Clarification of a Remarkable Chelate Effect Leads to Palladium-Catalyzed Base-Free Olefin Arylation

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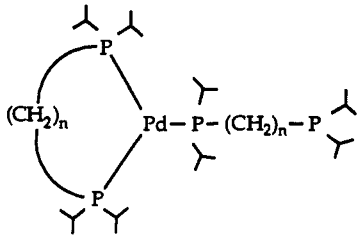
Summary: Palladium-catalyzed, base-free olefin arylation is possible. Thus, reaction of chlorobenzene with styrene and zinc to yield cis-stilbene is catalyzed by Pd(dippp)$_2$ (2) (or by Pd(OAc)$_2$ + 2dippp; dippp = 1,3-bis(diisopropylphosphino)propane). Other aryl chlorides are also reactive, whereas aryl bromides undergo substantial reduction and coupling. The reaction was discovered as a result of the observation that cis-(dippp)Pd(Ph)Cl, formed upon oxidative addition of PhCl to 2, reacts with excess styrene (in the presence or absence of base) to generate H_2 and yield (dippp)Pd(styrene) and (dippp)PdCl$_2$ (5). The latter complex is formed as a result of the instability of the putative cis-(dippp)Pd(H)Cl. 5 can be reduced to Pd(dippp)$_2$ with zinc in the presence of dippp. Pd(dippb)$_2$ (1) (dippb = 1,4-bis(diisopropylphosphino)butane), which yields a trans-oxidative-addition product with PhCl, is inactive in the base-free catalysis, and monophosphines are not effective. This novel reaction is complementary to the normal vinylation of aryl chlorides catalyzed by Pd(dippb)$_2$ under basic conditions, which leads to trans products.

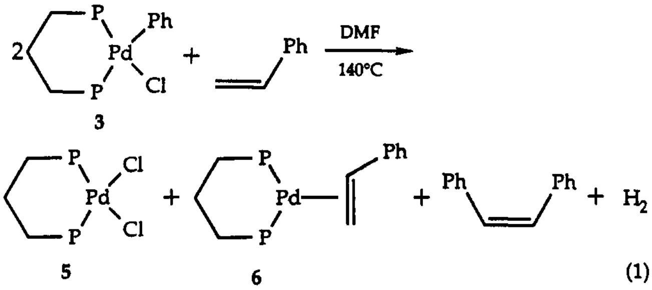
Arylation of olefins catalyzed by palladium, the "Heck reaction", is a very useful synthetic method for generating carbon–carbon bonds,[1] which has gained much laboratory and industrial interest. This reaction invariably requires the use of a base, the presence of which may be problematic at times, causing "ester hydrolysis, aldol condensations and other undesired site reactions".[1c] We report here that by proper choice of ligand it is possible to carry out this reaction under reducing conditions in the absence of a base. This reaction exhibits an unprecedented, very pronounced chelate effect, enabling the choice of reaction conditions and product stereochemistry by a mere one-carbon change in the chelate size. This also provides a new approach to the desirable utilization of aryl chlorides (rather than bromides or iodides, which are usually used) in arylation.

We have reported[2] that the Heck reaction can be carried out with aryl *chlorides* when Pd(dippb)$_2$ (1; dippb = 1,4-bis(diisopropylphosphino)butane) is used as a catalyst. Remarkably, the isostructural[3] Pd(dippp)$_2$ (2; dippp = 1,3-bis(diisopropylphosphino)propane) is essentially inactive in this process, although it is an excellent catalyst for carbonylation reactions of aryl chlorides.[4]



1, n = 4
2, n = 3

In order to understand the reason behind this phenomenon, we evaluated the reaction of complex **3**, obtained by oxidative addition of chlorobenzene to **2**,[3,5] with styrene. Interestingly, when 10 equiv of styrene is heated with **3** in DMF at 140 °C, two palladium complexes are formed in equivalent amounts: the dichloride **5**[6] and the Pd(0) complex **6**.[7,8] Stilbene (mainly the cis isomer) and hydrogen are also formed in this process (eq 1). Essentially, the same results are obtained in the presence of sodium acetate or triethylamine. In contrast, the complex *trans*-(η^1-dippb)$_2$Pd(Ph)Cl (4), obtained by oxidative addition of chlorobenzene to 1,[3] reacts with styrene in the presence of sodium acetate to regenerate complex **1** and produce *trans*-stilbene. Thus, the reason for the inefficiency of **2** as a catalyst is deactivation of half of the amount of the palladium complex in each cycle. The dichloride complex is not reduced under the reaction conditions and is catalytically inactive. Indeed, examination of the reaction mixture of attempted catalysis with **2** revealed that it was quantitatively transformed into **5**.



(1)

Formation of **5** is probably a result of reaction of HCl with the unobserved intermediate cis hydrido chloride complex **7**, which is apparently unstable and could not be prepared independently (Scheme I). Indeed, reacting the Pd(0) complex with 1 equiv of HCl gas generates $^1/_2$ equiv of **5** and no hydrido chloride complex (eq 2). This

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[1] (a) Heck, R. F. *Org. React.* **1982**, *27*, 345. (b) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: New York, 1985; pp 276–287. (c) Heck, R. F. In *Comprehensive Organic Chemistry*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 4, pp 833–863.

[2] Ben-David, Y.; Portnoy, M.; Gozin, M.; Milstein, D. *Organometallics* **1992**, *11*, 1995.

[3] Portnoy, M.; Milstein, D. *Organometallics* **1993**, *12*, 1655.

[4] (a) Ben-David, Y.; Portnoy, M.; Milstein, D. *J. Am. Chem. Soc.* **1989**, *111*, 8742. (b) Ben-David, Y.; Portnoy, M.; Milstein, D. *J. Chem. Soc., Chem. Commun.* **1989**, 1816.

[5] Portnoy, M.; Milstein, D. *Organometallics* **1993**, *12*, 1665.

[6] Portnoy, M.; Frolow, F.; Milstein, D. *Organometallics* **1991**, *10*, 3960.

[7] Excess olefin is required. Very little reaction takes place when equivalent amounts are used.

[8] Complex **6** was prepared independently by reaction of Pd(dippp)$_2$ with excess styrene in the presence of a phosphine scavenger: Portnoy, M.; Milstein, D., to be submitted for publication. It is stable only in the presence of excess styrene. $^{31}P\{^1H\}$ NMR (THF): δ 24.5 (d, J = 12 Hz, 1P), 34.0 (d, J = 12 Hz, 1P).

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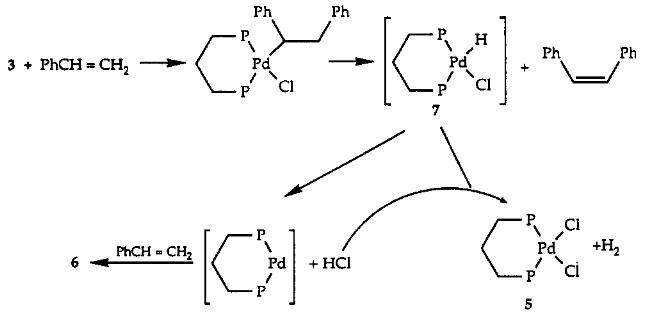
Table I[a]

$$PhCl + PhCH{=}CH_2 + {}^1/_2M \xrightarrow{Pd(OAc)_2 + 2L} PhCH{=}CHPh + {}^1/_2MCl_2 + {}^1/_2H_2$$

L	M	% PhCH=CHPh cis	% PhCH=CHPh trans	% PhH	% Ph—Ph	% Ph—Cl
dippp	Zn	81	7	2	0	10
dippp[b]	Zn	41	18	30	0	11
dippb	Zn	0	0	1	0	99
dippp	Cu	2	34	1	2	60
dippp	Fe	5	2	2	0	91
dippe	Zn	15	30	27	0	28
dippe + iPr$_3$P	Zn	1	0	98	1	0
2 iPr$_3$P	Zn	1	11	2	13	73

[a] Reaction conditions: a solution containing chlorobenzene (10 mmol), styrene (12 mmol), zinc (5 mmol), Pd(OAc)$_2$ (0.1 mmol), dippp (0.2 mmol), and DMF (4 mL) was heated at 140 °C for 24 h under argon in an open vessel equipped with an efficient condensor. Similar results are obtained when preformed Pd(dippp)$_2$ is used. [b] Reaction carried out in a closed vessel.

Scheme I



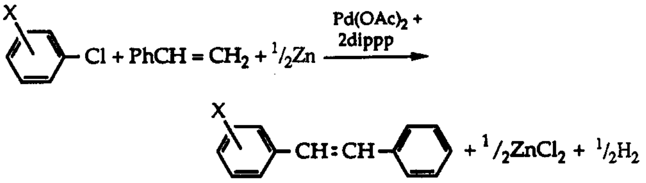
$$2 + HCl \overset{-dippp}{\rightleftharpoons} 7 \xrightarrow{HCl} 5 + H_2 \qquad (2)$$

instability is probably a result of the trans effect of the phosphine ligand, as contrasted with the stability of *trans*-hydridochloropalladium(II) complexes, in which this effect is absent.[9,10] Formation of 5 cannot be attributed to disproportionation of 3, since this complex is stable at 140 °C in the absence of styrene. The reason for the difference in catalytic activity between complexes 1 and 2 is undoubtedly related to formation of η^1-dippb complexes and is currently under study.

Several inorganic and organic bases have been tried in order to prevent this deactivation mode, with no success. Hence, in order to effect catalysis, we added a reducing agent, Zn powder, and omitted the base. Indeed, good yields of stilbene were obtained (Table I). Some reduction to the corresponding arene was observed, which could be minimized by efficient removal of the liberated H$_2$ by bubbling gas through the solution. This reduction becomes very significant when the aryl chloride is para-substituted with an electron-withdrawing group, undoubtedly because of more difficult olefin insertion into the stronger Pd–Ar bond.

Although, as expected, copper is far less effective than zinc, catalysis does take place. This suggests that the role of the metal is reduction of (dippp)PdCl$_2$ (5) rather than of the HCl produced. Indeed, reaction of 5 with Zn in the presence of dippp yields complex 2.

Table II[a]



X	solvent	% ArCH=CHAr cis	% ArCH=CHAr trans	% ArH	% ArCl
H	DMF	81	7	2	10
H	NMP	48	34	1	17
4-COMe	DMF	10	60	26	4
4-CO$_2$Me	NMP	0	65	20	15
4-OMe	DMF	37	12	12	39
3-OMe	DMF	46	18	6	30

[a] Reaction conditions are as described in Table I. Reaction temperatures: DMF, 140 °C; NMP, 160 °C.

It is noteworthy that the reaction mainly produces the kinetic product, *cis*-stilbene (except with the electron-withdrawing acetyl or carbomethoxy substituents). Under similar *basic* conditions with 1 as catalyst, the *trans* isomer is the major product. This is in line with the instability of the putative Pd–H complex 7 mentioned above. The cis to trans isomerization is probably catalyzed by Pd–H.

DMF is the solvent of choice. NMP (*N*-methylpyrrolidinone) can also be used, but a higher temperature (160 °C) is required, resulting in cis to trans isomerization. The reaction is mainly useful in the case of aryl chlorides. Aryl bromides yield, in addition to the desired stilbenes, substantial amounts of biphenyls.

The most effective catalyst in our hands for this "reductive Heck" reaction is 2. The dippe complex (dippe = 1,3-bis(diisopropylphosphino)ethane) also catalyzes the reaction, although less efficiently and selectively. The dippb complex is completely inefficient under the reducing conditions. We are unaware of other examples of selective catalytic vinylation of olefins with organic halides in the absence of a base.[11,12]

In summary, complexes 1 and 2 are complementary; whereas 1 is efficient under basic conditions, leading to *trans*-stilbenes, 2 is effective under reducing, nonbasic conditions and primarily produces *cis*-stilbene. This remarkable chelate effect clearly demonstrates the high sensitivity of homogeneous catalysis to "minor" ligand variations.

It is well-known that homogeneous catalysis can be very sensitive to the ligands used, although the reasons for this are generally not clear. Understanding the source of the ligand effect can lead to the discovery of new reactions, as demonstrated here.

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(9) See, for example: Saito, T.; Munakata, H.; Imoto, H. *Inorg. Synth.* **1977**, *17*, 83.

(10) A Pd(I) dippp complex containing *bridging* hydride trans to phosphorus is stable.[6]

(11) Synthesis of nortricyclenes from norbornadiene using palladium and zinc: Li, C.-S.; Chen, S.-S.; Shaw, J.-S. *J. Chem. Soc., Chem. Commun.* **1990**, 1774.

(12) Reaction of activated olefins with aryl halides, zinc, and NiCl$_2$(PPh$_3$)$_2$ results in low catalytic activity to give a mixture of various coupling and vinylation products: Boldrine, G. P.; Sovoia, D.; Tagliavini, E.; Trombini, C.; Umani Ronchi, A. *J. Organomet. Chem.* **1986**, *301*, C62.