Homogeneous Catalysis

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Ruthenium Hydride Catalyzed Regioselective Addition of Aldehydes to Enones To Give 1,3-Diketones**

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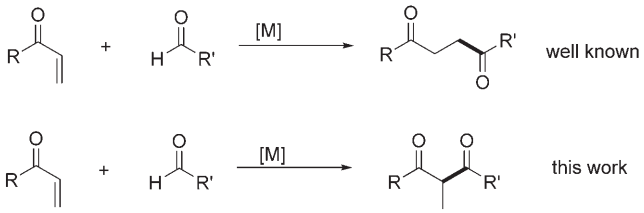
In memory of Yoshihiko Ito

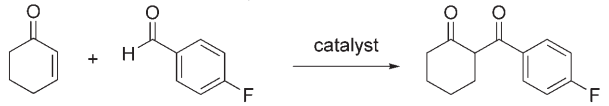
Despite the rapid progress in the development of metal-catalyzed cross-coupling reactions,[1] many challenges remain for the as yet unrealized classes of metal-catalyzed C–C bond-forming reactions. 1,3-Diketones are important basic building blocks, which are traditionally prepared by the acylation of ketone enolates, or by an aldol reaction of enolates with aldehydes followed by oxidation.[2,3] A transition-metal-based hydroacylation approach would give a short and atom-economic method to generate 1,3-diketones from readily available enones and aldehydes (Scheme 1, bottom). However, known examples of the hydroacylation of enones show that a reaction pathway that leads to 1,4-diketones is preferred (Scheme 1, top).[4] In principle, if the catalyst can support the three consecutive unit reaction processes of: 1) hydrometalation of enones to form metal enolates, 2) a cross-aldol reaction to form an alkoxymetal species, and 3) a β-metal hydride elimination of the resulting alkoxymetal species, it would give the desired 1,3-diketones with regeneration of the metal hydride. Herein we report an efficient method for the synthesis of 2-alkyl-substituted 1,3-diketones from readily available enones and aldehydes by using $[RuHCl(CO)(PPh_3)_3]$ as a catalyst.[5]

We surveyed a variety of ruthenium hydride complexes using the reaction of 2-cyclohexenone (**1d**) and *p*-fluorobenzaldehyde (**2c**) as a model system (Table 1). We thereby found that $[RuHCl(CO)(PPh_3)_3]$ catalyzed the required reaction of **1d** and **2c** effectively to give 2-(*p*-phenacyl)cyclohexanone **3f**. Thus, the reaction of **1d** with **2c** in the presence of 10 mol% $[RuHCl(CO)(PPh_3)_3]$ in benzene under reflux for 5 h gave **3f** in 75% yield after isolation by chromatography on silica gel (Table 1, entry 4). A phosphine-free ruthenium hydride system was unsuccessful as the catalyst (Table 1, entry 9).[6] Since PPh_3 is known to catalyze the Morita–Baylis–Hillman reaction,[7,8] we performed an experiment using 30 mol% PPh_3 under similar conditions (benzene, reflux, 5 h); the experiment gave neither **3f** nor the Morita–Baylis–Hillman product (Table 1, entry 10).[9]



Scheme 1. Two regiochemical pathways for the catalytic hydroacylation of aldehydes to enones.

Table 1: Effect of the Ru catalyst source on the reaction.[a]



1d **2c** **3f**

Entry	Catalyst	Quantity [mol%]	Solvent	*T* [°C]	Yield[b] **3f** [%]	Yield[b] **1d** [%]
1	$[RuH_2(PPh_3)_4]$	10	C_6H_6	80	0	87
2	$[RuHCl(PPh_3)_3]$	10	C_6H_6	80	0	94
3	$[RuH_2(CO)(PPh_3)_3]$	10	C_6H_6	80	9[c]	65
4	$[RuHCl(CO)(PPh_3)_3]$	10	C_6H_6	80	75[d]	0
5	$[RuHCl(CO)(PPh_3)_3]$	5	C_6H_6	80	49	35
6	$[RuHCl(CO)(PPh_3)_3]$	10	$(ClCH_2)_2$	80	83	40
7	$[RuHCl(CO)(PPh_3)_3]$	10	$tBuOCH_3$	55	10	75
8	$[Ru_3(CO)_{12}]$	10	C_6H_6	80	0	n.d.[e]
9	$[Ru_3(CO)_{12}]$/ $Et_2MeN{\cdot}HI$	10	C_6H_6	80	0	n.d.
10	PPh_3	30	C_6H_6	80	0	n.d.

[a] All reactions were performed using **1d** (0.4 mmol), **2c** (0.52 mmol), catalyst (5 or 10 mol%), and solvent (1.5 mL) for 5 h at reflux. [b] Yield based on GC analysis relative to dodecane as an internal standard. [c] Yield based on ^1H NMR analysis relative to $Cl_2CHCHCl_2$ as an internal standard. [d] Yield of isolated product. [e] Not determined.

We then examined the generality of the reaction by using a variety of unsaturated ketones and aldehydes (Table 2). The reaction of ethyl vinyl ketone (**1a**) with aldehydes **2a** and **2b** gave the corresponding 1,3-diketones **3a** and **3b** in good yields (Table 2, entries 1 and 2). The reaction was also effective for β-mono- and dialkyl-substituted enones such as **1b**, **1c**, and **1d** (Table 2, entries 3–6). On the other hand, the reaction of enone **1e**, which has an α-methyl substituent, failed to give the 2-ethyl-2-methyl-1,3-diketone (Table 2, entry 7); in this case, **1e** was recovered. Since the ruthenium hydride catalyst employed affects the isomerization of double bonds,[5a,10] we then tested enones with a remote C–C double

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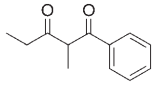
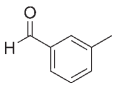
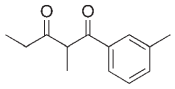
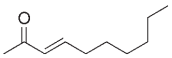
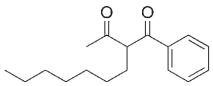
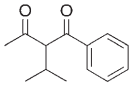
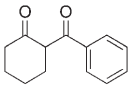
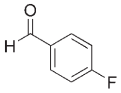
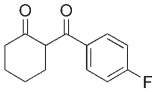
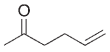
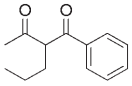
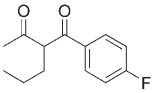
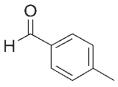
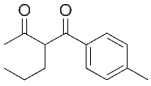
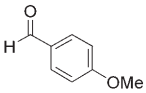
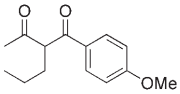
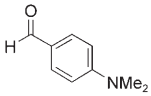
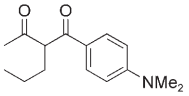
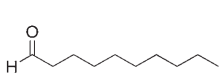
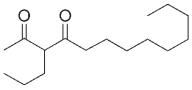
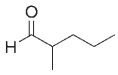
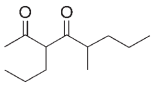
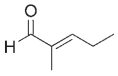
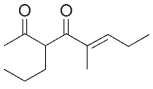
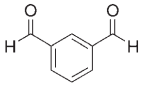
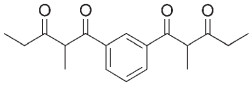
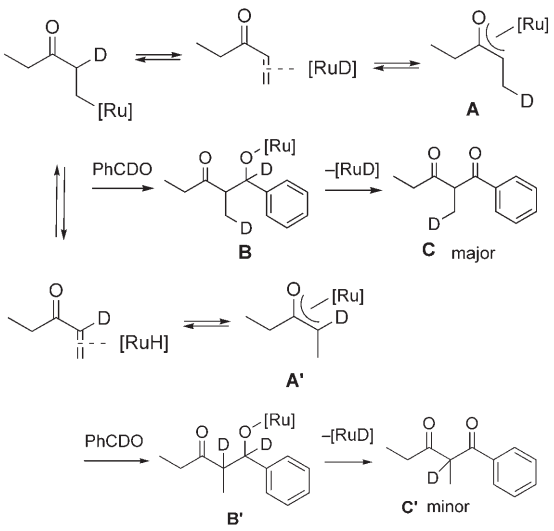
Table 2: Synthesis of β-diketones by a RuH-catalyzed regioselective addition of aldehydes to enones.[a]

Entry	Enones **1**		Aldehydes **2**		1,3-Diketones **3**		Yield [%][b]
1		**1a**		**2a**		**3a**	76
2		**1a**		**2b**		**3b**	72
3		**1b**		**2a**		**3c**	64
4		**1c**		**2a**		**3d**	73
5		**1d**		**2a**		**3e**	75[c]
6		**1d**		**2c**		**3f**	75[c]
7		**1e**		**2a**	n.r.[f]		
8		**1f**		**2a**		**3g**	92
9		**1f**		**2c**		**3h**	83
10		**1f**		**2d**		**3i**	85
11		**1f**		**2e**		**3j**	91
12		**1f**		**2f**		**3k**	95
13		**1f**		**2g**		**3l**	66[c]
14		**1f**		**2h**		**3m**	69[d]
15		**1f**		**2i**		**3n**	91
16[e]		**1a**		**2j**		**3o**	77[c,d]

[a] General conditions: enone **1** (1 mmol), aldehyde **2** (1.3 mmol), $[RuHCl(CO)(PPh_3)_3]$ (0.1 mmol), C_6H_6 (3.75 mL), reflux, 5 h. [b] Yields of isolated products after column chromatography on silica gel. [c] Obtained as a mixture of keto and enol forms. For details, see the Supporting Information. [d] d.r. = ca. 1:1 (^{13}C NMR). [e] 2.3 equivalents of **1a** and 20 mol% of catalyst were used. [f] No reaction.

bond, such as **1f**, in the hope that migration of the double bond would be followed by a coupling reaction to give 1,3-diketones. Indeed we were able to obtain good yields of 1,3-diketones by an alkene isomerization/dehydrogenative aldol reaction sequence (Table 2, entries 8–12). Aliphatic aldehydes **2g** and **2h** as well as α,β-unsaturated aldehyde **2i** were effective for the synthesis of 1,3-diketones (Table 2, entries 13–15). We examined the reaction of 2.3 equivalents of **1a** with dialdehyde **2j** in the hope of obtaining a three-component coupling product (Table 2, entry 16). As hoped,



Scheme 2. Possible reaction mechanism.

the envisaged tetracarbonyl compound **3o** was obtained (77% yield).

To get some insight into the mechanism, we carried out a separate experiment using [D]benzaldehyde (**2a′**). Deuterium was introduced mainly at the β-carbon atom of the enone (65%), which lends support for the proposed mechanism, however, deuterium incorporation at the α-carbon atom was also observed (35%). This finding may suggest that a hydroruthenation step leading to β-Ru ketones also exists in rapid equilibrium, which allows for the introduction of deuterium into the α-position of **1a** by a back β-hydride elimination (Scheme 2). Thus, the hydroruthenation of enones gives two types of ruthenium enolates, **A** and **A′**,[11,12] which then undergo an aldol reaction with the aldehydes to give β-keto alkoxyruthenium complexes **B** and **B′**. A β-elimination then takes place to give the 1,3-diketones **C** and **C′**, with regeneration of the ruthenium hydride catalyst for use in further reactions.

In summary, we have reported a novel regioselective addition reaction of aldehydes to enones, which provides an atom-economic and straightforward access to a wide variety of 2-alkyl-substituted 1,3-diketones. Synthetic applications of the present reaction as well as detailed mechanistic studies are currently underway.

Experimental Section

General procedure for the synthesis of 2-substituted 1,3-diketones catalyzed by $[RuHCl(CO)(PPh_3)_3]$: A mixture of ethyl vinyl ketone (**1a**; 86 mg, 1.03 mmol), benzaldehyde (**2a**; 138 mg, 1.3 mmol), and $[RuHCl(CO)(PPh_3)_3]$ (96.0 mg, 0.1 mmol) in benzene (3.75 mL) was stirred at reflux for 5 h under nitrogen. Purification by column chromatography on silica gel using 2% AcOEt in hexane as the eluent gave 2-propanoylpropiophenone (**3a**) (149 mg, 76%).

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