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Ruthenium-catalyzed regioselective α-alkylation of ketones with primary alcohols

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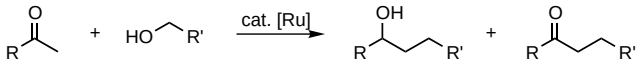
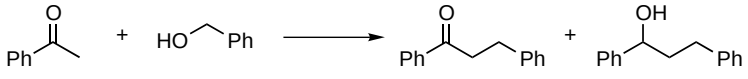
Abstract—Ketones are regioselectively alkylated with an array of primary alcohols in dioxane at 80°C in the presence of a catalytic amount of a ruthenium catalyst together with KOH and a hydrogen acceptor.

α-Alkylation of ketones has been known as a fundamental tool for a carbon–carbon σ-bond formation in synthetic organic chemistry.[1,2] The alkylation is generally achieved by the coupling between nucleophilic enolates (enolate equivalents) and electrophilic alkylating agents and regioselectivity is determined by initial enolate formation.[3] In connection with this report, during the course of our ongoing studies on ruthenium catalysis,[4–7] we recently found an unusual type of ruthenium-catalyzed transfer hydrogenation of ketones by primary alcohols.[8,9] The reaction gives mainly an unconventional transfer hydrogenated secondary alcohol accompanied by C–C coupling with concomitant formation of an alkylated ketone (Scheme 1). The preferential forma-



Scheme 1.

Table 1. Ruthenium-catalyzed α-alkylation of **1** with **2** under several conditions[a]



1 **2** **3** **4**

Entry	Hydrogen acceptor	Temp. (°C)	Time (h)	Yield[b] (%)	
				3	**4**
1	1-Dodecene	80	20	(82)	(2)
2	–	80	20	(70)	(14)
3	1-Dodecene	80	10	(61)	(6)
4	1-Dodecene	80	5	36	–[c]
5	1-Dodecene	50	20	25	–[c]
6[d]	–	180	20	(78)	(9)
7	1-Octyne	80	20	15	–[c]
8	Nitrobenzene	80	20	6	–[c]
9	1-Hexene	80	20	(79)	(2)

[a] *Reaction conditions*: **1** (1 mmol), **2** (1 mmol), hydrogen acceptor (1 mmol), $RuCl_2(PPh_3)_3$ (0.02 mmol), KOH (1 mmol), dioxane (3 ml).
[b] GLC yield. Isolated yield is shown in parentheses.
[c] Not determined.
[d] The reaction was carried out with autoclave.

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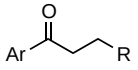
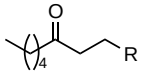
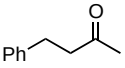
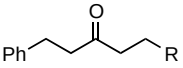
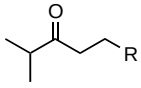
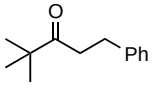
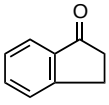
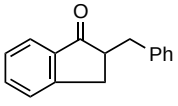
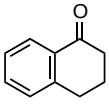
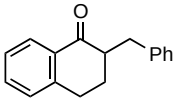
tion of alcohol to ketone may be due to the use of the molar ratio of alcohol/ketone = 3. This observation led us to seek an effective method for the ruthenium-catalyzed α-alkylation of ketones with primary alcohols. Herein we report on a ruthenium-catalyzed regioselective α-alkylation of ketones with primary alcohols in the presence of a hydrogen acceptor.

Table 1 shows optimization of the conditions for the α-alkylation of acetophenone (**1**) with benzyl alcohol (**2**). Treatment of an equimolar amount of **1** and **2** in dioxane in the presence of $RuCl_2(PPh_3)_3$ (2 mol%) and KOH together with 1-dodecene as hydrogen acceptor at 80°C for 20 h afforded 1,3-diphenylpropan-1-one (**3**) in 82% isolated yield with concomitant formation of further hydrogenated 1,3-diphenylpropan-1-ol (**4**, 2% yield) (entry 1). Only a trace amount of the direct transfer hydrogenation product, 1-phenylethanol was detected on GLC analysis of the crude reaction mixture.[10] On the other hand, when the reaction was carried out in the absence of 1-dodecene, the product **3** was produced in 70% yield along with considerable amount of **4** (14%) (entry 2). These results clearly indicate that 1-dodecene plays a role for the selectivity of **3** to **4**. The yield of **3** increases with prolonging the reaction time up to 20 h (entries 1, 3, 4). Lower reaction temperature resulted in lower yield of **3** (entry 5), but higher reaction temperature under the absence of 1-dodecene gave no significant change on the product yield and selectivity (entry 6). Other hydrogen acceptors such as 1-octyne and nitrobenzene deactivate the reaction itself (entries 7 and 8), but 1-hexene was effective as 1-dodecene for the yield and selectivity (entry 9).

Table 2. Ruthenium-catalyzed α-alkylation of ketones with primary alcohols[a]

Ketones	Alcohols	Products	Yield[b] (%)
			
Ar = Ph	R = Ph		82
Ar = Ph	R = 1-naphthyl		80
Ar = Ph	R = phenethyl		78
Ar = Ph	R = Pr		70
Ar = Ph	R = pentyl		78
Ar = Ph	R = *i*-Bu		80
Ar = 2-MeC_6H_4	R = Ph		81
Ar = 3-MeC_6H_4	R = Ph		79
Ar = 4-MeC_6H_4	R = Ph		78
Ar = 4-$MeOC_6H_4$	R = Ph		83
Ar = 4-FC_6H_4	R = Ph		76
Ar = 2-naphthyl	R = Ph		68
	R = phenethyl		55
	R = Pr		50
	R = phenethyl		59
	R = phenethyl		57
	R = Ph		48
	R = Ph		76
	R = Ph		52
	R = Ph		86

[a] Reaction conditions: ketone (1 mmol), primary alcohol (1 mmol), 1-dodecene (1 mmol), $RuCl_2(PPh_3)_3$ (0.02 mmol), KOH (1 mmol), dioxane (3 ml), 80 °C, for 20 h.

[b] Isolated yield.

Given the controlled conditions, with various ketones and primary alcohols the alkylation products were formed in the range of 48–86% yields with the minimal formation of coupled secondary alcohols (Table 2). From the reactions between **1** and several straight and branched primary alcohols, the corresponding alkylated ketones were produced in good yields. The alkylation was not significantly affected by the position and electronic nature of the substituent on the aromatic ring of ketones. In the case of dialkyl ketones, although the product yield was lower than that of the case of alkyl aryl ketones, the alkylation took place exclusively at less-hindered position over α-methylene and methine. Similar regioselectivity was observed by our recent reports[6] and others.[11] Benzo-fused cyclic ketones 1-indanone and 1-tetralone having only the methylene reaction site were readily alkylated with benzyl alcohol to give the corresponding products, whereas the reaction of cyclohexanone with primary alcohol afforded a complicated mixture on GLC analysis.

As the reaction pathway based on our recent report,[8] this involves a sequence such as oxidation of primary alcohol to aldehyde by a ruthenium, cross aldol reaction between the starting ketone and the aldehyde to produce α,β-unsaturated ketone, and selective reduction of the olefinic double bond of the unsaturated ketone. Although the role of 1-dodecene for the selectivity is not clear, it seems to both suppress further reduction of **3** to **4** by hydrogen transfer from solvent dioxane to 1-dodecene and reoxidize **4** back to **3** by transfer hydrogenation between **4** and 1-dodecene.[12,13] It is known that dioxane is used as a hydrogen donor in ruthenium- and rhodium-catalyzed transfer hydrogenation of olefins, aldehydes and ketones.[14]

General experimental procedure: a mixture of ketone (1 mmol), primary alcohol (1 mmol), 1-dodecene (1 mmol), $RuCl_2(PPh_3)_3$ (0.02 mmol) and KOH (1 mmol) in dioxane (3 ml) was placed in a 5 ml screw-capped vial and allowed to react at 80°C for 20 h. 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 thin layer chromatography (silica gel, ethyl acetate–hexane mixture) to give alkylated ketones.

In summary, we have shown that ketones can be regioselectively α-alkylated with various primary alcohols in the presence of a ruthenium catalyst and a hydrogen acceptor under a base. The present reaction will serve as an alternative α-alkylation route of ketones.

Acknowledgements

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