

## An Efficient Direct $\alpha$ -Alkylation of Ketones with Primary Alcohols Catalyzed by $[\text{Ir}(\text{cod})\text{Cl}]_2/\text{PPh}_3/\text{KOH}$ System without Solvent

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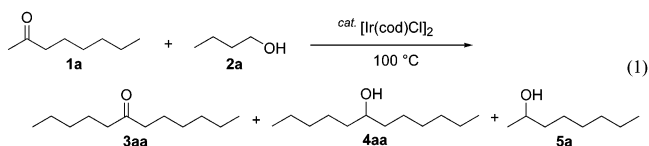
$\alpha$ -Alkylation of enolates derived from ketones with alkyl halides is one of the most important and frequently used methods in organic synthesis. During this reaction, however, the concurrent formation of undesirable waste salt is inherently unavoidable. In addition, treatment of unsymmetrical ketones with a base to generate enolates results in two possible enolate ions.<sup>1</sup> As a result, their subsequent alkylation leads to the formation of a mixture of  $\alpha$ - and  $\alpha'$ -alkylated products. If the  $\alpha$ -alkylation of enolates with alkyl halides can be replaced by the direct alkylation between ketones and alcohols, this method would provide a very useful green route to  $\alpha$ -alkylated ketones that does not produce any side products other than water. Recently, Cho et al. have reported the  $\alpha$ -alkylation of ketones with alcohols leading to  $\alpha$ -alkylated alcohols as major products. This reaction involves a Ru-catalyzed transformation of alcohols to aldehydes followed by a base-catalyzed aldol condensation of the parent ketones, with the formed aldehydes leading to  $\alpha,\beta$ -unsaturated ketones, which then undergo the hydrogenation to give saturated alcohols through  $\alpha$ -alkylated ketones.<sup>2a</sup> Hereafter, they showed that the same reaction is carried out in the presence of a hydrogen acceptor such as 1-dodecene to avoid the formation of  $\alpha$ -alkylated alcohols, since 1-dodecene is hydrogenated in preference to the  $\alpha$ -alkylated ketones formed by ruthenium dihydride.<sup>2b</sup>

Previously, we reported that iridium complexes such as  $[\text{Ir}(\text{cod})\text{Cl}]_2$  catalyze efficiently the selective transfer hydrogenation of  $\alpha,\beta$ -unsaturated carbonyl compounds with 2-propanol, giving saturated ketones.<sup>3</sup> In addition,  $[\text{Ir}(\text{cod})\text{Cl}]_2$  catalyzes an unusual exchange reaction between vinyl acetate and alcohols to give vinyl ethers.<sup>4</sup> By the use of  $[\text{Ir}(\text{cod})\text{Cl}]_2$  which catalyzes the transformation of alcohols to aldehydes, Williams et al. have reported the indirect Wittig reaction of alcohols.<sup>5</sup> Our attention has been focused on the unique catalysis of  $[\text{Ir}(\text{cod})\text{Cl}]_2$  to extend to the direct  $\alpha$ -alkylation of ketones with alcohols.

We have found that the selective  $\alpha$ -alkylation of ketones with alcohols is achieved under the influence of catalytic amounts of  $[\text{Ir}(\text{cod})\text{Cl}]_2$  and a base such as KOH without any solvent to give  $\alpha$ -alkylated ketones in good yields. This method provides a novel route to  $\alpha$ -alkylated ketones from ketones and alcohols without formation of any waste.

To confirm optimum reaction conditions, the reaction of 2-octanone (**1a**) with 1-butanol (**2a**) was chosen as a model reaction and carried out under various conditions (Table 1). The reaction of **1a** (2 mmol) with **2a** (4 mmol) in the presence of  $[\text{Ir}(\text{cod})\text{Cl}]_2$  (0.02 mmol), a ligand (0.04 mmol), and a base (0.2 mmol) at 100 °C for 4 h without any solvents afforded 6-dodecanone (80%) (**3aa**) along with small amounts of 5-decanol (2%) (**4aa**) and 2-octanol (**5a**) (7%) (run 1). It is interesting to note that the alkylation took place with complete regioselectivity at the less hindered side of **1a**. In the absence of a base under these conditions, no reaction took place except for the formation of a small amount of **5a** (run 2).

**Table 1.** Reaction of 2-Octanone (**1a**) with 1-Butanol (**2a**) Catalyzed by  $[\text{Ir}(\text{cod})\text{Cl}]_2$  and Base under Various Conditions<sup>a</sup>



run	ligand	base	conv. (%) <sup>b</sup>	product (%) <sup>c</sup>		
				3aa	4aa	5a
1	PPh <sub>3</sub>	KOH	96	80	2	7
2	PPh <sub>3</sub>		3	n.d.	n.d.	1
3	PPh <sub>3</sub>	CsOH	97	80	3	8
4	PPh <sub>3</sub>	NaOH	98	79	trace	8
5	PPh <sub>3</sub>	K <sub>2</sub> CO <sub>3</sub>	2	1	n.d.	2
6	PPh <sub>3</sub>	NEt <sub>3</sub>	2	n.d.	n.d.	2
7	PPh <sub>3</sub>	Ba(OH) <sub>2</sub>	44	27	1	15
8	PBu <sub>3</sub>	KOH	84	63	2	16
9	PCy <sub>3</sub>	KOH	82	48	2	15
10 <sup>d</sup>	dppe	KOH	85	28	2	26
11 <sup>d</sup>	dppp	KOH	92	23	3	27
12	P(OPh) <sub>3</sub>	KOH	7	2		5
13 <sup>e</sup>	PPh <sub>3</sub>	KOH	94	81	3	6
14 <sup>f</sup>	PPh <sub>3</sub>	KOH	90	76	1	7
15 <sup>g</sup>	PPh <sub>3</sub>	KOH	80	68	1	5

<sup>a</sup> **1a** (2 mmol) was reacted with **2a** (4 mmol) in the presence of  $[\text{Ir}(\text{cod})\text{Cl}]_2$  (0.02 mmol), base (0.2 mmol), and ligand (0.08 mmol) at 100 °C for 4 h without solvent. <sup>b</sup> Conversion of **1a**. <sup>c</sup> Based on **1a** used. <sup>d</sup> Ligand (0.04 mmol) was used. <sup>e</sup> At 110 °C. <sup>f</sup> At 90 °C. <sup>g</sup> **2a** (2 mmol) was used.



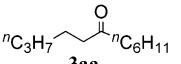

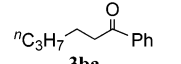

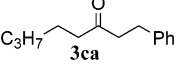

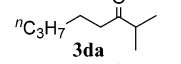

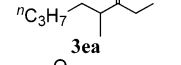

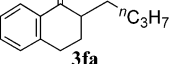

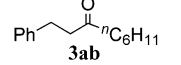
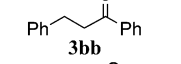

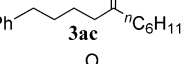

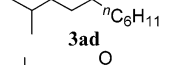

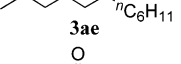

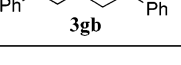
Although NaOH and CsOH served also as good bases, carbonates and an organic base such as triethylamine were inefficient as bases (runs 3–6). Ba(OH)<sub>2</sub> promoted slightly the alkylation to give **3aa** in a low yield (run 7). It was found that the reaction was considerably influenced by the ligands (runs 8–12). Among the ligands examined, PPh<sub>3</sub> was the best ligand followed by PBu<sub>3</sub> and PCy<sub>3</sub>, but bidentate ligands, dppe and dppp, promoted the transfer hydrogenation from **2a** to **1a** rather than the alkylation. When an electron-donating ligand such as P(OPh)<sub>3</sub> was added, no reaction took place. An equimolar reaction of **1a** and **2a** resulted in a slight decrease of **3aa** (run 15) (see Supporting Information).

The catalysis of several iridium complexes other than  $[\text{Ir}(\text{cod})\text{Cl}]_2$  is shown in Table 2. A cationic complex  $[\text{Ir}(\text{cod})_2]^+\text{BF}_4^-$  promoted the alkylation to some extent, but a considerable amount of Tishchenko product **5a** was formed (run 1).  $\text{IrCl}(\text{CO})(\text{PPh}_3)_2$  was found to slightly promote the alkylation, but the reaction was considerably retarded when a small amount of PPh<sub>3</sub> (4 mol %) was added to the  $\text{IrCl}(\text{CO})(\text{PPh}_3)_2$  (runs 2 and 3). It is thought that excess PPh<sub>3</sub> inhibits the coordination of alcohols to the iridium complex. In fact, even in the alkylation using the  $[\text{Ir}(\text{cod})\text{Cl}]_2$  catalyst, the addition of PPh<sub>3</sub> (8 mol %) resulted in a profound retardation of the reaction (run 4). A rhodium complex,  $[\text{Rh}(\text{cod})\text{Cl}]_2$ , was found to be less active than  $[\text{Ir}(\text{cod})\text{Cl}]_2$  under these conditions (run 5).

**Table 2.** Reaction of 2-Octanone (**1a**) with 1-Butanol (**2a**) Catalyzed by Several Ir and Rh Complexes<sup>a</sup>

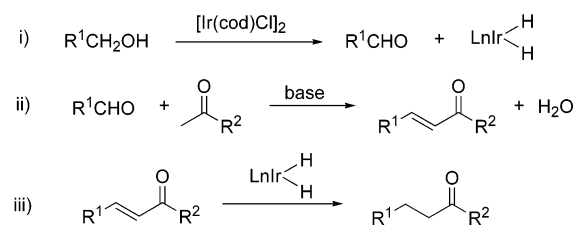
run	complex	conv. (%) <sup>b</sup>	product (%) <sup>c</sup>		
			3aa	4aa	5a
1	[Ir(cod) <sub>2</sub> ] <sup>+</sup> BF <sub>4</sub> <sup>-</sup>	84	31	2	20
2	IrCl(CO)(PPh <sub>3</sub> ) <sub>2</sub>	33	n.d.	n.d.	6
3 <sup>d</sup>	IrCl(CO)(PPh <sub>3</sub> ) <sub>2</sub>	54	11	trace	10
4 <sup>e</sup>	[Ir(cod)Cl] <sub>2</sub>	38	2	n.d.	6
5	Rh(cod)Cl] <sub>2</sub>	47	15	2	17

<sup>a</sup> Reaction conditions were the same as these of Table 1, Run 1.<sup>b</sup> Conversion of **1a**. <sup>c</sup> Based on **1a** used. <sup>d</sup> In the absence of PPh<sub>3</sub>. <sup>e</sup> In the presence of PPh<sub>3</sub> (0.16 mmol).**Table 3.** Reaction of Various Ketones with Alcohols Catalyzed by [Ir(cod)Cl]<sub>2</sub> and KOH<sup>a</sup>

Run	Ketone	Alcohol	Product (%) <sup>b</sup>
1			 80 (2)
2 <sup>c</sup>		<b>2a</b>	 88 (4)
3		<b>2a</b>	 71 (1)
4		<b>2a</b>	 80 (<1)
5 <sup>d</sup>		<b>2a</b>	 47 (<1)
6 <sup>d</sup>		<b>2a</b>	 88 (<1) [80] <sup>g</sup>
7	<b>1a</b>		 81 (3)
8	<b>1b</b>	<b>2b</b>	 86 (10)
9	<b>1a</b>		 81 (2)
10 <sup>e</sup>	<b>1a</b>		 96 (1)
11	<b>1a</b>		 84 (2)
12 <sup>f</sup>		<b>2b</b>	 86 (3) [79] <sup>g</sup>

<sup>a</sup> Reaction conditions were the same as these of Table 1, run 1.<sup>b</sup> Numbers in parentheses show the corresponding alcohol. <sup>c</sup> **1b** (8 mmol) was used. <sup>d</sup> KOH (0.6 mmol) was used. <sup>e</sup> KOH (0.4 mmol) was used. <sup>f</sup> **2b** (8 mmol) was used. <sup>g</sup> Isolated yield.

On the basis of these results, several ketones were allowed to react with alcohols under the selected reaction conditions (Table 3). The reaction of acetophenone (**1b**) with **2a** afforded 1-phenyl-1-hexanone (**3ba**) in 88% yield and a small amount of 1-phenyl-1-hexanol (**4ba**) (4%). In contrast to our results where **3ba** is obtained in high yield, the Ru-catalyzed reaction of **1b** with **2a** is reported to form a hydrogenated product, **4ba**, rather than **3ba**, as the principal product.<sup>2a</sup> 4-Phenyl-2-butanone (**1c**) reacted with **2a** to form 1-phenyl-3-octanone (**3ca**) (71%). For 3-methyl-2-butanone

**Scheme 1**

(**1d**), the coupling took place in the same way as **1a** to give 2-methyl-3-octanone (**3da**) (80%). Unlike methyl ketones, 3-pentanone (**1e**) reacted with some difficulty with **2a** to form 4-methyl-3-octanone (**3ea**) in 47% yield, but  $\alpha$ -tetralone (**1f**) was smoothly alkylated with **2a**, giving 2-butyl-1-tetralone (**3fa**) (88%). The reaction of **1a** and **1b** with benzyl alcohol (**2b**) under these conditions proceeded smoothly to form the corresponding alkylated products, 1-phenyl-3-nonanone (**3ab**) (81%) and 1,3-diphenyl-1-propanone (**3bb**) (86%), respectively. The alkylation of **1a** with substituted alcohols such as 2-methyl-1-propanol (**2d**) and 3-methyl-1-butanol (**2e**) resulted in 2-methyl-5-undecanone (**3ad**) (96%) and 2-methyl-6-dodecanone (**3ae**) (84%), respectively. When acetone (**1g**) was reacted with 4 equiv of **2b**,  $\alpha,\alpha'$ -alkylated product, 1,5-diphenyl-3-pentanone (**3gb**), was obtained in 86% yield without formation of  $\alpha$ -alkylated product (run 12).

Although a detailed reaction mechanism is not clear at this stage, the reaction is formally explained by the following sequential reactions through three key steps: (i) hydrogen transfer from alcohol to an iridium complex giving aldehyde and an iridium dihydride complex, (ii) base-catalyzed aldol condensation between the resulting aldehyde and ketone giving  $\alpha,\beta$ -unsaturated ketone, and (iii) selective hydrogenation of the  $\alpha,\beta$ -unsaturated ketone by an iridium dihydride complex in the reaction course, leading to an  $\alpha$ -alkylated ketone (Scheme 1). Although the in situ generation of an iridium dihydride complex from [Ir(cod)Cl]<sub>2</sub>, PPh<sub>3</sub>, and alcohol is not confirmed, various iridium dihydride complexes were prepared and are used in many reactions.<sup>6</sup> Since the present reaction is rationally explained by in situ generation of an iridium dihydride complex in the course of the reaction, it seems reasonable to assume the iridium dihydride complex as a key species in the present reaction.

In conclusion, we have developed the direct  $\alpha$ -alkylation method of ketones with alcohols catalyzed by iridium complexes without any solvents. This method provides a very convenient route to aliphatic ketones to which a carbonyl function can be introduced into the desired position by selecting the ketones and alcohols employed.

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**Supporting Information Available:** Experimental procedures and details of the reaction of **1a** and **2a** (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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