

## Communications

**High-Throughput Screening Studies of Fiber-Supported Catalysts Leading to Room-Temperature Suzuki Coupling**

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**Summary:** High-throughput screening of triphenylphosphine-based polymer-supported homogeneous catalysts (e.g., FibreCat™-1001) and selected Johnson Matthey Pd/C catalysts has achieved nearly quantitative conversion of activated and unactivated aryl bromides in Suzuki coupling using an ethanol–water solvent system. For more challenging substrates such as *p*-chloroacetophenone and 3-bromothiophene, coupling could be possible by tuning the FibreCat catalysts with *t*-Bu<sub>3</sub>P. These tuned catalysts (TunaCat) are air-stable.

During the past decade there has been a burgeoning of interest in the area of palladium-catalyzed Suzuki coupling reactions in academia as well as in the pharmaceutical and fine chemical industries to synthesize a wide variety of organic molecules.<sup>1</sup> Landmark publications by Fu<sup>2</sup> and Buchwald<sup>3</sup> in the late 1990s on the use of Pd complexes of electron-rich, bulky phosphines to carry out coupling reactions of more challenging substrates have also sparked a renewed interest in this area. Subsequently, Nolan,<sup>4</sup> Hermann,<sup>5</sup> Guram,<sup>6</sup> Reetz,<sup>7</sup> Beller,<sup>8</sup> Hartwig,<sup>9</sup> and Li<sup>10</sup> have also employed a similar approach. One of the major thrusts

in this area from an applied point of view is to utilize air-stable ligands, ligand precursors, or catalysts to carry out reactions under relatively mild conditions.<sup>4,10,11</sup> Another challenging aspect of Pd-catalysis is the effective separation of the catalysts/metals from the products. This report describes how high-throughput screening studies (HTS) can be effectively used to achieve Suzuki coupling under mild conditions, with minimal metal leaching, using supported homogeneous and heterogeneous catalysts.

For this work, we have been successful in anchoring Pd(OAc)<sub>2</sub>, Pd-dba, Pd(MeCN)Cl<sub>2</sub>, Pd(PhCN)Cl<sub>2</sub>, and (π-allyl)PdCl onto the polyethylene-based supported ligands, called FibreCat catalysts.<sup>12</sup> The skeletal structures of these complexes are shown in Figure 1. For all the above

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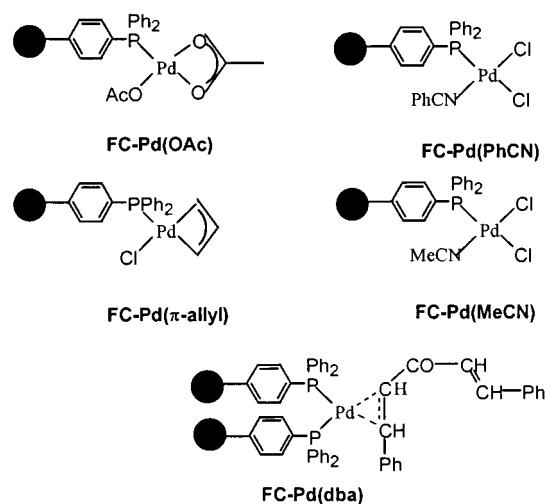
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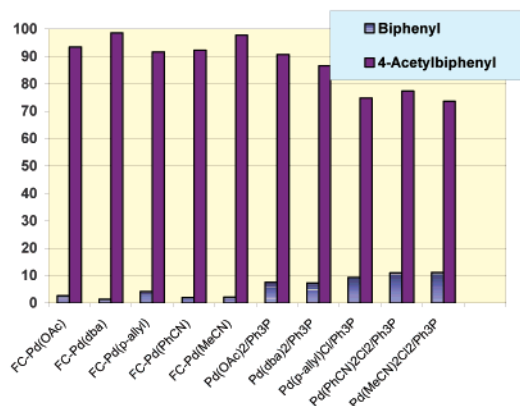
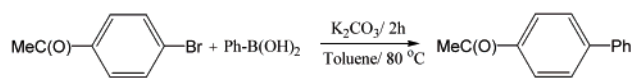


**Figure 1.** Basic structures of FibreCat catalysts synthesized for this study.

complexes, except for FC–Pd(dba), the Pd/ligand ratio is 1:1, as evidenced by 5–6% Pd loading, which corresponds to 0.5–0.6 mmol of P or Pd/gram of the FibreCat. In the case of FC–Pd(dba), the metal loading is only 2.5–3% (Pd/ligand is 1:2). This is in accordance with the reports by Herrmann<sup>13</sup> and Amatore<sup>14</sup> on the reaction of Pd<sub>2</sub>dba<sub>3</sub> and Pd(dba)<sub>2</sub> with Ph<sub>3</sub>P, which leads to L<sub>2</sub>Pd(dba).

**Screening Studies.** As stated by Fu, “there are a large number of parameters in a Suzuki reaction—palladium source, ligand, additive, solvent, temperature, etc.—and there are correspondingly, a large number of protocols for accomplishing the transformation, the choice of which depends on the structure of the reactants.”<sup>11a</sup> We found that HTS is one of the most efficient ways to optimize these parameters in a time efficient manner.

In this catalytic study,<sup>15</sup> we have taken these factors into account by selecting five Ph<sub>3</sub>P-based FibreCat catalysts (Figure 1), their corresponding homogeneous catalysts in the presence of Ph<sub>3</sub>P, and two 5% Pd/C catalysts, as well as by varying bases, solvents, temperatures, reaction time, and even the mode of agitation. Throughout the experiments we have used 0.005 mmol (1 mol % with respect to substrate) of Pd, 1.5 mmol of



**Figure 2.** Suzuki coupling screening of *p*-BrC<sub>6</sub>H<sub>4</sub>(CO)Me.

base, and 5 mL of solvent. The reaction was performed on a 0.5 mmol scale.

To test the five FibreCat compounds, we have performed the well-known reaction of *p*-bromoacetophenone with phenylboronic acid. The results are summarized in Figure 2. Interestingly, the supported catalysts gave slightly higher yields of the products with more selectivity, compared to their respective homogeneous catalysts under identical conditions. Since this is a rather facile system, no further optimization was done.

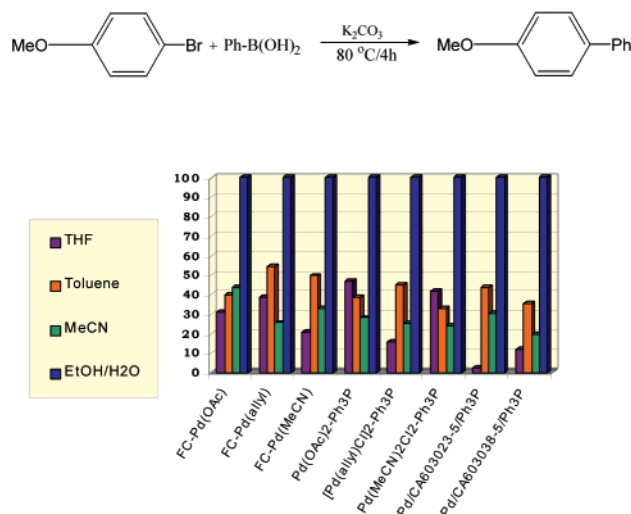
When a similar reaction was performed using an unactivated aryl bromide, *p*-bromoanisole, we observed a similar trend; however the reaction was not complete even after heating for 4 h. Preliminary screening studies using FC–Pd(OAc) (commercially available as FibreCat™-1001) with eight different solvents and three bases (K<sub>2</sub>CO<sub>3</sub>, Cs<sub>2</sub>CO<sub>3</sub>, K<sub>3</sub>PO<sub>4</sub>) indicated that the reaction would go to completion irrespective of the base, when ethanol–water was used as a solvent. A secondary screen was then performed using three FibreCat catalysts, and their respective homogeneous catalysts and two Pd/C catalysts in four different solvents using the

(12) (a) For general information on FibreCat products see: Buckley, S. *Manuf. Chem.* **2002**, January, 26–27. (b) General procedure for the synthesis of the FibreCat products employed in the study: Triphenylphosphine-supported fiber with a P loading of about 0.6 mmol/g (20 g; ca. 12 mmol P) obtained from Johnson Matthey/SMOP TECH, Finland, was charged to a 500 mL Schlenk flask and degassed with nitrogen for 10 min, followed by the addition of 100 mL of anhydrous CH<sub>2</sub>Cl<sub>2</sub>. To this stirred suspension was added the appropriate Pd-organometallics (Pd(OAc)<sub>2</sub>: 3.2 g, 14 mmol; [π-C<sub>3</sub>H<sub>5</sub>PdCl]<sub>2</sub>: 2.6 g, 7.1 mmol; (MeCN)<sub>2</sub>PdCl<sub>2</sub>: 3.63 g, 14 mmol; (PhCN)<sub>2</sub>PdCl<sub>2</sub>: 5.4 g, 14 mmol; Pd(dba)<sub>2</sub>: 4.3 g; 7.1 mmol) in 80 mL of dichloromethane and stirred for 3 h at room temperature. The mixture was filtered onto a sintered frit, and the solid was washed thoroughly with CH<sub>2</sub>Cl<sub>2</sub> (40 mL × 5) until the filtrate was colorless. The resulting solid was dried under vacuum in an oven with N<sub>2</sub> sweep at 30 °C to obtain about 21–23 g (ca. 95% yield) of the supported catalysts {FC–Pd(OAc): pale yellowish brown solid, Pd assay = 5.3% (0.5 mmol Pd/g); FC–Pd(π-allyl): cream-yellow solid, Pd assay = 4.5% (4.2 mmol Pd/g); FC–Pd(MeCN): orange-yellow solid, Pd assay = 6% (5.6 mmol Pd/g); FC–Pd(PhCN): orange-yellow solid, Pd assay = 5.8% (5.4 mmol Pd/g); FC–Pd(dba): pale violet solid, Pd assay = 2.5% (2.4 mmol Pd/g).

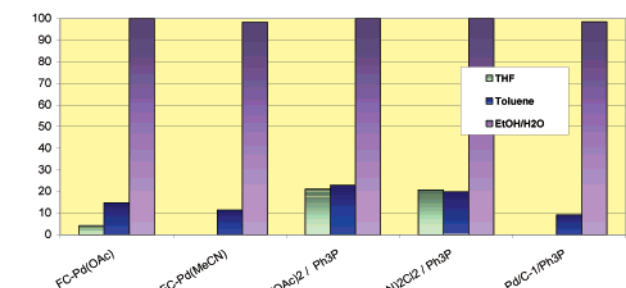
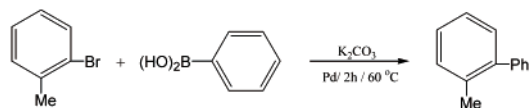
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(15) In a typical screening experiment, Radley's 12 test tube carousel or ChemSpeed's AS-200 automated 16 reactor-block was loaded with a base (e.g., K<sub>2</sub>CO<sub>3</sub>, 207 mg, 1.5 mmol), PhB(OH)<sub>2</sub> (65 mg, 0.54 mmol), and the catalysts (e.g., FC–Pd(OAc)<sub>2</sub>, 10 mg, 0.005 mmol Pd or Pd(OAc)<sub>2</sub>, 1.12 mg, 0.005 mmol with Ph<sub>3</sub>P, 0.01 mmol, or 5% Pd/C, 11 mg, 0.005 mmol) and were degassed for 10 min using vacuum and nitrogen. To this was added a solution (5 mL in the case of ethanol–water solvent system, 2.5 mL of ethanol solution followed by 2.5 mL water) of the substrate (e.g., *p*-bromoanisole, 93.6 mg, 0.5 mmol) using a manual syringe in the case of Radley's and a Robotic syringe in the case of ChemSpeed, and the mixture was heated to the desired temperature (25–80 °C) for a specified period of time (2–24 h). The reaction mixture was cooled to RT, extracted with 5 mL toluene in the case of the ethanol–water system, and filtered using a 0.45 μm syringe filter disk, and the filtrate was charged into the auto-sampler vials. These vials were then loaded into the auto-sampler of a precalibrated (reference samples of the substrate, product, and byproducts with known concentrations were injected earlier to identify the retention time and response factor) Perkin-Elmer XL Autosystem XL gas chromatograph equipped with both FID and MS detectors. An SPB column (30 m length, 0.25 mm diameter) with a temperature program (140 °C/0.5 min; 35 °C min<sup>-1</sup> to 200 °C, hold for 1 min; 40 °C min<sup>-1</sup> to 300 °C, hold for 4 min) was used to have a run time of 10 min. Apart from comparing the product and byproduct peaks to the standard peaks under identical conditions, their authenticity was further confirmed by comparing their mass spectra with those of the actual compound in the spectral library. These solutions were later precisely analyzed for PPM levels of Pd at our analytical lab using the wet ash method in an ICP-MS instrument.



**Figure 3.** Solvent effect in Suzuki coupling of *para*-BrC<sub>6</sub>H<sub>4</sub>OMe with PhB(OH)<sub>2</sub>.



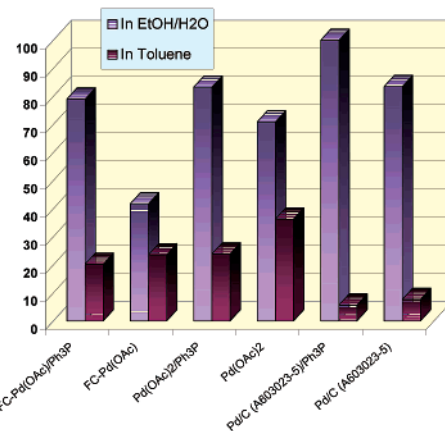
**Figure 4.** Suzuki coupling of 2-bromotoluene with phenylboronic acid.

fully automated ChemSpeed machine. The results are summarized in Figure 3.

It is interesting to note that, unlike the previous case, reactions in typical organic solvents did not give much conversion at all. However when the base was ground and the mode of agitation was changed from vortex to magnetic, much higher conversions were observed. The ethanol–water (1:1) system gave complete conversion when FibreCat catalysts, their homogeneous analogues, and 5% Pd/C were employed. We feel that this could be associated with the solubility of inorganic bases, which makes the reaction more “homogeneous”. Sowa<sup>16</sup> also observed the importance of DMA–water (20:1) in the coupling reactions of activated aryl chlorides when Pd/C was used. In their case the amount of water is very critical and ethanol–water does not seem to be a good solvent at all.

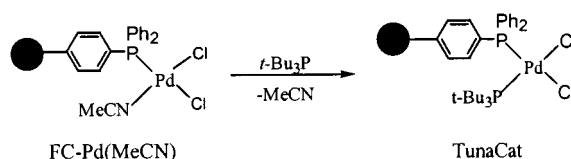
Results obtained from 2-bromotoluene were similar (Figure 4). However, for the heterocyclic system 2-bromopyridine, Pd/C seems to be better than the FibreCat catalysts and their corresponding homogeneous catalysts (Figure 5).

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**Figure 5.** Coupling of 2-bromopyridine in the absence and presence of Ph<sub>3</sub>P at 80 °C for 4 h.

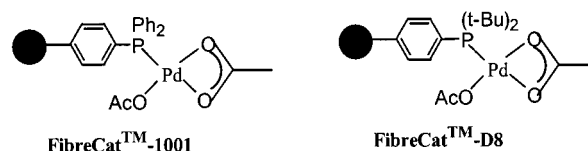
### Scheme 1. Synthesis of “Tunable” Supported Catalysts



In the case of 2-BrC<sub>5</sub>H<sub>4</sub>N, the substrate can also act as a ligand. When PPh<sub>3</sub> was added to the reaction, it competes with the substrate for coordination sites on Pd and the yield was improved as illustrated in Figure 5. In this case Pd/C seems to be the best catalyst in EtOH–H<sub>2</sub>O and the worst in toluene, highlighting the importance of HTS studies in catalysis.

Surprisingly our efforts to couple 3-bromothiophene using Ph<sub>3</sub>P-based FibreCat catalysts (see Figure 1), their corresponding homogeneous catalysts, or Pd/C were not very successful under identical conditions in EtOH–water as well as in dioxane. Furthermore, our *t*-Bu<sub>2</sub>P-based next generation FibreCat-D8 (D stands for development) was also not useful, although the same catalyst has been proven effective for aryl chloride and C–N coupling reactions.<sup>17</sup> High-throughput screening studies of the FibreCat compounds in the presence of *t*-Bu<sub>3</sub>P (in situ) prompted us to develop a *t*-Bu<sub>3</sub>P-based FibreCat (TunaCat). The synthesis of the complex is outlined in Scheme 1. The final product was washed several times with solvents until the washings contained undetectable amounts of Pd. This was to ensure the absence of any homogeneous catalysts generated.

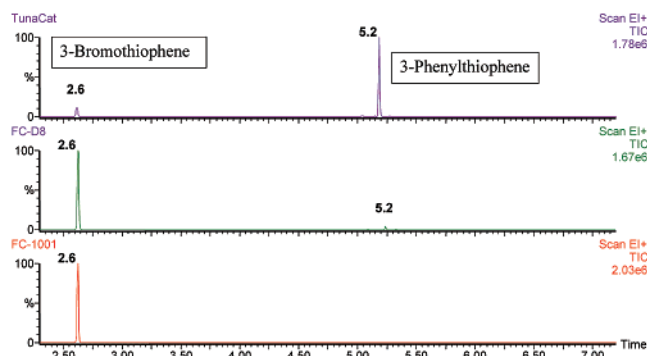
The concept of a tunable-supported catalyst is that one could design a catalyst to achieve selectivity. However, for this initial study, this was not elaborated. Figure 6 shows the superior activity of TunaCat compared to that of FibreCat-1001 or FibreCat-D8.



The activity of TunaCat in aryl chloride coupling (e.g., *para*-chloroacetophenone) was also successfully dem-

(17) Rowsell, E., and co-workers, Johnson Matthey Technology Center, Sonning, UK, personal communication.





**Figure 6.** Suzuki coupling of 3-bromothiophene with  $\text{PhB}(\text{OH})_2$  in  $\text{EtOH-H}_2\text{O}$  at  $80^\circ\text{C}/12\text{ h}$  with no Pd leaching.

**Table 1. Room-Temperature Suzuki Coupling of Aryl Bromides with  $\text{PhB}(\text{OH})_2$  with Yield/Reaction Time<sup>a</sup>**

substrate	FC-Pd(OAc)	Pd/C-1
<i>p</i> - $\text{BrC}_6\text{H}_4(\text{COMe})$	100%/1–2 h	100%/24 h
<i>p</i> - $\text{BrC}_6\text{H}_4(\text{OMe})$	100%/2–3 h	100%/24 h
<i>o</i> - $\text{BrC}_6\text{H}_4(\text{Me})$	98%/2–3 h	98%/24 h

<sup>a</sup> Pd was undetected (0 ppm) in the reaction mixture for all cases.

onstrated in this study with 100% conversion using  $\text{EtOH-H}_2\text{O}$  as a solvent. More details of the study with diverse examples will be published elsewhere.<sup>18</sup>

**Room-Temperature Suzuki Coupling.** To verify the effectiveness of  $\text{Ph}_3\text{P}$ -based FibreCat compounds in room-temperature Suzuki coupling, we reinvestigated the reactions of *p*-bromoacetophenone, *p*-bromoanisole, and *o*-bromotoluene by considering their electronic and steric effects. The heterocyclic systems were not included in the study, as the  $80^\circ\text{C}$  reactions did not give complete conversions. In this study, FC-Pd(OAc) (FibreCat-1001) and Pd/C in the absence of an external ligand were employed as the catalysts. The results are summarized in Table 1.

It is interesting to note that the  $\text{Ph}_3\text{P}$ -based polymer-supported catalyst is capable of coupling even an unactivated aryl bromide at room temperature in the presence of a commonly used base,  $\text{K}_2\text{CO}_3$ , without the use of any additives (e.g.,  $\text{CsF}$ ,  $\text{KF}$ ),<sup>11,19</sup> within 2–3 h. Our Pd/C also gave coupled product even without the use of  $\text{Ph}_3\text{P}$ . Fu has reported room-temperature reactions of the same substrates using  $\text{Pd}_2\text{dba}_3/t\text{-Bu}_3\text{P}$  in the presence of  $\text{KF}$  in THF,<sup>11a</sup> a condition somewhat similar to Buchwald's earlier work on the di(*tert*-butyl)phosphinobiphenyl ligand system.<sup>11b,20</sup> However the reaction period was much longer (20–24 h) than our results on FibreCat systems.

(18) Colacot, T. J. Unpublished results.

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**Table 2. Pd Leaching Data from the FC-1001 System for the Reaction of *p*-Bromoanisole with  $\text{PhB}(\text{OH})_2$ <sup>a</sup>**

solvent	base	Pd(PPM)
toluene	$\text{K}_2\text{CO}_3$	0
EtOH	$\text{K}_2\text{CO}_3$	0
DEM	$\text{K}_2\text{CO}_3$	0
THF	$\text{K}_2\text{CO}_3$	0
$\text{EtOH-H}_2\text{O}$	$\text{K}_2\text{CO}_3$	0
Dioxane	$\text{K}_2\text{CO}_3$	0
DMA	$\text{K}_2\text{CO}_3$	0
MIBK	$\text{K}_2\text{CO}_3$	15

<sup>a</sup>  $\text{EtOH-H}_2\text{O}$  system gave no Pd leaching in  $\text{K}_2\text{CO}_3$ ,  $\text{Cs}_2\text{CO}_3$ , and  $\text{K}_3\text{PO}_4$ ; however the catalyst turned black at the end of the reaction. For the same substrate–catalyst system, reactions in  $\text{Cs}_2\text{CO}_3$  and  $\text{K}_3\text{PO}_4$  bases gave pale colored solution in solvents such as dioxane, DMA, ethanol, and MIBK, indicating possible leaching.

**Leaching and Reuse.** Our studies on the nonheterocyclic systems indicate that the  $\text{EtOH-H}_2\text{O}$  system is useful for FibreCat catalysts in giving no Pd leaching. Analysis of Pd/FibreCat-catalyzed product solutions from the *p*-bromoanisole screen (Table 2) showed no Pd leaching when the solvent was  $\text{EtOH-H}_2\text{O}$  regardless of what inorganic base was used. However the catalyst turned black when the reaction was performed at high temperatures and could not be reused. With the exception of MIBK (methylisobutyl ketone), other solvents did not result in leaching when the base was only  $\text{K}_2\text{CO}_3$ . We also saw some leaching in the case of the bromopyridine system.

**Conclusion.** HTS screening is a powerful tool in optimizing the coupling reactions. Results from this study indicate that a judicious choice of conditions, optimized by HTS, can be used to achieve room-temperature Suzuki coupling of activated and unactivated bromides even with a  $\text{Ph}_3\text{P}$  ancillary ligand. This study also demonstrated that for challenging substrates one could effectively tune the FibreCat compounds relatively easily.

**Acknowledgment.** Prof. Barry Trost (Stanford University) is thanked for the useful discussions and suggestions pertaining to the characterization of FC-Pd(dba).

**Supporting Information Available:** Experimental details on the synthesis of TunaCat and its catalytic usage in the reaction of *p*-chloroacetophenone with  $\text{PhB}(\text{OH})_2$  as well as the GC–MS evidence, showing the quantitative conversion to the *p*-phenylacetophenone, are provided. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(20) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550–9561.