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Article

Continuous Process Improvement in the Manufacture of Carfilzomib, Part 1: Process Understanding and Improvements in the Commercial Route to Prepare the Epoxyketone Warhead

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ABSTRACT: Epoxyketone **4** is an isolated intermediate in the manufacturing route to the commercial proteasome inhibitor carfilzomib (Kyprolis). Commercial process development and optimization efforts toward the preparation of epoxyketone **4** highlighted several opportunities for process improvement. In this article, three case studies are presented that demonstrate how a detailed understanding of the reaction mechanism led to improvements that increased the overall robustness of the process. In the first case study, the mechanism of racemization of an α-chiral enone was investigated, resulting in the development of an improved aqueous workup procedure. Next, the stability of a bleach/pyridine mixture used for the step 3 epoxidation reaction was studied, leading to the identification of pyridine as a key raw material and improved reaction conditions and control strategy to meet the conversion target. Finally, oxidized butylated hydroxytoluene (oBHT) was identified as an impurity arising from the use of BHT-stabilized tetrahydrofuran in steps preceding the oxidation. The process understanding obtained from these investigations led to the implementation of process improvements that improved the robustness of the process. The development of a second-generation route to **4** is the subject of part 2 in this series (DOI: 10.1021/acs.oprd.0c00052).

KEYWORDS: *racemization, α-chiral enone, bleach, epoxidation, carfilzomib*

INTRODUCTION

Multiple myeloma is a cancer of plasma cells that originates in the bone marrow.[1] Carfilzomib is the active pharmaceutical ingredient (API) in the marketed proteasome inhibitor Kyprolis, initially approved by the U.S. Food and Drug Administration in 2012. Kyprolis is indicated for use in combination with dexamethasone or with lenalidomide plus dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy and as a single agent for the treatment of patients with relapsed or refractory multiple myeloma who have received one or more lines of therapy. Carfilzomib (Figure 1) is a synthetic epoxyketone-containing tetrapeptide inspired by the structure of epoxomicin, a natural product with proteosomal inhibition activity.[2] This article presents case studies in the continual drive to improve the manufacturing route to the key epoxyketone intermediate **4** in the synthesis of carfilzomib.

The route to prepare epoxyketone **4** involves three steps from L-Boc-leucine monohydrate: (1) Weinreb amide formation via the intermediacy of a mixed anhydride, (2) addition of isopropenylmagnesium bromide to generate enone **3**, and (3) epoxidation with bleach in pyridine to generate the isolated intermediate epoxyketone **4** (Scheme 1). Boc deprotection of **4** and subsequent coupling with intermediate **6** completes the synthesis of carfilzomib. Notable challenges identified during familiarization and process development activities include (1) the requirement for silica gel column

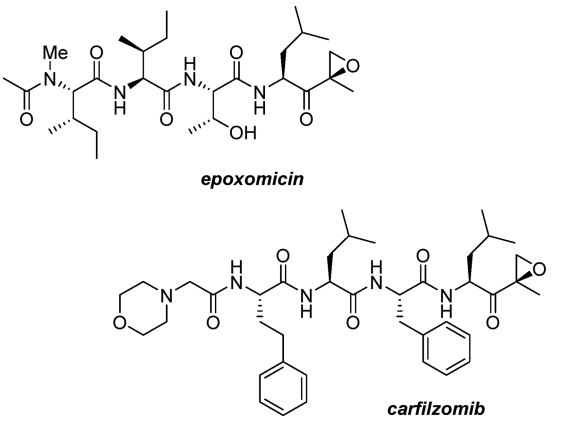

Figure 1. Structures of epoxomicin and carfilzomib.

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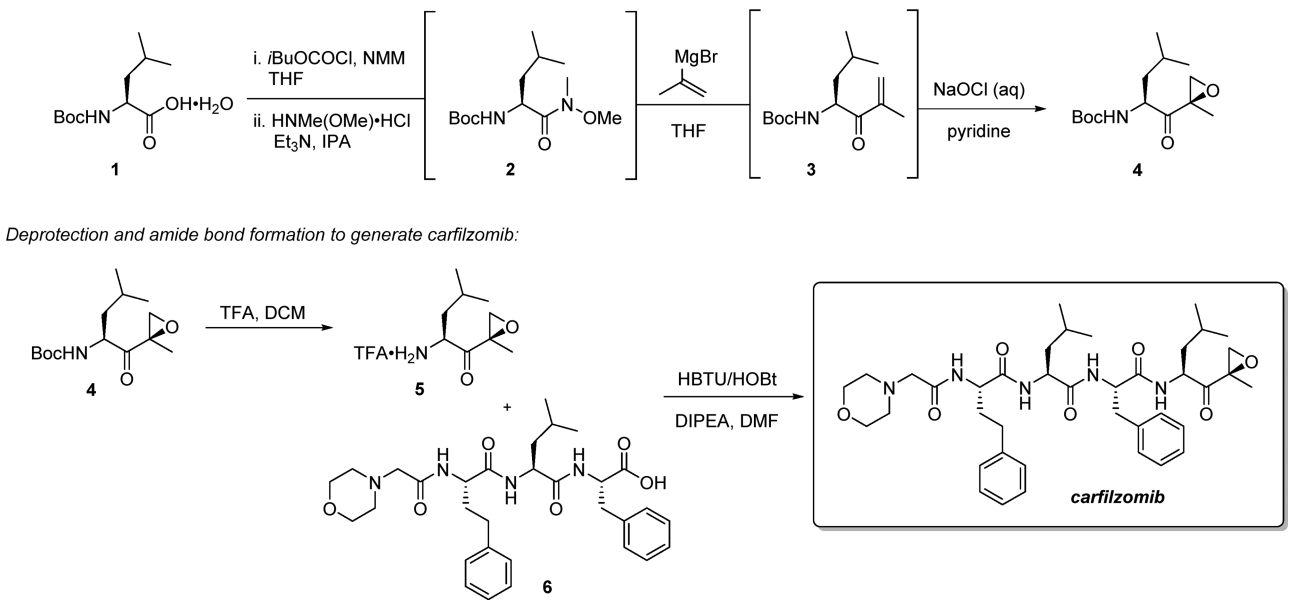
Scheme 1. Synthesis of Epoxyketone 4 and Conversion to Carfilzomib



chromatography and resulting stereochemical lability associated with purification of enone **3**, (2) latent exothermic activity observed for the bleach oxidation, (3) low diastereoselectivity (ca. 2:1) for the epoxidation to prepare epoxyketone **4**, and (4) the low melting point of the target compound **4** (mp = 41 °C), which challenges direct isolation from the crude reaction mixture.

Since carfilzomib was an in-licensed commercial program, to address these challenges a two-stage strategy was adopted to improve the robustness of the current route to epoxyketone **4** and deliver an improved synthesis in the life-cycle management stage of the program:

(1) Initiate process understanding workstreams to identify potential risks to process performance and implement solutions to mitigate these risks.

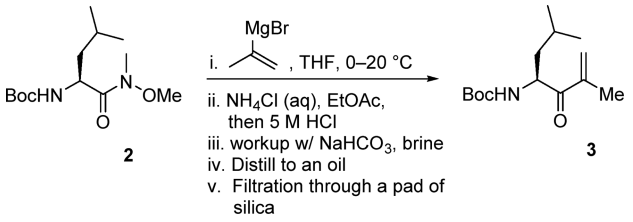
(2) Leverage process understanding gained from the first stage to deliver an improved second-generation process for the manufacture of epoxyketone **4**.

This article presents three case studies from the process understanding stage: (i) mechanism and mitigation of the racemization in the step 2 Grignard reaction, (ii) bleach decomposition in the step 3 epoxidation, and (iii) identification of an oxidized butylated hydroxytoluene (oBHT) impurity. In all cases, process improvements were implemented on the basis of a fundamental understanding of identified failure modes to improve the robustness of the process. The development of a second-generation process for the manufacture of epoxyketone **4** is the subject of part 2 of this series (DOI: 10.1021/acs.oprd.0c00052).

RACEMIZATION OF ENONE 3

Step 2 of the manufacturing route involves the preparation of enone **3** by addition of Weinreb amide **2** to a solution of isopropenylmagnesium bromide in tetrahydrofuran (THF) (Scheme 2). Aqueous ammonium chloride is charged upon confirmation of reaction completion, followed by acidification with 5 M HCl. After separation of the phases, the organic layer is washed with aqueous $NaHCO_3$ and brine. The final organic

Scheme 2. Synthesis of Enone 3



phase is then concentrated via distillation and filtered through a plug of silica gel with ethyl acetate and *n*-hexane to deliver enone **3** after concentration of the appropriate fractions.

Control of the stereochemical purity of enone **3** was critical because of the limited ability to purge stereoisomeric impurities in the downstream crystallization of epoxyketone **4**. However, during development it was noted that varying levels of racemization were observed (0.1 to >5%) confirming the lability of the α-enone stereocenter. In order to assess possible factors affecting racemization, an Ishikawa diagram[3] was constructed relating equipment, material, and process factors to racemization (Figure 2). A detailed sampling plan was then designed and implemented to identify the origin of racemization. Table 1 provides an overview of chiral purity data for four representative batches. Racemization was not detected in any unit operation prior to distillation of the final organic phase after aqueous workup (Table 1, entry 1).[4] Varying levels of racemization were observed after the distillation operation, with increased levels noted upon silica gel column chromatography for batches A and C (Table 1, entries 2 and 3). These data focused development efforts on evaluation of the distillation and chromatography unit operations.

An in-depth investigation of in-process samples for batch C highlighted the presence of white crystalline solids in distillation samples prior to the chromatography operation. The following observations were made with regard to these solids:

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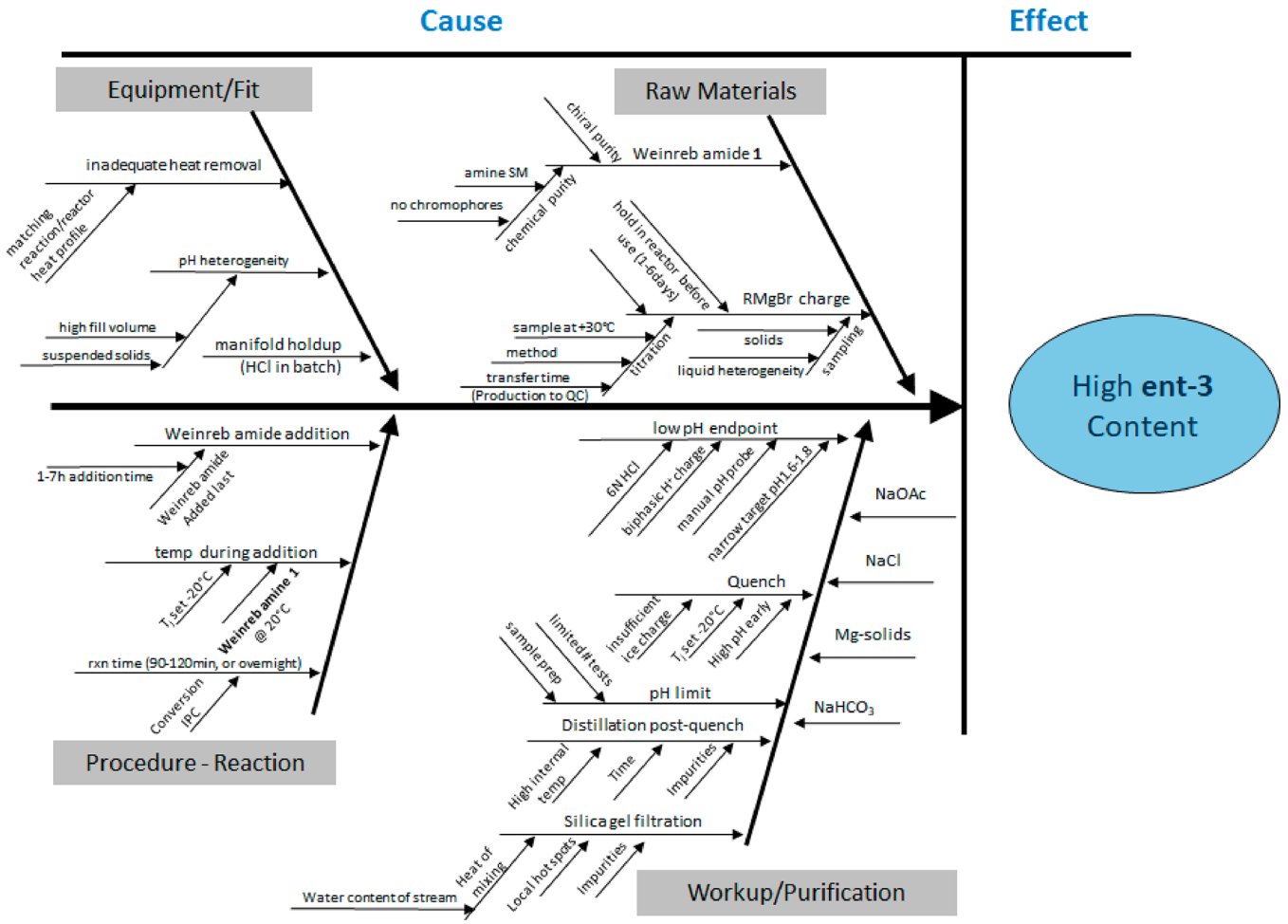

Figure 2. Ishikawa diagram to summarize potential root causes for racemization of enone **3**.

Table 1. Levels of *ent*-3 for Four Representative Batches A–D

entry	sampling point	A	B	C	D
1	prior to distillation (step iv)	<0.05%	<0.05%	<0.05%	<0.05%
2	after distillation (step iv)	0.19%	0.15%	0.66%	0.05%
3	after chromatography (step v)	0.41%	0.14%	3.39%	<0.05%

- They were soluble in water (>100 mg/mL).
- ^{1}H NMR spectra obtained in $CDCl_3$ or D_2O did not reveal organic impurities.
- ICP-MS analysis showed 30.5 wt % Na and 75 ppm Mg. All other metals (Si, V, Cr, Ni, Cu, As, Mo, Ru, Rh, Pd, Cd, Ir, Pt, Hg, Bi) were below the limit of detection.
- Capillary electrophoresis showed 8.2 wt % chloride and the presence of carbonate/bicarbonate (not quantified).
- The pH of a 6.7 mg/mL aqueous solution was 10.0 (cf. measured values of 8.4 for $NaHCO_3$ and 11.3 for Na_2CO_3).
- Addition of 1 M HCl to a 60 mg/mL aqueous solution produced vigorous bubbling.

Consistent with these observations, the white solids ("process salts") were shown to be a mixture of $NaHCO_3$, Na_2CO_3, and NaCl derived from precipitation during the aqueous wash and distillation sequence. Mg was found only in trace amounts in these solids, presumably because of efficient extraction in the upstream HCl wash.

The presence of process salts, combined with the high levels of racemization observed for batch C, led to the hypothesis that these salts caused the epimerization; however, exposure of enone **3** to these individual species did not result in the expected racemization (Figure 3). Silica gel alone also did not result in racemization of enone **3**. Notably, exposing enone **3** to a representative mixture of silica gel and the process salts resulted in significant levels of racemization. This unexpected cooperative effect could be reproduced by exposing enone **3** to silica in combination with either $NaHCO_3$ or Na_2CO_3. The magnitude of the effect is consistent with the observation that the pH of an aqueous solution of the isolated process salts is between that of $NaHCO_3$ and Na_2CO_3. These data suggest that a synergistic effect is operative where the interaction of silica with either $NaHCO_3$ or Na_2CO_3 produces a more potent racemizing medium than any of the individual components alone. We hypothesize that upon adsorption of the enone to silica gel, the acidity of the α-proton is enhanced either by the Lewis acidic nature of silica or through hydrogen bonding with silica,[5] facilitating a base-catalyzed deprotonation.[6] It should be noted that the carbonyl of the Boc group may also serve as a point of interaction with silica, increasing the extent of adsorption.

The observation that the recovered process salts were more basic than $NaHCO_3$ (used in the wash steps) warranted

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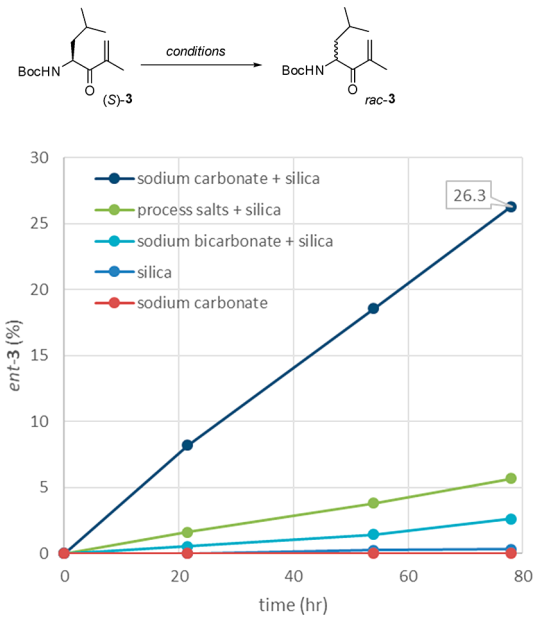

Figure 3. Racemization of enone **3** in the presence of additives at 35 °C.

additional consideration. We hypothesized that the distillation conditions employed in the production of enone **3** could impact the equilibrium described in Figure 4a through the continuous removal of CO_2 and H_2O. To probe the effect of CO_2 removal, the pH of an aqueous solution of $NaHCO_3$ was monitored under vacuum and constant-volume conditions (Figure 4b).[7] The pH of the aqueous solution was found to increase from 8.4 to 9.0, confirming that removal of CO_2 can drive the bicarbonate−carbonate equilibrium to higher pH. Additionally, under relevant process distillation conditions, the azeotropic removal of water would also be expected to drive the equilibrium from bicarbonate to carbonate.

With this understanding of the mechanism of racemization, the aqueous workup and purification process was redesigned to mitigate the risk of racemization of enone **3**. An inverse quench of the reaction stream into a mixture of 30 wt % aqueous citric acid and hexane resulted in a clean phase cut and the absence of precipitates. The organic layer was then washed sequentially with water, 5 wt % aqueous $NaHCO_3$, and water prior to a polish filtration operation to ensure complete purging of process salts from the organic layer or reactor walls. Finally, evaluation of the organic stream resulting from the optimized wash sequence demonstrated that the silica plug could be removed without any impact on the quality of epoxyketone **4**. These process changes, driven by a detailed understanding of the factors influencing racemization, resulted in an improved procedure for manufacturing that removed the risk of bicarbonate/carbonate-induced racemization.

EPOXIDATION TO PREPARE EPOXYKETONE 4

The manufacture of epoxyketone **4** proceeds via bleach-promoted epoxidation of enone **3** in pyridine.[8] In a typical process, a solution of enone **3** in pyridine is charged to a precooled (−15 °C) solution of commercial 10−15 wt % aqueous NaOCl and pyridine over 60−90 min. The crude reaction mixture is warmed to 0 °C, at which point an exotherm to 30 °C is observed at production scale. A lab-scale reaction was performed at −10 °C with slow addition (1 h) of the substrate solution to replicate the production-scale

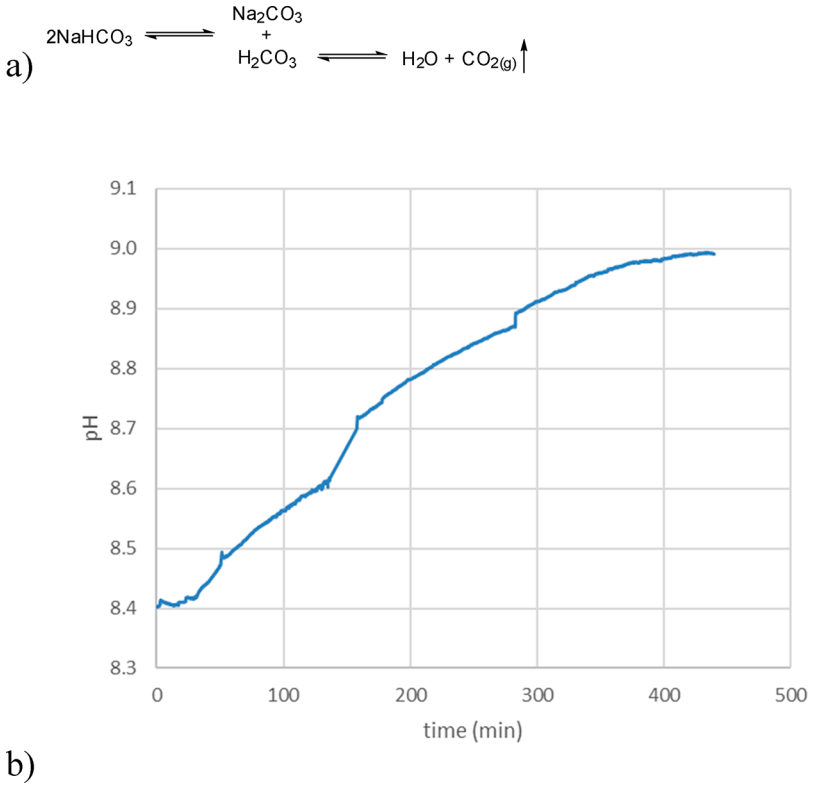

Figure 4. (a) Equilibrium between bicarbonate, carbonate, and carbonic acid species. (b) pH increase of an aqueous $NaHCO_3$ solution under representative distillation conditions.

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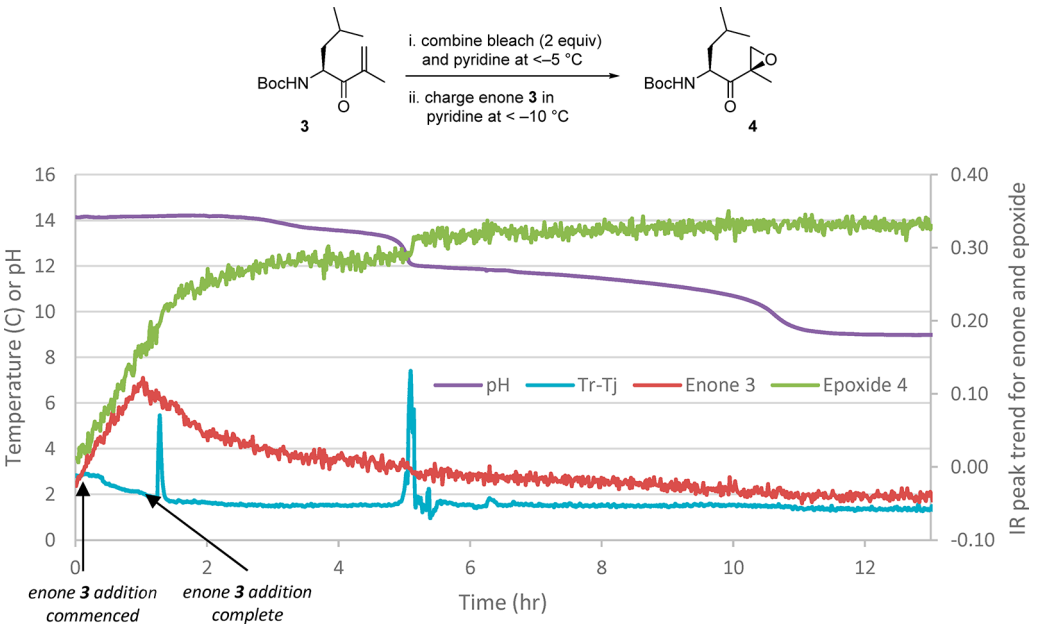
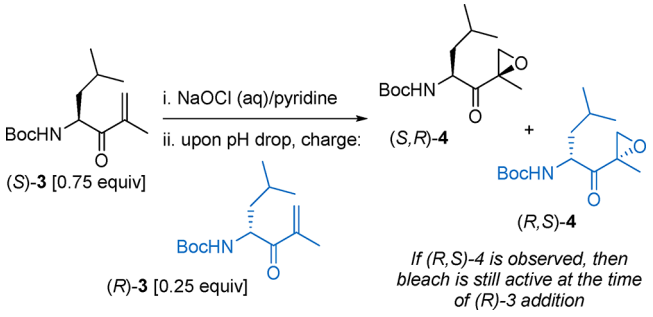


Figure 5. Reaction progress kinetics via *in situ* infrared spectroscopy[10] and corresponding pH and temperature profiles for the bleach epoxidation of enone **3**.

conditions but without purposefully warming to 0 °C. Evaluation of the reaction progress kinetics (as determined by *in situ* infrared spectroscopy) determined that this latent exothermic activity (at t = 5 h) was not associated with the productive reaction to generate epoxyketone **4** (Figure 5).[9] Product formation was observed during and after the addition of substrate, and a gradual decrease in pH was observed, corresponding to the consumption of bleach. At t = 5 h, a sudden decrease of pH was observed that coincided with the latent exotherm, at which point the desired reaction was nearly complete. The pH continued to decrease after the exothermic event, reaching a second inflection after an additional 5 h of aging.

Bleach stability is known to decrease at lower pH,[11] and therefore, we hypothesized that the spontaneous pH shift could be associated with a loss of hypochlorite. Because of the potential for incomplete reaction conversion upon bleach decomposition, an experiment was designed to assess the oxidative potential of residual bleach in the reaction mixture at various time points. As depicted in Table 2, the *R* enantiomer of enone **3** was introduced as a reactivity probe, since the reaction is known to retain the stereochemical integrity of the α-chiral center. At reaction completion, analysis of the chiral purity of crude epoxyketone **4** can provide a quantitative measure of bleach activity at the time of addition of (*R*)-**3**.

Table 2. Addition of (*R*)-3 as a Labeled Substrate to Assess Bleach Potency at Various Time Points



expt	pH at which (*R*)-**3** is charged	(*S*,*R*)-**4**:(*R*,*S*)-**4**
A	12.5	90:10
B	10	100:0

As shown in Table 2, 10% (*R*,*S*)-**4** was formed when (*R*)-**3** was added after the first pH drop (pH < 12.5), indicating that the bleach/pyridine mixture retains some oxidizing ability at this time point. Conversely, no (*R*,*S*)-**4** was observed upon addition of (*R*)-**3** at the second pH drop (pH < 10), consistent with the complete decomposition of bleach despite the excess (2.0 equiv) bleach charge. This study also indicates that the pyridine system may not have sufficient buffer capacity to maintain high pH throughout the reaction. As a preventative action, the addition time of the enone substrate must not be extended longer than necessary (typically <2 h) to ensure that the bleach is still active by the end of the substrate addition.

Continued familiarization and development activities revealed an unexpected dependence of the stability of the bleach solution on the source of pyridine. Bleach/pyridine mixtures prepared from a variety of pyridine lots under conditions representative of the process were titrated for hypochlorite content. As shown in Table 3, pyridine from vendor 1 (entry 1) retained a high titer of hypochlorite after the bleach was charged to pyridine. Conversely, pyridine from vendor 2 (entry 2) resulted in nearly complete decomposition of bleach as assayed after the bleach charge. Of note, a diagnostic brown color was observed during the bleach addition (Figure 6) that was associated with low bleach activity in the final mixture. A second lot from vendor 2 showed similar behavior (entry 3), demonstrating that the root cause of bleach decomposition was not limited to contamination of a single lot but instead linked to the manufacturing or storage method. Of note, the rate of bleach addition also impacted the titer; for example, the hypochlorite titer remained high when the bleach addition was performed quickly (10 min versus 100 min), as shown in entry 4.

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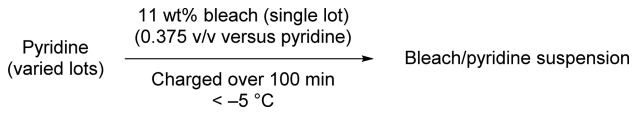
Table 3. Effect of the Pyridine Input on the Bleach Titer after Charging Bleach to Pyridine



entry	pyridine source	modification	bleach/pyridine activity[a]	color
1	vendor 1	none[b]	99%	pale yellow
2	vendor 2 (lot 1)	none	2.6%	brown
3	vendor 2 (lot 2)	none	2.3%	brown
4	vendor 2 (lot 1)	addition over 10 min	94%	pale yellow
5	vendor 2 (lot 1)	pyridine pretreated with K_2CO_3, then filtered	96%	pale yellow
6	vendor 1	20 ppm $FeCl_3$	1.9%	brown

[a]Relative to the theoretical amount of hypochlorite based on titration of bleach input. See the Experimental Section for the bleach titration method modified for use with pyridine. [b]Addition over 100 min.

Figure 6. Visual appearance of the bleach/pyridine mixture with vendor 1 pyridine (left) and vendor 2 pyridine (right).

Given the pH dependence of the stability of the bleach, we hypothesized that the difference in pyridine lots is related to trace acidic or basic impurities. To probe this possibility, pretreating the pyridine from vendor 2 with K_2CO_3 and then filtering led to retention of the hypochlorite titer. Furthermore, addition of 20 ppm $FeCl_3$ to the vendor 1 pyridine indeed led to loss of bleach activity. The binary response demonstrated in all of these studies (either full retention or absence of hypochlorite) suggests a catalytic and irreversible decomposition pathway. Given the effect of basic and acidic additives on the stability of bleach titer shown in Table 3, we next monitored the pH of the mixture throughout the course of the bleach addition. As shown in Figure 7, the pH measured for bleach addition to pyridine from vendor 1 showed a gradual increase from 12 to 14, consistent with slow charge of a basic species. When bleach was added to pyridine from vendor 2, the pH initially increased to a pH of 12 but then decreased over the remaining course of addition. These data suggest that below a critical pH, the bleach decomposed as it was being charged, leading to a drop in pH and continued decomposition. This can also explain the effect of the addition rate: a high pH is achieved immediately upon rapid bleach addition, resulting in a stable solution. This scenario is also consistent with the effect of added acid or base, which can trigger or prevent the decomposition (see Table 3, entries 5 and 6). Furthermore, the observed pH sensitivity of the bleach/pyridine mixture also explains the bleach decomposition behavior observed upon extended aging of the reaction mixture (Figure 5).

Although rapid (<10 min) addition of bleach in lab-scale experiments was shown to generate active bleach/pyridine mixtures with all lots of pyridine tested, this strategy is not practical on production scale because of the exotherm associated with the addition of bleach to pyridine caused by the heat of mixing and precipitation of solids. Therefore, several controls were used to ensure process robustness. First, the pyridine used in manufacturing was use-tested as a raw material under stressed conditions to ensure solution stability. Second, a use test of the bleach/pyridine mixture as an in-process control, which was already part of the procedure, was shown to be capable of detecting bleach decomposition, thus securing the batch.[12]

In summary, detailed understanding of the stability of bleach/pyridine mixtures before and after epoxidation facilitated the characterization of acceptable operating

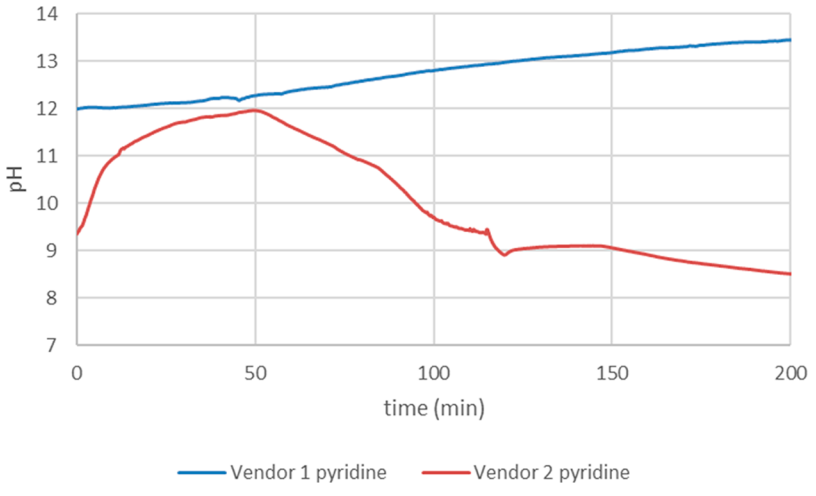


Figure 7. Variation of the pH of the mixture as bleach was added to pyridine from vendor 1 (blue) or vendor 2 (red) over 200 min.

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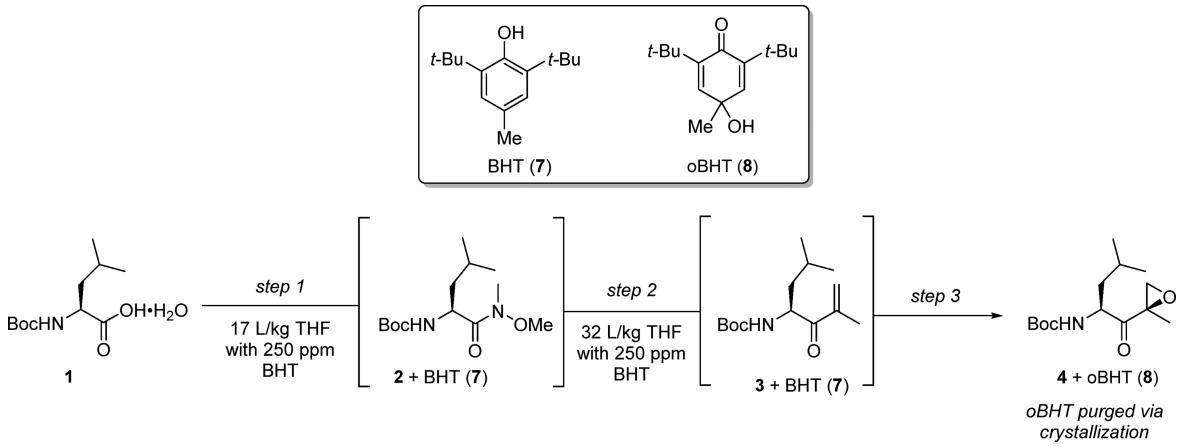
Scheme 3. Progression of BHT and oBHT through the Three-Step Synthesis of Epoxyketone 4



parameters and led to improvements that increase the process robustness.

IDENTIFICATION OF THE oBHT IMPURITY

BHT is an antioxidant and radical scavenging additive commonly found in many commercial ethereal solvents, commercial reagents supplied as solutions in these solvents,[13] various reagents that are prone to oxidative degradation, and certain commercial polymers. Impurity analysis performed in lab-scale studies identified oBHT (**8**) (Scheme 3) as an impurity formed during the bleach-mediated oxidation protocol (vide supra). In both of the preceding synthetic steps, Weinreb amide formation and Grignard addition, the reaction solvent is THF containing BHT as a stabilizer. The overall telescoped process results in accumulation of 3 wt % BHT (relative to enone **3**), which is converted to oBHT in the step 3 epoxidation reaction (Scheme 3).[14] By HPLC analysis, the liquid chromatography area percent (LCAP) of this impurity is amplified by the relative response factor of 4.3 relative to epoxyketone **4**. Crystallization was identified as the primary control point for purging of this impurity, as chromatographic separation was inefficient because of coelution of oBHT with epoxyketone **4**. An authentic sample of oBHT[15] was synthesized independently using $PhI(OAc)_2$ in order to perform fate-and-purge studies, which demonstrated that typical levels could be purged under the standard crystallization conditions. In view of the widespread use of ethereal solvents stabilized with BHT in manufacturing, this example highlights the importance of tracking related impurities, such as oBHT.

CONCLUSION

Detailed mechanistic understanding of the workup and isolation of an α-chiral enone, a bleach/pyridine epoxidation, and an impurity arising from the THF stabilizer BHT were performed that led to the identification of several opportunities for process improvements. Silica and carbonate/bicarbonate were found to have a synergistic effect leading to enhanced racemization of enone **3**, and bicarbonate was found to be partially converted to carbonate in the distillation step, exacerbating the effect. An improved workup procedure that prevents the entrainment of salts after workup, and removal of the silica plug, have been implemented. An investigation into the stability of bleach/pyridine mixtures for epoxidation showed that the quality of pyridine and the time for addition of bleach to pyridine were critical factors affecting the stability of bleach in pyridine. Furthermore, exothermic activity after reaction completion was found to be related to decomposition of residual bleach. Optimized processing conditions, testing of the pyridine raw material, and an in-process control to confirm the oxidizing power of the bleach/pyridine mixture resulted in a robust manufacturing process. Finally, oBHT was identified as an impurity resulting from the use of BHT in THF upstream of the oxidation step. Fate-and-purge studies of this impurity confirmed an effective control strategy. These three case studies demonstrate that detailed process understanding is critical to ensure robust commercial manufacturing. Part 2 in this series will present the development of a second-generation route to epoxyketone **4**.

EXPERIMENTAL SECTION

Preparation of *tert*-Butyl (*S*)-(2,6-Dimethyl-3-oxohept-1-en-4-yl)carbamate (3). Isopropenylmagnesium bromide (target 0.5 M in THF) was titrated prior to use, and charges were adjusted on the basis of the solution potency. Isopropenylmagnesium bromide (30.0 kg, 0.41 M, 13.3 mol) was charged to an inerted reactor, and the contents were cooled to an internal temperature of −10 °C. A solution of Weinreb amide **2** (1.46 kg, 5.30 mol) in THF (3.8 L, 2.6 L/kg) was then added to the reactor over 60 min while the internal temperature was maintained below −5 °C. The reaction mixture was warmed to an internal temperature of 25 °C and aged for 19 h. To a separate reactor, 30 wt % citric acid (8.7 L, 6.0 L/kg) and *n*-hexane (8.7 L, 6.0 L/kg) were charged, and the internal temperature was adjusted to 0 °C. The crude reaction mixture was charged to the biphasic citric acid/hexane mixture over 75 min while the internal temperature was maintained below 10 °C, and then the internal temperature was raised to 20 °C. The phases were allowed to separate, and the bottom aqueous phase was removed. The organic layer was washed sequentially with water (8.7 L, 6.0 L/kg), 8 wt % $NaHCO_3$ (8.7 L, 6.0 L/kg), and water (8.7 L, 6.0 L/kg). The resulting organic phase was concentrated to a volume of 2 L/kg under vacuum at a jacket temperature of 35 °C. *n*-Hexane (2.0 L, 1.4 L/kg) was charged, and the solution was polish-filtered. The solution was then concentrated to a volume of 2 L/kg under vacuum at a jacket temperature of 35 °C to afford a hexane solution of **2** (1.09 kg potency-corrected, 80% solution assay yield, 93.2 LCAP) with spectra identical to that previously reported in the literature.[16]

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Titration of Bleach/Pyridine Mixtures. Bleach concentration can be routinely measured by iodometric titration. This is typically accomplished by reducing hypochlorite using an excess of potassium iodide under acidic conditions according to

$$ClO^- + 2I^- + 2H^+ \rightarrow I_2 + Cl^- + H_2O$$

The I_2 species is then titrated with thiosulfate according to

$$I_2 + 2S_2O_3^{2-} \rightarrow 2I^- + S_4O_6^{2-}$$

However, pyridine has been observed to interfere with this method. To titrate bleach/pyridine mixtures, standard bleach titration protocols were adapted by adding additional HCl. In a typical procedure, a 0.2 M solution of sodium thiosulfate was standardized by titration of a solution of KIO_3. A bleach/pyridine mixture (prepared from addition of 11 wt % sodium hypochlorite (4.8 mL) to pyridine (12.9 mL) was diluted with water in a 100 mL volumetric flask. A 25 mL aliquot of this solution was then transferred to a conical flask and further diluted with ∼100 mL of water. Potassium iodide (2 g) was then added, and the flask was agitated until complete dissolution was observed. HCl (1 M, 200 mL) was then added. The solution was titrated with the standardized thiosulfate solution until a straw-yellow color was observed. A starch indicator solution (1 mL) was then added, forming a dark-blue solution. The titration was then continued until a clear end point was observed.

Preparation of *tert*-Butyl ((*S*)-4-Methyl-1-((*R*)-2-methyloxiran-2-yl)-1-oxopentan-2-yl)carbamate (4). Aqueous sodium hypochlorite (10 wt %, 3.4 L, 5.5 mol) was added over 90 min to a precooled (−10 °C) solution of pyridine (9.0 L, 13 L/kg) and water (0.84 L, 1.2 L/kg) at such a rate that the internal temperature remained below −5 °C. A sample of the bleach/pyridine suspension was pulled, and a use test was performed to ensure activity. A solution of enone **3** (700 g, 2.74 mol) in pyridine (0.78 L, 1.1 L/kg) was then charged over 45 min while the internal temperature was maintained below −10 °C. The batch was aged for an additional 4 h at −15 °C and then diluted with precooled (−10 °C) *n*-hexane (21 L, 30 L/kg) and water (5.6 L, 8.0 L/kg) at such a rate to maintain the internal temperature below −10 °C. The temperature of the biphasic mixture was adjusted to 0 °C, and the phases were allowed to separate. The lower aqueous layer was separated and back-extracted with *n*-hexane (14 L, 20 L/kg). The combined organic extracts were then washed sequentially with water (16 L/kg, 11.2 L), 10 wt % $NaHSO_4$ (10 kg/kg, 7 kg) two times, water (10 L/kg, 7.0 L), 30 wt % $Na_2S_2O_3$ (8 kg/kg, 5.6 kg), and water (10 L/kg, 7.0 L) two times. The resulting solution was distilled to an oil to provide crude epoxyketone **4** (284 g, 42% solution assay yield, 32.9 LCAP) with spectra identical to that previously reported in the literature.[17]

General Procedure for Racemization Studies. To a 2 dram vial were added enone **3** (25 mg), *n*-hexane (0.25 mL), and mesitylene as an internal standard. The appropriate solid (12.5 mg) was then added to the vials, and the mixtures were aged with stirring at the prescribed temperature. Samples were pulled for analysis via chiral HPLC.

2,6-Di-*tert*-butyl-4-hydroxy-4-methylcyclohexa-2,5-dien-1-one (oBHT). To a suspension of iodobenzene diacetate (93.2 g, 289 mmol) in MeCN (100 mL, 2.4 mL/g) and water (106 mL, 2.5 mL/g) at 20 °C was added a solution of BHT (42.5 g, 193 mmol) in MeCN (150 mL, 3.5 mL/g), followed by a rinse of the addition vessel with MeCN (70 mL, 1.6 mL/g). A modest exotherm was observed with a maximum internal temperature of 26 °C. The reaction mixture was aged at 20 °C for 18 h, diluted with EtOAc (340 mL, 8 mL/g), and washed twice with a saturated aqueous solution of NaCl (170 mL, 4 mL/g). The final organic phase was concentrated in vacuo and purified by column chromatography (5−15% EtOAc/heptane) to afford oBHT as a white crystalline solid (17.7 g, 38% yield, 97.1 wt %) with spectra identical to that previously reported in the literature.[18]

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Notes

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