

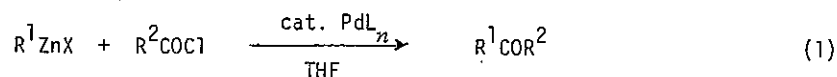
PALLADIUM-CATALYZED ACYLATION OF ORGANOZINCS AND OTHER ORGANOMETALLICS
AS A CONVENIENT ROUTE TO KETONES¹

Ei-ichi Negishi,* Vahid Bagheri, Sugata Chatterjee, Fen-Tair Luo,
Joseph A. Miller and A. Timothy Stoll

Department of Chemistry, Purdue University, W. Lafayette, Indiana 47907 U.S.A.

SUMMARY: The reaction of organozincs with acyl chlorides catalyzed by palladium-phosphine complexes, e.g., Pd(PPh₃)₄, provides a highly general and convenient route to ketones.

A wide variety of organometallics² are known to participate in acylation with acyl halides. Along with those containing Mg^{2a}, Cd^{2a}, and Cu^{2g}, organozincs^{2a} and organoaluminums^{2d} have been widely used. Contrary to our expectations, however, we have found that these organometallics often fail to react satisfactorily with acyl halides to provide ketones (*Table*). In light of recent papers describing the Pd-catalyzed acylation of organotin³ and organomercuries⁴ vis-à-vis our own finding that several other metals, especially Zn, also participate readily in the Pd-catalyzed cross coupling, we investigated the effect of Pd complexes on the reaction of organozincs with acyl chlorides⁵ (eq 1).



The experimental results are summarized in *Table*, and they indicate the following: (1) The uncatalyzed reaction of organozincs with acyl chlorides under the conditions used here indeed tends to fail to give high yields of the desired ketones. (2) The acylation reaction is however markedly catalyzed by Pd complexes, e.g., Pd(PPh₃)₄. Although we have arbitrarily used 5 mol % of a Pd-phosphine complex in most cases, its quantity may be substantially reduced, as judged by the results of a few experiments with 1 mol % of a catalyst. In some acylation reactions of alkenylzinc derivatives, a Pd catalyst generated in situ from Cl₂Pd(PPh₃)₂ and 2 equiv of *i*-Bu₂AlH was superior to Pd(PPh₃)₄ with respect to the product yield. (3) The scope of the acylation reaction with respect to the organic moieties of the reactants appears to be very broad. In fact, all Pd-catalyzed reactions of organozincs with acyl chlorides that we have run have yielded satisfactory results. (4) The preparation of alkenyl ketones via alkenylzinc derivatives is >98% stereospecific, and that via α,β -unsaturated acyl chlorides does not appear to involve stereoisomerization. The products do not undergo conjugate addition in competition with the desired acylation.

Organozinc compounds may be prepared by (i) treating organolithiums or Grignard reagents with dry ZnCl₂, (ii) direct metalation of organic halides with Zn metal, or (iii) carbocation⁶ of alkynes. Although the Pd-catalyzed acylation of organozincs proceeds readily in solvents containing THF, the corresponding reaction in diethyl ether is much more sluggish.

When (*E*)-1-heptenyllithium generated from the corresponding iodide in diethyl ether was used to prepare the corresponding alkenylzinc chloride, the reaction of the latter with acetyl chloride in THF after removal of diethyl ether proceeded satisfactorily (*Table*), whereas the same reaction in a mixture containing both diethyl ether and THF was very sluggish. In a few cases, acyl chlorides reacted to minor extents with THF to form ring-opened products, such as 1-acetoxy-4-chlorobutane. This side reaction, however, was not a serious problem in any of the experiments listed in *Table*.

The following preparation of (*E*)-4-methyl-3-decen-2-one is representative. (*E*)-2-Methyl-1-octenyl iodide (>99% *E*) was prepared by treating 1-octyne (2.75 g, 25 mmol) with Me_3Al (3.60 g, 50 mmol) and Cl_2ZrCp_2 (1.46 g, 5 mmol), followed by treatment with I_2 (7.61 g, 30 mmol), as described previously.^{7b} To 2.52 g (10 mmol) of the iodide in 10 mL of diethyl ether were added sequentially *n*-BuLi (4.8 mL of 2.3 M solution in hexane, -78°C) and dry ZnCl_2 (1.5 g, 11 mmol, -78°C to 0°C) in THF. After removing the solvents at reduced pressure, THF (10 mL), AcCl (0.94 g, 12 mmol), and a mixture of $\text{Cl}_2\text{Pd}(\text{PPh}_3)_2$ (0.08 g, 0.1 mmol) and *i*-Bu₂AlH (0.04 mL, 0.2 mmol) in 4 mL of benzene were added at 0°C , and the reaction mixture was stirred for 30 min at 0°C . Acidification (3N HCl), extraction (hexane), washing (aq NaHCO_3), drying (MgSO_4), and distillation provided 1.30 g (77%) of 4-methyl-3-decen-2-one (*E/Z* = 99): bp $55\text{--}57^\circ\text{C}$ (0.5 mm); IR (neat) 1740 (m), 1690 (s), 1615 (s) cm^{-1} ; ^1H NMR (CDCl_3 , Me_4Si) δ 0.89 (t, J = 7 Hz, 3 H), 1.1–1.7 (m, 8 H), 1.9–2.3 (m, 8 H), 6.05 (s, 1H); ^{13}C NMR (CDCl_3 , Me_4Si) δ 13.65, 18.35, 22.39, 27.39, 28.84, 31.54, 40.80, 123.10, 156.69, 195.73.

Although the Pd-catalyzed acylation of alkenylzinc derivatives is highly satisfactory, it is desirable to be able to use alkenylmetals containing Al, B, or Zr, that can, in many cases, be generated by either hydrometalation or carbometalation of alkynes. Neither alkenylboranes nor alkenylborates undergo clean acylation even in the presence of a Pd-phosphine catalyst. This is in sharp contrast with the corresponding acylation of alkyl- or arylborates reported earlier by us.^{2c} Alkenylalanes do react with acyl chlorides in CH_2Cl_2 or $(\text{CH}_2\text{Cl})_2$, and alkenylzinconium derivatives can be readily converted into alkenylalanes.^{2f} However, the reaction of (*E*)-(2-methyl-1-octenyl)dimethylalane⁷ with acetyl chloride in $(\text{CH}_2\text{Cl})_2$ at -30°C has produced stereoisomeric mixtures of 4-methyl-3-decen-2-one, in which the *E/Z* ratio has unpredictably ranged from 2 to 13.⁸ We have found, however, that both the above alkenylalane and its alanate, obtained by treatment of the alane with *n*-BuLi, react readily with acetyl chloride in THF at room temperature in the presence of a catalyst generated from $\text{Cl}_2\text{Pd}(\text{PPh}_3)_2$ and *i*-Bu₂AlH. In either case, the product yield is >90%. The stereospecificity in the alanate reaction is 96%, while that in the alane reaction is 92%. Thus, the Pd-catalyzed acylation of organoaluminums appears to be a viable alternative to the corresponding organozinc reaction. Our attempts to further improve the stereospecificity of the above reactions by the addition of ZnCl_2 as a co-catalyst⁹ led to an extensive formation of THF-derived byproducts.

Acknowledgments. We thank the National Science Foundation, the National Institutes of Health, and the Petroleum Research Fund, administered by the American Chemical Society, for support. S. Chatterjee is a recipient of a National Scholarship awarded by Ministry of Education, Government of India, and A. Stoil is a Ross Ade Fellow, Purdue University. We also thank Engelhardt Industries for a loan of palladium chloride.

Table Palladium-Catalyzed Reaction of Organozincs with Acyl Chlorides^a

R ¹	R ¹ ZnX ^b		R ² of R ² COCl	Catalyst ^c (mol %)	Yield ^d of R ¹ COR ² , %		Stereospecificity, %
	X				Pd-Catalyzed	Uncatalyzed	
<i>n</i> -Bu	Cl		Me	I (5)	— (80)	(10)	
Ph	Cl		Me	I (5)	— (80)	(<5) ^e	
(<i>E</i>)-1-Heptynyl	Cl		Me	II (1)	76 (98)	(<2)	>99% (<i>E</i>)
(<i>E</i>)-2-Methyl-1-octenyyl	Cl		Me	II (1)	77 (95)	(<2)	>98% (<i>E</i>)
1-Heptynyl	Cl		Me	I (5)	81 (97)	(<5)	
<i>n</i> -Bu	Cl		Ph	I (5)	— (90)	(52) ^f	
Ph	Cl		Ph	I (5)	— (93)	(<1) ^e	
<i>p</i> -Cl-C ₆ H ₄	Cl		Ph	I (5)	— (95)	— ^g	
1-Heptynyl	Cl		Ph	I (5)	73 (97)	(<1)	
<i>n</i> -Bu	Cl	Vinyl		I (5)	71 (91)	(<1)	
PhCH ₂ ^h	Cl	Vinyl		I (5)	77	(<1)	
Ph	Cl	(<i>E</i>)-Propenyl ⁱ		I (5)	92	(<2)	>98% (<i>E/Z</i> = 95/5)
1-Heptynyl	Cl	(<i>E</i>)-Propenyl ⁱ		I (5)	89	(<2)	>98% (<i>E/Z</i> = 95/5)
<i>n</i> -Octyl ^j	Cl	MeO		I (2.5)	78	(<1)	
<i>o</i> -Tolyl	Cl	MeO		I (2.5)	73	(<1)	
1-Octenyyl	Cl	MeO		I (2.5)	72	(<1)	
<i>k</i>	Br	MeO		I (1)	73	(<1)	>98% (<i>E/Z</i> = 85/15)
(<i>E</i>)-1-Octenyyl	Cl	MeO		II (5)	56	(<1)	>98% (<i>E</i>)
(<i>Z</i>)-1-Hexenyyl	Cl	MeO		II (5)	52	(<1)	>98% (<i>Z</i>)

^aThe reaction was carried out at ca. 25°C in mixed solvents containing THF. The time for completion of the Pd-catalyzed reaction is <6 h. Unless otherwise mentioned, the uncatalyzed reaction was run for the same amount of time as the catalyzed reaction. All isolated products were adequately characterized. All new compounds were additionally identified by elemental analysis. ^bUnless otherwise mentioned, the organozinc reagent was prepared by treating the corresponding organolithium with 1 equiv of dry ZnCl₂. ^cI = Pd(PPh₃)₄, II = Cl₂Pd(PPh₃)₂ + 2 *i*-Bu₂AlH. ^dIsolated yield. The numbers in parentheses are GLC yields. ^eThe uncatalyzed reaction was run for 1 h. The Pd catalyst was then added to the reaction mixture. ^fThe uncatalyzed reaction was run for 12 h at 25°C. The catalyzed reaction was complete within 30 min at 25°C. ^gThe uncatalyzed reaction was not carried out. ^hPrepared by treating benzyl bromide with Zn metal. ⁱ*E/Z* = 95/5. ^jPrepared from *n*-octylmagnesium bromide. ^k(*E*)-1-Trimethylsilyl-2-(*n*-hexyl)-1,4-pentadienyyl (*E/Z* = 85/15). Prepared by the reaction of 1-trimethylsilyl-1-octyne with allylzinc bromide.

REFERENCES AND NOTES

1. Selective Carbon-Carbon Bond Formation via Transition Metal Catalysis. 36. Part 35: Negishi, E.; Matsushita, H.; Kobayashi, M.; Rand, C. L. *Tetrahedron Lett.* in press.
2. (a) Mg, Zn, and Cd: Shirley, D. A. *Org. React.* 1954, *8*, 28. (b) Hg: Larock, R. C. *J. Organometal. Chem. Library* 1976, *1*, 257. (c) B: Negishi, E.; Chiu, K. W.; Yoshida, T. *J. Org. Chem.* 1975, *40*, 1675. (d) Al: Reinheckel, H.; Haage, K.; Jahnke, D. *Organometal. Chem. Rev. A* 1969, *4*, 47. (4) Si: Hudrlik, P. F. *J. Organometal. Chem. Library* 1976, *1*, 127. (f) Zr: Carr, D. B.; Schwartz, J. *J. Am. Chem. Soc.* 1979, *101*, 3521. (g) Cu: Posner, G. H.; Whitten, C. E.; McFarland, P. E. *J. Am. Chem. Soc.* 1972, *94*, 5106. (h) Fe: Collman, J. P. *Acc. Chem. Res.* 1975, *8*, 342. (i) Mn: Cahiez, G.; Bernard, D.; Normant, J. F. *Synthesis* 1977, 130. (j) Rh: Hegedus, L. S.; Kendall, P. M.; Lo, S. M.; Sheats, J. R. *J. Am. Chem. Soc.* 1975, *97*, 5448.
3. (a) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* 1978, *100*, 3636; *J. Org. Chem.* 1979, *44*, 1613. (b) Logue, M. W.; Teng, K. *J. Org. Chem.* 1982, *47*, 2549. (c) Soderquist, J. A.; Leong, W. H. *Tetrahedron Lett.* 1983, *24*, 2361.
4. Takagi, K.; Okamoto, T.; Sakakibara, Y.; Ohno, A.; Oka, S.; Hayama, N. *Chem. Lett.* 1975, 951.
5. A recent paper describes the reaction of benzyl bromides with acyl chlorides in the presence of Zn and a catalytic amount of a Pd complex: Sato, T.; Naruse, K.; Enokiya M.; Fujisawa, T. *Chem. Lett.* 1981, 1135.
6. (a) Negishi, E.; Van Horn, D. E.; Yoshida, T.; Rand, C. L. *Organometallics* 1983, *2*, 563. (b) Negishi, E.; Miller, J. A. unpublished results.
7. (a) Van Horn, D. E.; Negishi, E. *J. Am. Chem. Soc.* 1978, *100*, 2252. (b) Negishi, E.; Van Horn, D. E.; King, A. O.; Okukado, N. *Synthesis* 1979, 501. (c) Negishi, E. *Pure Appl. Chem.* 1981, *53*, 2333.
8. These results were obtained by L. D. Boardman of our laboratories.
9. Negishi, E.; Okukado, N.; King, A. O.; Van Horn, D. E.; Spiegel, B. I. *J. Am. Chem. Soc.* 1978, *100*, 2254.

(Received in USA 7 July 1983)