

Preparation of Titanated Alkoxyallenes from 3-Alkoxy-2-propyn-1-yl Carbonates and $(\eta^2\text{-Propene})\text{Ti}(\text{O-}i\text{-Pr})_2$ as an Efficient Ester Homoaldol Equivalent

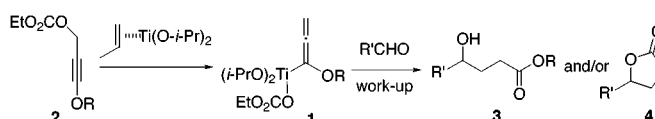
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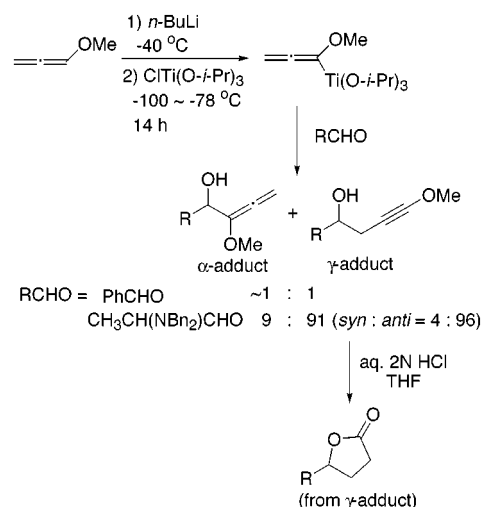
ABSTRACT



3-Alkoxy-2-propyn-1-yl carbonates (**2**) react with a divalent titanium reagent $(\eta^2\text{-propene})\text{Ti}(\text{O-}i\text{-Pr})_2$ to afford titanated alkoxyallenes **1** which, in turn, react with aldehydes regioselectively to provide the corresponding γ -addition products in good to excellent yields, thus affording a convenient method for synthesizing γ -hydroxy esters **3** and/or γ -butyrolactones **4**.

In 1993, titanated methoxyallene was introduced as a novel ester homoenolate equivalent. Thus, Dorsch and co-workers reported that successive treatment of methoxyallene with *n*-butyllithium and $\text{ClTi}(\text{O-}i\text{-Pr})_3$ furnishes titanated methoxyallene and that this reacts with some aldehydes with excellent regioselectivity to afford, after acidic hydration of the addition product, the corresponding γ -lactone as shown in Scheme 1.^{1–3} However, this method suffers from two drawbacks. First, to achieve a satisfactory yield and high γ -selectivity, the transmetalation reaction step from the lithium to the titanium needs to be carried out for as long as 14 hours at very low temperatures of -100 to -78 °C. Second, the regioselectivity is highly dependent on aldehydes; while the reaction with α -amino aldehydes afforded γ -addition products highly predominantly, the reaction with

Scheme 1



benzaldehyde provided almost equal amounts of the α - and γ -addition products (see Scheme 1).

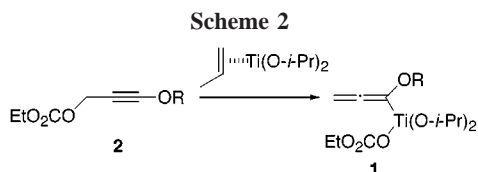
Recently, we developed an efficient and practical method for preparing allenyltitanium complexes by the reaction of

(1) Hormuth, S.; Reissig, H.-U.; Dorsch, D. *Angew. Chem., Int. Ed. Engl.* **1993**, 32, 1449.

(2) Titanium ester homoenolates: Nakamura, E.; Oshino, H.; Kuwajima, I. *J. Am. Chem. Soc.* **1986**, 108, 3745. Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1983**, 105, 651. Goswami, R. *J. Org. Chem.* **1985**, 50, 5907.

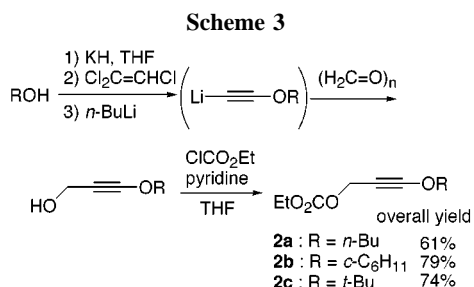
(3) Reviews for homoenolates and their equivalents, see: Kuwajima, I.; Nakamura, E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 2, p 441. Kuwajima, I.; Nakamura, E. *Top. Curr. Chem.* **1990**, 155, 1. Ryu, I.; Sonoda, N. *Synth. Org. Chem., Jpn.* **1985**, 43, 112. Werstiuk, N. H. *Tetrahedron* **1983**, 39, 205. Katritzky, A. R.; Piffel, M.; Lang, H.; Anders, E. *Chem. Rev.* **1999**, 99, 665. See also: Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1984**, 23, 932.

propargyl alcohol derivatives such as acetates or carbonates with the divalent titanium reagent (η^2 -propene)Ti(O-*i*-Pr)₂, generated in situ from Ti(O-*i*-Pr)₄ and 2 equiv of *i*-PrMgX, which proceeds via an oxidative addition pathway.^{4,5} We anticipated that titanated alkoxyallenes **1** with a different kind of alkoxy group might be prepared from (η^2 -propene)Ti(O-*i*-Pr)₂ and readily available 3-alkoxy-2-propyn-1-yl carbonates (**2**) (Scheme 2) and that among the obtained titanated



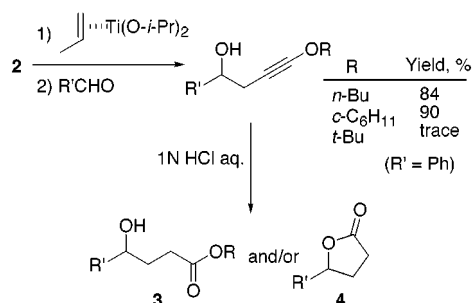
alkoxyallenes we could find one having the proper OR moiety which would react with aldehydes with excellent γ -selectivity, irrespective of the aldehyde.

The compounds **2a**, **2b**, and **2c** where RO is *n*-BuO, *c*-C₆H₁₁O, and *t*-BuO, respectively, were synthesized starting from 1,1,2-trichloroethylene, paraformaldehyde, and the corresponding alcohol according to the reported two-step reaction sequence shown in Scheme 3.⁶ The successive



treatment of **2a** or **2b** with (η^2 -propene)Ti(O-*i*-Pr)₂ and benzaldehyde provided the corresponding γ -addition product exclusively in excellent yield as shown in Scheme 4 (α -addition product was not observed); however, the anticipated titanated alkoxyallene was scarcely generated from **2c** under the same reaction conditions presumably due to the larger steric requirement of the tertiary alkoxy group. The γ -addition products obtained here could be easily converted to

Scheme 4



the corresponding γ -hydroxy ester **3** and/or γ -lactone **4** by treatment with aqueous 1 N HCl as shown in Scheme 4. These results strongly indicated that titanated alkoxyallenes **1** with primary and secondary alkoxy groups can be readily prepared from the corresponding **2** and that they serve as an efficient ester homoenolate equivalent. Compound **2a** seemed to be somewhat unstable for column chromatography on silica gel, and thus, the isolated yield of **2a** was lower than that of **2b** as shown in Scheme 3. We, therefore, used titanium reagent **1b** derived from **2b** for further reaction with other aldehydes. The results are summarized in Table 1.

Table 1. Reaction of Alkoxyallenyltitanium **1b** with Carbonyl Compounds

Entry	Carbonyl Compound	Work-up ^a	Product(s) [3 : 4]	Total Yield %
1	PhCHO	A	3 + 4 [3 : 1]	81
2		B	4	72
3	<i>n</i> -C ₇ H ₁₅ CHO	A	3 + 4 [3 : 1]	77
4		B	4	70
5	<i>c</i> -C ₆ H ₁₁ CHO	B	4	74
6		A	—	trace
7 ^b	<i>p</i> -NCC ₆ H ₄ CHO	B	4	52
8	<i>p</i> -AcOC ₆ H ₄ CHO	B	4	69
9		A	3 + 4 [3 : 1] ^c	78
10		A	3 (syn : anti = 6 : 94) ^d	76

^a Workup conditions: A, 1 N HCl (aq), THF, room temperature, 1 h; B, 1 N HCl (aq), THF, room temperature then, after extractive workup, the crude product was treated with NaH, THF, 0 °C to room temperature. ^b The aldehyde was added to the reaction mixture as a THF solution. ^c Both **3** and **4** thus obtained consist of two diastereomers in a ratio of 60:40. ^d Similar diastereoselectivity was reported in the reaction shown in Scheme 1.

It can be seen from Table 1 that **1b** reacts with a variety of aldehydes at the γ -position exclusively, thus affording **3**

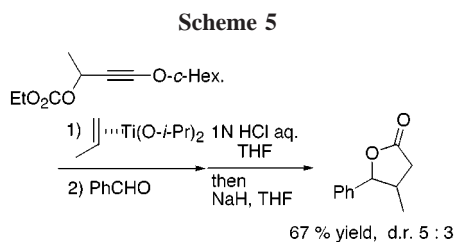
(4) Nakagawa, T.; Kasatkin, A.; Sato, F. *Tetrahedron Lett.* **1995**, 36, 3207. Yoshida, Y.; Nakagawa, T.; Sato, F. *Synlett* **1996**, 437. Kasatkin, A.; Sato, F. *Angew. Chem., Int. Ed. Engl.* **1996**, 35, 2848. An, D. K.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1998**, 39, 4861. An, D. K.; Hirakawa, K.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1999**, 40, 3737. Okamoto, S.; An, D. K.; Sato, F. *Tetrahedron Lett.* **1998**, 39, 4551. An, D. K.; Okamoto, S.; Sato, F. *Tetrahedron Lett.* **1998**, 39, 4555.

(5) For reviews for synthetic reactions mediated by (η^2 -propene)Ti(O-*i*-Pr)₂, see: Sato, F.; Urabe, H.; Okamoto, S. *Pure Appl. Chem.* **1999**, 71, 1511. Sato, F.; Urabe, H.; Okamoto, S. *Synlett* **2000**, 753. Sato, F.; Urabe, H.; Okamoto, S. *J. Synth. Org. Chem. Jpn.* **1998**, 56, 424.

(6) Porter, N. A.; Dussault, P.; Breyer, R. A.; Kaplan, J.; Morelli, J. *Chem. Res. Toxicol.* **1990**, 3, 236. Moyano, A.; Charbonnier, F.; Greene, A. E. *J. Org. Chem.* **1987**, 52, 2919.

and/or **4** in excellent yield. However, ketones did not react even though the reaction temperature was warmed to room temperature, presumably owing to their steric hindrance (entry 6). The results shown in Table 1 indicate the following other characteristic features of the reaction: **1b** works as highly chemoselective ester homoenolate equivalent; thus, functional groups present in aldehydes such as a cyano or an ester group were tolerated (entries 7 and 8). For the diastereoselectivity of the reaction with α -substituted aldehydes, the reaction with α -amino aldehydes proceeded with high diastereoselectivity to afford an *anti*-addition product highly predominantly (entry 10), as is the case shown in Scheme 1,¹ while α -silyloxy aldehydes gave a rather low selectivity (entry 9).

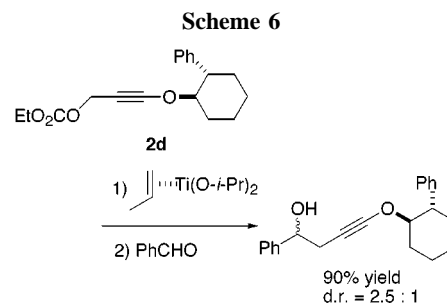
The reaction can be extended to the preparation of a β -substituted ester homoenolate equivalent. Thus, as shown in Scheme 5, reaction of the carbonates with a substituent



at the propargyl position with $(\eta^2\text{-propene})\text{Ti}(\text{O-}i\text{-Pr})_2$ and the following treatment with aldehydes afforded β,γ -disubstituted γ -lactones.⁷

Similarly, successive treatment of propargyl carbonate **2d** derived from *trans*-2-phenylcyclohexanol with $(\eta^2\text{-propene})\text{-Ti}(\text{O-}i\text{-Pr})_2$ and benzaldehyde afforded a diastereomeric

mixture of the corresponding addition products in a ratio of 2.5:1 (Scheme 6).^{7–9} Although the diastereoselectivity was



moderate, it may be improved by selecting a proper chiral alkoxy group, and further investigation to this end is underway in our laboratory.

In summary, a convenient ester homoenolate equivalent, titanated alkoxyallenes, can be readily prepared from 3-alkoxy-2-propyn-1-yl carbonates and $(\eta^2\text{-propene})\text{Ti}(\text{O-}i\text{-Pr})_2$.

Supporting Information Available: Experimental procedures and ^1H NMR and ^{13}C NMR data for compounds **2b**, **3** ($\text{R}' = \text{Ph}$), and **4** ($\text{R}' = \text{Ph}$). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(7) The starting carbonate for the reaction of Scheme 5 and Scheme 6 could readily be prepared from the corresponding alcohol and aldehyde according to a similar procedure shown in Scheme 3 in 70% and 72% overall yield, respectively.

(8) The ratio was determined by ^1H and ^{13}C NMR analyses. The stereochemistries of the products were not determined.

(9) For a review of chiral homoenolate equivalents, see: Ahlbrecht, H.; Beyer, U. *Synthesis* **1999**, 365.