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Synthesis of Chiral Alkynes Having ^2H or Halogen at the Secondary or Tertiary Propargylic Stereogenic Center by Hydrolysis and Halogenolysis of Optically Active Allenyltitaniums Having Axial Chirality

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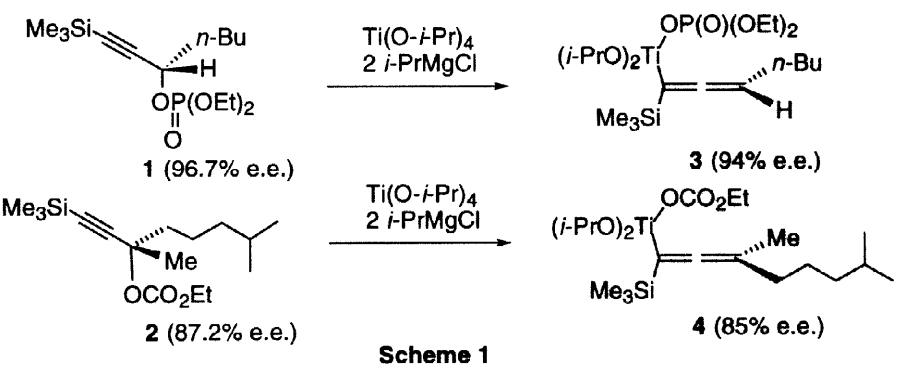
Abstract

The hydrolysis and halogenolysis of optically active allenyltitaniums, generated by the reaction of a Ti(O-*i*-Pr)4 / 2 *i*-PrMgCl reagent with optically active propargyl alcohol derivatives, proceed in a regioselective way and with excellent degree of chiral transfer, thus opening up a highly efficient and practical route to chiral alkynes having ^2H or Cl at the stereogenic propargylic center.

Keywords: titanium and compounds;asymmetric synthesis;alkynes;halogens and compounds

As described in the preceding paper, the reaction of a Ti(O-*i*-Pr)4 / 2 *i*-PrMgCl reagent with optically active propargylic alcohol derivatives proceeds with excellent chiral transfer to provide optically active allenyltitanium complexes.[1] Thus, the reaction of secondary propargyl phosphate **1** (96.7% e.e.) and tertiary propargyl carbonate **2** (87.2% e.e.) proceeded respectively with more than 97% chiral transfer, providing the corresponding di- or tri-substituted allenyltitaniums **3** (94% e.e.) and **4** (85% e.e.). (Scheme 1).



Scheme 1

We have shown the utility of allenyltitaniums thus obtained by preparation of optically active homopropargyl alcohols by their reaction with aldehydes.[1] The reaction of

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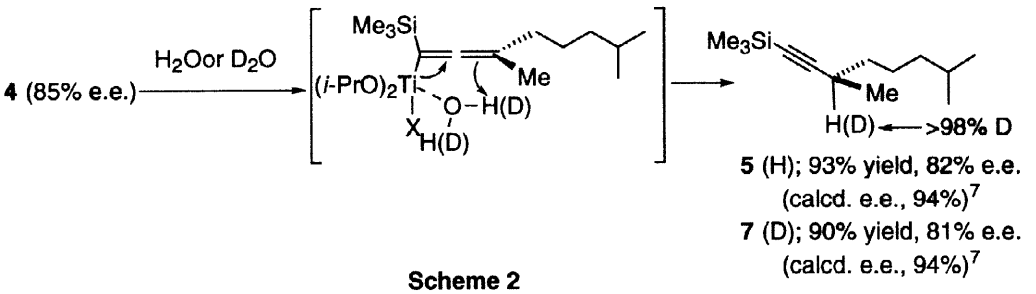
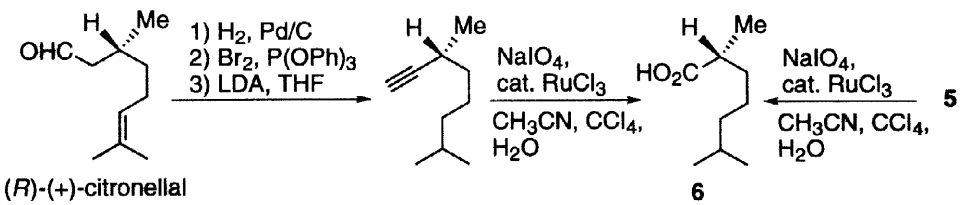
allenyltitaniums with electrophiles other than carbonyl compounds[2] and imines,[3] however, has scarcely been reported;[4] the paucity of relevant data is probably due to the fact that the allenyltitaniums have been usually prepared by transmetallation reaction using the corresponding organolithium compounds, and it is considered that this method offers no definite synthetical advantage in carrying out the reaction after transmetallation to titanium. However, the finding of a direct and easy access to optically active allenyltitaniums alters the case, and we thought that the reaction with other electrophiles might also become useful as an asymmetric synthetic method. We, moreover, anticipated that the stereochemical outcome of the reaction might provide significant information on the mechanism of electrophilic cleavage of the titanium-carbon bond. Herein reported are the results of the hydrolysis and halogenolysis of optically active allenyltitaniums.

Firstly, we investigated the hydrolysis of **4** (85% e.e.) by treatment with a large excess of H_2O at -78° C~0 °C which afforded the alkyne **5** in 93% yield (Scheme 2). The e.e. value and absolute configuration of **5** thus obtained were confirmed by GLC analysis using a chiral column after converting into 2,6-dimethylheptanoic acid (**6**) by treatment with $NaIO_4$ in the presence of $RuCl_3$[5] and comparison with the authentic (*R*)-**6** prepared from (*R*)-(+)-citronellal according to the procedure shown in Scheme 3.[6] It was found that **5** had an (*R*)-configuration and the e.e. value was 82% e.e. which indicated that the hydrolysis of **4** proceeded with a very high degree of chiral transfer of 94%. The regio- and stereochemical



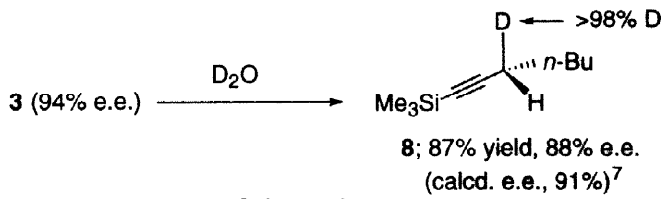
Scheme 2



Scheme 3

outcome of the reaction can be explained by assuming that the hydrolysis of titanium-carbon proceeds through the coordination of the H_2O to the titanium and the following electrophilic cleavage *via* an S_E2'-type reaction as shown in Scheme 2. With this result in hand, we carried out the deuterolysis of **4** which afforded optically active alkyne **7**[8] containing ^2H at the tertiary propargylic stereogenic center (Scheme 2). The deuterolysis of **3** also provided 87% yield of the chiral alkyne **8** (88% e.e.)[9] having ^2H at the secondary propargylic center

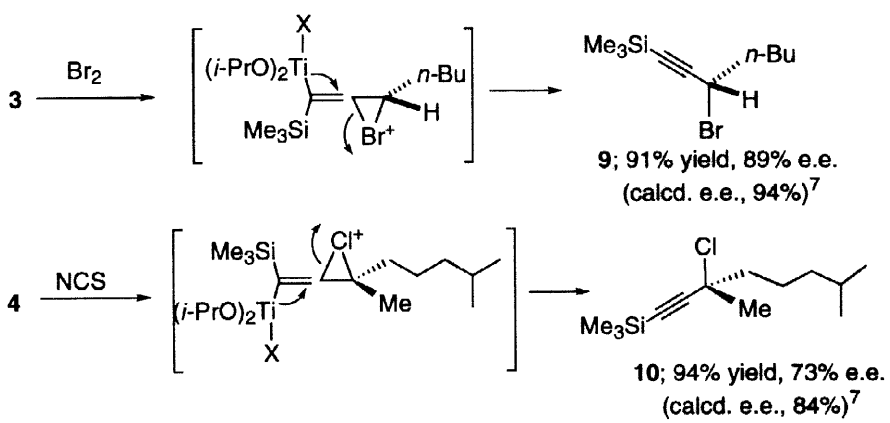
(Scheme 4),[10] the configuration of which is based on the analogy of the reactions of **4** providing **5** and **7**.



Scheme 4

In summary, a one-pot method for synthesizing optically active alkynes having a stereogenic propargylic center from readily available propargylic alcohol derivatives has been developed which proceeds with a very high degree of chiral transfer.[11,12] Noteworthy is the easy one-pot synthesis of deuterated compounds such as **7** and **8** because their synthetic methods so far developed require multi-step transformation.[13] Noteworthy also is the fact that the present method might allow the synthesis of alkynes having ^{3}H at the stereogenic propargylic center by workup with $^{3}H_2O$.

Halogenolysis of optically active allenyltitaniums also proceeds with a high to excellent degree of chiral transfer to provide optically active propargylic halides. Thus, the reaction of **3** with Br_2 (1.5 equiv., -78 °C~0 °C) proceeded with 94% chiral transfer to provide optically active secondary propargylic bromide **9** (Scheme 5). The e.e. value of **9** was determined by a chiral GLC analysis and the absolute configuration was confirmed to be (*S*) by comparing with the authentic compound.[14] Similarly, optically active tertiary propargylic chloride **10** (73% e.e.)[15,16] was obtained from **4** (85% e.e.) by treatment with NCS (1.5 equiv.).[17] The stereochemical outcome obtained here strongly indicates that the halogenolysis proceeds according to the mechanism shown in Scheme 5 which involves the generation of a halogenium cation intermediate and the following S_E2'-*anti*-type halodemetallation reaction.[18] We have now succeeded in developing an efficient access to optically active propargyl halides. Especially noteworthy is the easy entry to optically active tertiary propargylic chloride, which is otherwise difficult to synthesize.[19]



Scheme 5

In summary, we have developed a highly efficient one-pot method for synthesizing optically active alkynes having ^{2}H or halogen at the secondary or tertiary propargylic stereogenic center from readily available propargyl alcohol derivatives. The stereochemical

outcome obtained here provides important information for elucidation of the mechanism of hydrolysis and halogenolysis of allenyltitaniums.

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References and Footnotes

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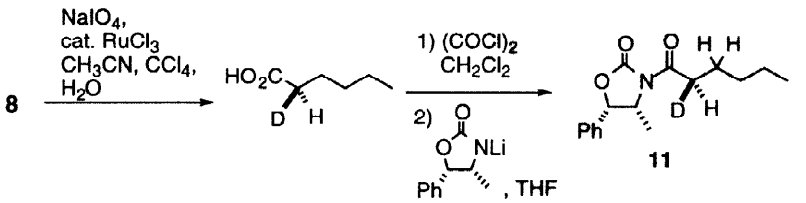
[2] Furuta K, Ishiguro M, Haruta R, Ikeda N, Yamamoto H. Bull. Chem. Soc. Jpn. 1984;57:2768-2776.
[3] Yamamoto Y, Ito W, Maruyama K. J. Chem. Soc., Chem. Commun. 1984;1004-1005.
[4] Yamamoto H. In: Trost BM. editor, Comprehensive Organic Synthesis, Oxford: Pergamon Press, 1991;Vol. 2:81-98. This is true not only of allenyltitaniums but also of other organotitaniums having an alkyl, aryl or allyl group, see: Reetz MT. Organotitanium Reagents in Organic Synthesis, Berlin/Heidelberg: Springer-Verlag, 1986.
[5] Carlsen PHJ, Katsuki T, Martin VS, Sharpless KB. J. Org. Chem. 1981;46:3936-3938.
[6] The enantiomers of 2,6-dimethylheptanoic acid were detected at the retention times of 4.8 min for (*S*)-isomer and 5.1 min for (*R*)-isomer by GLC analysis (Chirasil-DEX CB, Chrompack, 0.25 mm x 25 m, 2.0 $Kg \cdot cm^{-2}/H_2$, 130 °C).
[7] The value expected by simple extrapolation if the substrate is of 100% e.e.
[8] The e.e. value and configuration of **7** were confirmed by the same method applied to **5**.
[9] The e.e value was determined by 300MHz ^1H NMR analysis of the imide of [2-^2H]-heptanoic acid (**11**) derived from **8** according to the procedure shown below. The ^1H-homodecoupling NMR experiment of **11** by irradiation of methylene protons at the β-position showed two diastereomeric peaks at δ 2.88 (a minor isomer) and 2.95 (a major isomer) in a 6 : 94 ratio (88% d.s.).



[10] 9% yield of [1-^2H]-1-trimethylsilyl-1,2-heptadiene was co-produced which was easily separated by column chromatography.
[11] For other methods for preparation of optically active secondary alkynes, see: Corey EJ, Boaz NW. Tetrahedron Lett. 1984;25:3059-3062. Overman LE, Bell KL, Ito F. J. Am. Chem. Soc. 1984;106:4192-4201. Baker R, Head JC, Swain CJ. J. Chem. Soc., Perkin Trans. 1, 1988;85-97. Clasby MC, Craig D, Marsh A. Angew. Chem., Int. Ed. Engl. 1993;32:1444-1446. Norley M. Kocienski P, Faller A. Synlett, 1996;900-902. Shi Y, Peng LF, Kishi Y. J. Org. Chem. 1997;62:5666-5667. Marshall JA, Wang XJ. J. Org. Chem. 1992;57:1242-1252.
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[14] The authentic (*R*)-**9** was prepared from (*S*)-1-trimethylsilylheptyn-3-ol by the stereospecific S_N2 reaction using CBr_4, PPh_3 and pyridine in CCl_4. Gooding OW, Beard CC, Jackson DY, Wren DL, Cooper GF. J. Org. Chem. 1991;56:1083-1088. The enantiomers of **9** were detected at the retention times of 4.9 min for (*S*)-isomer and 4.6 min for (*R*)-isomer by GLC analysis (Chirasil-DEX CB, Chrompack, 0.25 mm x 25 m, 1.0 $Kg \cdot cm^{-2}/H_2$, 120 °C).
[15] Owing to somewhat low stability on column chromatography, pure **10** could not be isolated. Yield of **10** indicated in Scheme 5 was determined by ^1H NMR and GC analysis of the product obtained after passing through a pad of silica gel.
[16] The e.e value of **10** was determined by GLC analysis (Chirasil-DEX, Chrompack, 0.25 mm x 25 m, 1.0 $Kg \cdot cm^{-2}/H_2$, 120 °C) and the enantiomers were detected respectively at the retention times of 5.7 min and 5.6 min. The absolute configuration of **10** depicted in Scheme 5 was assigned on the analogy of the reaction of **3** providing **9**.
[17] The reaction of **4** with Br_2 gave a complicated mixture after workup.
[18] Similar S_E2' halodemetallation reactions of allenylstannyl compounds have been reported. Simo MS, Jean A, Lequan M. J. Organometal. Chem. 1972;35:C23-24. Cochran JC, Kuivila HG. Organometallics, 1982;1:97-103 and references cited therein.
[19] To the best of our knowledge, synthesis of optically active tertiary propargyl halide has not been reported. For preparation of racemic tertiary propargyl halide, see: Bentley TW, Dau-Schmidt JP, Llewellyn G, Mayr H. J. Org. Chem. 1992;57:2387-2392 and references cited therein.