Effective and Selective Mild Catalytic Hydrodehalogenation of Halocyclopropanes: Preparative Capabilities and Mechanistic Aspects[1]

A. V. Nizovtsev*, J. R. Al Dulayymi**, M. S. Baird**, I. G. Bolesov*, and V. V. Tverezovskii*

* Moscow State University, Moscow, 119899 Russia
** Department of Chemistry, University of Wales Bangor, Bangor, Gwynedd LL57 2UW, United Kingdom
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Abstract—This review surveys both data obtained by the authors and published data on the partial or full hydrodehalogenation of di- and polyhalocyclopropanes (chlorides and bromides) with Grignard reagents catalyzed by titanium or zirconium compounds. The factors affecting the efficiency and selectivity of the hydrodebromination of bromocyclopropanes are considered: the nature of Grignard reagents (including isotopically labeled reagents), their transformations and effects in catalyzed and uncatalyzed reactions, the participation of solvents, catalytic and stoichiometric amounts of the catalyst, etc. A scheme is proposed in which the key steps of the mechanism of hydrodebromination of bromocyclopropanes includes three blocks of reactions: (a) the generation of a catalytically active Ti(II) species; (b) the hydrodehalogenation of bromocyclopropanes involving electron transfer from a low-valent catalyst species, formation of the cyclopropyl radical, and stabilization of this radical as a result of hydrogen atom transfer from the solvent molecule; and (c) transformations of previously formed radical species, such as dimerization and disproportionation (for example, of radical species generated from Grignard reagents or ether molecules) or the linking of alkyl radicals to radical species produced from solvent molecules.

INTRODUCTION

Di- and polyhalocyclopropanes, which are readily available because methods used for the generation and addition of halocarbenes to various unsaturated compounds are highly efficient, have been of considerable interest to synthetic chemists for many years. As well as many other functional derivatives of cyclopropane, halocyclopropanes are characterized by high synthetic flexibility, which provides an opportunity to design aliphatic mono-, bi-, and polycyclic carbocycle and heterocycle systems with high selectivity. Among halocyclopropanes, 1-bromocyclopropanes are of particular interest; however, as a rule, the preparative synthesis of them is associated not with the generation of monobromocarbenes [1] and their addition to unsaturated compounds but with the partial reduction of readily available 1,1-dibromocyclopropanes, which can be used for the preparation of stereoisomeric monobromides in many cases [2, 3]. Of the most frequently used methods, radical reduction with tributyltin hydride [4], which primarily results in *cis-* or *endo*-monobromides, should be noted. A wide variety of reagents used for partial or full hydrodehalogenation are also well known: zinc–ethanol–potassium hydroxide [5, 6], a

zinc–copper couple [7], zinc–acetic acid [8], *O,O'*-diethyl-α-lithiomethyl phosphonate [9], complex hydrides [10], butyllithium in combination with subsequent treatment with methanol [11], and hydrogen in the presence of catalysts [12], as well as photochemical [13] and electrochemical [14, 15] techniques. Sodium in DMSO is also highly efficient; its key feature consists in the predominant formation of *trans-* or *exo*-monobromides [16]. Although all the above methods are quite efficient, they are not free of disadvantages. For example, the reduction with zinc in ethanol requires a long treatment of the reaction mixture, whereas toxic organotin compounds should be removed from the reaction mixtures formed with the use of tributyltin hydride. The method in which monobromocyclopropanes are obtained with high stereoselectivity using low-valent vanadium and diethyl phosphonate or triethyl phosphite at room temperature is time consuming. In this case, the yields of reaction products varied over a wide range [17].
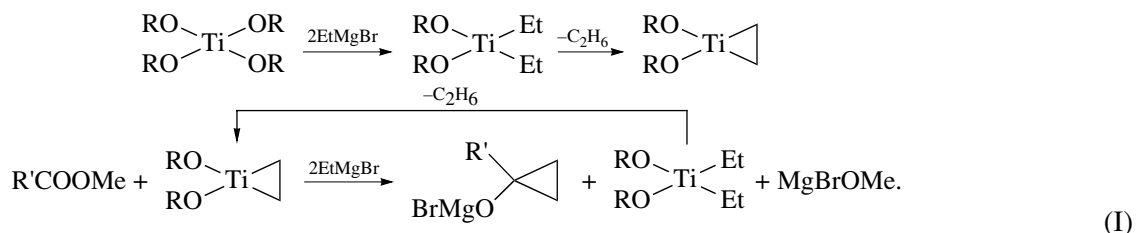
In this review, we survey some results obtained over the last six years in studies of the hydrodebromination of *gem-di-* and polyhalocyclopropanes with Grignard reagents catalyzed by titanium and zirconium compounds.

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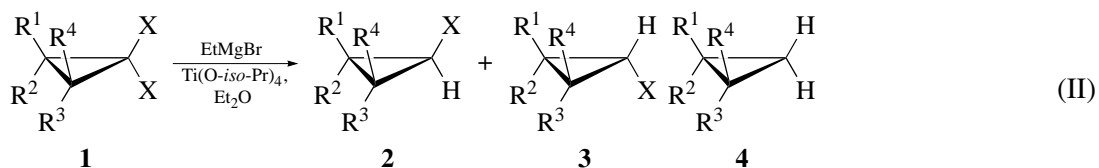## PREPARATIVE CAPABILITIES OF HALOCYCLOPROPANE HYDRODEBROMINATION

The reaction of ethylmagnesium bromide with esters in the presence of titanium isopropoxide to form cyclopropanol derivatives was discovered by Kulinkovich [18] (reaction (I)). The mechanism of this widely used reaction involves a catalytic cycle in which a diethyltitanium intermediate eliminates the ethane molecule.

$$
(RO)_2Ti(OR)_2 \xrightarrow{2EtMgBr} (RO)_2Ti(Et)_2 \xrightarrow{-C_2H_6} (RO)_2Ti\triangleleft
$$

$$
R'COOMe + (RO)_2Ti\triangleleft \xrightarrow{2EtMgBr} \underset{BrMgO}{\overset{R'}{\triangleright}} + (RO)_2Ti(Et)_2 + MgBrOMe. \qquad (I)
$$

This reaction was studied with 2,2-dibromocyclopropane carboxylates and other polybromocyclopropanes (and dichlorocyclopropanes) (reaction (II); Table 1). It was found that the same reagents can partially or completely hydrodebrominate tetra-, tri-, and *gem*-dibromocyclopropanes under mild conditions [19]. As can be seen in Table 1, dibromocyclopropane (**1a**) reacted with 1.3 mol equiv of ethylmagnesium bromide and 2 mol % titanium isopropoxide in ether (hereinafter, this refers to the use of diethyl ether) for 20 min at 20°C to form monobromides **2a** and **3a**, which were isolated in a 92% yield in a ratio of 2 : 1 after the treatment of the reaction mixture with water followed by distillation.

$$
\mathbf{1} \xrightarrow[\substack{Ti(O\text{-}iso\text{-}Pr)_4, \\ Et_2O}]{EtMgBr} \mathbf{2} + \mathbf{3} + \mathbf{4} \qquad (II)
$$

	a	b	c	d	e	f	g	h	i	j	k	l
R^1	Me	H	Me	H	H	H	$p\text{-}C_8H_{17}$	$p\text{-}C_4H_9$	Br	Ph	Me	H
R^2	Ph	Ph	Me	$-(CH_2)_2-$	$-(CH_2)_3-$	$p\text{-}C_6H_{13}$	Br	Br	Br	Ph	Ph	Ph
R^3	H	H	H	$-(CH_2)_2-$	$-(CH_2)_3-$	H	H	H	Me	H	H	H
R^4	H	H	H	H	H	H	H	H	Me	H	H	H
X	Br	Br	Br	Br	Br	Br	Br	Br	Br	Br	Cl	Cl

According to GLC data, under the specified conditions, the reaction mixture contained 1% parent dibromide and <1% completely reduced cyclopropane derivative **4a**. By varying the amount of titanium isopropoxide under the same conditions, it was found that the minimum catalyst amount that provides high conversion is 2%, because 0.5% catalyst reduced only 18% of starting dibromide **1a**. On the other hand, an increase in the catalyst amount up to 10% (Table 1, entries 5, 8, 10) apparently does not result in significant amounts of byproducts. An increase in the amount of the Grignard reagent up to 3 mol equiv in the reduction of compound **1a** in the presence of 10 mol % titanium isopropoxide afforded hydrocarbon **4a** in a 93% yield after allowing the reaction mixture to stand for 90 min (Table 1, entry 2).

Although it follows from Table 1 that the stereoselectivity of hydrodehalogenation is relatively low, this method is of special interest in cases when synthesized monobromides or monochlorides are used as the precursors of 3,3-disubstituted cyclopropenes [20, 21].

Note that an interesting result was obtained in the hydrodebromination of 1,1-dibromo-2-(but-3-enyl)cyclopropane with the use of 1.8 mol equiv of ethylmagnesium bromide in the presence of 5 mol % titanium isopropoxide. As the main product (according to GLC data, >55%), 1-bromo-2-methylbicyclo[3.1.0]hexane was obtained, which was isolated in a 27% yield by distillation (reaction (III)). Products that contain the

Table 1. Preparative reduction of *gem*-dihalocyclopropanes **1a**–**1m** with ethylmagnesium bromide in the presence of titanium compounds in catalytic amounts

Entry	Starting com- pound	EtMgBr, mol equiv	Ti(O-*iso*-Pr)$_4$, mol %	Time, min		Yield, % (according to GLC)			Yield,[a] %		2 : 3 product ratio
				addition	stirring	1	2 + 3	4	2 + 3	4	
1	**1a**	1.3	2	10	10	2	98	0	92		2.0 : 1
2	**1a**	3.0	10	60	20	0	0	97		93	–
3	**1b**	1.25	2	12	10	3	93	0	90		1 : 1.1
4	**1c**	1.3	5	30	10	0	99	[b]	85		–
5	**1d**	1.4	10	25	10	0	99	<1	90		1 : 3.8
6	**1e**	1.5	2	20	10	0	88	1	96		1 : 2.5
7	**1f**	1.45	5	20	10	1	95	<1	97		1 : 1.7
8	**1g**	1.0	10	10	10	1	89	0	96		3.5 : 1
9	**1h**	1.0	2	10	10	0	97	0	95		3.5 : 1
10	**1i**	1.05	10	10	10	3	92	4	95		–
11[c]	**1j**	1.5	2	10	10	0[d]	100[d]	0[d]	93[f]		–
12[e]	**1k**	2.0	10	20	120	1	96	1	94		2.0 : 1
13[e]	**1l**	2.0	10	30	30	3	94	<1	93		1 : 1.2
14[g]	**1m**	2.4	10	70	60	0	98	0	95		1 : 2.6

Note: [a] After filtration through a thin layer of silica gel. [b] The concentration of compound **4c** cannot be determined by GLC in this solvent. [c] The reaction was performed in THF; the TiCl$_4$ · 2THF complex was used as a catalyst. [d] According to ^{1}H NMR data. [e] The reaction was performed under reflux. [f] The resulting compound was pure, and it did not require additional filtration through a silica gel layer. [g] See reaction (VII).

CHBr fragment or unsaturated bonds were not detected in the reaction mixture by ^{1}H NMR spectroscopy [22].

$$endo : exo = 89 : 11 \qquad (III)$$
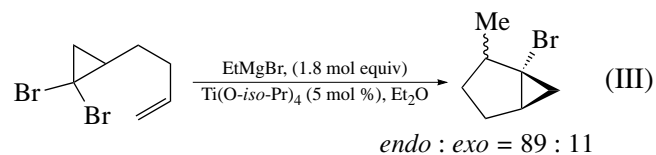
Along with titanium isopropoxide, titanium trichloride as a solution in dichloromethane and titanium tetrachloride in combination with phenylmagnesium bromide in ether can be effective catalysts for hydrodebromination with ethylmagnesium bromide [23].

The partial reduction of tricyclic tetrabromide **5a** (reaction (IV)) with the use of 2.3 mol equiv of ethylmagnesium bromide in the presence of 10 mol % titanium isopropoxide in ether also occurred rapidly and

efficiently: dibromide **5b** was prepared in an 84% yield as a mixture of three stereoisomers [23].


$$ (IV) $$
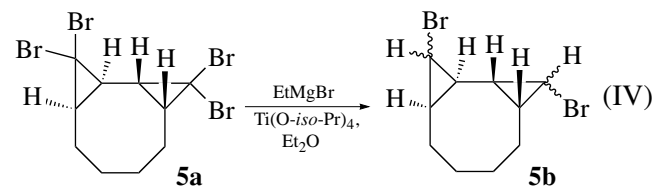
Interesting results were obtained in the reactions of 1,1,2-tribromo- (**1g**, **1h**) and 1,1,2,2-tetrabromocyclopropanes (**1i**): partial hydrodebromination with 1.00–1.05 mol equiv of ethylmagnesium bromide in ether in the presence of 2–10 mol % titanium isopropoxide resulted in only vicinal dibromides (**2g** + **3g** and **2h** + **3h**) and 1,1,2-tribromide **2i**, respectively, in ~95% yields.

These data, in combination with the results of the reduction of compound **5a**, indicate that the CBr$_2$ fragment exhibits a much higher activity than CHBr, no matter whether these structural fragments occur in the same or in different three-carbon rings. Another special feature of these transformations is that the reagents used (Grignard reagents and titanium isopropoxide) [23], similarly to lithium aluminum hydride, sodium borohydride in ethanol, or tributyltin hydride, result in only hydrodebromination and do not form 1,2-dehalo-

genation products. As a rule, these products are formed in high yields under the action of reagents such as alkyllithium, diethyl phosphite and triethylamine, or sodium hydride [24].

The found selectivity of the partial hydrodehalogenation of 1,1,2-tribromocyclopropanes was also accomplished in the synthesis of (*Z*)- and (*E*)-1,2-dibromo-1-(2-methoxymethoxyethyl)cyclopropanes(V), which were subsequently used as the precursors of new methylenecyclopropane analogs of adenosine [25]:

$$\text{(V)}$$

Yield 76%
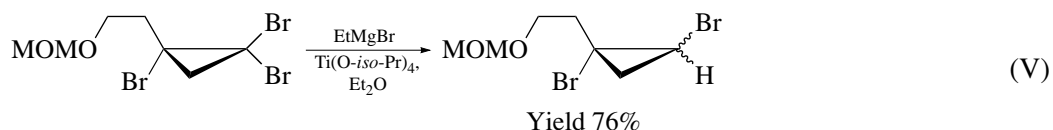
where MOMO is the fragment of the MeOCH$_2$O group.

Ethylmagnesium bromide in combination with titanium isopropoxide can also be used for the partial hydrodebromination of *gem*-dibromocyclopropyl derivatives of ferrocene. In this case, the yields of the corresponding monobromocyclopropanes are 60–80%. The reduction of these compounds using other methods resulted in lower yields [26].

Note that the high efficiency of hydrodebromination with the use of organomagnesium compounds and titanium derivatives cannot be extended to reactions with the participation of organolithium compounds. For example, the reaction of compound **1a** in ether with 1 mol equiv of *n*-butyllithium in hexane in the presence of 5 mol % titanium isopropoxide at 20°C for 1 h resulted in only 1% fully reduced cyclopropane derivative, 69% allene **6a**, 19% monobromides, and 11% of the parent substance [23].


6a
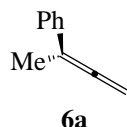
A similar mixture of products was obtained when the above reaction was performed at –90°C for 1 h. It is likely that the formation of allene **6a**, which is typical of the reactions of compound **1a** with organolithium compounds, occurs via a step of the intermediate generation of cyclopropylidene or a related carbenoid [27]. At the same time, it is well known that, on heating in dioxane, titanium tetrabutoxide promotes the conversion of dibromocyclopropanes into a mixture of monobromides and fully reduced cyclopropanes with the use of diisobutylaluminum hydride [28].

The reaction of dibromo ester **7** with ethylmagnesium bromide (4 mol equiv) in the presence of 10 mol % titanium isopropoxide resulted in the formation of stereoisomeric bicyclopropanols **8** in a ~65% yield (reaction (VI)). An analogous transformation of a salt of acid **9**, which was generated *in situ* from acid and

1 mol equiv of ethylmagnesium bromide, was less selective, although the main reaction product, monobromo acid **10**, which was isolated as a mixture of *cis* and *trans* isomers, was obtained in a 79% yield [23]. The other isolated substances were cyclopropanol derivative **8** (13%) and the parent acid (<1%).

$$\text{(VI)}$$
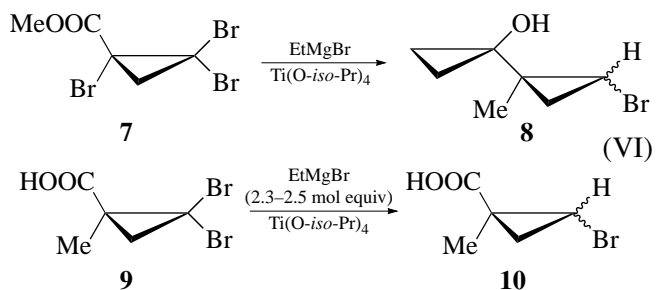
Data given in Table 1 and reaction (VII) suggest that dichlorocyclopropanes **1k–1m** can also be selectively converted into the corresponding monochlorides. Other examples of the reduction of chlorocyclopropanes with the use of Grignard reagents and titanium compounds will be published elsewhere.

$$\text{(VII)}$$
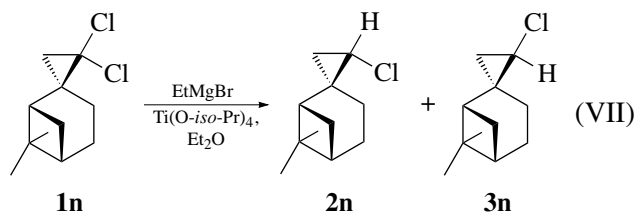
NATURE OF GRIGNARD REAGENTS

Note that the uncatalyzed reaction of methylmagnesium bromide with compound **1d** in boiling tetrahydrofuran (THF) is well known. It results in the formation of monobromides due to a radical mechanism, in accordance with which a halogen in compound **1d** is replaced by a hydrogen atom transferred from the α-position of the THF molecule [29]. However, it was

found that the yields of monobromides published for this reaction are lower than that under conditions of the reaction catalyzed by titanium isopropoxide. The addition of 2 mol equiv of methylmagnesium bromide to a solution of compound **1d** in an ether–THF–toluene mixture did not induce a fast reaction similar to the reaction that was observed with the use of EtMgBr and Ti(O–*iso*-Pr)$_4$. As a result, a considerable amount of **1d** had not managed to react even after 18 h. In this case, very similar stereoselectivities were observed both in the titanium isopropoxide–catalyzed reaction of ethylmagnesium bromide and, probably, in the uncatalyzed reaction of methylmagnesium bromide [23]. Compound **1a** reacted comparatively rapidly with 1.3 mol equiv of methylmagnesium bromide in an ether solution at room temperature: the yield of monobromides **2a** and **3a** after 1 h was 50–60%. In this case, the addition of 10 mol % Ti(O–*iso*-Pr)$_4$ to the reaction mixture increased the reaction rate only slightly: the degree of reduction over 1 h was almost 80%. To compare the activity of these two reagents, hydrodebromination was performed under standard conditions: the reagents (1.3 mol equiv) were added to solutions of dibromide **1a** for 10 min with stirring at 20°C (water bath), and the reaction mixtures were analyzed by GLC for a long time (see figure). This mode of adding reagents was chosen because the reduction with EtMgBr and Ti(O–*iso*-Pr)$_4$ is highly exothermic.

Evidently, the uncatalyzed reaction with EtMgBr was the slowest under these conditions, and the addition of 2 mol % Ti(O–*iso*-Pr)$_4$ allowed this reaction to be completed for the most part after the addition of the Grignard reagent. The subsequent reduction of **2a** and **3a** to **4a** occurred much more slowly.

The uncatalyzed reaction with MeMgBr was much more rapid than analogous reduction with EtMgBr. At the same time, the addition of 2 to 10 mol % Ti(O–*iso*-Pr)$_4$ caused only a slight increase in the rate.

If compound **1a** was mixed with 10 mol % Ti(O−*iso*-Pr)$_4$ and 0.2 mol equiv of EtMgBr and then 1.1 mol equiv of MeMgBr were added, the rate of reaction, which results in the corresponding monobromides, was much higher than that with the use of only MeMgBr. This fact suggests that an intermediate that promotes the subsequent reaction with MeMgBr is formed in the reaction between EtMgBr and Ti(O–*iso*-Pr)$_4$.

Note that metal derivatives capable of promoting the reactions of Grignard reagents with aliphatic and aromatic halides are known. For example, arylmagnesium halides reacted with cobalt(II) chloride in THF in the presence of haloalkanes to form alkylarenes; however, they were isolated in low yields [30, 31]. Next, methylmagnesium bromide reacted with bromobenzene in anisole in the presence of cobalt(II) chloride with the formation of a mixture of isomeric methoxybiphenyls and biphenyl in a small amount [32]. The intermediate formation of radicals in these reactions was supported by fixation with anthracene [33]. It is also well known

Concentration of **1a**, %

Reaction time, min
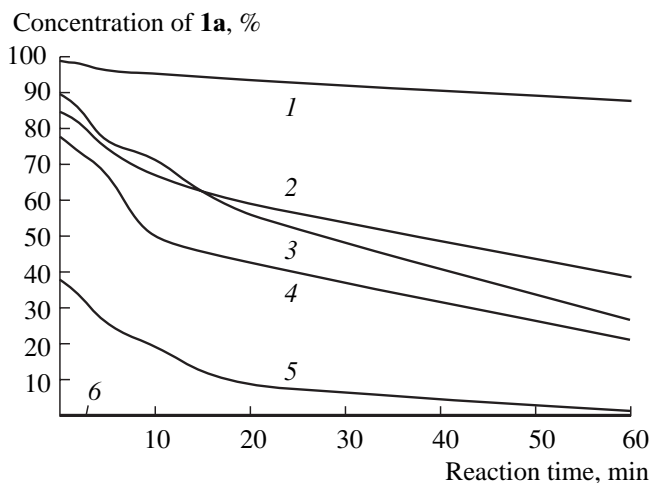
Reduction of compound **1a** with (*1*) EtMgBr, (*2*) MeMgBr, (*3*) MeMgBr + 2 mol % Ti(O–*iso*-Pr)$_4$, (*4*) MeMgBr + 10 mol % Ti(O–*iso*-Pr)$_4$, (*5*) 0.2 mol equiv of EtMgBr + 1.1 mol equiv of MeMgBr + 10 mol % Ti(O–iso-Pr)$_4$, and (*6*) EtMgBr + 2 mol % Ti(O–*iso*-Pr)$_4$ at 20°C (line *6* coincides with the axis of abscissas). The abscissa is the time after the addition of the Grignard reagent.

that cobalt halides [34], copper(I) bromide [35], and a number of other metals [36] promote the reaction of RMgX with R'X with the formation of RR'. Data on hydrodehalogenated compounds equivalent to those described in this work were not published. After the publication of the preliminary results of this study, the reduction of 1,1-dichlorocyclopropanes with Grignard reagents in the presence of cobalt(II) chloride or the Fe(dbm)$_3$ (dbm = dibenzoylmethanate) complex was reported [37].

To obtain information on the mechanism of hydrodehalogenation in the presence of Ti(O–*iso*-Pr)$_4$, a set of experiments was performed in which the reactivity of the series of alkylmagnesium bromides toward dibromocyclopropane **1a** was evaluated in the absence of titanium catalysts (Table 2).

The following conclusions can be drawn from data given in Table 2.

(a) Each of the tested Grignard reagents can accomplish hydrodebromination of dibromocyclopropane **1a**.

(b) With the use of 1.3 mol equiv of EtMgBr for 1 h, ~5% monobromides **2a** and **3a** and 7% allene **6a** were formed [38]. Even after 24 h, ~57% parent dibromide remained in the reaction mixture, and the ratio between the resulting monobromides and the allene was 1 : 4. It is generally agreed that 1-lithium-1-bromocyclopropanes are intermediate compounds in the formation of allenes by the well-known reactions of dibromocyclopropanes with alkyllithium reagents [27]. From this standpoint, 1-bromocyclopropyl anions (or corresponding organometallic compounds), which could be formed from both starting dibromides and one or both of the monobromocyclopropanes, can be intermediate compounds in the

Table 2. Reactions of dibromocyclopropane **1a** with various Grignard reagents in ether in the absence of catalysts

| Entry	RMgBr	RMgBr, mol equiv	Stirring time, h	Product yields,[a] %		
				1a	**2a + 3a**	**6a**
1	MeMgBr	1.3	24	13 [15]	85 [85(2.4 : 1)]	0 [0]
2	EtMgBr	1.3	24	43 [57]	10 [9(1.6 : 1)]	47 [31]
3	*sec*-BuMgBr	2.0	1	14 [21]	38 [53(1.5 : 1)]	49 [26]
4	Et$_2$CHMgBr	1.0	18	41 [43]	21 [18(1.6 : 1)]	38 [39]
5	*tert*-BuMgBr	2.0	8	23 [27]	77 [73(1.7 : 1)]	0 [0]
6	*tert*-BuMgBr	4.0	72	[4]	[96(1.7 : 1)]	0 [0]
7	PhMgBr	1.0	24	70 [74]	24 [26(2.3 : 1)]	6 [–]
8	PhCH$_2$MgBr	1.0	16	75 [78]	25 [22(1.8 : 1)]	0 [0]
9	PhCH$_2$CH$_2$MgBr	2.0	24	73 [65]	14 [23(2.8 : 1)]	13 [13]

Note: [a] All the data correspond to GLC values based on total products from the initial dibromocyclopropane and unreacted parent compound, which were taken as 100%; ^{1}H NMR data for the reaction mixture are given in brackets, and the **2a** : **3a** ratios are given in parentheses.

Table 3. Reduction of *gem*-dibromocyclopropanes with *tert*-butylmagnesium bromide in ether

Entry	Starting compound	Amount, mmol	*tert*-BuMgBr, mol equiv	Stirring time, h	Reaction mixture composition according to ^{1}H NMR data[a]			Yield, %	Ratio **2** : **3**
					1	**2 + 3**	**6[f]**		
1	**1a**	10	4.0	72	<1	>98	<1	80[b]	1.7 : 1
2	**1b**	1	3.0	24	0	92	8	–	1.6 : 1
3	**1j**	10	4.0	72	0	>96	<4	70[c]	–
4	**1n**	30	1.3	0.5	0	100	0	72[b]	1 : 2.6
5	**1o**	1	2.0	24	0	100	0	68[d] (44[e])	5 : 1

Note: [a] See footnote [a] in Table 2. [b] The yield after distillation. [c] The yield after recrystallization from a heptane–toluene mixture (10 : 1). [d] The yield of the crude product. [e] The yield of monobromo acids after the hydrolysis of the reaction mixture (second step) based on parent dibromide **1o**.
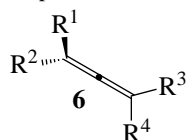
formation of allenes in uncatalyzed reactions of dibromocyclopropanes with Grignard reagents.

(c) Reduction with methylmagnesium bromide is much more rapid than that with the use of the other tested Grignard reagents, except for *tert*-butylmagnesium bromide.

(d) The reduction of compound **1a** with the use of 4 mol equiv of *tert*-butylmagnesium bromide (reac-

Table 4. Reactions of dibromocyclopropane **1a** with Grignard reagents in ether in the presence of titanium tetraisopropoxide

Entry	RMgBr	RMgBr, mol equiv	Ti(O-*iso*-Pr)$_4$, mol %	Stirring time	Product yields,[a] %			
					1a	**2a** + **3a**	**4a**	**6a**
1	MeMgBr	1.30	10	24 h	5 [6]	93 [94 (2.3 : 1)]	2 [0]	0 [0]
2	EtMgBr	1.30	2	10 min	2 [0]	98 [94[b] (2.0 : 1)]	0 [0]	0 [0]
3	EtMgBr	3.00	10	1.5 h	0 [0]	0 [0]	97 [93[b]]	0 [0]
4	*sec*-BuMgBr	1.04	5	30 min	<1 [0]	100 [97[b] (2.0 : 1)]	0 [0]	0 [0]
5	*sec*-BuMgBr	2.64	10	30 min	0 [0]	<1 [0]	>99 [95[b]]	0 [0]
6	Et$_2$CHMgBr	1.30	2	3 h	39 [33]	45 [49 (1.5 : 1)]	0 [0]	16 [18]
7	Et$_2$CHMgBr	1.30	10	10 min	3 [0]	97 [100 (2.0 : 1)]	0 [0]	0 [0]
8	Et$_2$CHMgBr	4.00	10	42 h	0 [0]	4 [0]	96 [100]	0 [0]
9	*tert*-BuMgBr	2.00	10	14 h	4 [3]	96 [97 (1.9 : 1)]	0 [0]	0 [0]
10	PhMgBr	1.50	2	20 min	5 [0]	93 [100 (2.6 : 1)]	3 [0]	0 [0]
11	PhMgBr	4.00	10	14 h	0 [0]	0 [0]	100 [100]	0 [0]
12	PhCH$_2$MgBr	1.00	10	16 h	59 [58]	41 [42 (1.8 : 1)]	0 [0]	0 [0]
13	PhCH$_2$MgBr	5.00	22	36 h	1 [0]	83 [88 (1.8 : 1)]	16 [12]	0 [0]
14[c]	PhCH$_2$CH$_2$MgBr	1.30	2	10 min	3 [0]	92 [100 (1.8 : 1)]	5 [0]	0 [0]
15	PhCH$_2$CH$_2$MgBr	5.00	10	24 h	0 [0]	3 [0]	97 [100]	0 [0]

Note: [a] See footnote [a] in Table 2. [b] The yield of the preparatively isolated compound. [c] The reaction mixture was treated with D$_2$O; according to chromatography–mass spectrometry and ^{1}H NMR data, the products contained no deuterium.

tion (VIII); Table 3) can be highly selective and preparative. *tert*-Butylmagnesium bromide can also be effective and selective in the partial hydrodebromina-tion of functional derivatives of *gem*-dibromocyclopropanes, such as 1,1-dibromo-2-cyano-2-methylcyclopropane (reaction (VIII); Table 3) [22].
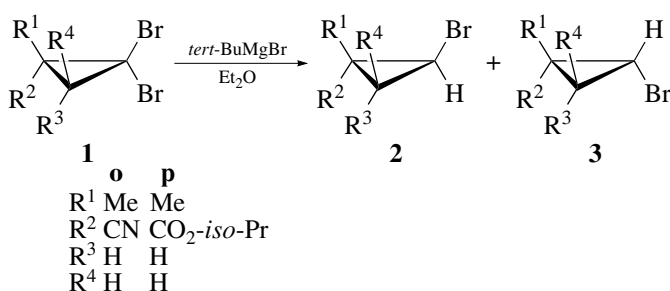
(VIII)

EFFECTS OF GRIGNARD REAGENTS IN CATALYZED REACTIONS

The reactions summarized in Table 4 were performed in the presence of titanium isopropoxide.

Examples of hydrodebromination that dramatically differed from uncatalyzed reactions (Table 2) in efficiency and selectivity were found.

The partial hydrodehalogenation of compound **1a** with *sec*-butylmagnesium bromide occurred with high

Table 5. Reactions of dibromide **1a** and monobromides **2a** + **3a** (entry 5) with phenylethylmagnesium bromide in ether

En-try	RMgBr,[b] mol equiv	Ti(O-*iso*-Pr)$_4$, mol %	Product yields,[a] %								
			1a	**2a** + **3a**	**4a**	**6a**	ethylbenzene	styrene	**13**	**14**	β-phenyleth-yl bromide
1	2.00	0	73 [65]	14 [23(2.8 : 1)]	0 [0]	13[13]	152 [166]	7 [7]	6	16	21 [19]
2[c]	0.80	2	35 [29]	65 [72(2.0 : 1)]	0 [0]	0 [0]	29 [64]	5 [2]	32	5	0 [0]
3[d]	1.30	2	3 [0]	92 [100(1.8 : 1)]	5 [0]	0 [0]	61 [100]	6 [6]	31	8	0 [0]
4	5.00	10	0 [0]	3 [0]	97[100]	0 [0]	479 [500]	32 [31]	28	46 [50]	0 [0]
5[e]	3.00	10	0 [0]	3 [0]	97[100]	0 [0]	273 [293]	25 [29]	6	16 [25]	0 [0]

Note: [a] See footnote[a] in Table 2.

[b] An aliquot portion of the Grignard reagent after treatment with D$_2$O contained, according to GLC data, ethylbenzene (>88%), styrene (<1.6%), and compound **14** (<10%); according to chromatography–mass spectrometry data, ethylbenzene-d (91%), styrene (1.6%), compound **14** (6%), and 2-phenylethanol (2%); all the ethylbenzene contained a deuterium label at the β-position of the alkyl group.

[c] The layers formed after the addition of 0.80 mol equiv of the Grignard reagent were separated: the bottom layer contained ether and 2-phenylethanol (according to ^{1}H NMR data in D$_2$O); the top layer was treated with D$_2$O; the aqueous layer contained only ether, whereas the top layer contained (according to ^{1}H NMR data) products specified in entry 2.

[d] A half of ether was distilled from the reaction mixture at atmospheric pressure and treated with bromine; the products of bromine addition to vinyl ethyl ether were not detected (according to ^{1}H NMR and GLC data). The remainder of the reaction mixture was treated with D$_2$O. Undeuterated monobromocyclopropanes were extracted from the organic phase. According to chromatography–mass spectrometry data, ethylbenzene was also free of deuterium labels.

[e] A mixture of monobromides **2a** + **3a** was reduced; the reaction mixture was treated with D$_2$O after 18 h; chromatography–mass spectrometry data gave the ratio PhCH$_2$CH$_2$D : PhCH$_2$CH$_3$ = 63 : 37.

selectivity, and it was almost completed with the use of 1.04 mol equiv of the reagent in the presence of 5 mol % catalyst for 30 min (entry 4). Ethylmagnesium bromide was found to be almost equally selective; however, it should be introduced into the reaction in an amount of 1.3 mol equiv; in this case, the reaction was completed after 10 min in the presence of 2 mol % Ti(O–*iso*-Pr)$_4$ (entry 2). Analogously, 1.3 mol equiv of 2-phenylethyl-magnesium bromide was required for almost complete monoreduction in the presence of 2 mol % Ti(O–*iso*-Pr)$_4$ (entry 14).

3-Pentylmagnesium bromide should also be used in an amount of 1.30 mol equiv, however, with 10 mol % catalyst (entry 7). In this case, the reaction was practically nonselective in the presence of 2 mol % Ti(O–*iso*-Pr)$_4$ (entry 6).

In each of the above examples, the reaction was completed within 10 min after the addition of the Grignard reagent, and the composition of the mixture subsequently remained almost unchanged for 20 min. Note that all four reagents were ineffective without a catalyst, and all the molecules had β-hydrogen atoms,

which are accessible to elimination and, for example, formation of substituted titanacyclopropanes.

Reduction with benzylmagnesium bromide was slower and less selective than that with the above four reagents. Note that ether **11** and 1,2-diphenylethane **12** (it is well known that they are formed in the production of Grignard reagents [39]) are also formed in catalyzed reactions. For example, it is well known that compound **11** is formed in benzylmagnesium bromide reactions with ether in the presence of xenon difluoride or titanium tetrachloride [40, 41], whereas compound **12** is formed on the decarboxylation of phenylacetic acid in the presence of Co(III) [42]. It is likely that compound **11** results from the interaction of benzyl and α-ethoxy-ethyl radicals, and compound **12** results from two benzyl radicals, which are either bound to a titanium center or independent of it.


11   **12**
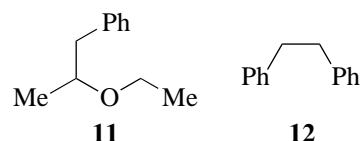
Dibromide **1a** reacted with 2.6–5.0 mol equiv of EtMgBr, *sec*-BuMgBr, 3-PentylMgBr, PhCH$_2$CH$_2$MgBr, or PhMgBr in the presence of a catalyst in each case with the formation of only doubly reduced compound **4a** containing no allene **6a**.

REACTION PATHWAYS OF ALKYL GROUPS

The complete analysis of reaction mixtures formed in the course of catalyzed partial reduction of 1,1-dibromocyclopropanes and the preparative isolation of all the products demonstrated that the alkyl and arylalkyl groups of starting Grignard reagents under-

went disproportionation and (or) dimerization with the formation of corresponding alkanes and alkenes, and the alkylation of ether, which is used as a solvent, also occurred (reaction (IX); Table 5). As a rule, reactions of this type are characteristic of radical intermediates (for example, the 2-phenylethyl radical could be formed from 2-phenylethylmagnesium bromide). The subsequent reactions of these intermediates, which result in the formation of R–H compounds, can be related to hydrogen-atom transfer, for example, from the α-position of the ether molecule.

(IX)
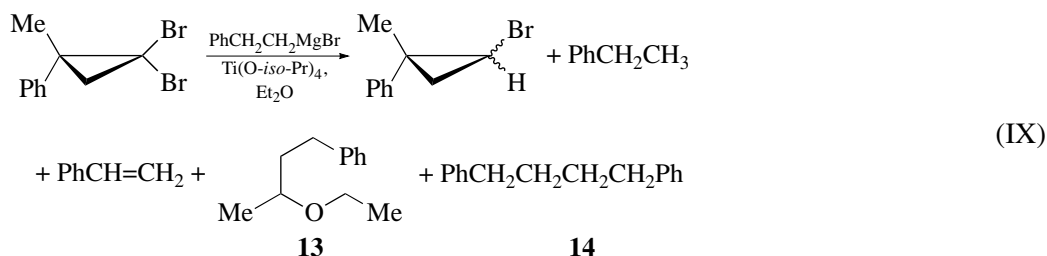
In all of the studied examples, the treatment of reaction mixtures with D$_2$O did not result in deuterated compounds **2a** and **3a** or ethylbenzene (if 2-phenylethylmagnesium bromide was used as a Grignard reagent). This result indicates that hydrogen, which is required for the replacement of bromine and the formation of ethylbenzene, was the constituent of the above molecules before the addition of D$_2$O.

The Grignard reagents used for the hydrodebromination of bromocyclopropanes were introduced into the reaction with Ti(O–*iso*-Pr)$_4$ in the absence of reduced substrates. The findings are the following:

(a) The treatment of 2-phenylethylmagnesium bromide in ether with water resulted in a small amount of styrene (<1.6%), 1,2-diphenylbutane (<10%), ethylbenzene, and phenylethanol (2%); the treatment of this reagent with D$_2$O after 84 h resulted in the formation of ethylbenzene containing >91% deuterium.

(b) The treatment of a mixture of 2-phenylethylmagnesium bromide and 10% Ti(O–*iso*-Pr)$_4$ with the use of D$_2$O after 84 h gave a mixture with a similar composition, although the level of styrene was ~6%. However, the deuterium content of ethylbenzene was considerably lower (50–60%).

(c) The treatment of the above Grignard reagent and 20 mol % Ti(O–*iso*-Pr)$_4$ with heavy water (D$_2$O) after 1 h gave ethylbenzene with a deuterium content as low as 13%.

These findings indicate that titanium isopropoxide promoted the decomposition of the Grignard reagent even in the absence of dibromocyclopropane, and radical intermediates were generated in this case.

Cp$_2$TiCl$_2$, Cp$_2$ZrCl$_2$, Zr(acac)$_4$, and other zirconium and titanium compounds can also be used as hydrodebromination catalysts. In this case, the reaction rate and selectivity remained unchanged. Hafnium compounds were found to be less effective catalysts.

PRODUCTS FORMED BY THE SOLVENT

The reaction of 2,2-dimethyl-1,1-dibromocyclopropane (**1c**) (300 mmol) with 1.2 mol equiv of EtMgBr and 5 mol % Ti(O–*iso*-Pr)$_4$ was performed for studying in more detail the composition of products formed by insertion into the ether molecule. The yields of the products were the following: *sec*-butyl ethyl ether (**15**), 66 mmol; *sec*-butyl isopropyl ether (**16**) [43], 28 mmol; 2,3-diethoxybutane (**17**), 36 mmol; conceivable ether oligomers, 3.59 g; ~49 mmol of monomeric ether; and 2,2-dimethyl-1-bromocyclopropane (**2c**), 240 mmol (according to ^{1}H NMR data).

It is likely that compound **15**, which is difficult to isolate on a small scale because it is highly volatile, results from solvent alkylation by the Grignard reagent. It is likely that compound **16** is formed by the exchange of one ethyl group of the solvent for an isopropyl unit of titanium isopropoxide. Correspondingly, it was not detected when the reaction was performed in the presence of titanium tetrachloride. Dimer **17** was obtained as a mixture of stereoisomers. It was reported that this compound in small amounts is formed in the photolysis of ether because of the dimerization of two radicals **18** [44] and in the photolysis of *cis*-bicyclo[6.1.0]nonan-2-one in an ether solvent [45]. It is formed as the main component in the photoinduced reduction of dibromocyclopropanes with lithium aluminum hydride in

Table 6. Reactions of dibromocyclopropane **1a** with phenylethylmagnesium bromide in THF (entry 1) and THF-d$_8$ (entry 2)

Entry	PhCH$_2$CH$_2$MgBr,[a] mol equiv	TiCl$_4$, mol %	Stirring time, h	Product yields,[b] %				
				1a	**2a** + **3a**	**4a**	ethylbenzene	styrene
1	1.0	5	1	40	60	0	68	16
	1.6		1	0 [0]	97 [100(1.5 : 1)]	3	129 [120]	16 [15]
2	1.2	5	1	57 [64]	43 [36(1.5 : 1)[c]]	0	111 [90][d]	9 [12]

Note: [a] The Grignard reagent treated with water contained (according to GLC data) 95% ethylbenzene, 1% styrene, and 2% 1,4-diphenylbutane.

[b] See footnote [a] in Table 2.

[c] The main monobromocyclopropane contained (according to chromatography–mass spectrometry and ^{1}H NMR data) 30% deuterium at the C[1] position; the second isomer contained 47% deuterium at this position.

[d] Ethylbenzene did not contain deuterium.

Table 7. Reaction of dibromocyclopropane **1a** with ethylmagnesium bromide in THF in the presence of 1.0 mol equiv of titanium tetrachloride (according to ^{1}H NMR data)

Entry	EtMgBr, mol equiv	Stirring time, min	Product yields, %		
			1a	**2a** + **3a**	**4a**
1	1.0	20	100	0	0
2	2.0	20	85	15 (1.6 : 1)	0
3	3.0	20	35	65 (1.6 : 1)	0
4	6.0	120	0	31 (1 : 4)	69

ether, for which the step of carbon–bromine bond cleavage is postulated as a homolytic process [46]. Under these conditions, compound **1d** forms a mixture of *endo-* and *exo*-monobromides in a ratio that is almost identical to that obtained in the hydrodebromination of **1d** with the use of EtMgBr and Ti(O–*iso*-Pr)$_4$. It was also published that compound **17** is formed in small amounts in a reaction of bromocyclopropane with magnesium in ether [47].

18
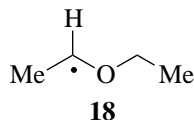
USE OF ISOTOPICALLY LABELED COMPOUNDS

The above results clearly indicate that the reactions of dibromocyclopropanes with the series of Grignard reagents in ether solutions occur more rapidly and selectively in the presence of Ti(O–*iso*-Pr)$_4$. However, the origin of hydrogen that is substituted for bromine remained unclear. Five hydrogen sources can be formally considered: the Grignard reagent, the solvent, the catalyst, the procedure of treating the reaction mixtures, and the C–H groups of the parent cyclopropane and other compounds formed from it. The last-named possibility seems improbable, at least for the type of reactions discussed, because products containing a three-carbon ring are formed in nearly quantitative yields and substances that would be formed by the loss of hydrogen atoms from parent bromocyclopropanes are absent from the reaction products. The fourth possibility can be easily excluded because in none of the cases did the treatment of reaction mixtures with D$_2$O result in the incorporation of deuterium into the products. Next, in many reactions, the catalyst was present in a 2% amount; therefore, it seemed highly improbable that it can provide a significant amount of the hydrogen required. Moreover, hydrodebromination also success-

fully occurred in the presence of catalysts such as $TiCl_3$ and $TiCl_4$. Hence, it follows that the catalyst cannot be the source of the full amount of required hydrogen.

The possibility of hydrogen transfer from the Grignard reagent was evaluated in the α- and β-deuterated compounds 3-deuterio-3-pentylmagnesium bromide and 1,1,1,3,3,3-hexadeuterio-2-propylmagnesium bromide. It was found that in none of the cases was deuterium transferred to a three-carbon ring.

Only with the use of the deuterated solvent THF-d_8 (Table 6) was it found that the hydrogen atom really can be transferred from the solvent molecule to a small ring in the course of the hydrodebromination of compound **1a** with 2-phenylethylmagnesium bromide catalyzed by $TiCl_4$. It is noteworthy that the deuteration levels of compounds **2a** and **3a** were only moderate and, interestingly, different for **2a** and **3a**. It is likely that the deuteration levels were low because of the small scale of the experiments, the alternative reactions that can result in the formation of other donors of hydrogen atoms, and the primary kinetic isotope effects in reactions with the participation of THF-d_8. The absence of deuterium from the resulting ethylbenzene is also noteworthy.

A similar deuteration level was found in the reaction of 1-bromo-1-methyl-2,2-diphenylcyclopropane with magnesium in THF-d_8, and an even lower level was found for the same reaction in ether (7%) [48].

However, note that the products of partial hydrodebromination contained no deuterium when the hydrodebromination of **1a** was performed in $CD_3OC_6H_5$.

USE OF CATALYSTS IN STOICHIOMETRIC AMOUNTS

The addition of 1.0 mol equiv of EtMgBr to an equimolar mixture of **1a** and titanium tetrachloride did not result in the appearance of compounds **2a** and **3a** (Table 7). The addition of a second mol equiv of EtMgBr was accompanied by the formation of 15% monobromides **2a** and **3a**. Even after the addition of a third mol equiv of the Grignard reagent, 35% dibromide **1a** remained in the reaction mixture. These results are consistent with the formation of Ti(II) derivatives, which are capable of reducing bromocyclopropanes, in the course of the reaction of titanium tetrachloride with 2.0 mol equiv of EtMgBr.

Thus, *gem*-dibromocyclopropanes form corresponding monobromocyclopropanes (including stereoisomers) in almost 95% yields upon treatment with 1.0–1.3 mol equiv of ethylmagnesium bromide and 2–10 mol % titanium isopropoxide in an ether solution at room temperature. An excess of the Grignard reagent provides an opportunity to obtain halogen-free cyclopropanes in >90% yields. The products of partial hydrodechlorination of *gem*-dichlorocyclopropanes can be obtained in 85–95% yields with the use of
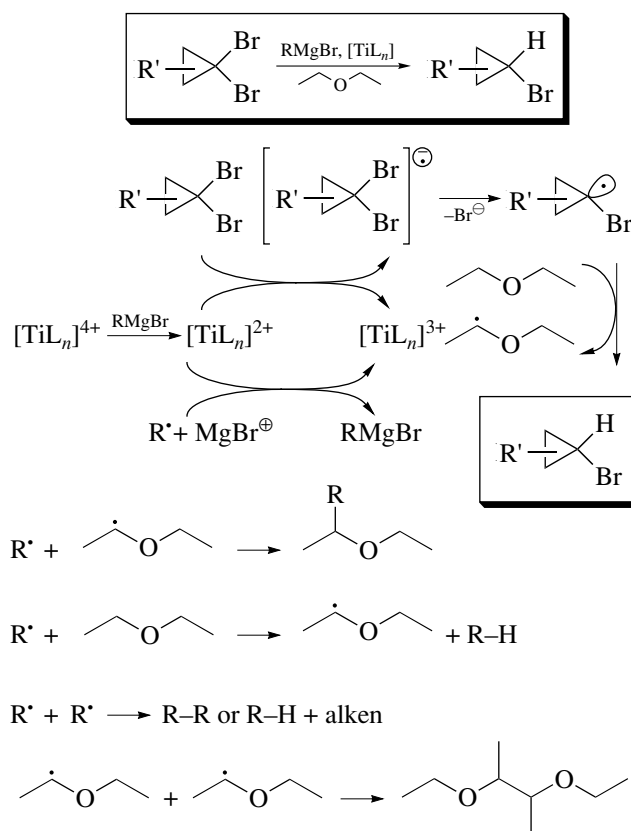
Scheme 1

2.0 mol equiv of EtMgBr and 10 mol % titanium isopropoxide in ether.

Along with ethylmagnesium bromide, *sec*-BuMgBr, 3-PentylMgBr, PhMgBr, and 2-PhCH$_2$CH$_2$MgBr were also found to be effective reagents for the hydrodebromination of *gem*-dibromocyclopropanes in the presence of titanium compounds. The complete analysis of such reaction mixtures demonstrated that they contained both the hydrodebromination products of bromocyclopropanes and other compounds formed from the Grignard reagents and solvent molecules. Note that substances that could result from the condensation of parent dibromocyclopropanes and the Grignard reagents or solvent molecules were not detected.

Although all of the examined Grignard reagents can accomplish comparatively slow hydrodebromination of *gem*-dibromocyclopropanes in the absence of catalysts, only *tert*-butylmagnesium bromide exhibited high selectivity: in the presence of 4.0 mol equiv of *tert*-BuMgBr, 1,1-dibromo-2-methyl-2-phenylcyclopropane formed 96% stereoisomeric monobromocyclopropanes and less than 1% 3-phenylbuta-1,2-diene after 72 h.
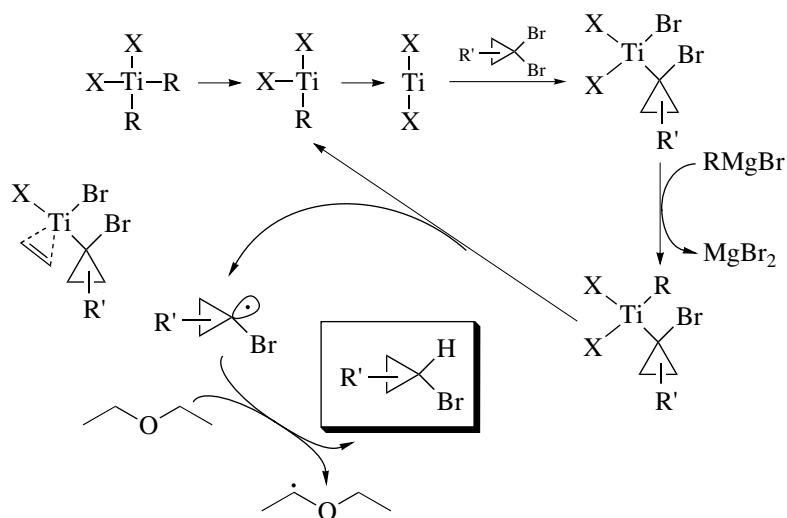
Deuterium labels were not detected in hydrodebromination products on the treatment of reaction mixtures with heavy water. Experiments with the use of α- and β-deuterated Grignard reagents (3-deuterio-3-pentyl-

magnesium bromide and 1,1,1,3,3,3-hexadeuterio-2-propylmagnesium bromide) or (methyl-d$_3$)anisole also did not result in the formation of deuterated monobromocyclopropanes. Only the hydrodebromination of 1,1-dibromo-2-methyl-2-phenylcyclopropane with 2-phenylethylmagnesium bromide in THF-d$_8$ was accompanied by partial deuterium transfer to C1 of the monobromocyclopropane formed.
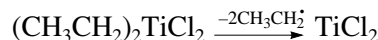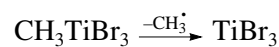
CONCLUSIONS ON THE MECHANISM OF HYDRODEBROMINATION

The above data on the hydrodebromination of mono-, di-, and polybromocyclopropanes allowed us to propose a scheme in which the key steps of the mechanism of bromocyclopropane hydrodebromination catalyzed by titanium compounds form three blocks of reactions (Scheme 1): (a) the generation of catalytically active Ti(II) species from Ti(IV) or Ti(III) at the initiation of reaction and then in a catalytic cycle due to the participation of a Grignard reagent; (b) the hydrodehalogenation of bromocyclopropanes, which involves electron transfer from a low-valent catalyst species, formation of a cyclopropyl radical, and stabilization of this radical as a result of hydrogen-atom transfer from the solvent molecule; (c) the reactions of previously formed radical species (for example, the dimerization and disproportionation of radical species generated from Grignard reagents or ether molecules, the linking of alkyl radicals to radical species produced from solvent molecules, etc.) [23].

The processes of electron transfer from a low-valent titanium species to dibromocyclopropane are difficult to describe. Nevertheless, it is well known that titanium(IV) alkyl halides can eliminate alkyl radicals (Scheme 2) [49].

$$CH_3TiBr_3 \xrightarrow{-CH_3^{\cdot}} TiBr_3$$

$$(CH_3CH_2)_2TiCl_2 \xrightarrow{-2CH_3CH_2^{\cdot}} TiCl_2$$

$$TiCl_4 + 2n\text{-BuLi} \longrightarrow n\text{-BuLi}_2TiCl_2 \xrightarrow{THF} TiCl_2 \cdot 2THF$$

Scheme 2

If the process under consideration is simply electron transfer from a low-valent titanium intermediate to dibromocyclopropane, the catalytic effects of particular Grignard reagents are difficult to explain. In particular, based on redox potentials, it is difficult to explain why the reactions of methylmagnesium bromide and *tert*-butylmagnesium bromide exhibited only small catalytic effects, whereas the catalytic effect of ethylmagnesium bromide was great. An alternative explanation is that intermediates with a bond between titanium and a cyclopropane fragment take part in the reaction. In this case, a catalytic cycle can involve the oxidative addition of a TiX$_2$ species at the carbon–bromine bond (Scheme 3). It is likely that the subsequent behavior of the oxidative addition product depends on the property of the titanium–three-carbon-ring bond. Formally, it is reasonable to expect that the homolytic cleavage of this bond results in the formation of the bromocyclopropyl radical and a Ti(III) derivative, which are specified in Schemes 1 and 3.

Previously [23], we considered the possible participation of other particular intermediates in the test reactions. In conclusion, note that, regardless of the results of a more detailed study of the mechanism of bromocyclopropane hydrodebromination, it is clear that a combination of appropriate Grignard reagents and catalytic amounts of TiX$_4$ or ZrX$_4$ is one of the most efficient combinations for the conversion of dibromocyclopropanes into the corresponding monobromides.

Scheme 3

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