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Preparation of *syn*-Tertiary Homoallylic Alcohols Utilizing Allenyltitanocenes Generated by Reductive Titanation of γ-Trimethylsilylpropargylic Carbonates

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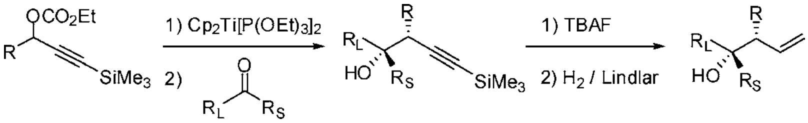
ABSTRACT



***syn*-Tertiary homoallylic alcohols were obtained by the reaction of α-silylallenyltitanocenes generated by the reductive titanation of γ-silylpropargylic carbonates with $Cp_2Ti[P(OEt)_3]_2$ with ketones and following desilylation and partial hydrogenation. High diastereoselectivity was observed when aromatic and α,β-unsaturated ketones were employed.**

Recently, much attention has been paid to the stereocontrolled construction of adjacent stereogenic centers. Addition of allylmetal species to ketones, therefore, has been extensively studied as a useful tool for the stereoselective preparation of *anti*-homoallylic alcohols bearing a quaternary center.[1] We have studied the reaction of allyltitanocenes generated by the reductive titanation of allylic sulfides or related allylic substrates with a titanocene(II) species with ketones. With this protocol, *anti*-tertiary homoallylic alcohols were obtained with unprecedentedly high diastereoselectivity even when sterically less congested methyl ethyl ketone and methyl vinyl ketone were employed.[2] In contrast to the preparation of *anti*-tertiary homoallylic alcohols, there are only a few reports on the diastereoselective preparation of *syn*-counterparts.[3−5] Knochel et al., for example, have recently achieved a highly diastereoselective preparation of *syn*-tertiary homoallylic alcohols by the reaction of β-silyl substituted crotylzinc reagents with acetophenone derivatives and subsequent desilylation.[3] Our recent results on the three-component coupling of thioacetals, alkynyl sulfones, and carbonyl compounds[6] prompted us to develop a new route to *syn*-tertiary homoallylic alcohols **1** utilizing γ-silylpropargyl carbonates **2** as starting materials (Scheme 1). Our new approach consists of the reaction of α-silylallenyltitanocenes **3**, generated by the reductive titanation of **2** with the

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(1) (a) Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; Chapter 10. (b) Chemler, S. R.; Roush, W. R. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: Weinheim, 2000; Chapter 11. (c) Risch, N.; Arend, M. In *Stereoselective Synthesis, Methods of Organic Chemistry (Houben-Weyl)*; Helmchen, G., Hoffmann, R., Mulzer, J., Schaumann, E., Eds.; Thieme: Stuttgart, 1996; Vol. 3, pp 1357−1602. (d) Szymoniak, J.; Moïse, C. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, 2002; Chapter 13. (e) Dunet, G.; Mayer, P.; Knochel, P. *Org. Lett.* **2008**, *9*, 117–120. (f) Ren, H.; Dunet, G.; Mayer, P.; Knochel, P. *J. Am. Chem. Soc.* **2007**, *129*, 5376–5377. (g) Li, S. W.; Batey, R. A. *Chem. Commun.* **2004**, 1382–1383. (h) Yasuda, M.; Hirata, K.; Nishino, M.; Yamamoto, A.; Baba, A. *J. Am. Chem. Soc.* **2002**, *124*, 13442–13447. (i) Thadani, A. N.; Batey, R. A. *Org. Lett.* **2002**, *4*, 3827–3830. (j) Kataoka, Y.; Makihara, I.; Yamahata, T.; Tani, K. *Organometallics* **1997**, *16*, 4788–4795. (k) Yamamoto, Y.; Yatagai, H.; Naruta, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1980**, *102*, 7107–7109.

(2) Yatsumonji, Y.; Nishimura, T.; Tsubouchi, A.; Noguchi, K.; Takeda, T. *Chem.*—*Eur. J.* **2009**, *15*, 2680–2686.

(3) Helm, M. D.; Mayer, P.; Knochel, P. *Chem. Commun.* **2008**, 1916–1917.

(4) Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8910–8911.

(5) Hayashi, N.; Honda, H.; Yasuda, M.; Shibata, I.; Baba, A. *Org. Lett.* **2006**, *8*, 4553–4556.

(6) Takeda, T.; Ando, M.; Sugita, T.; Tsubouchi, A. *Org. Lett.* **2007**, *9*, 2875–2878.

10.1021/ol100395n

Scheme 1

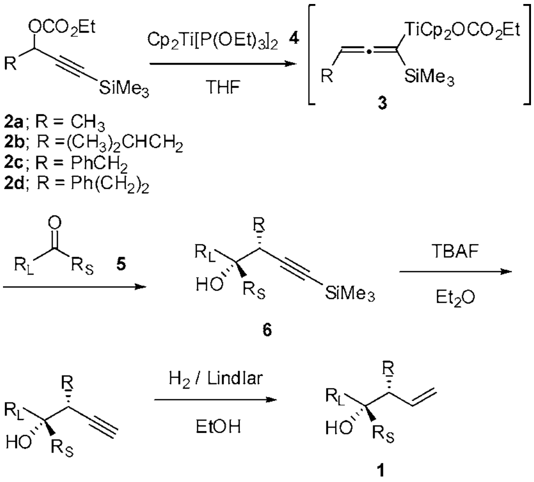
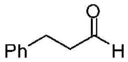
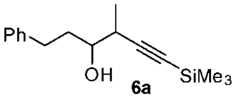
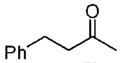
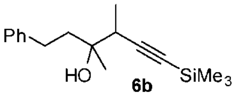
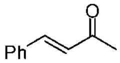
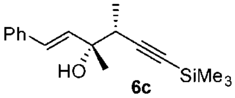
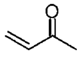
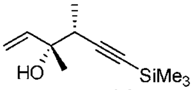
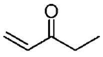
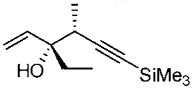
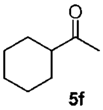
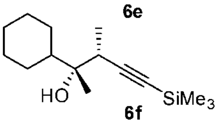
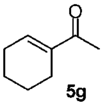
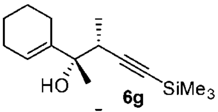
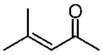
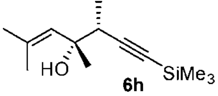
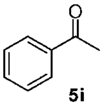
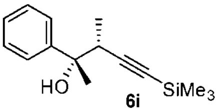
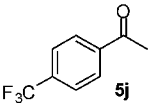
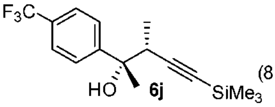
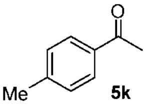
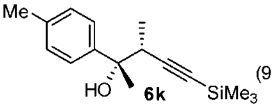
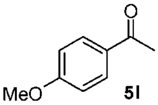
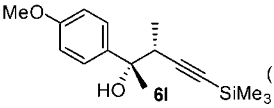


Table 1. Preparation of Homopropargylic Alcohols **6** Utilizing Propargylic Carbonate **2a**[a]

entry	carbonyl compound **5**	homopropargylic alcohol **6**	yield/%[b] (*syn*:*anti*[c])
1[d]	 **5a**	 **6a**	54[e] (53:47[f])
2	 **5b**	 **6b**	72 (64:36[f])
3	 **5c**	 **6c**	53 (85:15)
4[d]	 **5d**	 **6d**	39[e] (72:28)
5[d]	 **5e**	 **6e**	49[e] (81:19)
6	 **5f**	 **6f**	70 (57:43)
7	 **5g**	 **6g**	76 (79:21)
8	 **5h**	 **6h**	51 (95:5)
9	 **5i**	 **6i**	65 (87:13)
10	 **5j**	 **6j**	67 (81:19)
11	 **5k**	 **6k**	63 (90:10)
12	 **5l**	 **6l**	72 (95:5)

[a] Carried out using **2** (1.2 equiv) and **4** (1.8 equiv). [b] Isolated yield based on **5** used. [c] Determined by GLC analysis. [d] Carried out using **4** (1.5 equiv) and **5** (2 equiv). [e] Based on **2** used. [f] Ratio of diastereomers.

titanocene(II) reagent Cp$_2$Ti[P(OEt)$_3$]$_2$ **4**, with ketones **5** followed by desilylation and partial hydrogenation of the triple bond of the resulting δ-silylhomopropargylic alcohols **6**.

We first examined the regio- and diastereoselectivity of the addition of organotitanium species **3** to various carbonyl compounds **5** (Table 1). The treatment of allenyltitanium species **3a** generated from the propargyl carbonate **2a** with hydrocinnamaldehyde (**5a**) at 0 °C for 2 h regioselectively gave the homopropargyl alcohol **6a** as an almost 1:1 mixture of the diastereomers (entry 1). A similar reaction using the aralkyl methyl ketone **5b** produced the homopropargyl alcohol **6b** with moderate diastereoselectivity (entry 2). It is of interest that high *syn*-stereoselectivity was observed in the reaction of α,β-unsaturated ketone **5c** (entry 3). The same tendency of diastereoselectivity was also seen in the reactions of cyclic ketones **5f** and **g** (entries 6 and 7). Similarly to the α,β-unsaturated ketones, the reactions of acetophenones **5i**−**l** produced the homopropargylic alcohols **6i**−**l** with high *syn*-selectivity. The diastereoselectivity of these reactions was found to be dependent on the substituent on the aromatic ring; the *syn*-homopropargyl alcohol **6l** was obtained with high diastereoselectivity (95%), whereas the reaction of the acetophenone bearing an electron-withdrawing trifluoromethyl group gave the alcohol **6j** with lower selectivity (entries 10 and 12).

Several propargylic carbonates **2b**−**d** having an α-substituent other than a methyl group were also subjected to the titanocene(II)-promoted reaction with unsaturated ketones (Table 2). Over 85% diastereoselectivity in favor of the formation of *syn*-homopropargylic alcohols was achieved in these reactions.

The *syn*-tertiary homopropargylic alcohols **6**, separated from the *anti*-isomers, were successfully transformed into homoallylic alcohols **1** by the desilylation with tetrabutylammonium fluoride and subsequent hydrogenation using a Lindlar's catalyst (Table 3).

The stereochemistry of the homopropargylic alcohols **6** was determined as follows (details are provided in the Supporting Information). The *syn*-configuration of **6c** was unambiguously confirmed by X-ray single-crystal structural analysis after transformation into its pivalate. The configuration of propargylic alcohols **6f**,[7] **i**,[2] **p**[2] was determined at the stage of homoallylic alcohols **1** by comparison with the authentic *anti*-tertiary homoallylic alcohols.

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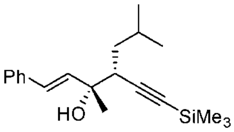
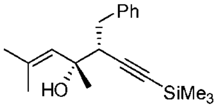
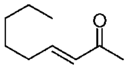
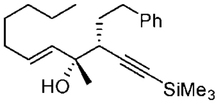
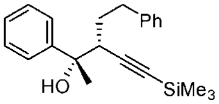
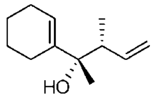
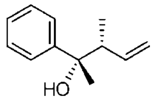
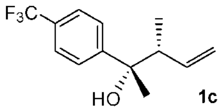
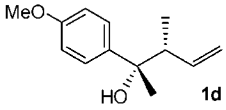
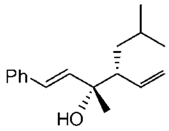
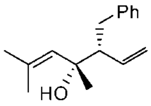
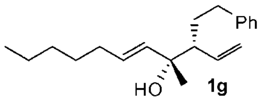
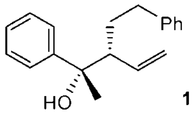
(7) Seebach, D.; Widler, L. *Helv. Chim. Acta* **1982**, *65*, 1972–1981.

Table 2. Preparation of Homopropargylic Alcohols **6** Utilizing Propargylic Carbonates **2b**−**d** Having an α-Substituent Other Than Methyl Group[a]

entry	propargylic carbonate **2**	carbonyl compound **5**	homopropargylic alcohol **6**		yield/%[b] (*syn*:*anti*[c])
1	**2b**	**5c**		**6m**	54 (85:15)
2	**2c**	**5h**		**6n**	53 (96:4)
3	**2d**	 **5m**		**6o**	73 (90:10)
4	**2d**	**5i**		**6p**	71 (100:0)

[a] Carried out using **2** (1.2 equiv) and **4** (1.8 equiv). [b] Isolated yield based on **5** used. [c] Determined by GLC analysis.

Table 3. Transformation of Homopropargylic Alcohols **6** into Homoallylic Alcohols **1**

entry	homopropargylic alcohol **6**	homoallylic alcohol **1**		overall yield/%[a]
1	**6g**		**1a**	73
2	**6i**		**1b**	90
3	**6j**		**1c**	94
4	**6l**		**1d**	58
5	**6m**		**1e**	80
6	**6n**		**1f**	81
7	**6o**		**1g**	72
8	**6p**		**1h**	84

[a] Isolated yield.

The *syn*-stereochemistry of the homopropargylic alcohol **6g** was determined after transformation to **6f**. The homopropargylic alcohol **6j** was transformed into the lactone by hydroboration/oxidation of the corresponding homoallyl alcohol **1c** and further oxidation of the resulting diol with PCC.[2] The X-ray analysis of the lactone clearly supported the *syn*-stereochemistry of **6j**. Alternatively, the stereochemistry of the homopropargylic alcohol **6d** was determined by its transformation to the stereochemically well-defined 2,3-dimethyl-4-pentene-1,2-diol.[8] The stereochemistry of other homopropargylic alcohols **6e**,**h**,**k**,**l**−**o** was estimated to be *syn* in analogy with other homopropargylic alcohols.

The reaction of allenylmetals with carbonyl compounds has been well studied.[9] Although highly diastereoselective addition of the allenylmetals to ketones has not appeared, various diastereoselective reactions with aldehydes have been reported. Yamamoto and co-workers reported that the allenyltitaniums, generated by the lithiation of alkynes followed by transmetalation with Ti(O^{i}Pr)$_4$, react with aldehydes to produce *anti*-secondary homopropargylic alcohols with high diastereoselectivity.[10] The similar preferential formation of *anti*-homopropargylic alcohols was observed in the reaction of allenyltitaniums, generated by the treatment of propargyl substrates with a titanium reagent prepared from Ti(O^{i}Pr)$_4$ and ^{i}PrMgBr, with aldehydes.[11] The stereoselectivity is rationalized by the reaction pathway involving a six-membered-ring transition state. These reac-

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(8) Chen, Y.; Eltepu, L.; Wentworth, P., Jr. *Tetrahedron Lett.* **2004**, *45*, 8285–8288.

(9) For recent examples, see: (a) Justicia, J.; Sancho-Sanz, I.; Álvarez-Manzaneda, E.; Oltra, J. E.; Cuerva, J. M. *Adv. Synth. Catal.* **2009**, *351*, 2295–2300. (b) Yanagisawa, A.; Suzuki, T.; Koide, T.; Okitsu, S.; Arai, T. *Chem. Asian J* **2008**, *3*, 1793–1800, and references cited therein.

(10) Furuta, K.; Ishiguro, M.; Haruta, R.; Ikeda, N.; Yamamoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2768–2776.

(11) Nakagawa, T.; Kasatkin, A.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 3207–3210.

tions, however, cannot be applied to ketones, and hence, the diastereoselectivity of the formation of tertiary homopropargylic alcohols using allenytitanium reagents has remained obscure.

In contrast to the preferential formation of *anti*-secondary homopropargylic alcohols described above, high *syn*-selectivity was observed in the reaction of allenyltitanocenes **3** with aromatic and α,*β*-unsaturated ketones. Although, without further study on the reaction mechanism, it is difficult to rationalize all the stereochemical results of the present reaction, high *syn*-selectivity would be explained by assuming the stereochemical pathway involving noncyclic transition sates.

In conclusion, we have developed a new method for the preparation of *syn*-tertiary homoallylic alcohols utilizing allenyltitanium species generated by the reductive titanation of propargylic carbonates with the titanocene(II) reagent. The results described here clearly show that our approach using the allenyltitanocene species and unsaturated ketones is extremely useful for the stereoselective preparation of *syn*-tertiary homoallylic alcohols. Further study on the origin of high *syn*-selectivity observed in the reaction of allenyltitaniums with unsaturated ketones is currently underway.

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Supporting Information Available: Experimental procedures and characterization data of all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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