Tetrahedron Letters, Vol.22, No.28, pp 2629 - 2632, 1981
Printed in Great Britain

0040-4039/81/282629-04$02.00/0

LIGAND CONTROL IN PALLADIUM-CATALYZED COUPLING REACTIONS BETWEEN ORGANOZIRCONIUM COMPOUNDS AND ALLYLIC SPECIES

Yosio Hayasi, Martin Riediker, James S. Temple, and Jeffrey Schwartz*
Department of Chemistry, Princeton University, Princeton, NJ 08544

SUMMARY: A (π-allylic)Pd(II) complex can serve as a catalyst precursor for selective coupling between allylic halides or acetates and alkenylzirconium complexes.

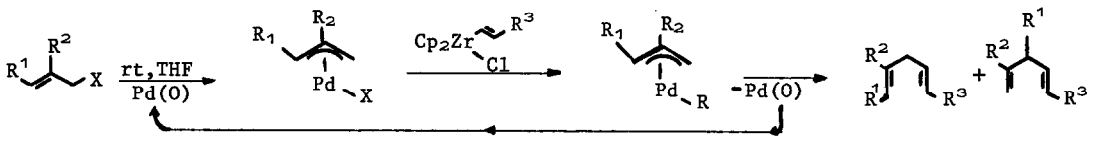
We have recently described the reaction between (π-allylic)Pd(II) halide species and alkenylzirconium complexes which gives rise to 1,4-dienes in high yield[1] and have reported that adding extrinsic ligands (for Pd) has a profound effect on the regiochemistry of coupling. We have also noted[1] that Pd(0) or Pd(II) species can serve as *catalysts* to effect coupling between alkenylzirconium complexes and allylic halides or acetates. Herein we wish to describe the details of this catalytic coupling reaction in terms of its stereochemical course, turnover efficiencies, and ligand regiochemical control of coupling.

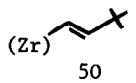
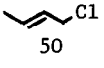
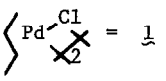
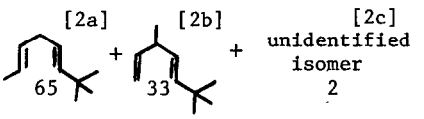
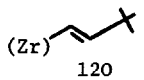
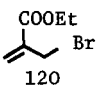
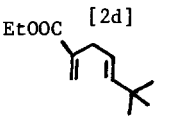
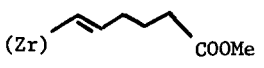
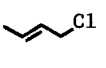
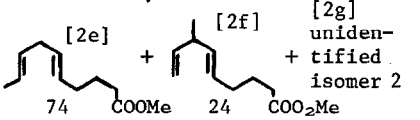
The general scheme is shown in Table 1. Under comparable conditions higher catalytic efficiencies are realized when allyl halides (vs. acetates) are employed; allylic bromides appear to be more reactive than the chlorides, too. Since transmetalation reactions involving organozirconium compounds and Pd(II) halide species are fast (and presumed to be fast for the acetates as well), and since reductive elimination from Pd(II) intermediates should be essentially independent of the nature of zirconium residues formed, we believe that the rate-limiting step for the catalytic cycle is the oxidative addition of the organic substrate to a reduced palladium species. Consistent with this notion we find that turnover rates are enhanced by increased concentrations of allylic substrates.

As shown in Table 2, the critical intermediate, from the point of view of control of carbon-carbon bond formation, is believed to be a (π-allylic)palladium-X species (where X is either halide or acetate). Ligand control of coupling regiochemistry, therefore, should be identical for the stoichiometric and catalytic sequences. Upon consideration of steric effects for the allylic complex intermediates, it can be determined whether a donor or an acceptor ligand should be added to promote coupling as desired.

In the stoichiometric reactions which we have described,[1] it was possible to assay the effect on coupling regiochemistry of added ligands since the Pd(II) halide species could be prepared in the absence of any other ligand (e.g., phosphines). Conventional reactions involving palladium *catalysis* utilize phosphine complexes of either Pd(0) (e.g., L_4Pd) or of Pd(II) (e.g., L_2PdCl_2). If these ligands were found to promote coupling regiochemistry contrary to that which is desired, it would be necessary to develop phosphine-free catalytic species. Since Pd(0) is formed upon reductive elimination in the stoichiometric reaction,[1] the catalytic utility of a

TABLE 1. PALLADIUM-CATALYZED COUPLING OF ALKENYLZIRCONIUM SPECIES WITH ALLYLIC HALIDES



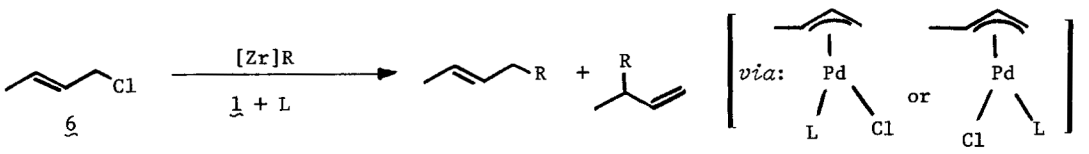
OrganoZr Complex Equiv (per Pd)	Allylic Compd Equiv (per Pd)	Pd Species Added	Turnovers Equiv (per Pd)	Ratio of Coupled Products
 50	 50	 = 1	35	 [2a] 65 + [2b] 33 + [2c] unidentified isomer 2
 120	 120	1	119	 [2d]
 72 72	 72	1	62	 [2e] 74 + [2f] 24 + [2g] unidentified isomer 2

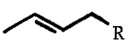
simple (π-allylic)palladium chloride complex, 1, was examined. Here the organozirconium compound would react with 1 and by sacrifice of one equivalent of the zirconium reagent (based on Pd) a potentially highly reactive "naked" Pd(0) catalyst species could be obtained on reductive elimination of the carbon-carbon bond.[3] Indeed, we find that 1, formed easily from crotyl chloride and $PdCl_2$,[4] serves as a highly efficient catalyst precursor for effecting these coupling transformations. It was now possible to determine the effect of intentionally added phosphine or other ligands upon the regiochemistry of the catalytic coupling reaction. Consistent with our observations for the stoichiometric reaction, we find that addition of phosphine ligands promotes coupling at the sterically *more* hindered terminus of the allylic unit; addition of maleic anhydride promotes coupling at the sterically less hindered terminus of the allylic fragment as shown in Table 2, which describes this feature for a case in which one terminus of the allylic unit is primary and the other is secondary.

In order to determine the stereochemical consequences of the catalytic coupling sequence, 3[5] was utilized as the starting material; net *inversion* of stereochemistry at C(20) was found, consistent with reported observations for oxidative addition-reductive elimination-based sequences.[1,5] It is important to note here that for the purpose of steroid synthesis utilizing palladium catalysis, high regiochemical control can be obtained *only* when the non-phosphinated catalyst precursor is employed; utilization of "conventional" catalysts such as L_4Pd gave rise to poor selectivity for coupling to steroidal product.[7] We describe below typical sequences employed to effect these catalytic coupling reactions. (All non-steroidal product ratios were determined by GLC analysis (20', 10% Carbowax, 20 M, 105°C) and all non-steroidal product

ratios are shown in Table 2).

TABLE 2. LIGAND EFFECTS ON CATALYTIC COUPLING (FOR X = Cl)



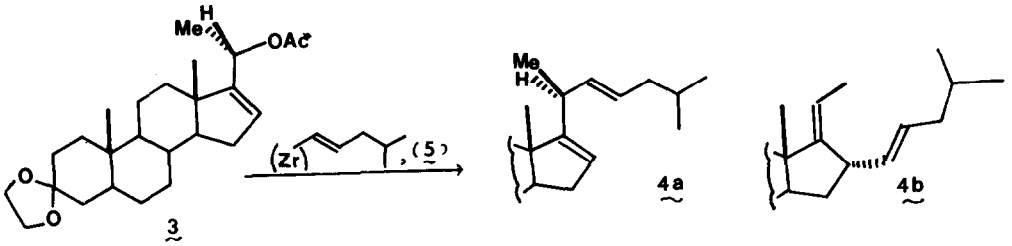
Ligand (equiv)		Product Ratio	
PPh_3	Maleic Anhydride		
0	0	65	35
2	0	45	55
4	0	20	80
9	0	10	90
0	3	92	8
$(PPh_3)_4Pd$,"cat"		15	85

Experimental Procedures. To 0.014 g ($7.10 \times 10^{-6} \times .5$ mol) of 1 (under argon) was added 0.588 mL (3.550×10^{-4} mol = 50 equiv) of a 0.60 M solution of (*E*)-2-butenyl chloride in THF to give a pale yellow solution. To this solution was added in one portion by syringe a solution of 2 (0.135 g; 3.972×10^{-4} mol = 55.9 equiv) and maleic anhydride (0.0021 g; 2.13×10^{-5} mol = 3 equiv) in 5 mL THF. The color of the reaction mixture changed to orange immediately after this addition. After ca. 5 min, the color changed again to pale yellow. The reaction mixture was stirred at room temperature for 2 days to give a pale yellow, clear solution, which was then analyzed by GLC using *n*-decane as internal standard. A similar reaction can be performed at 50°C and results in faster turnover with no appreciable decomposition of catalyst species. A comparable procedure, using 1 but omitting maleic anhydride, gave rise to a 65:35 mixture of coupled products.

To 0.0059 g (5.1×10^{-6} mol) of $Pd(P\phi_3)_4$ under Ar was added 1.239 mL (8.298×10^{-4} mol = 162.7 equiv) of a 0.670 M solution of 6 (98%) in THF. To this solution at room temperature was added a solution of 2 (0.235 g; 6.915×10^{-4} mol = 135.6 equiv) in THF 5 mL. The color of the reaction mixture did not change during addition of either the allylic halide or the organozirconium species. The mixture was stirred at room temperature for one day to give a clear, pale yellow (almost colorless) solution which was analyzed by GLC.

To a mixture of acetate 3 (0.4713 g; 1.1715×10^{-3} mol = 26.7 equiv), 1 (0.0086 g; 4.38 10^{-5} mol Pd) and maleic anhydride (0.0135 g; $1.376 \times 10^{-}$ mol = 3.14 equiv) (under Ar) was added 10 mL of THF, and the mixture was stirred for 10 min. To this solution was added a solution of 5 (1.0359 g; 3.0481×10^{-3} mol = 69.6 equiv) in THF (20 mL). The mixture was stirred at room temperature for 5 days to give a reddish-brown, clear solution. Preparative TLC (silica gel GF, *m*-xylene) of the residue of evaporation gave the coupled products as a viscous oil [6.75 turnovers based on Pd)]. Purification was carried out by using HPLC (Radial-Pak B, 0.5 AcOEt-hex). NMR analysis (90 MHz, C_6D_6) showed the desired product, 4a, but only a trace of 4b.

To 0.660 g (5.71×10^{-5} mol) of $Pd(P\phi_3)_4$ (under Ar) was added a solution of 3 (0.2417 g; 6.008×10^{-4} mol = 10.52 equiv) and ϕ_3P (0.0599 g; 2.284×10^{-4} mol = 4 equiv) in 20 mL THF. After stirring for 5 min, a solution of 5 (0.900 g; 2.6482×10^{-3} mol = 46.38 equiv) in 20 mL THF was added. Reaction procedures and analyses were as described above. In this way 0.599 g product (2.46 turnovers based on Pd) was obtained. The ^1H NMR spectrum of this material revealed that 4a and 4b were formed in an approximate ratio of 35:65. (For 4b the ^1H NMR spectrum was indicative:[1] (C_6D_6) 0.82 (s, CH_3(18)), 1.70 (d x d, J = 1, J' = 7, C(21)); ($CDCl_3$) 0.76 (s, CH_3(18)), 1.53 (d x d, J = 1, J' = 7, C(21)).



(3)

	a		b
Catalyst = $Pd(PPh_3)_4$ + 4 PPh_3	35	:	65
Catalyst = 1 + maleic anhydride	> 5	:	1

REFERENCES AND NOTES

(1) J. S. Temple and J. Schwartz, *J. Am. Chem. Soc.* 1980, *102*, 7381.

(2) Mass spectral characteristic peaks:

(a) *m/e* 138 (M^+, 7), 123 (M-CH_3, 9), 57 (69), 41 (100); ^{1}H NMR (C_6D_6): δ 1.00 (s, 9), 1.55 (m, 3), 2.71 (m, 2), 5.46 (m, 4 H);

(b) *m/e* 138 (very weak), 123 (10), 57 (100), 41 (80); ^{1}H NMR (C_6D_6): δ 0.99 (s, 9), 1.06 (d, 3, J = 6.7 Hz), 2.90 (m, 1), 4.90-5.95 (m, 5);

(c) *m/e* 138 (17), 123 (21), 57 (71), 41 (100);

(d) IR (CCl_4) 1720 cm^{-1}; ^{1}H NMR (CCl_4): δ 1.00 (s, 9), 1.29 (t, 3, J = 7.5 Hz), 2.92 (br d, 2, $J \simeq$ 5 Hz), 4.16 (q, 2, J = 7.5 Hz), 5.10-6.28 (m, 4);

(e) *m/e* 182 (M^+, 9), 108 (16), 93 (30), 41 (100); ^{1}H NMR (C_6D_6): δ 1.05-1.90 (m, 4), 1.57 (m, 3), 2.05 (q, 2, J = 6.6 Hz), 2.62 (m, 2), 3.32 (s, 3), 5.41 (m, 4);

(f) *m/e* 182 (4), 108 (34), 93 (73), 41 (100); ^{1}H NMR (C_6D_6): δ 1.05-1.85 (m, 4), 1.01 (d, 3, J = 7 Hz), 2.05 (q, 2, J = 6.6 Hz), 2.70 (m, 1), 3.33 (s, 3), 4.87-5.95 (m, 5);

(g) *m/e* 182 (7), 108 (41), 93 (88), 41 (99).

(3) We do not know what the nature is of Pd(0) species formed in these non-phosphine involved sequences. Only in one instance have we observed the formation of Pd metal; in all others reaction mixtures remained homogeneous.

(4) F. Jira and J. Sedlmeier, *Tetrahedron Lett.* 1971, 1227.

(5) B. M. Trost and T. R. Verhoeven, *J. Am. Chem. Soc.* 1978, *100*, 3435.

(6) For 4a, ^{1}H spectrum; (C_6D_6) 0.83 (s, CH_3(18)), 1.25 (d, J = 7, CH_3(21)); ($CDCl_3$) 0.77 (s, CH_3(18)), 1.13 (d, J = 7, CH_3(21)) was significantly different from that reported for the C(20) *nat* diene: (C_6D_6) 0.88 (s, CH_3(18)), 1.23 (d, J = 7, CH_3(21)); ($CDCl_3$) 0.77 (s, CH_3(18)), 1.09 (d, J = 7, CH_3(21)). Diene 4a was identical with material prepared from 3-oxo-*trans*-pregna-17(20)-ene ethylene ketal by a known route.[1]

(7) Utilization of the epimeric halide of 3 would yield steroidal product with C(20) *nat* configuration.

Acknowledgments. The authors acknowledge support for this work provided by the National Science Foundation, Grant No. CHE-79-00996. They also acknowledge Professor E. I. Negishi for informing them of his work done in a similar area.

(Received in USA 27 February 1981)