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Iridium-catalyzed reaction of enones with alcohols affording 1,3-diketones†

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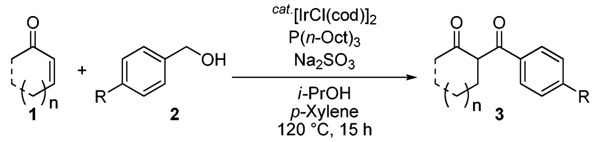
An iridium-catalyzed coupling reaction of alcohols with enones has been successfully developed providing access to 1,3-diketones with high selectivity in good yields. This reaction provides an atom-economical route to 1,3-diketones from readily available alcohols.

1,3-Diketones are an important class of compounds in organic synthesis and are widely employed as building blocks for the synthesis of a variety of heterocyclic compounds.[1] Classically, 1,3-diketones are prepared by the oxidation of aldol-type compounds, which are prepared from the reaction of the corresponding enolates with aldehydes[2] or by the acylation of acid chlorides/esters with ketone enolates.[3]

In contrast, Rh-catalyzed reductive aldol coupling reactions involving the hydrogenation of enones/enals to give β-hydroxyketones have attracted a great deal of interest and have been studied in great detail by Krische and coworkers.[4]

Furthermore, Ryu and coworkers have reported the Ru-catalyzed reaction of enals with alcohols leading to the formation of β-hydroxyketones as products.[5] In a recent publication, the same group reported the synthesis of 1,3-diketones by the Ru-catalyzed reaction of enals with aldehydes.[6]

It is well known that Ir and Ru complexes serve as efficient catalysts for hydrogen-transfer (also named as borrowing hydrogen) from alcohols to aldehydes.[7] To date, intense research efforts have been focused on both α-alkylation[8] and β-alkylation[9] reactions using alcohols as alkylating agents. The hydrogen-transfer methodology is also utilized in coupling reactions of alcohols and 2-alkynes to give homoallylic alcohols and α,β-enones by our group.[10] During the course of our own investigations into Ir-catalyzed transfer hydrogenation reactions using alcohols, we discovered an unprecedented route to 1,3-diketones by the reaction of enones (**1**) with alcohols (**2**) in the presence of an iridium complex catalyst (eqn (1)). This catalytic coupling process represents a highly atom-economical organic synthetic method using easily accessible starting materials.

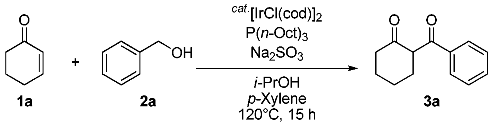


1 **2** **3**

(1)

The reaction of cyclohexenone (**1a**) and benzyl alcohol (**2a**) was employed as a model reaction and carried out under a variety of reaction conditions (Table 1). In one example, **1a**

Table 1 Ir-catalyzed reaction of cyclohexenone (**1a**) with benzyl alcohol (**2a**)[a]



1a **2a** **3a**

Entry	Ir-catalyst	Ligand (mol%)	Base (mol%)	Yield[b]/% **3a**
1	$[IrCl(cod)]_2$	P(*n*-Oct)$_3$ (20)	Na_2SO_3 (40)	82 (70)
2	$[IrCl(cod)]_2$	None	Na_2SO_3 (40)	n.d.[c]
3	$[IrCl(cod)]_2$	P(*n*-Bu)$_3$ (20)	Na_2SO_3 (40)	78
4	$[IrCl(cod)]_2$	PPh_3 (20)	Na_2SO_3 (40)	73
5	$[IrCl(cod)]_2$	$P(OPh)_3$ (20)	Na_2SO_3 (40)	Trace
6	$[IrCl(cod)]_2$	P(*n*-Oct)$_3$ (10)	Na_2SO_3 (40)	Trace
7	$[IrCl(cod)]_2$	P(*n*-Oct)$_3$ (30)	Na_2SO_3 (40)	70
8	$[IrCl(cod)]_2$	P(*n*-Oct)$_3$ (20)	None	71
9	$[IrCl(cod)]_2$	P(*n*-Oct)$_3$ (20)	$NaHCO_3$ (40)	67
10	$[IrCl(cod)]_2$	P(*n*-Oct)$_3$ (20)	Na_2SO_3 (20)	72
11	$[IrCl(cod)]_2$	P(*n*-Oct)$_3$ (20)	*t*-BuOK (40)	n.d.[c]
12[d]	$[IrCl(cod)]_2$	P(*n*-Oct)$_3$ (20)	Na_2SO_3 (40)	12
13[e]	$[IrCl(cod)]_2$	P(*n*-Oct)$_3$ (20)	Na_2SO_3 (40)	21
14[f]	$[IrCl(cod)]_2$	P(*n*-Oct)$_3$ (20)	Na_2SO_3 (40)	46
15	$[IrCl(coe)_2]_2$	P(*n*-Oct)$_3$ (20)	Na_2SO_3 (40)	39
16	$[Ir(OH)(cod)]_2$	P(*n*-Oct)$_3$ (20)	Na_2SO_3 (40)	7 (trace)[g]
17	$[Ir(OMe)(cod)]_2$	P(*n*-Oct)$_3$ (20)	Na_2SO_3 (40)	Trace
18	$[Cp^*IrCl_2]_2$	P(*n*-Oct)$_3$ (20)	Na_2SO_3 (40)	n.d.[c]

[a] Conditions: a mixture of **1a** (5 mmol) and **2a** (1 mmol) was reacted in the presence of an Ir-catalyst (0.2 mmol, 5 mol% based on **2a**), ligand (10–30 mol%), base (20–40 mol%), *i*-PrOH (3 mmol) and *p*-xylene (1 mL) at 120 °C for 15 h. [b] Yields were determined by GC based on the amount of **2a** used. The numbers in parentheses refer to isolated yields. [c] Not detected by GC. [d] **1a** (1 mmol) was used. [e] **1a** (2 mmol) was used. [f] The reaction was performed without *i*-PrOH. [g] The reaction was performed in the absence of base.

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† Electronic supplementary information (ESI) available: Experimental procedures and compound characterization data (^{1}H NMR, ^{13}C NMR). See DOI: 10.1039/c2cc32787b

(5 mmol) was reacted with **2a** (1 mmol) in the presence of a combination of $[IrCl(cod)]_2$ (0.05 mmol, 5 mol% based on **1a**), tri(*n*-octyl)phosphine (0.20 mmol) and isopropanol (3 mmol) in *p*-xylene (1 mL) at 120 °C for 15 h, providing 2-benzoyl cyclohexanone (**3a**) in 82% yield (entry 1). The addition of a phosphine ligand was found to be critical for the success of the reaction. Thus, in the absence of a phosphine ligand (entry 2), no **3a** was observed. With regard to the phosphine ligand, trialkylphosphines such as tri(*n*-octyl)phosphine and tri(*n*-butyl)phosphine were found to be the most suitable ligands (entries 1 and 3). Triphenyl phosphine showed comparable activity, whereas the use of triphenyl phosphite revealed low catalytic activity (entries 4 and 5, respectively). The optimized Ir : P ratio was determined to be 2. Smaller or larger amounts of tri(*n*-octyl)phosphine (10 mol%, Ir : P = 1 : 1 or 30 mol%, Ir : P = 1 : 3, respectively) resulted in lower yields of **3a** (entry 1 *vs.* entries 6 and 7). The reaction was found to proceed in substantial yield in the absence of a base (71%, entry 8). However, the addition of Na_2SO_3 (40 mol%, based on the amount of **2a**) increased the yield of **3a** to 82% (entry 1). The use of a weak base ($NaHCO_3$) or a smaller amount of Na_2SO_3 (20 mol%) did not reveal any additive effect (entries 9 and 10). In contrast, the use of a strong base, such as *t*-BuOK, completely deteriorated the catalytic activity and subsequent yield of **3a** (entry 11).

The reaction of an excess of **1a** (5 equiv.) with **2a** led to higher yield of **3a** (entry 1), owing to the formation of cyclohexanone from **1a**, which serves as a hydrogen acceptor in this reaction. Thus, the reaction of equimolar amounts of **1a** and **2a** under these conditions resulted in a decrease in the yield of **3a** (12%, entry 12). The addition of isopropanol (3 equiv.) to the reaction system effectively enhanced the reaction yield (entry 1 *vs.* entry 14). This result reveals that isopropanol serves as an external hydrogen atom donor for the iridium complex, assisting in the efficient formation of an iridium-hydride which is a key intermediate in this reaction (*vide infra*, eqn (2)). Furthermore, the reaction of **1a** with benzaldehyde did not lead to the formation of any 1,3-diketone (**3a**) under these conditions.

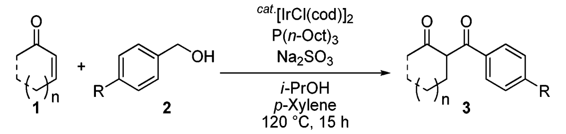
With regard to the iridium complex, $[IrCl(cod)]_2$ showed the best results and other selected iridium complexes, such as $[IrCl(coe)_2]_2$, $[Ir(OH)(cod)]_2$, $[Ir(OMe)(cod)]_2$ and $[Cp^*IrCl_2]_2$ which are known to function as efficient transfer hydrogenation catalysts, showed limited or no catalytic activities (entries 15–18). The reaction at 100 °C under these conditions gave **3a** in 45% yield. Needless to say, no **3a** was formed in the absence of an Ir complex. The use of a $[RhCl(cod)]_2$ complex in place of $[IrCl(cod)]_2$ under the conditions of entry 1, Table 1, did not afford **3a** at all.

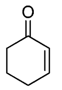
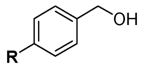
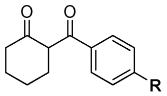
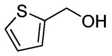
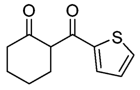
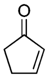
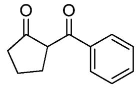
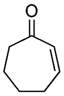
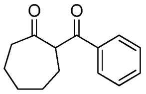
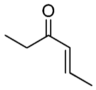
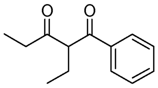
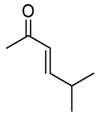
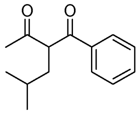
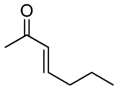
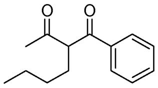
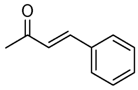
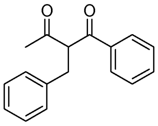
In the present reaction, various solvents were tolerated. According to the reaction conditions given in Table 1, the conditions associated with entry 1 in particular produced **3a** in a variety of yields depending upon the solvent used. Thus, toluene, 1,4-dioxane, mesitylene, DMF and DMSO gave yields of 74%, 72%, 56%, 44% and 40%, respectively.

The reactions of various enones (**1**) and alcohols (**2a**) were carried out under the optimized reaction conditions. The results are listed in Table 2. Various benzyl alcohol derivatives (**2a–2d**) and 2-thiophenemethanol (**2e**) were reacted with **1a** to give the corresponding 1,3-ketones (**3a–3e**) in good yields (entries 1–5). With regard to the enones, cyclopentenone (**1b**) and cycloheptenone (**1c**) were well tolerated under the reaction conditions (entries 6 and 7). In addition to cyclic enones, a variety of acyclic enones were also employed in the reaction, affording the corresponding products (entries 8–11).

Unfortunately, the use of aliphatic alcohols proved to be sluggish, providing the desired 1,3-diketones in less than 10% yield under the optimized conditions. The reaction with cinnamyl alcohol led to an intractable mixture under these conditions.

Table 2 Ir-catalyzed reactions of enones (**1**) with alcohols (**2**)[a]



Entry	Enone (**1**)	Alcohol (**2**)	Product (**3**)/yield[b] (%)
	 **1a**		
1	**1a**	R = H (**2a**)	70 (**3a**)
2	**1a**	R = CH_3 (**2b**)	77 (**3b**)
3	**1a**	R = OCH_3 (**2c**)	72 (**3c**)
4	**1a**	R = Cl (**2d**)	80 (**3d**)
5	**1a**	 **2e**	 79 (**3e**)
6	 **1b**	**2a**	 50 (**3f**)
7	 **1c**	**2a**	 32 (**3g**)
8	 **1d**	**2a**	 60 (**3h**)
9	 **1e**	**2a**	 49 (**3i**)
10	 **1f**	**2a**	 71 (**3j**)
11	 **1g**	**2a**	 73 (**3k**)

[a] Conditions: **1** (5 mmol) was allowed to react with **2a** (1 mmol) in the presence of $[IrCl(cod)]_2$ (0.05 mmol) combined with $P(n\text{-}Oct)_3$ (0.2 mmol), Na_2SO_3 (0.4 mmol) and *i*-PrOH (3 mmol) in *p*-xylene (1 mL) at 120 °C for 15 h. [b] Isolated yields.

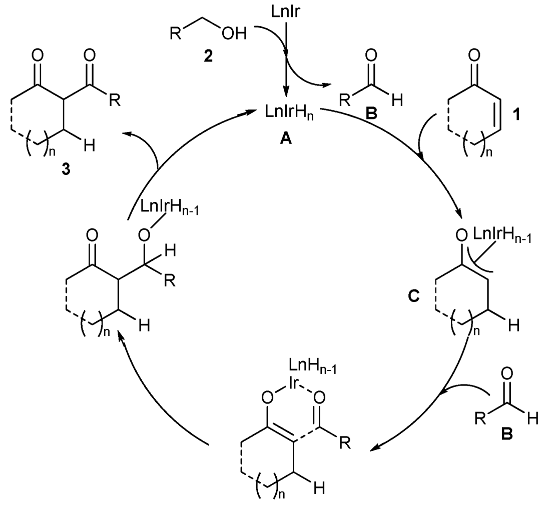
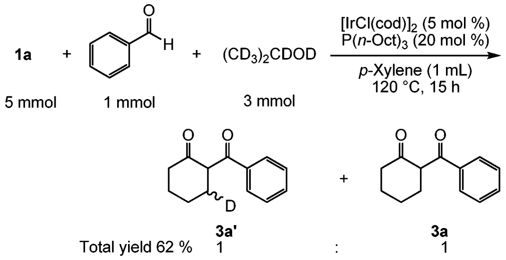


Fig. 1 A possible reaction pathway for the Ir-catalyzed formation of 1,3-diketones.

To further investigate the reaction mechanism, a deuterium labeling experiment was carried out. Thus, **1a** and benzaldehyde were reacted in the presence of isopropanol-d_8 under the conditions of entry 1 as documented in Table 1 (eqn (2)). Consequently, deuterium incorporation was observed at the β-alkenyl position of the product. The deuterium incorporation ratio at the β-alkenyl position was estimated to be 50% based on ^{1}H-NMR measurement.

This result strongly suggested that isopropanol serves as an effective hydrogen atom source for the formation of iridium-hydride.[7]



(2)

Based on these experimental results, the following reaction pathway was proposed as depicted in Fig. 1. The reaction is initiated by the formation of an iridium hydride (**A**) and an aldehyde (**B**) *via* hydrogen transfer from the alcohol to the iridium catalyst. Then enone (**1**) was inserted by an Ir–H bond of **A** to form the hydridooxa(π-allyl)iridium (**C**) as a key intermediate.[5] Subsequently, **C** reacts with aldehyde (**B**) to afford 1,3-diketones.

In conclusion, we have successfully developed an atom-economical synthesis for 1,3-diketones by the reaction of enones with alcohols in the presence of an Ir-catalyst. Further experimental investigations aimed at expanding the scope of this reaction are currently underway.

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