Selective Reaction of Aldehydes with Bicyclic Titanacyclopentadienes or Titanacyclopentenes Prepared *in Situ* from 1,6- or 1,7-Diynes or Enynes and (η^2-Propene)Ti(O-i-Pr)$_2$

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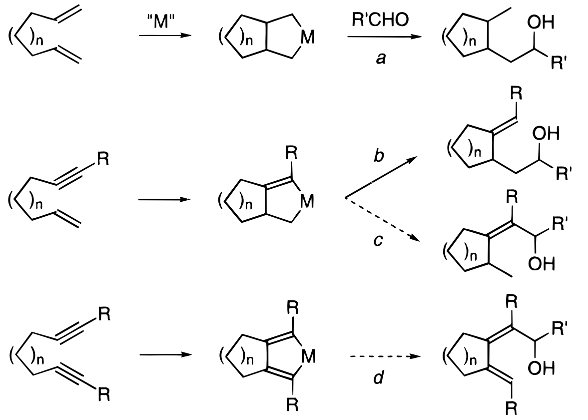
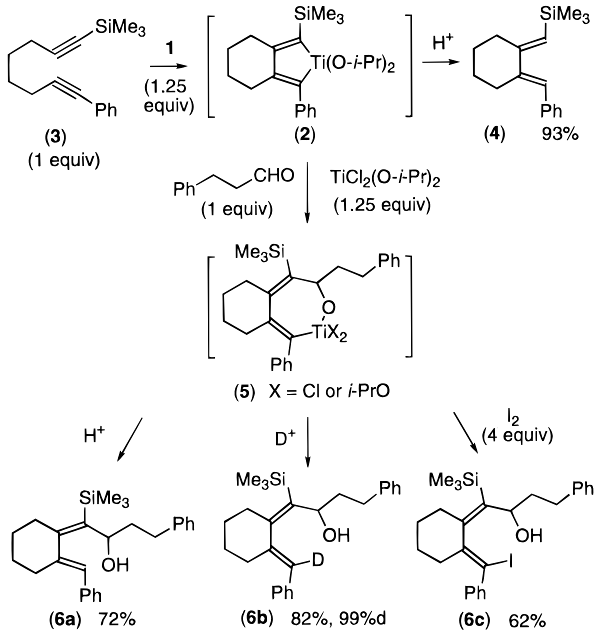
Bicyclic metallacycles of early transition metals such as titanium and zirconium (Scheme 1, M = metal), which are prepared from 1,6- or 1,7-dienes, -enynes, and -diynes and a stoichiometric amount of the low-valent metal complexes, have been widely accepted as useful reagents.[1] In addition to simple hydrolysis (or deuterolysis), their halogenolysis and reactions with other heteroatom electrophiles have been utilized to prepare functionalized 5- and 6-membered carbocycles.[2] The reaction of these metallacycles with aldehydes should provide a versatile method for the side chain extension after the cyclization. The known example involves the reactions of Cp$_2$-zirconacyclo*pentanes* and -cyclo*pentenes*, in which the *alkyl*−Zr bond is always transferred to aldehydes to give the corresponding 1:1 adducts (Scheme 1, paths *a* and *b*, but not *c*).[1a,3] Although the addition of bis(aryloxy)-titanacyclo*pentadienes* (generated from diethylacetylene or *tert*-butylacetylene) to benzophenone has been documented,[4] the application of metal-mediated bicyclization of diynes followed by aldehyde addition was not known (Scheme 1, path *d*).[5] Recently, we reported a low-valent titanium-mediated bicyclization of the aforementioned unsaturated compounds, in which a stoichiometric amount of (η^2-propene)Ti(O-i-Pr)$_2$ (**1**),[6,7] prepared *in situ* from inexpensive Ti(O-i-Pr)$_4$ and i-PrMgCl, was used.[8] In this paper, we will show selective reactions of path *d* as well as *c* by using this titanium complex.

Scheme 1



Scheme 2. Reaction of a Titanacyclopentadiene: Interception of Intermediates



Gratifyingly, titanacyclopentadiene **2** (>93% yield as estimated by protonolysis) generated from the diyne **3** and **1** reacted with an aldehyde preferably in the presence of an additional equivalent of TiCl$_2$(O-i-Pr)$_2$ (*vide infra*) to give the adduct **6a** in a good yield after hydrolysis (Scheme 2).[9] The reaction was highly regioselective: virtually no trace of another regioisomer formed. The reaction should proceed through the intermediate titanium species **5**, the presence of which was verified by its deuterolysis and iodinolysis as shown, to give the corresponding products **6b** and **c**.

This cyclization/aldehyde addition seems to be general for various 1,6- and 1,7-diynes as shown in Table 1, entries 1−7. A substituted nitrogen heterocycle (Table 1, entry 4) and cyclopentane frameworks (Table 1, entries 5−7) could be prepared as well. In the case of diynes having one trimethylsilyl group, the addition to alde-

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(1) (a) Buchwald, S. L.; Nielsen, R. B. *Chem. Rev.* **1988**, *88*, 1047. (b) Negishi, E. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, p 1163. (c) Negishi, E.; Takahashi, T. *Acc. Chem. Res.* **1994**, *27*, 124 and other review articles cited therein.

(2) For examples, see: Nugent, W. A.; Taber, D. F. *J. Am. Chem. Soc.* **1989**, *111*, 6435. Buchwald, S. L.; Nielsen, R. B. *J. Am. Chem. Soc.* **1989**, *111*, 2870. Fisher, R. A.; Nielsen R. B.; Davis, W. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 165. Fagan, P. J.; Nugent, W. A.; Calabrese, J. C. *J. Am. Chem. Soc.* **1994**, *116*, 1880 and references cited therein. Regioselective reactions of Cp$_2$-zirconacycles with heteroatom electrophiles are also possible; see: Takahashi, T.; Aoyagi, K.; Hara, R.; Suzuki, N. *Chem. Lett.* **1992**, 1693. Takahashi, T.; Aoyagi, K.; Hara, R.; Suzuki, N. *J. Chem. Soc., Chem. Commun.* **1993**, 1042. Takahashi, T.; Aoyagi, K.; Kondakov, D. Y. *J. Chem. Soc., Chem. Commun.* **1994**, 747. Mori, M.; Uesaka, N.; Saitoh, F.; Shibasaki, M. *J. Org. Chem.* **1994**, *59*, 5643.

(3) Copéret, C.; Negishi, E.; Xi, Z.; Takahashi, T. *Tetrahedron Lett.* **1994**, *35*, 695.

(4) Hill, J. E.; Balaich, G.; Fanwick, P. E.; Rothwell, I. P. *Organometallics* **1993**, *12*, 2911.

(5) Other methods for carbon−carbon bond formation based on metallacyclopentadienes of early transition metals have been reported. For ring closure with an olefin, acetylene, or nitrile, see ref 4. Takahashi, T.; Kotora, M.; Xi, Z. *J. Chem. Soc., Chem. Commun.* **1995**, 361. Balaich, G. J.; Rothwell, I. P. *Tetrahedron* **1995**, *51*, 4463. For copper-promoted allylation, see: Takahashi, T.; Kotora, M.; Kasai, K.; Suzuki, N. *Organometallics* **1994**, *13*, 4183.

(6) The generation of olefin (derived from the added Grignard reagent)−titanium complexes from Ti(OR)$_4$ and Grignard reagents was first reported by Kulinkovich *et al.* They utilized this complex as 1,2-bis-anionic species; see: Kulinkovich, O. G.; Sviridov, S. V.; Vasilevski, D. A. *Synthesis* **1991**, 234. See also: Corey, E. J.; Rao, S. A.; Noe, M. C. *J. Am. Chem. Soc.* **1994**, *116*, 9345.

(7) For the initial reports on the use of (η^2-propene)Ti(O-i-Pr)$_2$ prepared *in situ* from Ti(O-i-Pr)$_4$ and i-PrMgCl as a divalent titanium reagent, see: Harada, K.; Urabe, H.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 3203. Kasatkin, A.; Nakagawa, T.; Okamoto, S.; Sato, F. *J. Am. Chem. Soc.* **1995**, *117*, 3881. See also: Okamoto, S.; Kasatkin, A.; Zubaidha, P. K.; Sato, F. *J. Am. Chem. Soc.* **1996**, *118*, 2208. Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 4198.

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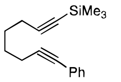
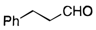
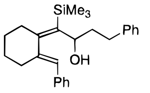
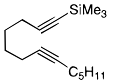
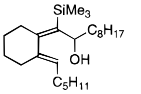
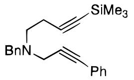
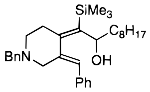
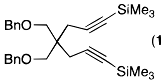
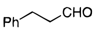
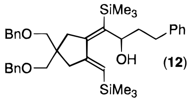
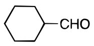
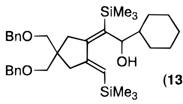
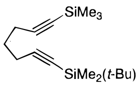
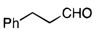
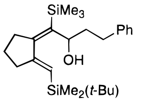
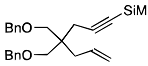
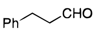
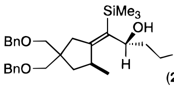
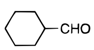
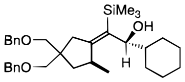
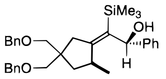
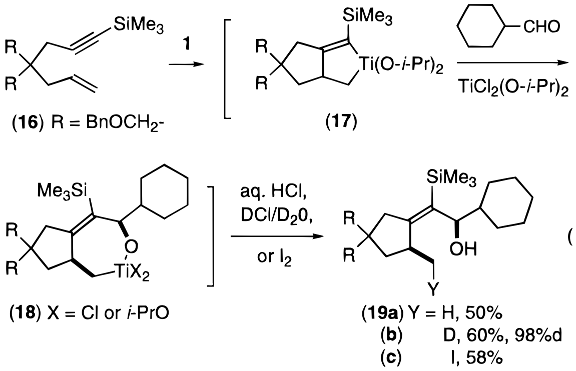
Table 1. Cyclization of Diynes or an Enyne and Subsequent Reaction with Aldehydes[a]

Entry	Diyne or enyne	Aldehyde (equiv)	Product	Yield (%)[b] [Ds][c]
1	 (**3**)	 (1)	 (**6a**)	72 (82)
2		(2)		80(quant)
3	 (**7**)	C$_8$H$_{17}$CHO (1)	 (**8**)	47
4	 (**9**)	C$_8$H$_{17}$CHO (1)	 (**10**)	73
5	 (**11**)	 (2)	 (**12**)	81
6		 (2)	 (**13**)	59
7	 (**14**)	 (2)	 (**15**)	41
8	 (**16**)	 (2)	 (**20**)[d]	66 [96: 4]
9		 (0.6)	 (**19a**)[d]	(62)[e]
10		(2)		50(53-60) [single[f]]
11		PhCHO[g] (1.5)	 (**21**)[d]	54 [>95:<5]

[a] See Scheme 2 and eq 1. [b] Isolated yields. Yields determined by ^{1}H NMR spectroscopy are shown in parentheses. [c] Diastereoselectivity. [d] For the assignment of stereochemistry see ref 9. [e] Based on aldehyde. [f] Product was isolated as a single isomer. [g] TiCl(O-i-Pr)$_3$ was used as the additive. With TiCl$_2$(O-i-Pr)$_2$, the yield of **21** decreased to 25%.

hydes always proceeded at the carbon having the silyl group. The α-anion stabilizing effect of the silyl group[10] to increase the reactivity of the R$_3$SiC−Ti bond in the titanacyclopentadiene toward aldehyde would account for this regioselectivity. When a diyne having two different silyl groups such as Me$_3$Si and (t-Bu)Me$_2$Si was employed (Table 1, entry 7), the addition to an aldehyde took place at the carbon bearing the less hindered trimethylsilyl group to yield **15**, the regioisomer of which could not be isolated. Thus, from the synthetic point of view, the appropriate choice of acetylenic substituent may discriminate between the two acetylenic termini. The absence of the externally added TiCl$_2$(O-i-Pr)$_2$ in the step of aldehyde addition decreased the product yields by 10−30%. Although the exact role of the titanium salt is unclear at present, it may activate the aldehyde as a Lewis acid and/or increase the reactivity of the titanacycle via ligand exchange reaction.[11]

The finding of the smooth transfer of the alkenyl−metal bond in the titanacyclopentadienes prompted us to investigate the addition of the metallacyclo*pentene* to aldehydes. When the titanabicycle **17**, generated *in situ* from **16** and **1** (in 90−97% yield determined by hydrolysis and deuterolysis),[8a] was allowed to react with cyclohexanecarbaldehyde in the presence of an extra equivalent of TiCl$_2$(O-i-Pr)$_2$ as above, the desired product **19a** was obtained in 50% yield with very high regio- and stereoselectivities (eq 1 and Table 1, entry 10).[9] The presence of the intermediate titanium species **18** was confirmed by subsequent deuterolysis or iodinolysis to give the corresponding deuterated product **19b** or the iodide **19c**. As shown in Table 1, aliphatic aldehydes afforded the products in good yields under standard reaction conditions; however, for an aromatic aldehyde, the use of TiCl(O-i-Pr)$_3$ in place of TiCl$_2$(O-i-Pr)$_2$ was recommended as the additive (Table 1, entry 11). The present reaction has two characteristic features. The first is that the aldehyde addition proceeded selectively at the alkenyl− rather than alkyl−metal bond of the titanacycle, which is in marked contrast to the aforementioned reactions of Cp$_2$-zirconacyclopentenes (Scheme 1, path *b vs c*).[12] The second point is the very high 1,4-diastereoselectivity of the resultant allyl alcohol (generally, >95:<5 by ^{1}H NMR analysis in comparison with an authentic sample), the relative stereochemistry of which was assigned as shown in Table 1.[9]



(**16**) R = BnOCH$_2$- (**17**)

(**18**) X = Cl or i-PrO

(**19a**) Y = H, 50%
(**b**) D, 60%, 98%d
(**c**) I, 58%

(1)

Supporting Information Available: Typical procedures for the preparation of **6a**−**c**, **19a**−**c**, and **21**, physical properties of all starting materials and products, and structural determination of several compounds (12 pages).

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(8) (a) Urabe, H.; Hata, T.; Sato, F. *Tetrahedron Lett.* **1995**, *36*, 4261. (b) Urabe, H.; Takeda, T.; Sato, F. *Tetrahedron Lett.* **1996**, *37*, 1253.

(9) The details are described in the supporting information.

(10) Weber, W. P. *Silicon Reagents for Organic Synthesis*; Springer-Verlag: Berlin, 1983. Colvin, E. W. *Silicon in Organic Synthesis*; Butterworth: London, 1981.

(11) 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., Ed.; Pergamon Press: Oxford, 1991; Vol. 1, p 139.

(12) Copper-promoted allylation and 1,4-addition to enones also proceeded at the vinyl-zirconium bond of Cp$_2$-zirconacyclopentenes; see: Kasai, K.; Kotora, M.; Suzuki, N.; Takahashi, T. *J. Chem. Soc., Chem. Commun.* **1995**, 109. Lipshutz, B. H.; Segi, M. *Tetrahedron* **1995**, *51*, 4407.