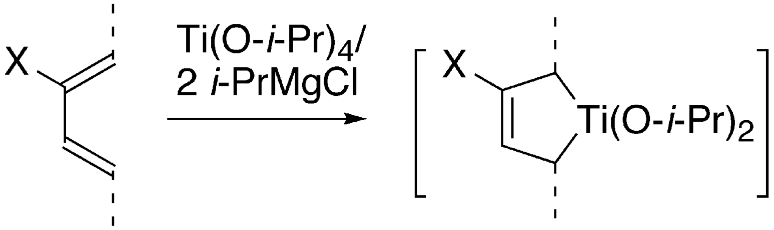
JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

Titanium Alkoxide Complex of Functionalized Conjugated Dienes. A Versatile Bis-anionic Template for Stereoselective Construction of Carbon Frameworks

Hirokazu Urabe, Kazuhisa Mitsui, Shinya Ohta, and Fumie Sato

J. Am. Chem. Soc., **2003**, 125 (20), 6074-6075• DOI: 10.1021/ja0341844 • Publication Date (Web): 26 April 2003



X = $CO_2R^{(*)}$, $CONR_2$, $OSiR_3$

ACS Publications
High quality. High impact.

Journal of the American Chemical Society is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

J|A|C|S
COMMUNICATIONS

Titanium Alkoxide Complex of Functionalized Conjugated Dienes. A Versatile Bis-anionic Template for Stereoselective Construction of Carbon Frameworks

Hirokazu Urabe,*,† Kazuhisa Mitsui,† Shinya Ohta,† and Fumie Sato*,‡

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

Received January 15, 2003; E-mail: hurabe@bio.titech.ac.jp; fsato@bio.titech.ac.jp

Conjugated diene-group 4 metal (Ti or Zr) complexes, hereby depicted as the form of Δ^3-metalacyclopentene **B** representative of the other possible structures **A** and **C** (Figure 1), have been generated from the corresponding dienes and a low-valent metal species.[1−3] While isomeric Δ^2-metalacyclopentenes **D** have found broad and intensive use in organic synthesis,[2,4] such applications of the Δ^3-isomer **B** are so far much less explored.[5] We report herein the generation and reactions of functionalized diene-titanium alkoxide complexes, where the functional groups play a pivotal role in the realization of unique synthetic transformations.

Functionalized conjugated diene **2**, readily prepared by the titanium-mediated coupling of acetylenes,[6] was treated with a titanium(II) alkoxide reagent, Ti(O-*i*-Pr)$_4$/2*i*-PrMgCl (**1**),[2,7] at −50 °C to generate titanacyclopentene **3**, the presence of which was verified by the production of monoolefin **4** (as a single *E*-isomer) or its deuterated counterpart **4**-d_2 (with almost complete deuterium incorporation, ds = diastereoselectivity) after hydrolysis or deuteriolysis (Scheme 1). Titanacycle **3** underwent the addition to aldehydes in a highly regio- and stereoselective manner to give adducts **6**−**9** involving a quaternary carbon center[8] and an (*E*)-olefin after hydroytic workup. The shown relative stereochemistry of representative **7a** was unambiguously determined by derivatization.[9] The Me$_3$Si group in the products could be desilylated in subsequent transformations (see Scheme 2), or the Me$_2$PhSi group in **7b** was converted to a hydroxy group by the Tamao−Fleming oxidation[10] to give **11** (Scheme 1).[9]

More importantly, iodinolysis of oxatitanacycles **5** gave iodides **10** as a 95:5 mixture of *two* isomers, which must reflect the diastereoselectivity of the step of aldehyde addition (93:7) rather than that of the iodination step. *Thus, the iodination itself proceeded with nearly complete stereoselectivity to create three stereogenic centers in one pot!* The shown stereochemistry of **10a** was verified by derivatization.[9,11]

Switching the *tert*-butyl ester of **2** to a chiral auxiliary would lead to asymmetric construction of multiple stereocenters (Scheme 2). Of several chiral substrates examined,[9] diene **12**[6,12] derived from (−)-8-phenylmenthol was found to be the most satisfactory one. The titanacycle from **12** reacted with an aldehyde to give adduct **13** with high asymmetric induction as well as diastereoselectivity. The absolute configuration of **13** was confirmed by derivatization.[9] Removal of the chiral auxiliary with Dibal (to **15**), followed by desilylation with a base,[13] gave pure stereodefined diol **16**. Alternatively, the stereoselective iodinolysis of the intermediate oxatitanacycle as described in Scheme 1 created three consecutive *chiral* centers to give optically active iodo alcohol **14**, which was isolated as a single isomer.

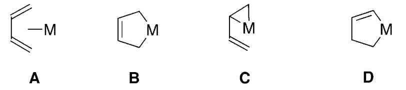
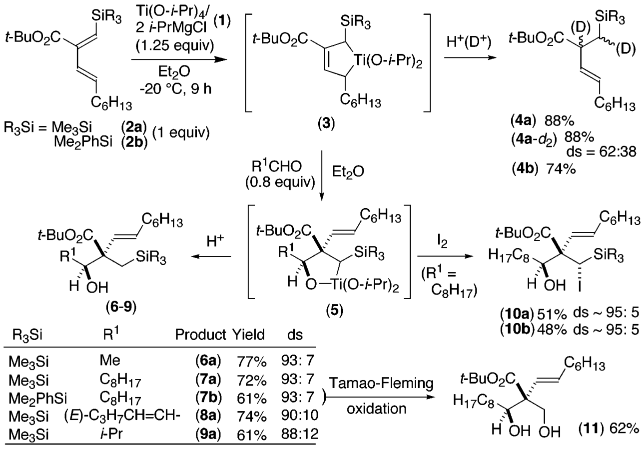


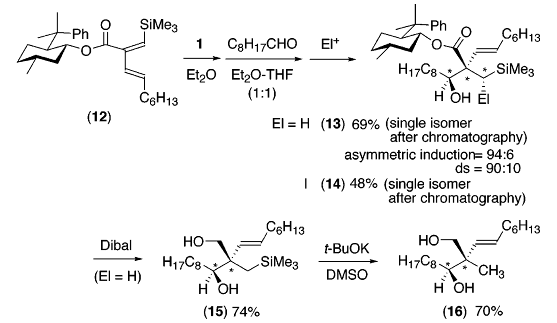
Figure 1. Conjugated diene-metal complexes **A**−**C** and Δ^2-metalacyclopentene **D** (M = metal).

Scheme 1. Construction of Multistereogenic Centers on the Template of Δ^3-Titanacyclopentene



R$_3$Si	R^1	Product	Yield	ds
Me$_3$Si	Me	(**6a**)	77%	93: 7
Me$_3$Si	C$_8$H$_{17}$	(**7a**)	72%	93: 7
Me$_2$PhSi	C$_8$H$_{17}$	(**7b**)	61%	93: 7
Me$_3$Si	(*E*)-C$_3$H$_7$CH=CH-	(**8a**)	74%	90:10
Me$_3$Si	*i*-Pr	(**9a**)	61%	88:12

Scheme 2. Asymmetric Induction to Multiple Centers via the Chiral Template



The titanacycle formation is also valid to cyclic dienes such as **17**,[6] giving monoolefins **19** after hydrolysis (Scheme 3). While the regioselective addition of titanacycle **18** to an aldehyde was again viable, the diastereoselectivity between the alcoholic and quaternary carbons of the products **20** (i.e., 1,2-ds) considerably decreased as compared to that of the open-chain products in Scheme 1. On the other hand, the stereocontrol of the incoming aldehyde by the lactam substituent R (=*i*-Pr) was virtually perfect to give **20b** with very high 1,3-ds as shown in Scheme 3.[9]

While other functionalized dienes **21** and **22**[6] in Figure 2 generated diene complexes as well,[9] nonfunctionalized **23** and **24**,[6] having an alkyl chain in place of the carbonyl group of **2** or **17**, did not form the complexes. Besides these dienes, the exposure of 2-siloxybutadienes **25**[14] to **1** generated the desired diene-titanium

---

† Department of Biological Information.
‡ Department of Biomolecular Engineering.

10.1021/ja0341844 CCC: $25.00

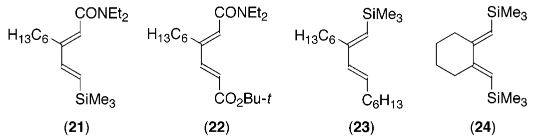
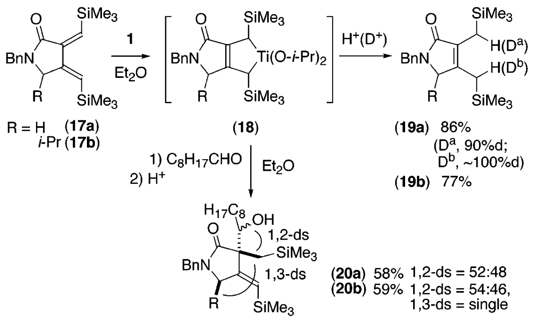
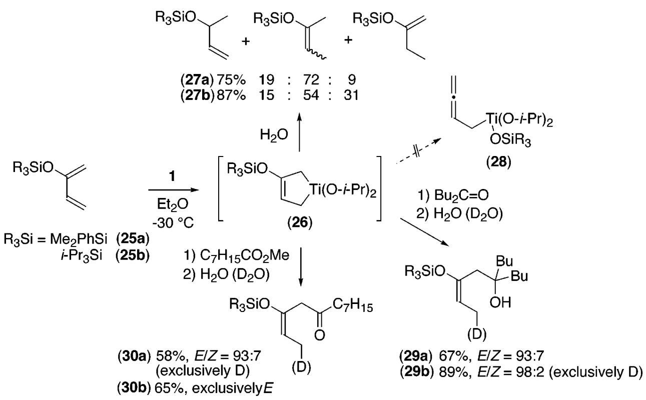


Figure 2.

Scheme 3. Generation and Reaction of Bicyclic Δ^3-Titanacyclopentene



Scheme 4. Siloxy-Substituted Δ^3-Titanacyclopentenes as a Reactive Template



alkoxide complexes **26** in good yields, as evidenced by their hydrolysis affording monoolefins **27** (Scheme 4). Elimination of the siloxy group from the titanacycle **26** (to (allenylmethyl)titanium species **28**) was not observed.[15] On the contrary, the coupling of **26** with carbonyl compounds followed by hydrolysis proceeded in a highly regio- and stereoselective manner to give stereodefined functionalized enol silyl ethers **29** and **30**, which are otherwise difficult to obtain.[14]

In conclusion, functionalized conjugated diene-titanium alkoxide complexes provide versatile templates for organic synthesis, where the functional group promotes the complex formation, controls regio- and stereoselectivities of the subsequent reactions, and imparts a chiral element to the template. Further applications of these complexes will be reported in due course.

Acknowledgment. We thank the Japan Society for the Promotion of Science and Kurata Foundation (to H.U.) for financial support.

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

References

(1) Yasuda, H.; Nakamura, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 723−742. Yasuda, H.; Tatsumi, K.; Nakamura, A. *Acc. Chem. Res.* **1985**, *18*, 120−126. Erker, G. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 397−412.

(2) Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev.* **2000**, *100*, 2835−2886.

(3) As far as titanium complexes are concerned, Δ^3-titanacyclopentene (**B** in Figure 1) was identified for the isoprene-titanium aryloxide complex: Balaich G. J.; Hill, J. E.; Waratuke, S. A.; Fanwick, P. E.; Rothwell, I. P. *Organometallics* **1995**, *14*, 656−665. For an example of structural variations **A** and **B**, see: Devore, D. D.; Timmers, F. J.; Hasha, D. L.; Rosen, R. K.; Marks, T. J.; Deck, P. A.; Stern, C. L. *Organometallics* **1995**, *14*, 3132−3134.

(4) For reviews, see: Aubert, C.; Buisine, O.; Malacria, M. *Chem. Rev.* **2002**, *102*, 813−834. Negishi, E.; Takahashi, T. *Acc. Chem. Res.* **1994**, *27*, 124−130. Negishi, E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, pp 1163−1184. Buchwald, S. L.; Nielsen, R. B. *Chem. Rev.* **1988**, *88*, 1047−1058.

(5) Although several synthetic reactions of nonfunctionalized diene-group 4 metal complexes have been reported, the lack of diversity in these complexes appears to intrinsically limit the development of broad synthetic applications. Ti: ref 3. Urabe, H.; Takeda, T.; Sato, F. *Tetrahedron Lett.* **1996**, *37*, 1253−1256. Zubaidha, P. K.; Kasatkin, A.; Sato, F. *Chem. Commun.* **1996**, 197−198. Williams, C. M.; Chaplinski, V.; Schreiner, P. R.; de Meijere, A. *Tetrahedron Lett.* **1998**, *39*, 7695−7698. Zr: Maye, J. P.; Negishi, E. *J. Chem. Soc., Chem. Commun.* **1993**, 1830−1831. López, L.; Berlekamp, M.; Kowalski, D.; Erker, G. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1114−1116. Erker, G.; Berlekamp, M.; Lopez, L.; Grehl, M.; Schönecker, B.; Krieg, R. *Synthesis* **1994**, 212−222. For relevant Δ^3-metalacyclopentenes of magnesium, see: Rieke, R. D.; Sell, M. S. In *Handbook of Grignard Reagents*; Silverman, G. S., Rakita, P. E., Eds.; Marcel Dekker: New York, 1996; pp 527−555.

(6) Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 1245−1255. Hamada, T.; Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 7342−7344. Urabe, H.; Nakajima, R.; Sato, F. *Org. Lett.* **2000**, *2*, 3481−3484.

(7) Kulinkovich, O. G.; de Meijere, A. *Chem. Rev.* **2000**, *100*, 2789−2834. Eisch, J. J. *J. Organomet. Chem.* **2001**, *617−618*, 148−157. Sato, F.; Okamoto, S. *Adv. Synth. Catal.* **2001**, *343*, 759−784. Sato, F.; Urabe, H. In *Titanium and Zirconium in Organic Synthesis*; Marek, I., Ed.; Wiley-VCH: Weinheim, 2002; pp 319−354.

(8) Fuji, K. *Chem. Rev.* **1993**, *93*, 2037−2066. Corey, E. J.; Guzman-Perez, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 388−401 and references therein.

(9) For details, see the Supporting Information.

(10) Tamao, K.; Ishida, N.; Kumada, M. *J. Org. Chem.* **1983**, *48*, 2120−2122. Fleming, I.; Henning, R.; Plaut, H. *J. Chem. Soc., Chem. Commun.* **1984**, 29−31. Benkeser, R. A.; Hoke, D. I.; Hickner, R. A. *J. Am. Chem. Soc.* **1958**, *80*, 5294−5297. For a review, see: Jones, G. R.; Landais, Y. *Tetrahedron* **1996**, *52*, 7599−7662.

(11) As far as we know, dependable data on the stereochemical course of iodination of an sp^3-carbon−titanium bond (either retention or inversion) are not available at present except for this work (see the Supporting Information). That the deuteriolysis in place of the iodinolysis also proceeds with complete stereoselectivity was separately observed (see **8a**-d_1 in the Supporting Information).

(12) Urabe, H.; Kusaka, K.; Suzuki, D.; Sato, F. *Tetrahedron Lett.* **2002**, *43*, 285−289.

(13) Trost, B. M.; Phan, L. T. *Tetrahedron Lett.* **1993**, *34*, 4735−4738.

(14) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063−2192. Pawlenko, S. In *Houben-Weyl Methods of Organic Chemistry*, 4th ed.; Kropf, H., Schaumann, E., Eds.; Thieme: Stuttgart, 1993; Vol. E15/1, pp 404−462. Weber, W. P. *Silicon Reagents for Organic Synthesis*; Springer-Verlag: Berlin, 1983; pp 206−272. Colvin, E. W. *Silicon in Organic Synthesis*; Butterworth: London, 1981; pp 198−287.

(15) Cf.: Chinkov, N.; Majumdar, S.; Marek, I. *J. Am. Chem. Soc.* **2002**, *124*, 10282−10283.

JA0341844