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Titanacyclopropanes as versatile intermediates for carbon–carbon bond formation in reactions with unsaturated compounds*

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Abstract: Dialkoxytitanacyclopropane intermediates [or titanium (II)-olefin complexes] generated *in situ* from ethylmagnesium bromide and titanium (IV) isopropoxide react with allylic alcohols and allylic ethers to afford S_N2' allylic ethylation products. The reaction proceeds with high regioselectivity and with low to high *trans-/cis-* stereoselectivity. This observation and others suggest a reaction mechanism involving an EtMgBr-initiated formation of titanacyclopentane ate complex **10** from titanacyclopropane-olefin complex **7** as a key step. Based on this assumption, a modified mechanism of titanium-mediated cyclopropanation of esters with Grignard reagents is proposed.

INTRODUCTION

Bis(pentamethylcyclopentadienyl)titanium-etylene complex has been prepared for the first time by Bercaw and coworkers in 1983 by the reduction of Cp'_2TiCl_2 with sodium amalgam in the presence of ethylene. The X-ray and reactivity patterns characterize the structure of the compound as an intermediate between Ti (II) ethylene and Ti (IV) metallacyclopropane limiting structures [1]. Some years ago [2] we found that the reaction of excess ethylmagnesium bromide with esters in the presence of titanium (IV) isopropoxide produces 1-substituted cyclopropanols **1**, and the formation of a key diisopropoxytitanacyclopropane intermediate **2** from diethyltitanium precursor **3** (Fig. 1) has been postulated.

Titanacyclopropane intermediates substituted at carbon atom can be generated using either higher homologues of ethylmagnesium bromide [3], or ligand exchange reactions [4].

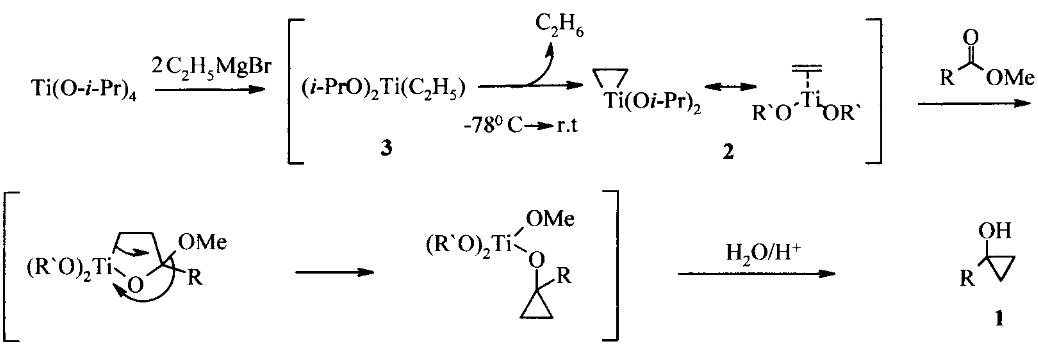

Fig. 1

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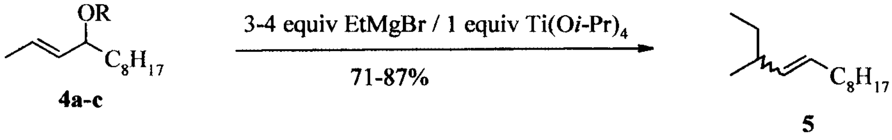
During the last five years, several research groups have performed a number of useful synthetic transformations based on generation of titanacyclopropane intermediates from Grignard reagents and titanium (IV) alkoxides. The most important results have been obtained using these reagents in transformations where C–C bonds are formed, for example, in syntheses of aminocyclopropanes [5], inter- or intramolecular hydroxy- or aminocyclopropanation of alkenes [6,7], olefin or acetylene couplings [8], as well as in generation of allyltitanium species [9].

ETHYLATION OF ALLYLIC ALCOHOLS AND ETHERS

We have found recently that the interaction of titanacyclopropane reagents with allylic alcohols and allylic ethers is also accompanied by the C–C bond formation, yielding formal S_N2' products of displacement of hydroxy or alkoxy leaving group by an alkyl group [10]. This reaction proceeds most smoothly if γ-substituted allylic alcohols are used in reaction with a nonsubstituted titanacyclopropane reagent **2**. Thus, the treatment of allylic alcohol **4a** with 4 equiv of EtMgBr and 1 equiv of $Ti(Oi\text{-}Pr)_4$ at room temperature affords a nearly equimolecular mixture of isomeric *cis*- and *trans*- alkenes **5** in 87% yield (Fig. 2). The same reaction of ether **4b** with 3 equiv of EtMgBr and 1 equiv of $Ti(Oi\text{-}Pr)_4$ gives a mixture (30:70) of *cis*- and *trans*-alkenes **5**, and, in the case of tetrahydropyranyl ether **4c,** a more than 90% stereoselectivity in favor of *trans*-alkene **5** is observed.

Capsaicin (II) synthesis

The synthetic utility of this highly regioselective and stereoselective carbon–carbon bond-forming reaction is demonstrated by a simple synthesis of capsaicin (II) **6** [11], which we have performed according to the following scheme (Fig. 3).



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

Fig. 2

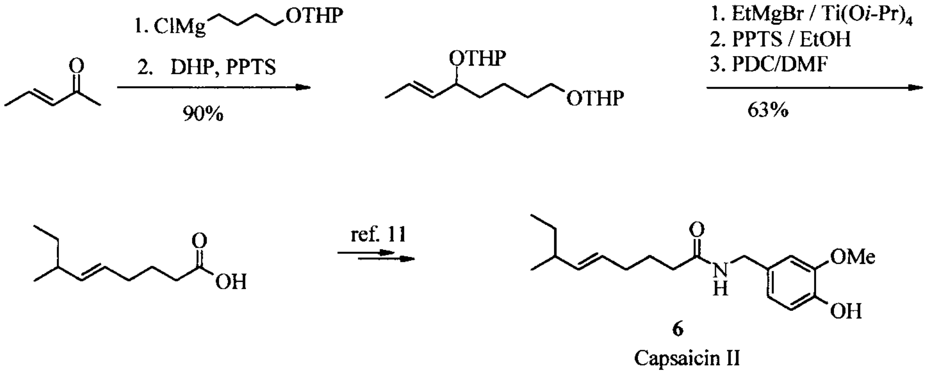


Fig. 3

Mechanistic considerations

By analogy with the mechanism of zirconium-catalyzed reactions of organomagnesium compounds with alkenes [12], the formation of alkene **5** from allylic derivatives **4** could be assumed to proceed through formation of a titanacyclopropane-olefin complex **7**, followed by rearrangement into titanacyclopentane species **8** and splitting of vicinal C–Ti and C–O- single bonds, giving an alkenyl titanium intermediate **9** (Fig. 4). However, all our attempts to trap the organotitanium compound **9** by reactions with various electrophiles (I_2, O_2, PhCHO) were unsuccessful, and only trace amounts of the corresponding products were detected. Moreover, the fact that three or more equivalents of EtMgBr are necessary for a complete consumption of the substrate **4** is difficult to account for by this mechanism.

The above-mentioned inconsistencies could be explained by a modified reaction mechanism including the reaction of titanacyclopropane-olefin complex **7** with EtMgBr leading to the formation of titanacyclopentane ate complex **10** (Fig. 5). The latter transforms further by intramolecular 1,2-elimination reaction into an unstable dialkyltitanium derivative **11** which decomposes into titanacyclopropane **2** and alkene **5**. If the alkoxide group at titanium is considered to be a 6e ligand, it could be concluded that the ate complex **10,** as well as the titanacyclopropane-olefin complex **6**, are 18e organometallic species, whereas the titanacyclopentane **8** is a 16e organometallic species. We assume that this circumstance could be a factor favoring the formation of the ate complex **10** as compared with titanacyclopentane **8**.

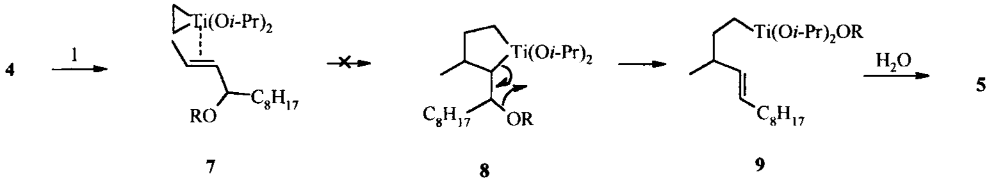


Fig. 4

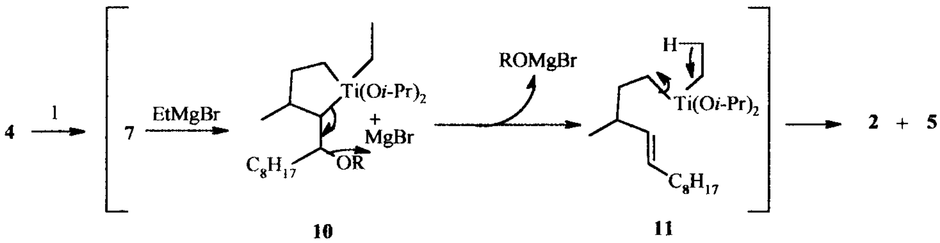


Fig. 5

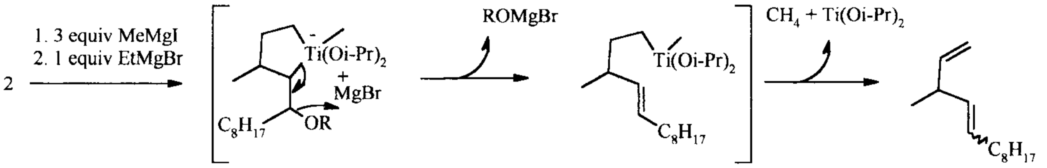


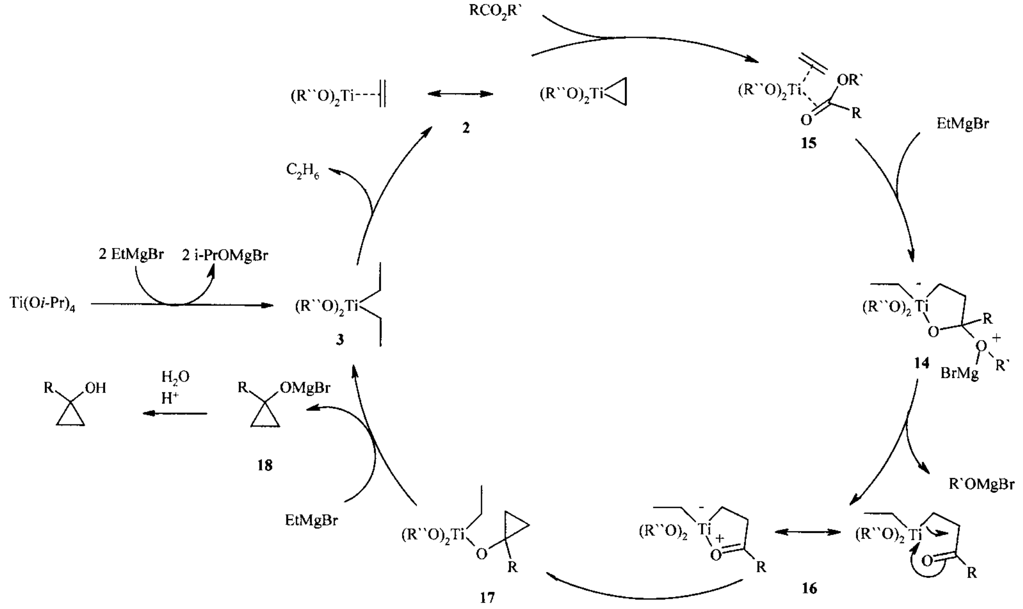
Fig. 6

The intermediate formation of dialkyltitanium species as alkene precursors is confirmed by obtaining 1,4-diene **12** in the reaction of allylic alcohol **4a** with 1 equiv of EtMgBr, 1 equiv of Ti(O*i*-Pr)$_4$, and 3 equiv of MeMgI (Fig. 6). It is obvious that the formation of vinylation product **12** in this reaction is due to the presence of β-hydrogen atoms only in alkenyl substituent of dialkyltitanium intermediate **13**.

Modified mechanism of cyclopropanation of esters

Expansion of the assumption on the EtMgBr-initiated formation of titanacyclopentane ate complexes onto titanium-mediated cyclopropanation of esters with Grignard reagents enabled us to propose a refinement of the original reaction mechanism. Thus, the formation of oxatitanacyclopentane ate complex **14** could also be initiated by the interaction of EtMgBr with titanacyclopropane-ester complex **15** (Fig. 7). Subsequent rearrangement of oxatitanacyclopentane **14** into homoenolate equivalent **16** by intramolecular ligand exchange at titanium followed by cyclization gives titanium cyclopropoxide **17.** Alkylation of the latter with EtMgBr results in diethyltitanium derivative **3**, and the catalytic cycle is completed. After hydrolysis of magnesium alkoxide **18**, the respective 1-substituted cyclopropanol **1** is formed. This refinement, as it seems, provides an explanation of the experimental data that could not find an adequate interpretation in the framework of the original mechanism. Thus, the necessity of using 3 equiv of Grignard reagent for cyclopropanation of carboxylic esters and dialkylamides in the noncatalytic version of this reaction is caused by the consumption of an additional equivalent for the formation of the ate complex **14,** which further transforms into the reaction products.

Furthermore, this mechanism explains higher reactivity of titanacyclopropane intermediates **1** in comparison with usual alkyltitanium compounds that do not react with carboxylic esters and dialkylamides at ambient temperatures.



R'' = *i*-Pr or R'.

Fig. 7

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REFERENCES

1. S. A. Cohen, P. R. Auburn, J. E. Bercaw. *J. Am. Chem. Soc.* **105**, 1136 (1983).
2. O. G. Kulinkovich, S. V. Sviridov, D. A. Vasilevskii, T. S. Pritytskaya. *Zh. Org. Khim.* **25**, 2245 (1989).
3. O. G. Kulinkovich, S. V. Sviridov, D. A.Vasilevskii, A. I. Savchenko, T. S. Pritytskaya. *Zhur. Org. Khim.* **27**, 294 (1991).
4. O. G. Kulinkovich, A. I. Savchenko, S. V. Sviridov, D. A. Vasilevskii. *Mendeleev Commun.* 230 (1993).
5. V. Chaplinski and A. de Meijere. *Angew. Chem. Int. Ed. Engl.* **35**, 413 (1996).
6. J. Lee, H. Kim, J. K. Cha. *J. Am. Chem. Soc.* **118**, 4198 (1996); J. Lee and J. K. Cha. *J. Org. Chem.* **62**, 1584 (1997).
7. J. Lee, C. H. Kang, H. Kim, J. K. Cha. *J. Am. Chem. Soc.*, **118**, 291, (1996); J. S. U, J. Lee, J. K. Cha. *Tetrahedron Lett.* **38**, 5233 (1997).
8. H. Urabe and F. Sato. *J. Org. Chem.*, **61**, 6756 (1996).
9. A. Kasatkin, T. Nakagawa, S. Okamoto, F. Sato. *J. Am. Chem. Soc.* **117**, 3881 (1995).
10. O. G. Kulinkovich, O. L. Epstein, V. E. Isakov, E. A. Khmel`nitskaya. *Synlett*. 101 (2000).
11. H. Kaga, K. Goto, T. Takahashi, M. Hino, T. Tokuhashi, K. Orito. *Tetrahedron* **52**, 8451 (1996).
12. E. Negishi and T. Takahashi. *Bull. Chem. Soc. Jpn.* **71**, 755 (1998).