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Pd-catalyzed acylation of α,β-ynone with acylzirconocene chloride and one-pot formation of cyclopentenone derivatives

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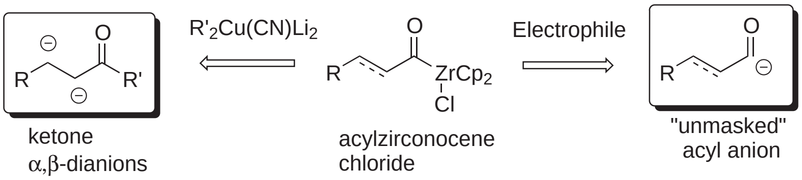
Abstract—Acylzirconocene chloride as an 'unmasked' acyl anion donor reacted with α,β-ynones to give 1,4-regioselective acylation products by the use of a catalytic amount of $PdCl_2(PPh_3)_2$ or $Pd(PPh_3)_4$, and a formation of a cyclopentenone derivative is observed through the reaction of α,β-unsaturated acylzirconocene chlorides and α,β-unsaturated ynones. © 2001 Elsevier Science Ltd. All rights reserved.

Exploration of new synthetic reactions by the use of acylzirconocene chloride is a matter of current interest to us. The acylzirconocene chloride is a stable complex at ambient temperature and can be prepared with ease through hydrozirconation of an unsaturated compound followed by the insertion of carbon monoxide.[1] Recently we revealed that the acylzirconocene chloride is not only a donor of an 'unmasked' acyl anion by reaction with electrophiles, but also a precursor of ketone α,β-dianions by treatment with a higher-order cyanocuprate reagent.[2,3]



Herein, we describe the results of the Pd-catalyzed 1,4-selective additions of acylzirconocene chlorides to an α,β-ynone system and a direct formation of cyclopentenone derivatives through the reaction of α,β-unsaturated acylzirconocene chloride with α,β-ynone. The $PdCl_2(PPh_3)_2$ or $Pd(PPh_3)_4$-catalyzed reaction of nonanoylzirconocene chloride (**1a**) with 1-phenyl-hept-2-yn-1-one (**2a**) showed the selective formation of 1,4-acylation product **3** in a slight preference of *Z*-isomers ($E/Z = 1/2.4$) in 85 or 68% yields, respectively, together with a trace amount (<5%) of diketone **4** generated by the homocoupling of **1a**. The results of the $PdCl_2(PPh_3)_2$ or $Pd(PPh_3)_4$-catalyzed reactions of α,β-ynone derivatives **2** with acylzirconocene chlorides **1** are listed in Table 1.

In all cases examined, the low *Z*-stereoselectivity of product **3** and a quite general 1,4-regioselectivity were realized. It is notable that the regioselectivity was unaffected even in the reactions of **2b** and **2d** which possess a bulky substituent at the *sp* carbon (entries 2 and 5, Table 1). Use of $Pd(acac)_2$ or $PdCl_2(CH_3CN)_2$ as a catalyst rendered the reaction complex and slow (by TLC), and a 1,2-adduct **5** was obtained in 40–47% yield together with a small amount (5–15%) of 1,4-adduct **3** (Scheme 1). Other catalysts [$PdCl_2DPPE$, $(dba)_3Pd_2\cdot CHCl_3$, $NiCl_2(PPh_3)_2$, $Ni(PPh_3)_4$, $Ni(acac)_2$ and $Ni(COD)_2$] ended with a recovery of the starting material or a formation of a complex mixture. The regioselectivity of α,β-ynone **2** shown in Table 1 and Scheme 1 was in remarkable contrast to that observed in the previously reported reactions of α,β-enone derivatives in which 1,2-regioselectivity has been attained by the use of a $PdCl_2(PPh_3)_2$ catalyst.[2]

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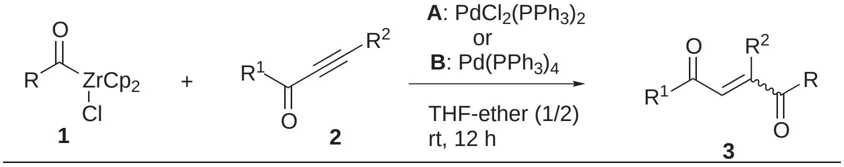
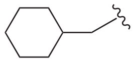
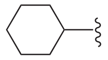
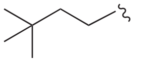
It is worth noting that ethyl phenylpropiolate and oct-4-yne did not react with **1**, and the starting materials were recovered unchanged. 1-Phenyl propynone, terminal acetylene derivative, ended with a formation of a complex mixture. The activation of the triple bond by an electron withdrawing ketone–carbonyl and the absence of alkynyl–hydrogen are requisite for bringing about the reaction. According to the facts that (i) either $PdCl_2(PPh_3)_2$ or $Pd(PPh_3)_4$ can be used as a catalyst, and (ii) the formation of a trace amount of diketone **4** by the use of $PdCl_2(PPh_3)_2$ catalyst, we assumed an analogous mechanism proposed for the Pd(0)-catalyzed reactions of α,β-unsaturated enone with acylzirconocene chloride.[2,4] Thus, a catalytic process; (i) an electron transfer from Pd(0) to α,β-ynone compounds, (ii) a formation of Pd–allenyl complex,[5] (iii) a transmetalation and (iv) a reductive elimination of Pd(0) would be involved (Scheme 2). However, the role of the triphenylphosphine ligand in bringing about the 1,4-selectivity in the present cases will be the subject of further studies.[6]

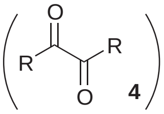
The reactions of α,β-unsaturated acylzirconocene chloride **6** with α,β-ynone compounds **2** under the identical conditions turned out to be a one-pot procedure for the preparation of cyclopentenone derivatives **7** (Scheme 3).

Table 1. $PdCl_2(PPh_3)_2$- and/or $Pd(PPh_3)_4$-catalyzed reactions of **2** with saturated acylzirconocene chlorides **1**[a]



entry	1	2			Pd	3	
	R	R^1		R^2	catalyst[b]	Yield (%)[c]	(E/Z)[d]
1	n-C_8H_{17} **1a**	Ph	**2a**	n-Bu	**A**	85	(1/2.4)
					B	68	(1/2.4)
2		CH_3	**2b**	t-Bu	**A**	71	(1/3)
					B	77	(1/2)
3		CH_3	**2c**	Ph	**A**	64	(1/5)
					B	45	(1/3)
4		Ph		$BnO(CH_2)_2$	**A**	59	(1/2)
					B	83	(1/1)
5		Ph	**2d**	t-Bu	**A**	82	(1/1)
					B	95	(1/2.5)
6		t-Bu		n-Bu	**A**	73	(1/3.5)
					B	73	(1/3)
7		Ph	**2a**	n-Bu	**A**	70	(1/3)
					B	51	(1/3)
8					**A**	54[e]	(1/2.8)
					B	40[f]	(1/4)
9					**A**	78	(1/3.6)
					B	71	(1/3)

[a] 2 equiv of **1**, 1 equiv of **2** and 5 mol % of catalyst (A or B) were used.
[b] Trace amount of diketone **4** was formed by the use of catalyst **A**.
[c] Isolated yield. [d] Determined by ^{1}H-NMR. [e] 21 % of **2a** was recovered.
[f] 49 % of **2a** was recovered.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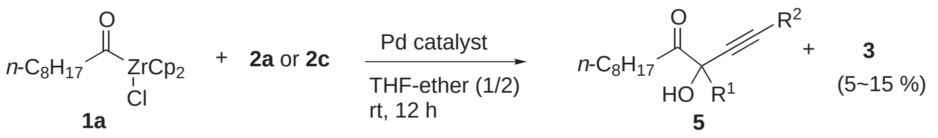
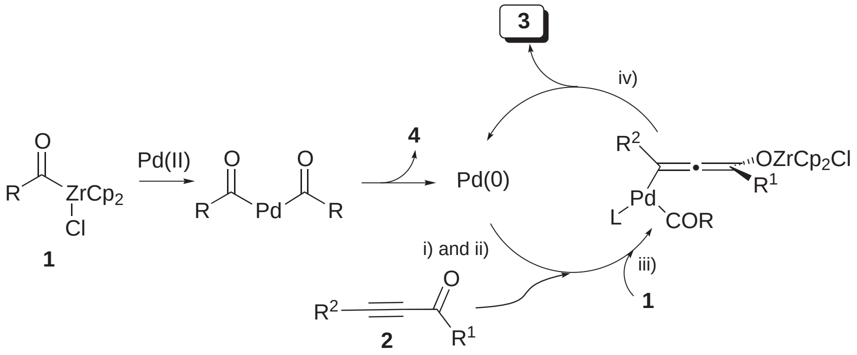
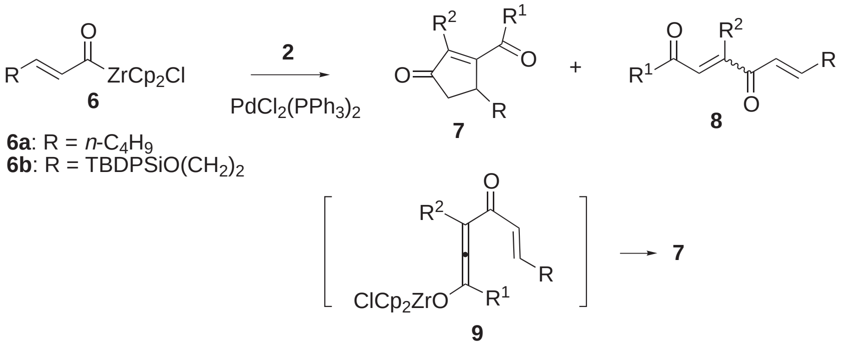


	Pd(acac)$_2$	PdCl$_2$(CH$_3$CN)$_2$
5a:	47 %	46 %
5c:	44 %	40 %

Scheme 1.



Scheme 2.



Scheme 3.

In the preliminary study of $PdCl_2(PPh_3)_2$ (5 mol%)-catalyzed reaction of **2c** with **6** (R = n-C_4H_9) in THF/toluene for 12 h at ambient temperature, cyclopentenone derivative **7** (R = n-C_4H_9, $R^1 = CH_3$, R^2 = Ph) in 21% yield together with the 1,4-addition products **8** (27% yield) were isolated. A prolonged stirring (48 h) of the reaction mixture increased the yields of **7**. Thus, the reaction of **6** [R = $TBDPSiO(CH_2)_2$] with **2a** in THF/toluene at ambient temperature for 48 h under $PdCl_2(PPh_3)_2$-catalyzed conditions gave **7** and **8** [R = $TBDPSiO(CH_2)_2$, R^1 = Ph, R^2 = n-Bu] in 63 and 23% yields, respectively.[7] The formation of **7** was a result of a secondary process of the enolate intermediate **9** through either the enolate assisted Nazarov reaction[8] or by an intramolecular Michael addition reaction.[9] In any event, easy access to highly substituted cyclopentenone derivatives **7** in a one-pot procedure from ynone **2** under mild conditions would render the present procedure useful.

In summary, the 1,4-selective acylation and a new and facile access to cyclopentenone derivatives are introduced through the $PdCl_2(PPh_3)_2$-catalyzed reactions of the α,β-ynone system with acylzirconocene chlorides. Our present Pd-catalyzed procedure has added a new and simple method for the preparation of cyclopentenone compounds, which constitute an important part of biologically active molecules.

References

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2. (a) Hanzawa, Y.; Tabuchi, N.; Saito, K.; Noguchi, S.; Taguchi, T. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 2395; (b) Hanzawa, Y.; Tabuchi, N.; Taguchi, T. *Tetrahedron Lett.* **1998**, *39*, 8141; (c) Hanzawa, Y.; Tabuchi, N.; Taguchi, T. *Tetrahedron Lett.* **1998**, *39*, 6249; (d) Harada, S.; Taguchi, T.; Tabuchi, N.; Narita, K.; Hanzawa, Y. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1696.
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4. (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.
5. Tsuji, J. *Palladium Reagents and Catalysts, Innovations in Organic Synthesis*; Wiley: UK, 1995.
6. It has been reported that the triphenylphosphine isomerizes α,β-ynone to conjugated dienone via allenyl ketone, see: Trost, B. M.; Kazmaier, U. *J. Am. Chem. Soc.* **1980**, *102*, 1333. Thus, it might be doubted that the Michael addition of **1** to the allenyl ketone intermediate followed by isomerization to **3**. However, in our case, this possibility is denied since t-Bu- or phenyl-substituted ynone (**2b**, **c** or **d**) yielded **3**.
7. Use of $Pd(PPh_3)_4$ (10 mol%) gave **7b** in 52% yield.
8. For Nazarov reaction, see: Denmark, S. E. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Paquette, L. A., Eds.; Pergamon: Oxford, 1991; Vol. 5, p. 751.
9. Although the intramolecular Michael addition is also a plausible mechanism, we believe that the concerted process is a prevailing process since the reactions of α,β-enone with **6** did not give cyclopentane compounds under 1,4-acylation conditions, see Ref. 2.