



Tetraalkylammonium-Free Heck Olefination of Deactivated Chloroarenes by Using a Macrocyclic Catalyst Precursor

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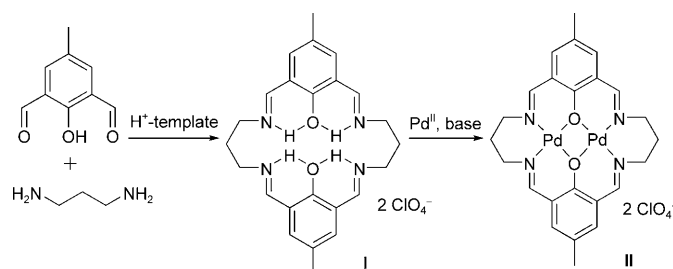
The palladium-catalyzed olefination of aryl halides (Mizoroki–Heck reaction) is a very versatile means of making new C–C bonds and continues to gain increasing importance in organic chemistry and fine chemical synthesis.^[1–3] Although seemingly any Pd species can achieve the coupling of aryl iodides and bromides under appropriate conditions, the industrially interesting activation of chloroarenes remains a challenging task and demands specific catalytic systems.^[4] Up to now, it has been stated by several groups that, unless exceptionally mild reaction conditions are applicable, any Pd precursor will release underligated free Pd⁰, which is the actual active species.^[4–11] This concerns both homogeneous and heterogeneous precatalysts. The released Pd species are unstable and likely to agglomerate and deactivate; therefore, stabilization is crucial for reasonable catalytic activity. As has been shown for heterogeneous Pd sources in the Heck coupling of aryl chlorides, the dissolution–reprecipitation equilibrium can provide sufficient stabilization for the active species, resulting in high activities. In some of these cases further stabilizers, such as tetrabutylammonium bromide (TBAB) are then unnecessary.^[11]

Macrocyclic complexes of Pd are characterized by an extraordinary stability, coordinative saturation of the central atom, and a preference for the Pd^{II} oxidation state. Although these qualities imply catalytic inactivity, a new concept of catalyst stabilization can be devised from them: If Pd was released from such complexes under C–C coupling reaction conditions, this release would be very slow and controlled. Reoordination of Pd into the macrocycle may also be possible and even favored. These processes would be similar to those for heterogeneous Pd precatalysts; however, by comparison, the equilibrium would be shifted to bound

Pd. In other words, the strong shift of the release–recapture equilibrium towards bound Pd should protect the catalytic species from fast deactivation under reaction conditions. Hence, macrocyclic Pd complexes may be suitable model systems to further utilize the stabilization of Pd species by controlled in situ generation from inactive precursors.

Herein, the successful application of this concept for the Heck olefination of highly deactivated chloroarenes will be shown. A bimetallic macrocyclic complex of the Robson type^[12a] is used as the precatalyst. As this paper will show, the new concept allows for very efficient Heck couplings with low catalyst loadings, even under additive-free conditions.

The bimetallic Pd complex **II** was prepared by first producing the free ligand **I** through proton-templated synthesis and subsequent metalation with two equivalents of palladium acetate (Scheme 1). This protocol gives complex **II** in very good yield and purity as a yellow powder.^[12b,c]



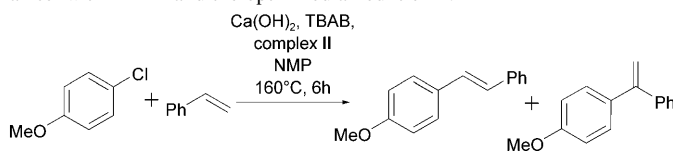
Scheme 1. Synthesis of the bimetallic Pd complex **II**.

As a model reaction for catalytic tests, we have chosen the Heck coupling of styrene with 4-chloroanisole, a highly deactivated aryl halide. The reaction was carried out under conditions that were applied in previous studies and were found to be suitable for the Heck coupling of aryl chlorides (Table 1).^[11] The initial catalyst amount was 0.5 mol % of **II** with respect to styrene.^[13] Under these conditions 48 % conversion of styrene and 36 % yield of 4-methoxy-*trans*-stilbene were obtained; the corresponding *cis*-stilbene was not

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Table 1. Catalytic results for the Heck coupling of styrene and 4-chloroanisole with TBAB and the optimized amount of **II**.^[a]



Entry	TBAB [mmol]	Conversion [%] ^[b]	Yield (t/g) [%] ^[c]
1	0.9	81	63/5
2	3.0	54	38/3
3	1.4	62	47/4
4	0.5	71	51/5
5	0.2	94	79/7
6	–	90	75/6
7 ^[d]	–	28	0/0
8 ^[d]	0.9	49	25/2

[a] Reaction conditions: styrene (1.5 mmol), 4-chloroanisole (3 mmol), Ca(OH)₂ (0.9 mmol), complex **II** (0.0375 mol %), N-methylpyrrolidone (NMP, 5 mL), air, 160 °C 6 h. [b] Conversion of styrene. [c] GC yields corresponding to the *trans* olefin (t) and the *gem* olefin (g). [d] Pd(OAc)₂ (0.075 mol %) was used as the catalyst.

found in this or any subsequent experiment. A 4 % yield of the *geminal*-substituted olefin 1-(4-methoxyphenyl)-1-phenylethene was also detected. In the following text the two Heck products will be regarded as the *trans* (t) and the *gem* product (g).

According to our concept, complex **II** releases ligand-free Pd into solution, which enters the catalytic cycle, is recaptured, or follows agglomeration pathways. It has been stated for ligandless Pd precatalysts (in the coupling of aryl bromides) that the catalyst performance highly depends on the initial Pd amount. Too low concentrations result in slow reaction progress, whereas higher amounts of catalyst lead to a more pronounced agglomeration of Pd.^[5,6] Thus, the same should apply to the Pd released from complex **II**. There should be an ideal initial amount of **II** that, in turn, generates the optimal amount of active Pd. A screening of different catalyst loadings showed an optimal initial loading of around 0.0375 mol % of **II**. With this amount of catalyst, conversion and yield were approximately doubled compared with the initial results with 0.5 mol % of catalyst, and the selectivity was also improved (Table 1, entry 1). Conversions and yields were lower with higher amounts of **II**. Moreover, a minimum catalyst loading of between 0.005 and 0.0125 mol % was found to be necessary for the reaction to occur. All of the subsequent experiments were conducted with the optimal amount of 0.0375 mol % of **II**.

If the controlled release and recapture of Pd by the macrocyclic ligand provides sufficient stabilization, it should render further stabilizers unnecessary. Accordingly, the reaction was also performed without TBAB. Under these additive-free conditions, a conversion of 90 % (Table 1, entry 6) and a selectivity of 90 % for the Heck products was obtained. This is one of the best reaction results reported in literature for these substrates (styrene and 4-chloroanisole). Similar results for the coupling of chloroanisole have, to the best of our knowledge, thus far only been achieved by using

phosphane ligands,^[15] or TBAB or comparable additives, including ionic liquids.^[16]

To further demonstrate the stabilizing effect, two comparison experiments were conducted, in which corresponding amounts of Pd(OAc)₂ (0.075 mol %) were used as the catalyst precursor instead of **II**. Without TBAB, Heck products were not observed. The addition of TBAB (0.9 mmol) led to a successful reaction, albeit with significantly lower conversion and selectivity than **II** without additives (Table 1, entries 7 and 8).

Screening the amount of TBAB even revealed that the conversions and yields decreased with a higher TBAB/**II** ratio (Table 1, entries 2 and 3) and increased when less TBAB was added (Table 1, entries 4 and 5). We suggest that, at the high reaction temperature, TBAB is partially converted to tributylamine through S_N2 substitution or Hofmann elimination.^[14] Although tributylamine has often been used as a base in Heck couplings, the amine may block coordination sites on Pd, and reduce Pd^{II} species, which facilitates the formation of Pd black.

Apart from the inhibitive effect of tetrabutylammonium ions, it has been stated in the literature that bromo ligands stabilize (low-nuclear) Pd species in solution, as well as enhance Pd dissolution from nanoclusters.^[17] In addition, Lewis acidic metal ions have been applied to improve chloroarene reactivity in coupling reactions.^[18] The Lewis acid may coordinate either to the chlorine or to the oxygen of the methoxy group of chloroanisole. As a result, the C–Cl bond is weakened, or electron density is drawn from the donor substituent and, therefore, from the aromatic ring. Both scenarios would make the oxidative addition of the chloroarene to Pd⁰ more feasible. Accordingly, addition of LiBr improved the reaction to give almost quantitative conversion. The optimal amount of LiBr was found to be 0.6–1 mmol for 1.5 mmol of styrene (Table 2, entries 2–4). Lower amounts of LiBr showed no improvement (Table 2, entry 1), and higher amounts were inhibitive to the reaction.

Under the optimized conditions, coupling can also be achieved at temperatures lower than 160 °C. At 150 °C, reasona-

Table 2. Catalytic results for Heck coupling of styrene and 4-chloroanisole with LiBr and the optimized amount of **II**.^[a]

Entry	LiBr [mmol]	T [°C]	t [h]	Conversion [%] ^[b]	Yield (t/g) [%] ^[c]
1	0.2	160	6	92	77/7
2	0.6	160	6	98	81/8
3	1.0	160	6	97	82/8
4	0.7	140	16	42	20/2
5	0.7	150	6	77	59/5
6	0.8	150	16	100	74/6
7 ^[d]	0.6	160	6	30	< 1/0
8 ^[e]	0.6	160	6	26	0/0
9 ^[f]	0.6	160	6	58	32/3

[a] Reaction conditions: styrene (1.5 mmol), 4-chloroanisole (3 mmol), Ca(OH)₂ (0.9 mmol), complex **II** (0.0375 mol %), NMP (5 mL), air. [b] Conversion of styrene. [c] GC yields corresponding to the *trans* olefin (t) and the *gem* olefin (g). [d] Ligand **I** (0.0375 mol %) was added. [e] Pd^{II}-tetraphenylporphyrin (0.075 mol %) was used as the precatalyst. [f] Pd^{II}-phthalocyanine (0.075 mol %) was used as the precatalyst.

ble conversions and yields are still obtained (Table 2, entry 5), and quantitative conversion of styrene can be achieved by prolonging the reaction time, albeit with lower selectivity (Table 2, entry 6). Heck coupling is also observed at 140 °C (Table 2, entry 4). However, at temperatures below 140 °C the reaction did not occur.

Finally, other macrocyclic Pd complexes were employed under these conditions. Pd^{II}-tetraphenylporphyrin did not show activity as a precatalyst. Modest conversion and yield could be achieved by using Pd^{II}-phthalocyanine (Table 2, entries 8 and 9). Clearly, these complexes behave differently to complex **II** with respect to Pd release, and may need a different set of conditions for better performance.

Based on our concept, addition of the free ligand to the reaction mixture should shift the release-recapture equilibrium towards bound Pd and stall the coupling catalysis. In fact, conducting the reaction by using complex **II** in the presence of ligand **I** (1 equiv) disrupts the Heck reaction (Table 2, entry 7). However, when corresponding amounts of the ligand **I** and Pd(OAc)₂ were added to the reaction mixture (before heating) instead of the preformed complex **II**, 89% conversion of styrene and 75% yield of the Heck products were still observed under the optimized conditions. These are comparable results to those obtained by directly using complex **II** (Table 2, entries 2 and 3). Thus, the formation (also in situ) of the macrocyclic complex **II** leads to highly effective catalytic coupling. On the other hand, direct exposure of free Pd to the warm reaction mixture should be disadvantageous for Heck coupling, even in the presence of **I**, because the initially unprotected Pd will enter deactivation pathways to a significant extent. Hence, adding Pd(OAc)₂ after 5 min to an already hot reaction mixture containing ligand **I**, led to significantly lower conversion (39%) and yield (15%). Moreover, when the ligand is added after 5 min to the hot reaction mixture containing Pd(OAc)₂, the Heck reaction proceeds to a lesser extent, or does not occur at all.

All of these results are consistent with a controlled release of active free Pd from complex **II** under the reaction conditions. It is this controlled release that prevents the formation of inactive Pd agglomerates under harsh conditions and leads to high catalytic performance even for deactivated substrates. Further stabilization by TBAB is then no longer necessary, and even inhibitive to the reaction.

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