J. Am. Chem. Soc. **2001,** *123,* 7937−7938 7937

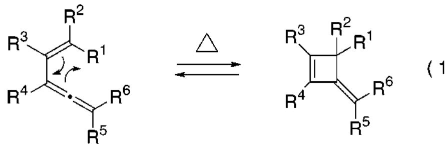
Remarkably Facile, Unidirectional Isomerization of Titanated Vinylallenes to Cyclobutenyltitanium Compounds. A Practical Construction of a Cyclobutene Framework

Christophe Delas,[†] Hirokazu Urabe,[‡] and Fumie Sato*,[†]

Departments of Biomolecular Engineering and Biological
Information, Graduate School of Bioscience and
Biotechnology, Tokyo Institute of Technology
4259 Nagatsuta-cho, Midori-ku, Yokohama
Kanagawa 226-8501, Japan

Received May 29, 2001
Revised Manuscript Received June 28, 2001

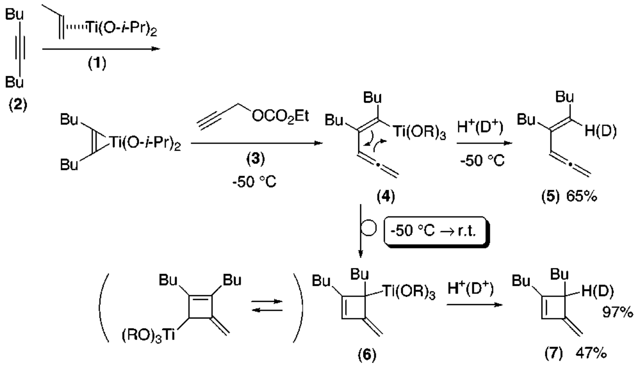
Electrocyclization of vinylallenes to methylenecyclobutenes as shown in eq 1 is a straightforward method to prepare cyclobutene derivatives from open-chain precursors.[1−4] However, this process often requires a very high reaction temperature of up to 350−450 °C, which is not recommended for routine laboratory equipment. Moreover, equilibrium between vinylallene and methylenecyclobutene tends to result in the formation of a mixture of the starting material and the product,[2−4] or the preferred production of vinylallene.[1a] These two weaknesses associated with this transformation so far detract from its practical value in the synthesis of cyclobutenes. To make this reaction a more routine synthetic method, efforts should be directed to find a unidirectional process under mild reaction conditions.[4] Herein we disclose that the isomerization of various titanated vinylallenes ($R^1 = Ti(OR)_3$ in eq 1), which most likely involves the electrocyclization as above, took place smoothly even at 0 °C to give the corresponding cyclobutenyltitanium species. The starting titanated vinylallenes are readily generated in situ via the acetylene coupling reaction with a divalent titanium alkoxide, which is another advantageous feature from the synthetic point of view.



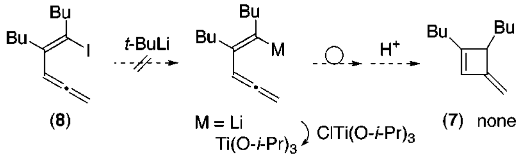
(1)

During the course of our study on the coupling of alkynes with a divalent titanium alkoxide complex, (η^2-propene)Ti(O-*i*-Pr)$_2$ (**1**)[5] prepared in situ from Ti(O-*i*-Pr)$_4$ and *i*-PrMgCl (Scheme 1), we were surprised to find that the coupling of an internal alkyne **2** and a propargyl carbonate **3** directly afforded methylenecyclobutene **7** after hydrolytic workup at room temperature.[6] As depicted in Scheme 1, this reaction involves (i) the first generation of the titanated vinylallene intermediate **4** at −50 °C, the presence of which was unambiguously verified by hydrolysis and deuteriolysis at the same temperature to give **5**,[7] and (ii) most likely, *electrocyclization of the metalated vinylallene* **4** *to methylenecyclobutene* **6** *during the warming from −50 °C to room temperature (or even 0 °C, vide infra)!* The presence of the intermediate methylenecyclobutenyltitanium species **6** was, in fact, confirmed by the deuteriolysis, giving **7**-d_1 with very high deuterium incorporation.

Scheme 1. Preparation of a Cyclobutene Derivative from a Titanated Vinylallene



A more detailed study on the formation of compound **6** (Scheme 1) revealed that the isomerization from **4** to **6** occurred even at 0 °C. Thus, the conversion reached around 50% at 0 °C for 3 h and, after 12 h at 0 °C, hydrolytic workup afforded the exclusive formation of the methylenecyclobutene **7** in the same yield as shown in Scheme 1, accompanied by no more than a trace amount of the uncyclized vinylallene **5**.[8] However, the isomerization did not reach completion at −10 °C for a prolonged period. Other control experiments confirmed the importance of the titanated moiety in this reaction. First, the electrocyclization of nonmetalated vinylallene **5** did not proceed at all under similar reaction conditions as shown in Scheme 1. Thus, on treatment with Ti(O-*i*-Pr)$_4$ and MgCl$_2$ in ether at room temperature for 18 h,[9] vinylallene **5** remained unchanged and was recovered in quantitative yield. Second, an attempt to obtain the cyclobutene from the lithiated or titanated vinylallene starting from the iodide **8**[7] was unsuccessful due to failure to achieve the clean formation of the intermediate vinyllithium species (eq 2). Thus, the method of Scheme 1 adopted by us appears to be an indispensable route to generate the metalated vinylallenes.



(2)

[†] Department of Biomolecular Engineering.

[‡] Department of Biological Information.

(1) For review, see: (a) Marvell, E. N. *Thermal Electrocyclic Reactions*; Academic Press: New York, 1980; pp 145−146. (b) Schuster, H. F.; Coppola, G. M. *Allenes in Organic Synthesis*; Wiley: New York, 1984; pp 89−104.

(2) Pasto, D. J.; Kong, W. *J. Org. Chem.* **1989**, *54*, 4028−4033.

(3) Gil-Av, E.; Herling, J. *Tetrahedron Lett.* **1967**, 1−4. Schneider, R.; Siegel, H.; Hopf, H. *Liebigs Ann. Chem.* **1981**, 1812−1825.

(4) A few recent examples that improved these limitations are as follows: (i) vinylallenes incorporated in the retinoid system participated in the unidirectional cyclization at a temperature as low as 90−110 °C to give cyclobutenes (ref 4a) and (ii) silylated vinylallenes (R^1 or $R^2 = SiR_3$ in eq 1) underwent the electrocyclization to give cyclobutenes at 145 °C (ref 4b). (a) Rey, J. G.; Rodríguez, J.; de Lera, A. R. *Tetrahedron Lett.* **1993**, *34*, 6293−6296. (b) Murakami, M.; Amii, H.; Itami, K.; Ito, Y. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1476−1477.

(5) Sato, F.; Urabe, H.; Okamoto, S. *Pure Appl. Chem.* **1999**, *71*, 1511−1519. Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2787−2834. Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835−2886. Sato, F.; Urabe, H.; Okamoto, S. *Synlett* **2000**, 753−775. Eisch, J. J. *J. Organomet. Chem.* **2001**, *617−618*, 148−157.

(6) Detailed procedures are shown in the Supporting Information.

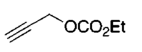
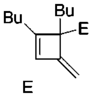
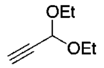
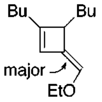
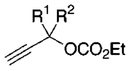
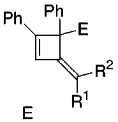
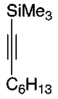
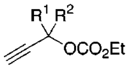
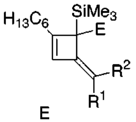
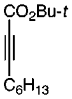
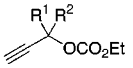
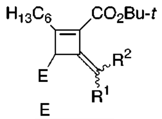
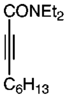
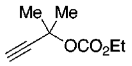
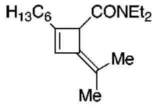
(7) Okamoto, S.; Takayama, Y.; Gao, Y.; Sato, F. *Synthesis* **2000**, 975−979.

(8) Thus, the reaction temperature necessary for the electrocyclization of vinylallenes seems to decrease in the following order: R^1 (in eq 1) = H (over 300 °C, refs 1a and 2−4) > SiR$_3$ (145 °C, ref 4b) > Ti(OR)$_3$ (0 °C, this work). Although the exact role of the metalated moiety to facilitate this vinylallene cyclization is a subject for further study, the generation of an allylmetal species that gains stabilization by allylic conjugation from the unstable vinylmetal compound may account for this fact.

(9) We, at first, suspected that the titanium or magnesium salts in the reaction medium might promote the isomerization of vinylallenes, because Lewis acids are effective in some concerted reactions. Urabe, H.; Sato, F. In *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, 2000; Vol. 2, pp 653−798. See also: Hopf, H.; Lenich, F. Th. *Chem. Ber.* **1973**, *106*, 3461−3462.

10.1021/ja016307v CCC: $20.00

Table 1. Preparation of Various Cyclobutene Derivatives According to Scheme 1

Entry	Acetylenes	Electrophile (E$^+$)	Product	Yield (%)[a]
	 			
			E	
1		H$^+$	H (**7**)	47
2		D$^+$	D (**7**-d$_1$)	46 (>97%d)
3		PhCHO	PhCH(OH)- (**9**)	51 (60:40)[b]
4	 	H$^+$	 (**10**)	85 (80:20)[c]
	 			
	R^1 R^2		E	
5	H H	H$^+$	H (**11**)	61
6	Me Me	H$^+$	H (**12**)	85
	 			
	R^1 R^2		E	
7	H H	H$^+$	H (**13**)	60
8	H H	D$^+$	D (**13**-d$_1$)	60 (>97%d)
9	Me Me	H$^+$	H (**14**)	72
	 			
	R^1 R^2		E	
10	H H	H$^+$	H (**15**)	55
11	H H	D$^+$	D (**15**-d$_1$)	55 (>97%d)
12	H C$_5$H$_{11}$	H$^+$	H (**16**)	55 (68:32)[c]
13	 	H$^+$	 (**17**)	71

[a] Isolated yields. [b] Diastereomeric ratio. Major and minor structures have not been assigned. [c] The ratio of olefinic geometry. Structural assignment has not been made except for entry 4.

The present ring closure of titanated vinylallenes at room temperature seems to be quite general as shown in Table 1.[6] The cyclobutenes **7** and **9**−**12** (entries 1−6) were obtained virtually as a single product with respect to the position of the double bonds. Moreover, as shown in entries 7−9, the first coupling of the two unsymmetrical acetylenes giving titanated vinylallenes was also highly regioselective[7,10] to give single cyclobutenes **13** or **14**. The intermediate organotitanium species served as a reagent for the introduction of a synthetically useful cyclobutenyl moiety to electrophiles, which was illustrated by the reaction with an aldehyde (entry 3), affording alcohol **9**. This cyclization is also applicable to the preparation of functionalized cyclobutenes such as those in entries 10−13. Thus, the coupling of the acetylenic ester and propargyl carbonate in entry 10 proceeded in a highly regioselective manner as reported previously[10] to give the titanated vinylallene intermediate,[11] which directly afforded the expected functionalized cyclobutene **15** upon hydrolysis. The presence of the titanated intermediate was confirmed analogously by deuteriolysis (entry 11). Acetylenic amide and the propargyl derivative in entry 13 behaved similarly to give the single cyclobutene **17** in good yield. The position of the introduced cyclobutene double bond is heavily dependent upon the kind of substrate as shown in entries 10−13, even though single olefinic isomers were always produced.

In summary, titanated vinylallenes underwent facile isomerization to cyclobutenyltitanium compounds[12] at room temperature (or even 0 °C). The overall ease of the experimental operations and the production of single olefinic isomers should make this transformation quite useful for the preparation of cyclobutene derivatives.[13]

Acknowledgment. We are grateful to the Japan Society for the Promotion of Science for financial support. C.D. thanks the same organization for a postdoctoral fellowship.

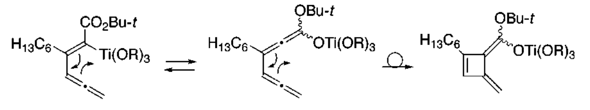
Supporting Information Available: Experimental procedures and physical properties of products (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

JA016307V

---

(10) Hamada, T.; Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 7342−7344.

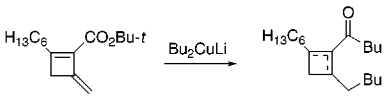
(11) The intermediate organotitanium species in this case would be the enolate form **ii** rather than C-metalated species **i**. The bis-allene structure found in **ii** is also a possible intermediate to give **iii**, because electrocyclization of bis-allenes is known to be more feasible than the vinylallene cyclizations. See refs 1a, 2, 4, and the following: Toda, F.; Garratt, P. *Chem. Rev.* **1992**, *92*, 1685−1707. The enolate form **iii** may account for the different regioselection of the protonation yielding **15** (and **16**) as compared to other entries of Table 1, where the intermediates before protonation are (entries 1−9) or would be (entry 13) C-titanated species.



(I) **(II)** **(III)**

(12) For synthetic application of organotitanium compounds, see: Reetz, M. T. *Organotitanium Reagents in Organic Synthesis*; Springer-Verlag: Berlin, 1986. Ferreri, C.; Palumbo, G.; Caputo, R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, pp 139−172. Reetz, M. T. In *Organometallics in Synthesis*; Schlosser, M., Ed.; Wiley: Chichester, 1994; pp 195−282.

(13) For most recent reports on the preparation and synthetic application of cyclobutenes, see: Durst, T.; Breau, L. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, pp 675−697. Bauvry, N.; Huet, F. *J. Org. Chem.* **2001**, *66*, 583−588. Takahashi, T.; Shen, B.; Nakajima, K.; Xi, Z. *J. Org. Chem.* **1999**, *64*, 8706−8708. Piers, E.; Boehringer, E. M.; Yee, J. G. K. *J. Org. Chem.* **1998**, *63*, 8642−8643. Barbero, A.; Cuadrado, P.; García, C.; Rincón, J. A.; Pulido, F. J. *J. Org. Chem.* **1998**, *63*, 7531−7533. Tallarico, J. A.; Randall, M. L.; Snapper, M. L. *Tetrahedron* **1997**, *53*, 16511−16520. Gourdel-Martin, M.-E.; Huet, F. *J. Org. Chem.* **1997**, *62*, 2166−2172. Niwayama, S.; Kallel, E. A.; Spellmeyer, D. C.; Sheu, C.; Houk, K. N. *J. Org. Chem.* **1996**, *61*, 2813−2825. We found that consecutive carbocupration (to the exo-cyclic double bond) and carbonyl addition of Bu$_2$CuLi to **15** afforded the bis-butylated product in good yield, some synthetic applications of which will be reported in due course.



(15) 80%