Intramolecular Coupling of Vinyl Ether and Olefins or Acetylenes with Ti(II) Reagent. Regio- and Stereo-selective Vinyltitanation of Carbon-Carbon Multiple Bonds

Ryota Nakajima, Hirokazu Urabe,† and Fumie Sato*
Department of Biomolecular Engineering, Graduate School of Bioscience and Biotechnology, Tokyo Institute of Technology,
4259 Nagatsuta-cho, Midori-ku, Yokohama, Kanagawa 226-8501
†*Department of Biological Information, Graduate School of Bioscience and Biotechnology, Tokyo Institute of Technology,*
4259 Nagatsuta-cho, Midori-ku, Yokohama, Kanagawa 226-8501

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Treatment of m-alkenyl (or m-alkynyl) vinyl ethers (m = 3,4) with a Ti(II) reagent generated most likely bicyclic oxatitanacycles, which eliminate the alkoxide tether to effect the selective vinyltitanation of the alkene or alkyne moiety to give m-vinyl-1-alkanols or m-vinyl-m-alken-1-ols.

Bicyclic metallacycles of group 4 transition metals **1** (Figure 1, M = Ti or Zr, L = ligand) have been utilized as versatile intermediates in organic synthesis.[1,2] Once such a metallacycle having a leaving group (X) at an appropriate position is generated from the corresponding diene, enyne, or diyne, and a metal constituent, one of the carbon-metal bonds of the metallacycle spontaneously eliminates the group X to form a new intermediate. The possible elimination patterns a-d are illustrated in Figure 1.[3,4] Although the first three types a,[4a–j] b,[4k] and c[4l] have been well documented, to our best knowledge, the last type d has not been reported yet. This fact prompted us to investigate the feasibility and synthetic application of the transformation of type d based on dialkoxytitanacycles (ML_2 = Ti(O-*i*-Pr)$_2$) recently introduced by us.[1]

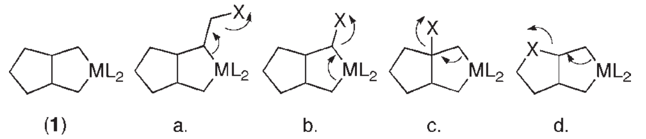
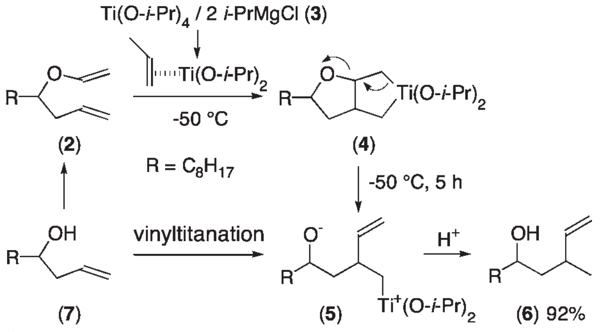


Figure 1. Elimination of the group X on bicyclic metallacycles.

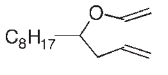
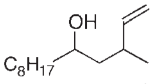
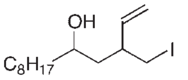
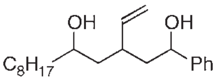
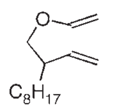
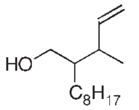
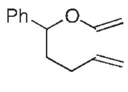
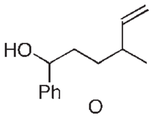
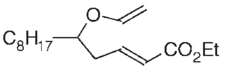
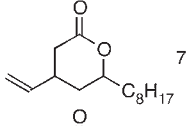
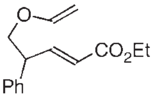
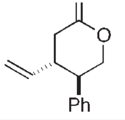
Vinyl ether **2** having an additional olefinic bond was treated at −50 °C with Ti(O-*i*-Pr)$_4$ / 2 *i*-PrMgCl (**3**),[1] which generates the actual Ti(II) reagent, (η^2-propene)Ti(O-*i*-Pr)$_2$, *in situ* (Scheme 1). After aqueous workup at the same temperature, the desired product **6**, having no longer a vinyl ether, but showing the presence of a hydroxy group as well as a terminal olefin, was obtained in excellent yield.[5] The presence of the intermediate alkyltitanium species **5** was, in fact, confirmed by iodinolysis and aldehyde addition to give the corresponding iodide and the diol, respectively, in good yields, which are shown in entries 2 and 3 of Table 1. As the starting vinyl ether is prepared from the parent alcohol **7** by ether exchange reaction,[6] the overall process could be considered as a hydroxy-mediated regioselective vinyltitanation of unactivated olefins[7] via dialkoxytitanacycle **4** generated with **2** and **3** (Scheme 1). Other examples of this transformation are collected in Table 1 to show its generality. Both the reactions starting from 3- and 4-alkenyl vinyl ethers are viable to give the desired unsaturated alcohols. This transformation is also applicable to the coupling of vinyl ether and functionalized olefins (entries 6 and 7), where good to excellent diastereoselectivities could be observed in the products.

Vinyl ethers incorporated in the enyne structure also



Scheme 1. Intramolecular coupling of vinyl ether and olefin.

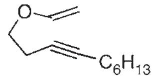
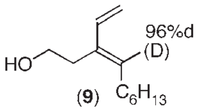
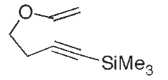
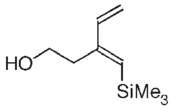
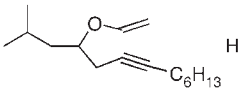
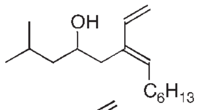
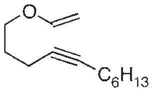
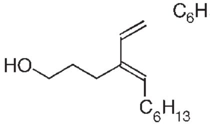
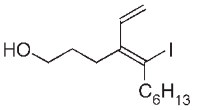
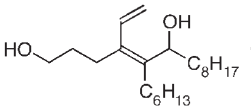
Table 1. Vinyltitanation of olefinic bond according to Scheme 1.

Entry	Substrate	Electrophile	Product	Yield/%[a]	Ds[b,c]
1		H^+		92	1:1
2		I_2		80	1:1
3		PhCHO		62	mixture
4		H^+		76	7:3
5		H^+		83	2:1
6		H^+		70[d]	85:15
7		H^+		53[d]	single

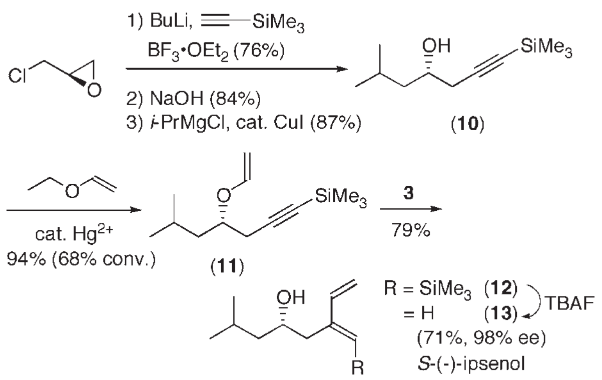
[a]Isolated yield. [b]Diastereoselectivity. [c]Stereochemistries have not been determined except entry 7. [d]After lactonization (CF_3CO_2H).

underwent the same reaction without any complication (Table 2). Vinyl ether **8** (entry 1) was treated with **3** under the same conditions as shown in Scheme 1 to afford diene alcohol **9** again in excellent yield after aqueous workup. The exclusive *E* stereoselectivity as well as the complete regioselectivity was confirmed by ^{1}H NMR analysis. The presence of the dienyltitanium species (corresponding to **5** in Scheme 1) was verified by deuteriolysis to give **9**-d$_1$, which showed a very high deuterium incorporation at the specified position. Other examples of this reaction are summarized in entries 2–6 of Table 2. Besides simple hydrolysis, interception of the remaining carbon-titanium bond with an electrophile such as iodine or aldehyde, as shown in entries 5 and 6, afforded the corresponding adducts that retain the depicted stereochemical integrity of the intermediate dienyltitanium species.

Table 2. Vinyltitanation of acetylenic bond according to Scheme 1.

Entry	Substrate	Electrophile	Product	Yield/%[a]
1	 (**8**)	H$^+$(D$^+$)	 (**9**)	91
2		H$^+$		47
3		H$^+$		91
4		H$^+$		90
5		I$_2$		61
6		C$_8$H$_{17}$CHO		63

[a]Isolated yields.



Scheme 2. Synthesis of optically active *S*-(-)-ipsenol.

A concise synthesis of optically active ipsenol in Scheme 2 demonstrates the synthetic utility of the above methodology. Commercially available, optically active epichlorohydrin was alkylated successively with (trimethylsilyl)acetylide and isopropyl Grignard reagent to give alcohol **10**, which was then subjected to ether exchange reaction to give vinyl ether **11**. Treatment of this with **3** under the reaction conditions of Scheme 1 furnished silyldiene alcohol **12**, which, upon desilylation with TBAF, gave (*S*)-(-)-ipsenol (**13**) (98% ee determined by Mosher's MTPA ester method), $[\alpha]_D^{26} - 15.3$ (*c* 1.06, ethanol).[8]

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This article is dedicated to Professor Teruaki Mukaiyama on the occasion of his 75th birthday.

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1 a) F. Sato, H. Urabe, and S. Okamoto, *Pure Appl. Chem.*, **71**, 1511 (1999). b) F. Sato, H. Urabe, and S. Okamoto, *Chem. Rev.*, **100**, 2835 (2000). c) F. Sato, H. Urabe, and S. Okamoto, *Synlett*, **2000**, 753. d) O. G. Kulinkovich and A. de Meijere, *Chem. Rev.*, **100**, 2787 (2000). e) J. J. Eisch, *J. Organomet. Chem.*, **617-618**, 148 (2001).

2 S. L. Buchwald and R. B. Nielsen, *Chem. Rev.*, **88**, 1047 (1988); E. Negishi, "Comprehensive Organic Synthesis," ed. by B. M. Trost and I. Fleming, Pergamon Press, Oxford (1991), Vol. 5, pp. 1163-1184; E. Negishi and T. Takahashi, *Acc. Chem. Res.*, **27**, 124 (1994); A. Ohff, S. Pulst, C. Lefeber, N. Peulecke, P. Arndt, V. V. Burlakov, and U. Rosenthal, *Synlett*, **1996**, 111; E. Negishi and T. Takahashi, *Bull. Chem. Soc. Jpn.*, **71**, 755 (1998).

3 This classification is a formal one and does not necessarily reflect the exact mechanism.

4 a) K. S. Knight and R. M. Waymouth, *Organometallics*, **13**, 2575 (1994). b) T. Takahashi, D. Y. Kondakov, and N. Suzuki, *Organometallics*, **13**, 3411 (1994). c) A. J. Bird, R. J. K. Taylor, and X. Wei, *Synlett*, **1995**, 1237. d) R. Hara, Y. Ura, S. Huo, K. Kasai, N. Suzuki, and T. Takahashi, *Inorg. Chim. Acta*, **300-302**, 741 (2000). e) Y. Takayama, Y. Gao, and F. Sato, *Angew. Chem. Int. Ed. Engl.*, **36**, 851 (1997). f) Y. Takayama, S. Okamoto, and F. Sato, *Tetrahedron Lett.*, **38**, 8351 (1997). g) T. Yamazaki, H. Urabe, and F. Sato, *Tetrahedron Lett.*, **39**, 7333 (1998). h) A. D. Campbell, T. M. Raynham, and R. J. K. Taylor, *J. Chem. Soc., Perkin Trans. 1*, **2000**, 3194. i) Y. Takayama, S. Okamoto, and F. Sato, *J. Am. Chem. Soc.*, **121**, 3559 (1999). j) C. Delas, H. Urabe, and F. Sato, *Tetrahedron Lett.*, **42**, 4147 (2001). k) T. Takahashi, Z. Xi, R. Fischer, S. Huo, C. Xi, and K. Nakajima, *J. Am. Chem. Soc.*, **119**, 4561 (1997). l) D. B. Millward and R. M. Waymouth, *Organometallics*, **16**, 1153 (1997). For an intermolecular reaction leading to vinylation: m) T. Takahashi, D. Y. Kondakov, Z. Xi, and N. Suzuki, *J. Am. Chem. Soc.*, **117**, 5871 (1995).

5 Preparation of **6**. To a stirred solution of Ti(O-*i*-Pr)$_4$ (0.088 mL, 0.298 mmol) and **2** (50 mg, 0.238 mmol) in Et$_2$O (3 mL) at −78 °C under argon was added *i*-PrMgCl (1.44 M in ether, 0.446 mL, 0.643 mmol). The reaction mixture was allowed to warm to −50 °C over 30 min and was stirred at this temperature for another 5 h. To this cold solution was added aqueous 1N HCl. Standard extractive workup and purification on silica gel afforded the title compound (46.7 mg, 92%) as an oil.

6 S. J. Rhoads and N. R. Raulins, "Organic Reactions," ed. by W. G. Dauben, Wiley, New York (1975), Vol. 22, pp. 1-252.

7 For other type of carbotitanations, see: E. Negishi and D. Y. Kondakov, *Chem. Soc. Rev.*, **1996**, 417; J. J. Eisch and M. P. Boleslawski, *J. Organomet. Chem.*, **334**, C1 (1987); P. Rigollier, J. R. Young, L. A. Fowley, and J. R. Stille, *J. Am. Chem. Soc.*, **112**, 9441 (1990).

8 Lit.[8b] $[\alpha]_D^{25} - 17.2$ (*c* 1.28, ethanol); lit.[8c] $[\alpha]_D^{24} - 16.5$ (*c* 1.47, ethanol). a) B. List, P. Pojarliev, and C. Castello, *Org. Lett.*, **3**, 573 (2001). b) T. Imai and S. Nishida, *J. Org. Chem.*, **55**, 4849 (1990). c) K. Mori, *Tetrahedron*, **32**, 1101 (1976).