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Org. Process Res. Dev., **Just Accepted Manuscript** • DOI: 10.1021/acs.oprd.8b00312 • Publication Date (Web): 07 Nov 2018

Process Development of a Suzuki Reaction used in the Manufacture of Lanabecestat

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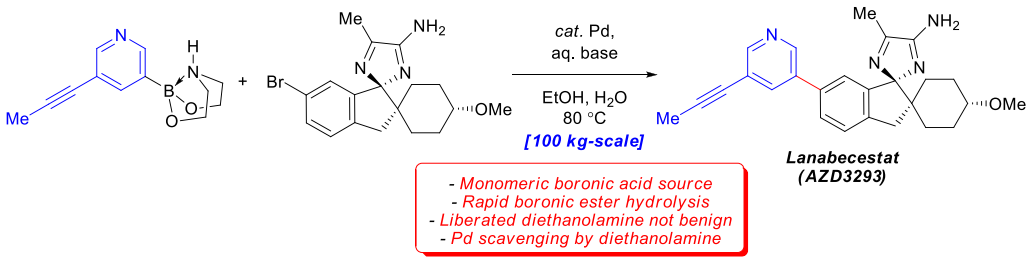


Keywords: Process Development – Suzuki – Kinetics – Scavenger – Manufacture – Lanabecestat.

Abstract

We have developed a scalable Suzuki process for the synthesis of lanabecestat (+)-camsylate, an active pharmaceutical ingredient that was recently investigated in a Phase III clinical program for the treatment of early Alzheimer's Disease. The evolution of this process has culminated with the use of a stable and crystalline diethanolamine boronic ester which rapidly hydrolyses under the reaction conditions. Herein, we report that the liberated diethanolamine plays an important role in the catalytic process, with supporting evidence for an equilibrium between an unbound and bound palladium complex. Additionally, the diethanolamine acts as an internal scavenger during the crystallization of lanabecestat by increasing the solubility of the palladium species, obviating the need for a discrete scavenging step.

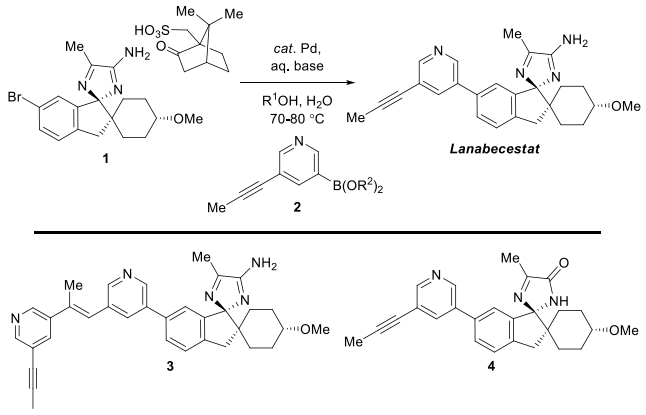
Introduction

Lanabecestat, co-developed by AstraZeneca (AZD3293) and Eli Lilly and Company (LY3314814), is a β-secretase inhibitor and was recently investigated in a Phase III clinical program for the treatment of early Alzheimer's disease (AD). Amyloid precursor proteins (APPs) are found within neurons and cleavage of these large membrane proteins result in elevated amyloid levels within the brain. Amyloid accumulation is thought to play a key role in the progression of AD and can result from changes in production, processing, and/or clearance of brain amyloid-β (Aβ) levels. β-Site amyloid precursor protein cleaving enzyme 1 (BACE-1) is the first step in the processing of APP to Aβ peptides, and its inhibition is an attractive target to stop the production of Aβ.[1]

We recently disclosed the Phase III route to lanabecestat, which involved a late-stage Suzuki coupling to install the pyridine side-chain (Scheme 1).[2] The Suzuki coupling is a common reaction used in the manufacture of pharmaceuticals and is the most common biaryl bond forming reaction.[3-5] The final stage, to generate the active pharmaceutical ingredient (API) (lanabecestat (+)-camsylate) is a salt formation with (+)-camphor sulfonic acid.

Several factors need to be understood when developing a chemical process with precious metals such as palladium. For example, the cost of the catalyst and subsequent loading can have a large impact on the overall cost-of-goods (CoGs) of the API and typically, tight controls of palladium levels in the final drug substance are necessary to ensure patient safety. There are several ways to remove such metals from a chemical process, for instance, *via* solid-supported scavengers, however, these steps can be expensive. Whilst the introduction of a palladium-catalyzed reaction can pose challenges to a control strategy, the late introduction of an expensive fragment, such as pyridine **2** (Scheme 1), is advantageous to cost.

Scheme 1. Suzuki coupling for the final step to Lanabecestat and associated known organic impurities.



The Suzuki process that was originally developed for kilo-scale manufacture in a large-scale laboratory (*Process A*) was not robust enough to deliver routinely on quality or quantity at full scale production. The reaction was performed in *n*-BuOH and the work-up involved numerous and lengthy phase separations with water to remove the potassium camsylate by-product. Furthermore, it involved a solid-supported scavenger step, a challenging solvent swap from *n*-BuOH to *n*-BuOAc, and an uncontrolled crystallization (precipitation) of lanabecestat, all of which were undesirable for scale-up.

Results and Discussion

In 2015, we developed a new Suzuki process (*Process B*) for Phase III clinical supply. High-throughput experimentation (HTE) was used to rapidly optimize the aryl bromide (**1**) and boronic acid (**2a**) charges,[6] the catalytic system (metal and ligand), solvent and base. The optimized process (*Process B*) used a 0.05 mol equivalent excess of boronic acid (relative to aryl bromide **1**), Na_2PdCl_4, 3-(di-*tert*-butylphosphonium)propane sulfonate (DTBPPS) and potassium phosphate, in aqueous ethanol at 70 °C. After removal of palladium on a solid-supported scavenger (PhosphonicS SPM32), lanabecestat was isolated *via* the addition of water as an antisolvent. Between 2015 and 2017, this process was successfully employed at AstraZeneca's Macclesfield pilot plant and delivered over 500 kg of lanabecestat in 15 batches.

A review of the manufacture highlighted several challenges associated with the testing, handling and charging of the boronic acid (**2a**). Development work had shown that undercharging the boronic acid led to an incomplete reaction and an overcharge gave rise to an over-coupled impurity (**3**);[6] both instances afford lanabecestat that does not meet the required specification. Charging was considered a potentially critical process parameter (CPP) since it had a narrow range of ±0.02 mol

equivalents (relative to **1**), and operating outside of this range was detrimental to the quality of the API. In this instance, we considered that the equipment had a control range of ±0.04 mol equivalents and since the boronic acid charge range did not extend beyond the plant control range, the process posed a significant quality risk to future manufactures. Additional learning from the manufacture and subsequent development work highlighted that analysis of the boronic acid was challenging due to difficulties in determining, unambiguously and with accuracy, the relative proportions of acid *vs.* boroxine (**2e**) present.[6] Furthermore, the preceding manufacturing process could not be confirmed as delivering solely either the boronic acid or boroxine species on a consistent basis. In addition to this, the material was a fine, amorphous and difficult-to-handle powder.

To circumvent the analytical and manufacturing challenges with the boronic acid, we investigated boronic esters in the Suzuki reaction, including diethanolamine (**2b**), neopentylglycol (**2c**) and pinacol (**2d**) esters.[6-8] The diethanolamine (DEA) boronic ester (**2b**) was selected as the coupling partner since; 1) the ester hydrolysis was assumed to be rapid (*vide infra*),[9] 2) the boronic ester was a monomeric and crystalline species that could be assayed, and charged, with greater accuracy than the boronic acid, 3) the preceding borylation process could easily be amended to manufacture the boronic ester,[10-12] and 4) the Suzuki reaction quality profile was comparable to that delivered by the boronic acid.

Diethanolamine boronic esters, often referred to as DABO boronates or dioxazaborocanes, are a class of *N*-coordinated cyclic boronic esters. They display tetrahedral geometry about boron and are advantageously air-stable, showing superior stability to the parent boronic acid, and can be used directly in subsequent Suzuki reactions. They are rarely used in synthetic organic chemistry, particularly in the context of process chemistry and manufacturing, and typically have significantly

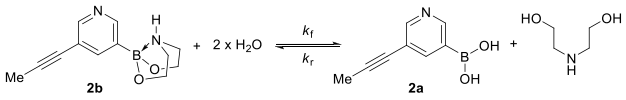
different physical properties from the parent boronic acid, making them easy to prepare without necessitating chromatography.[10-12]

With the newly selected diethanolamine boronic ester, a second round of high-throughput experimentation was initiated, identifying $Pd(AmPhos)_2Cl_2$ and $Pd(dtbpf)Cl_2$ as being superior to the previous catalytic system since both catalysts allowed a lower loading to be used as well as showing improved impurity profiles. Additionally, the pre-formed complexes were considered advantageous compared to the previous *in-situ* formed complex since there was no risk of over- or undercharging the ligand relative to the metal; this can be particularly challenging when charging relatively small quantities at production scale. The $Pd(AmPhos)_2Cl_2$ catalyst was chosen for further development based on its cost, reactivity, availability and safety. Following the high-throughput experiments, development work quickly showed that the catalyst loading could be reduced from 0.4 mol% with Na_2PdCl_4 (*Process B*) to 0.15 mol% with $Pd(AmPhos)_2Cl_2$ (*Process C*) and the charge range for the boronic ester could be widened to ±0.05 mol equivalents with no detrimental impact to quality. The increase in charge range beyond the plant control range meant that the boronic ester charge was no longer considered potentially critical and it reduced the risk of failing specification in future manufactures with respect to residual aryl bromide (**1**) and the over-coupled impurity (**3**).[6]

A drawback to the switch from the boronic acid (**2a**) to the boronic ester (**2b**) was that the rate of reaction was reduced; this was observed with all catalysts that were tested. An important factor in obtaining high yield with acceptable quality in this Suzuki coupling was achieving a fast reaction since a competitive non-palladium-catalyzed hydrolysis of the dihydroimidazole ring leads to an amide impurity (**4**).[6] The amide is an impurity controlled by the specification of drug substance (lanabecestat (+)-camsylate) and its formation in the Suzuki reaction was time and temperature

dependent. Ultimately however, the extent of hydrolysis was reduced to an acceptable level by increasing the reaction temperature to 80 °C (*vs.* 70 °C) and reducing the reaction time. Nevertheless, it was important for robustness reasons that we understood the cause for differences in rates between the boronic acid and ester, and we proposed that this could be due to one or more of the following factors; 1) the boronic ester may be the reactive species and inherently less reactive, 2) the boronic acid may be the reactive species and the boronic ester hydrolysis is slow (Scheme 2), and 3) the expelled diethanolamine may be compromising the catalyst. A series of studies was conducted to explore these potential effects.

Scheme 2. Hydrolysis of the diethanolamine boronic ester **2b** in water.



Hydrolysis of the Boronic Ester (2b) in Aqueous Ethanol. The amount of residual boronic ester (*vs.* boronic acid) is important for the lanabecestat (+)-camsylate control strategy. The boronic acid is Ames positive and is an impurity controlled by the specification of drug substance (lanabecestat (+)-camsylate). The acceptable level of the boronic acid is set at ≤128 ppm and this upper limit is based primarily on its mutagenicity and threshold of toxicological concern (TTC). It was therefore critical to understand how the switch from the boronic acid (**2a**) to the boronic ester (**2b**) impacted the control strategy. Specifically, it was important to determine if the boronic ester was retained or hydrolyzed to the boronic acid, and consequently whether additional controls and tests were required in the API.

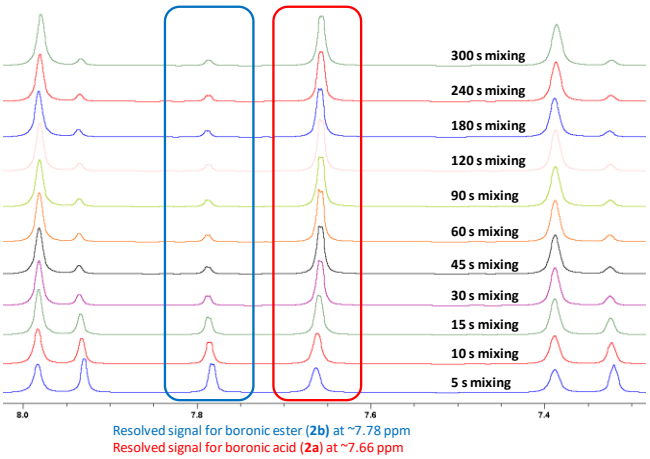


Figure 1: Stacked ^{1}H-NMR spectra between 5-300 seconds reaction time with highlighted regions of interest for **2a** and **2b**.[13] Reactions were run at 27 °C in a tube observing the organic fraction.

The diethanolamine boronic ester (**2b**) was dissolved in ethanol (0.56 M **2b**) and mixed with aqueous K_3PO_4 (1.2 M), which were the standard reaction conditions, and the concentration of each species (acid *vs.* ester) was measured *vs.* time.[14] It was possible to observe the hydrolysis to the boronic acid (**2a**) *via* ^{1}H-NMR analysis (Figure 1). The conversion times and final equilibrium positions were measured in a variety of conditions designed to simulate relevant process conditions.

The results provide evidence that the system tends towards equilibrium, favoring the boronic acid (**2a**), and that equilibrium is achieved in <2 minutes at 27 °C (Figure 2: Red data points). At the process temperature for the Suzuki reaction (80 °C), the rate of approach to equilibrium should be much quicker, meaning that an equilibrium position is reached before the Suzuki reaction starts.[15] In a separate experiment, diethanolamine was charged to a freshly prepared solution of **2b**

ethanol (0.56 M **2b**) in aqueous K_3PO_4 (1.2 M) and it was shown that this leads to an equilibrium that is shifted in favor of the boronic ester (**2b**) (Figure 2: Blue data points), consistent with our expectation (Scheme 2).

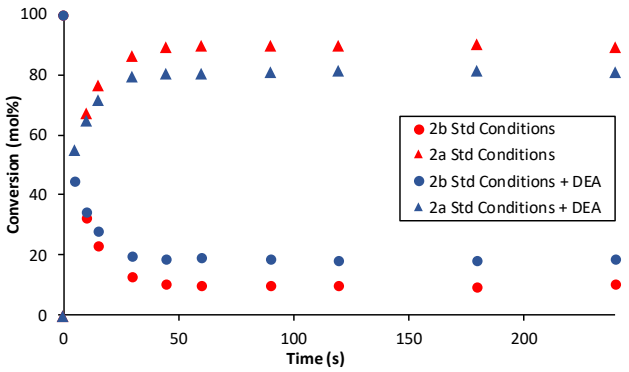


Figure 2: Hydrolysis of the diethanolamine boronic ester *vs.* time in ethanol/aqueous 1.2 M K_3PO_4 (3:2) at 27 °C demonstrating the effect of added DEA upon the final equilibrium position.

No evidence was found in the ^{1}H-NMR data (Figure 1) for the formation of the ring-opened, partially hydrolyzed intermediate. We therefore defined the equilibrium constant K_{EQ} (eq 1) based on a direct conversion of the boronic ester (**2b**) to acid (**2a**) (Scheme 2).

$$K_{EQ} = \frac{[\mathbf{2a}].[DEA]}{[\mathbf{2b}].[H_2O]^2} \quad (1)$$

However, the partially aqueous conditions used in the process mean that the concentration of water can be considered a constant and an apparent equilibrium constant, K_{EQ}' (eq 2) was therefore used.

$$K_{EQ}' = K_{EQ}[H_2O]^2 = \frac{[\mathbf{2a}].[DEA]}{[\mathbf{2b}]} \quad (2)$$

The experimental time course data for the approach to equilibrium were fitted to give a pseudo first order forward reaction rate constant (k_f) and the equilibrium constant K_{EQ}' (eq 2).[16] A good

agreement was generally obtained between the data and the model (Figure 3). Selected values of the best-fit constants and final equilibrium compositions are summarized in Table 1.

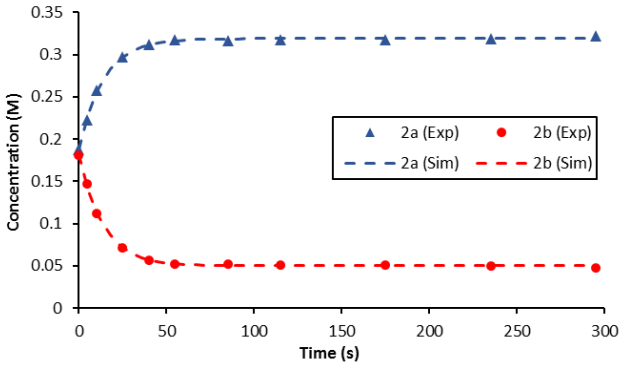


Figure 3: Result of fitting rate constants and equilibrium constants in DynoChem®.[16] Reaction approach to equilibrium with $k_f = 0.0559$ s^{-1} and K_{EQ}' = 2.03 M *vs.* experimental data.

Table 1: Summary of fitted constants and equilibrium compositions under the reaction and isolation conditions at 27 °C.

	Reaction (Experimental)	**Isolation (Predicted)**	**Isolation (Experimental)**
[H_2O] (M)	18.6	38	38
k_f (s^{-1})	0.056 ± 0.002	0.234	-
K_{EQ}' (M)	2.03 ± 0.06	8.47	6.37
[**2a**] (M)	0.034	0.0209	0.0205
[**2b**] (M)	0.016	0.0012	0.0016
% 2b	32	5.5	6.8

By applying eq 2 it was possible to estimate K_{EQ} under the process conditions and then use this value to predict K_{EQ}' and hence the equilibrium position at different water levels.[17] A comparison of the predicted and observed equilibrium positions (K_{EQ}') under the isolation conditions (Table 1) shows tolerable agreement between the predicted and actual results despite the difference between the predicted and observed equilibrium constant. This difference is likely to be due to the changes in the water/ethanol ratio in the solvent leading to changes in the bulk properties of the reaction solvent and thus changing the rate and equilibrium constants.

Assuming that the 0.05 mol equivalent overcharge of the boronic ester used in the reaction remains unreacted, it is possible to calculate how it will be speciated at the end of the Suzuki reaction (18.6 M water in ethanol) and during the isolation (38 M water in ethanol). The tabulated values (Table 1) show that the increased levels of water present in the isolation favors **2a** over **2b**, relative to the reaction conditions.[18]

With the knowledge that under the isolation conditions the boronic ester (**2b**) is predominantly hydrolyzed to the boronic acid (**2a**) (93.2% boronic acid, 6.8% boronic ester), it was concluded that it was not necessary to develop a separate analytical method capable of detecting ppm levels of the boronic ester. Consequently, we did not perform additional testing for residual levels of the boronic ester or amend the specification of lanabecestat (+)-camsylate.

Diethanolamine Effect on Catalytic Cycle. We were interested in investigating the fundamental reasons for the slower Suzuki reaction when the diethanolamine boronic ester was used because of the potential wider implications for analogous esters in other Suzuki reactions.

With the knowledge that the boronic ester hydrolyses in <2 minutes under the Suzuki conditions, the key question that we wanted to address was why is the rate of the Suzuki reaction

slower for the boronic ester than the boronic acid? A by-product from the boronic ester hydrolysis is diethanolamine (Scheme 2) and we questioned whether this could affect the catalysis. Palladium-diethanolamine complexes are known and diethanolamine-based solid-supported scavengers have been developed for metal removal.[19,20] It was therefore conceivable that diethanolamine was inhibiting the catalysis through the potentially reversible formation of a non-productive palladium-diethanolamine complex.

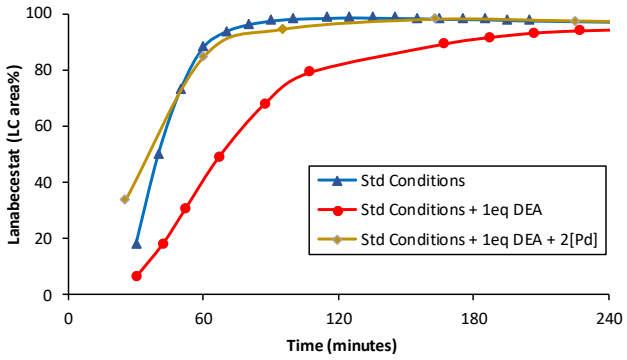


Figure 4: Effect of diethanolamine content on the rate of the Suzuki reaction at 80 °C.

The boronic ester (**2b**) was reacted under *Process* C conditions (at 80 °C) and passed its residual starting material in-process control (IPC) test after 90 minutes (Figure 4: Blue line). Conversely, when diethanolamine (1 equiv.) is charged to the reaction it is slower and requires over 240 minutes to reach its pass criteria (Figure 4: Red line). This result is consistent with deactivation of palladium by the diethanolamine. We speculate that there is an equilibrium between an unbound and active, and a bound and inactive palladium-diethanolamine species which, in the presence of additional diethanolamine, shifts to the bound and inactive form. It was postulated that if an equilibrium existed, charging 1 equiv. of diethanolamine whilst doubling the palladium loading should give a reaction profile similar to the standard conditions. This was indeed the case and the experimental observation was consistent with a palladium-diethanolamine deactivation hypothesis

(Figure 4: Gold line *vs.* Red line). Whilst additional work is required to unambiguously determine if there is an equilibrium, these results are consistent with this hypothesis.

It was important to understand how the control strategy would evolve to adapt to the changes in catalyst and catalyst loading (between *Process B* and *Process C*) prior to implementing them at production scale. For example, when the boronic acid (**2a**) was reacted with 0.4 mol% Na_2PdCl_4 under *Process B* conditions, the amount of palladium in the isolated solid was 204 ppm (Table 2, entry 1). This was not in line with our control strategy (≤200 ppm in the API, lanabecestat (+)-camsylate) since we had already determined that using lanabecestat from *Process B* in the API stage (salt formation with (+)-camphorsulfonic acid) led to no reduction in palladium level in lanabecestat (+)-camsylate. Hence, in *Process B* we implemented a solid-supported scavenger step during the work-up of the Suzuki stage which reduced the palladium level to <40 ppm (entry 2). The development of the new catalytic system for *Process C* ($Pd(AmPhos)_2Cl_2$) enabled the loading to be reduced to 0.15 mol%, which lowered the theoretical maximum palladium level in the isolated solid from 936 to 351 ppm. When the new catalyst was subjected to the same conditions as Na_2PdCl_4, albeit with a different catalyst loading and reaction dilution, the level of palladium in the solid was unexpectedly similar (entry 1 *vs.* 4). *Interestingly, when simply changing the boron species from the boronic acid (**2a**) to the diethanolamine boronic ester (**2b**), there was a 3.5-fold reduction in palladium (from 166 ppm to 48 ppm) in the isolated material (entry 4 vs. 7).*

Table 2: Diethanolamine effect on palladium removal

Entry	**2**	**Pd Loading / Cat.**	**Additive**	**Pd in lanabecestat (ppm)**	
				Theor.[a]	**Actual**

1	**2a**	0.40 mol% Na_2PdCl_4[b]	None	936	204[c]
2	"	"	Solid scavenger[d]	936	40[c]
3	"	"	DEA (1 equiv.)	936	96[c]
4	"	0.15 mol% $Pd(AmPhos)_2Cl_2$	None	351	166
5	"	"	DEA (1 equiv.)	351	143
6	**2b**	0.40 mol% Na_2PdCl_4 [b]	None	936	143
7	"	0.15 mol% $Pd(AmPhos)_2Cl_2$	None	351	48
8	"	"	DEA (1 equiv.)	351	36
9	"	0.75 mol% $Pd(AmPhos)_2Cl_2$	None	1755	405
10	"	1.50 mol% $Pd(AmPhos)_2Cl_2$	None	3150	1255

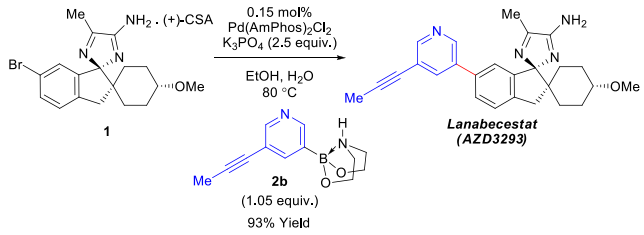
[a] Theoretical maximum palladium in the isolated lanabecestat assuming 100% yield and no purge of palladium. [b] Catalyst was modified with 0.4 mol% DTBPPS. [c] *Process B* was used (14 volumes) in entries 1 and 3. All other entries used *Process C* (9 volumes). [d] PhosphonicS SPM32 (20 wt%) or QuadraSil MP eco (12 wt%) was charged to the batch. The slurry was agitated and filtered before crystallizing lanabecestat.

The reduction in residual palladium level when we changed to the diethanolamine boronic ester may be explained by the formation of a palladium-diethanolamine complex. The diethanolamine-bound complex is likely to have superior solubility in the ethanol/water mixture (isolation conditions) compared to an unbound species. This coordination effect also supports our hypothesis on the rate differences between the boronic acid and ester (*vide supra*); additional control

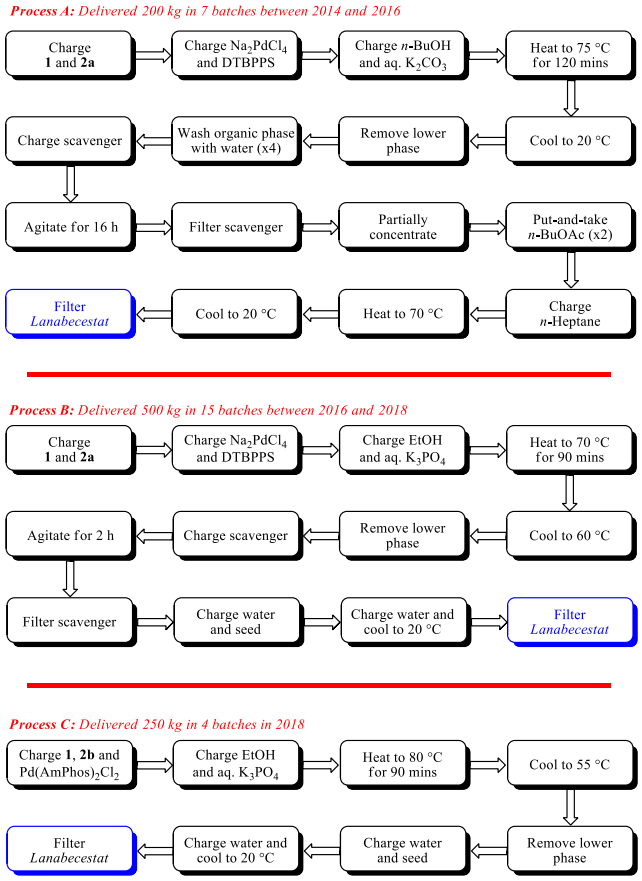
experiments were aimed at addressing this. Entry 3 was a repeat of Entry 1, albeit diethanolamine was charged after the reaction has reached its IPC criteria; the residual palladium was reduced 2-fold. This trend was not apparent across all reactions tested, for example, there was little difference between Entries 4 and 5 which mimicked Entries 1 and 3 albeit with a different catalyst. Additionally, Entry 5 was expected to have a similar palladium level to Entry 7 since the overall balanced equations for each reaction were equal, however, it was 3-fold higher. Nevertheless, the reduction in palladium loading and, more critically, the switch from the boronic acid (**2a**) to the diethanolamine boronic ester (**2b**) led to a reduction in palladium level in lanabecestat and advantageously removed the requirement for a scavenging step in the process.

Schemes 3-5 describe the final optimized conditions and process flow diagrams with associated timelines for the development history of the Suzuki reaction used in the manufacture of lanabecestat.

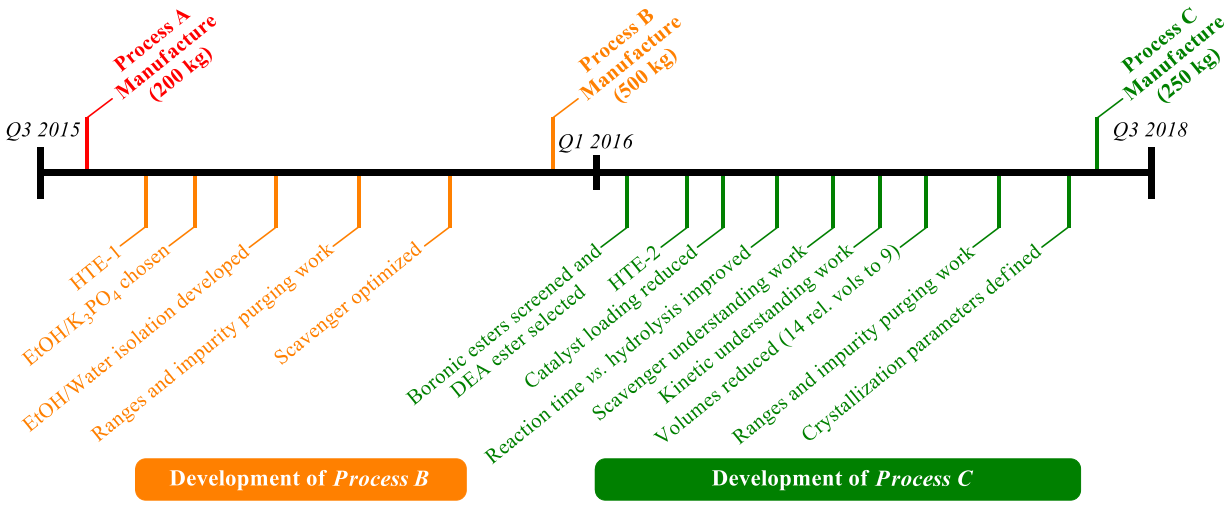
Scheme 3: Optimized *Process C* conditions for the manufacture of lanabecestat.



Scheme 4. Process flow diagrams showing the development history.



Scheme 5. Development timelines for Processes B and C and manufacturing dates for Processes A-C.



Summary

Process development between 2014 and 2018 successfully introduced an easily preparable diethanolamine boronic ester in the Suzuki process which improved accommodation for charging accuracy. High-throughput experimentation enabled rapid data collection across a broad chemical space and quickly identified a new catalyst for the process. In addition, the challenging solvent swaps, phase separations, solid-supported scavenger step and uncontrolled crystallization were all removed from the process. These improvements positively impacted the overall environmental and sustainability factors of the product; process mass intensity was reduced from 85 kg waste/kg lanabecestat in *Process A* to 35 kg waste/kg lanabecestat in *Process C*. Additionally, the changes provided a reduction in cost and time, and an increase in throughput. In 2018, *Process C* (Scheme 4) successfully manufactured 250 kg of lanabecestat in 4 batches.[21] The process was operated at 100 kg scale (based on input of **1**) and the palladium levels in lanabecestat, now without a discrete scavenging step, were an average of 37 ppm (*cf.* Table 2). Conversion of lanabecestat to the drug substance (lanabecestat (+)-camsylate) led to a further reduction in palladium (the average palladium level per batch was 19 ppm) to levels that were 10-fold below that set by the specification of drug substance ($\leq$200 ppm).

Changing from the boronic acid to the diethanolamine boronic ester required additional screening and mechanistic work. This process understanding work facilitated development of a simple and robust process with associated enhancements in the control of organic impurity levels. The liberated diethanolamine impacted both the catalysis and the purging of palladium, and as a result, we were able to remove the expensive and high risk solid-supported scavenging step from the process. The knowledge we obtained allowed for a process that was successfully scaled 200-fold, from 500 g in a laboratory to 100 kg in production and the demonstration at this scale has

highlighted the value of diethanolamine boronic esters. All these factors will likely stimulate further academic and industrial research into diethanolamine boronic esters as viable coupling partners, alternative to boronic acids, in Suzuki reactions.

EXPERIMENTAL

A process description for *Process C* is provided. In 2017, the process was operated on a 500 g scale in an R&D lab (5 L vessel) and in 2018 it was successfully scaled to 100 kg in a pilot plant.

Preparation of lanabecestat. To a 5 L jacketed vessel, equipped with an overhead agitator, temperature probe and condenser, was charged **1** (580.0 g, 924.4 mmol), **2b** (223.5 g, 970.6 mmol), $Pd(AmPhos)_2Cl_2$ (1.00 g, 1.39 mmol) and ethanol (3 mL/g, 1740 mL). The slurry was agitated at 20 °C and the oxygen was purged with a flow of nitrogen. Potassium phosphate tribasic (490.6 g, 2311 mmol) was dissolved in water (2 mL/g, 1160 mL) and the solution was charged to the 5 L vessel. The biphasic mixture was warmed to 80 °C and agitated for 90 minutes. The biphasic solution was cooled to 55 °C and the lower phase (~1 mL/g) was removed. Water (1 mL/g, 580 mL) was charged to supersaturate the solution and lanabecestat seed (0.15 wt%) was added. The thin slurry was held for 30 minutes and water (4 mL/g, 2320 mL) was added at a constant rate over 3 hours. The slurry was cooled to 20 °C over 3 hours, held for 1 hour, filtered and washed (displacement wash) with a mixture of water (1.6 mL/g, 928 mL) and ethanol (0.8 mL/g, 464 mL). The wet cake was dried under reduced pressure at 40 °C to afford lanabecestat (379.0 g) as a monohydrate in 93% yield (assay adjusted), 98.9% HPLC purity (area%) and 94.9% ^{1}H-QNMR assay (99.1% assay on anhydrous basis) as an off-white solid. ^{1}H NMR (400 MHz, d^6-DMSO) δ 8.65 (d, J = 2.3 Hz, 1H), 8.50 (d, J = 1.9 Hz, 1H), 7.88 (dd, J = 2.3, 1.9 Hz, 1H), 7.52 (dd, J = 7.8, 1.7 Hz, 1H), 7.39 (d, J = 7.8 Hz, 1H), 6.82 (d, J = 1.7 Hz, 1H), 6.52 (s, 2H), 3.19 (s, 3H), 3.08 (d,

J = 15.5 Hz, 1H), 2.99 (d, *J* = 15.5 Hz, 1H), 2.99 – 2.90 (m, 1H), 2.17 (s, 3H), 2.08 (s, 3H), 1.87-1.77 (m, 2H), 1.51-1.36 (m, 3H), 1.30-1.11 (m, 2H), 1.02-0.92 (m, 1H). ^{13}C NMR (101 MHz, d^6-DMSO): δ 161.5, 160.5, 149.9, 146.1, 145.0, 143.1, 135.8, 135.5, 134.1, 126.4, 125.9, 120.5, 120.2, 109.0, 90.3, 78.7, 76.5, 54.8, 52.2, 39.7, 30.0, 29.0, 28.5, 28.3, 14.2, 4.0.

Preparation of 2-(5-(prop-1-ynyl)pyridin-3-yl)-1,3,6,2-dioxazaborocane (2b).

To a vessel containing a solution of 3-bromo-5-(prop-1-ynyl)pyridine (697 kg, 8.49 w/w% in toluene, 301.9 mols) was charged tetrahydrofuran (2.5 kg/kg, 147 kg) and triisopropylborate (75.5 kg, 401.4 mols) at 25 °C. The solution was agitated, cooled to −70 °C and n-hexyllithium (108 kg, 33 w/w% in hexanes, 390.8 mols) was added over 3 hours. The reaction was quenched on a 15 °C stirred mixture of isopropyl acetate (2.7 kg/kg, 162 kg) and water (10.6 kg/kg, 633 kg). The bulk mixture was warmed to 25 °C, the layers were separated and the lower aqueous layer was washed twice with isopropyl acetate (2.7 kg/kg, 162 kg). The aqueous phase was charged to a clean vessel and 2-methyl tetrahydrofuran (8.6 kg/kg, 513 kg) was added followed by 13% sulfuric acid (2 kg/kg, 126 kg). The layers were separated and the organic layer was washed with water (4 kg/kg, 240 kg). The organic solution was distilled to 6.5 kg/kg (390 kg) at 100 mbar/40 °C, and azeotropically dried *via* continuous distillation with 2-methyl tetrahydrofuran (15.4 kg/kg, 924 kg). A solution of diethanolamine (13.5 kg, 128.4 mols) in isopropanol (0.1 kg/kg, 6.4 kg) was added to the 2-methyl tetrahydrofuran solution at 25 °C and after 15 minutes **2b** seed (0.15 wt%) was added. A solution of diethanolamine (13.5 kg, 128.4 mols) in isopropanol (0.1 kg/kg, 6.4 kg) was then added over 30 minutes and the slurry was held for 30 minutes. The slurry was cooled to 5 °C over 30 minutes, held for 1 hour and filtered. The filter cake was washed with methyl tert-butyl ether (1.5 kg/kg, 90 kg) and a mixture of methyl tert-butyl ether/acetonitrile (1:1 v/v, 1.5

kg/kg, 90 kg). The wet cake was dried under reduced pressure at 50 °C to afford **2b** (51.15 kg) in 71% yield (assay adjusted), 100% HPLC purity (area%) and 96.2% HPLC assay as an off-white solid. ^{1}H NMR (400 MHz, d^{6}-DMSO) δ 8.46 (d, *J* = 1.6 Hz, 1H), 8.36 (d, *J* = 2.3 Hz, 1H), 7.70 - 7.68 (m, 1H), 7.08 - 7.00 (m, 1H), 3.91 - 3.83 (m, 2H), 3.82 - 3.75 (m, 2H), 3.11 (tdd, *J* = 7.0, 9.2, 11.7 Hz, 2H), 2.91 - 2.84 (m, 2H), 2.04 (s, 3H). ^{13}C NMR (101 MHz, d^{6}-DMSO) δ 152.28, 149.50, 142.51, 118.88, 88.40, 77.67, 63.11, 50.64, 3.87.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website.

Process descriptions and kinetic data (PDF).

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Notes. The authors declare no competing financial interest.

Author Contributions

The manuscript was written by Phillip A. Inglesby. All authors have given approval to the final version of the manuscript.

Funding Sources. None

Notes. None

Any additional relevant notes should be placed here.

ACKNOWLEDGMENT

None

ABBREVIATIONS

None

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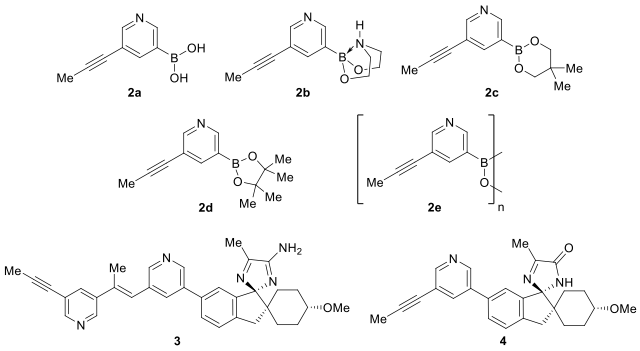

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10. The diethanolamine boronic ester (**2b**) crystallized upon charging a solution of diethanolamine in iso-propanol to a solution of the boronic acid/boroxine (generated *in-situ via* a Li-Br exchange borylation sequence) in Me-THF. The boronic ester (**2b**) was isolated as a monomeric, crystalline and stable solid. In 2018, 200 kg of **2b** was manufactured in 4 batches using this process. See Experimental section for further details.

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13. Although we could not unambiguously identify whether the protons of interest were at the 2- or 6-position of **2a** and **2b**, the chemical shifts suggest that we were observing the proton at the 2-position.

14. The reaction mixture was prepared by dissolving **2b** in ethanol (0.56 M) and mixing it with an aqueous solution of K_3PO_4 (1.2 M). This results in a biphasic mixture with much of the water from the K_3PO_4 solution absorbed into the ethanol fraction. It is assumed, based on the high ionic strength of the aqueous fraction, that all organic species are retained in the organic

fraction and that the volume increase of the organic fraction is due entirely to the addition of water. This volume increase is used to calculate the molarity of the water in ethanol.

15. The Suzuki reaction does not start until the batch temperature is >70 °C and typical heat-up rates in production are 0.5 °C/minute. Therefore, the boronic ester will have achieved equilibrium much before the Suzuki reaction starts.

16. Dynochem® 2011, V.4.0.0.0, www.scale-up.com. Details of the model used may be found in the Supporting Information.

17. An algebraic solution to the equilibrium problem was used to calculate the composition from the equilibrium constant and starting concentrations. This can be found in the Supporting Information.

18. The proven acceptable range for the boronic ester charge of 1.05 mol equivalents +/−0.05 mol equivalents means that an excess of 0.10 mol equivalents may be charged. In this worst-case scenario, the residual boron species will exist as 7.0% boronic ester (**2b**) and 93.0% boronic acid (**2a**).

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21. To the best of our knowledge, these are the first reported examples of a multi-kilo manufacture of a diethanolamine boronic ester and subsequent Suzuki coupling.