

Intramolecular carbometalation of functionalized terminal alkynes *via* low-valent titanium complexes

Natalia Morlender-Vais, Nicka Solodovnikova and Ilan Marek*

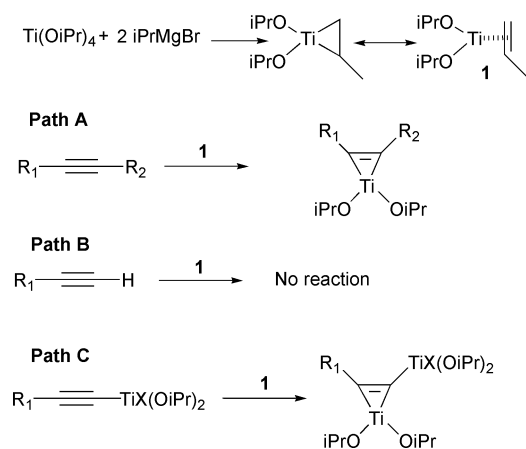
Department of Chemistry and Institute of Catalysis Science and Technology, Technion-Israel Institute of Technology, Technion City, Haifa 32 000 Israel. E-mail: chilann@tx.technion.ac.il

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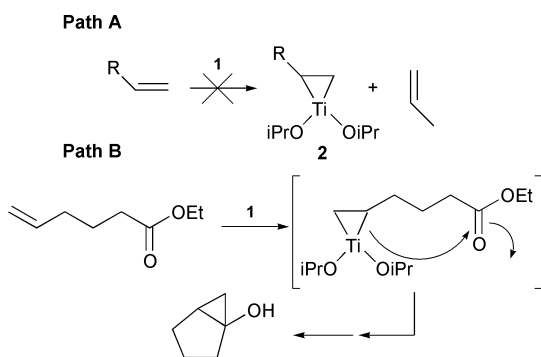
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Treatment of δ - and γ -functionalized monosubstituted alkynes with diisopropoxy(η^2 -propene)titanium induces an intramolecular cyclisation to afford the 4- and 5-membered cycloalkanols in good overall yields.

Various disubstituted alkynes react with diisopropoxy(η^2 -propene)titanium **1**, readily generated by the reaction of $\text{Ti}(\text{OiPr})_4$ with 2 eq. of iPrMgX (Sato's reagent), to give the corresponding titanacyclopropene derivatives as described in Scheme 1, path A.¹ However, as terminal alkynes failed to participate in the present reaction¹ (path B *vs.* path A), we have recently used the fact that a metalated alkyne can behave like a disubstituted alkyne to prepare the first titanacyclopropene in good overall yield (Scheme 1, path C).²



On the other hand, when **1** is opposed to an *unactivated* olefin, the ligand exchange is not efficient and therefore the desired olefin–titanium complex **2** is not formed (Scheme 2, path A). Only activated olefins undergo this exchange as styrene,³ conjugated dienes,⁴ vinyl silane⁵ or stannane.⁶ However, the presence of an electrophile in the carbon skeleton (Scheme 2, path B) promotes this reaction since an intramolecular nucleophilic acyl substitution⁷ reaction occurs in a

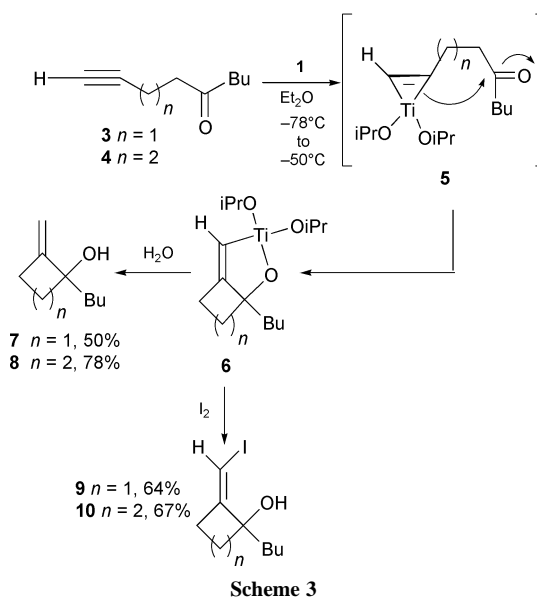


second step to give the cyclopropanolate derivative⁸ (known as the Kulinkovitch reaction).⁹

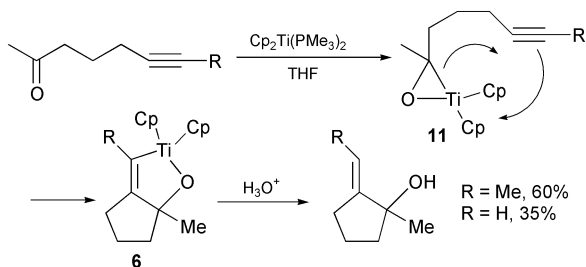
As part of our studies on the use of early transition metal complexes such as **1** for the carbometalation of unactivated alkynes,¹⁰ we anticipated by analogy with the results described in Scheme 2 that the facile intramolecular nucleophilic acyl substitution reaction of a functionalized *terminal* alkyne (known to be totally unreactive,^{1,11} Scheme 1, path B) might act as a driving force for shifting the equilibrium.⁷ In this case, a transient monosubstituted titanacyclopropene will be formed as intermediate before the carbocyclisation reaction. Indeed, treatment of dec-9-yn-5-one **4** ($n = 2$) with a stoichiometric amount of $\text{Ti}(\text{OiPr})_4$ and 2 eq. of iPrMgX at -78°C leads to the cyclic product **8**, after hydrolysis, in 78% isolated yield (Scheme 3).

In order to probe the existence of a remaining carbon–titanium bond in the molecule, iodine was added at the end of the reaction. The vinyl iodide **10** ($n = 2$) was isolated in 67% yield as single isomer (the stereochemistry was determined by NOE). Interestingly, this reaction can be applied to the formation of more strained carbocycles such as 4-membered ring derivatives in a very easy and straightforward manner (**3**, $n = 1$, Scheme 3). Here again, the non-isolated terminal titanacyclopropene **5** ($n = 1$) reacts intramolecularly with the ketone to give the organometallic derivative **6** ($n = 1$). Hydrolysis of the reaction mixture leads to the *exo*-methylene-cyclobutanol **7** in 50% isolated yield whereas the iodolysis gives only the *Z*-isomer of the vinyl iodide **9** in good chemical yield.¹²

Although the reaction mechanism described in Scheme 3 seems plausible, we have not been able to isolate even in very small amounts the transient titanacyclopropene derivative **5**. So, we have also considered an alternative mechanistic pathway for the formation of **6**. Indeed, it is known that early transition metal

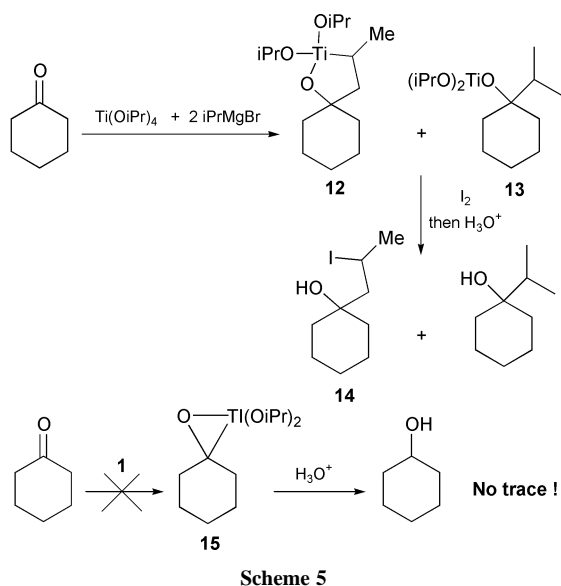


complexes can form some η^2 -ketone complexes, **11**, (metalloxiranes)¹³ which can further insert into an alkyne moiety to give the same oxatitanacyclopentene derivatives **6**. This mechanism was already reported for the reaction of δ -ynones with $[(C_5H_5)_2Ti(PMe_3)_2]$ to form 3-bis(cyclopentadienyl)-2-oxa-3-titanabicyclo[3.3.0]oct-4-ene in good overall yield.¹⁴ Although the intramolecular addition to a substituted alkyne to form the unsaturated oxatitanacycle worked well, here again the reaction on a terminal alkyne gives a low isolated yield (35%) of the cyclic product after hydrolysis, as described in Scheme 4.



So, in order to check if the first step of the reaction of **1** with **3** or **4** was a reaction at the alkynyl (Scheme 3) or at the carbonyl centers (Scheme 4), we decided to investigate the behavior of **1** with cyclohexanone as described in Scheme 5.

Treatment of 1 eq. of $Ti(OiPr)_4$ with 2 eq. of $iPrMgX$ in the presence of 1 eq. of cyclohexanone leads to two products, **12** and **13**, in a respectively 5 to 1 ratio and in quantitative yields. The major product **12** results from the reaction of diisopropoxy(η^2 -propene)titanium **1** with the carbonyl moiety which can further react with iodine to give **14** whereas **13** is formed from the direct attack of the Grignard reagent on the cyclohexanone.¹⁵ No trace of cyclohexanol was detected after hydrolysis in the crude reaction mixture which clearly indicates that the reaction does not proceed through the oxametallacycle



15. Thus, although **5** cannot be isolated, it is present as the first intermediate in the reaction before the nucleophilic attack on the carbonyl moiety occurs as described originally in Scheme 3.

In conclusion, the synthesis of *exo*-methylene-cyclopentane and -cyclobutane has been achieved in a one-pot sequence from readily available starting material with diisopropoxy(η^2 -propene)titanium. The mechanism of this reaction has been investigated and is composed by a carbometalation reaction of the monosubstituted-unactivated alkyne followed by intramolecular nucleophilic acyl substitution.

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