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Generation and Reactions of Low-Valent Titanium Alkoxide-Acetylene Complexes. A Practical Preparation of Allyl Alcohols

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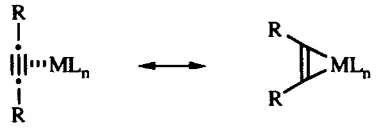
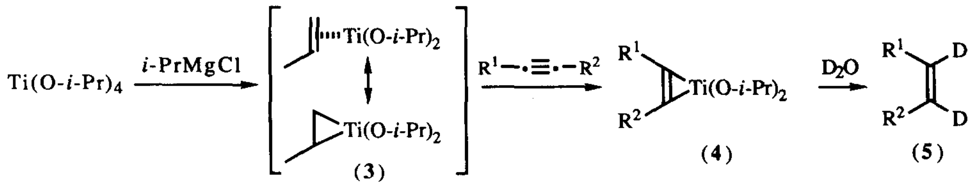
Abstract: *Low-valent titanium alkoxide prepared from Ti(O-i-Pr)4 and i-PrMgCl (1:2) incorporates acetylene to give an acetylene complex, titanacyclopropene, as evidenced by its reaction with deuterium oxide. Carbonyl compounds likewise reacted with the acetylene complex to give allyl alcohols. Introduction of two different electrophiles at each of both acetylenic termini was possible in a regio- and stereo-selective manner.*

Transition metal-acetylene complexes of the type **1** and/or **2** have attracted much interest recently as reaction intermediates or as stoichiometric reagents. Among them, Cp_2Ti-, Cp_2Zr-, Cl_nNb-, and Cl_nTa-acetylene complexes are frequently used in organic synthesis.[1] However, alkoxy complexes such as $(RO)_nZr$- or $(RO)_nTi$-acetylene complexes, which may be prepared from more economical starting materials, have not been utilized yet.



(1) (2)

Herein we wish to disclose efficient and practical method for the synthesis of alkoxytitanium-acetylene complex **4** (eq 1). The procedure is operationally simple: *i*-PrMgCl (2 equiv to the titanium) is added to an ethereal solution of Ti(O-*i*-Pr)$_4$ and an acetylene at -78 °C and the mixture is then stirred at -50 °C. The reaction most likely proceeds via a ligand exchange reaction between a low-valent titanium alkoxide[2] (likely exsisting as its propylene complex **3**)[3,4,5] and an acetylene.



(1)

Table 1. Generation and Deuteration of the Titanium Complex **4**[a]

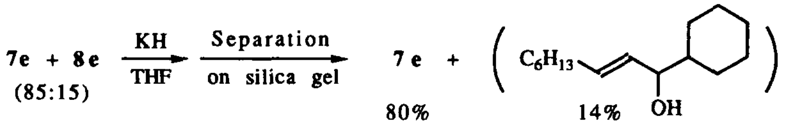
Entry	R^1	R^2	Period[b] (h)	**4**/**5**	Yield of **5** (%)[c,d]	Incorporation of D[e]			Z:E[c]
						d_2	d_1	d_0	
1	C_5H_{11}	C_5H_{11}	2	**a**	93 (81)	96	3	1	>99: 1
2	C_6H_{13}	Me	2	**b**	100	100	0	0	>99: 1
3	C_6H_{13}	CH_2OEE[f]	2	**c**	100(96)	94	6	0	>99: 1
4	Ph	Me	2	**d**	74	>86	- <14 -		>99: 1
5	Ph	Ph	2	**e**	(96)	>91	- <9 -		99.4: 0.6
6	Me_3Si	C_6H_{13}	2	**f**	94 (89)	96	4	0	>99: 1
7	Me_3Si	Me_3Si	5	**g**	100	100	0	0	>99: 1

[a] Reactant ratio: $Ti(O\text{-}i\text{-}Pr)_4$:$i$-PrMgCl:acetylene=1:2.5:0.8. In these experiments, a slight excess of the Grignard reagent (2.5 equiv to$Ti(O\text{-}i\text{-}Pr)_4$) was used to insure a complete reaction. [b] With respect to the generation of **4** (see text). [c] Determined by ^1H NMR and/or GC analysis. [d] Isolated yields in parentheses. [e] Determined by ^1H NMR and/or GC-MS analysis. [f] EE: 1-ethoxyethyl.

Although isolation and characterization of **4** were unsuccessful at present, the formation of **4** was verified by its reaction with deuterium oxide, which cleanly gave bis-deuterated alkene **5** in good yields with pure *Z* configuration as well as the high isotopic purities (Table 1). Terminal acetylenes failed to participate in the present reaction.

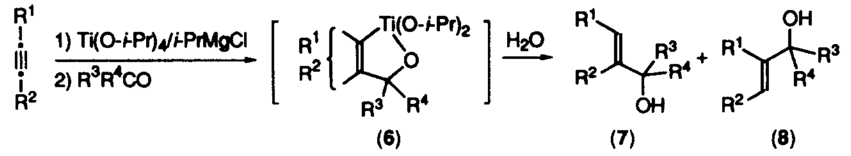
The acetylene complexes **4** were also reactive enough towards carbonyl compounds to give allyl alcohols (Table 2).[6,7] The addition step was completed at a temperature as low as -75 - -70 °C for a few hours. The reaction of **4** with carbonyl compounds cleanly stopped at the stage of the single addition to give the 1:1 adduct (**7** and **8**) in good yields due probably to the formation of less reactive alkenyltitanium species **6** (*vide infra*). No allylic diol arising from the double addition of a carbonyl compound was observed. The stereochemical assignments of the products were made based on the above deuteration experiments as well as comparison with authentic samples in a couple of cases.[8] In the case of unsymmetrical acetylenes, a regiochemical problem arises. It is interesting to note that **4** generated from a phenylacetylene preferentially reacted with an aldehyde at the carbon having the phenyl group (entries 2 and 3), while **4** from a silylacetylene gave a major product resulting from the reaction at the remote carbon from the silyl group (entries 4-12). Aldehydes having a normal alkyl chain afforded a mixture of **6** and **7** in a 79:21 ratio (entry 4), which was somewhat improved in the case of α-branched aldehydes (entries 2, 3, 5, 6, and 7). Crotonaldehyde and benzaldehyde showed much higher regioselectivities (entries 8 and 9). An excellent regioselectivitiy of 96:4 was also attained in the reaction of silylated titanacyclopropene **4f** and a ketone (entries 10-12). In addition to the generality of the present reaction as shown above, the titanium complex **4f** has an ability to discriminate between ketone and ester (entry 12) as other organotitanium reagents can.[9]

When a silylacetylene gave an inseparable mixture of the regioisomeric products **7** and **8**, hydroxy-assisted, selective desilylation was found to be useful for a facile separation of the minor isomer as illustrated in eq 2.[10]



(2)

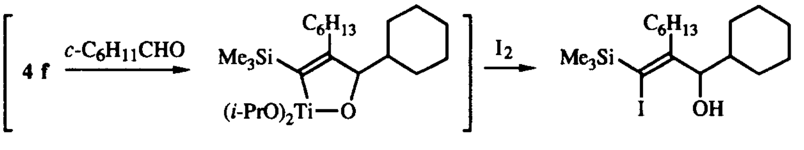
Table 2. Reaction of Titanium-Acetylene Complex with Carbonyl Compounds



Entry	R^1	R^2	R^3R^4CO	6/7/8	Yield (%)[a] Based on acetylene[b]	Yield (%)[a] Based on R^3R^4CO[c]	Ratio 7:8
1	C_5H_{11}	C_5H_{11}	cyclohexanecarbaldehyde	a	70		--
2	Ph	Me	"	b	81		16:84
3			"	"		90	14:86
4	Me_3Si	C_6H_{13}	hexanal	c	79		79:21
5			2-methylbutanal	d	84[d]		86:14
6			cyclohexanecarbaldehyde	e	86		85:15
7			"	"		84	86:14
8			crotonaldehyde	f	72		96: 4
9			benzaldehyde	g	47		93: 7
10			cyclohexanone	h	84		96: 4
11			"	"		83	96: 4
12			methyl 4-oxopentanoate	i	83[e]		exclusively 7
13	Me_3Si	Me_3Si	cyclohexanecarbaldehyde	j	70		--

[a] Isolated yield of a mixture of 7 and 8. [b] Reactant ratio: $Ti(O\text{-}i\text{-}Pr)_4$:i-PrMgCl:acetylene:$R^3R^4CO$=1:2.5:0.8:1. [c] Reactant ratio: $Ti(O\text{-}i\text{-}Pr)_4$:i-PrMgCl:acetylene:$R^3R^4CO$=1:2:1:0.7. [d] The major regioisomer was a 62:38 mixture of diastereoisomers. [e] The reaction took place at the ketone moiety and the product isolated was the corresponding lactone, 5-hexyl-4-methyl-7-(trimethylsilyl)-5-hexen-4-olide.

The presence of intermediate alkenyltitanium species **6**[11] before the aqueous workup of the reaction mixture was confirmed by its interception with iodine at -70 °C to room temperature to give the alkenyl iodide **9** and a small amount of its regioisomer (eq 3), the ratio of which was parallel to that of the protonated products as shown in entry 6, Table 2. Regio- and stereo-chemical assignments of **9** were unambiguously made by its conversion to **7e** via iodine/lithium exchange with *t*-BuLi and subsequent protonation. This reaction clearly demonstrated that double functionalization and/or carbon-carbon bond formation at the acetylene moiety was, in fact, possible with two different electrophiles.



(3)

In summary, the new low-valent titanium alkoxide-acetylene complex reported herein has the following advantageous feature: i) the starting materials, $Ti(O\text{-}i\text{-}Pr)_4$ and the Grignard reagent, are cheap and available in bulk, ii) the reaction shows good regio- stereo- and chemo-selectivities, and iii) a sequential reaction with two different electrophiles is feasible.

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4. At our hands, the use of isopropyl Grignard reagent for the generation of **3** was superior to other reagents such as ethyl Grignard reagent. See ref 5 for more details about this issue.
5. Other applications of this species: "A New Efficient Method for Synthesis of Allyltitanium Compounds from Allyl Halides or Allyl Alcohol Derivatives via Oxidative Addition Reaction. A Highly Efficient and Practical Synthesis of Homoallyl Alcohols," Kasatkin, A.; Nakagawa, T.; Okamoto, S.; Sato, F. *J. Am. Chem. Soc.* in press; "Highly Efficient Synthesis of Propargyl- and Allenyltitanium Reagents from Propargyl Halides or Propargyl Alcohol Derivatives. Practical Synthesis of Allenyl and Homopropargyl Alcohols," Nakagawa, T.; Kasatkin, A.; Sato, F. *Tetrahedron Lett.* in press.
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7. Preparation of **7h** (Table 1, entry 11) is typical. To a stirred solution of Ti(O-*i*-Pr)$_4$ (0.22 mL, 0.75 mmol) and 1-trimethylsilyl-1-octyne (0.14 g, 0.75 mmol) in ether (8.0 mL) was added a 1.25 M ethereal solution of *i*-PrMgCl (1.2 mL, 1.5 mmol) at -78 °C to give a yellow homogeneous mixture. The solution was warmed to -50 °C over 0.5 h, during which period its color turned brown. After stirring at the same temperature for 2 h, cyclohexanone (0.054 mL, 0.53 mmol) was added at -78 °C and the stirring was continued for 1 h at -75 - -70 °C. Then the reaction mixture was quenched with water (0.80 mL), allowed to warm to room temperature, and filtered through a short pad of Celite. The filtrate was dried over MgSO$_4$ and was concentrated *in vacuo* to give an oil. ^{1}H NMR analysis of this crude sample showed the presence of **7h** and **8h** in a ratio of 96:4. Purification on silica gel afforded a pure 96:4 mixture of **7h** and **8h** (0.12 g, 83%).
8. The alcohol **7a** is a known compound (ref 6f). The ^{1}H and ^{13}C NMR data of **7h** were compared to those of the known, homologous compound having decyl instead of hexyl group as R^2 (ref 6f) and these were in good agreement except the alkyl part.
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