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Rhodium-Catalyzed Synthesis of α,β-Unsaturated Ketones through Sequential C−C Coupling and Redox Isomerization

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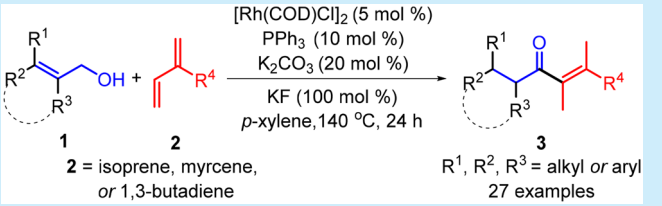
Supporting Information

ABSTRACT: A novel Rh(I)-catalyzed sequential C−C coupling and redox isomerization between allylic alcohols and 1,3-dienes has been accomplished. This versatile protocol provides expeditious access to a broad range of polysubstituted α,β-unsaturated ketones with excellent atom economy and regioselectivity.



Since extensive efforts were dedicated to the 1,3-diene-participated C−C coupling reaction, it has been illustrated as a robust and straightforward method to access a series of value-added compounds.[1] In connection with the field, the effects of various transition metal catalysts on the reductive coupling reactions of 1,3-dienes to alcohols or carbonyl compounds[1a] have been well-documented, including the limited examples depending on the rhodium catalysis system.[2] A superstoichiometric amount of external reductant, such as H_2,[2a] HCOOH,[3] *i*-PrOH,[3b,4] 1,4-butanediol,[5] Et_2Zn,[6] Et_3B,[2b,6a,7] or Et_3SiH,[8] was often required in the transformations to deliver the coupling products. In contrast, the hydrogen autotransfer process utilizing primary alcohols not only as the reactants but also as the hydrogen donors represented an excellent atom-economical method for the intermolecular reductive couplings.[4d,5a,9] Typically, the metal hydride species generated *in situ* is transferred to the diene pronucleophile to form the π-allylmetal precursor, which engages in a subsequent C−C coupling reaction with distinguished regioselectivity. In view of the inherent advantages highlighted, establishing a synthetic methodology with readily available simple primary alcohols as the substrates for versatile synthesis of functionalized ketones would be more broadly meaningful and constructive.

On the other hand, the redox isomerization of allylic alcohols relying on various transition-metal complexes,[10] including Pd,[11] Ir,[12] Ru,[13] and Rh,[14] has been viewed as an appealing approach to afford carbonyl-containing molecules because no external reagent is required in the redox-neutral process. Furthermore, significant advances in the stereospecific isomerization of allylic alcohols to α- or β-substituted ketones have been achieved.[15]

Enthused by the impressive allylic alcohol isomerization, we assumed that the coupling reactions of allylic alcohols with 1,3-dienes under Rh(I) catalysis might enable highly efficient synthesis of polyalkyl-substituted unsaturated ketones through tandem C−C coupling and transfer hydrogenation, with the explanation that the rhodium hydride formed *in situ* could serve as a crucial mediator in both processes. Herein, the successful establishment of the hypothesis is described. In contrast with other approaches for synthesizing polysubstituted enones (e.g., oxidation of cyclopropenylcarbinols,[16a] Pd-catalyzed formal hydroacylation of allenes,[16b] Pd-catalyzed oxidative coupling of allylic alcohols with nucleophiles,[16c] Ti-promoted coupling of alkynes with Weinreb amides,[16d] base-mediated conversion of propargylic tosylates,[16e] Pd-catalyzed cross-coupling of propargyl alcohols and allyl carbonates,[16f] Au-catalyzed acyl migration of propargylic esters,[16g] etc.), our protocol features ready availability of starting materials, good functional group compatibility, and excellent atom economy and reactant site selectivity.

To commence the study, we selected cinnamic alcohol **1a** and isoprene **2a** as the initial substrates for optimizing the reaction conditions (Table 1). When the reaction was performed in the presence of the $[Rh(COD)OH]_2/PPh_3$ catalytic couple under toluene refluxing conditions for 24 h, the C−C coupling/isomerization product **3a** was isolated in 9% yield (entry 1). Further screening of other rhodium catalysts revealed that $[Rh(COD)Cl]_2$ was the optimal choice (entries 2−6). To our delight, the product yield was increased to 41% when KF was used as an additive (entry 7). Switching PPh_3 to other ligands such as PCy_3, $(p\text{-Me-}C_6H_4)_3P$, and $(p\text{-MeO-}C_6H_4)_3P$ was found to be ineffective to improve the reaction conversion (entries 8−10). Among the bases evaluated, K_2CO_3 delivered a higher yield than other species (entries 11 and 12). It was observed that increasing the loading of isoprene **2a** or elevating the reaction temperature to 140 °C led to an enhanced yield of **3a** (entries 13 and 14). By simply changing the solvent to *p*-xylene, the enone could be provided

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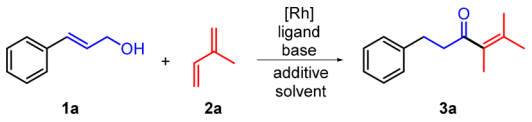
Table 1. Optimization of the Reaction Conditions[a]



1a 2a 3a

entry	Rh (5 mol %)	ligand (10 mol %)	base (10 mol %)	additive (100 mol %)	solvent	yield[b] (%)
1	$[Rh(COD)OH]_2$	PPh_3	K_2CO_3	\	toluene	9
2	$[Rh(COD)Cl]_2$	PPh_3	K_2CO_3	\	toluene	22
3	$Rh_2Cl_2(CO)_4$	PPh_3	K_2CO_3	\	toluene	8
4	$RhH(CO)(PPh_3)_3$	PPh_3	K_2CO_3	\	toluene	trace
5	$Rh(COD)_2SbF_6$	PPh_3	K_2CO_3	\	toluene	trace
6	$Rh(COD)_2BF_4$	PPh_3	K_2CO_3	\	toluene	trace
7	$[Rh(COD)Cl]_2$	PPh_3	K_2CO_3	KF	toluene	41
8	$[Rh(COD)Cl]_2$	PCy_3	K_2CO_3	KF	toluene	38
9	$[Rh(COD)Cl]_2$	$(p\text{-Me-}C_6H_4)_3P$	K_2CO_3	KF	toluene	21
10	$[Rh(COD)Cl]_2$	$(p\text{-MeO-}C_6H_4)_3P$	K_2CO_3	KF	toluene	16
11	$[Rh(COD)Cl]_2$	PPh_3	Cs_2CO_3	KF	toluene	33
12	$[Rh(COD)Cl]_2$	PPh_3	Ag_2CO_3	KF	toluene	21
13[c]	$[Rh(COD)Cl]_2$	PPh_3	K_2CO_3	KF	toluene	48
14[c,d]	$[Rh(COD)Cl]_2$	PPh_3	K_2CO_3	KF	toluene	56
15[c,d]	$[Rh(COD)Cl]_2$	PPh_3	K_2CO_3	KF	*p*-xylene	73
16[c,d,e]	$[Rh(COD)Cl]_2$	PPh_3	K_2CO_3	KF	*p*-xylene	60
17[c,d,f]	**$[Rh(COD)Cl]_2$**	**PPh_3**	**K_2CO_3**	**KF**	***p*-xylene**	**78**

[a]Unless otherwise noted, all reactions were carried out in N_2 atmosphere, using **1a** (0.3 mmol, 1 equiv) and **2a** (3.0 equiv) in 1.5 mL of solvent at 110 °C for 24 h. [b]Isolated yield. [c]**2a** (5.0 equiv). [d]140 °C. [e]PPh_3 (20 mol %). [f]K_2CO_3 (20 mol %).

in 73% isolated yield (entry 15). Variation of ligand loading suffered from an inferior yield (entry 16), whereas the employment of 20 mol % of the base allowed highly efficient formation of polysubstituted α,β-unsaturated ketone (entry 17), thus identifying the feasibility of this coupling reaction.

A variety of allylic alcohols were then examined for the C−C coupling/isomerization with isoprene (**2a**) under the optimized reaction conditions, and the results are presented in Scheme 1. Good compatibility with a wide range of functional groups for the construction of enones was observed, with methyl (**3b**), methoxy (**3c**), dimethylamino (**3d**), fluoro (**3e**, **3f**), and chloro (**3g**, **3h**) groups all being well-tolerated. However, the more electron-deficient cinnamic alcohols participated in the coupling reactions sluggishly (**3i**, **3j**). Interestingly, coniferyl alcohol bearing a free phenolic hydroxyl group expressed moderate reactivity to afford the anticipated compound **3k**. When our attention was turned to the transformation of the heterocycle-substituted allylic alcohol component, the corresponding trimethyl-substituted enone **3l** was produced in 64% yield. The good chemical yields achieved with the substrates bearing an alkyl group (**3m**) or aromatic rings (**3n**) at the α- or β-position of the hydroxyl group highlighted the generality of our catalytic system. It was found that the coupling reaction succeeded to proceed with 2-phenyl-substituted allylic alcohol to provide the desired product **3o**, albeit in low yield. In addition, cyclohex-1-en-1-yl methanol was a suitable substrate for the C−C coupling/isomerization (**3p**), and such a circumstance was the same as that of perillyl alcohol, regardless of the presence of a distal vinyl group (**3q**). It is worth mentioning that the linear substrates such as (*E*)-hept-2-en-1-ol and (*E*)-non-2-en-1-ol underwent the coupling reactions smoothly to obtain the high-boiling-point products (**3r**, **3s**) in yields of 56% and 65%, respectively. Unfortunately, 3-phenyl-2-propyn-1-ol was not allowed for this conversion, and only a trace amount of **3a** was detected.

Besides isoprene, other conjugated dienes were also inspected for the coupling reactions with the representative allylic alcohols to access polysubstituted α,β-unsaturated ketones (Scheme 2). For example, myrcene was successfully coupled with cinnamic alcohols together with 3-(furan-2-yl)prop-2-en-1-ol, generating the corresponding ketones in 43% to 69% yield (**3t**−**3v**). Alkyl-substituted linear allylic alcohols delivered higher isolated yields of C−C coupling/isomerization products (**3w**, **3x**) than the branched ones (**3y**, **3z**). Furthermore, the incorporation of 1,3-butadiene to cinnamic alcohol **1a** under $[Rh(COD)OH]_2$ catalysis led to a pair of dimethyl-substituted enones with a ratio of 1.6:1 in 65% combined yield (**3aa**, **3aa′**). However, only trace quantities of product were detected while performing the reactions of 1,3-pentadiene, 1-phenyl-1,3-butadiene, and 2-phenyl-1,3-butadiene with cinnamic alcohol.

Control experiments were carried out to probe the mechanism of the Rh-catalyzed synthesis of enones (Scheme 3). The C−C coupling reaction of 3-phenylpropan-1-ol **4** with isoprene **2a** under the standard conditions delivered a saturated ketone **5** in 51% yield (Scheme 3a). While conducting only cinnamic alcohol **1a** in another control experiment, 3-phenylpropanal **6** and an aldol condensation product **7** were isolated (Scheme 3b), which demonstrated that the transfer hydrogenation in the present catalytic system occurred in an intramolecular fashion.[15] Additionally, cinnamic aldehyde **8** was subjected to the standard conditions with isoprene **2a** by virtue of *i*-PrOH as an external reductant,[3b,4] furnishing the product **3a** in 62% yield (Scheme 3c). The results unambiguously suggest that **8** was involved in the coupling reaction as a key intermediate and that the Rh−H species formed *in situ* played a pivotal role in the C−C coupling/isomerization. Finally, an isotopic labeling experiment using deuterated cinnamic alcohol **1a-D_2** as the substrate was carried out (Scheme 3d). ^1H and ^2H NMR analysis of the product revealed that about 97% deuterium was incorporated

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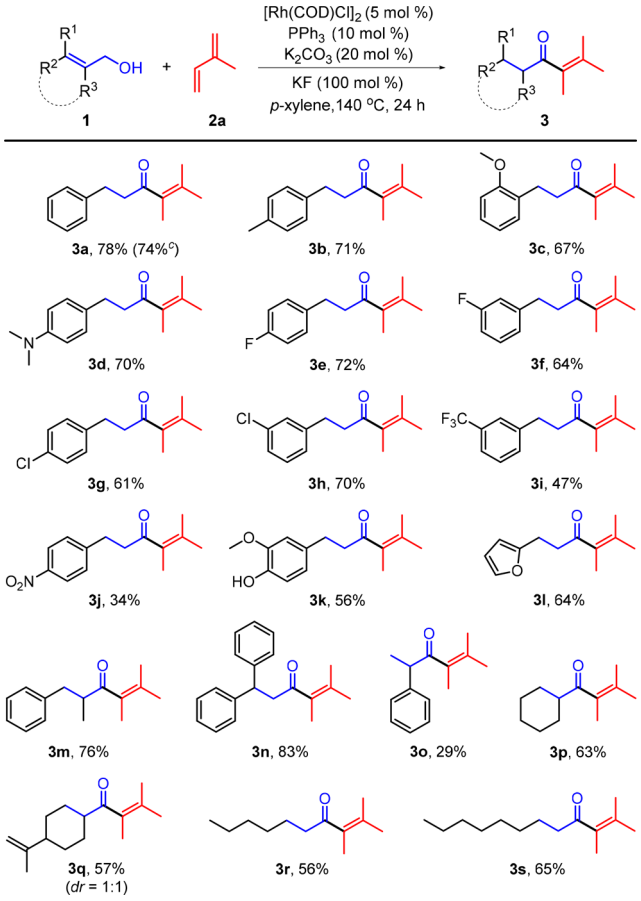
Scheme 1. Scope of the Allylic Alcohols for the C−C Coupling/Isomerization[a,b]

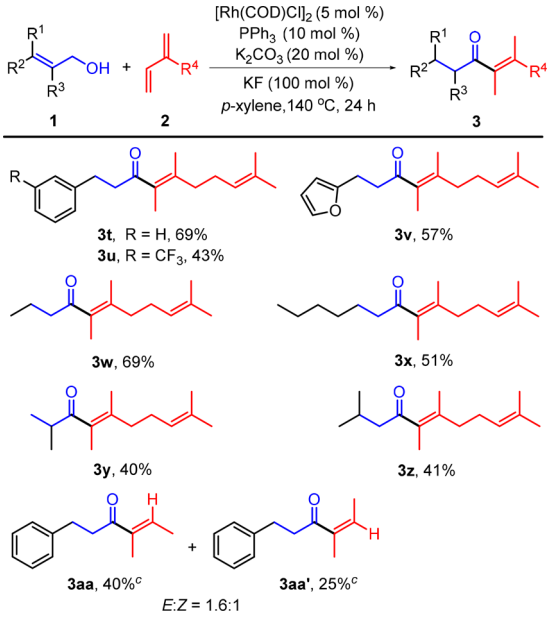


[a]Unless otherwise noted, all reactions were carried out with allylic alcohol **1** (0.3 mmol) and isoprene **2a** (1.5 mmol) in *p*-xylene (1.5 mL) at 140 °C under N_2 for 24 h. [b]Isolated yield. [c]Reaction was performed at a 1 mmol scale.

into the methylene carbon at the β-position of the carbonyl group, and about 71% of deuterium incorporation was at the methyl group β to the resulting ketone.

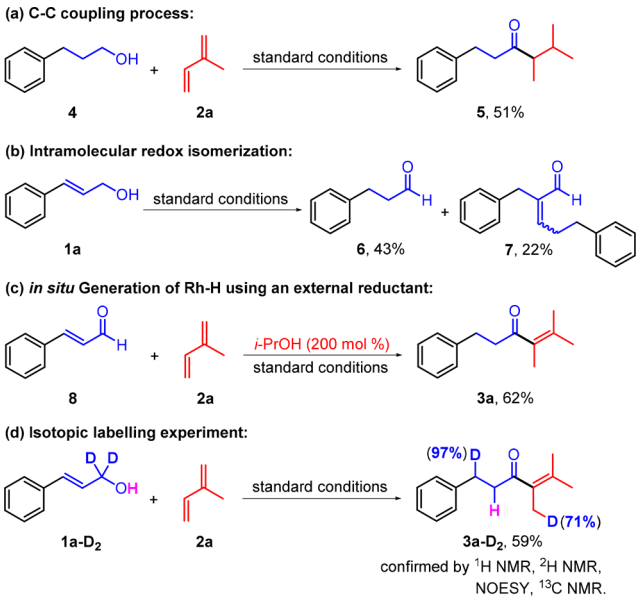
On the basis of the aforementioned experimentations as well as the previous documents on the functionalization of 1,3-dienes,[9a,17] a plausible mechanism is postulated (Scheme 4). The reaction of the rhodium catalyst with cinnamic alcohol **1a** in the presence of the base generates alkyloxyrhodium intermediate **I**,[18] which undergoes β-H elimination to give rise to the Rh−H active species and cinnamic aldehyde **8**. After the addition of the Rh−H species to isoprene **2a**, the resulting π-allylrhodium intermediate **II** nucleophilicly attacks the aldehyde **8** through the indicated six-centered transition state **III** to access homoallyloxyrhodium intermediate **IV**, which upon a second β-H elimination yields the complex **V** (C−C coupling process). Double bond isomerization exerted by the rhodium hydride through successive hydrorhodation/β-H elimination[17c,18] affords the more stable penta-1,4-dien-3-one **VI**. Note that reduction of the less sterically hindered double bond of the enone by the rhodium hydride is favorable to form the intermediate **VII**. Subsequent tautomerization and protonation delivers the target product **3a** with concomitant reproduction of the rhodium catalyst, thus achieving the redox isomerization process.[14b,15]

Scheme 2. Scope of 1,3-Dienes for the C−C Coupling/Isomerization[a,b]



[a]Unless otherwise noted, all reactions were carried out with allylic alcohol **1** (0.3 mmol) and 1,3-diene **2** (1.5 mmol) in *p*-xylene (1.5 mL) at 140 °C under N_2 for 24 h. [b]Isolated yield. [c]Reaction was performed using $[Rh(COD)OH]_2$ (5 mol %) as the catalyst in toluene (1.5 mL) at 110 °C under N_2 for 24 h.

Scheme 3. Control Experiments



In summary, a rhodium-catalyzed strategy enabling efficient construction of tetraalkyl-substituted α,β-unsaturated ketones has been developed from a host of allylic alcohols and 1,3-dienes, including isoprene, myrcene, and 1,3-butadiene. Mechanistic investigations show that this atom-economical, diene C3-regioselective[3b,4b] methodology proceeds through tandem C−C coupling and intramolecular redox isomerization. We optimistically think that the coupling reaction will find applications in the preparation of polyalkyl-substituted enones with pharmaceutical value.

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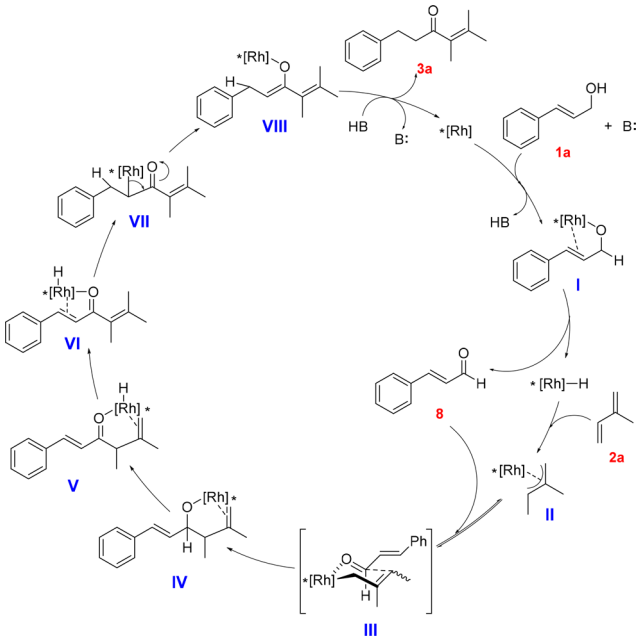
Scheme 4. Plausible Catalytic Mechanism



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b02190.

Experimental details, characterization data, and spectra (PDF)

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Notes

The authors declare no competing financial interest.

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