Angewandte Chemie

Homogeneous Catalysis

DOI: 10.1002/anie.200701005

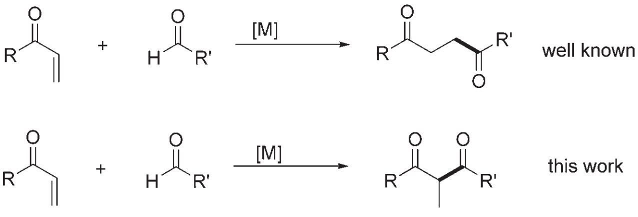
Ruthenium Hydride Catalyzed Regioselective Addition of Aldehydes to Enones To Give 1,3-Diketones**

*Takahide Fukuyama, Takashi Doi, Satoshi Minamino, Sohei Omura, and Ilhyong Ryu**

In memory of Yoshihiko Ito

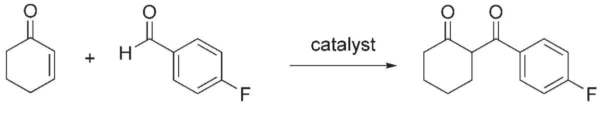
Despite the rapid progress in the development of metal-catalyzed cross-coupling reactions,[1] many challenges remain for the as yet unrealized classes of metal-catalyzed C−C bond-forming reactions. 1,3-Diketones are important basic building blocks, which are traditionally prepared by the acylation of 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$_6$H$_6$	80	0	87
2	[RuHCl(PPh$_3$)$_3$]	10	C$_6$H$_6$	80	0	94
3	[RuH$_2$(CO)(PPh$_3$)$_3$]	10	C$_6$H$_6$	80	9[c]	65
4	[RuHCl(CO)(PPh$_3$)$_3$]	10	C$_6$H$_6$	80	75[d]	0
5	[RuHCl(CO)(PPh$_3$)$_3$]	5	C$_6$H$_6$	80	49	35
6	[RuHCl(CO)(PPh$_3$)$_3$]	10	(ClCH$_2$)$_2$	80	83	40
7	[RuHCl(CO)(PPh$_3$)$_3$]	10	*t*BuOCH$_3$	55	10	75
8	[Ru$_3$(CO)$_{12}$]	10	C$_6$H$_6$	80	0	n.d.[e]
9	[Ru$_3$(CO)$_{12}$]/ Et$_2$MeN·HI	10	C$_6$H$_6$	80	0	n.d.
10	PPh$_3$	30	C$_6$H$_6$	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 ^{1}H NMR analysis relative to Cl$_2$CHCHCl$_2$ 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

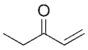
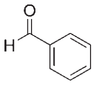
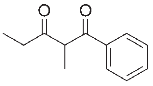
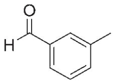
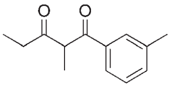
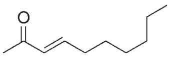
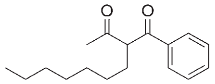
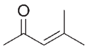
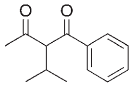
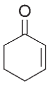
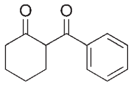
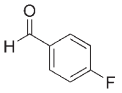
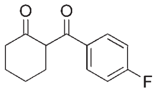
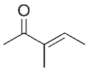
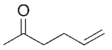
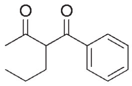
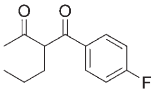
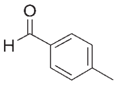
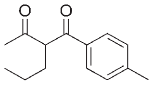
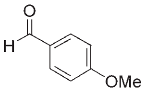
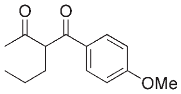
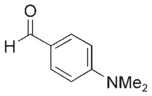
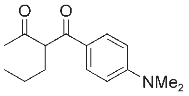
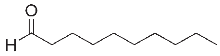
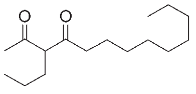
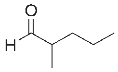
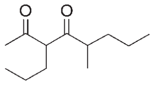
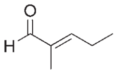
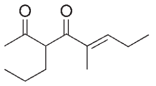
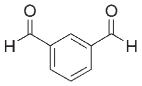
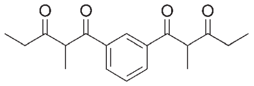
---

[*] Dr. T. Fukuyama, Dr. T. Doi, S. Minamino, S. Omura, Prof. Dr. I. Ryu
Department of Chemistry, Graduate School of Science
Osaka Prefecture University
Sakai, Osaka 599-8531 (Japan)
Fax: (+81) 72-254-9695
E-mail: ryu@c.s.osakafu-u.ac.jp

[**] I.R. acknowledges a Grant-in-Aid for Scientific Research from MEXT Japan and JSPS.

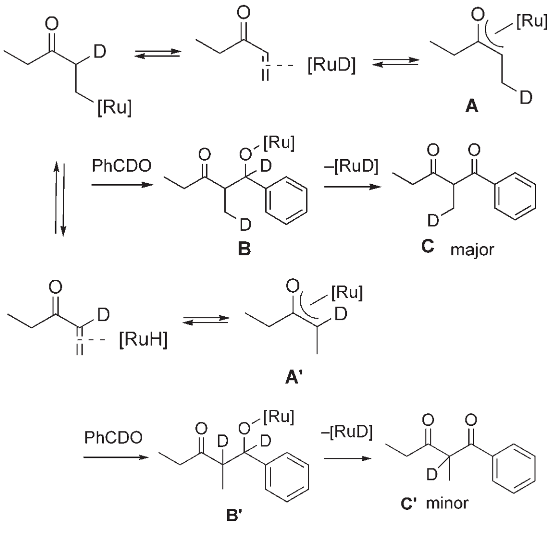
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

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$_6$H$_6$ (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 $[\mathrm{RuHCl(CO)(PPh_3)_3}]$: A mixture of ethyl vinyl ketone (**1a**; 86 mg, 1.03 mmol), benzaldehyde (**2a**; 138 mg, 1.3 mmol), and $[\mathrm{RuHCl(CO)(PPh_3)_3}]$ (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%).

Received: March 7, 2007

Keywords: addition · aldehydes · enones · homogeneous catalysis · ruthenium

---

[1] a) *Transition Metals for Organic Synthesis, Vol. 1 and 2* (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **1998**; b) *Applied Homogeneous Catalysis with Organometallic Compounds, Vol. 1 and 2* (Eds.: B. Cornils, W. A. Herrmann), VCH, Weinheim, **1996**.

[2] For recent work on the preparation of 1,3-diketones, see a) S. Kamijo, G. B. Dudley, *Org. Lett.* **2006**, *8*, 175; b) C. Wiles, P. Watts, S. J. Haswell, E. Pombo-Villar, *Tetrahedron Lett.* **2002**, *43*, 2945; c) V. Fargeas, M. Baalouch, E. Metay, J. Baffreau, D. Ménard, P. Gosselin, J.-P. Bergé, C. Barthmeuf, J. Lebreton, *Tetrahedron* **2004**, *60*, 10359; d) Z. Shen, B. L. Lu, Y. Zhang, *Tetrahedron Lett.* **2005**, *46*, 8785; e) K.-H. Park, L. J. Cox, *Tetrahedron Lett.* **2003**, *44*, 1067; f) K. Miura, M. Tojino, N. Fujisawa, A. Hosomi, I. Ryu, *Angew. Chem.* **2004**, *116*, 2477; *Angew. Chem. Int. Ed.* **2004**, *43*, 2423; see also the original work: g) G. Stork, R. Terrell, *J. Am. Chem. Soc.* **1954**, *76*, 2029.

[3] For recent methods for preparing 2-alkyl-substituted 1,3-diketones based on the catalytic alkylation of 1,3-diketones, see a) Z. Li, C. J. Li, *J. Am. Chem. Soc.* **2006**, *128*, 56; b) X. Yao, C. J. Li, *J. Am. Chem. Soc.* **2004**, *126*, 6884; c) X. Yao, C. J. Li, *J. Org. Chem.* **2005**, *70*, 5752; d) T. Pei, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2001**, *123*, 11290.

[4] For examples of transition-metal-catalyzed hydroacylation of enones leading to 1,4-diketones, see a) M. C. Willis, S. Sapmaz, *Chem. Commun.* **2001**, 2558; b) E.-A. Jo, C.-H. Jun, *Eur. J. Org. Chem.* **2006**, 2504.

[5] For our previous work on the use of the ruthenium hydride catalyst, see a) T. Doi, T. Fukuyama, S. Minamino, G. Husson, I. Ryu, *Chem. Commun.* **2006**, 1875; b) T. Doi, T. Fukuyama, J. Horiguchi, T. Okamura, I. Ryu, *Synlett* **2006**, 721; c) T. Doi, T. Fukuyama, S. Minamino, I. Ryu, *Synlett* **2006**, 3013.

[6] T. Fukuyama, Y. Higashibeppu, R. Yamaura, I. Ryu, *Org. Lett.* **2007**, *9*, 587.

[7] Using a similar system comprising α,β-unsaturated ketones, aldehydes, and $[\mathrm{RuH_2(PPh_3)_4}]$ under neat conditions, a Morita–Baylis—Hillman-type reaction was reported to take place, with $\mathrm{PPh_3}$ playing a role, see S. Sato, I. Matsuda, M. Shibata, *J. Organomet. Chem.* **1989**, *377*, 347.

[8] For a system using $\mathrm{PPh_3}$ and *p*-nitrophenol, see M. Shi, Y.-H. Liu, *Org. Biomol. Chem.* **2006**, *4*, 1468.

[9] We thank one of the referees for calling our attention to the mechanistic possibility in our system.

[10] a) H. Wakamatsu, M. Nishida, N. Adachi, M. Mori, *J. Org. Chem.* **2000**, *65*, 3966; b) S. Krompiec, M. Pigulla, W. Szczepankiewicz, T. Bieg, N. Kuznik, K. Leszczynska-Sejda, M. Kubicki, T. Borowiak, *Tetrahedron Lett.* **2001**, *42*, 7095; c) N. Kuznik, S. Krompiec, T. Bieg, S. Baj, K. Skutil, A. Chrobok, *J. Organomet. Chem.* **2003**, *665*, 167.

[11] For examples of catalytic transformations based on ruthenium enolates, see a) S.-I. Murahashi, T. Naota, H. Taki, M. Mizuno, H. Takaya, S. Komiya, Y. Mizuho, N. Oyasato, M. Hiraoka, M. Hirano, A. Fukuoka, *J. Am. Chem. Soc.* **1995**, *117*, 12436; b) R. Uma, M. Davies, C. Crévisy. R. Grée, *Tetrahedron Lett.* **2001**, *42*, 3069; c) B. M. Trost A. B. Pinkerton, *J. Am. Chem. Soc.* **2000**, *122*, 8081; d) S. Chang, Y. Na, E. Choi, S. Kim, *Org. Lett.* **2001**, *3*, 2089; e) H. Wang, M. Watanabe, T. Ikariya, *Tetrahedron Lett.* **2005**, *46*, 963.

[12] For isolated ruthenium enolate complexes, see a) J. F. Hartwig, R. A. Andersen, G. B. Bergman, *J. Am. Chem. Soc.* **1990**, *112*, 5670; b) J. F. Hartwig, R. G. Bergman, R. A. Andersen, *Organometallics* **1991**, *10*, 3326; c) B. T. Tasley, M. Rapta, R. J. Kulawiec, *Organometallics* **1996**, *15*, 2852.