On the Mechanism of Titanocenedichloride-catalysed Hydromagnesiation of Alkynes with Alkyl Grignard Reagents

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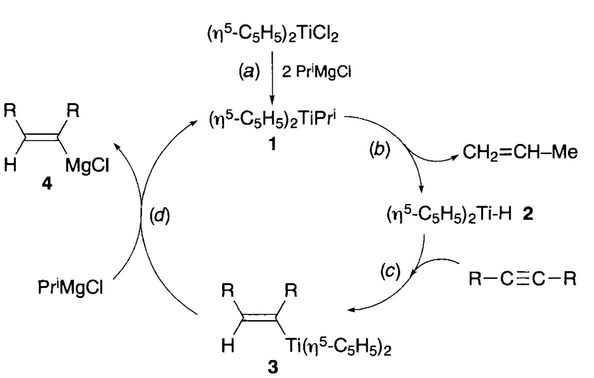
The mechanism of titanocenedichloride-catalysed hydromagnesiation reaction of alkynes with an alkyl Grignard reagent is elucidated and it is revealed that the regiochemistry of the reaction controlled at the step of transmetallation from titanium to magnesium.

Preparation of Grignard reagents by hydromagnesiation of alkenes and alkynes with alkyl Grignard reagents having a β-hydrogen atom(s) in the presence of titanium catalyst not only complements conventional methods but also enables a chemo-, regio- and stereo-selective formation of Grignard reagents which are otherwise difficult to prepare.[1] After the pioneering work of the hydromagnesiation of alkenes by Cooper and Finkbeiner,[2] we developed the $(\eta^5\text{-}C_5H_5)_2TiCl_2$-catalysed hydromagnesiation reaction of alkynes,[3] and proposed the reaction mechanism shown in Scheme 1 which is based on that proposed for alkenes.[2] Since then this reaction has become widely used in organic synthesis,[4] and its mechanism has continued to attract interest.[5] We have now succeeded in obtaining evidence to support the proposed reaction mechanism.

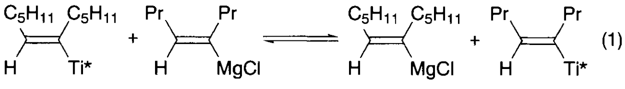
The reaction of $(\eta^5\text{-}C_5H_5)_2TiCl_2$ with 2 equiv. of $\mathrm{Pr^iMgCl}$ in diethyl ether (0 °C, 5 min), is known to afford $(\eta^5\text{-}C_5H_5)_2TiH$ **2** *via* $(\eta^5\text{-}C_5H_5)_2TiPr^i$ **1** according to paths (*a*) and (*b*) shown in Scheme 1.[6] After dodec-6-yne was added, the reaction mixture was stirred for 1 h at 0 °C to afford the alkenyltitanium compound **3** ($R = C_5H_{11}$) in essentially quantitative yield as evidenced by the following facts. Addition of D_2O to the reaction mixture furnished (*Z*)-6-deuteriododec-6-ene quantitatively (by ^1H NMR analysis), which suggested the presence of the alkenyl-titanium (**3**, $R = C_5H_{11}$) and/or -magnesium compound (**4**, $R = C_5H_{11}$). To clarify whether it was the titanium or the magnesium compound or both, benzaldehyde was added instead of D_2O to the reaction mixture, because **3** ($R = C_5H_{11}$) was expected to afford hydrobenzoin **5**[7] while **4** ($R = C_5H_{11}$) would give rise to the addition product, (*E*)-1-phenyl-2-pentyloct-2-en-1-ol **6**. We found that this reaction produced only **5** in 42% yield.

With the evidence of the hydrotitanation path (*c*) in Scheme 1, we tried to clarify the path (*d*). Thus, after the hydrotitanation reaction of dodec-6-yne, we added 1.2 equiv. of $\mathrm{Pr^iMgCl}$ to the reaction mixture at 0 °C. After stirring for 1 h at this temperature, benzaldehyde was added to the reaction mixture to afford **6** in 78% yield. This result strongly indicated the formation of **4** ($R = C_5H_{11}$) by transmetallation of the alkenyl group from titanium to magnesium as shown in path (*d*). We also confirmed this transmetallation reaction by synthesizing the alkenyl titanium compound **3** ($R = C_5H_{11}$) according to the reported procedure[8] and successive treatment with $\mathrm{Pr^iMgCl}$ (0 °C, 1 h) and benzaldehyde which provided **6** in 61% yield.

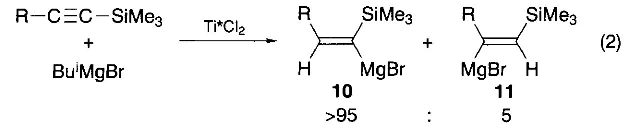


Scheme 1

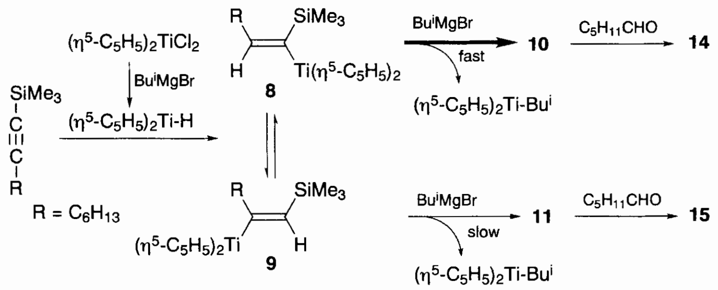
To get evidence for the formation of $(\eta^5\text{-}C_5H_5)_2TiH$ **2** *via* $(\eta^5\text{-}C_5H_5)_2TiPr^i$ **1** in the reaction path (*d*), before addition of benzaldehyde in the above reaction we added oct-4-yne to the reaction mixture at 0 °C and stirred for 30 min, which resulted in the formation of **6** and (*E*)-1-phenyl-2-propylhex-2-en-1-ol **7** [addition product of **4** ($R = C_3H_7$) and benzaldehyde] in a ratio of 45 : 55 in 72% total yield based on magnesium (or 36% yield based on the alkynes used). While the deuteriolysis of this reaction mixture resulted in the formation of (*Z*)-6-deuterioundec-6-ene and (*Z*)-4-deuteriooct-4-ene in 93 and 96% yields, respectively. These results indicating the essentially quantitative production of alkenyl metallic compounds (Ti and Mg compounds) from dodec-6-yne and oct-4-yne, which included almost equal amount of dodec-6-en-6-yl and oct-4-en-4-yl Grignard reagents (**4**, $R = C_5H_{11}$ and C_3H_7), can be explained by the hydrotitanation of oct-4-yne by the regenerated $(\eta^5\text{-}C_5H_5)_2TiH$ followed by the metal exchange reaction between the resulting oct-4-en-4-yl titanium compound and dodec-6-en-6-yl Grignard reagent as shown in eqn. (1) [$Ti^* = Ti(\eta^5\text{-}C_5H_5)_2$].[5]



Next we tried to clarify the origin of the regiochemistry of the hydromagnesiation of silylacetylenes, which furnishes the Grignard reagent in which magnesium is placed at the carbon bonded to the silyl group highly selectively as shown in eqn. (2) [$Ti^* = Ti(\eta^5\text{-}C_5H_5)_2$].[3]



After the hydrotitanation of 1-trimethylsilyloct-1-yne by $(\eta^5\text{-}C_5H_5)_2TiH$ prepared *in situ* by the reaction of $(\eta^5\text{-}C_5H_5)_2TiCl_2$ with 2 equiv. of $\mathrm{Bu^iMgBr}$, the reaction mixture was quenched with D_2O to afford the mixture of (*Z*)-1-trimethylsilyl-1-deuteriooct-1-ene **12** and (*Z*)-1-trimethylsilyl-2-deuteriooct-1-ene **13**. The ratio of **12** : **13** was dependent on the hydrotitanation reaction conditions: thus the ratio of **12** : **13** was 60 : 40 at 0 °C for 1 h, 83 : 17 at room temp. for 1 h, and 85 : 15 at the reflux temperature of diethyl ether for 2 h. These findings suggested that the 85 : 15 ratio of **12** : **13** is the mole ratio at equilibrium of the corresponding hydrotitanated compounds **8**/**9** ($R = C_6H_{13}$). We added $\mathrm{Bu^iMgBr}$ to the 83 : 17 mixture of the hydrotitanated compounds at room temp., stirred for 30 min and then added hexanal which resulted in the production of the addition products (*Z*)-7-trimethylsilyltetradec-7-en-6-ol **14** and (*E*)-1-trimethylsilyl-2-hexyloct-1-en-3-ol **15** in a ratio of >95 : 5 and 77% total yields (Scheme 2). These results which showed the presence of **10** ($R = C_6H_{13}$) and **11** ($R = C_6H_{13}$) in a ratio of >95 : 5 can be explained by



Scheme 2

assuming that the rate of transmetallation from titanium to magnesium in the case of **8** is much faster than that of **9** and that the mole ratio of **10** : **11** at equilibrium is >95 : 5 (Scheme 2).

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