ORGANIC LETTERS

2010
Vol. 12, No. 12
2844−2846

Direct Ruthenium-Catalyzed C−C Coupling of Ethanol: Diene Hydro-hydroxyethylation To Form All-Carbon Quaternary Centers

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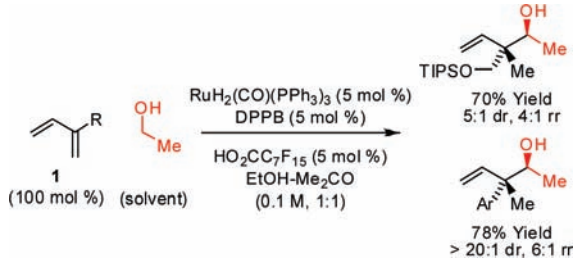
Received May 11, 2010

ABSTRACT



Under ruthenium-catalyzed transfer hydrogenation conditions, direct C−C coupling of ethanol and 2-substituted dienes occurs to furnish products of hydro-hydroxyethylation: *anti*-configured neopentyl homoallylic alcohols. Identical adducts are generated from acetaldehyde under related conditions employing isopropanol as reductant.

The majority of chemical commodities are made from rapidly depleting petrochemical feedstocks. The development of byproduct-free catalytic C−C bond-forming processes that exploit abundant, renewable resources would assist in defining a sustainable paradigm for chemical production.[1] With annual U.S. production now exceeding 10 billion gallons (2009),[2] ethanol is vastly abundant, yet its direct use as a C2 building block in homogeneous catalytic C−C coupling is largely unexplored.[3] Here, as part of a broad effort toward hydrogen-mediated C−C bond formations beyond hydroformylation,[4] we report the direct C−C coupling of ethanol and 2-substituted dienes to furnish products of hydroxyethylation: a ruthenium-catalyzed C−C bond-forming transfer hydrogenation (Scheme 1). This method enables diastereoselective formation of all-carbon quaternary centers under catalytic conditions in the absence of premetalated nucleophiles or resulting stoichiometric metallic byproducts. To our knowledge, this process, which enables direct, byproduct-free access to *anti*-configured neopentyl homoallylic alcohols, has no stereoselective counterpart in conventional allylmetal chemistry.[5]

In prior studies from our laboratory it was found that iridium and ruthenium catalysts promote hydrogen exchange between alcohols and π-unsaturated reactants to generate nucleophile−electrophile pairs that engage in byproduct-free C−C coupling.[4] This new pattern of reactivity availed the opportunity to explore the direct activation of renewable alcohols, such as methanol and ethanol, as C1 and C2 building blocks in catalytic C−C couplings to π-unsaturated reactants. Our initial efforts toward

(1) For selected reviews on sustainable chemical synthesis, see: (a) Anastas, P.; Eghbali, N. *Chem. Soc. Rev.* **2010**, *39*, 301. (b) Sheldon, R. A. *Green Chem.* **2007**, *9*, 1273. (c) Clark, J. H. *J. Chem. Technol. Biotechnol.* **2007**, *82*, 603. (d) Lange, J.-P. *ChemSusChem* **2009**, *2*, 587.

(2) Renewable Fuels Association (RFA): http://www.ethanolrfa.org/ (accessed March 1, 2010).

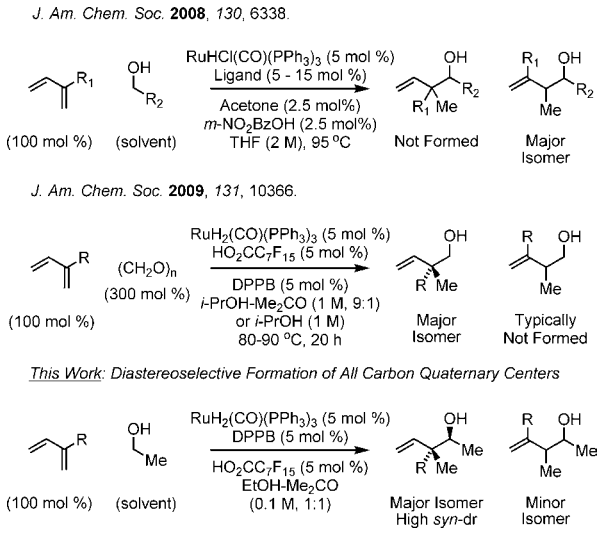
(3) Ethanol carbonylation to form propionic acid under the conditions of homogenous catalysis has been described: (a) Patil, R. P.; Kelkar, A. A.; Chaudhari, R. V. *J. Mol. Catal.* **1988**, *47*, 87. (b) Ubale, R. S.; Kelkar, A. A.; Chaudhari, R. V. *J. Mol. Catal. A: Chem.* **1997**, *118*, 9.

(4) For selected reviews on C−C bond-forming hydrogenation and transfer hydrogenation, see: (a) Shibahara, F.; Krische, M. J. *Chem. Lett.* **2008**, *37*, 1102. (b) Patman, R. L.; Bower, J. F.; Kim, I. S.; Krische, M. J. *Aldrichimica Acta* **2008**, *41*, 95. (c) Bower, J. F.; Kim, I. S.; Patman, R. L.; Krische, M. J. *Angew. Chem., Int. Ed.* **2009**, *48*, 34.

(5) For isolated examples of stereoselective carbonyl allylboration to furnish *syn*-configured neopentyl homoallylic alcohols, see: Ely, R. J.; Morken, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 2534, and ref 13.

10.1021/ol101077v
Published on Web 05/21/2010

Scheme 1. Carbonyl Addition via Ruthenium-Catalyzed C−C Coupling of Dienes[a]

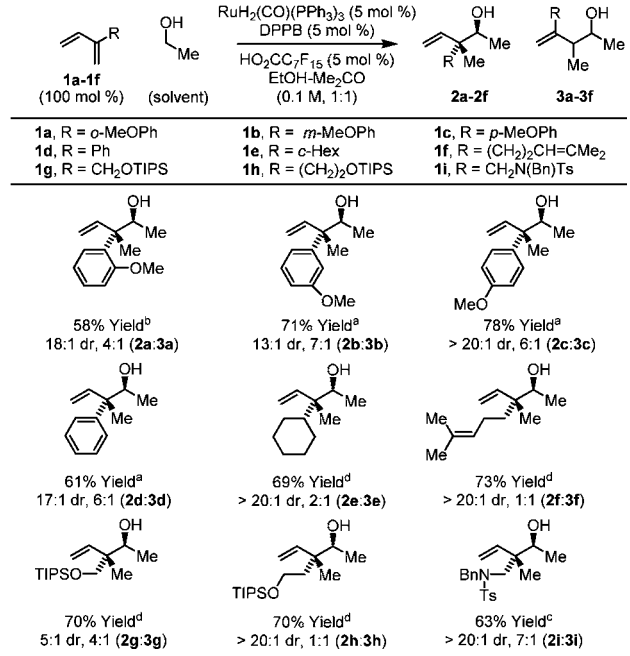


[a] For oxidative ruthenium-catalyzed diene-alcohol C−C coupling to form β,γ-enones, see ref 7c.

direct activation of methanol proved unfruitful, likely because methanol dehydrogenation is energetically demanding.[6] Indeed, whereas attempted C−C couplings of methanol fail, corresponding reactions of paraformaldehyde employing isopropanol as terminal reductant proceed readily, as demonstrated in ruthenium-catalyzed hydroxymethylations of 1,1-disubstituted allenes and 2-substituted dienes.[7b,d] As ethanol dehydrogenation occurs more readily than the dehydrogenation of methanol (ΔH = +68 vs +84 kJ/mol, respectively),[6] the direct activation of ethanol in couplings to 2-substituted diene **1c** was explored.[7−11]

Using $RuH(O_2CC_7F_{15})(CO)(dppb)(PPh_3)$ as catalyst,[12] a complex that was effective in related diene-formaldehyde couplings,[7b] diene **1c** was converted to the C−C coupling product **2c** and **3c** in 78% isolated yield as a 6:1 mixture of constitutional isomers. Notably, **2c** appears as a single diastereomer. Thus, C−C coupling occurs predominantly at the 2-position of the diene, resulting in diastereoselective formation of an all-carbon quaternary center. In most cases, regioisomers **2c** and **3c** differ substantially in polarity and are easily separated by silica gel chromatography. Under these conditions, ethanol was coupled to dienes **1a**−**1i**. With the exception of myrcene **1f** and diene **1h**, constitutional isomers **2** are the major products formed. Diastereoselectivities for adducts **2a**−**2i** range from 4:1 to >20:1 in favor of the indicated *anti*-isomer (Scheme 2). The

Scheme 2. Ruthenium-Catalyzed Coupling of Ethanol to 2-Substituted Dienes **1a**−**1i**[a]



[a] Cited yields are of material isolated by silica gel chromatography. Conditions: (a) 80 °C, 20 h; (b) 90 °C, 20 h; (c) 90 °C, 40 h; (d) 100 °C, 40 h. See Supporting Information for detailed experimental procedures.

stereochemical assignment of adducts **2a**−**2i** is tentatively assigned in analogy to that determined for the product obtained from the coupling of benzyl alcohol to myrcene **1f**.[13]

For most C−C bond-forming transfer hydrogenations developed in our laboratory,[4,7] carbonyl addition is possible from the alcohol or aldehyde oxidation level. In the latter case, a stoichiometric reductant such as isopropanol or formic acid is required. Accordingly, it was found that the reductive coupling of dienes **1a**−**1i** to acetaldehyde can be conducted using the same ruthenium catalyst under essentially identical conditions employing isopropanol/acetone (1:1) as solvent to furnish an equivalent set of adducts **2a**−**2i** with similar trends in regio- and diastereoselectivity (Scheme 3).

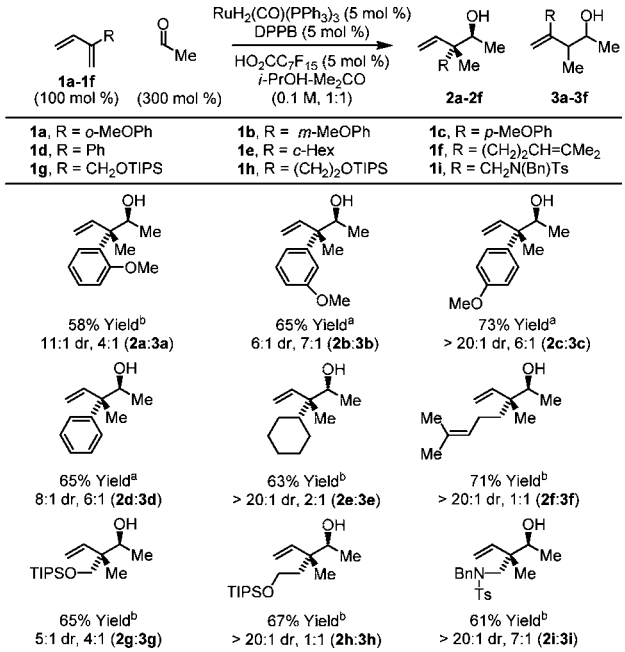
(6) For methanol dehydrogenation, DH = +84 kJ/mol. For ethanol dehydrogenation, DH = +68 kJ/mol: (a) Qian, M.; Liauw, M. A.; Emig, G. *Appl. Catal. A* **2003**, *238*, 211. (b) Lin, W.-H.; Chang, H.-F. *Catal. Today* **2004**, *97*, 181.

(7) For ruthenium catalyzed C−C bond-forming transfer hydrogenation developed in our laboratory, see the following. Dienes: (a) Shibahara, F.; Bower, J. F.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 6338. (b) Smejkal, T.; Han, H.; Breit, B.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 10366. (c) Shibahara, F.; Bower, J. F.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 14120. Allenes: (d) Ngai, M.-Y.; Skucas, E.; Krische, M. J. *Org. Lett.* **2008**, *10*, 2705. (e) Skucas, E.; Zbieg, J. R.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 5054. (f) Grant, C. D.; Krische, M. J. *Org. Lett.* **2009**, *11*, 4485. (g) Zbieg, J. R.; McInturff, E. L. *Org. Lett.* **2010**, published ASAP, DOI:, 10.1021/ol1007235. (h) Alkynes:; Patman, R. L.; Chaulagain, M. R.; Williams, V. M.; Krische, M. J. *J. Am. Chem. Soc.* **2009**, *131*, 2066. (i) Williams, V. M.; Leung, J. C.; Patman, R. L.; Krische, M. J. *Tetrahedron* **2009**, *65*, 5024. (j) Enynes: Patman, R. L.; Williams, V. M.; Bower, J. F.; Krische, M. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 5220.

(8) For related catalytic C−C couplings that occur by way of nucleophilic ruthenium *p*-allyls, see: (a) Tsuji, Y.; Mukai, T.; Kondo, T.; Watanabe, Y. *J. Organomet. Chem.* **1989**, *369*, C51. (b) Kondo, T.; Ono, H.; Satake, N.; Mitsudo, T.-a.; Watanabe, Y. *Organometallics* **1995**, *14*, 1945. (c) Kondo, T.; Hiraishi, N.; Morisaki, Y.; Wada, K.; Watanabe, Y.; Mitsudo, T.-a. *Organometallics* **1998**, *17*, 2131. (d) Yu, C.-M.; Lee, S.; Hong, Y.-T.; Yoon, S.-K. *Tetrahedron Lett.* **2004**, *45*, 6557. (e) Omura, S.; Fukuyama, T.; Horiguchi, J.; Murakami, Y.; Ryu, I. *J. Am. Chem. Soc.* **2008**, *130*, 14094.

(9) For selected reviews of ruthenium-catalyzed C−C coupling beyond olefin metathesis, see: (a) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067. (b) Kondo, T.; Mitsudo, T.-a. *Curr. Org. Chem.* **2002**, *6*, 1163. (c) Dérien, S.; Monnier, F.; Dixneuf, P. H. *Top. Organomet. Chem.* **2004**, *11*, 1.

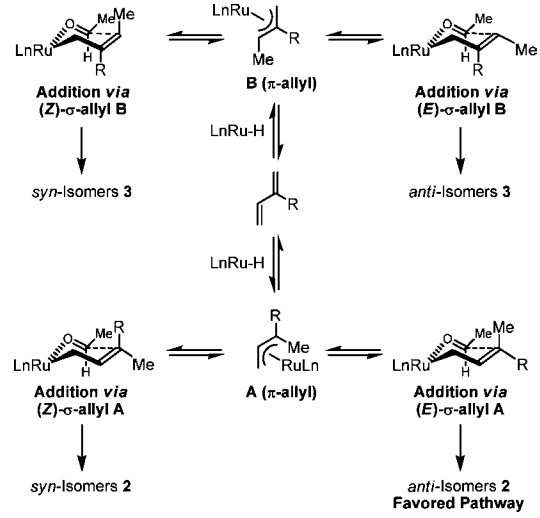
Scheme 3. Ruthenium-Catalyzed Coupling of Acetaldehyde to 2-Substituted Dienes **1a**−**1i**[a]



[a] Conditions: (a) 90 °C, 20 h; (b) 100 °C, 40 h. Otherwise, as described in Table 1.

Our collective data reveal that regioselectivity varies in response to steric features of the aldehyde, with small aldehydes such as formaldehyde[7b] delivering the greatest proportion of isomers **2**. These data are consistent with a Curtin−Hammett scenario involving rapid interconversion of isomeric π-allyls **A** and **B**.[14] Here, the relative energies of the competing transition structures for carbonyl addition determine regioselectivity. If one presumes a chairlike transition structure, additions from π-allyl **B** by way of (*E*)- and (*Z*)-σ-allyls **B** are likely disfavored as a result of strain arising from nonbonded interactions between the pseudoaxially oriented R-substituent with groups attached to the ruthenium center. Similarly, the transition state for carbonyl addition from π-allyl **A** by way of the (*Z*)-σ-allyl **A** is likely disfavored because of the pseudoaxial orientation of the R-substituent. In contrast to all other pathways, carbonyl addition from the (*E*)-σ-allyl **A** involves pseudoequatorial placement of the R-substituent, which directs preferential formation of *anti*-isomers **2**. Only through rapid interconversion of π-allyls and σ-allyls **A** and **B** can the minimum energy pathway en route to *anti*-isomers **2** be traversed (Scheme 4).

Scheme 4. Regio- and Diastereoselective Hydro-hydroxyethylation via Selective Carbonyl Addition from Isomeric Ruthenium π-Allyl and σ-Allyl Intermediates



In summary, we report a direct catalytic C−C coupling of ethanol, an abundant, renewable alcohol, which results in the diastereoselective formation of *anti*-configured homoallylic alcohols possessing all-carbon quaternary centers. These studies represent an important step toward the long-term objective of defining catalytic systems for the byproduct-free C−C coupling of abundant alcohols (methanol and ethanol) to α-olefins.[15] Future studies will focus on the development related hydro-hydroxyalkylations, including enantioselective variants of the process described herein.

Acknowledgment. The authors thank the Robert A. Welch Foundation and the NIH-NIGMS (RO1-GM069445) for partial support of this research.

Supporting Information Available: Spectral data for all new compounds (^{1}H NMR, ^{13}C NMR, IR, HRMS). This material is available free of charge via the Internet at http://pubs.acs.org.

OL101077V

(10) For catalytic intermolecular diene-aldehyde reductive coupling, see: (a) Kimura, M.; Ezoe, A.; Shibata, K.; Tamaru, Y. *J. Am. Chem. Soc.* **1998**, *120*, 4033. (b) Takimoto, M.; Hiraga, Y.; Sato, Y.; Mori, M. *Tetrahedron Lett.* **1998**, *39*, 4543. (c) Kimura, M.; Fujimatsu, H.; Ezoe, A.; Shibata, K.; Shimizu, M.; Matsumoto, S.; Tamaru, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 397. (d) Kimura, M.; Shibata, K.; Koudahashi, Y.; Tamaru, Y. *Tetrahedron Lett.* **2000**, *41*, 6789. (e) Kimura, M.; Ezoe, A.; Tanaka, S.; Tamaru, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 3600. (f) Loh, T.-P.; Song, H.-Y.; Zhou, Y. *Org. Lett.* **2002**, *4*, 2715. (g) Sato, Y.; Sawaki, R.; Saito, N.; Mori, M. *J. Org. Chem.* **2002**, *67*, 656. (h) Jang, H.-Y.; Huddleston, R. R.; Krische, M. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 4074. (i) Bareille, L.; Le Gendre, P.; Moïse, C. *Chem. Commun.* **2005**, 775. (j) Kimura, M.; Ezoe, A.; Mori, M.; Iwata, K.; Tamaru, Y. *J. Am. Chem. Soc.* **2006**, *128*, 8559. (k) Yang, Y.; Zhu, S.-F.; Duan, H.-F.; Zhou, C.-Y.; Wang, L.-X.; Zhou, Q.-L. *J. Am. Chem. Soc.* **2007**, *129*, 2248. (l) Sato, Y.; Hinata, Y.; Seki, R.; Oonishi, Y.; Saito, N. *Org. Lett.* **2007**, *9*, 5597.

(11) For a recent review encompassing nickel-catalyzed diene-aldehyde reductive coupling, see: Kimuara, M.; Tamaru, Y. *Top. Curr. Chem.* **2007**, *279*, 173.

(12) RuH($O_2CC_7F_{15}$)(CO)(dppb)(PPh_3) is prepared in situ from $RuH_2(CO)(PPh_3)_3$, $HO_2CC_7F_{15}$, and dppb: Dobson, A.; Robinson, S. R.; Uttley, M. F. *J. Chem. Soc., Dalton Trans.* **1974**, 370.

(13) Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2001**, *123*, 9488.

(14) For isomerization of ruthenium *p*-allyls, see: Xue, P.; Bi, S.; Sung, H. H. Y.; Williams, I. D.; Lin, Z.; Jia, G. *Organometallics* **2004**, *23*, 4735, and ref 7e.

(15) For related amine-mediated "hydro-aminoalkylation" of α-olefins, see: (a) Herzon, S. B.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 14940. (b) Herzon, S. B.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 6690, and references therein.