# Palladium Catalyst Systems for Cross-Coupling Reactions of Aryl Chlorides and Olefins**

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**Abstract:** A detailed investigation into the influence of phosphines, additives, bases and solvents on the Heck coupling reaction of 4-trifluoromethyl-1-chlorobenzene (**2**) is presented. It is shown that a number of catalyst systems exist for efficient cross coupling of electron-deficient aryl chlorides with various olefins. Basicity and steric demand of the ligand are two factors which determine the success of the reaction. In addition the phosphine/palladium ratio, the correct type and amount of additive, and finally the use of an appropriate base and solvent are also important. The optimised reaction conditions are applied for the arylation of styrene, 2-ethylhexyl acrylate and *N*,*N*-dimethyl acrylic amide with various aryl chlorides.

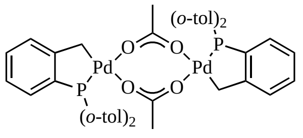
**Keywords:** additives · arylation · C–Cl activation · homogeneous catalysis · palladium

## Introduction

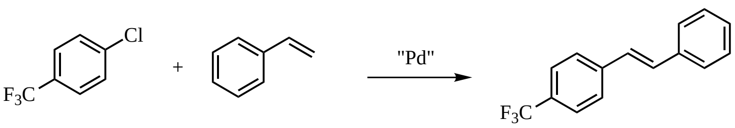
Among the various ways known to synthesise arylated olefins, probably the most powerful method is the construction of $C(sp^2)-C(sp^2)$ single bonds through the palladium-catalysed coupling reactions of olefins with aryl halides (Heck reaction).[1] In general, aryl bromides, iodides and triflates are used as starting materials for the Heck reaction. Due to the industrial importance of being able to functionalise easily accessible and cheap aryl chlorides,[2] there is currently a great deal of interest in the coupling of aryl chlorides with various nucleophiles.[3] While Bozell[4] demonstrated that nickel/palladium mixtures promote effective coupling reactions with olefins, most studies have focussed on palladium catalysts. Although initial work conducted by W. A. Herrmann and us,[5] as well as D. Milstein,[6] and more recently by M. T. Reetz,[7] G. Fu,[8] and J. F. Hartwig[9] led to significant breakthroughs in this area, the factors that affect the efficiency of the coupling of aryl chlorides with olefins are far from being understood. It is generally accepted that certain recipes for "good" reaction conditions exist, but the exact influence of most reaction parameters remains unclear. In this full paper we report in detail the effect of additives, bases and solvents on the catalytic performance of the palladacycle **1**, and of various palladium(II) acetate/phosphine in situ systems in the coupling reaction of 4-trifluoromethyl-1-chlorobenzene (**2**) and styrene (**3**). The optimised reaction conditions were applied to the Heck reaction of a variety of aryl chlorides with different olefins.

## Results and Discussion

Initially, we performed the coupling of 4-trifluoromethyl-1-chlorobenzene (**2**) and styrene (**3**) in the presence of palladacycle **1** as a model reaction (Scheme 1). Here, we studied the effect of added halide (cations and anions), bases and the olefin concentration on catalyst productivity. All reactions were run at a low catalyst concentration (0.05 mol% **1** = 0.1 mol% Pd). The negative inductive effect of the *para*-trifluoromethyl substituent leads to an activation of the C–Cl bond towards nucleophilic substitution.[10] Hence, compound **2** should be viewed as a moderately activated aryl chloride for palladium-catalysed coupling reactions.



**1**



Scheme 1. Heck reaction of **2** and **3**.

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In order to achieve significant conversion of chloroarenes in the palladacycle-catalysed Heck reaction comparatively high reaction temperatures (> 140 °C) are needed owing to the relative stability of the C–Cl bond towards oxidative addition.[2a] Only the highly basic catalyst systems developed very recently do not need this thermal activation and allow Heck coupling of aryl chlorides at 100–120 °C.[6, 8, 9]

The palladacycle **1** is an ideal source for the slow generation of palladium monophosphine species, which are most likely the active catalytic species in the reaction mixture.[5] In order to prevent deactivation (precipitation of palladium black) of these active species at higher reaction temperatures, it is necessary to add stabilising and/or activating agents to the reaction mixture. Soluble sources of bromide ions often show a beneficial effect in Heck reactions (Jeffery conditions).[1] Hence, we studied the influence of different concentrations of tetra-*n*-butylammonium bromide (TBAB) on the model reaction at 140 °C and 160 °C. Without any TBAB in the presence of 0.05 mol% **1** and 1.2 equivalents of sodium acetate as the base only 2% and 8% of 4-trifluoromethyl stilbene (**4**) is formed after 20 hours at 140 °C and 160 °C, respectively. Increasing the halide concentration leads to a higher product yield at both temperatures. However, there are significant differences depending on the reaction temperature. As shown in Figure 1 at 160 °C the optimum concentration of TBAB lies at 20 mol% relative to **2**, with 64% of **4** being formed (turnover number (TON) = 640). At higher concentrations of TBAB the yield decreases, with only 10% of **4** being obtained using 100 mol% TBAB. We explain this decrease in product yield at higher concentrations of TBAB by the blocking of free coordination sites of low-ligated palladium(0) complexes.

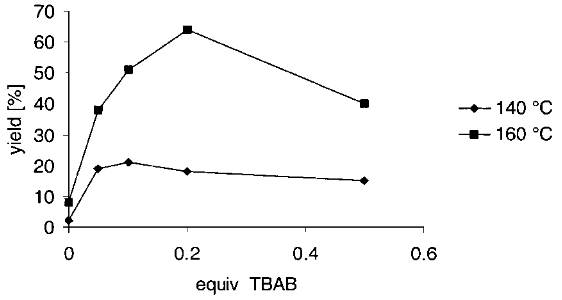
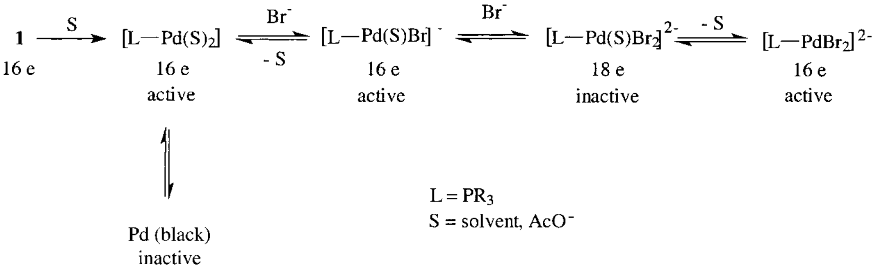


Figure 1. Effect of TBAB concentration (10 mmol **2**, 15 mmol **3**, 12 mmol sodium acetate, 0.005 mmol **1**, 10 mL DMAc, 20 h).

At 140 °C the yield of **4** is significantly lower compared to 160 °C; this demonstrates that a temperature of 140 °C is too low for an efficient activation of this substrate. After an initial increase in the yield by adding 5 mol% of TBAB the halide concentration has only a marginal influence on the reaction outcome. Hence, **4** is obtained in about 20% yield in the presence of 5–50 mol% TBAB. These results demonstrate that TBAB has both a positive and negative effect on the yield of **4** depending on the concentration and temperature. This can be explained by the fact that bromide ions facilitate the formation of anionic $14e^-$ and $16e^-$ $Pd^0$ monophosphine species (Scheme 2). At 160 °C the formation of these highly active species is fast and a higher halide concentration leads to the predominant formation of stable $18e^-$ complexes. At 140 °C the conversion of **1** to anionic $Pd^0$ complexes is low, hence a higher halide concentration is beneficial for the initial step. Nevertheless, reactivity of the $16e^-$ $Pd^0$ species is not high enough at 140 °C to ensure sufficient conversion of the test substrate.



Scheme 2. Proposed equilibrium of Pd complexes (for simplification there is no equilibrium with $12e^-$ and $14e^-$ Pd species shown).

While the initial catalyst tests were performed with sodium acetate as the base, we were also interested in the influence of other bases. Common bases for Heck reactions are the acetates, carbonates and bicarbonates of alkaline or earth alkaline metals, or alternatively organic bases such as trialkylamines.[2] These bases may also act as ligands at the Pd centre, thereby influencing the catalyst performance. Table 1 gives an overview of the results obtained in the presence of 1.2 equivalents of ten different bases. Sodium and potassium acetate and sodium carbonate lead to similar results in the presence of 20 mol% TBAB (64, 61 and 61% of **4**, respectively). Soluble tetra-*n*-butylammonium acetate leads, without added halide, to the formation of 32% of **4**. This is surprising because acetate ions should have a comparable stabilising effect on palladium(0) species as bromide ions due to *ate*-complex formation.[11] The expensive base cesium carbonate (25%) as

Table 1. Base effect on the coupling of **2** and **3**.[a]

| | Base | $Bu_4NBr$ [mol%] | Yield [%][b] |
|---|---|---|---|
| **1** | **NaOAc** | **20** | **64** |
| **2** | **KOAc** | **20** | **61** |
| 3 | $Bu_4NOAc$ | 0 | 32 |
| **4** | $\mathbf{Na_2CO_3}$ | **20** | **61** |
| 5 | $Cs_2CO_3$ | 20 | 25 |
| 6 | $K_3PO_4$ | 20 | 39 |
| 7 | $KO^tBu$ | 20 | 3 |
| 8 | NaOH | 20 | 4 |
| **9** | **CaO** | **20** | **67** |
| 10 | $NEt_3$ | 20 | 12 |

[a] Reaction conditions: 10 mmol **2**, 15 mmol **3**, 12 mmol base, 0.005 mmol **1**, 10 mL DMAc, 160 °C, 20 h. [b] Yield of **4**, determined by gas chromatography with diethyleneglycol di-*n*-butyl ether as the internal standard.

well as potassium phosphate (39%) gave lower yields of **4**. Both potassium *tert*-butoxide and sodium hydroxide lead to catalyst decomposition under these conditions. Much to our surprise, simple calcium oxide, almost insoluble in *N*,*N*-dimethyl acetamide (DMAc) and to the best of our knowledge not used before in palladium-catalysed coupling reactions, performs excellently under these reaction conditions (67% of **4**). Triethylamine is not suitable as base (12% of **4**) due to its ability to bind strongly to palladium. In all catalytic tests the selectivity for the *E* isomer of **4** lies between 94 and 98%, independent of the type of based used.

From these results we conclude that it is important to have a low concentration of basic anions in solution. Again the blocking of free coordination sites on the metal centre, which is necessary for the turnover of the catalyst, might be the reason for this effect.

Interestingly, the ratio of aryl chloride to olefin is crucial for the outcome of the coupling reaction (Figure 2). A yield of 91% of the desired stilbene **4** (relative to styrene) is observed by utilising 0.5 equivalents of styrene relative to **2**. Equimolar amounts of starting materials lead to a 66% yield of **4**. A further increase in the styrene/aryl chloride ratio (1.5–5 equiv) results in a continuous decrease in the product yield (64–23%).

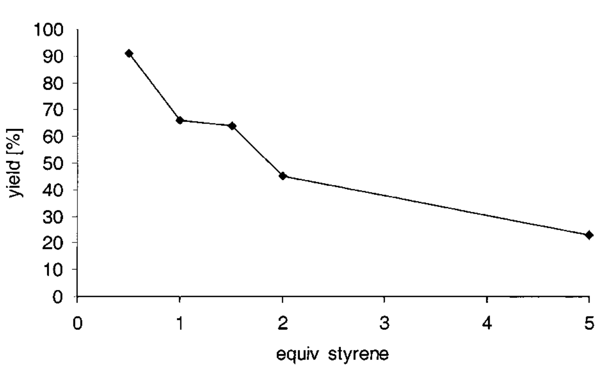


Figure 2. Influence of the styrene/aryl chloride ratio (10 mmol **2**, 2 mmol TBAB, 12 mmol sodium acetate, 0.005 mmol **1**, 10 mL DMAc, 160°C, 20 h).

Despite the lower yields, we decided to use 1–1.5 equivalents of the olefin throughout our study because this is the cheaper coupling partner relative to the aryl halide. The effect of olefin concentration on the catalyst performance is extremely important for an objective comparison of different catalyst systems. From the results shown above, we conclude that one can often influence the catalyst activity and productivity more by changing the concentration of olefin than by switching from one catalyst to another.

After considerable optimisation of the model reaction, we were interested in the outcome of this coupling reaction in the presence of a series of halides and other coordinating and non-coordinating salts. Investigations into the oxidative addition of aryl iodides to palladium(0) complexes confirm an activating and, hence, accelerating effect of added halide ions on this step of the catalytic cycle.[12] With regard to the results obtained with TBAB as the additive we believe that this is also valid for the coupling of aryl chlorides. Due to the fact that the addition of other anions (chloride,[13] iodide,[14] hydrogen sulfate,[15] acetate[16]) to palladium-catalysed coupling reactions is also beneficial in some cases, we tested various additives in the presence of sodium acetate and sodium carbonate (Tables 2 and 3). Table 2 gives a summary of the results observed in the presence of different tetra-*n*-butylammonium salts. As can be seen, bromide is the most effective counterion (TBAB) for this reaction if sodium acetate is used as the base. When sodium carbonate is utilised as the base, better results are obtained in the presence of tetra-*n*-butylammonium chloride hydrate (89% of **4**), followed then by the corresponding bromide and hydrogen sulfate (61 and 58% of **4**, respectively). By reaction with carbonate ions, the chloride's crystal water can form hydroxide ions that are able to coordinate to palladium and, hence, lead to considerable stabilisation of the active species. This formation of hydroxide ions seems to be responsible for the beneficial effect of chloride and water compared to chloride without water. The basicity of acetate ions is not sufficient to deprotonate water to a reasonable extent. In this case, the combination of water and chloride has no significant positive influence on the catalytic efficiency. Weakly coordinating anions (acetate, nitrate) as well as non-coordinating anions (tetrafluoroborate, sulfonic acid anions) do not stabilise low ligated palladium(0) complexes towards agglomeration and, hence, do not allow reasonable conversion of the test substrate.

During the investigations into the anion's influence on catalytic activity it became evident that the cation might also have a significant impact on the success of the reaction. The results of screening different halide additives are summarised in Table 3. Readily soluble tetraalkylammonium and lithium

Table 2. Anion effect on the coupling of **2** and **3**.[a]

| | Cation | Anion | NaOAc | | $Na_2CO_3$ | |
|---|---|---|---|---|---|---|
| | | | Yield [%][b] | Select. *E* [%] | Yield [%][b] | Select. *E* [%] |
| 1 | $Bu_4N^+$ | $Cl^-$ | 21 | 97 | 29 | 98 |
| **2** | **$Bu_4N^+$** | **$Cl^- \cdot H_2O$** | 36 | 96 | **89** | **95** |
| **3** | **$Bu_4N^+$** | **$Br^-$** | **64** | **94** | **61** | **94** |
| 4 | $Bu_4N^+$ | $I^-$ | 35 | 91 | 11 | 94 |
| 5 | $Bu_4N^+$ | $SCN^-$ | 1 | nd[c] | 0 | – |
| 6 | $Bu_4N^+$ | $SCN^-$ (0.1 mol%) | 1 | nd | 1 | nd |
| 7 | $Bu_4N^+$ | $OAc^-$ | 34 | 95 | 43 | 95 |
| 8 | $Bu_4N^+$ | $OH^-$ ($H_2O$ solvent) | 23 | 96 | 21 | 96 |
| 9 | $Bu_4N^+$ | $OH^-$ (MeOH solvent) | 0 | – | 0 | – |
| 10 | $Bu_4N^+$ | $NO_3^-$ | 5 | nd | 9 | nd |
| **11** | **$Bu_4N^+$** | **$HSO_4^-$** | 16 | 97 | **58** | **95** |
| 12 | $Bu_4N^+$ | $BF_4^-$ | 2 | nd | 0 | – |
| 13 | $Bu_4N^+$ | $OTs^-$ | 4 | nd | 10 | nd |
| 14 | $Bu_4N^+$ | $OTf^-$ | 1 | nd | 12 | nd |

[a] Reaction conditions: 10 mmol **2**, 15 mmol **3**, 12 mmol base, 2 mmol additive, 0.005 mmol **1**, 10 mL DMAc, 160°C, 20 h. [b] Yield of **4**, determined by gas chromatography with diethyleneglycol di-*n*-butyl ether as the internal standard. [c] Not determined.

Table 3. Cation effect on the coupling of **2** and **3**.[a]

| | Cation | Anion | NaOAc | | $Na_2CO_3$ | |
|---|---|---|---|---|---|---|
| | | | Yield [%][b] | Select. *E* [%] | Yield [%][b] | Select. *E* [%] |
| 1 | $Li^+$ | $Cl^-$ | 15 | 97 | 10 | nd[c] |
| 3 | $Cs^+$ | $Cl^-$ | 8 | nd | 13 | nd |
| 4 | $Bu_4N^+$ | $Cl^-$ | 21 | 97 | 29 | 98 |
| **5** | **$Bu_4N^+$** | **$Cl^- \cdot H_2O$** | 36 | 96 | **89** | **95** |
| 6 | $Li^+$ | $Br^-$ | 54 | 93 | 21 | 95 |
| 7 | $Na^+$ | $Br^-$ | 24 | 94 | 19 | 95 |
| 8 | $K^+$ | $Br^-$ | 29 | 94 | 53 | 95 |
| 9 | $NH_4^+$ | $Br^-$ | 22 | 95 | 28 | 96 |
| 10 | $Et_4N^+$ | $Br^-$ | 31 | 95 | 30 | 97 |
| **11** | **$Bu_4N^+$** | **$Br^-$** | **64** | **94** | **61** | **94** |
| **12** | **$Oc_4N^+$** | **$Br^-$** | 56 | 93 | **67** | **93** |
| **13** | **$Bu_4P^+$** | **$Br^-$** | **60** | **93** | **90** | **93** |
| **14** | **$(Et_2N)_4P^+$** | **$Br^-$** | 22 | 95 | **85** | **94** |
| 15 | $Me_4N^+$ | $I^-$ | 39 | 90 | 8 | 94 |
| 16 | $Et_4N^+$ | $I^-$ | 33 | 91 | 10 | nd |
| 17 | $Bu_4N^+$ | $I^-$ | 35 | 91 | 11 | 94 |

[a] Reaction conditions: 10 mmol **2**, 15 mmol **3**, 12 mmol base, 2 mmol additive, 0.005 mmol **1**, 10 mL DMAc, 160 °C, 20 h. [b] Yield of **4**, determined by gas chromatography with diethyleneglycol di-*n*-butyl ether as internal the standard. [c] Not determined.

bromides form the most active catalysts in combination with sodium acetate, while less soluble alkaline bromides lead to low conversions. Utilising sodium carbonate the Hofmann degradation of tetra-*n*-butylphosphonium bromide to form tri-*n*-butylphosphine, which leads to an active catalyst system itself, enhances the effect of simply added bromide. The reasons for the different results combining tetra(*N*,*N*-diethylamino)phosphonium bromide with sodium acetate and carbonate are not clear at the moment.

At this time the cationic effect of additives seems to depend solely on their solubility. However, other ways of interacting with the substrate or the catalyst system cannot be ruled out with certainty. Therefore we performed NMR experiments to detect an interaction between the added cation and the chlorine of the aryl chloride and to observe an interaction of the cation with palladium phosphine species. A change in the chemical shift of $^{13}C$ signal of the *ipso*-carbon atom could not be observed in DMAc/[D$_6$]DMSO (5:1) at room temperature ($\delta = 137.2-137.6$). Also an influence of the cation on the chemical shift of triphenylphosphine/palladium(0)/bromide *ate*-complexes could not be verified. In the $^{31}P$ NMR under reaction conditions, albeit at room temperature, two signals are observed for a mixture of $Pd(PPh_3)_4/Br^-$/DMAc/[D$_6$]DMSO (5:1). Both signals are broad and an assignment is difficult because the two signals represent a variety of both complexes and free phosphine that are all in fast equilibrium.

As shown in Tables 2 and 3 the additive did not significantly influence the geometry of the double bond formed (*E* vs *Z*). In all cases 93–97 % of the *E* isomer was obtained. However, iodide salts seem to decrease the selectivity marginally (ca. 91 % *E*) relative to the other anions investigated.

In the presence of 20 mol % of potassium trichlorostannate or various other transition metal halides as additives, for example, manganese(II), cobalt(II), nickel(II) (compare ref. [4]) or copper(I), no efficient conversion of **2** was observed (less than 20 % yield of **4**).

At this point three efficient catalyst systems based on the palladacycle **1** for the activation of **2** have been discovered. In the presence of the economically attractive base sodium carbonate an 85–90 % yield (TON = 850–900) of **4** was realised by applying either 0.2 equivalents tetra-*n*-butylphosphonium bromide, tetra(*N*,*N*-diethylamino)phosphonium bromide or tetra-*n*-butylammonium chloride hydrate.

Next, we were interested in a comparison of the molecularly defined complex **1** with traditional in situ catalyst systems. As stated previously palladium(II)/phosphine mixtures, which are generally applied for Heck and related reactions were not tested systematically for the activation of aryl chlorides at low catalyst loading (0.1 mol % Pd) prior to our investigations. In order to observe positive as well as negative influences of the different commercially available phosphine ligands, we performed the model reaction under standard reaction conditions (DMAc, 160 °C, 20 h) with tetra-*n*-butylammonium bromide as the additive. Typically, phosphines are applied in palladium-catalysed coupling reactions in a molar ratio of 1:1 to 4:1 with respect to palladium. It is said that higher phosphine/palladium ratios slow down the coupling reaction.[18] Therefore we chose a P/Pd ratio of 2:1 for the phosphine screening. As shown in Table 4 most of the investigated ligands do not catalyse the test reaction to an appreciable extent with or without 20 mol % of tetra-*n*-butylammonium bromide.

In each case less than 10 % of desired stilbene **4** was formed in the absence of TBAB. Only two phosphines led to significantly active catalyst systems under these conditions: tricyclohexylphosphine (71 % yield of **4** in the presence of sodium carbonate) and tri-*n*-butylphosphine (83 % yield of **4** in the presence of sodium carbonate), which are among the most basic ligands investigated in this study. However, basicity is not the only important factor that determines the success of the reaction: tris(dimethylamino)phosphine, which is only a bit less basic than tri-*n*-butylphosphine, is not suitable for the model reaction at all. On the other hand steric effects are also not the sole determining factor, for example, tricyclohexylphosphine and tri-*n*-butylphosphine work almost equally well. More electron-poor ligands whose size is comparable to the former [tris(perfluorophenyl)phosphine] or the latter [tris(2-cyanoethyl)phosphine] ligand do not support the reaction (< 10 % yield of **4**). Tri-*o*-tolylphosphine does not lead to an active catalyst system when applied in situ. Here, palladium precipitation occurs faster than complexation and concomitant cyclometallation. Surprisingly, tri-*tert*-butylphosphine/palladium(II) acetate does not catalyse the coupling of our test substrates under these conditions, although it is known to generate a highly efficient catalysts system in etheral solvents with cesium carbonate as a base.[8] In all reactions described here the selectivity towards the *E* double bond isomer lies

Table 4. Variation of phosphine ligands ($P/Pd(OAc)_2 = 2{:}1$) in the coupling of **2** and **3**.[a]

| | Phosphine | $\nu$ [$cm^{-1}$][b] | $\Theta$ [°][c] | $Bu_4NBr$ [mol%] | Yield [%][d] (NaOAc) | Yield [%][d] ($Na_2CO_3$) |
|---|---|---|---|---|---|---|
| 1 | $PCy_3$ | 2056 | 170 | 0 | 9 | 5 |
| **2** | **$PCy_3$** | 2056 | 170 | 20 | 39 (94) | **71 (94)** |
| 3 | $P(tBu)_3$ | 2056 | 182 | 20 | 26 (95) | 31 (94) |
| 4 | $P(nBu)_3$ | 2060 | 132 | 0 | 2 | 6 |
| **5** | **$P(nBu)_3$** | 2060 | 132 | 20 | 26 (96) | **83 (94)** |
| 6 | $P[2,4,6\text{-}(MeO)_3C_6H_2]_3$ | | | 20 | 22 | 47 (95) |
| 7 | $PCy_2(o\text{-biph})$ | | | 20 | 27 (95) | 38 (95) |
| 8 | $P(NMe_2)_3$ | 2062 | 157 | 20 | 2 | 0 |
| 9 | $PMe_2Ph$ | 2065 | 122 | 20 | 13 | 7 |
| 10 | dppb[e] | 2066 | | 20 | 21 (96) | 18 (96) |
| 11 | $PMePh_2$ | 2067 | 136 | 20 | 22 (95) | 14 |
| 12 | $PPh_2(2\text{-Py})$ | | | 20 | 0 | 0 |
| 13 | dppf[f] | | | 20 | 20 | 35 |
| 14 | $P(o\text{-Tol})_3$ | 2067 | 194 | 20 | 0 | 1 |
| 15 | dppt[g] | | | 20 | 18 (96) | 13 |
| 16 | $PPh_3$ | 2069 | 145 | 20 | 1 | 7 |
| 17 | $P(p\text{-}C_6H_4\text{-}F)_3$ | 2071 | 145 | 20 | 0 | 2 |
| 18 | $P(CH_2CH_2CN)_3$ | 2078 | 132 | 20 | 3 | 10 |
| 19 | $P(C_6F_5)_3$ | 2091 | 184 | 20 | 1 | 0 |

[a] Reaction conditions: 10 mmol **2**, 15 mmol **3**, 12 mmol base, 0 or 2 mmol TBAB, 0.01 mmol $Pd(OAc)_2$, 10 mL DMAc, 160 °C, 20 h. [b] $\nu_{CO}(A_1)$ of $Ni(CO)_3L$ in $CH_2Cl_2$.[17] [c] Tolman cone angle.[17] [d] Yield of **4** (selectivity of *E* isomer in parentheses), determined by gas chromatography with diethyleneglycol di-*n*-butyl ether as the internal standard. [e] 1,4-Bis(diphenylphosphino)butane. [f] 1,1′-Bis(diphenylphosphino)ferrocene. [g] 2,6-Bis-(diphenylphosphino)toluene.

between 94 and 96%, similar to that found for the palladacycle catalyst **1**. Hence, the same type of palladium species, which undergoes the $\beta$-hydride elimination, is likely.

In contrast to catalyst **1** the formation of palladium black is observed in the presence of most of the shown ligands. Thus, we assumed that the stabilisation of the active palladium species by a slight excess of ligand (2:1) is not sufficient. Therefore, the dependence of catalyst productivity on the phosphine/palladium ratio was investigated. As shown in Figure 3 the coupling of **2** with **3** can be affected efficiently by means of simple triphenylphosphine if the ligand is provided in an excess relative to palladium. The best yield of **4** (72%) is observed at a phosphine/palladium ratio of 15:1 in the presence of tetra-*n*-butylammonium bromide.

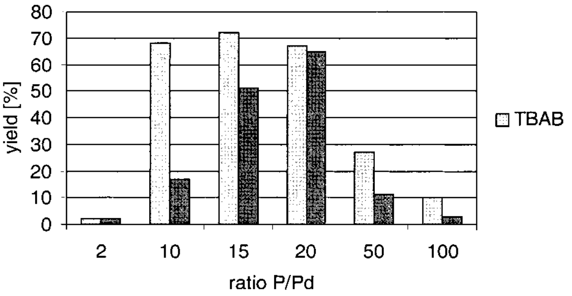


Figure 3. Influence of the P/Pd ratio (10 mmol **2**, 15 mmol **3**, 0 or 2 mmol TBAB, 12 mmol sodium acetate, 0.01 mmol palladium(II) acetate, 10 mL DMAc, 160 °C, 20 h).

If the co-catalyst is omitted comparable results (65%) are obtained at a slightly higher molar ratio of phosphine to palladium (20:1). This again supports the proposal that bromide ions and phosphines both act as ligands in the Heck reactions and may be substituted by each other. Higher concentrations of phosphine ligand lead to a decrease in catalyst activity (here the blocking of free coordination sites dominates), although the catalyst is stabilised against decomposition. Interestingly, increasing the phosphine/palladium ratio results in a significant decrease of *E* selectivity in the coupling product (P/Pd = 10:1, *E* selectivity of **4** = 91%; P/Pd = 100:1, *E* selectivity of **4** = 79%).

The success in coupling our test substrates in the presence of an excess of triphenylphosphine prompted us to re-investigate the ligand influence at higher phosphine/palladium ratios (Table 5). All reactions resulted in significantly higher product yields when a tenfold excess of ligand is applied compared with the initial twofold excess. The only exception was tri-*n*-butylphosphine which led to 53% of **4** compared with 83% at lower phosphine/palladium ratio in the presence of sodium carbonate.

Some important conclusions can be drawn from these results:

1) Regardless of the phosphine ligand employed, substantial yields of Heck products can be obtained even in the olefination of chloroarenes, if just the optimal conditions with respect to P/Pd ratio, base and co-catalyst are used.
2) An important but generally overlooked reaction parameter is the ligand/palladium ratio.
3) The combination of the right ligand/palladium ratio and the reaction temperature allows an efficient activation of C-Cl bonds at low catalyst loading.

Table 5. Variation of phosphine ligands ($P/Pd(OAc)_2 = 10{:}1$) in the coupling of **2** and **3**.[a]

| | Phosphine | $Bu_4NBr$ [mol%] | Yield [%][b] | Select. *E* [%] |
|---|---|---|---|---|
| 1 | $PCy_3$ | 0 | 40 | 92 |
| **2** | **$PCy_3$** | **20** | **72** | **92** |
| 3 | $P(tBu)_3$ | 20 | 29 | 93 |
| 4 | $P(nBu)_3$ | 0 | 12 | nd[c] |
| 5 | $P(nBu)_3$ | 20 | 23 | 91 |
| 6 | $P[2,4,6\text{-}(MeO)_3C_6H_2]_3$ | 20 | 31 | 94 |
| 7 | $PCy_2(o\text{-biph})$ | 20 | 29 | 94 |
| 8 | dppb[d] | 20 | 55 | 90 |
| 9 | $PMePh_2$ | 20 | 19 | 87 |
| 10 | $PAllPh_2$ | 20 | 50 | 92 |
| 11 | dppf[e] | 20 | 43 | 92 |
| 12 | $P(CH_2CH_2CN)_3$ | 20 | 17 | 90 |

[a] Reaction conditions: 10 mmol **2**, 15 mmol **3**, 12 mmol NaOAc, 0 or 2 mmol TBAB, 0.01 mmol $Pd(OAc)_2$, 10 mL DMAc, 160 °C, 20 h. [b] Yield of **4**, determined by gas chromatography with diethyleneglycol di-*n*-butyl ether as the internal standard. [c] Not determined. [d] 1,4-Bis(diphenylphosphino)butane. [e] 1,1′-Bis(diphenylphosphino)ferrocene.

Remarkably, even catalyst systems composed of electron-poor phosphite ligands efficiently catalyse the Heck coupling of chloroarenes with various olefins, if the ligand is provided in an excess.[19]

Table 6. Coupling of **2** and **3** in polar solvents.[a]

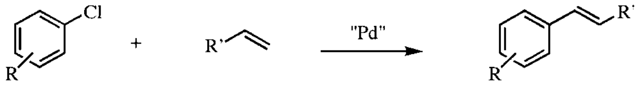
| | Solvent | Yield [%][b] (NaOAc) | Yield [%][b] ($Na_2CO_3$) |
|---|---|---|---|
| 1 | DMAc | 56 | 40 |
| **2** | **NMP** | **63** | **59** |
| 3 | TMU[c] | 48 | 48 |
| 4 | PEG 400[d] | 25 (10) | 2 (37) |
| 5 | ethylene glycol | 11 (28) | 2 (32) |

[a] Reaction conditions: 10 mmol **2**, 15 mmol **3**, 12 mmol base, 0.01 mmol $Pd(OAc)_2$, 0.15 mmol $PPh_3$, 9 mL solvent, 1 mL toluene, 160 °C, 20 h. [b] Yield of **4** (yield of trifluoromethylbenzene in parentheses), determined by gas chromatography with diethyleneglycol di-*n*-butyl ether as the internal standard. [c] *N,N,N′,N′*-Tetramethylurea. [d] Polyethylene glycol 400.

The last reaction parameter studied in the model reaction was the influence of the solvent (Table 6). Heck reactions are normally conducted in dipolar aprotic solvents like DMAc, DMF or acetonitrile. Therefore we investigated different polar solvents such as *N,N,N′,N′*-tetramethylurea (TMU), *N*-methylpyrrolidone (NMP), DMAc, polyethylene glycol and ethylene glycol in the presence of the most economically attractive catalyst system [$Pd(OAc)_2$/15 $PPh_3$]. Independent of the base used, NMP gave slightly better results with respect to DMAc and TMU. In ethylene glycol and polyethylene glycol 400 rapid palladium decomposition takes place; hence, these solvents do not allow an efficient coupling of **2** and **3**. Reductive dehalogenation of **2** to trifluoromethylbenzene is observed as a major side reaction (up to 37%).

The presented studies of the model reaction reveal that there are far more than ten different combinations of palladium source, ligand, co-catalyst (halide), base and P/Pd ratio that are able to catalyse the coupling of **2** and **3** in yields from 60–90% at a low catalyst loading. Some of these “best” catalyst systems were chosen and applied to the Heck reaction of various chloroarenes and different olefins (Scheme 3; Table 7).

All substrates tested here were converted to the desired coupling products in very good to excellent yields (85–100%) and with excellent turnover numbers (850–1000) with respect to Heck reactions of aryl chlorides. It is clear that for all shown combinations of substrates, more than one catalyst system exists that leads to similar good results; *ortho*-substituents at the aryl chloride are tolerated and electron-poor olefins can be coupled as well as electron-rich ones. Although in the latter case regio and stereochemical compli-

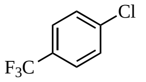
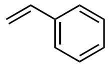
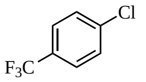
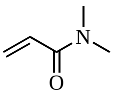
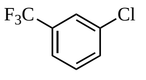
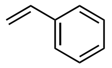
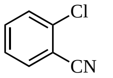
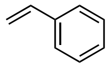
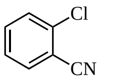
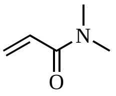
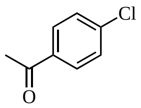
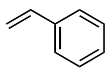
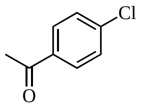
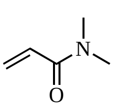
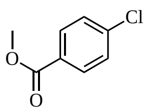
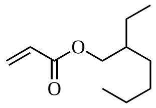


**2**: R = 4-$CF_3$
**5**: R = 3-$CF_3$
**6**: R = 2-CN
**7**: R = 4-COMe
**8**: R = 4-$CO_2Me$

**3**: R’ = Ph
**9**: R’ = $CONMe_2$
**10**: R’ = $CO_2$(2-ethylhexyl)

Scheme 3. Coupling of aryl chlorides and olefins in the presence of different catalyst systems.

Table 7. Coupling of aryl chlorides and different olefins.[a]

| | ArCl | Olefin | Pd source | Ligand[b] | $Bu_4NBr$ [mol%] | Yield [%][c] |
|---|---|---|---|---|---|---|
| 1 |  |  | $Pd(OAc)_2$ | 10 $P(OAr)_3$ | 20 | 90 |
| 2 |  |  | $Pd(OAc)_2$ | 10 $P(OAr)_3$ | 20 | 89 |
| 3 |  |  | $Pd(OAc)_2$ | 10 $P(OAr)_3$ | 20 | 93 |
| 4 |  |  | **1** | – | [d] | 94 |
| 5 |  |  | **1** | – | [d] | 100 |
| 6 |  |  | $Pd(OAc)_2$ | 2 $PBu_3$ | 20 | 85 |
| 7 |  |  | $Pd(OAc)_2$ | 10 $P(OAr)_3$ | 20 | 89 |
| 8 |  |  | $Pd(OAc)_2$ | 10 $PCy_3$ | 0 | 87 |

[a] Reaction conditions: 10 mmol ArCl, 15 mmol olefin, 12 mmol sodium carbonate, 0.01 mmol catalyst, 10 mL DMAc, 160 °C, 24 h. [b] Yield *E* product determined by gas chromatography with diethyleneglycol di-*n*-butyl ether as the internal standard. [c] Ar = 2,6-di-*tert*-butylphenyl. [d] 20 mol% $Bu_4NCl \cdot H_2O$.

cations arise from contrarily directing effects based on steric and electronic demands, respectively, which were not further investigated here. In the case of styrene, *E*/*Z* selectivity is about 95/5 in all cases, whereas acrylic esters and amides are coupled highly selectively ($>99$ %) to form the desired *E* $\beta$-product.

Utilising chlorobenzene and **3** as the substrates in the presence of 0.1 mol % of palladium catalysts never gave more than 13 % of coupling product. Reaction of 4-chloroanisole with styrene resulted in 17 % of 4-methoxy stilbene in the presence of palladium(II) acetate/20 triphenylphosphine. All other catalyst systems under investigation led to lower yields of the corresponding coupling product. Although the yields of the Heck reaction of non-activated aryl chlorides are not sufficient for organic synthesis, the achieved turnover numbers of 130–170 are similar to the best previously described catalysts with sterically hindered basic phosphines.

## Conclusion

What can we learn from this study of various catalyst systems for the Heck reaction of activated and non-activated aryl chlorides and olefins? Firstly, for activated aryl chlorides a number of useful catalyst systems exist that allow these reactions to proceed in good to excellent yield with catalyst turnover numbers of approximately 1000. The industrial realisation of coupling reactions with these substrates in the area of fine chemicals is nowadays, in our opinion, feasible. Importantly, the outcome of the many possible combinations of phosphine/additive/base is not easily predicted. While some general guidelines exist, for example, to use a higher P/Pd ratio, small changes in the co-catalyst or base may lead to a dramatic decrease in catalyst productivity. Contrary to traditional belief, basicity or steric demand of the ligand is not decisive for the success of the reaction. Here, the phosphine/palladium ratio and the olefin concentration are more important. In addition, one must note that the reaction conditions once optimised for a special pair of coupling partners are not automatically suitable for a similar coupling reaction.

With regard to the Heck coupling of non-activated aryl chlorides, more efficient catalyst systems are badly needed. Although the catalyst productivity of the simple Pd/excess PPh$_3$ catalysts presented here is in the range of 100–200, product yields are low. However, even the new basic and sterically demanding ligands such as tri-*tert*-butylphosphine[8] or the new adamantylphosphines[3q, 20] allow the reaction to proceed in good yield only at a comparable high catalyst concentration ($>1$ mol % of Pd catalyst).

## Experimental Section

**General**: All chemicals were commercially available and used without further purification. DMAc was distilled over calcium hydride and stored under argon. The coupling products synthesised were characterised using GC/MS, $^{1}$H and $^{13}$C NMR.

**General procedure**: In an ACE pressure tube (Aldrich) aryl halide (10 mmol), olefin (15 mmol), base (12 mmol), diethyleneglycol di-*n*-butyl ether (400 mg, as the internal standard), an appropriate amount of additive (if necessary), ligand and palladium source was suspended in dry DMAc (10 mL) under an atmosphere of argon. The tube was sealed and put in a preheated bath of silicon oil. After 20 hours the mixture was cooled to room temperature and CH$_2$Cl$_2$ (10 mL) and HCl (2 N, 10 mL) are added. The organic phase was analysed by gas chromatography. After washing the organic phase with water and brine, drying and evaporating the solvents, the products were isolated by crystallisation from methanol/acetone mixtures or by column chromatography (silica gel, hexane/ethyl acetate mixtures).

***E*-4-(Trifluoromethyl)stilbene**: $^{1}$H NMR (360 MHz, CDCl$_3$, 25 °C): $\delta = 7.60$ (m, 4 H), 7.54 (d, $^{3}J$(H,H) = 7.3 Hz, 2 H), 7.39 (m, 2 H), 7.31 (m, 1 H), 7.19 (d, $^{3}J$(H,H) = 16.4 Hz, 1 H), 7.11 (d, $^{3}J$(H,H) = 16.4 Hz, 1 H); $^{13}$C{$^{1}$H} NMR (90.6 MHz, CDCl$_3$, 25 °C): $\delta = 140.8$, 136.6, 131.2, 128.3, 127.1, 129.2 (q, $^{2}J$(C,F) = 32.3 Hz), 128.8, 126.8, 126.5, 125.6 (q, $^{3}J$(C,F) = 3.8 Hz), 124.2 (q, $^{1}J$(C,F) = 272 Hz); MS (70 eV, EI): *m*/*z*: 248 [*M*]$^{+}$, 179, 152, 89, 76.

***N*,*N*-Dimethyl-*p*-(trifluoromethyl)cinnamoyl amide**: $^{1}$H NMR (360 MHz, CDCl$_3$, 25 °C): $\delta = 7.64$ (d, $^{3}J$(H,H) = 15.5 Hz, 1 H), 7.58 (m, 4 H), 6.93 (d, $^{3}J$(H,H) = 15.5 Hz, 1 H), 3.10 (s, 6 H); $^{13}$C{$^{1}$H} NMR (90.6 MHz, CDCl$_3$, 25 °C): $\delta = 166.1$, 140.6, 138.8, 131.0 (q, $^{2}J$(C,F) = 32.4 Hz), 127.9, 125.7 (q, $^{3}J$(C,F) = 3.4 Hz), 123.9 (q, $^{1}J$(C,F) = 272 Hz), 120.0, 36.7; MS (70 eV, EI): *m*/*z*: 243 [*M*]$^{+}$, 224, 199, 171, 151, 98, 75.

***E*-3-(Trifluoromethyl)stilbene**: $^{1}$H NMR (360 MHz, CDCl$_3$, 25 °C): $\delta = 7.76$ (m, 1 H), 7.66 (m, 1 H), 7.54–7.44 (m, 4 H), 7.39 (m, 2 H), 7.31 (m, 1 H), 7.17 (d, $^{3}J$(H,H) = 16.4 Hz, 1 H), 7.10 (d, $^{3}J$(H,H) = 16.4 Hz, 1 H); $^{13}$C{$^{1}$H} NMR (90.6 MHz, CDCl$_3$, 25 °C): $\delta = 136.2$, 137.5, 131.1 (q, $^{2}J$(C,F) = 32.1 Hz), 130.6, 129.5, 129.1, 128.2, 127.1, 128.8, 126.7, 124.2 (q, $^{1}J$(C,F) = 272 Hz), 124.0 (q, $^{3}J$(C,F) = 3.8 Hz), 123.1 (q, $^{3}J$(C,F) = 3.8 Hz); MS (70 eV, EI): *m*/*z*: 248 [*M*]$^{+}$, 233, 179, 89.

**2-Cyanostilbene**: $^{1}$H NMR (400 MHz, CDCl$_3$, 25 °C): $\delta = 7.76$ (d, $^{2}J$(H,H) = 8.1 Hz, 1 H), 7.62–7.52 (m, 4 H), 7.44–7.22 (m, 6 H); $^{13}$C{$^{1}$H} NMR (101 MHz, CDCl$_3$, 25 °C): $\delta = 140.4$, 136.1, 133.3, 133.0, 132.7, 128.8, 128.7, 127.5, 127.0, 125.2, 123.9, 117.9, 111.1; MS (70 eV, EI): *m*/*z*: 205 [*M*]$^{+}$, 204, 190, 176, 102, 89.

***N*,*N*-Dimethyl-*o*-cyanocinnamoyl amide**: $^{1}$H NMR (400 MHz, CDCl$_3$, 25 °C): $\delta = 7.75$ (d, $^{2}J$(H,H) = 15.7 Hz, 1 H), 7.64–7.53 (m, 3 H), 7.37 (m, 1 H), 7.14 (d, $^{2}J$(H,H) = 15.7 Hz, 1 H), 3.13 (s, 3 H), 3.02 (s, 3 H); $^{13}$C{$^{1}$H} NMR (101 MHz, CDCl$_3$, 25 °C): $\delta = 165.7$, 138.3, 137.1, 133.6, 132.8, 129.1, 128.2, 123.1, 117.7, 111.3, 37.4, 35.8; MS (70 eV, EI): *m*/*z*: 200 [*M*]$^{+}$, 156, 128, 98.

***E*-4-Acetylstilbene**: $^{1}$H NMR (360 MHz, CDCl$_3$, 25 °C): $\delta = 7.92$ (d, $^{3}J$(H,H) = 8.2 Hz, 2 H), 7.54 (d, $^{3}J$(H,H) = 8.2 Hz, 2 H), 7.51 (d, $^{3}J$(H,H) = 7.3 Hz, 2 H), 7.34 (m, 3 H), 7.19 (d, $^{3}J$(H,H) = 16.3 Hz, 1 H), 7.09 (d, $^{3}J$(H,H) = 16.4 Hz, 1 H), 2.56 (s, 3 H); $^{13}$C{$^{1}$H} NMR (90.6 MHz, CDCl$_3$, 25 °C): $\delta = 197.3$, 141.9, 136.7, 135.9, 131.4, 128.8, 128.7, 128.3, 127.4, 126.8, 126.4, 26.5; MS (70 eV, EI): *m*/*z*: 222 [*M*]$^{+}$, 207, 178, 152, 89.

***p*-Acetyl-*N*,*N*-dimethylcinnamoyl amide**: $^{1}$H NMR (360 MHz, CDCl$_3$, 25 °C): $\delta = 7.87$ (d, $^{3}J$(H,H) = 8.0 Hz, 2 H), 7.59 (d, $^{3}J$(H,H) = 15.5 Hz, 1 H), 7.52 (d, $^{3}J$(H,H) = 8.0 Hz, 2 H), 6.92 (d, $^{3}J$(H,H) = 15.5 Hz, 1 H), 3.12 (s, 3 H), 3.00 (s, 3 H), 2.52 (s, 3 H); $^{13}$C{$^{1}$H} NMR (90.6 MHz, CDCl$_3$, 25 °C): $\delta = 197.2$, 165.9, 140.6, 119.9, 139.6, 137.3, 128.6, 127.7, 37.3, 35.8, 26.5; MS (70 eV, EI): *m*/*z*: 217 [*M*]$^{+}$, 202, 173, 131, 102, 98, 76.

**2-Ethylhexyl *p*-methoxycarbonylcinnamate**: $^{1}$H NMR (400 MHz, CDCl$_3$, 25 °C): $\delta = 7.99$ (d, $^{2}J$(H,H) = 8.3 Hz, 2 H), 7.64 (d, $^{2}J$(H,H) = 16.1 Hz, 1 H), 7.54 (d, $^{2}J$(H,H) = 8.2 Hz, 2 H), 6.48 (d, $^{2}J$(H,H) = 16.1 Hz, 1 H), 4.09 (m, 2 H), 3.87 (s, 3 H), 1.61 (quint, $^{2}J$(H,H) = 6.0 Hz, 1 H), 1.41–1.26 (m, 8 H), 0.87 (m, 6 H); $^{13}$C{$^{1}$H} NMR (101 MHz, CDCl$_3$, 25 °C): $\delta = 166.6$, 166.3, 142.9, 138.6, 131.2, 130.0, 127.8, 120.6, 67.0, 52.1, 38.7, 30.3, 28.9, 23.7, 22.9, 14.0, 10.8; MS (70 eV, EI): *m*/*z*: 318 [*M*]$^{+}$, 287, 207, 189, 175, 145, 112, 70.

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