

## Titanium(IV) isopropoxide-catalysed reaction of alkylmagnesium halides with ethyl acetate in the presence of styrene. Non-hydride mechanism of ligand exchange in the titanacyclopropanes

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## Abstract

The dependence of the yields of (E)-1-methyl-2-phenyl-1-cyclopropanol (3) on the structure of the organomagnesium compounds and reagents ratio in the reaction of ethyl acetate with Grignard reagents, in the presence of styrene and catalytic amounts of Ti(OPr<sup>1</sup>)<sub>4</sub>, has been investigated. Butylmagnesium bromide has been found to be the most suitable organomagnesium for the preparation of 3 by this method. The use of  $(CD_3)_2CHMgBr$  for the generation of the titanacyclopropane intermediates led to the formation of 3. This result disagreed with the hydride mechanism of the ligand exchange for 2-phenyltitanacyclopropane (4) formation. @ 1999 Elsevier Science Ltd. All rights reserved.

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Some years ago we discovered the titanium(IV) isopropoxide catalysed reaction of alkyl alkanecarboxylates with ethylmagnesium bromide yielding 1-substituted cyclopropanols [1]. It was surmised that the key step of this transformation is disproportionation of diethyltitanium alkoxide 1 into the corresponding titanacyclopropane 2 which acts as an ethylene dianion (CH<sub>2</sub>-CH<sub>2</sub>)<sup>2-</sup> equivalent [1, 2]. The use of higher alkylmagnesium halides yielded the corresponding 1,2-disubstituted cyclopropanols [3]. Taking into account that titanacyclopropanes exhibit the properties of titanium-olefin complexes, an alternative method for the preparation of 1,2-disubstituted cyclopropanols by ethylene displacement in the titanacyclopropane 2 with other unsaturated compounds was proposed [4]. In fact, (E)-1-methyl-2-phenyl-1-cyclopropanol (3) was

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obtained in 42% yield by dropwise addition of ethylmagnesium bromide to a boiling ethereal solution of ethyl acetate, styrene and 0.05 equiv. of titanium(IV) isopropoxide. Ethylene was detected in the gaseous reaction products serving as indirect evidence of the formation of 4 from 2 [4].

Later, Cha and coworkers [5-7] as well as Sato and coworkers [8], rediscovered this method for the preparation of 1,2-disubstituted cyclopropanols. Cyclohexyl- [5], cyclopentyl- [6], n-butyl- [7] and isopropylmagnesium [8] halides were recommended for the generation of the titanacyclopropane intermediates from equimolar quantities of  $Ti(OPr^{i})_{4}$  with respect to the ester. These results allow inter- and intramolecular hydroxycyclopropanation reactions to be carried out using a wide range of alkenes [5-9].



In all of these reports [5-9] as well as in our first communication [4], it was assumed that alkenes transform into titanacyclopropanes by means of ligand exchange as shown in Scheme 1; however, no clear evidence in support of this mechanism had been proposed. In particular, since decomposition of alkyl derivatives of transition metals may occur through  $\beta$ -hydrogen abstraction, with the formation of intermediate metal hydrides like 5 [10], the possibility of its further addition to styrene, followed by transformation of **6** into 2-phenyltitanacyclopropane (4) as shown in Scheme 2, *a priori* cannot be ruled out. Thus, in the case of a Grignard reagent fully deuterated in its  $\beta$ -position one might expect the formation of the corresponding titanium deuteride derivative. Its further addition to styrene and disproportionation would then lead to the formation of deuterated phenyltitanacyclopropane 4, especially as the  $\beta$ -abstraction reactions in alkyl derivatives of transition metals display a significant isotope effect [11]. In the present work we have found that the reaction of (CD<sub>3</sub>)<sub>2</sub>CHMgBr (3 equiv.) with ethyl acetate (1 equiv.), styrene (2 equiv.) and Ti(OPr<sup>i</sup>)<sub>4</sub> (0.2 equiv.) did not lead to the deuterated cyclopropanol 3. Only

non-deuterated (*E*)-1-methyl-2-phenyl-1-cyclopropanol (3) was isolated in 68% yield as indicated by <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra of 3 prepared using deuterated and non-deuterated isopropylmagnesium bromides. Therefore, the hydride mechanism for ligand exchange for 2phenyltitanacyclopropane (4) formation may be excluded and we believe that it proceeds by means of direct olefin displacement in the corresponding titanacyclopropane intermediate [11].

We also examined how the nature of the Grignard reagent, and the stoichiometry of the reagents influenced the yield of (E)-1-methyl-2-phenyl-1-cyclopropanol (3). The results are summarised in the following Table.

Table

Yields of (E)-1-methyl-2-phenyl-1-cyclopropanol (3)<sup>4</sup>):

Entry	R	Equiv. of RMgBr	Equiv. of styrene	Equiv. of Ti(OPr')4	Yield of 3, % <sup>b)</sup>
1	Et	2.5	2	0.05	42 [4]
2	Et	2	2	0.1	36
3	Et	2.5	2	0.1	54
4	Et	2.5	2	0.2	55
5	Et	2.5	2	0.5	53
6	Et	2.5	2	1.0	41
7	Et	2.5	1	0.2	35
8	Et	2.5	3	0.2	53
9	<i>l</i> -Pr	2.5	2	0.2	72
10	<i>i</i> -Pr	2.5	2	0.05	32
11	<i>i</i> -Pr	2	2	0.1	55
12	<i>n</i> -Pr	2.5	2	0.2	71
13	n-Bu	2.5	2	0.2	78
14	<b>≁Bu</b>	2.5	2	0.2	27
15	c-Hex <sup>c)</sup>	4.5	2	1.0	53
16	c-Hex <sup>c)</sup>	2.5	2	0.2	30

<sup>a)</sup> Reaction procedure: to a solution of ethyl acetate (0.97 mL, 10 mmol), styrene (10 - 30 mmol) and Ti(QPr)<sub>4</sub> (0.5 -1 mmol) in 15 mL of Et<sub>2</sub>O, a solution (1.5 - 2.0 M) of 20 - 45 mmol of Grignard reagent in Et<sub>2</sub>O was added dropwise, over 1 h, at reflux. The mixture was stirred for an additional 30 min, then was poured into ice-cold 10% sulfuric acid (50 mL). The organic layer was separated and the aqueous layer was extracted with ether (2×20 mL). The combined organic extracts were washed with saturated NaHCO<sub>3</sub> and brine, dried over MgSO<sub>4</sub> and concentrated under reduced pressure. The residue was diluted with cold hexane and the crystalline 3 was filtered off and dried. The product obtained had satisfactory <sup>1</sup>H and <sup>13</sup>C NMR spectra [12]. <sup>b</sup>) Yield of the crude crystalline product is given. <sup>c)</sup>Cyclohexylmagnesium chloride was used.

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When EtMgBr was used, better yields of cyclopropanol 3 were achieved by the combination of 2.5 equiv. of Grignard reagent and 0.1-0.2 equiv. of  $Ti(OPr')_4$  (entries 1-4). The use of a two-fold excess of styrene versus equimolar quantities significantly increased the yield of 3 (entries 4 and 7) although a three-fold excess did not further increase the yield (entries 4 and 8).

Variation of Grignard reagents (entries 4, 9-16) revealed that *n*-BuMgBr was the most efficient in this reaction (entry 13) and slight differences were observed between *n*-PrMgBr and *i*-PrMgBr (entry 9 and 12). As was found in the case of EtMgBr, the use of *i*-PrMgBr in the presence of 0.2 equiv. in comparison with 0.05 equiv. of  $Ti(OPr')_4$  gave better yield (entries 9 and 10). Carrying out this reaction under non-catalytic conditions did not lead to higher yields of 3 (entries 5 and 6), which underscores the benefits of the catalytic variant. It should also be mentioned that this procedure was successfully applied to the hydroxycyclopropanation of aliphatic alkenes. Thus, 1-methyl-2-octyl-1-cyclopropanol was obtained in 61% yield using ethyl acetate (1 equiv.) with *n*-BuMgBr (2.5 equiv.) and 1-decene (2 equiv.) in the presence of 0.2 equiv. of Ti(OPr')<sub>4</sub>.

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