Regioselective Carbon-Carbon Bond Formation in Titanium Mediated Reaction of Ethylmagnesium Bromide with Allylic Alcohols and Allylic Ethers

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Abstract: In the presence of Ti(O*i*-Pr)$_4$ reaction of EtMgBr with allylic alcohols and allylic ethers affords the products of formal S$_N$2' substitution of hydroxy or alkoxy groups with ethyl groups in moderate to good yields and excellent regioselectivity. The mechanism of the reaction includes the formation of titanacyclopropanes as the key organometallic intermediates. Promoting action of EtMgBr on the process of C-C bond formation in the transformation of titanacyclopropane-olefin complex **5** into the titanacyclopentane ate complex **6** is proposed.

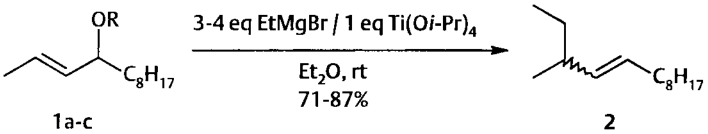
Key words: titanium alkoxides, Grignard reagents, allylic compounds, alkylations, alkenes

Alkene complexes of the Group IV transition metals show properties of metallacyclopropane reagents in the reactions with electrophiles.[1] Until now, the properties of titanocene and zirconocene derivatives are the most studied. Some years ago, we found that the reaction of ethylmagnesium bromide with carboxylic esters in the presence of titanium alkoxides smoothly results in formation of 1-substituted cyclopropanols.[2] It was supposed that the key organometallic intermediate in this reaction is diisopropoxytitanacyclopropane (diisopropoxytitanium-ethylene complex) which acts like a 1,2-dicarbanionic equivalent. To the best of our knowledge, it was the first synthetically useful transformation for the generation of titanacyclopropane reagents where inexpensive and easy-to-use titanium alkoxides were used instead of titanocene derivatives. Later, it was shown that dialkoxytitanacyclopropane reagents react with *N,N*-dialkylcarboxamides to form the corresponding aminocyclopropanes,[3] and are involved in the ligand exchange[4] as well as in inter- and intramolecular olefins and acetylenes coupling reactions.[5] Dialkoxytitanacyclopropane 1,2-dicarbanionic equivalents have also been successfully used in consecutive reactions with two different electrophiles.[6]

We report herein the titanium alkoxide mediated reaction of ethylmagnesium bromide with allylic alcohols and allylic ethers, resulting in the formation of the products of formal S$_N$2' allylic ethylation.[7] As shown in Scheme 1, when 2-undecen-4-ol (**1a**) or its methyl (**1b**) and THP (**1c**) ethers are treated with 3-4 equiv EtMgBr in the presence of 1 equiv Ti(O*i*-Pr)$_4$ at room temperature in Et$_2$O, alkene **2** is obtained in good yields.[8] Carbon-carbon bond formation occurred exclusively at the γ-carbon and no formation of regioisomeric olefins, the α-attack products, was detected by GC-MS analysis.

As illustrated in the Table, the reaction of the allylic alcohol **1a** with EtMgBr in the presence of equimolecular amounts of Ti(O*i*-Pr)$_4$ provided much better yields of substitution product **2** in comparison with catalytic conditions (entry1-4). Full consumption of substrate occurred after addition of 4 equiv of the Grignard reagent. When the ethers **1b** and **1c** were used, 3 equiv of EtMgBr were sufficient for their full involvement in the reaction (entries 5-11). Under similar reaction conditions, the primary allylic alcohol with disubstituted double bond (entry 12) as well as primary and tertiary allylic alcohols and 2-tetrahydropyranyl ethers with mono- (entries 13-17) and trisubstituted (entries 18 and 19) double bonds are also involved in this transformation. However, in the case of allylic alcohols with monosubstituted double bond[9] and, especially, their THP ethers, reaction was accompanied with the formation of appreciable amounts of hydroxyl group reductive elimination products derived from the corresponding allyltitanium species.[10] It is also noteworthy that in the case of linalool (entry 16), the product of allylic substitution in geraniol was obtained in good yield only in the presence of excess of reagents (entries 18 and 19).

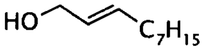
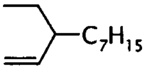
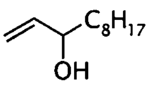
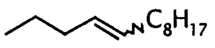
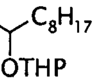
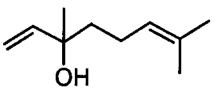
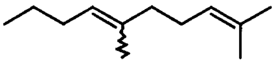
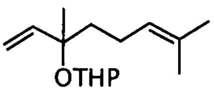
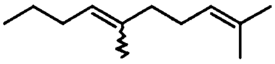
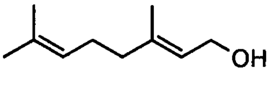
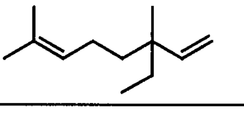
Substitution of hydroxyl group in allylic alcohols occurs with low *cis/trans* stereoselectivity (entries 1-4, 13-16). Predominant formation of *trans*-alkenes is observed in titanium-mediated reaction of EtMgBr with allylic ethers (entries 5-11, 17), especially in the case of 2-tetrahydropyranyl ethers with disubstituted and monosubstituted double bond (entries 8-11, 17) where up to 95% of *trans*-isomer is formed (entry 8-11).



R = H (a), Me (b), 2-tetrahydropyranyl (c)

Scheme 1

Table Yields of Substitution Products in the Reaction of Allylic Alcohols and Allylic Ethers with EtMgBr in the Presence of Ti(O*i*-Pr)$_4$.

Entry	Substrate	Equiv		Substitution product	Yield, [%][a)]
		EtMgBr	Ti(O*i*-Pr)$_4$		
1	**1a**	3.2	0.1	**2**	35
2		4	0.2	*trans/cis*=1:1	52
3		3	1		67
4		4	1		87
5	**1b**	2.2	0.1	**2**	50
6		2.2	1	*trans/cis* =70/30	30
7		3	1		72
8	**1c**	1.5	0.1	**2**	35
9		2.2	0.1	*trans/cis* =95/5	30
10		2	1		47
11		3	1		71
12		4	1		51[b]
13		4	1		70[c,d]
14		6	1	*trans/cis* =1:1	77[c,d]
15		3	1	 *trans/cis* =1:1	45[c]
16		6	1	 *trans/cis* =1:1	68[b]
17		5	1	 *trans/cis* =70:30	42[e]
18		6	1		56[b]
19		7	1.5		84[b]

[a)] Isolated yield.

[b)] Near 10% (GC-MS) of reductive elimination products are formed as a mixture of regioisomers.

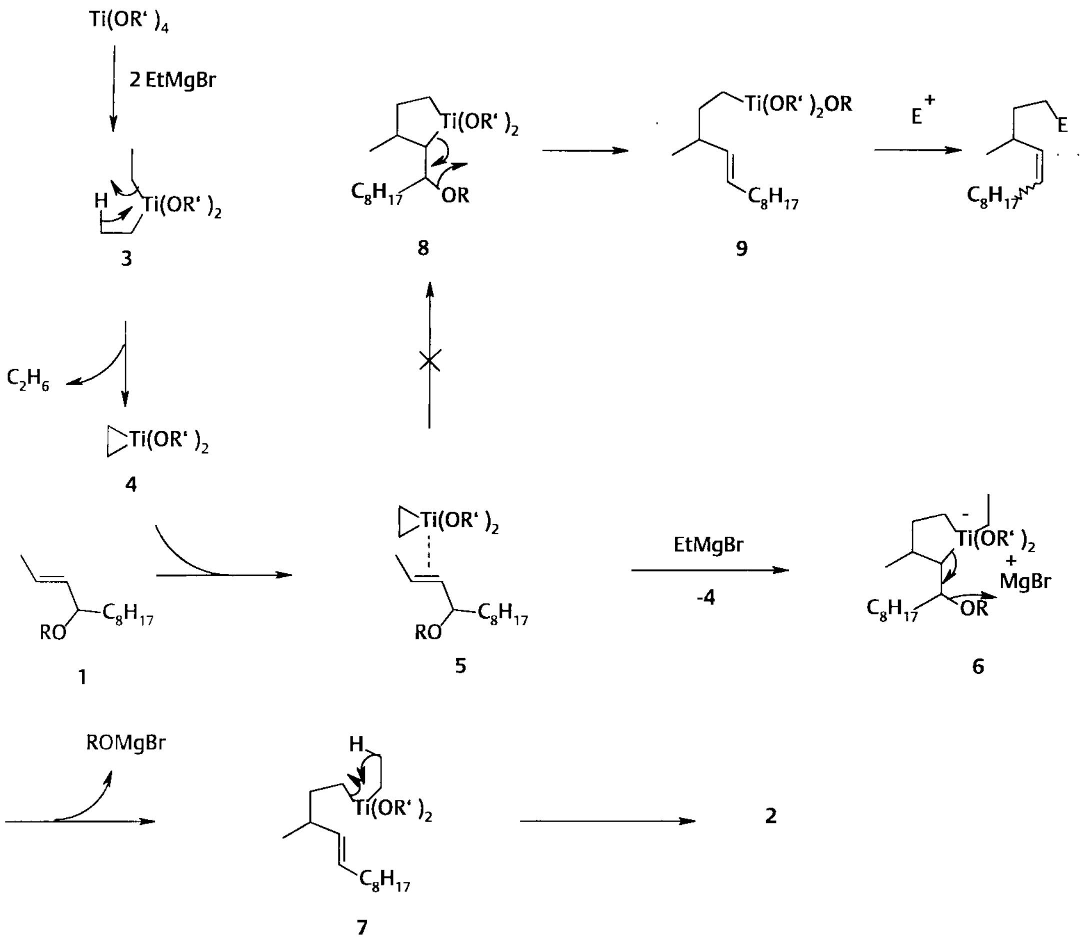
[c)] Near 20% (GC-MS) of reductive elimination products are formed as a mixture of regioisomers.

[d)] Near 20% (GC-MS) of ethane addition product is formed (M/e = 200).

[e)] Near 50%(GC-MS) of reductive elimination products are formed as a mixture of regioisomers.

A plausible mechanism for this reaction is shown in Scheme 2. Ethylation of Ti(O*i*-Pr)$_4$ with EtMgBr affords diethyltitanium derivative **3**, which disproportionates to give diisopropoxytitanacyclopropane **4**.[2] If each of the isopropoxy groups are considered as six-electron ligand, then titanacyclopropane **4** is formally a 16e organometallic species. Its coordination with substrate **1** gives an 18e olefin complex **5**. We propose that EtMgBr addition to the complex **5** possibly induces its transformation into titanacyclopentane ate complex **6**. Sequential Ti-C and C-O bond cleavages of **6** afford dialkylated titanium species **7**, which easily undergoes ethane elimination to provide the alkene **2** and titanacyclopropane **4**.

Our supposition that titanacyclopropane-olefin complexes **5** under the reaction conditions do not transform directly into titanacyclopentane derivatives **8**[7] is grounded on the fact that all our efforts to fix any organometallic products of this reaction were unsuccessful. In fact, sequential cleavage of Ti-C and C-O bonds in the intermediate **8** would lead to bis-homoallylic organometallic species **9**, which like analogous zirconocene intermediates could be fixed by the reactions with electrophiles.[7] However, passing an excess of gaseous oxygen through a reaction mixture derived from the reaction of allylic alcohol **1a** with 3 equiv EtMgBr and 1 equiv Ti(O*i*-Pr)$_4$ as well as addition of I$_2$ or benzaldehyde does not lead to a considerable de-



R = H, Me, THP, MgBr, Ti(OR')$_3$
R' = O*i*-Pr, $OC_{12}H_{23}$

Scheme 2

crease of the yield of **2**, as compared with the yield obtained by treatment with water. We suppose that the substitution product **2** forms before treatment of the reaction mixture with the electrophile (Scheme 2). Easier formation of titanacyclopentane ate complex **6** in comparison with the parent titanacyclopentane **8** can be explained by the fact that the titanacyclopropane-olefin complex **5** is an 18e species whereas the titanacyclopentane ate complex **8** is a 16e species.

Within the framework of this mechanism the necessity to use different relative amounts of EtMgBr and Ti(O*i*-Pr)$_4$ for full consumption of the substrate (Table) can also be explained. Near equimolar amounts of Ti(O*i*-Pr)$_4$ in the case of allylic alcohols are necessary because of the corresponding titanium oxides formation which, probably, could not be involved into a catalytic cycle.[3] Full consumption of the substrate in the reaction of alcohol **1a** with 4 equiv of EtMgBr (entry 4) can be explained by spending of 1 equiv of Grignard reagent for magnesium alkoxide **1** (R = MgBr) and *i*-PrOMgBr formation, additional 2 equivalents for titanacyclopropane intermediate **4** generation and one more equivalent for the initiation of titanacyclopentane ate complex formation step.

In summary, high regioselective ethylation of allylic alcohols and allylic ethers by the action of EtMgBr in the presence of titanium(IV) isopropoxide have been found.

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(8) **Typical procedure for *(E)*-3-methyl-4-tridecene (2).** To a solution of allylic ether **1c** (1.38 g, 5 mmol) and Ti(O*i*-Pr)$_4$ (1.5 mL, 5 mmol) in Et_2O (15 mL), EtMgBr (15 mL of 1 M solution in Et_2O) was added dropwise in 1 h at room temperature, and the mixture was stirred for an additional 30 min. After acidic work up (20 mL of 10% aq. H_2SO_4) and extraction with ether, organic layers were washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$ and evaporated. *(E)*-3-Methyl-4-tridecene (*(E)*-**2**) (containing less than 5% of *Z*-isomer by GC-MS-analysis) (0.69 g, 71%) was isolated by column chromatography on silica gel (eluent - cyclohexane). NMR ^{1}H (200 MHz, $CDCl_3$): 0.86 (t, J = 7.2 Hz, 3H), 0.90(t, J = 7.2 Hz, 3H), 0.96(d, J = 6.9 Hz, 3H), 1.18-1.41 (m, 14H), 1.88-2.06 (m, 3H), 5.14-5.23 (m, 2H). NMR ^{13}C (50 MHz, $CDCl_3$): 11.63, 14.16, 20.56, 22.81, 29.29, 29.46, 29.64, 29.87, 30.01, 32.74, 33.51, 38.56, 128.79, 136.19. MS (70eV), m/z 196(M^+), 167, 154, 139, 125, 111, 97, 83, 70, 55(100%), 41, 29. IR (CCl_4), ν, cm^{-1}: 2973, 2853, 1453, 1373, 1200, 1026, 973.

(9) In the case of 1-undecen-3-ol (entries 13 and 14) in the reaction mixture by GC-MS analysis the alcohol with M/z = 200 (product of ethane addition to the allylic alcohol) was fixed. Its formation can be explained by the β-attack of titanacyclopropane reagent on the double bond of substrate following by protolytic cleavage of titanacyclopentane intermediate. See ref. 7.

(10) The formation of allyltitanium compounds from allylic esters and allyl halides by the action 2 *i*-PrMgCl/Ti(O*i*-Pr)$_4$ have been reported by Sato et al. See: Kasatkin, A.; Nakagawa, T.; Okamoto, S.; Sato, F. *J. Am. Chem. Soc.* **1995**, *117*, 3881. Hikichi, S.; Gao, Y.; Sato, F. *Tetrahedron Lett.* **1997**, *38*, 2867. Teng, S.; Kasatkin, A.; Kawanaka, Y.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1997**, *38*, 8977. Teng, S.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1998**, *39*, 6927. Kasatkin, A.; Sato, F. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 2848. Matsuda, S.; An, D. K.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1998**, *39*, 7513.

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