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Titanium-Mediated Alkylative Cyclizations of 1,3-Diene-Tethered Esters

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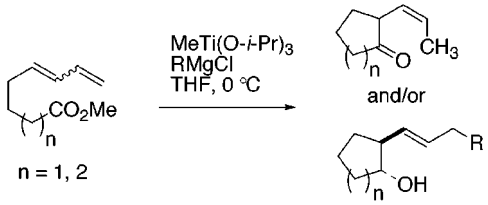
ABSTRACT



An alkylative titanium-mediated cyclization reaction of 1,3-diene-tethered carboxylic esters has been developed by employing an in situ generated titanacyclopropane intermediate to afford *trans*-2-alkenyl cyclohexanols.

Transition-metal-promoted carbocyclizations of unsaturated functionalities have been demonstrated to provide convenient methods for the facile formation of rings. Procedures that involve the formation of metallacycle intermediates by means of low valent metals such as Zr, Ti, or Ni have been frequently employed.[1] For example, cyclizations of enynes, diynes, and dienes have been extensively investigated, since they proceed with good diastereoselectivity and tolerate several functional groups. Related reactions of saturated or α,β-unsaturated carbonyl derivatives with tethered unsaturated functionalities have also been developed as useful methods for the construction of carbocyclic rings.[2] Recently, 1,3-dienes have been successfully employed for coupling to carbonyl compounds.[3] As part of our research program expanding upon the Kulinkovich cyclopropanation reaction,[4] herein we report the titanium-mediated alkylative cyclizations of 1,3-diene-tethered carboxylic esters.

For convenience, the requisite ω-dienyl esters **1** and **2**[5] were prepared as a 1:1 mixture of *E* and *Z* isomers (in good yields) by standard Wittig olefination of the corresponding aldehydes with the ylide prepared from allyltriphenylphosphonium bromide. Treatment of **1** with cyclopentylmagnesium chloride (1.8 equiv) in the presence of methyltitanium triisopropoxide (1.1 equiv) at 0 °C afforded cyclopentanone **3a** (62%) and cyclopentanol **4a** (21%) (Scheme 1).[6] Hy-

(1) For general reviews, see: (a) Negishi, E.-i. *Acc. Chem. Res*. **1987**, *20*, 65. (b) Negishi, E.-i.; Takahashi, T. *Synthesis* **1988**, 1. (c) Buchwald, S. L.; Nielsen, R. B. *Chem. Rev*. **1988**, *88*, 1047. (d) Takahashi, T. *J. Synth. Org. Jpn*. **1993**, *51*, 1145. (e) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev*. **1996**, *96*, 635.

(2) For representative examples, see: (a) Hewlett, D. F.; Whitby, R. J. *J. Chem. Soc., Chem. Commun*. **1990**, 1684. (b) Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc*. **1995**, *117*, 6785. (c) Crowe, W. E.; Rachita, M. J. *J. Am. Chem. Soc*. **1995**, *117*, 6787. (d) Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc*. **1996**, *118*, 3182. (e) Montgomery, J. *Acc. Chem. Res*. **2000**, *33*, 467.

(3) See, inter alia: (a) Yasuda, H.; Tatsumi, K.; Nakamura, A. *Acc. Chem. Res*. **1985**, *18*, 120. (b) Sato, Y.; Takimoto, M.; Hayashi, K.; Katsuhara, T.; Takagi, K.; Mori, M. *J. Am. Chem. Soc*. **1994**, *116*, 9771. (c) Sato, Y.; Takimoto, M.; Mori, M. *Tetrahedron Lett*. **1996**, *37*, 887. (d) Gao, Y.; Urabe, H.; Sato, F. *J. Org. Chem*. **1994**, *59*, 5521. (e) Kimura, M.; Ezoe, A.; Shibata, K.; Tamaru, Y. *J. Am. Chem. Soc*. **1998**, *120*, 4033. (f) Kimura, M.; Fujimatsu, H.; Ezoe, A.; Shibata, K.; Shimizu, M.; Matsumoto, S.; Tamaru, Y. *Angew. Chem., Int. Ed*. **1999**, *38*, 397.

(4) For recent reviews, see: (a) Kulinkovich, O. G.; de Meijere, A. *Chem. Rev*. **2000**, *100*, 2789. (b) Sato, F.; Urabe, H.; Okamoto, S. *Chem. Rev*. **2000**, *100*, 2835. (c) Sato, F.; Urabe, H.; Okamoto, S. *Synlett* **2000**, 753.

(5) Compare Hudlicky, T.; Sheth, J. P. *Tetrahedron Lett*. **1979**, 2667.

(6) **Typical Experimental Procedure.** A 3.0 M solution of methylmagnesium chloride (0.2 mL) in THF was added at 0 °C over a period of 5 min to a solution of Ti(O-*i*-Pr)$_4$ (0.16 mL, 0.55 mmol) in anhydrous THF (5 mL). After the mixture had been stirred for an additional 5 min, **2** (84 mg, 0.5 mmol) was added, followed by slow addition (over a period of 1 h) of a 2.0 M solution of cyclopentylmagnesium chloride (0.75 mL) in THF. The reaction mixture was then stirred for 10 min and quenched with addition of water (0.5 mL). The resulting mixture was stirred for an additional 1 h, dried over sodium sulfate, and filtered. The filter cake was washed with CH_2Cl_2 (10 mL), and the combined filtrates were concentrated under vacuum. Purification by column chromatography on silica gel afforded

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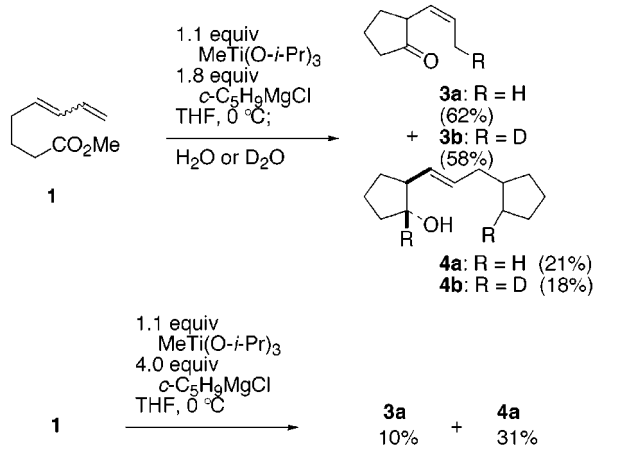
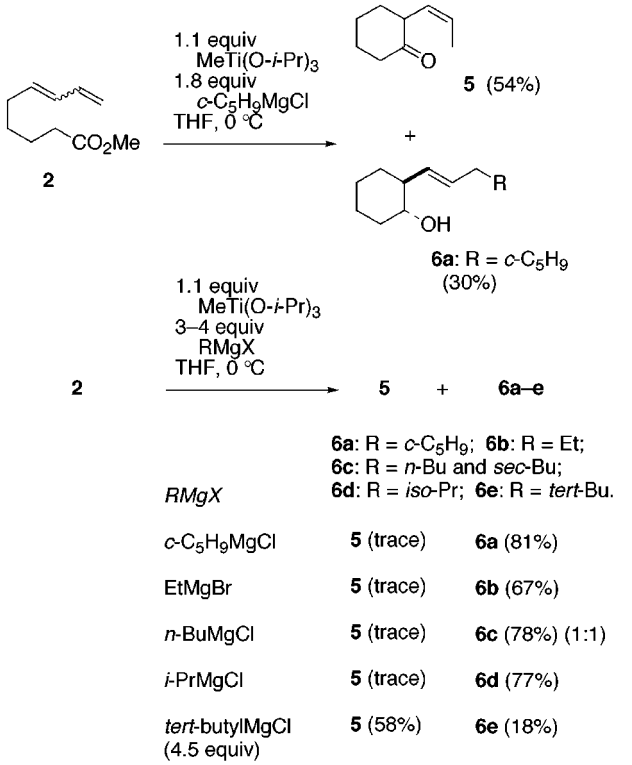
Scheme 1



Scheme 2



RMgX		
c-C_5H_9MgCl	**5** (trace)	**6a** (81%)
EtMgBr	**5** (trace)	**6b** (67%)
n-BuMgCl	**5** (trace)	**6c** (78%) (1:1)
i-PrMgCl	**5** (trace)	**6d** (77%)
tert-butylMgCl (4.5 equiv)	**5** (58%)	**6e** (18%)

drolysis of the reaction mixture with D_2O provided monodeuterated **3b** (58%) and dideuterated **4b** (18%). When a larger excess (4 equiv) of the Grignard reagent was added, a mixture of **3a** (10%) and **4a** (31%) was obtained with considerably lower material balance. The structures (including the stereochemistry) of **4a** and **4b** were determined by ^{1}H NMR, ^{13}C NMR, and mass spectral analysis, along with comparison of the ^{1}H NMR chemical shifts of the methine proton α to the hydroxyl group with those of closely related known cyclopentanol isomers.[7]

Similarly, cyclization of the homologue **2** under identical conditions using 1.8 equiv of cyclopentylmagnesium chloride produced a mixture of **5** (54%) and **6a** (30%) (Scheme 2). By utilizing an additional amount of the Grignard reagent, the isolated yield of **6a** was increased at the expense of **5**. When 3 equiv of the Grignard reagent was added slowly over a period of 1 h, the *trans*-substituted cyclohexanol **6a**, the stereochemistry of which was unequivocally established by the observation of a diaxial coupling (J = 9.9 Hz) for the methine proton (3.17 ppm, dt, J = 4.0, 9.9 Hz, 1 H) α to the hydroxyl group, was obtained in 81% yield, along with a trace amount of **5**.[6] This observation clearly indicated that both **5** and **6a** were derived from a common reaction intermediate. Additionally, the titanium-mediated cyclization reaction of **2** appears to be general with a range of Grignard reagents. For example, use of ethyl, *n*-butyl, and isopropyl Grignard reagents afforded the corresponding adducts **6b**−**d** in comparable yields, whereas *tert*-butyl Grignard reagent afforded a mixture of **5** (58%) and **6e** (18%). Only the *E*-olefin isomers, free from *Z*-isomers, were found for **6a**−**e**. It is interesting that **6c** was obtained as a 1:1 mixture of the two regioisomers. Not surprisingly, extension of this procedure to methyl 7,9-decadienoate gave complex mixtures containing only trace amounts of the respective cycloheptanol products. Thus, the titanium-mediated cyclizations were limited to the formation of five- and six-membered rings.

Although the Kulinkovich cyclopropanation reactions of carboxylic esters were in general marginally affected by the nature of a titanium alkoxide,[4,8] the choice of methyltitanium triisopropoxide[9] proved to be critical for the successful cyclization. Titanium tetraisopropoxide or chlorotitanium triisopropoxide was ineffective. An unexpected advantage of MeTi(O-*i*-Pr)$_3$, compared to Ti(O-*i*-Pr)$_4$ and ClTi(O-*i*-Pr)$_3$, can be attributed to its efficacy in inducing the requisite β-elimination (vide infra). A stoichiometric amount of MeTi(O-*i*-Pr)$_3$ was also necessary to obtain good yields of **5** and/or **6**. No attempt was made to develop a variant that was catalytic in titanium.

A plausible mechanism for the formation of the cyclization products is outlined in Scheme 3. β-Elimination of the dialkyltitanium intermediate **7** would be expected to generate a titanacyclopropane intermediate or a Ti(II)-alkene complex. Subsequent ligand exchange with diene **1** or **2** would then afford **8a**,**b**,[4,10] which could exist in equilibrium with titanacyclopentene **9a**,**b**.[11,12] Subsequent addition of **8a**,**b** or **9a**,**b** to the tethered ester function would then lead to the

84.3 mg (81%) of **6**. When 1.8 equiv of cyclopentylmagnesium chloride (e.g., 0.45 mL of a 2.0 M solution in THF) was employed under otherwise identical conditions, **1** (77 mg, 0.5 mmol) gave 38.5 mg (62%) of **3a** and 20.4 mg (21%) of **4a**.

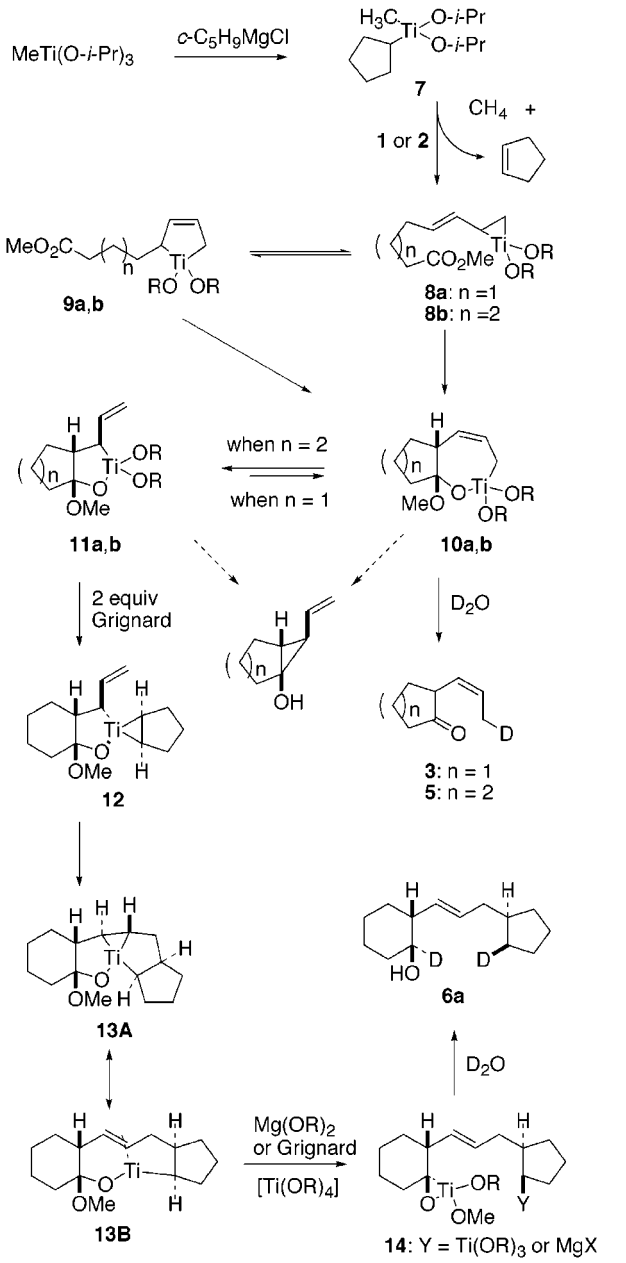
(7) The stereochemistry of 2-alkenylcyclopentanols and -cyclohexanols can be easily determined by the diagnostic chemical shift of the methine proton, which is more shielded in *trans* isomers than in *cis* isomers: Snider, B. B.; Karras, M.; Price, R. T.; Rodini, D. J. *J. Org. Chem*. **1982**, *47*, 4538.

(8) Compare Lee, J. C.; Sung, M. J.; Cha, J. K. *Tetrahedron Lett*. **2001**, *42*, 2059.

(9) Chaplinski, V.; Winsel, H.; Kordes, M.; de Meijere, A. *Synlett* **1997**, 111.

(10) Compare (a) Kulinkovich, O. G.; Savchenko, A. I.; Sviridov, S. V.; Vasilevski, D. A. *Mendeleev Commun*. **1993**, 230. (b) Kasatkin, A.; Sato, F. *Tetrahedron Lett*. **1995**, *36*, 6079. (c) Lee, J.; Kang, C. H.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc*. **1996**, *118*, 291. (d) Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc*. **1996**, *118*, 4198.

Scheme 3



formation of **10a**,**b**, which could undergo an allylic rearrangement to give **11a**,**b**. When $n = 1$, **10a** would be preferred to **11a** in the latter interconversion, as might be expected on the basis of strain associated with a titanaoxabicyclo[3.3.0]octane ring system. Hydrolysis of **10a**,**b** would afford **3a**,**b** or **5** with the *Z* configuration of the double bond ($J = 10.8$ Hz). On the other hand, it is evident that **11b** ($n = 2$) should be favored over **10b**, and it could react with an additional 2 equiv of the Grignard reagent to provide **12**. The ensuing cyclization of **12** to **13A**/**13B**, the two limiting resonance structures for the resulting metal−*E*-alkene complex, can be viewed as an intramolecular diene cyclization.[1] While tentative, it is tempting to speculate that the relative configuration of **13A**/**13B**, based on steric considerations, is as shown in Scheme 3. Subsequent reduction of the hemiacetal functionality would occur next, via a ketone intermediate (formed by the initial migration of the methoxy group to the titanium), from the bottom face directed by the *E*-olefin functionality to give the *trans*-substituted cyclohexanol isomer **6a**. A priori, there was another reaction manifold possibly available for **10a**,**b** or **11a**,**b**, but no corresponding bicyclic cyclopropanol was found in the crude reaction mixture.

The stereoselective formation of **6b**−**e** by use of other Grignard reagents in place of cyclopentylmagnesium chloride can be rationalized by an identical pathway. As evidenced in the formation of both regioisomers of **6c**, little regioselectivity was observed for **12** → **13** with a primary Grignard reagent. On the other hand, use of a secondary or a tertiary Grignard reagent afforded excellent regiocontrol, where the subsequent carbocyclization took place at the more substituted olefinic carbon. Attempts to intercept the presumed intermediate **12** by exchange with an excess (5 equiv) of an external alkene were unsuccessful. Apparently, **12** → **13** must take place more rapidly than an intermolecular olefin exchange of **12**. These results, taken together, suggest that the formation of **12** by β-elimination is the slowest step for **11b** → **12** → **13**. The different regiochemical outcome between the reaction of primary and secondary/tertiary Grignard reagents with **11b** can be attributed to preferential β-elimination by one of the two diastereotopic alkyl groups bound to the titanium metal with the latter reagents.

Sato and co-workers reported a related intramolecular coupling of alka-3,5-dienyl carbonates by employing (η^2-propene)Ti(O-*i*-Pr)$_2$.[13] The present work differs from Sato's previous cyclization in the subsequent incorporation of various alkyl groups arising from the Grignard reagents. Also, a similar mechanism has previously been advanced by de Meijere for the preparation of alkenyl cyclopropylamines from the titanium-mediated intermolecular cyclopropanation of *N*,*N*-dibenzylformamide with a diene or a triene.[11] Surprisingly, an intramolecular variant of 1,3-diene-tethered tertiary amides, which is analogous to the present study, gave only an intractable reaction mixture.[14b] To make an additional comparison, the titanium-mediated intermolecular cyclopropanation of esters with dienes afforded little of the corresponding cyclopropanols.[14] The divergence in the reactivity of esters and amides in their intramolecular and intermolecular titanium-induced coupling reactions with dienes was atypical, especially in view of comparable reactivities with terminal olefins, yet their origin is unclear.

In summary, an alkylative titanium-mediated cyclization reaction of 1,3-diene-tethered carboxylic esters has been

(11) Williams, C. M.; Chaplinski, V.; Schreiner, P. R.; de Meijere, A. *Tetrahedron Lett*. **1998**, *39*, 7695.

(12) Similar rearrangements have been reported for zirconocene−diene complexes: (a) Erker, G.; Dorf, U. *Angew. Chem., Int. Ed. Engl*. **1983**, *22*, 777. (b) Erker, G. *Angew. Chem., Int. Ed. Engl*. **1989**, *28*, 397.

(13) (a) Zubaidha, P. K.; Kasatkin, A.; Sato, F. *J. Chem. Soc., Chem. Commun*. **1996**, 197. Compare (b) Yoshida, Y.; Okamoto, S.; Sato, F. *J. Org. Chem*. **1996**, *61*, 7826.

(14) (a) See footnote 11 of ref 11. (b) Lee, J.; Quan, L. G.; Cha, J. K., unpublished observations. (c) For an alternative approach, see: Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc*. **1995**, *117*, 9919.

developed by employing an in situ generated titanacyclopropane intermediate to afford *trans*-2-alkenyl cyclohexanols.[15] Mechanistic and synthetic studies will be reported in due course.

(15) The internal double bond of the 1,3-diene functionality can accommodate alkyl substituents (e.g., methyl 6-methyl-octa-5,7-dienoate, methyl 7-methyl-nona-6,8-dienoate): Quan, L. G.; Cha, J. K., unpublished results.

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Supporting Information Available: Characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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