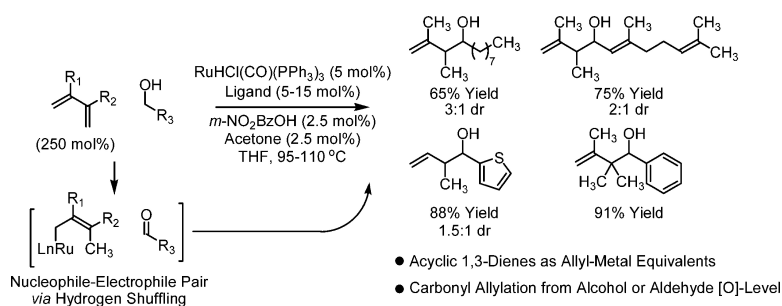


Ruthenium-Catalyzed C#C Bond Forming Transfer Hydrogenation: Carbonyl Allylation from the Alcohol or Aldehyde Oxidation Level Employing Acyclic 1,3-Dienes as Surrogates to Preformed Allyl Metal Reagents

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Ruthenium-Catalyzed C–C Bond Forming Transfer Hydrogenation: Carbonyl Allylation from the Alcohol or Aldehyde Oxidation Level Employing Acyclic 1,3-Dienes as Surrogates to Preformed Allyl Metal Reagents

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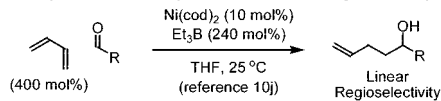
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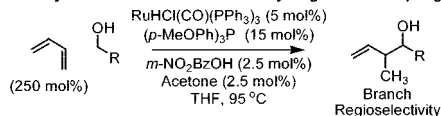
Ruthenium-catalyzed transfer hydrogenation ranks among the most powerful methods available for the reduction of polar functional groups,¹ yet reductive C–C bond formations catalyzed by ruthenium are highly uncommon.^{2–4} We have shown that reductive C–C bond formation may be achieved under the conditions of catalytic hydrogenation^{5,6} and, more recently, under the conditions of iridium-catalyzed transfer hydrogenation.⁷ The iridium-catalyzed processes enable direct coupling of allenes^{7a} and 1,3-cyclohexadiene^{7b} to aldehydes or alcohols to furnish products of carbonyl allylation. While these proof of concept studies establish the use of allenes and dienes as surrogates to preformed allyl metal reagents, the iridium-catalyzed couplings were not applicable to acyclic 1,3-dienes.

Here, we report that under the conditions of ruthenium-catalyzed hydrogen autotransfer^{8,9} 1,3-butadiene, isoprene, and 2,3-dimethylbutadiene couple to alcohols **1a–6a** to furnish products of carbonyl allylation **1b–6b**, **1c–6c**, and **1d–6d**, respectively. Under related transfer hydrogenation conditions employing isopropanol or formic acid as terminal reductant, aldehydes **7a–9a** couple to isoprene to furnish products of carbonyl allylation **1c–3c**, respectively. Thus, carbonyl allylation is achieved from the alcohol or aldehyde oxidation level. To our knowledge, these are the first examples of ruthenium-catalyzed C–C bond formation under the conditions of alcohol-mediated transfer hydrogenation.^{2–4} The branched regioselectivity observed in these couplings complements the linear regioselectivity observed in nickel-catalyzed diene–aldehyde reductive couplings.^{10–12} The transfer hydrogenative couplings reported in this account enable byproduct-free carbonyl allylation that transcends the boundaries of oxidation level and represent an important step in the departure from preformed organometallic reagents in carbonyl addition chemistry.^{6h,7,13,14}

Ni-Catalyzed Diene–Aldehyde Reductive Coupling - Homoallylation



Ru-Catalyzed Diene–Alcohol Transfer Hydrogenative Coupling - Allylation



Initially, a range of commercially available ruthenium catalysts were evaluated for their potential to couple isoprene to *p*-nitrobenzylalcohol under the conditions of hydrogen autotransfer. It was found that RuHCl(CO)(PPh₃)₃ promotes formation of the desired adduct with excellent levels of regioselectivity (>95:5) and in good isolated yield using only 2.5 equiv of diene. The addition of *m*-nitrobenzoic acid (2.5 mol %) proved to be critical as only trace quantities of product are observed in the absence of acid. Additionally, acetone (2.5 mol %) was found to confer a small but reproducible improvement in reaction efficiency. Finally, in most cases, isolated yields are improved upon addition of exogenous phosphine ligand, (*p*-MeOPh)₃P or *rac*-BINAP.¹⁵ Under optimal conditions, benzylic alcohols **1a–6a** couple

Table 1. Ruthenium-Catalyzed Coupling of Acyclic Dienes to Alcohols **1a–6a**^a

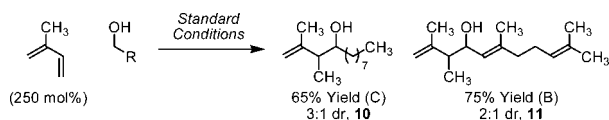
Entry	Alcohol	Product	Aryl	Conditions	Yield (dr)
1	1a	1b	<i>p</i> -NO ₂ Ph	B	84% (1.5:1)
2	2a	2b	Ph	B	61% (2:1)
3	3a	3b	<i>p</i> -MeOPh	C	76% (2:1)
4	4a	4b	<i>m</i> -MeOPh	C	87% (2:1)
5	5a	5b	2-Thienyl	C	87% (1.5:1)
6	6a	6b	Ar = <i>p</i> -BrPh	C	90% (2:1)

Entry	Alcohol	Product	Aryl	Conditions	Yield (dr)
1	1a	1c	<i>p</i> -NO ₂ Ph	A	84% (2:1)
2	2a	2c	Ph	C	93% (1:1)
3	3a	3c	<i>p</i> -MeOPh	C	84% (1.5:1)
4	4a	4c	<i>m</i> -MeOPh	C	93% (1:1)
5	5a	5c	2-Thienyl	C	82% (1:1)
6	6a	6c	Ar = <i>p</i> -BrPh	C	75% (1:1)

Entry	Alcohol	Product	Aryl	Conditions	Yield
1	1a	1d	<i>p</i> -NO ₂ Ph	B	89%
2	2a	2d	Ph	B	91%
3	3a	3d	<i>p</i> -MeOPh	B	67%
4	4a	4d	<i>m</i> -MeOPh	B	67%
5	5a	5d	2-Thienyl	B	63%
6	6a	6d	Ar = <i>p</i> -BrPh	B	61%




^a Cited yields are of isolated material. Conditions A employ no added ligand. Conditions B employ (*p*-MeOPh)₃P (15 mol %) as ligand. Conditions C employ *rac*-BINAP (5 mol %) as ligand. See Supporting Information for detailed experimental procedures.

to isoprene to furnish products of carbonyl isoprenylation **1c–6c** in good to excellent yield. Similarly, benzylic alcohols **1a–6a** couple to butadiene to furnish products of crotylation **1b–6b**, and use of 2,3-dimethylbutadiene as an allyl donor delivers products of reverse 2-methyl prenylation **1d–6d** (Table 1). Aliphatic alcohols couple in diminished yield, however, allylic alcohols couple more efficiently. For example, isoprene couples to 1-nonanol and geraniol in 65% and 75% isolated yields, respectively.



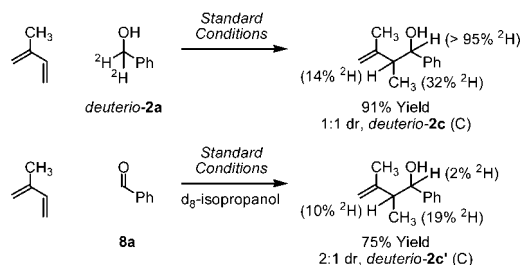
Carbonyl allylation can also be achieved from the aldehyde oxidation level employing isopropanol or formic acid as terminal reductant, although increased loadings of diene are required. For example, under standard conditions, aldehydes **7a–9a** couple to isoprene to furnish products of carbonyl allylation **1c–3c**, respectively, in good to excellent yield. Thus, carbonyl allylation from the alcohol or aldehyde oxidation level is possible (Table 2).

Table 2. Coupling of Isoprene to Representative Aldehydes under Conditions of Ruthenium-Catalyzed Transfer Hydrogenation^a

	Standard Conditions (Reductant)		
 (20 equiv.)			
	7a , Ar = <i>p</i> -NO ₂ Ph, 8a , Ar = Ph, 9a , Ar = <i>p</i> -MeOPh		
<i>i</i> -PROH (400 mol%) 90 °C	84% Yield (B) 2:1 dr, 1c	82% Yield (C) 2:1 dr, 2c	68% Yield (C) 1:1 dr, 3c
HCO ₂ H (200 mol%) 90 °C	89% Yield (A) 3:1 dr, 1c	64% Yield (C) 2:1 dr, 2c	68% Yield (C) 1:1 dr, 3c

^a See Table 1 footnotes for details. *m*-NO₂BzOH and acetone were not employed as additives.

A plausible mechanism involves alcohol dehydrogenation to generate a ruthenium hydride, which hydrometalates the less substituted olefin of isoprene to deliver the secondary σ -allyl metal haptomer. Carbonyl addition from the more stable primary σ -allyl haptomer through a six-centered transition structure accounts for branched regioselectivity. Consistent with this interpretation, coupling of isoprene to *deuterio-2a* provides *deuterio-2c*, with deuterium at the benzylic position (>95%), the allylic methyl (32%), and the allylic methine (14%). Coupling of isoprene to aldehyde **8a** using isopropanol-*d*₈ as terminal reductant provides *deuterio-2c'*, which incorporates deuterium at the allylic methyl (19%) and the allylic methine (10%). Incomplete deuterium incorporation likely stems from reversible hydrometalation of isoprene. Mechanisms involving reversible diene hydrometalation in advance of diene–aldehyde oxidative coupling cannot be excluded on the basis of available data.



In summary, we report the first C–C couplings under the conditions of ruthenium-catalyzed transfer hydrogenation employing alcohols as terminal reductants. For such transfer hydrogenative couplings, hydrogen embedded within isopropanol or an alcohol substrate is redistributed among reactants to generate nucleophile–electrophile pairs, enabling carbonyl addition from the aldehyde or alcohol oxidation level. Stereoselective variants of these and other alcohol–unsaturated couplings are currently under investigation.

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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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