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# A tertiary phosphine oxide ligand-based recyclable system for the Suzuki–Miyaura and Negishi reactions: evidence for pseudo-homogeneous catalysis†

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A recoverable catalyst system has been developed and its application in both Suzuki–Miyaura and Negishi coupling reactions has been demonstrated. We have also investigated the nature of the active catalyst in solution – a controversial topic as recent reports describe 'metal-free' coupling chemistry and whether heterogeneous reactions are actually homogeneous. We classify our catalytic system as 'pseudo-homogeneous' and employ Pd(OAc)$_2$ and a commercially available cyclohexyldiphenyl phosphine oxide ligand. The system can be reused in up to 10 cycles while retaining good to excellent isolated yields.

Palladium-catalysed cross-coupling reactions between an aryl halide electrophile and an organoboron nucleophile are a clean and efficient strategy for the formation of biaryls; which facilitates a myriad of applications in the synthesis of pharmaceutical precursors, agrochemicals, and high-tech materials.[1–4] The cross-coupling reaction using boronic acid/esters, known as the Suzuki–Miyaura[5] reaction has been investigated extensively because of the broad availability and relative air and moisture stability of boronic acids and their derivatives.[6] In parallel, the development of other cross-coupling methodology has resulted in a number of different strategies. For example, the Negishi coupling is a valuable alternative due to the fast transmetalation of organozinc reagents to palladium in comparison with boronic acids.[7] Generally, the Suzuki–Miyaura coupling reaction is performed using palladium catalysts in the presence of ancillary ligands, most often N-heterocyclic carbenes or tertiary phosphines.[8] Phosphine oxides have also seen widespread application as

ligands for cross-coupling reactions arising from their pentavalent nature, which provides air and moisture stability.[9–11] Denmark and co-workers employed triphenyl phosphine oxide as a ligand in the cross-coupling of arylsilanolates with aryl bromides; where they described phosphine oxide as a 'buffering ligand' that stabilises the highly active palladium nanoparticles formed *in situ* which govern catalysis.[12] Later, Ackermann reported the first use of secondary phosphine oxides in the arylation of α C–H acidic compounds.[13]

The dominant role palladium plays in cross-coupling reactions presents a sustainability issue as palladium is a non-abundant metal. In developing more sustainable approaches to chemical synthesis, it would be desirable to either replace or, at least, recycle palladium catalysts over multiple catalytic runs.[14,15] Different approaches to catalyst reuse have previously been reported, including work by Fan and co-workers where a palladium/phosphine dendrimer system was successfully re-used up to 9 times in Suzuki–Miyaura cross-coupling reactions.[16] Impressively, only 0.2 mol% of Pd catalyst is required to reach full conversion, however reaction conditions are rather forcing – heating at reflux in dioxane. A report by Afewerki *et al.* described the use of a Pd heterogeneous catalyst derived from rice husk waste which could be reused in up to 6 cycles in Suzuki–Miyaura chemistry.[17] Ye and co-workers reported the recyclability of a Pd-based electride material Y$_3$Pd$_2$; which was recycled 20 times. The catalyst recyclability is excellent but 40 mol% of catalyst was required![18] In any attempt to make a more cost-effective and sustainable catalytic system the importance of palladium recovery and reuse is integral to newly developed methods.[19,20]

Recent work by Ananikov and co-workers introduced the concept of "cocktail" catalysis.[21–26] The Ananikov group demonstrated that rather than being homogenous or heterogenous the nature of the metal catalyst can be mixed, with a "cocktail" of metal species responsible for driving reactions. Hence a dynamic metal catalyst system can contain multiple species which are key to catalytic activity with nanoparticle and molecular catalysts both present. Leaching

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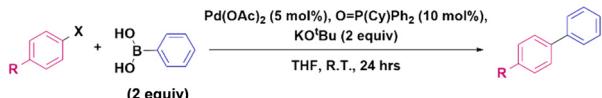
**Scheme 1** Tertiary phosphine oxide palladium-catalysed Suzuki–Miyaura cross-coupling.

of heterogenous species can occur giving the same phenomena observed with pseudo-homogenous catalysis. These systems then comprise potentially reusable and recyclable catalysts.

Thus, we sought a simple approach to palladium recycling which employs inexpensive and readily available ligands under ambient conditions; we investigated the use of tertiary phosphine oxides as ligands in palladium-catalysed Suzuki–Miyaura and Negishi coupling reactions.

### Suzuki–Miyaura coupling

The coupling reaction between iodotoluene and phenylboronic acid (Scheme 1) was chosen as a model reaction with which to study the effectiveness of our catalytic system. Different commercially available phosphine oxide ligands and solvents were screened (Table S1, ESI†) and the use of cyclohexyl diphenylphosphine oxide as ligand and THF as solvent were found to provide optimal reaction conditions. Although the goal of our work was to investigate recyclable palladium catalysts, we considered it important to demonstrate that a robust Suzuki–Miyaura catalyst had been achieved. Thus, we explored a limited scope of substrates (Table 1).

**Table 1** Scope of substrate in Suzuki–Miyaura coupling reaction
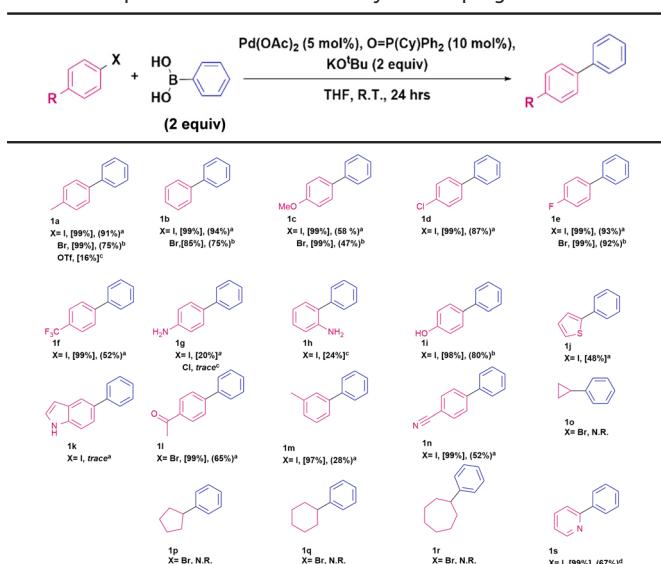


[a] Pd(OAc)$_2$ (0.015 mmol), ligand (0.03 mmol), aryl halide (0.3 mmol), phenylboronic acid (0.6 mmol), potassium *tert*-butoxide (0.6 mmol), THF (2 mL), reaction time = 24 hours. Conversion calculated by Gas Chromatography coupled with Mass Spectrometry (GC-MS), isolated yields []. [b] Temperature = 70 °C. [c] Solvent = toluene, temperature = 100 °C. [d] Solvent = EtOH:H$_2$O.

To demonstrate the further utility of this system we ran a series of coupling reactions between aryl halides or aryl triflates and phenyl boronic acid. As summarized in Table 1, our catalytic system demonstrated a respectable reactivity profile and good functional group tolerance under mild reaction conditions. Most functional groups investigated were well tolerated, and isolated biphenyls were obtained in good to excellent yields. An unsuccessful attempt was made to effect sp$^2$–sp$^3$ couplings with cyclic alkyl bromides. Additional experiments were carried out with 4-iodopyridine and 2-iodopyridine, spectroscopic conversion of the starting materials proved to be poor (26% and 13% respectively). We hypothesize that this is due to the coordination of the pyridine moiety to the Pd nanoparticles thus hindering catalytic turnover. When the solvent system is changed to a mixture of ethanol and water the reaction exhibits full conversion and 2-phenylpyridine (**1s**) was isolated in good yield.

### Recycling studies

We investigated the recyclability of Pd(OAc)$_2$ with cyclohexyl diphenylphosphine oxide for Suzuki–Miyaura coupling. As illustrated in Table 2, the catalyst system could be recycled through 10 consecutive coupling reactions without any loss of activity and good yields of the coupled product in each run were obtained (see ESI† for description of recycling method). Catalyst and product were readily separable in hexane, and the recovered (precipitated) catalyst was re-used directly in subsequent catalytic cycles. Separation was achieved *via* a simple filtration operation akin to a heterogeneous process.

### Negishi coupling

To further explore potential applications of our catalytic system, we decided to investigate the Negishi coupling. The coupling reaction between iodotoluene and tolylzinc iodide (Scheme 2) was performed and was found to proceed cleanly and in good to excellent yield.

Substrate scope and recyclability were subsequently explored in a manner consistent with earlier Suzuki–Miyaura studies (see ESI,† Tables S2 and S3). Once more, the catalyst and product were readily separable *via* hexane addition to spent reaction mixture; with simple filtration allowing reclamation of the catalyst. The recovered catalyst was re-used in subsequent catalytic cycles after readdition of the reagents. The palladium catalyst could be re-used up to ten times without significant loss of yields (see ESI†). The scope of our Negishi coupling chemistry was explored using phenyl zinc bromide and a total of eight substrates and isolated yields of up to 85% were obtained (see ESI†).

### Homogenous, heterogenous and pseudo-homogenous catalysis

To determine the nature of the active catalytic species present in solution, several test reactions were carried out. In testing catalyst homogeneity a mercury drop test is typically

**Table 2** Recylability of Suzuki–Miyaura catalyst

| Cycle[a] | Temperature (°C) | Yield (%) (spectroscopic (isolated)) | Selectivity (**1a** : **1a′**) |
|---|---|---|---|
| 1 | R.T. | >99 | 7 : 1 |
| 2 | R.T. | >99 | 55 : 1 |
| 3 | R.T. | >99 (96) | 105 : 1 |
| 4 | R.T. | >99 (90) | 400 : 1 |
| 5 | R.T. | >99 | >400 : 1 |
| 6 | R.T. | >99 | 150 : 1 |
| 7 | R.T. | >99 | 280 : 1 |
| 8 | R.T. | >99 | 400 : 1 |
| 9 | R.T. | >99 | 400 : 1 |
| 10 | R.T. | >99 | 400 : 1 |

Conditions: recyclability studies w/ O=PCyPh$_2$, Pd(OAc)$_2$. [a] Pd(OAc)$_2$ (0.015 mmol), ligand (0.03 mmol), iodotoluene (0.3 mmol), phenylboronic acid (0.6 mmol), potassium *tert*-butoxide (0.6 mmol), solvent = 2 mL, reaction time = 24 h. Spectroscopic yield calculated with tetramethylsilane as an internal standard. Ratio of heterocoupled product 4-methyl-1,1-biphenyl (**1a**) to homocoupled product 4,4-dimethyl-1,1-biphenyl (**1a′**).

employed, however this can often lead to inconclusive results due to the fact that mercury only forms amalgams with certain metals.[27] A Suzuki–Miyaura reaction between 4-iodotoluene and phenylboronic acid was conducted under standard conditions and allowed to stir for three hours, the reaction was then filtered and allowed to stir for a further 21 hours (24 hours total).[28] From the precipitate, black palladium species were observable suggesting the formation of nanocomposites, surprisingly the reaction still proceeded to completion suggesting that even after filtration catalytically active Pd species remain present in solution (*i.e.* homogenous reactivity).[16,29]

Recent reports suggest that many supposed heterogenous systems actually operate in a pseudo-homogenous regime in which the heterogeneous species acts as a "well" of active Pd species which can 'break off' and be catalytically active in solution.[30,31] To probe for such behaviour, further tests were then performed in an effort to "trap" nanocomposite palladium structures. Thus, poly(vinylpyridine) was added to a standard Suzuki–Miyaura reaction (7.5 mol% polymer); the polymer acts to suppress heterogeneous catalysis by nanocomposites. The reaction mixture was allowed to stir at room temperature for 24 hours. The reaction proceeded to completion, further suggesting that the catalytically active Pd species are homogeneous in nature. Analogous tests were carried out for Negishi coupling reactions (see ESI†). Previous reports have demonstrated the use of heterogenous catalysts in palladium-catalysed Negishi couplings.[32,33]

To further characterise the palladium nanostructures formed during the reaction, transmission electron microscope (TEM) imaging was used to explore heterogeneous structural details. As evidenced by TEM imaging the recovered Pd

catalyst is nanoparticulate in nature (Fig. 1). Given the evidence, we propose that the active palladium species responsible for Suzuki–Miyaura coupling are homogenous in nature but are sourced from a heterogeneous palladium nanocomposite; our catalyst is pseudo-homogenous.

To further interrogate the nature of the catalytically relevant species, $^{31}$P NMR was carried out in both the solid-state (SSNMR) and in the solution state. Analysis of the catalyst both before and after precipitation from solution affords a signal in the $^{31}$P NMR at 35.9 ppm (see ESI†), consistent with the phosphine oxide being present in both solution and the solid-state.

In conclusion, we have developed a highly recyclable catalyst system from commercially available cyclohexyl diphenyl phosphine oxide and Pd(OAc)$_2$ capable of effecting both Suzuki–Miyaura and Negishi couplings. The robust
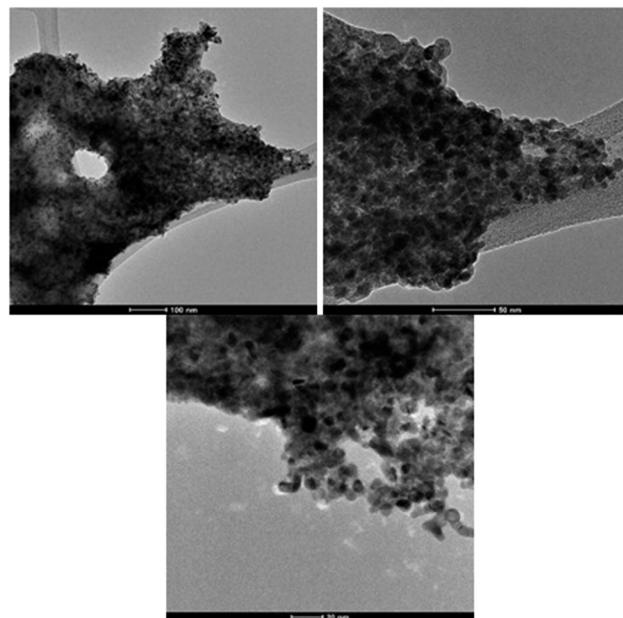


**Fig. 1** TEM images of Pd nanocomposites generated in catalytic Suzuki–Miyaura reactions, at 100, 50 and, 20 nm magnification.
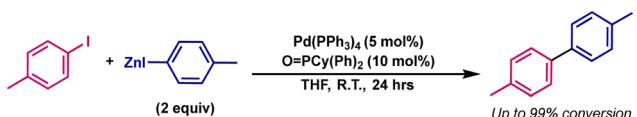


**Scheme 2** Tertiary phosphine oxide palladium-catalysed Negishi cross-coupling.

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nature of this system is demonstrated *via* recycling experiments which deliver high yields in up to 10 catalytic cycles. Finally, investigation into the nature of the active catalyst species *via* TEM, poisoning experiments and both solution and solid-state NMR analysis strongly supports a pseudo-homogenous catalytic system.

## Author contributions

AKK, AB and MF designed the experimental studies, which AKK and AB performed. AKK, AB and MF wrote the manuscript.

## Conflicts of interest

There are no conflict of interests to declare.

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