ORGANOMETALLICS

Volume 19, Number 8, April 17, 2000

Communications

Titanium-Catalyzed Cycloisomerization of 1,6-Dienes. Regio- and Stereoselective Synthesis of *exo*-Methylenecycloalkanes

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Received December 22, 1999

Summary: Cycloisomerization of 1,6-dienes **1** *in the presence of a catalytic amount of n-BuMgBr and a variety of organotitanium complexes such as* Cp_2TiCl_2, $Cp(MeO)TiCl_2$, $Cp(Me_2N)TiCl_2$, *or* $CpTi[(TMS)_2NC(NCy)_2)Cl_2$ *provided the corresponding 2-methyl-1-methylenecyclopentanes* **2** *with high efficiency. In contrast, catalysis using the more sterically encumbered complex ethylenebis(tetrahydroindenyl)titanium dichloride led to the predominant formation of methylenecyclohexanes* **3**.

Cycloisomerization reactions of 1,6-dienes **1** catalyzed by organotransition metal complexes have recently attracted attention as a useful means for regiodefined carboannulation.[2−6] Analogous cycloisomerization of appropriate heteroatom-containing precursors has also been utilized for the synthesis of the corresponding heterocycles.[7] Transformations of this variety are attractive by virtue of their intrinsic atom economy,[8] as well as the importance of the product alkenes as synthetic intermediates. Although complexes of several late transition metals (e.g., Pd,[2a,b,3b] Ni,[2a] Rh,[3] and Ru[4]) have been shown to be effective catalysts for this process, catalytically active complexes derived from early transition metals are comparatively rare.[5,6,9] Cy-

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

[2] (a) Radetich, B.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1998**, *120*, 8007. (b) Heumann, A.; Moukhliss, M. *Synlett* **1998**, 1211. For palladium-catalyzed cycloisomerizations of enynes, see: (c) Trost, B. M. *Acc. Chem. Res.* **1990**, *23*, 34.

[3] (a) Schmitz, E.; Hench, U.; Habisch, D. *J. Prakt. Chem.* **1976**, *318*, 471. (b) Grigg, R.; Malone, J. F.; Mitchell, T. R. B.; Ramasubbu, A.; Scott, R. M. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1745. (c) Grigg, R.; Mitchell, T. R. B.; Ramasubbu, A. *J. Chem. Soc., Chem. Commun.* **1980**, 27. (d) Bright, A.; Malone, J. F.; Nicholson, J. K.; Powell, J.; Shaw, B. L. *J. Chem Soc., Chem. Commun.* **1971**, 712.

[4] Yamamoto, Y.; Ohkoshi, N.; Kameda, M.; Itoh, K. *J. Org. Chem.* **1999**, *64*, 2178, and references therein.

[5] Cp_2TiCl_2/*i*-PrMgBr-catalyzed cycloisomerization of 1,5-hexadiene, which gave 1-methylcyclopentene as a byproduct, has been reported, see: (a) Akita, M.; Yasuda, H.; Nagasuna, K.; Nakamura, A. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 554. Cycloisomerization of 1,7-octadiene to 2-methyl-1-methylenecyclohexane catalyzed by the cyclotitanacyclopentane derived from 1,7-octadiene and $(ArO)_2TiCl_2$/2 BuLi has been reported, see: (b) Thorn, M. G.; Hill, J. E.; Waratuke, S. A.; Johnson, E. S.; Fanwick, P. E.; Rothwell, I. P. *J. Am. Chem. Soc.* **1997**, *119*, 8630. (c) Waratuke, S. A.; Johnson, E. S.; Thorn, M. G.; Fanwick, P. E.; Rothwell, I. P. *J. Chem. Soc., Chem. Commun.* **1996**, 2617. Cp_2ZrCl_2/MAO-catalyzed cycloisomerization of 1,2-diallylbenzene to the corresponding methylenecycloheptane has been reported, see: (d) Christoffers, J.; Bergman, R. G. *J. Am. Chem. Soc.* **1996**, *118*, 4715. Thermal decomposition of bicyclometallacyclopentanes, derived from Cp_2MCl_2 (M = Ti, Zr) and 1,7-dienes, at high temperature to provide 2-methyl-1-methylenecyclohexanes has been reported, see: (e) McDermott, J. X.; Wilson, M. E.; Whitesides, G. M. *J. Am. Chem. Soc.* **1976**, *98*, 6529. (f) Takahashi, T.; Kotora, M.; Kasai, K. *J. Chem. Soc., Chem. Commun.* **1994**, 2693.

[6] For cycloisomerizations of dienes catalyzed by lanthanide and Ta complexes, see: (Ta): Smith, G.; McLain, S. J.; Schrock, R. R. *J. Organomet. Chem.* **1980**, *202*, 269. (Lanthanide): Bunel, E.; Burger, B. J.; Bercaw, J. E. *J. Am. Chem. Soc.* **1988**, *110*, 976. Piers, W. E.; Shapiro, P. J.; Bunel, E. E.; Bercaw, J. E. *Synlett* **1990**, 74.

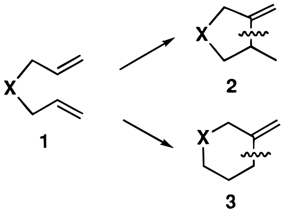
[7] See refs 2a,b and 3a,d.

[8] Trost, B. M.; Krishe, M. J. *Synlett* **1998**, 1.

[9] For other titanium-catalyzed cycloisomerization of enynes, see: Sturla, S. J.; Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 1976.

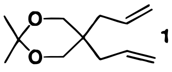
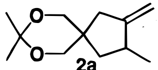
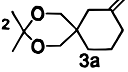
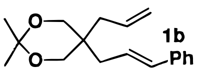
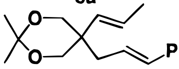
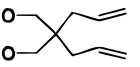
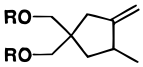
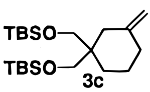
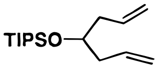
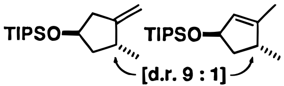
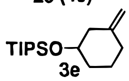
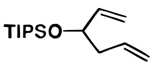
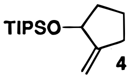
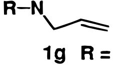
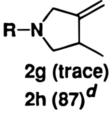
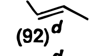
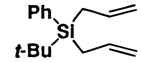
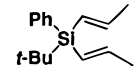
10.1021/om991024l CCC: $19.00 © 2000 American Chemical Society
Publication on Web 03/17/2000

clization reactions of the above variety can be classified into two types. The coupling reaction may proceed in a tail-to-tail fashion providing 2-methyl-1-methylenecycloalkanes (**2**) (eq 1)[10] or to afford methylenecycloalkanes (**3**) via head-to-tail coupling (eq 2).[11] Herein we wish to report an efficient cycloisomerization reaction catalyzed by titanium complexes, which includes regioselective (eq 1 vs eq 2) and diastereoselective formation of *exo*-methylenecycloalkanes from 1,6-dienes and related, heteroatom-containing, substrates.



In a representative diene cycloisomerization, a simple metallocene, Cp$_2$TiCl$_2$ (5 mol %, Cp = cyclopentadienyl), was activated with *n*-BuMgBr (15 mol %)[12] in the presence of diene **1a** (1 equiv) in diethyl ether. The resulting mixture was stirred at 25−30 °C for 24 h under argon to afford 2-methyl-1-methylenecyclopentane **2a** in 92% yield (Table 1, entry 1). In contrast, cycloisomerization of **1a** with *racemic*-EBTHI−TiCl$_2$[13] (5 mol %, EBTHI = ethylenebis(tetrahydroindenyl)) and *n*-BuMgBr (15 mol %) provided methylenecyclohexane **3a** (49% yield) admixed with **2a** (11%) (entry 2). These results indicate not only that the cycloisomerization reaction can be efficiently catalyzed by titanocene type complexes but also that selective formation of **2** or **3** can be realized by a simple change of Ti-precatalysts.[14]

Table 1. Cp$_2$TiCl$_2$- or (±)-EBTHI−TiCl$_2$-Catalyzed Cycloisomerization Reaction of 1,6-Dienes[a]

Entry	Substrate, 1	Catalyst[b]	Product(s) (Yield, %)[c]
1	 **1a**	Cp$_2$TiCl$_2$ (A)	 **2a** (92)
2		(±)-EBTHI-TiCl$_2$ (B)	 **3a** (49) + **2a** (11)
3	 **1b**	A	 (93)[d]
			
4	**1c** (R = TBS)	A	**2c** (71), (84)[e]
5	**1d** (R = PhCH$_2$)	A	**2d** (92)
6	**1c**	B[f]	 **3c** (76) + **2c** (5)
	 **1e**		
7		A	**2e** (49)[e] (21)[e]
8		B	 **3e** (70) + **2e** (13) [>10:1 *trans*]
9	 **1f**	A	 **4** (76)
			 
10	**1g** R = PhCH$_2$	A[f]	**2g** (trace)[d] (92)[d]
11	**1h** R = *tert*-Bu	A[f]	**2h** (87)[d] (11)[d]
12	 **1i**	A	 **5** (95) [>95% *E*]

[a] The reaction mixture was stirred under argon at 28 °C for 24−48 h. [b] Unless otherwise indicated, 5 mol % of catalyst and 15 mol % of *n*-BuMgBr were used. [c] Unless otherwise indicated, values correspond to isolated yields. [d] Yield was determined by ^{1}H NMR analysis of the crude mixture using an internal standard. [e] The reaction was performed in toluene. [f] 10 mol % of catalyst and 30 mol % of *n*-BuMgBr were used.

Representitive cycloisomerizations of a variety of 1,6-dienes to the corresponding methylenecycloalkanes **2** and/or **3** under these conditions (5 mol % of a Ti-complex and 15 mol % of *n*-BuMgBr) are illustrated in Table 1. In general, reactions using Cp$_2$TiCl$_2$ as the precatalyst led to the specific formation of five-membered rings, while six-membered ring formation was the primary reaction mode with EBTHI−TiCl$_2$ (entries 2, 6, and 8). With regard to the reactions with the Cp$_2$TiCl$_2$-derived catalyst, 4-substituted and 4,4-disubstituted 1,6-heptadienes were superior substrates, presumably as a consequence of the Thorpe−Ingold conformational effect. In addition, successful cyclization of diallylamine derivatives was limited to those having a bulky substituent on the nitrogen atom (entry 11) to avoid olefin isomerization leading to the corresponding bisenamine derivative (entry 10).[15] Surprisingly, diallylsilane **1i** did not undergo cyclization but gave dipropenylsilane **5** quantitatively (>95% *E*) (entry 12). Olefinic substitution prohibited cyclization, as is exemplified by entry 3, where olefin isomerization to the 2-alkene was once again observed.[15] This method could also be extended to the cycloisomerization of 1,5-dienes. Accordingly, 1,5-hexadiene **1f** underwent facile cycloisomerization in the presence of the Cp$_2$TiCl$_2$-derived catalyst to provide the 2-methylenecyclopentanol derivative **4** regioselectively via a head-to-tail coupling (entry 9).[5a] It should be noted that the reaction of **1e** afforded the corresponding 2-methyl-1-methylenecyclopentane with good 1,3-diastereoselectivity (entry 7). To our best knowledge, this is the first example of a diastereoselective cycloisomerization of a 1,6-diene. Hydrocarbon solvents, such as toluene, can be used instead of diethyl ether (entries 4 and 7 and footnote e, Table 1) and, in some cases, provided slightly better yields.

As shown in Table 2, other Ti-catalysts such as Cp(MeO)TiCl$_2$ (**C**),[16] Cp(Me$_2$N)TiCl$_2$ (**D**),[17] or CpTi[(TMS)$_2$-

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[10] See refs 2−4 and 5b,c.

[11] See refs 2a and 5a,d.

[12] Effectively 2 equiv of the Grignard reagent is required for the Ti-precatalyst that is utilized. In initial investigations, we determined that *i*-PrMgCl, *i*-BuMgBr, cyclo-HexMgCl, and *n*-BuMgBr could be used for the reaction, but that EtMgBr did not afford any cyclized product. Use of Cp$_2$ZrCl$_2$ as a precatalyst also did not afford **2** under these conditions.

[13] Collins, S.; Kuntz, B. A.; Taylor, N. J.; Ward, D. G. *J. Organomet. Chem.* **1988**, *342*, 21. Schäfer, A.; Karl, E.; Zsoinai, L.; Gottfried, H.; Brintzinger, H. H. *J. Organomet. Chem.* **1987**, *328*, 87. Collins, S.; Kuntz, B. A.; Hong, Y. *J. Org. Chem.* **1989**, *54*, 4154.

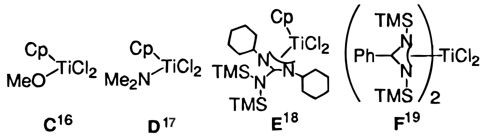
[14] In the palladium-catalyzed cycloisomerization of 1,6-dienes, a ligand effect (phosphine) on the selectivity between five- and six-membered ring formation has also been observed; see ref 2a.

[15] Selective titanium-catalyzed isomerization of 1-alkenes to 2-alkenes has been reported; see ref 5a.

[16] Gorsich, R. D. *J. Am. Chem. Soc.* **1960**, *82*, 4211.

[17] Prepared from CpTiCl$_3$ and Me$_2$NSiMe$_3$ in CH$_2$Cl$_2$ (0 °C to rt).

Table 2. Cycloisomerization Reaction of 1 to 2 Catalyzed by a Variety of Titanium Compounds[a]



C[16] **D**[17] **E**[18] **F**[19]

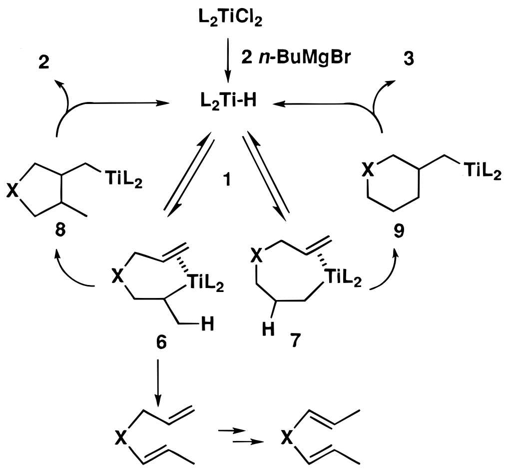
entry	substrate, **1**	catalyst[b]	products	yield, %[c]
1	**1a**	**C**	**2a**	82
2		**D**		78
3		**E**		75[d]
4		**F**		trace
5	**1c**	**E**[e]	**2c**	71[d]

[a] The reaction mixture was stirred under argon at 28 °C for 24−30 h. [b] The structure of catalyst is illustrated above. Unless otherwise indicated, 10 mol % of catalyst and 30 mol % of *n*-BuMgBr were used. [c] Unless otherwise indicated, yields were determined by ^{1}H NMR analysis of the crude product mixture. [d] Isolated yield. [e] 5 mol % of catalyst and 15 mol % of *n*-BuMgBr were used.

$NC(NCy)_2)Cl_2$ (**E**)[18] can be used for the formation of five-membered rings (entries 1−3 and 5, Table 2). The amidinato moiety has recently been utilized as an alternative to cyclopentadienyl-based ligands in early transition metal chemistry.[20] It is noteworthy that the conversion of **1a** to **2a** and **1c** to **2c** represent what are, to the best of our knowledge, the first examples of the use of a CpTiCl(amidinato) complex as a catalyst in organic synthesis, other than the polymerization reactions of olefins.

The mechanism of cycloisomerization can be explained by the postulated catalytic cycle outlined in Scheme 1, in which all of individual steps are well precedented.[21] The intermediates **6** and **7** may be in equilibrium through hydrotitanation/β-hydride elimination reactions. The resulting substitution pattern (**2** or **3**) of the product will depend on the relative reactivity exhibited by the catalyst in the initial insertion event (**6** to **8** or **7** to **9**). The reaction with titanium complexes having a comparatively small ligand (L) such as Cp can easily undergo cyclization via **6**−**8**−**2**, while the more sterically encumbered EBTHI ligand can deflect the reaction pathway toward the formation of **3**. Alkene isomerization is observed when the olefin insertion steps are much slower than the abstraction of a β-hydride from the internal carbon in **6**.

Scheme 1



In summary, we have demonstrated that Cp_2TiCl_2 or EBTHI−$TiCl_2$/RMgX reagents are useful catalysts for the regio- and diastereoselective cycloisomerization of 1,5- and 1,6-dienes to a variety of *exo*-methylenecycloalkanes. We have further shown that Ti complexes bearing a variety of heteroatom ligands are active catalysts for the conversion of 1,6-dienes to the corresponding methylenecyclopentanes. Methods to prepare methylenecycloalkanes via asymmetric variations of this reaction are currently under study.

Acknowledgment. Support for this research by a generous grant from the National Science Foundation is gratefully acknowledged.

Supporting Information Available: Experimental procedures and characterization of cycloisomerization products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Gómez, R.; Duchateau, R.; Chernega, A. N.; Teuben, J. H.; Edelmann, F. T.; Green, L. H. *J. Organomet. Chem.* **1995**, *491*, 153. Littke, A.; Sleiman, N.; Bensimon, C.; Richeson, D. S. *Organometallics* **1998**, *17*, 446.

(19) Roesky, H. W.; Meller, B.; Noltemeyer, M.; Schmidt, H. G.; Scholz, U.; Sheldrick, G. M. *Chem. Ber.* **1988**, *121*, 1403. Dick, D. G.; Duchateau, R.; Edema, J. H.; Gambarotta, S. *Inorg. Chem.* **1993**, *32*, 1959.

(20) For reviews of transition metal amidinates, see: Edelmann, F. T. *Coord. Chem. Rev.* **1994**, *137*, 403. Dehnicke, K. *Chem.-Ztg.* **1990**, *114*, 295. Barker, J.; Kilner, M. *Coord. Chem. Rev.* **1994**, *133*, 219.

(21) See ref 5a and references therein. Observed olefin isomerization to 2-alkenes (entries 10 and 12, Table 1) strongly supports the formation of a transient Ti−H compound as an active catalyst.