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A polymer-supported salen-type palladium complex as a catalyst for the Suzuki–Miyaura cross-coupling reaction

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Abstract—A salen-type palladium(II) complex was readily immobilised onto a Merrifield resin. The supported complex is an effective recyclable heterogeneous catalyst for the Suzuki cross-coupling reaction without the use of phosphine ligands. Leaching of the metal into solution from the supported catalyst proved negligible.

The importance of biaryl units as molecular components in pharmaceuticals, herbicides and natural products, as well as in engineering materials such as conducting polymers, molecular wires and liquid crystals, has attracted enormous interest.[1] The Suzuki cross-coupling reaction (coupling of an organoborane and an aryl halide) is an increasingly popular method for the construction of unsymmetrical biaryl compounds as it represents an attractive alternative over methods that use organometallic species since the organoboranes used in the Suzuki reaction are air and moisture stable with relatively low toxicity.[2] Catalysts used in the Suzuki reaction have been traditionally based on homogeneous palladium phosphine complexes, which are rarely recoverable without elaborate and wasteful procedures, and therefore commercially unfavourable.[3] Moreover, phosphine ligands are expensive, toxic; and in large-scale applications the phosphines may be more costly than the metal itself.[4] In recent years there has been an increasing interest in developing greener processes. In this context, heterogeneous catalysis is emerging as an alternative to homogeneous processes since the catalysts can be recovered and reused. Catalyst recovery also decreases contamination of products with residual metal species. Previously, catalysts based on palladium species immobilised on cross-linked polystyrene resins or silica gels have been used in Suzuki reactions.[5,6] However, these catalysts have generally suffered from limited mass transfer, low specificity and selectivity in addition to leaching of the catalytic species from the surface of the support.[5,7]

Recently we reported the synthesis and characterisation of an unsymmetrical salen-type palladium(II) complex and its immobilisation onto a polystyrene–divinylbenzene cross-linked Merrifield resin.[8] The polymer-supported catalyst was shown to be effective in the Heck reaction between 4-bromobenzene and styrene. In this paper we report the use of the supported palladium complex as an active and stable heterogeneous catalyst for the Suzuki cross-coupling reaction of a variety of aryl bromides. The supported catalyst can be reused several times without a significant degradation in catalytic activity. Leaching of the palladium into solution is negligible. We believe that this catalyst is unique in Suzuki chemistry because it is more active than its homogeneous analogue yet is truly heterogeneous, being easily removed from the reaction mixture by filtration and recycled. Leached metal is shown to play no part in the catalysis. Another advantage of the catalyst is that addition of phosphines is not required, thus reducing process costs and eliminating toxic materials that can prove difficult to separate. Furthermore, the absence of phosphines also eliminates the possibility of side reactions that may occur between arylphosphines and the boronic acid.[3,9,10] The resulting product is therefore

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Keywords: Suzuki–Miyaura reaction; Solid-supported catalysis; Palladium; Phosphine-free.

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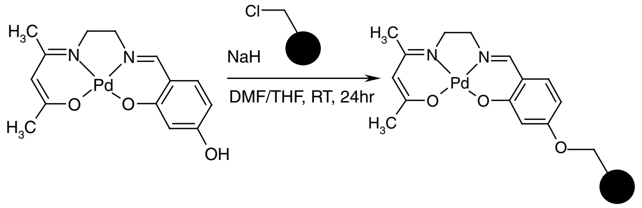


Scheme 1. The immobilisation of the salen-type palladium(II) complex.

isolated from the reaction mixture with a high degree of inherent purity.

The Merrifield resin-supported salen-type palladium catalyst was prepared according to the procedures reported previously (Scheme 1).[8,11] A study of the homogeneous analogue of the immobilised palladium complex [Pd(salenac-OMe)] (Fig. 1) was also undertaken as a comparison. The synthesis of the [Pd(salenac-OMe)] has been reported previously.[8] ICP–AE spectroscopy analyses indicated there to be ca. 4% (wt/wt) palladium on the Merrifield beads, corresponding to a catalyst loading of 0.4 mmol palladium/g of resin.[†]

The supported palladium catalyst was assessed for its activity in the Suzuki reaction initially by studying the coupling of 4-bromoanisole with phenylboronic acid to form 4-methoxybiphenyl as the principal product (Scheme 2). We adopted reaction conditions that have been widely used for Suzuki coupling reactions.[12] A mixture of 4-bromoanisole, a base, phenylboronic acid and a predetermined quantity of the catalyst resin in DME/water (1:1) was heated at a constant temperature for 24 h.[‡] The resin of the supported palladium catalyst is initially bright yellow in colour. Generally, at the end of the reaction the colour of the resin has faded slightly, displaying a yellow/pale-brown colour. Initial studies addressed the catalyst concentration, reaction temperature and the base used in the reaction. The results are summarised in Table 1. The catalyst concentration, with respect to the palladium complex immobilised on the support, was studied in the range 0.1–1.0 mol% relative to the organobromide with a reaction temperature of 100 °C. The best catalyst concentration was observed for 0.5 mol% palladium with the principal product 4-methoxybiphenyl being formed in a conversion of 89%. Less than 0.5 mol% palladium resulted in a drop in this conversion, and more than 0.5 mol% palladium was found unnecessary as the conversion did not increase further. The optimum catalyst concentration found in this study, in terms of highest turnover frequency, is comparable to that of previous reports.[13] The reaction temperature was varied from 80 to 100 °C using 0.5 mol% catalyst. It was found that at 90 °C the most efficient conversion was achieved.

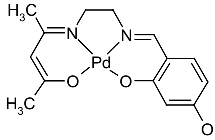


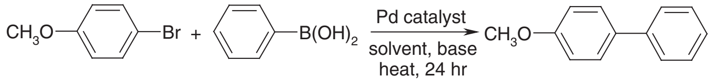
Figure 1. Chemical structure of the [Pd(salenac-OMe)] complex.

Experimental data presented in Table 1 show that K_3PO_4 and NaOH gave the best conversion, with around 90% of 4-bromoanisole being converted to 4-methoxybiphenyl. The reaction with the most commonly used base, Na_2CO_3, afforded the cross-coupling product in a conversion of only 46%. It has been reported that weak bases give better results for less hindered arylboronic acids, and that the order of reactivity for more sterically hindered boronic acids such as mesitylboronic acid corresponded to the basic strength: $Ba(OH)_2 > NaOH > K_3PO_4 > Na_2CO_3 > NaHCO_3$ in homogeneous systems.[14] When the weak base $NaHCO_3$ was used in this study it gave a lower conversion than when Na_2CO_3 was used. Similarly, Cs_2CO_3, which has been reported to be much more effective in the Suzuki reaction than K_2CO_3,[15] gave one of the lowest conversions. Interestingly, although phenylboronic acid is not sterically hindered, the order of reactivity in this study was still found to correspond to the basic strength: $NaOH > K_3PO_4 > Na_2CO_3 > NaHCO_3$. Both triethylamine and *N*,*N*-diisopropylethylamine gave relatively good conversions (>75%). DBU was completely ineffective for the system, possibly due to the steric hindrance of DBU or another side reaction. The coupling reaction using tri-*n*-butylamine as a base also failed, achieving a conversion of only 16%, possibly due also to the increased steric bulk of the *n*-butyl groups.

Further studies focused on varying the solvent system, using 0.5 mol% palladium resin catalyst with K_3PO_4 at 90 °C for 24 h for which DME/water (1:1) gave 89% conversion of 4-bromoanisole to 4-methoxybiphenyl.

[†] ICP–AE spectroscopy analyses of the palladium resin catalyst were performed on a Spectro Ciros^{CDD} instrument (Spectro Analytical, UK) by Alan Cox and Ian Staton from the Department of Chemistry, The University of Sheffield. Calibration against a palladium standard and a blank was linear, using 2% nitric acid solutions containing 0, 1, 5 and 10 ppm palladium made from 1000 ppm stock solution (Aristar). Weighed samples (20.0 mg) of the palladium resin catalyst were placed in glass tubes and digested at 180 °C in a mixture of concentrated nitric acid (5 cm^3, Aristar) and concentrated perchloric acid (0.5 cm^3, Aristar). Three parallel samples were digested over 2, 4 and 6 h, respectively. The yellow palladium resin catalyst became a white residue after digestion. The digest was then diluted to 50 cm^3 with water. Analysis showed that all the metal was removed from the support within 2 h as increasing the digestion time to 4 and 6 h achieved no increase in the amount of the metal in the digest.

[‡] In a typical experiment, a solution of 4-bromoanisole (0.0474 g, 0.25 mmol) in DME (0.5 mL) was added to a Radley's Carousel reaction tube containing the required amount of the palladium catalyst. A solution of a base (0.75 mmol) in water (1 mL) and a solution of phenylboronic acid (0.0462 g, 0.38 mmol) in DME (0.5 mL) were then added and the tube was heated at the required temperature for 24 h with magnetic stirring under a nitrogen atmosphere. To work-up, the mixture was allowed to cool to room temperature and saturated aqueous NaCl solution (3 mL) was added. The organic components were extracted into diethyl ether (2 × 3 mL), which was dried over anhydrous $MgSO_4$ and the resulting solution analysed by GC and GC–MS with reference to standard solutions of 4-methoxybiphenyl.



Scheme 2. The Suzuki reaction of 4-bromoanisole and phenylboronic acid.

Table 1. Study of the reaction conditions in the Suzuki reaction using the palladium resin catalyst in DME/water (1:1) with 1.5 equiv $PhB(OH)_2$ and 1 equiv 4-bromoanisole for 24 h under a nitrogen atmosphere

	Conversion (%)	TOF (mol/mol/h)
Conditions: 100 °C, 3 equiv K_3PO_4		
Mol% Pd catalyst		
1.0	89	3.7
0.5	89	7.4
0.1	33	13.8
Conditions: 0.5 mol% Pd resin catalyst, 3 equiv K_3PO_4		
Temperature (°C)		
80	40	3.3
90	89	7.4
100	85	7.1
Conditions: 90 °C, 0.5 mol% Pd resin catalyst, 3 equiv base		
Base		
K_3PO_4	89	7.4
$NaHCO_3$	36	3.0
Na_2CO_3	46	3.8
Cs_2CO_3	17	1.4
NaOH	92	7.7
Et_3N	76	6.3
$(i\text{-}Pr)_2NEt$	77	6.4
Bu_3N	16	1.3
DBU	1	—

The data represent conversions of 4-bromoanisole to 4-methoxybiphenyl (based on GC data).

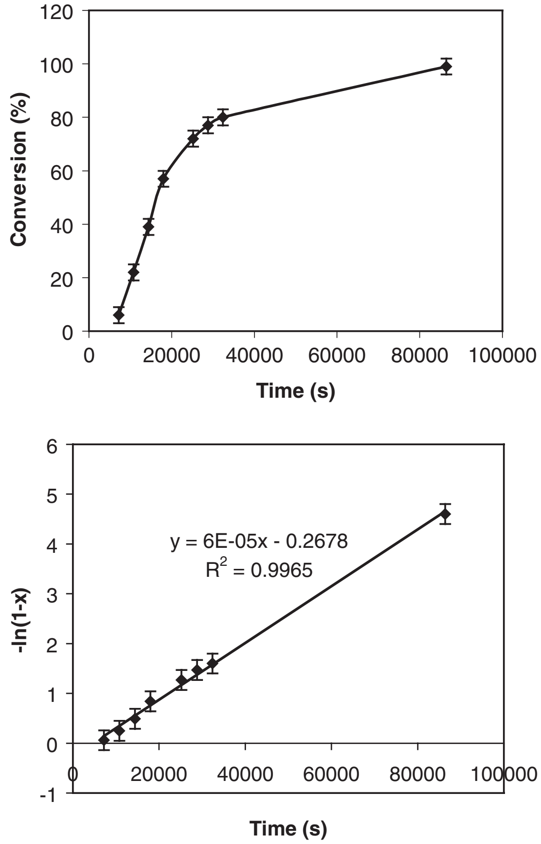


Figure 2. Kinetic data of the Suzuki reaction using 0.5 mol% palladium resin in DMF at 90 °C over 24 h, showing an observed *pseudo* first order rate constant of $6 \times 10^{-5} s^{-1}$.

Screening for other solvents revealed that pure DME was totally ineffective with only 2% 4-methoxybiphenyl being formed, however, pure DMF was an excellent solvent, which gave a 99% conversion based on 4-bromoanisole. The use of K_3PO_4 suspended in DMF has been found to efficiently promote the coupling of aryl bromides with phenylboronic acid, which is in accordance with our own results.[16] In light of these results we carried out a kinetic study of the reaction at 90 °C using K_3PO_4 in DMF. A plot of $-\ln(1-x)$ against reaction time (Fig. 2) where x is the mole fraction of 4-methoxybiphenyl produced indicates the reaction to be *pseudo* first order overall, with an observed overall rate constant of $6 \times 10^{-5} s^{-1}$.

The palladium catalyst was found to give up to 99% conversion based on 4-bromoanisole. This result proved to be highly dependent on the solvent system and conditions used. Less than 0.5% biphenyl was observed, formed by homo-coupling of the phenylboronic acid. No 4,4′-dimethoxybiphenyl, which could be formed by homo-coupling of 4-bromoanisole, was detected. It has been also reported that homo-coupling of the arylboronic acid can occur when the cross-coupling reaction is very slow,[17] in addition palladium-catalysed homocoupling has also been proposed.[18] In fact it has been reported that in the Suzuki reaction mixtures can be produced containing up to 10% biphenyl,[19] formed either by homo-coupling of the phenylboronic acid or by coupling with a phenyl group of a phosphine ligand. The fact that less than 0.5% biphenyl is formed in this study is therefore an advantage.

When using a supported metal catalyst a crucial issue is the deactivation and reusability of the catalyst, especially when a precious metal is involved. The palladium resin catalyst was therefore tested for recoverability and reusability over five successive runs. After each run, the original palladium resin was filtered off, washed several times with THF and water to remove any excess reagents and reused under the same reaction conditions as for the initial run without any regeneration. Results from Table 2 show that the palladium resin catalyst can be recovered and reused in further reaction without a significant degradation in activity. Although the catalytic activity was gradually diminished, a conversion of over 80% was still achieved in the third run, and 60% conversion was still achieved in the fifth run. Another point of great concern for most anchored catalysts is

Table 2. Study of catalyst recycling in the Suzuki reaction using 0.5 mol% of the palladium resin catalyst in DMF with 1.5 equiv $PhB(OH)_2$, 1 equiv 4-bromoanisole and 3 equiv K_3PO_4 at 90 °C for 24 h under a nitrogen atmosphere

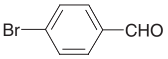
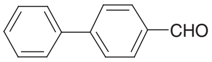
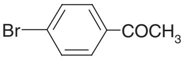
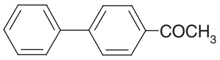
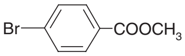
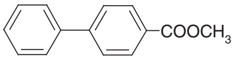
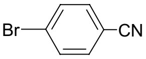
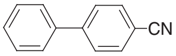
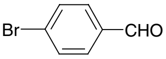
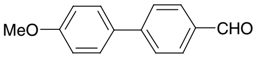
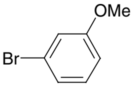
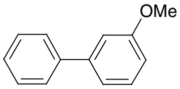
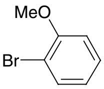
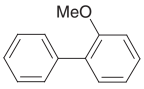
Run	Conversion (%)	TOF (mol/mol/h)
1	99	8.3
2	96	8.0
3	82	6.8
4	67	5.6
5	60	5.0

The data represent conversions of 4-bromoanisole to 4-methoxybiphenyl (based on GC data).

the possibility that some active metal migrates from the solid support to the liquid phase and that this leached metal would become responsible for a significant part of the catalytic activity.[1,3] In order to determine if leaching was a problem an experiment was performed to estimate the contribution of leached palladium to the catalytic activity by performing a filtration during the course of the reaction to remove the solid phase. If the catalytic reaction continued this would indicate that the active species was leached metal rather than the supported catalyst. The organic phase was separated from the solids after 2-hour reaction time, having used fresh supported catalyst. Additional K_3PO_4 was added to the clear filtrate (same amount as the original base). The composition of the reaction mixture was determined using GC at this point and then at regular intervals after continuing the reaction for 22 h at 90 °C, in the absence of the supported catalyst. The data from GC determinations gave quantitative information about residual, catalytically active palladium in solution after supported catalyst separation. Within experimental error, no increase in the amount of product, was detected, proving there to be no contribution from leached species (homogeneous catalysis). In order to determine the absolute amount of the palladium species dissolved into solution caused by leaching, the crude reaction mixtures were evaporated to dryness and analysed using ICP–AE. It was shown that less than 1% of the total amount of the original palladium species was lost into solution during the course of a reaction. This almost negligible leaching level, which is at the limit of detection of the ICP–AE, accounts for the recoverability and reusability of the palladium resin catalyst.

The study was then extended to the reaction of a diversity of substituted bromobenzenes containing electron-withdrawing and electron-donating groups, in order to test the tolerance of functional groups. Isomers of 4-bromoanisole were also investigated in order to determine the selectivity of bromine substitution position on the anisole ring. Excellent yields of biphenyls were achieved in most cases, as shown in Table 3. K_2CO_3 was used instead of K_3PO_4 for the base-sensitive cyano group (entry 4): the reaction using K_3PO_4 yielded the corresponding carboxylic acid. The use of electron-withdrawing ring substituents normally leads to enhanced reactivity in palladium-catalysed coupling reactions.[20] However, the Suzuki reaction of 4-bromonitrobenzene failed completely with the coupling product being detected only in trace amounts, despite the fact that the nitro group is strongly electron withdrawing. All attempts to carry out the reaction of 4-bromoaniline were also unsuccessful. This behaviour of the system requires further studies. It was also shown that the Suzuki reaction using the supported catalyst offers a selectivity for 3- and 4-bromoanisole over 2-bromoanisole, being around

Table 3. The Suzuki reactions of substituted bromobenzenes using 0.5 mol% palladium resin catalyst, 1.5 equiv $PhB(OH)_2$, 3 equiv K_3PO_4 in DMF at 90 °C for 24 h under a nitrogen atmosphere

Entry	Substrate	Product	Conversion (%)
1			100
2			100
3			100
4			100[a]
5			100[b]
6			100
7			40

The data represent conversions of bromobenzenes to biphenyls (based on GC–MS data).

[a] K_2CO_3 was used instead of K_3PO_4.

[b] 4-Methoxybenzeneboronic acid was used instead of benzeneboronic acid.

100% conversion for the 3-isomer and only 40% for the 2-isomer. Furthermore, 60% unreacted starting material in the case of the 2-isomer led us to believe that this was a rate limited selectivity based on the increased steric bulk at the 2-position inhibiting substitution.

In addition to the experiments reported above, we also performed homogeneously catalysed Suzuki reactions using the homogeneous analogue of the immobilised complex, [Pd(salenac-OMe)] (Fig. 1). The synthesis, purification and characterisation of this complex, and its use as homogeneous catalyst for the Heck coupling reaction has been published previously.[8] Unfortunately, despite the fact that the analogous heterogeneous reactions proceed close to completion, the reaction using 0.5 mol% [Pd(salenac-OMe)] complex with K_3PO_4 in DMF at 90 °C for 24 h resulted in only 1% conversion of 4-bromoanisole to 4-methoxybiphenyl, while the analogous heterogeneous reactions were performed successfully with 99% conversion by GC. Increasing the reaction temperature was shown to have little or no apparent effect on the reaction rate, with only 7% conversion being achieved at 100 °C. The colour of the reaction solution was yellow and there was no apparent change in colour during the course of the homogeneous catalyst reactions. A series of bases such as NaOH, Na_2CO_3, $NaHCO_3$, Cs_2CO_3 and *N*,*N*-diisopropyl ethylamine were also used for the homogeneous reactions but no improvement was achieved. Changing the reaction solvent to DME, DME/water (1:1) and DMF/water (1:1) still failed to give an improvement in the yield of 4-methoxybiphenyl. Furthermore, the addition of 2.5 mol% triphenylphosphine as a homogeneous additive had no effect on the conversion. However, it was found that reasonable yields were obtained using a much higher catalyst concentration. The homogeneous reactions using 5 mol% palladium complex in DME/water (1:1) afforded 4-methoxybiphenyl in conversions of 84%, 82% and 74% using K_3PO_4, NaOH and Na_2CO_3 as bases, respectively. This means that the Merrifield resin support has a significant effect on the activity of the catalyst. Varma et al. have reported a significant improvement in reaction rate using a heterogeneous palladium chloride and tetraphenylphosphonium bromide intercalated clay catalyst, when compared to the corresponding homogeneous palladium chloride catalyst under identical reaction conditions.[21]

In summary, the polymer-supported palladium catalyst exhibits a high activity towards the Suzuki cross-coupling reaction. The catalyst can be easily separated from the reaction mixture by simple filtration and reused after washing. Very little palladium leaches into solution from the catalyst during the course of the reaction. The polymer-supported catalyst was considerably more active than the homogeneous analogue. This unexpected and surprising behaviour of the homogeneous analogue of the immobilised complex still needs further studies and these are underway.

Acknowledgements

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