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

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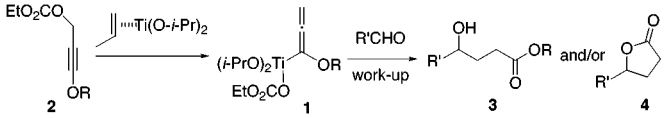
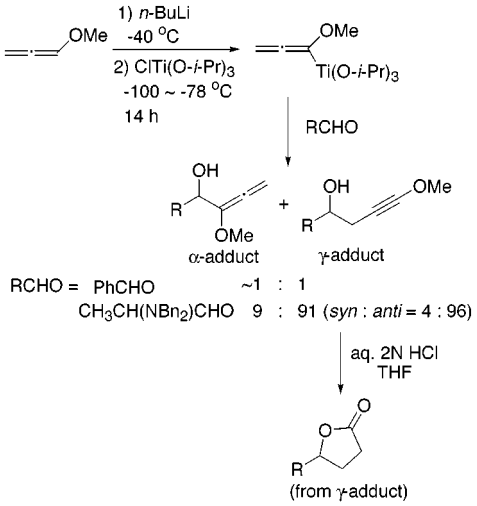
ABSTRACT



3-Alkoxy-2-propyn-1-yl carbonates (2) react with a divalent titanium reagent (η^2-propene)Ti(O-*i*-Pr)$_2$ to afford titanated alkoxyallenes 1 which, in turn, react with aldehydes regiospecifically 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 ClTi(O-*i*-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 benzaldehyde provided almost equal amounts of the α- and γ-addition products (see Scheme 1).

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.; Piffl, M.; Lang, H.; Anders, E. *Chem. Rev.* **1999**, *99*, 665. See also: Hoppe, D. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 932.

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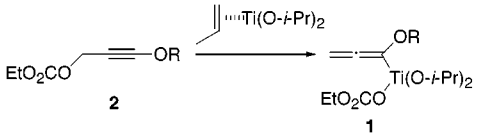
propargyl alcohol derivatives such as acetates or carbonates with the divalent titanium reagent (η^2-propene)Ti(O-*i*-Pr)$_2$, generated in situ from Ti(O-*i*-Pr)$_4$ and 2 equiv of *i*-PrMgX, which proceeds via an oxidative addition pathway.[4,5] We anticipated that titanated alkoxyallenes **1** with 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

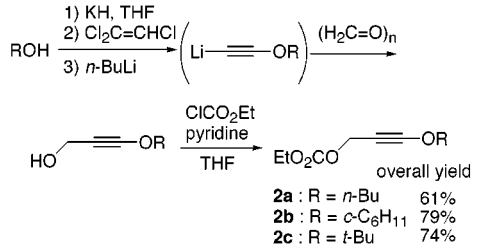
Scheme 2



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*-C$_6$H$_{11}$O, 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

Scheme 3



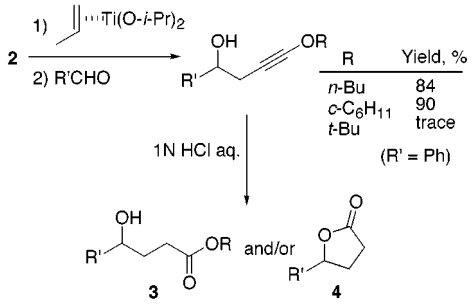
treatment of **2a** or **2b** with (η^2-propene)Ti(O-*i*-Pr)$_2$ and benzaldehyde provided the corresponding γ-addition product exclusively in excellent yield as shown in Scheme 4 (α-addition product was not observed); however, the anticipated titanated alkoxyallene was scarcely generated from **2c** 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

(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.

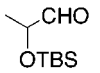
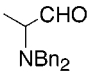
(6) Porter, N. A.; Dussault, P.; Breyer, R. A.; Kaplan, J.; Morelli, J. *Chem. Res. Toxicol.* **1990**, *3*, 236. Moyano, A.; Charbonnier, F.; Greene, A. E. *J. Org. Chem.* **1987**, *52*, 2919.

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	*n*-C$_7$H$_{15}$CHO	A	**3** + **4** [3 : 1]	77
4		B	**4**	70
5	*c*-C$_6$H$_{11}$CHO	B	**4**	74
6		A	—	trace
7[b]	*p*-NCC$_6$H$_4$CHO	B	**4**	52
8	*p*-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

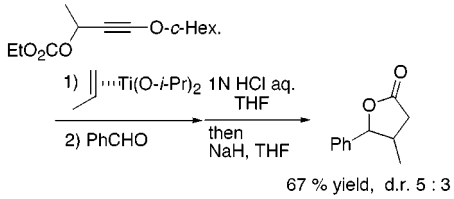
[a] Workup conditions: A, 1 N HCl (aq), THF, room temperature, 1 h; B, 1 N HCl (aq), THF, room temperature then, after extractive workup, the crude product was treated with NaH, THF, 0 °C to room temperature. [b] The aldehyde was added to the reaction mixture as a THF solution. [c] Both **3** and **4** 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**

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 diasteroselectivity 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

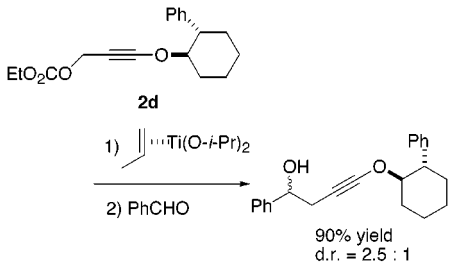
Scheme 5



at the propargyl position with (η^2-propene)Ti(O-*i*-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 (η^2-propene)-Ti(O-*i*-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

Scheme 6



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 (η^2-propene)Ti(O-*i*-Pr)$_2$.

Supporting Information Available: Experimental procedures and ^{1}H NMR and ^{13}C NMR data for compounds **2b**, **3** (R′ = Ph), and **4** (R′ = 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 ^{1}H 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.