ORGANIC LETTERS

2012
Vol. 14, No. 18
4703–4705

$RuHCl(CO)(PPh_3)_3$-Catalyzed α-Alkylation of Ketones with Primary Alcohols

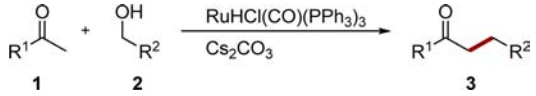
Takashi Kuwahara, Takahide Fukuyama, and Ilhyong Ryu*

Department of Chemistry, Graduate School of Science, Osaka Prefecture University,
Sakai, Osaka 599-8531, Japan

ryu@c.s.osakafu-u.ac.jp

Received August 4, 2012

ABSTRACT



The α-alkylation reaction of ketones with primary alcohols to give α-alkylated ketones was achieved using $RuHCl(CO)(PPh_3)_3$ as a catalyst in the presence of Cs_2CO_3 as a base. This reaction proceeds via an aldol condensation of ketones with aldehydes, formed via transfer dehydrogenation of alcohols, to give α,*β*-unsaturated ketones, which then undergo transfer hydrogenation with primary alcohols to give α-alkylated ketones and aldehydes, the latter of which participate in the next catalytic cycle. While the reaction of aliphatic primary alcohols was sluggish compared with that of benzylic alcohols, a catalytic amount of 1,10-phenanthroline was found to promote the alkylation dramatically.

α-Alkylation of ketones is one of the most fundamental reactions in organic synthesis. In the most common protocols, ketones are transferred to metal enolates[1] or enamines,[2] which are ready to react with carbon electrophiles to give α-alkylated ketones. In recent years, alternative approaches based on the transition-metal-catalyzed α-alkylation of ketones have been developed,[3−8] in which alcohols are employed as *latent* aldehydes by catalytic transfer dehydrogenation. In 2002, Shim and co-workers reported that $RuCl_2(PPh_3)_3$ can catalyze α-alkylation of ketones with primary alcohols. In this Ru-catalyzed reaction, to avoid the reduction of product ketones a stoichiometric amount of a terminal alkene, such as 1-dodecene, is used as a hydrogen trap.[4] The Pd/C system can also be used as a catalyst in combination with 1-decene as a hydrogen trap.[5] In a similar transformation but without the need for the addition of alkenes, Ishii and co-workers found that $[IrCl(cod)]_2$ is an excellent catalyst for the α-alkylation of ketones with primary alcohols.[6] Yus and co-workers also reported that $[Ru(dmso)_4]Cl_2$ catalyzed the α-alkylation of ketones with benzylic alcohols.[7] Recyclable catalyst systems such as Pd/AlO(OH)[8a] and viologen polymers[8b,c] and a heterogeneous system using Ag/Mo oxides[8d] are also actively being pursued. In these studies, the metal-catalyzed transfer hydrogenation reaction is combined with a classical aldol condensation using a strong base, which is typically KOH, and the overall transformation is highly atom-economical, since the only byproduct is water (Scheme 1).

We have been interested in the potential of RuHCl(CO)-$(PPh_3)_3$ as a multitask catalyst[9] for atom-economical cross-addition reactions and previously reported that the reaction of α,*β*-unsaturated aldehydes with primary

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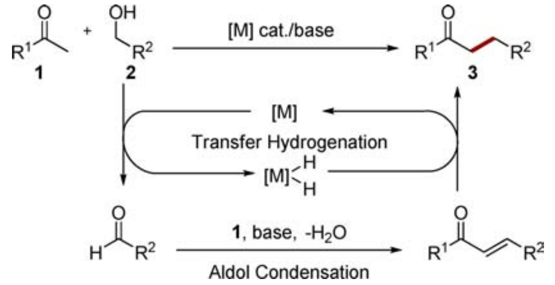
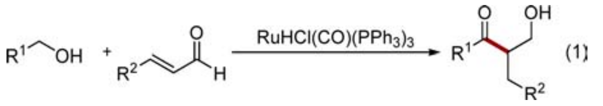
10.1021/ol302145a

Scheme 1. Concept of the Metal-Catalyzed α-Alkylation of Ketones

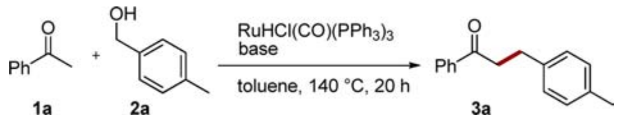


alcohols gave good yields of α-hydroxymethyl ketones (eq 1).[9b] Since this reaction involves an effective transfer dehydrogenation of primary alcohols to give aldehydes, we believed that this Ru-H catalyst would also be useful even for the α-alkylation of ketones. Herein we report the results.



Using RuHCl(CO)(PPh$_3$)$_3$ as a catalyst and acetophenone (**1a**) and 4-methylbenzyl alcohol (**2a**) as test substrates, we examined the α-alkylation of ketones under several conditions (Table 1). When **1a** was reacted with **2a** in the presence of 5 mol % of RuHCl(CO)(PPh$_3$)$_3$ and 1.5 equiv of potassium carbonate at 140 °C (bath temp) for 20 h, the desired α-alkylated ketone **3a** was formed in 7% yield (entry 1). After survey of several bases, we found that Cs$_2$CO$_3$ gave good yield of **3a** (entry 4). Catalyst loading as low as 1 mol % gave **3a** in 86% yield (entry 5). Even a reduced amount of Cs$_2$CO$_3$ (30 mol %) sufficed for the reaction (entry 6). A lower temperature (110 °C) resulted in

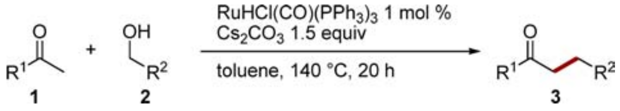
Table 1. Optimization of the Reaction Conditions[a]

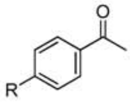
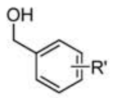
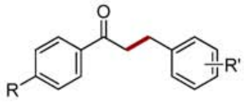
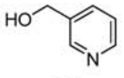
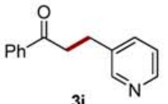
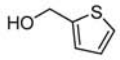
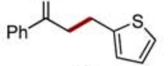
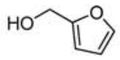
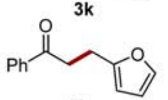
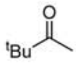
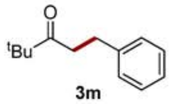
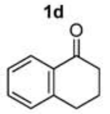
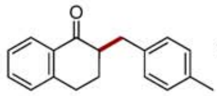
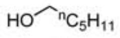
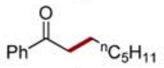
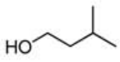
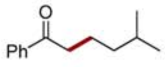
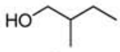
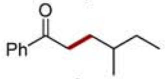
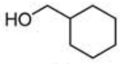
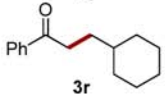


entry	cat. (mol %)	base (mol %)	yield[b] (%)
1	5	K$_2$CO$_3$ (150)	7[c]
2	5	Na$_2$CO$_3$ (150)	nd[d]
3	5	NEt$_3$ (150)	nd[d]
4	5	Cs$_2$CO$_3$ (150)	73
5	1	Cs$_2$CO$_3$ (150)	86
6	1	Cs$_2$CO$_3$ (30)	74
7[e]	1	Cs$_2$CO$_3$ (150)	14[c]
8[f]	1	Cs$_2$CO$_3$ (150)	69
9[f,g]	1	Cs$_2$CO$_3$ (150)	79

[a] Reaction conditions: **1a** (1.3 mmol), **2a** (1.0 mmol), RuHCl(CO)(PPh$_3$)$_3$, base, toluene (3 mL), 140 °C (bath temp). [b] Isolated yield. [c] NMR yield. [d] Not detected. [e] 110 °C (bath temp). [f] 5 h. [g] 1,10-phenanthroline (3 mol %) was used.

Table 2. RuHCl(CO)(PPh$_3$)$_3$-Catalyzed α-Alkylation Reactions of Ketones with Nonbenzylic Alcohols[a]



entry	ketone **1**	alcohol **2**	product **3**	yield (%)[b]
				
1	R = H **1a**	R′ = *p*-Me **2a**	**3a**	86
2	**1a**	= H **2b**	**3b**	92
3	**1a**	= *p*-Ph **2c**	**3c**	88
4	**1a**	= *m*-CF$_3$ **2d**	**3d**	75
5	**1a**	= *o*-MeO **2e**	**3e**	76
6	**1a**	= *m*-MeO **2f**	**3f**	82
7	**1a**	= *p*-MeO **2g**	**3g**	70
8	= *p*-MeO **1b**	= *p*-Me **2a**	**3h**	55
9	= *p*-Br **1c**	= *p*-Me **2a**	**3i**	87
10	**1a**	 **2h**	 **3j**	89
11	**1a**	 **2i**	 **3k**	71
12	**1a**	 **2j**	 **3l**	65
13[c]	 **1d**	**2b**	 **3m**	85
14	 **1e**	**2a**	 **3n**	64
15	**1a**	 **2k**	 **3o**	22
16[d]	**1a**	**2k**	**3o**	88
17[d]	**1a**	 **2l**	 **3p**	67
18[e]	**1a**	 **2m**	 **3q**	83
19[e]	**1a**	 **2n**	 **3r**	72

[a] Reaction conditions: ketone **1** (1.3 mmol), alcohol **2** (1.0 mmol), RuHCl(CO)(PPh$_3$)$_3$ (1 mol %), Cs$_2$CO$_3$ (1.5 mmol), toluene (3 mL), 140 °C (bath temp), 20 h. [b] Isolated yields. [c] KOH (1.5 mmol) was used instead of Cs$_2$CO$_3$. [d] 1,10-phenanthroline (Phen; 3 mol %) was used as an additive. [e] RuHCl(CO)(PPh$_3$)$_3$ (3 mol %) and Phen (6 mol %) were used.

lower conversion (entry 7). Although the reaction was not complete in 5 h (entry 8), acceleration of the reaction was observed with the addition of 1,10-phenanthroline as an additive (entry 9).

Having the optimized conditions in hand (Table 1, entry 5), we then examined the generality of the present α-alkylation of ketones, and the results are summarized in Table 2. α-Alkylation of acetophenone (**1a**) with a variety of substituted benzyl alcohols **2b**–**g** proceeded well to give the corresponding α-substituted ketones **3b**–**g** in good yields (entries 2–7). The reaction of *p*-methoxyacetophenone (**1b**) with **2a** gave **3h** in 55% yield due to a low conversion under the employed conditions (entry 8). In contrast, *p*-bromoacetophenone (**1c**) was alkylated in excellent yield (entry 9). Several hydroxymethyl heteroaryls such as 3-pyridinemethanol (**2h**) and 2-thiophenemethanol (**2i**) also reacted with acetophenone to give **3j** and **3k** in good yields, respectively (entries 10 and 11). Furfuryl alcohol (**2j**) gave the corresponding ketone **3l** in 65% yield (entry 12). Although the alkylation of pinacolone (**1d**) was sluggish under the standard conditions, the use of KOH in place of Cs_2CO_3 significantly promoted the reaction to deliver the corresponding ketone **3m** in 85% yield (entry 13). α-Tetralone (**1e**) was alkylated by **2a** to give **3n** in 64% yield (entry 14).

We also examined the alkylation of ketones using nonbenzylic primary alcohols; however, the results were poor. For example, when the alkylation of **1a** using 1-hexanol (**2k**) was carried out in the presence of 3 mol % of $RuHCl(CO)(PPh_3)_3$, the desired ketone **3o** was obtained in only 22% yield (entry 15). However, we were delighted to find that the addition of 1,10-phenanthroline (Phen) dramatically accelerated the reaction, thus delivering **3o** in 88% yield (entry 16). Other additives such as DPPB (40%), 2,2′-bipyridine (24%), and PCy_3 (43%) did not work as effectively as 1,10-phenanthroline. In a similar manner, branched alcohol **2l** and **2m** also particpated in the alkylation of **1a**, giving good yields of the corresponding ketones **3p** and **3q**, respectively (entries 17 and 18). The reaction of cyclohexanemethanol **2n** with **1a** gave the corresponding ketone **3r** in 72% yield (entry 19).

In summary, we have found that the α-alkylation reaction of ketones with primary alcohols can be effectively catalyzed by $RuHCl(CO)(PPh_3)_3$ in the presence of Cs_2CO_3 as a base. We also found that a catalytic amount of 1,10-phenanthroline dramatically promoted α-alkylation using nonbenzylic aliphatic alcohols. A detailed mechanistic study involving the precise role of 1,10-phenanthroline in the promotion of alkylation using aliphatic alcohols as well as synthetic applications of the present reactions is currently underway in this laboratory.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research on Innovative Areas (No. 2105) from the MEXT. T.F. acknowledges a Grant-in-Aid for Scientific Research (C) from JSPS for financial support.

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

The authors declare no competing financial interest.

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(9) For our recent work on $RuHCl(CO)(PPh_3)_3$-catalyzed transformation, see: (a) Fukuyama, T.; Okamoto, H.; Ryu, I. *Chem. Lett.* **2011**, *40*, 1453. (b) Denichoux, A.; Fukuyama, T.; Doi, T.; Horiguchi, J.; Ryu, I. *Org. Lett.* **2010**, *12*, 1. (c) Omura, S.; Fukuyama, T.; Murakami, Y.; Okamoto, H.; Ryu, I. *Chem. Commun.* **2009**, 6741. (d) Omura, S.; Fukuyama, T.; Horiguchi, J.; Murakami, Y.; Ryu, I. *J. Am. Chem. Soc.* **2008**, *130*, 14094. (e) Fukuyama, T.; Doi, T.; Minamino, S.; Omura, S.; Ryu, I. *Angew. Chem., Int. Ed.* **2007**, *46*, 5559. (f) Doi, T.; Fukuyama, T.; Minamino, S.; Ryu, I. *Synlett* **2006**, 3013. (g) Doi, T.; Fukuyama, T.; Horiguchi, J.; Okamura, T.; Ryu, I. *Synlett* **2006**, 721. (h) Doi, T.; Fukuyama, T.; Minamino, S.; Husson, G.; Ryu, I. *Chem. Commun.* **2006**, 1875.