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A Highly Active Phosphine-free Catalyst System for Heck Reactions of Aryl Bromides

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Abstract

Palladium salts such as $Pd(OAc)_2$ or $PdCl_2(PhCN)_2$ in the presence of *N,N*-dimethylglycine (DMG) constitute the simplest and one of the most reactive and selective catalyst systems for the Heck reaction of aryl bromides with olefins known to date.

The palladium-catalyzed Heck reaction of aryl halides ArX (X = Cl, Br, I) with olefins is a widely used C-C bond forming process in academic institutions,[1] but industrial applications are rare.[2] This is due to the fact that the reactivity of aryl halides decreases drastically in the order ArI > ArBr > ArCl, which means that most of the cheap chlorides and many readily available bromides do not react with sufficiently high yields, turnover numbers and selectivities, even if the traditional catalysts $Pd(PPh_3)_4$ or PdX_2/PPh_3 (excess) are used in relatively large amounts ($\geq$ 5 mol-%)[1,2] or new variations such as palladacycles[3] are employed. Another challenge of equal importance is the desire to simplify the catalyst by working under phosphine-free conditions.[4] Recently we reported that catalytic amounts of $PdX_2/6\ Ph_4PCl$ constitute the first effective catalyst system for the Heck reaction of aryl chlorides, especially in the presence of 10 – 12 mol-% of the cheap additive *N,N*-dimethylglycine (DMG).[5] In the absence of the phosphonium salt Ph_4PCl, no reaction takes place, i.e., PdX_2/DMG fails to catalyze the reaction of ArCl. We now report that the phosphine-free system $PdCl_2(PhCN)_2$/DMG or $Pd(OAc)_2$/DMG is in fact an excellent catalyst in the Heck reaction of aryl bromides.[6]

In a model reaction the Heck coupling of bromobenzene **1** with styrene **2** was carefully monitored with respect to conversion and selectivity of product formation (**3**, **4** and **5**).[7] Table 1 shows that in the case of 1 – 1.5 mol-% of $PdCl_2(PhCN)_2$/20 DMG and NaOAc as base in *N*-methyl-2-pyrrolidone (NMP) as solvent the reaction is essentially complete within 10 h at 130 °C, selectivity being high (**3** : **4** : **5** = 96.4 : 0.6 : 3.0).[8] Similar results were obtained with $Pd(OAc)_2$ in the presence of DMG. In contrast, $PdCl_2(PhCN)_2$ or $Pd(OAc)_2$ in the absence of the additive lead to poor conversions (40% and 38%, respectively) and lower selectivities under otherwise identical conditions (Table 1). In the case of $Pd(OAc)_2$ alone respectable conversion (70%) was obtained only upon extending the reaction time (30 h) and applying drastic conditions (150 °C). But even then conversion and selectivity are considerably lower than in the case of $PdCl_2(PhCN)_2$ in the presence of DMG at lower temperatures and shorter reaction times (Table 1). In the latter case the amount of Pd-catalyst can be reduced to 0.0009 mol-% while obtaining essentially the same conversion. This corresponds to a turnover number

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of TON = 106700. However, the reaction time is long (4 days) and selectivity is lower. Even higher TONs are possible at lower conversions, but this was not optimized.

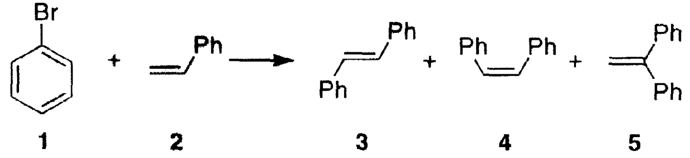


Table 1

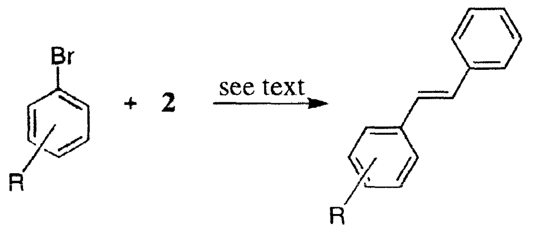
Heck Reaction[a] of **1** with **2** in the Presence or Absence of $(CH_3)_2NCH_2CO_2H$ (DMG)

Catalyst (mol-%)	Solvent	DMG : Pd	Temp. (°C)	Time (h)	Conversion[b] (%)	Selectivity[b] (**3** : **4** : **5**)
$PdCl_2(PhCN)_2$ (1.5)	NMP[c]	20 : 1	130	10	98	96.4 : 0.6 : 3.0
$PdCl_2(PhCN)_2$ (1.1)[d]	NMP	20 : 1	130	10	99	95.7 : 0.6 : 3.7
$PdCl_2(PhCN)_2$ (0.1)	NMP	20 : 1	130	10	96	93.7 : 1.1 : 5.2
$PdCl_2(PhCN)_2$ (0.03)[e]	NMP	20 : 1	130	10	99	93.3 : 0.7 : 6.0
$PdCl_2(PhCN)_2$ (0.01)	NMP	20 : 1	130	24	98	92.7 : 0.7 : 6.6
$PdCl_2(PhCN)_2$ (0.0009)	NMP	20 : 1	130	96	96	92.9 : 0.7 : 6.4
$PdCl_2(PhCN)_2$ (1.5)	NMP	20 : 1	110	10	98	96.6 : 0.4 : 2.9
$PdCl_2(PhCN)_2$ (1.5)	NMP	20 : 1	100	10	79	96.6 : 0.4 : 2.9
$PdCl_2(PhCN)_2$ (1.5)	CH_3OH	20 : 1	130	10	99	97.0 : 0.5 : 2.5
$PdCl_2(PhCN)_2$ (1.5)	CH_3OH	7 : 1	130	10	99	96.7 : 0.3 : 3.0
$PdCl_2(PhCN)_2$ (1.5)	EtOH	20 : 1	130	10	79	97.0 : 0.5 : 2.5
$PdCl_2(PhCN)_2$ (1.5)	DEG[f]	20 : 1	130	10	99	96.6 : 0.4 : 3.0
$PdCl_2(PhCN)_2$ (1.5)	DMA[g]	20 : 1	130	10	81	96.0 : 0.9 : 3.1
$PdCl_2(PhCN)_2$ (1.5)	DMSO[h]	20 : 1	130	10	8	97.3 : 0.9 : 1.8
$PdCl_2(PhCN)_2$ (1.5)	CH_3CN	20 : 1	130	10	25	93.7 : 3.9 : 2.3
$PdCl_2(PhCN)_2$ (1.5)	DMF[i]	20 : 1	130	10	54	96.0 : 0.7 : 2.6
$Pd(OAc)_2$ (1.5)	CH_3OH	20 : 1	130	10	99	96.5 : 0.3 : 3.1
$Pd(OAc)_2$ (1.5)	NMP	20 : 1	130	10	99	96.0 : 0.6 : 3.4
$PdCl_2(CH_3CN)_2$ (2.0)	CH_3OH	20 : 1	130	10	98	96.4 : 0.3 : 3.3
$PdCl_2(PhCN)_2$ (1.5)	NMP	no DMG	130	10	40	93.5 : 0.7 : 5.8
$PdCl_2(PhCN)_2$ (1.5)	CH_3OH	no DMG	130	10	8	not determined
$PdCl_2(PhCN)_2$ (1.5)	DEG	no DMG	130	10	36	90.0 : 1.3 : 8.7
$Pd(OAc)_2$ (1.5)	NMP	no DMG	130	10	18	94.0 : 0.8 : 5.2
$Pd(OAc)_2$ (1.5)	CH_3OH	no DMG	130	10	8	not determined
$Pd(OAc)_2$ (1.5)	DMSO	no DMG	130	10	38	93 : 1.0 : 6.0
$Pd(OAc)_2$ (1.5)	CH_3CN	no DMG	130	10	2	not determined
$Pd(OAc)_2$ (1.5)	NMP	no DMG	130	30	51	93.0 : 1.0 : 6.0
$Pd(OAc)_2$ (1.5)	NMP	no DMG	150	30	70	92.0 : 1.0 : 7.0
$Pd(OAc)_2$ (0.009)	NMP	no DMG	130	24	77	92.7 : 0.8 : 6.5
$Pd(OAc)_2$ (0.0009)	NMP	no DMG	130	96	85	93.0 : 0.7 : 6.3

a) Generally 1 mmol of **1**, 1.5 mmol of **2** and 2 mmol of sodium acetate were used under an atmosphere of argon. b) Conversion and selectivity were determined by gas chromatography using decane and hexadecane as internal standards. c) NMP = *N*-methyl-2-pyrrolidone. d) In this case 2.3 mmol of **1**, 3.5 mmol of **2** and 4.6 mmol of sodium acetate were used. e) In this case 40.0 mmol of **1**, 60 mmol of **2** and 80 mmol of sodium acetate were used. f) DEG = diethylene glycol. g) DMA = dimethylacetamide. h) DMSO = dimethylsulfoxide. i) DMF = dimethylformamide.

Applying the standard conditions [$PdCl_2(PhCN)_2$ (1.5 mol-%)/20 parts DMG and NaOAc as base in NMP at 130 °C for 10 h],[8] several other aryl bromides were subjected to the Heck reaction of styrene **2**. In all cases >95% trans-selectivity was observed with only traces of the side-products. As expected the activated substrates with electron-withdrawing groups react very smoothly. *p*-Methoxybenzene (**6e**), being a de-activated aryl bromide,[2] reacts with remarkably high conversion (89%), and even the *p*-dimethylamino derivative **6g** participates in the reaction. The reactions were not optimized.

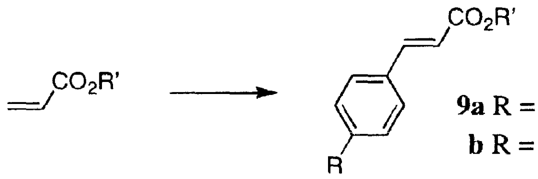
6 a R = *p*-NO_2
b R = *p*-CF_3
c R = *p*-CN
d R = *p*-$COCH_3$
e R = *p*-OCH_3
f R = *m*-OCH_3
g R = *p*-$N(CH_3)_2$



7 a 100% conversion
b 96% conversion
c 100% conversion
d 100% conversion
e 89% conversion
f 60% conversion
g 60% conversion

Finally, the olefinic substrate was varied to include the acrylate **8**. Under the standard conditions[8] smooth formation of products **9** was observed. More than 97% trans-selectivity at 97% conversion was detected by GC analysis. Here again optimization was not strived for, i.e., the use of less catalyst may well be possible.

8 R' = 2-ethylhexyl



9a R = H 97%
b R = CH_3 97%

The precise function of the additive DMG is currently unknown. However, when using 1.5 mol-% of $PdCl_2(PhCN)_2$ in the presence of DMG it was observed experimentally that the color of the reaction mixtures remains yellowish/light brown until essentially all of the aryl bromide had been consumed (after which the solution turns black). In contrast, working in the absence of DMG resulted in an immediate color change from light yellow to black at the beginning of the reaction at 130 °C. At these catalyst concentrations the DMG-based system is much more efficient than $Pd(OAc)_2$ alone, which means that excellent conversion and maximum selectivity can be achieved within 10 hours. At very low catalyst concentrations the two systems start to converge as far as performance is concerned (Table 1). High TONs are then possible at the expense of very long reaction times (4 days) which may impede real applications. Interestingly, at such low catalyst concentrations the $Pd(OAc)_2$ system improves in efficiency.[9] We have previously shown that the thermolysis of $Pd(OAc)_2$ at 100 °C in a polar solvent such as propylene carbonate (PC) results in the ready formation of black PC-stabilized nanostructured Pd-colloids (8 – 10 nm in size as shown by transmission electron microscopy), and that these preformed clusters catalyze Heck reactions.[10] It is thus possible (although not proven) that the protocols described above using PdX_2/NaOAc at 130 °C involve solvent-stabilized nanoparticles of palladium.[11] Experimentally, other nitrogen-containing compounds such as picolinic acid are also useful additives, although less effective than DMG.

In summary, although mechanistic details need to be illuminated in future work, we have discovered extremely efficient catalyst systems for Heck reactions of aryl bromides. It remains to be seen if related coupling processes such as the amination of aryl bromides as well as Suzuki and Stille reactions can also be catalyzed by the phosphine-free system PdX_2/DMG or $Pd(OAc)_2$.

Acknowledgement
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7. In some cases extremely small amounts (< 0.4%) of the double Heck reaction product triphenylethylene are formed.
8. Typical procedure: In the reaction flask were placed $PdCl_2(PhCN)_2$ (0.015 mmol) and *N,N*-dimethylglycine (0.3 mmol). After evacuating and purging under argon, 2 mmol sodium acetate, 1 mmol bromobenzene, 1.4 mmol styrene were added, dissolved in 1 ml dry solvent and stirred at 130 °C for 10 h. After cooling, 2 ml diethylether and the GC-standards were added. The reaction mixture was filtered through Al_2O_3 and analyzed by gas chromatography.
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