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Highly Efficient Synthesis of Allylic Alcohols Having an α-Alkoxyalkyl Group at Their β-Position *via* Regioselective Addition Reaction of Titanium-Propargyl Ether Complexes with Carbonyl Compounds

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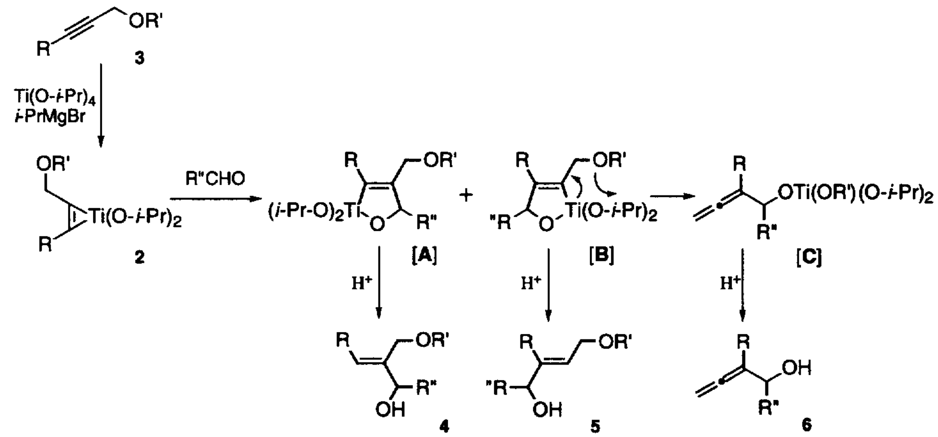
Abstract: Diisopropoxytitanium-propargyl ether complexes **2**, readily generated *in situ* from Ti(OPr^i)$_4$/ 2 ^{i}PrMgBr reagent and propargylic ethers **3**, react with aldehydes and ketones highly regioselectively at the carbon having an α-alkoxyalkyl group, thus affording an efficient and practical method for synthesizing allylic alcohols **4** having an α-alkoxyalkyl group at the β-position. The synthesis of conjugated dienes **7h** and **8h** from the resulting **4h** is also described.

The reaction of metal-alkyne complexes of the type L$_n$M(η^2-alkyne) (**1**) with aldehydes or ketones provides an efficient, stereoselective method for synthesizing allylic alcohols.[1,2] In the case of **1** derived from unsymmetrical alkynes, however, a regiochemical problem arises. Several alkynes show high regioselectivity, although it depends on the nature of the metal (M) and ligands (L$_n$); these alkynes include terminal acetylenes, alkylarylacetylenes, and alkynes having a heteroatom or an electron-withdrawing alkoxycarbonyl group as the acetylenic substituent.

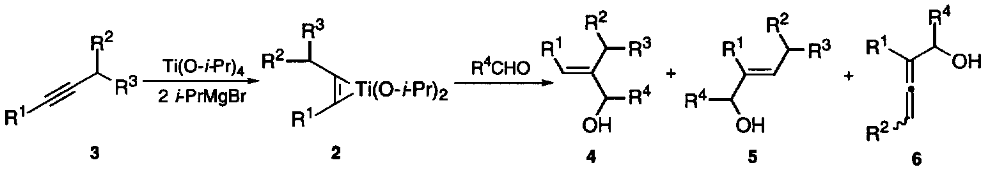
Recently, we have reported that the titanium-alkyne complexes, (η^2-alkyne)Ti(OPr^i)$_2$, can be readily synthesized from alkynes and Ti(OPr^i)$_4$ / 2 ^{i}PrMgX (X= Cl or Br) reagent, and which, in turn, react with carbonyl compounds to furnish allylic alcohols in excellent yields.[1,3] We have now found that the titanium-alkyne complexes (^{i}PrO)$_2$Ti(η^2-propargylic ether) (**2**) derived from propargylic ethers (**3**) react with aldehydes other than formaldehyde[4] and ketones at the carbon having the α-alkoxyalkyl group highly selectively to afford, after hydrolysis, the alcohols **4** exclusively or predominantly as shown in Table 1.[5]

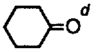
Scheme 1



The fact that there are few efficient methods for synthesizing alcohols **4**, compared to their regioisomers **5**, starting from readily available propargylic alcohols[6,7] prompted us to plan the reaction. We initially did not expect especially high selectivity; however, we envisioned that one of the titanium compounds **B** generated might be converted into the corresponding allene compound **C** under the reaction conditions through β-elimination as shown in Scheme 1, thus providing, after hydrolysis, allenylic alcohols **6** which should be readily separable from **4**. We found that this type of elimination actually occurred, thus making it easy to isolate **4** (see Table 1).

Tablel: Reactions of Titanium-Propargylic Ether Complexes with Carbonyl Compounds [a]



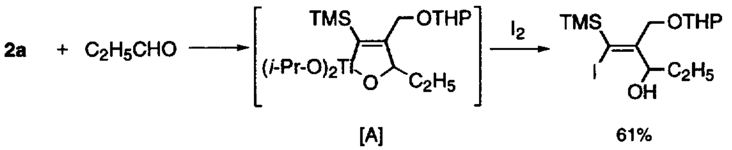
Entry	3			2	R^4CHO	Isolated Yield of 4 (%) [b]	Ratio of Products [c]		
	R^1	R^2	R^3				4	5	6
1	TMS	H	OTHP	a	$C_5H_{11}CHO$	78	96	—	4
2					PhCHO	78	>98	—	<2
3					 [d]	82	>98	—	<2
4	TMS	H	OEE	b	C_2H_5CHO	72	>98	—	<2
5	TMS	H	OTBS	c	C_2H_5CHO	71	>98	—	<2
6	n-Bu	H	OTHP	d	$C_5H_{11}CHO$	46	79	—	21
7	Ph	H	OTHP	e	C_2H_5CHO	63	80	12	8
8	TMS	n-Bu	OTHP	f	C_2H_5CHO	71	90	—	10
9	TMS	OEt	OEt	g	C_2H_5CHO	64	>98	—	<2
10	$TMSCH_2$	H	OTHP	h	$C_5H_{11}CHO$	78	95	—	5
11	TMS	H	CH_2OTHP	i	$C_5H_{11}CHO$	75	76	24	—

[a] Reactant ratio; **3** : $Ti(O\text{-}i\text{-}Pr)_4$: i-PrMgBr: carbonyl compound=1.0:1.3:2.5:1.3. [b] Isolated yield based on **3**.
[c] Determined by ^1H-NMR analysis of the crude reaction mixture. [d] Ketone was used instead of aldehyde.

Several aspects of the reaction as revealed in Table 1 deserve further comment. The titanium complexes **2a, b, c** generated from $Me_3SiC{\equiv}CCH_2OR'$ reacted with aldehydes and ketones to furnish the corresponding

4 almost exclusively regardless of R' (entries 1-5). Although $Ti(OPr^i)_2$-alkyne complexes derived from alkylsilylacetylenes provided mainly the product resulting from the carbonyl addition at the remote carbon from the silyl group, its regioselectivity was moderate as was observed by the production of the two regioisomers in 79:21 ratio in the reaction of the complex derived from 1-trimethylsilyl-1-hexyne with hexanal.[1] The fact that the complex **2e** preferentially reacted with an aldehyde at the remote carbon having a phenyl group (entry 7) strongly indicates the regio-controlling nature of the α-alkoxylalkyl group because $Ti(OPr^i)_2$-phenylalkylacetylene complexes were found to react preferentially with an aldehyde at the carbon having the phenyl group.[1] The finding that the titanium-homopropargylic ether complex **2i** did not show especially high regioselectivity (entry 11) might suggest that the regio-controlling nature of the α-alkoxyalkyl group is attributable to its electronic character.

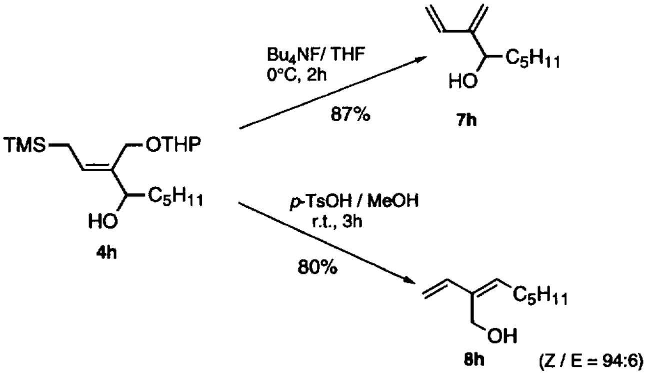
The iodionolysis of the reaction product of **2a** with C_2H_5CHO shown in eq 1 not only indicates the formation of the titanacycle [A] in the present reaction but also the synthetic usefulness of the reaction.



(1)

The application of the allyl alcohols **4**, which have now become readily accessible, in organic syntheses is currently underway in our laboratory, and the reactions shown in Scheme 2 demonstrate one of such applications; treatment of **4h** with Bu_4NF in THF or *p*-TsOH in MeOH resulted in the regiospecific Peterson olefination reaction leading to **7h** or **8h**, respectively, in excellent yields. Highly stereoselective formation of **8h** with Z-stereochemistry is also noteworthy. The combination of the reactions shown in Schemes 1 and 2 starting from **3h** provides a highly efficient method for synthesizing 1,3-butadiene having an α-hydroxyalkyl moiety at the 2-position as well as 1,3-alkadiene having a hydroxymethyl group at the 3-position, both of which have been accepted as useful synthetic intermediates.[8]

Scheme 2



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4. The reaction of **2a** with HCHO afforded complicated mixtures including the corresponding **4** in 18% yield.
5. A typical procedure is as follows: to a stirred solution of **2a** (0.097 g, 0.46 mmol) and $Ti(OPr^i)_4$ (0.171 g, 0.60 mmol) in ether (3.5 ml) was added ^{i}PrMgBr (2.27 M in ether, 0.50 ml, 1.15 mmol) at -78 °C. The resulting yellow solution was warmed to -50 °C over 1 h, during which period its color turned brown. After stirring at the same temperature for 2 h, hexanal (0.060 g, 0.60 mmol) was added at -78 °C and the stirring was continued for 30 min at -78 °C. Then the reaction mixture was warmed to 0 °C over 30 min and quenched with 1 N HCl (2.5 ml). The organic layer was separated and the aqueous layer was extracted with ether. 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 the corresponding **4** (0.113 g) in 78%.
6. Synthesis of **5** from propargyl alcohols can be readily carried out using hydromagnesiation reaction. see: Sato, F.; Ishikawa, H.; Watanabe, H.; Miyake, T.; Sato. M. *J. Chem. Soc. Chem. Commun.* **1981**, *22*, 718-720; Sato, F.; Watanabe, H.; Tanaka, Y.; Sato, M. *J. Chem. Soc. Chem. Commun.* **1982**, 1126-1127; Sato, F.; Kobayashi, Y. In *Organic Synthesis*; Paquette, L. A., Ed.; John Wiley & Sons Inc.: New York, 1990; Vol. 69, pp. 106-112.
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