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Diene Hydroacylation from the Alcohol or Aldehyde Oxidation Level via Ruthenium-Catalyzed C−C Bond-Forming Transfer Hydrogenation: Synthesis of β,γ-Unsaturated Ketones

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Abstract: Under the conditions of ruthenium-catalyzed transfer hydrogenation, isoprene couples to benzylic and aliphatic alcohols **1a**−**g** to deliver β,γ-unsaturated ketones **3a**−**g** in good to excellent isolated yields. Under identical conditions, aldehydes **2a**−**g** couple to isoprene to provide an identical set of β,γ-unsaturated ketones **3a**−**g** in good to excellent isolated yields. As demonstrated by the coupling of butadiene, myrcene, and 1,2-dimethylbutadiene to representative alcohols **1b**, **1c**, and **1e**, diverse acyclic dienes participate in transfer hydrogenative coupling to form β,γ-unsaturated ketones. In all cases, complete branch regioselectivity is observed, and, with the exception of adduct **3j**, isomerization to the conjugated enone is not detected. Thus, formal intermolecular diene hydroacylation is achieved from the alcohol or aldehyde oxidation level. In earlier studies employing a related ruthenium catalyst, acyclic dienes were coupled to carbonyl partners from the alcohol or aldehyde oxidation level to furnish branched homoallylic alcohols. Thus, under transfer hydrogenative coupling conditions, all oxidation levels of substrate (alcohol or aldehyde) and product (homoallyl alcohol or β,γ-unsaturated ketone) are accessible.

Introduction

We have found that diverse unsaturated compounds are subject to reductive C−C coupling under the conditions of rhodium- and iridium-catalyzed hydrogenation.[1,2] More recently, we have found that catalytic C−C coupling may be achieved under the conditions of transfer hydrogenation employing iridium[3] or ruthenium catalysts.[4] A remarkable feature of such "transfer hydrogenative couplings" resides in the ability to promote C−C bond formation between unsaturates and carbonyl compounds from the alcohol or aldehyde oxidation level, thereby circumventing redox manipulations often required to convert alcohols to aldehydes. These studies represent a departure from the use of preformed organometallics in an ever-increasing range of carbonyl additions and are unique in their ability to promote direct C−H functionalization of alcohols at the carbinol carbon.[5]

Recently, we disclosed a method for the direct coupling of acyclic dienes to carbonyl partners from the alcohol or aldehyde oxidation level to furnish branched products of carbonyl addition with complete levels of regiocontrol.[4a] Here, 1,3-butadiene, isoprene, and 2,3-dimethylbutadiene were found to deliver products of carbonyl crotylation, isoprenylation, and reverse (methyl)prenylation. These studies establish the use of acyclic dienes as surrogates to preformed allyl metal reagents in carbonyl allylations from the alcohol or aldehyde oxidation level. In this article, we report a related catalytic system based on ruthenium that promotes branch-selective coupling of 1,3-butadiene, isoprene, 2,3-dimethylbutadiene, and myrcene to diverse alcohols and aldehydes to furnish β,γ-unsaturated ketones, representing a formal hydroacylation of acyclic dienes

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

(2) For recent examples, see the following. C=X vinylation: (a) Kong, J.-R.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 718. (b) Skucas, E.; Kong, J.-R.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 7242. (c) Barchuk, A.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 8432. (d) Barchuk, A.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 12644. Aldol and Mannich addition: (e) Jung, C.-K.; Garner, S. A.; Krische, M. J. *Org. Lett.* **2006**, *8*, 519. (f) Jung, C.-K.; Krische, M. J. *J. Am. Chem. Soc.* **2006**, *128*, 17051. (g) Bee, C.; Han, S. B.; Hassan, A.; Iida, H.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 2747. C=O allylation: (h) Skucas, E.; Bower, J. F.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 12678.

(3) For iridium-catalyzed transfer hydrogenative C−C couplings, see: (a) Bower, J. F.; Skucas, E.; Patman, R. L.; Krische, M. J. *J. Am. Chem. Soc.* **2007**, *129*, 15134. (b) Bower, J. F.; Patman, R. L.; Krische, M. J. *Org. Lett.* **2008**, *10*, 1033. (c) Kim, I. S.; Ngai, M.-Y.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 6340.

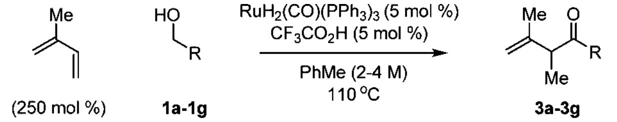
(4) For ruthenium-catalyzed transfer hydrogenative C−C couplings, see: (a) Shibahara, F.; Bower, J. F.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 6338. (b) Patman, R. L.; Williams, V. M.; Bower, J. F.; Krische, M. J. *Angew. Chem., Int. Ed.* **2008**, *47*, 5220. (c) Ngai, M.-Y.; Skucas, E.; Krische, M. J. *Org. Lett.* **2008**, *10*, 2705.

(5) Alcohols participate in formal substitution under the conditions of hydrogen autotransfer to furnish products of C−C bond formation. These processes employ preformed nucleophiles that olefinate the transient carbonyl, which is then reduced to the saturated adduct. In contrast, the processes developed in our laboratory employ unsaturates as pronucleophiles and deliver products of carbonyl addition. For reviews of hydrogen autotransfer, see: (a) Guillena, G.; Ramón, D. J.; Yus, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 2358. (b) Hamid, M. H. S. A.; Slatford, P. A.; Williams, J. M. J. *Adv. Synth. Catal.* **2007**, *349*, 1555.

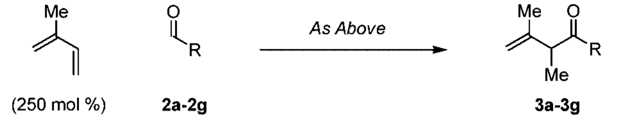
(6) For intermolecular ruthenium-catalyzed hydroacylation, see: (a) Isnard, P.; Denise, B.; Sneeden, R. P. A.; Cognion, J. M.; Durual, P. *J. Organomet. Chem.* **1982**, *240*, 285. (b) Isnard, P.; Denise, B.; Sneeden, R. P. A.; Cognion, J. M.; Durual, P. *J. Organomet. Chem.* **1983**, *256*, 135. (c) Kondo, T.; Tsuji, Y.; Watanabe, Y. *Tetrahedron Lett.* **1987**, *28*, 6229. (d) Kondo, T.; Akazome, M.; Tsuji, Y.; Watanabe, Y. *J. Org. Chem.* **1990**, *55*, 1286. (e) Kondo, T.; Hiraishi, N.; Morisaki, Y.; Wada, K.; Watanabe, Y.; Mitsudo, T.-A. *Organometallics* **1998**, *17*, 2131.

10.1021/ja805356j CCC: $40.75

Table 1. Ruthenium-Catalyzed Transfer Hydrogenative Coupling of Isoprene to Alcohols **1a**−**g** or Aldehydes **2a**−**g** To Furnish *β,γ*-Unsaturated Ketones **3a**−**g**[a]



entry	alcohol	product	R group	yield
1	**1a**	**3a**	*o*-MeOPh	94%
2	**1b**	**3b**	*m*-MeOPh	70%
3	**1c**	**3c**	*p*-MeOPh	81%
4	**1d**	**3d**	*p*-(MeO_2C)Ph	91%
5	**1e**	**3e**	*p*-BrPh	80%
6	**1f**	**3f**	2-Thienyl	71%
7	**1g**	**3g**	*n*-Octyl	87%



entry	aldehyde	product	R group	yield
8	**2a**	**3a**	*o*-MeOPh	98%
9	**2b**	**3b**	*m*-MeOPh	98%
10	**2c**	**3c**	*p*-MeOPh	92%
11	**2d**	**3d**	*p*-(MeO_2C)Ph	62%
12	**2e**	**3e**	*p*-BrPh	96%
13	**2f**	**3f**	2-Thienyl	94%
14	**2g**	**3g**	*n*-Octyl	84%

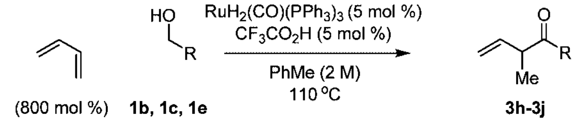
[a] Cited yields are of material isolated by silica gel chromatography. See Supporting Information for detailed experimental procedures.

from the alcohol or aldehyde oxidation level.[6,7] Thus, under the conditions of transfer hydrogenative coupling, all oxidation levels of substrate (alcohol or aldehyde) and product (homoallyl alcohol or *β,γ*-unsaturated ketone) are accessible (Scheme 1).

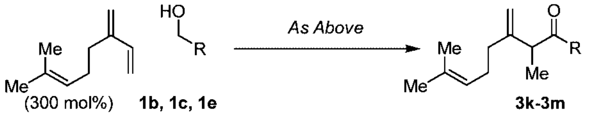
Results and Discussion

In our prior studies of the ruthenium-catalyzed transfer hydrogenative coupling of acyclic dienes to carbonyl partners employing $RuHCl(CO)(PPh_3)_3$ as precatalyst, oxidation of the initially formed homoallylic alcohol was observed to give the corresponding *β,γ*-unsaturated ketones as a side product. It was found that ketone formation is suppressed upon introduction of additional phosphine ligand, which presumably occupies coordination sites required for *β*-hydride elimination. A corollary to this effect is that ketone formation should be favored for ruthenium complexes that are more highly coordinatively unsaturated. To challenge this hypothesis, isoprene was coupled to *p*-methoxybenzyl alcohol (**1c**) using $RuHCl(CO)(PPh_3)_3$ as the precatalyst, but in the absence of added phosphine. To our delight, the *β,γ*-unsaturated ketone **3c** was produced in 55% isolated yield, accompanied by 28% isolated yield of the homoallylic alcohol. Again, predicated on the assumption that coordinative unsaturation should promote oxidation of the initially formed homoallylic alcohol, a ruthenium complex possessing a counterion less strongly coordinating than chloride was sought. As it is known that $RuH_2(CO)(PPh_3)_3$ reacts with acids HX to generate complexes of the type $RuHX(CO)(PPh_3)_3$,[8] an assay of acidic additives was undertaken. It was found that coupling of

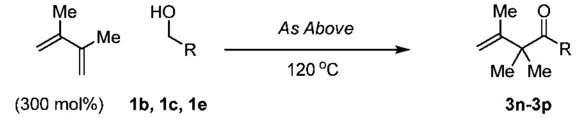
Table 2. Ruthenium-Catalyzed Transfer Hydrogenative Coupling of Butadiene, Myrcene, and 1,2-Dimethylbutadiene to Representative Alcohols **1b**, **1c**, and **1e** To Furnish *β,γ*-Unsaturated Ketones **3h**−**j**, **3k**−**m**, and **3n**−**p**[a]



entry	alcohol	product	R group	yield
1	**1b**	**3h**	*m*-MeOPh	75%
2	**1c**	**3i**	*p*-MeOPh	96%
3	**1e**	**3j**	*p*-BrPh	62%[b]



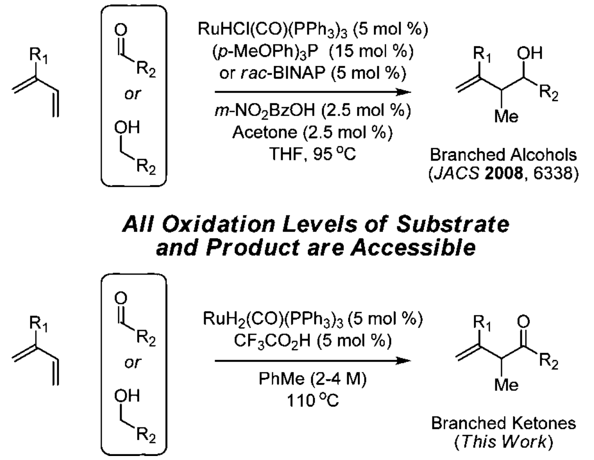
entry	alcohol	product	R group	yield
4	**1b**	**3k**	*m*-MeOPh	91%
5	**1c**	**3l**	*p*-MeOPh	96%
6	**1e**	**3m**	*p*-BrPh	85%



entry	alcohol	product	R group	yield
4	**1b**	**3n**	*m*-MeOPh	93%
5	**1c**	**3o**	*p*-MeOPh	80%
6	**1e**	**3p**	*p*-BrPh	91%

[a] Cited yields are of material isolated by silica gel chromatography. See Supporting Information for detailed experimental procedures. [b] The reaction product **3j** was contaminated with approximately 10% of the α,*β*-unsaturated ketone.

Scheme 1. Carbonyl Allylation and Hydroacylation from the Aldehyde or Alcohol Oxidation Level via Transfer Hydrogenative C−C Coupling of Dienes



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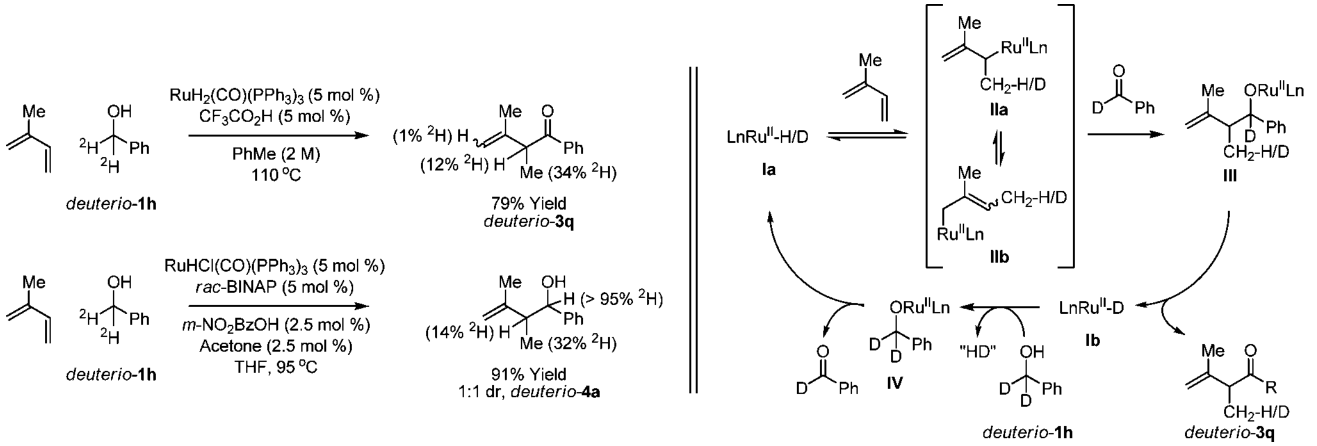
(7) Concurrent with submission of our work, an aligned study was disclosed by Ryu: Omura, S.; Fukuyama, T.; Horiguchi, J.; Murakami, Y.; Ryu, I. *J. Am. Chem. Soc.* **2008**, *130*, in press (http://dx.doi.org/10.1021/ja806929y).

(8) Dobson, A.; Robinson, S. R.; Uttley, M. F. *J. Chem. Soc., Dalton Trans.* **1974**, 370.

Scheme 2. (Left) Ru-Catalyzed Coupling of Isoprene to *deuterio*-**1h** To Provide Deuterated Ketone **3q** and Deuterated Alcohol **4a**[a] and (Right) A Simplified Catalytic Mechanism Accounting for the Formation of *deuterio*-**3q**



[a] Cited yields are of pure isolated material. See Supporting Information for detailed experimental procedures.

isoprene to *p*-methoxybenzyl alcohol (**1c**) performed in the presence of trifluoroacetic acid (TFA) gives the β,γ-unsaturated ketone **3c** in 70% isolated yield, accompanied by 12% isolated yield of the homoallylic alcohol. Here, RuH$_2$(CO)(PPh$_3$)$_3$ presumably reacts with TFA to generate RuH(O$_2$CCF$_3$)(CO)(PPh$_3$)$_3$. Finally, by performing the coupling at higher temperature, which should further enhance the degree of coordinative unsaturation via ligand dissociation, using RuH$_2$(CO)(PPh$_3$)$_3$ (5 mol%) and TFA (5 mol%), the desired β,γ-unsaturated ketone **3c** was generated in 81% yield in the absence of any homoallylic alcohol (Table 1, entry 1). Under these optimized conditions, isoprene couples to alcohols **1a**−**g** to deliver β,γ-unsaturated ketones **3a**−**g** in good to excellent isolated yields. Remarkably, under identical conditions, aldehydes **2a**−**g** couple to isoprene to provide an identical set of β,γ-unsaturated ketones **3a**−**g** in good to excellent isolated yields (Table 1).

To further evaluate the scope of this process, butadiene, myrcene, and 1,2-dimethylbutadiene were coupled to representative alcohols **1b**, **1c**, and **1e** under the optimum conditions cited in Table 1. The corresponding β,γ-unsaturated ketones **3h**−**j**, **3k**−**m**, and **3n**−**p** were produced in good to excellent isolated yields. In all cases, complete branch regioselectivity is observed, and, with the exception of adduct **3j**, isomerization to the conjugated enone is not detected. The efficient formation of all-carbon quaternary centers, as demonstrated by the formation of ketones **3n**−**p**, is noteworthy (Table 2).

The coupling of isoprene to *deuterio*-**1h** under standard conditions delivers the β,γ-unsaturated ketone *deuterio*-**3q**, which incorporates deuterium primarily at the allylic methyl (34%) and the allylic methine (12%). This pattern of deuterium incorporation closely matches that obtained in the related coupling reaction of *deuterio*-**1h** to furnish homoallylic alcohol **4a**.[4a] Hence, a mechanism akin to that previously postulated appears operative. A simplified account is as follows. Ruthenium hydride **Ia** hydrometalates the less substituted olefin of isoprene to deliver the secondary σ-allyl haptomer **IIa**, which isomerizes the more stable primary σ-allyl haptomer **IIb**. Carbonyl addition from the primary σ-allyl haptomer occurs through a six-centered transition structure with allylic inversion to deliver ruthenium alkoxide **III**, which upon β-hydride elimination delivers the β,γ-unsaturated ketone *deuterio*-**3q** along with ruthenium deuteride **Ib**. The reaction of **Ib** with *deuterio*-**1h** provides the ruthenium alkoxide **IV**, from which β-hydride is eliminated to provide the deuterated aldehyde with concomitant regeneration of **1a**. Partial deuteration of the allylic methyl (34%) and the allylic methine (12%) is attributed to reversible and regio-promiscuous hydrometalation of isoprene (Scheme 2).

It should be noted that a conventional hydroacylation mechanism was proposed by Kondo in closely aligned studies on ruthenium-catalyzed diene−aldehyde hydroacylation.[6e] However, the selective formation of homoallylic alcohols under our previously described conditions,[4a] along with the fact that activated ketones such as isatins couple to dienes to form homoallylic alcohols (albeit in poor yield) in reactions employing isopropanol as terminal reductant, suggests that such pathways are not operative under the conditions we report.

Summary

Through transfer hydrogenative C−C coupling, one may transcend the boundaries imposed by oxidation level and the use of stoichiometric organometallic reagents. In the specific case of carbonyl allylation,[9] addition may be achieved from the alcohol or aldehyde oxidation level using acyclic dienes as surrogates to preformed allyl metal reagents. Further, one may access the product of carbonyl allylation as the homoallylic alcohol or, as established in the present study, as the β,γ-unsaturated ketone. *Thus, all oxidation levels of substrate (alcohol or aldehyde) and product (homoallyl alcohol or β,γ-unsaturated ketone) are accessible.* Future studies are aimed at the development of catalytic systems applicable to the transfer hydrogenative coupling of petrochemical and renewable feedstocks, such as α-olefins and ethanol.

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Supporting Information Available: Experimental procedures and 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.

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(9) For reviews on enantioselective carbonyl allylation, see: (a) Ramachandran, P. V. *Aldrichimica Acta* **2002**, *35*, 23. (b) Kennedy, J. W. J.; Hall, D. G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4732. (c) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. (d) Yu, C.-M.; Youn, J.; Jung, H.-K. *Bull. Korean Chem. Soc.* **2006**, *27*, 463. (e) Marek, I.; Sklute, G. *Chem. Commun.* **2007**, 1683. (f) Hall, D. G. *Synlett* **2007**, 1644.