species was calculated by interpolation of a standard curve of carbonic anhydrase, cytochrome C, and aprotinin.

Reaction conditions: Mixtures of K1 (240 μM) and K2 (240 μM) were incubated at 23°C in 250 mM MOPS (1% (v/v) 3-mercaptopropionic acid), 0 to 2.0 M $NaClO_4$, at pH 7.5. At the indicated time interval 50 μL of the reaction mixture was evaluated by reversed-phase HPLC. The reaction products were identified by direct isolation and characterization by mass spectrometry, or by HPLC coinjection with authentic samples. Concentrations of product were determined by interpolation of peak areas from a standard curve.

Received: July 24, 1997 [Z10729IE]
German version: *Angew. Chem.* **1998**, *110*, 489–492

Keywords: bioorganic chemistry · peptides · self-replication · template synthesis

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A New Catalyst System for the Heck Reaction of Unreactive Aryl Halides

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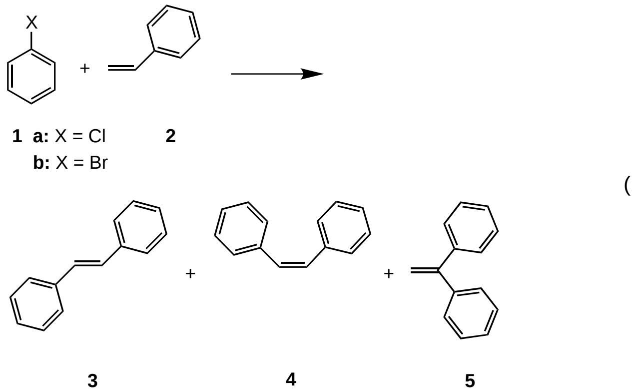
Although the palladium-catalyzed Heck reaction of aryl halides ArX (X = Cl, Br, I) with olefins is a standard C–C bond-forming reaction,[1] industrial applications are rare,[2] because the reactivity of aryl halides decreases drastically in the order ArI > ArBr > ArCl, which means that the cheap chlorides and even some bromides do not react with sufficiently high yields, turnover numbers (TON), and selectivities. In spite of recent progress, for example, use of certain palladacycles prepared from tris(*o*-tolyl)phosphane as catalysts in Heck reactions of bromo and activated chloro arenes,[3] the activation of unreactive aryl halides such as chlorobenzene remains a real challenge.[4] We report on a new and surprisingly simple catalyst system, which for the first time makes such coupling reactions possible in an unusually efficient manner.[5] We serendipitously discovered that the use of simple Pd salts such as $PdCl_2$ or $Pd(OAc)_2$ in the presence of tetraphenylphosphonium salts Ph_4PX (X = Cl, Br, I) leads to unexpectedly high catalytic activities.[6] Optimization of the reaction of chlorobenzene (**1a**) with styrene (**2**) to form the Heck products **3**, **4**, and **5** [Eq. (1)] showed that a ratio of Pd to Ph_4PX of 1:6 leads to the best results; sodium acetate is suitable as base and *N*,*N*-dimethylformamide (DMF) or *N*-methylpyrrolidinone (NMP) as solvent (Table 1).[7]



(1)

Another surprising discovery is that the use of small amounts of *N*,*N*-dimethylglycine (DMG) as additive leads to a pronounced improvement in regioselectivity.[7] Upon employing six equivalents of DMG relative to Pd and only 2 mol% of the Pd catalyst, the proportion of undesired regioisomer **5** is significantly reduced. Although no chemically engineered optimization was carried out, simple exploratory experiments showed that a further decrease in the amount of catalyst is certainly possible. Using 0.5 mol% catalyst a TON of 130 is reached. The same reaction with

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1433-7851/98/3704-0481 $ 17.50+.50/0

Table 1. Heck reaction of chlorobenzene (**1a**) with styrene (**2**) at 150°C.[a]

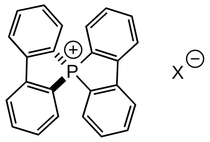
Catalyst	Solvent	t [h]	DMG [mol%]	Conversion [%]	Side products [%]	Selectivity [**3**:**4**:**5**]
$[Pd(CH_3CN)_2Cl_2]$	NMP	12	–	6	6	–
$[Pd(CH_3CN)_2Cl_2]\cdot 6\,Ph_4PCl$	DMF	8	–	89	11	86:1:13
$[Pd(CH_3CN)_2Cl_2]\cdot 6\,Ph_4PCl$	NMP	12	–	79	<1	84:1:15
$[Pd(CH_3CN)_2Cl_2]\cdot 6\,Ph_4PCl$	NMP	12	12	96	<1	96:1:3
$[Pd(CH_3CN)_2Cl_2]\cdot 6\,Ph_4PCl$	DMF	12	12	95	12	96:1:3
$[Pd(CH_3)_2(tmeda)]\cdot 6\,Ph_4PCl$[b]	NMP	12	9	85	<1	97:1:2
$[PdCl_2(Ph_3P)_2]\cdot 4\,Ph_4PCl$	DMF	6	–	77	7	85:1:14
$[\{Pd(\mu\text{-}Cl)(Ph_3P)(Ph)\}_2]$	NMP	12	–	14	8	83:2:15
$[\{Pd(\mu\text{-}Cl)(Ph_3P)(Ph)\}_2]\cdot 6\,Ph_4PCl$	NMP	12	–	86	<1	85:1:14
$[\{Pd(\mu\text{-}Cl)(Ph_3P)(Ph)\}_2]\cdot 6\,Ph_4PCl$	NMP	12	12	80	<1	97:1:2
$Pd(OAc)_2\cdot 6\,Ph_4PCl$	NMP	12	12	79	<2	97:1:2

[a] [a] Sodium acetate (2 equiv) as base; 2 mol% Pd catalyst. [b] tmeda = *N,N,N',N'*-tetramethylethylenediamine.

bromobenzene (**1b**) and styrene (**2**) in NMP in the presence of as little as 0.05 mol% of the catalyst $[Pd(CH_3CN)_2Cl_2]\cdot 6\,Ph_4PCl$ also proceeded smoothly (24 h; 140°C; 77% Heck products **3**, **4**, and **5** in a ratio of 90:1:9; TON = 1300).

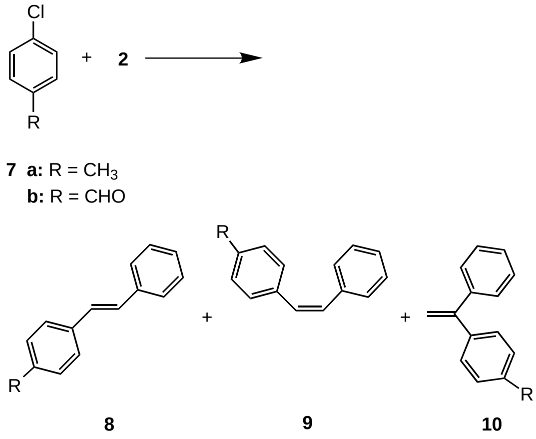
Interestingly, the influence of the phosphonium salt depends upon the nature of the halide counterion. Whereas the bromide is somewhat less effective than the chloride, the iodide turns out to be practically ineffective (<16% conversion after 8 h). Although detailed mechanistic studies remain to be carried out, we currently suspect that part or all of the reaction proceeds via the phosphonium salt. Ph_4PX are known to function as stoichiometric arylating agents in Pd-catalyzed Heck reactions, albeit in moderate yields.[8] Triphenylphosphane is thereby generated, which in our case becomes arylated back to the phosphonium salt in a known Pd-catalyzed process.[9]

It is currently unclear why the presence of Ph_4PX stabilizes the palladium so effectively, that is, why practically no undesired Pd precipitate is observed at such high temperatures. Anionic complexes[10] are probably formed on halide addition of Ph_4PX to such possible intermediates as $[(Ph_3P)Pd(Ph)X]$ or the dimeric form $[\{Pd(\mu\text{-}X)(Ph_3P)(Ph)\}_2]$. Indeed, the latter compound (X = Cl), which we were able to prepare easily as a relatively insoluble and difficult to characterize complex by reaction of $Pd(OAC)_2$ with Ph_4PCl in the presence of ethanol as the reducing agent,[11] is a highly active and thermally stable catalyst or precatalyst in the presence of excess Ph_4PCl. Accordingly, at 60–70°C the dimeric precursor is converted into a soluble and presumably anionic form. In addition, synthetically and mechanistically significant is the observation that the use of the spiro-type phosphonium salt **6a**,**b**[12] under the usual conditions of the test reaction leads to less than 4% conversion. This special phosphonium salt is particularly stable and does not undergo ring-opening arylation.



6 **a:** X = Cl
b: X = I

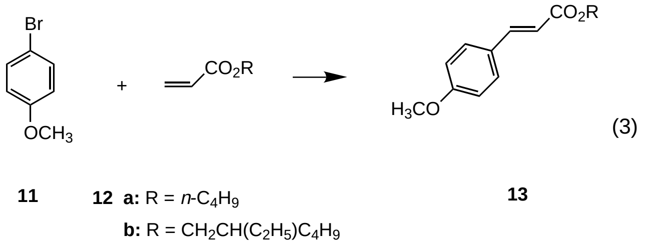
Should these hypotheses pertain, then the use of stoichiometric amounts of substituted aryl halides and catalytic amounts of $[Pd(CH_3CN)_2Cl_2]\cdot 6\,Ph_4PCl$ should afford scrambling products,[13] the amount of which is expected to depend upon the ratio of ArX to Ph_4PCl. Indeed, this was observed. For example, upon treating *p*-chlorotoluene (**7a**) with styrene (**2**) in the presence of $[Pd(CH_3CN)_2Cl_2]\cdot 6\,Ph_4PCl$ [2 mol%, NMP, 8 h, 150°C; Eq. (2)], not only the "normal" products **8a**, **9a**, and **10a** were formed in a ratio of 90: <1:10, but also the scrambling products **3**–**5** in a ratio of about 85:1:14 (conversion relative to **7a**: 66%; 30% normal products, 27% scrambling products). In the presence of DMG (12 mol%) the reaction proceeds similarly, but with increased regioselectivity (**8a**:**9a**:**10a** = 97: <1:3). The use of $[Pd(CH_3CN)_2Cl_2]\cdot 6\,(p\text{-tolyl})_4PCl$ as the catalyst (2 mol%, NaOAc, NMP, 19 h, 150°C) affords by nature solely the desired products **8a**, **9a**, and **10a** in a ratio of 90: <1:10 (58% conversion, 4% side products).



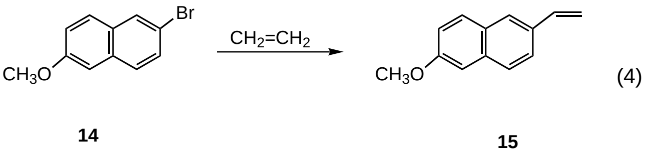
(2)

To suppress the amount of undesired scrambling products generally, it is not mandatory to prepare and use the corresponding phosphonium salt. Rather, it is simply necessary to reduce the amount of the catalyst $[Pd(CH_3CN)_2Cl_2]\cdot 6\,Ph_4PCl$. For example, the reaction of *p*-chlorobenzaldehyde (**7b**) with styrene (**2**) in presence of 0.1 mol% of $[Pd(CH_3CN)_2Cl_2]\cdot 6\,Ph_4PCl\cdot 6\,DMG$ (NaOAc, NMP, 48 h, 150°C) affords the desired products **8b**, **9b** and **10b** in a ratio of 98: <1:2 (98% conversion; TON = 950), and only 1% of undesired scrambling products **3**, **4**, and **5** [Eq. (2)].

The method can be applied to other substrates such as acrylates (**12**). Bromobenzene (**1b**) reacts smoothly with acrylate **12a** (0.01 mol% $[Pd(CH_3CN)_2Cl_2]\cdot 6\,Ph_4PCl$, NMP, 130°C; >97% yield, TON 9800). Reaction of the normally sluggishly reacting *p*-bromoanisol **11** with the acrylate **12b** [Eq. (3)] leads to 71 % of the desired product (TON 1300); only 1 % scrambling product and no 1,1-regioisomers are formed.[14]



In a further experiment the industrially relevant 2-bromo-6-methoxynaphthalene **14**[15] was treated with ethylene in the presence of 0.05 mol % $[Pd(CH_3CN)_2Cl_2] \cdot 6\,Ph_4PCl$ in a steel autoclave [NaOAc, *N*,*N*-dimethylacetamide as solvent, 24 h, 140°C, 20 bar; Eq. (4)]. The desired product **15** was obtained in 89 % yield (conversion 97 %, TON = 1800).



In summary, the combination of PdX_2 and Ph_4PX in the presence of DMG represents the currently most active and selective catalyst system for Heck reactions of normally unreactive aryl halides. Even the special palladacycles, recently described as being particularly active, fail in reactions of such substrates as chlorobenzene (**1a**).[3] Indeed, in our hands the coupling of **1a** and **2** with the usual palladacycle *trans*-di(μ-acetato)-bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium[3] with or without DMG as an additive proceeded to less than 2 % (TON = 1). The turnover number in the reaction of bromobenzene (**1b**) with acrylate (**12a**) is also significantly higher in our catalyst system (TON 9800 versus 48 for the palladacycle[3]). The same pertains to the reaction of *p*-bromoanisol (**11**; TON 1300 versus 87).[16] It remains to be seen whether our catalyst system is also effective in Suzuki coupling reactions, carbonylations, and aminations.

Received: September 3, 1997 [Z10884IE]
German version: *Angew. Chem.* **1998**, *110*, 492–495

Keywords: C–C coupling · Heck reaction · homogeneous catalysis · palladium · regioselectivity

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[7] Typical procedure: A pyrex reaction flask was charged with $Pd(CH_3CN)_2Cl_2$ (5.2 mg, 0.02 mmol) and Ph_4PCl (45.0 mg, 0.12 mmol), degassed three times under vacuum, and then flushed with argon. Anhydrous sodium acetate (164.0 mg, 2.0 mmol), chlorobenzene (**1a**; 112.6 mg, 1.0 mmol) and styrene (**2**; 130.2 mg, 1.25 mmol) were added. Following the addition of 1 mL NMP (or DMF) the flask was closed, and the contents stirred for 30 min at 120°C and then 12 h at 150°C. After the usual workup, the mixture was analyzed by gas chromatography. The reaction was performed analogously with *N*,*N*-dimethylglycine (DMG) as additive.

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