

## Palladium-Catalyzed Acylation Reactions of $\alpha,\beta$ -Unsaturated Ketones with Acylzirconocene Chloride: Remarkable Control of 1,2- and 1,4-Selectivity by the Catalyst

Yuji Hanzawa,\* Nobuhito Tabuchi and Takeo Taguchi\*

School of Pharmacy, Tokyo University of Pharmacy and Life Science  
1432-1 Horinouchi, Hachioji, Tokyo 192-0392, Japan

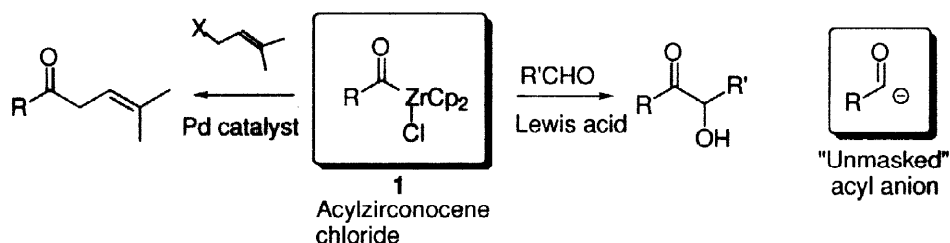
Received 16 July 1998; revised 24 August 1998; accepted 28 August 1998

**Abstract:** Palladium-catalyzed reactions of  $\alpha,\beta$ -unsaturated ketones with acylzirconocene chloride showed not only an efficient acyl transfer to  $\alpha,\beta$ -unsaturated ketones but also a remarkable regiochemical control by selecting  $\text{PdCl}_2(\text{Ph}_3)_2$  or  $\text{Pd}(\text{OAc})_2$ .

© 1998 Elsevier Science Ltd. All rights reserved.

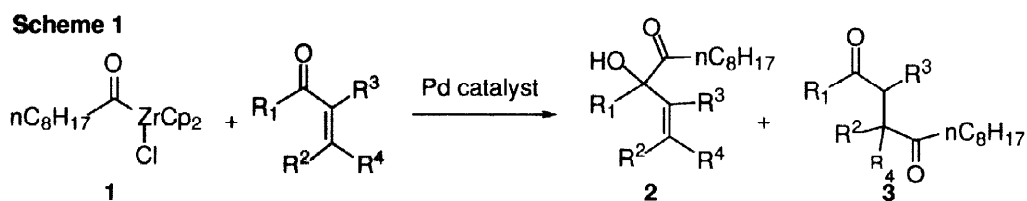
**Keywords:** Acylation; Michael reactions; Palladium and compounds; Zirconium and compounds

Recently, we devoted much time to exploring new reactions of easily accessible acylzirconocene chloride **1**, and reported the efficient formation of  $\alpha$ -ketol derivatives through Lewis acid-mediated reactions of **1** with aldehydes.<sup>1</sup> These results imply that the acyl group of **1** reacts as an “unmasked” acyl anion which is a convenient and attractive species in organic synthesis.<sup>2</sup> The reactivity of the acyl group in **1** as an “unmasked” acyl anion was also confirmed in the palladium  $[\text{PdCl}_2(\text{PPh}_3)_2]$ -catalyzed coupling reactions with organic halides and/or allylic acetates.<sup>3</sup> As we have noted previously, *acylzirconocene chloride 1 is unreactive toward carbonyls other than aldehydes under the Lewis acid-mediated conditions.*<sup>1</sup>



In the literature,<sup>4</sup> reactions of  $\alpha,\beta$ -unsaturated ketones with acylate transition metal complexes have been reported to give 1,4-dicarbonyls through a Michael-type addition of the acyl anion. Although these reagents constitute useful transformations of organic molecules, there is a serious drawback in the preparation of acylate transition metal complexes due to the high toxicity of the starting metal carbonyls such as nickel carbonyl, etc. In our continuous effort in acylzirconocene chloride **1** chemistry, we found that *the reactions of 1 (R =  $n\text{C}_8\text{H}_{17}$ ) with  $\alpha,\beta$ -unsaturated ketones did proceed efficiently to give acylated products in the presence of a catalytic amount of a palladium complex and, furthermore, the catalyst showed a striking effect on the selectivity for 1,2- and 1,4-acylated products (2 and 3) (Scheme 1).* In this communication, we describe the scope of the palladium-catalyzed regioselective acylation of  $\alpha,\beta$ -unsaturated ketones with **1** (R =  $n\text{C}_8\text{H}_{17}$ ). The results of the reactions

of **1** ( $R = nC_8H_{17}$ ) with  $\alpha,\beta$ -unsaturated ketones in the presence of Pd(II) catalyst [ $PdCl_2(PPh_3)_2$  or  $Pd(OAc)_2$ ] in toluene or  $Et_2O$ -THF (2 : 1) are listed in Table 1.



**Table 1.** Pd-catalyzed reactions of **1** ( $R = nC_8H_{17}$ ) with  $\alpha,\beta$ -unsaturated ketones

Entry	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	R <sup>4</sup>	Conditions <sup>a</sup>	product <sup>b</sup>	Yield (%) <sup>c</sup>
1	—(CH <sub>2</sub> ) <sub>2</sub> —		H	H	A	complex mixture	
2					B	<b>3</b>	70
3	—(CH <sub>2</sub> ) <sub>3</sub> —		H	H	A	<b>2</b>	81
4					B	<b>3</b>	55
5	—(CH <sub>2</sub> ) <sub>3</sub> —		H	CH <sub>3</sub>	A	<b>2</b>	21
6					B	<b>3</b>	47
7	—(CH <sub>2</sub> ) <sub>4</sub> —		H	H	A	<b>2</b>	77
8					B	<b>3</b>	60
9	nC <sub>4</sub> H <sub>9</sub>	H	H	CH <sub>3</sub>	A	<b>2</b>	75
10					B	<b>3</b>	97
11	CH <sub>3</sub>	H	H	Ph	A	<b>2</b>	95
12					B	<b>3</b>	96
13	Ph	H	H	CH <sub>3</sub>	A	<b>2</b>	91
14					B	<b>3</b>	96
15	Ph(CH <sub>2</sub> ) <sub>2</sub>	H	H	H	A	<b>2 + 3</b> <sup>d</sup>	76 <sup>e</sup>
16					B <sup>f</sup>	<b>3</b>	78
17	Ph(CH <sub>2</sub> ) <sub>2</sub>	H	CH <sub>3</sub>	H	A	<b>2</b>	87
18					B	<b>3</b>	98
19	Ph	CH <sub>3</sub>	H	CH <sub>3</sub>	A	no reaction	
20					B	no reaction	

<sup>a</sup> A:  $\alpha,\beta$ -Unsaturated ketone (1 mmol), **1** (1.5 mmol),  $PdCl_2(PPh_3)_2$  (5 mol%) in toluene (15 mL) at ambient temperature for 20 h. B:  $\alpha,\beta$ -Unsaturated ketone (1 mmol), **1** (2.0 mmol),  $Pd(OAc)_2$  (10 mol%) and  $BF_3 \cdot OEt_2$  (1 mmol) in  $Et_2O$ -THF (2 : 1) (15 mL) at 0 °C for 12 h. <sup>b</sup> Ratios of **2/3** or **3/2** were greater than 95% by NMR analysis of the crude reaction mixture except for entry 15. <sup>c</sup> Isolated yields. <sup>d</sup> **2** : **3** = 1 : 1.2. <sup>e</sup> Combined yield. <sup>f</sup>  $BF_3 \cdot OEt_2$  was not used.

It should be mentioned that the reactions of simple ketone and/or the  $\gamma,\delta$ -unsaturated ketone with **1** ( $R = nC_8H_{17}$ ) in the presence of a palladium catalyst did not give an acylation product.<sup>5</sup> The 1,2- and 1,4-selectivity in the acylation of  $\alpha,\beta$ -unsaturated ketones is heavily dependent on the palladium catalyst. Thus, the use of  $PdCl_2(PPh_3)_2$  (5 mol%) in toluene (conditions A) gave carbonyl acylation products **2** (1,2-selective) while the use of  $Pd(OAc)_2$  (10 mol%) in  $Et_2O$ -THF (2 : 1) (conditions B) gave  $\beta$ -acyl adducts **3**, 1,4-dicarbonyls, (1,4-selective).<sup>6</sup> Under both reaction conditions A and B, products **2** and **3** are obtained in mostly good to excellent yields. It is curious that the reaction of cyclopentenone with **1** ( $R = nC_8H_{17}$ ) gave a complex reaction mixture under the conditions A (entry 1) while the 1,4-product **3** was obtained in good yield under the conditions B (entry 2). Although a reasonable explanation for this observation is not available yet, this is the first example of acylzirconocene chloride as an acyl Michael donor. Interestingly, an introduction of substituents at the  $\beta,\beta'$ -positions of  $\alpha,\beta$ -unsaturated ketone retards not only the formation of **3** but also the formation of **2** (entries 19, 20). In the case of non-substituted  $\alpha,\beta$ -unsaturated ketone, a considerable amount of 1,4-product **3** along with 1,2-product **2** was obtained under the conditions A (entry 15). Use of nickel complexes  $[Ni(acac)_2]$  and other palladium complexes  $[Pd(Ph_3)_4]$ ,  $Pd_2(dba)_3-PPh_3$ ,  $Pd(acac)_2$ -DIBAL or  $PdCl_2(dppe)$  as a catalyst gave less satisfactory yields and ratios of the products.<sup>7</sup> It is worth mentioning that the addition of  $BF_3 \cdot OEt_2$  (1 equiv with respect to  $\alpha,\beta$ -unsaturated ketones) to a mixture of  $\alpha,\beta$ -unsaturated ketones and  $Pd(OAc)_2$  (10 mol%) in  $Et_2O$ -THF (2 : 1) improved the yield of the 1,4-dicarbonyl products **3**.<sup>8</sup> In  $PdCl_2(PPh_3)_2$ -catalyzed reactions (conditions A), the addition of  $BF_3 \cdot OEt_2$  and/or the use of  $Et_2O$ -THF (2 : 1) as a solvent did not alter the 1,2-regioselectivity or the yields of the products **2**. A conjugated ester such as methyl cinnamate was inert under the same reaction conditions. Although the present reaction revealed that the acylzirconocene chloride species **1** ( $R = nC_8H_{17}$ )<sup>9</sup> can be enrolled as a very handy substitute for toxic acylate metal carbonyl complexes, we must await further study to explain the alteration in the regioselectivity by changing the palladium catalyst from  $PdCl_2(PPh_3)_2$  to  $Pd(OAc)_2$  and the role of  $BF_3 \cdot OEt_2$  as a co-additive.

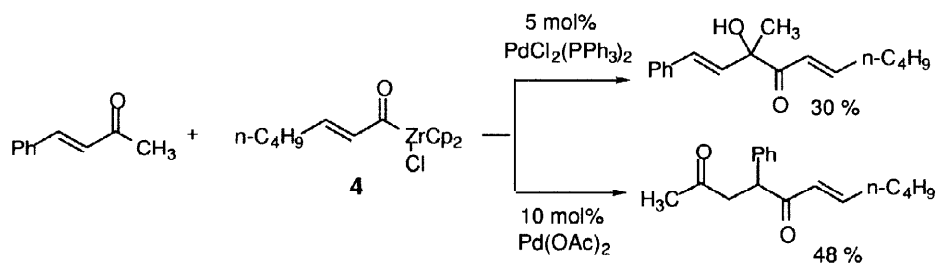
*Typical experimental procedure:* (Conditions A); Under an argon atmosphere, to a suspension of  $Cp_2ZrHCl$  (1.5 mmol) in  $CH_2Cl_2$  (6 mL) was added 1-octene (3 mmol) and the mixture was stirred for 0.5 h at ambient temperature. After the mixture was stirred under CO atmosphere for 2 h, the solution was concentrated under vacuum to dryness to give crystals of **1** ( $R = nC_8H_{17}$ ). To the crystals was added toluene (15 mL),  $\alpha,\beta$ -unsaturated ketone (1 mmol) and  $PdCl_2(PPh_3)_2$  (5 mol%) at ambient temperature and the mixture was stirred at the same temperature for 20 h. The reaction mixture was treated with aqueous  $NaHCO_3$  and extracted with ether (3 x 15 mL). The combined ethereal extracts were washed with saturated sodium chloride solution, dried over  $MgSO_4$  and concentrated under reduced pressure to give a crude oil, which was purified by column chromatography to give **2**. (Conditions B); To a solution of **1** in  $Et_2O$  (10 mL)-THF (5 mL), which is prepared as described in Conditions A, was added  $\alpha,\beta$ -unsaturated ketone (1 mmol),  $BF_3 \cdot OEt_2$  (1 mmol) and  $Pd(OAc)_2$  (10 mol%) at 0 °C and the mixture was stirred for 12 h at 0 °C. After the same workup and purification procedure of Conditions A, product **3** was isolated.

In summary, palladium-catalyzed reactions of acylzirconocene chloride complex with  $\alpha,\beta$ -unsaturated ketones constitute not only a clean acyl transfer reaction but also a very notable regiochemical control by selection of the catalysts. Particularly, very efficient Michael addition of the acyl group of **1** ( $R = nC_8H_{17}$ ) opened a new synthetic possibility since a variety of acylzirconocene chloride derivatives are easily available by an established procedure.<sup>10</sup>

**Acknowledgment:** This work was supported by a Grant-in-Aid for Science Research (C) from the Ministry of Education, Science and Culture, Japan (No. 10672000).

## References and Note

- Harada, S.; Taguchi, T.; Tabuchi, N.; Narita, K.; Hanzawa, Y. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 1696.
- a) Collin, J.; Namy, J.-L.; Dallemer, F.; Kagan, H. B. *J. Org. Chem.* **1991**, *56*, 3118. b) Namy, J.-L.; Colomb, M.; Kagan, H. B. *Tetrahedron Lett.* **1994**, *35*, 1723. c) Seyferth, D.; Weinstein, R. M.; Hui, R. C.; Wang, W.-L.; Archer, C. M. *J. Org. Chem.* **1992**, *57*, 5620 and the references cited therein. d) Ving, J. L. in *Comprehensive Organic Synthesis*; Vol. 4 (Eds.: B. M. Trost and I. Fleming), Pergamon Press, Oxford, 1991, p. 115.
- Hanzawa, Y.; Tabuchi, N.; Taguchi, T. *Tetrahedron Lett.* **1998**, *39*, 6249.
- a) Cooke, Jr., M. P.; Parlman, R. M. *J. Am. Chem. Soc.* **1977**, *99*, 5222. b) Corey, E. J.; Hegedus, L. S. *J. Am. Chem. Soc.* **1969**, *91*, 4926. c) Hegedus, L. S.; Perry, R. J. *J. Org. Chem.* **1985**, *50*, 4955. d) Semmelhack, M. F.; Keller, L.; Sato, T.; Spiess, E. J.; Wulff, W. *J. Org. Chem.* **1985**, *50*, 5566. e) Yamashita, M.; Takashika, H.; Uchida, M. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1257.
- Reactions of cyclohexanone and/or 1-phenylhex-5-en-3-one with **1** ( $R = nC_8H_{17}$ ) in the presence of  $PdCl_2(PPh_3)_2$  or  $Pd(OAc)_2$  catalyst ended with the recovery of the starting ketones.
- Structures of new compounds were unambiguously determined by spectroscopic means ( $^1H$ -,  $^{13}C$ -NMR, IR and MS) and combustion analysis.
- Nickel-catalyzed conjugated addition of alkenylzirconium species to  $\alpha,\beta$ -unsaturated ketones has been reported. a) Schwartz, J.; Loots, M.; Kosugi, H. *J. Am. Chem. Soc.* **1980**, *102*, 1333. b) Dayrit, F. M.; Schwartz, J. *J. Am. Chem. Soc.* **1981**, *103*, 4466. In our present reactions of cyclohexenone with **1**, the results obtained by the examined catalysts other than  $PdCl_2(PPh_3)_2$  and  $Pd(OAc)_2$  are as follows:  $Pd(PPh_3)_4$ ; 34 % (**2/3** = 2/1).  $Pd(acac)_2$ -DIBAH; 36 % (**2** only).  $PdCl_2(dppe)$ ; 51 % (**2/3** = 2/1).  $Pd_2(dba)_3 \cdot CHCl_3$ - $PPh_3$ ; 29 % (**2** only).  $Ni(acac)_2$ ; 54 % (**2/3** = 1/3).
- Although the role of the added  $BF_3 \cdot OEt_2$  is not clear in the present cases, the reactions of **1** with  $\alpha,\beta$ -unsaturated ketone without adding  $BF_3 \cdot OEt_2$  gave constantly 10–30 % lower yields of **3**. It is worth commenting that an addition of  $BF_3 \cdot OEt_2$  to a cobalt acylate complex has been reported to reduce the reducing ability of the acylate complex by complexation. See ref. 4c.
- Reactions of  $\alpha,\beta$ -unsaturated acylzirconocene chloride **4** with  $\alpha,\beta$ -unsaturated ketone under the Pd-catalyzed conditions also gave 1,2- and 1,4-acylation products, selectively, while the yields of the products were lower compared with **1** ( $R = nC_8H_{17}$ ).



- a) Wipf, P.; Jahn, H. *Tetrahedron* **1996**, *52*, 12853. b) Labinger, J. A. in *Comprehensive Organic Synthesis*; Vol. 8 (Eds.: B. M. Trost and I. Fleming), Pergamon Press, Oxford, 1991, p. 667. c) Schwartz, J.; Labinger, J. A.; *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 333.