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Synthesis of Optically Active Allenyltitaniums Having Axial Chirality by the Reaction of Optically Active Propargylic Compounds with a Ti(O-*i*-Pr)4/2*i*-PrMgCl Reagent

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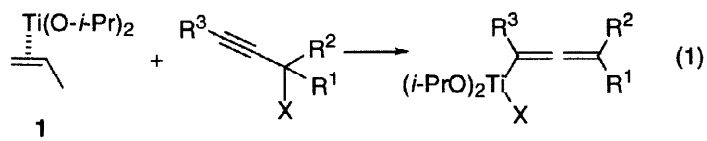
Abstract

The reaction of a titanium(II) complex (η^2-propene)Ti(O-*i*-Pr)$_2$, generated *in situ* from Ti(O-*i*-Pr)4 and 2 equiv of *i*-PrMgCl, with optically active secondary propargyl phosphate and tertiary propargyl carbonate proceeds with more than 97% chiral transfer, thus providing an efficient and practical method for synthesizing di- and tri-substituted allenyltitaniums with high optical purity.

Keywords: titanium and compounds;asymmetric synthesis;elimination;alcohols

Recently, we have revealed that the titanium(II) complex (η^2-propene)Ti(O-*i*-Pr)$_2$ (**1**), generated *in situ* by the reaction of Ti(O-*i*-Pr)4 with 2 equiv of *i*-PrMgX (X = Cl or Br),[1] reacts with propargyl alcohol derivatives *via* an oxidative addition pathway to give allenyltitanium complexes in excellent yields (eq 1).[2] With these results in hand, we anticipated that optically active allenyltitaniums having axial chirality might be obtained by starting with optically active propargyl alcohol derivatives and, thus, a new efficient asymmetric synthetic method might be developed.[3] We also expected that the stereochemical outcome of the reactions would provide valuable information on the mechanism of the reaction of eq 1.



1

X = OCO_2Et, $OP(O)(OEt)_2$

Optically active propargyl carbonates or phosphates **2-5**, readily prepared according to the reported procedure using the Katsuki and Sharpless asymmetric epoxidation as the key reaction,[4] were reacted with **1** and subsequently with benzaldehyde to afford the corresponding homopropargylic alcohols **6** as a mixture of two diastereomers. The absolute configuration of **6** was determined by derivatization to the known compound[5] while its

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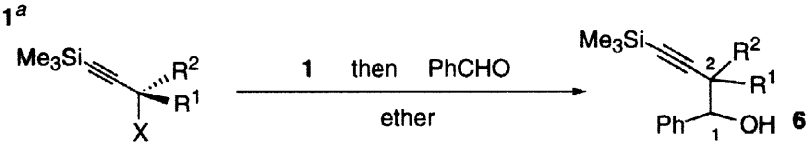
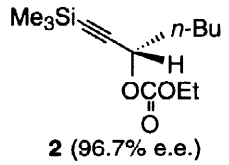
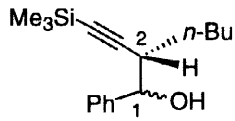
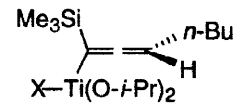
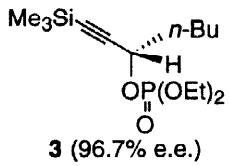
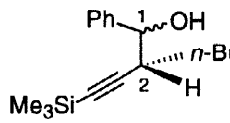
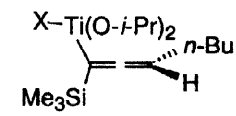
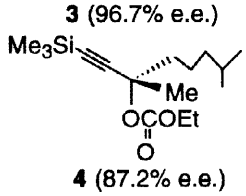
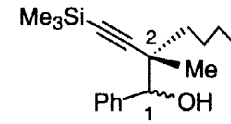
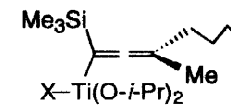
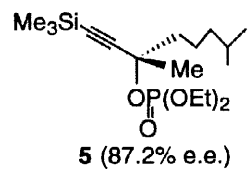
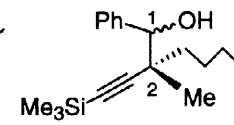
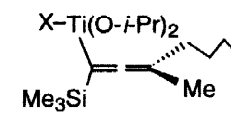
Table 1[a]



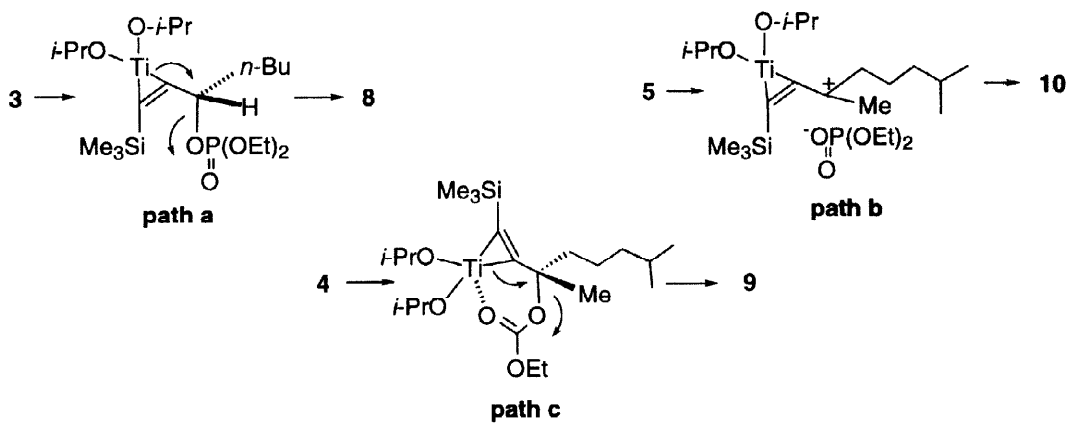
Entry	Substrate (e.e., %)[b]	Product 6[c] E.e., % / Configuration[d]	Structure of Major Isomer of Allenyltitanium E.e., %[e]
1	 **2** (96.7% e.e.)	 49[f] / (1*R*,2*S*) 49[f] / (1*S*,2*S*)	 **7** 49 (50)
2	 **3** (96.7% e.e.)	 94[f,g] / (1*S*,2*R*) 94[f,g] / (1*R*,2*R*)	 **8** 94 (97)
3	 **4** (87.2% e.e.)	 85[h] / (2*S*)	 **9** 85 (98)
4	 **5** (87.2% e.e.)	 8.3[h] / (2*R*)	 **10** 8.3 (9.5)

[a]Reaction conditions: substrate (0.5 mmol), Ti(O-*i*-Pr)$_4$ (0.75 mmol), *i*-PrMgCl (1.5 mmol) and ether (5 mL) at -50 ~ -40 °C for 2 h under an Ar atmosphere and then benzaldehyde (0.4 mmol) at -78 °C. [b] See note 4. [c]Total yields of both diastereomers based on benzaldehyde and diastereoselectivities (*erythro* : *threo*)[12] are as follows; 87% (62 : 38) for entry 1, 98% (54 : 46) for entry 2, 86% (55 : 45) for entry 3, 72% (55 : 45) for entry 4. [d]For determination of configurations, see note 5. [e]E.e. is based on that of **6**. The calculated values expected by simple extrapolation if the substrate is of 100% ee are shown in parenthesis. [f]Determined by GC analysis using a chiral capillary column (Chirasil-DEX, Chrompack, 0.25 mm x 25 m) after separation of diastereomers. [g]The same e.e. was obtained when a solution of the allenyltitanium prepared at -50 ~ -40 °C for 2 h was warmed to 20 °C over 0.5 h and stirred for 2 h at this temperature, and then benzaldehyde was added at -78 °C. [h]Two diastereomers were inseparable. E.e. value was determined after derivatization, see note 5.

enantiomeric excess (e.e.) was determined by GLC analysis using a chiral column. The results are summarized in Table 1. It can be seen that the absolute configuration and enantiomeric excess (e.e.) of the resulting **6** are highly dependent on whether the propargyl compound is secondary or tertiary and also on the leaving group X. Thus, with respect to the configuration, the carbonates **2** and **4** furnished the corresponding **6** where the addition reaction proceeded with retention while phosphates **3** and **5** afforded the inversion products. Since the reaction of allenyltitaniums with aldehydes is well-established to proceed at the γ-allenylic carbon *via* a chelate-type transition state, i.e., with allenyl inversion,[6] the major

configuration of the allenyltitaniums generated by these reactions can be assigned as **7-10**, respectively, as depicted in Table 1. With respect to the e.e. of the allenyltitanium, and thus eventually that of **6**, it was excellent for secondary phosphate **3** and tertiary carbonate **4**; meanwhile, it was moderate for secondary carbonate **2** and low for tertiary phosphate **5**. In conclusion, the reaction with optically active secondary propargyl phosphate and tertiary propargylic carbonate proceeds with more than 97% chiral transfer, thus providing an efficient and practical method for synthesizing di- and tri-substituted allenyltitaniums with high optical purity. We also confirmed that allenyltitaniums thus obtained are stable to racemization at least up to room temperature as reported by Hoffman and Hoppe[7] (see note g in Table 1).

The most plausible mechanism for the oxidative addition reaction of eq 1 involves the exchange of the propene ligand in **1** with the acetylenic moiety of propargyl compounds and the subsequent β-elimination reaction of the resulting titanium-alkyne intermediate.[2] The stereochemical outcome of the reaction and the degree of chiral transfer shown in Table 1 can be explained by assuming a different elimination pathway from the titanium-alkyne intermediate. Thus, as shown in Scheme 1,[8] in the case of secondary phosphate **3**, the titanium-alkyne intermediate may readily undergo an anti β-elimination through an anti-coplanar transition state, thus providing **8** with excellent e.e. (path a). However, the tertiary phosphate **5** proceeds mainly *via* an E1-elimination pathway (path b), rather than the concerted one due to the steric congestion, providing **10** with low e.e.[9] Since carbonate is a weaker leaving group than phosphate, the β-elimination of tertiary carbonate **4** proceeds *via* a syn-elimination pathway almost exclusively to afford **9** where intramolecular coordination acts as the driving force (path c);[10] however, for the secondary carbonate **2**, an anti-elimination pathway also might be involved (path c and partly *via* path a).



Scheme 1. Elimination Pathway of Alkyne-titanium Intermediates to Allenyltitaniums

In summary, an efficient and practical method for synthesizing optically active allenyltitaniums with excellent optical purity has been developed. We believe that this finding opens up a new efficient entry to optically active compounds including homopropargyl alcohols as described here;[11] further application of the optically active allenyltitaniums to asymmetric synthesis will be reported in the following paper.

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References and Footnotes

[1] Kulinkovich OG, Sviridov SV, Vasilevski DA. Synthesis 1991;234. Kasatkin A, Nakagawa T, Okamoto S, Sato F. J. Am. Chem. Soc. 1995;117:3881-3882. Harada K, Urabe H, Sato F. Tetrahedron Lett. 1995;36:3203-3206. Takayanagi Y, Yamashita K, Yoshida Y, Sato F. J. Chem. Soc., Chem. Commun. 1996;1725-1726.

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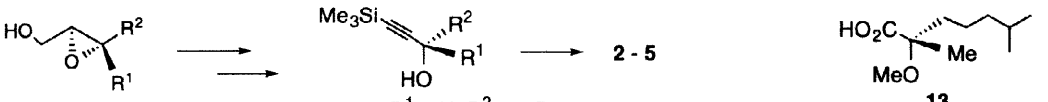
[3] For synthesis of chiral allenyl metals having axial chirality and their synthetic applications; see, Si: Masse CE, Panek JS. Chem. Rev. 1995;95:1293-1316. Sn: Marshall JA. Chem. Rev. 1996;96:31-47. B: Matsumoto Y, Naito M, Uozumi Y, Hayashi T. J. Chem. Soc. Chem. Commun. 1993;1468-1469.

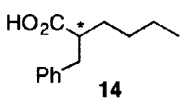
[4] The preparation of **2-5** was carried out from the corresponding optically active epoxy alcohols *via* **11** or **12** according to the reported procedure; Takano S, Samizu K, Sugihara T, Ogasawara K. J. Chem. Soc., Chem. Commun. 1989;1344-1345. Yadav JS, Deshpande PK, Sharma GVM. Tetrahedron 1990;46:7033-7046. E.e. value of **2** (and **3**) was determined by GLC analysis using a chiral column (Chirasil-DEX, Chrompack). Meanwhile, e.e. value of **4** and **5** is based on that of the α-methoxycarboxylic acid **13** derived from **12**, which was determined by GLC analysis (Chirasil-DEX, Chrompack).



11 ; R^1 = H, R^2 = *n*-Bu

12 ; R^1 = Me, R^2 = $(CH_2)_3CHMe_2$

[5] The absolute configuration of **6** shown in entries 1 and 2 in Table 1 was confirmed by derivatization to the known 2-benzylhexanoic acid (**14**) by deoxygenation to 3-benzyl-1-heptyne using Et_3SiH in the presence of BF_3[13] (91% yield) and the following oxidative cleavage of the acetylenic moiety using $NaIO_4$ in the presence of $RuCl_3$ (63% yield);[14] the $[\alpha]_D$ values observed were as follows.



14

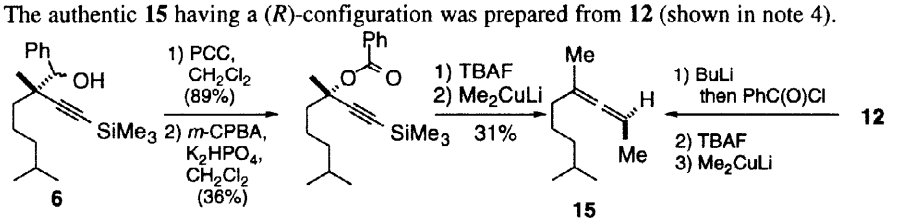
$[\alpha]^{20}_D$ -12.2 (*c* 3.85, C_6H_6) (entry 1)

$[\alpha]^{22}_D$ +22.9 (*c* 2.44, C_6H_6) (entry 2)

lit., $[\alpha]^{24}_D$ -19.6 (*c* 5, C_6H_6) for (*R*)-enantiomer with 86% ee

(Meyers AI, Knaus G, Kamata K, Ford ME. J. Am. Chem. Soc. 1976;98:567-576).

The e.e. value and absolute configuration of **6** shown in entries 3 and 4 were determined by GLC analysis (Chirasil-DEX CB, Chrompack) after derivatization to 4,8-dimethyl-2,3-nonadiene (**15**). The procedure for conversion of **6** (entry 3) to **15** is shown below. The authentic **15** having a (*R*)-configuration was prepared from **12** (shown in note 4).



[6] Furuta K, Ishiguro M, Haruta R, Ikeda N, Yamamoto H. Bull. Chem. Soc. Jpn. 1984;57:2768-2776. Yamamoto H. In: Trost BM, editor. Comprehensive Organic Synthesis. Oxford: Pergamon Press, 1991:Vol. 2:81-98.

[7] Hoffmann RW, Lanz J, Metternich R, Tarara G, Hoppe D. Angew. Chem., Int. Ed. Engl. 1987;26:1145-1146.

[8] A similar reaction mechanism to that outlined in Scheme 1 has been proposed for the organocopper-induced substitution reaction of propargylic compounds which involves the formation of the π-complex between the copper and the acetylenic moiety of propargylic derivatives and subsequent elimination of the leaving group *via* a *syn* or *anti* pathway. Alexakis A. Pure Appl. Chem. 1992;64:387-392 and references cited therein.

[9] March J. :Advanced Organic Chemistry: Reactions, Mechanism, and Structure. Tokyo: McGraw-Hill Kogakusha, 1977;Chapter 9.

[10] *Syn*-elimination reactions of β-oxysubstituted organometallics *via* the metal-oxygen coordination have been reported. Sugita T, Nishimoto K, Ichikawa K. Chem. Lett. 1973;607-610. Brown HC, Hamaoka T, Ravindran N. J. Am. Chem. Soc. 1973;95:6456-6457. Shimizu N, Sakai M, Tsuno Y. Chem. Lett. 1990;2207-2208. Maeda, K, Shinokubo H, Oshima K. J. Org. Chem. 1996;61:6770-6771 and references cited therein. See also ref. 8.

[11] Although the diastereoselectivity of the reaction of allenyltitaniums with benzaldehyde or primary alkyl aldehyde is moderate, it is excellent with secondary alkyl aldehyde.[6]

[12] *Threo/erythro* notation conforms to the definition suggested by Noyori and co-workers. Noyori R, Nishida I, Sakata J. J. Am. Chem. Soc. 1981;103:2106-2108.

[13] Adlington MG, Orfanopoulos M, Fry JL. Tetrahedron Lett. 1976;2955-2958.

[14] Carlsen PHJ, Katsuki T, Martin VS, Sharpless KB. J. Org. Chem. 1981;46:3936-3938.