

Synthesis of 2-Hydroxymethyl Ketones by Ruthenium Hydride-Catalyzed Cross-Coupling Reaction of α,β -Unsaturated Aldehydes with Primary Alcohols

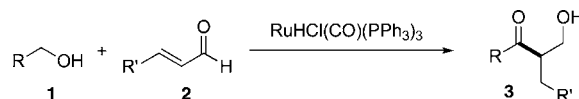
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ABSTRACT



The cross-coupling reaction of α,β -unsaturated aldehydes with primary alcohols to give 2-hydroxymethyl ketones was achieved using $\text{RuHCl}(\text{CO})(\text{PPh}_3)_3$ as a catalyst. This atom-economical reaction is likely to proceed via the hydorruthenation of α,β -unsaturated aldehydes followed by an aldol reaction of the resultant enolates with aldehydes to give α -formylated ketones, which undergo transfer hydrogenation with primary alcohols leading to α -hydroxymethyl ketones. The reduction step can generate aldehydes, participating in the next catalytic cycle.

Development of new catalytic coupling processes accompanied with atom economy is highly desirable in organic synthesis.^{1,2} In this regard, we are interested in the potentials of ruthenium hydride-catalyzed bond forming reactions in conjunction with the use of readily available oxygenated substrates, such as alcohols, ketones, and aldehydes.^{3–5} Recently, we have reported that dimerization of primary

unsaturated alcohols^{4a} and reductive dimerization of α,β -unsaturated aldehydes⁵ were effectively catalyzed by $\text{RuHCl}(\text{CO})(\text{PPh}_3)_3$. In the latter homocoupling reaction of enals, secondary alcohols such as isopropanol act as a hydrogen source, which is converted to acetone, an inert compound in the system (Scheme 1, eq 1). Since the pioneering work of Gregorio and co-workers on catalytic dimerization of primary alcohols,⁶ many researchers have pursued the potential of cross-coupling reactions of primary alcohols via transfer hydrogenation.⁷ In this regard, recent work by

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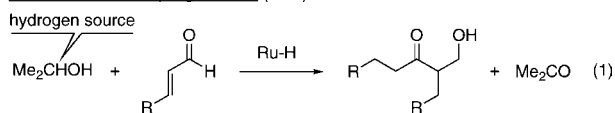
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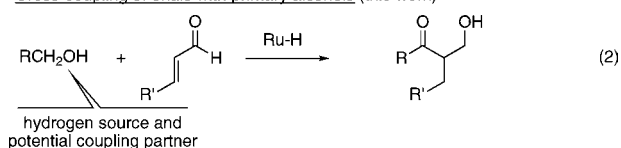
Krische and co-workers that demonstrates Ru- and Ir-catalyzed cross-coupling of alcohols with unsaturated C–C double and triple bonds is noteworthy.⁸ We thought that if primary alcohols, such as benzyl alcohol, are employed as a hydrogen source, the resulting aldehydes would act as a coupling partner to give cross-coupling products (Scheme 1, eq 2). We report herein the Ru–H-catalyzed atom-economical cross-coupling reaction of α,β -unsaturated aldehydes with primary alcohols leading to α -hydroxymethyl ketones.

Scheme 1. Ru–H Catalyzed Coupling Reactions of Enals

Reductive homocoupling of enals (ref 5)

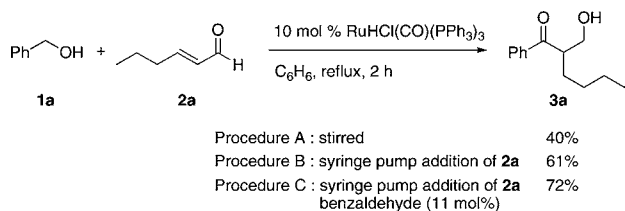


Cross-coupling of enals with primary alcohols (this work)



When a benzene solution of benzyl alcohol (**1a**, 1.2 equiv) and 2-hexenal (**2a**) in the presence of $\text{RuHCl}(\text{CO})(\text{PPh}_3)_3$ (10 mol %) was heated under reflux for 2 h (Procedure A, Scheme 2), 2-hydroxymethyl-1-phenyl-1-hexanone (**3a**) was obtained in 40% yield. In this case, a significant amount of dimer derived by reductive coupling of **2a** was formed as byproduct (**3a**/dimer = 5/1). To suppress the undesired dimerization course, **2a** was added slowly using a syringe pump over the period of 1 h, then the resulting mixture was stirred for another 1 h (Procedure B). In this case, the desired **3a** was obtained in 61% yield. Since in the initial stage of the reaction **2a** was consumed by transfer hydrogenation to produce benzaldehyde, we decided to add a small amount of aldehyde beforehand (Procedure C). This caused further improvement of the yield of **3a** up to 72%.

Scheme 2. Optimization of the Reaction Conditions



Having an optimized procedure C in hand, we then examined the generality of the present cross-coupling reaction with various alcohols and enals (Table 1). The reactions of 2-hexenal (**2a**) with several benzylic alcohols, having an

Table 1. Cross-Coupling Reaction of α,β -Unsaturated Aldehydes with Benzylic Alcohols^a

entry	benzyl alcohol 1	enal 2	β -hydroxymethyl ketone 3	yield ^b
1				72%
2		2a		53%
3		2a		66%
4		2a		59%
5		2a		74%
6		2a		67%
7 ^c		2a		64%
8		2a		66%
9	1a			66%
10	1a			45%
11	1a			60%
12 ^c	1e			69%
13		2a		30%

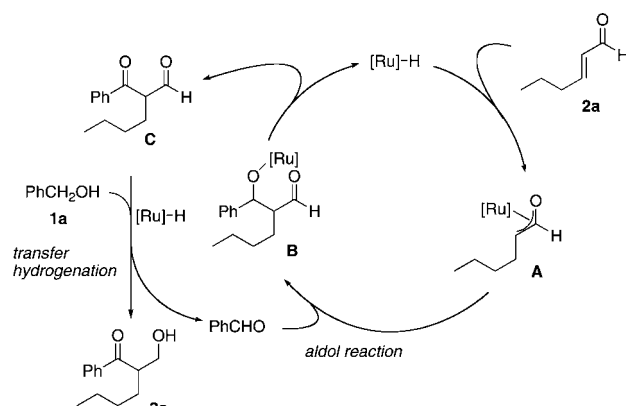
^a Conditions: **1** (1.2 equiv), **2** (0.8 mmol), corresponding aldehyde (10 mol %), $\text{RuHCl}(\text{CO})(\text{PPh}_3)_3$ (0.08 mmol), benzene (4 mL). A benzene solution of **1** (5 mL) was added using a syringe pump over the period of 1 h, then the mixture was heated at reflux for 1 h. ^b Isolated yield after flash chromatography on SiO_2 . ^c A benzene solution of **1g** and **2a** was added over the period of 1 h.

electron-donating substituent or an electron-withdrawing substituent, gave the 2-hydroxymethyl ketone **3** in good yields (entries 1–6). The reaction also worked well with alcohols having heteroaromatic rings such as 2-thiophenemethanol (**1g**) and 2-furanmethanol (**1h**) (entries 7 and 8). In the case of the alcohol **1g**, transfer hydrogenation of **1g** and **2a** leading to 2-thiophenecarboxyaldehyde and 1-hexanol was fast with the procedure C. Thus, syringe pump addition of a mixture solution of **1g** and **2a** was examined, giving the desired coupling product **3g** in good yield. Disubstituted enal **2c** also reacted with **1a**, whereas the yield of **3j** was rather modest (entry 10). Enals having an aromatic substituent

at the β -position, such as **2d** and **2e**, gave the corresponding 2-hydroxymethyl ketones in good yields (entries 11 and 12). The reaction of nonbenzylic type alcohol **1i** also gave the coupling **3m** in 30%, which requires further efforts for yield optimization.

A possible mechanism for this enal/alcohol coupling reaction is shown in Scheme 3 with an example of the reaction of **1a** and **2a**. The hydroruthenation of **2a** would give ruthenium enolate **A**,^{9,10} which then undergoes aldol reaction with benzaldehyde.^{11,12} β -Elimination from the resulting aldol adduct **B** would lead to the keto aldehyde **C**. Finally, transfer hydrogenation¹³ between the aldehyde moiety of **C** and benzyl alcohol (**1a**) gives 2-hydroxymethyl ketone **3a** and benzaldehyde which then reacts with another molecule of ruthenium enolate **A**, creating a catalytic cycle.

Scheme 3. Possible Mechanism for the Coupling of **1a** and **2a**



In summary, we have shown that a novel cross-coupling reaction of enals with primary alcohols is effectively catalyzed by $\text{RuHCl}(\text{CO})(\text{PPh}_3)_3$, which leads to good yields of 2-hydroxymethyl ketones. The reaction is likely to proceed via an aldol reaction of a ruthenium enolate followed by a transfer hydrogenation, where primary alcohols act as both a hydrogen source and a latent aldehyde. The simplicity, atom efficiency, mild reaction conditions, and short reaction times make this an appealing methodology for accessing 2-hydroxymethyl ketones. Synthetic applications of the present reaction are currently underway in this laboratory.

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Supporting Information Available: Experimental procedure and compound characterization. This material is available free of charge via the Internet at <http://pubs.acs.org>. OL902289R

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