Advanced Synthesis & Catalysis

Accepted Article

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To be cited as: *Adv. Synth. Catal.* 10.1002/adsc.201800262

Link to VoR: http://dx.doi.org/10.1002/adsc.201800262

10.1002/adsc.201800262

UPDATE

DOI: 10.1002/adsc.201((will be filled in by the editorial staff))

An efficient benzoxaborole one-pot synthesis by Silia*Cat* DPP-Pd heterogeneous catalysis using diboronic acid

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Received: ((will be filled in by the editorial staff))

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201######.((Please delete if not appropriate))

Abstract. Organoboron compounds are valuable molecules of increasing interest in organic synthesis, catalysis, biology and medicine. Among them, benzoxaboroles emerged as promising building blocks for numerous research programs. In this letter, we communicate the development of new conditions for the one-pot benzoxaborole synthesis by Silia*Cat* DPP-Pd catalysis using diboronic acid as the boron source. This low cost and sustainable strategy permitted the preparation of a useful range of benzoxaborole building blocks. Finally, the transformation was extended to a continuous flow process using our Vapourtec system.

Keywords: Benzoxaborole synthesis; cross-coupling; flow chemistry; heterogeneous catalysis; Borylation.

Benzoxaboroles are hemi-esters of arylboronic acids that have been known for over 60 years when the unsubstituted 1-hydroxy-1,3-dihydrobenzoxaborole (benzoxaborole, Bbzx, Figure 1) was first synthesized and characterized by Torssell in 1957.[1] During the last 50 years, these compounds have attracted much attention in various fields, exemplified in material science, organic synthesis and since 2006, medicinal chemistry.[2] Indeed, thanks to their physical and chemical properties, benzoxaboroles were recognized as important boron-containing molecules able to interact selectively with biomolecules.[3] Recently, several derivatives have been accepted by the FDA for topical treatment of onychomycosis[4] (AN2690, Figure 1) and atopic dermatitis or psoriasis (AN2728, Figure 1).[5]

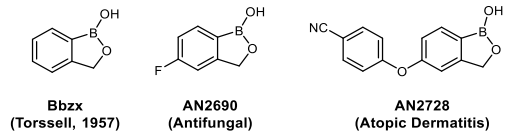


Figure 1. Benzoxaboroles of interest.

Over the years, at Nestlé Skin Health (NSH), several research programs have targeted these specific scaffolds for the topical treatment of acne or psoriasis.[6] In a recent letter, we disclosed a new versatile one-pot strategy to prepare benzoxaboroles derived from Molander's borylation conditions[7] with diboronic acid (BBA) and using a second generation Buchwald catalyst (Figure 2).[6] These conditions were more atom economical and provided boroxole products that were easier to purify, being free of pinacol, compared to a recent process using Bis(pinacolato)diboron (B_2pin_2) reported by Huang *et al.*.[8] However, despite this advance, occasional difficulties were still encountered to purify some of our benzoxaborole products to an acceptable purity for biological assay, mainly because of the remaining 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (XPhos) by-products and the [1,1'-biphenyl]-2-amine side product arising from breakdown of the XPhos-Pd-G2 catalyst (**1**). To circumvent these difficulties and offer a more sustainable and cost-efficient methodology, herein, we describe the discovery of a new benzoxaborole synthesis under heterogeneous palladium catalysis (Figure 2).

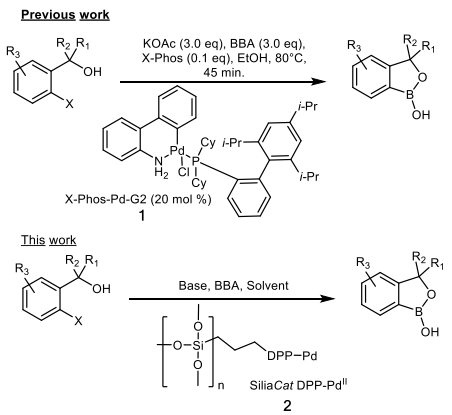
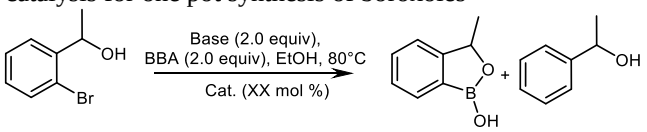


Figure 2. New benzoxaborole synthesis under heterogeneous palladium catalysis.

During the last few years, Silia*Cat* DPP-Pd (**2**, Figure 2) has been reported in numerous palladium-catalyzed batch reactions,[9] including the Suzuki–Miyaura, Heck–Mizoroki, Sonogashira, Kumada, Stille and Buchwald reactions. This palladium catalyst, produced by SiliCycle, is a diphenylphosphine based Pd^{II} heterogeneous catalyst entrapped in a functionalized organosilica matrix. It presents the advantages of having a fairly accurate loading (0.2-0.3 $mmol.g^{-1}$) with good physical robustness that lowering the risk of leaching and ultimately of poor turnover capacity.[10] Therefore, it was decided to focus our route optimization using this catalyst. Our first attempt to transfer from homogeneous to heterogeneous catalysis was explored and the results are summarized in Table 1. Under both homogeneous (Table 1, entry 1) and heterogeneous conditions (Table 1, entry 2) the conversion was complete. Interestingly, the reaction appeared to be quicker with Silia*Cat* DPP-Pd than with the XPhos Pd G2 catalyst but led to lower selectivity toward the desired product (**4**) compared to the proto-dehalogenated side product (**5**). Reduction of the catalyst loading to 10 mol% (Table 1, entry 3) demonstrated very little impact on the reaction and encouraged us to continue our exploration with this lower loading. To further improve our system, we envisioned that the low solubility of potassium acetate (KOAc) in ethanol may not be optimal for our heterogeneous catalytic method. Indeed, switching for the more soluble tetrabutylammonium acetate (Bu_4NOAc) (entry 4, Table 1) allowed to accomplish the same reaction rates but with much promising selectivity (70:30). Alternatively, the reaction with the organic tertiary base triethylamine (Et_3N) did not give satisfactory results (Table 1, entry 5).

Table 1. Transfer from homogeneous to heterogeneous catalysis for one pot synthesis of boroxoles



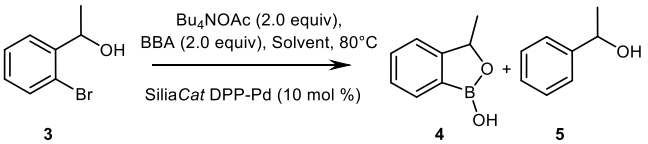
3 4 5

Entry	Catalyst	Base	Conv. [%][a]	Time (min)	Sel.[b]	Yield [%].[c]
1	**1** (20 mol %)	KOAc	Full	10	75:25	56
2	**2** (20 mol %)	KOAc	Full	2	50:50	41
3	**2** (10 mol %)	KOAc	Full	2	45:55	-
4	**2** (10 mol %)	Bu_4NOAc	Full	2	70:30	-
5	**2** (10 mol %)	Et_3N	90	2	50:50	-

[a] Conversion was determined by ^1H NMR. [b] As a ratio of **4**:**5** determined by ^1H NMR. [c] Isolated yield after purification by chromatography.

The new optimized conditions permitted us to achieve a full conversion but with only a moderate selectivity in favor of the desired product. To reduce the formation of proto-dehalogenated side product (**5**), it was postulated that changing the solvent to an aprotic one should increase selectivity.[11] Table 2 displays the different solvent effects observed. In all cases, a full conversion was observed in less than 15 minutes. As expected, low to acceptable selectivity (from a ratio of 45:55 to 70:30) was observed for protic polar solvents such as methanol, isopropanol and ethanol (Table 2, entries 1-3). Interestingly, besides toluene (Table 2, entry 5) in which the reaction was slower and 1,4-dioxane (Table 2, entry 4) that gave similar results to ethanol, all aprotic solvents afforded promising results (Table 2, entries 6-8). With these results in hand, it was decided to further explore the scope of the reaction in acetonitrile (selectivity of 80:20) which is a safer and more practical solvent in comparison to *N*,*N*-dimethylformamide (DMF) or dimethyl sulfoxide (DMSO).

Table 2. Solvent screening for boroxole synthesis by Silia*Cat* DPP-Pd catalysis.



3 4 5

Entry	Solvent	Conv. [%][a]	Time (min)	Sel.[b]
1	Ethanol	Full	2	70:30
2	Methanol	Full	7	45:55
3	Isopropanol	Full	5	60:40
4	1,4-Dioxane	Full	7	70:30
5	Toluene	Full	15	55:45
6	DMF	Full	5	80:20
7	DMSO	Full	7	80:20
8	Acetonitrile	Full	5	80:20

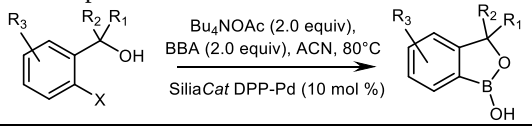
[a] Determined by NMR. [b] As a ratio of **4**:**5** determined by ^1H NMR.

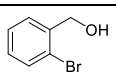
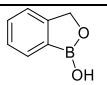
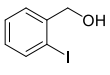
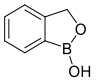
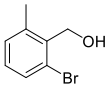
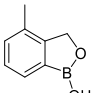
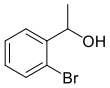
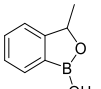
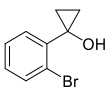
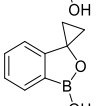
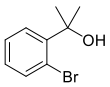
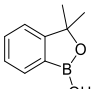
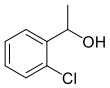
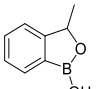
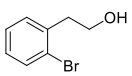
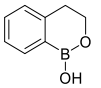
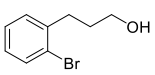
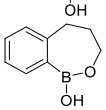
In order to address the question of heterogenous catalyst choice, a rapid comparative study was realized with a selection of immobilized Pd-catalysts such as dichlorobis(triphenylphosphine) Pd^{II} polymer-bound, Pd^{II} EnCat 30TPP, di(acetato)-dicyclohexylphenylphosphine Pd^{II} polymer-bound FibreCat and Silia*Cat* Pd^0.[12] This short screen confirmed that Silia*Cat* DPP-Pd was the best catalyst, affording a rapid conversion to boroxole **4** while minimising the formation of side product **5**.

To conclude our study, we decided to evaluate the scope of this new process using the same substrates as were used for the homogenous catalytic process (Table 3).[6] As expected from the solvent optimization, all substrates were fully converted within a minute. Both bromides and iodides were equally good substrates for this process and performed as well as for homogeneous catalysis with

isolated yields of 61 and 58 % (Table 3, entries 1 and 2). In the case of (2-bromo-6-methylphenyl)methanol (Table 3, entry 3), the corresponding boroxole was obtained in 73 % yield which was higher than the result obtained with our previous conditions. Indeed, 4-methylbenzo[*c*][1,2]oxaborol-1(3*H*)-ol was particularly difficult to purify using our homogenous catalytic conditions[6] and this example clearly shows the superiority of these new heterogenous conditions, permitting the recovery of the desired product with little effort in both high purity and yield. Increasing steric hindrance at the benzylic position with one, two methyl groups or a cyclopropyl group also afforded boroxole products with good yields (Table 3, entries 4-6). Despite the steric hindrance, the supported catalyst was well tolerated and gave comparable results to the homogeneous process. Unfortunately, going from an aryl bromide to an aryl chloride (Table 3, entry 4 v entry 7) gave a significantly lower yield (3 %) and demonstrates the limitations of Silia*Cat* DPP-Pd to catalyze the desired reaction with weakly reactive aryl chloride substrates. Finally, six and seven membered boroxoles were also recovered with acceptable isolated yields using this convenient one-pot approach (entries 8–9).

Table 3. Scope of the reaction.



Entry	Substrate	Product	Conv. [%][a]	Time [min]	Yield [%][b]
1			Full	1	**61** *(69)*[c]
2			Full	1	**58** (59)[c]
3			Full	1	**73** (35)[c]
4			Full	1	**52** (57)[c]
5			Full	1	**55** (51)[c]
6			Full	1	**71** (42)[c]
7			70	10	**3** (32)[c]
8			Full	1	**51** (37)[c]
9			Full	1	**33** (45)[c]

[a] Conversion was determined by ^{1}H NMR. [b] Isolated yield. [c] Isolated yield in brackets was obtained under homogeneous XPhos-Pd-G2 process previously reported.[6]

The successful transfer from homogeneous to heterogeneous catalysis encouraged us to see how this process would perform in flow with our Vapourtec R-series system.[13] Lately, flow chemistry has been intensively developed to improve the performance of known chemical synthesis.[14] Indeed, the capacity of the flow chemistry to rapidly deliver product in a more sustainable working environment and facilitate rapid conditions' scouting and optimization represents a great interest to save time and accelerate our research programs. Moreover, coupling this technique with heterogeneous catalysis represents a powerful strategy due to the simple reuse and recovery of the catalyst.[15] As shown in Figure 3, we started our investigation by preparing a solution of the aryl bromide (**3**), BBA and Bu_4NOAc in acetonitrile and pumping it through an omnifit column packed with Silia*Cat* DPP-Pd (Figure 3). As clogging was observed due to particle formation, the solvent was switched from pure acetonitrile to an acetonitrile:ethanol mixture (5:1).[16] The preliminary results obtained by the flow process are summarized in Table 4.

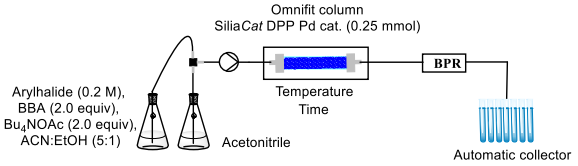
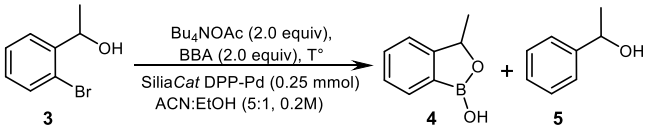
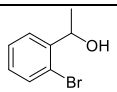
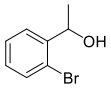
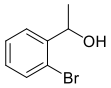
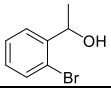


Figure 3. Experimental set-up of the flow system.

Table 4. Optimization of flow Silia*Cat* DPP-Pd catalysed boroxole synthesis.



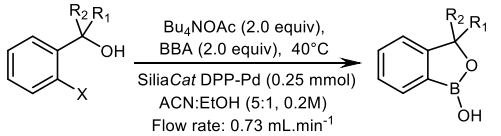
3 4 5

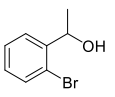
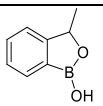
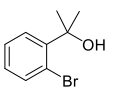
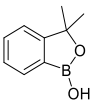
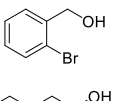
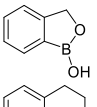
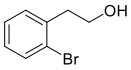
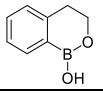
Entry	Substrate	Time [a] [min]	Temp. (°C)	Conv. [%]	Sel.[b]	Yield [%].[c]
1		10	r.t.	70	60:40	-
2		10	40	full	40:60	-
3		2	40	80	75:25	-
4		3	40	full	70:30	51 44[d]

[a] Residence time. [b] As a ratio of **4**:**5** determined by ^{1}H NMR. [c] Isolated yield. [d] Yield after 8 consecutive runs with the same column of catalyst.

After a rapid optimization of the flow process through temperature and residence time tuning (Table 4, Entries 1-4), we were able to propose an acceptable condition for a first flow process for benzoxaborole synthesis. A residence time of 3 min, combined with a reaction temperature of 40 °C allowed us to obtain the desired product with acceptable selectivity and isolated yield (Table 4, Entry 4). Indeed, a lower temperature compared to batch process was required to limit the formation of side product (**5**) while maintaining full conversion. Additionaly, reusability of the catalyst was assessed by running the reaction eight times in a row with little change in conversion or selectivity highlighting the interest of using automated system for benzoxaborole production.[17] Finally, the conditions were applied to four different substrates on a 500 mg scale (Table 5, Entry 1-3). In all cases, acceptable yields were obtained and allowed us to validate the unoptimized flow process conditions as an interesting alternative for rapid scale up of product. Indeed, by using a flow rate of 0.73 mL.min^{-1} we were able to produce up to 633 mg.h^{-1} of benzo[*c*][1,2]oxaborol-1(*3H*)-ol.

Table 5. Flow Silia*Cat* DPP-Pd catalysed boroxole synthesis.



Entry	Substrate	Product	Yield [%][a]
1			52
2			54
3			54
4			42

[a] Isolated yield.

In summary, a concise and efficient synthesis of substituted benzoxaboroles has been developed based on the one-pot borylation cyclocondensation cascade reaction of unprotected *ortho* halogen substituted benzyl alkanols and diboronic acid under heterogeneous catalysis. The reaction features mild conditions and high efficiency. In addition, the use of supported Silia*Cat* DPP-Pd showed yields as high as those obtained with the second generation Buchwald catalyst and displays the added advantages of being easy to purify, recyclable as well as being less expensive. Finally, the transfer from batch to flow led to a simple and rapid process to give access to boroxoles in continuous flow. Although, further optimization of the reaction is still necessary, this first example should be of interest as a practical strategy to rapidly produce valuable benzoxaborole derivatives as building blocks for research programs.

Experimental Section

General batch procedure: A glass vial equipped with a magnetic stir bar and fitted with a Teflon screw cap was charged with BBA (90 mg, 1.0 mmol), base (1.0 mmol), the aryl halide (0.50 mmol) and the solvent (2.5 mL, 0.4 M). The supported Pd catalyst (10 mol %) was then added, and the suspension was stirred (750 rpm) and heated at 80°C until full conversion was observed. The reaction was cooled to room temperature, filtered over celite and concentrated under reduced pressure. The crude mixture was purified using silica gel column chromatography.

General flow procedure: A solution of diboronic acid (2.0 equiv), tetrabutylamonium acetate (2.0 equiv) and 2-halogeno benzyl alkanol (1.0 equiv) in an ACN:EtOH mixture (5:1, 0.2M) was pumped at 0.73 mL.min^{-1} using the Vapourtec R2+ system (one pump only). The solution was driven to an omnifit colum (6.6 mm x 100 mm) preheated at 40°C, containing Silia*Cat* DPP-Pd (1.0 g, 0.25 mmol/g) and giving a residence time of 3 min. After pumping of the whole solution the outlet crude mixture was concentrated and directly purified using silica gel column chromatography.

Acknowledgements

The authors would like to acknowledge Mr. Grégoire Mouis for his help for structural analysis of the compounds.

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[16] No difference in conversion and selectivity was observed in batch by switching from Acetonitrile to Acetonitrile:Ethanol 9:1.

[17] Data from the 8 consecutive runs are reported in supplementary material.

10.1002/adsc.201800262

UPDATE

An efficient benzoxaborole one-pot synthesis by Silia*Cat* DPP-Pd heterogeneous catalysis using diboronic acid

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