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Heck Reactions of Aryl Chlorides Catalyzed by Ligand Free Palladium Salts

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Abstract Palladium acetate has been shown to be a highly active catalyst for Heck reactions of aryl chlorides even in the absence of organic ligands. Bromobenzene can efficiently be coupled in presence of negligible traces of Pd, resulting in the highest TON (4.7×10^7) and TOF (1.2×10^7 h^{-1}) values that have ever been reported for this system up to now.

Keywords Aryl chlorides · CC coupling · Ligand free · Palladium

1 Introduction

In the last few years, mechanistic investigations on palladium catalyzed coupling reactions which focus on the identification of the truly catalytically active species during the reaction cycle have attracted considerable attention. Although a great variety of different—homogeneous [1] as well as supported [2–4]—Pd catalysts have been employed in, e.g. Heck-type coupling reactions (Scheme 1), the question arises whether these Pd compounds contain Pd in an active form or they act only as a pre-catalyst from which the active species is generated or released in situ. Careful interpretation of literature results corroborates the latter assumption since homogeneous catalysis is induced by either in situ reduction of Pd(II) complexes and/or ligand dissociation to generate active Pd(0) species bearing free coordination sites for oxidative addition of the aryl halide as the first step of the catalytic cycle. Several recent investigations have shown that in presence of supported Pd (pre-)catalysts the active species is generated in situ by dissolution of Pd species from the support [5].

Experimental results and spectroscopic observations have, however, been misinterpreted in many cases, because the Pd precursor might be transferred only partially into the active component. Thus, an observable amount of the initial Pd can be detected, which is often described as catalytically active, although it in fact represents a precursor or spectator species only. There are various examples in literature where catalytic activity is attributed to heterogeneous Pd surface sites arguing that the concentration found in solution is “not sufficiently high to explain the catalytic activity of the system”. In contrast to such claims, we were able to prove that dissolved Pd species which were generated from supported catalysts are catalytically active in low concentrations below 1 ppm [6, 7]. In this contribution, we will provide evidence that highly catalytically active species can also be generated from simple inorganic Pd salts and compounds, like $Pd(OAc)_2$, $Pd(OH)_2$, or $PdCl_2$.

For a classification of the activity of different catalysts, it is a reasonable approach to survey the substrate scope which is available for Heck couplings in presence of the respective catalysts. Due to the increasing aryl-X bond strengths of the different halides, the reactivity of aryl halides decreases in the order $I > Br \gg Cl$. In accordance, activation of aryl iodides and (activated) aryl bromides is feasible in presence of almost any kind of Pd pre-catalyst. In contrast, activation of aryl chlorides remains a major challenge which has to be met by a “highly active” catalyst system.

Application of $Pd(OAc)_2$ in quite low concentration (typically down to 10^{-3} mol%) has been reported for a variety of different CC couplings, including Heck [8–12]

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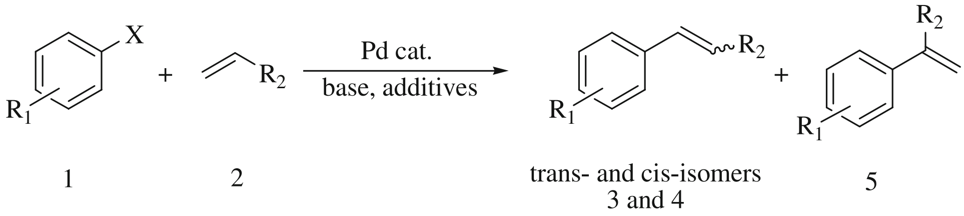
Scheme 1 Heck reaction of aryl halides and olefins



X = Cl, Br, I
R_1 = NO_2, CN, $COCH_3$, H, CH_3, OCH_3, etc.
R_2 = phenyl, COO(alkyl), etc.

and Suzuki [13, 14] reactions of aryl iodides and bromides. The addition of n-tetrabutylammonium bromide (NBu_4Br) facilitated even reactions of aryl chlorides in reactions of Suzuki-type while chlorides were not accessible for Heck reactions up to now under comparable conditions. Consequently, it has become a widespread and established presumption in the Heck community that such simple salts are absolutely unsuitable for reacting aryl chlorides.

2 Experimental

General procedure for Heck reactions of aryl chlorides: Pd catalyst, 12 mmol $Ca(OH)_2$, 6 mmol NBu_4Br, 10 mmol aryl chloride, and 500 mg diethylene glycol dibutylether as internal standard were weighed out into a pressure tube. After addition of 6 mL *N*-methylpyrrolidone (NMP) and 12 mmol styrene, the mixture was purged for 5 min with oxygen and the sealed pressure tube was put in a preheated oil bath (160 °C) for 6 h.

General procedure for Heck reactions of bromobenzene: Pd catalyst, 12 mmol NaOAc, 10 mmol bromobenzene, and 500 mg diethylene glycol dibutylether as internal standard were weighed out into a pressure tube. After addition of 10 mL NMP and 15 mmol styrene, the mixture was purged for 5 min with argon and the sealed pressure tube was put in a preheated oil bath (140 °C) for 4 h.

For experiments with ultra-low Pd amount, Pd was added as a NMP solution in appropriate concentration. "Pd free" experiments were performed using new pressure tubes and stirring bars (without possible Pd contamination).

General work-up procedure: After the end of the reaction, 2 mL of the reaction mixture are sampled and extracted with dichloromethane and water (2 mL each). The organic layer is dried over sodium or magnesium sulfate and analyzed by GC and GC-MS.

3 Results and Discussion

Recently, we reported on the generation and stabilization of soluble Pd species from solid catalysts, which are highly active in Heck reactions of even deactivated aryl chlorides [5, 6]. Strictly speaking the support functions just as a reservoir for the (ligand free) active species and the dissolution and re-deposition have to be controlled by careful choice of appropriate reaction parameters [4].

In this paper, we report on the transfer of this concept to homogeneous ligand free palladium salts. We demonstrate that homogeneously dissolved palladium acetate can as well be stabilized against agglomeration and deactivation by addition of NBu_4Br (formation of $[PdBr_n]^{m-}$ complexes) under optimized reaction conditions. The resulting catalyst system represents the first application of a soluble Pd catalyst which affords the activation of aryl chlorides in Heck reactions in absence of additional organic ligands. Thus, the presented results clearly disprove the current conceptions that have been made for Heck reactions of aryl chlorides up to now. In addition, reactions of bromobenzene could be performed in the presence of traces of Pd which were introduced only as "impurities" of common inorganic bases (= "palladium free" Heck reaction). In contrast to the known works in this area made by, e.g. Arai, Leadbeater, de Vries and Reetz [8–12], Pd concentrations in the range of even 10^{-7} mol% were found to be sufficient for activation of bromobenzene. The reactions could be performed using conventional heating to elevated temperatures (160 °C), application of microwave heating techniques (which is required, e.g. by Leadbeater [12]) was not necessary.

Table 1 visualizes the catalytic results of Heck reactions of various aryl chlorides and styrene in presence of $Pd(OAc)_2$ as the only catalyst. The choice of appropriate reaction conditions emerged to be crucial. Like in the case of highly active supported Pd catalysts [5, 6], $Ca(OH)_2$ as the base and oxygen atmosphere provided the best results. The addition of NBu_4Br was inevitable to achieve product formation with aryl chlorides. Probably, the bromide ions stabilize Pd against agglomeration by formation of inorganic Pd(0) and Pd(II) complexes, like $[PdBr_n]^{m-}$, and, thus, against catalyst deactivation.

In reactions of the activated 4-chloroacetophenone, the variation of the catalyst amount showed that the formation of the desired coupling products was comparatively low in presence of too high Pd amounts (1 mol%). This fact might

Table 1 Ligand free $Pd(OAc)_2$ as catalyst for Heck reactions of aryl chlorides and styrene

Cat. amount (mol%)	X	R_1	Conversion (%)	Yield **3** (%)	TON
1	Cl	$COCH_3$	99	49	49
0.1	Cl	$COCH_3$	98	67	670
0.01	Cl	$COCH_3$	100	94	9400
0.001	Cl	$COCH_3$	73	20	20000
0.01	Cl	H	71	38	3800
0.01	Cl	CH_3	9	3	300

be explained by an increased tendency towards particle agglomeration of the Pd species under these conditions as discussed already by de Vries [15]. This results in the formation of colloidal Pd which might promote dehalogenation reactions (leading to decreased selectivity) and finally in larger metallic Pd particles that are inactive (deactivation by Pd black formation). Reduction of the catalyst amount down to 0.01 mol% led to an optimized system, resulting in remarkable TON up to 10,000 and selectivity (94%) within short reaction times of 6 h. Application of lower Pd concentrations caused a significant loss of selectivity (only 20% yield at 0.001 mol% Pd). While activated aryl chlorides, like 4-chloroacetophenone, can be converted efficiently with remarkable selectivity under the chosen reaction conditions, non- and deactivated aryl chlorides are less reactive. The reaction of chlorobenzene yielded 38% of the coupling product at a conversion of 71%, while deactivated 4-chlorotoluene was almost inert under the chosen conditions. Benzene (or its derivatives) is found as an undesired side-product which is built via a dehalogenation route.

Table 2 demonstrates that several other simple inorganic Pd salts, including $Pd(OH)_2$, PdO, and $PdCl_2$, are suitable catalysts for reactions of bromobenzene. Under reaction conditions, which have been optimized for the coupling of aryl bromides and styrene [16, 17], 0.1 mol% of these cheap and readily available Pd salts are sufficient to obtain complete conversion and high selectivity towards the desired *trans*-product (≈90%) within 4 h. Reactions of non-activated aryl bromides in presence of ligand free $PdCl_2$ have been reported recently also by Schmidt et al. [18].

Table 2 Ligand free Pd salts in ultra-low concentrations as catalyst for Heck reactions of bromobenzene and styrene

Pd catalyst	Cat. amount (mol%)	Conv. (%)	Yield **3** (%)	TON	TOF (h^{-1})
$Pd(OH)_2$	0.1	99	89	890	225
$PdO \cdot H_2O$	0.1	100	92	920	230
$PdCl_2$	0.1	98	88	880	220
$Pd(OAc)_2$	10^{-5}	99	90	9.0×10^6	2.3×10^6
$Pd(OAc)_2$	3×10^{-7}	15	14	4.7×10^7	1.2×10^7
None[a,b]	1.3×10^{-5}	45	42	3.2×10^6	1.9×10^5

[a] Pd is introduced as "impurity" in NaHCOO

[b] 10 mmol bromobenzene, 18 mmol sodium formate, 6 mmol NBu_4Br, 3 mL NMP, 1 mL water, 140 °C, 17 h

$Pd(OAc)_2$ emerged to be an extremely efficient catalyst under the given reaction conditions. A drastic decrease of the Pd amount down to 10^{-5} mol% still provided complete conversion, resulting in TONs in the range of 10^7. Even negligible traces (3×10^{-7} mol%) of Pd promoted the Heck coupling. "Pd free" Heck couplings were also feasible under the optimized reaction conditions.

However, in accordance to the results of Leadbeater et al. (who found the same for "Pd free" Suzuki reactions [19]), Pd trace analysis (ICP-OES) proved that negligible amounts of Pd have been introduced to the system as an "impurity" in the applied base. The "ultra-low Pd concentrations" in ligand free Heck reactions that have been reported up to now by the groups of Arai, Reetz, de Vries and Leadbeater worked with Pd amounts in the range of 10^{-3} mol% [8–12]. In contrast to our work the catalyst loadings presented in these publications are higher by factors of 100–10,000. Consequently, the observed TON (4.7×10^7) and TOF (1.2×10^7 h^{-1}) of our systems are higher by several orders of magnitude and represent the highest numbers ever reported for Pd catalyzed coupling reactions of non-activated aryl bromides.

4 Conclusions

In summary, we have shown that simple palladium salts can act as efficient pre-catalysts for Heck-type coupling reactions of aryl chlorides and bromides in absence of any organic ligand. Under optimized reaction conditions (esp. use of NBu_4Br as additive for the stabilization of Pd species), activation of aryl chlorides in presence of simple $Pd(OAc)_2$ became feasible for the first time. $Pd(OAc)_2$ and other inorganic Pd salts turned out to be extremely efficient catalysts for reactions of bromobenzene, resulting in the highest TON (4.7×10^7) and TOF (1.2×10^7 h^{-1}) values that have been reported for this substrate up to now. In conclusion, each new Pd system called "highly active" in Heck reactions should be compared to these simple ligand free systems. In addition, the order of magnitude of activity and necessary Pd concentrations must be regarded in mechanistic investigations and conclusions.

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