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# Carbon – carbon bond formation between secondary alcohols and aldehydes under ruthenium-catalyzed redox shuttle

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# Chan Sik Cho<sup>a</sup>\*, Bok Tae Kim<sup>a</sup> and Nam Sik Yoon<sup>b</sup>

Secondary alcohols are coupled with aldehydes in dioxane in the presence of a catalytic amount of a ruthenium catalyst along with KOH to give coupled ketones or coupled secondary alcohols depending on the molar ratio of secondary alcohols to aldehydes and the presence (or absence) of a sacrificial hydrogen acceptor. Copyright © 2011 John Wiley & Sons, Ltd.

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## Introduction

It is well known that the carbon-carbon bond forming reaction plays a pivotal role in organic synthesis. Thus, many practical methods catalyzed by transition metals have been developed for such a carbon – carbon bond-forming reaction.<sup>[1,2]</sup> We also recently found several sp<sup>3</sup>-carbon-sp<sup>3</sup>-carbon bond forming-reactions between ketones (or secondary alcohols) and primary alcohols under a ruthenium-catalyzed redox shuttle.<sup>[3,4]</sup> The cross-coupling between ketones 1 and primary alcohols 2 selectively gives coupled ketones **3** ( $\alpha$ -alkylation of **1** with **2**; Scheme 1, route a)<sup>[5]</sup> or coupled secondary alcohols 4 (Scheme 1, route b)<sup>[6]</sup> according to the molar ratio of [2]:[1]. An atom economical reductive crosscoupling of 1 with 2 leading to 4 under the molar ratio of [2]:[1] = 1 - 1.2 by the addition of ethylenediamine has also been reported.<sup>[7]</sup> Similar one-pot multicatalytic cross-coupling between secondary alcohols **5** and **2** leading to **4** ( $\beta$ -alkylation of **5** with **2**) was also disclosed by the addition of a sacrificial hydrogen acceptor (Scheme 1, route c).<sup>[8]</sup> In addition, it was also demonstrated that ketones 1 were found to be coupled with aldehydes 6 to give coupled ketones **3** (Scheme 1, route d).<sup>[9]</sup> Several other transition metal precursors have also been introduced for such sp<sup>3</sup>-carbon – sp<sup>3</sup>-carbon bond-forming reactions,<sup>[10-16]</sup> and this coupling protocol could be applied to modified Friedländer guinoline synthesis.<sup>[17–26]</sup> Prompted by these findings, this report describes another ruthenium-catalyzed one-pot multicatalytic coupling mode between secondary alcohols 5 and aldehydes 6, leading to coupled ketones 3 or coupled secondary alcohols 4 by the tuning of the molar ratio of [5]:[6] and the presence (or absence) of a hydrogen acceptor (Scheme 1, routes e and f).

## **Results and Discussion**

Table 1 shows optimization of the conditions for the carbon-carbon bond formation between 1-phenylethanol (**5a**) and benzaldehyde (**6a**) under a ruthenium-catalyzed redox shuttle leading to selective formation of either coupled ketone, 1,3-diphenylpropan-1-one (**3a**), or coupled secondary alcohol, 1,3-diphenylpropan-1-ol (**4a**). Treatment of equimolar amounts of

5a and 6a in dioxane in the presence of RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub> (2 mol%) and KOH at 80  $^{\circ}$ C for 20 h afforded **3a** (48% yield) and **4a** (10% yield) with concomitant formation of acetophenone (9%; entry 1). The product yield and distribution were slightly increased by the addition of 1-dodecene as a hydrogen acceptor (entry 2). However, when the reaction was carried out in the presence of much greater amount of 1-dodecene, no significant change in the product yield and selectivity was observed (entry 3). It has been found that the reaction rate on the coupling between secondary alcohols and primary alcohols towards coupled secondary alcohols is dramatically enhanced by the addition of a sacrificial hydrogen acceptor.<sup>[8]</sup> Treatment of equimolar amounts of **5a** and **6a** is desirable from an atom economy point of view since the reaction under the molar ratio of [5a]:[6a] = 0.5 results in a slightly increased yield of 3a (68% yield; entry 4). The best result in terms of both overall yield and the selectivity of coupled ketone to coupled secondary alcohol is best accomplished by further tuning of the reaction time (entry 5). Finally, when the reaction was carried out under the molar ratio of [5a]: [6a] = 3 in the absence of 1-dodecene, coupled secondary alcohol 4a was selectively formed in preference to coupled ketone 3a (entry 6).

Reaction conditions having been established for the formation of coupled ketone, various secondary alcohols **5** were subjected to the reaction with **6a** in order to investigate the reaction scope, and several representative results are summarized in Table 2. Various aryl(methyl) carbinols (**5a**–**f**) having electron-donating and -withdrawing substituents on the aromatic ring were readily coupled with **6a** to give the corresponding coupled ketones (**3a**–**f**) in the range of 42–63% yields along with a small amount of coupled secondary alcohols **4** in several cases (<3%) and uncoupled ketones (<11%) produced from **5**. The reaction proceeded likewise

<sup>\*</sup> Correspondence to: Chan Sik Cho, Department of Applied Chemistry, Kyungpook National University, Daegu 702-701, South Korea. E-mail: cscho@knu.ac.kr

a Department of Applied Chemistry, Kyungpook National University, Daegu 702-701, South Korea

b Department of Textile System Engineering, Kyungpook National University, Daegu 702-701, South Korea



Scheme 1. Cross-coupling routes.



Scheme 2. A reaction pathway.

with  $\alpha$ -methyl-1-naphthalenemethanol (**5g**) to afford the coupled ketone **3g** in 40% yield. In the reaction of heteroaryl(methyl) carbinol **5h** with **6a**, the corresponding coupled ketone **3h** was also obtained in similar yield. Benzo-fused cyclic carbinol **5i** also

reacted with **6a** to give 2-benzyl-1-tetralone (**3i**) in 49% yield. With alkyl(methyl) carbinols (**5j** and **5k**), the product yield was lower than when aryl(methyl) carbinols were introduced. On the other hand (not shown in Table 2), **5a** was also cross-coupled with aliphatic aldehyde and octyl aldehyde. However, in contrast to the cross-coupling between aryl(methyl) carbinols and **6a**, lower reaction rate and yield were observed with octyl aldehyde (the yield of 1-phenyldecan-1-one was 31%).

Table 3 shows the preferential formation of coupled secondary alcohols 4 by the cross-coupling between various secondary alcohols 5 and aldehydes 6 under the standard set of reaction conditions (entry 6 of Table 1). The reactions of 5a with various aromatic and heteroaromatic aldehydes (6a-e) proceeded to give the corresponding coupled secondary alcohols (4a-e) in the range of 32-81% yields along with coupled ketones. The product yield and selectivity were considerably affected by the electronic nature of the substituent on the aromatic ring of (6a - d). With aldehyde having an electron-withdrawing Cl substituent, the product yield and selectivity were lower than when aldehydes having an electron-donating character were used. In the reaction of ferrocenecarboxaldehyde (6f), the corresponding coupled secondary alcohol 4f was also obtained in 75% yield with a small amount of coupled ketone (19% yield). Various aryl(methyl) and heteroaryl(methyl) carbinols (5b-h) were also reacted with **6a** to give the corresponding coupled secondary alcohols (**4g**-**m**) in the range of 64-88% yields. Here again, similar selectivity in favor of coupled secondary alcohols to coupled ketones was observed. Benzo-fused cyclic carbinol 5i and alkyl(methyl) carbinol 5k were also coupled with 6a to give 2-benzyl-1,2,3,4tetrahydronaphthalen-1-ol (4n) as a diastereoisomeric mixture and 1,5-diphenylpentan-3-ol (40), respectively. However, the product yield and selectivity were lower than when aryl(methyl) carbinols were employed.

For the reaction pathway, it seemed to proceed via initial oxidation of **5** to ketone **1** (Scheme 2). Compounds **1** and **6** then underwent a cross-aldol reaction under KOH to give the  $\alpha$ , $\beta$ -unsaturated ketone **7**, which was hydrogenated to **3** and **4** by a dihydridoruthenium species generated in the initial oxidation stage of **5**. A similar catalytic cycle has been proposed by us in ruthenium-catalyzed cross-coupling reactions.<sup>[6,8,9]</sup>

Table 1.	Optimization of cond	itions for the reaction of <b>5a</b> w	ith <b>6a</b> ª			
		$\begin{array}{cccc} OH & & O & & OH \\ Ph & + & PhCHO & \longrightarrow & Ph & Ph & Ph & Ph & Ph \end{array}$				
		5a 6a	3a	4a		
					Yie	eld (%)
Entry	[5a]:[6a]	1-Dodecene (mmol)	Time (h)	Conversion <sup>b</sup> (%) of <b>5a</b>	3a	4a
1	1	_	20	75	48	10
2	1	1	20	82	60	6
3	1	5	20	82	59	4
4 <sup>c</sup>	0.5	5	40	90	68	Trace
5	1	5	40	85	63	Trace
6 <sup>d</sup>	3	-	40	69	15	75

 $^a$  Reaction conditions: **6a** (1 mmol), RuCl $_2$ (PPh $_3$ ) $_3$  (0.02 mmol), KOH (1 mmol), dioxane (2 ml), 80  $^\circ$ C.

<sup>b</sup> Determined by GLC.

<sup>c</sup> **6a** (2 mmol).

<sup>d</sup> RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub> (0.05 mmol), KOH (3 mmol).





 $^a$  Reaction conditions:  ${\bf 5}$  (1 mmol),  ${\bf 6a}$  (1 mmol), 1-dodecene (5 mmol), RuCl\_2(PPh\_3)\_3 (0.02 mmol), and KOH (1 mmol) in dioxane (2 ml), 80  $^\circ$ C, 40 h.

<sup>b</sup> Isolated yield. Numbers in parentheses indicate the corresponding coupled secondary alcohols.

# Conclusion

In summary, it has been shown that secondary alcohols undergo a one-pot multicatalytic carbon–carbon bond forming reaction with aldehydes under a ruthenium-catalyzed redox shuttle to give preferentially coupled ketones or coupled secondary alcohols according to the molar ratio of substrates and whether a sacrificial hydrogen acceptor is added or not.

## Experimental

<sup>1</sup>H and <sup>13</sup>C NMR (400 and 100 MHz) spectra were recorded on a Bruker Avance Digital 400 spectrometer using Me<sub>4</sub>Si as an internal standard. GLC analyses were carried out with Shimadzu GC-17A (FID) equipped with a CBP10-S25-050 column (Shimadzu, a silica fused capillary column, 0.33 mm  $\times$  25 m, 0.25 µm film thickness) using N<sub>2</sub> as carrier gas. The isolation of pure products was carried out via thin-layer (silica gel 60 GF<sub>254</sub>, Merck) chromatography. Commercially available organic and inorganic compounds were used without further purification. Secondary alcohols (**5b**-**h**) were prepared by reduction of the corresponding ketones with NaBH<sub>4</sub> in MeOH.



Table 3. Ruthenium-catalyzed cross-coupling between secondary

coupled ketones.

#### **General Experimental Procedure**

A mixture of secondary alcohols (1–3 mmol), aldehydes (1 mmol), RuCl<sub>2</sub>(PPh<sub>3</sub>)<sub>3</sub> (0.02–0.05 mmol), KOH (1–3 mmol) and 1-dodecene (0–5 mmol) in dioxane (2–3 ml) was placed in a 5 ml screw-capped vial and the system was allowed to react at 80 °C for an appropriate time. The reaction mixture was filtered through a short silica gel column (ethyl acetate) to eliminate inorganic salts. Removal of the solvent left a crude mixture, which was separated by thinlayer chromatography (silica gel, ethyl acetate–hexane mixture) to give coupled secondary alcohols and coupled ketones. All coupled ketones and secondary alcohols were identified by GLC and spectroscopic comparison with authentic samples synthesized by recent reports.<sup>[5,7–9,27]</sup>

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