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Titanium-Mediated [2 + 2 + 2] Coupling of Diynes with Homoallylic Alcohols

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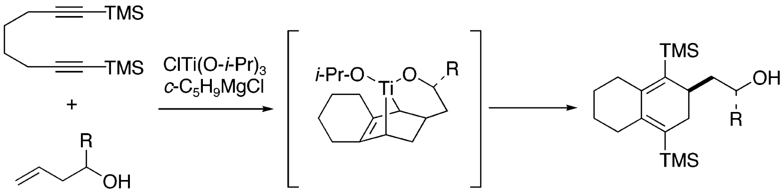
ABSTRACT



In connection with the known diyne-ene [2 + 2 + 2] cycloaddition reactions mediated by titanium aryloxides, the ability of titanium alkoxides to promote coupling of a titanacyclopentadiene with an alkene has been assessed for the isomerization-free preparation of 1,3-cyclohexadienes. The successful cycloaddition by titanium alkoxides is predicated on the use of homoallylic alcohols as the olefin component. With secondary homoallylic alcohols, high 1,3-diastereoselectivity is observed, which lends itself to enantioselective preparation of functionalized 1,3-cyclohexadienes.

Transition metal-mediated [2 + 2 + 2] cycloadditions of three unsaturated components have been extensively investigated for direct formation of benzenes, six-membered heterocycles, and related compounds.[1] Late transition metals such as cobalt, rhodium, nickel, and ruthenium complexes have been shown to be effective for the conceptually appealing cyclotrimerization reactions, and a majority of known examples have been directed at rapid assembly of polycyclic aromatic compounds. One useful variant involves coupling of two alkyne molecules with an alkene for the synthesis of 1,3-cyclohexadienes, where intramolecular processes have frequently been adopted in order to avoid regiochemical complications in intermolecular diyne-ene [2 + 2 + 2] cycloaddition reactions. Particular emphasis was placed on improving the efficiency and also controlling the regio- and stereochemistry of these cycloadditions. Titanium aryloxides were shown to be effective under mild conditions by Rothwell and co-workers, but the initially formed 1,3-cyclohexadiene products were found to undergo extensive isomerization by metal-mediated 1,5-hydrogen shifts (see **7A** → **7B** in Scheme 1).[2,3] We herein report isomerization-free coupling of diynes with homoallylic alcohols in the presence of a titanium alkoxide and a Grignard reagent.

As an extension of the Kulinkovich cyclopropanation,[4] we investigated the utility of a presumed dialkoxytitanacyclopropane intermediate in the [2 + 2 + 2] cycloaddition reaction for the synthesis of functionalized bicyclic cyclohexadienes. Of particular interest was the comparison of the reactivity profiles of titanium aryloxides and alkoxides in the context of this metal-mediated cycloaddition:[5] in contrast to Rothwell's pioneering work on sterically demanding titanium aryloxides,[2] the use of titanium alkoxides had been limited to either intramolecular coupling of two components

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(1) For general reviews, see: (a) Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539. (b) Buchwald, S. L.; Nielsen, R. B. *Chem. Rev.* **1988**, *88*, 1047. (c) Shore, N. E. *Chem. Rev.* **1988**, *88*, 1081. (d) Negishi, E.; Takahashi, T. *Acc. Chem. Res.* **1994**, *27*, 124. (e) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259. (f) Grotjahn, D. B. In *Comprehensive Organometallic Chemistry II*; Hegedus, L. S., Ed.; Pergamon: Oxford, 1995; Vol. 12, p 741. (g) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (h) Ojima, I.; Tzamarioudaki, M.; Li, Z.; Donovan, R. J. *Chem. Rev.* **1996**, *96*, 635. (i) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901.

(2) (a) Balaich, G. J.; Rothwell, I. P. *J. Am. Chem. Soc.* **1993**, *115*, 1581. (b) Johnson, E. S.; Balaich, G. J.; Rothwell, I. P. *J. Am. Chem. Soc.* **1997**, *119*, 7685. (c) Use of allyl phenyl ether allowed formation of substituted methylenecyclohex-3-enes as single regioisomers: Balaich, G. J.; Rothwell, I. P. *Tetrahedron* **1995**, *51*, 4463.

(3) Cf.: Karel, K. J.; Brookhart, M.; Aumann, R. *J. Am. Chem. Soc.* **1981**, *103*, 2695.

(4) For excellent 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.

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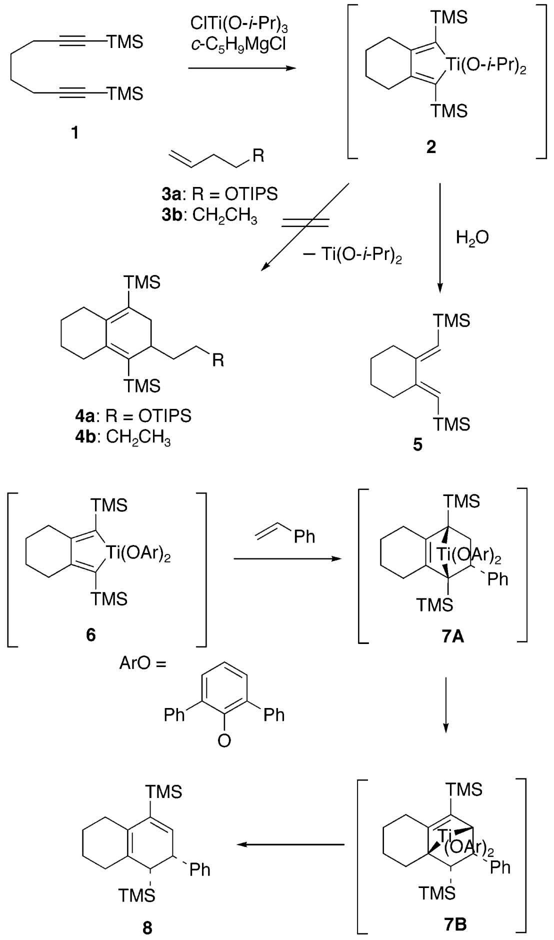
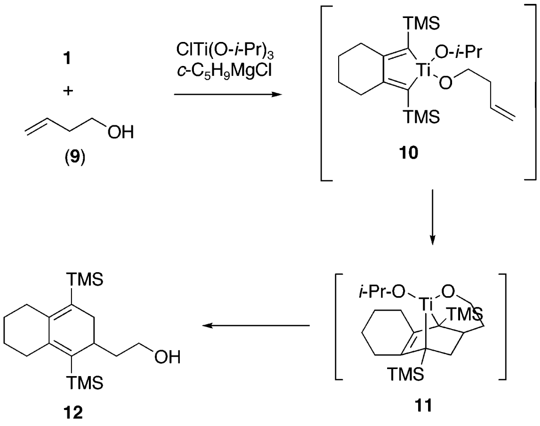
Scheme 1



involving olefins and acetylenes or the availability of aromaticity to drive the equilibrium.[6,7] When a mixture of 1,8-bis(trimethylsily)-1,7-octadiyne (**1**) and 1-triisopropylsiloxy-3-butene (**3a**) [or 1-hexene (**3b**)] was subjected to typical modified Kulinkovich conditions involving 1.0 equiv of ClTi(O-*i*-Pr)$_3$ and 4.0 equiv of cyclopentylmagnesium chloride,[8] no [2 + 2 + 2] cycloadduct **4a**,**b** was found in the crude reaction mixtures (Scheme 1). Instead, the cyclization product **5** was isolated in 82% yield after aqueous workup. Formation of diene **5** indicates facile generation of **2**, which is well precedented for early transition metals (containing cyclopentadiene or alkoxide ligands). The subsequent, rate-determining attack of an olefin on **2** appeared to be unfavorable. In marked contrast, the corresponding aryloxy derivatives **6** were shown by Rothwell to readily undergo the metal-mediated Diels−Alder reaction with several olefins to afford **8**.[2] This noticeable difference in reactivity between ligands containing aryloxides and alkoxides could be attributed to electronic effects.[5b]

To overcome the apparently unfavorable reaction of **2** with an alkene, we decided to rely on intramolecularity by employing an alcohol-tethered olefin: the titanium metal could serve as a suitable matrix as a result of in situ exchange between **2** and the alcohol functionality, as we previously demonstrated in the diastereoselective hydroxycyclopropanation reactions of homoallylic alcohols.[9] Indeed, the use of 3-buten-1-ol (**9**) afforded the desired cycloadduct **12** in 85% yield, when ClTi(O-*i*-Pr)$_3$ and cyclopentylmagnesium chloride were used and the reaction mixture was heated at 50 °C for several hours prior to aqueous workup (Scheme 2).[10]

Scheme 2[a]



titanium reagent	Grignard reagent	yield (%)
Ti(O-*i*-Pr)$_4$	*c*-C$_5$H$_9$MgCl	41
ClTi(O-*i*-Pr)$_3$	*c*-C$_5$H$_9$MgCl	85
Cl$_2$Ti(O-*i*-Pr)$_2$	*c*-C$_5$H$_9$MgCl	53
ClTi(O-*i*-Pr)$_3$	*i*-PrMgCl	44
ClTi(O-*i*-Pr)$_3$	*c*-C$_6$H$_{11}$MgCl	73

[a] Reaction conditions:[10] 1 equiv of **1**; 3 equiv of **9**; 1 equiv of a titanium reagent; 4 equiv of a Grignard reagent.

When no heating was applied, only trace amounts of **12** were found in the crude reaction mixture. According to a brief survey of several titanium alkoxide reagents and Grignard reagents, the best yields were obtained by employing ClTi(O-*i*-Pr)$_3$ and cyclopentylmagnesium chloride. Prefabrication of a mixed titanate **10** from a titanium alkoxide and **9** proved to be unnecessary. It is interesting to note that addition of

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(5) (a) For related comparison studies in the titanium-mediated cyclopropanation of esters, see: Lee, J. C.; Sung, M. J.; Cha, J. K. *Tetrahedron Lett*. **2001**, *42*, 2059. (b) In a recent investigation, titanium alkoxides [e.g., Ti(OCH$_2$CF$_3$)$_4$ and Ti(OCH(CF$_3$)$_2$)$_4$] bearing electronegative substituents seemed to be more effective than ClTi(O-*i*-Pr)$_3$ for the cycloaddition reaction: Pang, J.-H.; Cha, J. K. Unpublished results. An electron-deficient titanium species would bind more tightly to unsaturated groups and thus be beneficial.

(6) (a) Urabe, H.; Suzuki, K.; Sato, F. *J. Am. Chem. Soc*. **1997**, *119*, 10014 and references therein. (b) For an excellent review, see: Sato, F.; Urabe, H.; Okamoto, S. *Synlett* **2000**, 753.

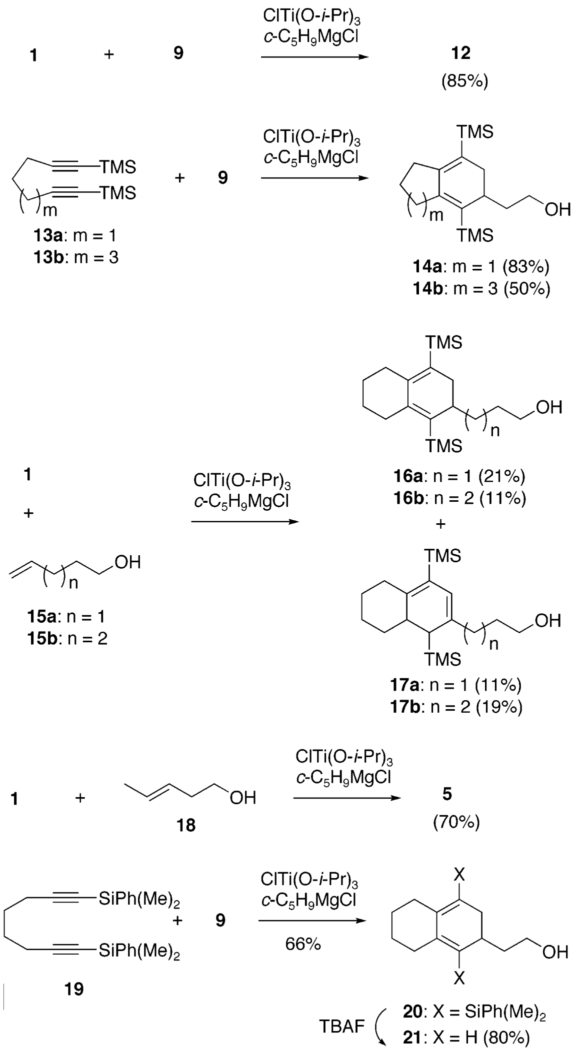
(7) Recently, there appeared examples on coupling of three alkynes or nitriles: (a) Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc*. **2001**, *123*, 7925. (b) Suzuki, D.; Tanaka, R.; Urabe, H.; Sato, F. *J. Am. Chem. Soc*. **2002**, *124*, 3518. (c) Tanaka, R.; Nakano, Y.; Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc*. **2002**, *124*, 9682.

(8) Lee, J.; Kim, H.; Cha, J. K. *J. Am. Chem. Soc*. **1996**, *118*, 4198.

(9) Quan, L. G.; Kim, S.-H.; Lee, J. C.; Cha, J. K. *Angew. Chem., Int. Ed*. **2002**, *41*, 2160.

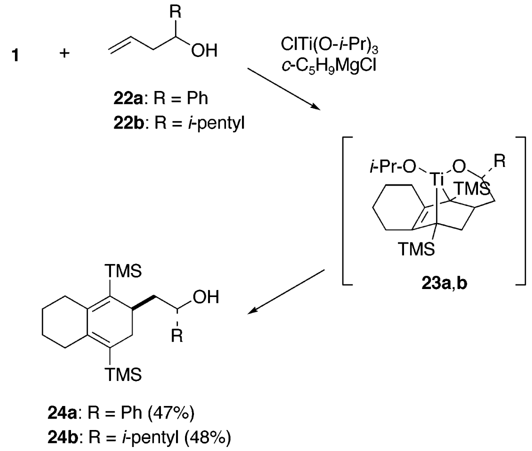
the Grignard reagent at 0 °C or room temperature resulted in lower yields (50 and 55%, respectively) than at −78 °C. This unexpected temperature dependence is in conspicuous contrast to that of the olefin exchange-mediated cyclopropanation reactions of carboxylic esters and derivatives.[8,11]

Scheme 3



Under optimized reaction conditions, several alcohols containing longer tethers and also different diynes were next examined (Scheme 3); the homoallylic alcohol group proved to be optimal. Allylic alcohols were not examined because they were already known to react under identical conditions to yield the corresponding allylic titanium reagents.[4] Longer tethers resulted in not only lower yields but also competing isomerization. It is clear that the homoallylic tether is useful in promoting the desired Diels−Alder reaction,[12] as well as preventing subsequent metal-mediated 1,5-hydrogen shift (e.g., **17a** and **17b**) due to geometrical constraints imposed by the six-membered titanate in **11**. As was the case in the titanium-mediated cyclopropanations, disubstituted olefins (e.g., **18**) did not undergo the [2 + 2 + 2] cycloaddition. To facilitate the removal of the vinylsilyl groups, use of **19** was next examined to afford the cycloadduct **20** in 66% yield. Treatment of **20** with TBAF in 2:1 THF−DMSO at 80 °C cleanly gave **21** in 80% yield.[13,14] In the above-mentioned preliminary study, no attempt was made to develop a catalytic procedure with respect to a titanium reagent since it is inexpensive and readily available. However, successful development of such a catalytic process would seem feasible, as **7** was shown to enter a catalytic cycle presumably because of instability of a Ti(II) species.[2b]

Scheme 4



Finally, the 1,3-diastereoselectivity, which was previously utilized for the stereoselective synthesis of *trans*-1,2-dialkylcyclopropanols,[9] was examined by employing secondary homoallylic alcohols **22a**,**b**. In both cases, the cycloadducts **24a**,**b** were obtained as single diastereomers in 47 and 48% (unoptimized) yields, respectively.[15] The stereochemistry of **24a**,**b** was tentatively assigned as shown in Scheme 4 on the basis of the expected bias for the transition state having an alkyl substituent in the equatorial position leading to

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(10) **Typical Experimental Procedure.** To a mixture of **1** (72.8 mg, 0.29 mmol) and ClTi(O-*i*-Pr)$_3$ (0.29 mL of a 1 M solution in THF) was added **9** (75 μL, 0.87 mmol). After the mixture had been stirred at room temperature for 1 h and then cooled to −78 °C, cyclopentylmagnesium chloride (1.45 mL of a 1 M solution in THF) was added over a period of 10 min. The reaction mixture was stirred at −20 °C for 1 h and then allowed to warm to room temperature. Benzene (0.3 mL) was added, and the resulting mixture was heated at 50 °C for 8−10 h (monitored by TLC). The reaction was quenched by addition of water, and the mixture was extracted with EtOAc. The extract was washed with brine and dried over MgSO$_4$. Purification by column chromatography (1:5 EtOAc−hexane) afforded **12** (80 mg, 85%) as a colorless oil.

(11) Origin of the observed temperature dependence is unclear. In the present case, the requisite low valent titanium was readily generated at low temperatures, as the presence of coordinating alkynes would facilitate reductive elimination.

(12) Rothwell and co-workers presented strong evidence in favor of the Diels−Alder-like cyclization of a titanacyclopentadiene rather than an alternate, stepwise insertion of an olefin into the Ti−C bonds.[2b]

(13) (a) Oda, H.; Sato, M.; Morizawa, Y.; Oshima, K.; Nozaki, H. *Tetrahedron* **1985**, *41*, 3257. (b) Other procedures for desilylation by employing HI or I$_2$ were unsuccessful.

(14) Diels−Alder reaction of the acetate of diene **21** and maleic anhydride gave the corresponding adduct as a single diastereomer in excellent yield.

(15) Compounds **24a** and **24b** were found to undergo a 1,5-hydrogen shift in a CDCl$_3$ solution.

23a,**b**. The exceptional level of the diastereoselectivity lends itself to a convenient, enantioselective synthesis of 1,3-cyclohexadienes by starting with enantiomerically pure homoallylic alcohols.

In summary, the ability of titanium alkoxides to promote the diyne-ene [2 + 2 + 2] cycloaddition reaction has been evaluated in comparison to the known examples involving titanium aryloxides: unlike the latter, the titanium alkoxide-mediated cycloaddition requires the use of homoallylic alcohols as the olefin component. Of particular importance is high 1,3-diastereoselectivity offered by secondary homoallylic alcohols, which should be of general utility in titanium-mediated C−C bond-forming reactions. Further refinement of this strategy, along with mechanistic studies and synthetic applications, will be reported in due course.

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