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Advanced Procedure for the Preparation of *cis*-1,2-Dialkylcyclopropanols – Modified Ate Complex Mechanism for Titanium-Mediated Cyclopropanation of Carboxylic Esters with Grignard Reagents

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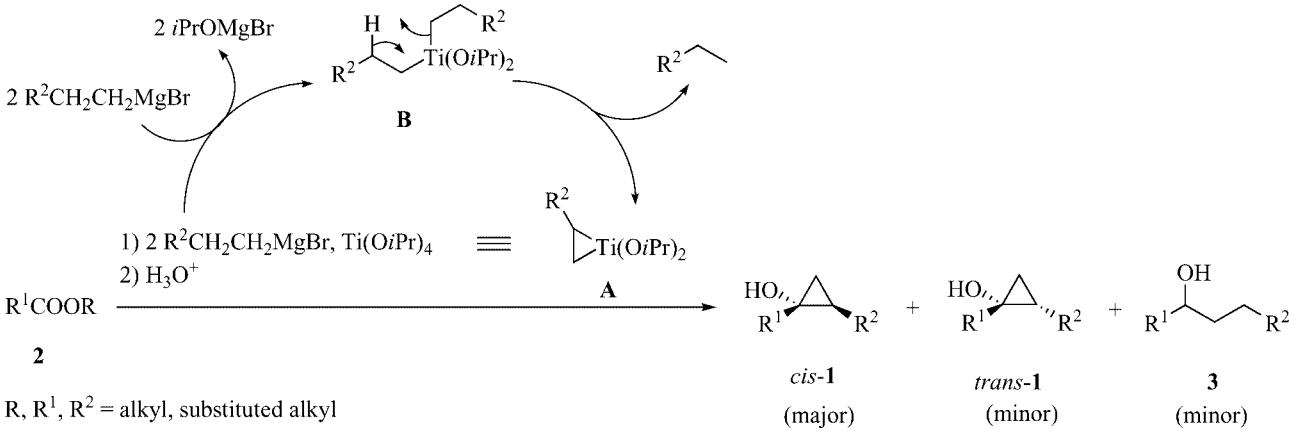
A procedure for the preparation of *cis*-1,2-dialkylcyclopropanols by titanium(IV) alkoxide-mediated cyclopropanation of carboxylic esters with Grignard reagents, involving the addition of 1.5 equiv. of a higher homologue of ethylmagnesium halide to a mixture of 1 equiv. of carboxylic ester, 1 equiv. of titanium(IV) isopropoxide, and 1.5 equiv. of methylmagnesium halide in ether or tetrahydrofuran at room temperature, has been elaborated. This procedure minimizes the formation of secondary alcohol side products with chromatographic retention factors close to those of the *cis*-1,2-disubstituted cyclopropanols. Inhibitory action of carboxylic esters toward the reduction of titanium(IV) isopropoxide with Grignard reagents was observed. This observation, along with some other data, allowed us to suggest a modified ate complex mechanism for the cyclopropanation, proceeding via the corresponding octahedral titanium intermediates. In the context of this mechanism, a suitable explanation for the necessity to use an additional equivalent of Grignard reagent in a stoichiometric version of the reaction was found and experimentally verified.

Introduction

Substituted cyclopropanols are readily available compounds with considerable synthetic potential, due to their ready ability to engage in various three-carbon ring-cleavage reactions.[1,2] In our studies on the elaboration of a stereoselective method for the preparation of trisubstituted olefins through cationic cyclopropyl-allyl rearrangements of cyclopropyl sulfonates[3,4] we needed to operate with stereochemically pure *cis*-1,2-dialkylcyclopropanols (*cis*-**1**). A convenient approach to the synthesis of these compounds is the titanium(IV) alkoxide-catalyzed cyclopropanation of carboxylic esters **2** with higher homologues of ethylmagnesium halides (Scheme 1), acting in this transformation as equivalents of dialkoxytitanacyclopropane reagents **A**,[5–8] which, it had been suggested, might be formed by elimination of alkanes from dialkyltitanium precursors **B**.[5,9,10] Preferential formation of *cis* isomeric cyclopropanols in the reactions between esters and the alkoxytitanacyclopropane reagents was explained theoretically in terms of stabilizing



Scheme 1. Synthesis of 1,2-disubstituted cyclopropanols.

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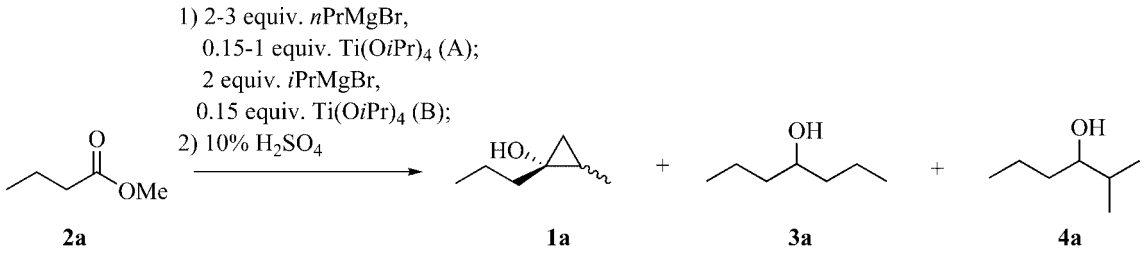
agostic interactions between the Ti atom and the geminal hydrogen in the transition state of the three-carbon ring-closing step.[11] Cyclopropanols *cis*-**1** were produced in the

reaction as major products and could be easily separated from the corresponding minor *trans* isomers by column chromatography. However, up to 10–20% of secondary alcohols **3** were also generated as by-products under these conditions, and the retention factors (R_f values) of alcohols **3** and cyclopropanols *cis*-**1** were close when chromatographic separation was performed over silica gel or alumina, which enormously complicates the chromatographic isolation of *cis*-**1** in a pure form.

Here we have managed to develop an advanced procedure for the preparation of cyclopropanols *cis*-**1** by titanium-mediated cyclopropanation of carboxylic esters with Grignard reagents in a modified procedure that gives no appreciable quantities of the by-products possessing chromatographic properties similar to those of *cis*-**1**. A stabilizing effect of esters on titanium(IV) alkoxide ate complexes with the Grignard reagents was also revealed during this study. These findings and several other results obtained enabled us to propose the modified ate complex mechanism for the cyclopropanation of carboxylic esters with alkoxytitanacyclopropane reagents.

Results and Discussion

Methyl butyrate (**2a**) was chosen as a model compound with which to clarify general tendencies in secondary alcohol formation during titanium-mediated cyclopropanation of esters. Treatment of *n*-propylmagnesium bromide with ester **2a** in diethyl ether in the presence of catalytic amounts of titanium(IV) isopropoxide (Procedure A, catalytic mode) produced a mixture of stereoisomeric cyclopropanols *cis*/*trans*-**1a** together with heptan-4-ol (**3a**) in good yield (Scheme 2). Product ratios depended slightly on reaction times (Table 1, Entries 1 and 2), changing of titanium(IV) isopropoxide to titanium chlorotriisopropoxide (Entries 2 and 3), relative quantities of titanium(IV) alkoxide (Entries 4 and 5), the alkoxide moiety structure in the substrate (Entries 2 and 6), and temperature (Entries 4, 7 and 8). Minor quantities of cyclopropanol *trans*-**1a** were formed in somewhat lower amounts when the reaction was performed in THF (Entries 4, 5, 7, and 8). In the case of the titanium(IV) isopropoxide-catalyzed reaction between methyl butyrate (**2a**) and isopropylmagnesium bromide



Scheme 2. Cyclopropanation of methyl butyrate (**2a**).

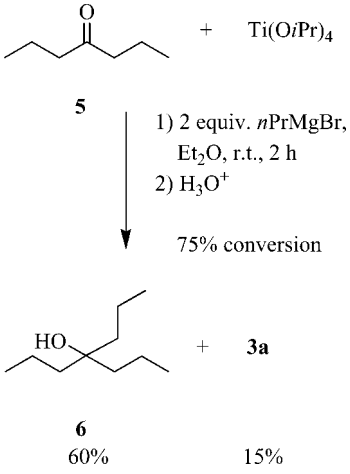
Table 1. Cyclopropanation of methyl butyrate (**2a**).

Entry	RMgBr[a]	Ti(O*i*Pr)$_4$ (equiv.)	Conditions[b]	Yields (%) of products[c] **1a** (*cis*/*trans*)	**3a**
1	*n*PrMgBr	0.15	Et_2O, room temp., 3 h	76 (86:14)	12
2	*n*PrMgBr	0.15	Et_2O, room temp., 1.5 h	76 (85:15)	13
3	*n*PrMgBr	0.15[d]	Et_2O, room temp., 1.5 h	81 (88:12)	10
4	*n*PrMgBr	0.15	THF, room temp., 1.5 h	84 (93:7)	10
5	*n*PrMgBr	1	THF, room temp., 1.5 h	71 (90:10)	13
6[e]	*n*PrMgBr	0.15	Et_2O, room temp., 1.5 h	79 (80:20)	10
7	*n*PrMgBr	0.15	THF, reflux, 1 h	79 (91:9)	11
8[f]	*n*PrMgBr	1	THF, –78→0 °C	75 (90:10)	12
9	*i*PrMgBr	0.15	Et_2O, room temp., 1.5 h	70 (80:20)	7[g]
10	*i*PrMgBr	0.15	THF, room temp., 1.5 h	73 (90:10)	8[h]

[a] 2.2 Equiv. of Grignard reagent were employed in the catalytic version, and 3 equiv. in the stoichiometric version of the reaction. [b] Time of Grignard reagent addition is indicated. [c] Determined from the ^{1}H NMR spectrum of the reaction mixture after the aqueous workup and solvent removal. [d] TiCl(O*i*Pr)$_3$ was used in place of Ti(O*i*Pr)$_4$. [e] Isopropyl butyrate was used in place of methyl butyrate (**2a**). [f] Ester **2a** was added to a mixture of 1 equiv. Ti(O*i*Pr)$_4$ and 3 equiv. *n*PrMgBr at –78 °C. [g] Alcohol **4a** (11%) was also detected. [h] Alcohol **4a** (15%) was also detected.

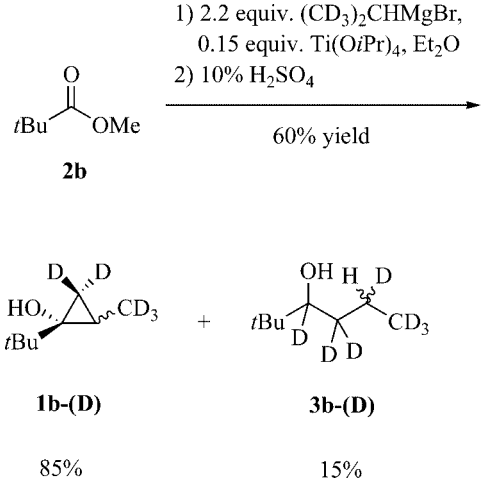
(Procedure B, catalytic mode), branched secondary alcohol **4a** was formed as a by-product along with unbranched alcohol **3a**.

It could be suggested that the precursors to secondary alcohols **3a** and **4a** were the corresponding ketones. However, when *n*-propylmagnesium bromide (2 equiv.) was added at room temperature to an equimolar mixture of titanium(IV) isopropoxide and dipropyl ketone (**5**) in diethyl ether, only minor amounts of secondary alcohol **3a** (ca. 15%) were obtained and tertiary alcohol **6** was mainly formed (Scheme 3). Since this had not been detected in substantial amounts in the products of the titanium-catalyzed cyclopropanation of ester **2a**, it could be concluded that the appearance of secondary alcohol **3a** among the reaction products was by a different route.



Scheme 3. Reaction between ketone **5** and 2 equiv. *n*PrMgBr and 1 equiv. Ti(O*i*Pr)$_4$.

We further studied deuterium distribution in secondary alcohol **3d-(D)** obtained from the reaction between methyl pivalate (**2b**) and $(CD_3)_2CHMgBr$ in the presence of catalytic amounts of titanium(IV) isopropoxide in diethyl ether (Scheme 4). The selection of the substrate **2b** simplified the assignment of the resonance signals in the ^1H and ^{13}C NMR spectra of the alcohol **3b-(D)**, since the singlet signals from the *tert*-butyl group did not complicate the spectral analysis. After removal of the solvent and the remaining starting ester **2b** by evaporation, a mixture of *cis*- and *trans*-cyclopropanols **1b-(D)** (*cis*/*trans* = 30:70), along with secondary alcohol **3b-(D)**, was isolated in 60% overall yield. Preferential formation of *trans*-cyclopropanol **1b-(D)** is observed in this case as a result of unfavorable steric repulsion between CD_3 and *tert*-butyl groups in the transition state leading to cyclopropanol *cis*-**1b-(D)**.[12] Alcohol **3b-(D)** was isolated as a major by-product by column chromatography after treatment of the reaction mixture with an appropriate amount of *N*-bromosuccinimide to convert cyclopropanols **1b-(D)** into the corresponding bromoketone with a higher R_f value.[13]



Scheme 4. Cyclopropanation of methyl pivalate (**2b**) with $(CD)_3$-CHMgBr.

Incorporation of deuterium at C3 and C5 in compound **3b-(D)** was confirmed by its ^{13}C NMR spectrum, showing triplet signals for carbon atoms C3 (δ = 79.0 ppm, J = 21.2 Hz) and C5 (δ = 19.3 ppm, J = 19.2 Hz), shifted upfield in comparison with the same signals in undeuterated alcohol **3b** (see Exp. Sect.). The deuterium contents at C3 and C5 in compound **3b-(D)** were estimated from the ^1H NMR spectroscopic data as 95% and 85%, respectively (see Exp. Sect.). Interestingly, deuterium insertion had occurred diastereoselectively, with one of the diastereomers of alcohol **3b-(D)** predominating (>85:15 ratio), as was deduced by comparison of the ^1H NMR spectrum of **3b-(D)** with that of undeuterated alcohol **3b**. The spectrum of the latter compound showed two different signals with comparable intensities for the diastereotopic protons at C5, whereas compound **3b-(D)** gave predominantly only one of the corresponding signals.

A possible pathway for deuterium incorporation at C3 and C5 in compound **3b-(D)** would be β-hydride shifts in the corresponding dialkyltitanium species (vide infra, Scheme 8).[10] It was conjectured that the generation of titanacyclopropane intermediates from organomagnesium compounds not possessing hydrogens β to the metal atom as sacrificial alkylating agents should minimize the formation of secondary alcohols by this route. Methyltitanium triisopropoxide had successfully been used earlier for the cyclopropanation of esters and *N*,*N*-dialkylcarboxamides with Grignard reagents.[14–16] To avoid an additional methyltitanium triisopropoxide preparation procedure, we studied the possibility of employing the sequential addition of organomagnesium reagents to a mixture of titanium(IV) isopropoxide and a carboxylic ester under conventional conditions.

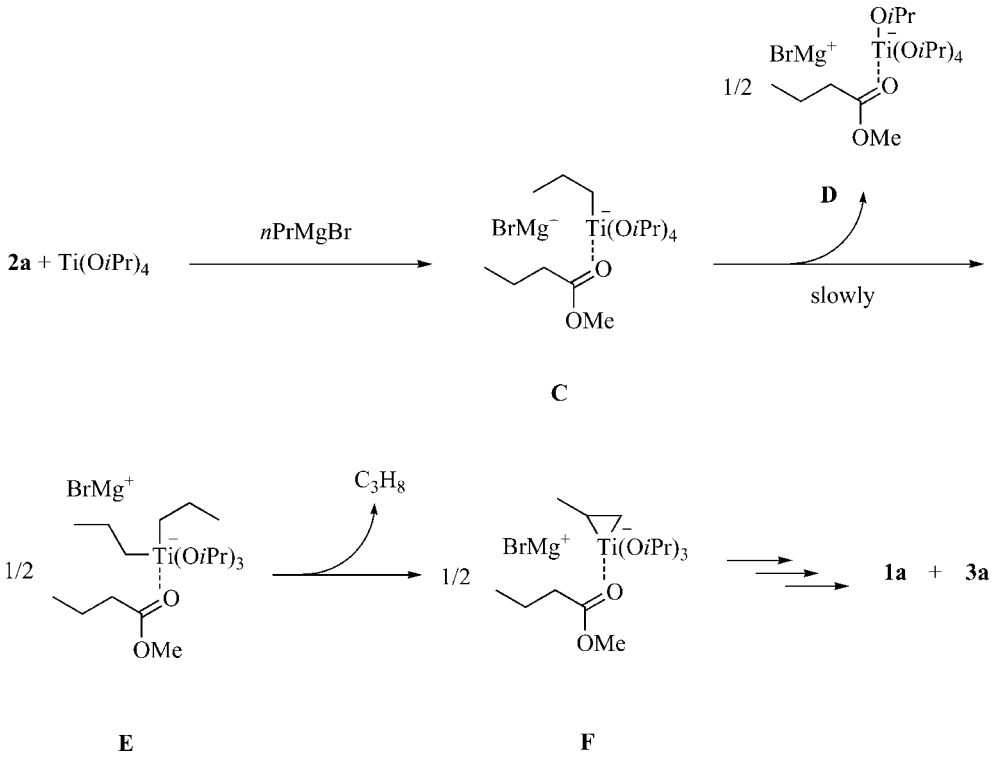
Addition of *n*-propylmagnesium bromide (1 equiv.) to an equimolar mixture of titanium(IV) isopropoxide and ester **2a** in diethyl ether at room temperature resulted, after 15 h and aqueous workup, in the formation of isomeric cyclopropanols **1a** (14%) and alcohol **3a** (4%), along with starting compound **2a** (2%) and isopropyl butyrate (**7a**) (80%). The slow reaction rate between the Grignard reagent and the mixture of ester **2a** and titanium(IV) isopropoxide under the studied conditions was surprising because we had recently reported evidence on the fast generation of titani-

um(III) isopropoxide on treatment of titanium(IV) isopropoxide with ethylmagnesium bromide in diethyl ether at room temperature.[17] Similarly, in the absence of the ester **2a**, *n*-propylmagnesium bromide reacted rapidly with titanium(IV) isopropoxide with intense gas evolution, and the reaction mixture turned black due to the formation of low-valent titanium species. These results indicate that *ester* **2a** *inhibits titanium(IV) alkoxide reduction with the Grignard reagent* and we believe that the inhibition may be caused by the formation of relatively stable octahedral ate complex **C**[18] (Scheme 5). This is slowly transformed into the reaction products through intermolecular alkyl ligand exchange, resulting in the formation of alkoxide ate complex **D** and dialkyltitanium ate complex **E**. Elimination of propane from complex **E** gives titanacyclopropane ate complex **F**, which is further transformed into cyclopropanol **1a** and alcohol **3a** (see below).

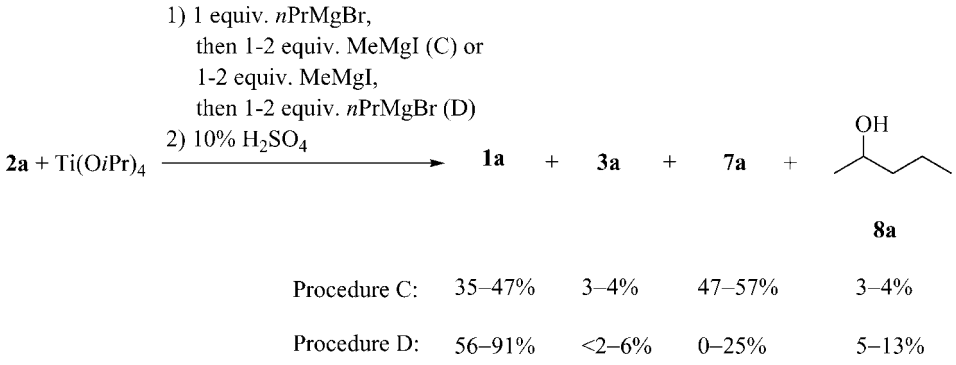
The inhibition by ester **2a** of titanium(IV) alkoxide reduction with alkylmagnesium halides allowed us to infer potential for the generation of dialkyltitanium intermediates merely by sequential addition of Grignard reagents to equimolar mixtures of titanium(IV) isopropoxide and the carboxylic ester. In fact, addition of *n*-propylmagnesium bromide (1 equiv.) and then methylmagnesium iodide (1–2 equiv.) to a mixture of methyl butyrate (**2a**, 1 equiv.) and titanium(IV) isopropoxide (1 equiv.) in diethyl ether (Procedure C) resulted in the formation of stereoisomeric cyclopropanols **1a**, secondary alcohol **3a**, transesterification product **7a**, and secondary alcohol **8a** (Scheme 6, Table 2, Entries 1 and 2). Although this procedure gave cyclopropanol **1a** in only about 40% yield, the content of alcohol **3a** in the reaction mixture was lower than 5%.

The reactivity of methylmagnesium halides toward equimolar mixtures of ester **2a** and titanium(IV) isopropoxide proved to be significantly lower than that of propylmagnesium bromide. Addition of methylmagnesium iodide or methylmagnesium bromide (1 or 2 equiv.) to titanium(IV) isopropoxide (1 equiv.) in diethyl ether or THF at room temperature thus gave yellow or orange solutions that were stable for several hours, with the mixture turning black due to the formation of low-valent titanium species only when a third equivalent of methylmagnesium halide was added. When a mixture of methyl butyrate (**2a**, 1 equiv.), titanium(IV) isopropoxide (1 equiv.), and methylmagnesium iodide (2 equiv.) in diethyl ether was kept at room temp. for 0.5 h, only a 40% yield of isopropylbutyrate **7a**, along with 60% of starting compound **2a**, was detected after hydrolysis, and no products of ester alkylation with methylmagnesium iodide were found.

The dependence of the yields of cyclopropanols **1a** and alcohols **3a** and **8a** on the ratio of organomagnesium compounds when *n*-propylmagnesium bromide was added to an equimolar mixture of ester **2a**, titanium(IV) isopropoxide, and methylmagnesium iodide (procedure D) are summarized in Table 2 (Entries 3–9).[19] This order of mixing of the reagents resulted in significant enhancement of the yields of cyclopropanols **1a**, while the combined yields of by-products **3a** and **8a** remained nearly the same as those obtained in Procedure C (Table 2, Entries 1–4). Use of increasing amounts of methylmagnesium iodide gave lower quantities



Scheme 5. Reaction between ester **2a** and 1 equiv. of *n*PrMgBr and 1 equiv. of Ti(O*i*Pr)$_4$.



Scheme 6. Cyclopropanation of methyl butyrate (**2a**) with *n*PrMgBr and MeMgI.

Table 2. Cyclopropanation of methyl butyrate (**2a**) with *n*PrMgBr and MeMgI in Et_2O.

Entry	MeMgI (equiv.)	*n*PrMgBr (equiv.)	Procedure[a]	Yields (%) of products[b,c] **1a**	**3a**	**8a**	**2a+7a**
1	1	1	C	35	4	4	57
2	2	1	C	47	3	3	47
3	1	1	D	56	5	5	34
4	2	1	D	60	<2	13	25
5	1	2	D	77	6	6	11
6	2	2	D	85	<2	13	0
7	1.5	2	D	88	<2	10	0
8	1.5	1.5	D	88	<2	10	0
9	1.5	1.5	D[d]	91	<2	7	0

[a] Procedure C: *n*PrMgBr (1 equiv.) and then MeMgI (1–2 equiv.) were added at room temp. to an equimolar mixture of ester **2a** and Ti(O*i*Pr)$_4$ in diethyl ether. Procedure D: ester **2a** (1 equiv.) and then *n*PrMgBr (1–2 equiv.) were added at room temp. to an equimolar mixture of 1–2 equiv. MeMgI and Ti(O*i*Pr)$_4$ in diethyl ether. [b] Determined by ^{1}H NMR spectroscopy. [c] Combined yields of *cis*-**1a** and *trans*-**1a**. [d] At 0 °C.

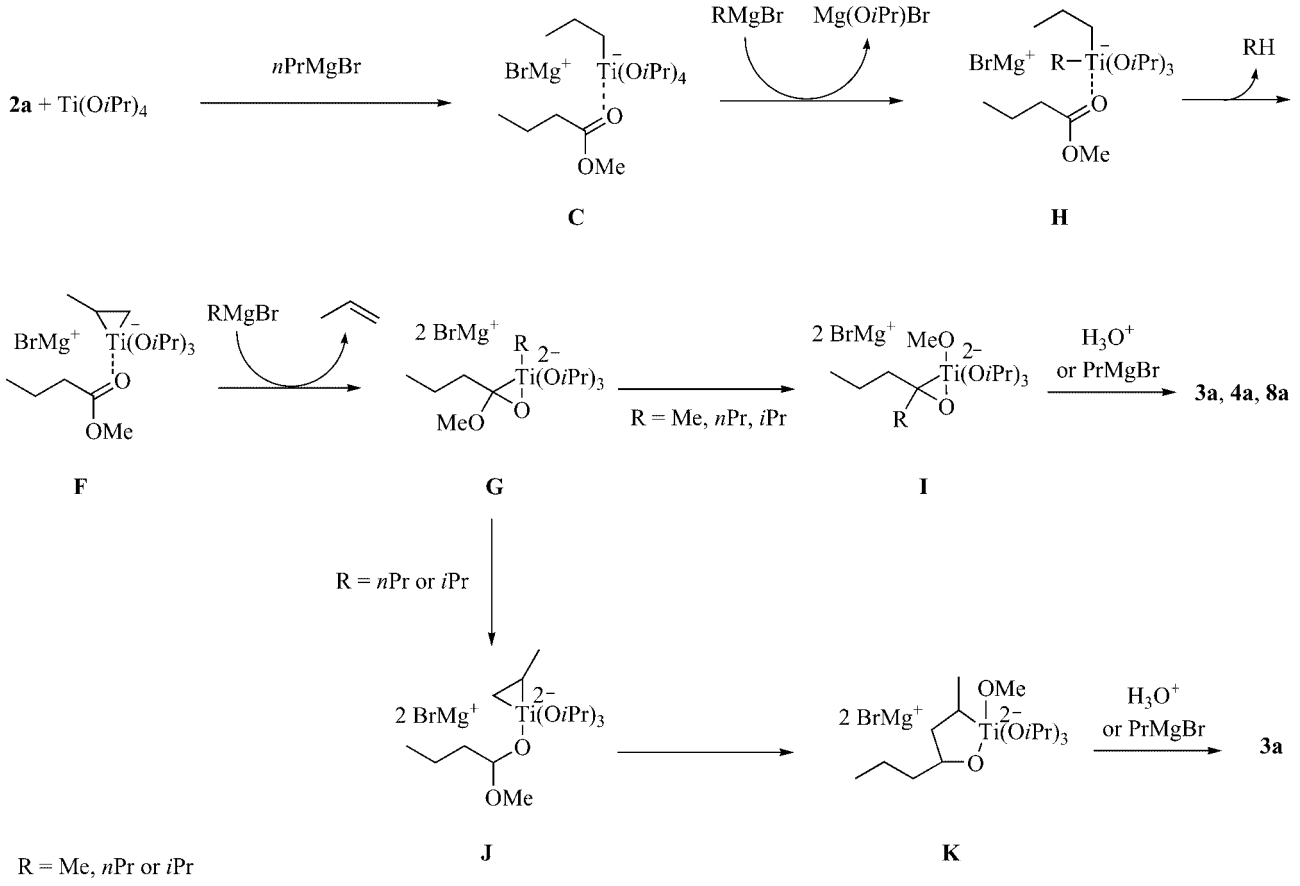
of alcohol **3a**, but almost proportional increases in the yields of pentan-2-ol (**8a**) took place in these cases (Entries 3–9). The lowest yield of secondary alcohol **8a** was observed when 1.5 equiv. of methylmagnesium iodide were used and the reaction was performed at 0 °C (Entry 9).

We believe that the secondary alcohols **3a**, **4a**, and **8a** are formed from a common intermediate, since their combined yields remained nearly constant in all cases examined (Table 1 and Table 2). This intermediate is probably oxatitanacyclopropane intermediate **G**,[20] generated through the alkylation of ate complex **C**, followed by elimination of alkane in dialkyltitanium intermediate **H** (**E** when R = *n*Pr) and propene displacement in the resulting titanacyclopropane complex **F** with the Grignard reagent (Scheme 7). In view of the evidence of the ate complex **C** intermediate formation discussed above, along with the high oxophilicity of titanium and its tendency to form octahedral complexes,[21] all putative intermediates will from now on be depicted as octahedral complexes.

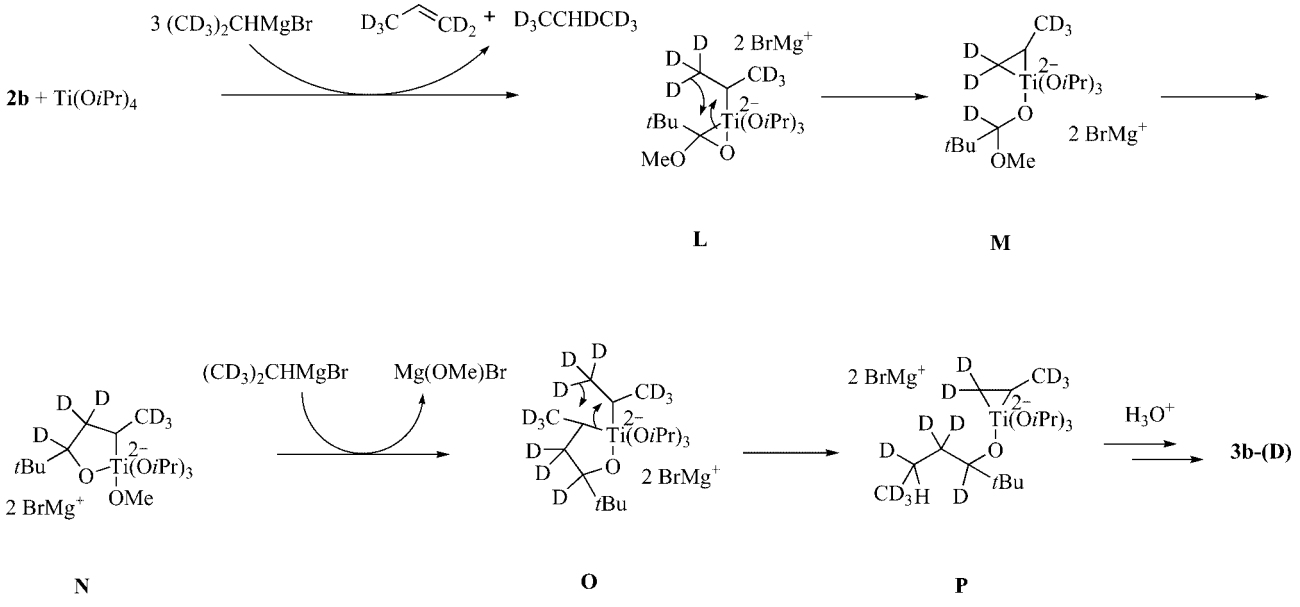
Consistently with this hypothesis, the transformation of oxatitanacyclopropane intermediate **G** into secondary alcohols **3a** (R = Pr), **4a** (R = *i*Pr), and **8a** (R = Me) could be assumed to proceed through heterolytic rearrangement and subsequent hydrolysis of the resulting oxatitanacyclopropane intermediate **I**. The main driving forces for the rearrangement of intermediate **G** to **I** could be stabilization of carbocationic species by oxygen as well as the strength of the Ti–O bond.[21]

In oxatitanacyclopropane **G**, containing an alkyl group with β-hydrogens, the β-hydride shift process evidently competes with the **G** to **I** rearrangement, resulting in titanacyclopropane intermediate **J**. This in turn rearranges to oxatitanacyclopentane **K**, which after hydrolysis gives alcohol **3a** (Scheme 7). This reaction channel is blocked when methylmagnesium halide is used as a sacrificial reagent, since this results in the generation of intermediate **G** (R = Me) without hydrogens β to the metal atom, resulting in a decrease in the yield of alcohol **3a** (Table 2). When an excess of *n*-propylmagnesium bromide or isopropylmagnesium bromide is present, intermediates **I** and **K** can also be transformed into alcohols **3a**, **4a**, and **8a** through disproportionation of the corresponding dialkyltitanium intermediates (vide infra).

The deuterium distribution in by-product **3b-(D)** from the titanium(IV) isopropoxide-catalyzed reaction between methyl pivalate (**2b**) and $(CD_3)_2CHMgBr$ (Scheme 4) fits with the proposed mechanism. Oxatitanacyclopropane intermediate **L** [**L** equals **G** when R = $CH(CD_3)_2$ and Pr is replaced with *t*Bu] undergoes a β-hydride shift, forming titanacyclopropane **M**. Rearrangement of this gives oxatitanacyclopentane **N**, which again undergoes alkylation followed by a β-hydride shift in the dialkyltitanium intermediate **O**



Scheme 7. Proposed mechanism for the formation of secondary alcohols **3a**, **4a**, and **8a**.

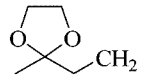


Scheme 8. Proposed mechanism for the formation of alcohol **3b-(D)**.

to afford the titanacyclopropane intermediate **P**. This in turn participates in further reactions without structural transformations of alkoxide moieties, finally resulting after hydrolysis in heptadeuterated alcohol **3b-(D)** (Scheme 8).

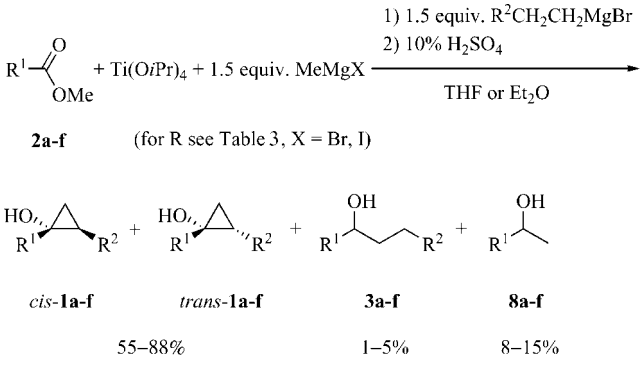
Table 3 presents the yields of cyclopropanols **1a**–**f**, along with the corresponding by-products, obtained in the reactions between esters **2a**–**f** and titanacyclopropane reagents, generated by a standard catalytic procedure (procedure A), and by the stoichiometric version proposed here (pro-

Table 3. Synthesis of 1,2-disubstituted cyclopropanols from esters **2a**–**f**.

Entry	Ester	R^1	R^2	Procedure[a], solvent	Yield (%) of *cis*-**1**[b]	Yield (%) of *trans*-**1**[c]	Content (%) of impurity **3** in *cis*-**1**[c]	Yield (%) of **8**[c]
1	**2a**	*n*Pr	Me	A, THF	68	5	16	-
				D, THF	67	8	<1	13
				D, Et_2O	65	12	<1	8
2	**2b**	*t*Bu	Me	A, Et_2O	49 (*cis*:*trans* = 25:75)[d]		18	-
				D, Et_2O	55 (*cis*:*trans* = 40:60)[d]		3	15
3	**2c**	Me	*n*Bu	A, THF	70	3	12	-
				D, THF	80	2	<2	-[e]
				D, Et_2O	82	2	<2	-[e]
4	**2d**	nC_5H_{11}	Me	A, THF	71	5	15	-
				D, THF	75	8	<1	13
				D, Et_2O	75	13	<1	8
5	**2e**	$Cl(CH_2)_3$	Me	A, THF	67	7	20	-
				D, THF	73	5	-[f]	15
				D, Et_2O	74	10	-[f]	8
6	**2f**		Me	A, THF- Et_2O	80 (*cis*:*trans* = 95:5)[g]		20	-
				D, THF	80[h]	3	<1	14

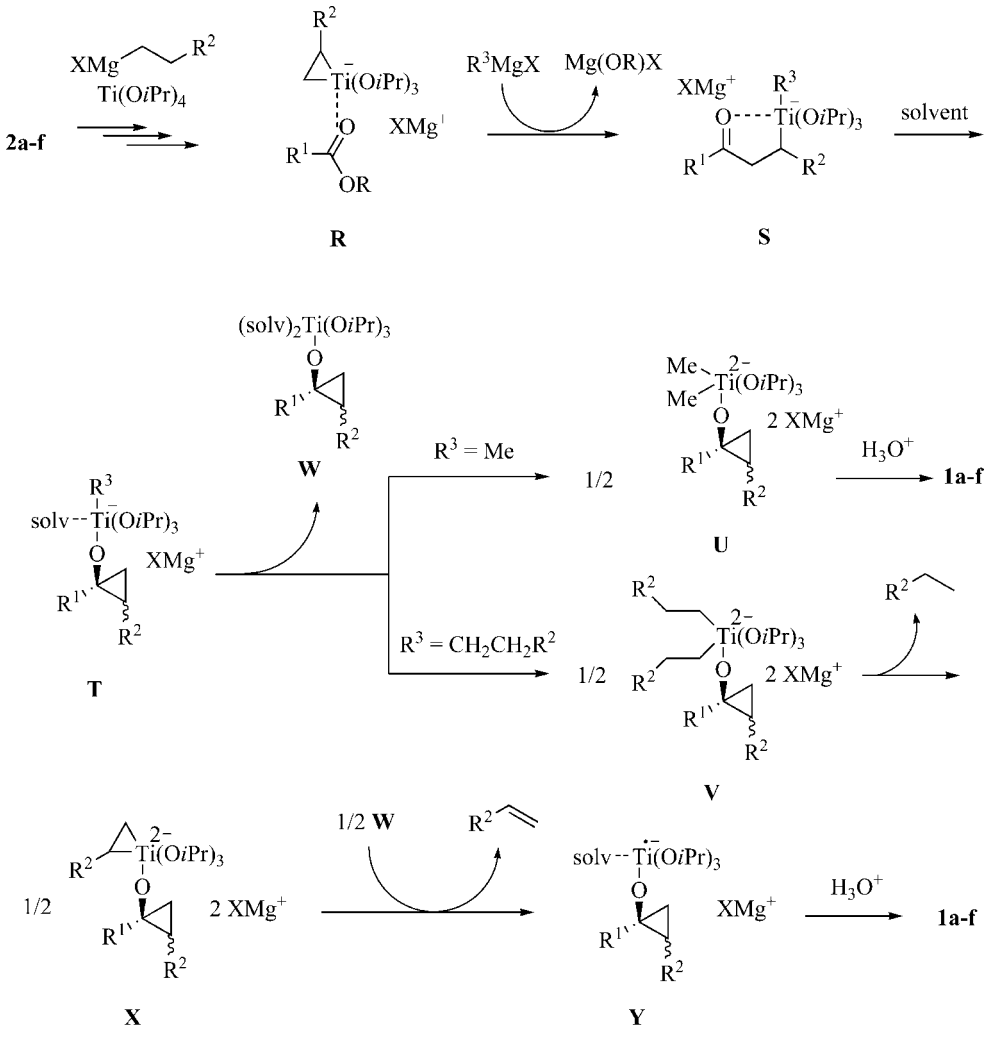
[a] Procedure A: 0.15 equiv. $Ti(OiPr)_4$, 2.2 equiv. $R^2(CH_2)_2MgBr$, THF or Et_2O, room temp. Procedure D: 1 equiv. $Ti(OiPr)_4$, 1.5 equiv. MeMgI (in ether) or MeMgBr (in THF), then 1.5 equiv. $R^2(CH_2)_2MgBr$, Et_2O or THF, 0 °C. [b] Isolated yields. [c] Determined by ^1H NMR spectroscopy. [d] Determined by ^1H NMR spectroscopy. Products were not isolated. [e] The yield was not determined (**8c** = *i*PrOH). [f] Not detected. [g] See ref.[22] [h] 2.5 equiv. of *n*PrMgBr were used to achieve full conversion of **2f**.

cedure D) (Scheme 9). As in the example of ester **2a**, cyclopropanation of esters **2b**–**f** by procedure A in most cases gave the corresponding 1,2-disubstituted cyclopropanols **1b**–**f** with 90% or higher *cis* stereoselectivity. The only exception was the sterically hindered methyl pivalate (**2b**), which gave mainly *trans*-cyclopropanol **1b** in moderate yields (Table 3, Entry 2). Again, the *cis* stereoselectivity of the reaction was slightly higher in THF than in diethyl ether, and secondary alcohols **3b**–**f** (12–20%) were formed as by-products in all cases. Although employment of procedure D gave similar results with respect to product yields and stereoisomer ratios, dramatic decrease in yields of alcohols **3** was observed in all examined cases (Table 3). Alcohols **8** have substantially lower R_f values, due to their lower molecular weights in comparison with corresponding secondary alcohols **3** and, accordingly, *cis*-cyclopropanols **1**.



Scheme 9. Advanced procedure for the preparation of 1,2-disubstituted cyclopropanols.

One more remarkable feature of the studied reaction was the achievement of full substrate conversion only when 3 equiv. of Grignard reagent had been totally consumed. It should also be pointed out that not less than 1.5 equiv. of *n*PrMgBr was necessary for full conversion of ester **2a** (Table 2). Excessive quantities of Grignard reagents are usually applied in the presence of equimolar amounts of titanium(IV) alkoxides for full consumption of the substrates in the cyclopropanation of carboxylic acid derivatives and in some other transformations promoted by titanacyclopropane reagents.[8,23] The results obtained in this work allowed us to surmise that *an extra equivalent of Grignard reagent is consumed for the reduction of titanium(IV) alkoxides to low-valent titanium species.* We believe that a Grignard reagent attack on titanacyclopropane intermediate **R** (**F**, when R^2 = Me and R^1 = Pr, Scheme 5) results in the formation of octahedral β-oxotitanium intermediates **S** and that the 18-electron shell on titanium atom is formally saved[23] during this transformation (Scheme 10). Cyclopropane ring-closure in intermediate **S** affords the titanium cyclopropanolate **T**, which has no "protecting" ester ligand and disproportionates to give dimethyltitanium ate complex **U** (when R^3 = Me) or an unstable dialkyltitanium ate complex **V** (when $R^3 = R^2CH_2CH_2$), along with alkoxytitanium intermediate **W** (Scheme 10). Dialkyltitanium intermediate **V** undergoes further elimination of an alkane, giving titanacyclopropane intermediate **X**. An alkene displacement from this intermediate with alkoxytitanium complex **W** and subsequent redistribution of electrons and alkoxide ligands in the formed adduct give rise to titanium(III) cyclopropanolate ate complex **Y**. This, and the dimethyltitanium complex **U**, are direct precursors of cyclopropanols **1a**–**f**. Evi-



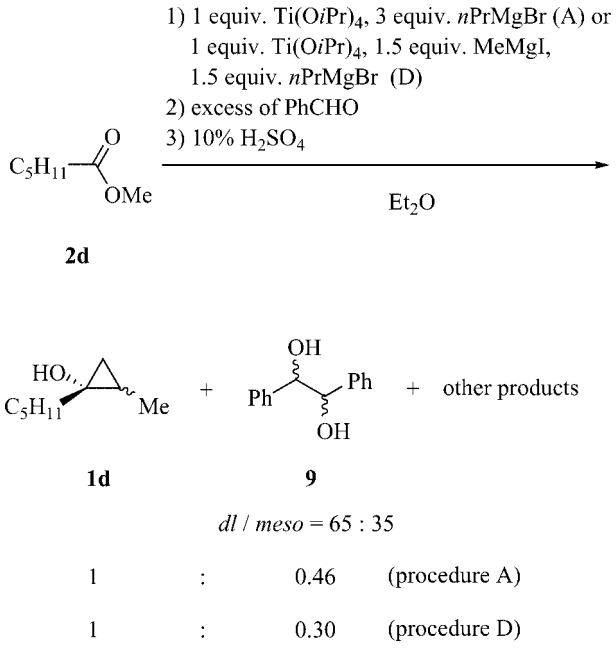
For R, R^1, R^2 see Table 3; R^3 = Me or $CH_2CH_2R^2$; X = Br, I

Scheme 10. Modified ate complex mechanism for the cyclopropanation of esters.

dently, in the catalytic version of the reaction, a carboxylic ester remains in excess in relation to the titanium catalyst, protecting this from reduction with Grignard reagent. This hypothesis explains the adequacy of the use of stoichiometric amounts (ca. 2 equiv.) of Grignard reagents in the catalytic titanium-mediated cyclopropanation of carboxylic esters.

The consumption of an additional equivalent of Grignard reagent for the reduction of titanium(IV) alkoxides to titanium(III) alkoxides was confirmed by the results of experiments based on smooth reduction of benzaldehyde to hydrobenzoin with titanium(III) isopropoxide.[17] When an excess of benzaldehyde (4 equiv.) was added to a reaction mixture obtained by cyclopropanation of methyl hexanoate $C_5H_{11}CO_2Me$ (**2d**) in diethyl ether under the conditions of Procedure D, ^{1}H NMR analysis of the products showed the formation of, among other products, hydrobenzoin (**9**, *meso*:*dl* = 35:65) (Scheme 11).[24] This compound was not formed in the control experiment when an excess of benzaldehyde was added to a mixture of 1 equiv. of titanium(IV) isopropoxide and 2 equiv. of methylmagnesium iodide in ether at room temperature under the same conditions.

The ratio of cyclopropanol **1d** and hydrobenzoin **9** formed (**1d/9** = 1:0.3) indicates the consumption of ca. 0.6 equiv. of the Grignard reagent for the reduction of titanium(IV) alkoxides **X** to titanium(III) species **Y**.[17] Treatment of the reaction mixture obtained by the stoichiometric Procedure A with an excess of benzaldehyde produced cyclopropanol **1d** and hydrobenzoin (**9**) in 1:0.46 ratio. This ratio corresponds to consumption of ca. 0.9 equiv. of the Grignard reagent for the formation of titanium(III) alkoxides **Y**. The relatively large amount of hydrobenzoin (**9**) in the last experiment probably arises as a result of a higher stability of dimethyltitanium intermediates **V** toward formation of low-valent titanium species in comparison with less stable dialkyltitanium intermediates **U**, disposed to elimination of an alkane and formation of the corresponding titanacyclopropane [titanium(II)–olefin complex] species.



Scheme 11. Trapping of titanium(III) alkoxides with PhCHO.

Conclusions

In conclusion, an advanced procedure for the preparation of *cis*-1,2-disubstituted cyclopropanols by titanium alkoxide-mediated cyclopropanation of esters with Grignard reagents, minimizing the formation of secondary alcohols with chromatographic retention factors close to those of *cis*-cyclopropanols, has been elaborated. The modified ate complex mechanism of the reaction, proposed on the evidence of a stabilizing effect of carboxylic esters on the reduction of titanium(IV) isopropoxide with Grignard reagents, including the formation of octahedral titanium species, is suggested. A suitable explanation for the necessity to use an additional equivalent of Grignard reagent in the stoichiometric version of the cyclopropanation reaction has been proposed and confirmed experimentally.

Experimental Section

General: All solvents were purified and dried by conventional methods prior to use. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were freshly distilled from sodium/benzophenone. Titanium(IV) isopropoxide [Ti(O*i*Pr)$_4$] was purified by distillation, other reagents were used as purchased from commercial suppliers. All reactions were carried out under dry argon. 2-Bromo-1,1,1,3,3,3-hexadeuteriopropane, containing 95 atom-% deuterium by ^{1}H NMR, was prepared from [D$_6$]acetone.[25] Column chromatography was performed on Merck 60 silica gel (70–230 mesh). IR spectra were recorded with Specord IR-75 or Vertex 70 spectrometers. ^{1}H and ^{13}C NMR spectra were obtained with a Bruker AC 400 instrument at 400 and 100 MHz, respectively, in $CDCl_3$ ($CHCl_3$ at δ = 7.26 ppm for ^{1}H and $CDCl_3$ at δ = 77.0 ppm for ^{13}C as an internal standard). The multiplicities of carbon signals were determined by use of the DEPT technique. The presence of by-products **3a**, **3b**, **4a**, **6**, **7a**, and **8a** in the reaction mixtures was confirmed by comparison of the corresponding NMR spectra with those of the authentic samples.

Cyclopropanation of Methyl Butyrate (2a) with *n*-Propylmagnesium Bromide in the Presence of Catalytic Amounts of Ti(O*i*Pr)$_4$ (Procedure A, Catalytic Mode, Table 1 and Table 3): *n*-Propylmagnesium bromide (12 mL, 0.9 M in Et_2O or THF, 11 mmol) was slowly added (over 1.5 h) at room temperature to a solution of Ti(O*i*Pr)$_4$ (0.21 g, 0.75 mmol, 15 mol.%) and methyl butyrate (**2a**, 0.51 g, 5 mmol) in Et_2O or THF (10 mL). The brown reaction mixture was stirred for an additional hour, and quenched by careful addition of sulfuric acid (10%, 10 mL) at 0 °C. The aqueous phase was extracted with Et_2O (3 × 5 mL), and the combined organic phases were washed with satd. $NaHCO_3$ and brine and dried with Na_2SO_4. Solvent was carefully removed in vacuo, and the residue (0.5–0.6 g) was analyzed by NMR spectroscopy, revealing the formation of a mixture of (*E*)- and (*Z*)-2-methyl-1-propylcyclopropanols [**1a**, 76%, (*E*)/(*Z*) 86:14 in Et_2O; 84%, (*E*)/(*Z*) 93:7 in THF] and heptan-4-ol (**3a**, 12% in Et_2O; 10% in THF), along with small amounts (12% in Et_2O; 6% in THF) of starting ester **2a** and isopropyl butyrate (**7a**). Reproduction of this procedure on a 10-fold scale in THF gave, after column chromatography over silica gel (hexane/ethyl acetate), cyclopropanol *trans*-**1a** (0.28 g, 5%) and an 84:16 mixture of cyclopropanol *cis*-**1a** and hexan-4-ol (**3a**) (4.63 g, 81% overall yield). Modification of the experimental conditions gave similar yields of products and stereoisomer ratios (see Table 1, Entries 1, 3, 5–7).

(*E*)-2-Methyl-1-propylcyclopropanol (*cis*-1a): ^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.01 to 0.04 (m, 1 H, cycloprop. 3-*H*), 0.77–0.84 (m, 1 H, cycloprop. 3-*H*), 0.87–1.06 (m, 1 H, cycloprop. 2-*H*), 0.96 (t, *J* = 7.0 Hz, 3 H, C*H*$_3$ in *n*Pr), 1.00 (d, *J* = 2.0 Hz, 3 H, cycloprop. 2-C*H*$_3$), 1.48–1.61 (m, 4 H, C*H*$_2$C*H*$_2$), 1.96 (br s, 1 H, O*H*) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.2 (*C*H$_3$), 14.2 (*C*H$_3$), 19.0 (*C*H$_2$), 19.5 (*C*H), 20.6 (*C*H$_2$), 36.0 (*C*H$_2$), 58.8 (*C*OH) ppm. Vide infra for IR data.

(*Z*)-2-Methyl-1-propylcyclopropanol (*trans*-1a): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.22 (m, 1 H, cycloprop. 3-*H*), 0.55 (dd, *J* = 9.3, 5.1 Hz, 1 H, cycloprop. 3-*H*), 0.60–0.69 (m, 1 H, cycloprop. 2-*H*), 0.93 (t, *J* = 7.1 Hz, 3 H, C*H*$_3$ in *n*Pr), 1.12 (d, *J* = 6.1 Hz, 3 H, cycloprop. 2-C*H*$_3$), 1.39–1.57 (m, 4 H, C*H*$_2$C*H*$_2$), 1.80 (br s, 1 H, O*H*) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 12.3 (*C*H$_3$), 14.1(*C*H$_3$), 18.1 (*C*H), 18.9 (*C*H$_2$), 19.5 (*C*H$_2$), 41.5 (*C*H$_2$), 58.4 (*C*OH) ppm.

Reaction between Methyl Butyrate (2a) and Isopropylmagnesium Bromide in the Presence of Catalytic Amounts of Ti(O*i*Pr)$_4$ (Procedure B, Table 1, Entries 9 and 10): The reaction was carried out as described above in diethyl ether or THF, except that isopropylmagnesium bromide (12 mL, 0.9 M in Et_2O or THF, 11 mmol) was used instead of *n*-propylmagnesium bromide. NMR spectroscopy revealed the formation of a mixture of cyclopropanols **1a** [70%, (*E*)/(*Z*) 80:20 in Et_2O; 73%, (*E*)/(*Z*) 90:10 in THF], 2-methylhexan-3-ol (**4a**, 11 and 15% in Et_2O and THF, respectively) and heptan-4-ol (**3a**, 7–8%), along with 4–12% of starting ester **2a** and isopropyl butyrate (**7a**).

Reaction between Methyl Butyrate (2a) and *n*-Propylmagnesium Bromide with Stoichiometric Amounts of Ti(O*i*Pr)$_4$ (Procedure A, Stoichiometric Mode, Table 1, Entry 8): A solution of *n*-propylmagnesium bromide (15 mL, 1 M in THF, 15 mmol) was cooled to –78 °C, and Ti(O*i*Pr)$_4$ (5 mmol, 1.42 g) in THF (5 mL) was then added by syringe. Methyl butyrate (**2a**, 5 mmol, 0.51 g) in THF (3 mL) was added to the obtained orange mixture, and the reaction mixture was allowed to warm to 0 °C and quenched with sulfuric acid (10%, 18 mL). The aqueous phase was extracted with Et_2O

(3 × 5 mL), and the combined organic phases were washed with satd. $NaHCO_3$ and brine and dried with Na_2SO_4. After removal of the solvent the residue was analyzed by NMR spectroscopy. The 2-methyl-1-propylcyclopropanols [**1a**, 75%, (*E*)/(*Z*) 90:10], heptan-4-ol (**3a**, 12%), 4-propylheptan-4-ol (**6**, 7%), and starting compound **2a** (6%) were detected as the reaction products.

Reaction between Methyl Pivalate (2b) and $(CD_3)_2CHMgBr$ in the Presence of Ti(O*i*Pr)$_4$: $(CD_3)_2CHMgBr$, prepared from Mg (0.60 g, 25 mmol) and 2-bromo-1,1,1,3,3,3-hexadeuteriopropane[25] (3.23 g, 25 mmol), in Et_2O (20 mL) was added slowly (over 1 h) at room temperature to a solution of Ti(O*i*Pr)$_4$ (0.43 g, 1.5 mmol) and methyl pivalate (**2b**, 1.16 g, 10 mmol) in Et_2O (10 mL). The resulting dark brown solution was stirred for an hour and quenched by careful addition of sulfuric acid (10%, 20 mL) at 0 °C. The aqueous phase was extracted with Et_2O (3 × 10 mL) and the combined organic phases were washed with satd. $NaHCO_3$ and brine and dried with Na_2SO_4. NMR analysis of the crude product (0.80 g, ca. 60% yield) after solvent evaporation and removal of starting compound **2b** in vacuo gave a mixture of deuterated cyclopropanols *trans*-**1b-(D)** and *cis*-**1b-(D)** (85%, *trans*/*cis* 70:30) and alcohol **3b-(D)** (15%).

To obtain secondary alcohol **3b-(D)** in pure form, the reaction mixture was treated with an excess of *N*-bromosuccinimide (1.07 g, 6 mmol) in CCl_4 (7 mL). After the reaction was complete (TLC monitoring, ca. 2 h), the mixture was passed through the layer of silica. The solvent was removed under reduced pressure and the residue was subjected to column chromatography over silica gel (petroleum ether/ethyl acetate), to afford 1-bromo-1,1-dideuterio-4,4-trimethyl-2-(trideuteriomethyl)pentan-3-one (0.76 g, 36% yield from **2b**) as the first fraction and deuterated 2,2-dimethyl-3-hexanols **3b-(D)** (0.062 g, 5% yield from **2b**) as the second fraction.

(*Z*)-1-*tert*-Butyl-3,3-dideuterio-2-(trideuteriomethyl)cyclopropanol [*trans*-1b-(D)]: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.86 (brs, 1 H, cycloprop. 2-C*H*), 0.88 [s, 9 H, C(CH_3)$_3$], 1.90 (brs, 1 H, O*H*) ppm. ^{13}C NMR ($CDCl_3$, 400 MHz): δ = 11.5 (sept, J = 19.4 Hz, *C*D$_3$), 13.8 (cyclopr. 2-*C*H), 15.8 (quint, J = 24.2 Hz, *C*D$_2$), 25.6 [C(*C*H$_3$)$_3$], 34.1 [*C*(CH$_3$)$_3$], 64.5 (*C*OH) ppm.

(*E*)-1-*tert*-Butyl-3,3-dideuterio-2-(trideuteriomethyl)cyclopropanol [*cis*-1b-(D)]: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.03 [s, 9 H, C(CH_3)$_3$], 1.04 (brs, 1 H, cycloprop. 2-C*H*), 1.83 (brs, 1 H, O*H*) ppm. ^{13}C NMR ($CDCl_3$, 400 MHz): δ = 21.3 (cycloprop. 2-*C*H), 27.4 [C(*C*H$_3$)$_3$], 34.6 [*C*(CH$_3$)$_3$], 64.2 (*C*OH) ppm, signals from both CD_3 and CD_2 were not detected due to low intensity.

1-Bromo-1,1-dideuterio-4,4-trimethyl-2-(trideuteriomethyl)pentan-3-one: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.17 [s, 9 H, C(CH_3)$_3$], 3.40 (brs, 1 H, 2-C*H*) ppm. ^{13}C NMR ($CDCl_3$, 400 MHz): δ = 26.1 [C(*C*H$_3$)$_3$], 42.3 (2-*C*H), 44.5 [*C*(CH$_3$)$_3$], 216.5 (*C*O) ppm, signals from both CD_3 and CD_2 were not detected due to low intensity.

Deuterated 2,2-Dimethyl-3-hexanols [3b-(D)]: ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.88 [s, 9 H, C(CH_3)$_3$], 1.25 (brs, 0.7 H, 5-C*H*D, major diastereomer), 1.27 (brd, J = 14 Hz, 0.15 H, 5-CH_2, residual protons at C5), 1.37 (brs, 1 H, O*H*), 1.52 (brs, 0.15 H, 5-C*H*D, minor diastereomer), 1.54 (brd, J = 14 Hz, 0.15 H, 5-CH_2, residual protons at C5), 3.17 (brs, 0.05 H, 3-C*H*OH, residual protons at C3) ppm. ^{13}C NMR ($CDCl_3$, 400 MHz): δ = 13.0 (sept, J = 19.0 Hz, 6-*C*D$_3$), 19.3 (t, J = 19.2 Hz, 5-CHD), 19.6 (5-*C*H$_2$), 25.6 [C(*C*H$_3$)$_3$], 32.6 (quint, J = 19.0 Hz, 4-*C*D$_2$), 34.7 [*C*(CH$_3$)$_3$], 79.0 (t, J = 21.2 Hz, 3-*C*DOH), 79.6 (3-*C*HOH) ppm.

Reactions between Methyl Butyrate (2a), *n*-Propylmagnesium Bromide, and Methylmagnesium Iodide in the Presence of Ti(O*i*Pr)$_4$ (Procedure C, Table 2, Entries 1–2): *n*-Propylmagnesium bromide (1 M in Et_2O, 5 mL, 5 mmol) and then methylmagnesium iodide (5 or 10 mL, 1 M in Et_2O, 5 or 10 mmol) were added slowly at room temp to a solution of Ti(O*i*Pr)$_4$ (1.42 g, 5 mmol) and methyl butyrate (**2a**, 0.51 g, 5 mmol) in Et_2O (10 mL). The brown reaction mixture was kept overnight, and quenched by careful addition of sulfuric acid (10%) at 0 °C. The aqueous phase was extracted with Et_2O (3 × 5 mL), and the combined organic phases were washed with satd. $NaHCO_3$ and brine and dried with Na_2SO_4. Solvent was carefully removed in vacuo, and the residue was analyzed by NMR spectroscopy, showing mixtures of cyclopropanols **1a**, secondary alcohols **3a** and **8a**, and isopropyl butyrate (**7a**).

Reactions between Methyl Butyrate (2a), *n*-Propylmagnesium Bromide, and Methylmagnesium Iodide in the Presence of Ti(O*i*Pr)$_4$ (Table 2, Entries 3–9): Methylmagnesium iodide (5–10 mL, 1 M in Et_2O, 5–10 mmol) was added over 5 min to a solution of Ti(O*i*Pr)$_4$ (1.42 g, 5 mmol) in Et_2O (10 mL). Methyl butyrate (**2a**, 0.51 g, 5 mmol) and, over 20–30 min, *n*-propylmagnesium bromide (5–10 mL, 1 M in Et_2O, 5–10 mmol) were then added. The brown reaction mixture was stirred for an hour and quenched by addition of sulfuric acid (10%) at 0 °C. The aqueous phase was extracted with Et_2O (3 × 5 mL) and the combined organic phases were washed with satd. $NaHCO_3$ and brine and dried with Na_2SO_4. Solvent was carefully removed in vacuo, and the residue was analyzed by NMR spectroscopy, showing mixtures of cyclopropanols **1a**, secondary alcohols **3a** and **8a**, isopropyl butyrate (**7a**), and methyl butyrate (**2a**).

General Procedure for the Preparation of *cis*-1,2-Disubstituted Cyclopropanols 1a–f from Esters 2a–f with Methylmagnesium Halides (Procedure D, Table 3): A solution of methylmagnesium iodide in ether or methylmagnesium bromide in THF (20 mL, 1.5 M, 30 mmol) was added over 5 min at room temperature to a solution of Ti(O*i*Pr)$_4$ (5.68 g, 20 mmol, in 20 mL of Et_2O or THF). The obtained yellow or orange solution was cooled to 0 °C and ester **2a**–**f** (20 mmol, in 10 mL of Et_2O or THF) was added. *n*-Propylmagnesium bromide or its higher homologue (20–23 mL, 1.5 M in Et_2O or THF, 30–34 mmol) was added to the reaction mixture over 30–40 min, and the resulting solution was allowed to warm to room temperature and stirred for an hour. The reaction mixture was quenched by careful addition of sulfuric acid (10%, 70–80 mL) at 0 °C, the aqueous phase was extracted with Et_2O (3 × 20 mL), and the combined organic layers were washed with satd. $NaHCO_3$ and brine and dried with Na_2SO_4 or $MgSO_4$. After removal of the solvent, the 1,2-disubstituted cyclopropanols **1a**–**e** were isolated by column chromatography over silica gel (petroleum ether/ethyl acetate). The corresponding alcohols **8a**–**e** were formed as the main by-products.

(*E*)-2-Methyl-1-propylcyclopropanol (*cis*-1a): Yield 1.48–1.53 g (65–67%) in Et_2O and THF, colorless oil. Vide supra for NMR spectroscopic data. IR (CCl_4): $\tilde{\nu}$ = 3600, 3350, 3070 cm^{-1}. $C_7H_{14}O$ (114.19): C 73.63, H 12.36; found: C 73.15, H 12.21.

(*E*)- and (*Z*)-1-*tert*-Butyl-2-methylcyclopropanols 1b: These were obtained in ca. 55% yield, (*E*)/(*Z*) 40:60 (by ^{1}H NMR), along with 3,3-dimethyl-2-butanol (15%) and traces of 2,2-dimethyl-3-hexanol (**3b**, 3%).

(*E*)-1-*tert*-Butyl-2-methylcyclopropanol (*cis*-1b): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.44 (dd, J = 7.0, 5.2 Hz, 1 H, cycloprop. 3-*H*), 0.71 (dd, J = 10.3, 5.2 Hz, 1 H, cycloprop. 3-*H*), 1.04 [s, 9 H, C(CH_3)$_3$], 0.99–1.14 (m, 1 H, cycloprop. 2-*H*), 1.21 (d, J = 6.7 Hz, 3 H, cycloprop. 2-CH_3), 2.20 (brs, 1 H, O*H*) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.6 (cycloprop. 2-*C*H$_3$), 17.8 (*C*H$_2$), 21.7 (*C*H), 27.4 [C(*C*H$_3$)$_3$], 34.6 [*C*(CH$_3$)$_3$], 64.0 (*C*OH) ppm.

(*Z*)-1-*tert*-Butyl-2-methylcyclopropanol (*trans*-1b): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.10 (m, 1 H, cycloprop. 3-*H*), 0.74 (dd, *J* = 9.7, 5.4 Hz, 1 H, cycloprop. 3-*H*), 0.90 [s, 9 H, C(CH_3)$_3$], 0.84–0.93 (m, 1 H, cycloprop. 2-*H*), 1.14 (d, *J* = 6.0 Hz, 3 H, cycloprop. 2-CH_3), 2.20 (br s, 1 H, O*H*) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 12.5 (cycloprop. 2-*C*H$_3$), 14.2 (*C*H), 16.6 (*C*H$_2$), 26.1 [C(*C*H$_3$)$_3$], 34.2 [*C*(CH$_3$)$_3$], 64.5 (*C*OH) ppm.

(*E*)-2-Butyl-1-methylcyclopropanol (*cis*-1c): Yield 2.05–2.10 g (80–82%) in Et_2O and THF, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04 (dd, *J* = 6.4, 5.1 Hz, 1 H, cycloprop. 3-*H*), 0.81 (ddq, *J* = 10.8, 5.1, 0.6 Hz, 1 H, cycloprop. 3-*H*), 0.89 (t, *J* = 6.9 Hz, 3 H, CH_3 in *n*Bu), 0.90–1.02 (m, 1 H, cycloprop. 2-*H*), 1.05–1.20 (m, 1 H, 1*H* in *n*Bu), 1.22–1.45 (m, 5 H, 5*H* in *n*Bu), 1.39 (d, *J* = 0.6 Hz, 3 H, cycloprop. 1-CH_3), 1.97 (br s, 1 H, O*H*) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.1, 20.2, 20.5, 22.5, 25.6, 29.5, 31.9, 55.6 ppm. IR (CCl_4): $\tilde{\nu}$ = 3602, 3325, 3071 cm^{-1}. Spectral data are consistent with those previously reported for this compound in Ref.[14]

(*E*)-2-Methyl-1-pentylcyclopropanol (*cis*-1d): Yield 2.13 g (75%) in Et_2O and THF, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.01 to 0.05 (m, 1 H, cycloprop. 3-*H*), 0.78–0.85 (m, 1 H, cycloprop. 3-*H*), 0.90 (t, *J* = 6.9 Hz, 3 H, CH_3 in *n*-C$_5$H$_{11}$), 1.01 (d, *J* = 1.8 Hz, 3 H, cycloprop. 2-CH_3), 0.98–1.10 (m, 1 H, cycloprop. 2-*H*), 1.23–1.40 (m, 4 H, 2 × CH_2 in *n*-C$_5$H$_{11}$), 1.47–1.60 (m, 4 H, 2 × CH_2 in *n*-C$_5$H$_{11}$), 1.82 (br s, 1 H, O*H*) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.0, 14.2, 19.6, 20.6, 22.7, 25.5, 32.0, 33.9, 58.8 ppm. IR (CCl_4): $\tilde{\nu}$ = 3600, 3350, 3070 cm^{-1}. $C_9H_{18}O$ (142.24): C 76.00, H 12.76; found: C 75.65, H 12.43.

(*E*)-1-(3-Chloropropyl)-2-methylcyclopropanol (*cis*-1e): Yield 2.17–2.20 g (73–74%) in Et_2O and THF, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.04–0.12 (m, 1 H, cycloprop. 3-*H*), 0.82–0.90 (m, 1 H, cycloprop. 3-*H*), 1.00–1.10 (m, 4 H, cycloprop. 2-*H*, CH_3), 1.67–1.74 (m, 2 H, CH_2CH$_2$CH$_2$Cl), 1.82 (br s, 1 H, O*H*), 1.95–2.15 (m, 2 H, CH$_2$CH_2CH$_2$Cl), 3.64 (t, *J* = 6.5 Hz, 2 H, CH$_2$CH$_2$CH_2Cl) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.1, 19.7, 20.7, 29.1, 31.3, 45.3, 58.2 ppm. IR (CCl_4): $\tilde{\nu}$ = 3599, 3350, 3076 cm^{-1}. $C_7H_{13}ClO$ (148.63): C 56.57, H 8.82; found: C 56.31, H 8.47.

(*E*)-2-Methyl-1-[2-(2-methyl-1,3-dioxolan-2-yl)ethyl]cyclopropanol (*cis*-1f): This compound was prepared by a slight modification of Procedure D. Methylmagnesium bromide (10 mL, 1.5 M in THF, 15 mmol) was added over 5 min at room temperature to a solution of Ti(O*i*Pr)$_4$ (2.84 g, 10 mmol) in THF (20 mL), and the resulting yellow solution was cooled to 0 °C. Ester **2f** (10 mmol) in THF (10 mL) and, over 30 min, *n*-propylmagnesium bromide (27 mL, 0.9 M solution in THF, 24 mmol) were then added. The slurry mixture was warmed to room temperature and stirred for 2 h and the reaction was quenched by addition of water (5 mL). The obtained heterogeneous mixture was vigorously stirred for 40 min, and the white precipitate was filtered off and washed with THF (3 × 20 mL). Solvent was evaporated under reduced pressure, the residue was diluted with Et_2O (50 mL), and the aqueous phase was separated. The organic phase was washed with brine and dried with Na_2SO_4. After removal of the solvent, cyclopropanol *cis*-**1f** was purified by column chromatography over silica gel (hexane/ethyl acetate), to afford (*E*)-2-methyl-1-[2-(2-methyl-1,3-dioxolan-2-yl)-ethyl]cyclopropanol **1f** (1.48 g, 80%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = –0.02 to 0.03 (m, 1 H, cycloprop. 3-*H*), 0.77–0.83 (m, 1 H, cycloprop. 3-*H*), 0.98–1.08 (m, 1 H, cycloprop. 2-*H*), 1.02 (d, *J* = 1.5 Hz, 3 H, cycloprop. 2-CH_3), 1.36 (s, 3 H, CH_3), 1.65–1.71 (m, 2 H, CH_2), 1.90–1.96 (m, 2 H, CH_2), 3.06 (br s, 1 H, O*H*), 3.95–4.00 (m, 4 H, OCH_2CH_2O) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.2, 19.5, 20.5, 23.6, 28.2, 35.6, 58.5, 64.5, 64.5, 110.1 ppm. IR (CCl_4): $\tilde{\nu}$ = 3600, 3475, 3072 cm^{-1}.

Reaction between Benzaldehyde and a Mixture Obtained after Treatment of Methyl Hexanoate (2d) with *n*-Propylmagnesium Bromide, Ti(O*i*Pr)$_4$, and MeMgI: Methylmagnesium iodide (5.4 mL, 1.4 M in Et_2O, 7.5 mmol) was added over 1–2 min at room temperature to a solution of Ti(O*i*Pr)$_4$ (1.42 g, 5 mmol in 5 mL of Et_2O) and the mixture was cooled to 0 °C. Methyl hexanoate (**2d**, 0.65 g, 5 mmol) in Et_2O (3 mL) and, over 10 min, *n*-propylmagnesium bromide (6.3 mL, 1.2 M in Et_2O, 7.5 mmol) were then added. The red-brown mixture was stirred for 40 min at room temperature, and benzaldehyde (2.12 g, 20 mmol) in Et_2O (5 mL) was added in one portion at 0 °C. The reaction mixture was kept overnight and hydrolyzed with sulfuric acid (10%, 18 mL) at 0 °C. The aqueous phase was extracted with Et_2O (3 × 5 mL), and the combined organic phases were washed with satd. $NaHCO_3$ and brine and dried with $MgSO_4$. The ^{1}H NMR spectrum of the residue obtained after evaporation of Et_2O showed the absence of the starting compound and the formation of 2-methyl-1-pentylcyclopropanol [**1d**, (*E*)/(*Z*) 85:15], 1-phenylethanol, hydrobenzoin (**9**, *dl*/*meso* 65:35), and benzyl alcohol in a molar ratio of 1:0.15:0.30:2.6.

Reaction between Benzaldehyde and a Mixture Obtained after Treatment of Methyl Hexanoate (2d) with *n*-Propylmagnesium Bromide and Ti(O*i*Pr)$_4$: *n*-Propylmagnesium bromide (12.5 mL, 1.2 M in Et_2O, 15 mmol) was added at 0 °C over 15 min to a solution of Ti(O*i*Pr)$_4$ (1.42 g, 5 mmol) and methyl hexanoate (**2d**, 0.65 g, 5 mmol) in Et_2O (8 mL). The red-brown mixture was stirred for 40 min at room temperature. Benzaldehyde (2.12 g, 20 mmol) in Et_2O (5 mL) was then added in one portion at 0 °C, and the reaction mixture was kept overnight and hydrolyzed with sulfuric acid (10%, 18 mL) at 0 °C. The aqueous phase was extracted with Et_2O (3 × 5 mL), and the combined organic phases were washed with satd. $NaHCO_3$ and brine and dried with $MgSO_4$. The ^{1}H NMR spectrum of the residue after evaporation of Et_2O showed the absence of the starting compound. 2-Methyl-1-pentylcyclopropanol [**1d**, (*E*)/(*Z*) 85:15], hydrobenzoin (**9**, *dl*/*meso* 65:35), and benzyl alcohol were found in a molar ratio of 1:0.46:2.7.

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