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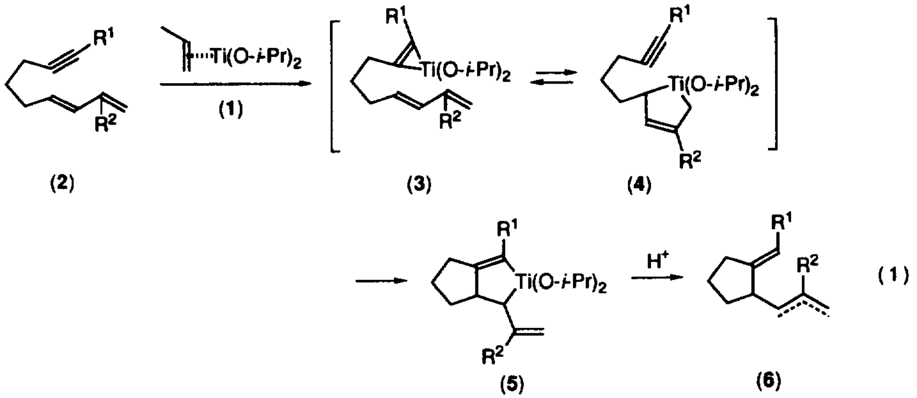
Intramolecular Cyclization of Conjugated Diene and Acetylene with (η^2-Propene)Ti(O-*i*-Pr)$_2$. Generation and Reaction of Titanabicycles Having an Allyltitanium Moiety

Hirokazu Urabe, Tohru Takeda, and Fumie Sato*

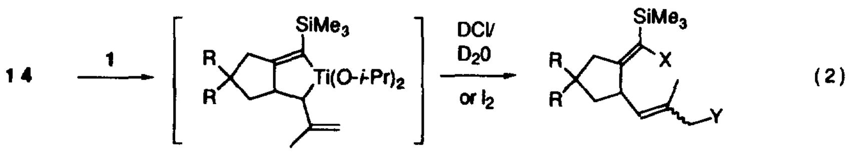
Department of Biomolecular Engineering, Tokyo Institute of Technology,
4259, Nagatsuta-cho, Midori-ku, Yokohama, Kanagawa 226, Japan

Abstract: Intramolecular cyclization of conjugated diene and acetylene with (η^2-propene)Ti(O-*i*-Pr)$_2$ affords titanabicycles **5** having an allyltitanium moiety. Upon hydrolysis, **5** afforded cyclopentanes **6**. Moreover, selective extension of the carbon-carbon bond is feasible by the reaction of **5** and aldehydes to give the products such as **9**, **10**, **13**, and **16**.

Cyclization of unsaturated compounds such as dienes, diynes, and enynes by a catalytic or stoichiometric amount of a metal species continues to be a versatile method to prepare cyclic compounds.[1] Recently, we reported a low-valent titanium-mediated cyclization of these unsaturated compounds in which a stoichiometric amount of (η^2-propene)Ti(O-*i*-Pr)$_2$ (**1**), prepared *in situ* from inexpensive Ti(O-*i*-Pr)$_4$ and *i*-PrMgCl, was used.[2] During the course of our study, we were interested in the titanium-mediated cyclization of dienyne **2** (eq 1), which proceeds most likely via an acetylene complex **3**[3] and/or a diene complex **4**.[4] Herein we report that this reaction is, in fact, mediated by **1**,[5,6] and, more importantly, we will show the high reactivity of the allyltitanium moiety of the resultant titanabicycle **5**[7] toward aldehydes, which permits selective carbon-carbon bond elongation after the cyclization.



As revealed from the results in Table 1, the reaction of dienynes **7**, **11**, and **14**[8] took place without any difficulty under our standard reaction conditions[2] to give the cyclized products after hydrolysis. The ease of cyclization was unaffected by the stereochemistry of diene (either *E* or *Z*) (entries 1 and 2). Unfortunately, upon simple hydrolysis with hydrochloric acid, the substrates **7** or **11** afforded a mixture of regio- and stereoisomers with respect to the newly formed olefinic bond coming from the diene part (**8a+b** or **12a+b** in entries 1, 2, or 5). The regioselection of protonation, however, was highly regulated by a methyl substituent of the diene moiety in **14** to give a single isomer (**15**, entry 7). The presence of an intermediate titanabicycle such as **5** was verified by its deuterolysis and iodinolysis. Thus, after the cyclization of **14** (*E*/*Z* >95: 5), the reaction mixture was treated with DCl/D_2O or I_2 in place of hydrochloric acid to give bis-deuterated or -iodinated product (**18** or **19**, the shown *E*/*Z* ratio refers to that of $CH{=}C(Me)CH_2Y$, eq 2). The iodinolysis of the allyltitanium portion of **17** again proceeded in a highly regioselective manner.



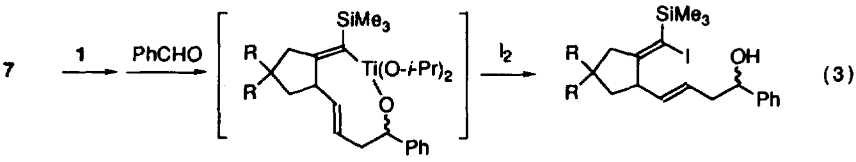
(17)

R = $BnOCH_2$-

(18) X = D (>99%d), Y = D (93%d)
90% *E*/*Z* = 29:71

(19) X = Y = I
79% *E*/*Z* (or *Z*/*E*) = 26:74

This cyclization should be more highlighted in the successive reaction with aldehydes (entries 3, 4, 6, and 8 in Table 1),[9] which has some characteristic features. The first is the high reactivity of the intermediate titanabicycle **5** toward aldehydes. The addition took place smoothly and exclusively at the allyl rather than vinyltitanium site of **5**.[10,11,12] The second point is that the addition is always regioselective: aldehydes reacted at the less substituted terminus of the allylic system, which is in marked contrast with reactions with ordinary allyltitanium reagents, which usually react with aldehydes at the more substituted position.[13,14] In addition to these regioselectivities, the highly stereoselective formation of the *E* double bonds from the substrates having an unsubstituted diene moiety should be noted (entries 3, 4, and 6).[12,13,15] Achievement of moderate to good 1,5-chirality induction with respect to the hydroxy groups (their configurations have not been elucidated yet) is also not trivial. However, a diene substituent such as the methyl group in **14** considerably decreased the olefinic stereoselectivity in the step of aldehyde addition to give a mixture of isomers **16** (entry 8). The remaining vinyltitanium moiety of **20** after the reaction of **7** (*E*/*Z* = 57:43), **1**, and PhCHO could be intercepted with iodine to give **21** (eq 3), which demonstrates that both carbon-titanium bonds in **5** may participate in selective synthetic transformations under an appropriate choice of reagents.

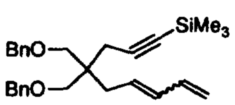
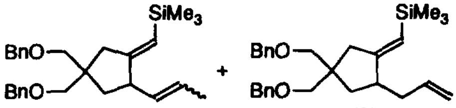
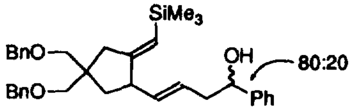
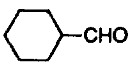
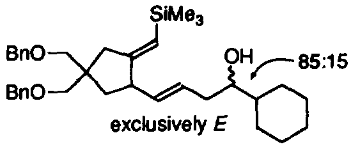
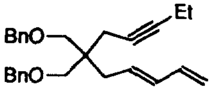
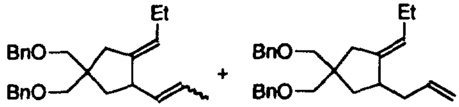
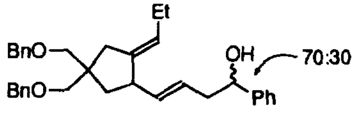
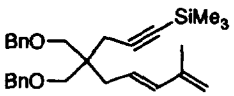
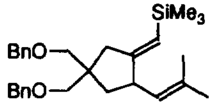
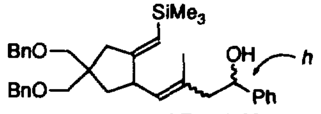


(20) R = $BnOCH_2$-

(21) 66%

The present reaction mediated by **1** should be a new and facile entry to metal-promoted cyclizations that are quite efficient for the construction of substituted cyclic compounds. Study on the applicability to other ring systems is now underway.

Table 1. (η^2-Propene)Ti(O-*i*-Pr)$_2$-Mediated Intramolecular Cyclization of Diene and Acetylene and Successive Reaction with Aldehydes.[a]

Entry	Substrate	Electrophile[b]	Product(s)[c] (Yield (%)[d])
			 (**8a**) (**8b**)
1	(**7**) *E*/*Z* = 57:43	HCl	9 (*E*/*Z* = 4 : 6) : 1 (quant)[e]
2	*E*/*Z* = 93: 7	HCl	8 (*E*/*Z* = 5 : 5) : 2 (quant)[e]
3	"	PhCHO	 *E*/*Z* > 95: 5 (**9**) (96)
4	"		 exclusively *E* (**10**) (75)
5	 (**11**) *E*/*Z* > 95:5	HCl	 (**12a**) (**12b**) 2 (*E*/*Z* = 5 : 5) : 1 (quant)[e]
6	"	PhCHO	 exclusively *E* (**13**) (60)
7	 (**14**) *E*/*Z* > 95:5	HCl	 (**15**) (80)[e,f,g]
8	"	PhCHO	 *E*/*Z* = 40:60 (**16**) (80-88)

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[a] See eqs 1 and 2. Bn = benzyl. [b] HCl refers to 1 N hydrochloric acid. [c] Specified configurations of olefinic moieties were determined by ^{1}H NMR coupling constants and/or NOE studies. [d] Isolated yields unless otherwise noted. [e] Yield determined by ^{1}H NMR spectroscopy. [f] Another regioisomer arising from protonation was less than a trace amount. [g] Remainder is an uncyclized compound, 6,6-bis(benzyloxymethyl)-2-methyl-9-(trimethylsilyl)-1,3,8-nonatriene. [h] For each olefinic isomer, configuration of the hydroxy group is most likely single.

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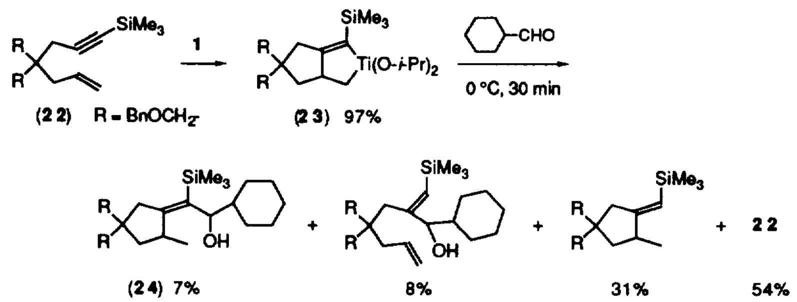
1. For a most recent review: Trost, B. M. *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 259. See also literature cited in Ref 2.
2. Urabe, H.; Hata, T.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 4261.
3. Harada, K.; Urabe, H.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 3203.
4. Yasuda, H.; Tatsumi, K.; Nakamura, A. *Acc. Chem. Res.* **1985**, *18*, 120. See note 25 in this literature.
5. Intramolecular cyclization of unsaturated compounds including conjugated diene with Ti and Zr species has not been addressed: see the following reviews. Negishi, E. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, p 1163. Negishi, E.; Takahashi, T. *Acc. Chem. Res.* **1994**, *27*, 124. Intermolecular reactions of a diene-zirconium complex with acetylene or olefin: Ref 4. Yasuda, H.; Nakamura, A. *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 723. Reactions of an olefin- or (strained) acetylene-zirconium complex with diene have also been reported: Negishi, E.; Miller, S. R. *J. Org. Chem.* **1989**, *54*, 6014. Buchwald, S. L.; Nielsen, R. B. *Chem. Rev.* **1988**, *88*, 1047. Buchwald, S. L.; Lum, R. T.; Dewan, J. C. *J. Am. Chem. Soc.* **1986**, *108*, 7441.
6. Other metal-catalyzed intramolecular cyclizations of conjugated diene and olefin (or acetylene), see: Wender, P. A.; Smith, T. E. *J. Org. Chem.* **1995**, *60*, 2962. McKinstry, L.; Livinghouse, T. *Tetrahedron* **1994**, *50*, 6145. Takacs, J. M.; Chandramouli, S. V. *J. Org. Chem.* **1993**, *58*, 7315. Takacs, J. M.; Boito, S. C. *Tetrahedron Lett.* **1995**, *36*, 2941, and references cited therein. Although the products are Diels-Alder-type compounds in the first two reports, such products were not observed in the present titanium-mediated reaction.
7. Although the exact nature of **5** is unclear, it is tentatively drawn as in a σ-allyl form and, accordingly, it may be the corresponding π-allyl structure.
8. Dienynes **7**, **11**, and **14** were prepared from appropriate acetylenic aldehydes with the following reagents: $Ph_3(CH_2{=}CHCH_2)P^+Br^-$ (Heck, R. F. *J. Am. Chem. Soc.* **1963**, *85*, 3387) and $Ph_2(CH_2{=}CRCH_2)PO$ (R = H, Me) (Ukai, J.; Ikeda, Y.; Ikeda, N.; Yamamoto, H. *Tetrahedron Lett.* **1983**, *24*, 4029).
9. Reaction of entry 4, Table 1 is representative. **4-[2-[(Trimethylsilyl)methylene]-4,4-bis(benzyloxymethyl)cyclopentyl]-1-cyclohexyl-3(*E*)-buten-1-ol (10).** To a mixture of $Ti(O\text{-}i\text{-}Pr)_4$ (0.059 mL, 0.201 mmol) and **7** (69 mg, 0.160 mmol, *E/Z* = 93:7) in 2 mL of Et_2O was added *i*-PrMgCl (1.50 M in ether, 0.294 mL, 0.441 mmol) dropwise at -78 °C under nitrogen. After stirring for 30 min, the solution was warmed to -50 °C over 30 min and kept at this temperature for 2 h. Cyclohexanecarbaldehyde (0.029 mL, 0.241 mmol) was then added and the reaction mixture was stirred at the same temperature for 20 min and at 0 °C for 30 min. The reaction was terminated by the dropwise addition of 1 N HCl (4 mL). The organic layer was separated and washed with aqueous $NaHCO_3$ solution, dried ($MgSO_4$), and concentrated to an oil, which was chromatographed on silica gel (hexane-ether) to afford the title compound (66 mg, 75%). The ratio of the diastereoisomers, which could not be separated by the chromatography, was determined by ^{13}C NMR spectroscopy.
10. It is interesting to compare the result of entry 4 in Table 1 with the following observation. The titanabicycle **23** (Ref 2) afforded the adduct **24** with cyclohexanecarbaldehyde only in a low yield under similar reaction conditions and the reaction preferentially occurred at the alkenyl-Ti bond.



11. Transfer of an allyl group in titanium reagents to carbonyl compounds is one of the most feasible reactions: see, Reetz, M. T. In *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: Berlin, 1986; p 116.
12. Among metallacycles of early transition metals, zirconacycles have been shown to react with a few carbon electrophiles, see: Copéret, C.; Negishi, E.; Xi, Z.; Takahashi, T. *Tetrahedron Lett.* **1994**, *35*, 695. Gordon, G. J.; Whitby, R. J. *Synlett* **1995**, 77. Luker, T.; Whitby, R. J. *Tetrahedron Lett.* **1995**, *36*, 4109. Takahashi, T.; Kotora, M.; Kasai, K.; Suzuki, N. *Organometallics* **1994**, *13*, 4183. Kasai, K.; Kotora, M.; Suzuki, N.; Takahashi, T. *J. Chem. Soc., Chem. Commun.* **1995**, 109. Takahashi, T.; Kotora, M.; Xi, Z. *J. Chem. Soc., Chem. Commun.* **1995**, 361.
13. Review on reactions of allyltitanium reagents: Ferreri, C.; Palumbo, G.; Caputo, R. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 1, p 139 and other review articles cited therein. Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207.
14. For our recent work on the generation and application of allyltitanium reagents, see: Urabe, H.; Yoshikawa, K.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 5595. Kasatkin, A.; Nakagawa, T.; Okamoto, S.; Sato, F. *J. Am. Chem. Soc.* **1995**, *117*, 3881. Zubaidha, P. K.; Kasatkin, A.; Sato, F. *J. Chem. Soc., Chem. Commun.*, in press.
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