Fast and Clean Borylation of Aryl Halides Under Flow Using Sol–Gel Entrapped SiliaCat DPP-Pd

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ABSTRACT: The fast and clean synthesis of boronic acid pinacol esters starting from aryl halides and bis(pinacolato)diboron is heterogeneously carried out over the SiliaCat DPP-Pd solid catalyst with largely enhanced reaction rate and catalyst stability. This opens the route to the transfer of cross-coupling borylation in a flow microreactor from the research level to process development.

1. INTRODUCTION

The Miyaura borylation reaction rapidly affords aryl- and heteroaryl boronates,† that are widely used in place of boronic acids in the Suzuki–Miyaura reaction, when reactive functional groups are present in the electrophilic aryl halides.‡ The original reaction offering easy and greater access to diverse borylated species involves the cross-coupling of bis(pinacolato)diboron (B₂Pin₂) with aryl halides and vinyl halides catalyzed at 80 °C in dioxane or DMF by 3 mol % PdCl₂(dppf) (1,1′-bis(diphenylphosphino)ferrocene dichloropalladium(II)) in the presence of a 3 equiv excess of KOAc. The Miyaura reaction eventually made the Suzuki–Miyaura C–C coupling reaction the routine method used both in industry and in academia, for the synthesis of diverse biaryls and heterobiaryls, ubiquitous motifs in established organic synthesis technology both in the academia and in the pharmaceutical and fine chemicals industries.10 Mesoporous, free-flowing organosilica catalytic xerogels indeed have a number of distinct advantages over traditional polymer resin beads, including faster kinetics, solvent independence, ease of use, and pronounced chemical and physical stabilities.11

In this report, we show how the catalytic borylation mediated by SiliaCat DPP-Pd can be carried out under flow with dramatic enhancement in reaction rate and catalyst stability, compared to reaction under batch conditions, while retaining the pronounced yield and selectivity observed for the catalytic reaction under batch conditions. The mesoporous catalyst’s excellent textural properties, indeed, make it ideally suited for application in a flow microreactor.

2. EXPERIMENTAL SECTION

Catalyst and Reagents. The SiliaCat DPP-Pd employed (0.25 mmol/g palladium loading, 573 m²/g BET specific surface area; 1.13 cm³/g total pore volume; 7.5 nm BJH desorption average mesopore diameter; 0.354 g/mL density) was obtained from SiliCycle, Inc. The flow rate was increased up to 0.5 mL/min threshold by using particle size of the catalyst functionalized with diphosphine ligand bound to Pd²⁺ (with typical 0.2–0.3 mmol/g palladium loading, high surface area 300–650 m²/g; depending on the applied parameters of the sol–gel synthesis), which is highly active in C–C coupling reactions.

A major advance enabled by these new silica-based materials made of catalytic species entrapped in mesoporous organosilica lies in the possibility to carry out solid-phase syntheses under flow and under automated conditions, nowadays a well-established organic synthesis technology both in the academia and in the pharmaceutical and fine chemicals industries.10 Special Issue: Continuous Processes 14
Table 1. SiliaCat DPP-Pd-catalysed borylation of aryl bromides: batch versus flow

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate (scale-up)</th>
<th>Catalyst (mol %)</th>
<th>Solvent (M)</th>
<th>Batch or Flow conditions</th>
<th>Conv (%)</th>
<th>Select (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1'</td>
<td>(5 mmol, 20 mL solvent)</td>
<td>SiliaCat DPP-Pd 1 mol%</td>
<td>i-PrOH (0.50)</td>
<td>Batch Method A</td>
<td>60</td>
<td>100</td>
</tr>
<tr>
<td>2'</td>
<td>(5 mmol, 40 mL solvent)</td>
<td>SiliaCat DPP-Pd catalyst reactor (R1)</td>
<td>i-PrOH (0.25)</td>
<td>Flow</td>
<td>0.75</td>
<td>1.37</td>
</tr>
<tr>
<td>3'</td>
<td>(5 mmol, 40 mL solvent)</td>
<td>SiliaCat DPP-Pd catalyst reactor (R1)</td>
<td>i-PrOH (0.25)</td>
<td>Flow</td>
<td>0.50</td>
<td>2.05</td>
</tr>
<tr>
<td>4'</td>
<td>(5 mmol/14 mL solvent)</td>
<td>SiliaCat DPP-Pd 2 mol%</td>
<td>i-PrOH (0.75)</td>
<td>Batch Method B</td>
<td>180</td>
<td>100</td>
</tr>
<tr>
<td>5'</td>
<td>(5 mmol/50 mL solvent)</td>
<td>SiliaCat DPP-Pd catalyst reactor (R1)</td>
<td>i-PrOH (0.21)</td>
<td>Flow</td>
<td>0.50</td>
<td>2.05</td>
</tr>
<tr>
<td>6'</td>
<td>(5 mmol/50 mL solvent)</td>
<td>SiliaCat DPP-Pd catalyst reactor (R2)</td>
<td>i-PrOH (0.21)</td>
<td>Flow</td>
<td>0.25</td>
<td>4.10</td>
</tr>
<tr>
<td>7'</td>
<td>(5 mmol/14 mL solvent)</td>
<td>SiliaCat DPP-Pd 2 mol%</td>
<td>i-PrOH (0.75)</td>
<td>Batch Method B</td>
<td>120</td>
<td>100</td>
</tr>
<tr>
<td>8'</td>
<td>(5 mmol/50 mL solvent)</td>
<td>SiliaCat DPP-Pd catalyst reactor (R1)</td>
<td>i-PrOH (0.21)</td>
<td>Flow</td>
<td>0.50</td>
<td>2.05</td>
</tr>
<tr>
<td>9'</td>
<td>(5 mmol/50 mL solvent)</td>
<td>SiliaCat DPP-Pd catalyst reactor (R2)</td>
<td>i-PrOH (0.21)</td>
<td>Flow</td>
<td>0.50</td>
<td>4.34</td>
</tr>
<tr>
<td>10'</td>
<td>(10 mmol/100 mL solvent)</td>
<td>SiliaCat DPP-Pd catalyst reactor (R2)</td>
<td>i-PrOH (0.21)</td>
<td>Flow</td>
<td>0.25</td>
<td>8.67</td>
</tr>
</tbody>
</table>

*Bath reaction. Method A: substrate (5 mmol, 1 equiv), bis(pinacolato)diboron (1 equiv), potassium acetate (2 equiv) in 2-propanol (20 mL, 0.50 M), 1 mol % SiliaCat DPP-Pd. *Flow reaction: in the solution of the batch reaction, Method A, 40 mL of solvent were used. The solution was pumped through the catalyst bed preheated at 82 °C at 0.50 mL/min or 0.75 mL/min flow rate. *Batch reaction. Method B: substrate (5 mmol, 1 equiv), bis(pinacolato)diboron (1.1 equiv) potassium acetate (2.2 equiv) in 2-propanol (14 mL, 0.75 M, molar concentration). *Flow reaction: in the solution of the batch reaction, Method B, 50 mL of solvent were used. The solution was pumped through the catalyst bed preheated at 82 °C at 0.25 mL/min or 0.50 mL/min flow rate. Column reactor (R1) (0.342 ID × 7 cm, 2.4 mL) was charged with 0.8 g SiliaCat DPP-Pd (0.25 mmol/g Pd loading). Column reactor (R2) (0.785 ID × 6.5 cm, 5.1 mL) was charged with 1.76 g SiliaCat DPP-Pd (0.25 mmol/g Pd loading). Scale-up 2 times the conditions of footnote d. Molar concentration with respect to the reagents (substrate + B₂Pin₂). The solution was pumped through the catalyst bed preheated at 82 °C at 0.25 mL/min or 0.50 mL/min flow rate. All experiments were conducted at 82 °C ± 1 °C. Residence time in the column reactor charged with the heterogeneous catalyst. The solution of product was collected in a separate vessel for analysis. Conversion/selectivity determined by GC−MS analysis.
bigger than 200 μm to avoid pressure drop throughout the catalyst packed in the microreactor ($d_{50} = 224$, $d_{90}/d_{10} = 5.9$). All other reagents of pure grade were received from Aldrich (St. Louis, MI) and were used as such without further purification.

**Reaction Set-Up and Conditions.** The optimal reaction conditions developed in the batch reaction over SiliaCat DPP-Pd for the borylation reaction of 4-bromobenzonitrile (Method A) and of 4-bromoanisole or 2-bromotoluene (Method B) were tested under flow in the modular Asia 220 flow chemistry system commercialized by Syrris, using a more diluted solution to ensure a homogeneous reaction mixture.

The system, whose setup is displayed in Figure 2, allows fast and reproducible mixing of liquid reactants in the presence of the solid catalyst. Only one solution was prepared mixing the substrate, bis(pinacolato)diboron and base (KOAc) in i-PrOH solvent. The column reactor (R1) with adjustable end charged with 1.76 g SiliaCat DPP-Pd, and the flow system was initialized during 20 min at room temperature when only the i-PrOH solvent was processed using both pump channels directly through the solid-phase reactor via a T-piece (a tube reactor adaptor enabling up to 4 reagents to be combined at the input of the reactor charged with the solid phase) at 0.50 mL/min or at 0.25 mL/min. After 20 min the solid-phase reactor was heated at 82 °C. The homogeneous regents solution containing 5–10 mmol substrate kept at room temperature was processed using either pump channel directly through the solid-phase reactor preheated at 82 °C.

**3. RESULTS AND DISCUSSIONS**

First, we tested the borylation of 4-bromobenzonitrile. Results in Table 1 show the excellent applicability of the mesoporous SiliaCat DPP-Pd heterogeneous catalyst under flow conditions. Hence, while under batch conditions complete conversion was obtained in 1 h (entry 1 in Table 1), under flow at 0.75 mL/min flow rate the conversion was 90% in 1.37 min residence time in the column reactor (entry 2). For the quantitative conversion of 4-bromobenzonitrile into the corresponding arylboronate, the residence time in the column reactor was increased to 2.05 min by increasing the flow rate to 0.5 mL/min (entry 3).

When electronically deactivated 4-bromoanisole was reacted in batch, the quantitative conversion to the corresponding arylboronate required 3 h (entry 4). Under flow conditions, 72% conversion was obtained at 0.5 mL/min flow rate, with 2.05 min residence time (entry 5). When the latter time was increased to 4.1 min, for 0.25 mL/min flow rate, conversion increased to 83% (entry 5). Eventually, 92% conversion was obtained under 0.25 mL/min flow rate, in 8.67 min residence time (entry 6), by replacing the 2.4 mL column reactor (R1) with a column reactor (R2) with an adjustable end (0.785 ID × 6.5 cm) charged with twice the original amount of SiliaCat DPP-Pd (1.76 g).

A sterically hindered substrate such as ortho-substituted 2-bromotoluene that, under batch conditions is quantitatively converted into the corresponding arylboronates in 2 h (entry 7), under flow is converted in 82% yield within the 2.4 mL column reactor (R1) column reactor in 2.05 min (entry 8). Using the column reactor (R2) with adjustable end charged with 1.76 g SiliaCat DPP-Pd, the conversion after 8.67 min residence time to 97% (entry 9). Almost complete conversion (98%) could be reached when the conditions developed in entry 9 were repeated for a much longer period of time (7 h, entry 10).

To investigate the stability of the nanoencapsulated catalyst the reaction using 2-bromotoluene as substrate was carried out, feeding the reagents continuously into the 5.1 mL R2 reactor for a much longer period of time (7 h) under the conditions developed in entry 9. Conversion levels were then checked every hour. Figure 3 clearly shows that the outcome of the reaction does not change with time, thus proving the required long-term stability of solid catalysts needed for practical synthetic applications.

Leaching of Pd and Si from the SiliaCat DPP-Pd catalyst during catalysis was indirectly assessed by analyzing the metals content in the isolated crude product by ICP-OES (inductively coupled plasma optical emission spectroscopy) in DMF solvent (100 mg/mL concentration)\(^{14}\). The low values detected for both Pd (0.12 mg/kg) and Si (0.28 mg/kg) clearly point to low metal contamination of the reaction product.

This result markedly differs from that obtained carrying out the reaction in batch under fast (600 rpm) mechanical stirring, when considerable mechanical and chemical degradation of the
xerogel microparticles comprising the catalyst is observed after the fourth consecutive reaction run.

### OUTLOOK AND CONCLUSIONS

In summary, the direct synthesis of boronic acid pinacol esters starting from different aryl bromides and bis(pinacolato)diboron can now be heterogeneously carried out using the SilicaCatalystedPP-dicatalyst packed within the microreactor of a commercial flow chemistry module. In accordance with results of the reaction in batch, similar excellent results (not reported herein) have been obtained also for aryl chloride and iodide derivatives.

Comparison of reaction under batch and flow chemistry conditions generally shows that flow chemistry results in a much enhanced reaction rate with further enhancement in catalyst stability. This is due to the high reactivity of the silica-entrapped Pd catalyst, and to the intrinsic versatility of catalyst stability. This is due to the high reactivity of the silica-entrapped Pd catalyst, and to the intrinsic versatility of catalyst stability, as well as the reaction rate with further enhancement in catalyst stability. This is due to the high reactivity of the silica-entrapped Pd catalyst, and to the intrinsic versatility of catalyst stability, as well as the reaction rate with further enhancement in catalyst stability.

The catalyst is an organosilica xerogel that adsorbs and concentrates external reactants at the surface of its large mesoporosity, without shrinking or swelling in any solvent and withstanding temperatures of over 200 °C. The catalyst is stable in air, and thus, the method does not require the use of inert conditions that are common when employing delicate Pd complexes used in cross-coupling reactions.

The use of anhydrous, non-toxic isopropanol as solvent coupled to the lack of the catalyst-product separation step further adds to the environmental benefits of this new method of broad scope, that opens the route to easier, greater access to arylboronates via the heterogeneously catalyzed borylation of readily available aryl halides. In conclusion, these results provide for the synthetically relevant cross-coupling borylation reaction, another of those "missing method and technology" required for the transfer of flow-through processes in flow microreactors from the research level to process development invoked by Kirschning a decade ago.

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**Notes**

The authors declare no competing financial interest.

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8. (See also at the URL: www.silicycle.com/eu/applications/catalysis/use-of-silicacat-dpp-pd (last time accessed, 18 February 2014)).
12. (Batch reaction. Method A: substrate (5 mmol, 1 equiv), bis(pinacolato)diboron, BPin₂ (1 equiv), KOAc (2 equiv), 20 mL anhydrous i-PrOH (0.5 M molar concentration in respect to aryl bromide and to bis(pinacolato)diboron) over 1 mol% SilicaCatalystedPP-dicatalyst at 82 °C; Method B: substrate (5 mmol, 1 equiv), bis(pinacolato)diboron, BPin₂ (1.1 equiv), KOAc (2.2 equiv), 14 mL anhydrous i-PrOH (0.75 M molar concentration in respect to aryl bromide and to bis(pinacolato)diboron) over 2 mol % SilicaCatalystedPP-dicatalyst at 82 °C. (Flow reaction. One solution, substrate (1 equiv), B₂Pin₂ (from 1 to 2 equiv) in i-PrOH (0.21 M) was prepared. The resulting homogenous solution was processed at room temperature using the channels of both pumps (but a single pump could also be used) directly through the solid-phase recirculation of the reaction system through the catalyst bed, that in itself can lead to very long residence times and catalyst utilisation.)