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Titanium(IV) Aryloxide Catalyzed Cyclization Reactions of 1,6- and 1,7-Dienes

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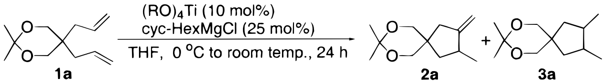
Transformations of unsaturated compounds mediated by stoichiometric quantities of zirconocene or titanocene complexes have received widespread acceptance as valuable methods in organic synthesis, and have been used as key reactions for the total synthesis of natural products.[2] Recently, the generation and subsequent utilization of low-valent complexes of the type $(RO)_2Ti(L)_n$ as alternatives to $Cp_2M(L)_n$ (M = Ti, Zr) in many reactions has been popularized.[3,4] With the exception of a few catalytic reactions,[5−7] the vast majority of transformations involving $(RO)_2Ti(L)_n$ equivalents require stoichiometric amounts of the reagent.[4] Although stoichiometric reactions utilizing inexpensive $(i\text{-PrO})_3TiX$ reagents often generate intermediates containing nucleophilic Ti−C bonds that can be used for further manipulations, the discovery of new *catalytic* processes should permit the use of *specialized* RO− ligands for reaction profile alteration as well as increased efficiency.[5e] In this context, it is noteworthy that all of the catalytic transformations involving $(RO)_2Ti(L)_n$ complexes recorded to date require the use of at least stoichiometric amounts of the driving organometallic reagent.[5−7]

Table 1. Effect of $(RO)_4Ti$ on Catalyzed Cyclisomerization Reaction of 1,6-Dienes **1a** to **2a**



(1)

entry	$(RO)_4Ti$	yield of **2a** (%)[a]
1	$(i\text{-PrO})_4Ti$	(9)
2	$(cyc\text{-HexO})_4Ti$	(38)
3	$(cyc\text{-HexO})_4Ti$ (48 h)	(39)
4	$(PhO)_4Ti$	(68)
5	$(2,6\text{-}Ph_2C_6H_3O)_2TiCl_2$	(14)
6	$(2,6\text{-}Me_2C_6H_3O)_4Ti$	(85)[b]
7[c]	$(2,6\text{-}Me_2C_6H_3O)_4Ti$ (5 mol %)	(85)[b]

In this communication, we wish to report the $(ArO)_2Ti$-catalyzed cycloisomerization of 1,6- and 1,7-dienes to methylenecycloalkanes using catalytic amounts of both $(ArO)_4Ti$ and a Grignard reagent.[8]

In an initial experiment, we found that the reaction of 1,6-diene **1a** with catalytic amounts of $Ti(O\text{-}i\text{-}Pr)_4$ (10 mol %) and $cyc\text{-}C_6H_{11}MgCl$[9] (25 mol %) in THF (0 °C to room temperature, 24 h) afforded methylenecyclopentane **2a** (9%), the corresponding saturated cyclopentane **3a** (7%), and recovered **1a** (84%) (eq 1 and entry 1 in Table 1). This result suggested that the reaction could be rendered catalytic since the conversion (combined yield of **2a** and **3a**) was greater than the amount of the titanium complex. Accordingly, we investigated the reaction using several $Ti(OR)_4$ species to find the appropriate conditions for predominant production of **2a** (entries 1−6, Table 1). It was discovered that the use of $(2,6\text{-}Me_2C_6H_3O)_4Ti$[7a] as a precatalyst provided **2a** in excellent yield (entry 6) and the amount of this titanium compound could be reduced (entry 7). As is also revealed from these data, the nature of the RO group affects the reaction both sterically and electronically. In addition, the reaction may be subject to termination by decomposition of active catalyst (entries 2 and 3). Under identical reaction conditions, $(2,6\text{-}Ph_2C_6H_3O)_2TiCl_2$ did not provide a good yield of **2a**.[7] This is presumably due to steric hindrance of the ArO groups and/or the diminished ability of the Ti center to form an "ate" complex.

Table 2 summarizes representative examples of this reaction using a variety of diene substrates **1b**−**i**. These results show the following features of this cyclization: (1) All of the reactions gave 2-methyl-1-methylenecycloalkanes, i.e., the coupling pro-

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[1] Visiting Research Associate, Montana State University (1998−1999).

[2] (a) Yasuda, H.; Nakamura, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 723. Buchwald, S. L.; Neilsen, R. B. *Chem. Rev.* **1988**, *88*, 1047. (b) Negishi, E. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 5, p 1163. (c) Broene, R. D.; Buchwald, S. L. *Science* **1993**, *261*, 1696. Negishi, E.; Takahashi, T. *Acc. Chem. Res.* **1994**, *27*, 124. Hanzawa, Y.; Ito, H.; Taguchi, T. *Synlett* **1995**, 299. Ohff, A.; Pulst, S.; Lefeber, C.; Peulecke, N.; Arndt, P.; Burkalov, V. V.; Rosenthal, U. *Synlett* **1996**, 111. See also ref 3q. (d) For the stoichiometric use of $CpTi(CH_3)_2Cl$ in synthesis, see: Fairfax, D.; Stein, M.; Livinghouse, T. *Organometallics*, **1997**, *16*, 1523. McGrane, P. L.; Livinghouse, T. *J. Am. Chem. Soc.* **1993**, *115*, 11485 and references therein.

[3] For generation and utility of $(RO)_2Ti(\eta^2\text{-alkene})$ or $(RO)_2Ti(\eta^2\text{-alkyne})$ derived from $Ti(O\text{-}i\text{-}Pr)_4$/Grignard reagent and alkene or alkyne, see: (a) Hamada, T.; Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 7342. (b) Takayama, Y.; Okamoto, S.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 3559. (c) Urabe, H.; Hamada, T.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 2931. (d) Hareau, G. P.-J.; Koiwa, M.; Hikichi, S.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 3640. (e) Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 1245 and references cited therein. Reviews, see: (f) Sato, F.; Urabe, H.; Okamoto, S. *J. Synth. Org. Chem. Jpn.* **1998**, *56*, 424. For generation and utility of (η2-alkene or -alkyne)$Ti(OAr)_2$: (g) Johnson, E. S.; Balaich, G. J.; Rothwell, I. P. *J. Am. Chem. Soc.* **1997**, *119*, 7685. (h) Johnson, E. S.; Balich, G. J.; Fanwick, P. E.; Rothwell, I. P. *J. Am. Chem. Soc.* **1997**, *119*, 11086 and see also ref 7.

[4] After the pioneering work by Kulinkovich and co-workers, in which the alkoxytitanium−alkene complexes were depicted as titanacycloalkene compounds, $(RO)_2Ti^{(IV)}[-CH_2\text{-}CH(R)-]$ and used as vicinal dianionic species, it has been discovered that the alkoxytitanium−alkene complexes could be utilized as a low-valent titanium equivalent via ligand-exchange reactions with double or triple bond(s) present in the substrates.[3,5,6] For exchange reactions involving double bonds, the intermediate alkoxytitanium−alkene complexes have been depicted as $(RO)_2Ti^{II}\text{-}(\eta^2\text{-alkene})$.[3] Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A.; Pritytskaya, T. S. *Zh. Org. Khim.* **1989**, *25*, 2244. Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A.; Savchenko, A. I.; Prityrskaya, T. S. *Zh. Org. Khim.* **1991**, *27*, 294. Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1995**, *117*, 9919. See also: Chaplinski, V.; de Meijere, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 413 and refs 5a,b,e.

[5] For the use of catalytic amounts of a $(RO)_2Ti(L)_n$ equivalent in the synthesis of cyclopropanols, see: (a) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A. *Synthesis* **1991**, 234. (b) Kulinkovich, O. G.; Vasilevskii, D. A.; Savchenko, A. I.; Sviridov, S. V. *Zh. Org. Khim.* **1991**, *27*, 1428. For catalytic cyclo-bis-zincation of enynes, see: (c) Montchamp, J.-L.; Negishi, E. *J. Am. Chem. Soc.* **1998**, *120*, 5345. For catalytic carbometalation of dienes, see: (d) Negishi, E.; Jensen, M. D.; Kondakov, D. Y.; Wang, S. *J. Am. Chem. Soc.* **1994**, *116*, 8404. For ligand modification leading to optically enriched cyclopropanols, see: (e) Corey, E. J.; Rao, S. A.; Noe, M. C. *J. Am. Chem. Soc.* **1994**, *116*, 9345.

[6] Cha has reported *semi*-catalytic hydroxycyclopropanation of olefins using 0.5 equiv of $ClTi(O\text{-}i\text{-}Pr)_3$ and 5 equiv of Grignard reagents: Lee, J.; Kang, C. H.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 291. Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc.* **1996**, *118*, 4198.

[7] (a) $(2,6\text{-}Me_2C_6H_3O)_4Ti$ was prepared by a modification of the literature procedure: Durfee, L. D.; Latesky, S. L.; Rothwell, I. P.; Huffman, J. C.; Folting, K. *Inorg. Chem.* **1985**, *24*, 4569. (b) Rothwell has investigated the cycloisomerization reaction of 1,7-octadiene catalyzed by the bicyclotitanacyclopentane compound, derived from $(2,6\text{-}Ph_2C_6H_3O)TiCl_2$, 2BuLi, and 1,7-octadiene, but this titanacycle could not catalyze the cyclization of 1,6-heptadiene: Waratuke, S. A.; Thorn, M. G.; Hill, J. E.; Waratuke, A. S.; Johnson, E. S.; Fanwick, P. E.; Rothwell, I. P. *J. Am. Chem. Soc.* **1997**, *119*, 8630 and references therein.

[8] Titanocene derivative-catalyzed cyclization of enynes and alkenones has been reported: Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 3182. Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 11688. Kablaoui, N. M.; Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 5818; Kablaoui, N. M.; Hicks, F. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1997**, *119*, 4424. Montchamp, J.-L.; Negishi, E. *J. Am. Chem. Soc.* **1998**, *120*, 5345. Sturla, S. J.; Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 1976.

[9] The ratio of Grignard reagent to $Ti(OAr)_4$ is 2:1. The reaction of **1a** with 50 mol % of $(2,6\text{-}Me_2C_6H_3O)_4Ti$ and 50 mol % of cyc-HexMgCl did not give cyclized product. In initial investigations, we found that the reaction could be carried out by using *i*-PrMgCl, *i*-BuMgCl, *n*-BuMgBr, or cyc-HexMgCl. Among these activators, cyc-HexMgCl gave slightly better yields. The use of EtMgBr did not provide cyclized product.

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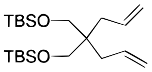
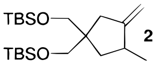
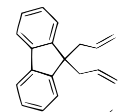
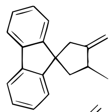
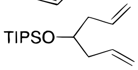
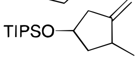
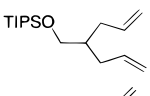
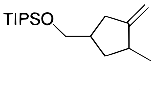
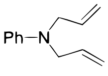
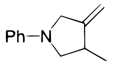
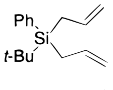
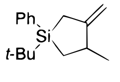
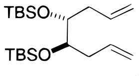
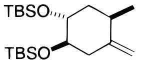
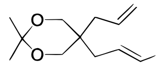
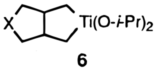
Table 2. Cyclisomerization Reaction of 1,6-Dienes Catalyzed by $(2,6\text{-}Me_2H_3O)_4Ti$ and cyc-HexMgCl

Entry	Substrate, **1**	Product(s) (Yield, %)[a]
1	 **1b**	 **2b** (90)
2	 **1c**	 **2c** (88)
3	 **1d**	 **2d** (85) [d.r. 52:48][b]
4	 **1e**	 **2e** (92) [d.r. 55:45][b]
5[c]	 **1f**	 **2f** (44)[d,e]
6[c]	 **1g**	 **2g** (73)[e] [d.r. 60:40][b]
7	 **1h**	 **2h** (71) [d.r. 96 : 4][b,f]
8	 **1i**	no reaction[e]

[a] Isolated yield. In all entries, a small amount of the saturated compound **3** (5−10% yield) was produced. [b] Ratio was determined by ^1H NMR and/or GC analysis. [c] 20 mol % of a Ti compound and 45 mol % of cyc-HexMgCl were used. [d] The reaction mixture was stirred for 48 h. 29% of **1f** was recovered. [e] Yield was determined by NMR analysis of the crude mixture using an internal standard. [f] For determination of the stereochemistry, see the Supporting Information.

ceeded in a *tail-to-tail* fashion; (2) 4-substituted or 4,4-disubstituted 1,6-dienes are superior substrates for the formation of five-membered-ring compounds; (3) the reaction can be applied to the formation of six-membered-ring carbocycles (entry 7); (4) highly diastereoselective cyclizations can be realized for appropriate substrates (entry 7); (5) heterocycles, such as **2f** and **2g**, can be synthesized by this methodology (entries 5 and 6); and (6) the reaction is not suitable for 1,6-dienes possessing terminal alkene substitution (entry 8).

It has been widely accepted that alkoxides of the type $(RO)_4Ti$ can be easily reduced by Grignard reagents to provide a $(RO)_2Ti$ equivalent in situ.[3−7,10] In addition, Ti(III) hydride complexes are known to be highly active catalysts for alkene isomerization.[11a] In light of these considerations, the active catalyst in the present reaction is postulated to be a transient complex of the type $(2,6\text{-}Me_2C_6H_3O)_2Ti(\eta^2\text{-alkene})$.[11b] On this basis, a possible catalytic cycle is illustrated in Scheme 1. Reaction of the $(RO)_2Ti$ equivalent (prepared in situ *in the presence of diene*) with the diene substrate should generate a metastable bicyclotitanacyclopentane **4**. Complex **4**, in turn, undergoes β-hydride elimination to provide the corresponding Ti−H compound **5**, from which reductive elimination of $Ti(OR)_2$ occurs to produce methylenecyclopentane **2**.[12]



6

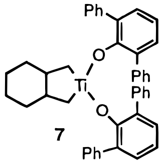


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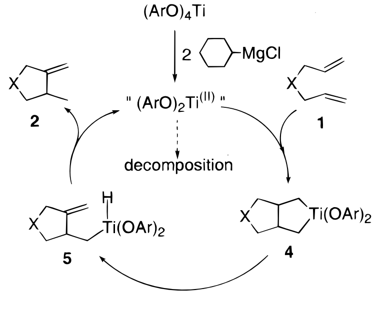
Figure 1. Structures **6** and **7**.

Scheme 1



Sato has reported the quantitative preparation of bicyclotitanapentanes (i.e., **6**) from 1,6-dienes and a stoichiometric amount of a $Ti(O\text{-}i\text{-}Pr)_4/2\ i\text{-}PrMgX$ reagent and these are stable at −50 °C (Figure 1).[3i,j] Similarly, Rothwell has reported that the titanium compound **7** catalyzes the cycloisomerization of 1,7-octadiene to 2-methyl-1-methylenecyclohexane *at high temperature (100 °C)*, but that the complex is stable enough below room temperature to be isolated.[7b] Furthermore, the bicyclometallacyclopentanes derived from Cp_2TiCl_2 or Cp_2ZrCl_2 and an appropriate reducing agent are usually stable at up to room temperature for further manipulations such as CO insertion and electrophilic functionalization of the Ti−C bond(s) with carbonyl compounds.[2,13] In the present transformation, it can be considered that the nature of the RO group plays an important role. The bulkiness of the $2,6\text{-}Me_2C_6H_3O$ moiety may decrease the decomposition rate of the active Ti(II) species, but this ligand is small enough not to retard β-hydride elimination. In addition, the electron-deficient character of the phenoxide ligands relative to aliphatic alkoxy moieties provides an electron-poor Ti center that should facilitate both β-hydrogen abstraction and alkene coordination. These stereoelectronic effects enhance the viability of the catalytic manifold so that efficient cycloisomerization occurs *at 0 °C to ambient temperature*.

In summary, we have developed a catalyst system derived from $(2,6\text{-}Me_2C_6H_3O)_4Ti$ and RMgX and shown this to be effective for cycloisomerization reactions of 1,6- and 1,7-dienes. The present transformation provides a highly efficient means to synthesize methylenecycloalkanes, including heterocyclic compounds.[14]

Supporting Information Available: Preparation details and experimental results (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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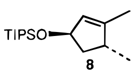
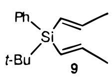
(10) $(RO)_2Ti$ equivalents are believed to be stabilized as alkene or alkyne complexes such as $(\eta^2\text{-alkene})Ti(OR)_2$, see refs 3−7.

(11) (a) Akita, M.; Yasuda, H.; Nagasuna, K.; Nakamura, A. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 554 and references therein. (b) In control experiments, dienes **1d** and **1g** were subjected to cyclization in the presence of a Cp_2Ti−H source derived from Cp_2TiCl_2 (5 mol %) and *n*-BuMgBr (15 mol %). In the case of **1d**, **2d** was obtained admixed with the isomerized product **8** (**2d**:**8** = 49:21) whereas for **1g**, the *E,E*-diene **9** was obtained in 95% isolated yield. The absence of similar alkene isomerization products in the present $(ArO)_4Ti$/RMgCl-catalyzed diene cyclizations is therefore inconsistent with the participation of a Ti(III) intermediate in the catalytic cycle.



8



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(12) A similar mechanism to explain the formation of 2-methyl-1-methylenecycloalkanes from bicyclometallacyclopentenes has been discussed: (a) Smith, G.; McLain, S. J.; Schrock, R. R. *J. Organomet. Chem.* **1980**, *202*, 269. (b) Yamamoto, Y.; Ohkoshi, N.; Kameda, M.; Itoh, K. *J. Org. Chem.* **1999**, *64*, 2178, and refs 7 and 13.

(13) Thermal decomposition of bicyclic titana- and zirconacyclopentanes to provide 2-methyl-1-methylenecycloalkanes has been reported: McDermott, J. X.; Wilson, M. E.; Whitesides, G. M. *J. Am. Chem. Soc.* **1976**, *98*, 6529. Takahashi, T.; Kotora, M.; Kasai, K. *J. Chem. Soc., Chem. Commun.* **1994**, 2693.

(14) For additional examples of transition metal-catalyzed cycloisomerization of 1,6-dienes, see: Radetich, B.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1998**, *120*, 8007. Heumann, A.; Moukhliss, M. *Synlett* **1998**, 1211. Christoffers, J.; Bergman, R. G. *J. Am. Chem. Soc.* **1996**, *118*, 4715. Piers, W. E.; Shapiro, P. J.; Bunel, E. E.; Bewcaw, J. E. *Synlett* **1990**, 74.