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Hydroxyl-Directed Cyclizations of 1,6-Enynes

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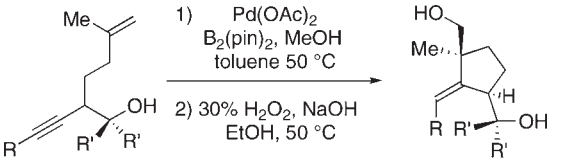
ABSTRACT

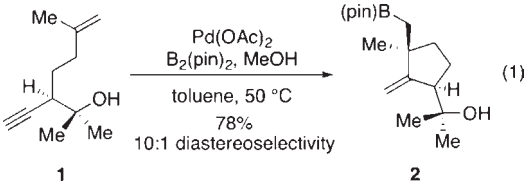


High selectivities for *cis*-products

The palladium-catalyzed, hydroxyl-directed cyclization reactions of 1,6-enynes provide a highly diastereoselective process for the syntheses of stereochemically defined cyclopentanes. Consistently high levels of *cis*-selectivity are possible using homopropargyl alcohols in contrast to the corresponding propargyl alcohols. Hydroborylative enyne cyclizations coupled with this directing group effect provide a useful method for the syntheses of multifaceted compounds bearing all carbon quaternary centers.

The intuitive implementation and reliability of substrate-directed reactions makes them ideal transformations for complex molecule syntheses. The noncovalent interactions that direct these reactions provide outcomes that oppose the typically repulsive effects of adjacent substituents.[1] The ability to diastereoselectively perform the cyclization reactions of 1,6-enynes provides an added attribute to this already useful transformation.[2] Recently, the use of ester functionalities as directing groups has provided remarkable control, allowing alternative products to be formed depending on the metal catalyst used.[2c] Herein we report the pronounced directing group effects of homopropargyl alcohols on the borylative cyclization reactions of 1,6-enynes.

In the course of our efforts to develop a synthetic route to stolonidiol, a marine derived diterpenoid capable of inducing the biosynthesis of choline acetyltransferase (ChAT),[3,4] we plan to implement a key Pd-catalyzed enyne cyclization to form the 5- and 11-membered rings of the natural product in a single operation. To test the potential directing effect of homopropargyl alcohol within our system on the enyne cyclization we examined the reaction using a borylative enyne cyclization.[5] The initial study examined the cyclization reaction of homopropargyl alcohol **1** which was shown to proceed with good diastereoselectivity (10:1), providing the *cis*-product **2** as the major diastereomer (eq 1).



1 2

To test the generality of this diastereocontrol several cyclization substrates, propargyl and homopropargyl alcohols, were synthesized and subjected to the borylative cyclization. The addition of acetylide anions into 4-methyl-4-pentenal (**3**) provided the corresponding propargyl alcohols represented by **4** (Scheme 1).[6,7] In addition to providing access to the corresponding homopropargylic system these alcohols were used to study the diastereoselectivities possible using propargyl alcohols as directing groups.

(1) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.

(2) For review, see: (a) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1. (b) Michelet, V.; Toullec, P. Y.; Genêt, J.-P. *Angew. Chem., Int. Ed.* **2008**, *47*, 4268. Recent example of an ester directed enyne cyclizations: (c) Trost, B. M.; Ferreira, E. M.; Gutierrez, A. C. *J. Am. Chem. Soc.* **2008**, *130*, 16176.

(3) (a) Mori, K.; Iguchi, K.; Yamada, N.; Yamada, Y.; Inouye, Y. *Tetrahedron Lett.* **1987**, *28*, 5673. (b) Yabe, T.; Yamada, H.; Shimomura, M.; Miyaoka, H.; Yamada, Y. *J. Nat. Prod.* **2000**, *63*, 433.

(4) Miyaoka, H.; Baba, T.; Mitome, H.; Yamada, Y. *Tetrahedron Lett.* **2001**, *42*, 9233.

(5) (a) Marco-Martinez, J.; Lopez-Carrillo, V.; Bunuel, E.; Simancas, R.; Cardenas, D. J. *J. Am. Chem. Soc.* **2007**, *129*, 1874. (b) Marco-Martinez, J.; Buñuel, E.; Muñoz-Rodriguez, R.; Cárdenas, D. J. *Org. Lett.* **2008**, *10*, 3619.

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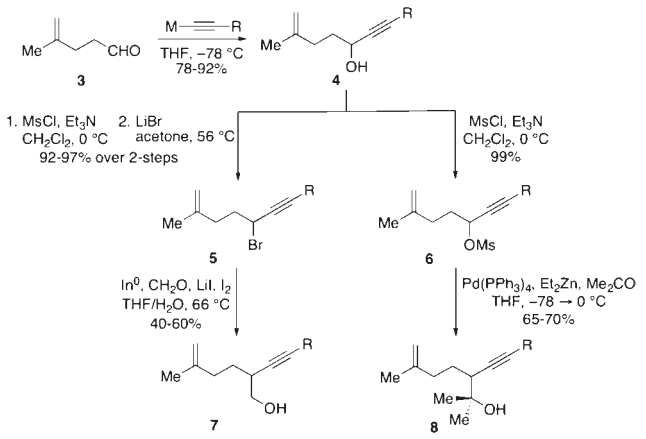
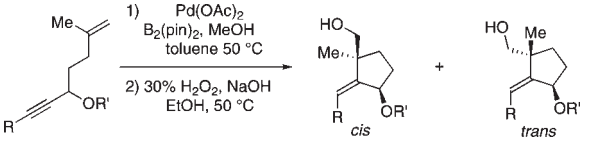
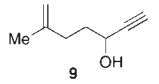
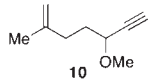
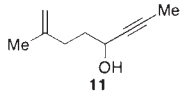
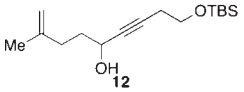
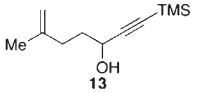
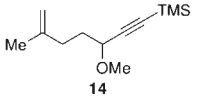
Scheme 1



Alternatively, conversion of the alcohols to either propargyl bromides or mesylates generated precursors for reactions with either formaldehyde or acetone, yielding a series of homopropargyl alcohols exemplified by **7** and **8**. Barbier-type reactions with formaldehyde were optimally performed using indium, formalin, and bromides **5** providing

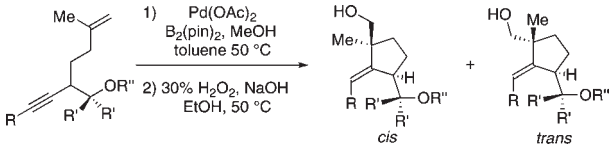
Table 1. Diastereoselective, Borylative Enyne Cyclizations of Propargyl Alcohols[a]

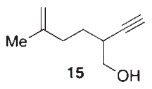
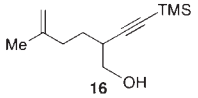
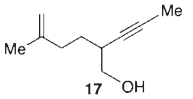
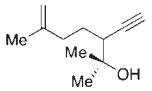
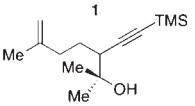
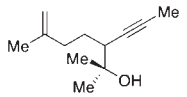
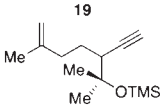


Substrate	mol % Pd	yield (%)	dr (*cis*:*trans*)
 **9**	25	n.r.	
 **10**	5	57	1:1
 **11**	15	91	2.5:1
 **12**	15	46	1:1
 **13**	5	87	8.5:1
 **14**	25	23	1:1

[a] Yields quoted are isolated yields. Stereoselectivities were determined by ^{1}H NMR spectroscopy of the crude mixture, with relative stereochemistries determined by NOE measurements.

Table 2. Diastereoselective, Borylative Enyne Cyclizations of Homopropargyl Alcohols[a]



Substrate	mol % Pd	yield (%)	dr (*cis*:*trans*)
 **15**	5	75	10:1
 **16**	25	72	>19:1
 **17**	25	85	>19:1
 **1**	5	76	13:1
 **18**	25	n.r.	
 **19**	25	90	>19:1
 **20**	5	81	1:1.2

[a] Yields quoted are isolated yields. Stereoselectivities were determined by ^{1}H NMR spectroscopy of the crude mixture. The relative stereochemistries were determined by NOE measurements and X-ray crystallography.

the primary alcohols **7**.[8] The reaction of the propargyl mesylates **11** with acetone was accomplished using diethyl zinc and tetrakis(triphenylphosphine)palladium, forming the corresponding tertiary alcohol products **9**.[9]

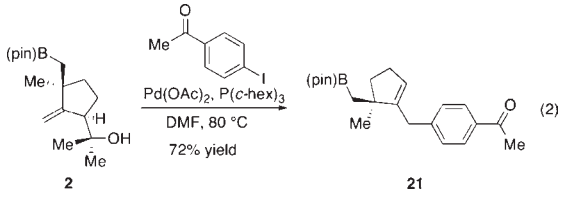
The cyclization reactions of propargyl alcohols and ethers using the palladium catalyzed borylative cyclization were examined using substrates **9**−**14** (Table 1).[5] Treatment of the propargyl alcohols with palladium acetate, methanol, and bis(pinicolato)diborane provided the cyclized products with no to moderate selectivity and variable yields. To facilitate the determination of the ratios of the products, the boronate esters were oxidized using basic solutions of hydrogen peroxide generating the corresponding diol products.[10] Propargyl alcohol **9** proved to be

(6) Padwa, A.; Kulkarni, Y. S.; Zhang, Z. *J. Org. Chem.* **1990**, *55*, 4144.
(7) Wakefield, B. J. *Organolithium Methods*; Academic: London, 1988; pp 32−44.
(8) Chan, T.-H.; Li, C.-J. *Tetrahedron* **1999**, *55*, 11149.
(9) Marshall, J. A.; Adams, N. D. *J. Org. Chem.* **1999**, *64*, 5201.

unreactive under the cyclization conditions; however, the corresponding methyl ether **10** formed the expected products in 57% yield and as a 1:1 mixture of isomers. Enyne **11** provided the corresponding diols in 91% yield (2.5:1 ratio *cis*/*trans*), and enyne **12** proved nonselective in the cyclization reaction proceeding with a yield of 46%. An interesting exception in the propargyl alcohol series, the TMS substituted alkyne **13** cyclized providing an 8.5:1 *cis*/*trans* ratio of products in good yield. The related methyl ether **14** proved a poor candidate for cyclization and generated a 1:1 ratio of diastereomers.

The cyclizations of the homopropargyl alcohols using the ligandless palladium conditions provided the *cis*-product with good to excellent diastereoselectivities and moderate to good yields (Table 2). Enyne **15** cyclized providing the *cis* product as the major isomer in a ratio of 10:1 (*cis*/*trans*) in 75% yield. Substrates with additional substitution on the alkyne, **16** and **17**, generated the cyclized products with excellent selectivity in excess of 19:1. The cyclizations of tertiary alcohols **1** and **19** were accomplished with good and excellent selectivities, respectively, demonstrating the strong directing effect from the homopropargyl position. The sterically congested enyne **18** proved resistant to the reaction conditions returning unchanged starting material. Cyclization of silyl ether **20** resulted in a nonselective reaction providing support for the importance of the alcohol in directing the reaction.

Aside from reactions of the boronate esters generated through the course of the reactions the homoallylic alcohols also provide a handle for carbon bond formation. The conversion of homoallyl alcohol **2** to acetophenone **21** through a palladium-catalyzed retro-allylation provides an example of a useful carbon−carbon bond forming transformation (eq 2).[11]



The directing effects of propargyl alcohols have proven variable; however, the cyclizations of homopropargyl alcohols proceed with high levels of diastereoselectivity. The directing group effects of the homopropargyl alcohols leads to the *cis*-placement of the boronate esters even when sterically congested tertiary alcohols are used as directing groups. Starting from simple precursors the boronic esters and diol products are expected to provide new, stereochemically defined compounds for complex molecule synthesis.

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Supporting Information Available. Detailed experimental procedures and full spectroscopic characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(10) Brown, H. C.; Zweifel, G. *J. Am. Chem. Soc.* **1959**, *81*, 247.

(11) (a) Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2006**, *128*, 2210. (b) Iwasaki, M.; Hayashi, S.; Hirano, K.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2007**, *129*, 4463.