# The Suzuki Coupling of Aryl Chlorides under Microwave Heating

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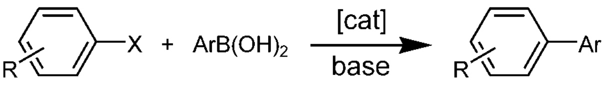
**Abstract:** Simple, inexpensive catalysts formed *in situ* from tricyclohexylphosphine and palladium acetate or a phosphite-based palladacycle show unprecedented activity in the Suzuki coupling of deactivated, non-activated and activated aryl chloride substrates under microwave heating.

**Keywords:** aryl chlorides; C–C bond formation; metallacycles; microwaves; palladium; Suzuki coupling

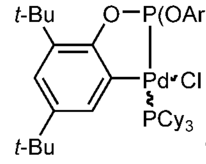
The use of microwave heating has led to the facilitation of a great number of reactions[1] and, with recent changes in microwave design, can now be applied to parallel screening programmes. The Suzuki reaction (Scheme 1) is a powerful technique for the formation of biaryl species.[2]



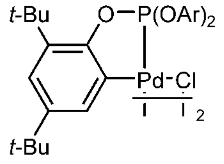
**Scheme 1.** The Suzuki biaryl coupling reaction.

Many recent studies on this process have focussed on the development of catalyst systems that are able to activate electronically challenging aryl chloride substrates.[3] It would therefore be highly desirable if a catalyst system could be designed for the Suzuki coupling of aryl chloride substrates under microwave heating.[4,5] As yet, to the best of our knowledge, the only catalyst that shows reasonable activity in the coupling of deactivated aryl chlorides under microwave heating is one formed *in situ* from palladium acetate and tetrabutylammonium bromide (TBAB) in the presence of water.[6] The active catalyst in this case is presumably colloidal palladium supported by the TBAB.[7]

The lack of homogeneous catalysts for the coupling of aryl chlorides under microwave heating may be due to the fact that many of the alkylphosphine-based catalysts used in such reactions under 'classical' heating conditions do not prove to have particularly high thermal stability. We have recently reported that the pre-catalyst **1**, typically formed *in situ* from **2** and $PCy_3$ not only shows extremely high activity in the Suzuki coupling of aryl chlorides, but also is very long-lived.[8]



**1**



**2**

Ar = $C_6H_3$-2,4-*t*-$Bu_2$

We wondered whether the high longevity of **2** would enable it to be used effectively in the coupling of aryl chloride substrates under microwave heating. This indeed proved to be the case, but surprisingly we found that even simpler systems based on $PCy_3$ and palladium acetate are equally effective. The preliminary findings of this study are presented below.

Rather than perform extensive base optimisation, we focussed on the use of $K_3PO_4$ as this is both inexpensive and tolerant of a wide range of substrate functionality. While some activity is observed in toluene, far better results are obtained in 1,4-dioxane and this solvent was used for the rest of the study.

Initial studies were performed on the coupling of phenylboronic acid with 4-chloroanisole since this aryl chloride is electronically deactivated and thus provides a challenging and useful indication of catalyst performance. Representative results are summarised in Table 1.

We were pleased to find that the coupling proceeds with high conversion at 180 °C within 10 min (entry 1) with a catalyst formed *in situ* from **2** and one equivalent of $PCy_3$ per Pd. Increasing the time to 20 min leads to a slight increase in conversion but also to an increased amount of biphenyl impurity due to homo-coupling of the boronic acid, which is used in excess (entry 2).

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**Table 1.** Suzuki coupling of 4-chloroanisole with phenylboronic acid.[a]

| Entry | Catalyst [mol % Pd] | Temperature [°C] | Time [min] | Conversion [%][b] | Biphenyl [%] |
|---|---|---|---|---|---|
| 1 | **2**+$PCy_3$ (1.0) | 180 | 10 | 89 | <1 |
| 2 | **2**+$PCy_3$ (1.0) | 180 | 20 | 93 | 2 |
| 3 | **2**+$PCy_3$ (1.0) | 150 | 30 | 92 | <1 |
| 4 | **2**+$PCy_3$ (1.0) | 150 | 20 | 79 | 2 |
| 5 | **2**+$PCy_3$ (1.0) | 150 | 10 | 48 | 2 |
| 6 | **2**+$PCy_3$ (1.0) | 150 | 20 | 73[c] | 2 |
| 7 | **2**+$PCy_3$ (1.0) | 150 | 20 | 78[d, e] | 1 |
| 8 | **2**+$P(t\text{-Bu})_3$ (1.0) | 150 | 10 | 16 | 4 |
| 9 | $Pd(OAc)_2$ (1.0) | 150 | 20 | 0 | 1 |
| 10 | $Pd(OAc)_2$+$PCy_3$ (1.0) | 150 | 20 | 4 | 2 |
| 11 | $Pd(OAc)_2$+2 $PCy_3$ (1.0) | 150 | 30 | 98 | 2 |
| 12 | $Pd(OAc)_2$+2 $PCy_3$ (1.0) | 150 | 20 | 90[c] | <1[e] |
| 13 | $Pd(OAc)_2$+2 $PCy_3$ (1.0) | 150 | 20 | 7[d] | 3 |
| 14 | $Pd(OAc)_2$+2 $PCy_3$ (0.05) | 150 | 20 | 61 | 1 |
| 15 | $[Pd(dba)_2]$ | 150 | 20 | 50 | 14 |

[a] Conditions: 4-chloroanisole (1.0 mmol), phenylboronic acid (1.5 mmol), $K_3PO_4$ (2.0 mmol), 1,4-dioxone (4 mL).
[b] Conversion to coupled product determined by GC (hexadecane standard).
[c] Water (0.5 mL) added (total solvent volume = 4 mL).
[d] Under air.
[e] GC analysis shows the presence of an unidentified side product.

Good activity is also seen when the temperature is reduced to 150 °C (entries 3–5), although slightly longer reaction times (20–30 min) are required for optimal conversions. Comparing entries 4, 6 and 7 it can be seen that the catalyst system is remarkably stable with respect to both air and water with essentially no change in activity observed. As we have previously observed with classical heating, $P(t\text{-Bu})_3$ is not as effective a ligand as $PCy_3$ for the Suzuki coupling of aryl chlorides when used in conjunction with a palladacyclic precursor (entry 8).[8,9] In addition, a larger amount of biphenyl impurity is observed. For these reasons we focussed on catalysts containing $PCy_3$ for the rest of the study.

We were surprised to find that while both palladium acetate and catalysts formed *in situ* from palladium acetate and one equivalent of $PCy_3$ are inactive (entries 9 and 10), increasing the P:Pd ratio to 2:1 gives an extremely active catalyst system (entry 11). As with the catalyst formed from **2** and $PCy_3$, this system is also tolerant to added water (entry 12). However, it is not stable with respect to air, with very low activity observed when the reaction is performed under aerobic conditions (entry 13). Reasonable conversion is seen at catalyst loadings as low as 0.05 mol % Pd (entry 14). By contrast, when the experiment outlined in entry 11 was repeated under thermal conditions in a sealed tube, conversions were somewhat lower at 45% at 30 min and 64% after 18 hours. We have previously shown that dibenzylideneacetone-containing palladium complexes do not make particularly useful precursors for aryl chloride Suzuki catalysts formed *in situ* from $PCy_3$,[9] possibly as a result of the often non-innocent nature of the tenacious dba ligand.[10] Here we find that whilst $[Pd(dba)_2]$ can be used as a precursor for a catalyst that can be used under microwave heating (entry 15) it is somewhat less active than either **2** or palladium acetate and leads to a far higher contamination of the product with biphenyl.

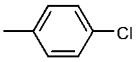
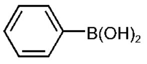
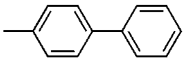
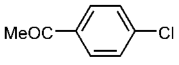
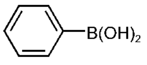
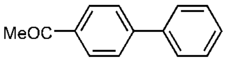
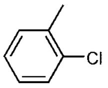
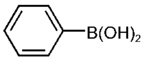
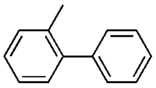
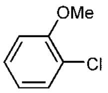
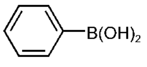
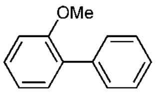
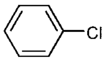
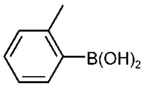
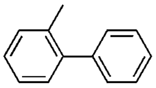
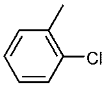
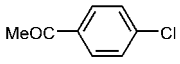
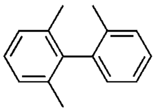
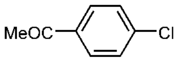
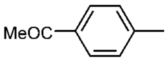
Having established that a palladium acetate/$PCy_3$ mixture is an excellent catalyst for the coupling of an electronically deactivated aryl chloride we next undertook a brief investigation of its performance with a range of aryl chlorides and both aryl- and alkylboronic acids, the results of which are outlined in Table 2.

The high temperature and short reaction time (180 °C, 10 min) used in this study gave very satisfactory results in most cases although the increased temperature often led to the formation of side products. Thus, all of the reactions with phenylboronic acid show the presence of some biphenyl, as does the coupling of chlorobenzene with 2-tolylboronic acid (entry 5). In this case the biphenyl results from an Ullmann coupling of the chloride. As with 4-chloroanisole, it should be possible to circumvent this by using less forcing conditions.

Steric hindrance in the 2-position of either the aryl chloride or the boronic acid is tolerated, but the introduction of three *ortho*-functions into the biaryl product is difficult and only low yields of product are formed (entry 6).[11] In this case substantial amounts of *meta*-xylene are observed as a result of hydrodeboration of the xylylboronic acid. Methylboronic acid can also be used as a substrate, albeit with somewhat limited success.

In summary, catalysts formed *in situ* from the inexpensive, readily available and comparatively easily handled phosphine, tricyclohexylphosphine, and either the palladacyclic precursor **2** or palladium acetate show very good activity in the Suzuki coupling of aryl chloride sub-

**Table 2.** Suzuki coupling of aryl chlorides with aryl and alkyl boronic acids catalysed by $Pd(OAc)_2/PCy_3$. [a]

| Entry | Aryl chloride | Boronic acid | Product | Conversion [%][b] |
|---|---|---|---|---|
| 1 |  |  |  | 87[c] |
| 2 |  |  |  | 81[c, d] |
| 3 |  |  |  | 94[c] |
| 4 |  |  |  | 85[c] |
| 5 |  |  |  | 94[c] |
| 6 |  |  |  | 31[e] |
| 7 |  | $MeB(OH)_2$ |  | 33 |

[a] Conditions: aryl chloride (1.0 mmol), boronic acid (1.5 mmol), $K_3PO_4$ (2.0 mmol), 1,4-dioxane (3.5 mL), $H_2O$ (0.5 mL).
[b] Conversion to coupled product determined by GC (hexadecane standard).
[c] Contains 3–10% biphenyl.
[d] Contains an unidentified side-product.
[e] Contains 28% *meta*-xylene.

strates under microwave heating. While palladium acetate is obviously a highly useful palladium precursor and appropriate for most applications, the greater air tolerance of the catalyst formed from **2** may sometimes prove advantageous, for instance, in high throughput screening programmes.

## Experimental Section

### General Method for the Suzuki Coupling of Aryl Chlorides

Stock solutions of the appropriate palladium precursor and phosphine, made up under nitrogen, each in 1,4-dioxane (1 mL) were added to a 5-mL microwave reaction vial, the aryl chloride (1.0 mmol), boronic acid (1.5 mmol) and $K_3PO_4$ (2.0 mmol) were added and then the total solvent volume was corrected to 4 mL with 1,4-dioxane or dioxane and water. The mixture was heated in a Personal Chemistry Emrys™ Liberator at the appropriate temperature, under 'fixed hold time' conditions for the appropriate time in either 'normal absorption' (neat dioxane) or 'high absorption' (water/dioxane mix) modes. After cooling, water (10 mL) was added and the product mixture was extracted with $CH_2Cl_2$ ($3 \times 40$ mL), dried ($MgSO_4$), concentrated under vacuum, hexadecane (internal standard, 0.068 M in dioxane, 1 mL) added and conversion to product determined by GC.

## Acknowledgements

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