ORGANIC PROCESS RESEARCH & DEVELOPMENT

Subscriber access provided by University of Otago Library

Full Paper

Development and scale up of an efficient Miyaura borylation process using tetrahydroxydiboron

Sing R. Gurung, Christopher Mitchell, Jie Huang, Marco Jonas, Josiah D Strawser, Elena Daia, Andrew Hardy, Erin O'Brien, Frederick Hicks, and Charles Dimitrios Papageorgiou

Org. Process Res. Dev., **Just Accepted Manuscript** • DOI: 10.1021/acs.oprd.6b00345 • Publication Date (Web): 20 Nov 2016

Downloaded from http://pubs.acs.org on November 23, 2016

Just Accepted

"Just Accepted" manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides "Just Accepted" as a free service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. "Just Accepted" manuscripts appear in full in PDF format accompanied by an HTML abstract. "Just Accepted" manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are accessible to all readers and citable by the Digital Object Identifier (DOI®). "Just Accepted" is an optional service offered to authors. Therefore, the "Just Accepted" Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the "Just Accepted" Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these "Just Accepted" manuscripts.

ACS Publications

Organic Process Research & Development is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Published by American Chemical Society. Copyright © American Chemical Society. However, no copyright claim is made to original U.S. Government works, or works produced by employees of any Commonwealth realm Crown government in the course of their duties.

Development and scale up of an efficient Miyaura borylation process using tetrahydroxydiboron

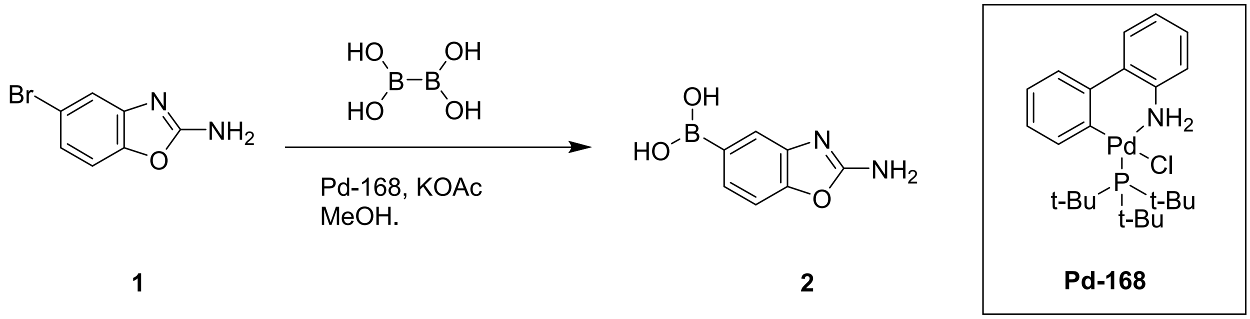
Sing R. Gurung[1], Christopher Mitchell[2], Jie Huang[1], Marco Jonas[1], Josiah D. Strawser[2], Elena Daia[3], Andrew Hardy[2], Erin O'Brien[2], Frederick Hicks[2], Charles D. Papageorgiou[2]*

1 Albany Molecular Research Inc, 21 Corporate Circle, Albany, NY, 12203

2 Takeda Pharmaceuticals International Co., Process Chemistry, 40 Landsdowne St., Cambridge, MA, 02139

3 Carbogen AMCIS Ltd, 303 Clayton Lane, Manchester, M11 4SX

Table of Contents Graphic



Keywords: tetrahydroxydiboron, Miyaura borylation, oxygen sensitivity, ethylene glycol, cost analysis

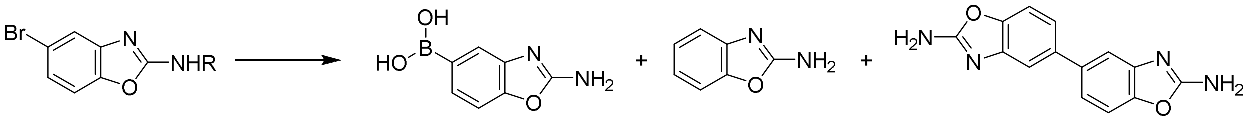
Abstract

A revised Miyaura borylation process has been developed using tetrahydroxydiboron that avoids the use of bis(pinacolato) diboron and hence the need to hydrolyze the resulting boronic ester to its corresponding acid. The process was greatly simplified and successfully scaled-up in the pilot plant on a 65 kg scale, reducing plant cycle time and resulting in a 47 % overall cost reduction. Furthermore, methodology for the study of the oxygen sensitivity of the process is reported that allowed for optimization of the amount of tetrahydroxydiboron and catalyst used. These studies also demonstrated an oxygen-induced decomposition of tetrahydroxydiboron.

INTRODUCTION

Boronic acids are not only extremely useful reagents in a number of cross-coupling reactions, but they are also of great interest in medicinal chemistry. Their synthesis typically relies on one of two main methods. [1, 2] The most atom efficient and cost effective approach involves a metal-halogen exchange of the corresponding halide using an organolithium or organomagnesium reagent followed by quench with a trialkyl borate.[3] However, this method presents limitations with respect to functional group tolerance, as many pharmaceutically relevant substrates contain base sensitive moieties within their structures. An alternative, more versatile strategy involves a transition metal-catalyzed borylation that provides access to a wide range of aryl and heteroarylboron derivatives with a high degree of complexity. These methods are less cost effective and atom efficient typically utilizing palladium (Pd) catalysts and bis(pinacolato) diboron (B_2Pin_2) as the boron source.[4-7] The resulting boronic esters are then typically hydrolyzed, in an additional step to their corresponding boronic acids, a process that can be challenging given its reversible nature, and that affords large amounts of pinacol waste.[8] Removal of this pinacol waste from the reaction mixture can also be troublesome, requiring laborious extraction and distillation techniques as the development of suitable crystallization processes is often plagued by oiling issues. Finally, reaction conditions need to be identified that minimize the competing de-halogenation and homo-coupling of the aryl halide starting material, that can significantly impact the overall process yield and isolated product purity.

Figure 1. Synthesis of arylboronic acid **2** and related impurities

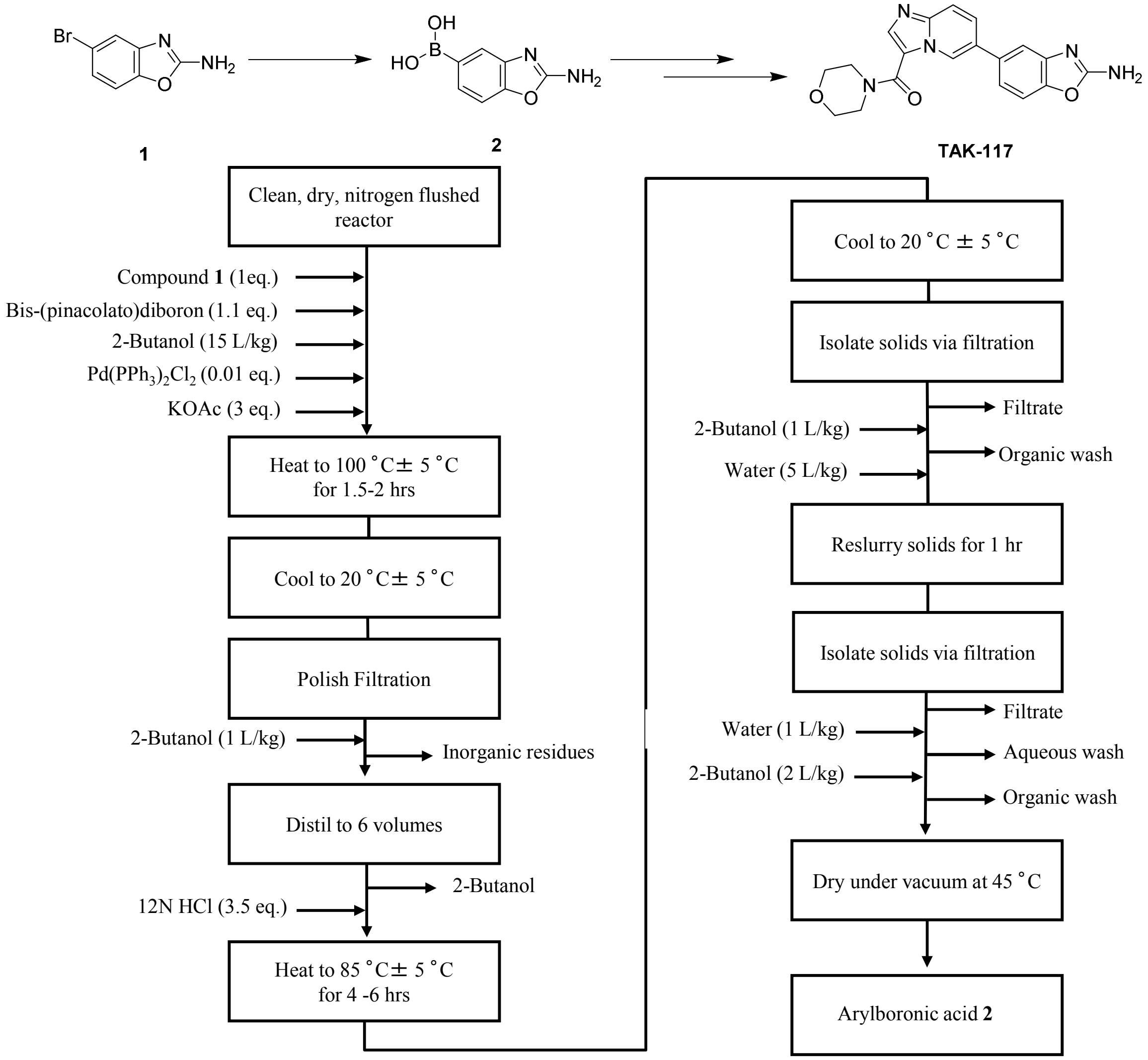


1 R= H, Boc **2** **3** **4**

Arylboronic acid **2** is a key starting material in the manufacturing process for TAK-117, a selective PI3Kα inhibitor currently in Phase 1b clinical trials (Figures 1 & 2). Treatment of the boc-protected aryl bromide **1** with stoichiometric quantities of sec-BuLi under a wide range of conditions followed by a quench with $B(OMe)_3$ resulted predominantly in de-bromination. This indicates that the metal-halogen exchange may be faster than the deprotonation of the free hydrogen on the nitrogen, this internal proton source effectively quenching the desired lithiated species. A rapid reverse addition of the aryl-bromide to an excess of sec-BuLi was shown to enable both complete lithium-halogen exchange and nitrogen deprotonation. However the rapid heat evolution associated with this approach makes it unsuitable for batch processing.[8]

Therefore a Pd mediated process was developed, outlined in Figure 2 that employed B_2Pin_2 as the borylating agent and utilized a relatively high loading of bis(triphenylphosphine)palladium (II) chloride catalyst (0.01 eq.). Aryl bromide **1**, B_2Pin_2 and KOAc were charged to a clean and dry reactor, flushed with nitrogen followed by 15 volumes of 2-BuOH. Oxygen was removed from the suspension by conducting 3 vacuum/ N_2 purge cycles before adding the catalyst. The reaction mixture was then heated to 100 °C for 1-2 hours after which time an in-process control (IPC) sample was removed to confirm that the overall conversion was within the set specification of no-less-than (NLT) 99.0%. The reaction mixture was cooled to 20 °C and a polish filtration was conducted to remove the generated KBr salts. The solids were washed with 2-BuOH and the filtrate concentrated to 6 volumes. Concentrated HCl was finally added to mediate the hydrolysis of the ester that took place within 4-6 hours at 85 °C. Once the hydrolysis was complete (achieved a NLT 98.0% conversion), the suspension was cooled to 20 °C, filtered and the wet-cake washed with 2-BuOH and water. The wet-cake was re-slurried in water to remove the residual inorganics (mainly boric acid) and then filtered and washed with water and 2-BuOH before being dried under vacuum at 45 °C.

Figure 2. Original B_2Pin_2-mediated Miyaura borylation of aryl bromide **1**



A total of 5 batches were manufactured according to this process on a 20-50 kg scale that afforded product with good overall purity (95.8-97.5%), with the main impurities being the de-brominated (**3**) and homo-coupled (**4**) side products that were each observed, during IPC analysis, in 7-13% (Figure 1). The process yield was also low and variable, between 60 and 75%, which was of great importance as the boronic acid is a significant cost contributor, accounting for approximately 19 % of the overall active pharmaceutical ingredient (API) cost. As highlighted in Figure 2, the process was extremely laborious with a large number of unit operations that resulted in a long average batch cycle time of approximately 9.25 days. There were also significant challenges with determining the end point of the hydrolysis step as appropriate conditions to quench the reaction during sample preparation for IPC analysis could not be identified, due to the reversible nature of the boronate hydrolysis. This resulted in a number of batches being stopped before the desired end-point had been reached. Finally, conversion was highly variable on scale, taking 2 to greater than 12 hrs, and in some cases it stalled and needed additional B_2Pin_2 and catalyst to reach full conversion.

This paper describes the subsequent studies conducted toward developing and scaling up into the pilot plant an alternative more atom economical, higher yielding and robust process utilizing tetrahydroxydiboron (BBA). BBA has only recently been reported by Molander et al. in the direct metal-catalyzed synthesis of arylboronic acids and there is only one report of its use in the large scale manufacture of boronic acids.[9-14] This method utilized Buchwald's second generation XPhos Pd-G2 catalyst that lead to a more rapid in situ formation of the requisite Pd(0) species.

EXPERIMENTAL SECTION

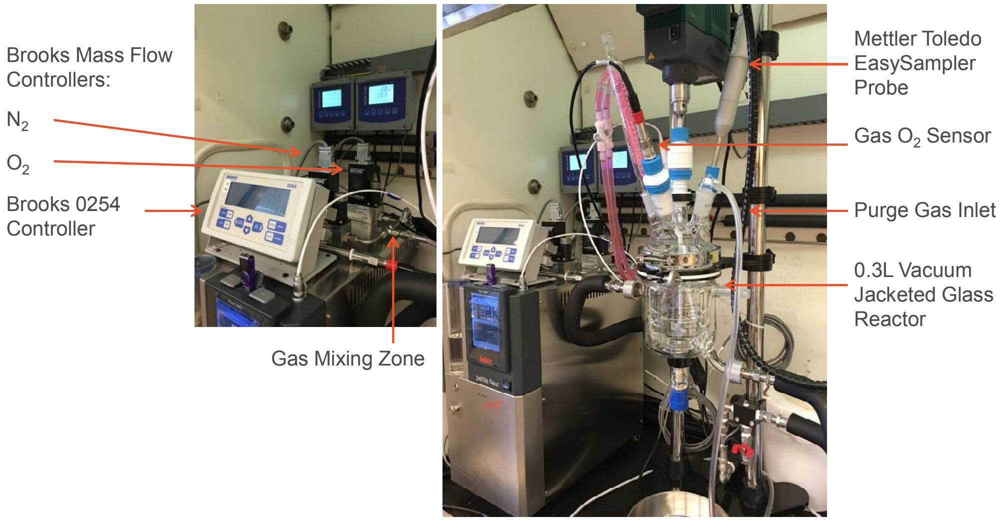
General high throughput screening experimental procedure. All reactions were performed using 0.75 mmol (160 mg) of aryl bromide **1**. All solid reagents were placed in 24 x 150 mm Radley glass reaction tubes. The tubes were placed in the Radley Carousel Reaction Station equipped with a cooling reservoir and lid, and were evacuated under vacuum and purged with nitrogen for a total of 5 cycles. Solvent (25 vol.) and liquid reagents were then added using syringes, and the resulting mixtures were heated to 90 °C for a total of 16 hours. For all reactions, 3 eq. of base and corresponding borylating reagent were used. The reaction mixtures were then analyzed by HPLC.

General experimental procedure. All reactions were performed in a 3-neck 100 mL cylindrical jacketed reactor equipped with an overhead stirrer, temperature probe and condenser. Aryl bromide **1** (5.0 g, 23.4 mmol, 1 eq.), BBA (1.0-6.0 eq.), KOAc (2.5-3.0 eq.) and Pd-168 (0.01-0.25 mol %) were charged to the reactor that was then subjected to three vacuum/ N_2 purge cycles. MeOH (50.0 mL, 10 vol.), followed by ethylene glycol (3.0 vol.) if applicable, was charged and agitation was initiated at 200 rpm. Three additional vacuum/ N_2 purge cycles were conducted and the reaction mixture was heated to the desired temperature over 0.5-3 hrs. When the reaction was complete, as determined by HPLC analysis, water (50 mL, 10 vol.) was charged over 1 hr and the resulting slurry aged for 2-16 hrs. The slurry was filtered under vacuum and the wet-cake washed with MeOH:Water/ 1:1 (25 mL, 5 vol.) and water (25 mL, 5 vol.) before being dried under vacuum at 50 °C to afford boronic acid **2** as an off-white solid.

Oxygen sensitivity studies. All reactions were performed in a 0.3 L vacuum jacketed dish bottom reactor equipped with an overhead stirrer, temperature probe, Mettler-Toledo Ingold Inpro 6850iG gas oxygen sensor (part number: 52 206 435), Mettler-Toledo Ingold Inpro 6850i dissolved oxygen sensor (DO, part number: 52 206 121) and Mettler Toledo Easysampler 1210 (part number: 30083901). The oxygen composition in the reactor headspace was controlled with a Brooks 0254 controller (part number: 0254AB1B15A) that controlled two Brooks SLA5850 thermal mass flow controllers calibrated for each N_2 and O_2 (part number: SLA5850S1BAB1C2A1, Figure 3).

The O_2 headspace composition of the reactor was set to the desired level and a slight positive pressure was maintained in the reactor (by setting the total gas flow rate to 100 mL/min), which was typically higher when the reagents were charged than during the course of the reaction (total gas flow rate was typically 30 mL/min during the course of the reaction) to minimize the introduction of air into the reactor headspace. Aryl bromide **1** (20.0 g, 93.9 mmol, 1 eq.) and KOAc (23.0 g, 234.8 mmol, 2.5 eq.) were charged to the reactor followed by MeOH (150 mL, 7.5 vol.) and ethylene glycol as applicable (60 mL, 3.0 vol.), and the reaction mixture agitated at the desired agitation speed for 30 min to allow for the liquid and headspace O_2 concentrations to equilibrate. A mixture of BBA (10.5 g, 117.3 mmol, 1.25 eq.) and Pd-168 (24 mg, 0.0470 mmol, 0.05 mol%) was charged, and the reaction temperature was quickly adjusted to 35 °C taking advantage of the reaction exotherm to reach the set-point. Sampling was initiated using the Easysampler (a total of 24 samples were taken) and the reaction mixture aged for a total of 24 hrs, after which time it was discarded.

Figure 3. Experimental set-up for conducting the oxygen sensitivity studies



Pilot plant experimental procedure. Scale-up was performed in a 2800 L GLMS Pfaudler jacketed reactor equipped with temperature and pressure probes, a Mettler-Toledo Ingold Inpro 6850iG gas oxygen sensor and a Mettler-Toledo Ingold Inpro 6850i dissolved oxygen sensor. Each oxygen sensor was connected to an M400 Type 2 single-channel multiparameter transmitter and the data was recorded using a Yokogawa datalogger. The oxygen composition in the reactor headspace was modified and controlled using two 40-400 mL/min flow meters manufactured by PLATON (part number: PGU #24SS/Vit) one for each N_2 and compressed air. The reactor was charged with aryl bromide **1** (65 kg, 305 mol, 1 eq.), KOAc (74.6 kg, 760 mol, 2.5 eq.) and MeOH (475 L, 7.5 vol.) followed by ethylene glycol (51.3 L, 3 eq). During the charge of these materials, a positive N_2 pressure was maintained by flowing N_2 at 10L/min to minimize the introduction of air into the reactor headspace. At the end of the charge, stirring was initiated at 54 rpm and the mixture was cooled to 5 °C. A cycle of five vacuum/ N_2 purge cycles was then performed and the oxygen content was confirmed to be 0.18 ppm in solution and 0.4 % in the headspace.

The agitator was stopped and a mixture of BBA (34.1 kg, 380.4 mol, 1.25 eq.) and Pd-168 (78 g, 152 mmol, 0.05 mol %) was charged. Five additional vacuum/ N_2 purge cycles were conducted, the stirring was re-initiated at 54 rpm, and the reaction temperature was adjusted to 35 °C.

The mixture was aged at this temperature for 12 hrs after which time IPC analysis indicated that it had reached full conversion (100.0 %). Water (650 kg, 10 vols) was charged over 1 hr and the mixture was cooled to 20±5 °C over 1 hr, stirred at this temperature for 1 hr and sampled for the determination of the crystallization end-point. In process analysis showed that the concentration of the product in the mother liquors was below the specification of NMT 3.0 mg/mL (2.5 mg/mL), and therefore the product was filtered. The wet-cake was washed with a 1:1 mixture of MeOH:water (97.5 kg, 3.0 vol.) and then three times with water (97.5 kg, 3 x 3.0 vol.) and finally dried under vacuum at 45 °C to afford 50.7 kg of boronic acid **2** (91.1%) as an off white solid with an HPLC purity of 98.8 % containing 1.4 % of compound **3** and 0.4 % of compound **4**.

^{11}B NMR analysis. 200 mg of BBA was placed in a 25 mL round bottom flask and the headspace was displaced with nitrogen (if applicable) via a sequence of vacuum/ N_2 pressure cycles. In a separate 25 mL round bottom flask, KOAc, Pd-168 and/ or ethylene glycol were added, as applicable followed by 9 mL of MeOD. The mixture was then purged with nitrogen or air for 1 hour before being transferred to the flask containing the BBA. The resulting mixture was agitated at ambient temperature until fully dissolved and a sample transferred to an appropriate quartz NMR tube for ^{11}B NMR analysis using a Bruker 400 MHz instrument and a relaxation time of 1.0 sec. The extent of degradation was calculated according to equation 1.

$$\%\,\text{degradation} = \left[\left(\frac{1}{\int BBA \times 2 + \int B(OH)_3}\right) \times 2 \times \int B(OH)_3\right] \times 100 \qquad (1)$$

HPLC Method. The HPLC method used for IPC analysis as well as for analyzing the purity of boronic acid **2** employed a Symmetry Shield RP1 Column, 100 Å, 3.3 µm, 4.6 x 150 mm maintained at 25 °C. A 20 mM NH_4OAc Buffer/ CH_3CN, 90/10 (v/v) solution was used as Mobile Phase A and a 20 mM NH_4OAc Buffer/ CH_3CN, 10/90 (v/v) solution as Mobile Phase B. The total flow rate was set to 1.0 mL/min, the injection volume was 5.0 µL and the detection was carried out at 285 nm. The total method analysis time was 20 min. A gradient was used starting at 100 % of Mobile Phase A, moving to 69 % after 5 min, 50 % after 7 min and ending at 38 % at 10 min. The latter composition was maintained for 2 min after which time the eluent was switched to 100 % Mobile Phase B for 4 min. Finally, the column was re-equilibrated at 100 % Mobile Phase A for a total of 4 min.

The sample preparation procedure was as follows: 1) for IPC analysis, 25 µL of the reaction mixture was diluted with MeOH:H_2O/ 70:30 in a 2 mL volumetric flask; 2) for purity analysis, 25 mg of boronic acid **2** was dissolved in a 50 mL volumetric flask using MeOH:H_2O/ 70:30.

Compounds **2**, **3** and **1** eluted at a relative retention time (RRT) of 1.40, 1.86 and 1.98 min respectively.

RESULTS AND DISCUSSION

High throughput screen. Pinacolborane (HBPin), neopentylglycolborane (HBNpt), bisboronic acid (BBA) and tetrakis(dimethylamino)diboron ($B_2(NMe_2)_4$) were screened using Pd-100 ($Pd(PPh_3)_2Cl_2$), Pd-106 ($PdCl_2(dppf)\cdot CH_2Cl_2$) and the second generation SPhos palladacycle.[9, 15-19] Three solvents were screened at 25 vol. (2-BuOH, toluene and 1,4-dioxane) using 2 mol % of the catalyst, 3 eq. of KOAc and 3 eq. of the borylating reagent at 90 °C. HBPin and HBNpt did not lead to any significant conversions and mostly de-bromination was observed with HBPin while the aryl bromide **1** was recovered with HBNpt. $B_2(NMe_2)_4$ resulted in poor conversions (<40 %) and high levels of **3**. All reactions using BBA in 2-BuOH went to completion (>99 % conversion), however with relatively high levels (5-15 %) of both de-bromination and homo-coupling.

BBA was selected and a high throughput catalyst screen was conducted using a 2 mol % loading investigating both preformed and in situ generated catalysts (using a $Pd(OAc)_2/L$ ratio of 1:2). The catalyst loading for the hits out of this screen was then progressively lowered to 0.5 mol %. Pd-127 ($PdCl_2$(dcypf), Pd-116 ($Pd[P(tBu)_3]_2$) and Pd-168[20] emerged as the front runners from this screen affording >99 % conversion with ~5 % of **3**. Pd-127 afforded significantly higher levels of **4** than either Pd-116 or Pd-168 (7 % *vs.* 3 %).

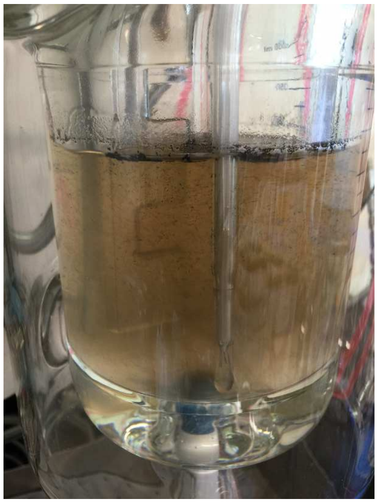
The catalyst loading was further reduced to 0.25 mol %, and the 3 hits were subjected to a solvent screen investigating 1-BuOH, EtOH and MeOH. The levels of both compounds **3** and **4** were reduced to 1-3 % for Pd-118 and Pd-168 in MeOH, while high levels (9.1 %) of compound **3** were observed for Pd-127.

Further reduction of the catalyst loading to 0.1 mol % and 0.05 mol % demonstrated that Pd-168 was the more active catalyst and was subsequently selected for further process optimization. At 0.05 mol % a 96 % conversion was observed for Pd-168, with 4.1 % of **3** and 2.4 % of **4**, compared to only 45 % conversion for Pd-118.

Evaluation of the screening hit. The conditions identified from the screen were successfully scaled up to 5 g (Table 1, Entry 8) using 0.25 mol % of the Pd-168 catalyst. However, a large excess of BBA was used (2.0 eq.) which is a major cost contributor ($750/ kg) for the boronic acid (Figure 11). Reduction of the amount of this reagent resulted, as expected, to larger levels of homo-coupling (**4**; Table 1, Entries 7-9 & 4), which was found to be an impurity that was difficult to purge during the isolation of the product and in downstream processing, and therefore needed to be controlled to no-more-than (NMT) 3.0 %. Furthermore, the amount of compound **3** formed as a result of de-bromination increased from 4.3 % to 8.4 %, as the BBA stoichiometry increased from 2 to 6 eq. Using only 1.0 eq., resulted in a 50.7 % conversion and therefore, 2.0 eq. offered the optimal compromise between cost, conversion and reaction impurity profile. Under these conditions the reaction tolerated up to 2.5 vol % water, reaching complete conversion within 4 hrs affording 4.7 % and 3.5 % of compounds **3** and **4** respectively.

Figure 4. Reaction mixture at the end of the reaction: A) at 65 °C, B) at 35 °C, 1.0 eq. **1**, 3.0 eq. KOAc, 0.25 mol % Pd-168, 2.0 eq. BBA, 10 vol. MeOH, 4 hrs

A)



B)

Significant base and Pd catalyzed proto-deboronation of **2** was observed at 65 °C, which could account for the varying levels of **3** observed. However, under the reaction conditions at 25 °C, boronic acid **2** was found to be stable for >22 hrs, suggesting that elevated temperatures should be avoided for this reaction. It was also observed that at 65 °C a large amount of black particulates were formed that were very difficult to clean from the reactor walls, requiring extensive mechanical scrubbing (Figure 4a). This material was thought to be a result of the polymerization of BBA and not the precipitation of a Pd species, as it was not soluble in nitric acid and its quantity appeared to be related to the amount of BBA used.[21] It was then postulated that lower temperatures may reduce the amount of the polymerization and hence black particulates. Gratifyingly, complete conversions were achieved within 16 hrs at temperatures as low as 35 °C (Table 1, Entries 1-3 & 5-6), and at these lower temperatures the levels of impurities **3** and **4** were further reduced. Indeed the postulated polymerization was significantly reduced, but not completely suppressed, as demonstrated by the presence of fewer black particulates (Figure 4b). At 25 °C, the reaction rate was greatly reduced and 94% conversion was obtained after 42 hrs, so that 35 °C appeared to be the lowest practical reaction temperature (Table 1, entry 5).

Table 1. Effect of temperature and amount of BBA on the conversion and reaction impurity profile -1.0 eq. **1**, 3.0 eq. KOAc, 0.25 mol % Pd-168, BBA, 10 vol. MeOH

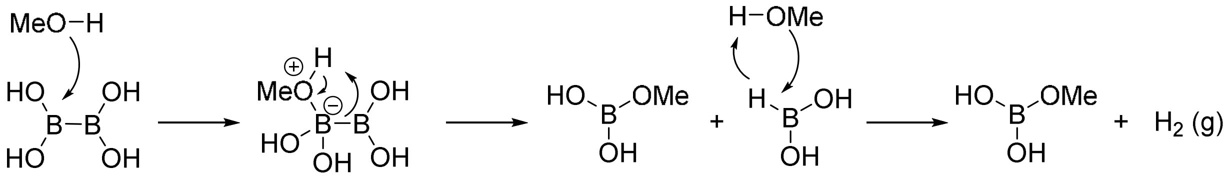
Entry	BBA eq.	Time/ hrs	T/ °C	*LCAP*[1]			
				2	**3**	**4**	**1**
1	1.0	4	35	49.1	1.3	1.6	47.7
2	1.5	16	35	94.0	2.4	2.5	0.3
3	1.5	16	45	91.9	3.6	3.3	ND
4	1.5	16	65	85.3	6.1	6.9	1.4
5	2.0	42	25	90.1	2.5	0.8	5.3
6	2.0	4	35	94.0	3.6	1.3	0.3
7	2.0	4	65	92.8	4.3	2.5	ND
8	3.0	4	65	93.3	5.8	0.7	ND
9	6.0	4	65	90.5	8.4	0.6	ND

1. LCAP = Liquid Chromatography Area Percent

In the absence of a suitable in-process analytical method for monitoring BBA during the reaction, a series of experiments were conducted using a stoichiometric amount of the reagent. This allowed for better discrimination of the key process parameters as well as understanding of its stability. BBA has been shown by Molander et al. using ^{11}B NMR to decompose almost instantaneously in the presence of various Pd(II) species to boric acid.[9] The kinetics of this degradation were greatly reduced by pre-forming the Pd(0) catalyst and using an excess amount of ligand to ensure its efficient formation. Therefore it was postulated that the degradation was a result of the Pd catalyst and that a semi batch process could improve conversions at lower BBA stoichiometries. Accordingly 1.0 eq. of BBA was dissolved in 4 vol. of MeOH that was then added to a solution of **1**, KOAc and catalyst in 6 vol. of MeOH. This reaction only went to

35.7 % conversion vs. 50.7 % in the case where MeOH was added to the solid reagents. Moreover, when the BBA solution in MeOH was aged for 16 hrs prior to being added to the remainder of the reagents, the conversion dropped to 27.4 %, highlighting its instability in the reaction solvent. Alternative non-protic solvents were also considered and after an extensive solubility screen, BBA was found to be only appreciably soluble in DMAc. The borylation was unsuccessful in pure DMAc but found to proceed to 53.6 % conversion when a solution in 4 vol. of DMAc was added to 10 vol. of MeOH. However, when the DMAc solution was added over 6 hrs, only a 33.2 % conversion was observed offering no advantage over using a pure MeOH solvent system.

Figure 5. Tentative BBA decomposition pathway



Stability of BBA. Accelerating Rate Calorimetry (ARC) was performed on BBA in the solid state in order to determine its thermal stability. The results indicated a catastrophic decomposition reaction at 85 °C possibly as a result of rapid polymerization.[21] The time to maximum rate under adiabatic conditions (TMR_{ad}), which is a measure of the probability of occurrence of a decomposition reaction, was calculated to be 165 hr at 35 °C and only 5 hr at 65 °C further supporting the need for a lower reaction temperature. It was noted that upon addition of BBA to MeOH effervescence was observed, presumably as a result of the evolution of hydrogen gas which raised into question its stability in the solvent used (Figure 5). Boronic acids are well known to be unstable even at room temperature, to transesterify with alcohols and readily form dimeric and cyclic trimeric anhydrides, making their in process monitoring particularly challenging.[22] Extensive NMR studies were performed in an attempt to better understand its stability (Figure 6 and Table 2). It was found that BBA significantly degraded to boric acid after prolonged aging at room temperature under all conditions explored. In general oxygen, water and Pd-168 significantly accelerated its hydrolysis, while KOAc appeared to have no impact. In the presence of Pd-168, 63 % of BBA had degraded by the time the first NMR sample was taken and it was fully hydrolyzed within just 4 hours (Entry 5, Table 2). The addition of ethylene glycol has been shown to result in the in situ formation of a much more stable boronate ester that can significantly accelerate reaction rates and allow for the amount of BBA and catalyst used to be reduced.[12] Indeed this greatly increased its stability so that in the presence of water after 20 hours 13.8 % of BBA was hydrolyzed compared to 47.4 % in the absence of ethylene glycol (Entries 4 & 3, Table 2). Similar trends were observed for air and Pd-168. Therefore it was suspected that BBA was hydroscopic and that it was the residual water that was responsible for its hydrolysis when dissolved in MeOH (e.g. Table 2, entry 1). Karl Fischer analysis resulted in 7.1 % water which corresponded to 3.0 % surface water once the water generated from the transesterification occurring in MeOH was accounted for.

Figure 6. ^{11}B NMR of BBA in MeOH under nitrogen after 21 hrs of aging

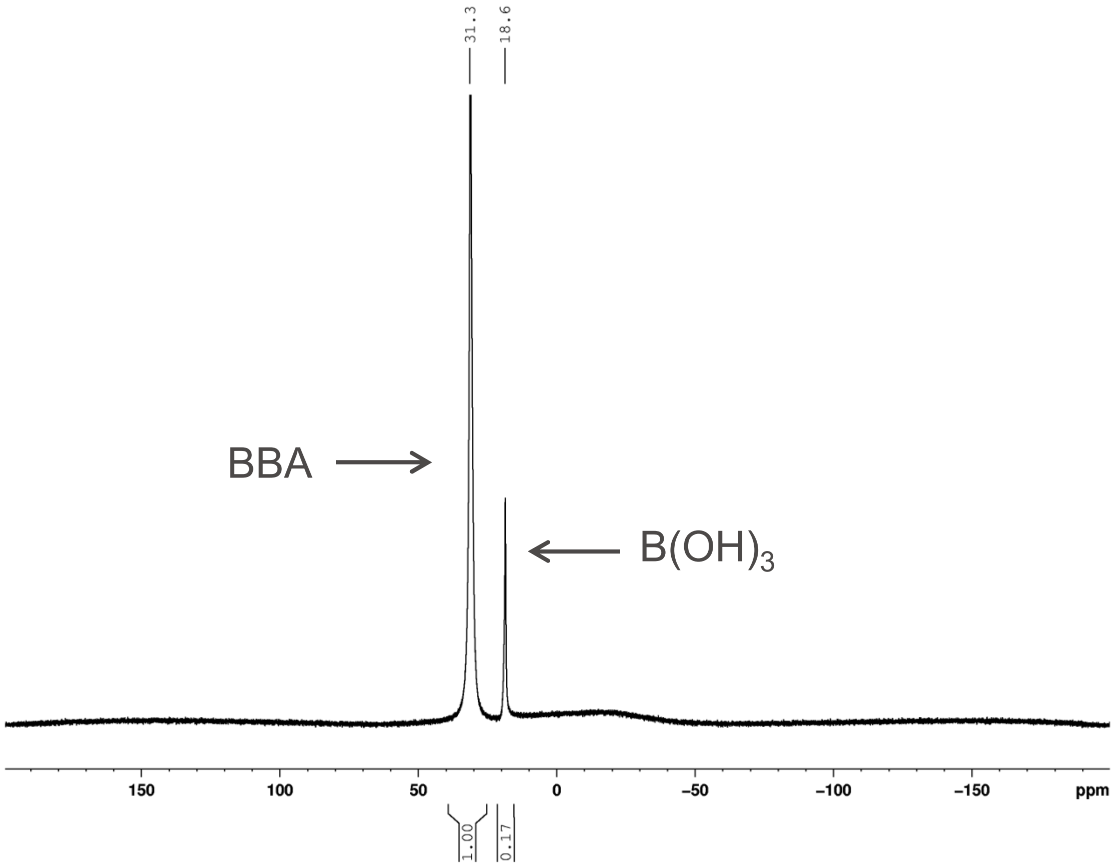


Table 2. Stability studies of BBA using ^{11}B NMR.

Entry	Conditions	Ethylene Glycol	H_2O	KOAc	Pd-168	Time/ hr	Degradation / %
1	Inert	-	-	-	-	0	2.0
						21	19.4
2	Inert	-	-	🟩	-	0	3.8
						20	19.4
3	Inert	-	🟩	-	-	0	7.4
						20	47.4
4	Inert	🟩	🟩	-	-	0	3.8
						20	13.8
5	Inert	-	-	-	🟩	0	63.0
						4	99.3
6	Inert	🟩	-	-	🟩	0	21.9
						4	88.0
7	Air	-	-	-	-	0	54.1

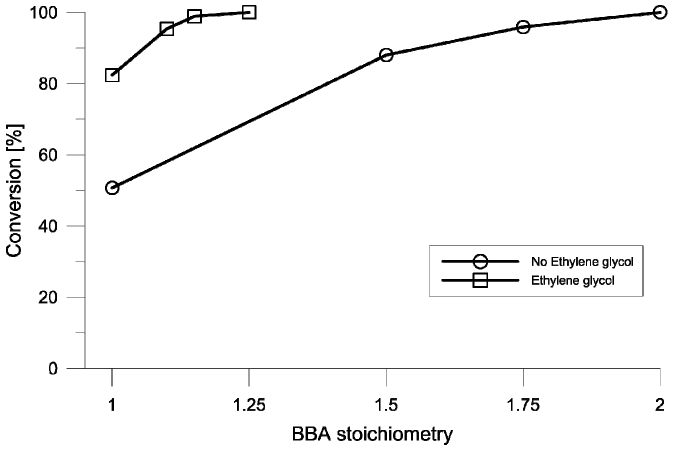
						23	55.4
8	Air	🟩	-	-	-	0	16.7
						20	33.3
9	Air	-	🟩	-	-	0	66.2
						20	68.4
10	Air	🟩	🟩	-	-	0	33.3
						20	43.2

Effect of ethylene glycol. As expected, ethylene glycol was found to have a profound effect on both the reaction rate and amount of BBA and Pd-168 required to achieve complete conversions. Under the reaction conditions, BBA presumably exists as a mixture of species. Once ethylene glycol is added the equilibrium will shift in favor of the more stable bidentate ethylene glycol ester which is anticipated to be less Lewis acidic than the methyl ester or the boronic acid as a result of the favorable overlap of the B-O σ bond with the vacant B p orbital. Indeed, adding just 1 eq. of ethylene glycol with respect to the BBA used, increased the overall conversion from 48.4 % to 85.6 %, while 5 eq. resulted in >99 % conversion after just 6 hrs of reaction.

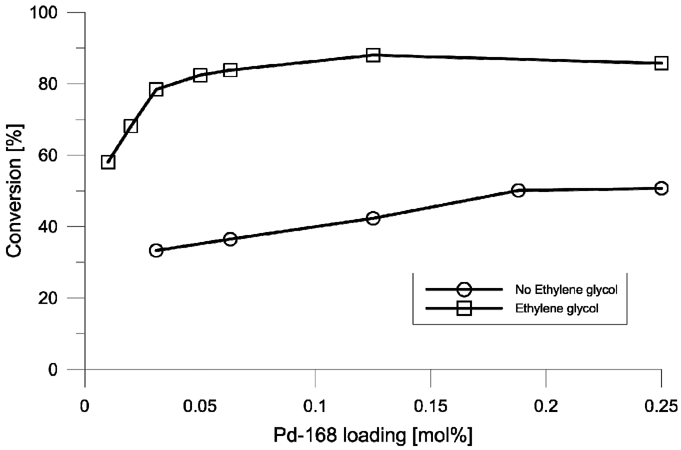
Use of ethylene glycol therefore allowed for the amount of BBA required to achieve the target conversion specification of NLT 99.0 % to be reduced from 2.0 eq. to 1.15 eq., greatly improving the efficiency of the process (Figures 7A & 11). In its absence conversion dropped dramatically when less than 1.75 eq. of BBA were used to afford <95.9 % conversion. If stalled, due to for example poor BBA quality, the reaction was found to be readily recovered by simply adding more BBA. Therefore, 1.25 eq. of BBA was selected to afford a reasonable safety margin from the determined edge of failure. The catalyst loading could also be reduced 5-fold (from 0.25 mol % to 0.05 mol %) with no impact on the observed impurity profile, reaction rate and overall conversion (Figure 7B; 85.7 % vs. 85.0 % respectively), which was otherwise impossible to achieve.

Figure 7. Effect of ethylene glycol on: A) the BBA stoichoimetry -1.0 eq. **1**, 3.0 eq. KOAc, BBA, 15.2 eq. ethylene glycol (if applicable), 0.05 & 0.25 mol % Pd-168, 10 vol. MeOH, 35 °C, 4 hrs, 200 RPM; B) the catalyst loading, -1.0 eq. **1**, 3.0 eq. KOAc, 1.0 equiv. BBA, 15.2 eq. ethylene glycol (if applicable), Pd-168, 10 vol. MeOH, 35 °C, 4 hrs, 200 RPM

A)



B)

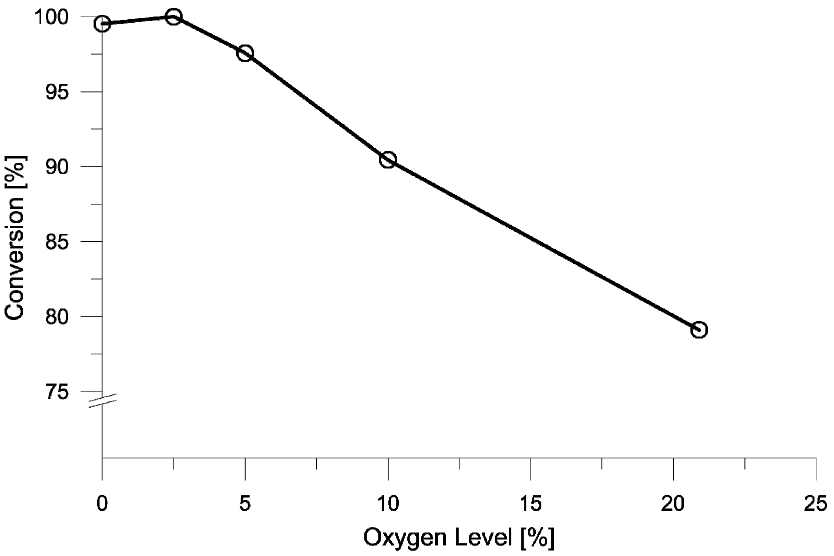


Effect of oxygen. The process in the absence of ethylene glycol, using 2.0 eq. of BBA and 0.25 mol % Pd-168 catalyst was not found to be particularly sensitive to oxygen, tolerating up to 5 % without an appreciable impact on the overall conversion or reaction impurity profile (Figure 8A).

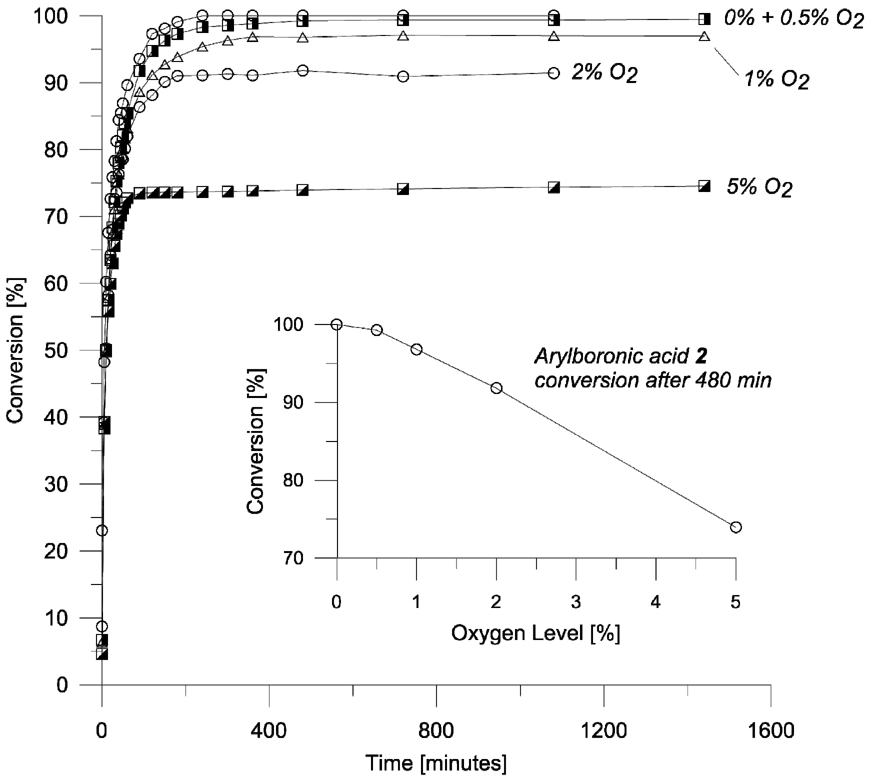
Above 5 %, the conversion dropped significantly and when run under air (20.9 % O_2) the reaction stalled at 63.0 % conversion. On the other hand, when ethylene glycol was used, that allowed for the amount of BBA and catalyst used to be reduced significantly, the process was found to be greatly dependent on the reactor headspace oxygen levels and a significant drop in the overall conversion was observed at levels above 0.5 % (Figure 8B). For example, under an atmosphere of 2.0 % O_2, the conversion dropped to 91.4 %, while under 5.0 % O_2 the reaction stalled at just 74.6 % conversion. Therefore the amount of O_2 in the headspace was determined to be a key process parameter, and a specification of NMT 0.5 % O_2 was set. Interestingly, oxygen did not appear to impact the levels of de-bromination and homo-coupling, which were 1.2-3.0 % and <0.5 % respectively for all conditions investigated.

Figure 8. Effect of oxygen on the arylboronic acid **2**conversion: A) under the optimal process conditions without using ethylene glycol -1.0 eq. **1**, 3.0 eq. KOAc, 2.0 eq. BBA, 0.25 mol % Pd-168, 10 vol. MeOH, 35 °C, 4 hrs, 200 RPM; B) under the optimal process conditions using ethylene glycol -1.0 eq. **1**, 2.5 eq. KOAc, 1.25 eq. BBA, 15.2 eq. ethylene glycol, 0.05 mol % Pd-168, 10 vol. MeOH, 35 °C, 4 hrs, 200 RPM

A)

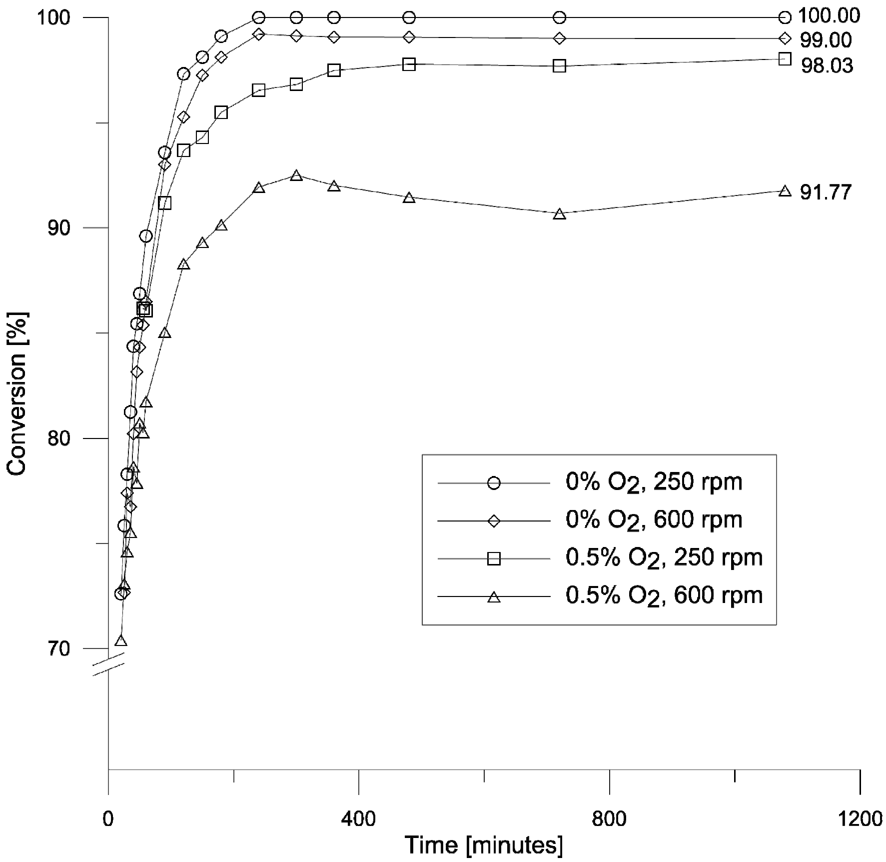


B)



Effect of agitation speed. Surprisingly the reaction agitation speed only had an impact on conversion when the process was run under a headspace containing some amount of O_2. For example when run under an atmosphere of 0.5 % O_2, the overall conversion dropped from 98.0 % to 91.8 % as the agitation speed increased from 250 to 600 RPM (Figure 9). Addition of supplemental BBA alone was sufficient to push the reaction to completion, suggesting that the catalyst was active and that the reaction performance was compromised as a result of the degradation of the BBA. This mixing dependency suggested that the observed degradation was O_2-mediated, as at higher agitation speeds the mass transfer of the O_2 gas to the liquid is higher leading to faster dissolution of the gas into the liquid layer and therefore faster degradation.

Figure 9. Effect of agitation speed on the arylboronic acid **2**conversion at different O_2 headspace levels -1.0 eq. **1**, 2.5 eq. KOAc, 1.25 eq. BBA, 15.2 eq. ethylene glycol, 0.05 mol % Pd-168, 10 vol. MeOH, 35 °C, 4 hrs

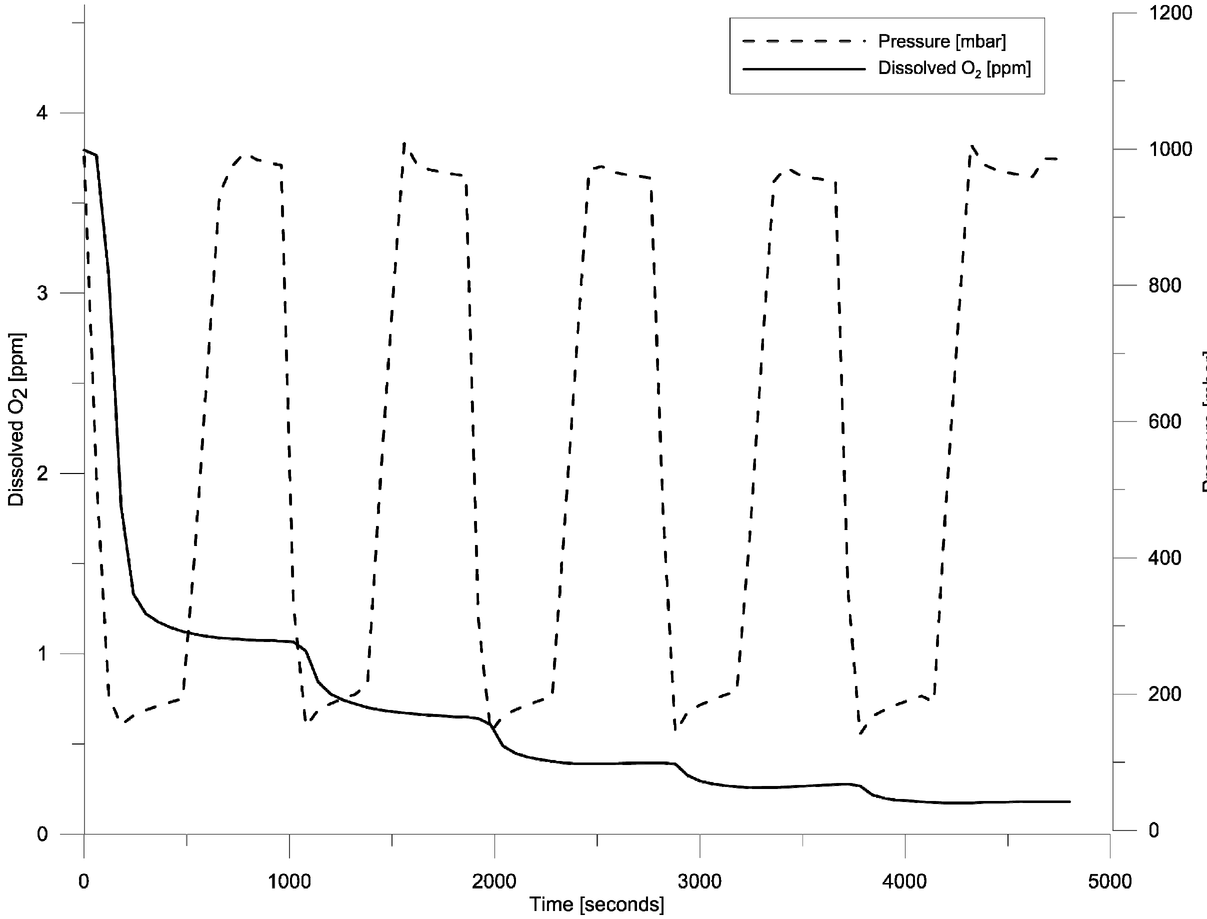


Scale-up. The previously described lab-scale experimentation demonstrated how the dissolved oxygen (DO) level is expected to be a key process parameter upon scale-up. The speed and efficiency with which a target DO level can be obtained is a factor of both the headspace oxygen content, which provides the driving force for gas exchange, and the gas-liquid mass-transfer coefficient (k_La) which determines the rate at which gas is able to move across the gas-liquid phase boundary. The choice of the inertion technique and operating parameters are crucial in obtaining an acceptable DO level.[23] The two most common approaches for the inertion of a reactor at any scale are either a flow-through of inert gas to dilute the headspace or the use of variable-pressure cycles to exchange the headspace. Both are typically performed while the liquid mass is being agitated to maximize the gas-liquid mass-transfer rate. The first, headspace flow-through method, can take many hours on scale as the inert gas flow rates are typically low compared to the large headspace volumes. Variable-pressure cycles are typically quicker and use less nitrogen to achieve a target headspace oxygen concentration, however when vacuum is used there is the risk of losing solvent via evaporation as well as pulling in air through the inevitable leaks that are present in a typical plant reactor. Pressurization with inert gas followed by release to atmosphere avoids pulling air into the reactor but is typically not possible when low-pressure and/or glass components are used as part of the reactor. On the basis of this, agitated variable-pressure vacuum and release cycles were selected as the inertion technique. The vacuum set-point was 200 mbar, to minimize solvent loss (the vapor pressure of methanol at 20 °C is 130 mbar) and the nitrogen gas flow rate was set to 400 L/min in order to vigorously mix the headspace and ensure homogeneity and efficient dilution. To ensure the effectiveness of this proposed inertion sequence an at-scale solvent pilot run was performed. For this the plant reactor was flushed with nitrogen before 1,800 L of methanol was charged. After commencing agitation at the intended set-point of 54 rpm, vacuum was applied and the headspace pressure reduced to 200 mbar i.e. above the boiling point. After a 5 minute hold the reactor was backfilled with nitrogen at a flowrate of 400 L/min and held once more for 5 minutes. This cycle was repeated a further four times and ultimately yielded a dissolved oxygen content of 0.85 ppm and a headspace oxygen level of 0.2 %. This was deemed to be sufficiently below the 0.5 % requirement where at a lab-scale the reaction had been demonstrated to proceed to full conversion without stalling. Further to this, additional inertion runs were performed which allowed the reactor k_La coefficient to be calculated.

Figure 10 shows a typical data set of dissolved oxygen collected across a total of five vacuum and nitrogen release cycles. The behavior of the probe as well as its response time when experiencing variable pressure is not well characterized and must be considered when analyzing the data in order to extract, for example, the $k_L a$. However it can clearly be seen that each successive vacuum-release cycle reduces the dissolved oxygen level, and the extent with which it drops diminishes with each successive cycle as the headspace O_2 level decreases and the driving force is reduced.

It is also worth noting that once BBA is charged to the reaction the dissolved oxygen sensor fails to return a value. This is suggesting that the presence of the boron species either depolarizes the sensor or otherwise interferes with the electrochemical reaction resulting in a failure to produce a reading. Due to this effect the amphoteric probe cannot be used to monitor dissolved oxygen levels over the course of the reaction and is solely used to confirm the inertion of the reaction solvent prior to the reagent addition. The gaseous O_2 sensor installed in the headspace continues to read throughout the reaction and its value is used to provide assurance that the blanket of inert gas remains within the desired specifications throughout the reaction.

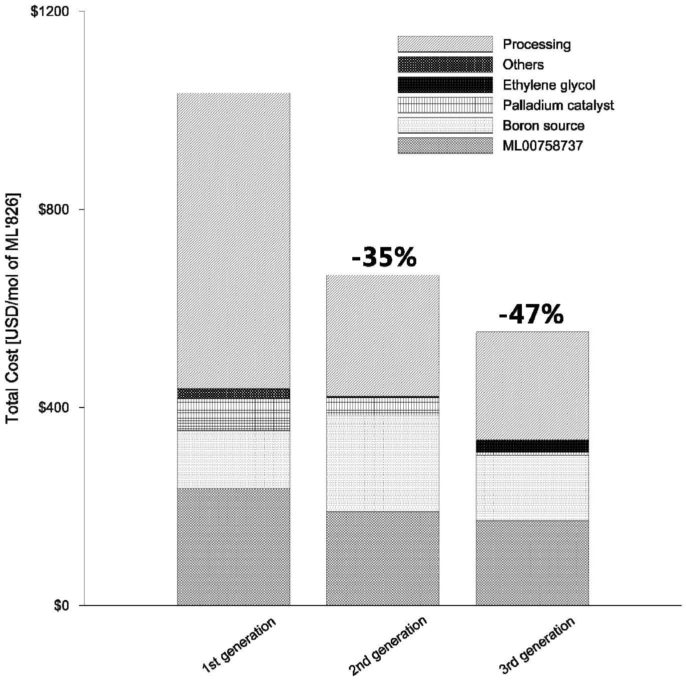
Figure 10. Typical dissolved oxygen data collected across a total of five vacuum and nitrogen release cycles in a 2,800 L reactor charged with 1,800 L of MeOH and agitated at 54 rpm



The validated inertion protocol was successfully applied on pilot scale at 65 kg and achieved, after five cycles a headspace oxygen level of 0.2 % and a dissolved oxygen level of 0.18 ppm. The borylation reaction met all specifications with a >99.9 % conversion to boronic acid **2** and a yield of 91.4 % with an HPLC purity of 98.8 %. The levels of de-brominated and homo-coupled impurities were within the typical ranges at 1.4 % and 0.4 %, respectively.

Cost analysis. The 3rd generation ethylene glycol-BBA process was shown to afford significant cost savings over the previous synthetic routes (Figure 11). The data that showed this reduction was obtained directly from the contract manufacturer and included separate line items for individual raw material costs and total processing costs. While the exact factors and each one's significance in reducing the processing cost are unknown (being proprietary CMO costing information), a number of improvements made to the process are likely large contributors. Beyond the obvious reduction in BBA stoichiometry and Pd loading, the ethylene glycol process was significantly streamlined and reduced the number of unit operations compared to the previous iterations (Figures 2 & 12). The 2-butanol distillation was removed, as was the polish filtration previously needed to remove inorganic residues. The synthesis directly afforded the boronic acid and bypassed the need to hydrolyze it. In making these changes the number of vessels required dropped from 2 to 1 and the overall processing time from 9.25 days to 2.5. The yield also improved from 60 % in the 1st generation B_2Pin_2 process to 80 % in the 2nd generation BBA process and finally to 90 % with the 3rd generation ethylene glycol-BBA process – this achieves an overall increase in efficiency and throughput. When considering solely the processing costs per mole the 2nd generation BBA process achieved a 59 % reduction compared to the 1st generation B_2Pin_2 process while the 3rd generation ethylene glycol-BBA process achieved a 63 % reduction. When the savings in raw material costs are also included, the 2nd generation BBA process was found to offer a total 35 % reduction in cost per mole as compared to the 1st generation B_2Pin_2 process while the 3rd generation process offered a total 47 % cost reduction compared to the 1st generation B_2Pin_2 process.

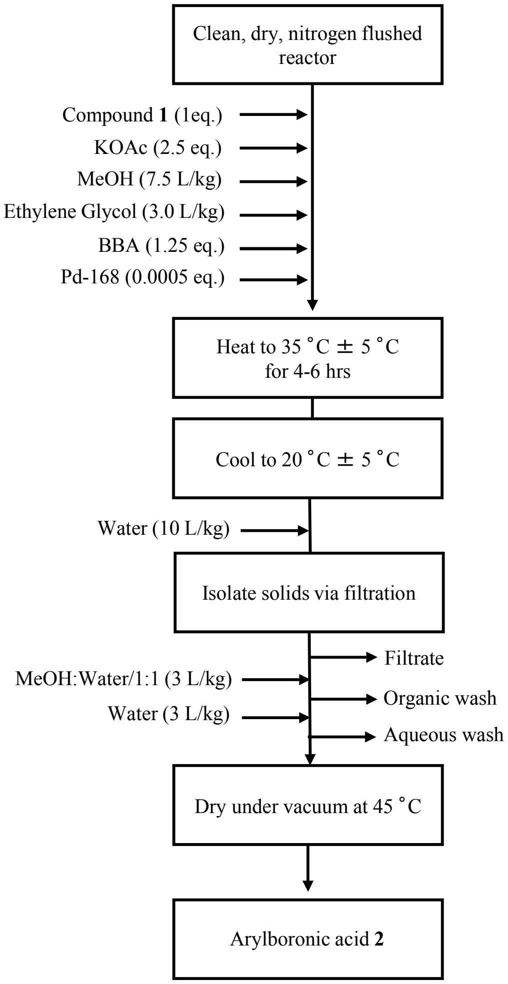
Figure 11. Costs analysis of the three borylation processes: 1st generation, being the original B_2Pin_2; 2nd generation, being the original BBA mediated process; 3rd generation, being the modified with ethylene glycol BBA process



CONCLUSION

A Miyaura borylation process utilizing BBA was developed to afford a key fragment of TAK-117, an API currently being developed by Takeda Pharmaceuticals as an oncolytic agent. The stability of BBA was evaluated under the reaction conditions using a combination of ^{11}B NMR, calorimetry and targeted experiments using a stoichiometric amount of BBA, and found to be greatly improved by the addition of ethylene glycol. Data was presented to suggest an O_2-mediated degradation of BBA that was determined to be the root cause for the observed inconsistent reaction conversions. Methodology was developed for both the study and scale-up of O_2 sensitive processes that enabled the tight control of both the dissolved and headspace O_2 concentrations, allowing for the identification of suitable O_2 specifications. Finally, the revised process was demonstrated to be significantly more efficient than the original process that utilized B_2Pin_2, offering a cost saving of 47 %.

Figure 12. Revised BBA-mediated Miyaura borylation of aryl bromide **1**



AUTHOR INFORMATION

Corresponding Author

*E-mail: charles.papageorgiou@takeda.com

ACKNOWLEDGMENTS

The authors would like to thank Corina Scriban and Andreas Seger from Johnson Matthey Catalysis and Chiral Technologies for their support with the high throughput screening as well as S. Trice and G. Molander for useful discussions.

REFERENCES

(1) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419.

(2) Kotha, A.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633.

(3) Suzuki, A.; Brown, H. C. *Organic Syntheses via Boranes*; Aldrich Chemical Company: Milwakee, 2003; Vol. 3.

(4) Ishiyama, T.; Murata, M.; Miyaura, N.; *J. Org. Chem*. **1995**, *60*, 7508.

(5) Murata, M.; Watanabe, S.; Masuda, Y.; *J. Org. Chem*. **1997**, *62*, 6458.

(6) Tang, W.; Keshipeddy, S.; Zhang, Y.; Wei, X.; Savoie, J.; Patel, N. D.; Yee, N. K.; Senanayake, C. H. *Org. Lett*. **2011**, *13*, 1366.

(7) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(8) Results using flow chemistry have been promising and will be reported in a subsequent publication.

(9) Molander, G. A.; Trice, S. L. J.; Dreher, S. D. *J. Am. Chem. Soc.* **2010**, *132*, 17701.

(10) Molander, G. A.; Trice, S. L. J.; Kennedy, S. M. *J. Org. Chem.* **2012**, *77*, 8678.

(11) Molander, G. A.; Cavalcanti, L. N.; García- García C. *J. Org. Chem.* **2013**, *78*, 6427.

(12) Molander, G. A.; Trice, S. L. J.; Tschaen, B. *Tetrahedron* **2015**, *71*, 5758.

(13) Molander, G. A.; Trice, S. L. J.; Kennedy, S. M. *Org. Lett.* **2012**, *14*, 4814.

(14) Williams, M. J.; Chen, Q.; Codan, L.; Dermenjian, R. K.; Dreher, S.; Gibson, A. W.; He, X.; Jin, Y.; Keen, S. P.; Lee, A. Y.; Lieberman, D. R.; Lin, W.; Liu, G.; McLaughlin, M.; Reibarkh, M.; Scott, J. P.; Strickfuss, S.; Tan, T.; Varsolona, R. J.; Wen, F. *Org. Process Res. Dev.* **2016**, *20*, 1227.

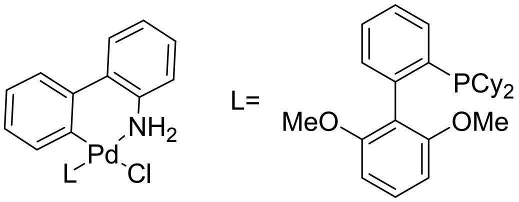
(15) Miyaura, N.; Yamada, K.; Suzuki, A. *Tetrahedron Lett.* **1979**, *20*, 3437.

(16) Billingsley, K. L.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 5589.

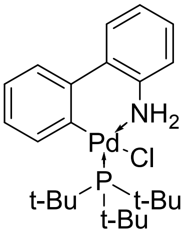
(17) Rosen, B. M.; Huang, C; Percec, V. *Org. Lett.* **2008**, *10*, 2597.

(18) Moldoveanu, C.; Wilson, D. A.; Wilson, C. J.; Leowanawat, P.; Resmerita, A.-M.; Liu, C.; Rosen, B. M.; Percec, V. *J. Org. Chem*. **2010**, *75*, 5438.

(19) The structure of the second generation SPhos palladacycle used is:



(20) The structure of Pd-168 is:



(21) Wartik, T.; Apple, E. F. *J. Am. Chem. Soc.* **1955**, *77*(23), 6400.

(22) Hall, D. G. Boronic Acids, 2nd edition, Wiley-VCH, Chapter 1, 1-134.

(23) Merritt, J. M.; Buser, J. Y.; Campbell, A. N.; Fennell, J. F.; Kallman, N. J.; Koenig, T. M.; Moursy, H.; Pietz, M. A.; Scully, N.; Singh U. K. *Org. Process Res. Dev.* **2014**, *18*, 246.