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PALLADIUM-CATALYZED ACYLATION OF ORGANOZINCS AND OTHER ORGANOMETALLICS AS A CONVENIENT ROUTE TO KETONES[1]

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SUMMARY: The reaction of organozincs with acyl chlorides catalyzed by palladium-phosphine complexes, e.g., $Pd(PPh_3)_4$, provides a highly general and convenient route to ketones.

A wide variety of organometallics[2] 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 organotins[3] and organomercuries[4] 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 chlorides[5] (eq 1).

$$R^1ZnX \ + \ R^2COCl \ \xrightarrow[\text{THF}]{\text{cat. PdL}_n} \ R^1COR^2 \qquad (1)$$

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., $Pd(PPh_3)_4$. 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 $Cl_2Pd(PPh_3)_2$ and 2 equiv of i-Bu_2AlH was superior to $Pd(PPh_3)_4$ 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 $ZnCl_2$, (ii) direct metalation of organic halides with Zn metal, or (iii) carbozincation[6] 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 ($\geq$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 $Cl_2Pd(PPh_3)_2$ (0.08 g, 0.1 mmol) and *i*-Bu_2AlH (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 55-57°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 $(CH_2Cl)_2$, and alkenylzirconium derivatives can be readily converted into alkenylalanes.[2f] However, the reaction of (*E*)-(2-methyl-1-octenyl)dimethylalane[7] with acetyl chloride in $(CH_2Cl)_2$ 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 $Cl_2Pd(PPh_3)_2$ and *i*-Bu_2AlH. 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-catalyst[9] led to an extensive formation of THF-derived byproducts.

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Table Palladium-Catalyzed Reaction of Organozincs with Acyl Chlorides[a]

R^1ZnX[b]		R^2 of R^2COCl	Catalyst[c] (mol %)	Yield[d] of R^1COR^2, %		
R^1	X			Pd-Catalyzed	Uncatalyzed	Stereospecifity, %
n-Bu	Cl	Me	I (5)	— (80)	(10)	
Ph	Cl	Me	I (5)	— (80)	(<5)[e]	
(*E*)-1-Heptenyl	Cl	Me	II (1)	76 (98)	(<2)	>99% (*E*)
(*E*)-2-Methyl-1-octenyl	Cl	Me	II (1)	77 (95)	(<2)	>98% (*E*)
1-Heptynyl	Cl	Me	I (5)	81 (97)	(<5)	
n-Bu	Cl	Ph	I (5)	— (90)	(52)[f]	
Ph	Cl	Ph	I (5)	— (93)	(<1)[e]	
p-Cl-C_6H_4	Cl	Ph	I (5)	— (95)	—[g]	
1-Heptynyl	Cl	Ph	I (5)	73 (97)	(<1)	
n-Bu	Cl	Vinyl	I (5)	71 (91)	(<1)	
$PhCH_2$[h]	Cl	Vinyl	I (5)	77	(<1)	
Ph	Cl	(*E*)-Propenyl[i]	I (5)	92	(<2)	>98% (*E*/*Z* = 95/5)
1-Heptynyl	Cl	(*E*)-Propenyl[i]	I (5)	89	(<2)	>98% (*E*/*Z* = 95/5)
n-Octyl[j]	Cl	MeO	I (2.5)	78	(<1)	
o-Tolyl	Cl	MeO	I (2.5)	73	(<1)	
1-Octynyl	Cl	MeO	I (2.5)	72	(<1)	
k	Br	MeO	I (1)	73	(<1)	>98% (*E*/*Z* = 85/15)
(*E*)-1-Octenyl	Cl	MeO	II (5)	56	(<1)	>98% (*E*)
(*Z*)-1-Hexenyl	Cl	MeO	II (5)	52	(<1)	>98% (*Z*)

[a] The 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. [b] Unless otherwise mentioned, the organozinc reagent was prepared by treating the corresponding organolithium with 1 equiv of dry $ZnCl_2$. [c] I = $Pd(PPh_3)_4$. II = $Cl_2Pd(PPh_3)_2$ + 2 *i*-Bu_2AlH. [d] Isolated yield. The numbers in parentheses are GLC yields. [e] The uncatalyzed reaction was run for 1 h. The Pd catalyst was then added to the reaction mixture. [f] The uncatalyzed reaction was run for 12 h at 25°C. The catalyzed reaction was complete within 30 min at 25°C. [g] The uncatalyzed reaction was not carried out. [h] Prepared by treating benzyl bromide with Zn metal. [i] *E*/*Z* = 95/5. [j] Prepared from *n*-octylmagnesium bromide. [k] (*E*)-1-Trimethylsilyl-2-(*n*-hexyl)-1,4-pentadienyl (*E*/*Z* = 85/15). Prepared by the reaction of 1-trimethylsilyl-1-octyne with allylzinc bromide.

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