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

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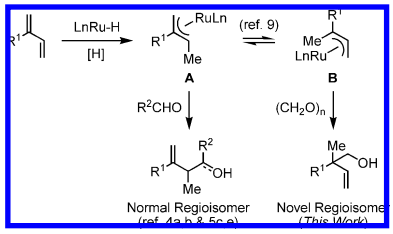
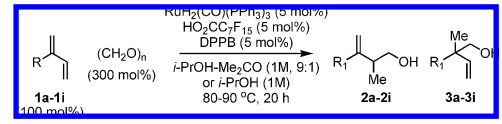
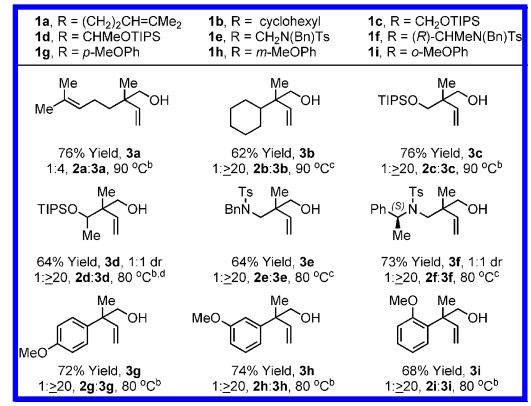
Hydroformylation is the largest-volume application of homogeneous metal catalysis and the prototypical C−C bond-forming hydrogenation.[1] Whereas alkene hydroformylation is well-developed, the hydroformylation of conjugated dienes has proven especially challenging.[2] As part of a broad program aimed 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 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 the 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 isomer **B** by way of reversible β-hydride elimination−diene hydrometalation. On the basis of 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 $RuH(O_2CC_7F_{15})(CO)(dppb)(PPh_3)$, 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.

Table 1. Ruthenium-Catalyzed Reductive Coupling of 2-Substituted Dienes **1a**−**i** to Paraformaldehyde via Transfer Hydrogenation[a]





[a] In each case, the cited yield is of isolated material and represents the average of two runs. See the Supporting Information for detailed experimental procedures. [b] 2-Propanol/Me_2CO (1 M, 9:1) was used as the solvent. [c] 2-Propanol (1 M) was used as the solvent. [d] The reaction time was extended to 40 h.

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 chairlike transition structure, the path to isomers **2** mandates pseudoaxial 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 resulted in formation of the primary neopentyl alcohol **3b** as a single regioisomer (Table 1). Branching directly adjacent to the 2-position is not required, as illustrated by the formation of adducts **3c** and **3e**. However, sterically demanding groups are required at O and N, respectively, to maintain complete levels of regioselectivity. To probe the potential for substrate-induced diastereoselectivity, dienes **1d** and **1f**, which possess a preexisting stereogenic center, were subjected to the standard reaction conditions. However, the resulting neopentyl alcohols were formed as equimolar mixtures of diastereomers. Finally, as demonstrated by the formation of adducts **3g**−**i**,[11] 2-aryl-1,3-butadienes are subject to highly regioselective hydroxymethylation.

To gain further mechanistic insight, isotopic labeling studies were undertaken. Diene **1g** was subjected to three separate experiments employing *deuterio*-paraformaldehyde, 2-propanol-d_8, or both *deuterio*-paraformaldehyde and 2-propanol-d_8 under otherwise standard

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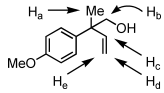
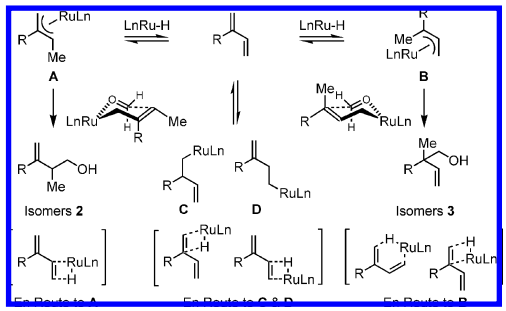
Table 2. Isotopic Labeling Studies Exclude Hydroformylation Pathways and Corroborate Reversible Diene Hydrometallation[a]



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

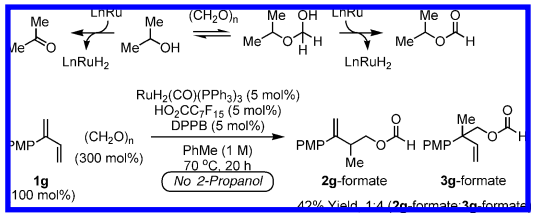
[a] The extent of ^{2}H incorporation was determined using ^{1}H and ^{2}H NMR spectroscopy. The indicated values represent averages of two runs.

Scheme 1. Plausible Catalytic Mechanism Accounting for the Results of Isotopic Labeling



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 hydrometalation−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 chairlike transition structure is postulated to provide isomers **3** (Scheme 1). As previously discussed, strain associated with the pseudoaxial orientation of large diene 2-substituents appears to disfavor formation of isomers **2**. In contrast, the transition structure en route to isomers **3** involves pseudoequatorial orientation of the diene 2-substituents and projection of these groups into open volumes of space.

Formaldehyde hemiacetals mediate reductive coupling in competition with 2-propanol. ^{1}H NMR analyses of the crude reaction mixtures reveal both acetone and isopropyl formate. Additionally, in the absence of 2-propanol 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, solubility between paraformaldehyde and *deuterio*-paraformaldehyde may account for the observed drop in deuterium incorporation for H_a upon use of *deuterio*-paraformaldehyde and 2-propanol-d_8 instead of paraformaldehyde and 2-propanol-d_8.



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.

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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.

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