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Rhodium-Catalyzed Remote Isomerization of Alkenyl Alcohols to Ketones

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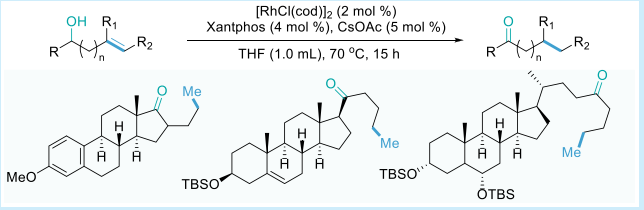
ABSTRACT: We develop herein an efficient rhodium-catalyzed remote isomerization of aromatic and aliphatic alkenyl alcohols into ketones. This catalytic process, with a commercially available catalyst and ligand ($[RhCl(cod)]_2$ and Xantphos), features high efficiency, low catalyst loading, good functional group tolerance, a broad substrate scope, and no (sub)stoichiometric additive. Preliminary mechanistic studies suggest that this transformation involves an iterative dissociative β-hydride elimination−migration insertion process.



The catalytic isomerization of alkenes is a green and sustainable process featuring atom, step, and redox economy and has attracted considerable attention in the last decades.[1,2] In this context, the isomerization of alkenyl alcohols is probably one of the most studied transformations and has proved to be a powerful platform to deliver synthetically valuable carbonyl compounds with high atom and step economy. Among them, the allylic-alcohol isomerization has been well documented using various transition metals,[3] including Ru,[4] Rh,[5] Ir,[6] Pd,[7] and Fe[8] (Figure 1a). In contrast, the long-distance isomerization of alkenyl alcohols is much less developed and still remains challenging despite its highly potential application in the rapid generation of molecular complexity.

The remote isomerization of alkenyl alcohols usually undergoes a transition-metal-catalyzed chain-walking mechanism, which involves consecutive migration insertion/β-hydride elimination.[9] In the past decade, the field has received increasing attention; however, only a few impressive examples of efficient synthetic methods have been described (Figure 1b).[2a,10] For example, the Grotjahn group developed a bifunctional Ru complex as the catalyst for the remote isomerization of linear alkenyl alcohols.[2a] Of note, this robust catalyst could realize an efficient movement of an alkene double bond over 30 positions along a linear alkyl chain but is not suitable for branched substrates. In addition, Mazet and coworkers reported an efficient palladium-catalyzed short- and long-distance isomerization of highly substituted allylic, homoallylic, and alkenyl alcohols using a preprepared Pd catalyst and substoichiometric cyclohexene as an additive.[10b] Later, they successfully extended this catalytic system to the remote deconjugative isomerization of highly substituted α,β-unsaturated carbonyl compounds.[10c] Recently, the Zhao group reported an impressive example of the rhodium-catalyzed enantioselective isomerization of homoallylic and bishomoallylic secondary alcohols.[10d] Despite these significant advances, the development of new efficient catalytic systems, featuring

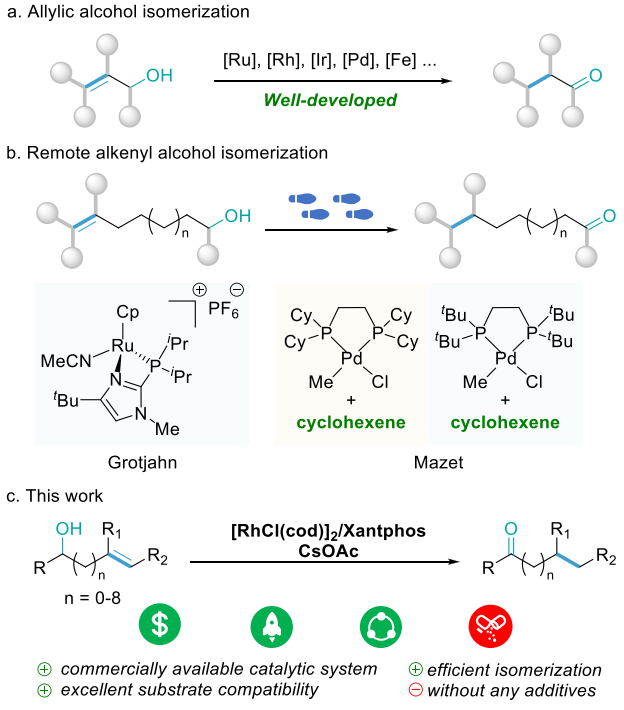


Figure 1. Isomerization of alkenyl alcohols.

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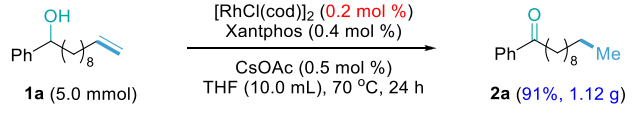
easy accessibility, excellent substrate compatibility, and environmental friendliness, is still in high demand for this useful transformation.[11]

In this Letter, we demonstrate a practical and easy-handling method for the catalytic synthesis of a variety of ketones from alkenyl alcohols under simple and mild reaction conditions. Specifically, the alkenyl alcohols undergo a Rh-catalyzed remote isomerization (chain-walking) with excellent efficiency in the presence of commercially and readily available $[RhCl(cod)]_2$, Xantphos, and CsOAc. If desired, this protocol can also be employed to prepare other synthetically valuable compounds through the functionalization of the ketones.

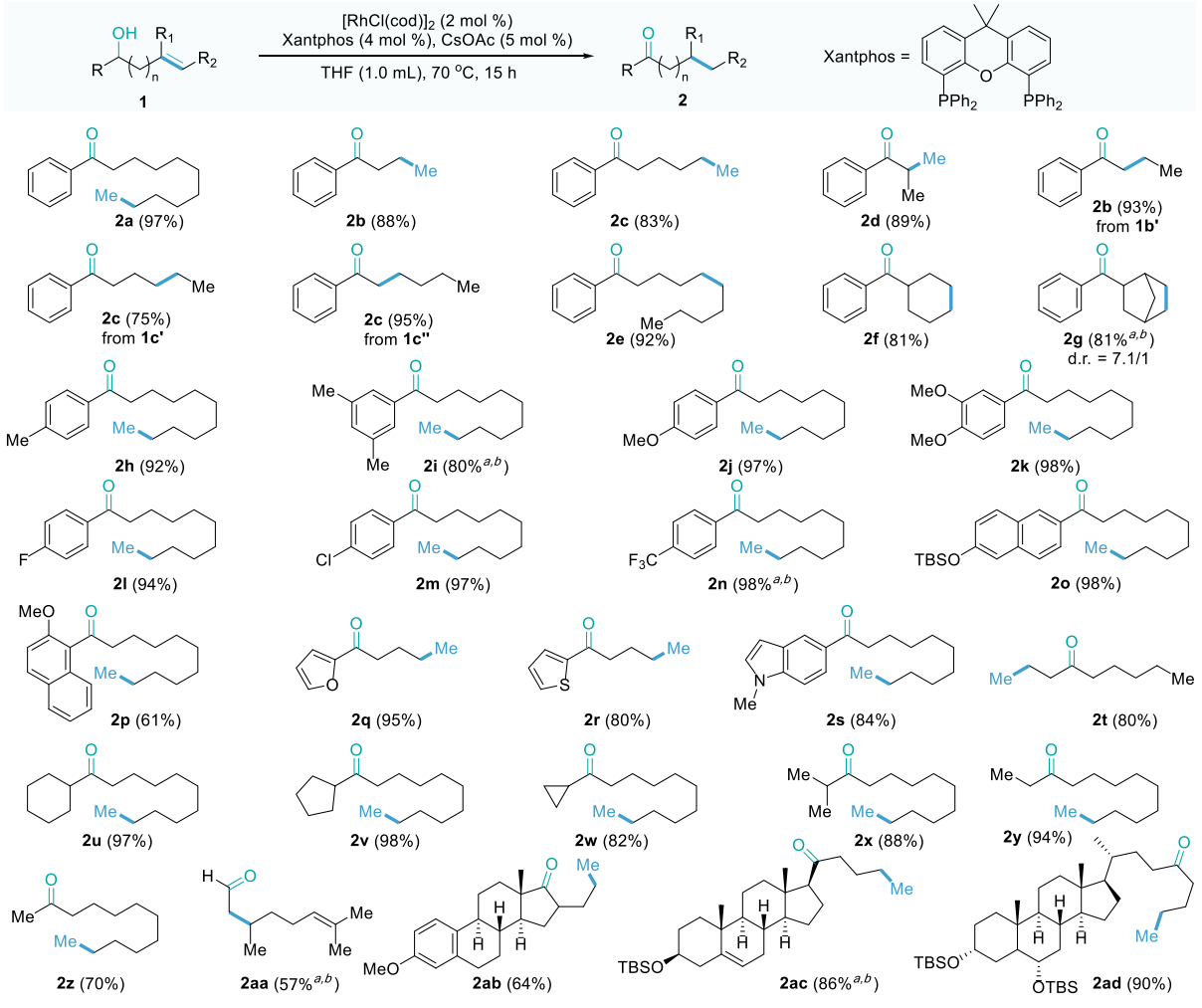
We began our study with 1-phenylundec-10-en-1-ol **1a** as the model substrate. Initially, the isomerization of **1a** was performed in the presence of $[RhCl(cod)]_2$, Xantphos, and K_2CO_3 in tetrahydrofuran (THF) at 70 °C for 15 h. Encouragingly, the desired ketone **2a** was formed in 43% yield, albeit along with 57% of carbon−carbon double-bond isomerized byproduct **3a**, a mixture of different alkenyl alcohols (Table 1, entry 1). The formation of **3a** was confirmed by ^{13}C NMR. (See more details in the Supporting Information.) With this promising result, we then set out to examine various reaction parameters (Table 1). A series of bases were first examined, and CsOAc was identified as the choice of base (Table 1, entries 2−4). To our delight, the desired ketone **2a** was obtained in quantitative yield when the CsOAc was used as the base (Table 1, entry 4). On the contrary, a trace amount of the ketone **2a** was observed in the absence of base, indicating the crucial role of the base in this isomerization (Table1, entry 5). Subsequently, solvent screening indicated that THF was the best. Other solvents, such as 1,4-dioxane, dimethylacetamide (DMA), and ethyl acetate (EtOAc), all proved to be inferior (Table 1, entries 6−8). Furthermore, the ligands had a dramatic effect on the ketone formation. For instance, the formation of **3a** became significant with Cy-Xantphos as the ligand (Table 1, entry 9), and a mixture of **2a** and **3a** (1:1) was afforded when PPh_3 was employed (Table 1, entry 10).

With the optimal conditions in hand, we next explored the substrate scope of this remote isomerization. A wide range of

Scheme 2. Gram-Scale Reaction



Scheme 1. Scope of Substrates



[a]Performed with 5 mol % $[RhCl(cod)]_2$, 10 mol % Xantphos, and 10 mol % CsOAc. [b]24 h. **1b′** = (*E*)-1-phenylbut-2-en-1-ol; **1c′** = (*E*)-1-phenylhex-4-en-1-ol; **1c′′** = (*E*)-1-phenylhex-2-en-1-ol.

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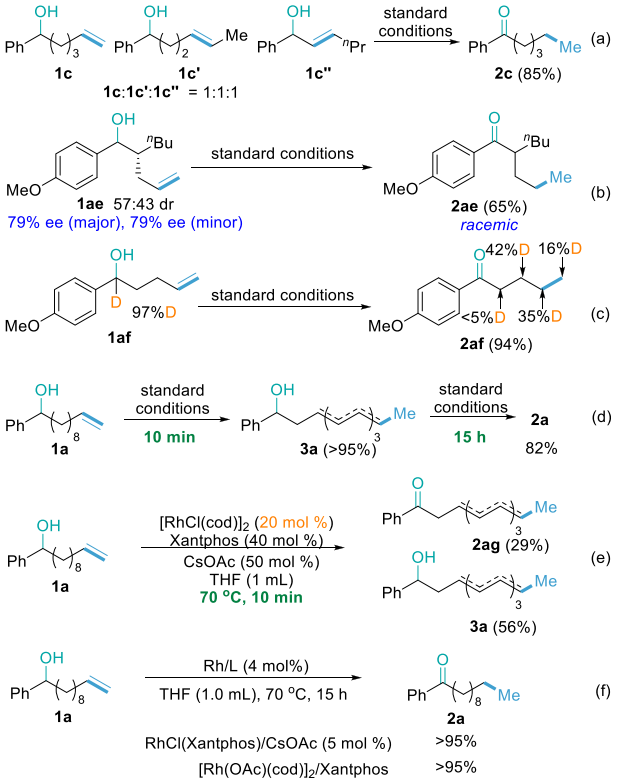
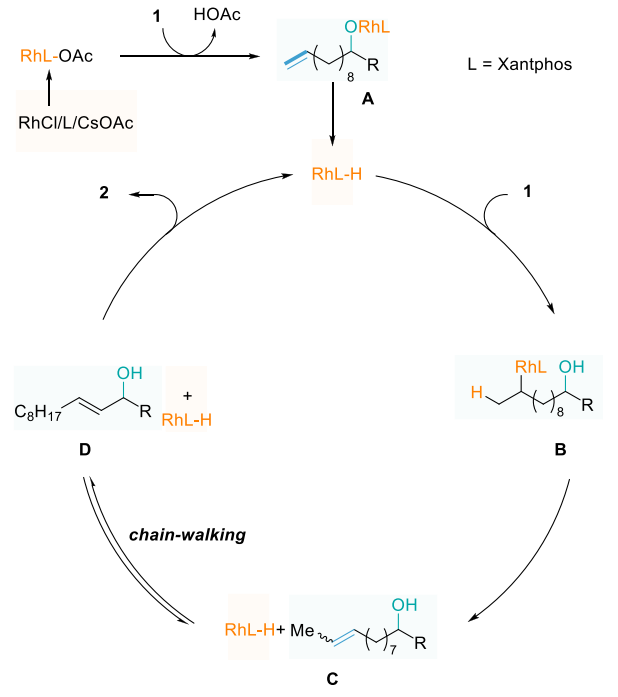
Scheme 3. Mechanistic Studies

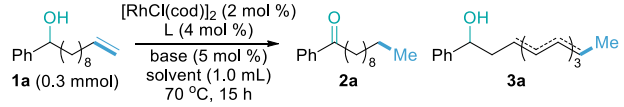


Scheme 4. Proposed Reaction Mechanism



alkenyl alcohols **1** were examined, and the results are shown in Scheme 1. First, the effect of different olefin substitution patterns was investigated. Substrates **1a**−**d** bearing a terminal olefin moiety, regardless of the chain length, all exclusively provided the corresponding ketones **2a**−**d** with high efficiency (83−97% yield). 1,2-Disubstituted alkenyl alcohols **1b′**−**c′′** with a carbon−carbon double bond at different positions were also suitable substrates and afforded the desired products **2b,c**

Table 1. Optimization of the Reaction Conditions



entry	ligand	solvent	base	2a/3a[a]
1	Xantphos	THF	K_2CO_3	43/57
2	Xantphos	THF	DABCO	17/83
3	Xantphos	THF	NaF	3/97
4	**Xantphos**	**THF**	**CsOAc**	**>99/<1**
5	Xantphos	THF		4/96
6	Xantphos	1,4-dioxane	CsOAc	80/20
7	Xantphos	DMA	CsOAc	<1/>99
8	Xantphos	EtOAc	CsOAc	54/46
9	Cy-Xantphos	THF	CsOAc	8/92
10	PPh_3	THF	CsOAc	50/50

[a]Determined by ^{1}H NMR using CH_2Br_2 an internal standard. Cy-Xantphos = (9,9-dimethyl-4*a*,9*a*-dihydro-9*H*-xanthene-4,5-diyl)-bis-(dicyclohexylphosphane).

in good to excellent yield. Additionally, the *Z*-alkenyl substrate **1e** also successfully participated in this distant isomerization to give **2e** in 92% yield. Remarkably, cyclic olefins were found to be compatible with this protocol (**2f,g**). Subsequently, the tolerance of functional groups on the aromatic ring was tested. Both electron-donating (Me and OMe) and -withdrawing groups (F, Cl, CF_3) were applicable to give the corresponding ketones in excellent yield (**2h**−**n**). Naphthalenes and heterocycles, such as furan, thiophene, and indole, could be incorporated into the products with good to high efficiency (**2o**−**s**, 61−98% yield). The conjugation between the aromatic ring and the carbonyl group is probably a key driving force for this isomerization process. We then wondered if the alkyl alkenyl alcohols would be feasible to undergo the isomerization. To this end, an array of alkyl alkenyl alcohols was examined, and the results are summarized in Scheme 1. As shown, all aliphatic alkenyl alcohols **1t**−**z** proceeded smoothly to furnish the corresponding ketone products (**2t**−**z**) in good to excellent yield. This isomerization reaction can tolerate relatively steric-hindered alkyl substituents next to the hydroxyl group, such as cyclohexyl, cyclopentyl, cyclopropyl, and isopropyl groups (**2u**−**x**). Prominently, trisubstituted allylic alcohol **1aa** (nerol) is competent for this remote isomerization to afford citronellal **2aa** in 57% yield. It is worth noting that this transformation is also compatible with numerous complex molecules. For example, esterone- and cholesterol-derived alkenyl alcohols **1ab**−**ad** isomerized smoothly to give the corresponding products in 64, 86, and 90% yield, respectively, suggesting that this method has great potential applications in the synthesis or late-stage modification of biologically active complex molecules, such as natural products and pharmaceuticals.[12]

To demonstrate the practicability of this method, a gram-scale catalytic reaction was carried out. Substrate **1a** was treated with $[RhCl(cod)]_2$ and Xantphos, but the catalyst loading was decreased to 0.2 mol %. Pleasingly, the isomerized product **2a** was isolated without an essential erosion in yield (91%, 5.0 mmol, Scheme 2), which further proves the application potential of this method in synthetic chemistry.

To gain more insights into the reaction mechanism, we carried out a series of control experiments (Scheme 3). As demonstrated in Scheme 3a, the single isomerization product

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2c was obtained in 85% yield when a mixture of alkenyl alcohols **1c**, **1c′**, and **1c′′** were subjected to the standard reaction conditions. In addition, the racemic ketone **2ae** was isolated in 65% yield when the chiral alcohol **1ae** was used (Scheme 3b). Moreover, a deuterated reaction was carried out, and the deuteration was found along the alkyl chain (Scheme 3c). These results suggested that this reaction involves a dissociative chain-walking process.[2f,10b] Surprisingly, although full conversion was observed when the reaction was quenched after 10 min under the standard conditions, the byproduct **3a** was obtained in almost quantitative yield, which could be further converted into the ketone **2a** (Scheme 3d). Additionally, ketone **2ag** was isolated in 29% yield along with 56% of **3a** when the reaction was treated with 20 mol % of $[RhCl(cod)]_2$ and quenched after 10 min (Scheme 3e), indicating that the alkenyl alcohol first underwent β-H elimination to generate the unsaturated ketone and then the chain-walking process. To establish what the true catalyst is, we synthesized RhCl(Xantphos) and used it to catalyze the isomerization of **1a**.[13] Pleasingly, the catalysts RhCl(Xantphos) and $[RhCl(cod)]_2$/Xantphos gave identical results (Scheme 3f). Furthermore, in the absence of CsOAc, $[Rh(OAc)(cod)]_2$/Xantphos afforded the same results as the standard conditions provided. On the basis of the results, we believe that Rh(OAc)(Xantphos) should be the true catalyst.

On the basis of the observed results, we proposed a plausible mechanism for this isomerization (Scheme 4). Initially, the reaction of $[RhCl(cod)]_2$ with CsOAc produces Rh−OAc, which then reacts with **1** to afford intermediate **A**. Subsequent β-H elimination results in the formation of Rh−H, which undergoes migratory insertion with **1** to give intermediate **B**. The following β-H elimination provides intermediate **C** and Rh−H. The intermediate **C** then goes through dissociative migration insertions/β-hydride elimination (chain-walking) to give intermediate **D**, followed by the Rh-catalyzed isomerization of allylic alcohol[5] to deliver the desired ketone **2** and regenerate the Rh−H species.

In summary, we have developed an efficient rhodium-catalyzed remote olefin isomerization reaction in which a variety of aromatic and alkyl alkenyl alcohols were transformed to ketones in good to excellent yield. This catalytic redox-neutral process employed a commercially available catalyst and ligand ($[RhCl(cod)]_2$ and Xantphos), and no additive was required. Moreover, this protocol features high efficiency, good functional group tolerance, a broad substrate scope, and excellent compatibility with complex molecules. Noticeably, the catalyst loading can be reduced to 0.2 mol % without any detrimental effect on the yield. Preliminary mechanistic studies provide support for the dissociative chain-walking mechanism.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04508.

Experimental procedures, characterization, and NMR spectra for obtained compounds (PDF)

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Notes

The authors declare no competing financial interest.

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