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

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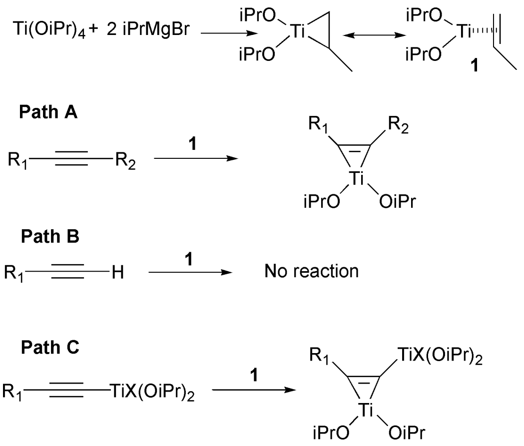
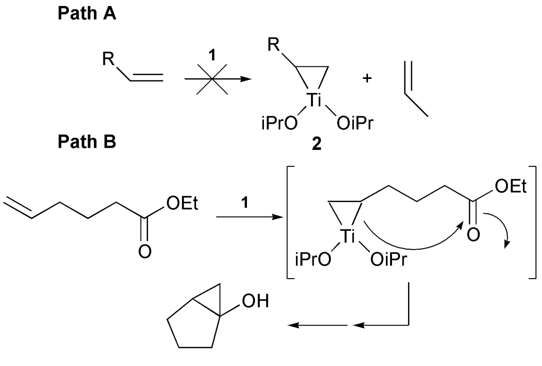
Treatment of δ- and γ-functionalized monosubstituted alkynes with diisopropoxy(η^2-propene)titanium induces an intramolecular cyclisation to afford the 4- and 5-membered cycloalkanols in good overall yields.

Various disubstituted alkynes react with diisopropoxy(η^2-propene)titanium **1**, readily generated by the reaction of $Ti(OiPr)_4$ 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 reaction[1] (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 titano–titanacyclopropene in good overall yield (Scheme 1, path C).[2]



Scheme 1

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 silane[5] 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 substitution[7] reaction occurs in a second step to give the cyclopropanolate derivative[8] (known as the Kulinkovitch reaction).[9]

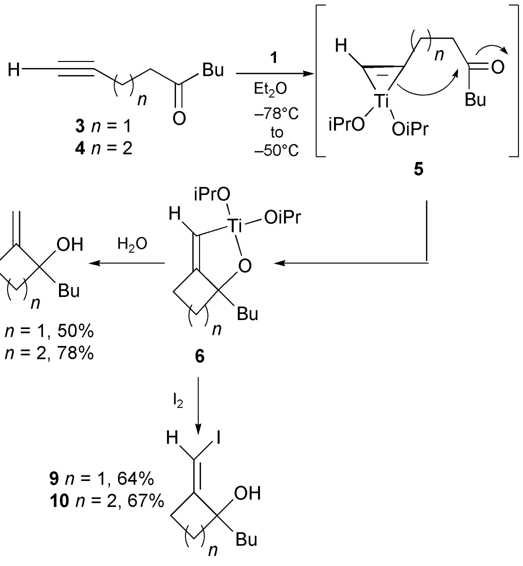


Scheme 2

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 $Ti(OiPr)_4$ 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*-methylenecyclobutanol **7** in 50% isolated yield whereas the iodinolysis 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



Scheme 3

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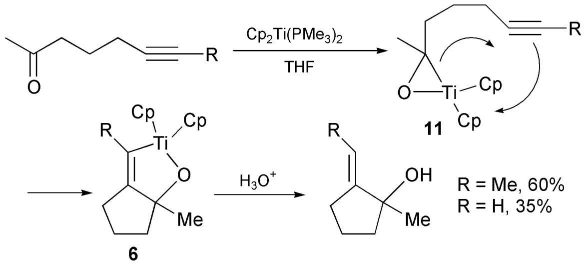
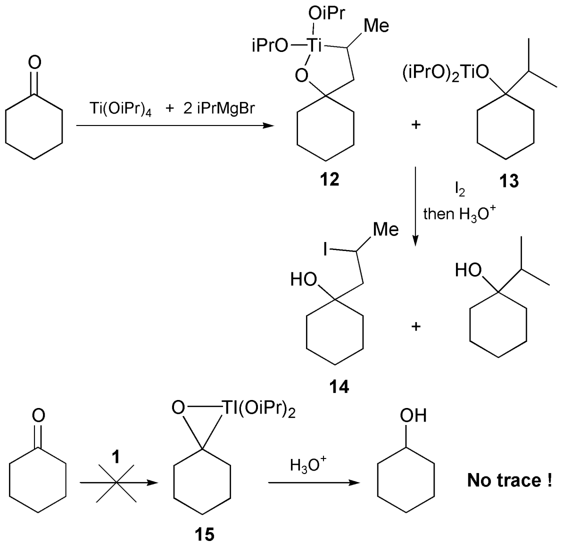
complexes can form some η^2-ketone complexes, **11**, (metallaoxiranes)[13] which can further insert into an alkyne moiety to give the same oxatitanacyclopentene derivatives **6**. This mechanism was already reported for the reaction of δ-ynones with $[(C_5H_5)_2Ti(PMe_3)_2]$ to form 3-bis(cyclopentadienyl)-2-oxa-3-titanabicyclo[3.3.0]oct-4-ene 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.



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.



Scheme 5

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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