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Generation of Allylic Titanocene Derivatives from Vinyl Halides and a Cp_2TiCl_2-Me_3Al Reagent System

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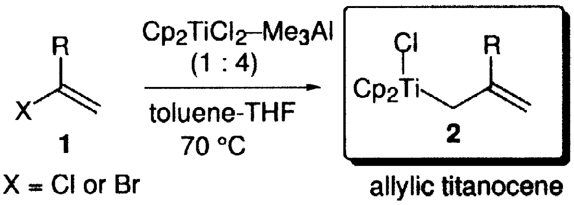
Abstract: The reagent prepared in advance by stirring a mixture of a Cp_2TiCl_2–Me_3Al reagent system in the ratio of 1 : 4 in toluene for 3 days is found to be effective in generating allylic titanocene on treatment with vinyl halides in THF.

Allylic organometals occupy an important position in diastereo- and/or enantioselective synthesis of organic molecules. The generation of many kinds of allylic organometals, thus, has been earnestly contrived by many research groups.[1] Among the allylic organometals, group 4 early transition metals (Ti and Zr) as a metal component have attracted much attention not only for the reactivity and selectivity but also for the way of generation.[2] Search for new methods for generating allylic metal derivatives from a simple organic molecule is considered to be a significant subject since the methodology should present interesting possibilities in organic synthesis. We report herein an efficient generation of allylic titanocene species **2**[3] from a solution of vinyl halides **1** in tetrahydrofuran (THF) and a reagent which is prepared in advance by stirring a mixture of titanocene dichloride (Cp_2TiCl_2) and trimethylaluminum (Me_3Al) in the ratio of 1 : 4 in toluene.[4]



In all the preparations of the allylic titanocene derivatives **2** described in the present paper, a stoichiometric amount of Cp_2TiCl_2 to vinyl halides **1** and a mixture of Cp_2TiCl_2 – Me_3Al reagent system in the ratio of 1 : 4 were the optimized conditions to attain reasonable amounts of the allylic titanocene species **2**.[5] Two more prerequisite conditions are: i) premixing[6] of a toluene solution of Cp_2TiCl_2 and Me_3Al (1 : 4 ratio) at ambient temperature for 3 days prior to the addition of vinyl halides and ii) the use of THF as a co-solvent[7] at the stage of the addition of vinyl halides **1**. The results of the formation of homoallylic alcohols **3** by the reactions of the generated allylic titanocene derivatives **2** from **1** with carbonyls are listed in Table 1.

Typical experimental procedure: Under an Ar atmosphere, a solution of Me_3Al (15 % in toluene, 2.9 ml, 6.0 mmol) was added to a solution of Cp_2TiCl_2 (374 mg, 1.5 mmol) in toluene (3 ml) at ambient temperature. After the mixture was stirred at the same temperature for 3 d, a solution of α-chlorostyrene

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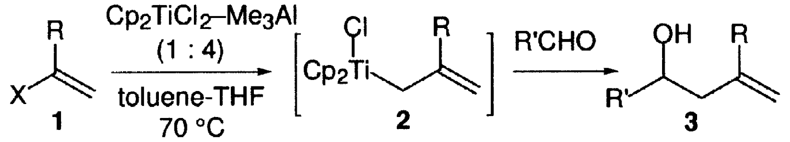
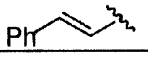
(139 mg, 1.0 mmol) in THF (5 ml) was added at 0 °C and the mixture was gradually warmed to ambient temperature and finally heated to reflux overnight. To the thus-generated 2-phenyl allyltitanocene was added a solution of 3-phenylpropanal (200 mg, 1.5 mmol) in THF (5 ml) under ice cooling and the mixture was stirred at ambient temperature fo 3 h. The reaction was terminated by the addition of aq NaOH (1M solution) at 0 °C and the mixture was filtered through a Celite pad. The filtrate was extracted with ether and the combined organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The crude oily material was purified by silica gel column chromatography (hexane – ethyl acetate = 10 : 1 ~ 3 : 1) to give pure 2,6-diphenyl-1-hexen-4-ol (187 mg, 0,74 mmol) in 74 % yield.[8]

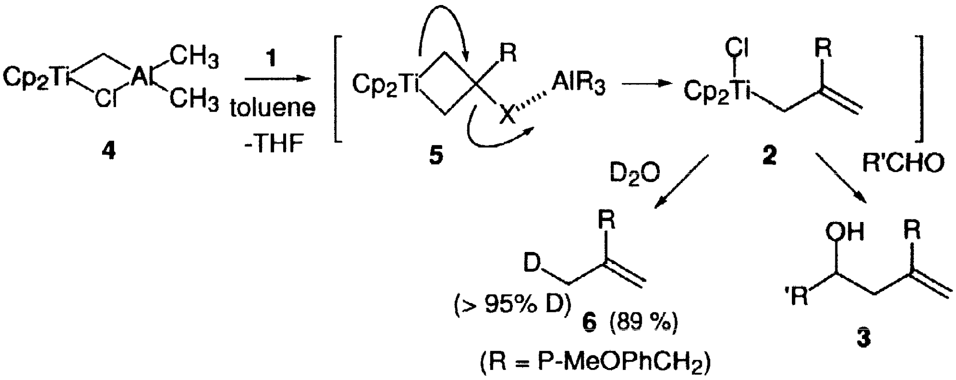
Table 1. Generation and Reactions of Allylic Titanocene 2 with Aldehydes[a]



R	X	R'	Yield of **3** (%)[b]
Ph	Cl	Ph	50
		$PhCH_2CH_2$	74
p-$MeOPhCH_2$	Cl	$PhCH_2CH_2$	93
CH_3	Cl	Ph	58
		$PhCH_2CH_2$	58
	Br	Ph	60
		$PhCH_2CH_2$	80
$cyC_6H_{11}CH_2$	Cl	Ph	60
	Br	$PhCH_2CH_2$	87
		cyC_6H_{11}	60
		 Ph	66

a Experimental procedure, see the text.
b Isolated yield.

The reaction of vinyl halides **1**[9] with the premixed Cp_2TiCl_2 – Me_3Al (1 : 4) reagent system did not show a significant difference between chloride and bromide in the formation of allylic titanocene derivatives **2**, and **2** prepared under the present conditions showed the standard reactivity of allylic titanocene derivatives with aldehydes including α,β-unsaturated aldehyde. The reaction of cyclohexanone with allylic titanocene **2** generated from **1** (R = $CH_2cyC_6H_{11}$, X = Br) also gave homoallylic alcohol in 69 % yield.[10] It has been well established that the reaction of Cp_2TiCl_2 with 2 equiv of Me_3Al at ambient temperature for 3 days yields a heterobimetalic species, the so-called Tebbe reagent **4**.[11] The reaction of the Tebbe reagent **4** with olefinic compounds in the presence of a basic solvent or compound, such as THF or dimethylaminopyridine (DMAP), has been reported to give a titanacyclobutane compound, an intermediate of the olefin methathesis, through a reaction of titanocene methylidene complex ($Cp_2Ti{=}CH_2$) with olefin.[12] In our present cases, heating of a mixture of the Tebbe reagent **4**, which is generated in toluene, with vinylhalide **1** (R = Ph, X = Cl) in toluene-THF at 70 °C did not generate an appreciable amount of allylorganometallic compounds since no allylation product could be isolated by the treatment of the reaction mixture with aldehyde. Addition of 2 more equiv of Me_3Al to the mixture of the Tebbe reagent **4** and vinyl halide **1** (R = Ph, X = Cl) in toluene-THF and the heating of the mixture at 70 °C indicated a formation of allylic titanocene species **2** (R = Ph) whose presence was confirmed by the formation of the allylation product **3** (R = Ph, R' = CH_2CH_2Ph, 30 % yield) in the reaction with 3-phenylpropanal. The use of 0.5 equiv of Cp_2TiCl_2 and 2 equiv of Me_3Al to vinyl halide **1** (R = Ph, X = Cl) according to the typical experimental procedure and the treatment with benzaldehyde in THF yielded an allylation product **3** (R = R' = Ph) in 25 ~ 30 % yield. Furthermore, the semicatalytic use of Cp_2TiCl_2 (0.1 mol) in the presence of 4 moles of Me_3Al to vinyl halide **1** (R = Ph, X = Cl) in the same way yielded the allylation product **3** (R = R' = Ph) in ~ 5 % yield. These observations imply that the reaction must be stoichiometric with respect to Cp_2TiCl_2 and the presence of 2 moles or more of Me_3Al relative to the Tebbe reagent **4** is necessary for the formation of allylic titanocene derivatives **2**. Further evidence for the formation of allylic titanocene derivatives **2** was obtained by the deuteration of the allyic organometal intermediate **2** (R = p-$MeOPhCH_2$) with deuterium oxide to give deuterated compound **6** at allylic position in more than 95 % D content (by ^1H NMR) in 89 % chemical yield. Reactions of alkyl halide with titanocenemethyledene complex have been reported to proceed through a radical mechanism.[13] However, the present procedure for the generation of allylic titanocene derivatives **2** is likely to proceed through a titanacyclobutane **5** followed by Me_3Al-mediated β-elimination of chloride[14,15] since the reaction of **1** with $Cp_2Ti{=}CH_2$, which is generated from dimethyltitanocene,[16] in the absence of Me_3Al did not generate **2**.[17]



In conclusion, we have shown a new method to generate allylic taitanium species from vinyl halides and a $Cp_2TiCl_2 - Me_3Al$ (1 : 4) reagent system using a toluene-THF solvent system.

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4. Reactions of **1** with "Cp_2Zr" has been reported to give an oxidatively Cp_2Zr-inserted product. Takahashi, T.; Kotora, M.; Fischer, R.; Nishihara, Y.; Nakajima, K. *J. Am. Chem. Soc.* **1995**, *117*, 11039.
5. Use of 1 : 1 or 1 : 2 (see text) $Cp_2TiCl_2 - Me_3Al$ reagent system under otherwise identical conditions to the typical experiment did not show the formation of homoallylic alcohol derivative in the reaction with aldehyde. Use of 1 : 3 $Cp_2TiCl_2 - Me_3Al$ reagent system gave a lower yield (25 %) of the allylation product in the reaction with aldehyde. The reaction of monosubstituted olefin with 1 : 1 $Cp_2TiCl_2 - Me_3Al$ reagent system has been reported. Barber, J. J.; Willis, C.; Whitesides, G. M. *J. Org. Chem.* **1979**, *44*, 3603.
6. Reaction (70 °C, 24 h) of vinyl halides in THF with a toluene solution of Cp_2TiCl_2–Me_3Al (1 : 4) which was used without premixing failed to generate allylic titanocene.
7. Reaction did not take place without using THF. Use of DMAP instead of THF did not give satisfactory results.
8. All new compounds were characterized by NMR (^1H, ^{13}C), IR, MS and combustion analysis.
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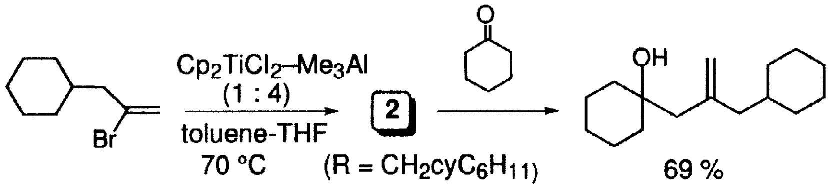
10.



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14. The reaction of acylchloride with the Tebbe reagent has been known to give titanocene enolate through a β-elimination process of the cyclooxatitanabutane intermediate. Stille, J. R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1983**, *105*, 1664. However, the complex and multi-mechanistic nature of the $Me_3Al - Cp_2TiCl_2$ reagent system depending on the reaction conditions in carbometalation reactions of acetylenes has also been reported. Negishi, E.; Kondakov, D. Y.; van Horn, D. E. *Organometallics* **1997**, *16*, 951. Thus, we cannot definitely rule out the possibility that another reaction mechanism leading to allylic titanocene **2** might take part in some extent in our cases.
15. A referee pointed out the possibility of the formation of η^3-allyltitanocene instead of **2**. We can rule out this possibility by the fact that the allylation of aldehyde proceeds even after the treatment of the present allylic titanocene species with excess CH_2Cl_2. It has been reported that the η^3-allyltitanocene complex reacts with CH_2Cl_2 to give Cp_2TiCl_2.[2e] We have confirmed that no reaction took place through the reaction of η^3-allyltitanocene with aldehyde in the presence of CH_2Cl_2.
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17. In the presence of Me_3Al (2 equiv) under otherwise identical conditions, **3** (R = $cyC_6H_{11}CH_2$, R' = $PhCH_2CH_2$) was isolated in a lower yield (20 %) through the reaction with aldehyde. We appreciate one of the referees for the kind suggestion to test about this reaction.