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Ti-TADDOLate-Catalyzed, Highly Enantioselective Addition of Alkyl- and Aryl-Titanium Derivatives to Aldehydes

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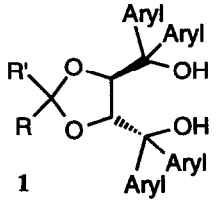
Abstract: Toluene-ether or toluene-hexane solutions of aryl and alkyl triisopropoxy titanium reagents (free of Li, Mg, or Zn salts) are prepared from the corresponding Li or *Grignard* reagents and $ClTi(O^iPr)_3$, with careful removal of salts (centrifugation of LiCl or of dioxane•MgX_2, and addition of 12-crown-4). The solutions of the organotitanium compounds are combined with one equiv. of an aldehyde and 0.2 equiv. of (*R,R*)-diisopropoxy-(α,α,α',α'-tetraphenyl-2,2-dimethyl-1,3-dioxolane-4,5-dimethanolato) titanium (Ti-TADDOLate **3**) at dry-ice temperature. Warming up to room temperature leads to nucleophilic addition to the (*Si*)-face of the aldehydes with enantioselectivities as high as 99.5 : 0.5 (products **4** - **33** in *Scheme 4*). Functional groups or protecting groups and branching in the Ti-R group and in the aldehyde must be remote from the reacting centers. Aryl groups can be added to aldehydes by this method. - In contrast to all the enantioselective R_2Zn additions to aldehydes, in which only one R-group is actually transferred, a twice as economic use is made of the originally employed R-metal reagent in the method described here. - A procedure for multigram preparation of the spiro-Ti-TADDOLate (**2**) employed for the *in situ* generation of the catalyst (**3**) is described, and details of the determination of enantiomer ratios (er) by GC and NMR methods are given (Tab. 2, 3). The mechanistic interpretation of Ti-TADDOLate-mediated nucleophilic additions as derived previously (ref.[4e]) is also compatible with this monometallic variant of the method.

INTRODUCTION

There has been much effort to achieve enantioselective C,C-bond formation between a carbonyl compound - usually an aldehyde - and an organometallic alkyl or aryl species. The most successful examples using catalytic amounts of a chiral catalyst were performed with dialkyl zinc reagents in combination with chiral aminoalcohols[2] or *Lewis* acid[3] systems, and enantioselectivities better than 99 : 1 were found quite often.

Among these reactions the Ti-catalyzed ones play a prominent role, since they give high selectivities with both, aromatic and aliphatic (alkyl, alkenyl, and alkynyl) aldehydes, and even solvents others than saturated or aromatic hydrocarbons may be used, e. g. ether or THF. Using the chiral diol ligands **1** (TADDOLs = α,α,α',α'-tetraaryl-1,3-dioxolane-4,5-dimethanols), which can be easily prepared from tartrate acetals and aryl *Grignard* reagents, selectivities up to er 99.5 : 0.5 are achieved[3b,4].

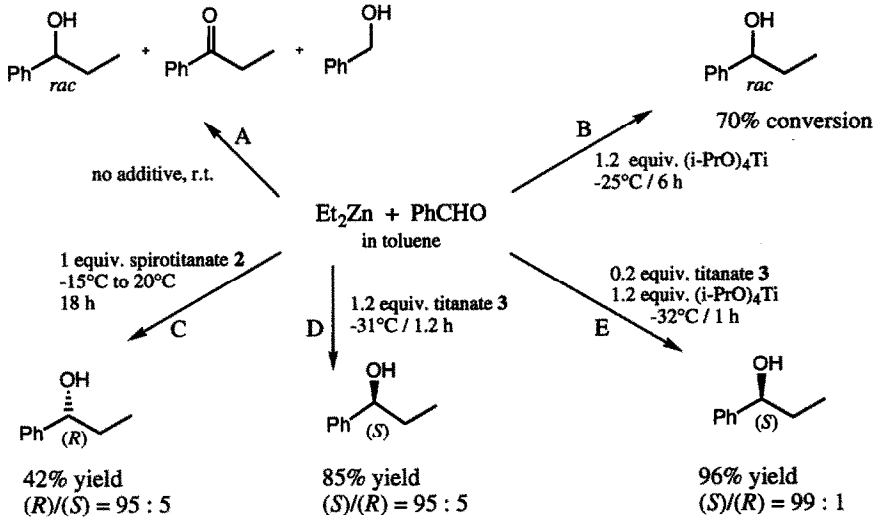


1 **1a**: R = R' = Me, Aryl = Ph

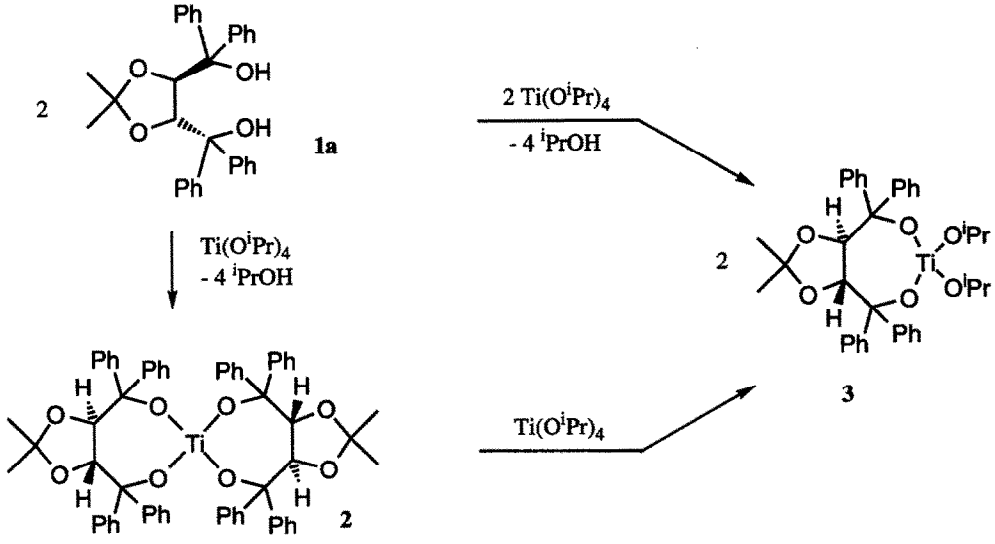
The results of our previous studies about the TADDOL-titanate mediated addition of Et_2Zn to benzaldehyde are summarized in *Scheme 1*. *Path A*: Et_2Zn does not react with benzaldehyde to any appreciable

extent in toluene at temperatures around -30°C, whereas at room temperature, benzyl alcohol, 1-phenylpropan-1-ol, and propiophenone are produced. *Path B*: In contrast, the nucleophilic transfer of an Et group to benzaldehyde from Et_2Zn occurs at *ca.* -25°C in the presence of 1.2 equiv. of $Ti(O^iPr)_4$. *Path C*: The corresponding experiment with the chiral spiro-titanate **2** (*Scheme 2*) leads to a 95 : 5 mixture of (*R*)- and (*S*)-alcohols in a slow reaction requiring temperatures above 0°C. *Path D*: On the other hand the titanate **3** (*Scheme 2*) leads to the formation of a 95 : 5 mixture, with the (*S*)-enantiomer predominant under identical conditions. *Path E*: Finally, an improvement of the enantioselectivity, from 95 : 5 to 99.5 : 0.5 for the formation of the

Scheme 1. Reactions of Et_2Zn with PhCHO under Various Conditions. *The structures of the titanates 2 and 3 are shown in* Scheme 2.



Scheme 2. Preparation of the Spirotitanate **2** and of the Bicyclic Titanate **3**.



(*S*)-enantiomer, is achieved by applying 0.2 equiv. of **3** and 1.2 equiv. of $Ti(O^iPr)_4$. Thus, reducing the amount of the chiral titanate by a factor of six and adding a six fold excess of the achiral titanate gives the best result (for a mechanistic investigation see ref.[4e]).

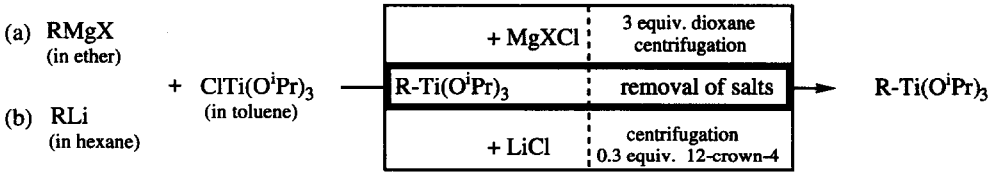
Although there are impressive selectivities[4,5], there remains an inherent disadvantage in all of these dialkyl zinc additions: Only one of the two alkyl groups from dialkyl zinc is transferred to the aldehyde. Therefore we developed a method using $R\text{-}Ti(O^iPr)_3$ as the organometallic partner for the addition to aldehydes, and the Ti-TADDOLate **3** as the catalyst[6]. This zinc-free, monometallic system is also more promising for large-scale applications, and there is less ambiguity in its mechanistic interpretations.

PREPARATIVE RESULTS

The **catalyst** (**3**) is generated *in situ* either by ligand exchange from the TADDOL **1a** and $Ti(O^iPr)_4$ or by metathesis form the spiro-titanate **2** and $Ti(O^iPr)_4$ (see *Scheme 2*). The second route is our favoured one since **3** is generated with the least number of manipulations, just by mixing the air stable spirotitanate **2** with an equimolar amount of the commercially available $Ti(O^iPr)_4$ in toluene. A procedure for the multi-gram preparation of **2** is described in the experimental part.

The **enantioselective addition** to aldehydes is performed with 1.2 equiv. of freshly prepared $R\text{-}Ti(O^iPr)_3$ (*vide infra*), 0.2 equiv. of **3**, and 1.0 equiv. of an aldehyde in toluene. The reactants are mixed at -78°C and are allowed to warm to room temperature overnight (*Scheme 3*). Both, alkyl- and aryl-tetraisopropoxy-titanium compounds are used which are generated *in situ* from the corresponding alkyl- or aryl-lithium or *Grignard* compounds and $Cl\text{-}Ti(O^iPr)_3$. It turns out that the presence of the salts, which are formed in the transmetallation step, LiCl and MgXCl, respectively, drastically reduces the enantioselectivity (see the data in *Table 1*, entries 1 and 2). In toluene these salts are insoluble and therefore can be separated by centrifugation (cf. entries 3 and 4). The best results were obtained when 1,4-dioxane is added [method (a) in *Scheme 3*] to complete the precipitation of magnesium salts, or when the remaining traces of Li cations were removed by complexation with 12-crown-4 [method (b) in *Scheme 3*] (cf. entries 5 - 7 in *Table 1*).

Scheme 3. Generation of $R\text{-}Ti(O^iPr)_3$ and its Ti-TADDOLate Catalyzed Addition to Aldehydes. *The best methods for the removal of the salts (MgXCl, and LiCl, respectively) are specified as (a) and (b).*



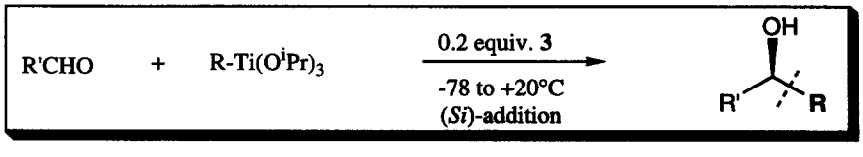


Table 1. Ti-TADDOLate Catalyzed Addition of Et-Ti(O^iPr)$_3$ and Bu-Ti(O^iPr)$_3$ to PhCHO with Different Methods for the Removal of the Salts (cf. *Scheme 3*). *For the* formulae *of products 4 and 5 see* Scheme 4.

Entry	RM	Removal of Salts	Product	Yield[%]	er
1	EtMgBr	none	(*S*) **4**	66	68 : 32
2	BuLi	none	(*S*) **5**	90	80 : 20
3	EtMgBr	centrifugation	(*S*) **4**	42	94 : 6
4	BuLi	centrifugation	(*S*) **5**	76	98 : 2
5	EtMgBr	addition of 3 equiv. 1,4-dioxane and centrifugation	(*S*) **4**	59	>99 : 1
6	BuMgI	addition of 3 equiv. 1,4-dioxane and centrifugation	(*S*) **5**	97	>99 : 1
7	BuLi	centrifugation and addition of 0.3 equiv. 12-crown-4	(*S*) **5**	81	99 : 1

By inspection of *Table 1* (entries 5 - 7) it can be seen that both methods (a) and (b) for the removal of the salts give essentially the same enantioselectivities in the subsequent addition reaction.

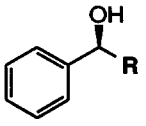
The centrifugation can be performed at room temperature in a tube sealed with a rubber septum and flushed with argon without any remarkable decomposition of R-Ti(O^iPr)$_3$ even though the color of the solution turned black in most cases. Et-Ti(O^iPr)$_3$ is the only exception: its solutions have to be handled at temperatures below -10°C using a refrigerated centrifuge.

The reaction of benzaldehyde with simple Alkyl-Ti(O^iPr)$_3$ and CH_2=$CHCH_2CH_2$-Ti(O^iPr)$_3$ gives selectivities of ≥99 : 1 (products **4** - **8** in *Scheme 4*) under standard conditions. $PhCH_2$-Ti(O^iPr)$_3$ is added at -90°C with a 83 : 17 selectivity (product **9**). Substituted benzaldehyde derivatives with *ortho* and *meta* substituents give low to moderate selectivities, but excellent selectivities (≥97.5 : 2.5) are found for the *para* substituted products (**10** - **15**). Aliphatic aldehydes give high selectivities, too (≥96 : 4, products **16** - **18**). It must be pointed out that even Ph-Ti(O^iPr)$_3$ can be added selecively to both, substituted benzaldehyde derivatives and aliphatic aldehydes (products **14** - **16**). The reaction is very sensitive to steric hindrance: Cyclohexane carboxaldehyde and pivaldehyde give enantiomer ratios of 86 : 14 and 63 : 37 only (products **19** and **20**). Unsaturated and α,β-acetylenic aldehydes (products **21** - **23**) give selectivities ≥96.5 : 3.5. The only exception in the acetylenic aldehyde series is product **24** with a (poor) 90 : 10 selectivity (*Scheme 4*).

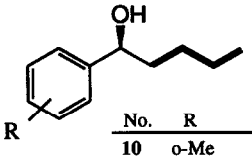
The tested nucleophiles with functionalyzed alkyl groups can be added with selectivities ≥96 : 4 as long as the hetero-atom is separated from the nucleophilic carbanionic C-atom by at least three C-atoms (products **25** - **27**). If the hetero-atom is closer to the metal substituted C-atom the selectivity drops. Product **28** with two "spacer atoms" is formed with only 85 : 15 selectivity. Products **29** - **33** with hetero-atoms in the transferred alkyl or aryl group are formed in poor selectivities or even as racemic mixtures.

All **enantiomer ratios** (er) were determined by non-optical methods. We used either capillary gas chromatography with chiral cyclodextrin derivatives as stationary phase (*Table 2* in the Experimental Part), or *Mosher* ester derivatives[7] (*Table 3* in the Experimental Part) of the alcohols for analysis of the ratios of the resulting diastereoisomers by ^{19}F-NMR or ^{1}H-NMR spectroscopy, or Eu(hfc)$_3$ as NMR-shift reagent. To find the best analysis of the enantiomeric ratios we first prepared racemic samples of the compounds **4** - **33** by addition of an organometallic compound (R-MgX, R-Li, or R-Ti(O^iPr)$_3$) to the appropriate aldehyde.

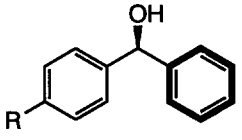
Scheme 4. Secondary Alcohols Obtained in Enantiomerically Enriched Form Using the Procedures Outlined in Scheme 3. *The groups printed in bold face are those introduced with the R-Ti(O^{i}Pr)$_3$ by addition to the corresponding aldehydes. The selectivities are given as enantiomer ratios (er).*



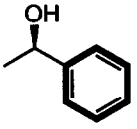
No.	R	% y	er
4	Et	59	99.5 : 0.5
5	Pr	82	99.5 : 0.5
6	Bu	97	99.5 : 0.5
7	Hex	66	99 : 1
8	$CH_2CH_2CH{=}CH_2$	52	99 : 1
9	CH_2Ph	13	83 : 17



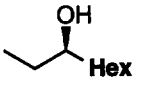
No.	R	% y	er
10	o-Me	79	80 : 20
11	o-MeO	98	58 : 42
12	m-MeO	98	85 : 15
13	p-MeO	98	98.5 : 1.5



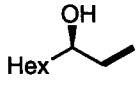
No.	R	% y	er
14	Me	96	98 : 2
15	NO_2	79	97.5 : 2.5



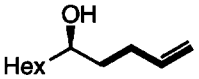
16 72% y, er 98.5 : 1.5



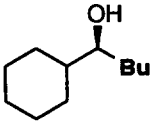
17 66% y, er 98.5 : 1.5



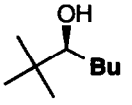
ent-**17** 57% y, er 98 : 2



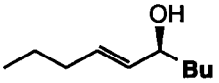
18 71% y, er 96 : 4



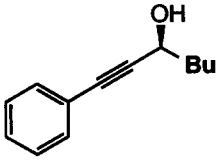
19 72% y, er 81 : 19



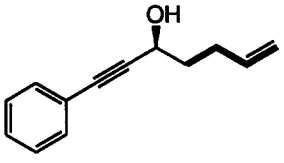
20 26% y, er 56 : 44



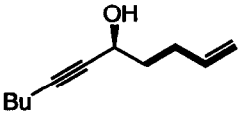
21 94% y, er 98.5 : 1.5



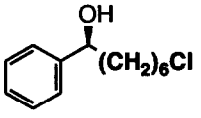
22 60% y, er 98 : 2



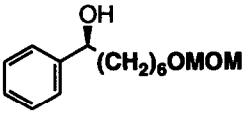
23 33% y, er 96 : 4



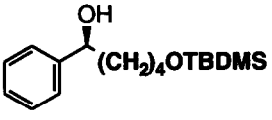
24 38% y, er 90 : 10



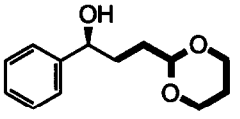
25 67% y, er 98 : 2



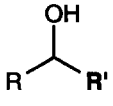
26 66% y, er 98 : 2



27 30% y, er 96 : 4



28 87% y, er 85 : 15



No.	R	R'	er
29	Ph	CH_2SMe	69 : 31
30	Ph	2-dithianyl	50 : 50
31	Ph	$CH_2CH_2CO_2Et$	65 : 35
32	Et	2-F-C_6H_4	58 : 42
33	Me	2-MeO-C_6H_4	50 : 50

CONCLUSIONS

In general we can state, that the characteristic features of this reaction are very similar to those of the Ti-TADDOLate catalyzed dialkyl zinc addition to aldehydes[3b,4]. It is therefore entirely possible that no zinc center is involved in the rate-determining C,C bond-forming step of the previously reported reaction (in the bimetallic mechanism proposed[4e] both metal centers could be titanium!).

In those examples, where the absolute configuration of the product is known, the addition occurred from the *Si*-face of the aldehyde. In those examples where no literature data are available we assume an (*Si*)-addition.

Both, aliphatic and aromatic aldehydes are good substrates, and as long as hetero-atoms are separated by "some" carbon atoms from the reacting part of the molecule, or if they are geometrically not available for intramolecular complexation with a carbonyl activating Ti-atom, they do not essentially affect the selectivity. Steric hindrance of the reacting centers is not compatible with this method of enantioselecive nucleophilic addition to aldehydes.

In some examples where the dialkyl zinc additions give moderate selectivities higher er values can be achieved by the present method. E.g. products **25** and **26** are formed with a 98 : 2 selectivity using the reaction sequence described in this paper, but an er of only 92 : 8 is found in the corresponding dialkyl zinc reaction. In the aryl transfer and for aliphatic aldehydes this "zinc free" reaction is superior, as well.

Last but not least, we want to emphasize the fact that here the alkyl transfer is twice as efficient as in any dialkyl zinc addition, since only one equiv. of RM is requiered (RM *vs.* RMR).

EXPERIMENTAL PART

General Remarks. *Abbreviations:* FC (flash chromatography), GP (general procedure), KD (bulb to bulb distillation).

Starting materials and reagents: A 2 M stock soln. of Cl-Ti(O^iPr)$_3$ was prepared according to ref.[8]. Dioxane was freshly distilled over sodium. Toluene and ether were dried over MS 4 Å. The liquid aldehydes were distilled, and Ti(O^iPr)$_4$ (*Hüls AG*) was used without further purification.

Equipment: All reactions were performed under an inert argon atmosphere in oven-dried equipment. Thin layer chromatography (TLC): precoated silica gel 60 F_{254} plates (*Merck*); visualisation by UV_{254} light, development using vanilline soln. (4.0 g anisaldehyde, 20 g ice, 374 mL EtOH, 6 mL H_2SO_4) or phosphomolybdic acid soln. (25 g phosphomolybdic acid, 10 g $Ce(SO_4)_2 \cdot 4H_2O$, 60 mL H_2SO_4, 940 mL H_2O). Flash chromatography: SiO_2 60 (0.040 - 0.063 mm, *Fluka*), pressure: 0.2 bar. Distillation for purification of the products: *Büchi GKR-50* bulb to bulb distillation apparatus; boiling points (bp.): correspond to uncorrected air bath temp. Melting points (mp.): open glass capillaries, *Büchi 510* (*Tottoli* apparatus), uncorrected. $[\alpha]_D$ at r.t. (*ca.* 20°C) *Perkin-Elmer 241* polarimeter (*p.a.* solvents, *Fluka*). Capillary gas chromatography (CGC): *HRGC* or *MEGA HRGC 5160* (*Carlo Erba*); injector temp.: 230°C, detector temp.: 250°C, carrier gas: H_2. Columns: S1: WCOT Fused Silica, Cyclodextrin-ß-2,3,6-M-19, 50 m x 0.25 mm (*Chrompack*); S2: Heptakis(2,3,6-tri-O-ethyl)-ß-cyclodextrin in OV 1701 Vi (1 : 4), 10 m x 0.27 mm (self-made). ^{1}H-NMR spectra: *Varian Gemini 200* (200 MHz) or *Varian Gemini 300* (300 MHz), δ in ppm down field of TMS (δ = 0), J in Hz. ^{19}F-NMR spectra: *Varian Gemini 300* (282 MHz), δ in ppm down field of CCl_3F (δ = 0).

Preparation of the Mosher-*esters: Ca.* 5 mg of the alcohol, 30 mg *N,N*-dimethyl-4-amino pyridine, and 10 mg of (*S*)-α-methoxy-α-triflouromethyl-acetic acid chloride were dissolved in 0.5 mL of $CHCl_3$. After 30 min the reaction mixture was poured into 2 M HCl, the organic layer extracted with ether, washed with brine and satd. $NaHCO_3$ soln. and evaporated in vacuo. The residue was analysed without further purification.

GP1 - Enantioselective Alkyl or Aryl Titanium Addition - Using RMgX as the Original Reagent: A centrifuge tube equipped with rubber septum and magnetic stirring bar flushed with argon and filled with 2 mL (4 mmol) of a 2 M Cl-Ti(O^iPr)$_3$ soln. in hexane, and *ca.*15 mL of toluene was cooled to -78°C. An ethereal *Grignard*-soln. (3.5 mmol) and 1 mL of 1,4-dioxane was added, the cooling bath was removed and the tube was allowed to reach 0°C under vigorous stirring. The magnesium complex was precipitated by centrifugation and the supernatant R-Ti(O^iPr)$_3$ soln. was used immediately.

In a two neck flask, a soln. of 0.1 equiv. **2** and 0.12 equiv. Ti(O^iPr)$_4$ in toluene was stirred for a few minutes at room temperature, and 1.2 equiv. of the R-Ti(O^iPr)$_3$ soln. was added. The temperature was maintained at -78°C for 0.5 to 1.5 h, 1.0 equiv. of the aldehyde (neat or dissolved in toluene) was added, and the reaction was allowed to warm to room temperature overnight without removing the cooling bath. The reaction was quenched with aqueous 5 M NaOH (0.3 mL per 1 mmol aldehyde). Stirring was continued for 10 min, Na_2SO_4 was added, and after an additional stirring of 10 min the reaction mixture was filtered through a celite pad. The solvent was evaporated *in vacuo,* and the product was separated from the TADDOL either by KD or by FC.

GP2 - Enantioselective Alkyl or Aryl Titanium Addition - Using RLi as the Original Reagent: A centrifuge tube equipped with rubber septum and magnetic stirring bar flushed with argon and filled with 2 mL (4 mmol) of a 2 M Cl-Ti(O^iPr)$_3$ soln. in hexane, and *ca.*15 mL of toluene was cooled to -78°C. An alkyl or aryl lithium soln. (3.5 mmol) was added, the cooling bath was removed and the tube was allowed to reach 0°C under vigorous stirring. The LiCl was precipitated by centrifugation and the supernatant R-Ti(O^iPr)$_3$ soln. was used immediately.

In a two neck flask, a soln. of 0.1 equiv. **2** and 0.12 equiv. Ti(O^iPr)$_4$ in toluene was stirred for a few minutes at room temperature, 1.2 equiv. of the R-Ti(O^iPr)$_3$ soln. and 0.3 equiv. of 12-crown-4 were added. The temperature was maintained at -78°C for 0.5 to 1.5 h, 1.0 equiv. of the aldehyde (neat or dissolved in toluene) was added, and the reaction was allowed to warm to room temperature overnight without removing the cooling bath. The reaction was quenched with aqueous 5 M NaOH (0.3 mL per 1 mmol aldehyde). Stirring was continued for 10 min, and the reaction mixture was filtered through a Celite pad. Water and ether were added, the organic layer was washed four times with water, and dried over Na_2SO_4. The solvent was evaporated *in vacuo,* and the product was separated from the TADDOL either by KD or by FC.

Spirotitanate 2: In a flame dried 250 mL two neck flask equipped with a reflux condenser, a magnetic stirring bar, a rubber septum, and an argon vacuum inlet at the top of the condenser was placed 9.33 g (20 mmol) of (*R,R*)-2,2-dimethyl-α,α,α',α'-tetraphenyl-1,3-dioxolane-4,5-dimethanol[9], 2.3 g (11 mmol) of Ti(O^iPr)$_4$, and 20 mL of toluene. The slurry was refluxed for 3 h to give a pale yellow solution. Then, the temperature of the heating bath was maintained at 100 to 110°C. The solvent was evaporated slowly (30 to 60 min) *in vacuo*, and condensed in a cold trap. The rate of evaporation was controlled by the vacuum and the

cooling rate of the condenser. The remaining pale yellow solid was dried for an additional 1 to 2 h in an oil pump vacuum (0.1 Torr). The product (*ca.* 10 g) contained, according to the ^{1}H-NMR spectrum less than 1% of uncomplexed diol, and could be used without further purification. Spectra see ref.[4d].

Table 2. GC Separation of Enriched Products (see *Scheme 4*).

Compound	Column[a)]	Initial Temperature [°C]	Heating Rate [°C/min]	Inlet Pressure [bar]	Approximate Retention Time [min]	Ratio of Enantiomers 1st : 2nd eluted	Configuration / Sense of Optical Rotation[b)]
4	S1	80	1.0	1.2	33	0.5 : 99.5	(*S*) (-)
5	S2	70	1.0	0.5	22	99.5 : 0.5	(*S*) (-)
6	S1	85	0.4	1.2	82	99.5 : 0.5	(*S*) (-)
7	S1	110	0.8	1.2	65	99 : 1	(*S*) (-)
10	S1	120	0.5	1.2	50	91 : 9	(-)
11	S1	120	1.0	1.2	40	58 : 42.5	
16	S1	80	1.0	1.3	25	98.5 : 1.5	(*R*) (+)
19	S1	85	0.5	1.2	78	81 : 19	(*S*) (-)
29	S1	115	0.5	1.4	65	31 : 68.5	(-)
33	S1	100	1.0	1.2	31	50 : 50	

a) S1: Heptakis(2,3,6-tri-*O*-methyl)-β-cyclodextrin, 50 m x 0.25 mm, *Chrompack* CP Cyclodextrin, β-2,3,6-m-19. S2: Heptakis(2,3,6-tri-*O*-ethyl)-β-cyclodextrin in OV1701 1 : 4, 10 m x 0.25 mm. b) Of the major enantiomer, measured in MeOH.

Table 3. Determination*via* the *Mosher* Esters of the Ratios of Enantiomers in Products Shown in *Scheme 4*.

Compound	Observed Group	Chemical Shift δ [ppm]	Ratio of enantiomers er	Configuration / Sense of Optical Rotation (Solvent)
8	CF_3	-71.28 and -72.08	1 : 99	(–) (MeOH)
9	CF_3	-71.68 and -71.90	83 : 17	(*S*) (+) (EtOH)
12	CF_3	-71.90 and - 72.04	15 : 85	(–) (MeOH)
13	CF_3	-71.95 and -72.19	1.5 : 98.5	(–) (MeOH)
14	CH_3	2.27 and 2.25	2 : 98	(*S*) (–) (benzene)
15	CF_3	-71.70 and -71.79	97.5 : 2.5	(*S*) (+) (MeOH)
17	CF_3	-71.77 and -71.85	98.5 : 1.5	(*R*) (–) (MeOH)
18	CF_3	-71.68 and -71.76	4 : 96	(+) (MeOH)
20	CF_3	-71.16 and -71.54	56 : 44	
21	CF_3	-71.92 and -72.00	1.5 : 98.5	(+) (MeOH)
22	CF_3	-72.08 and -72.36	2 : 98	(–) (MeOH)
23	CF_3	-72.00 and -72.35	4 : 96	(+) ($CHCl_3$)
24	CF_3	-72.09 and -72.42	10 : 90	
25	CF_3	-71.76 and -72.00	2 : 98	(–) (EtOH)
26	CF_3	-71.79 and -72.02	2 : 98	(–) (EtOH)
27	1-CH	5.96 and 5.89	4 : 96	(–) (EtOH)
28	CF_3	-71.80 and -72.10	15 : 85	(–) (MeOH)
30	1-CH	6.17 and 6.05	50 : 50	
32	CF_3	-71.90 and -72.19	58 : 42	(+) (MeOH)

(*S*)-1-Phenyl-propan-1-ol ((*S*)-4): Following GP1 84 mg (0.79 mmol) benzaldehyde and EtMgBr gave after KD (0.3 Torr, 150°C) 72 mg **4** (GC purity: 89%) (59%). Er 99.5 : 0.5. $[\alpha]_D$ = (-) (MeOH). [Lit.[10]: $[\alpha]_D^{25}$ = -22.2 (neat), (*S*)-form].

(*S*)-1-Phenyl-butan-1-ol ((*S*)-5): Following GP1 73 mg (0.69 mmol) benzaldehyde and PrMgBr gave after KD (0.1 Torr, 150°C) 82 mg **5** (82%). Er 99.5 : 0.5. $[\alpha]_D$ = -35.2 (c = 1.2, MeOH). [Lit.[11]: $[\alpha]_D^{27}$ = -45.9 (c = 5.0, C_6H_6), (*S*)-form]. Mp.: 46.5-47.5°C.

(*S*)-1-Phenyl-pentan-1-ol ((*S*)-6): Following GP1 106 mg (1.00 mmol) benzaldehyde and BuMgI gave after KD (0.3 Torr, 150°C) 160 mg **6** (97%). Er 99.5 : 0.5 $[\alpha]_D$ = -25.9 (c = 3.1, MeOH) [Lit.[12]: $[\alpha]_D^{24}$ = +17.2 (neat), (*R*)-form].

Following GP2 0.70 mL (7.0 mmol) benzaldehyde and BuLi gave after KD (0.3 Torr, 150°C) 1.05 g **6** (91%). Er 98.5 : 1.5.

(*S*)-1-Phenyl-heptan-1-ol ((*S*)-7): Following GP1 88 mg (0.83 mmol) benzaldehyde and HexMgBr gave after KD (0.2 Torr, 150°C) 105 mg **7** (66%). Er 99 : 1. $[\alpha]_D$ = -31.4 (c = 1.7, benzene) [Lit.[13]: $[\alpha]_D^{25}$ = +22.6 (Benzene), with er 85 : 15, (*R*)-form].

(-)-1-Phenyl-pent-4-en-1-ol ((-)-8): Following GP1 106 mg (1.00 mmol) benzaldehyde and homoallyl-MgBr gave after KD (0.1 Torr, 150°C) 85 mg **8** (52%). Er 99 : 1. $[\alpha]_D$ = (-) (c = 1, MeOH) [Lit.[4d]: $[\alpha]_D^{RT}$ = -31.9 (c =3.2, $CHCl_3$) with er 95 : 5].

(*S*)-1,2-Diphenyl-ethan-1-ol ((*S*)-9): Following GP1 (reaction temperature -95°C → RT) 106 mg benzaldehyde and BnMgBr gave after FC (hexane / ether 3 : 1) 25 mg **9** (13%). Er 83 : 17. $[\alpha]_D$ = +37.7 (c = 1, EtOH) [Lit.[14]: $[\alpha]_D^{18}$ = +55.9 (c =1.4, EtOH), (*S*)-form].

(-)-1-(2-Methyl-phenyl)-pentan-1-ol ((-)-10): Following GP1 90 mg (0.75 mmol) *o*-methyl benzaldehyde and BuMgI gave after KD (0.2 Torr, 160°C) 105 mg **10** (79%). Er 80 : 20. Using 1 Eq. **2** 79% **10** with er 91 : 9 was isolated. $[\alpha]_D$ = -37.5 (c = 1.1, MeOH).

1-(2-Methoxy-phenyl)-pentan-1-ol (11): Following GP2 150 mg (1.10 mmol) *o*-anisaldehyde and BuLi gave after KD (0.3 Torr, 150°C) 220 mg **11** (>98%). Er 58 : 42.

(-)-1-(3-Methoxy-phenyl)-pentan-1-ol ((-)-12): Following GP2 135 mg (1.00 mmol) *m*-anisaldehyde and BuLi gave after KD (0.3 Torr, 150°C) 200 mg **12** (98%). Er 85 : 15. $[\alpha]_D$ = -11.3 (c = 1.3, MeOH).

(-)-1-(4-Methoxy-phenyl)-pentan-1-ol ((-)-13): Following GP2 135 mg (1.00 mmol) anisaldehyde and BuLi gave after KD (0.3 Torr, 150°C) 190 mg **13** (98%). Er 98.5 : 1.5. $[\alpha]_D$ = -22.5 (c = 1.1, MeOH). Mp.: 41.5-43°C. Following GP2 1.36 g (10.0 mmol) anisaldehyde and BuLi gave after KD (0.2 Torr, 150°C) 1.80 g **13** (93%). Er 98.5 : 1.5. Mp.: 41-42.5°C.

(*S*)-Phenyl-*p*-tolyl-methanol ((*S*)-14): Following GP2 120 mg (1.00 mmol) 4-tolyl-aldehyde and PhLi gave after KD (0.07 Torr, 100-160°C) 190 mg **14** (96%). Er 98 : 2. $[\alpha]_D$ = -9.7 (c = 4.4, benzene) [Lit.[15]: $[\alpha]_D^{25}$ = -8.84 (c = 4.8, benzene), with er 94 : 6, (*S*)-form]. Mp.: 66-69°C.

(*S*)-(4-Nitro-phenyl)-phenyl-methanol ((*S*)-15): Following GP2 150 mg (1.00 mmol) *p*-nitro-benzaldehyde and PhLi gave after KD (0.07 Torr, 200°C) 180 mg **15** (79%). Er 97.5 : 2.5. $[\alpha]_D$ = +43.3 (c = 1, MeOH) [Lit.[16]: $[\alpha]_D$ = +50.0 (c = 0.62, MeOH), with er 93 : 7, (*S*)-form].

(*R*)-1-Phenyl-ethan-1-ol ((*R*)-16): Following GP2 0.15 mL acetaldehyde and 1.75 mmol $PhTi(O^iPr)_3$ gave after KD (15 Torr, 150°C) 155 mg **16** (72%). Er 98.5 : 1.5. Assignment by comparison with authentic ((*R*)-**16**).

(*R*)-3-Nonanol ((*R*)-17): Following GP1 58 mg (1.0 mmol) propionaldehyde and HexMgBr gave after KD (0.2 Torr, 150°C) 95 mg **17** (66%). Er 98.5 : 1.5. $[\alpha]_D$ = -8.4 (c = 1.5, MeOH) [Lit.[17]: $[M]_D^{RT}$ = -11.6 (neat), (*R*)-form].

(+)-Undec-1-en-5-ol ((+)-18): Following GP1 0.92 g (8.1 mmol) enanthaldehyde and homoallyl-MgBr gave after KD (0.1 Torr, 150°C) 0.96 g **18** (71%). Er 96 : 4. $[\alpha]_D$ = +1.4, $[\alpha]_{365}$ = +3.1 (c = 1.5, MeOH).

(*S*)-1-Cyclohexyl-pentan-1-ol ((*S*)-19): Following GP2 112 mg (1.00 mmol) 1-cyclohexane carboxaldehyde and BuLi gave after KD (0.3 Torr, 150°C) 130 mg **19** (76%). Er 81 : 19. $[\alpha]_D$ = -10.2 (c = 1.0, MeOH) [Lit.[18]: $[\alpha]_D^{30}$ = -12.9 (neat), (*S*)-form].

2,2-Dimethyl-heptan-3-ol (20): Following GP2 87 mg (1.00 mmol) pivaldehyde and BuLi gave after KD (15 Torr, 130°C) 38 mg **20** (26%). Er 56 : 44.

(+)-(*E*)-Dec-6-en-5-ol ((+)-21): Following GP1 73 mg (0.74 mmol) (*E*)-hex-2-enal and BuMgI gave after KD (0.3 Torr, 150°C) 110 mg **21** (94%). Er 98.5 : 1.5. $[\alpha]_D$ = +7.7 (c = 1.7, MeOH).

(-)-1-Phenyl-hept-1-yn-3-ol ((-)-22): Following GP1 130 mg (1.00 mmol) phenyl-propiol aldehyde and BuMgBr gave after KD (0.1 Torr, 170°C) 110 mg **22** (60%). Er 98 : 2. $[\alpha]_D$ = -5.2 (c = 1.7 MeOH) [Lit.[19]: $[\alpha]_D^{25}$ = +6.24 (c = 1.33 $CHCl_3$), with er 83.5 : 16.5].

(+)-1-Phenyl-hept-6-en-1-yn-3-ol ((+)-23): Following GP1 0.34 g (2.6 mmol) phenyl-propiol aldehyde and homoallyl-MgBr gave after FC (hexane / ethyl acetate 10 : 1) 0.16 g **23** (33%). Er 96 : 4. $[\alpha]_D$ = +18.2 (c = 0.7, $CHCl_3$). ^{1}H-NMR (200 MHz) δ = 7.60-7.25 (m, 5, Ph), 6.00-5.75 (m, 1, 6-CH), 5.20-5.00 (m, 2, 7-CH_2), 4.70-4.55 (m, 1, 3-CH), 2.90-2.70 (m, 2, 5-CH_2), 2.10-1.85 (m, 3, HO and 4-CH_2).

Undec-1-en-6-yn-5-ol (24): Following GP1 1.00 g (9.08 mmol) hept-2-ynal and homoallyl-MgBr gave after KD (0.1 Torr, 150°C) 0.57 g **24** (38%). Er 90 : 10. ^{1}H-NMR (200 MHz) δ = 5.95-5.70 (m, 1, 2-CH), 5.10-4.90 (m, 2, 1-CH_2), 4.45-4.30 (m, 1, 5-CH), 2.30-2.15 (m, 4, 3-CH_2 and 8-CH_2), 1.85-1.65 (m, 3, 4-CH_2 and OH), 1.60-1.30 (m, 4, 9-CH_2 and 10-CH_2), 0.91 (t, 3, J = 7, CH_3).

(-)-7-Chloro-1-phenyl-heptan-1-ol ((-)-25): A soln. of 1.0 g (4.0 mmol) 1-chloro-6-iodo-hexane in 1 mL ether and 14 mL toluene was cooled to -78°C. 1.46 mL (6.77 mmol) of a 4.64 M *tert*-butyl-lithium soln. was added and stirring was continued at this temperature for additional 30 min. The resulting pale yellow soln. of Cl-$(CH_2)_6$-Li was used without further purification following GP2. 305 mg (2.88 mmol) benzaldehyde gave after FC (pentane / ether 3 : 1) 442 mg **25** (67%) . Er 98 : 2. $[\alpha]_D$ = -14.8 (c = 1.6 EtOH) [Lit.[20]: $[\alpha]_D^{RT}$ = -15.5 (c = 1.3, EtOH), with er 92 : 8].

(-)-7Methoxymethoxy-1-phenyl-heptan-1-ol ((-)-26): Following GP1 0.10 mL (1.0 mmol) benzaldehyde and 7,9-dioxadecyl magnesium bromide gave after FC (hexane / ethyl acetate 6 : 1) 167 mg **26** (66%). Er 98 : 2. $[\alpha]_D$ = (-) (c = 1, MeOH) [Lit.[4d]: $[\alpha]_D^{RT}$ = -10.3 (c = 3, EtOH), with er 92 : 8].

(-)-5-[(*tert*-Butyl-dimethyl-silyl)-oxy]-1-phenyl-pentan-1-ol ((-)-27): Following GP1 0.10 mL (1.0 mmol) benzaldehyde and TBDMSO$(CH_2)_4$-MgBr gave after FC (hexane / acetone 7 : 1) 90 mg **27** (30%). Er 96 : 4. $[\alpha]_D$ = -15.5 (c = 0.7, EtOH). ^{1}H-NMR (200 MHz) δ = 7.40-7.20 (m, 5, Ph), 4.70-4.60 (m, 1, 1-CH), 3.60 (t, 2, J = 6, 5-CH_2), 1.95-1.20 (m, 6, 2-$CH_2CH_2CH_2$), 0.86 (s, 9, ^{t}Bu), 0.02 (s, 6, $SiMe_2$).

(-)-3-[1,3]Dioxan-2-yl-1-phenyl-propan-1-ol ((-)-28): Following GP1 160 mg (1.51 mmol) benzaldehyde and 2-[1,3]dioxan-2-yl-ethyl magnesium bromide gave after FC (hexane / ethyl acetate 2 : 1) 290 mg **28** (87%). Er 85 : 15. $[\alpha]_D$ = -12.5, $[\alpha]_{365}$ = -39.9 (c = 1.2, MeOH).

(*R*)-(-)-1-Phenyl-3-thiabutan-1-ol ((*R*)-29): A soln. of 1.5 mL of dimethyl sulfide in 2 mL ether was cooled to -78°C. 1.0 mL (4.6 mmol) of a 4.6 M *tert*-butyl-lithium soln. was added, stirring was continued and

the temperature was allowed to warm to room temperature within 2 h. The resulting pale yellow suspension of $LiCH_2SMe$ was used without further purification following GP2. 106 mg (1.00 mmol) benzaldehyde gave after KD (0.1 Torr, 170°C) 150 mg **29** (90%). Er 69 : 31. $[\alpha]_D$ = -8.4 (c = 1.3, MeOH) [Lit.[21]: $[\alpha]_D^{20}$ = +63.8 (c = 5.63, cyclopentane), (*S*)-form]

[1,3]Dithian-2-yl-phenyl-methanol (30): A soln. of 480 mg (4.00 mmol) 1,3-dithiane and 2.50 mL (4.00 mmol) BuLi (1.6 M in hexane) in 6 mL toluene was stirred at room temperature for 1 h. The resulting pale yellow suspension of was used without further steps following GP2. 170 mL (1.6 mmol) benzaldehyde gave after FC (pentane / ether 3 : 1) 200 mg **30** (55%). Er 50 : 50.

4-Hydroxy-4-phenyl-butyric acid ethyl ester (31): A soln. of 0.8 mL (4 mmol) 1-ethoxy-cyclopropyloxy-trimethylsilane in 10 mL toluene was stirred with 0.44 mL $TiCl_4$ for 0.5 h. Then a soln. of 0.92 mL (12 mmol) ^{i}PrOH and 2.6 mL (12 mmol) ^{t}BuLi (4.64 M in pentane) in 7.25 mL toluene was added and the LiCl was removed by centrifugation. 75% of the supernatant was used following GP2. 0.30 mL (3.0 mmol) benzaldehyde gave after FC (hexane / ether 9 : 1) 83 mg **31** (13%) . Er 65 : 35. Determination of the ratio of enantiomers: a) Transesterification with MeOH / H_2SO_4 b) $Eu(hfc)_3$ in C_6D_6 (shift of the OMe signal 3.66 ppm → 4.73 and 4.70 ppm, respectively)

(+)-1-(2-Fluoro-phenyl)-propan-1-ol ((+)-32): Following GP2 58 mg (1.00 mmol) propionaldehyde and 1.3 mmol *o*-F-C_6H_4-Li (generated *in situ* from ^{t}BuLi and *o*-F-C_6H_4-Br in ether at -90 to -80°C) gave after KD (0.1 Torr, 150°C) 0.15 g **32** (96%). Er 58 : 42. $[\alpha]_D$ = (+) (c = 1, MeOH).

1-(2-Methoxy-phenyl)-ethan-1-ol (33): Following GP2 0.10 mL acetaldehyde and 1.30 mmol *o*-MeO-C_6H_4-Li (generated *in situ* from BuLi and o-MeO-C_6H_4-Br in toluene at -78°C to RT) gave after and KD (0.3 Torr, 150°C), 130 mg **33** (GC purity: 70%). Er 50 : 50.

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