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Research Article

Redox-Triggered Ruthenium-Catalyzed Remote C−H Acylation with Primary Alcohols

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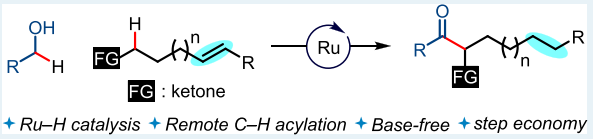
ABSTRACT: Redox-triggered metal-catalyzed cross-coupling reactions from readily available alcohols provide a step economical means to synthesize ketones and related compounds. Prior examples for hydrogenative remote C(sp^3)−H functionalization of olefins via a metal walking process featured external reducing agents. Here, we report a strategy for redox-triggered hydrogenative remote C(sp^3)−H acylation of olefins with primary alcohols both as an acylating agent and a reductant, which is validated by the base-free 1,3-diketone synthesis. Mechanistic studies have confirmed that the reaction takes place via an aldehyde intermediate and a metal walking process.



KEYWORDS: *redox strategy, remote C−H functionalization, metal walking, acylation, borrowing hydrogen*

INTRODUCTION

Development of catalytic atom- and step-economic sustainable transformations from readily available materials has been among the central topics of modern synthetic chemistry.[1] In the past few decades, selective C−H functionalization has emerged to be a powerful method to synthesize various valuable compounds.[2] To control the selectivity of C(sp^3)−H functionalization, the substrate bearing inherent directionality or utilization of additional directing groups or mediators has been widely exploited.[3] Another approach for selective C(sp^3)−H functionalization relies on a metal walking strategy via metal-catalyzed rapid olefin isomerization along the saturated hydrocarbon chain to form alkyl metal species at a remote C(sp^3)−H site.[4] This strategy has been used in several types of transition metal-catalyzed hydrogenative remote C(sp^3)−H functionalization of olefins, such as boration,[5] silylation,[6] zirconation,[7] formylation,[8] amination,[9] arylation,[10] cyclization,[11] carboxylation,[12] and related functionalized isomerization of olefins.[13] Recently, nickel-catalyzed remote C(sp^3)−H cross-coupling of olefins with organic halides has emerged to be a powerful tool for C−C bond construction.[14] However, stoichiometric hydride sources such as hydrosilane are usually needed to generate the active metal hydride species in this overall reductive process.

In synthetic chemistry, it is usually necessary to adjust the oxidation state of reactants to generate the required functionality, making the anticipated bond formation to take place.[15] For instance, the addition of Grignard reagents to an aldehyde remains among the most used reactions to form C−C bonds in the medicinal industry. However, the aldehyde is usually obtained by oxidation of a more abundant and stable alcohol precursor. Furthermore, if ketone is the target product, an additional step of oxidation is required (Figure 1a).[16] This well-established classical route for ketone synthesis relies on a multistep sequence involving two oxidative manipulations. Similarly, the classical 1,3-diketone synthesis needs an aldol reaction and two oxidations from alcohols (Figure 1b).[17] Obviously, poor efficiency exists for these transformations because of step count and generation of stoichiometric waste products.[18] To avoid the poor step economy and large quantities of waste production, the incorporation of redox manipulation and bond formation into a single reaction is a powerful strategy. In the past decade, borrowing hydrogen and the related hydrogen transfer reactions have been widely applied in catalytic redox-neutral transformations.[19] Without the utilization of oxidizing agents, metal-catalyzed alcohol dehydrogenation directly affords an aldehyde or a ketone, which reacts with another component producing various products via C−C or C−X (heteroatom) bond formation. If the metal catalyst is not only able to remove the hydrogen from the alcohol but also return the hydrogen to the unsaturated product or another unsaturated reactant via metal-hydride catalysis, an overall redox-triggered process will be realized. For instance, pioneering studies by Krische et al. reported that redox-triggered transfer hydrogenative C−C formation can be achieved via in situ-generated electrophiles from alcohols and nucleophiles from dienes or other unsaturated compounds (Figure 1c).[20] Recently, this dehydrogenative strategy has been expanded to ketone synthesis via cross-coupling with organic halides or pseudohalides.[21]

Continuing our interest in the catalytic synthesis of carbonyl compounds,[22] we recently questioned whether remote C(sp^3)−H acylation with primary alcohols could be achieved via borrowing

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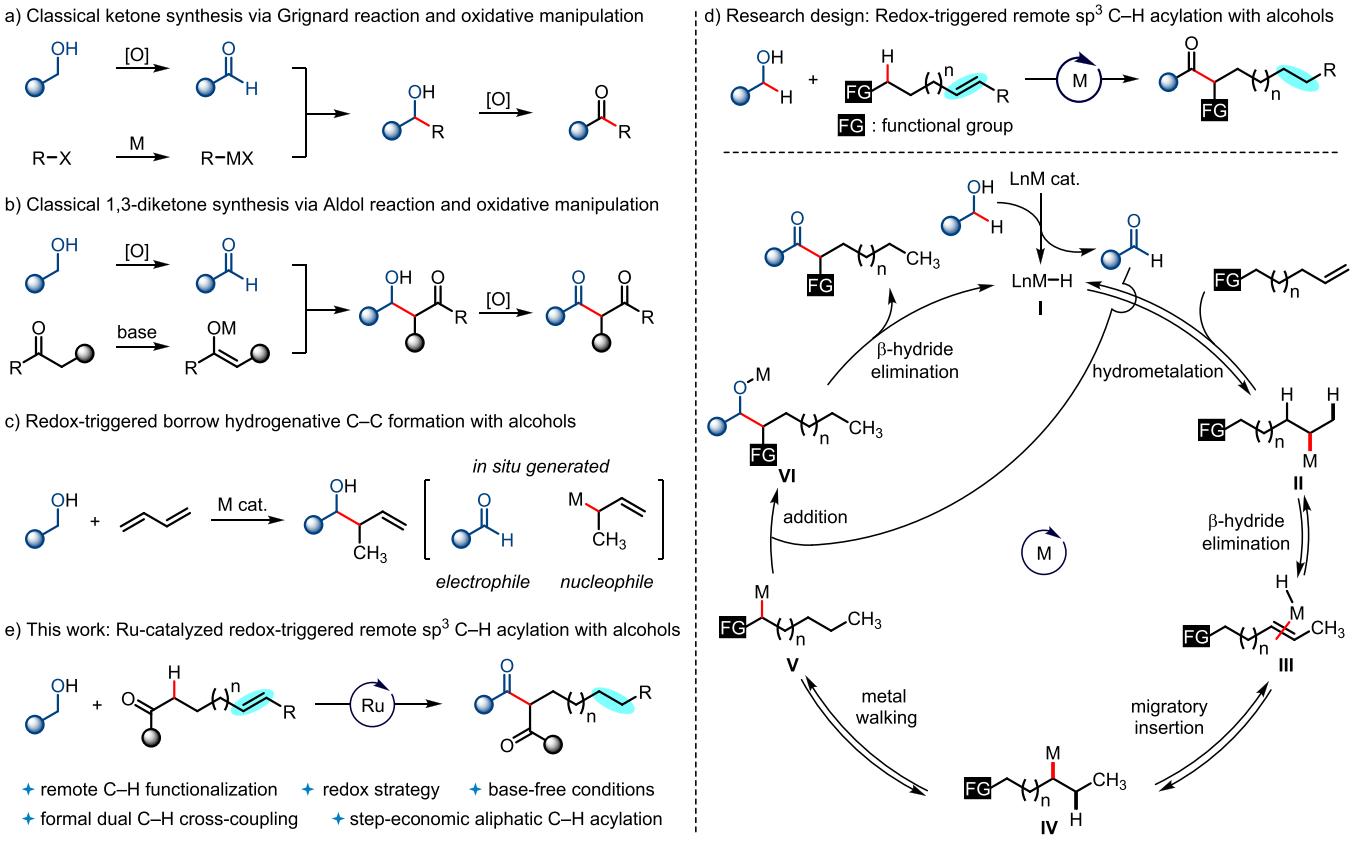
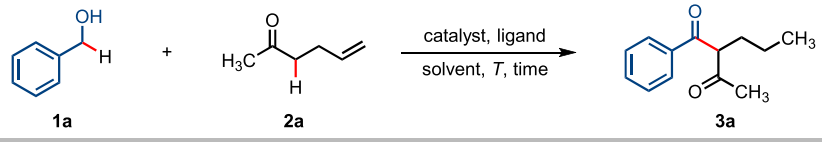
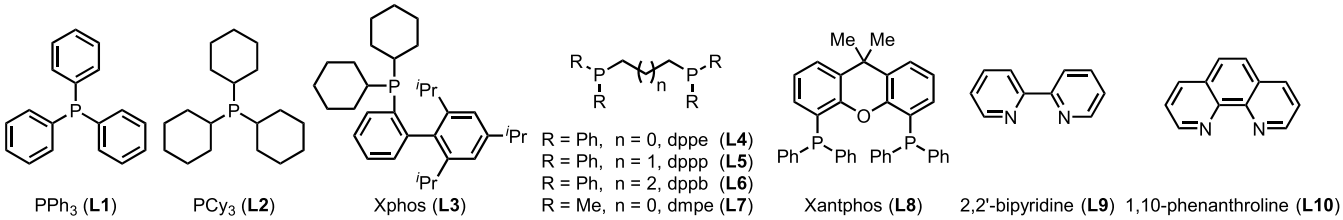


Figure 1. Redox-triggered ketone synthesis with primary alcohols.

Table 1. Optimization of the Reaction Conditions[a]



1a **2a** **3a**



PPh_3 (**L1**) PCy_3 (**L2**) Xphos (**L3**) Xantphos (**L8**) 2,2'-bipyridine (**L9**) 1,10-phenanthroline (**L10**)

entry	catalyst (x mol %)	ligand (x mol %)	solvent	T (°C)	t (h)	yield (%)[b]
1	$RuHCl(CO)(PPh_3)_3$ (5)		toluene	110	16	13
2	$RuH_2(CO)(PPh_3)_3$ (5)		toluene	110	16	<5
3	$RuClCp(PPh_3)_2$ (5)		toluene	110	16	0
4	$RuHCl(CO)(PPh_3)_3$ (5)		1,4-dioxane	110	16	43
5	$RuHCl(CO)(PPh_3)_3$ (5)		1,4-dioxane	120	16	48
6	$RuHCl(CO)(PPh_3)_3$ (5)		1,4-dioxane	130	16	49
7	$RuHCl(CO)(PPh_3)_3$ (5)		1,4-dioxane	90	16	18
8	$RuHCl(CO)(PPh_3)_3$ (5)		1,4-dioxane	120	24	62
9	$RuHCl(CO)(PPh_3)_3$ (5)	**L1** (10)	1,4-dioxane	120	24	52
10	$RuHCl(CO)(PPh_3)_3$ (5)	**L2** (10)	1,4-dioxane	120	24	23
11	$RuHCl(CO)(PPh_3)_3$ (5)	**L3** (10)	1,4-dioxane	120	24	49
12	$RuHCl(CO)(PPh_3)_3$ (5)	**L4** (5)	1,4-dioxane	120	24	48
13	$RuHCl(CO)(PPh_3)_3$ (5)	**L5** (5)	1,4-dioxane	120	24	<5
14	$RuHCl(CO)(PPh_3)_3$ (5)	**L6** (5)	1,4-dioxane	120	24	18
15	$RuHCl(CO)(PPh_3)_3$ (5)	**L7** (5)	1,4-dioxane	120	24	44
16	$RuHCl(CO)(PPh_3)_3$ (5)	**L8** (5)	1,4-dioxane	120	24	46
17	$RuHCl(CO)(PPh_3)_3$ (5)	**L9** (5)	1,4-dioxane	120	24	0

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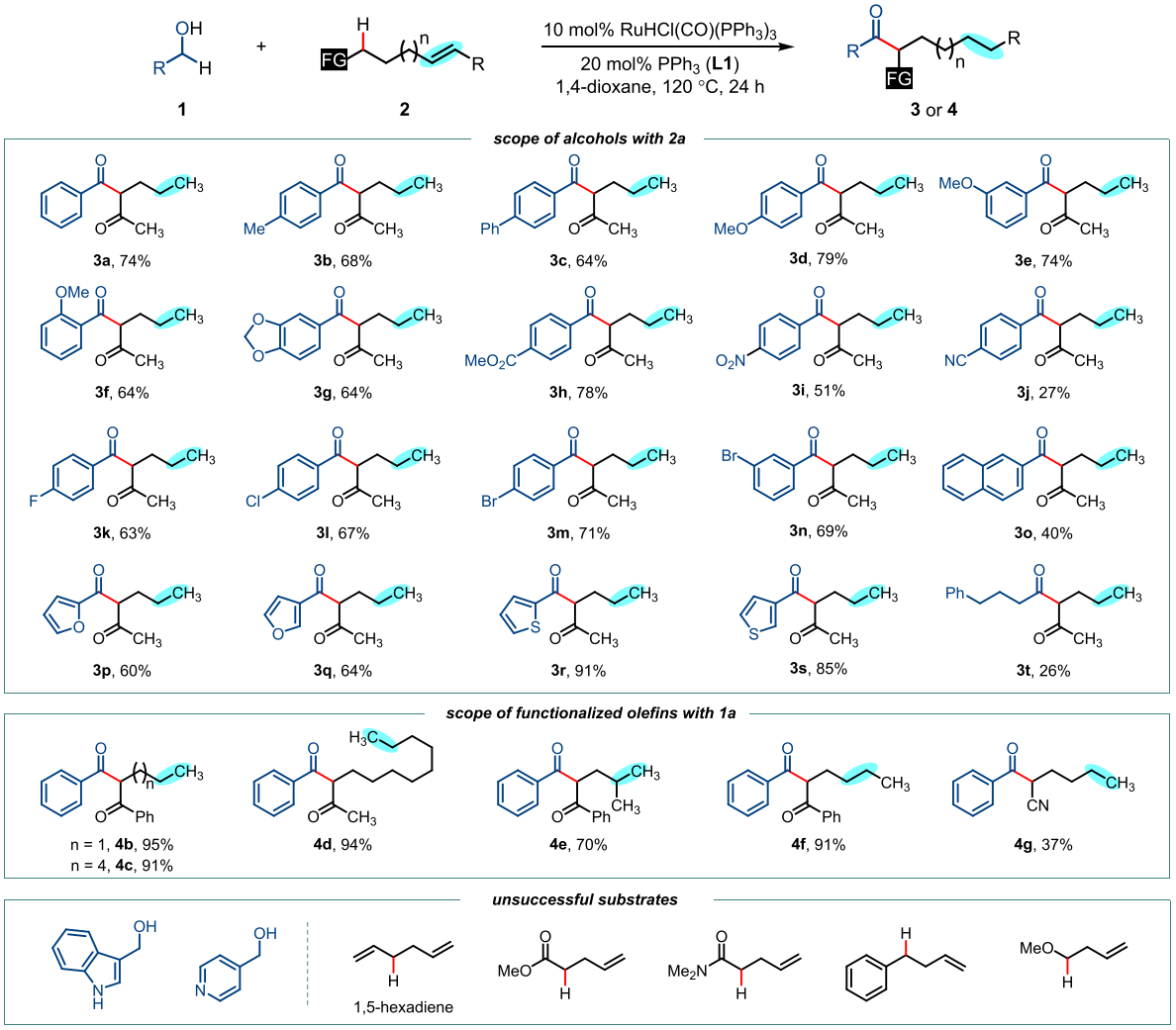
Table 1. continued

entry	catalyst (x mol %)	ligand (x mol %)	solvent	T (°C)	t (h)	yield (%)[b]
18	$RuHCl(CO)(PPh_3)_3$ (5)	**L10** (5)	1,4-dioxane	120	24	0
19	$RuHCl(CO)(PPh_3)_3$ (10)		1,4-dioxane	120	24	67
20	$RuHCl(CO)(PPh_3)_3$ (10)	**L1** (20)	1,4-dioxane	120	24	80 (74)[c]

[a]All reactions were carried out with **1a** (0.2 mmol) and **2a** (0.6 mmol) in 1 mL solvent unless otherwise noted. [b]The yield is determined by calibrated gas chromatography (GC) with *n*-dodecane as an internal standard. [c]Isolated yield in the parenthesis.

Table 2. Reaction Scope of Ru-Catalyzed Remote C−H Acylation with Primary Alcohols[a]



[a]Reaction conditions: **1** (0.2 mmol), **2** (0.6 mmol), $RuHCl(CO)(PPh_3)_3$ (10 mol %), PPh_3 (20 mol %), 1,4-dioxane (1.0 mL), 120 °C, 24 h. The isolated yield is provided.

hydrogen hydrometalation of unactivated olefins followed by the metal walking process. The detailed depiction of the presumed mechanism for the remote C−H acylation is shown in Figure 1d. First, the alcohol-coordinated metal complex undergoes β-hydride elimination, generating an aldehyde and a metal hydride **I**. Hydrometalation of an unactivated alkene with **I** produces an alkyl metal intermediate **II**, which can undergo β-hydride elimination to provide the isomeric complex **III**. After reinsertion of the metal hydride to the generated internal olefin, an alkyl metal species **IV** is formed. Iteration of this process finally leads to the thermodynamically favored alkyl metal intermediate **V**, which is stabilized with a suitable functional group, such as a heteroatom or π-conjugated group. Then, addition of the alkyl metal intermediate **V** to the aldehyde generated by in situ dehydrogenation of alcohol would deliver alkoxy metal species **VI**. Finally, the following β-hydride elimination leads to a ketone product and regenerates the metal hydride **I**. A suitable catalytic system must meet several requirements. First, the metal walking process must be rapid compared to the carbonyl addition reaction. Second, the stabilized alkyl metal intermediate **V** is more prone to carbonyl addition in the presence of many normal alkyl metal intermediates (**II** and **III**). Herein, we report an step-economic redox-triggered Ru-catalyzed remote C(sp^3)−H acylation with primary alcohols for the synthesis of 1,3-diketones to validate such a strategy (Figure 1e).

RESULTS AND DISCUSSION

Reaction Development. We began by investigating the reaction of benzyl alcohol **1a** with 1,5-hexadiene. A stable allyl

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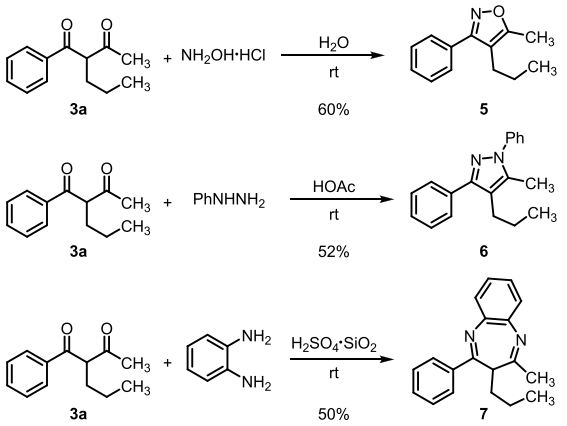
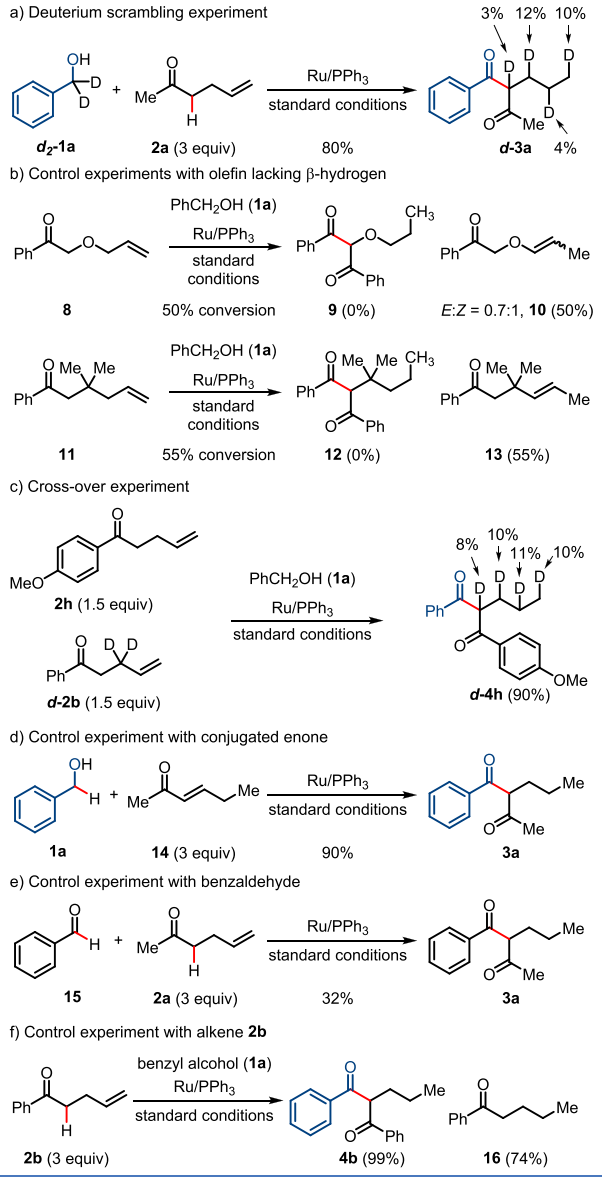
metal species is supposed to be generated via alcohol dehydrogenation, hydrometalation, and then metal walking, which is prone to aldehyde addition. However, no desired C−H acylation product is observed between 1,5-hexadiene and **1a** under various metal catalysis, except for the benzaldehyde byproduct. We then turn to the substrate of α-olefin with a carbonyl group at the terminal carbon. We assumed that a metal enolate species would be formed via hydrometalation followed by metal walking under suitable conditions. It is well known that an aldol product can be easily obtained by the reaction of an aldehyde with a metal enolate.[23] Furthermore, a ruthenium hydride catalyst has been used in the isomerization of alkenes[24] and dehydrogenative aldol-type reaction of an alcohol with an acraldehyde.[25] Inspired by these reports, we found that the reaction between **1a** and 5-hexen-2-one (**2a**) afforded the desired 1,3-diketone **3a** in 13% yield with 5 mol % $RuHCl(CO)(PPh_3)_3$ as the catalyst in toluene at 110 °C (Table 1, entry 1). A trace amount of **3a** was observed with $RuH_2(CO)(PPh_3)_3$ as the catalyst (Table 1, entry 2). No reaction occurred with $RuClCp(PPh_3)_2$ or $Ru_3(CO)_{12}$ as the catalyst (Table 1, entry 3 and Table S1 in Supporting Information). The yield was increased to 43% when 1,4-dioxane was used as a solvent (Table 1, entry 4). When raising the reaction temperature to 120 °C, **3a** was obtained in 48% yield (Table 1, entry 5). The yield did not change too much on further increasing the temperature (Table 1, entry 6). However, the yield of **3a** dropped a lot when decreasing the temperature to 90 °C (Table 1, entry 7). By simply prolonging the reaction time to 24 h, **3a** was obtained in 62% yield (Table 1, entry 8). Then, a variety of ligands were investigated in this Ru-catalyzed remote C(sp^3)−H acylation. The results showed that the ligand has a significant effect on the reaction. A monodentate phosphine ligand gave **3a** in 23−53% yields, such as PPh_3 (**L1**), PCy_3 (**L2**), and Xphos (**L3**) (Table 1, entries 9−11). For a bidentate phosphine ligand, moderate yields were obtained with dppe (**L4**), dmpe (**L7**), and Xantphos (**L8**), but lower yields were obtained with dppp (**L5**) and dppb (**L6**) (Table 1, entries 12−16), which may be due to the different bite angles of these ligands. Moreover, no reaction occurred with nitrogen-containing bidentate ligands, such as 2,2′-bipyridine (**L9**) and 1,10-phenanthroline (**L10**) (Table 1, entries 17−18). When tridentate triphos was used, **3a** was obtained in 9% yield (Table S1 in Supporting Information). So far, the simplest PPh_3 (**L1**) has been proved to be the optimal ligand. Then, a slightly higher yield was obtained when 10 mol % $RuHCl(CO)(PPh_3)_3$ was used (Table 1, entry 19). Finally, addition of PPh_3 as an additional ligand delivered **3a** in 80% yield (Table 1, entry 20).

Reaction Scope. With the optimized conditions in hand, we next explored the substrate scope of this reaction (Table 2). A variety of benzylic alcohols were first investigated. The reaction tolerated both electron-donating (Me, Ph, and MeO) and electron-withdrawing (ester and nitro) groups on the phenyl ring of the benzyl alcohols. Notably, the *para*-, *meta*-, and *ortho*-methoxy benzyl alcohols all reacted smoothly affording the corresponding products in 64−79% yields (**3d**−**3f**). Moderate to good yields were obtained with *para*-CO_2Me and *para*-NO_2 substituted benzyl alcohol (**3h**−**3i**). The strong electron-withdrawing cyano group could also be tolerated, delivering the product **3j** in an acceptable yield. On the other hand, benzyl alcohols bearing halogen atoms (F, Cl, and Br) were also compatible, providing the corresponding 1,3-diketones in 63−71% yields (**3k**−**3n**). Furthermore, alcohols containing π-conjugated arene (naphthalene) and heteroarenes (furan and thiophene) also proceeded well delivering the products **3o**−**3s** in 40−91% yields. Finally, when aliphatic 4-phenylbutan-1-ol was used as the substrate, a slow reaction was observed producing the desired product **3t** in a low yield

Scheme 1. Synthetic Applications



Scheme 2. Mechanistic Studies



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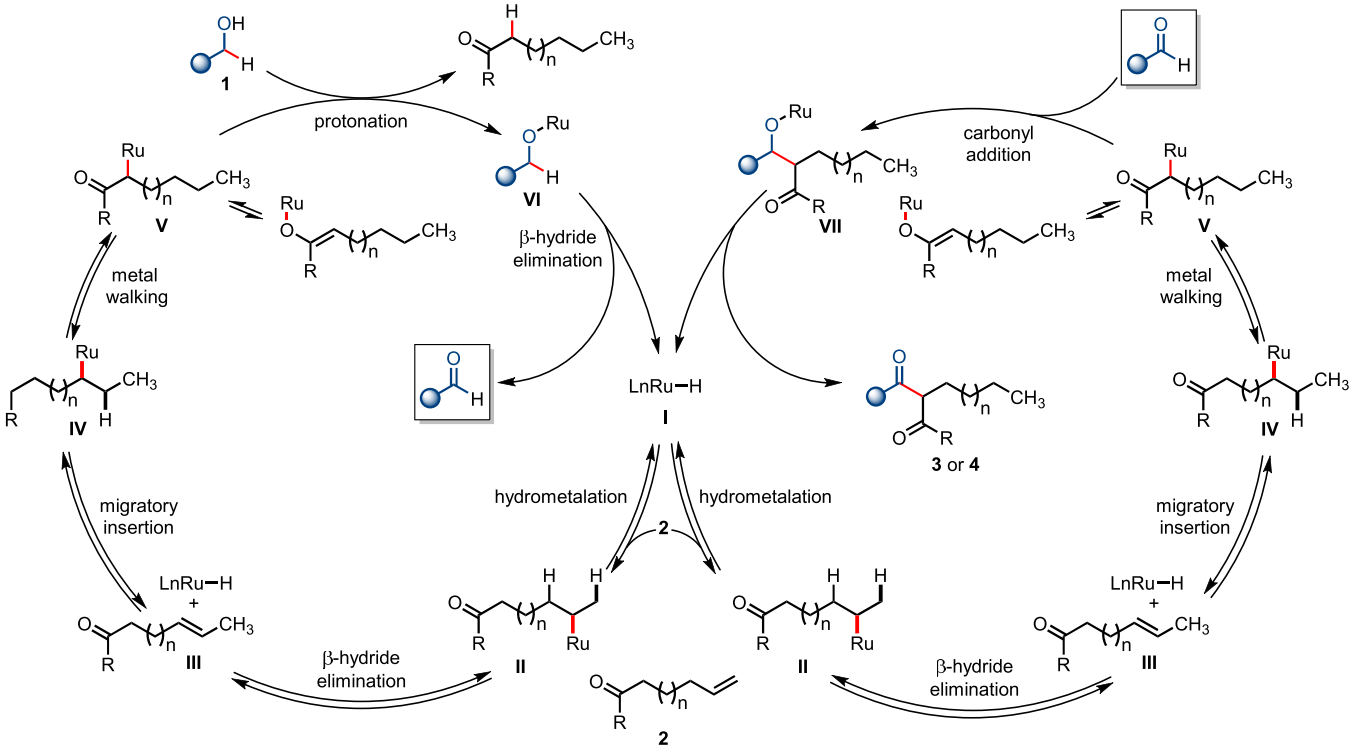
Scheme 3. Plausible Catalytic Pathway



under the standard conditions. Unfortunately, no C−H acylation reaction occurred with alcohols containing an indole or a pyridine subunit, even with an *N*-methyl-protected indole substrate.

Then, a variety of functional group-tethered linear α-olefins were investigated. The reactions occurred smoothly with ketone-tethered α-olefins. Acylation of 1-phenylpent-4-en-1-one, 1-phenylnon-8-en-1-one, and dodec-11-en-2-one with benzyl alcohol **1a** afforded the corresponding products **4b**−**4d** in excellent yields. Obviously, the metal walking process is rapid and efficient in this remote C(sp^3)−H acylation. Notably, 2,2-disubstituted and internal olefin are well tolerated, delivering the products **4e** and **4f** in good to excellent yields. Finally, a moderate yield was obtained with a nitrile-linked alkene, hex-5-enenitrile, under the standard conditions (**4g**). Unfortunately, no desired diketone product was obtained when switching the ketone with other functional groups, such as alkene, ester, amide, phenyl, and methoxy under the standard conditions. Benzaldehyde and an alkene hydrogenation product were observed in these reactions.

Synthetic Applications. As a versatile intermediate in synthetic chemistry, 1,3-diketones can be converted into many useful compounds by routine manipulations. To demonstrate the potential utility of 1,3-diketone, we simply performed several condensation reactions with **3a** for the synthesis of nitrogen-containing heterocycles, which have been widely present in marketed drug molecules and active pharmaceutical ingredients (Scheme 1). The reaction of **3a** with hydroxylamine, phenylhydrazine, and 1,2-phenylenediamine afforded the corresponding isoxazole **5**, pyrazole **6**, and diazepin **7**, respectively, under mild conditions.

Mechanistic Studies. To gain insights into the reaction mechanism, a number of control experiments were carried out. First, a deuterium scrambling experiment with alcohol d_2-**1a** as the acylating agent was performed under standard conditions to prove the metal walking pathway. As expected, remote C(sp^3)−H acylation of **2a** gave *d*-**3a** in 80% yield with clear deuterium labeling at the sp^3 carbon of the alkyl chain (Scheme 2a). Next, no desired C(sp^3)−H acylation occurred with the substrate including an oxygen atom or a gem-dimethyl spacer in the hydrocarbon chain between the ketone group and the double bond. For instance, the reaction of **8** or **11** with alcohol **1a** only afforded the olefin isomerization product **10** and **13** (Scheme 2b). These results indicate that the reaction takes place via Ru-hydride-catalyzed reversible hydrometalation and isomerization of olefin. A cross-over experiment was performed with **2h** and deuterated *d*-**2b** as the substrates, and H/D scrambled *d*-**4h** was obtained in an excellent yield (Scheme 2c). This result indicates that Ru−H species are dissociated from alkenes during the metal walking process.[26] Furthermore, a reaction of conjugated enone **14** with alcohol **1a** occurred smoothly producing **3a** in 90% yield, suggesting that **14** might be the isomerization intermediate of olefin **1a** (Scheme 2d). When benzaldehyde (**15**) was used instead of benzyl alcohol (**1a**), diketone **3a** was obtained in a moderate yield, demonstrating that the aldehyde in situ-generated from the dehydrogenation of alcohol could be the reaction intermediate (Scheme 2e). Further experiments were then carried out. No benzaldehyde (**15**) was generated when mixing benzyl alcohol (**1a**) with $RuHCl(CO)(PPh_3)_3$ in dioxane at 120 °C for 2 h without 5-hexen-2-one (**2a**). However, the benzaldehyde (**15**) and diketone product **3a** were quickly generated when **2a** was added into the above reaction mixture. Then, acylation of benzoyl-linked alkene **2b** was performed to trace the excess amount of alkene (Scheme 2f). In addition to the desired diketone product **4b**, the alkene hydrogenation product **16** is obtained in a good yield. This result demonstrates that the alkene **2** also serves as a H_2 acceptor.

Based on these control experiments, a detailed mechanism was proposed as shown in Scheme 3. First, hydrometalation of ketone-tethered alkene **2** with a Ru−H complex (**I**) generates the alkyl ruthenium intermediate **II**, which can undergo

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β-hydride elimination to provide the isomeric alkene **III** and regenerate the Ru−H species. After reinsertion of the ruthenium hydride species to the generated internal olefin, an alkyl ruthenium species **IV** is formed. Iteration of this process finally leads to the alkyl ruthenium intermediate **V**, which is stabilized as a ruthenium enolate. Ligand exchange and protonation of the intermediate **V** with alcohol **1** generate the corresponding alkyl ketone product and the alkoxy ruthenium species **VI**. The following β-hydride elimination produces the aldehyde intermediate and the ruthenium hydride catalyst **I**. Iteration of hydrometalation of alkene, β-hydride elimination, migratory insertion, and metal walking process would give the alkyl ruthenium species **V**. Then, the addition of the alkyl ruthenium intermediate **V** to the above aldehyde intermediate delivers alkoxyl metal species **VII**. Finally, β-hydride elimination leads to the desired diketone product and regenerates the ruthenium hydride catalyst **I**. The control experiments are consistent with the proposed catalytic cycle.

CONCLUSIONS

In summary, we have developed a novel protocol for the remote C(sp^3)−H acylation of olefins with primary alcohols. The ruthenium-catalyzed alpha acylation of a ketone with an alcohol has been achieved affording 1,3-diketones through a redox strategy. The reaction takes place smoothly without a base as an additive. This step-economic reaction features an efficient multistep process involving borrowing hydrogen, hydrometalation, and metal walking, which has been confirmed by mechanistic studies. Development of remote C(sp^3)−H acylation of other functionalized olefins with primary alcohols is ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acscatal.0c03343.

Experimental procedures, optimization of the reaction conditions, substrates used in the Ru-catalyzed remote C−H acylation, general procedure for Ru-catalyzed remote C−H acylation, synthetic applications, control experiments, and NMR characterization data (PDF)

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Author Contributions

#X.G. and Y.W. contributed equally to this work.

Notes

The authors declare no competing financial interest.

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