Efficient Screening and Library Generation in Parallel C–C Coupling Reactions Mediated by Organosilica SiliaCat Palladium Catalysts

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ABSTRACT: Organosilica SiliaCat palladium catalysts applied to the conversion of widely different substrates in Suzuki, Sonogashira, and Heck coupling reactions run in a parallel synthesizer enable quick screening of the reaction system with identification of the best reaction conditions and rapid library generation.

INTRODUCTION

Palladium-catalyzed cross-coupling reactions for carbon–carbon bond formation impact a broad spectrum of the chemical sciences from medicinal and materials chemistry to polymer and synthetic organic chemistry.1 These reactions are powerful because, along with broad versatility, they generally tolerate the presence of functional groups in the coupling partners and thus do not require protection and deprotection of functional groups in the reagents. We have recently reported that carbon–carbon Suzuki–Miyaura, Mizoroki–Heck, Negishi, and Sonogashira coupling reactions can be heterogeneously carried out using new solid organosilica palladium catalysts such as SiliaCat S-Pd (1) and SiliaCat DPP-Pd (2) as well as SiliaCat Pd0 (3).3 SiliaCat is a registered trademark of SiliCycle, Inc. and SiliaCat DPP-Pd and SiliaCat S-Pd are respectively a diphenylphosphine and a sulfur-based palladium(II) heterogeneous catalyst, whereas SiliaCat Pd0 is an organoceramic matrix entrapping ultra-small Pd(0) nanocrystallites (Figure 1).

Solid catalysts such as the latter materials can be easily separated from the reaction products by simple filtration, are easier to handle, and can be easily reused.

Parallel synthesis over solid reagents or catalysts is now a powerful tool for the synthesis of libraries or collections of new compounds in essentially a single operation4 using effective tools such as the MiniBlock Synthesizer (MiniBlock is a registered trademark of Mettler-Toledo, Inc.), namely a compact device that enables synthesis via solid- or solution phase under widely controlled environmental conditions inside the reactor (temperature, atmosphere, agitation) as well as purification to be carried out on the same platform.5 In this report we show that SiliaCat palladium catalysts can be applied to the rapid conversion of widely different substrates in Suzuki, Sonogashira, and Heck coupling reactions run in parallel in the MiniBlock Synthesizer. The method allows quick screening with identification of the best reaction conditions and fast library generation of useful compounds.

RESULTS AND DISCUSSION

In general all reagents (solids, substrates, base) and catalyst were preweighed in the reaction tubes using the Mini-Block reaction block for parallel synthesis and reaction screening.6 Solvent was added along with the liquid substrate to each tube. Each Block indeed can be used at different temperatures, from 20 to 100 °C. The palladium loading values in the SiliaCat S-Pd, Silia Cat DPP-Pd, and SiliaCat Pd0 are respectively 0.30, 0.20, and 0.05 mmol/g. When reaction was complete (determined by TLC and GC/MS), the solid catalyst was filtered and the reaction mixture analyzed by GC/MS. Conversions and selectivity with respect to the coupling products are determined by GC/MS analysis, and yields are obtained by isolation of the product via flash chromatography. In the reusability tests the solid catalyst was filtered using the Mettler-Toledo MiniBlock system, rinsed with MeOH and water, and dried under vacuum, directly in the tube, prior to reuse.

Suzuki–Miyaura Reaction. Screening and optimisation was first aimed to investigate different solvents and bases in the coupling conversion of an aryl chloride with phenylboronic acid with 2 mol % entrapped Pd in the SiliaCat DPP-Pd (Scheme 1).

The results in Table 1 show that total conversions were obtained in ethanol, ethanol/water, and the propanols, whereas reactions in THF, dioxane, toluene, and in DMF were slow. The best base was K2CO3.

Base facilitates the otherwise slow transmetalation of boronic acid. Inorganic bases work better and, in general, reactivity is in the order Cs2CO3 > CsF > K2CO3 > KOAc > Na2CO3 > Et3N.7 Milder bases such as Na2CO3 or K3PO4 are suitable if unprotected phenols or acids are present.8 For Suzuki coupling on commercial scale, cesium base is generally avoided, owing to high cost.

Parallel Syntheses. The MiniBlock device permits running 24 reactions in parallel. First we studied the Suzuki–Miyaura...
The results in Table 2 show that SiliaCat DPP-Pd allows access to chlorinated substrates with either electron-withdrawing (entries 2/C0 and 3) or electron-donating groups (entries 6/12) as well as with more sterically hindered molecules (entries 7 and 12).

We then studied the Suzuki/Miyaura coupling reactions of different aryl bromide substrates with phenylboronic acid in the presence of the heterogeneous catalysts SiliaCat DPP-Pd, SiliaCat S-Pd (Table 3), and SiliaCat Pd/0 (Table 4).

For maximum conversion the molar concentration of the mixture with respect to the substrate has a crucial role. Hence, Table 3 shows that for the SiliaCat S-Pd the best results were obtained using EtOH/H₂O solvent (0.1 M with respect to the substrate). Table 4, on the other hand, shows that for the SiliaCat Pd/0 the best results were obtained using EtOH (0.12 M) as solvent.

These optimized conditions were therefore used in parallel Suzuki/Miyaura coupling of different aryl bromide substrates without substituents, with different electron-withdrawing (nitro, nitrile, carbonyl groups) or electron-donating (methoxy, methyl, phenol, amine) groups, and with different heteroatoms such as pyridine and quinoline were tested.
The results in Table 5 show very good conversions for all catalysts. However, for the same reactions the catalytic activity of the SiliaCat DPP-Pd and SiliaCat Pd0 catalysts were higher than that of the SiliaCat S-Pd. In each case, the best catalyst was SiliaCat Pd0 according complete conversion with only 0.5 mol % catalytic amount.

**Sonogashira Coupling Reactions.** We then investigated SiliaCat DPP-Pd, SiliaCat S-Pd, and SiliaCat Pd0 in the heterogeneous Sonogashira coupling reactions of different iodide substrates with phenylacetylene. Again aryl iodides with different electron-withdrawing or -donating groups and different heteroatoms were tested (Scheme 3). Remarkably, the presence of a cocatalyst was not required.

Results in Table 6 show that in general yields are high for all catalysts. Only substrate 2-ido-aniline (entry 8) could not be converted.

### Table 2. Suzuki–Miyaura coupling of different aryl chlorides run in MiniBlock mediated by SiliaCat DPP-Pd

<table>
<thead>
<tr>
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<th>Substrate</th>
<th>Conversion/Selectivity (%)</th>
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</thead>
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</tr>
<tr>
<td>2</td>
<td>O,N</td>
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<td>3</td>
<td>N,O</td>
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<tr>
<td>4</td>
<td>Cl</td>
<td>98/99 100/98 78/99 55/98</td>
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<td>5</td>
<td>Cl</td>
<td>100/99 78/84 80/97 25/96</td>
</tr>
<tr>
<td>6</td>
<td>MeO</td>
<td>85/96 45/100 53/98 31/94</td>
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<td>7</td>
<td>MeO</td>
<td>75/96 30/98 25/95 30/100</td>
</tr>
<tr>
<td>8</td>
<td>HO</td>
<td>67/98 72/97 75/97 10/95</td>
</tr>
<tr>
<td>9</td>
<td>Cl</td>
<td>92/100 82/93 60/96 45/100</td>
</tr>
<tr>
<td>10</td>
<td>Cl</td>
<td>100/99 67/100 57/94 36/94</td>
</tr>
<tr>
<td>11</td>
<td>Cl</td>
<td>77/100 45/93 58/96 35/94</td>
</tr>
</tbody>
</table>

*General experimental conditions: 1 equiv substrate, 1.25 equiv PhB(OH)2; 2 equiv K2CO3, EtOH/H2O 15%, 0.12 M, 2 mol % SiliaCat DPP-Pd, reaction time: 6 h.

### Table 3. Suzuki–Miyaura coupling reactions run in MiniBlock mediated by SiliaCat S-Pd

<table>
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<th>Substrate</th>
<th>Conversion/Selectivity (%)</th>
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<td>Cl</td>
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<tr>
<td>2</td>
<td>Cl</td>
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<tr>
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<td>Cl</td>
<td>77/100 80/100 80/98 65/100 60/100 85/100</td>
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<td>4</td>
<td>Cl</td>
<td>75/92 62/100 74/97 60/100 50/98 69/99</td>
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<td>Cl</td>
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</tr>
<tr>
<td>8</td>
<td>Cl</td>
<td>45/96 40/95 52/100 40/100 59/98 45/100</td>
</tr>
</tbody>
</table>

*Conditions: 1 equiv substrate, 1.2 equiv PhB(OH)2; 2 equiv K2CO3, 1 mol % SiliaCat S-Pd, reaction time: 4 h; under reflux.

### Table 4. Suzuki–Miyaura coupling run in MiniBlock mediated by SiliaCat Pd0

<table>
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<th>Substrate</th>
<th>Conversion/Selectivity (%)</th>
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<td>Br</td>
<td>100/100 100/100 100/100 100/100</td>
</tr>
<tr>
<td>2</td>
<td>Br</td>
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<td>Br</td>
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<td>4</td>
<td>Br</td>
<td>100/98 98/98 100/100 93/98</td>
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<tr>
<td>5</td>
<td>Br</td>
<td>100/100 95/98 100/100 91/95</td>
</tr>
<tr>
<td>6</td>
<td>Br</td>
<td>75/98 75/100 83/98 100/100</td>
</tr>
</tbody>
</table>

*Conditions: 1 equiv substrate, 1.2 equiv PhB(OH)2; 2 equiv K2CO3, 0.5 mol % SiliaCat Pd0, 2 h reflux.

### Table 5. Suzuki–Miyaura coupling of different aryl bromides run in MiniBlock in the presence of different SiliaCat palladium catalysts

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<th>Substrate</th>
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<th>Conversion/Selectivity (%)</th>
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<td>Ph</td>
<td>92/100 95/100 90/100</td>
</tr>
<tr>
<td>2</td>
<td>Br</td>
<td>Ph</td>
<td>82/92 96/98 100/98</td>
</tr>
<tr>
<td>3</td>
<td>Br</td>
<td>Ph</td>
<td>100/100 100/100 100/99</td>
</tr>
<tr>
<td>4</td>
<td>Br</td>
<td>Ph</td>
<td>100/100 100/100 100/99</td>
</tr>
<tr>
<td>5</td>
<td>Br</td>
<td>Ph</td>
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<td>Ph</td>
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</tr>
<tr>
<td>10</td>
<td>Br</td>
<td>Ph</td>
<td>97/100 78/100 95/99</td>
</tr>
<tr>
<td>11</td>
<td>Br</td>
<td>Ph</td>
<td>100/100 78/100 95/99</td>
</tr>
<tr>
<td>12</td>
<td>Br</td>
<td>Ph</td>
<td>82/90 45/100 83/98 100/100</td>
</tr>
</tbody>
</table>

*General experimental conditions: 1 equiv substrate, 1.2 equiv PhB(OH)2; 2 equiv K2CO3.

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fully coupled with phenylacetylene. However, SiliaCat Pd$^0$ is the most selective catalyst with minimum 94% selectivity in the conversion of 2-iodo-phenol (entry 6).

** Heck–Mizoroki Coupling.** Different aryl iodides and aryl bromides were thus tested in the Heck coupling reaction with different olefins such as styrene and methyl acrylate, in the presence of SiliaCat DPP-Pd in DMF (Scheme 4) at 90–100 °C, namely the maximum temperature permitted by the thermostatic Huber Visco-bath$^9$ connected to the MiniBlock.

The results in Table 7 show good conversions, from 80% to 100%, only for aryl iodide and bromide substrates with different electron-withdrawing groups (entries 1, 5–8). These results are in correlation with batch results (see Table 8, entries 1, 5–7), in DMF solvents at 90 °C. For aryl iodide and bromide substrates with different electron-donating groups, the conversions obtained in MiniBlock were much lower than in batch where the temperature used was 120 °C (Table 8, entries 2–4, 9–11).

**Reusability.** The fact the SiliaCat heterogeneous catalysts are leach-resistant suggests that these materials might be well suited for reuse in subsequent catalytic reactions. All aryl bromides used in Suzuki coupling reaction with the SiliaCat DPP-Pd (Table 5) were thus reused in five

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**Table 6.** Sonogashira coupling of different aryl iodides run in MiniBlock in the presence of different SiliaCat palladium catalysts

<table>
<thead>
<tr>
<th>#</th>
<th>Substrate</th>
<th>Product</th>
<th>Conversion / Selectivity (%)</th>
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</thead>
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<td></td>
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<td>SiliaCat DPP-Pd</td>
</tr>
<tr>
<td>1</td>
<td>I$_2$NH$_2$-I</td>
<td>O$_2$N-</td>
<td>100 /100</td>
</tr>
<tr>
<td>2</td>
<td>Me$_2$-I</td>
<td>Me$_2$-</td>
<td>100 /100</td>
</tr>
<tr>
<td>3</td>
<td>MeO-</td>
<td>MeO-</td>
<td>99 /98</td>
</tr>
<tr>
<td>4</td>
<td>I$_2$</td>
<td>I$_2$</td>
<td>100 /100</td>
</tr>
<tr>
<td>5</td>
<td>I$_2$</td>
<td>I$_2$</td>
<td>100 /100</td>
</tr>
<tr>
<td>6</td>
<td>H$_2$I</td>
<td>H$_2$I</td>
<td>90 /98</td>
</tr>
<tr>
<td>7</td>
<td>Os$_2$I$_2$</td>
<td>Os$_2$I$_2$</td>
<td>83 /98</td>
</tr>
<tr>
<td>8</td>
<td>Br$_2$</td>
<td>Br$_2$</td>
<td>55 /96</td>
</tr>
</tbody>
</table>

*Reactions performed in ethanol solvent (0.08 M) at reflux, 4 h. Substrate/phenylacetylene/K$_2$CO$_3$ = 1/1.2/2 equiv, 1 mol % catalyst. The presence of a cocatalyst is not required.

**Table 7.** Heck–Mizoroki coupling of different aryl halides and different olefins run in MiniBlock mediated by SiliaCat DPP-Pd

<table>
<thead>
<tr>
<th>#</th>
<th>Substrate</th>
<th>Olefin</th>
<th>Conversion / Selectivity (%)</th>
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<tbody>
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<td>1</td>
<td>O$_2$N-</td>
<td>88 /96</td>
<td>100 /99</td>
</tr>
<tr>
<td>2</td>
<td>51 /98</td>
<td>73 /97</td>
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</tr>
<tr>
<td>3</td>
<td>MeO-</td>
<td>54 /91</td>
<td>69 /100</td>
</tr>
<tr>
<td>4</td>
<td>I$_2$</td>
<td>43 /88</td>
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<td>O$_2$N-</td>
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<td>50 /97</td>
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<td>Br$_2$</td>
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<td>61 /98</td>
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<td>8</td>
<td>Br$_2$</td>
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<td>55 /97</td>
</tr>
<tr>
<td>9</td>
<td>Br$_2$</td>
<td>25 /82</td>
<td>-</td>
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<tr>
<td>10</td>
<td>Br$_2$</td>
<td>33 /91</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>Br$_2$</td>
<td>traces</td>
<td>-</td>
</tr>
</tbody>
</table>

*Reactions conditions: DMF solvent (0.65 M) at 90 °C for 20 h. Substrate/olefin/NaOAc = 1/1.5/1.5 equiv, 1 mol % SiliaCat DPP-Pd. Conversion determined by GC/MS analysis. Selectivity in trans-isomers.

**Table 8.** Heck–Mizoroki coupling of different aryl halides and different olefins mediated by SiliaCat DPP-Pd under batch conditions.

<table>
<thead>
<tr>
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<th>Substrate</th>
<th>Olefin</th>
<th>Conversion / Selectivity (%)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>O$_2$N-</td>
<td>100 /97</td>
<td>98 /99</td>
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<td>2</td>
<td>80 /78</td>
<td>100/99</td>
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</tr>
<tr>
<td>3</td>
<td>MeO-</td>
<td>99 /91</td>
<td>100 /99</td>
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<tr>
<td>4</td>
<td>I$_2$</td>
<td>92 /75</td>
<td>85 /89</td>
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<td>O$_2$N-</td>
<td>100 /97</td>
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<td>Br$_2$</td>
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<td>7</td>
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<td>Br$_2$</td>
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*Reactions conditions: DMF solvent (0.65 M), T = 90–120 °C for 20 h. Substrate: olefin: NaOAc = 1:1.5:1.5 equiv, 0.5 mol % SiliaCat DPP-Pd. Conversion determined by GC/MS analysis. Selectivity in trans-isomers.
Table 9. Reusability of SiliaCat DPP-Pd in Suzuki coupling of different aryl bromides run in MiniBlock

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<th>Substrate Products</th>
<th>Conversion/Selectivity (%)</th>
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<th>Run 3</th>
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<tbody>
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<td>16</td>
<td>H2N-Br</td>
<td>98/94</td>
<td>85/93</td>
<td>65/92</td>
<td>30/67</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>H3N-Br</td>
<td>95/93</td>
<td>92/97</td>
<td>91/82</td>
<td>65/89</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>NH2-Br</td>
<td>97/100</td>
<td>78/96</td>
<td>20/98</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>NBr</td>
<td>80/90</td>
<td>75/95</td>
<td>70/93</td>
<td>50/96</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>N2Br</td>
<td>100/99</td>
<td>88/90</td>
<td>75/95</td>
<td>67/99</td>
<td>68/96</td>
<td></td>
</tr>
</tbody>
</table>

consecutive reaction runs. Results in Table 9 show that, for substrates without substituent groups or with different electron-withdrawing groups such as, nitro, nitril, or carbonyl, the SiliaCat DPP-Pd catalyst can perform more than five cycles with minimal loss of activity. This is not the case for the substrates with different electron-donating groups, such as amine, methoxy, methyl, or for heteroaryl bromide substrates, such as pyridines and quinoline, when the SiliaCat DPP-Pd can perform three or five cycles with noticeable loss of activity.

Leaching. Possible leaching of palladium (and silicon) was determined for all SiliaCat DPP-Pd, SiliaCat S-Pd, and SiliaCat Pd0 catalysts employed in Suzuki–Miyaura (Table 5) and in Sonogashira (Table 6) coupling reactions. Results in Table 10 show minimal leaching of palladium for all the catalysts, with again best (minimal) values obtained for SiliaCat Pd0 catalyst.

The same general findings were observed (Table 11) for Pd and Si leaching in all Sonogashira reactions investigated in Table 6.

Leaching of Pd and Si was also assessed for SiliaCat DPP-Pd catalyst after each reuse of the catalyst for all bromide substrates analysed in Table 9. Results in Table 12 show that gain, leaching of palladium, is generally low (<10 ppm) and rather constant in each reaction run.

Table 10. Conversion vs leaching of Pd and Si from the SiliaCat DPP-Pd, SiliaCat S-Pd, and SiliaCat Pd0 catalysts employed in Suzuki–Miyaura reactions of Table 5

<table>
<thead>
<tr>
<th>#</th>
<th>Substrate Product</th>
<th>SiliaCat DPP-Pd</th>
<th>SiliaCat S-Pd</th>
<th>SiliaCat Pd0</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0-Br</td>
<td>92/100</td>
<td>0.1</td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>1.0-Br</td>
<td>100/92</td>
<td>0.3</td>
<td>1.0</td>
</tr>
<tr>
<td>3</td>
<td>1.0-Br</td>
<td>100/100</td>
<td>0.1</td>
<td>1.0</td>
</tr>
<tr>
<td>4</td>
<td>1.0-Br</td>
<td>100/100</td>
<td>0.1</td>
<td>1.0</td>
</tr>
<tr>
<td>5</td>
<td>1.0-Br</td>
<td>100/100</td>
<td>0.1</td>
<td>1.0</td>
</tr>
<tr>
<td>6</td>
<td>1.0-Br</td>
<td>100/100</td>
<td>0.1</td>
<td>1.0</td>
</tr>
<tr>
<td>7</td>
<td>1.0-Br</td>
<td>100/100</td>
<td>0.1</td>
<td>1.0</td>
</tr>
</tbody>
</table>

* Leaching determined by ICP-OES analysis. The solvent was evaporated and replaced by DMF/EtOH (3:1 v/v).

Table 11. Conversion vs leaching of Pd and Si from the SiliaCat DPP-Pd, SiliaCat S-Pd, and SiliaCat Pd0 catalysts employed in the Sonogashira reactions of Table 6

<table>
<thead>
<tr>
<th>#</th>
<th>Substrate Product</th>
<th>SiliaCat DPP-Pd</th>
<th>SiliaCat S-Pd</th>
<th>SiliaCat Pd0</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0-Br</td>
<td>100/100</td>
<td>1.5</td>
<td>1.0</td>
</tr>
<tr>
<td>2</td>
<td>1.0-Br</td>
<td>100/100</td>
<td>1.5</td>
<td>1.0</td>
</tr>
<tr>
<td>3</td>
<td>1.0-Br</td>
<td>100/100</td>
<td>1.5</td>
<td>1.0</td>
</tr>
<tr>
<td>4</td>
<td>1.0-Br</td>
<td>100/100</td>
<td>1.5</td>
<td>1.0</td>
</tr>
</tbody>
</table>

* Leaching determined by ICP-OES analysis. The solvent was evaporated and replaced by DMF/EtOH (3:1 v/v).

Overall, the results of the leaching tests show that, in general when reactivity decreases, leaching of palladium becomes more relevant. Furthermore, leaching depends on the substrates with heteroaryl bromides such as pyridines and quinoline affording the highest leaching levels.
Organically modified silica-based SiliaCat palladium catalysts, SiliaCat DPP-Pd, SiliaCat S-Pd, and SiliaCat Pd\(^0\), are robust and efficient heterogeneous catalysts for C–C cross-coupling reactions run in the parallel synthesizer Mettler-Toledo’s MiniBlock. This allows fast screening for optimal results in terms of selective activity, easy filtration, and reuse of the catalyst in Suzuki–Miyaura coupling reactions with different aryl bromides and chlorides, Sonogashira coupling reactions with different aryl iodides, and Heck–Mizoroki reactions with aryl iodide and bromide substrates. In general, SiliaCat Pd\(^0\) made of ultra-small Pd nanocrystals entrapped in amorphous sol-gel organosilica is the most selective, active, and leach-proof catalyst. The catalysts are reusable, and leaching of active Pd species is limited, even if leaching increases with decreasing reactivity. In all reactions inert or anhydrous conditions were not necessary. The method, in conclusion, offers the rapid synthesis of a library of useful coupled reaction products, while the ease of catalyst recovery and recycle and the low Pd-leaching potential are key attractions of this technology for scale-up.

### Table 12. Conversion vs leaching of Pd and Si from the SiliaCat DPP-Pd catalyst employed in the Suzuki–Miyaura coupling reactions of Table 9

<table>
<thead>
<tr>
<th>#</th>
<th>Substrate</th>
<th>Products</th>
<th>Pd</th>
<th>Si</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td>Run 1</td>
<td>Run 2</td>
</tr>
<tr>
<td>2</td>
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<td></td>
<td>0.1</td>
<td>0.1</td>
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<tr>
<td>7</td>
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<td>0.1</td>
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<td>0.1</td>
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<td>13</td>
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<td>10</td>
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<td>17</td>
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<td>1.7</td>
<td>2.2</td>
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<td>18</td>
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<td>3.2</td>
<td>25</td>
</tr>
<tr>
<td>19</td>
<td></td>
<td></td>
<td>1.4</td>
<td>12</td>
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<tr>
<td>20</td>
<td></td>
<td></td>
<td>2.1</td>
<td>0.3</td>
</tr>
</tbody>
</table>

*Leaching determined by ICP-OES analysis. The solvent was evaporated and replaced by DMF/EtOH (3:1 v/v).*

### CONCLUSIONS

Organically modified silica-based SiliaCat palladium catalysts, SiliaCat DPP-Pd, SiliaCat S-Pd, and SiliaCat Pd\(^0\), are robust and efficient heterogeneous catalysts for C–C cross-coupling reactions run in the parallel synthesizer Mettler-Toledo’s MiniBlock. This allows fast screening for optimal results in terms of selective activity, easy filtration, and reuse of the catalyst in Suzuki–Miyaura coupling reactions with different aryl bromides and chlorides, Sonogashira coupling reactions with different aryl iodides, and Heck–Mizoroki reactions with aryl iodide and bromide substrates. In general, SiliaCat Pd\(^0\) made of ultra-small Pd nanocrystals entrapped in amorphous sol–gel organosilica is the most selective, active, and leach-proof catalyst. The catalysts are reusable, and leaching of active Pd species is limited, even if leaching increases with decreasing reactivity. In all reactions inert or anhydrous conditions were not necessary. The method, in conclusion, affords the rapid synthesis of a library of useful coupled reaction products, while the ease of catalyst recovery and recycle and the low Pd-leaching potential are key attractions of this technology for scale-up.

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### REFERENCES

(1) For a recent account on cross-coupling reactions, see the themed issue (Buchwald, S. L., Ed.): *Acc. Chem. Res.* 2008, 41, 1439.


