

# The development of efficient catalysts for palladium-catalyzed coupling reactions of aryl halides†

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In the mid 1990s, we started a program on the development of more efficient palladium catalysts for the C–C and C–N coupling reactions of aryl halides, especially aryl chlorides. In this contribution, our investigations on new catalyst systems and their application in organic synthesis are summarized.

## Introduction

The functionalization of aryl halides is of major importance in the field of modern arene chemistry due to the ubiquity of aromatic and heteroaromatic units in fine chemical intermediates,

† Dedicated with deep respect to Professor Dr Klaus Kühlein without whom this chemistry would not have been started.

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pharmaceuticals, agrochemicals, and new materials.<sup>1</sup> Among the different aromatic functionalization reactions, palladium-catalyzed coupling processes such as the Heck,<sup>2</sup> Suzuki,<sup>3</sup> Kumada,<sup>4</sup> Sonogashira,<sup>5</sup> Buchwald–Hartwig amination<sup>6</sup> and other C–C and C–O bond forming reactions offer elegant possibilities for the synthesis of a multitude of substituted arenes (Scheme 1). The increasing popularity of these methods in synthesis is seen in every issue of modern scientific journals dedicated to organic synthesis or organometallic chemistry and catalysis.<sup>7</sup> The main advantages of the coupling processes shown in Scheme 1 are based on the ready availability of starting materials, the simplicity and generality of the methods, and the broad tolerance of palladium catalysts towards various functional groups.

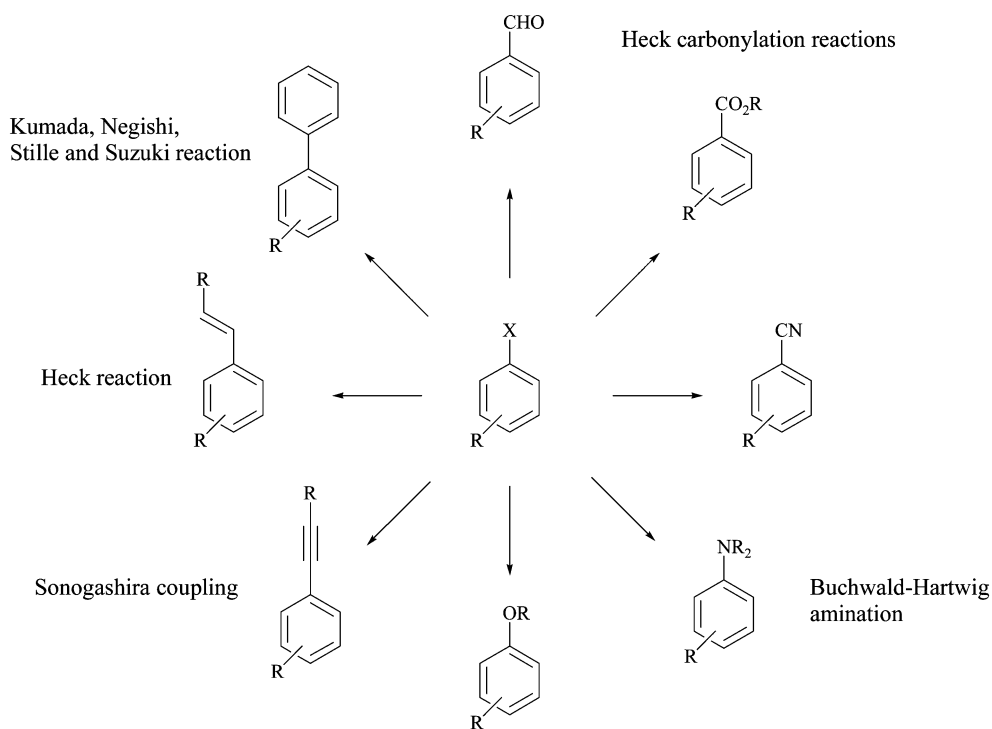
With regard to application in industry, the shown coupling reactions offer the opportunity of shorter and more selective routes for a number of currently used fine chemicals compared to traditional stoichiometric organic transformations. Thus, it is not surprising that since the early 1990s, more and more palladium-catalyzed reactions are transferred from academic protocols to industrial scale.<sup>8</sup> Selected examples of processes, which are used nowadays (or have been used) on production or pilot plant scale are shown in Scheme 2.

Due to the synthetic power of the methods, we believe that this type of homogeneous catalysis is well suited for further use in the chemical industry. However, future applications of palladium-catalyzed aryl–X refinement reactions on a commercial scale will rely on two factors: (a) the availability of “cheap” starting materials, and (b) the use of efficient (TON >10 000) and practical (no expensive ligands or co-catalysts needed, etc.) catalysts for the desired transformation. Therefore, during the last decade, the development of new catalysts which are more productive and more active has been and continues to be a major goal in this area of organometallic chemistry and homogeneous catalysis.

## Results and discussion

### The development of palladacycle catalysts

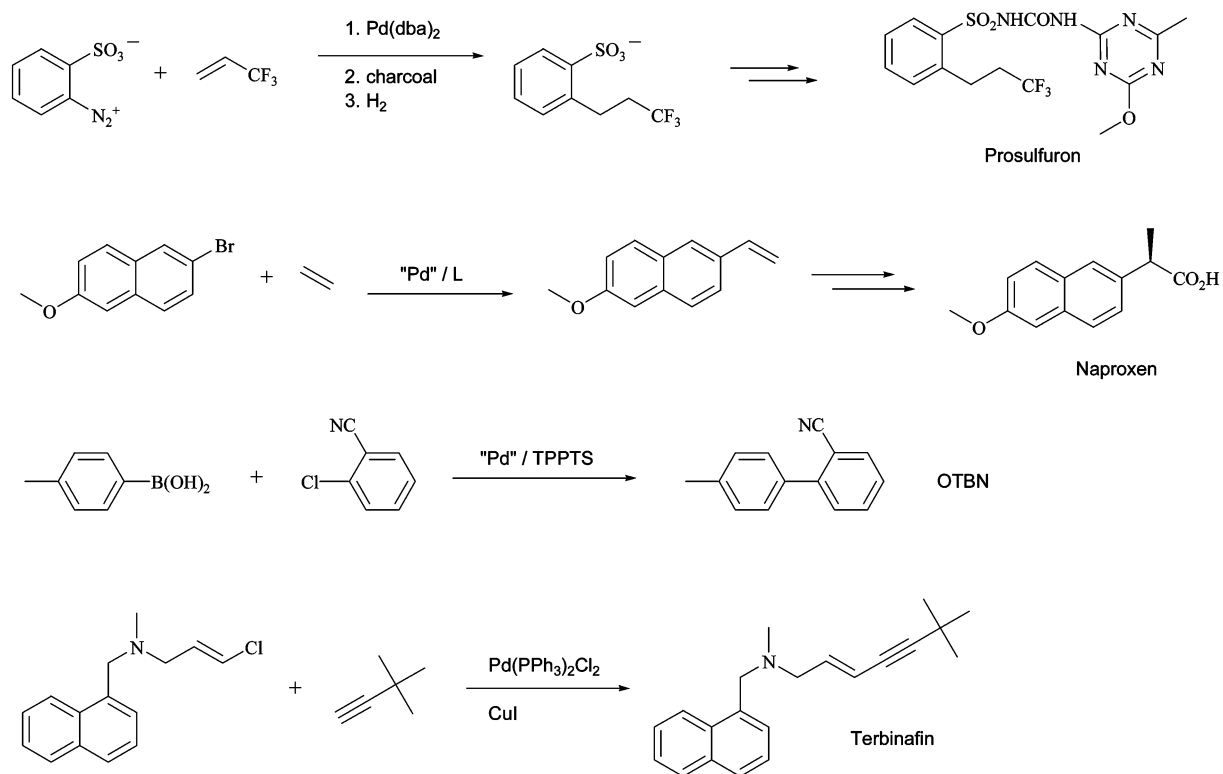
It is interesting to note that until the mid 1990s, most palladium-catalyzed coupling reactions of aryl halides utilized simple triphenylphosphine as a ligand for stabilizing the active metal centre<sup>13</sup> although relatively soon it was found that



**Scheme 1** Selected examples of palladium-catalyzed coupling reactions of aryl-X derivatives.

tri(*o*-tolyl)phosphine gives significantly better results, for example in the Heck reaction of 4-bromophenol and methyl acrylate (>95% after 38 h at 75 °C vs. 3% after 48 h with

$\text{PPh}_3$ ).<sup>14</sup> In the 1980s, Alwyn Spencer in the group of Hans-Ulrich Blaser at Ciba-Geigy investigated the effect of reaction conditions on Heck olefinations of aryl bromides and was able



**Scheme 2** Examples of industrially feasible palladium-catalyzed C-C coupling reactions: syntheses of Prosulfuron,<sup>9</sup> Naproxen,<sup>10</sup> OTBN,<sup>11</sup> Terbinafin.<sup>12</sup>

to reach for the first time turnover numbers (TON) >100 000 with activated (electron deficient) aryl bromides.<sup>15</sup>

Our interest in the palladium-catalyzed coupling reactions of aryl chlorides and anilines<sup>16</sup> started in the early 1990s. At that time, Matthias Beller was working as a research chemist in the Central Research of Hoechst AG in Frankfurt, and a project on this topic was initiated by the former director of the Central Research, Klaus Kühlein. Shortly after the start of the project in-house at Hoechst, fruitful collaborations with academic groups, *e.g.*, with David Milstein<sup>17</sup> and mainly Wolfgang A. Herrmann<sup>18</sup> at the Technical University of Munich, were initiated in 1992/3. It was Christoph Broßmer<sup>19</sup> in Herrmann's group who discovered that high catalyst activity and productivity is obtained when the cyclometallated complex **1** ("palladacycle")<sup>20</sup> (Fig. 1) is applied in the Heck reactions of aryl bromides and chlorides instead of an *in situ* mixture of palladium acetate and tri(*o*-tolyl)phosphine.<sup>21</sup>

Soon after this finding, Claus-Peter Reisinger (from Herrmann's group), Thomas Riermeier, and Alexander Zapf joined the project in Frankfurt and Munich and explored the organometallic chemistry and catalytic performance of **1**. In general, excellent productivities and activities with a wide range of aryl halides were obtained. For example, with activated substrates, *e.g.*, 4-bromoacetophenone, TONs of up to 1 000 000 were achieved (Scheme 3).

Deactivated (electron rich) aryl bromides require somewhat higher catalyst concentrations for high yields (*ca.* 0.1 mol%). Notably, electron deficient chloroarenes, which had rarely been coupled successfully at that time, could also be reacted in the presence of a comparably low palladium concentration of 0.1 mol% provided that at least 20 mol% of a soluble bromide salt (LiBr or *n*-Bu<sub>4</sub>NBr) is added. The role of the added bromide is both that of an activating and stabilizing agent for the palladium catalyst through ate-complex formation.<sup>22</sup> Other coordinating (chloride, iodide, acetate *etc.*) or non-coordinating anions (nitrate, triflate *etc.*) do not increase the catalytic productivity at all or increase it slightly compared to a catalyst system without any additive.<sup>23,24</sup> Interestingly, it turned out that the olefin-aryl chloride ratio dramatically

influences the reaction outcome. Often a small excess of olefin (1.2–1.5 equiv.) over aryl halide is applied due to possible side reactions of the olefin such as dimerization or polymerization. However, olefins act as  $\pi$ -acidic ligands for the palladium center resulting in a significant decrease of electron density and, thus, a lower reactivity towards oxidative addition to the aryl chloride. As a consequence, an improved catalytic performance is obtained when an olefin-chloroarene ratio <1 is chosen.<sup>24</sup>

Although the reasons for the improved productivity of **1** were initially unclear,<sup>25</sup> this finding led to an enormous activity by various groups in the following years to develop improved metallacycle-type catalysts and other palladium-phosphine catalysts for Heck and Suzuki reactions. A selection of other palladacycle catalysts is shown in Fig. 2.<sup>26</sup>

Kinetic investigations showed that palladacycle **1** is more stable than simple palladium phosphine complexes under reaction conditions and, thus, the catalytic activity is maintained for a longer period. Apparently **1** acts as temperature-stable pre-catalyst, which slowly releases the active monophosphine palladium species. One more reason for the unexpected catalyst productivity seems to be the resistance of **1** towards aryl-aryl scrambling on the phosphine which leads to fast ligand degradation in the case of "simple" phosphines such as triphenylphosphine.<sup>27</sup>

When alkyl methacrylates instead of unsubstituted acrylates or styrene are coupled with bromoarenes, two regioisomers are formed because  $\beta$ -hydride elimination from the intermediate alkyl-Pd complex can occur in two directions (Scheme 4).<sup>28</sup> Furthermore, double arylated products **4** are obtained by a second Heck reaction of **3**. We demonstrated that the ratio of the two isomers **2** and **3** can be controlled by a suitable choice of base: with strongly coordinating tertiary amines (*e.g.*, *n*-Bu<sub>3</sub>N), the cinnamic acid derivative **2** is formed in *ca.* 10-fold excess, whereas weakly coordinating inorganic bases such as

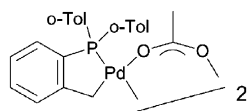
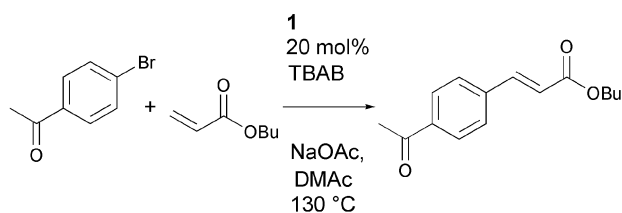


Fig. 1 Palladacycle **1**.



**Scheme 3** Heck reaction of 4-bromoacetophenone and methyl acrylate (TON 1 000 000; TOF 42 000; >99% yield; TBAB = tetra-*n*-butylammonium bromide, DMAc = *N,N*-dimethylacetamide).

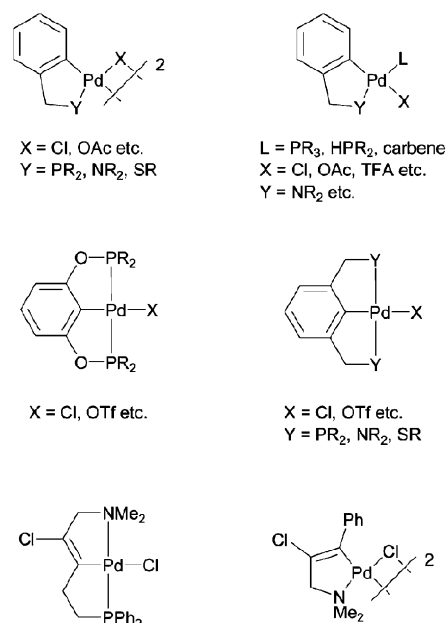
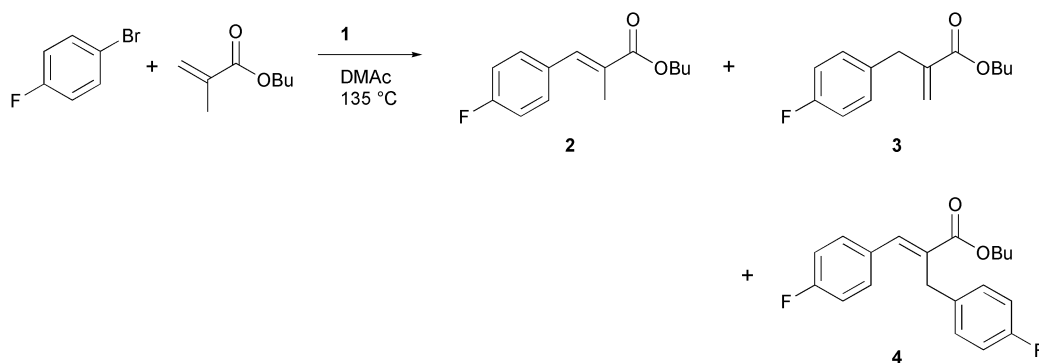


Fig. 2 Selected palladacycle catalysts.

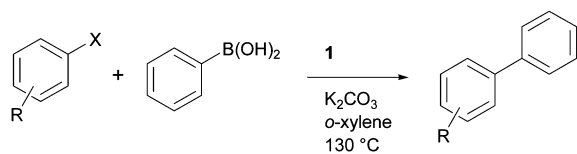


**Scheme 4** Heck reaction of methacrylates.

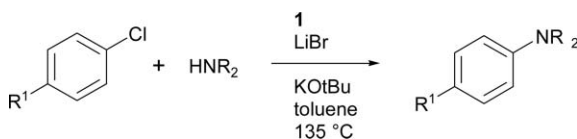
sodium acetate lead to a statistically determined ratio of *ca.* 2 : 3.

Palladacycle **1** turned out to be an efficient catalyst for Suzuki and Buchwald–Hartwig amination reactions, too. For example, aryl bromides can be coupled with phenylboronic acid, applying catalyst concentrations as low as 0.001–0.02 mol% (TON >70 000; Scheme 5).<sup>29</sup> 4-Chloroacetophenone as an activated aryl chloride was arylated with TONs in the range of 1000 under identical conditions. The addition of a soluble halide source is not required here. In contrast to the Heck coupling with palladacycle **1**, non-polar solvents such as *o*-xylene give the best results.

The first example of an amination reaction with aryl chlorides (now called the Buchwald–Hartwig amination) has also been described by us using catalyst **1**.<sup>23,30</sup> Electron deficient *para*-substituted chloroarenes were reacted with secondary aliphatic (*e.g.*, piperidine) or aromatic (*e.g.*, *N*-methylaniline) amines yielding the corresponding tertiary anilines with TONs of up to 800 at 135 °C (Scheme 6). Crucial for the success of this reaction is the use of potassium *tert*-butoxide as a base. Toluene is the solvent of choice, and 20 mol% lithium bromide has to be added to increase the catalytic activity and selectivity. Competing with the palladium-catalyzed reaction, a second pathway *via* aryne intermediates<sup>31</sup> has been observed under these conditions



**Scheme 5** Suzuki reaction using palladacycle **1** as a catalyst.



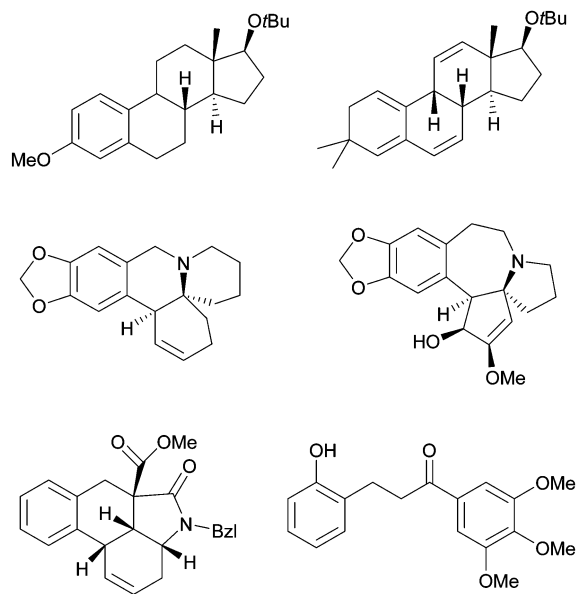
**Scheme 6** Buchwald–Hartwig amination of aryl chlorides.

(strong base at high temperatures) resulting in up to 9% of the corresponding *meta*-isomer.

Apart from our own work on synthetic applications, palladacycle catalyst **1** proved to be superior to other palladium catalysts in various syntheses of natural products and organic building blocks. A selection of applications is shown in Fig. 3. To be noted are the examples presented by Tietze<sup>32</sup> and other groups.<sup>33</sup>

#### Catalyst systems with high ligand–Pd ratio

After moving from industry to the Technical University in Munich in early 1996 (MB), a small research group was formed which basically focused on three topics: (a) improved catalysts for palladium-catalyzed coupling reactions, (b) amidocarbonylation reactions,<sup>34</sup> and (c) amination of olefins.<sup>35</sup> In the area of aryl–X activation reactions, on the one hand we continued to explore the synthetic potential of **1**, on the other hand we looked for alternative palladium catalysts. As mentioned above, the success of palladacycle **1** is based



**Fig. 3** Synthesis of natural products and building blocks using **1**.<sup>32,33</sup>

largely on its stability, which prevents the formation of palladium black. Along this line we thought that *in situ* catalyst systems which are intrinsically stabilized should show similar catalytic behaviour. Indeed, the agglomeration of palladium(0) can easily be prevented by the addition of bromide ions and/or by applying a higher phosphine–palladium ratio. For example, in the case of simple triphenylphosphine, an increase in the P–Pd ratio from 2 : 1 to 20 : 1 in the Heck reaction of 4-chlorobenzotrifluoride and styrene under standard conditions (0.1 mol% Pd(OAc)<sub>2</sub>, DMAc, 160 °C) leads to a dramatic increase in product yield from 1 to 65%. In the presence of 20 mol% tetra-*n*-butylammonium bromide as a stabilizing additive, the ligand–metal optimum lies at a somewhat lower phosphine–palladium ratio of 15 : 1 (72% yield). This finding has been in contrast to the general belief that high P–Pd ratios suppress catalytic activity by blocking free coordination sites on the palladium center.<sup>36</sup>

The concept of using an excess of phosphine ligands for the activation of aryl chlorides in palladium-catalyzed cross-coupling reactions could even be applied to phosphite ligands, which have formerly been judged as intrinsically unsuitable for these types of reactions due to their ability to withdraw electron density from a coordinated palladium centre. Applying economically attractive triethylphosphite as a ligand in the Heck reaction of 4-chlorobenzotrifluoride and styrene gave >70% of the desired product (0.1 mol% Pd(OAc)<sub>2</sub>, P–Pd 100 : 1).<sup>37</sup> Other trialkyl- or triarylphosphites are also suitable for the olefination of electron deficient aryl chlorides and all types of aryl bromides.

Similarly, in the Suzuki reaction of 4-chlorobenzotrifluoride and phenylboronic acid, good yields (>75%) are obtained with tri(*i*-propyl)phosphite or tris(2,4-di-*tert*-butylphenyl)phosphite (P–Pd 10 : 1).<sup>38</sup> Interestingly, the addition of 20 mol% tetra-*n*-butylammonium bromide suppresses almost all catalytic activity. On the other hand, additives that activate the boronic acid towards transmetalation of the phenyl rest to the palladium centre significantly improve the reaction outcome. Fluoride is well suited to this purpose, but simple water in combination with a strong base (sodium carbonate) is also effective. Interestingly, triarylphosphites are not hydrolyzed under these conditions. It is not only activated aryl chlorides that can be coupled using this protocol, but also non-activated chlorobenzene and 4-chlorotoluene (*ca.* 50% yield). Both electron rich and electron poor aryl bromides can be reacted with high efficiency: only 0.0001 mol% of palladium is required for good yields.

#### Palladium catalysts based on sterically demanding and basic phosphines

Based on the pioneering work of Osborne,<sup>39</sup> Alper,<sup>40</sup> and Milstein<sup>41</sup> since the mid to late 1990s, it was mainly Fu<sup>42,43</sup> Buchwald,<sup>44</sup> and Hartwig<sup>45</sup> that developed basic, sterically demanding phosphine ligands for palladium-catalyzed cross-coupling reactions. The resulting catalysts are especially active when applied at a low ligand–palladium ratio (1 : 1 to 2 : 1).

We also became interested in this type of catalyst in 1998. During the summer of that year, we moved from Munich to Rostock to the now-called Leibniz-Institut für Organische

Katalyse (IfOK), which is a state-funded but independent research institute for applied homogeneous catalysis. After reorganization of the institute, twelve technology platforms were created, among them the topic “aryl–X activation reactions”. Since that time, Alexander Zapf has acted as the group leader of this project. In Rostock, Andreas Ehrentraut joined the group as a PhD student and his goal was to develop bulky, electron rich phosphines which should be active even under mild conditions (room temperature up to 80 °C). First we focused on adamantylphosphines—a class of ligands that has been scarcely known,<sup>46</sup> and which has never been applied in palladium-catalyzed reactions before. We were pleased to find that among the various alkyladamantylphosphines, di-(1-adamantyl)-*n*-butylphosphine (**5**) is an excellent ligand for the different functionalization reactions of aryl chlorides (Fig. 4). Interestingly, the group of John Hartwig also developed at the same time, in a parallel attempt, efficient ligands with similar substituents.<sup>47</sup> Fortunately from our point of view we had previously claimed the corresponding ligands in a patent application.<sup>48</sup>

In contrast to Heck reactions with **1** as a catalyst, relatively non-polar solvents such as dioxane give the best results here.<sup>49</sup> Typical TONs for the reaction of deactivated aryl chlorides are in the range of 50–100 with **5** at 120 °C. In the Suzuki reaction of aryl chlorides, even 0.001 to 0.005 mol% of a palladium acetate–**5** catalyst is sufficient for high yields! Electron rich chloroarenes can be arylated with TONs of up to almost 20 000, electron deficient chloroarenes with TONs of more than 60 000 at 100 °C. Toluene is the solvent of choice and potassium triphosphate is a well suited base.<sup>50</sup> Ligands with similar steric properties, *e.g.*, di(1-adamantyl)allylphosphine, give comparable results as does **5**, but more congested ones lead to lower yields in the Suzuki reactions of aryl chlorides.<sup>51</sup> Ligand **5** (cataCXium® A) and similar derivatives are nowadays commercially available from Strem and have been up-scaled by Degussa Homogeneous Catalysts up to kg-scale. An important advantage of this class of ligands compared to similar *tert*-butylphosphines is their significantly increased stability towards air and moisture. In general, **5** can be handled in air without problems. Interestingly, the corresponding HBr or HI salts of adamantylphosphine ligands are equally efficient precursors for *in situ* catalyst systems. Their synthesis requires just one step less than that of the corresponding phosphines.<sup>51</sup>

The new ligands have also been applied successfully in the Buchwald–Hartwig amination of aryl chlorides and the  $\alpha$ -arylation of ketones. The coupling of non-activated chloroarenes with primary or secondary alkylamines or with anilines is possible in toluene at 120 °C with sodium *tert*-butoxide as a base (0.5 mol% Pd(OAc)<sub>2</sub>, P–Pd = 2 : 1).<sup>52</sup> In the case of bulky

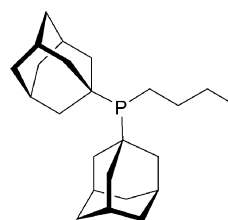


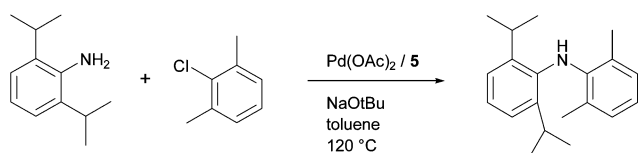
Fig. 4 Di(1-adamantyl)-*n*-butylphosphine (**5**, cataCXium® A).

2,6-disubstituted anilines and congested aryl chlorides, the new phosphines (especially **5**) are superior to all other previously known ligands (Scheme 7).

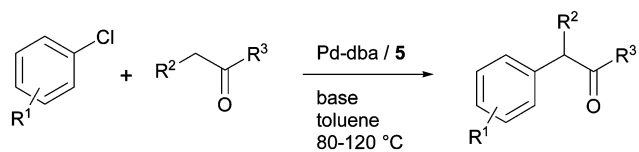
Another interesting cross-coupling reaction is the palladium-catalyzed  $\alpha$ -arylation of ketones with aryl halides yielding arylmethyl ketones (Scheme 8). Here again, **5** is one of the best ligands for the reaction of aryl chlorides.<sup>53</sup> Applying sodium *tert*-butoxide as a base in toluene, high turnover numbers of more than 4000 are found. For substrates with base sensitive functional groups, potassium carbonate and phosphate, respectively, can be used. The selectivity towards mono- or diarylation can be influenced to some extent by a suitable choice of base and the ketone-aryl chloride ratio.

In addition, Plenio and co-workers<sup>54</sup> and other groups<sup>55</sup> demonstrated elegantly the usefulness of 1-adamantylphosphines such as **5** in different palladium-catalyzed coupling reactions.

Recently, another class of basic, sterically hindered phosphines has been developed in our group. Inspired by Buchwald's biarylphosphine motif<sup>44</sup> our ligands are characterized by an *N*-aryl heterocyclic backbone, which is substituted by a bulky dialkylphosphino group in the  $\alpha$ -position to the nitrogen atom (Fig. 5).<sup>56</sup> So far, more than 20 different phosphines have been synthesized based on *N*-arylpyrrole (e.g., **6–8**), -indole (e.g., **9**) and -(benz)imidazole (e.g., **10**). Again, some of the ligands (cataCXium® P ligands) are commercially available from Strem and Degussa Homogeneous Catalysts. An important feature of the ligands is their easy preparation in one or two steps, even on a large scale (up to kg-scale), by selective deprotonation of the *N*-aryl



Scheme 7 Coupling of 2,6-di(*i*-propyl)aniline and 2-chloro-*m*-xylene.



Scheme 8  $\alpha$ -Arylation of ketones.

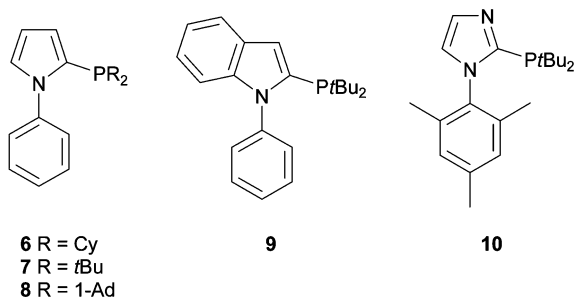


Fig. 5 Some cataCXium® P ligands.

heterocycle and quenching with the corresponding chlorophosphine. Hence, the synthesis of ligand libraries is easy compared with other similar phosphines.

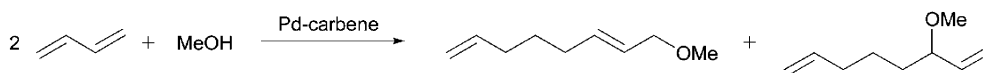
Due to their basicity and steric bulkiness, they constitute excellent ligands for palladium-catalyzed coupling reactions. For example, an *in situ* mixture of palladium acetate and ligand **7** catalyzes the Suzuki reactions of both electron rich and electron deficient aryl chlorides with TONs of up to 10 000 at 60 °C.<sup>57</sup> At room temperature, unprecedented TONs are obtained: only 0.1 mol% of catalyst is required for good yields of the desired biaryls. In the case of sterically demanding aryl chlorides (e.g., 2-chloro-*m*-xylene), superior results are obtained with the less bulky ligand **6** with two cyclohexyl instead of *tert*-butyl groups at the phosphorus. The new ligands also work excellently in the amination of aryl chlorides.<sup>58</sup> Among the different ligands prepared, 2-(di-*tert*-butylphosphino)-*N*-phenylindole (**9**) shows the best performance in most cases. Coupling reactions of both activated and deactivated chloroarenes can be performed under mild conditions (room temperature to 60 °C). Secondary aliphatic and aromatic amines react successfully, as well as primary amines. Remarkable catalyst productivities (TON of up to 8000) and activities (TOF 14 000 h<sup>-1</sup> at 75% conversion) are obtained.

#### Palladium catalysts based on *N*-heterocyclic carbene ligands

Apart from P-donor ligands, in recent years *N*-heterocyclic carbenes have gained some importance as ligands for palladium-catalyzed coupling reactions.<sup>59</sup> Although carbenes can act as  $\pi$ -acceptor ligands, it has become the commonly held opinion that they can be viewed as simple  $\sigma$ -donor ligands. Accordingly, carbenes show behaviour similar to electron rich phosphines in many reactions. Initially, palladium(II) complexes with two carbene ligands have been described by Herrmann *et al.* for the Heck reactions of aryl bromides and activated aryl chlorides.<sup>60</sup> Later on Herrmann,<sup>61</sup> Nolan,<sup>62</sup> Cavell,<sup>63</sup> and others<sup>64</sup> described various applications of palladium carbene catalysts for aryl-X functionalizations.

We became interested in this class of catalysts with respect to the synthesis of monophosphine<sup>65</sup> and monocarbene palladium(0) catalysts. We thought that such complexes constitute ideal pre-catalysts for various coupling reactions at a low reaction temperature due to the defined amount of strongly coordinating ligands and the omission of catalyst preformation [*e.g.*, reduction of Pd(II) to Pd(0)] under reaction conditions. Hence, Mario Gómez Andreu and later on Kumaravel Selvakumar, Ralf Jackstell, and Anja Frisch in particular were able to prepare various monocarbene palladium(0) complexes with stabilizing olefinic co-ligands, for example **11** turned out to be the most efficient catalysts known to date in the telomerization of 1,3-butadiene with various alcohols (Scheme 9).<sup>66</sup>

Thus, for the first time, bulk telomerization reactions appear to be commercially viable and are not limited by catalyst costs. The industrial applicability of similar catalyst systems has already been demonstrated by the production of telomeres on a tonne-scale!<sup>67</sup> Unfortunately, in palladium-catalyzed



**Scheme 9** Telomerization of 1,3-butadiene with methanol.

cross-coupling reactions, 1,6-dienes do not seem to be ideal co-ligands. In most cases, a significant decrease in catalytic activity, probably due to the dienes' strong binding to the palladium centre is observed resulting in the blocking of free coordination sites on the catalyst.<sup>68</sup> Co-ligands that are easily removed under reaction conditions are quinones. For example, naphthoquinone can be used, which coordinates to palladium(0) *via* the non-aromatic double bond. Additional coordination of a carbonyl oxygen of a second molecule leads to the formation of a naphthoquinone bridged palladium dimer (*e.g.*, **12**) (Fig. 6).<sup>69</sup> Complexes of this type are active catalysts for the Heck and Suzuki reactions of aryldiazonium salts. Here, protic solvents are advantageous and mild conditions are feasible (*ca.* 50 °C, no base, 0.1–1 mol% Pd).

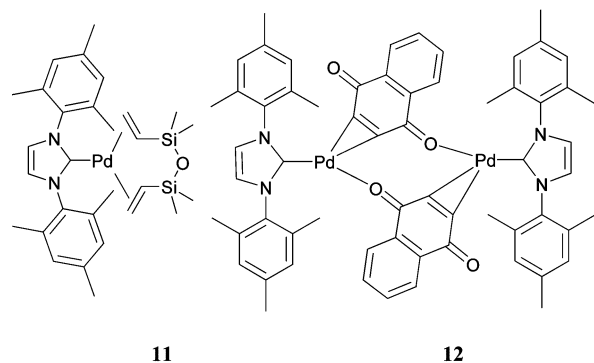
In addition, we tested monocarbene palladium(0) quinone complexes in the Heck reaction using tetra-*n*-butylammonium bromide as an ionic liquid. Here, we obtained reasonable to good activity for both electron deficient and electron rich aryl chlorides.<sup>70</sup>

A recent comparison of phosphine and carbene based palladium catalysts under identical conditions revealed that for Suzuki and Buchwald–Hartwig amination reactions, phosphines lead to more productive catalysts, whereas for Kumada reactions, generally carbene ligands are superior.<sup>68</sup> However, it cannot be ruled out that there are other reaction conditions which show the opposite results.

### Miscellaneous

In addition to the examples mentioned above, we also pursued other ideas for catalyst development. Already in 1995, we had described the first examples of the coupling reactions of aryl halides in the presence of colloidal palladium catalysts.<sup>71</sup> Here, aryl bromides were olefinated in high yields at excellent reaction rates. It is interesting to note that this area has been of significant interest in recent years due to the design of potentially more active palladium nanoparticles.<sup>72</sup>

An early attempt of our group to design ligands for Heck and Suzuki reactions under biphasic conditions was based on

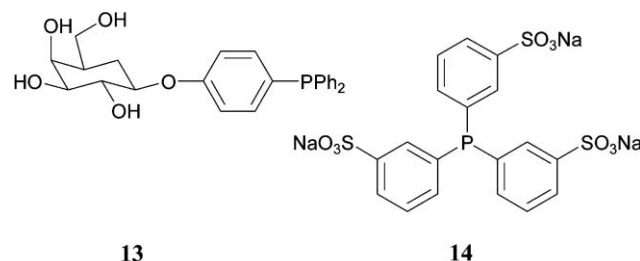


**Fig. 6** Monocarbene palladium(0) complexes.

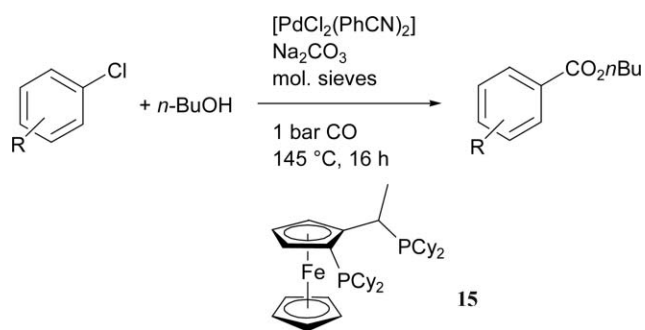
the attachment of carbohydrates to triphenylphosphine *via* O-glycosidic bonds, *e.g.* in **13**. Performing Heck and Suzuki reactions of aryl bromides in alcohols as solvents, the carbohydrate-substituted ligands performed better than the “standard ligand” TPPTS (**14**) (Fig. 7).<sup>73</sup>

Since 2000, we have become more interested in “more difficult” coupling reactions such as the carbonylation (“Heck carbonylation reaction”)<sup>74</sup> and cyanation of aryl halides.<sup>75</sup> In contrast to most palladium-catalyzed coupling reactions, here the reaction partners strongly deactivate the metal center due to their  $\pi$ -acidic nature or due to the formation of palladium clusters. We showed that bidentate ligands offer significant advantages for the carbonylation of aryl bromides and chlorides. Good to excellent yields of a number of *N*-heterocyclic carboxylic acid esters were realized by applying the appropriate ligand [1,4-bis(diphenylphosphino)butane (dppb), 1,1'-bis(diphenylphosphino)ferrocene (dppf) or 1,4-bis(dicyclohexylphosphino)butane (dcpb)] in the right concentration at low catalyst loadings (0.005–0.5 mol% Pd). Catalyst turnover numbers of up to 13 000 were obtained. Our investigations on the palladium-catalyzed alkoxy carbonylation reaction of activated and deactivated aryl chlorides resulted in the development of a new and efficient catalyst system based on cyclohexyl-substituted ferrocenylphosphine ligands for the carbonylation of aryl chlorides.<sup>76</sup> Again, the considerable advantages are that these ligands are air stable and commercially available.<sup>77</sup> With the PdCl<sub>2</sub>(PhCN)<sub>2</sub>-**15** catalyst (0.5 mol% Pd) in the presence of sodium carbonate as the base, chlorobenzene was converted to *n*-butyl benzoate in an essentially quantitative yield within 16 h (130–145 °C) (Scheme 10). The CO pressure can be as low as 1 bar. After optimization, a catalyst turnover number of almost 1600 was observed at Pd loadings of only 0.05 mol%, underlining the high productivity of the catalyst system. This catalyst productivity is almost one order of magnitude higher than that previously reported with non-activated chloroarenes.

Finally, it is worth mentioning that we started to investigate the palladium-catalyzed coupling reactions of *alkyl* chlorides in 2002. The activation of C(sp<sup>3</sup>)-Cl bonds has so far been much less studied. We showed that PCy<sub>3</sub><sup>78</sup> and *N*-heterocyclic carbenes<sup>79</sup> are suitable ligands for the palladium-catalyzed coupling of alkyl chlorides with aryl Grignard reagents. A



**Fig. 7** Phosphine ligands for two phase catalysis.



**Scheme 10** Carbonylation of aryl chlorides.

variety of simple as well as functionalized primary alkyl chlorides provided the corresponding alkyl benzenes generally in good to very good yields. By comparing the 1,3-dimesitylimidazol-2-ylidene (IMes) palladium(0) naphthoquinone complex (**12**) with the previously known palladium phosphine catalyst, improved yields and catalyst activities were observed.

## Summary and outlook

We have summarized the development of several new catalysts for palladium-catalyzed cross-coupling reactions of aryl halides, especially aryl chlorides, in our group. Starting from palladacycle **1**, we found that a plethora of *in situ* catalysts with high ligand–palladium ratios are suitable for aryl–X activation reactions at elevated temperatures. However, specially designed basic and sterically demanding phosphines show superior performance under milder reaction conditions. Different ligand concepts have proved successful for Heck and Suzuki reactions as well as Buchwald–Hartwig aminations, cyanations, and carbonylations. Currently, further investigations on the scope and limitations of di(1-adamantyl)alkylphosphines and *N*-aryl-2-(dialkylphosphino)pyrrole type ligands are performed within our group. Due to their facile synthesis and their commercial availability, we are optimistic that technical processes based on these ligands will be launched in the near future.

Nowadays, cross-coupling reactions appear as reliable transformations in more complex natural product syntheses. Apparently, a number of reactions are efficient enough to run in industry on a tonne-scale. This has been made possible by the important advancements in cross-coupling chemistry, which took place during the last decade. Nevertheless, we believe that these methods still offer significant challenges for the future. For example, catalyst efficiency (activity and productivity) is still comparably low using substrates such as (nitrogen)heteroarenes and more functionalized coupling partners. Here, the development of better catalysts should be very useful. Clearly, new catalyst systems should be tested initially in more simple benchmark reactions, however, this should only be the start and not the end of catalyst development! Thus, we encourage our colleagues to test novel catalysts with challenging substrates. In this regard, it is also interesting to note that already in 1997 we had mentioned that the Heck or Suzuki reaction of 4-bromoacetophenone is not a useful benchmark test for catalysts, because

any palladium source gives very good results under appropriate conditions.<sup>21b</sup>

Apart from that, another major challenge for the next few years will be the development of cross-coupling alternatives which do not use aryl halides as substrates but directly employ arenes. The advantages of such methods are obvious: cheaper substrates and less waste. Here, the development of selective CH-transformation reactions, either *via* metal-catalyzed CH-activation or *via* catalytic Friedel–Crafts variants, is the crucial point. Despite the general problem of regioselectivity, more and more interesting examples demonstrate the potential of this approach.<sup>80</sup>

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