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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 $Ti(OPr^i)_4$, 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.

Keywords: Grignard reagents, titanium compounds, cyclopropanation, alkenes

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 $(CH_2\text{-}CH_2)^{2-}$ 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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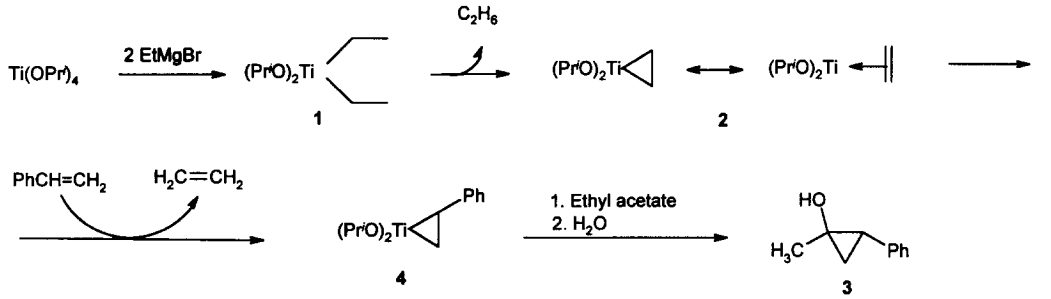
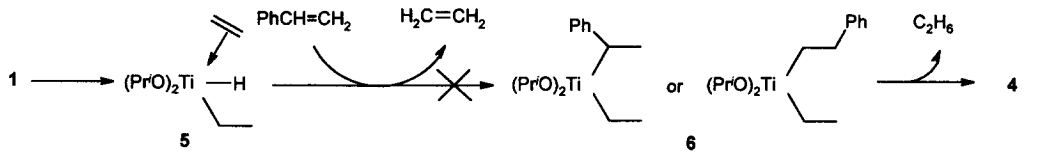
obtained in 42% yield by dropwise addition of ethylmagnesium bromide to a boiling ethereal solution of ethyl acetate, styrene and 0.05 equiv. of titanium(IV) isopropoxide. Ethylene was detected in the gaseous reaction products serving as indirect evidence of the formation of **4** from **2** [4].

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].



Scheme 1

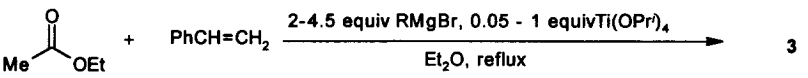


Scheme 2

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 β-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 β-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 β-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 $(CD_3)_2CHMgBr$ (3 equiv.) with ethyl acetate (1 equiv.), styrene (2 equiv.) and $Ti(OPr^i)_4$ (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 ^{1}H NMR and ^{13}C NMR spectra of **3** prepared using deuterated and non-deuterated isopropylmagnesium bromides. Therefore, the hydride mechanism for ligand exchange for 2-phenyltitanacyclopropane (**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**) [a]:

Entry	R	Equiv. of RMgBr	Equiv. of styrene	Equiv. of $Ti(OPr^{i})_4$	Yield of 3, % [b]
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*-Pr**	2.5	2	0.2	72
10	***i*-Pr**	2.5	2	0.05	32
11	***i*-Pr**	2	2	0.1	55
12	***n*-Pr**	2.5	2	0.2	71
13	***n*-Bu**	2.5	2	0.2	78
14	***i*-Bu**	2.5	2	0.2	27
15	***c*-Hex**[c]	4.5	2	1.0	53
16	***c*-Hex**[c]	2.5	2	0.2	30

[a] Reaction procedure: to a solution of ethyl acetate (0.97 mL, 10 mmol), styrene (10 - 30 mmol) and $Ti(OPr^{i})_4$ (0.5 -1 mmol) in 15 mL of Et_2O, a solution (1.5 - 2.0 M) of 20 - 45 mmol of Grignard reagent in Et_2O 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 $NaHCO_3$ and brine, dried over $MgSO_4$ 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 ^{1}H and ^{13}C NMR spectra [12]. [b] Yield of the crude crystalline product is given. [c] Cyclohexylmagnesium chloride was used.

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 $Ti(OPr^i)_4$ (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 $Ti(OPr^i)_4$ 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 $Ti(OPr^i)_4$.

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