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Regio- and Stereoselective Ruthenium-Catalyzed Hydrovinylation of 1,3-Dienes: Application to the Generation of a 20(*S*) Steroidal Side Chain

Zhengjie He, Chae S. Yi,* and William A. Donaldson*

Department of Chemistry, Marquette University, P.O. Box 1881, Milwaukee, Wisconsin 53201-1881

william.donaldson@marquette.edu

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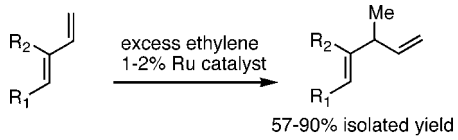
ABSTRACT



The addition of ethylene to 1,3-dienes and 1-vinylcycloalkenes, catalyzed by two ruthenium complexes, proceeds in a regioselective fashion to afford 3-methyl-1,4-dienes as products. For a steroidal-based 1-vinylcycloalkene, the addition is stereospecific, giving a product with a 20(*S*) configuration.

Transition metal-catalyzed hydrovinylation[1] holds tremendous potential as a generally useful C−C bond-forming reaction, since it uses a cheap feedstock (ethylene) and proceeds in an "atom economical" fashion.[2] This reaction has largely focused on 1-arylethylenes as substrates since the products, 3-aryl-1-butenes, may be transformed into useful analgesics (e.g., ibuprofen, naproxen). While a number of recent reports describe highly enantioselective hydrovinylation of styrenes,[3] further development of this reaction as a general synthetic tool will require broadening the scope of applicable substrates. Only limited examples of the hydrovinylation of cyclic dienes have been reported.[4] In the course of examining the ruthenium-catalyzed coupling of ethylene with alkynes, one of our labs recently reported the use of two ruthenium catalytic systems **1** and **2** for the coupling of ethylene with alkynes and alkenes.[5] We herein report the ruthenium-catalyzed hydrovinylation of unsymmetrically substituted 1,3-dienes. Reaction of 1,3-dienes

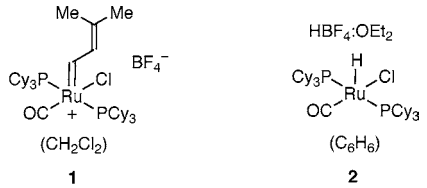


Figure 1. Ruthenium catalyst structures.

3a−**h** with excess ethylene, in the presence of either catalyst **1** or **2** gave predominantly the corresponding 3-methyl-1,4-dienes **4a**−**h**, the products resulting from 1,2-hydrovinylation (Table 1).[6] The structural assignment for **4** was based on its ^{1}H NMR spectral data. In particular, signals at ca. δ 5.9 (ddd, 1H), 5.05 (m, 2H), and 1.2 ppm (d, 3H) are characteristic of the vinyl and methyl groups of a 3-substituted-1-butenyl

(1) (a) Jolly, P. W.; Wilke, G. In *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B., Herrmann, W. A., Eds.; Wiley-VCH: New York, 2000; pp 1024−1072. (b) Goossen, L. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 3775−3778.

(2) (a) Trost, B. M. *Science* **1991**, *254*, 1471−1477. (b) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 259−281.

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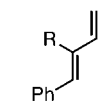
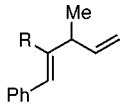
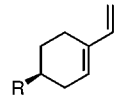
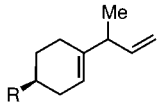
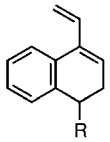
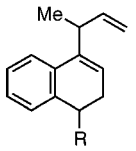
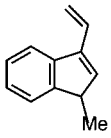
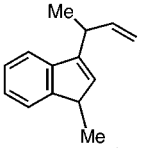
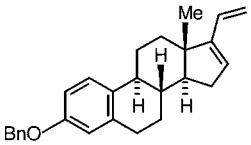
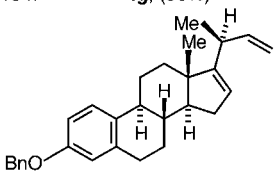
Table 1. Ru-Catalyzed Hydrovinylation of 1,3-Dienes

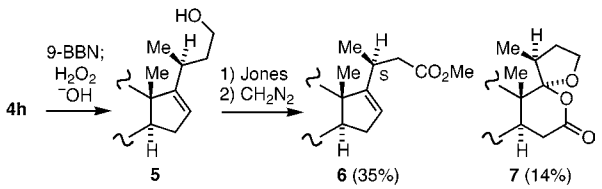
1-vinylcycloalkene	catalyst/rxn time	product (isolated yield)
 **3a**, R = Ph **3b**, R = Me	1% **2**, 6 h 1% **1**, 16 h	 **4a**, R = Ph (90%)[a] **4b**, R = Me (75%)
 **3c**, R = H **3d**, R = C(Me)=CH$_2$	1% **1**, 22 h 1% **2**, 20 h	 **4c**, R = H (62%) **4d**, R = C(Me)=CH$_2$ (57%)[b]
 **3e**, R = H **3f**, R = Me	1% **2**, 20 h 1.5% **1**, 15 h	 **4e**, R = H (67%) **4f**, R = Me (75%)[b]
 **3g**	1.5% **1**, 15 h	 **4g**, (56%)[b]
 **3h**	2% **2**, 7 h	 **4h**, (88%)[c]

[a] From ref 5b. [b] Mixture of diastereomers (1:1). [c] Single diastereomer.

functionality. In certain cases, the reaction was terminated prior to complete consumption of starting material **3**, as prolonged contact with the catalyst led to isomerization of the initially formed **4** to the more stable conjugated 3-methyl-1,3-diene.[7] Any unreacted starting material or the isomerized 1,3-diene product could be chemically separated from the desired 1,4-diene **4** by treatment of the reaction mixture with phenyl triazodione (PTAD); the PTAD undergoes cycloaddition with the conjugated dienes, and the desired product **4** can be cleanly separated from these cycloaddition products.

Hydrovinylation of dienes bearing aryl substituents (**3a**,**b**) as well as 1-vinylcycloalkenes (**3c**−**h**) proceeded with excellent 1,2-addition regioselectivity. For certain substrates bearing a resident stereocenter (e.g., **3d**,**f**,**g**), hydrovinylation was not stereoselective, giving a 1:1 mixture of diastereomeric products. In contrast, hydrovinylation of the steroidal diene **3h** proceeded with excellent regio- and stereoselectivity, giving a single diastereomer **4h** in good isolated yield. Since assignment of the C20 configuration of the product **4h** was not possible on the basis of NMR spectral data, a crystalline derivative was sought. To this end, hydroboration/oxidation of **4h** proceeded only at the vinyl group to afford the primary alcohol **5** (Scheme 1). Oxidation of **5** with Jones reagent, followed by treatment of the crude product with diazomethane, gave a separable mixture of ester **6**[8] and spirocyclic lactone **7**.[9] Crystals of **7** suitable for X-ray diffraction analysis revealed the relative configurations within the molecule;[10] since the precursor **3h** was prepared from optically pure estrone,[11] the absolute configurations at the C17 and C20 stereocenters of **7** were assigned as (*R*) and (*S*), respectively. Thus, the hydrovinylation product **4h** has the 20(*S*) configuration, which is opposite to the configuration of most naturally occurring steroids [i.e., 20(*R*)]. Recently, a nonnatural 20(*S*) vitamin D$_3$ analogue has been reported that selectively induces bone formation.[12] While there are many strategies for the preparation of the 20(*R*) side chain,[13] there is a general lack of *stereoselective* routes to side chains with the 20(*S*) configuration.[14]

Scheme 1



(3) (a) Bayersdorfer, R.; Ganter, B.; Englert, U.; Keim, W.; Vogt, D. *J. Organomet. Chem.* **1998**, *552*, 187−194. (b) Albert, J.; Cadena, M.; Granell, J.; Muller, G.; Ordinas, J. I.; Panyella, D.; Puerta, C.; Sanudo, C.; Valerga, P. *Organometallics* **1999**, *18*, 3511−3518. (c) Englert, U.; Haerter, R.; Vasen, D.; Salzer, A.; Eggerling, E. B.; Vogt, D. *Organometallics* **1999**, *18*, 4390−4398. (d) Wegner, A.; Leitner, W. *J. Chem. Soc., Chem. Commun.* **1999**, 1583−1584. (e) Bosmann, A.; Francio, G.; Jenssen, E.; Solinas, M.; Leitner, W.; Wasserscheid, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 2697−2699. (f) Francio, G.; Faraone, F.; Leitner, W. *J. Am. Chem. Soc.* **2002**, *124*, 736−737. (g) Nomura, N.; Jin, J.; Park, H.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1998**, *120*, 459−460. (h) Nandi, M.; Jin, J.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1999**, *121*, 9899−9900. (i) Park, H.; RajanBabu, T. V. *J. Am. Chem. Soc.* **2002**, *124*, 734−735.

(4) (a) Beger, J.; Duschek, C.; Gericke, C. *J. Prakt. Chem.* **1974**, *316*, 952−962. (b) Buono, G.; Siv, C.; Peiffer, G.; Triantaphylides, C.; Denis, P.; Mortreux, A.; Petit, F. *J. Org. Chem.* **1985**, *50*, 1781−1782. (c) Hilt, G.; du Mesnil, F.-X.; Luers, S. *Angew. Chem., Int. Ed.* **2001**, *40*, 387−389.

(5) (a) Yi, C. S.; Lee, D. W.; Chen, Y. *Organometallics* **1999**, *18*, 2043−2045. (b) Yi, C. S.; He, Z.; Lee, D. W. *Organometallics* **2001**, *20*, 802−804.

(6) Neither 1,4-diphenyl-1,3-butadiene or 2,5-dimethyl-2,4-hexadiene reacted with ethylene in the presence of either **1** or **2**.

(7) Isomerization (over longer reaction periods) is observed with both catalysts **1** and **2**. Thus, at least for catalyst **1**, this isomerization cannot be attributed to the presence of acid.

(8) Both the 20(*S*)- and 20(*R*)-isomers of the methyl ether corresponding to benzyl ether **6** have been previously prepared. The close similarity of their literature NMR spectral data does not allow for an unambiguous assignment. Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1978**, *100*, 3435−3443.

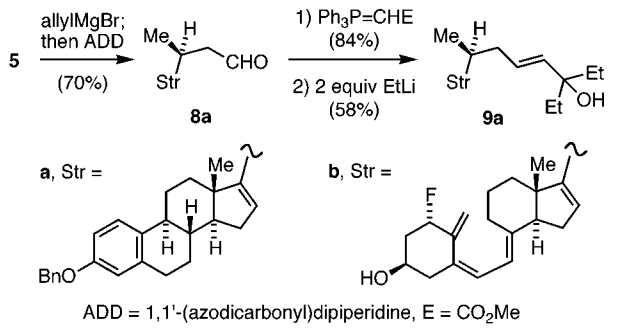
(9) Formation of γ-lactones from 4-penten-1-ols or δ-lactones from 5-hexen-1-ols via oxidation with chromium reagents has been previously reported. (a) Chakraborty, T. K.; Chandrasekaran, S. *Tetrahedron Lett.* **1984**, *25*, 2895−2896. (b) Schlecht, M. F.; Kim, H. *Tetrahedron Lett.* **1985**, *26*, 127−130. (c) Rathore, R.; Vankar, P. S.; Chandrasekaran, S. *Tetrahedron Lett.* **1986**, *27*, 4079−4082.

(10) Bennett, D. W.; Siddiquee, T. A.; Murphy, K. L.; Haworth, D. T.; He, Z.; Donaldson, W. A. *J. Chem. Cryst.* Submitted for publication. CCDC number 201892.

(11) De Riccardis, F.; Meo, D.; Izzo, I.; Di Filippo, M.; Casapullo, A. *Eur. J. Org. Chem.* **1998**, 1965−1970.

To demonstrate the synthetic potential of this diastereoselective hydrovinylation reaction, alcohol **5** was transformed into unsaturated alcohol **9a** via a three-step protocol (Scheme 2). Structure **9a** is a hybrid between estrone and the Roche

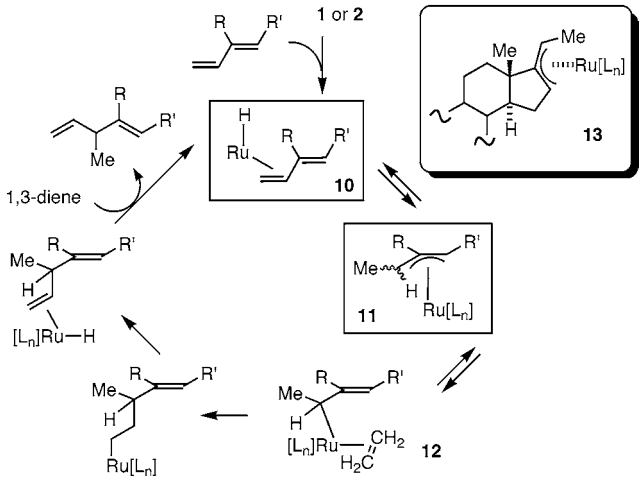
Scheme 2



vitamin D_3 analogue, Ro 26-9228 (**9b**), which is reported to increase bone mineral density in rats.[12a] Additionally, functionalized estrone analogues structurally similar to **9a** are described as agents for the modulation of cell growth and differentiation.[12d]

The hydrovinylation of 1,3-dienes with either **1** or **2** is proposed to involve a ruthenium hydride species **10** in which the less substituted olefin of the diene is coordinated to Ru (Scheme 3).[15] Insertion of the conjugated diene into the Ru−H bond generates the 1-methyl-π-allyl intermediate **11** in a reversible fashion. Ethylene insertion into the σ-allyl species **12**, with retention of configuration, followed by

Scheme 3



β-hydride and subsequent ligand exchange with a 1,3-diene, regenerates species **10**, and affords the product 1,4-diene. The stereoselective formation of **4h** may be rationalized on the preferential formation of π-allyl intermediate **13** (Scheme 3) in which Ru is trans to the sterically bulky angular methyl group and the allylic methyl group occupies the anti position in order to avoid steric interaction with the C12 methylene (steroid numbering).

In summary, regio- and stereoselective hydrovinylation of 1,3-dienes **3** has been achieved by using Ru catalysts **1** or **2**. Further developments in the scope of this reaction as well as synthetic applications will be reported in due course.

Acknowledgment. Financial support for this work was provided by the National Institutes of Health (GM-42641 to W.A.D. and GM-55987 to C.S.Y.). High-resolution mass-spectral determinations were made at the Washington University Mass Spectrometry Resource, an NIH Research Resource (Grant P41RR0954). W.A.D. acknowledges stimulating discussions with Prof. T. V. RajanBabu.

Supporting Information Available: Details of experimental procedures, characterization, and analytical data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) (a) Kabat, M. M.; Garofalo, L. M.; Daniewski, A. R.; Hutchings, S. D.; Liu, W.; Okabe, M.; Radinov, R.; Zhou, Y. *J. Org. Chem.* **2001**, *66*, 6141−6150. (b) Sicinski, R. R.; Rotkewicz, P.; Kolinski, A.; Sicinska, W.; Prahl, J. M.; Smith, C. M.; DeLuca, H. F. *J. Med. Chem.* **2002**, *45*, 3366−3380. (c) Shevde, N. K.; Plum, L. A.; Clagett-Dame, M.; Yamamoto, H.; Pike, J. W.; DeLuca, H. F. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 13487−13491. (d) Hesse, R. H.; Setty, S. K. S.; Ramgopal, M.; Kugabalusooriar, S. Patent WO 2000068246, 2000; CAN 133 350395, 2000.

(13) For a review, see: Gui-Dong, Z.; Okamura, W. H. *Chem. Rev.* **1995**, *95*, 1877−1952. For a more recent synthesis, see: Yan, J.; Herndon, J. W. *J. Org. Chem.* **1998**, *63*, 2325−2331 and references therein.

(14) 20(*S*) vitamin D_3 precursors have been prepared by ozonolytic degradation of ergocalciferol, followed by a base-catalyzed epimerization and separation of the 20(*R*)- and 20(*S*)-diastereomers: Hijikuro, D. T.; Takahashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 3716−3722. For a route to the 20(*S*) side chain that uses stoichiometric palladium, see ref 8.

(15) Notably, the Ru−H species **10** has been proposed as an intermediate in the coupling of alkynes with ethylene using catalyst **1** (see ref 5a).