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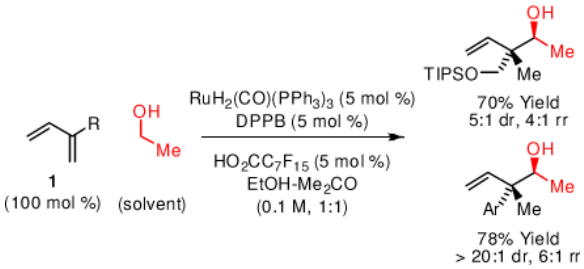
Direct Ruthenium Catalyzed C-C Coupling of Ethanol: Diene Hydro-Hydroxyethylation to Form All Carbon Quaternary Centers

Hoon Han and **Michael J. Krische***
University of Texas at Austin, Department of Chemistry and Biochemistry, Austin, TX 78712.

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 pre-metallated 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 direct activation of methanol proved unfruitful, likely due to the fact that methanol dehydrogenation is energetically demanding.[6] Indeed, whereas attempted C-C

mkrische@mail.utexas.edu .

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.

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.7 b,d As ethanol dehydrogenation occurs more readily than the dehydrogenation of methanol ($\Delta H = +68$ *vs.* +84 kJ/mol, respectively),[6] the direct activation of ethanol in couplings to 2-substituted diene **1c** was explored.[7,8,9,10,11]

Gratifyingly, using $RuH(O_2CC_7F_{15})(CO)(dppb)(PPh_3)$ as catalyst,[12] a complex that was effective in related diene-formaldehyde couplings,[7b] a 78% isolated yield of C-C coupling product as a 6:1 mixture of constitutional isomers **2c** and **3c**. Notably, **2c** appears as a single diastereomer. Thus, C-C coupling occurs 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 between 4:1 to > 20:1 in favor of the indicated *anti*-isomer (Scheme 2). The stereochemical assignment of adducts **2a-2i** is made 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 isopropanolacetone (1:1) as solvent to furnish an equivalent set of adducts **2a-2i** with similar trends in regio- and diastereoselectivity **2a-2i** (Scheme 3).

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 chair-like transition structure, additions from π-allyl **B** by way of (*E*)- and (*Z*)-σ-allyls **B** are likely disfavored due to strain arising from non-bonded interactions between the pseudo-axially 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 due to pseudo-axial orientation of the “R-substituent”. In contrast to all other pathways, carbonyl addition from the (*E*)-σ-allyl **A** involves pseudo-equatorial 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).

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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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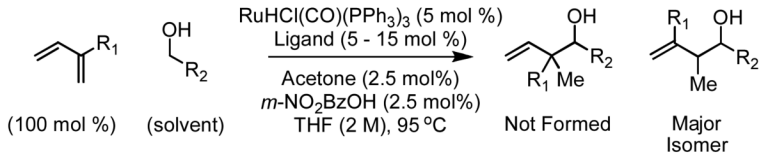

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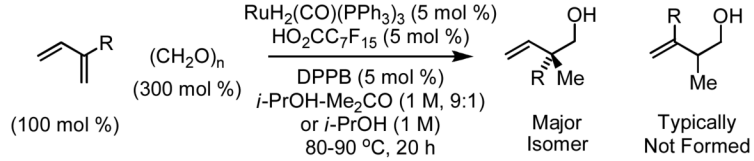
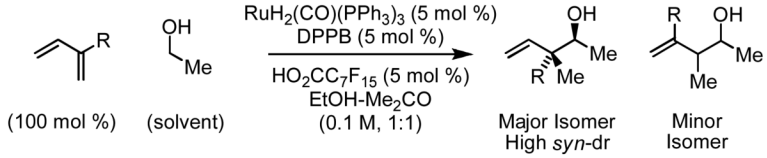


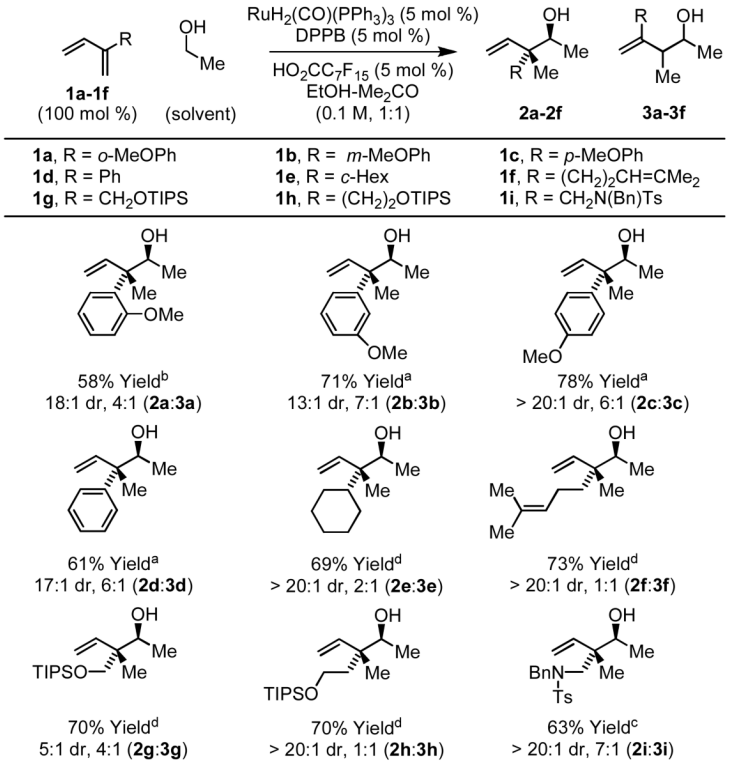
This Work: Diastereoselective Formation of All Carbon Quaternary Centers



Scheme 1.

Carbonyl addition via ruthenium catalyzed C-C coupling of dienes.

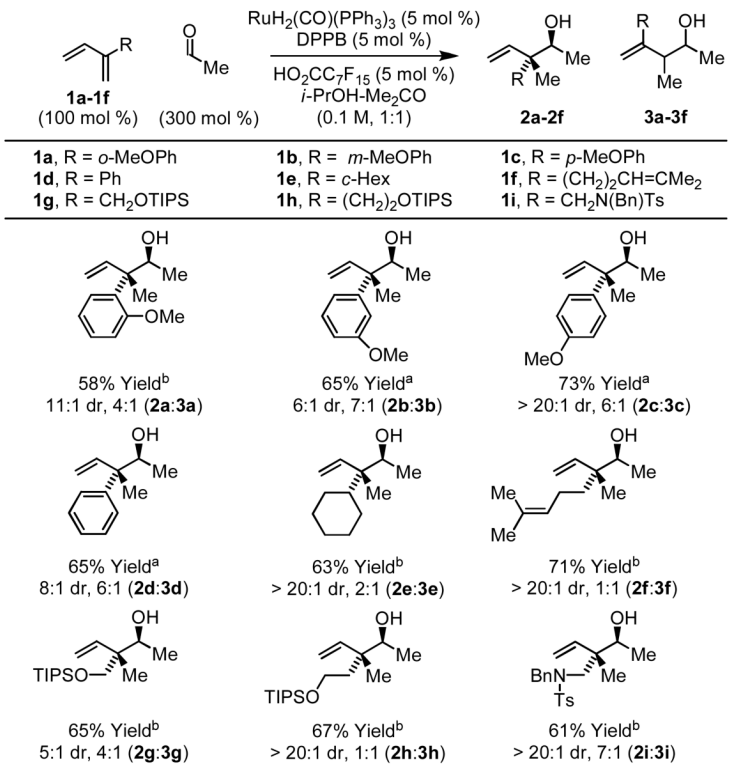
[a]For oxidative ruthenium catalyzed diene-alcohol C-C coupling to form β,γ-enones, see reference [7c].



Scheme 2.

Ruthenium catalyzed coupling of ethanol to 2-substituted dienes **1a-1i**.[a]

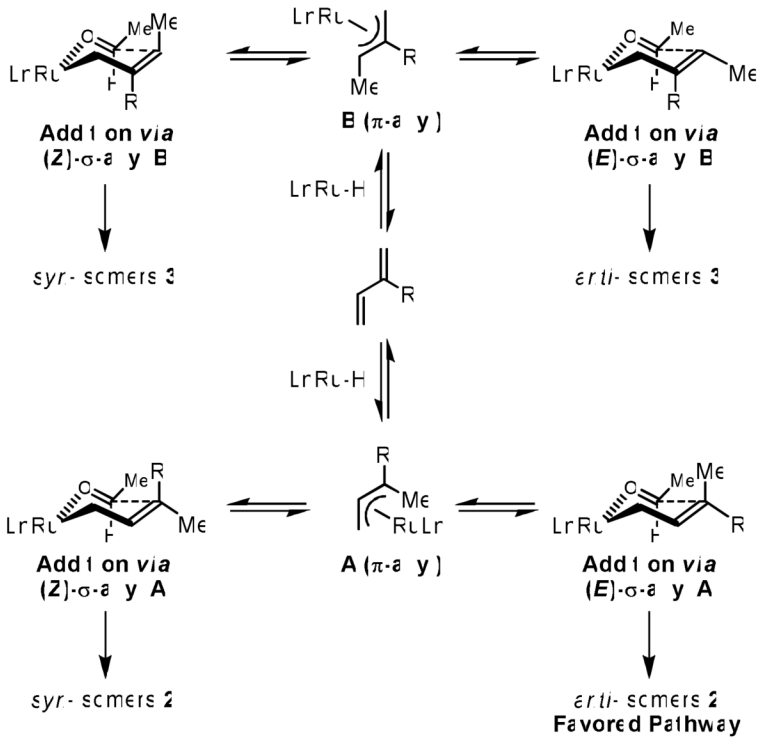
[a]Cited yields are of material isolated by silica gel chromatography. Conditions: (a) 80 °C, 20 h; (b) 90 °C, 20 h; (c) 90 °C, 40 h; (d) 100 °C, 40 h. See Supporting Information for detailed experimental procedures.



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.



Scheme 4.

Regio- and diastereoselective hydro-hydroxyethylation via selective carbonyl addition from isomeric ruthenium π-allyl and σ-allyl intermediates.[a]