ChemInform Abstract: Ruthenium–Catalyzed C —C Bond Forming Transfer Hydrogenation: Carbonyl Allylation from the Alcohol or Aldehyde Oxidation Level Employing Acyclic 1,3–Dienes as S...

3 AUTHORS, INCLUDING:

John F Bower
University of Bristol
63 PUBLICATIONS **1,353** CITATIONS

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

Fumitoshi Shibahara, **John F. Bower**, and **Michael J. Krische**[*]
Department of Chemistry and Biochemistry, University of Texas at Austin, Austin, Texas 78712

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-dimethyl-butadiene 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**
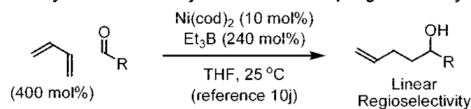
Ru-Catalyzed Diene-Alcohol Transfer Hydrogenative Coupling - Allylation
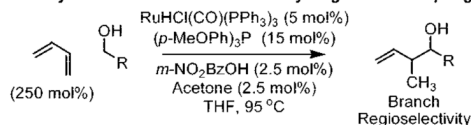
mkrische@mail.utexas.edu.

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.

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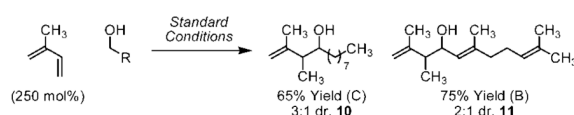
Carbonyl allylation can also be achieved from the aldehyde oxidation level employing isopropanol or formic acid as terminal reductant, although increased loadings of diene are required. For example, under standard conditions, aldehydes **7a–9a** couple to isoprene to furnish products of carbonyl allylation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

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 methane (14%). Coupling of isoprene to aldehyde **8a** using isopropanol-*d₈* 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.
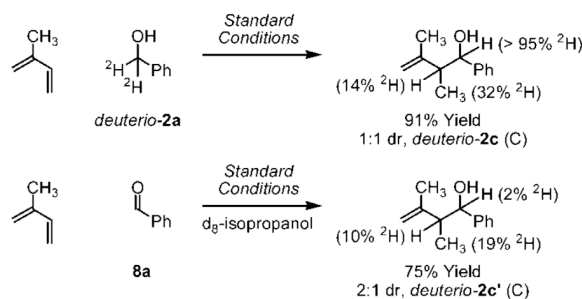
In summary, we report the first C–C couplings under the conditions of ruthenium-catalyzed transfer hydrogenation employing alcohols as terminal reductants. For such transfer hydrogenative couplings, hydrogen embedded within isopropanol or an alcohol substrate is redistributed among reactants to generate 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

References

1. For selected reviews of ruthenium-catalyzed transfer hydrogenation, see: (a) Zassinovich G, Mestroni G, Gladiali S. Chem. Rev 1992;92:1051. (b) Noyori R, Hashiguchi S. Acc. Chem. Res 1997;30:97. (c) Noyori R, Yamakawa M, Hashiguchi S. J. Org. Chem 2001;66:7031. (d) Noyori R, Ohkuma T. Angew. Chem., Int. Ed 2001;40:40. (e) Noyori R. Angew. Chem., Int. Ed 2002;41:2008. (f) Noyori R. Adv. Synth. Catal 2003;345:15. (g) Muňiz K. Angew. Chem., Int. Ed 2005;44:6622. (h) Noyori R. Chem. Commun 2005:1807. (i) Gladiali S, Alberico E. Chem. Soc. Rev 2006;35:226. [PubMed: 16505917] (j) Ikariya T, Murata K, Noyori R. Org. Biomol. Chem 2006;4:393. [PubMed: 16446796] (k) Ikariya T, Blacker AJ. Acc. Chem. Res 2007;40:1300. [PubMed: 17960897]

2. For a review of ruthenium-catalyzed alkene hydroformylation, see: Kalck P, Peres Y, Jenck J. Adv. Organomet. Chem 1991;32:121.

3. For ruthenium-catalyzed reductive C–C bond formations beyond alkene hydroformylation, 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) Yu C-M, Lee S, Hong Y-T, Yoon S-K. Tetrahedron Lett 2004;45:6557.

4. For selected reviews of ruthenium-catalyzed C–C coupling, see: (a) Trost BM, Toste FD, Pinkerton AB. Chem. Rev 2001;101:2067. [PubMed: 11710241] (b) Kondo T, Mitsudo T-a. Curr. Org. Chem 2002;6:1163. (c) Dérien S, Monnier F, Dixneuf PH. Top. Organomet. Chem 2004;11:1.

5. For selected reviews of hydrogenative C–C coupling, see: (a) Ngai M-Y, Kong J-R, Krische MJ. J. Org. Chem 2007;72:1063. [PubMed: 17288361] (b) Iida H, Krische MJ. Top. Curr. Chem 2007;279:77. (c) Skucas E, Ngai M-Y, Komanduri V, Krische MJ. Acc. Chem. Res 2007;40:1394. [PubMed: 17784728]

6. For recent examples, see: C=X vinylation: (a) Kong J-R, Ngai M-Y, Krische MJ. J. Am. Chem. Soc 2006;128:718. [PubMed: 16417351] (b) Skucas E, Kong J-R, Krische MJ. J. Am. Chem. Soc 2007;129:7242. [PubMed: 17511459] (c) Barchuk A, Ngai M-Y, Krische MJ. J. Am. Chem. Soc 2007;129:8432. [PubMed: 17571894] (d) Barchuk A, Ngai M-Y, Krische MJ. J. Am. Chem. Soc 2007;129:12644. [PubMed: 17914825] Aldol and Mannich addition: (d) Jung C-K, Garner SA, Krische MJ. Org. Lett 2006;8:519. [PubMed: 16435874] (e) Jung C-K, Krische MJ. J. Am. Chem. Soc 2006;128:17051. [PubMed: 17177457] (f) Garner SA, Krische MJ. J. Org. Chem 2007;72:5843. [PubMed: 17583961] (g) Bee C, Iida H, Han SB, Hassan A, Krische MJ. J. Am. Chem. Soc 2008;130:2747. C=O Allylation: (h) Skucas E, Bower JF, Krische MJ. J. Am. Chem. Soc 2007;129:12678. [PubMed: 17900123]

7. (a) Bower JF, Skucas E, Patman RL, Krische MJ. J. Am. Chem. Soc 2007;129:15134. [PubMed: 18020342] (b) Bower JF, Patman RL, Krische MJ. Org. Lett 2008;10:1033. [PubMed: 18254642]

8. For reviews of hydrogen autotransfer, see: (a) Guillena G, Ramón DJ, Yus M. Angew. Chem., Int. Ed 2007;46:2358. (b) Hamid MHSA, Slatford PA, Williams JMJ. Adv. Synth. Catal 2007;349:1555.

9. For examples of C–C coupling that proceed by way of C–C bond forming redox isomerization, see: (a) Herath A, Li W, Montgomery J. J. Am. Chem. Soc 2008;130:469. [PubMed: 18081296] (b) Herzon SB, Hartwig JF. J. Am. Chem. Soc 2007;129:6690. and references cited therein. [PubMed: 17474747]

10. Catalytic intermolecular diene–aldehyde reductive coupling: (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,
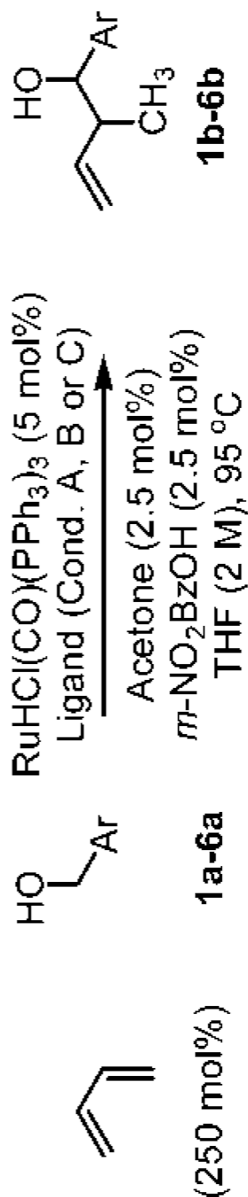
Matsumoto S, Tamaru Y. Angew. Chem., Int. Ed 1999;38:397. (d) Kimura M, Shibata K, Koudahashi Y, Tamaru Y. Tetrahedron Lett 2000;41:6789. (e) Kimura M, Ezoe A, Tanaka S, Tamaru Y. Angew. Chem., Int. Ed 2001;40:3600. (f) Loh T-P, Song H-Y, Zhou Y. Org. Lett 2002;4:2715. [PubMed: 12153217] (g) Sato Y, Sawaki R, Saito N, Mori M. J. Org. Chem 2002;67:656. [PubMed: 11856003] (h) Jang H-Y, Huddleston RR, Krische MJ. 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. [PubMed: 16802822] (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. [PubMed: 17269780] (l) Sato Y, Hinata Y, Seki R, Oonishi Y, Saito N. Org. Lett 2007;9:5597. [PubMed: 18020355]

11. For reviews encompassing nickel-catalyzed diene–aldehyde reductive coupling, see: (a) Tamaru Y. J. Organomet. Chem 1999;576:215. (b) Ikeda, S-i. Angew. Chem., Int. Ed 2003;42:5120. (c) Montgomery J. Angew. Chem., Int. Ed 2004;43:3890. (d) Tamaru, Y., editor. Modern Organo Nickel Chemistry. Weinheim, Germany: Wiley-VCH; 2005. (e) Kimuara M, Tamaru Y. Top. Curr. Chem 2007;279:173.

12. For ruthenium-catalyzed hydroacylation of 1,3-dienes empolying aldehydes as acyl donors, see: Mitsudo, T-a; Kondo, T.; Hiraishi, N.; Morisaki, Y.; Wada, K.; Watanabe, Y. Organometallics 1998;17:2131.

13. Carbonyl allylation via ene-type reaction typically requires highly activated aldehydes: (a) Mikami K, Shimizu M. Chem. Rev 1992;92:1021. (b) Berrisford DJ, Bolm C. Angew. Chem., Int. Ed. Engl 1995;34:1717. (c) Johnson JS, Evans DA. Acc. Chem. Res 2000;33:325. [PubMed: 10891050]

14. Carbonylallylation employing allylic acetates requires metallic reductants: Tamaru, Y. Handbook of Organopalladium Chemistry for Organic Synthesis. Negishi, E-i, editor. Vol. Vol. 2. New York: Wiley-Interscience; 2002. p. 1917Also, see ref 4b

15. RuHCl(CO)(L)$_3$ (L = (*p*-MeOPh)$_3$P) is not an efficient catalyst, suggesting the active catalyst is ligated to both Ph$_3$P and (*p*-MeOPh)$_3$P.

Table 1

Ruthenium-Catalyzed Coupling of Acyclic Dienes to Alcohols **1a–6a**[a]
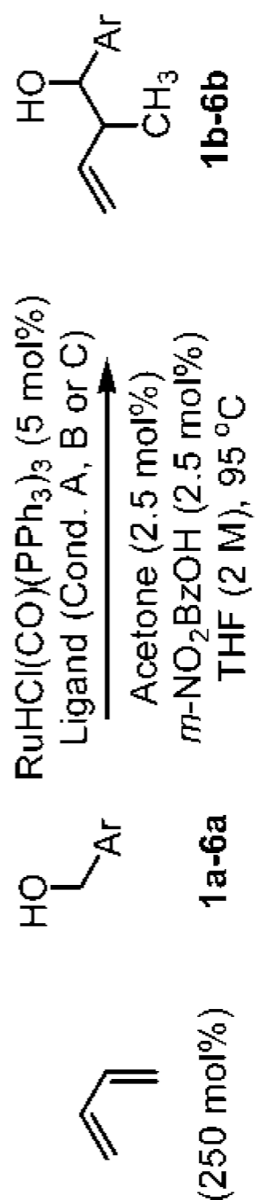
Entry	Alcohol	Product	Aryl	Conditions	Yield (dr)
1	1a	1b	p-NO₂Ph	B	84% (1.5:1)
2	2a	2b	Ph	B	61% (2:1)
3	3a	3b	p-MeOPh	C	76% (2:1)
4	4a	4b	m-MeOPh	C	87% (2:1)
5	5a	5b	2-Thienyl	C	87% (1.5:1)
6	6a	6b	Ar = p-BrPh	C	90% (2:1)

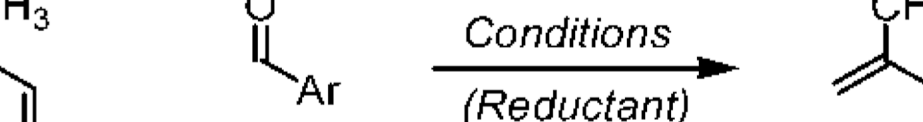| Entry	Alcohol	Product	Aryl	Conditions	Yield (dr)
1	1a	1c	p-NO₂Ph	A	84% (2:1)
2	2a	2c	Ph	C	93% (1:1)
3	3a	3c	p-MeOPh	C	84% (1.5:1)
4	4a	4c	m-MeOPh	C	93% (1:1)

Entry	Alcohol	Product	Aryl	Conditions	Yield (dr)
5	5a	5c	2-Thienyl	C	82% (1:1)
6	6a	6c	Ar = p-BrPh	C	75% (1:1)

Entry	Alcohol	Product	Aryl	Conditions	Yield
1	1a	1d	p-NO₂Ph	B	89%
2	2a	2d	Ph	B	91%
3	3a	3d	p-MeOPh	B	67%
4	4a	4d	m-MeOPh	B	67%
5	5a	5d	2-Thienyl	B	63%
6	6a	6d	Ar = p-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.

Table 2

Coupling of Isoprene to Representative Aldehydes under Conditions of Ruthenium-Catalyzed Transfer Hydrogenation[a]

	7a, Ar = p-NO₂Ph, 8a, Ar = Ph, 9a, Ar = p-MeOPh		
i-PrOH (400 mol%)	84% Yield (B)	82% Yield (C)	68% Yield (C)
90 °C	2:1 dr, **1c**	2:1 dr, **2c**	1:1 dr, **3c**
HCO₂H (200 mol%)	89% Yield (A)	64% Yield (C)	68% Yield (C)
90 °C	3:1 dr, **1c**	2:1 dr, **2c**	**1:1** dr, **3c**

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