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EFFECTS OF ORGANOMETALS ON THE PALLADIUM-CATALYZED TANDEM CARBOPALLADATION-CROSS COUPLING FOR PREPARING STEREODEFINED EXOCYCLIC ALKENES

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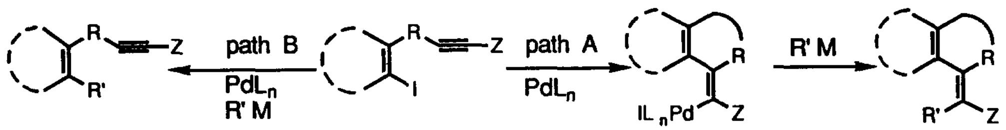
Summary: The reaction of ω-(o-iodoaryl)- and ω-(Z-β-iodoalkenyl)alkynes with organometals containing Zr, Sn, Al, or B in the presence of a catalytic amount of a palladium-phosphine complex, such as $Pd(PPh_3)_4$, proceeds predominantly via initial cyclic carbopalladation followed by cross coupling, whereas the corresponding reaction of organozincs tends to be dominated by direct cross coupling.

In contrast to the reaction of organopalladium derivatives with alkenes, which has been widely utilized in the development of Pd-catalyzed carbon-carbon bond forming processes, such as the Heck reaction,[2] the corresponding reaction of alkynes had until recently been far less well developed.[3] One crucial difference between them is that, while alkylpalladiums containing β hydrogens, formed as intermediates in the former, readily undergo elimination for catalytic recycling of Pd, alkenylpalladium intermediates in the latter do not. This necessitates additional transformations for catalytic processes. Mainly over the past few years, some Pd-catalyzed processes have been developed by combining the carbopalladation step with trapping of alkenylpalladium intermediates with proton donors,[4] CO,[5] alkenes,[5,6] or organometals.[7] Our own earlier attempts to trap alkenylpalladiums via cross coupling (Path A) with organozincs, e.g., vinylzinc bromide, were disappointing due to direct cross coupling before cyclic carbopalladation[8] (Path B).



Our previous finding[9] that organozincs undergo the Pd-catalyzed cross-coupling reaction much faster than other organometals, such as those containing Al, B, Cu, Sn, and Zr, suggested to us that, for the very reason, organozincs might actually be unsuitable reagents for achieving tandem carbopalladation-cross coupling. We have therefore screened various metals known to participate in Pd-catalyzed cross coupling including Li, Mg, Zn, B, Al, Sn, Zr, and Cu and have found that the course of the Pd-catalyzed reaction of o-iodo-(3-pentynyl)benzene (1), chosen as a test system, with alkenylmetals strongly depends on the metals as well as the organic ligands. As we suspected, the reaction of 1 with (*E*)-1-hexenylzinc chloride is dominated by direct cross coupling to produce 2 as the major product (68%) along with only a 19% yield of the desired product 3. On the other hand, the corresponding reactions of (*E*)-1-hexenylmetals containing Zr[10] or Sn[11] have produced the desired tandem carbopalladation-cross coupling product (3) in high yields along with traces (< 3%) of 2. The use of (*E*)-1-hexenyl(diisobutyl)alane[12] led to a 57% yield of 3 along with a 32% yield of 2, and that of B-[(*E*)-1-hexenyl]catechol-borane[13] gave 3 in 41% yield, which did not further increase with time. In contrast, the reactions of (*E*)-1-hexenylmetals containing Li and Mg with 1 did not produce detectable amounts of 3. The organolithium reaction gave a 41% yield of the deiodinated derivative of 1 along with a minor amount (~20%) of an unidentified product, while the organomagnesium reaction mixture contained the unreacted starting material (48%) and the deiodinated product (15%). These results are summarized in Table I.[14]

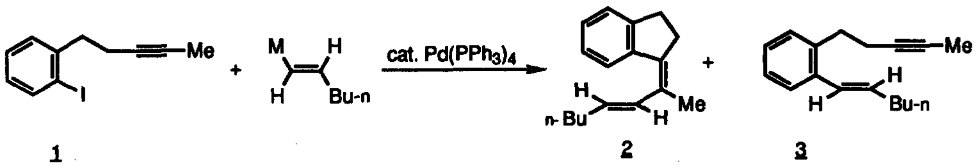
Although similar trends have been observed in other cases as well, it has been noted that the relative effectiveness of various metals also depends on the carbon ligands. As can be seen from the results summarized in Table I and Scheme I, zirconium is probably the most effective metal for introducing an alkenyl group but not for introducing aryl or alkynyl groups, in part because there is no satisfactory route to R(Cl)ZrCp$_2$ where R is aryl or alkynyl. On the other hand, tin is effective for incorporating alkenyl or alkynyl groups but not aryl groups. The reaction of 1 with PhSn(Bu-*n*)$_3$, for example, caused the disappearance of 1 without producing either 4 or 5. Triarylalanes have been the most effective cyclization-arylation agents. The stereochemical assignments of the cyclization-cross coupling products were based on ^{1}H 2D NOESY NMR spectroscopy. The stereoselectivity in each case was >98%.

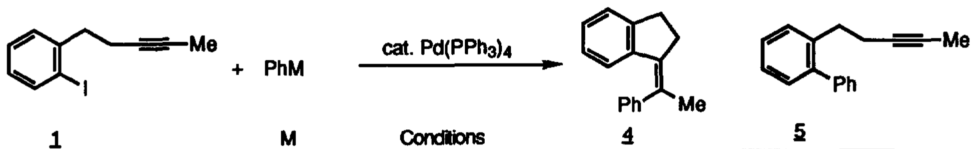
Table I. Reaction of *o*-Iodo-3-pentynylbenzene (1) with (*E*)-1-Hexenylmetals Catalyzed by Pd(PPh$_3$)$_4$[a]

M of MCH=CHBu-*n*[b]	Solvent	Temp.	Yield by GLC (%)			
			1	2	3	Others
ZnCl	THF	25°C	trace	68	19	trace
ZrCp$_2$Cl	THF	reflux	10	$\le$3	84	trace
SnMe$_3$	THF-HMPA[c]	reflux	18	$\le$2	69	trace
Al(Bu-*i*)$_2$	THF	reflux	trace	32	57	trace
BO$_2$C$_6$H$_4$[d]	benzene[e]	reflux	37	$\le$4	41	trace
Li	THF	25°C	trace	trace	trace	60[f]
MgI	THF	reflux	48	trace	trace	15[g]

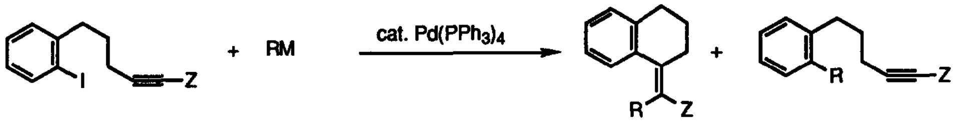
[a] The reaction times varied from 1 to 10 h. [b] Organometals containing Zn, Sn, and Li were prepared from 1.2-1.3 equivalents of (*E*)-1-hexenyl iodide via Li-I exchange, while the Mg derivative was prepared via direct metalation. Those containing Zr and Al were prepared via the respective hydrometallation of 1-hexyne. [c] Two molar equiv of HMPA was added. [d] BO$_2$C$_6$H$_4$ = catecholborane. [e] Two equivalents of NaOEt in EtOH were added. [f] Deiodinated product (41%) and an unidentified product. [g] Deiodinated product.

Scheme I

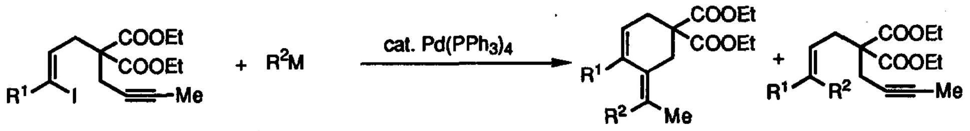




M	Conditions	4	5
ZnCl	THF, 25°C	34%	57%
$AlPh_2$	benzene, reflux	93%	<2%
$AlMe_2$	THF, reflux	40%	5%
$Sn(Bu\text{-}n)_3$	THF-HMPA, reflux	trace	trace



6 Z	RM	Conditions	7	8
Me	$H_2C{=}CHZnCl$	THF, 25°C	trace	63%
n-Bu	$H_2C{=}CHSn(Bu\text{-}n)_3$	THF-HMPA, reflux	89%	<5%



9 R^1	R^2M	Conditions	10	11
n-Bu	$(n\text{-}BuC{\equiv}C)_2Zn$	THF, 25°C	8%	75%
n-Bu	$n\text{-}BuC{\equiv}CSnMe_3$	THF-HMPA, reflux	73%	<5%
n-Bu	$n\text{-}BuC{\equiv}CB(Bu\text{-}n)_3Li$	THF, 25°C	45%	not determined
n-Bu	$n\text{-}BuC{\equiv}CH$ + CuI (5%) $n\text{-}BuNH_2$ (5 equiv)	benzene, 25°C	16%	49%
n-Bu	$[(E)\text{-}1\text{-}Hexenyl]_2Zn$	THF, 25°C	trace	50%
n-Pr	$[(E)\text{-}1\text{-}Hexenyl]ZrCp_2Cl$	THF, reflux	85%	not determined

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(14) The following procedure for the conversion of 1 into 3 is representative. To a slurry of $Cp_2Zr(H)Cl$ (0.38 g, 1.5 mmol) in 3 mL of benzene was added 1-hexyne (0.23 mL, 2.0 mmol) under nitrogen at 25°C. After 3 h the volatiles were evaporated under reduced pressure, and 2 mL of THF was added to the residue. The resultant solution was added to a mixture of 1 (0.26 g, 0.95 mmol) and $Pd(PPh_3)_4$ (0.055 g, 0.05 mmol) in 2 mL of THF. After 5 h of refluxing, the reaction mixture was cooled to 0°C and quenched with water. Its analysis by GLC indicated the formation of 3 in 84% yield. The amount of 2 was $\leq$ 3%. Extractive workup followed by chromatography (silica gel, hexane) afforded a 70% yield (0.14 g, 0.62 mmol) of 3: IR (neat) 1610(w), 1460(m), 970(s), 750(s) cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.94 (t, *J* = 7.1 Hz, 3H), 1.3-1.5 (m, 4H), 1.97 (s, 3H), 2.15-2.3 (m, 2H), 2.7-2.9 (m, 2H), 2.9-3.0 (m, 2H), 5.84 (dt, *J* = 15.5 and 7.1 Hz, 1H), 6.99 (d, *J* = 15.5 Hz, 1H), 7.1-7.7 (m, 4H). ^{13}C NMR ($CDCl_3$, Me_4Si) 14.23, 17.87, 22.57, 30.54, 32.20, 32.55, 33.32, 125.62, 125.96, 126.65, 127.19, 127.52, 130.40, 131.31, 139.32, 141.92, 148.56. High resolution MS Calcd for $C_{17}H_{22}$ 226.1722, found 226.1722.

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