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Highly Efficient Synthesis of Propargyl- and Allenyltitanium Reagents from Propargyl Halides or Propargyl Alcohol Derivatives. Practical Synthesis of Allenyl and Homopropargyl Alcohols

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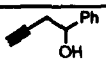
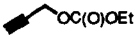
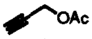
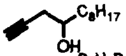
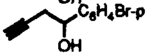
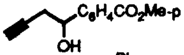
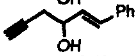
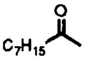
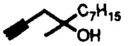
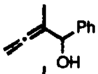
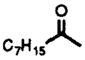
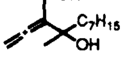
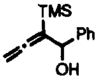
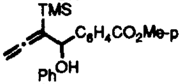
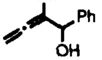
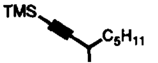
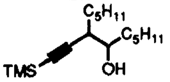
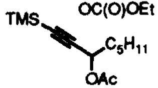
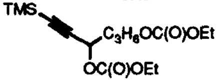
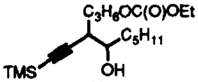
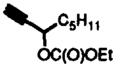
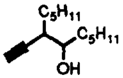
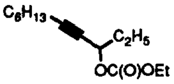
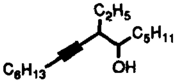
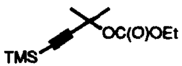
Abstract: *Reaction of $Ti(O\text{-}i\text{-}Pr)_4$ / 2 i-PrMgBr, synthetic equivalent of practical Ti(II) reagent, with propargyl halides or propargyl alcohol derivatives affords allenyl titanium compounds in excellent yields, thus providing an efficient and practical method for synthesis of both allenyl and homopropargyl alcohols by the successive treatment with aldehydes or ketones.*

The preparation of allenyl and propargyl organometallics and their application in organic synthesis have attracted much interest in recent years.[2] Yamamoto and his coworkers reported the synthesis of propargyl- and allenyltitanium reagents and their use for the preparation of α-allenyl and homopropargyl alcohols, respectively.[3] Thus, propargyl- and allenyltitanium reagents were prepared from 1-substituted and 1,3-disubstituted 1-propynes, respectively, by lithiation with *t*-butyllithium followed by the reaction with $Ti(O\text{-}i\text{-}Pr)_4$. The organotitanium reagents thus prepared reacted with aldehydes in a regio- and stereocontrolled manner to afford either α-allenyl or homopropargyl alcohols. We report here a new efficient and practical synthetic method for preparation of propargyl and allenyltitanium reagents including those that have been difficult to prepare by Yamamoto's method.

Recently we have found that allyl halides or allyl alcohol derivatives react with a low-valent titanium compound (presumablly diisopropoxy(η^2-propene) titanium) derived from the reaction of $Ti(O\text{-}i\text{-}Pr)_4$ with 2 eq of *i*-PrMgBr[4] to afford allyltitanium compounds in excellent yields.[5] With this finding, we expected the formation of allenyl- and/or propargyltitanium reagents by the reaction of propargyl halides or propargyl alcohol derivatives with the $Ti(O\text{-}i\text{-}Pr)_4$ / 2 *i*-PrMgBr reagent.

As expected, the addition of 2 eq of *i*-PrMgBr to a mixture of $Ti(O\text{-}i\text{-}Pr)_4$ and propargyl substrates at -50 °C followed by stirring the reaction mixture for 1 h at -50 °C ~ -40 °C generated the corresponding organotitanium reagents *in situ*, which, in turn, reacted with carbonyl compounds to provide the addition products.[6] The results are summarized in Table 1.

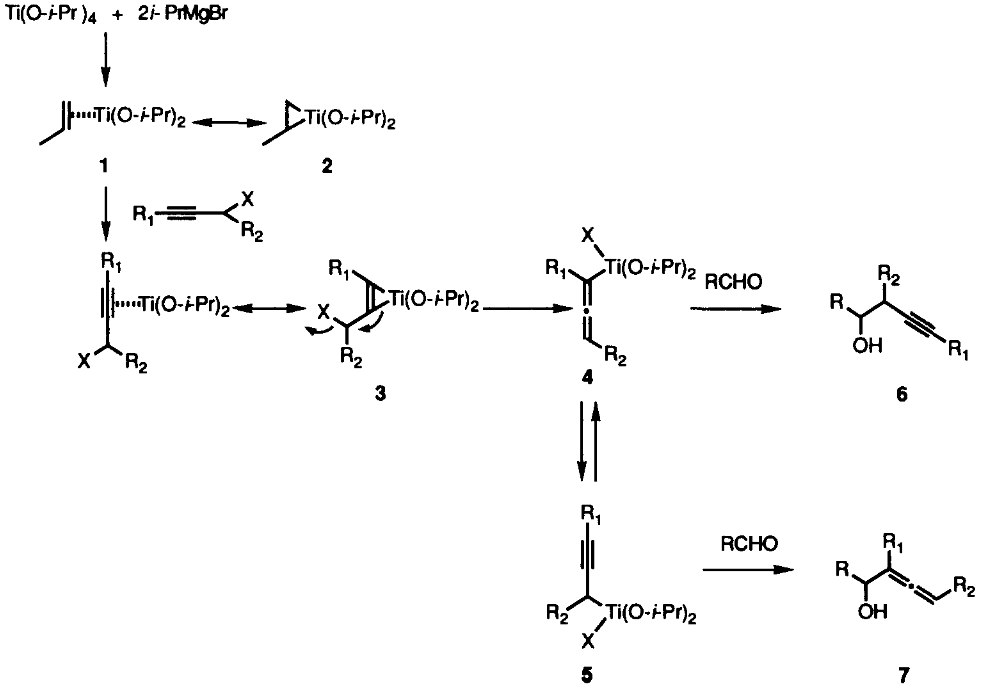
Table 1. Synthesis of various allenyl and homopropargyl alcohols using a variety of propargyl and carbonyl compounds.[a]

entry	propargyl compound	carbonyl compound	product		
				yield (%)[b]	(*threo*:*erythro*)[c]
1		PhCHO		85	
2				82	
3				74	
4				36	
5		$C_8H_{17}CHO$		91	
6		*p*-BrC_6H_4CHO		91	
7		*p*-$MeO_2CC_6H_4CHO$		86	
8				74	
9				85	
10		BuC(O)Bu		78	
11		PhCHO		89	
12				83	
13		PhCHO		83	
14		*p*-$MeO_2CC_6H_4CHO$		79	
15		PhCHO		86	
16[d]		$C_5H_{11}CHO$		70	(80 : 20)
17[d]				77	(80 : 20)
18[d]				88	(76 : 24)
19[d]				89	(75 : 25)
20[d]				89	(72 : 28)
21		PhCHO		78	

[a] Reaction conditions: propargyl compound:Ti(O-*i*-Pr)$_4$:*i*-PrMgBr:carbonyl compound=1.0:1.0:1.9:0.7. Allenyl titanium compounds were prepared at -50 °C ~ -40 °C (1 h) and then a carbonyl compound was added at -40 °C. [b] Isolated yield based on carbonyl compound. [c] Determined by ^1H-NMR analysis. [d] Carbonyl compound was added at -78°C.

It can be seen from Table 1 that titanium reagents derived from 3-halo-1-propyne or 2-propyn-1-ol derivatives such as acetate and carbonate reacted with aldehydes or ketones to provide the corresponding homopropargyl alcohols in excellent yields without contamination of any allenyl alcohols (entries 1~10), while the titanium reagents derived from 1-substituted 3-halo-1-propyne condensed with carbonyl compounds to afford allenyl alcohols exclusively (entries 11~15). Titanium reagents derived from secondary or tertiary propargyl alcohol derivatives furnished the corresponding β-alkyl homopropargyl alcohols exclusively (entries 16~21).

These results strongly indicated the formation of allenyl titanium compounds from 3-halo-1-propyne, 2-propyn-1-ol derivatives, and secondary and tertiary propargyl alcohol derivatives, and the formation of propargyl titanium compounds from 1-substituted 3-halo-1-propyne, according to a plausible reaction mechanism shown in Scheme 1. First, diisopropoxy(η^2-propene)titanium complex **1** which can also be regarded as diisopropoxytitanacyclopropane complex **2** generated by the reaction of $Ti(O\text{-}i\text{-}Pr)_4$ / 2 i-PrMgBr[4] reacts with propargyl compounds to form titanacyclopropene complexes **3**. Elimination of the halide or OC(O)R group from **3** was followed to generate allenyltitanium reagents **4**. In the case of the allenyltitanium reagents derived from 1-substituted 3-halo-1-propyne (i.e. R_1=alkyl, R_2=H), metallotropic rearrangement of titanium occurred to afford more stable propargyltitanium reagents **5** as suggested by Yamamoto. The titanium reagents thus produced reacted with carbonyl compounds via a chelate-type transition state to afford either homopropargyl alcohols **6** (from **4**) or allenyl alcohols **7** (from **5**).[2]



Scheme 1

Other noteworthy facts of the present reaction are as follows. (1) Although the titanium reagents derived from secondary or tertiary propargyl alcohol derivatives did not react with ketones presumably due to steric hindrance as reported by Yamamoto, those derived from 3-halo-1-propyne or 1-substituted 3-halo-1-propyne reacted with ketones to afford tertiary homopropargyl alcohols (entries 9 and 10) or tertiary allenyl alcohols (entry 12) respectively. (2) The titanium reagents which are not accessible by Yamamoto's method such as these shown in entries 1, 18, 19 and 20 could be readily prepared. (3) Owing to the high chemoselectivity of the organotitanium compounds,[7] the synthesis of allenyl and propargyl alcohols having various functional groups could be readily carried out by the reaction with functionalized carbonyl compounds (entries 6, 7, 8 and 14).

In conclusion, $Ti(O\text{-}i\text{-}Pr)_4$ / 2 *i*-PrMgBr reagent can be successfully used to transform readily available propargyl halides, acetates and carbonates into propargyl- or allenyltitanium reagents, thus opening up a highly efficient and practical way to synthesize both homopropargyl and α-allenyl alcohols.[8] Further synthetic applications of $Ti(O\text{-}i\text{-}Pr)_4$ / 2 *i*-PrMgBr reagent which acts as a very active $Ti(O\text{-}i\text{-}Pr)_2$ equivalent are in progress in our laboratory.

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5. Kasatkin, A.; Nakagawa, T.; Okamoto, S.; Sato, F., *J. Am. Chem. Soc.*, in press.
6. A typical procedure is as follows: to a stirred solution of 3-bromo-1-propyne (0.127 ml, 1.43 mmol) and $Ti(O\text{-}i\text{-}Pr)_4$ (0.425 ml, 1.43 mmol) in Et_2O (10 ml) was added *i*-PrMgBr (1.90 ml, 1.43 M in Et_2O, 2.72 mmol) at -50 °C and the mixture was stirred for 1 h at -50 °C ~ -40 °C. Then benzaldehyde (0.102 ml, 1.00 mmol) was added at -40 °C and the mixture was warmed up to -20 °C for 0.5 h. The reaction mixture was quenched with aq.1 N HCl at -20 °C. The organic layer was separated and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The resulting oil was purified by chromatography on silica gel to give 1-phenyl-3-butyn-1-ol (0.124 g) in 85% yield.
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8. The synthesis of allenyl zirconium compounds by the reaction of $Cp_2Zr(n\text{-}Bu)_2$ (Cp_2Zr equivalent) with propargyl ether derivatives and their reaction with aldehydes in the presence of $BF_3{\cdot}OEt_2$ providing homopropargyl alcohols have been reported, however, it suffers from several limitations in their synthetic applicability as compared to the present methodology: it affords a mixture of homopropargyl and allenyl alcohols, and it is only applicable for synthesis of β-substituted homopropargyl alcohols, Ito, H.; Nakamura, T.; Taguchi, T.; Hanzawa, Y. *Tetrahedron Lett.* **1992**, *33*, 3769.

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