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Studies on the origin of cis-diastereoselectivity of the titanium-mediated cyclopropanation of carboxylic esters with Grignard reagents. Stereochemistry of the intramolecular cyclization of β-metalloketones

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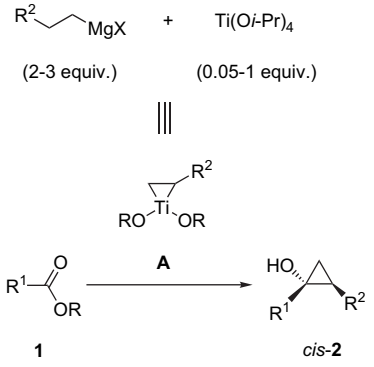
Abstract

Data on the stereochemistry of the intramolecular cyclization of β-metaloketones into 1,2-disubstituted cyclopropanols are in agreement with the cyclopropanation of carboxylic esters with alkoxytitanacyclopropane reagents proceeding via the β-titanoketone intermediates with the metal atom bound to a secondary carbon. Hypothesis for the origin of cis-diastereoselectivity of the cyclization of the β-titanoketones is suggested. It explains the tendency for the preferable formation of *cis*-1,2-disubstituted cyclopropanols by relief of repulsion strain between the ligands at the octahedral titanium atom.

Keywords: Diastereoselectivity; Cyclopropanols; Titanacyclopropanes; Ate complexes

1. Introduction

1,2-Disubstituted cyclopropanols are useful synthetic intermediates due to their ability to be involved in regioselective C1–C2, C1–C3 or C2–C3 three-carbon ring bonds' cleavage reactions to give functionalized compounds with a linear or branched carbon skeleton.[1,2] Titanium(IV) alkoxide-catalyzed cyclopropanation of carboxylic esters **1** with higher homologues of ethylmagnesium halides is a convenient approach to 1,2-disubstituted cyclopropanols.[3,4] It has been suggested that the reaction proceeded through the two-fold alkylation of titanium(IV) isopropoxide to give dialkyltitanium intermediate. Subsequent disproportonation of the latter lead to the key intermediate, dialkoxytitanacyclopropane **A**, acting in this transformation as an equivalent of a 1,2-dicarbanion.[3,5] Preferable formation of *cis*-1,2-disubstituted cyclopropanols *cis*-**2** (Scheme 1) is a distinctive stereochemical feature of the cyclopropanation of carboxylic esters.[3b,6–8]



Scheme 1.

Two models were proposed to explain the experimentally-observed cis-selectivity. In the first,[7] the insertion of the ester carbonyl group into intermediate **A** between Ti and the secondary carbon was supposed[3b,7,9] (Scheme 2, 2°C–Ti bond insertion) to afford the less sterically hindered oxatitanacyclopentane intermediate *trans*-**B**. The authors postulated that the migration of an alkoxy-group was accompanied by face-specific π-donor coordination of the carbonyl group to the

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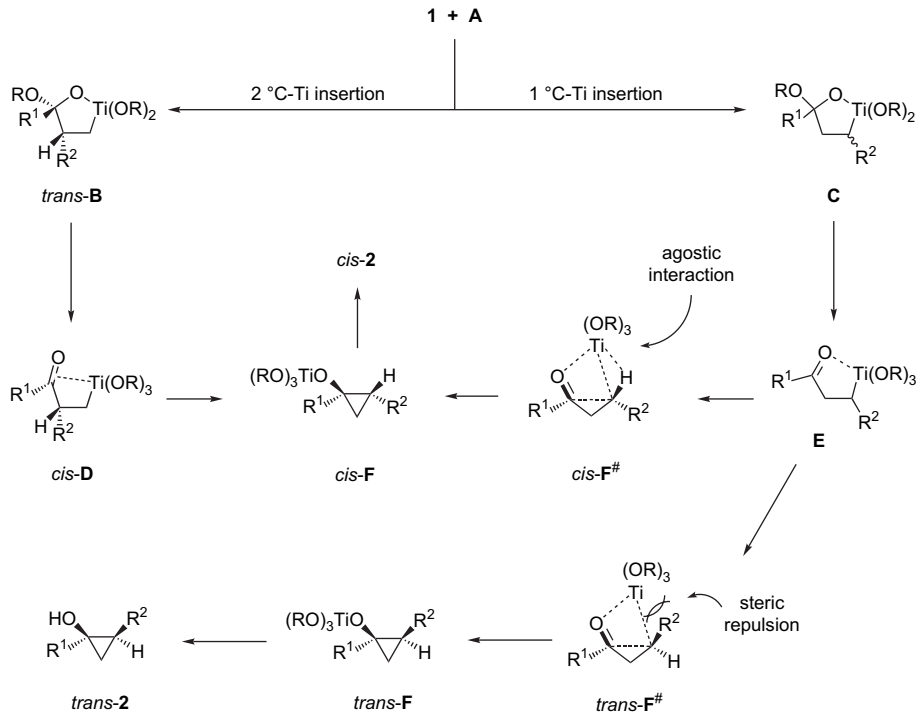


Scheme 2.

titanium atom to give a pentacoordinated titanium complex **D**. Although the reasons for stereoselective formation of **D** were not discussed, the absolute configuration of 1-methyl-2-phenylcyclopropanol, obtained by cyclopropanation of ethyl acetate with 2-phenylethylmagnesium bromide in the presence of a chiral titanium(IV) catalyst, was in agreement with this model.[7]

An alternative model was based on the results of DFT calculations for the reactions between carboxylic esters and a dimethoxytitanacyclopropane species.[10] In accordance with the obtained results, the insertion of the ester carbonyl into intermediate **A** between Ti and the primary carbon was preferred, and the corresponding oxatitanacyclopentane intermediate **C** further transformed into cyclopropanol **2** through the β-oxotitanium intermediate **E** (Scheme 2, 1°C–Ti bond insertion). cis-Diastereoselectivity was attributed to an agostic interaction between an α-hydrogen and the pentacoordinated titanium atom, which stabilized transition state *cis*-**F**$^{\#}$ leading to *cis*-cyclopropanolate *cis*-**F** with retention of the configuration at the carbon bound to titanium.[11] The agostic interaction is weakened in the transition state *trans*-**F**$^{\#}$, which is destabilized by unfavorable steric repulsion between the titanium atom and an alkyl group R^2. It was also concluded, that an alternative mode of insertion of the ester carbonyl into intermediate **A** (2°C–Ti bond insertion) should result in preferable formation of cyclopropanolate *trans*-**F**.[10]

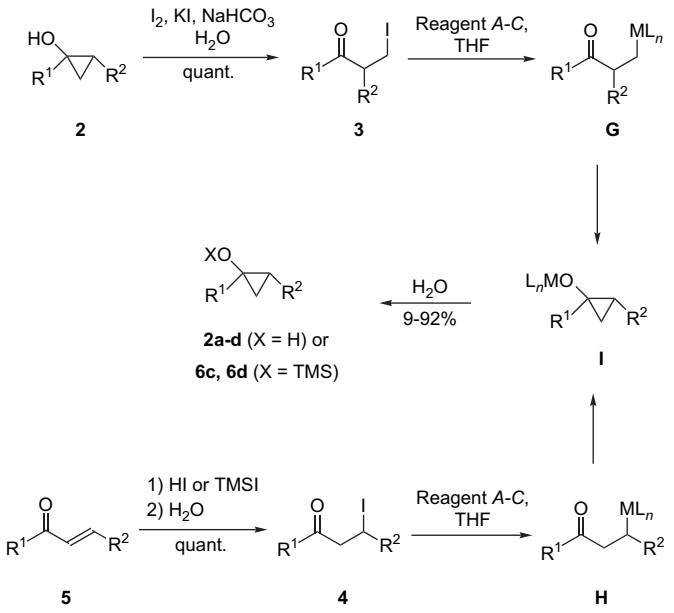
Although the 1°C–Ti bond insertion of ester carbonyl in the reactions between alkoxytitanacyclopropane reagents **A** and carboxylic esters was suggested by the structure of some by-products,[6,12] the formation of cyclopropanols in the same way, was not experimentally confirmed. We supposed that a study of the stereochemistry of the intramolecular cyclization of β-metalloketones might be helpful in elucidation of this question as well as in confirmation or not of a specific influence of the titanium atom on the stereoselectivity of formation of 1,2-disubstituted cyclopropanols. Here, we also attempted to detect the influence of an α-agostic interaction on the stereochemistry of the cyclopropanation of carboxylic esters by means of the deuterium isotope effect.

2. Results and discussion

2.1. Stereochemistry of the intramolecular cyclization of β-metalloketones

The reactions of β-iodoketones **3**, **4** with zinc, organotitanium, and organomagnesium reagents were tested to generate the β-metalloketone intermediates **G** and **H** with the metal atom bound to primary and secondary carbon, respectively, by halogen–metal exchange (Scheme 3). We found that β-iodoketones **3** could be conveniently prepared from 1,2-disubstituted cyclopropanols **2** by the reaction with iodine in aqueous KI/$NaHCO_3$.[13] The yields of β-iodoketones **3** were nearly quantitative, and no isomeric products **4** with the iodine atom bound to a secondary carbon were found in the reaction mixtures by ^{1}H NMR spectroscopy. The secondary iodides **4** were obtained from the corresponding α,β-unsaturated ketones **5** by treatment with hydrogen iodide in CH_2Cl_2 or trimethyliodosilane in CH_3CN (Scheme 3).[14]

β-Iodoketones **3**, **4** under the treatment with 1.1–1.5 equiv of zinc dust in THF in the presence of trimethylchlorosilane (reagent *A*)[15–17] followed by aqueous work-up, gave



R^1, R^2 = alkyl; reagents: Zn, TMSCl (*A*); R^3MgBr, $Ti(Oi\text{-}Pr)_4$ (*B*); R^3MgBr (*C*); M = Zn, Ti or Mg; L = I, Br, O*i*-Pr, solvent or another ligand (see also Table 1)

Scheme 3.

cyclopropanols **2a**, **2b** (for R^1=linear alkyl) or trimethylsilyl ethers **6c**, **6d** (R^1=branched alkyl) in high yield (Scheme 3, Table 1).[18,19] Reaction with zinc dust or zinc–copper couple in the absence of TMSCl gave lower yields and proceeded more slowly.[20] As indicated in Table 1, intramolecular cyclization of iodoketones **3a–d**, probably proceeding through the β-zincketone intermediates **G** (M=Zn) with the metal atom bound to the primary carbon, gave cyclopropanols **2a**, **2b** or trimethylsilyl ethers **6c** with low stereoselectivity (entries 1–4, reagent *A*). The only exception was *tert*-butyl ketone **3d**, giving exclusively the sterically less hindered *trans*-product **6d**. In contrast, secondary iodides **4** gave cyclopropanols **2a**, **2b** or silyl ethers **6c**, **6d** with medium or good trans-diastereoselectivity under these conditions (entries 5–8, reagent *A*).[21]

The preparation of cyclopropanols **2** from β-iodoketones **3**, **4** via putative β-titanoketone intermediates **G**, **H** (M=Ti) was a somewhat more complex task. Our attempts to generate β-titanoketones by the reaction of iodoketones **3b**, **4b** with zinc in the presence of $ClTi(Oi\text{-}Pr)_3$[22] or low-valent titanium alkoxides[23] were unsuccessful. Nevertheless, cyclopropanols **2a–d** were obtained in low or moderate yields by treatment of iodoketones **3**, **4** with 3.5–4 equiv of cyclohexylmagnesium bromide in the presence of 1 equiv of titanium(IV) isopropoxide (reagent *B*)[24] in THF (Scheme 3, Table 1).

Cyclization of primary iodides **3a–d**, promoted by the magnesium–titanium reagent *B*, proceeded with low diastereoselectivity, and gave nearly the same ratios of isomeric cyclopropanols as obtained in the zinc-mediated reaction (Table 1, entries 1–4). When secondary iodide **4a** was treated with the magnesium–titanium reagent *B*, no cyclopropanols **2a** (entry 5, reagent *B*) were found in the reaction mixture, whereas compounds **4b**, **4c** gave cyclopropanols **2b**, **2c** with

Table 1
Yields and diastereomer ratios of cyclopropanols **2** and siloxycyclopropanes **6** obtained by the reductive cyclization of iodoketones **3**, **4**

Entry	Starting iodoketone	R^1	R^2	Reagent[a]	Product	Yield[b] (%)	cis/trans[c,d]
1	**3a**	Me	*n*-Pr	*A*	**2a**	91	1:1
				B		35	2:1
2	**3b**	*n*-Pr	Me	*A*	**2b**	92	1:1
				B		50	1:1
				C		22	1:1.5
3	**3c**	*i*-Pr	Me	*A*	**6c**	88	1:1
				B	**2c**	42	1:1
4	**3d**	*t*-Bu	Me	*A*	**6d**	85	<1:99
				B	**2d**	33	1:4.5
5	**4a**	Me	*n*-Pr	*A*	**2a**	86	1:3.5
				B		0	—
6	**4b**	*n*-Pr	Me	*A*	**2b**	85	1:3
				B		35[e]	4.5:1
				C		9	1:1.2
7	**4c**	*i*-Pr	Me	*A*	**6c**	84	1:2
				B	**2c**	24	2:1
8	**4d**	*t*-Bu	Me	*A*	**6d**	84	1:11
				B	**2d**	21	1:1

[a] Regent *A*: 1.1–1.5 equiv Zn, 1–1.5 equiv TMSCl, THF, room temperature; reagent *B*: 3.5–4 equiv *c*-$C_6H_{11}MgBr$, 1 equiv $Ti(Oi\text{-}Pr)_4$, THF, room temperature; reagent *C*: 3.5–4 equiv *c*-$C_6H_{11}MgBr$, THF, room temperature.

[b] Isolated yields for procedure *A* and determined by ^1H NMR spectra using $PhCO_2Et$ as an internal standard for procedures *B*, *C*.

[c] Determined by the integration of the signals from the CH_2-cyclopropane protons in ^1H NMR spectra.

[d] cis and trans configurations are referred to relative arrangement of R^1 and R^2 groups.

[e] A trace amount of cyclopropanol **2b** was obtained when the reaction was performed in ether.

the pronounced cis-diastereoselectivity (entries 6, 7). Even in the case of iodoketone **4d** (R^1=*t*-Bu), highly sterically hindered cyclopropanol *cis*-**2d** was obtained in the same yield as the corresponding trans isomer (entry 8, reagent *B*). When iodoketones **3b**, **4b** were treated with cyclohexylmagnesium bromide (reagent *C*) in the absence of titanium(IV) isopropoxide, isomeric cyclopropanols **2b** were obtained in lower yields (entries 2 and 6). Noticeably, in the case of linear iodoketone **4b** the stereoisomer ratios were dramatically different from those observed in the reactions with the magnesium–titanium reagent *B* (entry 6) indicating the important role of titanium atom in a process of formation of cyclopropanol **2b** under treatment of iodoketones **3b** and **4b** with reagent *B*.

Although we assume that the reactions between iodoketones **3** and **4** and reagents *A–B* proceed via corresponding β-metalloketones **G**, **H** (Scheme 3), which formed as a result of a well-known halogen–metal exchange or by a different route,[25] alternative mechanisms for the transformation of the iodoketones **3**, **4** to cyclopropanolates **I** under treatment of reagents *A–C*, involving generation of the corresponding radical,[26] carbenoid[27] or oxametallacyclopropane intermediates[6,28] could be also assumed. These possibilities are not discussed here in detail for reason of space, however, it is worth noting that the transition states for the corresponding three-carbon ring forming steps have to possess a certain geometrical similarity, reflecting the structure of cyclopropanolates **I**.

For this reason, the similarity of the obtained stereochemical results with the data on influence of steric effects on the stereochemistry of the cyclopropanation of esters with alkoxytitanacyclopropane reagents have to be taken into account, independently from the mechanisms realized (see below).

2.2. Stereochemistry of the titanium-mediated cyclopropanation of esters

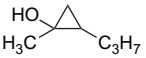
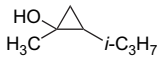
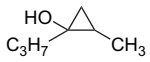
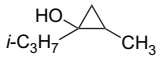
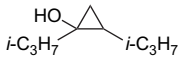
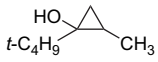
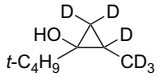
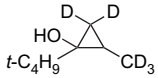
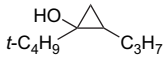
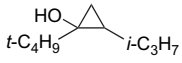
The contrast in stereochemistry for Zn, Mg (Table 1, reagents *A* and *C*), and Ti-mediated (Table 1, reagent *B*) cyclizations of secondary iodoketones **4** confirms, as mentioned above, a specific role of the titanium atom in providing the cis-stereoselectivity. Moreover, the stereoisomer ratios of cyclopropanols **2b–d**, observed in the reactions between the magnesium–titanium reagent *B* and iodoketones **4b–d** in THF *were very close to those obtained by cyclopropanation of corresponding esters **1** with alkoxytitanacyclopropane reagents*, generated by reaction of 3 equiv of isopropylmagnesium bromide with 1 equiv of titanium(IV) isopropoxide. The comparison of the stereochemical outcomes for both reactions showed that the contents of *cis*-cyclopropanols **2b**, **2c**, and **2d** in stereoisomeric mixtures were 4.5:1 versus 10:1, 2:1 versus 2:1, and 1:1 versus 1:1, respectively (Table 1, entries 6–8, reagent *B*; Table 2, entries 3, 4, 6). We consider this result as a reliable evidence for the formation of cyclopropane rings in both reactions via similar transition states, i.e., the insertion of an ester carbonyl into the less substituted Ti–C bond of the titanacyclopropane reagent (Scheme 2, 1°C–Ti bond insertion).

If the diastereoselectivity of β-titanaketone **E** cyclization is determined by an α-agostic interaction (Scheme 2, *cis*-$F^{\#}$),[10] deuterium substitution would have an affect on the stereochemistry of the cyclopropanation.[29] We studied the reaction of methyl pivalate with deuterated isopropyl Grignard reagents in the presence of titanium(IV) isopropoxide and the ratio of 1:1.4 for cis/trans isomers of d_6-**2d** cyclopropanol (Table 2, entry 7) formed in the reaction with $(CD_3)_2CDMgBr$ was slightly less than the ratio of 1:1.6 for cis/trans isomers of cyclopropanol **2d** obtained with undeuterated Grignard reagent $(CH_3)_2CHMgBr$ (Table 2, entry 6). This could be attributed to the smaller size of the CD_3 group in comparison with the CH_3 group.[30] The reaction with $(CD_3)_2CHMgBr$ gave a somewhat higher cis/trans ratio of 1:1.2 than obtained in the reaction with $(CD_3)_2CDMgBr$ (cis/trans=1:1.4) (Table 2, entries 7 and 8). The observed change in stereoisomer ratios is formally consistent with the α-agostic stabilization of the transition state *cis*-$\mathbf{F}^{\#}$,[10] because the agostic bonding is more preferred for H rather than for D atom.[29,31] However, an observed difference in cis/trans-ratios between d_6-**2d** and d_5-**2d** corresponds to a difference in activations energies for the formation of the corresponding cyclopropanolates of about 0.08 kcal/mol, and this value is close to the difference in energy between deuterium–protium and protium–protium eclipsed pairs (0.07 kcal/mol[32]) and influence of isotope substitution on the stereochemistry of the cyclopropanation of methyl pivalate with deuterated alkoxytitanacyclopropane reagents could be attributed to a steric isotope effect[33] without taking into account an α-agostic interaction of the titanium atom.

As mentioned above, a destabilizing $R^2\cdots Ti$ repulsion in the transition state *trans*-$\mathbf{F}^{\#}$ (Scheme 1) was suggested as another possible factor leading to the cis-selectivity.[10] In accordance with this supposition, the increase of cis-diastereoselectivity for cyclization of β-metalloketone intermediates **H** in the order Zn<Ti<Mg, corresponding to the order of increasing covalent radii for these metals, should be expected. Nevertheless, cis-stereoselectivity of the cyclization of iodoketone **4b** under treatment with reagents *A–C* increased in a different order: Zn<Mg≪Ti (Table 1, entry 6). Moreover, *the cyclopropanation of carboxylic esters with bulky alkoxytitanacyclopropane reagents led to enhancement of the cis-diastereoselectivity*, and high cis-selectivity was observed even in the case of sterically hindered *cis*-1,2-diisopropylcyclopropanol (**2f**) and *cis*-1-*tert*-butyl-2-isopropylcyclopropanol (**2h**) (Table 2, entries 5 and 10). These results indicate that the energy, which provides the formation of sterically crowded *cis*-1,2-disubstituted cyclopropanols, accumulates in β-titanoketones **E** in proportion to increasing size of R^2 group. We suppose that repulsive interactions between the R^2 group and substituents at titanium are a source of this energy and these interactions could be especially significant for the highly coordinated titanium atom. The formation of such species is envisaged in the ate complex mechanism of the titanium-mediated cyclopropanation of carboxylic esters.[6] In accordance with this mechanism, alkylation of octahedral titanium species **J**, followed by elimination of an alkane from dialkyltitanium ate complex **K** and addition of a Grignard reagent to titanacyclopropane intermediate **L** gives octahedral oxatitanacyclopentane intermediate **M** (Scheme 4). Intermediate **M** further converts into β-oxotitanium intermediate **N** and the cyclopropane ring closure affords the titanium cyclopropanolate **O**. In a non-catalytic version of the reaction, intermediate **O** disproportionates to afford titanium(III) cyclopropanolate ate complex **P** as the immediate precursor of cyclopropanols **2a–h**.

Conversion of the β-titanoketone **N** into *cis* and *trans* cyclopropanolates **O** proceeds through the corresponding bicyclic transition states $\mathbf{O}^{\#}$ (Scheme 5). A decrease in the cis/trans ratio of cyclopropanols **2** when the R^1 group increases its size (Table 2, entries 3, 4, 6) looks as a trivial trend caused by steric destabilization due to approach of the groups R^1 and R^2 to each other when the three-carbon ring is closing. In contrast, increase in cis-diastereoselectivity of the cyclopropanation reaction when the R^2 group increases its size (Table 2, entries 2, 5, 10) is very unusual. Noticeably, among the couples of isomeric cyclopropanols with the same alkyl groups (e.g., **2a**, **2b**; **2e**, **2c**), better cis-selectivity was observed when the R^2 group was larger than R^1 (Table 2, entries 1,3 and 2,4). We hypothesize that the driving force for cis-stereoselectivity of the ester cyclopropanation *is a relief of the steric strain* during the transformation of β-titanaketone **N** into cyclopropanolates **O**. Evidently, if the transition states $\mathbf{O}^{\#}$ (Scheme 5) are not too early, the repulsive interactions for R^2 and ligands at the

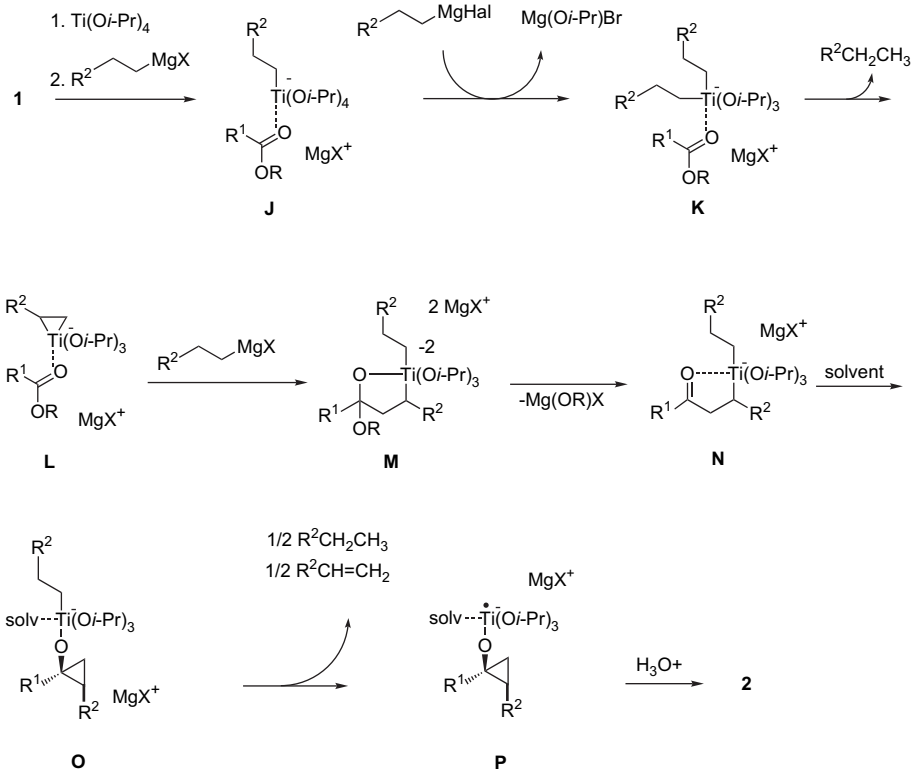
Table 2
Yields and diastereomer ratios for the cyclopropanols **2** obtained from carboxylic esters **1** by cyclopropanation with Grignard reagents in the presence of titanium(IV) isopropoxide

Entry	Ester **1**	Grignard reagent	Cyclopropanol **2**	Solvent	Yield of **2**[a,b] (%)	cis/trans[c]
1	$CH_3CO_2C_2H_5$	$C_5H_{11}MgBr$	 **2a**	Et_2O or THF	75	20:1
2	$CH_3CO_2C_2H_5$	i-$C_5H_{11}MgBr$	 **2e**	Et_2O	67[d]	23:1
3	$C_3H_7CO_2CH_3$	C_3H_7MgBr	 **2b**	Et_2O	76	5.5:1
				THF	84	14:1
				THF	71[d]	10:1
				Et_2O	70	4:1
		i-C_3H_7MgBr		THF	73	10:1
				THF	68[d]	10:1
4	i-$C_3H_7CO_2CH_3$	C_3H_7MgBr	 **2c**	Et_2O	67	1:1
				THF	58	2:1
		i-C_3H_7MgBr		Et_2O	47	1:1
				THF	60	2:1
				THF	50[d]	2:1
5	i-$C_3H_7CO_2CH_3$	i-$C_5H_{11}MgBr$	 **2f**	Et_2O	45[d]	4:1
6	t-$C_4H_9CO_2CH_3$	C_3H_7MgBr	 **2d**	Et_2O	49	1:3
				THF	45	1:3
		i-C_3H_7MgBr		Et_2O	44	1:3
				Et_2O	54[d]	1:1.6
				THF	53	1:3
				THF	44[d]	1:1
7	t-$C_4H_9CO_2CH_3$	i-C_3D_7MgBr	 d_6-**2d**	Et_2O	55[d]	1:1.4
8	t-$C_4H_9CO_2CH_3$	$(CD_3)_2CHMgBr$	 d_5-**2d**	Et_2O	50[d]	1:1.2
9	t-$C_4H_9CO_2CH_3$	$C_5H_{11}MgBr$	 **2g**	Et_2O	48[d]	1:1.2
10	t-$C_4H_9CO_2CH_3$	i-$C_5H_{11}MgBr$	 **2h**	Et_2O	37[d]	3:1

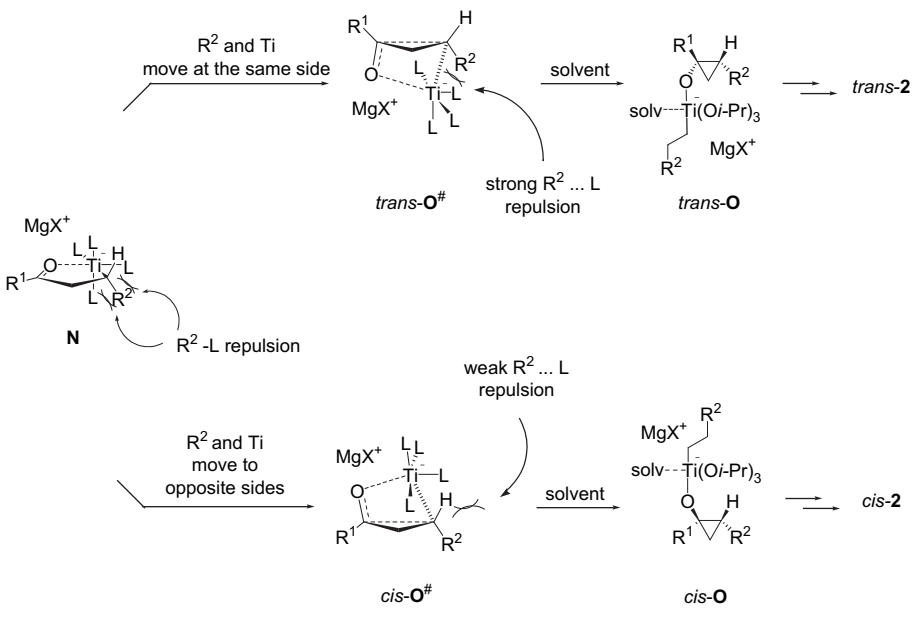
[a] In the presence of catalytic (15 mol %) amounts of Ti(O*i*-Pr)$_4$.
[b] Estimated by ^{1}H NMR.
[c] Determined by ^{1}H NMR.
[d] In the presence of stoichiometric amounts of Ti(O*i*-Pr)$_4$.

titanium atom have to be substantially high for transition state *trans*-**O**$^{\#}$ than for *cis*-**O**$^{\#}$. In the latter, the R^2 alkyl group and titanium atom coordinated to carbonyl move away toward the opposite sides of the cyclopropane ring and finally occupy trans-position in cyclopropanolate *cis*-**O**. In contrast, conversion of β-titanoketone **N** to cyclopropanolate *trans*-**O** has both R^2 and the titanium atom at the same side of the cyclopropane ring (Scheme 5). Evidently, the relief of the $R^2\cdots L$ repulsion strain should stabilize transition state *cis*-**O**$^{\#}$ to a greater extent than transition state *trans*-**O**$^{\#}$, and the difference in energies between both transition states should increase when R^2 increases its size. Thus, the equilibrium between the repulsive interactions $R^2\cdots R^1$ and $R^2\cdots L$ (which favor the formation of *trans*-**2** and *cis*-**2**, respectively) determines the stereochemical outcome for the cyclopropanation of carboxylic esters with the alkoxytitanacyclopropane reagents. Remarkably, the $R^2\cdots L$ repulsive interaction is more sensitive to the size of the R^2 group, than the $R^1\cdots R^2$ interaction and this may be important for synthetic applications.

In contrast to β-titanoketones **N**, octahedral complexes for the corresponding zinc and magnesium intermediates **H** (M=Zn, Mg) are less typical, such species are usually not so



Scheme 4.



Scheme 5.

stable as the corresponding tetrahedral complexes and are inclined to easy dissociation.[34] This leads to a reduction of the $R^2\cdots L$ repulsion and formation of the thermodynamically more stable cyclopropanols *trans*-**2** from the corresponding β-metalloketones is favored. In other words, a more effective extrication from repulsive interactions between ligands at octahedral titanium atom in β-titanoketone ate complexes determinates cis-stereoselectivity for their intramolecular conversion into 1,2-disubstituted cyclopropanols.

3. Conclusion

The comparison of diastereoisomer ratios of cyclopropanols, obtained by the reductive cyclization of β-iodoketones

under treatment of zinc, *c*-$C_6H_{11}MgBr$ or *c*-$C_6H_{11}MgBr$/$Ti(Oi\text{-}Pr)_4$ with the ratios observed in the cyclopropanation of carboxylic esters by substituted alkoxytitanacyclopropane reagents, suggests formation of the *cis*-1,2-disubstituted cyclopropanols in the latter reaction from the β-titanoketone intermediates with the metal atom bound to a secondary carbon. The influence of deuterium substitution in isopropyl Grignard reagent on the stereochemistry of the titanium-mediated cyclopropanation reaction could arise from the steric isotope effect. The determining role of repulsive interactions between ligands at the titanium on the stereochemistry of intramolecular cyclization of β-titanoketones is hypothesized. These interactions were visualized in the context of an ate complex mechanism of the titanium-mediated cyclopropanation of carboxylic esters.

4. Experimental

4.1. 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. Trimethylchlorosilane (TMSCl) was distilled and kept over sodium. Commercial zinc dust was successively washed with aqueous HCl, water, ethanol, acetone, diethyl ether and dried in vacuo at 100 °C. 2-Bromo-1,1,1,3,3,3-hexadeuteriopropane and 2-bromo-1,1,1,2,3,3,3-heptadeuteriopropane were prepared from acetone-d_6 and propan-2-ol-d_8, respectively.[35] Unsaturated ketones **5** were prepared by dehydration of corresponding aldols or by oxidation of appropriate allylic alcohols.[36] Titanium(IV) isopropoxide [$Ti(Oi\text{-}Pr)_4$] was purified by distillation, other reagents were used as purchased from commercial suppliers. All reactions with organometallics were carried out under dry argon. Chromatographical separations were performed on Merck 60 silica gel (70–230 mesh). IR spectra were recorded with Specord IR-75 or Vertex 70 spectrometers. ^1H NMR (400 MHz) and ^{13}C NMR (100.6 MHz) spectra were taken on a Bruker AC 400 spectrometer in $CDCl_3$ as a solvent. Chemical shifts were given in δ value with $CHCl_3$ (δ=7.26 ppm) and $CDCl_3$ (δ=77.0 ppm) as internal standards for ^1H NMR and ^{13}C NMR spectra, respectively. The multiplicities of carbon signals were determined by use of the DEPT techniques. The stereochemical configurations for compounds **2a–h** were confirmed by 1D NOESY or NOE difference experiments.

4.2. Synthesis of β-iodoketones

4.2.1. General procedure for the preparation of β-iodoketones *4* from α,β-unsaturated ketones *5* with hydrogen iodide[14a]

A gaseous hydrogen iodide (generated by dropping 57% hydroiodic acid upon phosphorus pentoxide; *CAUTION*: violent reaction!) was passed through the solution of unsaturated ketone **5** (10–15 mmol) in CH_2Cl_2 (10–15 mL). After the reaction was complete (TLC monitoring, ca. 10–15 min), the solution was washed with water, satd Na_2SO_3, brine and dried with Na_2SO_4. After filtration and removal of the solvent under reduced pressure, the corresponding iodoketones **4a–d** were obtained in 95–100% yields as pale-yellow or orange oils, and were used without further purification. All compounds were unstable, and decomposed while keeping at room temperature. However, they could be stored at low temperatures and protected from direct light for several days without noticeable decomposition.

4.2.2. General procedure for the preparation of β-iodoketones *4* from α,β-unsaturated ketones *5* with trimethyliodosilane[14c]

A solution of sodium iodide (2.70 g, 18 mmol) in anhydrous CH_3CN (20 mL) and then TMSCl (1.95 g, 18 mmol) were added to a solution of unsaturated ketone **5** (15 mmol) in anhydrous CH_3CN (3 mL) at room temperature. After the reaction was complete (TLC monitoring, 10–15 min), 20 mL of Et_2O was added, the reaction mixture was washed with Na_2SO_3, brine and dried with $MgSO_4$. After evaporation of the volatiles in vacuo, corresponding iodoketones **4a**, **4d** were obtained in 90–95% yield as orange oils and were used without further purification.

*4.2.2.1. 4-Iodoheptan-2-one (compound **4a**).* ^1H NMR ($CDCl_3$) δ 0.92 (t, J=7.3 Hz, 3H, 7-CH_3), 1.33–1.46 (m, 1H, CH_2CH_2), 1.46–1.63 (m, 2H, CH_2CH_2), 1.70–1.82 (m, 1H, CH_2CH_2), 2.16 (s, 3H, 1-CH_3), 3.03 (dd, J=17.5, 5.6 Hz, 1H, 3-CH_2), 3.22 (dd, J=17.5, 8.3 Hz, 1H, 3-CH_2), 4.38 (m, 1H, CHI); ^{13}C NMR ($CDCl_3$) δ 13.0, 22.7, 27.3, 30.5, 42.2, 54.1, 205.5; IR (CCl_4) ν_{max}: 1720 cm^{-1}.

*4.2.2.2. 2-Iodoheptan-4-one (compound **4b**).* ^1H NMR ($CDCl_3$) δ 0.90 (t, J=7.4 Hz, 3H, 7-CH_3), 1.59 (m, 2H, 6-CH_2), 1.88 (d, J=6.9 Hz, 3H, 1-CH_3), 2.36 (m, 2H, 5-CH_2), 2.91 (dd, J=17.4, 6.3 Hz, 1H, 3-CH_2), 3.15 (dd, J=17.4, 7.8 Hz, 1H, 3-CH_2), 4.48 (m, 1H, CHI); ^{13}C NMR ($CDCl_3$) δ 14.1, 17.3, 18.7, 29.2, 45.7, 55.6, 208.0; IR (CCl_4) ν_{max}: 1710 cm^{-1}.

*4.2.2.3. 5-Iodo-2-methylhexan-3-one (compound **4c**).* ^1H NMR ($CDCl_3$) δ 1.08 (d, J=7.0 Hz, 3H, CH_3 in *i*-Pr), 1.09 (d, J=7.0 Hz, 3H, CH_3 in *i*-Pr), 1.89 (d, J=6.8 Hz, 3H, 6-CH_3), 2.55 (sept, J=7.0 Hz, 1H, CH in *i*-Pr), 2.97 (dd, J=17.5, 6.4 Hz, 1H, 4-CH_2), 3.23 (dd, J=17.5, 7.7 Hz, 1H, 4-CH_2), 4.50 (m, 1H, CHI); ^{13}C NMR ($CDCl_3$) δ 17.6, 17.8, 18.5, 28.8, 41.0, 53.0, 211.0; IR (CCl_4) ν_{max}: 1720 cm^{-1}.

*4.2.2.4. 5-Iodo-2,2-dimethylhexan-3-one (compound **4d**).* ^1H NMR ($CDCl_3$) δ 1.13 (s, 9H, CH_3 in *t*-Bu), 1.89 (d, J=6.9 Hz, 3H, 6-CH_3), 2.98 (dd, J=17.9, 6.4 Hz, 1H, 4-CH_2), 3.31 (dd, J=17.9, 7.4 Hz, 1H, 4-CH_2), 4.55 (m, 1H, CHI); ^{13}C NMR ($CDCl_3$) δ 19.0, 26.0, 28.7, 43.8, 49.7, 212.1; IR (CCl_4) ν_{max}: 1707 cm^{-1}.

4.2.3. General procedure for the preparation of β-iodoketones *3* from 1,2-disubstituted cyclopropanols *2*

An appropriate cyclopropanol **2** (10 mmol) was added to the solution of iodine (3.05 g, 12 mmol), potassium iodide

(6.6–8.3 g, 40–50 mmol), and sodium hydrocarbonate (1.2–1.5 g, 15–18 mmol) in water (50–60 mL) at vigorous stirring. After 10–15 min (TLC monitoring) the reaction mixture was treated with satd Na_2SO_3 to remove an excess of iodine, and extracted with CH_2Cl_2 (3×10 mL). The organic layer was washed with brine and dried with Na_2SO_4. After removal of the solvent under reduced pressure, corresponding iodoketones **3a–d** were purified by column chromatography over silica gel (hexane/ethyl acetate) and isolated in 95–100% yields as pale-yellow or orange oils.

*4.2.3.1. 3-(Iodomethyl)hexan-2-one (compound **3a**).* ^{1}H NMR ($CDCl_3$) δ 0.91 (t, J=7.3 Hz, 3H, 6-CH_3), 1.23–1.34 (m, 2H, CH_2CH_2), 1.42–1.51 (m, 1H, CH_2CH_2), 1.59–1.68 (m, 1H, CH_2CH_2), 2.20 (s, 3H, 1-CH_3), 2.84 (m, 1H, 3-CH), 3.16 (dd, J=9.8, 5.1 Hz, 1H, CH_2I), 3.29 (dd, J=9.8, 8.6 Hz, 1H, CH_2I); ^{13}C NMR ($CDCl_3$) δ 3.9, 13.9, 20.0, 29.6, 34.9, 54.5, 209.3; IR (CCl_4) ν_{max}: 1715 cm^{-1}.

*4.2.3.2. 1-Iodo-2-methylhexan-3-one (compound **3b**).* ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J=7.4 Hz, 3H, 6-CH_3), 1.15 (d, J=7.1 Hz, 3H, CH_3), 1.58 (m, 2H, 5-CH_2), 2.44 (m, 2H, 4-CH_2), 2.86 (m, 1H, 2-CH), 3.08 (dd, J=9.8, 6.2 Hz, 1H, CH_2I), 3.34 (dd, J=9.8, 7.2 Hz, 1H, CH_2I); ^{13}C NMR ($CDCl_3$) δ 6.1, 13.6, 16.8, 18.0, 43.3, 48.4, 211.0; IR (CCl_4) ν_{max}: 1720 cm^{-1}.

*4.2.3.3. 1-Iodo-2,4-dimethylpentan-3-one (compound **3c**).* ^{1}H NMR ($CDCl_3$) δ 1.10 (d, J=6.9 Hz, 3H, CH_3 in *i*-Pr), 1.11 (d, J=6.9 Hz, 3H, CH_3 in *i*-Pr), 1.17 (d, J=6.9 Hz, 3H, CH_3), 2.75 (sept, J=6.9 Hz, 1H, CH in *i*-Pr), 3.04–3.15 (m, 2H, 2-CH, CH_2I), 3.33–3.41 (m, 1H, CH_2I); ^{13}C NMR ($CDCl_3$) δ 6.1, 18.0, 18.1, 18.7, 39.7, 47.0, 215.0; IR (CCl_4) ν_{max}: 1718 cm^{-1}.

*4.2.3.4. 1-Iodo-2,4,4-trimethylpentan-3-one (compound **3d**).* ^{1}H NMR ($CDCl_3$) δ 1.16 (d, J=6.9 Hz, 3H, CH_3), 1.18 (s, 9H, CH_3 in *t*-Bu), 3.04 (dd, J=9.1, 6.6 Hz, 1H, CH_2I), 3.31–3.44 (m, 2H, 2-CH, CH_2I); ^{13}C NMR ($CDCl_3$) δ 7.1, 20.0, 26.2, 43.2, 44.4, 216.4; IR (CCl_4) ν_{max}: 1707 cm^{-1}.

4.3. Cyclizations of β-iodoketones

4.3.1. General procedure for the preparation of 1,2-disubstituted cyclopropanols **2** (or its TMS-derivatives **6**) from β-iodoketones **3**, **4** with Zn/TMSCl (reagent A)

TMSCl (0.22–0.33 g, 2–3 mmol) was added to a stirred zinc dust (2.2–3 mmol) in THF (5 mL). After 5 min, a solution of iodoketone **3** or **4** (2 mmol) in THF (2 mL) was added via syringe, and the reaction mixture was stirred at room temperature. After the reaction was complete (TLC monitoring, ca. 3–6 h), the reaction mixture was diluted with ether (5 mL) and hydrolyzed with aq K_2CO_3 (10%, 10 mL). Precipitate was filtered off and washed with ether (3×5 mL). Aqueous layer was separated from the filtrate and extracted with ether (3×3 mL). Combined organic layers were dried with Na_2SO_4. After solvent evaporation, cyclopropanols *cis*/*trans*-**2a**, **2b** (or siloxycyclopropanes **6c**, **6d**) were purified by column chromatography (pentane/diethyl ether or hexane/ethyl acetate) and isolated in 84–92% combined yields.

*4.3.1.1. (*E*)- and (*Z*)-1-Methyl-2-propylcyclopropanols (compounds *cis*/*trans*-**2a**).* Yield, 0.207 g, (91%, (*E*)/(*Z*) 1:1) from **3a**; 0.196 g, (86%, (*E*)/(*Z*) 1:3.5) from **4a**.

*4.3.1.2. (*E*)-1-Methyl-2-propylcyclopropanol (compound *cis*-**2a**).* ^{1}H NMR ($CDCl_3$) δ 0.05 (dd, J=6.3, 5.1 Hz, 1H, cycloprop. 3-H), 0.82 (dd, J=10.0, 5.1 Hz, 1H, cycloprop. 3-H), 0.91 (t, J=7.3 Hz, 3H, CH_3 in *n*-Pr), 0.98 (m, 1H, cycloprop. 2-H), 1.05–1.16 (m, 1H, 1H in *n*-Pr), 1.24–1.48 (m, 3H, in *n*-Pr), 1.39 (s, 3H, cycloprop. 1-CH_3), 2.04 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 13.9, 20.2, 20.5, 22.7, 25.4, 32.0, 55.6; IR (CCl_4) ν_{max}: 3600, 3350, 3070 cm^{-1}. Anal. Calcd for $C_7H_{14}O$: C, 73.63; H, 12.36. Found: C, 73.55; H, 12.30.

*4.3.1.3. (*Z*)-1-Methyl-2-propylcyclopropanol (compound *trans*-**2a**).* ^{1}H NMR ($CDCl_3$) δ 0.30 (m, 1H, cycloprop. 3-H), 0.50–0.64 (m, 2H, cycloprop. 3-H+2-H), 0.92 (t, J=7.2 Hz, 3H, CH_3 in *n*-Pr), 1.36–1.50 (m, 4H, 4H in *n*-Pr), 1.39 (s, 3H, cycloprop. 1-CH_3), 1.77 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 13.9, 19.5, 23.0, 24.9, 26.0, 29.8, 55.4; IR (CCl_4) ν_{max}: 3615, 3370, 3075 cm^{-1}. Anal. Calcd for $C_7H_{14}O$: C, 73.63; H, 12.36. Found: C, 73.45; H, 12.31.

*4.3.1.4. (*E*) and (*Z*)-2-Methyl-1-propylcyclopropanols (compounds *cis*/*trans*-**2b**).* Yield 0.210 g (92%, (*E*)/(*Z*) 1:1) from **3b**, 0.194 g (85%, (*E*)/(*Z*) 1:3) from **4b**. See Ref. 6 for spectral data.

*4.3.1.5. (*E*)- and (*Z*)-1-Isopropyl-2-methyl-1-(trimethylsiloxy)-cyclopropanes (compounds *cis*/*trans*-**6c**).* Yield 0.327 g (88%, (*E*)/(*Z*) 1:1) from **3c**, 0.312 g (84%, (*E*)/(*Z*) 1:2) from **4c**. Spectral data are given for a 2:1 mixture of (*Z*) and (*E*) isomers. ^{1}H NMR ($CDCl_3$) δ 0.00 (m, 0.5H, cycloprop. 3-H, (*E*)-isomer), 0.09 (s, 4.5H, $Si(CH_3)_3$, (*E*)-isomer), 0.14 (s, 9H, $Si(CH_3)_3$, (*Z*)-isomer), 0.19 (m, 1H, cycloprop. 3-H, (*Z*)-isomer), 0.53–0.67 (m, 2.5H, cycloprop. 2H, (*Z*)-isomer, cycloprop. 1H, (*E*)-isomer), 0.80–1.15 (m, 5H, $3CH_3$+cycloprop. CH, (*E*)-isomer), 0.86 (d, J=6.9 Hz, 3H, CH_3, (*Z*)-isomer), 0.94 (d, J=6.9 Hz, 3H, CH_3, (*Z*)-isomer), 1.07 (d, J=5.6 Hz, 3H, CH_3, (*Z*)-isomer), 1.22 (m, 0.5H, CH in *i*-Pr, (*E*)-isomer), 1.40 (sept, J=6.9 Hz, 1H, CH in *i*-Pr, (*Z*)-isomer); ^{13}C NMR ($CDCl_3$) δ 1.5, 1.6, 12.7, 13.8, 15.0, 18.5 (2C), 18.6, 19.0 (2C), 19.7, 19.8, 32.2, 36.2, 64.2, 64.8; IR (CCl_4) ν_{max}: 3070 cm^{-1}. Anal. Calcd for $C_{10}H_{22}OSi$: C, 64.45; H, 11.90. Found: C, 64.38; H, 11.81.

*4.3.1.6. (*E*)-1-Isopropyl-2-methylcyclopropanol (compound *cis*-**2c**).* This compound was obtained from **6c** by refluxing in anhydrous methanol and isolated by column chromatography. ^{1}H NMR ($CDCl_3$) δ −0.01 (m, 1H, cycloprop. 3-H), 0.79 (m, 1H, cycloprop. 3-H), 0.95–1.12 (m, 10H, cycloprop. 2-H, $3CH_3$), 1.34 (m, 1H, CH in *i*-Pr), 1.64 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 13.7, 18.0, 18.3, 20.5, 20.7, 31.1, 62.5; IR

(CCl_4) ν_{max}: 3600, 3450, 3065 cm^{-1}. Anal. Calcd for $C_7H_{14}O$: C, 73.63; H, 12.36. Found: C, 73.70; H, 12.28.

*4.3.1.7. (Z)-1-Isopropyl-2-methylcyclopropanol (compound trans-**2c**).* This compound was obtained from **6c** by refluxing in anhydrous methanol and isolated by column chromatography. ^1H NMR ($CDCl_3$) δ 0.21 (m, 1H, cycloprop. 3-H), 0.55 (dd, J=9.2, 5.1, 1H, cycloprop. 3-H), 0.67 (m, 1H, cycloprop. 2-H), 0.97 (d, J=6.8 Hz, 3H, CH_3), 1.00 (d, J=6.8 Hz, 3H, CH_3), 1.11 (d, J=6.1 Hz, 3H, CH_3), 1.15 (m, 1H, CH in *i*-Pr), 1.67 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 12.4, 17.9, 18.0, 18.2, 19.4, 36.3, 62.7; IR (CCl_4) ν_{max}: 3600, 3450, 3065 cm^{-1}. Anal. Calcd for $C_7H_{14}O$: C, 73.63; H, 12.36. Found: C, 73.60; H, 12.32.

*4.3.1.8. (Z)-1-tert-Butyl-2-methyl-1-(trimethylsiloxy)cyclopropane (compound trans-**6d**).* Yield 0.340 g (85%, (*Z*)/(*E*)>99:1) from **3d**, 0.336 g (84%, (*Z*)/(*E*) 92:8) from **4d**. ^1H NMR ($CDCl_3$) δ 0.14 (s, 9H, $Si(CH_3)_3$), 0.74–0.83 (m, 2H, cycloprop. 2H), 0.88 (m, 1H, cycloprop. 1H), 0.86 (s, 9H, $C(CH_3)_3$), 1.06 (d, J=6.1 Hz, 3H, cycloprop. 2-CH_3); ^{13}C NMR ($CDCl_3$) δ 1.9, 12.3, 12.5, 16.6, 26.9, 35.0, 67.2; IR (CCl_4) ν_{max}: 3070 cm^{-1}. Anal. Calcd for $C_{11}H_{24}OSi$: C, 65.93; H, 12.07. Found: C, 66.00; H, 12.18.

*4.3.1.9. (Z)-1-tert-Butyl-2-methylcyclopropanol (compound trans-**2d**).* This compound was obtained from **6c** by refluxing in anhydrous methanol and isolated by column chromatography. See Ref. 6 for spectral data.

*4.3.2. Preparation of (E)- and (Z)-1-methyl-2-propyl-1-(trimethylsiloxy)cyclopropanes (compounds cis/trans-**6a**)*

Triethylamine (0.40–0.61 g, 4–6 mmol) was added when the reaction of iodoketone **4a** with Zn/TMSCl (reagent *A*, vide supra) had been complete and the reaction mixture was stirred for 1–1.5 h before the aqueous work-up. Then ether (10 mL) was added and the reaction mixture was hydrolyzed with satd NH_4Cl. Organic phase was washed with water, brine and dried with Na_2SO_4. Solvent was removed under reduced pressure, and the residue was purified by column chromatography (hexane/ethyl acetate), to afford 1-methyl-2-propyl-1-(trimethylsiloxy)cyclopropanes (**6a**) (0.29 g, 78% combined yield, (*Z*)/(*E*) 3:1).

*4.3.2.1. (E)-1-Methyl-2-propyl-1-(trimethylsiloxy)cyclopropane (compound cis-**6a**).* ^1H NMR ($CDCl_3$) δ 0.00 (dd, J=6.0, 5.1 Hz, 1H, cycloprop. 3-H), 0.12 (s, 9H, $Si(CH_3)_3$), 0.82 (dd, J=10.0, 5.1 Hz, 1H, cycloprop. 3-H), 0.91 (t, J=7.1 Hz, 3H, CH_3 in *n*-Pr), 0.88–1.10 (m, 2H, cycloprop. 2-H, 1H in *n*-Pr), 1.35 (s, 3H, cycloprop. 1-CH_3), 1.34–1.47 (m, 3H, 3H in *n*-Pr); ^{13}C NMR ($CDCl_3$) δ 1.3, 14.0, 20.1, 20.9, 22.7, 25.0, 32.2, 56.7 ppm. Anal. Calcd for $C_{10}H_{22}OSi$: C, 64.45; H, 11.90. Found: C, 64.50; H, 11.97.

*4.3.2.2. (Z)-1-Methyl-2-propyl-1-(trimethylsiloxy)cyclopropane (compound trans-**6a**).* ^1H NMR ($CDCl_3$) δ 0.13 (s, 9H, $Si(CH_3)_3$), 0.28 (m, 1H, cycloprop. 1H), 0.46–0.56 (m, 2H, cycloprop. 2H), 0.90 (t, J=7.2 Hz, 3H, CH_3 in *n*-Pr), 1.12–1.25 (m, 1H, 1H in *n*-Pr), 1.38 (s, 3H, cycloprop. 1-CH_3), 1.35–1.54 (m, 3H, 3H in *n*-Pr); ^{13}C NMR ($CDCl_3$) δ 1.3, 14.0, 19.4, 22.7, 24.1, 26.6, 30.0, 56.7. Anal. Calcd for $C_{10}H_{22}OSi$: C, 64.45; H, 11.90. Found: C, 64.50; H, 11.97.

*4.3.3. Reaction of iodoketones **3**, **4** with cyclohexylmagnesium bromide in the presence of Ti(Oi-Pr)$_4$ (reagent B)*

Cyclohexylmagnesium bromide, prepared from Mg (0.194 g, 8 mmol) and bromocyclohexane (1.30 g, 8 mmol) in THF (8 mL), was added dropwise to the mixture of iodoketone **3** or **4** (2 mmol) and Ti(O*i*-Pr)$_4$ (0.57 g, 2 mmol) in THF (5 mL) at room temperature over 50–60 min. The reaction mixture was stirred for an hour, cooled to 0 °C, diluted with ether (10 mL) and hydrolyzed by cold sulfuric acid (10%, 10 mL). Aqueous phase was separated and extracted with ether (3×5 mL). Combined organic phases were washed with satd Na_2SO_3, $NaHCO_3$, brine and dried with $MgSO_4$. Yield of cyclopropanols and diastereomer ratios were determined by ^1H NMR of the crude product after solvent evaporation using ethyl benzoate as an internal standard (see Table 1, reagent *B*).

*4.3.4. Reaction between iodoketones **3b**, **4b** and cyclohexylmagnesium bromide (reagent C)*

The reaction was carried out as described above, except that Ti(O*i*-Pr)$_4$ was not added. See Table 1 (entries 2 and 6, reagent *C*) for yields and diastereomer ratios.

4.4. Cyclopropanation of carboxylic esters

4.4.1. General procedure for the cyclopropanation of carboxylic esters with Grignard reagents in the presence of Ti(Oi-Pr)$_4$ (catalytic mode)

Alkylmagnesium bromide (11 mL, 1 M in Et_2O or THF, 11 mmol) was added dropwise to the solution of carboxylic ester (5 mmol) and Ti(O*i*-Pr)$_4$ (0.21 g, 0.75 mmol, 15 mol %) in Et_2O or THF (10 mL) at room temperature. The brown reaction mixture was stirred for an 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 $NaHCO_3$, brine and dried with Na_2SO_4. Solvent was removed in vacuo, and the residue was analyzed by NMR spectroscopy. See Table 2 for yields and diastereomer ratios.

4.4.2. General procedure for the cyclopropanation of carboxylic esters with Grignard reagents in the presence of Ti(Oi-Pr)$_4$ (stoichiometric mode)

Alkylmagnesium bromide (15 mL, 1 M in Et_2O or THF, 15 mmol) was added dropwise to the solution of carboxylic ester (5 mmol) and Ti(O*i*-Pr)$_4$ (1.42 g, 5 mmol) in Et_2O or THF (10 mL) at room temperature. The brown reaction mixture 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 (3×5 mL), and the combined organic phases were washed with satd $NaHCO_3$, brine and dried

with Na_2SO_4. Solvent was removed in vacuo, and the residue was analyzed by NMR spectroscopy. See Table 2 for yields and diastereomer ratios. Vide supra for NMR spectroscopic data for compounds **2a**, **2c** and Ref. 6 for compounds **2b** and **2d**.[37]

*4.4.2.1. (E)-2-Isopropyl-1-methylcyclopropanol (compound cis-**2e**).* ^{1}H NMR ($CDCl_3$) δ 0.04–0.09 (m, 1H, cycloprop. 3-H), 0.70–0.99 (m, 6H, cycloprop. 3-H, cycloprop. 2-H, CH in *i*-Pr, CH_3 in *i*-Pr), 1.00–1.05 (m, 3H, CH_3 in *i*-Pr), 1.44 (s, 3H, CH_3), 1.87 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 19.6 (CH_2), 20.5(CH_3), 22.2 (CH_3), 22.9 (CH_3), 30.2 (CH), 34.0 (CH), 55.9 (COH); IR (CCl_4) ν_{max}: 3602, 3070 cm^{-1}. Anal. Calcd for $C_7H_{14}O$: C, 73.63; H, 12.36. Found: C, 73.70; H, 12.24.

*4.4.2.2. (E)-1,2-Diisopropylcyclopropanol (compound cis-**2f**).* ^{1}H NMR ($CDCl_3$) δ 0.00 (dd, J=6.7, 5.0 Hz, 1H, cycloprop. 3-H), 0.75 (dd, J=10.2, 5.0 Hz, 1H, cycloprop. 3-H), 0.80–1.00 (m, 5H, cycloprop. CH, CH in *i*-Pr, CH_3 in 2-*i*-Pr), 1.05–1.10 (m, 9H, $3CH_3$), 1.38 (m, 1H, CH in *i*-Pr), 1.74 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 18.5 (CH_2), 18.7 (CH_3), 19.0 (CH_3), 22.6 (CH_3), 23.9 (CH_3), 28.2 (CH), 30.9 (CH), 36.0 (CH), 63.8 (COH); IR (CCl_4) ν_{max}: 3608, 3066 cm^{-1}. Anal. Calcd for $C_9H_{18}O$: C, 76.00; H, 12.76. Found: C, 75.55; H, 12.88.

*4.4.2.3. (Z)-1,2-Diisopropylcyclopropanol (compound trans-**2f**).* ^{1}H NMR ($CDCl_3$) δ 0.30 (dd, J=6.3, 5.0 Hz, 1H, cycloprop. 3-H), 0.38 (m, 1H, cycloprop. 2-H), 0.54 (dd, J=9.1, 5.0 Hz, 1H, cycloprop. 3-H), 0.98 (d, J=6.7 Hz, 3H, CH_3 in 1-*i*-Pr), 0.99 (d, J=6.7 Hz, 3H, CH_3 in 2-*i*-Pr), 1.02 (d, J=6.5 Hz, 3H, CH_3 in 1-*i*-Pr), 1.03 (d, J=6.8 Hz, 3H, CH_3 in 2-*i*-Pr), 1.13 (m, 1H, CH in 1-*i*-Pr), 1.45 (m, 1H, CH in 2-*i*-Pr), 1.48 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 17.9 (CH_3), 18.08 (CH_2), 18.12 (CH_3), 22.5 (CH_3), 23.4 (CH_3), 27.6 (CH), 32.8 (CH), 36.1 (CH), 63.5 (COH). Anal. Calcd for $C_9H_{18}O$: C, 76.00; H, 12.76. Found: C, 76.10; H, 12.81.

*4.4.2.4. (E)-1-tert-Butyl-2-propylcyclopropanol (compound cis-**2g**).* ^{1}H NMR ($CDCl_3$) δ 0.42 (dd, J=7.3, 5.4 Hz, 1H, cycloprop. 3-H), 0.70 (dd, J=10.5, 5.4 Hz, 1H, cycloprop. 3-H), 0.87 (m, 1H, cycloprop. 2-H), 0.92 (t, J=7.3 Hz, 3H, CH_3 in *n*-Pr), 1.02 (s, 9H, CH_3 in *t*-Bu), 1.14–1.28 (m, 1H, CH_2 in *n*-Pr), 1.34–1.49 (m, 2H, CH_2 in *n*-Pr), 1.63–1.73 (m, 1H, CH_2 in *n*-Pr), 1.90 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 13.9 (CH_3 in *n*-Pr), 17.0 (cycloprop. CH_2), 23.8 (CH_2), 27.4 [$C(CH_3)_3$], 28.3 (CH), 31.5 (CH_2), 34.6 [$C(CH_3)_3$], 64.6 (COH); IR (CCl_4) ν_{max}: 3612, 3074 cm^{-1}. Anal. Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 76.53; H, 12.74.

*4.4.2.5. (Z)-1-tert-Butyl-2-propylcyclopropanol (compound trans-**2g**).* ^{1}H NMR ($CDCl_3$) δ 0.15 (dd, J=6.1, 5.4 Hz, 1H, cycloprop. 3-H), 0.73 (dd, J=9.6, 5.4 Hz, 1H, cycloprop. 3-H), 0.84 (m, 1H, cycloprop. 2-H), 0.91 (s, 9H, CH_3 in *t*-Bu), 0.94 (t, J=7.2 Hz, 3H, CH_3 in *n*-Pr), 1.33–1.50 (m, 4H, CH_2 in *n*-Pr), 1.59 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 14.1 (CH_3), 15.7 (CH_2), 20.3 (CH), 23.4 (CH_2), 26.1 [$C(CH_3)_3$], 30.0 (CH_2), 34.0 [$C(CH_3)_3$], 65.0 (COH); IR (CCl_4) ν_{max}: 3606, 3074 cm^{-1}. Anal. Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 76.72; H, 12.80.

*4.4.2.6. (E)-1-tert-Butyl-2-isopropylcyclopropanol (compound cis-**2h**).* ^{1}H NMR ($CDCl_3$) δ 0.39 (dd, J=7.7, 5.4 Hz, 1H, cycloprop. 3-H), 0.65 (dd, J=10.8, 5.4 Hz, 1H, cycloprop. 3-H), 0.83 (m, 1H, cycloprop. 2-H), 0.96 (d, J=6.5 Hz, 3H, CH_3 in *i*-Pr), 1.04 (s, 9H, CH_3 in *t*-Bu), 1.08 (d, J=6.5 Hz, 3H, CH_3 in *i*-Pr), 1.46 (m, 1H, CH in *i*-Pr), 1.81 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 15.5 (CH_2), 23.5 (CH_3 in *i*-Pr), 23.9 (CH_3 in *i*-Pr), 27.7 (CH_3 in *t*-Bu), 28.1 (CH), 34.8 [$C(CH_3)_3$], 38.2 (CH), 66.1 (COH); IR (CCl_4) ν_{max}: 3612, 3074 cm^{-1}. Anal. Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 76.63; H, 12.81.

*4.4.2.7. (Z)-1-tert-Butyl-2-isopropylcyclopropanol (compound trans-**2h**).* ^{1}H NMR ($CDCl_3$) δ 0.17 (dd, J=6.4, 5.5 Hz, 1H, cycloprop. 3-H), 0.58 (m, 1H, cycloprop. 2-H), 0.71 (dd, J=9.7, 5.5 Hz, 1H, cycloprop. 3-H), 0.90 (s, 9H, CH_3 in *t*-Bu), 0.96 (d, J=6.6 Hz, 3H, CH_3 in *i*-Pr), 1.03 (d, J=6.8 Hz, 3H, CH_3 in *i*-Pr), 1.48 (m, 1H, CH in *i*-Pr), 1.60 (br s, 1H, OH); ^{13}C NMR ($CDCl_3$) δ 15.2 (CH_2), 22.5 (CH_3 in *i*-Pr), 23.5 (CH_3 in *i*-Pr), 26.1 (CH_3 in *t*-Bu), 27.6 (CH), 29.1 (CH), 33.7 [$C(CH_3)_3$], 65.6 (COH); IR (CCl_4) ν_{max}: 3619, 3074 cm^{-1}. Anal. Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 76.70; H, 12.83.

4.4.3. Reaction between methyl pivalate and deuterated Grignard reagents in the presence of Ti(Oi-Pr)$_4$[38]

$(CD_3)_2CHMgBr$ or $(CD_3)_2CDMgBr$ (10 mL, 0.9 M in Et_2O, 9 mmol) was added slowly (over 20 min) at room temperature to a solution of $Ti(Oi\text{-}Pr)_4$ (0.85 g, 3 mmol) and methyl pivalate (0.35 g, 3 mmol) in Et_2O (5 mL). The resulting mixture was stirred for 50 min and quenched by careful addition of sulfuric acid (10%, 11 mL) at 0 °C. The aqueous phase was extracted with Et_2O (2×3 mL), and the combined organic phases were washed with satd $NaHCO_3$, brine and dried with Na_2SO_4. Solvent was removed carefully, and the residue was analyzed by ^{1}H NMR spectroscopy, revealing the formation of a mixture of (*E*)- and (*Z*)-deuterated cyclopropanols **2d** in ca. 50–55% combined yields.

For determination of diastereomer ratios, ^{1}H NMR spectra were acquired and processed in conditions adequate for accurate quantitative measurements.[39] All spectra were acquired with a single scan using 64k data points and a sweep width of 20 ppm. The resulted FID was zero-filled to 128k data points and a mild Gaussian window (GB=0.1) was applied to the FID before the Fourier transformation. For an accurate and reproducible integration, calculation of the peak areas was performed using curve fitting routines in Bruker XWINNMR 3.5 program, and signals from *t*-Bu groups from both of the diastereomers were fit by a mixed Lorenzian–Gaussian line shape. Our own experiment with the test sample in accordance with published procedure[40] confirmed that the error of integration not exceeded 1% in this case.

*4.4.3.1. (E)-1-tert-Butyl-2,3,3-trideuterio-2-(trideuteriomethyl)-cyclopropanol (compound cis-d_6-**2d**).* ^{1}H NMR ($CDCl_3$) δ 1.03 (s, 9H, CH_3 in *t*-Bu), 1.50 (br s, 1H, OH).

*4.4.3.2. (Z)-1-tert-Butyl-2,3,3-trideuterio-2-(trideuteriomethyl)-cyclopropanol (compound trans-d_6-**2d**).* ^{1}H NMR ($CDCl_3$) δ 0.90 (s, 9H, CH_3 in *t*-Bu), 1.50 (br s, 1H, OH). See Ref. 6 for NMR spectral data for compounds d_5-**2d**.

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