243. Enantioselective Addition of Chiral Organotitanium Derivatives to Aldehydes

Preliminary Communication

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Summary

Alkoxy- and aryloxy-organotitanium compounds **2**-**4** derived from (*S*)-2-methyl-1-butanol, (*R*)-2-butanol, (−)-menthol, quinine, cinchonine, and (*S*)-1.1′-binaphthol are added to aromatic aldehydes to give optically active alcohols **5**-**10** in enantioselectivities of up to 88% e.e., with nucleophilic transfer of methyl, phenyl, and 1-naphthyl groups. The *Tables 1-3* list the effects of varying the reagents, the substrates, and the reaction conditions of the new asymmetric synthesis.

Based on *single* experiments, there was an earlier optimistic ('8% e.e.... promising') [1] and a later pessimistic ('13% e.e.... disappointingly low') [2] statement concerning enantiomeric excess in asymmetric synthesis with chiral organotitanium reagents. Based on more *extensive* experimentation, we are pleased to announce, that for once the optimists were right, and that we have been able to achieve enantiomeric excesses of up to 88% in such reactions. This result is comparable with or superior to the best data reported in the literature about enantioselective organometallic additions to aldehydes [3-5].

In fact, our activity [1] [6-8] in the field of organotitanium and -zirconium reagents was triggered by the desire to plan asymmetric carbonyl additions more rationally than was possible by exploiting the elusive effects between lithium reagents and chiral solvents [3] [9]. The 'more solid' bonds [10] between titanium and (chiral) OR*-groups (* designating the chirality) are readily made by *iso*-propoxy/R*O-substitution in chloro-triisopropoxytitanium [1] [6] with azeotropic removal of the 2-propanol[3]) formed.

The chiral chlorotitanates **1** thus prepared are converted *in situ* to the organotitanates **2** by reaction with RLi- or RMgX-derivatives, as described previously [1]

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[1]) Undergraduate research student at ETH-Zürich (1980/81).

[2]) Part of the projected Ph.D. thesis of *B. Weidmann*, ETH-Zürich.

[3]) Benzene can be used as solvent for the azeotropic distillation; it is removed and replaced by the solvent in which the Cl/R-exchange **1** → **2** and the subsequent reactions are carried out.

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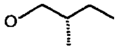
$$\text{Cl-Ti[OCH(CH}_3)_2]_3 + 3\text{R*OH} \xrightarrow{-3\,\text{Me}_2\text{CHOH}} \text{Cl-Ti(OR*)}_3$$

1

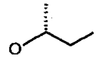
R-Ti(OR*)_3

2

a $R = CH_3$, OR* =

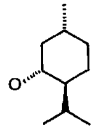


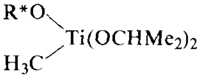
b $R = CH_3$, OR* =



c $R = CH_3$
d $R = C_6H_6$
e 1-naphthyl

OR* =

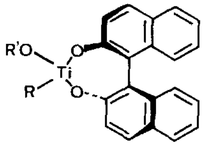




$$\text{R*O}\diagdown\text{Ti(OCHMe}_2)_2 / \text{H}_3\text{C}$$

3

a R*O from quinine
b R*O from cinchonine



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a $R = CH_3$, $R' = C_2H_5$
b $R = CH_3$, $R' = CH(CH_3)_2$
c $R = C_6H_5$, $R' = CH(CH_3)_2$

[6]. Solutions of the reagents **3** and **4** derived from quinine and cinchonine[4]), and from (*S*)-binaphthol [11][5]), respectively are obtained similarly. The results of the asymmetric syntheses of the alcohols **5**, **6**, **7**, **9** and **10** and of the lactone **8** by enantioselective addition[6]) of the reagents **2**-**4** to aldehydes are described in the *Tables 1*, *2* and *3*, with variations of the OR*-group, of the aldehyde, and of the reaction conditions, respectively.

Table 1. *Additions of differently chirally modified methyl and phenyl titatnium reagents* **2**-**4** *to benzaldehyde (entries 1-7) and to* p-*tolylaldehyde (entries 8 and 9).* With **2** and **3** diethyl ether is used as solvent, reaction conditions: 3 h/ − 60°, then + 20°; with **4**, solvent: THF, 3 h/ − 20°. Conditions of α_D-measurement and optical purities see [5] and [12]. Work-up see previous papers [1] [6] [7] and footnote 6.

Entry	Reagent	Product		
			$[\alpha]_D$	% e.e.
1	**2a**	(*S*)-**5**	− 3.64°	8
2	**2b**	(*S*)-**5**	− 5.42°	12
3	**2c**	(*S*)-**5**	− 10.46°	23
4	**3a**	(*S*)-**5**	− 6.32°	14
5	**3b**	(*R*)-**5**	+ 4.50°	10
6	**4a**	(*S*)-**5**	− 12.58°	28
7	**4b**	(*S*)-**5**	− 26.90°	59
8	**2d**	(*R*)-**10**	+ 2.87°	29
9	**4c**	(*S*)-**10**	− 8.84°	88

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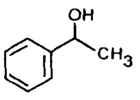
[4]) Since the Cl of **1** is also replaced by OR in the presence of amines, we used the sequence [Ti $(OCHMe_2)_4$ + R*OH → Ti (OR*) $(OCHMe_2)_3$ (**A**); **A** + ½ $TiCl_4$ → ClTi (OR*) $(OCHMe_2)_2$ (**B**) + ClTi $(OCHMe_2)_3$ (**C**); **B**/**C** + CH_3Li → **3** + $CH_3Ti(OCHMe_2)_3$] for preparation of **3**, with the obvious disadvantage of achiral dilution of the reagent.

[5]) Precursors of **4** (R = Cl) are obtained directly from ClTi(OR')$_3$ and the binaphthol of $[\alpha]_D = -34.1°$ ($c = 1$, THF) [11] with removal of 2 R'OH.

[6]) The conversions are > 95% in all cases. The yields of isolated products depend upon the ease of separation from R*OH, which is volatile in the case of **2a** and **2b**, and which is soluble in acid or base in the cases of **3** and **4**, respectively; with menthol (from **2c**-**2e**) we encountered problems when the product volatility was too high (*cf.* **5**, **8**).



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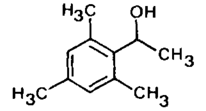

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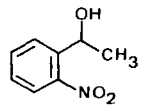

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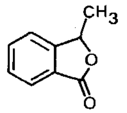

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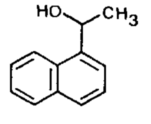

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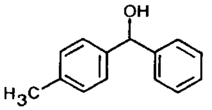

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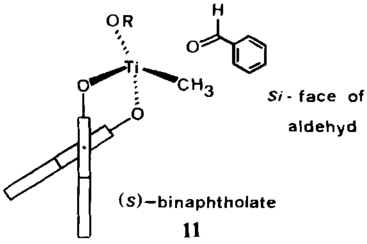

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Table 2. *Additions of chiral methyl and naphthyl titanium reagents of type* **2** *and* **4** *to different aldehydes.* For conditions see head of *Table 1.* The $[\alpha]_D$-values of optically pure samples and the conditions of measurement were taken from the following references: **6** [3], **8** [13], **9** [3]; **7** was converted to **5** [3] by reduction (Na_2S: $NO_2 \rightarrow NH_2$), diazotation ($NaNO_2$/HCl, 0°; $NH_2 \rightarrow N_2^{\oplus}$), and reduction (HOAc/NaOAc, THF, 20°; $N_2^{\oplus} \rightarrow H$).

Entry	Aldehyde	Reagent	Product		
				$[\alpha]_D$	% e.e.
1	Mesityl aldehyde	**2c**	(*R*)-**6**	+ 6.34°	12
2	*o*-Nitro-benzaldehyde	**2c**	(*S*)-**7**	+ 140°	76
3		**4b**	(*S*)-**7**	+ 7.49°	4
4	Methyl *o*-formyl-benzoate	**2c**	(*S*)-**8**	− 7.58°	25
5	1-Naphthaldehyde	**2c**	(*S*)-**9**	− 46°	58
6		**4b**	(*S*)-**9**	− 37°	46
7	Acetaldehyde	**2e**	(*R*)-**9**	+ 3.81°	5

Table 3. *Preparation of alcohol* **7** *from methyl-trimethoxy-titanium* (**2c**) *and* o-*nitrobenzaldehyde under different reaction conditions.* For optical purity of **7** see head of *Table 2.* Preparation of the solutions of **2c**:**1** was freed from benzene[3]), dissolved (*ca.* 0.1M) in the desired solvent, and combined with a mol-equiv. of CH_3Li (1.7M in ether). The aldehyde was added at −60°, after 3 h the mixture was warmed to +20° within 12 h. A kryostat with temperature control was used for the experiment of entry 5.

Entry	Solvent	Product 7	
		$[\alpha]_D^{25}$	% e.e.
1	Pentane	+ 11.2°	6
2	Ether	+ 140°	76
3	Ether + 1 mol-equiv. $LiClO_4$	+ 16.7°	9
4	THF	− 10.4°	5.5
5	Ether (with warming from − 100 to − 40° in 60 h)	+ 40°	22

It can be seen, that the highest selectivities are obtained with the menthol⁶)⁷)⁸) and with the binaphthol derivatives (entries 7 and 9 in *Table 1*, entries 2, 5, and 6 in *Table 2*). With the axially chiral binaphtholates **4**, the nature of the third OR-group appears to be crucial (entries 6 and 7 of *Table 1*), see the topology in **11**.

The examples in *Table 2* indicate that the reaction is strongly substrate-dependant [*cf.* entry 1 (*Re*-approach) with entry 2 (*Si*-approach)] and that it is better to add methyl to naphthaldehyde than naphthyl to acetaldehyde (*cf.* entry 5 with entry 7), other things being equal.

Finally, the strong solvent (5.5% (*R*) e.e. in THF, 76% (*S*) e.e. in ether) and temperature (22% e.e. at -100 to $-40°$, 76% at -60 to $+20°$) effects are evident from *Table 3*, entries 4 *vs.* 2 and entry 5 *vs.* 2, respectively.

The approach to enantioselective carbonyl additions⁹) by use of simple non-alkali or -alkaline earth alkyl- and aryl-organometallic reagents⁹) described here has the following advantages: *(i)* It makes use of the full equivalent of the organometallic reagent; *(ii)* it exhibits a high functional-group selectivity - only aldehydes and ketones are attacked (see products **7** and **8**, *Tables 2* and *3*, and [1] [6] [7]); *(iii)* it can be successful in asymmetric methyl *and* phenyl transfers (*Table 1*, entry 9, and *Table 2*, entry 2).

We trust, that it is only a matter of time, until the most generally applicable combination of chiral OR*-groups, conditions, and substrate-types for these enantioselective additions will be elucidated.

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⁷) This 'auxiliary' is *cheap* in both enantiomeric forms.

⁸) Other monoterpenes such as borneol, *iso*-borneol, fenchol *etc.* are being tested.

⁹) Ketones with enantiotopic carbonyl group faces, as well as the use of zirconium analogues are being tested.