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Org. Process Res. Dev., **Just Accepted Manuscript** • DOI: 10.1021/acs.oprd.7b00049 • Publication Date (Web): 02 Mar 2017

A Plant Process for the Preparation of Cinchona Alkaloid-Based Thiourea Catalysts

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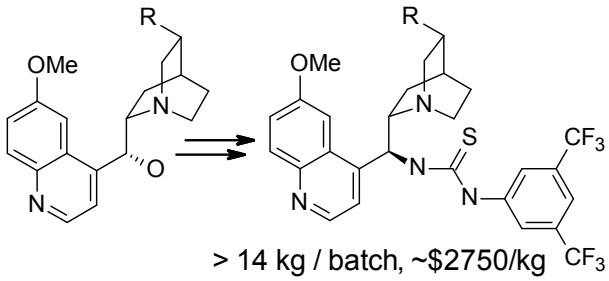

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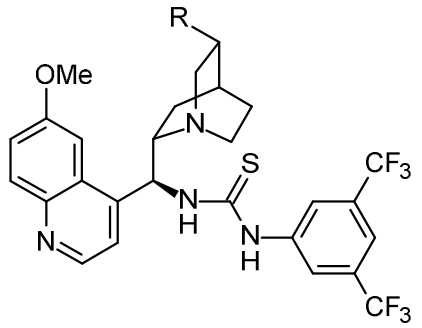
ABSTRACT Cinchona alkaloid-based thiourea catalysts (**1a** and **1b**) belong to an important class of bifunctional organocatalysts, which has been widely used for a variety of asymmetric reactions. The commercial availability of these catalysts is sporadic, and limited to the sub-gram quantities. Herein is described a general, scalable, and practicable process for the preparation of these catalysts that was used to synthesize more than 14 kg of catalyst per batch.

KEYWORDS Thiourea Cinchona Alkaloid Scaling-up

Introduction

Bifunctional, modified cinchona alkaloids represent a very important class of chiral organocatalysts.[1] The unique, bulky basic quinuclidine moiety, along with the incorporated hydrogen bond donors such as hydroxyl or thiourea groups, enables the simultaneous activation of both the nucleophilic and electrophilic reactants, enhancing the activity and enantioselectivity of a variety of reactions with a broad substrate scope. Unlike metal-based chiral catalysts, organocatalysts also have the advantage of removability, recoverability, and moisture and air stability. These attributes are highly desirable for the development of greener processes in the pharmaceutical industry.[2]



R = CH_2CH_3, **1a**; R = $CHCH_2$, **1b**

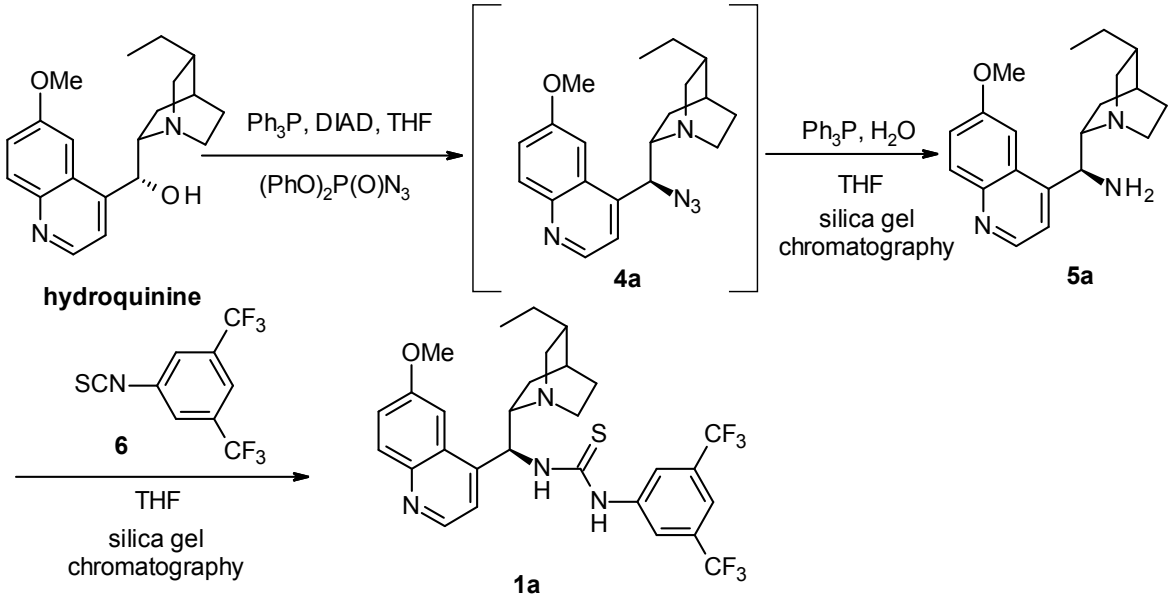
Figure 1. Cinchona Alkaloid-Based Thiourea Catalysts

With the progress made in one of our clinical programs, it became a high priority to have multi-kilogram quantities of the catalyst (**Figure 1**, **1a** or **1b**) at a reasonable price. Unfortunately, the commercial supply for both catalysts was limited to sporadic availability of sub-gram quantities at a premium cost.[3] The decision was made to prepare the catalyst in-house. Herein, we detail our efforts toward the development of a highly efficient process for the preparation of catalysts **1a** and **1b** with significant improvements on the robustness, scalability,

and practicability. The process was used to prepare kilo gram quantities of **1a** and **1b** in our kilo labs, and 25 kg of **1b** in our pilot plant at a cost of approximately $2750/kg.

Original Synthesis

The first synthesis of hydroquinine-based catalyst **1a** was reported by Soós's group in 2005 (**Scheme 1**).[4] The procedure consisted of three steps, including a Mitsunobu reaction, reduction, and coupling with isothiocyanate **6**. The isolation and chromatographic purifications were required for both intermediate **5a** and **1a** to furnish the product in over 95% purity. Although the procedure readily provided grams of product, it was not feasible to carry out on a much larger scale without modifications.



Scheme 1. Soós's Synthesis of **1a**

Process Development

Process improvement work using hydroquinine as the starting material began with screening solvents for the first stage Mitsunobu reaction in order to replace the water-miscible solvent THF

and thus simplify the workup. LC-MS analysis of the reaction mixture revealed the major side-product was the enamine **7a** (**Figure 2**), generated by the elimination of the secondary hydroxyl functionality. As shown in Table 1, several non-miscible solvents were found to provide similar or better impurity profiles, with CH_2Cl_2 affording the cleanest reaction (**Table 1**, Entry 3). Other benefits of CH_2Cl_2 included the possible reduction of the solvent volume by 50% (**Table 1**, Entry 5), and having the organic wash at the bottom layer, simplifying the workup.

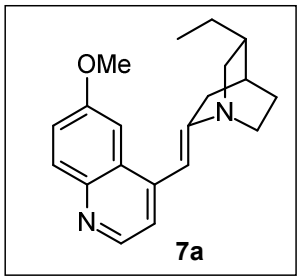


Figure 2. A possible structure of impurity **7a.**

Table1. Solvent Screening for Stage 1 Mitsunobu Reaction

Entry	Solvent	Azide 4a (A%)	Enamine 7a (A%)
1	2-MeTHF	85.7	7.1
2	THF	84.1	10.2
3	CH_2Cl_2	94.5	2.5
4	toluene	87.0	7.2
5	CH_2Cl_2*	92.1	3.0

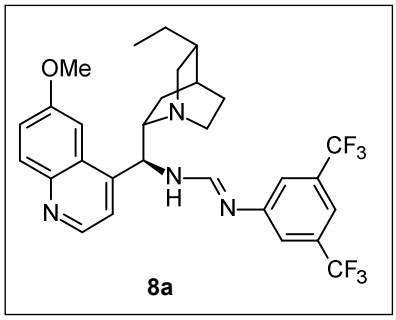
*The solvent volume was reduced by half.

The stage 2 reduction of azide **4a** required 1.8 equivalents of PPh_3 for complete conversion. Generally, the starting material disappeared in 3-4 hours, but the reaction was held for additional 7 hours to fully consume the intermediate.

The workup started by charging 3N HCl directly into the reaction mixture and allowing for a phase separation, which was easily achieved using CH_2Cl_2 as the solvent. Of note, the clear phase-cut was reached faster than when ethyl acetate was used as in the original process. The product amine **5a** and side product enamine **7a** stayed in the upper aqueous layer at acidic pH, while the unreacted triphenylphosphine and the side-product triphenylphosphine oxide remained in the bottom organic wash. It was found that the pH of the aqueous layer need to be adjusted to 2.0-2.5 for complete removal of the side products. Lower pH hinder the removal of triphenylphosphine oxide from the aqueous phase. The resulting acidic aqueous solution was basified with aqueous ammonia, and back-extracted with CH_2Cl_2. The product-containing organic phase was azeotropically dried until the water content was less than 1000 ppm. The residual solution was used directly in the next stage, coupling with the isothiocyanate **6**.

The stage 3 coupling reaction proceeded smoothly in methylene chloride with 3-4 small impurities (< 2 A% in total by HPLC analysis), including the remaining unreacted amine **5a**, and the carried-over enamine **7a**. These very polar impurities were found to be impossible to remove solely by recrystallization. An acid wash was developed to remove these impurities. Interestingly, only ethyl acetate could be used as the extraction solvent to facilitate this wash. Thus, the workup of stage 3 occurred with a solvent swap from methylene chloride to ethyl acetate, followed by an adjustment to pH 2-2.5 with 3N HCl. The very polar impurities formed HCl salts, staying in the bottom aqueous layer. The HCl salt of **1a**, however, stayed in the upper ethyl acetate layer as determined by LC-MS analysis. After the phase cut and subsequent removal of those impurities, the crude product solution was basified with aqueous ammonia and recrystallized to reach the target purity. It is worth noting that the basification step increased the amount of a new unknown impurity **8a** to 2-4 A%, as determined by LCMS. Further

optimization of the recrystallization reduced this impurity to less than 0.5 A% in the final product.



8a

Figure 3. A possible structure of impurity **8a.**

For the recrystallization of the final product, having the dissolution solvent boiling point higher than ethyl acetate was ideal to facilitate a complete solvent exchange before the recrystallization. Based on this, a small set of recrystallization experiments using either a single solvent or solvent mixtures were performed. The experiments started with dissolving crude **1a** at room temperature or elevated temperature in the selected solvents, then precipitating the product by either cooling down or by a charge of anti-solvents (**Table 2**). These experiments identified two solvent systems that gave a precipitate with good physical properties (**Table 2**, Entries 4 and 5). Between two solvent systems, acetonitrile provided better purity as it rejected impurity **8a** (**Figure 3**) more efficiently than *i*-PrOAc/heptanes solvent system. However, none of the recrystallizations reduced the polar impurities such as enamine **7a** or unreacted starting material amine **5a**, which confirmed the need for the acid wash described above. As expected, the recrystallization of the crude catalyst **1a** after the acid-base wash furnished more than 99 A% purity (**Table 2**, Entry 8) with preferred ACN system.

Table 2. Recrystallization Experiments of **1a**

Entry	Initial Purity (A%)	Solvent System (vol/vol)	Result	Purity (A%)
1	87.6	2-MeTHF/heptanes= 1/10	Gum first, then solid	90.0
2	87.6	MTBE/heptanes = 10/50	Gum first, then solid	95.4
3	87.6	*i*-PrOH/H_2O =2/4	Gum	89.4
4	87.6	*i*-PrOAc/heptanes = 2/20	Solid	95.6
5	87.6	CH_3CN = 4	Solid	97.6
6	87.6	*n*-BuOH/heptanes = 1/10	Solution	NA
7	87.6	$PhCH_3$ = 2	Gum	NA
8	95.0	CH_3CN = 4	Solid	99.2

An additional solubility study of **1a** in acetonitrile was carried out with Crystal-16® using pure **1a**, and the data was worked up with Crystalclear® to generate the solubility curve.[5] It was found that the solubility depended dramatically on the temperature, indicating a simple heating and cooling sequence should be able to achieve a crystallization with reasonable recovery. Finally, after further optimization of conditions, the recrystallization was performed in 1.8-2.0 volumes of acetonitrile. Typically losses were 7-10% when the product was collected at 0 °C. However, it was occasionally found that the slurry was too thick to stir. A few control experiments determined that residual water was the cause. As a result, the control of the solvent swapping process was modified to not only monitor the complete replacement of ethyl acetate, but also to control the water level below 1000 ppm.

When the process was scaled up in the kilo lab, two batches, each starting with 1.2 kg of hydroquinine, were carried out smoothly. Crude **1a** was obtained by concentrating the workup

mixture to dryness on the rotary evaporator. Two batches of crude **1a** were combined and recrystallized. Interestingly, upon the charge of acetonitrile, the product first dissolved and then precipitated immediately at room temperature, affecting the efficiency of the mixing. Good mixing could resume after heating the batch to 80 °C, and the recrystallization proceeded as expected from that point forward. Finally, 3.2 kg of **1a** was obtained, representing a 73.3% overall yield with 98 A% purity (**Table 3**).

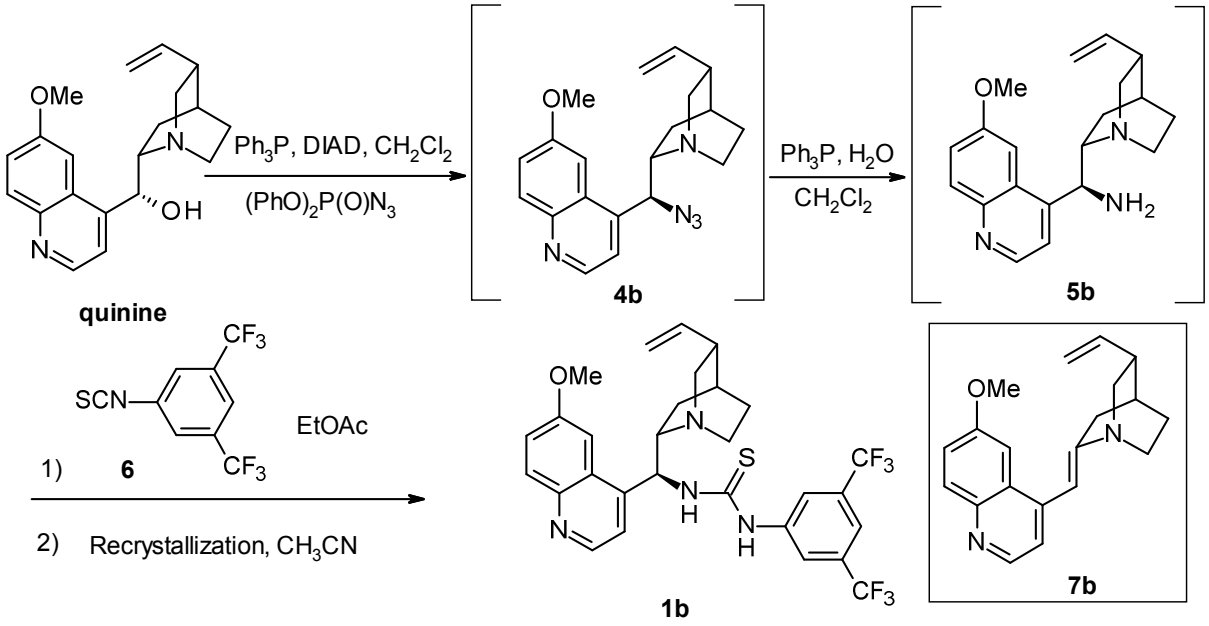
Table 3. Kilo Lab Synthesis of **1a**

Batch	Scale (kg)	Amine 5a (A%)	1a			
			Crude (A%)	Yield (kg)	Yield (%)	Purity (A%)
1	1.2	89.6	95.4	3.2	73.3	98.3
2	1.2	91.9	93.7			

When planning for further scale-up, it was found that sourcing of high-quality hydroquinine at more than 10 kg scale was surprisingly challenging and only possible through custom synthesis. On the other hand, quinine-based **1b** behaved similarly to **1a** in the targeted asymmetric reaction. The alternative starting material, quinine, was commercially readily available.

The process was further optimized for the preparation of **1b** by using ethyl acetate as both the extraction solvent for amine **5b** and the reaction solvent for the stage 3 coupling, eliminating the second solvent swap. Moreover, the final solvent swap from ethyl acetate to acetonitrile was performed without concentrating to dryness, eliminating the problem of fast precipitation

observed in the previous kilo lab campaign for the synthesis of **1a**, making the new process suitable for a pilot plant operation (**Scheme 2**).



Scheme 2. Final Plant Process for the Synthesis of **1b**

A complete hazard evaluation for the process of **1b** was performed before the pilot plant campaign. The reactants and intermediate streams were analyzed by Thermos Screening Unit (TSU) and Differential Scanning Calorimetry (DSC), indicating thermal stability up to at least 265 °C. The synthesis of **1b** from quinine is a three-step process containing at least 10 thermal events. The calorimetry of each thermal event was analyzed independently using the HEL Auto-MATE software, and results are summarized in **Table 4**.

In general, the thermal events were not significant because the maximum achievable temperatures were below the boiling points of the solvents and at least 200 °C below any potential thermal decomposition points. The only noteworthy event was triphenylphosphine solution dosing. If there were complete loss of control during the dosing, the maximum

achievable temperature would be sufficient to cause the solvent to boil. However, this boiling was a cooling event and served as an additional safety factor for the process. In the new process, the triphenylphosphine is dosed as a solution to provide better control than does portion-wise addition of the solid.

Table 4. Summary of Thermal Events for the Synthesis of **1b**

Process Step	**Total E in kJ (Q_r)**	**Q_r (kJ/kg of limiting reagent)**	**Q_r (kJ/kg of reaction mass)**	**Molar Heat of Reaction. [kJ / mole of Quinine (LR)]**	**ΔT K (°C)**
DIAD Dosing	5.00	500	51.5	162.1	34.3
Diphenyl Phosphoryl Azide Solution Dosing	4.69	469	44.9	152.0	28.0
DI Water Dosing	0.14	14	1.12	4.4	0.7
Triphenylphosphine Solution Dosing	9.70	970	70.3	314.7	37.0
3N HCl Dosing	2.37	237	14.1	76.8	6.7
Conc. Aqueous Ammonia Dosing	2.11	211	24.4	68.5	5.8
6 Solution Dosing	2.90	29	30.3	94.0	14.4
1N HCl Solution Dosing	0.74	74	6.3	23.9	3.0
Conc. Aqueous Ammonia Dosing	0.41	41	3.3	13.2	1.6
DI Water Dosing	0.48	48	3.3	15.6	1.7

Two batches were performed in the pilot plant at approximately 10 kg scale. The starting quinine was > 95% pure, and contained less than 5% hydroquinine. The process proceeded as

expected (**Table 5**), affording a total 26 kg of **1b** in two batches. The assay of approximately 96 wt% was dictated by the purity of the starting quinine. Fortunately, the major impurity **1a** is a similarly effective catalyst for the targeted reaction. Hence, **1a** as an impurity is not a concern for the present application.

Table 5. Pilot Plant Synthesis of **1b**

Batch	Quinine (kg)	1b			1a (A%)
		Yield (kg)	Yield (%)	Assay (wt%)	
1	11.0	14.2	70	95.3	3.9
2	10.3	12.2	65	96.4	2.8

Conclusion

In summary, we have demonstrated a robust, cost effective scalable process for the synthesis of hydroquinine- or quinine-based thiourea catalysts **1a** and **1b**. The process was successfully demonstrated in the pilot plant, affording over 14 kg of **1b** over four stages in a single 100 gal reactor. Moreover, the new process, consisting of three chemical reactions and one recrystallization, was performed in a single reactor, significantly improving the practicability and productivity of the synthesis.

Experimental Section

All materials were purchased from commercial suppliers. Unless otherwise noted, all reagents and solvents were used as supplied. NMR spectra were obtained using a Bruker 400 MHz spectrometer in the solvents indicated. HPLC spectra were collected on an Agilent 1200 series

instrument. Solubility was measured by Crystal 16® and the data was worked up with Crystalclear®.

Kilo lab Preparation of **1a**

To a 20 L jacketed glass reactor, equipped with condenser, thermocouple, and nitrogen sweep, was charged hydroquinine (1.20 kg, 3.68 mole, limiting reagent), and triphenyphosphine (1.16 kg, 4.41 mole, 1.2 equiv.). The batch was purged with nitrogen, dichloromethane (7.2 L, 6.0 V) was added, and the batch stirred at room temperature for approximately 30 minutes to obtain a clear solution. After cooling to approximately 0 °C, diisopropyl azodicarboxylate (DIAD, 0.888 kg, 4.41 mole, 1.2 equiv.) was charged through an addition funnel while keeping the batch below 5 °C. The addition funnel was rinsed with an additional dichloromethane (40 mL) and the wash was combined with the batch. After the batch temperature was stabilized at 0-5 °C, a solution of diphenyl phosphoryl azide (DPPA, 1.22 kg, 4.41 mole, 1.2 equiv.) in dichloromethane (1.2 L, 1.0 V) was charged while keeping the batch temperature at approximately 0 °C. The addition line was rinsed again with dichloromethane (100 mL) and combined with the batch. This addition took approximately 1 hour. The batch was warmed to approximately 20 °C, and stirring continued at this temperature for approximately 2 hours before an in-process control indicated a complete reaction.

The reduction procedure started with cooling the batch to approximately 15 °C. A total of 1.62 kg (1.35 V) of DI water was charged, followed by a solution of triphenylphosphine (1.74 kg, 6.62 mole, 1.8 equiv.) in dichloromethane (1.8 L, 1.5 V) at approximately 20 °C (Caution: N_2 off-gassing!). The batch was stirred at approximately 23 °C for 15-18 hours before quenching with 3N HCl (2.8 L) to pH 2.2. After partitioning, the product was in the upper aqueous layer,

which was washed twice with 3.12 L (2.6 V) of dichloromethane at ambient temperature. The dichloromethane layers were discarded. The pH of the aqueous layer was adjusted to > 10 with 28% aqueous ammonia (750 mL, 0.625 V), and extracted with two 3.12 L (2.6 V) portions of dichloromethane. The dichloromethane layers were combined and concentrated to dryness on rotary evaporator, affording 1.52 kg of crude **5a** as a yellow oil. The residue was dissolved in dichloromethane (3.0 L, 2.5 V) and concentrated to dryness. The residue was dissolved again in dichloromethane (3.0 L, 2.5 V), at which point the water content was 328 ppm by KF analysis. This solution of crude **5a** was used in the next step without further manipulation.

The coupling reaction commenced with charging the above solution into a 20 L jacketed glass reactor, equipped with a condenser, thermocouple and nitrogen sweep. The container was rinsed with dichloromethane (3.0 L, 2.5 V) and the rinse combined with the batch. The reaction mixture was cooled to approximately 0 °C, and 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**6**) (898 g, 3.31 mole, 0.9 equiv.) in dichloromethane (2.4 L, 2 V) was charged while keeping the reaction temperature below 10 °C. The addition took approximately 35 minutes to complete. The resulting solution was warmed to approximately 20 °C and stirred for 1 hour until in-process control indicated a complete reaction. The batch was transferred into a rotary evaporator and concentrated to dryness under vacuum. The residue was re-dissolved in ethyl acetate (9.6 L, 8 V) and charged back to the reactor. The batch was acidified with 1N HCl (4.0 L, 3.3 V) to approximately pH 2. The batch was partitioned, and the upper organic layer was washed with of DI water (4 L, 3.3 V), and then adjusted to pH >10 with 28% aqueous ammonia (950 mL, 0.8 V). The reaction mixture was partitioned again and the bottom aqueous layer was discarded. The upper organic layer was washed with DI water (2.4 L, 2 V), and concentrated to dryness on a

rotary evaporator. The residue was azeotropically dried with dichloromethane (39 L, 32.5 V) to afford a waxy yellow solid, which was further dried under full house vacuum with a nitrogen sweep at ambient temperature for an additional 2 days to furnish 1.99 kg (90.7% yield) of crude **1a** in 95.2 A% purity with 614 ppm of water.

The second lot of crude **1a** was prepared with 1.20 kg of hydroquinine using the same process, affording 2.13 kg (97.1% yield) of product in 95.1 A% purity with 461 ppm of water.

The above two lots of crude **1a** (4.12 kg) were combined and charged into a 20 L jacketed glass reactor, equipped with a condenser, thermocouple and nitrogen sweep. The containers were each rinsed with 2L (0.49 V) of acetonitrile and the rinse combined with the batch. An additional portion of acetonitrile (3.4 L, 0.83 V) was charged. The product precipitated immediately, and the stirrer was blocked. The reactor was opened and the solid was broken up manually with a paddle. After the stirring was resumed, the reactor was re-sealed and the atmosphere rendered inert with nitrogen. The batch was heated to 80 °C to furnish a clear solution, cooled back to approximately 20 °C, and stirred for 1 hour before cooling further to approximately 0 °C. The batch was stirred at this temperature for an additional 17 hours then filtered on a 6 L Büchner funnel. The filter cake was washed twice with 2.0 L (0.49 V) of cold acetonitrile, and dried in the funnel for approximately 42 hours until no weight loss was observed over a period of 2 hours. Finally, 3.21 kg of **1a** was obtained, representing a 73.3% overall yield in 98.3 A% purity. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 0.75-0.82 (m, 4H), 1.15-1.27 (m, 3H), 1.39-1.46 (m, 2H), 1.55 (brs, 1H), 1.60-1.63 (m, 1H), 2.40-2.44 (m, 1H), 2.65-2.73 (m, 1H), 3.18 (dd, J = 3.6, 13.2 Hz, 1H), 3.26-3.29 (m, 1H), 3.97 (s, 3H), 6.02 (brs, 1H), 7.45 (dd, J = 2.4, 9.2

Hz, 1H), 7.61 (d, J = 4.8 Hz, 1H), 7.69 (s, 1H), 7.94 (brs, 1H), 7.96 (d, J = 9.2 Hz, 1H), 8.15 (s, 2H), 8.74 (d, J = 4.4 Hz, 1H), 8.92 (brs, 1H). 10.22 (brs, 1H). ^{13}C NMR (100.59 MHz, DMSO-d_6) δ 11.79, 24.73, 25.06, 26.73, 28.04, 36.57, 41.01, 55.55, 56.71, 59.27, 102.98, 119.07, 120.54, 123.14 (d, J_{CF} = 273.6 Hz), 121.21, 127.96, 130.31 (q, J_{CF} = 33.2 Hz), 131.13, 141.67, 143.96, 145.05, 147.58, 157.01, 179.37. HRMS-ESI (m/z): $[M+H]^+$ Calcd for $C_{29}H_{31}F_6N_4OS$: 597.2117; found: 597.2123.

Pilot Plant Synthesis of **1b**:

A 100 gallon glass-lined jacketed reactor was inerted with nitrogen. Quinine (11.0 kg, 33.9 mole, limiting reagent) and triphenylphosphine (10.7 kg, 40.7 mole, 1.2 equiv.) were charged via EZDock bags. This was followed by the charge of methylene chloride (88.2 kg, 6 V). The batch was agitated at about 26 °C for approximately 2 hours to obtain a clear solution. After cooling the batch to approximately 5 °C, a solution of diisopropyl azodicarboxylate (DIAD, 8.20 kg, 40.7 mole, 1.2 equiv.) was charged from an addition tank over approximately 1 hour while maintaining the temperature below 10 °C. The addition tank and transfer lines were rinsed with additional methylene chloride (2.70 kg, 1V), and the rinse combined with the batch. This was followed by the charge of a solution of diphenylphosphoryl azide (DPPA, 11.3 kg, 40.7 mole, 1.2 equiv.) in methylene chloride (14.8 kg, 1 V) over approximately 2.5 hours while maintaining the batch temperature below 10 °C. Following the addition, the batch was heated to approximately 20 °C and agitated for an additional 19 hours until HPLC indicated a complete reaction.

The batch was cooled to approximately 15 °C, and DI water (14.9 kg, 1.35 V) was charged, followed by a solution of triphenylphosphine (16.0 kg, 61.0 mole, 1.8 equiv.) in methylene

chloride (21.7 kg, 1.5 V) over approximately 50 minutes (Caution: Off-gassing!). After the addition, the batch was warmed to approximately 25 °C and stirred overnight until the reaction was complete. Workup started with quenching the batch with 3 N HCl over approximately 1 hour until the pH reached 2.5. The agitation was stopped, and the batch was held at ambient temperature for approximately 1 hour to obtain a clear phase cut. The upper aqueous layer was washed twice with 38.4 kg of methylene chloride (5.2 V). The batch was adjusted with 28% aqueous ammonia (15.8 kg) to pH 10.0, extracted with ethyl acetate (98.7 kg, 10 V), and washed with saturated brine (37.2 kg). The resulting solution was distilled under vacuum (ca. 250 mmHg), while charging ethyl acetate in portions, until KF analysis indicated 410 ppm of water in the solution. At the end of the distillation, the batch consisted of approximately 8 V of ethyl acetate.

The batch was cooled to approximately 0 °C, and a solution of 3,5-bis(trifluoromethyl)phenyl isothiocyanate (**6**) (8.30 kg, 30.5 mole, 0.9 equiv.) in ethyl acetate (19.8 kg, 2V) was charged into the batch over 30 minutes while maintaining the temperature at approximately 0 °C. After the addition, the batch was warmed to approximately 20 °C and stirred for an additional 1 hour until reaction completion. The batch was quenched with 1N HCl (37 L) until the pH reached 2.0-2.5, stirred for an additional 20 minutes, and held until a clear phase cut was reached. The lower aqueous layer was drained and discarded. The upper organic layer was washed with DI water (37.5 kg, 3.4 V), and the pH was adjusted to over 10 with 28% aqueous ammonia. Additional DI water (34.1 kg, 3.1 V) was charged, and the batch was agitated for 10 minutes. The agitation was stopped, and the layers were allowed to separate. The lower aqueous layer was drained and discarded. The upper organic layer was heated to 40 °C and washed with an additional portion of DI water (34.4 kg, 3.1 V). Agitation was stopped and the batch was held for approximately 5

hours at 40 °C, allowing for a clear phase cut. The lower aqueous layer was drained and discarded. The upper organic layer was vacuum distillated (ca. 200 mmHg) while charging acetonitrile (10 V) in portions, until the KF analysis indicated 339 ppm of water remaining. The solution contained 43.3 wt% of **1b**.

The batch was cooled to approximately 0 °C over 1 hour, and agitated at 0 °C for an additional 16 hours. Solids precipitated when the batch reached 31.5 °C. The product was isolated in an Aurora filter, and the filter cake was washed with approximately 8.80 kg of acetonitrile. The product was dried under vacuum at 50 °C for 3 days, affording 14.2 kg of catalyst **1b** as a white solid, representing a 70.7 % yield. The HPLC assay was 95.3 wt%, with 3.9 A% of the hydroquinine-based catalyst **1a** as the major impurity. ^{1}H NMR (DMSO-d_6, 400 MHz): δ = 0.77-0.83 (m, 1H), 1.22-1.28 (m, 1H), 1.56-1.63 (m, 3H), 2.28 (brm, 1H), 2.67-2.72 (m, 2H), 3.21 (dd, *J* = 10.0, 13.2 Hz, 1H), 3.24-3.33 (m, 2H), 3.97 (s, 3H), 4.94 (d, *J* = 10.4 Hz, 1H), 5.00 (d, *J* = 17.2 Hz, 1H), 5.83 (ddd, *J* = 7.6, 10.4, 17.2 Hz, 1H), 6.04 (brs, 1H), 7.45 (dd, *J* = 2.8, 9.2 Hz, 1H), 7.62 (d, *J* = 4.8 Hz, 1H), 7.70 (S, 1H), 7.94 (S, 1H), 7.96 (d, *J* = 9.2 Hz, 1H), 8.15 (s, 2H), 8.74 (d, J = 4.8 Hz, 1H), 8.96 (d, J = 4.8 Hz, 1H), 10.21 (brs, 1H). ^{13}C NMR (100.59 MHz, DMSO-d_6) δ 25.27, 26.92, 27.34, 40.96, 55.05, 55.61, 59.33, 103.02, 114.22, 115.78, 120.62 (brs), 121.24, 123.18 (q, *J* = 272.6 Hz), 127.97, 130.36 (q, *J* = 33.2 Hz), 131.18, 141.68, 141.89, 144.01, 144.91, 147.61, 157.08, 179.43. HRMS-ESI (m/z): $[M+H]^+$ Calcd for $C_{29}H_{29}F_6N_4OS$: 595.1961; found: 595.1975.

ASSOCIATED CONTENT

Supporting Information. HPLC methods used for in process control and final product analysis. HPLC spectrums of the intermediates and final products **1a** and **1b**. NMR spectral data of

compounds **1a** and **1b**. Solubility curves of **1a** and **1b** in acetonitrile. These materials are available free of charge via the Internet at http://pubs.acs.org.

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

ACKNOWLEDGMENT

We wish to thank Jianzhong Li, Jennifer Van De Rijn, and Raeann Wu for analytical assistance; Vincent Djuhadi and Shahar Barak for procurement support. We also thank the operation team including Crispin Cebula, Russell Craig, Robert Cummins, and Steven Mangos for pilot plant support, as well as helpful discussion with Partha Mudipalli and Jing Fang.

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