

Scale-up of Azide Chemistry: A Case Study

Francisco González-Bobes,^{*,†} Nathaniel Kopp,^{*,†} Li Li,[‡] Joerg Deerberg,[†] Praveen Sharma,[†] Simon Leung,[§] Merrill Davies,[†] Joseph Bush,[§] Jason Hamm,[§] and Michael Hrytsak[§][†]Chemical Development, [‡]Analytical and Bioanalytical Development, and [§]Chemical Development Operations, Bristol-Myers Squibb Company, One Squibb Drive, New Brunswick, New Jersey 08903, United States

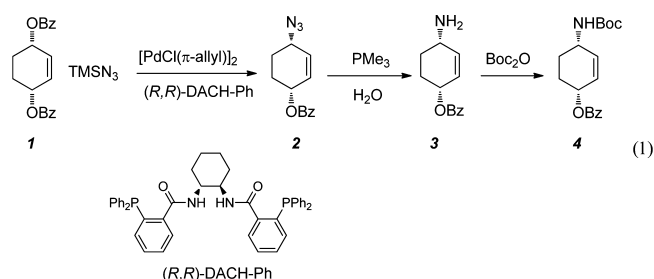
S Supporting Information

ABSTRACT: We report research and development conducted to enable the safe implementation of a highly enantioselective palladium-catalyzed desymmetrization of a *meso*-bis-ester using trimethylsilylazide (TMSN₃) as the nucleophile. This work is used as a case example to discuss safe practices when considering the use of azide reagents or intermediates, with a focus on the thermodynamic and quantitative analysis of the hazards associated with hydrazoic acid (HN₃).

INTRODUCTION

Azide chemistry offers an efficient entry to synthesize a range of nitrogen-containing compounds with a wide variety of functional groups.^{1,2} When considering a reaction involving azide reagents and intermediates, safety aspects, such as material compatibility, exposure, and explosivity, must be evaluated and addressed prior to large scale execution. Specifically, the incompatibility of azide reagents with some metals³ and with certain chlorinated solvents,⁴ and the thermal instability of azide intermediates⁵ constitute major hurdles when developing routes that involve azide-containing intermediates. A topic of even greater concern is the potential for generation of hydrazoic acid (HN₃).⁶ HN₃ is a relatively weak acid (pK_a = 4.7),⁷ with a low boiling point (37 °C).⁸ The recommended NIOSH exposure limit for inhalation, expressed as the threshold limit value (TLV), is 0.11 ppm for HN₃.⁹ Exposure above these levels has been shown to lower blood pressure in animals and humans. Other symptoms often associated with inhalation of HN₃ include the following: bronchitis, eye, nose, throat, and lung irritation, headache, and weakness that can lead to collapse. There is no specific antidote for azide intoxication.^{9d} In addition to exposure, HN₃ is an unstable and shock sensitive compound that can decompose to generate large amounts of gas and energy.¹⁰ Equilibrium concentrations of HN₃ can be formed under a range of pH conditions,¹¹ and its volatile nature creates the potential for explosions.¹² Despite these concerns, azide chemistry has been employed on large scale,¹³ primarily by the implementation of process and engineering controls.¹⁴ For example, there are several reports involving the scale-up of azide reactions, in many cases carrying out critical operations in bunkers.¹⁵

During the development of a synthetic route to a pharmaceutical candidate, we became interested in accessing an intermediate via a highly enantioselective palladium-catalyzed desymmetrization of a *meso*-bis-ester **1** using TMSN₃ as the nucleophile (eq 1).¹⁶ The process requires three chemical



transformations: (a) the formation of the allylic azide intermediate **2**; (b) the reduction of the azide intermediate to the amine **3**; and (c) the formation of the desired allylic carbamate **4**. Herein, we report a detailed safety analysis and process assessment that enabled the safe scale up of this chemistry without the need of specialized facilities. Whereas most published approaches rely on preventing accumulation of HN₃ in the condensate by implementing engineering controls, we considered the risks associated with this approach not acceptable for implementation in our multipurpose scale up facilities. We focused on a *quantitative approach* in which, even in the event of enriched condensate accumulation, the lower explosive limit (LEL)¹⁷ would not be reached. To the best of our knowledge, such an approach has not been previously disclosed in the context of preparation of pharmaceutical intermediates.

RESULTS AND DISCUSSION

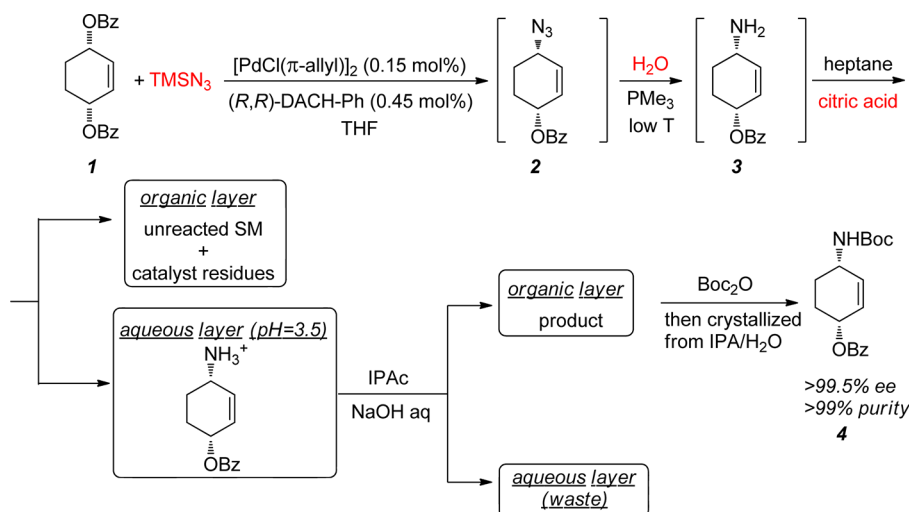
Initial Assessment: First Generation Process. We undertook development efforts with two major goals: (a) to design a safe and scalable process to support downstream route development and (b) to develop a safe and robust process to support long-term project needs. Our first step to assess the viability of using this reaction on scale was to evaluate the thermo-stability of the allylic azide **2** in THF. The decomposition of **2** was highly exothermic (−388.4 J/g), yet it rated as low in probability (ADT 24 was 93 °C by ARC and 94 °C by Setaram C80 and AKTS Thermokinetic analysis).¹⁸ This did not pose a reactivity problem, since the palladium-catalyzed desymmetrization proceeds efficiently at 0 °C.^{16,19} Based on the thermochemistry data, we also decided that the allylic azide **2** would not be isolated but used directly in the next step, which would be carried out in the same solvent system as the desymmetrization reaction to avoid the need for distillations.

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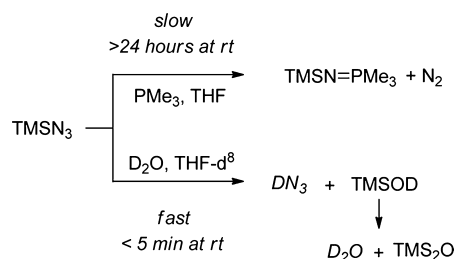
Scheme 1. Description of the First Generation Process



Our initial process development relied heavily on the literature conditions.¹⁶ We quickly established a basic understanding of the unit operations required to obtain **4** with the desired quality attributes (Scheme 1).

The desymmetrization performed well in THF as the solvent,¹⁶ and the reaction mixture could be easily telescoped into the Staudinger reaction via addition of water and a dilute solution of trimethylphosphine in THF.²⁰ The thermochemistry of the azide reduction was also evaluated. The reaction was highly exothermic (-161.6 J/g) and produced significant amounts of nitrogen as a byproduct. Nonetheless, the thermal profile and gas evolution were addition-controlled and easily managed by adjusting the rate of addition of the reactants to adapt to the cooling and venting capacities of the equipment. Extracting the allylic amine **3** into the aqueous phase by acidification with diluted aqueous acid was crucial to ensure stability of the process stream and process robustness. Addition of *n*-heptane allowed for an easy phase separation, in which most of the process- and catalyst-derived impurities remained in the organic phase and could be removed via a simple liquid–liquid separation. The aqueous solution was then treated with isopropyl acetate (IPAc) and an excess of aqueous sodium hydroxide to efficiently partition the allylic amine **3** into the organic phase. After a phase separation, the IPAc layer was treated with di-*tert*-butyl dicarbonate (Boc_2O) to afford the desired allylic carbamate **4**. Finally, solvent exchange from IPAc²¹ to IPA followed by addition of water as antisolvent allowed for the isolation of the product in excellent chemical and optical purity (>99.5% *e.e.*; >99% pure).

Through a basic risk analysis we identified two transformations that could generate HN_3 during the process (highlighted in red in Scheme 1). The formation of HN_3 from hydrolysis of TMSN_3 due to residual water during the desymmetrization reaction and during the downstream processing from any unreacted TMSN_3 (Staudinger reaction and acidification) posed a safety concern. The hydrolysis during the desymmetrization reaction could be minimized by controlling the water content of the input reagents and solvent. In addition, we reasoned that HN_3 would be a competent nucleophile in the desymmetrization reaction. The potential for formation of HN_3 from residual TMSN_3 upon addition of water required the development of a control strategy to establish safe operating limits for HN_3 after the desymmetrization reaction (Scheme 2).²²

Scheme 2. Secondary Reactions for Residual TMSN_3 under Processing Conditions

We then focused on the development of an in-process control (IPC) for residual azide to guarantee that the solution, gas, and enriched condensate phases would remain below the LEL.^{10,23}

Development of the Process Control Strategy: Vapor–Liquid Equilibrium (VLE) Assessment. We conducted a complete assessment of the three phases in two steps: (a) evaluation of the process vapor–liquid equilibrium with respect to reaction completion (azide consumption); and (b) determination of the process IPC limit through interpolation of literature data for the LEL of the enriched condensate in equilibrium with the solution and vapor phase.

Due to the issues associated with the preparation and handling of HN_3 , few studies have developed complete vapor–liquid equilibrium profiles. However, independent reports have reasonably agreed on the Henry's law constant (K_H) to describe the equilibrium at concentrations ranging from 11 M to 10 μM .^{11,24} The Henry's law constant is expressed as the ratio between the aqueous phase solution concentration $[\text{HN}_3]$ and the partial pressure of HN_3 in the gas phase, P_{HN_3} (eq 2):

$$K_H = \frac{[\text{HN}_3]_{\text{aq}}}{P_{\text{HN}_3}} \quad (2)$$

Betterton and Robinson¹¹ determined this value at 25 °C (aq) as 12.0 ± 0.7 M/atm, which may be adjusted based on the pH and temperature of the system. Our study specifically examined the effect of pH, as the downstream addition of aqueous acid significantly lowers the pH and increases the HN_3 vapor pressure in the system.

The pH dependence of the Henry's law constant (K_H) may be described through calculation of the effective Henry's law

constant (K'_H) with respect to the $[H^+]$ concentration and the acidity constant for HN_3 ($K_a = 2.24 \times 10^{-5}$) (eq 3):

$$K'_H = K_H(1 + K_a/[H^+]) \quad (3)$$

Figure 1 highlights the relationship between the vapor–liquid equilibrium and pH derived from eq 3. This plot

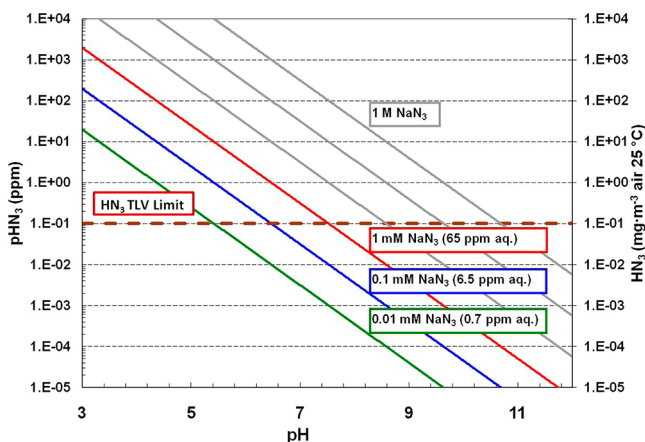


Figure 1. Combined effects of solution free azide concentration and pH on the partial pressure of HN_3 in the gas phase over H_2O at 25 °C. Adapted with permission: 1997 Taylor & Francis Group.¹¹

quantitatively shows that a higher solution concentration of azide and/or a lower pH both increase the gas phase partial pressure significantly. The TLV at 0.11 ppm^{9a} illustrates that azide solution concentrations must be kept very low or at high pH in order to maintain safe exposure levels. Since the chemistry was conducted in an inert, closed environment, the safe solution azide level did not depend on the TLV but focused on the LEL.

The Henry's law approximation afforded a method to evaluate the vapor–liquid equilibrium relationship with respect to reaction conversion and pH for our process (Figure 2). It must be noted that these calculations are based on a purely

aqueous system at 25 °C. The process conditions added a buffer into the approximation, since the temperature was controlled below 15 °C in a volatile organic solvent. As presented in Figure 2, the effects of pH dominate the HN_3 gas phase concentration (vol %). To maintain safety during downstream processing, a high pH and/or near complete reaction conversion must be achieved. Since the process required an acidification for intermediate stabilization (approximate pH 3.5), our control strategy relied on achieving high reaction conversions (low residual free azide). Therefore, the next step in the quantitative analysis became the determination of the acceptable residual free azide level after the palladium-catalyzed desymmetrization reaction. To accomplish this, we first interpolated equilibrium data from the PUREX process, a nuclear fuel reprocessing method which forms HN_3 as a byproduct.^{23a} Using this data, we established a gas phase limit of 0.625 vol % which is based on the enriched condensate LEL in equilibrium with the solution and gas phases. As an additional layer of safety, our IPC limit calculation used a more conservative HN_3 gas phase limit of 0.30 vol %, which translated to a final limit of 200 ppm of free azide after the desymmetrization reaction.²⁵ By using substoichiometric amounts of $TMSN_3$ (0.95 equiv), we were able to comfortably meet the proposed IPC (typical experimental values of <100 ppm). This strategy was employed during scale-up.

First Generation Process: Process Execution and Results. Although the focus of our control strategy was limiting the level of free azide in solution post-desymmetrization, the process execution included a comprehensive evaluation from reagent and waste handling to emergency preparedness. Before processing, an inert transfer of the azide reagent to a compatible pressure container was conducted to minimize exposure to moisture during charging and limit personnel exposure. A nitrogen sweep was implemented during processing to purge the process train, and the vent line was sent through a caustic scrubber. Waste streams were segregated and treated with excess base prior to disposal by a qualified contractor.

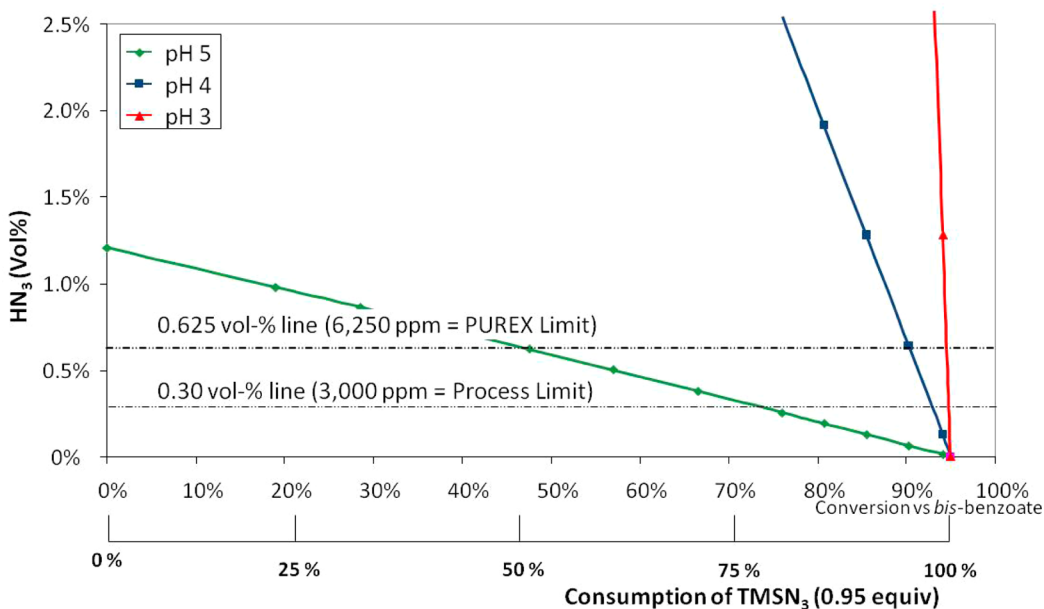
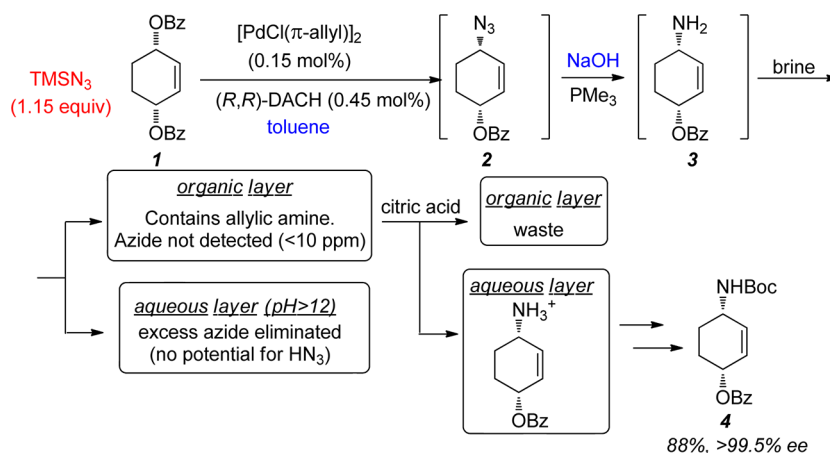


Figure 2. The vol % of HN_3 in the gas phase corresponding to conversion of starting material or consumption of trimethylsilyl azide reagent with respect to pH.

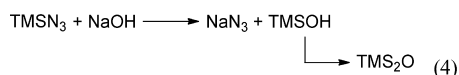
Scheme 3. Description of the Second Generation Process



The process was successfully scaled-up in two batches to deliver 8.42 kg of **4** (76% yield based on TMSN_3) in high purity (>99%), potency ($\geq 99\%$), and enantiomeric excess ($\geq 99.5\%$). In both cases the reaction IPC for residual azide after the desymmetrization reaction met the proposed limit.²⁶

Second Generation Process. Although we successfully demonstrated our first generation process at kilogram scale and thus met the first objective of our development work, we recognized that the process had some key limitations that would need to be addressed before considering larger scale operations. Specifically, in order to meet the IPC for residual azide, a very accurate charge of TMSN_3 would be critical. The use of TMSN_3 as the limiting reagent resulted in the undesirable sacrifice of variable amounts of the more elaborate meso-*bis*-benzoate starting material. More importantly, the control strategy was based on minimizing the generation of HN_3 whereas avoiding its formation altogether would be intrinsically safer. We decided to pursue the development of an alternative process in which the stoichiometry of TMSN_3 would not play a critical role.²⁷

We were interested in leveraging the chemical properties of HN_3 to aid its efficient removal. We envisioned that, upon completion of the desymmetrization reaction, the reaction media could be adjusted to a basic pH via addition of an aqueous solution of sodium hydroxide (eq 4). This would



immediately convert any excess of TMSN_3 present in the reaction mixture to aqueous sodium azide, which could be easily removed via extractive workup, hence eliminating any concerns about formation of HN_3 .²⁸

To use this strategy, a series of requirements would need to be met: (a) the desymmetrization reaction should proceed in a solvent that allows for an efficient phase separation from the aqueous phase; (b) the Staudinger reaction should also proceed efficiently in that same solvent at low temperature;¹⁹ (c) the sodium azide generated as byproduct should efficiently partition into the aqueous phase to allow for quantitative removal. With these objectives in mind, we found that toluene could be used as the solvent in the palladium-catalyzed desymmetrization reaction without compromising chemical and optical purity. The allylic azide intermediate **2** in toluene also exhibited highly

exothermic decomposition behavior (-326.5 J/g) upon evaluation with the ARSST (advance reactive system screening tool) and DSC (differential scanning calorimetry). This decomposition was also rated as low in probability (ADT 24 was 71°C by the ARSST and 80°C by DSC and AKTS Thermokinetics Analysis),¹⁸ and it did not pose a problem since the palladium-catalyzed desymmetrization proceeded efficiently at 0°C . Upon reaction completion (30 min), the mixture was treated with excess aqueous sodium hydroxide (2 N), followed by azide reduction, which proceeded smoothly under the basic conditions of the reaction media.²⁹ The concentration of azide in the organic layer was <10 ppm, well below the 200 ppm limit previously discussed, showcasing that the residual levels of azide after the desymmetrization were no longer critical (Scheme 3).³⁰

A comparison of both processes against different key parameters is presented in Table 1. The initial process required

Table 1. Comparison of the Process against Key Parameters

key parameters	1st generation	2nd generation
stoichiometry of TMSN_3	critical	not critical
azide levels post-desymmetrization	control to ppm level	not critical
potential to form HN_3 downstream	yes	no
HN_3 control strategy	IPC control	process design
yield	76%	88%
PMI (kg total process input/kg product)	85	52

tight control of the stoichiometry and a highly sensitive IPC. In contrast, the second generation process addresses the topic of HN_3 generation through an improved process design in which neither the stoichiometry nor the levels post-desymmetrization of azide play a critical role. Importantly, significant yield improvement and waste reduction were realized while maintaining the desired product quality.

CONCLUSION

We have described the safe implementation of a highly enantioselective palladium-catalyzed desymmetrization using an azide nucleophile. We conducted a quantitative analysis of the vapor–liquid–condensate equilibrium using Henry's law based on the literature data for HN_3 , which shows that the safe operating limits are dictated by the enriched condensate. This is in contrast with most published reports which either do not

consider enriched condensate or mitigate the risk by implementing engineering controls. This quantitative analysis allowed for the establishment of a successful strategy to address explosivity concerns associated with HN_3 generation. We used this approach to prepare a key intermediate in kilogram amounts with excellent quality in our multipurpose scale up facilities. In addition, we also designed and demonstrated a more efficient process based on an understanding of the secondary reactions involved in the fate of TMSN_3 under the reaction conditions. The learnings from this case example may be applicable to other reactions involving azides.

■ EXPERIMENTAL SECTION

General. TMSN_3 was transferred from the commercial container to a pressure bomb excluding air and moisture. In laboratory scale, TMSN_3 was always handled in a ventilated enclosure (fume hood) to prevent exposure to HN_3 vapors. On kilogram scale, handling of TMSN_3 was done using double gloves (inner-nitrile surgical style, outer-silvershield), a silver-shield apron, and a supplied air respirator.

The potency of *cis*-cyclohex-2-ene-1,4-diyl dibenzoate was determined by HPLC, and the stoichiometry of TMSN_3 was corrected accordingly. For details on the analytical method, see the Supporting Information.

Waste treatments to eliminate azide were not conducted on site. The waste streams containing azide were adjusted to $\text{pH} \geq 12$ with aqueous NaOH and handled by a qualified contractor.

The palladium-catalyzed reaction is oxygen sensitive, and inefficient inertion could cause catalyst deactivation and stalling, thus compromising the ability to meet the IPC. The following actions were taken to ensure adequate inertion: (a) extensive evacuation/refilling cycles with nitrogen and (b) circulation of the nitrogen gas through a gas purifier to adsorb residual oxygen (Oxyclear).

A scrubber with 5 wt % sodium hypochlorite was used to collect the PMe_3 vapors from the vent line.

The Staudinger reaction and the addition of Boc_2O produced gaseous byproducts. The rate of addition was adjusted to the cooling and venting capacities of the equipment.

Preparation of (1*R*,4*S*)-4-(*tert*-Butoxycarbonylamino)-cyclohex-2-enyl Benzoate (4). *a. First Generation Process (TMSN₃ as the Limiting Reagent).* A 200 L lined-glass reactor was inerted via three consecutive vacuum/nitrogen/refilling cycles (vacuum pressure: -0.8 bar). *cis*-Cyclohex-2-ene-1,4-diyl dibenzoate (5.465 kg, 1.0 equiv) (1), $[\text{Pd}(\pi\text{-allyl})\text{Cl}]_2$ (9.44 g, 0.0015 equiv), and (*R,R*)-DACH-Ph (54.12 g, 0.0045 equiv, Chirotech) were charged to the reactor, followed by three additional inertion cycles (vacuum pressure: -0.8 bar). THF (12.200 kg, 13.7 L) was added, and the mixture was first stirred until a homogeneous solution was obtained (<10 min, endothermic process) and then cooled to -5°C . TMSN_3 (1.785 kg, 0.95 equiv, Sigma Aldrich) was then added to the reaction mixture over approximately 20–25 min in order to maintain the temperature at $0 \pm 5^\circ\text{C}$. An additional THF charge (1.900 kg) was conducted to remove any residual TMSN_3 from the transfer line. The reaction was stirred at $0 \pm 5^\circ\text{C}$ for an additional 2 h and then sampled for residual azide in solution (<70 ppm of azide versus <200 ppm target). Water (11.030 kg) and 1 M trimethylphosphine in THF (17.075 kg, Sigma Aldrich) were then sequentially added to the reactor at such a rate that the internal temperature remained 0 – 15°C . Once the phosphine had been charged, the transfer line was rinsed with THF (1.15 kg) and the reaction mixture was stirred at 0 – 5°C for 1 h. An aliquot was then analyzed by HPLC to verify that

the allylic azide had been successfully converted to the allylic amine intermediate. *n*-Heptane (15.020 kg), water (11.935 kg), brine (20 wt %, 11.985 kg), and aqueous citric acid (20 wt %, 41.00 kg) were sequentially added. The reaction mixture was then allowed to warm up (15 – 25°C) and stirred for at least 15 min. The layers were allowed to split. The aqueous layer, which contained the allylic amine, was pressure-transferred into a clean 200 L reactor, and was held overnight. The organic layer was disposed of and treated as azide containing waste. To the aqueous solution containing the product was added IPAc (24.086 kg). The mixture was then cooled to 0°C , followed by the addition of aqueous sodium hydroxide (25 wt %, 23.207 kg). The addition was done at such a rate that the temperature stayed in the desired range (0 – 10°C). The mixture was warmed to room temperature (15 – 25°C), and after no less than 15 min the phases were allowed to split. The lean aqueous was discharged, and the rich organic layer was washed with brine (20 wt %, 18.162 kg) and diluted with water (17.948 kg). After no less than 15 min of contact time, the phases were allowed to split and the aqueous layer was discharged. A solution of Boc_2O (3.540 kg) in IPAc (9.551 kg) was then added to the reactor over a period of 1 h. After 90 min the reaction mixture was sampled for completion. A put and take distillation was implemented to remove IPAc and replace it in solution with IPA for crystallization of the allylic carbamate. Distillation was continued until an IPA/IPAc ratio of $>95:5$ was obtained as measured by GC-FID. The concentration of the product was adjusted with IPA to ~ 200 mg/mL, and a seeded/cooling crystallization using water as antisolvent was conducted. The slurry was filtered and then washed with IPA/ H_2O ($1/3$). The wet cake was placed into a vacuum oven, and it was dried at 40 – 45°C under vacuum. 3.67 kg of product were obtained. 99% wt; 99.9 area %; 76% corrected yield (based on azide).

b. Second Generation Process. *cis*-cyclohex-2-ene-1,4-diyl dibenzoate (1 equiv, 874.8 mol (corrected for purity), 300 g) (1), $[\text{Pd}(\pi\text{-allyl})\text{Cl}]_2$ (0.0015 equiv, 1.31 mmol, 0.48 g, 0.15 mol %), and (*R,R*)-DACH-Ph (0.0045 equiv, 3.94 mmol, 2.77 g, 0.45 mol %, Chirotech) were introduced in a 5 L reactor equipped with a mechanical stirrer. The reactor was placed under a nitrogen atmosphere (three vacuum/refilling cycles over 45 min, 100 Torr). Toluene ($<0.003\%$ H_2O by KF; 3 L/kg of crude *meso*-ester, 900 mL) was then added, and the resulting mixture was stirred for 5–10 min at room temperature. The resulting homogeneous solution was then cooled. Once the internal temperature reached -3°C to -5°C , TMSN_3 (98% wt, 1.15 equiv, 118 g, 137 mL, Sigma Aldrich) was added at such a rate that the internal temperature was kept below 0°C . After the addition was complete, the jacket temperature was adjusted to -5°C , and the mixture was stirred for 1 h. A sample was analyzed by HPLC (residual starting material <1 area %). 2 N NaOH (1.4 equiv, 703 g, 651 mL, ~ 2 L/kg crude *meso*-ester) and a 1 M solution of PMe_3 in toluene (1.25 equiv, 1165 mol, 988 g, 1165 mL, Sigma Aldrich) were sequentially added at such a rate that the internal temperature stayed at 0 – 10°C . The reaction mixture was stirred for 1 h at 0 – 10°C , and then an aliquot was taken to ensure complete conversion of the allylic azide to the allylic amine had occurred. The reaction mixture was then treated with NaCl 10% (2 L/kg of crude *meso*-ester, 600 mL), warmed to 18 – 22°C , and held for 5 min with stirring, and then the phases were allowed to split. The aqueous layer was collected and was segregated to be disposed as azide containing waste. TBME was added (2 L/kg of crude *meso*-ester, 600 mL), and the organic layer was then cooled to $\sim +15^\circ\text{C}$. A sample of the

organic layer was analyzed for azide concentration (<10 ppm azide observed with a target of <200 ppm). Aqueous citric acid 20% (2 equiv, 1.86 mol, 1.79 kg) was added with vigorous stirring, maintaining the internal temperature within the range 10–20 °C. The mixture was stirred for 15 min, and then the phases were allowed to split. A sample of the aqueous phase was taken to check the pH (pH 3–4 was targeted). The reaction mixture was held overnight. The rich aqueous layer was placed into a clean 5 L reactor and treated with IPAc (4 L/kg of *meso*-bis-ester, 1.2 L) and the resulting mixture was cooled to 0–5 °C. 10 N NaOH (5.5 equiv, 5.1 mol, 773 g, 512 mL) was then slowly added at such a rate that the internal temperature did not exceed 10 °C. The reaction mixture was warmed to 15–25 °C and held for at least 15 min with stirring, and then the phases were allowed to split. The aqueous layer was collected and was disposed as waste. The organic layer was then washed with 10 wt % brine (4 L/kg of *meso*-bis-ester, 1.2 L). The mixture was vigorously stirred for no less than 15 min, and then the phases were allowed to split. The lean aqueous layer was collected and was disposed of as waste. The rich IPAc phase was then cooled to 0–5 °C. A solution of Boc₂O (1 equiv, 930.6 mmol, 204 g) in IPAc (1–1.5 L/kg of Boc₂O) was prepared (endothermic). This solution was added to the reaction mixture over approximately 1 h to control the carbon dioxide evolution. The reaction mixture was stirred at 10 °C for 90 min, and then a sample was collected and was analyzed by HPLC to ensure the allylic amine had been efficiently converted to the allylic carbamate. The reaction mixture was then warmed to room temperature and was held overnight. A put and take distillation strategy was implemented to remove IPAc and replace it in solution with IPA for crystallization of the allylic carbamate. Distillation was continued until an IPA/IPAc ratio of >95:5 was obtained as measured by GC-FID. The concentration of the product was adjusted with IPA to ~200 mg/mL, and a seeded/cooling crystallization using water as antisolvent was conducted. The slurry was filtered and then washed with an IPA/H₂O ratio of 1/3. The wet cake was dried at 40–45 °C under vacuum. 244.79 g of product was obtained. 98% wt; >99.9 area %; 88% corrected yield.

■ ASSOCIATED CONTENT

■ Supporting Information

Analytical methods and compound characterization data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: francisco.gonzalezbobes@bms.com; nathaniel.kopp@bms.com.

Notes

The authors declare no competing financial interest.

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(26) We developed contingency plans to be used in the case that the IPC was not met when working on scale. For a discussion, see the Supporting Information.

(27) The use of nonazide nucleophiles was also considered. A discussion on this topic is beyond the scope of this manuscript.

(28) A target pH of ≥ 12 was set for the aqueous layer.

(29) The palladium-catalyzed desymmetrization–basification–Staudinger sequence also worked well in 2-MeTHF. Toluene was chosen due to its lower price.

(30) These results show that the sodium azide partitions exclusively into the aqueous layer. In the unlikely scenario that higher levels were observed after the first split, a simple recourse would be to conduct an additional wash with 2 N NaOH.