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All Carbon Quaternary Centers *via* Ruthenium-Catalyzed Hydroxymethylation of 2-Substituted Butadienes Mediated by Formaldehyde: Beyond Hydroformylation

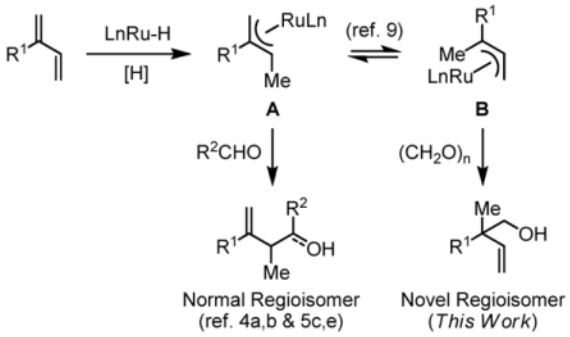
Tomas Smejkal[a,b,c], **Hoon Han**[c], **Bernhard Breit**[a,b,*], and **Michael J. Krische**[b,c,*]

[a] Albert-Ludwigs-Universität Freiburg, Institut für Organische Chemie und Biochemie, 79104 Freiburg, Germany

[b] Albert-Ludwigs-Universität Freiburg, Freiburg Institute for Advanced Studies (FRIAS), 79104 Freiburg, Germany

[c] University of Texas at Austin, Department of Chemistry and Biochemistry, Austin, TX 78712

Abstract



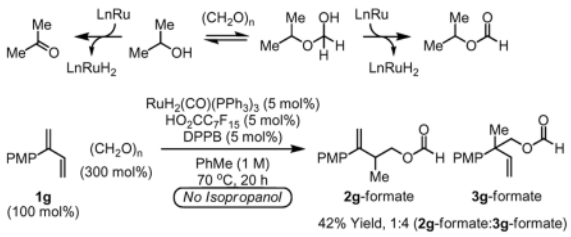
Ruthenium catalyzed transfer hydrogenation of 2-substituted dienes **1a**-**1i** in the presence of paraformaldehyde results in reductive coupling at the 2-position to furnish products of hydroxymethylation **3a**-**3i**, which embody all carbon quaternary centers. Reductive coupling of diene **1g** to paraformaldehyde under standard conditions, but employing either *deuterio*-paraformaldehyde or d_8-isopropanol, or both *deuterio*-paraformaldehyde corroborate a catalytic mechanism involving rapid and reversible diene hydrometallation with incomplete regioselectivity in advance of C-C coupling. These present method provides an alternative to the hydroformylation of conjugated dienes, for which efficient, regioselective catalytic systems remain undeveloped.

Hydroformylation is the largest volume application of homogenous metal catalysis and the prototypical C-C bond forming hydrogenation.[1] Whereas alkene hydroformylation is well developed, the hydroformylation of conjugated dienes has proven especially challenging.[2] As part of a broad program aimed at the development of hydrogen-mediated C-C bond formations beyond hydroformylation,[3] one of the present authors reported ruthenium catalyzed reductive couplings of carbonyl compounds to various unsaturates,[4–6] including dienes,[4a,b] allenes,[4c,d] alkynes[4e,f] and enynes.[4g] In lieu of efficient protocols for diene hydroformylation, the ruthenium catalyzed reductive coupling of dienes to paraformaldehyde, an abundant C1-

mkrische@mail.utexas.edu; bernhard.breit@chemie.unifreiburg.de.

Supporting information available: Experimental procedures and spectral data for new compounds. This material is available free of charge *via* the internet at http://pubs.acs.org.

feedstock, was investigated. Here, we report that ruthenium catalyzed transfer hydrogenation of 2-substituted dienes in the presence of paraformaldehyde delivers products of reductive C-C coupling in good yield. Remarkably, and in contrast to prior work on diene-carbonyl reductive coupling,[4–8] conditions that promote interconversion of π-allyl **A** to the isomeric π-allyl **B** were identified,[9] enabling C-C coupling at the 2-position of the diene to furnish products incorporating all carbon quaternary centers.



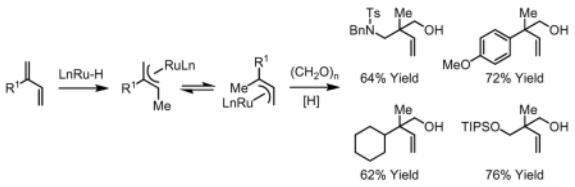
Initial studies focused on the reductive coupling of myrcene **1a** to paraformaldehyde. Upon an assay of our previously disclosed conditions,[4a,b] the catalyst prepared in situ from RuHCl(CO)$(PPh_3)_3$ and *rac*-BINAP was most effective, providing an 18% isolated yield of C-C coupling product. Surprisingly, this product appeared as an equimolar mixture of the anticipated adduct **2a** and its regioisomer **3a**, wherein coupling occurs at the substituted position of the diene to furnish the all carbon quaternary center. It was postulated that product **3a** forms through isomerization of π-allyl isomer **A** to π-allyl **B** by way of reversible β-hydride elimination-diene hydrometallation. Based on this hypothesis, ruthenium catalysts that embody greater cationic character were assayed, as coordinative unsaturation should promote β-hydride elimination, potentially accelerating isomerization. Indeed, upon an assay of counterions, it was found that $RuH(O_2CC_7F_{15})(CO)(dppb)(PPh_3)$, which is prepared in situ from $RuH_2(CO)(PPh_3)_3$ and $HO_2CC_7F_{15}$,[10] provides a 76% isolated yield of C-C coupling product as a 1:4 mixture of isomers **2a** and **3a**, respectively, in the presence of dppb.

It was hypothesized that the relative energies of the competing transition structures for carbonyl addition dictate the distribution of products **2** and **3**. If one assumes intervention of a chair-like transition structure, the path to isomers 2 mandates pseudo-axial orientation of the diene 2-substituent (Scheme 1). Hence, a larger 2-substituent should disfavor formation of isomers **2**. Indeed, exposure of the cyclohexyl-substituted diene **1b** to the aforementioned reaction conditions results in formation of the primary neopentyl alcohol **3b** as a single regioisomer. Branching directly adjacent to the 2-position is not required, as illustrated by formation of adducts **3c** and **3e**. However, sterically demanding groups are required at oxygen and nitrogen, respectively, to maintain complete levels of regioselectivity. To probe potential for substrate-induced diastereoselectivity, dienes **1d** and **1f**, which possess a preexisting stereogenic center, were subjected to standard reaction conditions. However, the resulting neopentyl alcohols were formed as equimolar mixtures of diastereomers. Finally, as demonstrated by formation of adducts **3g**-**3i**,[11] 2-aryl-1,3-butadienes are subject to highly regioselective hydroxymethylation (Table 1).

To gain further mechanistic insight, isotopic labeling studies were undertaken. Diene **1g** was subjected to three separate experiments employing *deuterio*-paraformaldehyde, d_8-isopropanol and both *deuterio*-paraformaldehyde and d_8- isopropanol under otherwise standard conditions (Table 2). The observed patterns of deuterium incorporation exclude pathways involving ruthenium catalyzed hydroformylation,[12] potentially enabled through decomposition of paraformaldehyde to form syngas (CO/H_2). Rather, these data are consistent with a scenario involving diene hydrometallation-β-hydride elimination at different positions of the diene by way of intermediates **A–D**. Formaldehyde addition from the primary σ-allyl haptomer derived from **B** through a chair-like transition structure is postulated to provide isomers **3** (Scheme 1).

As previously discussed, strain associated with pseudo-axial orientation of large diene 2-substituents appears to disfavor formation of isomers **2**. In contrast, the transition structure en route to isomers **3** involves pseudo-equatorial orientation of the diene 2-substituents and projection of these groups into open volumes of space.

Formaldehyde hemiacetals mediate reductive coupling in competition with isopropanol. ^{1}H NMR analysis of crude reaction mixtures reveal both acetone and isopropyl formate. Additionally, in the absence of isopropanol, but under otherwise standard conditions, diene **1g** is converted to formate esters **2g**-formate and **3g**-formate in 42% isolated yield as a 1:4 ratio of regioisomers, respectively. The difference in crystallinity and, hence, reactivity between paraformaldehyde and *deuterio*-paraformaldehyde may account for the observed drop in deuterium incorporation for "**Ha**" upon use of *deuterio*-paraformaldehyde and d_8-isopropanol compared to paraformaldehyde and d_8-isopropanol.



In summary, ruthenium catalyzed transfer hydrogenation of 2-substituted dienes in the presence of paraformaldehyde results in reductive coupling at the 2-position to furnish products of hydroxymethylation that contain all carbon quaternary centers. This process represents an alternative to 1,3-diene hydroformylation, for which efficient regioselective catalytic systems remain undeveloped.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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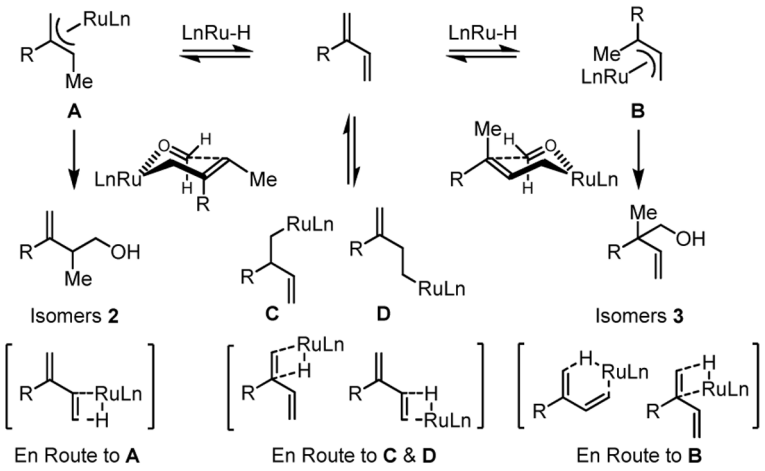


Scheme 1.
Plausible catalytic mechanism accounting for the results of isotopic labelling.

Table 1

Ruthenium catalyzed reductive coupling of 2-substituted dienes **1a**-**1i** to paraformaldehyde via transfer hydrogenation.[a]

1a, R = $(CH_2)_2CH=CMe_2$

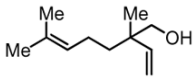
1b, R = cyclohexyl

1d, R = CHMeOTIPS

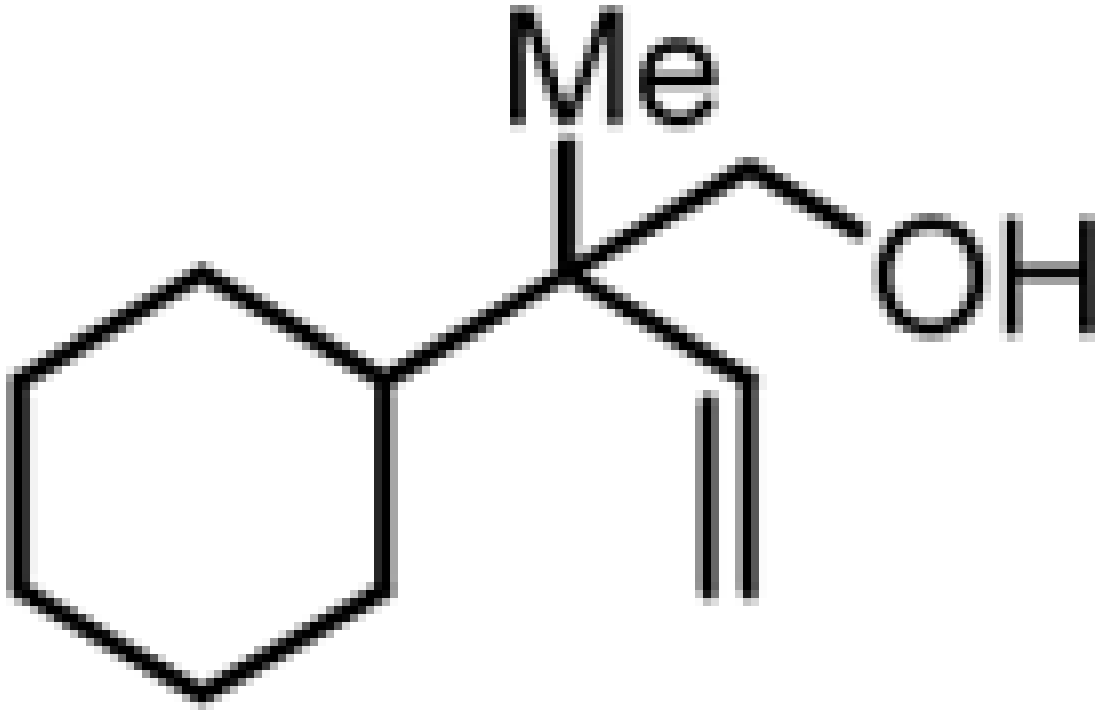
1e, R = $CH_2N(Bn)Ts$

1g, R = *p*-MeOPH

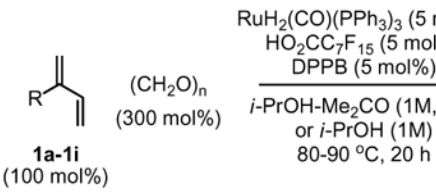
1h, R = *m*-MeOPH



76% Yield, **3a**
1:4, **2a:3a**, 90 °C[b]



62% Yield, **3b**
1:≥20, **2b:3b**, 90 °C[c]



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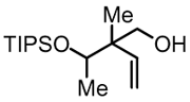
1b, R = cyclohexyl

1d, R = CHMeOTIPS

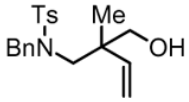
1e, R = $CH_2N(Bn)Ts$

1g, R = *p*-MeOPH

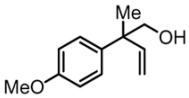
1h, R = *m*-MeOPH



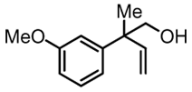
64% Yield, **3d**, 1:1 dr
1:≥20, **2d:3d**, 80 °C[b,d]



64% Yield, **3e**
1:≥20, **2e:3e**, 80 °C[c]



72% Yield, **3g**
1:≥20, **2g:3g**, 80 °C[b]



74% Yeild, **3h**
1:≥20, **2h:3h**, 80 °C[b]

[a] In all cases, cited yields are of isolated material and represent the average of two runs.

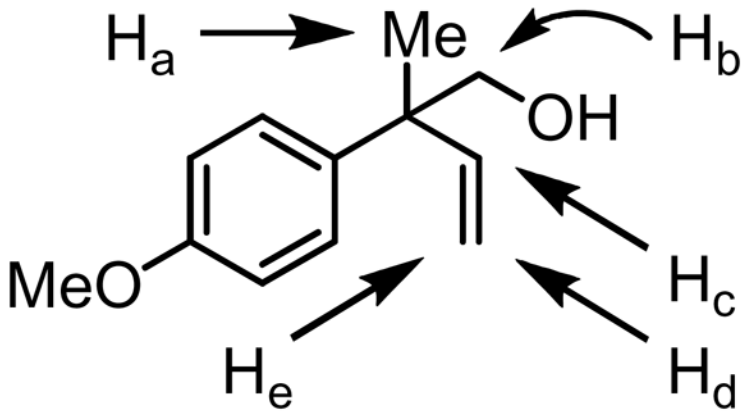
[b] Isopropanol-Me_2CO (1 M, 9:1) was used as solvent.

[c] Isopropanol (1 M) was used as solvent.

[d] Reaction time was extended to 40 h. See Supporting Information for detailed experimental procedures.

Table 2

Isotopic labeling studies exclude hydroformylation pathways and corroborate reversible diene hydrometallation.[a]



$(CD_2O)_n$, *i*-PrOH	$(CH_2O)_n$, d_8-*i*-PrOH	$(CD_2O)_n$, d_8-*i*-PrOH
H_a (5% ^2H)	H_a (51.5% ^2H)	H_a (17% ^2H)
H_b (100% ^2H)	H_b (0% ^2H)	H_b (100% ^2H)
H_c (16.5% ^2H)	H_c (46% ^2H)	H_c (76.5% ^2H)
H_d (12% ^2H)	H_d (51% ^2H)	H_d (58.5% ^2H)
H_e (14% ^2H)	H_e (50% ^2H)	H_e (57.5% ^2H)

[a] The extent of ^2H incorporation was determined using ^1H and ^2H NMR. The indicated values represent the average of two runs.