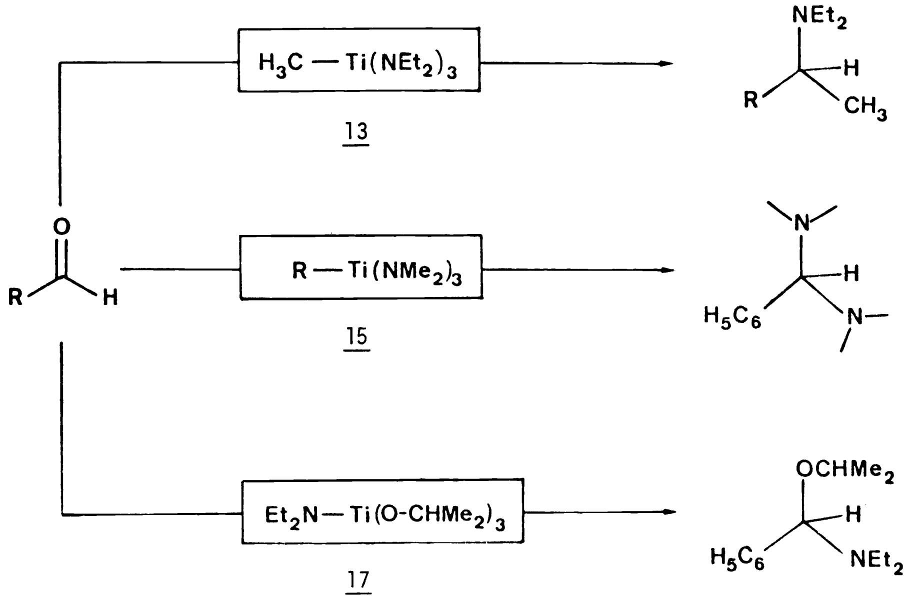
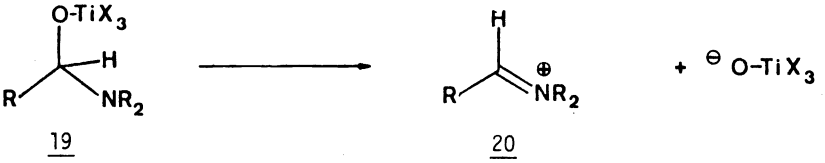
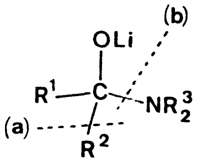




only with the methyl-titanium reagent, while higher alkyl groups are transferred poorly from the metal to the carbonyl centre; (iv) the diethylamino-group of 13 can not be replaced by other dialkylamino-groups with equal success: the tris(dimethylamino)-titanium analogue 15 reacts with benzaldehyde to give the aminal 16 rather than a product of C,C-bond formation, and very poor yields are obtained with, for instance, a piperidino-group; (v) finally, only non-enolizable aldehydes could be employed in the original procedure.[24]

Obviously, the rate of and the driving force for transfer of a dialkylamino-group from titanium to carbon is very large, see 19. From the primary adducts, formation of iminiumsalts 20 is favorable, not only because of the high stability of such cations,[23b] but also due to the high affinity of titanium for oxygen as compared with nitrogen, [cf. the bond energies[25] Ti-O (115 kcal/mole) and Ti-N(81 kcal/mole) and the conversion of benzaldehyde to the N,O-acetal 18 with diethylamino-triisopropoxy-titanium (17)[20b]]. Taking advantage of this situation, we have developed quite different, simple procedures for achieving overall transformations leading to tertiary amines of type 12.

From considerations about the mechanism of the alkylative amination with 13, it occurred to us that the metal-O-group in alkoxides of type 21 might be rendered a better leaving group by a transmetallation to titanium derivatives 22. Lithioxides 21 are the supposed intermediates of R^2Li additions (a) to carboxamides;[26] they have recently been shown to be quite stable when formed from aromatic[27,28] or other non-enolizable[29] aldehydes and lithium amides, see (b) in 21, $R^2 = H$. Thus, we added[20b] chloro- or bromo-tris(diethylamino)-, chloro-triisopropoxy-, or tetrachloro-titanium to solutions containing equivalent amounts of such adducts 21 to aldehydes, and combined the resulting mixtures with organolithium compounds. The desired products of alkylative amination were not formed with RO-substituents on titanium (22, X = $OCHMe_2$). With amino-substituted titanium (22, X = NEt_2), the same products 14 were isolated as with the original procedure using the reagent 13. Best yields were obtained with the (trichlorotitanio)-group (22, X = Cl). Its titanium has obviously both, a large affinity for oxygen and strong Lewis-acid character. The results are presented in Scheme 4, in which a comparison with the yields of the "direct" method using 13 is also made.



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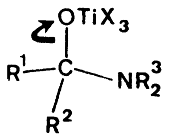

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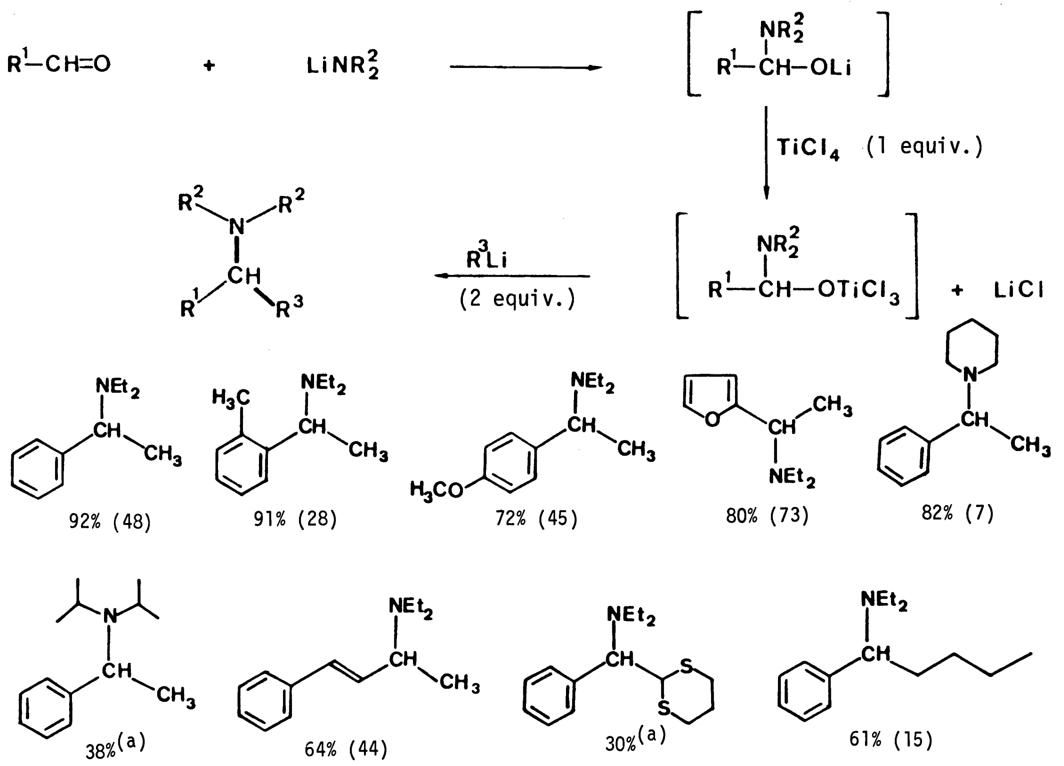
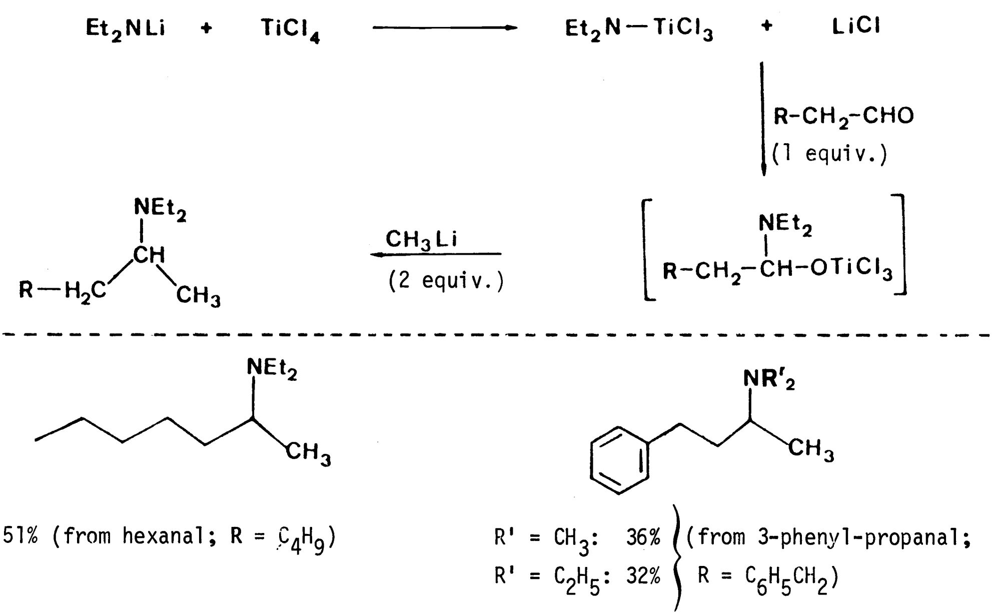
For enolizable aldehydes neither the "direct" method with reagent 13 nor the modification described in Scheme 4 is applicable. In the first case enamine formation, i.e. recovery of unreacted aldehyde after aqueous workup, prevails, cf. the Weingarten-method of preparing enamines from aldehydes or ketones, excess secondary amine, and titanium tetrachloride. In the second case, the lithium amide acts primarily as a base, rather than as a nucleophile, which again leads to recovery of unreacted aldehyde after workup. On the other hand, it is

Scheme 4



% yields calculated from R^1-CHO (for comparison, values in parentheses are the yields obtained with reagent 13, ref.[24]). (a) Results of preliminary, non-optimized experiments.

Scheme 5

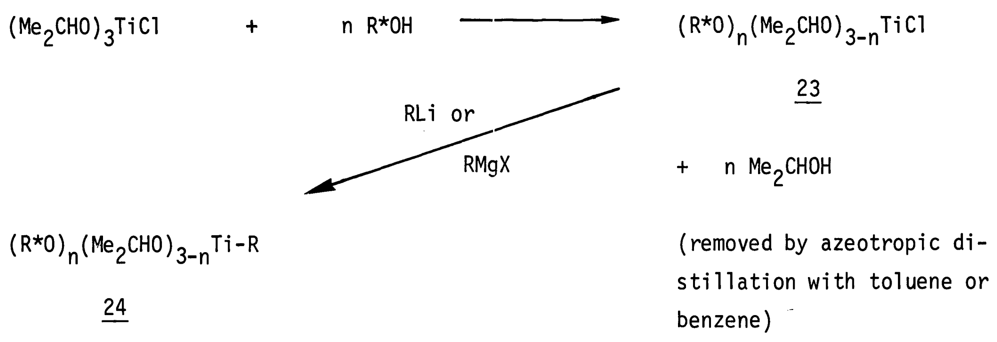


These yields were obtained in preliminary experiments and were not optimized.

known, that the various amino-titanium reagents have a great tendency to transfer the amino-group to aldehydes, with simultaneous attachment of titanium to oxygen.[1-3,20b,24] We therefore prepared solutions of diethylamino-trichloro-titanium, first added an aliphatic aldehyde, and then methyllithium, to find[20b] that the products of alkylative amination are formed in reasonable yields, see Scheme 5. We have no doubt that this procedure is applicable to other enolizable and non-enolizable aldehydes, and possibly also to ketones, as well as to secondary amines other than diethylamine.

E) Asymmetric Synthesis of Secondary Alcohols by Enantioselective Additions of Organotitanium Reagents to Aldehydes

It is very easy to prepare chiral, non-racemic organotitanium reagents 24: the isopropoxy-groups of the commercially available triisopropoxy-chloro-titanium are replaced by chiral R*O-groups, simply by mixing with the desired number of equivalents of a chiral alcohol in a solvent which forms azeotropes with isopropanol, distilling off this alcohol, and treating the resulting chlorotitanium derivative 23 with an organolithium or -magnesium compound.[1,2,30] These latter reagents have been made chiral and thus enantioselective by addition of optically active ethers, amines, aminoethers, aminoalkoxides, aminoamides etc.[31]. However, the use of these modified Li- and Mg-organic compounds is rather limited, because they can be aggregates, reacting in very complicated sequences of steps which may show different selectivities, cf. a recent discussion about aggregates of Li-enolates.[32] So far, high enantioselecitvities were only observed when an excess of such reagents was employed in additions to aldehydes. The only enantiomeric excesses exceeding 90% were obtained when butyllithium was added to benzaldehyde. In contrast to the alkali and alkaline earth metal derivatives, the titanates of type 24 are not aggregated, if the OR-groups are α-branched or otherwise bulky.[33] Not surprisingly, the first attempts at using chiral derivatives 24 in asymmetric syntheses have been very promising, up to 92% enantiomeric excess (ratio of enantiomers 96:4) [30,34,35] was achieved. To avoid repetition of results which we have already reported elsewhere,[1,2,30] we concentrate our discussion here to just two types of reagents. They show high selectivity in the enantioselective transfers of phenyl and methyl groups to aromatic and aliphatic aldehydes, conversions which could not be performed successfully by previous methods.



The chiral ligands used are the binaphthol of P-configuration,[36] now commercially available,[37] and the diols obtained from (R.R)-tartaric ester acetonide or pivalaldehyde acetal with excess phenyl Grignard-reagent. From these, the reagents 25-28 were prepared and allowed to react with various aldehydes. The highest asymmetric inductions are shown in Scheme 6. Obviously, chiral diarylcarbinols are best prepared with the phenyl-titanium reagent 26 bearing the binaphtholate ligand. For methyl-group transfer to benzaldehyde, and maybe other aromatic aldehydes, the tartaric acid-derived pivalaldehyde acetal 28 appears to be best. Finally, secondary alcohols without aromatic groups on the carbinol centre have so far been obtained in highest optical activities using the acetonide 27 for methyl-group transfer to aliphatic aldehydes, see also Table 2. All reactions were carried out by adding equimolar amounts of the aldehyde to the nucleophilic Ti-derivative, which had been prepared with methyl or phenyllithium. Diaryl- and dialkyl-carbinols thus obtained can not be prepared in equally high optical purity by asymmetric reduction of the corresponding ketones with chiral complex boron^{38a} or aluminum^{39} hydrides or with chiral boranes.^{38b,c} Thus, for in-

Scheme 6

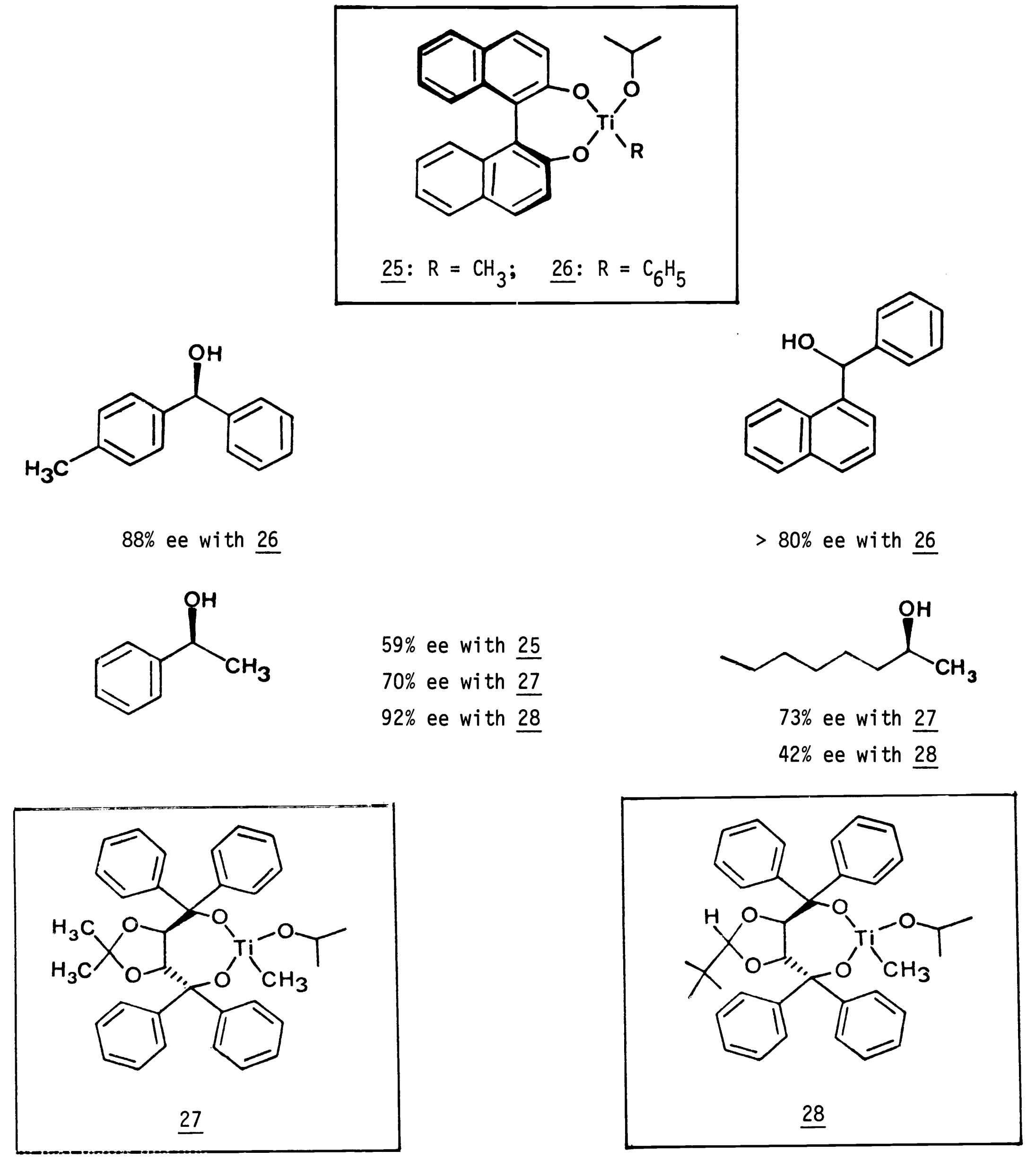


Table 2. Addition of the chiral methyl-titanium derivative 27 to aliphatic aldehydes with relative topicity ul.

The aldehyde was added to the diethylether solution of 27 at -15°C, and the mixture was allowed to warm up to +25°C before workup. For reference specific rotations see[40].

Aldehyde (R)	(S)-Alcohol		
	Chem. yield [%]	$[\alpha]_D^{RT}$	% enantiomeric excess
butanal (C_3H_7)	35	+7.8	58
hexanal (C_5H_{11})	67	+9.4	83
heptanal (C_6H_{13})	83	+7.4	73
nonanal (C_8H_{17})	75	+5.0	58
undecanal ($C_{10}H_{21}$)	82	+4.4	56
cyclohexylcarboxaldehyde (c-C_6H_{11})	78	+2.1	39

stance, the lithium aluminum hydride bearing the binaphtholate and an alkoxide group reduces - if employed in twofold excess - aryl, vinyl, and alkynyl alkyl ketones with excellent enantioselectivity, but not diaryl or dialkyl ketones.[39]

As may be expected, the enantioselectivity increases with decreasing reaction temperature, see Table 3. Much to our surprise, however, the result also depends strongly upon the method of generation of the reagent 27, and upon the presence of certain impurities! Thus, with methyllithium from a freshly opened bottle (commercial solution in diethyl ether, LiCl-containing) the above mentioned results could not be reproduced until 10% methanol had been added to generate lithium methoxide. Also, when the reagent 27 was prepared from methyl magnesium bromide, the (R)-(-)- rather than the (S)-(+)-enantiomer of 2-octanol was formed in excess, see Table 4.

Table 3. Effect of temperature on the enantioselectivity of the methyl transfer from 27 to heptanal. The reaction proceeds only above -50°C.

Temperature [°C]	(S)-2-Octanol	
	$[\alpha]_D^{RT}$	% ee
+24	+3.7	37
-15	+7.4	73
-50	+8.4	83

Table 4. Enantiomeric excesses with which 2-octanol is produced from heptanal and 27, depending upon the source of the methyl group. In all cases, the reaction was carried out in ether, between -15°C and ambient temperature. The methyllithium was purchased as ether solutions, either containing LiCl (a) (Metallgesellschaft AG, D-Frankfurt) or containing LiBr(b) (Aldrich Chemical Company, Inc., Milwaukee, USA). The Grignard-solution was purchased as ether solution from Cilag Chemie AG, CH-Schaffhausen.

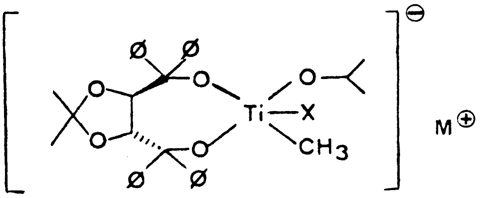
Preparation of 27 from the chloro-titanium compound of type 23 and heptanal	2-Octanol	
	$[\alpha]_D^{RT}$	% ee
methyllithium(a), containing insoluble precipitate (old bottle), 1.40 M titration following ref.[41]	+7.40	73
methyllithium(a), freshly opened bottle, clear solution without deposit; titer: 1.54 M	+5.50	54
methyllithium(a), fresh bottle, 10% CH_3OH added before use, titer: 1.33 M	+7.02	70
methyllithium-lithiumbromide(b), fresh bottle, clear solution without deposit; titer: 2.50 M	+5.07	50
methyl magnesium bromide, titer: 3.75 M	-3.86	38(c)

(a) Fresh bottles contain 5% CH_3Li and 0.4% LiCl (1.60 M in CH_3Li, 0.07 M in LiCl).

(b) Fresh bottles contain 6% CH_3Li, 12% LiBr, and 0.5% LiCl (2.5 M in CH_3Li, 1.1 M in LiBr, 0.1 M in LiCl).

(c) Nonanal gave 37% ee of (R)-(-)-2-decanol and cyclohexyl-carboxaldehyde gave 35% ee of (R)-(-)-1-cyclohexyl-ethanol under the same conditions.

These results suggest, that the actual reagent in the transformations is not the simple methyl-titanium derivative 27, but an ate-complex 29. In this case, the nature of the group X and of the counter ion can be decisive. Also, the fact that only 10% lithium methoxide increases the % ee appreciably (Table 4), might be interpreted as a result of higher reactivity of the ate-complex 29 as compared with the simple reagent 27. A systematic investigation of these effects is undertaken in our laboratories. Similar effects due to ate-complexes are also observed with chiral lithium aluminium hydrides of the type $[(RO)_n(R^*O)_{3-n}AlH]Li$. for examples see[39,42].



29

X = Cl, Br, OCH_3
M = Li, MgCl, MgBr

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14. Methyl cyclohexenyl-carboxylate is reduced to the alcohol with $LiAlH_4$ (LAH). Conversion of the alcohol to the bromide with PBr_3, transformation[12] to the *Grignard*-reagent, and transmetallation with $ClTi(OC_6H_5)_3$ gives solutions of the Ti-reagent shown at the top of *Scheme 2*.
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