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Efficient Diastereoselective Synthesis of α,β-Dihydroxyesters from Methyl Phenylglyoxylate and Aldehydes Mediated by Titanium Trichloride/Pyridine System Ψ

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Abstract: The reductive coupling of methyl phenylglyoxylate **2** with aliphatic and aromatic aldehydes **3**, promoted by $TiCl_3$/Py system in anhydrous THF, affords α,β-dihydroxyesters **4** in good yields (60-94%) and high *syn*-diastereoselectivity (up to 85%). The type of ligand at the metal ion necessary to achieve a high level of diastereocontrol and the possible mechanism involved are discussed.

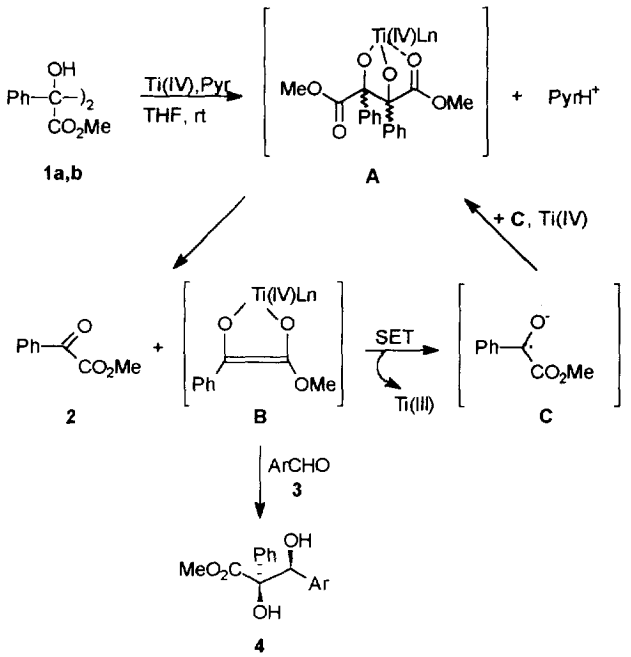
Introduction

The Lewis acid catalyzed reaction of nucleophiles with aldehydes constitutes an important part of organic synthesis, since it frequently results in stereoselective carbon-carbon bond formation in conformationally non rigid open-chain compounds.[1] The properties of Lewis acid-carbonyl complexes are ultimately responsible for determining the reactivity of the reagents and, very often, dictate the stereochemical course of the reaction.[2]

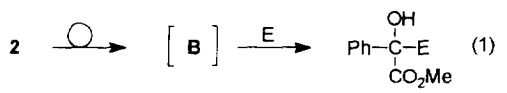
In our previous paper[3] we have shown that *meso* and *dl* dimethyl diphenyltartrates, **1a and 1b**, undergo rapid oxidative cleavage, at room temperature, on treatment with $TiCl_4$ in THF/Py solution. The Ti(IV)-ene-diolate **B**, formed by heterolytic cleavage of the bidentate Ti(IV)-diol complex **A**,[4] was assumed to be the reactive intermediate (Scheme I).

Whereas in the absence of electrophiles, subsequent oxidative dimerization of **B**, *via* coupling of **C**, accounted for the high yield of methyl phenylglyoxylate **2** (77%) and Ti(III) (25%), in the presence of aromatic aldehydes **3**, quantitative *syn*-diastereoselective aldol condensation of **B** with **3** gives rise to α,β-dihydroxyesters **4** (50% yield, 90% *syn*-diastereoselectivity).[3]

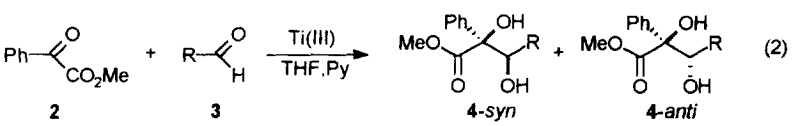
Scheme I



In the course of our studies, we found that reduction of **2** by an excess of $TiCl_3$ in anhydrous THF solution, provided that Pyr was present, afforded **1a,b** (yield, 59%; meso/*dl*, 98/2). This result prompted us to explore the possibility that **2** itself might serve as a "methyl mandelate anion equivalent" to achieve carbon-carbon bond formation in reaction with electrophiles under Lewis acid-reductive conditions (eq 1).



In this context we now report a widely applicable new methodology for *syn*-diastereoselective construction of α,β-dihydroxyesters **4** (60-94% yield; up to 85% *syn*-diastereoselectivity) by reacting an equimolar amount of **2** and aromatic or aliphatic aldehydes **3** with two equivalents of $TiCl_3$ in anhydrous THF/Py solution at room temperature (eq 2).



The type of ligand (Ln) at the titanium ion, which possesses reductive and Lewis acid properties, is ultimately responsible for both determining the nucleophilic reactivity of **B** and achieving high diastereocontrol in the formation of **4**.

Results and Discussion

After some optimizations, the following conditions (method A) proved to be effective: equimolar amounts of **2** and **3** (2.5 mmol) in anhydrous THF (10 mL) and Pyr[5] (3 mmol) were treated with a 1 M $TiCl_3$-THF/CH_2Cl_2 (2:1) solution[6] (5 mmol) under N_2 at r.t. (20°C). Quenching with water after 30 min, followed by usual workup, afforded **4** as the sole reaction product.

As it is apparent from Table I, the yields of **4a-q** range from 60 to 94%, based on the starting **2**, and are always quantitative, based on the converted **2**. The level of stereocontrol is uniformly high (*ca* 90%) regardless of the steric bulk of the substituent R in the aldehyde. The only exception is the lack of selectivity found with acetaldehyde (entry k).

An X-ray diffraction analysis of the prevailing isomer **4i** (isomer ratio, 96:4), the ORTEP representation of which is depicted in Fig. 1, shows that the structure corresponds to a simple *syn* diastereoselectivity[7] (Masamune nomenclature).[8]

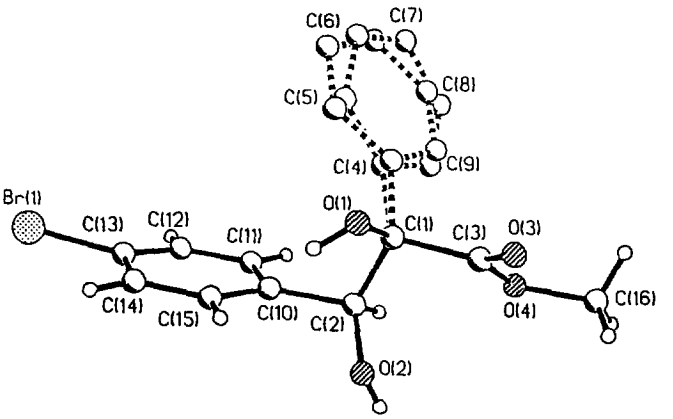


Fig. 1 ORTEP representation of isomer **4i** with the atom-labeling scheme

By analogy with the major isomer **4i** and by assuming an analogous topology in the transition state leading to carbon-carbon bond formation, the prevailing diastereoisomer of compounds **4a-q** should have *syn* relative configuration. The only available literature synthesis[9] concerns **4a** and one report[9d] tentatively ascribes the *syn* (≡ threo) configuration to the isomer melting at 144 °C. Since this isomer prevails (90:10 ratio) under our reaction conditions, we are in a position to confirm the stereochemical assignment proposed.

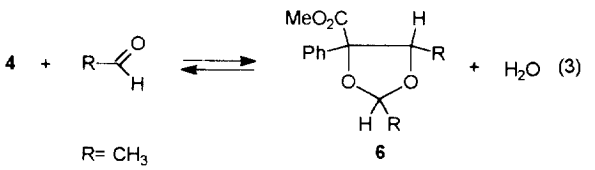
Two physical properties differentiate well the *syn* from the *anti* isomer **4a-q**: the chromatographic mobility ($R_{f\ syn} < R_{f\ anti}$) and the field (δ ppm) at which the CO_2Me singlet resonates in the ^1H NMR spectrum ($\delta_{syn} > \delta_{anti}$). As a consequence, α,β-dihydroxyesters **4** were easily separated into pure

diastereoisomers by chromatography (flash column)[10] and the *syn*:*anti* ratios were determined by ^1H NMR analysis of the crude reaction mixture.

As evidenced in Table I, the highest yields of **4** and the highest *syn* selectivity were observed by employing a Ti(III)/Py molar ratio close to 2:1 and an equimolar amount of **2** and **3** (entries a-q). In the absence of Pyr (entries a", b", and i"), a considerable decrease of **4**, a concomitant formation of methyl mandelate **5** (10-17% yield), and a lower *syn*:*anti* ratio were observed. A RC(O)H/PhC(O)CO_2Me molar ratio of 2:1 decreased the yield of **4** without affecting the diastereoselectivity (entries a', b', g', and i').

When water (0.25 mL) was used (entry i'"), as an additive instead of Pyr, a poor *anti*-diastereoselectivity was observed (*syn*:*anti* ratio, 41:59) and the yield of **4i** dropped from 85 to 20% in favor of **5** (40%). **3i** was choosen as a representative aldehyde, but controlling experiments with other aldehydes afforded similar results as far as product distribution and diastereoselectivity are concerned.

The only exception to this general behavior was found with acetaldehyde (entry k): the reaction was stereorandom even in the presence of Pyr and, when two equivalents of acetaldehyde were used (entry k'), formation of dioxolanes **6**[11,12] (mixture of inseparable isomers) also occurred (eq 3), raising the combined reaction yield (**4** + **6**) to 93%.



The synthesis of **4** was also achieved by performing the reductive coupling of **2** and **3** with an aqueous acidic $TiCl_3$ solution in glacial CH_3CO_2H, as a solvent (method B, see experimental).

However, the data reported in Table I for method B, as compared with those obtained with method A, are striking in several regards: 1) poor *anti*-diastereoselectivity was always found; 2) yields of **4a-i** were uniformly high (71-83%) and, notwithstanding the aqueous acidic medium (pH ≅ 1), **5** was always formed in a very minute amount (< 5%): this product distribution is in sharp contrast with the extensive formation of **5** (40-50% yield), to the detriment of **4**, observed in THF solution when traces of water (0.25 mL) were present (entry i'" and controlling experiments with other aldehydes); 3) with aliphatic aldehydes (entries k-n) formation of acetals **6** (eq 3) occurred even at a RC(O)H/**2** molar ratio of 1:1.

The easy acetalization step in aqueous solution,[11,12] cessation of the reaction at the 1,2-diol stage in anhydrous THF (it should be exactly the opposite!),[13] the reversed diastereoselectivity and, above all, the yield of **5**, higher in THF/H_2O than in aqueous acidic solution, suggest that dramatically different transition-state structures are involved in these two protocols.

Whereas the mechanism postulated in earlier papers[14] for the Ti(III)-mediated addition of α-X-substituted benzoyl compounds (PhC(O)X) to carbonyls in aqueous acidic solution (method B) is still open to question (radical or organometallic addition?), we report herein experimental evidence (data of **Table II**) that strongly supports the intermediacy of a Ti(IV)-ene diolate **B** (Scheme I) as the reactive partner in condensation with **3** under protocol A.

Table I. Yields of Isolated Products from the Ti(III) Mediated Reaction

$PhC(O)CO_2Me$ + RC(O)H → $PhC(OH)(CO_2Me)C(OH)(H)R$

2 **3a-q** **4a-q**

		Method A[a]		Method B[b]	
entry	R	**4**	*syn*:*anti*[c]	**4**	*syn*/*anti*[c]
a	Ph	70	90:10	76	41:59
a'	"	55[d]	90:10		
a"	"	50[e]	75:25		
b	*p*-CH_3Ph	70	90:10	81	36:64
b'	"	65[d]	90:10		
b"	"	53[e]	76:24		
c	*o*-CH_3Ph	84	94:6	82	41:59
d	*o*-CH_3OPh	94	86:14	83	43:57
e	*m*-CH_3OPh	69	85:15		
f	*p*-CH_3OPh	67	92:8	81	41:59
g	*p*-CNPh	84	90:10	71	52:48
g'	"	65[d]	90:10		
h	*o*-(CO_2H)Ph	84[f]	85:15		
i	*p*-BrPh	85	96:4	81	48:52
i'	"	75[d]	93:7		
i"	"	49[e]	84:16		
i"'	"	20[g]	41:59		
j	2-furyl	84	85:15		
k	CH_3	61	50:50	43(36)[h]	
k'	"	60[d](33)[h]			
m	CH_3CH_2	73	83:17	34(20)[h]	
n	$(CH_3)_2CH$	60	95:5	26(20)[h]	
p	$(CH_3)_3C$	13	99:1	28	35:65
q	$PhCH_2$	75	85:15		

[a]Reduction performed in anhydrous THF. [b]Reduction performed in aqueous CH_3COOH. [c]Determined by ^1H NMR spectroscopy. [d]2 equivalents of RC(O)H were used. [e]Pyr was not used as an additive, and **5** was formed as a byproduct (10-17%). [f]Isolated as lactone. [g]Water (0.25 mL) was used as an additive instead of Pyr. Methyl mandelate **5** was formed as the main product (40%). [h]Numbers in parentheses refers to yields of dioxolane **6**.

Table II. Product Yields[a] from the Ti(III) Mediated Reduction of $PhC(O)CO_2Me$ in Anhydrous THF under Various Conditions

entry	additive[b]	**4i**(*syn*:*anti*)	**5**	**1**(meso:*dl*)
1	Py		6	59 (92:8)
2	Py[c]		traces	25 (91:9)
3	Py, D_2O		58 (90% D)	24 (62:38)
4	Py, D_2O[d]		22 (89% D)	66 (80:20
5	Py, *t*-BuOH		21	72 (93:7)
6	Py, **3i**	85 (96:4)		
7	Py, **3i**[d]	92 (97:3)		
8	D_2O, **3i**	20 (43:57)	40 (94% D)	traces
9	Py, D_2O, **3i**	38 (49:51)	25 (93% D)	traces
10	Py, *t*-BuOH, **3i**	40 (90:10)	30	27 (60:40)
11	none		60	traces
12	none[c]		28	traces

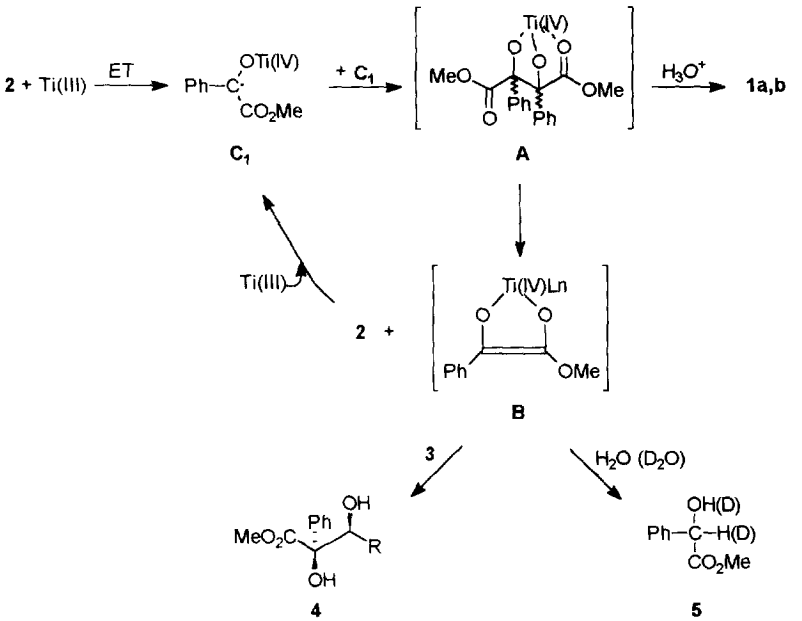
[a] ^1H NMR yields based on the starting **2**. [b] 0.25 mL of each additive and 2.5 mmol of **3i** were used. [c] One equivalent of $TiCl_3$ was used. [d] D_2O or **3i** was added after 10 min and the mixture was allowed to react for additional 30 min.

Reduction of **2** (2.5 mmol) by $TiCl_3$ (5 mmol) in THF(10 mL)/Py(0.25 mL) solution progressed very rapidly (less than 5 min.) at room temperature and afforded dimer **1** as the almost exclusive product (59% yield, entry 1) after aqueous workup. This result suggests a mechanism in which the first step is the formation of a radical, followed by its dimerization.

This radical coupling is not consistent with an organometallic intermediate, unless such an intermediate reforms the dimer in the absence of a carbonyl substrate but is trapped *in situ* when an aldehyde is present. In this regard, the most significant result comes from entry 7 in which the addition of $TiCl_3$ to **2** was followed by addition of **3i** after 10 min. and the reaction mixture was allowed to react for an additional 30 min before quenching with water. Indeed, the addition of the aldehyde last provided **4i** in 92% yield, which is better than the yield obtained for the reaction in the presence of **3i** from the beginning (85%, entry 6).

Considering that the aldehyde was added after the onset of the reaction, *eg* after the dimerization had taken place, **4i** could not arise from a radical addition mechanism, unless dimerization is a reversible process. Since dimer **1**, under the paragonable experimental conditions of Scheme I, underwent Ti(IV)-promoted heterolytic cleavage, but not reversible homolysis,[3] we then formulate the mechanistic model shown in Scheme II to explain the formation of **4a-q** under protocol A.

Scheme II



An initial inner-sphere electron transfer from Ti(III) to **2** affords the carbon centered radical $\mathbf{C_1}$ which irreversibly dimerizes to **A**. A sequential Ti(IV)-catalyzed intramolecular two-electron cleavage of **A** gives rise to **2** and the stabilized Ti(IV)-ene-diolate **B**. In the absence of electrophiles, both **2** and **B** may regenerate **A**, the former by reductive and the latter by oxidative dimerization (Scheme I), so that the equilibrium concentrations of **2**, **A** and **B**, at the time of quenching, is settled either by the relative concentration of Ti(III) and Ti(IV) (entries 1 and 2) or by the relative stabilities of **A** and **B**, which are determined by the type of ligand at Ti(IV) (see later).

However, if an aldehyde is present, the heterolytic cleavage of **A** is continuously shifted in favor of **B** and **2**, since **B** is drained from the equilibrium by fast addition to **3**, and **2** is removed by fast Ti(III) reduction to $\mathbf{C_1}$. As a consequence, the yield of **4**, based on the starting **2**, reached 94% with the most reactive aldehyde (entry d)[15] whereas, in the absence of **3**, not more than 59% of **2** was converted to **1**. These results imply that the addition of **B** to the carbonyl substrate becomes faster than any other process under these conditions. The amount of **4** produced will depend upon how the aldehyde effectively competes for the Ti(IV)-ene-diolate with the other electrophiles present; accordingly, the high yield of **5** (40%) formed when water was used, instead of Pyr (entry i[m]), may easily be explained by the competitive protolysis of **B**. To prove it, we tried to trap the intermediate **B** by replacing H_2O with D_2O: the labeling experiment succeeded and 94% of **5** (40% yield) resulted deuterated (entry 8).

In the presence of both Pyr and D_2O (entry 9), the yield of **5** decreases (25%) in favor of **4i** (38%), since Pyr competes with **B** in scavenging the hydrogen ions formed, following acid hydrolysis of $TiCl_3$ in the presence of water.

It must be highlighted that whenever H_2O or D_2O was used, together with Pyr, the yellow precipitate Ti(IV)THFPy[5] (oligomer of undefined composition) did not form and the blue color of Ti(III) slowly faded to a pale violet, as it was observed under the conditions of method B. That is, in the presence of H_2O, Pyr does not act as a proper ligand to the metal ion, but rather as a base in competition with **B** for hydrogen ions. This proposal is further supported by the reversed *syn/anti* ratio found for **4i** in entries 8 and 9.

However, D_2O added either at the beginning or at a settled equilibrium concentration of **A** (*eg* after 10 min) is less efficient than an aldehyde in removing **B** from the whole equilibrium (*cfr* entries 3 and 4 with 6 and 7). In fact, when D_2O was the only electrophile present, protonation of **A** to **1**[16] (24% and 66% in entries 3 and 4, respectively) was competing with its cleavage to **B**, whilst in the presence of both D_2O and **3i**, only a trace of **1** was found (entry 9).

A result that needs to be stressed because, at a first glance, it seems inconsistent with an anionic intermediate, is the high yield of dimer **1** (72%, entry 5) obtained by reducing **2** in the presence of *t*-BuOH.

The preferential formation of **1**, instead of alcohol **5**, when the protic additive was present[17] is in line with our mechanistic proposal: a reasonable interpretation of this result is that coordination of the bulky *t*-BuOH ligand at Ti(IV) inhibits, owing to steric hindrance, the further formation of the chelate complex **A** (a pre-requisite for the cleavage to occur) and/or increases the hydrogen ion concentration (n *t*-BuOH + Ti(IV) $\rightarrow$ n H^+ + Ti(IV)(*t*-BuO)$_n$), thereby shifting the whole equilibrium towards **1**.[16] However, in the presence of **3i**, the fast aldol condensation intervenes and only 27% of **1** was found unreacted (entry 10).

As stated above, Pyr was essential to ensure both high yields of **4** and high *syn* diastereoselectivity. Concerning the role of Pyr in facilitating the formation of **4**, we believe that the basicity of the ligand (THF or Pyr), which saturates the coordinative valences of Ti(IV) in **A** and **B**, strongly influences both the inherent stability of **A** towards heterolytic cleavage and the nucleophilic reactivity of **B** towards a carbonyl carbon atom.

Pyr is a better donor ligand than THF: when it is present, it preferentially complexes with Ti(IV)[5] and displaces THF from the coordinative sphere of the metal.[18] In this fashion, Pyr increases the electron density at titanium, but strongly decreases its Lewis acidity.

Whereas a high electron density would enhance the nucleophilic reactivity of **B** and, hence, its rate of addition to **3**, a lower Lewis acidity of the metal in **A** may decrease the equilibrium concentration of **B**. In fact, the cleavage of **A**, which is probably favored by further complexation of Ti(IV) with one ester carbonyl,[19] may not be so efficient when the chelating properties of the metal ion are reduced[20] by coordination with Pyr.

These hypotheses are supported by the following data: reduction of **2** afforded mainly **1** in the presence of Pyr (entries 1-2), but gave only **5** in its absence (entries 11-12). Nevertheless, if an aldehyde is added, **B** (Ln= Py) is consumed as it is formed by a very fast addition process (entries a-q); the more stable and less nucleophilic analogue **B** (Ln= THF), though present in high concentration, is not so efficiently consumed and partially survives until aqueous workup, affording **5** (10-17% yield) to the detriment of **4** (entries a", b", and i").

Stereochemical Outcome

The low yields of **4**, observed when two equivalents of RC(O)H were used (entries a', b', f', and i') tend to substantiate that solely the aldehyde complexed with titanium[21] is the reactive counterpart of **B**.

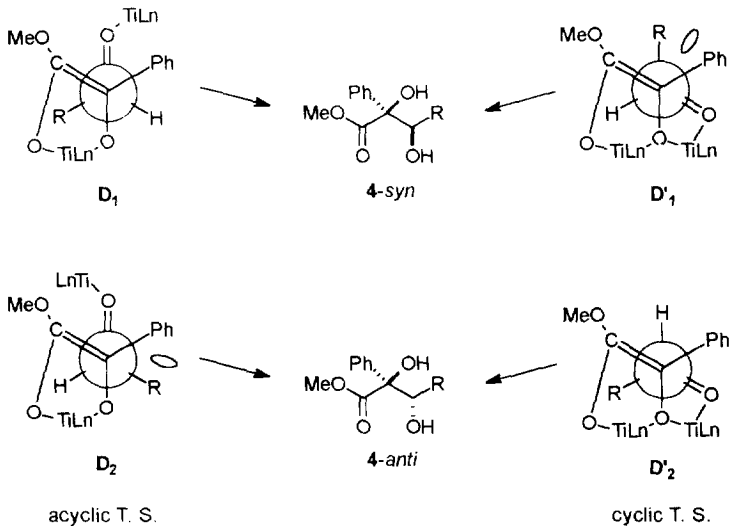
Considering that the coordinative valences of titanium are then completed by molecules of THF and Pyr, the steric environment around the metal ion should be fairly bulky and minimization of steric interactions in such intermediates, at the time of carbon-carbon bond formation, is readily compatible with an acyclic transition state in which the more demanding steric interaction would involve the two O-Ti-Ln groups of the coordinated reactants (Scheme III).

Between the two possible geometries $\mathbf{D_1}$ and $\mathbf{D_2}$, in which the two bulky O-Ti-Ln are antiparallel, the latter (non bonded interaction between Ph and R groups) is destabilized as compared with the former, and the *syn*-**4** isomer is obtained.

Accordingly, irrespective of the size of the R group attached to the aldehyde, the *syn*-selectivity greatly decreases by decreasing the bulk of the ligands at the metal ion (*eg*, on going from THF-Pyr, THF, THF-H_2O to H_2O).

In fact, when the ligand is H_2O, the environment around the metal ion is less bulky, scrambling of ligands would be easier and a Ti-bridging[22] between the reactants would permit, at the time of carbon-carbon bond formation, a cyclic transition state in which the more demanding steric interaction R⇔Ph destabilizes $\mathbf{D'_1}$ with respect to $\mathbf{D'_2}$ geometry, leading preferentially to the *anti* isomer.

Scheme III



Conclusions

In summary, a new reaction sequence, in which an intermediate Ti(IV)-ene-diolate adds to aromatic and aliphatic aldehydes has been examined. The proposed intermediate is easily formed *in situ* from the corresponding α-ketoester in sequential key steps in which the titanium ion performs two important functions: as a reducing agent, it promotes the one-electron dimerization of the ketoester and, as a Lewis acid, it facilitates the heterolytic cleavage of the dimer. The strong donor ligand Pyr enhances the nucleophilic reactivity of the Ti(IV)-ene-diolate and, by adding steric congestion in the addition transition state, increases the *syn*-diastereoselectivity.

The remarkably simple experimental conditions make this reaction of interest both for the high yields of isolated products obtained and for the good level of diastereoselectivity observed. We anticipate that this reaction may be the prototype for other novel transformations based on the reactivity of the Ti(IV)-ene-diolate towards electrophiles.

Experimental Section

General. All reactions were run under N_2 at room temperature (20 °C). Commercially available aldehydes were distilled before use. THF was distilled over Na and benzophenone. An anhydrous $TiCl_3$ solution (1.0 M) in CH_2Cl_2/THF (2:1) from Aldrich and an aqueous acidic $TiCl_3$ solution (15% w/v) from C. Erba were used for method A and B, respectively. Flash column chromatography was carried out by using Merck silica gel (particle size 0.004-0.063 mm). ^1H NMR spectra were recorded in $CDCl_3$ solutions on a Bruker AC-250 MHz instrument. Me_4Si served as an internal standard. Mass spectra were taken on a Hitachi-Perkin-Elmer RMU-6D spectrometer at 70 eV with an IS temperature of 100°C. IR spectra were recorded on a Perkin-Elmer Model E 177 instrument. Melting points were taken on a Kofler apparatus (uncorrected). Diastereoselectivity was determined by ^1H NMR analysis of the crude reaction mixture prior to any purification.

General Procedure for Method A (Table 1). A 50 mL two-necked flask, equipped with a septum cap, magnetic stirrer bar and N_2 inlet, was charged with $PhC(O)CO_2Me$ **2** (2.5 mmol), aldehyde **3a-q** (2.5 mmol), anhydrous THF (10 mL) and anhydrous Pyr (3 mmol). To the well stirred solution, 5 mL (5 mmol) of anhydrous $TiCl_3$ solution was added, in one portion, with a syringe. The blue color of $TiCl_3$ immediately turned to green and a yellow precipitate appeared in a few seconds.[5] After 15 min stirring, the color faded to pale-yellow. Upon additional 20 min stirring, the reaction mixture was quenched with water (15 mL) and extracted with EtOAc (3x50 mL). The extracts were washed until neutrality, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by flash column chromatography on silica gel, eluting with hexane/Et_2O/$CHCl_3$ (from 5:2.5:2.5 to 4:3:3). The structure of the major isomer **4i** corresponded to a *syn* diastereoselectivity. By analogy, a *syn* configuration was assigned to the more abundant isomer **4a-q**. As a rule, unreacted **2**, *anti* **4a-q**, *syn* **4a-q** were eluted in that order.

General Procedure for Method B (Table I). To a well stirred solution of **2** (2.5 mmol) and **3** (2.5 mmol) in CH_3CO_2H (10 mL), at room temperature under N_2, was added, in one portion, a 15% aqueous $TiCl_3$ solution (5 mmol). The blue color of $TiCl_3$ slowly faded to pale-violet. After 1 h, the reaction mixture was extracted with EtOAc (3x50 mL) and workup as in method A was adopted. With aliphatic aldehydes **3k-n**, diaxolanes **6** were also formed, as a mixture of inseparable isomers which were eluted, as a first fraction, from flash column chromatography. No attempt was made to fully characterize **6**, being the effort beyond the scope of the present work.

X Ray Crystallography of 4i. $C_{16}H_{15}O_4Br$, M= 351.2, monoclinic, $P2_{1/C}$, a= 13.366(3), b= 5.689(3), c= 19.562(16) A°, β= 91.67(3)°, Z= 4, V= 1487(2) $A^{\circ 3}$, λ= 1.54180 A°, D_c= 1.57 g cm^{-3}, F(000)= 712, μ (CuKα)= 3.89 mm^{-1}, room temperature, Philips PW1100 modified diffractometer, 8686 total reflections ($3 \leq \vartheta \leq 65$) of which 2481 were independent. The structure was solved by heavy-atom method using the SHELXS-86 program.[23] Full matrix least-square refinement for 134 parameters. The phenyl group appeared disordered. The final result was obtained with the phenyl ring refined as a rigid group disordered over two sets of positions with site occupancy factors of 0.6 and 0.4, respectively. The H atoms were refined with geometrical constraints (riding model). Final refinement, with anisotropic non-H and non-ring C atoms, converged at R1= 0.080 for 890 observed reflections with $I \geq 2\sigma(T)$.

Atomic coordinates and thermal parameters, bond lengths and angles, list of the observed and calculated structure factors have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue 1.

Spectroscopic Data. Compounds **4a-q** of Table I were isolated as pure diastereoisomers and their structural assignments were deduced from the following data.

Methyl-2,3-dihydroxy-2,3-diphenylpropanoate (4a). *Syn* isomer: mp 144 °C (Et_2O/p. ether) (lit. mp 144 °C,[9c] 149 °C[9a]); IR (nujol) υ_{max} 3300 (OH), 1710 (CO), 1260 (C-O-C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.95 (1H, OH, d, J= 7 Hz, D_2O exchangeable), 3.88 (3H, OCH_3, s), 4.0 (1H, OH, s, D_2O exchangeable), 5.41 (1H, CH, d, J= 7 Hz, s after D_2O exchange), 7.12 (8H, Ph H, m), 7.5 (2H, Ph H, m). *Anti* isomer: mp 165-7 °C (Et_2O) (lit. mp 153 °C,[9c] 164-5 °C[9a]); IR (nujol) υ_{max} 3500, 1720, 1260 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.7 (1H, OH, s, D_2O exchangeable), 3.62 (3H, OCH_3, s), 3.7 (1H, OH, s, D_2O exchangeable), 5.43 (1H, CH, s), 7.3 (8H, Ph H, m), 7.8 (2H, Ph H, m).

Methyl-2,3-dihydroxy-2-phenyl-3-(4-methylphenyl)propanoate (4b). *Syn* isomer: mp 167-70 °C (Et_2O/EtOAc, 8:2), 174-6 °C (EtOAc); IR (nujol) υ_{max} 3400 (OH), 1720 (CO), 1240 (C-O-C) cm^{-1}; MS, *m/z* 286 ($M^{\cdot+}$, < 1), 269, 252, 227, 209, 181, 166 (100), 151, 134, 121, 105, 93, 91, 77; ^1H NMR ($CDCl_3$) δ 2.22 (3H, CH_3, s), 2.85 (1H, OH, d, J= 7 Hz, D_2O exchangeable), 3.90 (3H, OCH_3, s), 4.0 (1H, OH, s, D_2O exchangeable), 5.40 (1H, CH, d, J= 7 Hz, s after D_2O exchange), 6.98 (4H, m, Ar H), 7.24 (3H, Ph H, m), 7.52 (2H, Ph H, m). Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.30; H, 6.34. Found: C, 71.26; H, 6.31. *Anti* isomer: mp 128-31 °C (Et_2O); ^1H NMR ($CDCl_3$) δ 2.33 (3H, CH_3, s), 2.66 (1H, OH, sbr, D_2O exchangeable), 3.62 (3H, OCH_3, s), 3.69 (1H, OH, s, D_2O exchangeable), 5.41 (1H, CH, s), 7.12 (2H, Ar H, d, J= 6Hz), 7.25 (2H, Ar H, d, J= 6 Hz), 7.38 (3H, Ph H, m), 7.78 (2H, Ph H, m).

Methyl-2,3-dihydroxy-2-phenyl-3-(2-methylphenyl)propanoate (4c). *Syn* isomer: mp 108-10 °C (Et_2O/hexane, 2:1); IR (nujol) υ_{max} 3500, 3400 (OH), 1730 (CO), 1250 (C-O-C) cm^{-1}; MS, *m/z* 286 ($M^{\cdot+}$, < 1), 166, 120, 119, 107 (100), 105, 91, 77; ^1H NMR ($CDCl_3$) δ 1.97 (3H, CH_3, s), 2.82 (1H, OH, d, J= 6 Hz, D_2O exchangeable), 3.92 (3H, OCH_3, s), 4.13 (1H, OH, s, D_2O exchangeable), 5.68 (1H, CH, d, J= 6 Hz, s after D_2O exchange), 6.91 (1H, Ph H, m), 7.07 (2H, Ph H, m), 7.17 (3H, Ph H, m), 7.40 (2H, Ph H, m), 7.64 (1H, Ph H, m). Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.30; H, 6.34. Found: C, 71.33; H, 6.36. *Anti* isomer: mp 96-7 °C (hexane), ^1H NMR ($CDCl_3$) δ 2.39 (3H, CH_3, s), 2.85 (1H, OH, d, J= 6.5 Hz, D_2O exchangeable), 3.58 (3H, OCH_3, s), 3.92 (1H, OH, D_2O exchangeable), 5.61 (1H, CH, d, J= 6.5 Hz, s after D_2O exchange), 7.16 (3H, Ph H, m), 7.38 (3H, Ph H, m), 7.56 (1H, Ph H, m), 7.73 (2H, Ph H, m).

Methyl-2,3-dihydroxy-2-phenyl-3-(2-methoxyphenyl)propanoate (4d). *Syn* isomer: mp 95-8 °C (Et_2O/hexane, 1:1); IR (nujol) υ_{max} 3580, 3480 (OH), 1730 (CO), 1250 (C-O-C) cm^{-1}; MS, *m/z* 302 ($M^{\cdot+}$, < 1), 285, 268, 225, 166, 136 (100), 121, 107, 105, 91, 77, 51; ^1H NMR ($CDCl_3$) δ 3.52 (1H, OH, d, J= 9 Hz, D_2O exchangeable), 3.60 (3H, OCH_3, s), 3.90 (3H, OCH_3, s), 4.13 (1H, OH, s, D_2O exchangeable), 5.87, (1H, CH, d, J= 9 Hz, s after D_2O exchange), 6.67 (1H, Ar H, m), 6.76 (1H, Ar H, m), 7.16 (5H, 2Ar H+3Ph H, m), 7.50 (2H, Ph H, m). Anal. Calcd for $C_{17}H_{18}O_5$: C, 67.52; H, 6.00. Found: C, 67.56; H, 6.07. *Anti* isomer: 147-8 °C (EtOAc/Et_2O); ^1H NMR ($CDCl_3$) δ 3.36 (1H, OH, d, J= 8.5 Hz, D_2O exchangeable), 3.60 (3H, OCH_3, s), 3.84 (3H, OCH_3, s), 4.02 (1H, OH, s, D_2O exchangeable), 5.76 (1H, CH, d, J= 8.5 Hz, s after D_2O exchange), 6 .94 (2H, Ar H, m), 7.35 (5H, 2ArH+3Ph H, m), 7.72 (2H, Ph H, m).

Methyl-2,3-dihydroxy-2-phenyl-3-(3-methoxyphenyl)propanoate (4e). *Syn* isomer: mp 108-10 °C (Et_2O); IR (KBr) υ_{max} 3480, 3430 (OH), 1700 (CO), 1250 (C-O-C) cm^{-1}; MS, *m/z* 302 ($M^{\cdot+}$, < 1), 243, 225, 197, 166 (100), 151, 137, 136, 135, 107, 105, 77, 51; ^1H NMR ($CDCl_3$) δ 2.96 (1H, OH, s br, D_2O exchangeable), 3.60 (3H, OCH_3, s), 3.90 (3H, OCH_3, s), 3.98 (1H, OH, s, D_2O exchangeable), 5.40 (1H, CH, s), 6.61 (1H, Ar H, m), 6.68 (2H, Ar H, m) 7.03 (1H, Ar H, m). 7.24 (3H, Ph H, m), 7.50 (2H, Ph H, m). Anal. Calcd for $C_{17}H_{18}O_5$: C, 67.52; H, 6.00. Found: C, 67.46; H, 5.98.

Methyl-2,3-dihydroxy-2-phenyl-3-(4-methoxymethyl)propanoate (4f). *Syn* isomer: mp 148-9 °C (Et_2O/hexane, 2:1); IR (KBr) υ_{max} 3450 (OH), 1720 (CO), 1250 (C-O-C) cm^{-1}; MS, *m/z* 302 ($M^{\cdot+}$, < 1), 268, 225, 197, 166, 137 (100), 121, 107, 105, 79, 77, 51; ^1H NMR ($CDCl_3$) δ 2.80 (1H, OH, d, J= 7.8 Hz, D_2O exchangeable), 3.70 (3H, OCH_3, s), 3.90 (3H, OCH_3, s), 3.98 (1H, OH, s, D_2O exchangeable), 5.38 (1H, OH, d, J= 7.8 Hz, s after D_2O exchange), 6.66 (2H, Ar H, d, J= 8.4 Hz), 7.04 (2H, Ar H, d, J= 8.4 Hz), 7.23 (3H, Ph H, m), 7.50 (2H, Ph H, m). Anal. Calcd for $C_{17}H_{18}O_5$: C, 67.52; H, 6.00. Found: C, 67.60; H, 6.06. *Anti* isomer: mp 128-31 °C (Et_2O); ^1H NMR ($CDCl_3$) δ 2.61 (1H, OH, s br, D_2O exchangeable), 3.64 (3H, OCH_3, s), 3.68 (1H, OH, s, D_2O exchangeable), 3.80 (3H, OCH_3, s), 5.38 (1H, CH, s), 6.36 (2H, Ar H, m), 7.88 (5H, 2Ar H+3Ph H, m), 7.79 (2H, Ph H, m).

Methyl-2,3-dixydroxy-2-phenyl-3-(4-cyanophenyl)propanoate (4g). *Syn* isomer: mp 133-5 °C (Et_2O/hexane, 1:1); IR (nujol) υ_{max} 3430, 3390 (OH), 2220 (CN), 1740 (CO), 1250 (C-O-C) cm^{-1}; MS, *m/z* 238 ($M^{\cdot+}$-COOMe), 220, 192, 190, 166 (100), 133, 131, 130, 107, 106, 105, 102, 77; ^1H NMR ($CDCl_3$) δ 3.03 (1H, OH, d, J= 8.5 Hz, D_2O exchangeable), 3.94 (3H, OCH_3, s), 4.00 (1H, OH, s, D_2O exchangeable), 5.45 (1H, CH, d, J= 8.5 Hz, s after D_2O exchange), 7.14 (2H, Ar H, d, J= 7.5 Hz), 7.25 (3H, Ph H, m), 7.40 (2H, Ar H, d, J= 7.5 Hz), 7.42 (2H, Ph H, m). Anal. Calcd for $C_{17}H_{15}NO_4$: C, 68.66; H, 5.09; N, 4.71. Found: C, 68.60; H, 5.06; N, 4.75. *Anti* isomer mp 137-9 °C (Et_2O/hexane, 1:1); ^1H NMR ($CDCl_3$) δ 2.92

(1H, OH, d, J= 5.5 Hz, D_2O exchangeable), 3.66 (1H, OH, s, D_2O exchangeable), 3.72 (3H, OCH_3, s), 5.42 (1H, CH, d, J= 5.5 Hz, s after D_2O exchange), 7.42 (5H, Ph H, m), 7.63 (4H, Ph H, m).

Methyl-2-hydroxy-2-phenyl-2-phthalidylacetate (4h). mp 198-200 °C (AcOEt/Et_2O, 1:1); IR (nujol) υ_{max} 3470 (OH), 1770 (CO lactone), 1730 (CO), 1270 (C-O-C) cm^{-1}; MS, *m/z* 298 ($M^{\cdot+}$, 5), 239 (M-COOMe), 221, 165, 134 (100), 105, 77; ^1H NMR ($CDCl_3$) δ 3.86 (1H, OH, s, D_2O exchangeable), 3.96 (3H, OCH_3, s), 6.11 (1H, Ar H, d, J= 8.5 Hz)[24], 6.20 (1H, CH, s), 7.33 (1H, Ar H, m), 7.48 (4H, 3Ph H+ Ar H, m), 7.75 (2H, Ph H, m), 7.88 (1H, Ar H, d, J= 8.5 Hz). Anal. Calcd for $C_{17}H_{14}O_5$: C, 68.44; H, 4.73. Found: C, 68.48; H, 4.77.

Methyl-2,3-dihydroxy-2-phenyl-3-(4-bromophenyl)propanoate (4i). *Syn* isomer: it was shown to have the *syn* configuration by single crystal X-ray difractometry; mp 173-5 °C (EtOAc/hexane, 8:2); IR (KBr) υ_{max} 3440 (OH), 1720 (CO), 1240 (C-O-C) cm^{-1}; MS, *m/z* 334-332 (M-H_2O, < 1), 317-315, 293-291 (M-COOMe), 276-274, 275-273, 247-245, 187-185, 166 (100), 107, 77, 51; ^1H NMR ($CDCl_3$+DMSO) δ 3.85 (3H, OCH_3, s), 4.85 (1H, OH, s, D_2O exchangeable), 5.34 (1H, CH, d, J= 6 Hz, s after D_2O exchange), 5.55 (1H, OH, d, J= 6 Hz, D_2O exchangeable), 6.96 (2H, Ar H, m), 7.20 (5H, 3Ph H+2 Ar H, m), 7.50 (2H, Ph H, m). Anal Calcd for: $C_{16}H_{15}O_4Br$: C, 54.85; H, 4.32. Found: C, 54.81; H, 4.36. *Anti* isomer: mp 158-61 °C (EtOAc/hexane, 8:2); ^1H NMR ($CDCl_3$) δ 2.72 (1H, OH, s br, D_2O exchangeable), 3.67 (3H, OCH_3, s), 3.67 (1H, OH, s, D_2O exchangeable), 5.36 (1H, CH, s), 7.24 (2H, Ar H, m), 7.40 (5H, 2Ar H+3Ph H, m), 7.72 (2H, Ph H, m)

Methyl-2,3-dihydroxy-2-phenyl-3-(2-furyl)propanoate (4j). *Syn* isomer: mp 119 °C (Et_2O); IR (KBr) υ_{max} 3520, 3430 (OH), 1730 (CO), 1250 (C-O-C) cm^{-1}; MS, *m z* 262 ($M^{\cdot+}$, 2), 244 (M-H_2O), 227, 203, 185, 166, 105 (100), 97, 77; ^1H NMR ($CDCl_3$) δ 3.02 (1H, OH, d, J= 6 Hz, D_2O exchangeable), 3.89 (3H, OCH_3, s), 4.20 (1H, OH, s, D_2O exchangeable), 5.50 (1H, CH, d, J= 6 Hz, s after D_2O exchange), 6.02 (1H, furan H, d, J= 3.5 Hz), 6.14 (1H, furan H, dd, J= 3.5, 2 Hz), 7.25 (3H, 2Ph H+furan H, m), 7.55 (2H, Ph H, m). Anal. Calcd for $C_{14}H_{14}O_5$: C, 64.10; H, 5.38. Found: C, 64.05; H, 5.35. *Anti* isomer: mp 104-6 °C (Hexane/$CHCl_3$, 9:1); ^1H NMR ($CDCl_3$) δ 2.70 (1H, OH, d, J= 8.5 Hz, D_2O exchangeable), 3.71 (3H, OCH_3, s), 3.86 (1H, OH, s, D_2O exchangeable), 5.46 (1H, CH, d, J= 8.5 Hz, s after D_2O exchange), 6.38 (2H, furan H, m), 7.40 (4H, 3Ph H+furan H, m), 7.74 (2H, Ph H, m).

Methyl-2,3-dihydroxy-2-phenylbutanoate (4k). Isomeric mixture (thick liquid): IR (film) υ_{max} 3500 (OH), 1740 (CO), 1260 (C-O-C) cm^{-1}; MS, *m/z* 192 (M-H_2O, < 1), 176, 175, 166, 165, 151, 134, 133, 105 (100), 77. One isomer: ^1H NMR ($CDCl_3$) δ 0.98 (3H, CH_3, d, J= 6.5 Hz), 2.1 (1H, OH, s br, D_2O exchangeable), 3.8 (1H, OH, s, D_2O exchangeable), 3.82 (3H, OCH_3, s), 4.55 (1H, CH, q, J= 6.5 Hz), 7.35 (3H, Ph H, m), 7.64 (2H, Ph H, m). The other isomer.: ^1H NMR ($CDCl_3$) δ 1.24 (3H, CH_3, d, J= 6 Hz), 2.3 (1H, OH, s br, D_2O exchangeable), 3.80 (3H, OCH_3, s), 3.98 (1H, OH, s, D_2O exchangeable), 4.44 (1H, CH, q, J= 6 Hz), 7.35 (3H, Ph H, m), 7.64 (2H, Ph H, m).

Methyl-2,3-dihydroxy-2-phenylpentanoate (4m). *Syn* isomer: mp 77-80 °C (Et_2O); IR (KBr) υ_{max} 3520, 3480 (OH), 1735 (CO), 1260 (C-O-C) cm^{-1}; MS, *m/z* 225 (M+1, < 1), 207, 190, 166, 151, 134, 105 (100), 77; ^1H NMR ($CDCl_3$) δ 0.9 (3H, CH_3, t, J= 7 Hz), 1.18 (1H, CH_2, ddq, J= 15, 2.5, 7 Hz), 1.31 (1H, CH_2, ddq, J= 15, 10, 7 Hz), 2.10 (1H, OH, s br, D_2O exchangeable), 3.83 (3H, OCH_3, s), 4.0 (1H, OH, s, D_2O exchangeable), 4.22 (1H, CH, dd, J= 2.5, 10 Hz), 7.35 (3H, Ph H, m), 7.61 (2H, Ph H, m). Anal. Calcd for $C_{12}H_{16}O_4$: C, 64.26; H, 7.20. Found: C, 64.30, H, 7.17. *Anti* isomer: mp 99-102 °C (Et_2O); ^1H NMR

($CDCl_3$) δ 1.04 (3H, CH_3, t, J= 7.5 Hz), 1.42 (1H, CH_2, ddq, J= 14, 2.5, 7.5 Hz), 1.63 (1H, CH_2, ddq, J= 14, 10, 7.5 Hz), 1.90 (1H, OH, s br, D_2O exchangeable), 3.80 (3H, OCH_3, s), 3.96 (1H, OH, s, D_2O exchangeable), 4.13 (1H, CH, dd, J= 2.5, 10 Hz), 7.35 (3H, Ph H, m), 7.66 (2H, Ph H, m).

Methyl-2,3-dihydroxy-2-phenyl-4-methylpentanoate (4n). *Syn* isomer: mp 55-7 °C (Hexane/Et_2O, 8:2); IR (nujol) υ_{max} 3500 (OH), 1720 (CO), 1280 (C-O-C) cm^{-1}; MS, *m/z* 179 ($M^{\cdot+}$-COOMe), 166, 151, 134, 106, 105 (100), 77; ^1H NMR ($CDCl_3$) δ 0.81 (3H, CH_3, d, J= 6.8 Hz), 0.85 (3H, CH_3, d, J= 6.8 Hz), 1.58 (1H, CH, m, J= 6.8, 3 Hz), 2.32 (1H, OH, d, J= 11 Hz, D_2O exchangeable), 3.82 (3H, OCH_3, s), 4.3 (1H, OH, s, D_2O exchangeable), 4.28 (1H, CH, dd, J= 11, 3 Hz, d after D_2O exchange), 7.34 (3H, Ph H, m), 7.64 (2H, Ph H, m). Anal: Calcd for $C_{13}H_{18}O_4$: C, 65.51; H, 7.62: Found: C, 65.57; H, 7.63.

Methyl-2,3-dihydroxy-2-phenyl, 4,4-dimethylpentanoate (4p). *Syn* isomer: 88-91 °C (petroleum ether), IR (nujol) υ_{max} 3500 (OH), 1740 (CO), 1250 1120 (C-O-C) cm^{-1}; MS, *m/z* 193 ($M^{\cdot+}$-COOMe), 177, 166 (100), 151, 134, 105, 87, 77, 57, 41; ^1H NMR ($CDCl_3$) δ 0.74 (9H, CH_3, s), 2.47 (1H, OH, d, J= 10.5 Hz, D_2O exchangeable), 3.83 (3H, OCH_3, s), 4.02 (1H, OH, s, D_2O exchangeable), 4.18 (1H, CH, d, J= 10.5 Hz, s after D_2O exchange), 7.32 (3H, Ph H, m), 7.72 (2H, Ph H, m). Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.63; H, 7.99. Found: C, 66.59; H, 7.82. *Anti* isomer: mp 118-20 °C (Et_2O); ^1H NMR ($CDCl_3$) δ 1.06 (9H, CH_3, s), 1.83 (1H, OH, s br, D_2O exchange), 3.70 (1H, OH, s, D_2O exchangeable), 3.74 (3H, OCH_3, s), 4.16 (1H, CH, s), 7.35 (3H, Ph H, m), 7.70 (2H, Ph H, m).

Methyl-2,3-dihydroxy-2,4-diphenylbutanoate (4q). *Syn* isomer: mp 121-2 °C (Et_2O/petroleum ether, 1:1); IR (nujol) υ_{max} 3460 (OH), 1720 (CO), 1250 (C-O-C) cm^{-1}; MS, *m/z* 286 ($M^{\cdot+}$, < 1), 269, 257, 227, 209, 166 (100), 151, 134, 105, 91, 77; ^1H NMR ($CDCl_3$) δ 2.22 (1H, OH, s br, D_2O exchangeable), 2.48 (1H, CH_2, dd, J= 14.5, 2.8 Hz), 2.59 (1H, CH_2, dd, J= 14.5, 10 Hz), 3.78 (3H, OCH_3, s), 4.06 (1H, OH, s, D_2O exchangeable), 4.59 (1H, CH, dd, J= 10, 2.8 Hz), 7.10 (2H, Ph H, m), 7.22 (3H, Ph H, m), 7.38 (3H, Ph H, m), 7.71 (2H, Ph H, m). Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.30; H, 6.34. Found: C, 71.26; H, 6.35. *Anti* isomer: mp 104-5 °C (Et_2O/petroleum ether, 1:1), ^{1}1H NMR ($CDCl_3$) δ 2.0 (1H, OH, s br, D_2O exchangeable), 2.80 (1H, CH_2, dd, J= 14, 4 Hz), 2.88 (1H, CH_2, dd, J= 14, 9 Hz), 3.70 (3H, OCH_3, s), 3.85 (1H, OH, s; D_2O exchangeable), 4.52 (1H, CH, dd, J= 4, 9 Hz). 7.30 (8H, Ph H, m), 7.66 (2H, Ph H, m).

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References and Notes

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1. (a) Gung, B. W.; Wolf, M. A. *J. Org. Chem.* **1992**, *57*, 1370 and references therein. (b) For a review on titanium-catalyzed reactions: Duthaler, R. O.; Hafner, A. *Chem. Rev.* **1992**, *92*, 807. (c) Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*, Springer-Verlag: Berlin, **1986**; pp 123-88.
2. (a) For a review on crystal structures of Lewis acid carbonyl complexes: Shambayati, S.; Crowe, W. E.; Shreiber, S. L. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 272. (b) Kijooka, S.; Nakano, M.; Shiota, F.;

Fujiyama, R. *J. Org. Chem.* **1989**, *54*, 5409. (c) Shirodkar, S.; Stormes, M. N.; Thornton, E. *Tetrahedron Lett.*, **1990**, *31*, 4699. (d) Harrison, C. R. *Tetrahedron Lett.*, **1987**, *28*, 4135. (e) Nakada, M.; Urano. Y.; Kabayashi, S.; Ohno, M. *Tetrahedron Lett.*, **1994**, *35*, 741. (f) Pellisier, H.; Toupet, L.; Santelli, M. *J. Org. Chem.*, **1994**, *59*, 1709.

3. Clerici, A.; Clerici, L.; Porta, O. *J. Org. Chem.*, **1995**, *60*, 480.
4. Ti(IV)-complex **A** may not be the monomer shown in Scheme I. The most famous example is the Sharpless catalyst in which the strained $(i\text{-PrO})_2$Ti-tartrate monomer is stabilized by dimerization or similar aggregates: ref 1b, p 813 and references therein. Besides, the coordinative valences of Ti(IV) in complexes **A** and **B** may well be saturated by coordination with the solvent (THF and Pyr).
5. Pyr acts as a proper ligand at the metal ion since, upon addition of $TiCl_3$ to the solution of **2** and **3** in THF, a yellow precipitate is formed in a few seconds. ^{1}H NMR (DMSO) spectrum of the solid evidences the presence of Pyr and THF in the ratio 4:1. The adduct, probably a Ti(IV)THFPy oligomer, is very sensitive to moisture and is completely destroyed by quenching the reaction with water.
6. Solutions of $TiCl_3$ in THF/CH_2Cl_2 (2:1) are, now, commercially available from Aldrich and are stable for long periods, provided air and moisture are excluded.
7. The term "*simple diastereoselectivity*" refers to the relative stereochemistry of two newly created chiral carbon centers formed by the union of two prochiral sp^2 hybridized carbon atoms of achiral molecules. Heathcock, C. H. *Asymmetric Synthesis*, Academic Press: Orlando, **1984**, Vol 3, part B.
8. Masamune, S.; Ali, A. S. K.; Snitman, D. L.; Garvey, D. S. *Angew. Chem., Int. Ed. Engl.* **1980**, 557.
9. (a) Beccalli, E. M.; Marchesini, A. *Gazz. Chim. Ital.* **1984**, *114*, 389. (b) Dahn, H.; Fisher, R.; Loewe, L. *Helv. Chim. Acta* **1956**, *39*, 1774. (c) Kohler, E. P.; Brown, F. W. *J. Am. Chem. Soc.* **1933**, *55*, 4299. For configurational assignments: (d) Zimmerman, H. E.; Singr, L.; Thyagarayan, B. S. *J. Am. Chem. Soc.* **1959**, *81*, 108. (e) *Beilstein*, *10*, E III, 1966.
10. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
11. For as concern formation of acetals **6**, aldehyde-Lewis acid 2:1 complexes may well be involved: (a) Clerici, A.; Porta, O. *Synth. Commun.* **1988**, *18*, 2281. (b) Clerici, A.; Porta, O. *J. Org. Chem.* **1990**, *55*, 1240. (c) Szymaniak, J.; Besançon, J.; Moise, C. *Tetrahedron* **1994**, *50*, 2841. (d) Szymaniak, J.; Besançon, J.; Moise, C. *Ibid.* **1992**, *48*, 3867.
12. The existence of RC(O)H-Lewis acid 2:1 complexes has been previously reported in solid and/or solution state: (a) Kijooka, S.; Nakano, M.; Shiota, F.; Fujiyama, R. *J. Org: Chem.* **1989**, *54*, 5409. (b) Ref 2f.
13. Acetalization (eq 3) is a reversible process that can be shifted to the side of acetal only by removal of the water formed: Flawers, H. M. *The Chemistry of the Hydroxyl Group*, Patai, S. Ed.: London, **1971**; p 1029.
14. Clerici, A.; Porta, O. *J. Org. Chem.* **1993**, *58*, 2889 and references cited therein.
15. The high reactivity of *o*-CH_3O-benzaldehyde **3d** is well explained by intramolecular titanium-chelation, which reverses the polar nature of the methoxy group.
16. $TiCl_4$-catalyzed cleavage of **1** does not occur when traces of protic additive, such as water or *t*-BuOH, is present in the reaction mixture: ref 3.
17. Reduction of carbonyls by SmI_2 in THF gives diols but, in the presence of *t*-BuOH affords the corresponding alcohols. (a) Giraud, P.; Namy, J. L.; Kagan, H. B. *J. Am. Chem. Soc.* **1980**, *102*, 2693.

(b) Namy, J. L., Souppe, J.; Kagan, H. B. *Tetrahedron Lett.* **1983**, *24*, 765. (c) Shine, J-S.; Fang, J. M. *Tetrahedron Lett.* **1993**, *34*, 335.

18. Since ligand displacement reactions with Ti(IV)-alkoxides are very fast, there should be no kinetic obstacles to this ligand exchange.
19. In the Sharpless catalyst $(i\text{-PrO})_2$Ti-tartrate, the metal ion reaches an octahedral coordination by dimerization and complexation with one ester carbonyl: ref 1b, p 813.
20. High Lewis acidity is a pre-requisite for Ti(IV)-chelation controlled processes.
21. Supposing a stoichiometric 1:1 complexation of Ti(III) with either RC(O)H or $PhC(O)CO_2Me$, an excess of free carbonyl was left when a molar ratio Ti(III)/RC(O)H/$PhC(O)CO_2Me$ of 2:2:1 was used. It is assumed that the Lewis acid occupies a coordinative site on the carbonyl oxygen that is *cis* to the aldehydic hydrogen: (a) Reetz, M. T.; Hullmann M.; Massa, W.; Berger, S.; Rademacher, P.; Heymanns, P. *J. Am. Chem. Soc.* **1986**, *108*, 2405. (b) Heathcoch, C. H.; Davidsen, S. K.; Hug, K. T.; Flippin, L. A. *J. Org. Chem.* **1986**, *51*, *3027*.
22. Clerici, A.; Porta, O. *J. Org. Chem.* **1985**, *50*, 76.
23. Sheldrick, G. M. *Program for the solution of crystal structures*, **1986**, University of Gottingen, Germany.
24. The proton at 6.11 ppm is the proton at position-4 of the isobenzofuran-1-one ring. The high field, at which resonates, indicates that the proton lies within the shielding cone of one of the two phenyl rings present in the molecule: (a) Clerici, A.; Porta, O. *J. Org. Chem.* **1989**, *54*, 3872. (b) Malpezzi, L. *Acta Cryst.* **1991**, *C 47*, 676.

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