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.

Figure 1. Chemical structure of SiliaCat DPP-Pd (A); and chemical structure of SiliaCat DPP diphenylphosphine heterogeneous ligand (B).

1. INTRODUCTION

The Miyaura borylation reaction rapidly affords aryl- and heteroaryl boronates,[1] 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.[2] The original reaction offering easy and greater access to diverse borylated species involves the cross-coupling of bis-(pinacolato)diboron (B_2Pin_2) with aryl halides and vinyl halides catalyzed at 80 °C in dioxane or DMSO by 3 mol % $PdCl_2(dppf)$ [1,1′-bis(diphenylphosphino)ferrocene dichloropalladium(II)] in the presence of a 3 equiv excess of base (KOAc). The Miyaura reaction eventually made the Suzuki−Miyaura C−C coupling reaction the routine method used both in industry and in academia,[3] for the synthesis of diverse biaryls and heterobiaryls, ubiquitous motifs in pharmaceuticals, natural products, liquid crystals, and many other valued products used in different industrial sectors.[4]

Since the 1995 introduction of the original Miyaura borylation protocol, other homogeneous palladium catalysts of enhanced versatility for the cross-coupling of pinacolborane with aryl halides have been introduced, including palladium coordinated by (dicyclohexylphosphino)biphenyl-type ligands such as SPhos and XPhos.[5]

Furthermore, intense research attempts were devoted to efficiently heterogenize palladium catalytic species used in cross-coupling reactions,[6] with the aim to obtain selective and reusable solid cross-coupling catalysts avoiding contamination of the product with Pd. In this context, we have recently described the heterogeneously catalyzed synthesis of boronic acid pinacol esters using a wide range of aryl chlorides, bromides and iodides and bis(pinacolato)diboron as borylating agent over the sol−gel entrapped SiliaCat DPP-Pd catalyst (eq 1):[7] SiliaCat DPP-Pd[8] (Figure 1) is an organosilica matrix
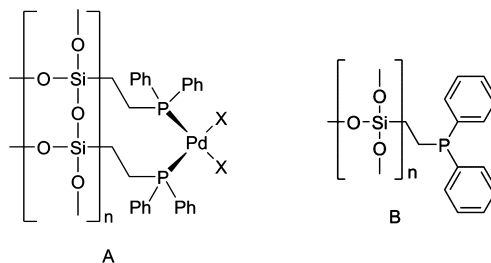
functionalized with diphenylphosphine ligand bound to Pd^{2+} (with typical 0.2−0.3 mmol/g palladium loading, high surface area 300−650 m^2/g; depending on the applied parameters of the sol−gel synthesis), which is highly active in C−C coupling reactions.[9]

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] 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 m^2/g BET specific surface area; 1.13 cm^3/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
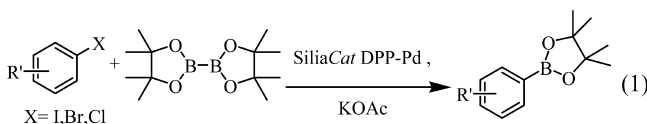
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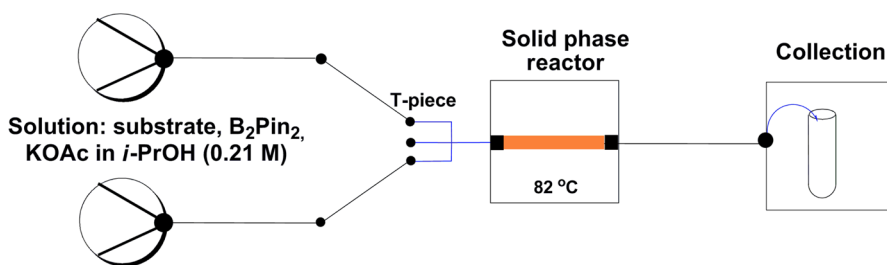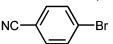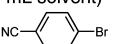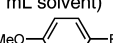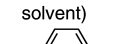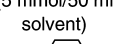
Figure 2. Flow borylation reaction over Silia*Cat* DPP-Pd.

Table 1. Silia*Cat* DPP-Pd-catalysed borylation of aryl bromides: batch versus flow

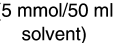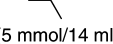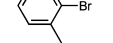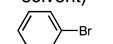| Entry	Substrate (scale-up)	Catalyst (mol %)	Solvent (M)[h]	Batch or Flow conditions — Flow (mL/min)	RT[i] (min)	Conv[j] (%)	Select[i] (%)
1[a]	NC–C6H4–Br (5 mmol, 20 mL solvent)	Silia*Cat* DPP-Pd 1 mol%	*i*-PrOH (0.50)	Batch Methode A	60	100	99
2[b]	NC–C6H4–Br (5 mmol, 40 mL solvent)	Silia*Cat* DPP-Pd catalyst reactor (R1)[e]	*i*-PrOH (0.25)	0.75	1.37	90	95
3[b]	NC–C6H4–Br (5 mmol, 40 mL solvent)	Silia*Cat* DPP-Pd catalyst reactor (R1)[e]	*i*-PrOH (0.25)	0.50	2.05	100	95
4[c]	MeO–C6H4–Br (5 mmol/14 ml solvent)	Silia*Cat* DPP-Pd 2 mol%	*i*-PrOH (0.75)	Batch Methode B	180	100	99
5[d]	MeO–C6H4–Br (5 mmol/50 ml solvent)	Silia*Cat* DPP-Pd catalyst reactor (R1)[e]	*i*-PrOH (0.21)	0.50 / 0.25	2.05 / 4.10	72 / 83	97 / 98
6[d]	MeO–C6H4–Br (5 mmol/50 ml solvent)	Silia*Cat* DPP-Pd catalyst reactor (R2)[f]	*i*-PrOH (0.21)	0.25	8.67	92	95
7[c]	(2-methylphenyl)–Br (5 mmol/14 ml solvent)	Silia*Cat* DPP-Pd 2 mol%	*i*-PrOH (0.75)	Batch Methode B	120	100	98
8[d]	(2-methylphenyl)–Br (5 mmol/50 ml solvent)	Silia*Cat* DPP-Pd catalyst reactor (R1)[e]	*i*-PrOH (0.21)	0.50	2.05	82	98
9[d]	(2-methylphenyl)–Br (5 mmol/50 ml solvent)	Silia*Cat* DPP-Pd catalyst reactor (R2)[f]	*i*-PrOH (0.21)	0.50 / 0.25	4.34 / 8.67	91 / 97	96 / 98
10[g]	(2-methylphenyl)–Br (10 mmol/100 ml solvent)	Silia*Cat* DPP-Pd catalyst reactor (R2)[f]	*i*-PrOH (0.21)	0.25	8.67	98	98

[a]*Batch* 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 % Silia*Cat* DPP-Pd. [b]*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. [c]*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). [d]*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. [e]Column reactor (R1) (0.342 ID × 7 cm, 2.4 mL) was charged with 0.8 g Silia*Cat* DPP-Pd (0.25 mmol/g Pd loading). [f]Column reactor (R2) (0.785 ID × 6.5 cm, 5.1 mL) was charged with 1.76 g Silia*Cat* DPP-Pd (0.25 mmol/g Pd loading). [g]Scale-up 2 times the conditions of footnote d. [h]Molar concentration with respect to the reagents (substrate + B_2Pin_2). 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. [i]Residence time in the column reactor charged with the heterogeneous catalyst. [j]The solution of product was collected in a separate vessel for analysis. Conversion/selectivity determined by GC−MS analysis.
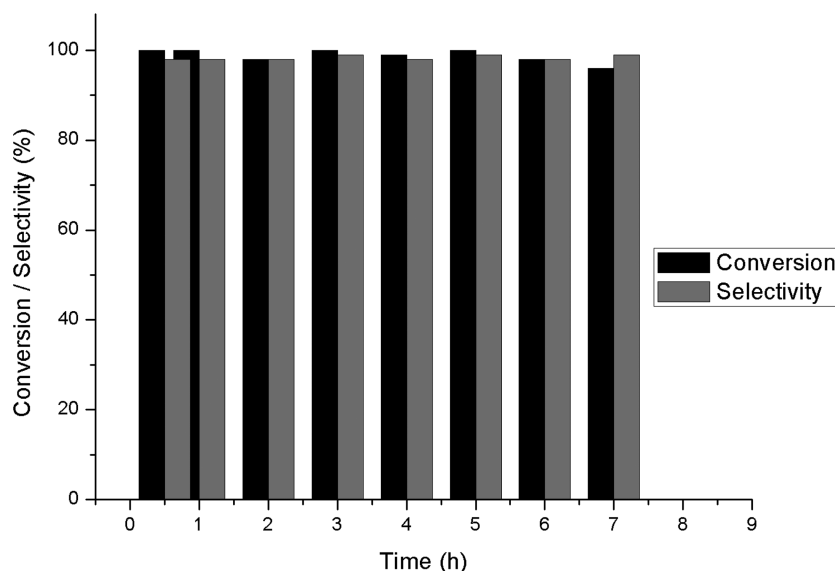
Figure 3. Stability of the Silia*Cat* DPP-Pd supported catalyst in borylation reaction under flow chemistry.

bigger than 200 μm to avoid pressure drop throughout the catalyst packed in the microreactor ($d50 = 224$, $d90/d10 = 5.9$). 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 Silia*Cat* DPP-Pd for the borylation reaction of 4-bromobenzonitrile (Method A) and of 4-bromoanisole or 2-bromotoluene (Method B)[12] were tested under flow in the modular Asia 220 flow chemistry system commercialized by Syrris,[13] 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 2.4 mL (R1) was thus charged (simply packing the column) with 0.8 g Silia*Cat* 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 three flows of 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 Silia*Cat* 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 Silia*Cat* 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 (R1) column reactor in 2.05 min (entry 8). Using the column reactor (R2) with adjustable end charged with 1.76 g Silia*Cat* DPP-Pd brings 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 Silia*Cat* 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 SiliaCat DPP-Pd solid catalyst packed within the microreactor of a commercial flow chemistry module. In accordance with results of the reaction in batch,[7] 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,[15] and to the intrinsic versatility of chemical processes under flow in which the time of contact between the catalyst and the reactants can be tuned simply by varying the reactor volume and/or the flow rate until optimal conditions are identified.

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"[16] 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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(12) Batch reaction. *Method A*: substrate (5 mmol, 1 equiv), bis(pinacolato)diboron, B_2Pin_2 (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% SiliaCat DPP-Pd, 82 °C; *Method B*: substrate (5 mmol, 1 equiv), bis(pinacolato) diboron, B_2Pin_2 (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 % SiliaCat DPP-Pd, 82 °C.

(13) Flow reaction. One solution, substrate (1 equiv), B_2Pin_2 (from 1 equiv to 1.1 equiv), KOAc (from 2 equiv to 2.2 equiv) in *i*-PrOH (0.21M) 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 reactor preheated at 82 °C via a T-piece (a tube reactor adaptor enabling up to three flows of 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 (0.25 mL/min or 0.125 mL/min each pump). The outcome solution was collected over water and extracted with ethyl acetate. The organic layer was separated, dried under $MgSO_4$ and filtered, and the solvents were evaporated under vacuum. For detailed information, see at the URL: http://syrris.com/flow-products/asia-automated-systems/asia-220-flow-chemistry (last time accessed, January 10, 2014).

(14) Leaching values are given in mg/kg APIs (active pharmaceutical ingredients). Limit of detection: LOD_{Pd} = 0.01 ppm in solution (100 mg/mL concentration) or 0.10 mg/kg in the crude product; LOD_{Si} = 0.005 ppm in solution (100 mg/mL concentration) or 0.05 mg/kg in the crude product.

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(16) Kirschning, A.; Jas, G. *Top. Curr. Chem.* **2004**, *242*, 209−239 Industrial chemists, interested in using the absolute minimum amount of Pd, even in an immobilised system, will be able to examine recirculation of the reaction system through the catalyst bed, that in itself can lead to very long residence times and catalyst utilisation..