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Multikilogram Synthesis of a Hepatoselective Glucokinase Activator

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Supporting Information

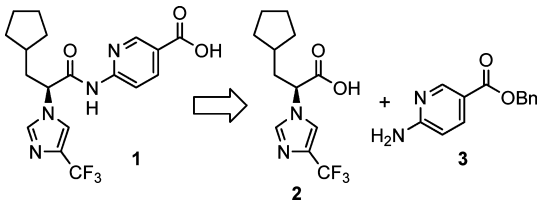
ABSTRACT: This work describes the process development and manufacture of early-stage clinical supplies of a hepatoselective glucokinase activator, a potential therapy for type 2 diabetes mellitus. Critical issues centered on challenges associated with the synthesis of intermediates and API bearing a particularly racemization-prone α-aryl carboxylate functionality. In particular, a T3P-mediated amidation process was optimized for the coupling of a racemization-prone acid substrate and a relatively non-nucleophilic amine. Furthermore, an unusually hydrolytically-labile amide in the API also complicated the synthesis and isolation of drug substance. The evolution of the process over multiple campaigns is presented, resulting in the preparation of over 110 kg of glucokinase activator.

INTRODUCTION

Glucokinase (GK, also known as hexokinase IV) is an enzyme which mediates glucose metabolism in the liver and insulin release in the pancreas.[1] Pharmaceutical agents that act as glucokinase activators have been shown to increase the activity of GK and have been positioned as promising therapies for the treatment of type 2 diabetes mellitus,[2] a condition afflicting over 340 million people worldwide.[3] Systemic glucokinase activators impact the activities of this enzyme in both the liver and pancreas,[4] whereas hepatoselective activators are specific to the enzyme in the liver and are hypothesized to have better safety profiles with respect to hypoglycemia.[5] While there are no GK activators approved for market, this field is very active,[6] and several activators are currently in clinical trials.[2]

Herein, we describe the development of a manufacturing route to hepatoselective glucokinase activator **1** for early-phase clinical studies. Our convergent approach to **1** relies on the penultimate amide condensation of acid **2** and aminonicotinate **3** (Scheme 1), a strategy derived from the original medicinal chemistry synthesis.[5] As outlined in Scheme 2, the discovery route comprises six steps and starts with copper-catalyzed alkylation of (*R*)-methyl glycidate (**4**) by cyclopentylmagnesium bromide to provide hydroxy ester **6**. Activation of the hydroxyl group as its triflate ester (**7**) was followed by an alkylation with 4-(trifluoromethyl)imidazole (**8**) to generate an 85:15 mixture of regioisomers **9** and **10** that were separated by chromatography. This alkylation was particularly sensitive as excess base promoted racemization of the product, and so the reaction was conducted with excess triflate (1.5 equiv relative to imidazole **8**) and a substoichiometric amount of LHMDS (0.9 equiv) as the limiting reagent. Hydrolysis of ester **9** to acid **2** was accomplished in 6 M aq HCl at near-reflux temperature. With **2** in hand, the amide bond was formed in a two-step process involving activation of the acid as its acid chloride followed by isolation and treatment with aminonicotinate **3** and pyridine. Final hydrogenation of the benzyl ester with H_2 and Pd/C in a pressure vessel provided crude **1** which was reslurried in Et_2O to crystalline active pharmaceutical ingredient (API).

Scheme 1. Retrosynthetic Approach to 1



Aggressive project timelines allowed us only a brief opportunity to explore alternative synthetic routes to **1**. We decided to retain the existing end-game coupling of acid **2** and aminonicotinate **3** and initially focused our efforts on developing an alternative preparation of **2**. One promising approach installs the stereogenic center via asymmetric hydrogenation of an enamine precursor (Scheme 3). Enamine **15** was prepared as a 93:7 mixture of *Z*/*E*-isomers over two steps from **12** by enolate addition to aldehyde **13** and subsequent dehydration.[7] Unfortunately, asymmetric hydrogenation of enamine **15** via dynamic kinetic resolution[8] provided **16** with only low to moderate chiral purity, the best result being 73% ee from the complexed catalyst [$Rh(cod)_2BF_4$/Josiphos (*R*,*S*)-PPF-P(*t*-Bu)$_2$].[9]

We also investigated alternative preparations of the chiral hydroxy ester **6** (Scheme 4). Screening the enzymatic reduction[10] of keto ester **17** identified several hits, and ADH-T[11] in isopropanol (IPA) and pH 6.5−7.5 buffer provided the best results with

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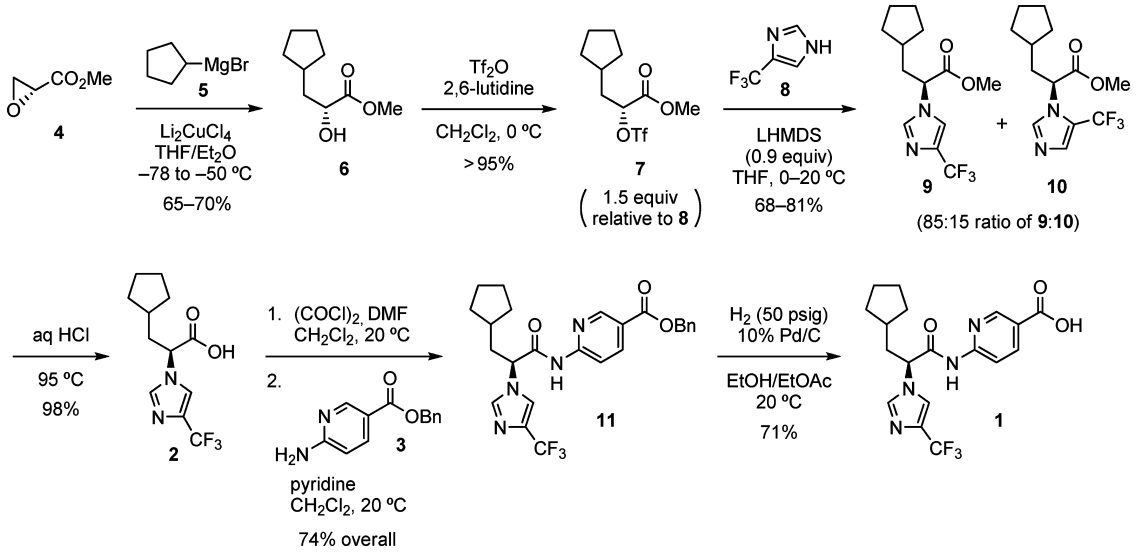
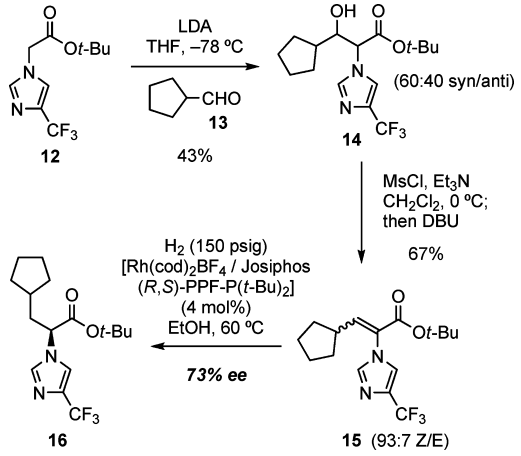
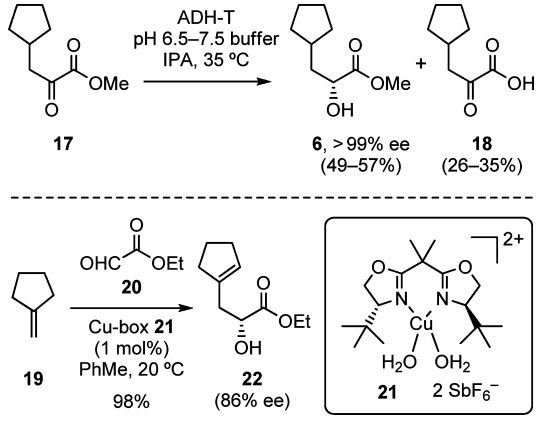
Scheme 2. Medicinal Chemistry Synthesis of 1



Scheme 3. Asymmetric Hydrogenation of Enamine 15



Scheme 4. Alternative Preparations of the α-Hydroxy Ester

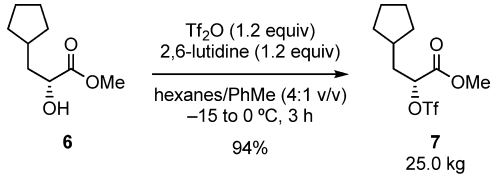


>99% ee **6** but also keto acid **18** as a substantial byproduct. Unfortunately, pH adjustment did not suppress hydrolysis to **18**, and time constraints did not allow for the investigation of more robust keto esters. The preparation of α-hydroxy ester **22** via asymmetric carbonyl-ene reaction of methylenecyclopentane (**19**) and ethyl glyoxalate (**20**) was also explored. Adduct **22** was synthesized in high yield using the Evans protocol[12] with Cu(II) complex **21**; however, this method provided the hydroxy ester with lower chiral purity (86% ee) than other approaches and required eventual hydrogenation of the cyclopentene. On the basis of these results, we elected to externalize the synthesis of **6** from methyl glycidate (which itself was prepared from serine[13]) and enable the medicinal chemistry route.

PROCESS DEVELOPMENT

Triflation of 6 to 7. Using the discovery conditions (1.7 equiv of Tf_2O, 2.1 equiv of 2,6-lutidine, CH_2Cl_2)[5] as a starting point for optimization, we determined that the triflation proceeded to completion using as little as 1.2 equiv each of Tf_2O and 2,6-lutidine at 0 °C (Scheme 5).[14] The reaction is

Scheme 5. Triflation of 6



dose-controlled and strongly exothermic (250 kJ/mol) with respect to Tf_2O addition. To minimize chlorinated solvents, heptane and mixtures of heptane/CH_2Cl_2 were initially explored for triflation; ultimately, heptane was replaced with lower-boiling hexanes as a precaution to allow for concentration at lower temperatures, thus minimizing the risk of thermal decomposition of **7** on workup. The choice of 20 vol% CH_2Cl_2 in hexanes proved optimal as the lutidinium triflate salts formed in the process are insoluble in hexanes and interfered with reaction agitation in the absence of cosolvent, but with a small amount of dichloromethane present they crystallized gradually during Tf_2O addition. In subsequent campaigns, the CH_2Cl_2 was replaced with toluene which performed similarly, and the higher boiling point of toluene proved not to be an issue during vacuum concentration on workup.[15]

Quenching with aq HCl extracted the 2,6-lutidine and triflate salts, and phase separation was greatly facilitated by hexanes as the primary solvent. On gram scale, it was possible to dry the crude product solution with $MgSO_4$ and concentrate to obtain

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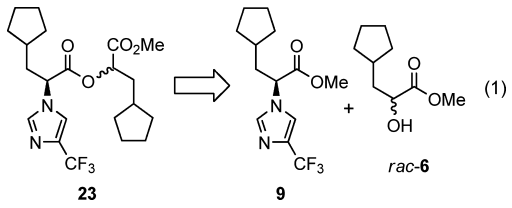
triflate **7** as an oil; however, this approach afforded product which decomposed on storage with the development of color and precipitation of polymeric impurities. We recognized during workup development that most of the color from the reaction mixture remained with the drying agent ($MgSO_4$) after filtration, and we substituted silica gel with improved results. Thus, the shelf life and quality of the triflate **7** were extended substantially by simple filtration through silica gel, and after concentration, the resulting oil was stable for several days. On scale, the solution was concentrated to low volume and used directly in the subsequent step without additional manipulation. This process was executed several times on 20 kg scale with yields always greater than 90%.

Imidazole Alkylation to 9. While seemingly a straightforward transformation, the alkylation of 4-(trifluoromethyl)imidazole (**8**)[16] with triflate **7** proved quite complex. The discovery conditions treated 1.0 equiv of imidazole **8** with 0.9 equiv of LHMDS in THF at 0 °C followed by 1.5 equiv of triflate **7** and warming to 20 °C (Scheme 2).[5] These conditions provided inconsistent results, and under the best of circumstances the alkylation proceeded with some racemization (1% *ent*-**7** to 7% *ent*-**9**) to afford an 85:15 mixture of regioisomers **9** and **10**, both oils requiring chromatography for separation. Moreover, any excess base from the incidental overcharge of LHMDS resulted in additional loss of stereochemical fidelity in the product, and LiOH from adventitious water led to competitive ester hydrolysis. The reaction demonstrated only modest regioselectivity and poor overall economy, as a substantial excess of the costly **7** and **8** were used relative to the base.

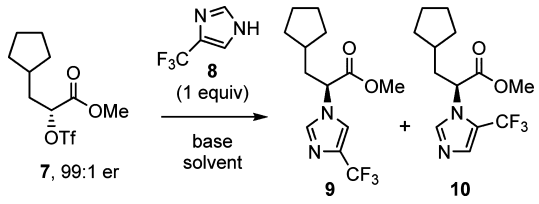
Process development began with the screening of milder bases while restricting the reaction stoichiometry to equimolar **7** and **8** and optimizing for rate, regioselectivity, and extent of racemization (Table 1). Reactions with carbonate or phosphate bases in THF generated heterogeneous slurries that could be filtered on workup for simple base removal. Alkylations promoted by K_3PO_4 proceeded with excellent regioselectivity (96:4) at 20 °C but with substantial racemization (65:35 er). Switching to K_2CO_3, a slightly weaker base, suppressed formation of *ent*-**9** while still providing excellent regioselectivity for **9** over **10**, and replacing THF with MeCN increased the rate of alkylation (entries 10−12).[17] Slower reactions were observed when switching from stir-bar agitation (on a smaller scale) to overhead mixing (on a larger scale), which suggests the benefit of particle size reduction in this process even when employing powdered K_2CO_3.[18] On a larger scale, complications from using MeCN as solvent became more apparent. First, the higher solubilities of K_2CO_3, $KHCO_3$, and KOTf complicated the separation of these salts by simple filtration. Second, pseudodimer **23** (<10%; ∼1:1 dr) was detected from the transesterification of **9** with the racemate of alcohol **6** (eq 1). The latter presumably



was racemized via carbonate displacement of the triflate,[19] although **6** can also be regenerated from triflate hydrolysis by water derived from the disproportionation of $KHCO_3$.[20] Switching to less-polar EtOAc (entry 15) provided **9** with excellent regioselectivity (96:4) and chiral purity (97:3 er) while also suppressing the formation of pseudodimer **23**. This latter benefit is likely due to the lower solubility of K_2CO_3 in EtOAc.[21]

When this chemistry was scaled in the kilo lab (Scheme 6), the alkylation proceeded with 96:4 regioselectivity and modest racemization (∼1% *ent*-**7** to 3.0% *ent*-**9**). The triflate was fully consumed within 2 h, and the batch was expedited to workup, as laboratory pilots demonstrated that prolonged reaction times erode the chiral purity of product (10% *ent*-**9** after 24 h). Filtration of the suspended potassium salts was aided by first diluting with methyl *tert*-butyl ether (MTBE), and solvent exchange to toluene provided a 50 wt% solution of **9** (containing 4% **10**; 98% combined yield) for subsequent ester hydrolysis. Optimizations prior to larger-scale processing resulted in the further suppression of racemization to 1.6% *ent*-**9** by replacing K_2CO_3 with K_3PO_4 and cooling the process to 0 °C. This result is notable considering the substantial racemization observed when using K_3PO_4 at 20 °C in THF (Table 1, entry 7). Adding MTBE to the reaction mixture prior to workup lowered the solubility of phosphate salts and suppressed further chiral degradation

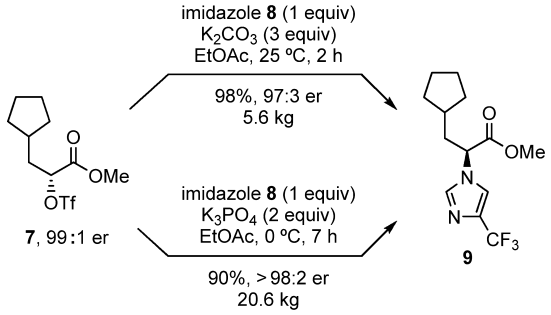
Table 1. Conditions for Imidazole Alkylation



entry	base (equiv)	solvent	*T* (°C)	yield[a] (%)	**9**:**10**	er (**9**)
1	LHMDS (0.9)	THF	0	---	85:15	93:7
2	*i*-Pr_2NH (3)	THF	0	46	94:6	---
3	Et_3N (3)	THF	20	43	89:11	---
4	*i*-Pr_2NEt (3)	THF	20	73	83:17	---
5	K_2HPO_4 (3)	THF	20	<5	---	---
6	K_3PO_4 (1)	THF	20	79	96:4	---
7	K_3PO_4 (3)	THF	20	98	96:4	65:35
8	Na_2CO_3 (3)	THF	20	<5	---	---
9	$KHCO_3$ (3)	THF	20	<5	---	---
10	K_2CO_3 (3)	THF	0	80	96:4	96:4
11	K_2CO_3 (3)	THF	20	90	96:4	96:4
12	K_2CO_3 (3)	MeCN	20	96	95:5	97:3
13	K_2CO_3 (3)	THF/PhMe	20	67	96:4	---
14	K_2CO_3 (3)	2-MeTHF	20	58	96:4	---
15	**K_2CO_3 (3)**	**EtOAc**	**20**	**95**	**96:4**	**97:3**

[a]In situ yield based on conversion after 1 h (stir-bar agitation).

Scheme 6. Alkylation of Imidazole 8



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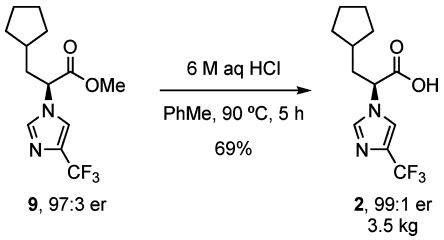
which was otherwise observed during the filtration as the mixture warmed in the filter. This reoptimized process provided multiple 20 kg batches of **9** (containing 4% **10**) typically with >90% yields. Of note, some variability in reaction outcomes (degradation in alkylation rate and chiral purity of the product) appears to stem from variations in the purity and particle size of K_2CO_3 and K_3PO_4, and efforts are underway to quantify these influences.

Ester Hydrolysis of 9 to 2. Medicinal chemistry accomplished the hydrolysis of methyl ester **9** in 6 M aq HCl (20 vol) at 95 °C (Scheme 2).[5,22] These conditions were evaluated, and after reducing the HCl to 6 vol, the hydrolysis proceeded to 90% conversion within 15 min at 90 °C but stalled at 95% with extended heating. We suspected the residual ester was due to an equilibrium between acid **2** and starting material, and the removal of MeOH via distillation during heating drove the hydrolysis to completion. No racemization was detected under these strongly acidic conditions.

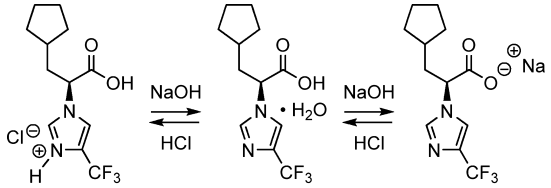
On scale-up in the kilo lab, ester **9** was carried into the hydrolysis as a toluene solution telescoped from the previous step. After HCl addition, the biphasic mixture was heated until hydrolysis proceeded to completion (Scheme 7). One benefit of

Scheme 7. Acid-Catalyzed Hydrolysis of 9



this biphasic system is that acid **2** partitions to the aqueous phase as the hydrochloride salt, whereas toluene retains trace organic impurities that are removed upon phase separation. Initially, we tried a "bottom-up" approach[23] to crystallize **2** directly from the aqueous phase for convenient isolation. To this end, the aqueous phase was neutralized with NaOH to pH 3 and **2·HCl** oiled from solution and quickly hardened to amorphous solids which converted to crystalline monohydrate (**2·H₂O**) on extended granulation (Scheme 8).[24] The equilibration of **2·HCl**

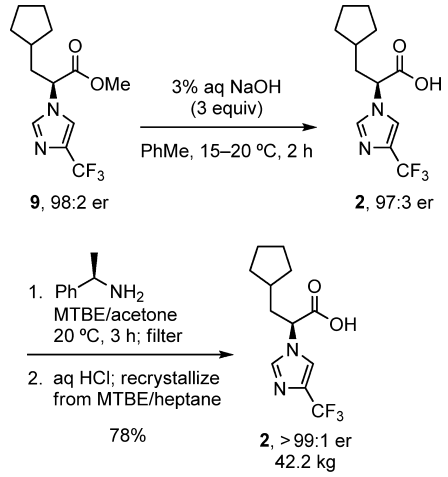
Scheme 8. pH Effect on the Solubility of 2



to **2·H₂O** releases HCl to the aqueous mother liquor, and careful monitoring was necessary to maintain pH 3 during crystallization. (Incidental overcharging of NaOH redissolves the solids as the sodium carboxylate **2·Na** which can be converted back to **2·H₂O** without degradation by readjusting to pH 3 with HCl.) Although modest yields (40–45%) of **2·H₂O** could be obtained directly by filtration, this material cocrystallized with varying amounts of NaCl and performed poorly in subsequent amide couplings due to the presence of water. Alternatively, **2** was extracted from the aqueous slurry into EtOAc and recrystallized from heptane. This purification provided 3.5 kg of anhydrous acid (<0.1% H_2O; 69% yield) as dense white solids while reducing *ent*-**2** to 0.7% and completely purging the regioisomer derived from **10**.

An alternative, base-catalyzed hydrolysis proved more amenable to larger-scale operations (Scheme 9). By replacing HCl

Scheme 9. Base-Catalyzed Hydrolysis of 9 and Classical Resolution



with aq NaOH, saponification proceeded in the biphasic toluene/aqueous mixture at 15–20 °C with only slight racemization (1.6% *ent*-**9** to 2.8% *ent*-**2**). Hydrolysis was complete within 2 h, and extending the reaction times did not degrade the chiral purity, which is consistent with our previous observation that the sodium salt of **2** (**2·Na**; Scheme 8) is stable in alkaline solutions. Acidifying the aqueous phase to pH 3 crystallized **2** from the biphasic mixture, and the crude acid was collected by filtration. Although recrystallization of this filtered material from EtOAc/heptane provided **2** in 50–60% yield (99:1 er), greater yields and chiral purities were obtained via an intermediate crystallization of a salt prepared by mixing the crude acid with (*R*)-α-methylbenzylamine. After breaking this salt, the free acid was isolated from MTBE/heptane to provide 40 kg batches of **2** (78% yield for hydrolysis and resolution) with only 0.5% *ent*-**2** and complete purging of the regioisomer derived from **10**.

Amide Coupling of 2 and 3. In the discovery process, **2** was converted to the acid chloride under standard conditions (oxalyl chloride, CH_2Cl_2, catalytic DMF), and the reaction mixture was concentrated to an oil and reconcentrated twice from dichloroethane (Scheme 2).[5] The acid chloride was then redissolved in CH_2Cl_2 and treated with aminonicotinate **3**[25] and pyridine. After an aqueous workup and solvent removal, the crude amide **11** was either recrystallized from EtOAc or purified through silica gel to provide off-white solids. While this approach was serviceable for small-scale work, we preferred a one-step amidation on a larger scale to avoid the handling and isolation of a sensitive, activated acid intermediate. It seemed likely that the substrate would be susceptible to racemization based on the sensitivity of previous intermediates. Compounding this concern, aminonicotinate **3** appeared to be a relatively poor nucleophile that might require a strongly-activated electrophile or

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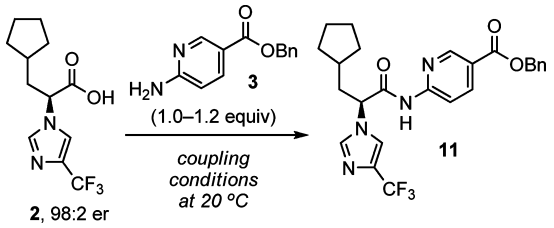
forcing conditions for coupling. Thus, what initially seemed a relatively straightforward amidation required a rather extensive development effort. Furthermore, efforts to reproduce medicinal chemistry's recrystallization of amide **11** from EtOAc provided inconsistent results.

An early screen of amide coupling reagents[26] validated our concerns about substrate racemization, as activated intermediates derived from **2** proved sensitive to chiral degradation under various conditions (Table 2).[27] Initial couplings of **2** and **3** with

Table 2. Screening Reagents for the Coupling of 2 and 3

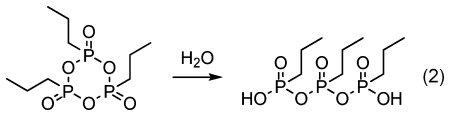


entry	conditions	er (**11**)[a]
1	CDI, THF	50:50
2	CDMT, NMM, MeCN	70:30
3	CDMT, 2,6-lutidine, MeCN	ND[b]
4	DEPBT, EtN(*i*-Pr)$_2$, THF	50:50
5	DCC, HOAt, DMF	93:7
6	DCC, HOAt, CH_2Cl_2	98:2
7	DCC, CH_2Cl_2	98:2
8	EDC, CH_2Cl_2	ND[b]
9	EDC·HCl, CH_2Cl_2	94:6
10	EDC·HCl, HOAt, DMF	60:40
11	HATU, EtN(*i*-Pr)$_2$, DMF	86:14
12	HATU, EtN(*i*-Pr)$_2$, CH_2Cl_2	96:4
13	HATU, 2,6-lutidine, CH_2Cl_2	87:13
14	HATU, pyridine, CH_2Cl_2	97:3

[a]In situ ratio prior to workup. [b]Not determined due to poor conversion.

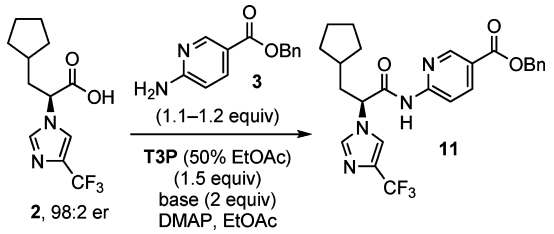
CDI, CDMT, EDC, or DEPBT[28] proceeded with substantial or complete racemization and were abandoned. The best conditions with DCC and HATU provided the amide with only slight racemization; however, these reagents are not ideal for large-scale processing and were not optimized further.

Greater success was achieved using T3P (**24**; *n*-propanephosphonic acid anhydride; eq 2)[29] for the one-pot conden-



sation of **2** and **3**.[30,31] Upon dosing mixtures of **2** and **3** with T3P in the presence of base, it was not surprising to observe a correlation between base strength and racemization, with weaker bases providing the amide with less *ent*-**11** (Table 3).[27] As a general trend, bulkier bases also provided **11** with greater enantiopurity, which is illustrated by comparing the results from TMP (80:20 er) versus Et_3N (54:46 er) or *N*-ethylmorpholine (94:6 er) versus *N*-methylmorpholine (92:8 er). The use of 4-(dimethylamino)pyridine (DMAP) as a nucleophilic catalyst diminished the chiral purity of **11**, as the resulting acylpyridinium species appears more susceptible to racemization than its T3P-activated precursor. Ultimately, the best results were obtained

Table 3. Optimizing T3P-Mediated Amidation to Minimize Racemization



entry	base[a]	DMAP	*T* (°C)	er (**11**)[b]
1	none	none	20	NR
2	Et_3N	20 mol%	20	54:46
3	TMP	20 mol%	20	80:20
4	TMP	none	20	90:10
5	NMM	20 mol%	20	80:20
6	NMM	none	20	92:8
7	NEM	none	20	94:6
8	2,6-lutidine	20 mol%	20	93:7
9	2,6-lutidine	20 mol%	0	95:5
10	2,6-lutidine	none	20	95:5
11	2,6-*t*-Bu-4-Me-py	20 mol%	20	96:4
12	pyridine	20 mol%	20	96:4
13	pyridine	none	20	97:3
14	**pyridine**	**none**	**0**	**98:2**

[a]TMP = 2,2,6,6-tetramethylpiperidine; NMM = *N*-methylmorpholine; NEM = *N*-ethylmorpholine. [b]In situ ratio prior to workup.

using pyridine bases, and combinations of T3P and 2,6-lutidine or pyridine proved sufficiently robust to execute on scale.

Table 4 details the evolution of T3P conditions for the coupling of **2** and **3** over several campaigns. For initial scale-up (entry 1), a mixture of acid, aminonicotinate, and 2,6-lutidine in EtOAc was dosed with T3P (50% in EtOAc)[32] while cooling to control a mild exotherm, and holding the homogeneous mixture at 20 °C afforded amide **11** with ~3% racemization (0.7% *ent*-**2** to 4.0% *ent*-**11**). After a water quench, 2,6-lutidine and residual **3** were extracted with a series of aq citric acid and water washes. Interestingly, the final water wash triggered an uncontrolled crystallization of amide from the water-saturated EtOAc phase. These solids were collected and combined with the organic phase, and processing concluded with a slurry of amide in EtOAc/CH_2Cl_2 to provide 4.3 kg of **11** (75% yield) with >99% achiral purity and only 1.4% *ent*-**11**.

For subsequent campaigns, a series of process changes were implemented to improve reaction performance. Replacing 2,6-lutidine with pyridine[33] at 0 °C further suppressed racemization (Table 3, entry 14), the charge of **3** was reduced to 1.1 equiv, and the solvent loading was reduced from 10 to 2 vol (Table 4, entries 2 and 3). These more-concentrated conditions led to a viscous but homogeneous solution in which amide **11** was formed with only slight racemization (0.5% *ent*-**2** to 1.3−1.8% *ent*-**11** over multiple batches). Since the amide precipitates readily from water-saturated EtOAc, we were able to implement an efficient direct-drop isolation[23] by quenching with aqueous HCl to crystallize **11** as the free base with 0.7−0.9% *ent*-**9** and rejection of excess **3** and pyridine. However, this isolation also required some optimization prior to scaling. When the reaction solvent was EtOAc, the resulting solids were gummy and slow to filter from the biphasic mother liquor.[34] The filtered amide also contained 0.5−1.0% phosphonate **25** from T3P hydrolysis (eq 2) that poisoned the catalyst in downstream hydrogenation.

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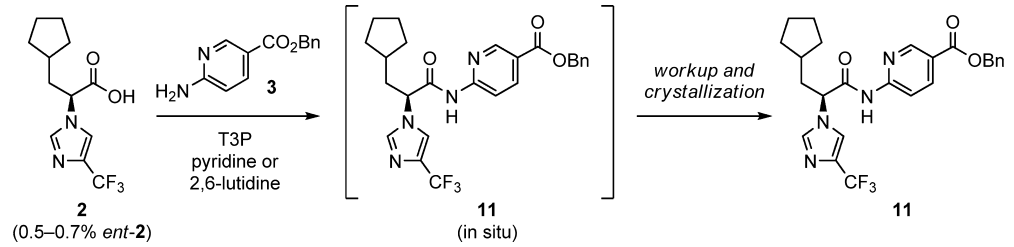
Table 4. Evolution of T3P Conditions for the Coupling of Acid 2 and Amine 3



2 (0.5–0.7% *ent*-**2**) **11** (in situ) **11**

campaign	conditions	*ent*-**11** (in situ)	workup	**11** (isolated)[a]
1	amine **3** (1.2 equiv), T3P (50% EtOAc), 2,6-lutidine EtOAc (10 vol), 20 °C, 6 h	4.0%	H_2O quench; aq citric acid washes; slurry in EtOAc/CH_2Cl_2	4.3 kg (1.4% *ent*-**11**), 75% yield
2	amine **3** (1.1 equiv), T3P (50% EtOAc), pyridine EtOAc (2 vol), 0 °C, 20 h	1.3–1.8%	aq HCl quench; filter and reslurry in H_2O	44.1 kg (0.7–0.9% *ent*-**11**), 86% yield
3	amine **3** (1.1 equiv), T3P (50% EtOAc), pyridine EtOAc (2 vol), 0 °C, 20 h	1.3–1.8%	aq HCl quench; add MeCN and slurry	62.0 kg (0.3–0.5% *ent*-**11**), 84% yield
4	amine **3** (1.1 equiv), T3P (50% MeCN), pyridine MeCN/EtOAc (2:1 v/v; 8 vol), 0 °C, 20 h	1.6%	aq HCl quench and slurry	34.1 kg (0.5% *ent*-**11**), 88% yield

[a]All batches isolated with >99% achiral purity.

This impurity was purged to <0.1% by reslurrying the filtered material in water, and the purified solids (>44 kg; 86% yield over two batches) proved easy to filter (Table 4, entry 2).

Before the next scale-up, the workup was modified to provide well-filtered and phosphonate-free material without a rework. To this end, in laboratory pilots, EtOAc was distilled from the crystallization slurry after HCl quench and replaced with a water-miscible cosolvent to generate a fine suspension of **11** that was easily filtered (Figure 1). MeCN proved superior to

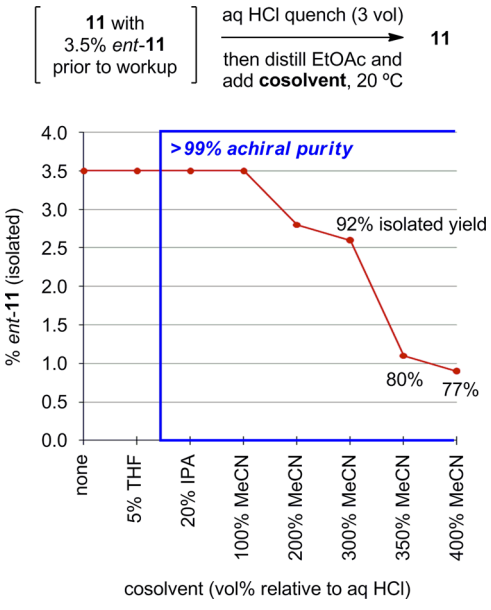


Figure 1. Exchanging EtOAc with water-miscible cosolvents for the improved crystallization of amide **11**.

other cosolvents with respect to the purging of **3**, pyridine, and phosphonate **25** (<0.1%), although substantial dilution (400 vol%) was needed to reduce *ent*-**11** to <1%. As a more-straightforward alternative to solvent exchange, simple dilution of the quenched EtOAc/aq HCl mixture with MeCN afforded the amide with the same purity upgrade (Table 4, entry 3). A large volume of MeCN (15 vol) was required to create a well-filtered suspension of amide in a monophasic mother liquor; with less added solvent, the solids still retained a gummy texture and rafted at the interface of the organic and aqueous layers of the mother liquor. In the plant, this revised workup was used to crystallize 62 kg of **11** (84% yield over two batches) directly from the reaction mixture without the need for a rework (0.3–0.5% *ent*-**11**; <0.05% **25**). On the basis of the success of MeCN as a cosolvent for this crystallization, the process was further refined to employ acetonitrile as the primary solvent for amide formation. As such, an optimal ratio of 2:1 v/v MeCN/EtOAc improved the mobility of the reaction mixture and allowed for enhanced stirring during amide formation, crystallization, and filtration (Table 4, entry 4). This solvent system was incorporated into a fourth-generation process in which T3P was charged as a 50% solution in MeCN, and simply quenching with aq HCl crystallized **11** (>34 kg; 88% yield) in excellent purity (>99% achiral, 0.5% *ent*-**11**, <0.05% **25**) without the need for additional MeCN dilution or rework.

Hydrogenation of 11 to 1. In the final deprotection, the discovery conditions for the synthesis of **1** from benzyl ester **11** employed 10% Pd/C (10 wt%) and H_2 (50 psig) in large volumes of EtOH/EtOAc (Scheme 2).[5] The mixture was filtered and concentrated to a foam that was reslurried in Et_2O to provide crystalline **1**. This process was slightly modified for the first scale-up in the kilo lab (Scheme 10), with the most notable changes being the replacement of EtOH/EtOAc with IPA, a reduction in catalyst loading (10 to 5 wt%) and solvent volume (20 to 6 vol), and the direct crystallization of **1** from IPA/heptane. Interestingly, no difference in reaction rate was observed when varying concentrations, as **11** has low solubility in IPA, and the rate of hydrogenation appears to be dissolution limited. Under 50 psig of H_2, debenzylation proceeded without racemization. Dilution of the mixture with heptane prior to filtration facilitated the removal of colloidal Pd residues and provided a clear and colorless filtrate. Concentration at 45 °C followed by heptane dilution and gradual cooling to 15 °C crystallized 2.7 kg of **1** (75% yield) as the desired polymorph[35]

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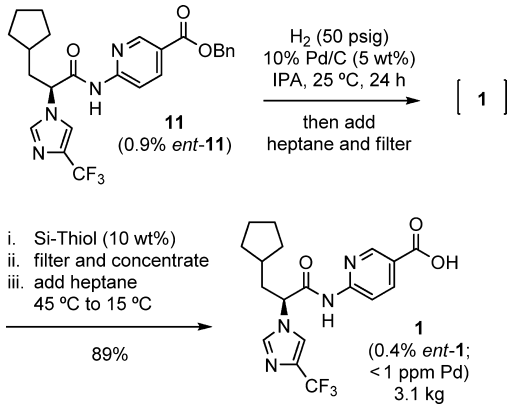
Scheme 10. Optimized Pressure Hydrogenation of Benzyl Ester 11 to API 1



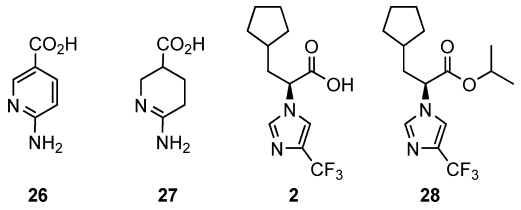


Figure 2. Byproducts from hydrogenation in wet IPA.

with 0.6% *ent*-**1** and 78 ppm Pd. The crystallized API also contained 0.1% aminonicotinic acid (**26**) and 0.5% reduced aminonicotinic acid **27**, two byproducts from amide bond cleavage (Figure 2, vide infra). For a reload campaign, this process was modified to incorporate Si-Thiol as a metal scavenger after the IPA/heptane filtration, and reducing the amount of IPA relative to heptane for crystallization provided **1** with improved yield (3.1 kg; 89% yield), a similar purity profile including 0.4% *ent*-**1**, and substantially improved metal content (<1 ppm Pd).

An unexpected sensitivity of the amide bond to hydrolysis and solvolysis from hydrogenation in wet IPA (~50% water-wet Pd/C) became apparent when analyzing the mother liquors from these crystallizations. In addition to the 0.1% **26** and 0.5% **27** that were observed in the isolated API, the filtrate also contained 5% acid **2** and 5% isopropyl ester **28** (Figure 2). The lack of pyridine-reduction byproducts with the amide still intact suggests that **27** is derived from **26** (or its benzyl ester **3**) after amide bond cleavage. Stability studies also revealed the slow decomposition of **1** to **2** and **28** in wet IPA, illustrating the susceptibility of **1** to hydrolysis and solvolysis during the relatively benign conditions employed for the workup and crystallization.

The need to address these degradation issues and accommodate larger batch sizes drove a redevelopment of the hydrogenation process. To avoid operational constraints associated with limited pressure vessel availability and size, we implemented a transfer hydrogenation process.[36] 1-Methyl-1,4-cyclohexadiene[37] and formic acid[38] were screened as possible hydrogen donors, and IPA[36] was avoided as a hydrogen source due to concerns over amide solvolysis. Debenzylation was not observed using wet Pd/C and methylcyclohexadiene, whereas formic acid facilitated the clean conversion of benzyl ester **11** to **1** without racemization. Remarkably, no amide hydrolysis was observed from transfer hydrogenation using water-wet catalyst and formic acid, even at elevated temperatures. Initial pilots in 10% v/v HCO_2H in EtOAc (10 vol total; 13 equiv of HCO_2H) at 55 °C proceeded to completion within 3 h using 20 wt% of

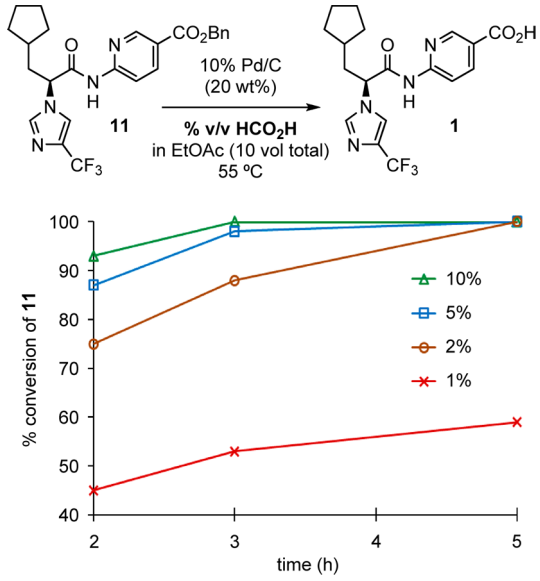


Figure 3. Relative conversions of **11** in HCO_2H/EtOAc mixtures with different vol% HCO_2H.

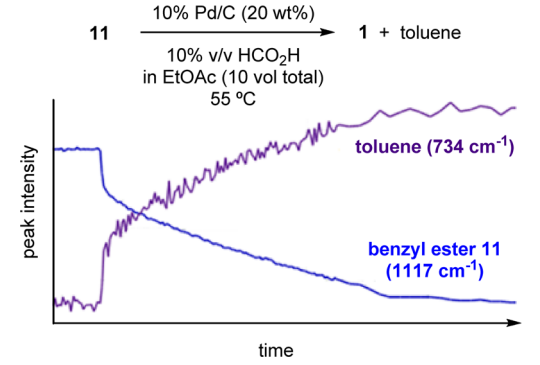


Figure 4. FTIR monitoring of the transfer hydrogenation of benzyl ester **11** to API **1**.

10% Pd/C. As expected, the rate decreases with the volume percentage of formic acid (Figure 3) and also varies with the type of Pd/C.[39] The catalyst loading was held at 20 wt% for transfer hydrogenation on large scale, as reaction times doubled with only 10 wt%. Real-time reaction monitoring via FTIR (Figure 4) revealed an induction period in which a period of zero conversion is followed by a very sharp increase in reaction rate. The length of the induction period (typically <2 h) varies between Pd/C types (and batches of the same type) due to factors that have yet to be fully elucidated.

On scale, this process performed exactly as anticipated. Interestingly, the initial run using Johnson Matthey (JM) type A402028−10 catalyst required a second charge of Pd/C to drive the hydrogenation to completion, whereas all subsequent runs used JM type 10R487 catalyst and proceeded to completion without requiring an additional catalyst charge. The reaction proceeded without racemization or amide hydrolysis, which is consistent with laboratory pilots and again noteworthy considering the presence of water in the reaction mixture from the catalyst and also from the observed competitive dehydration of HCO_2H to CO and H_2O.[40] We measured 40−50 L of gas per mole of **11** released to the headspace over the course of this transfer hydrogenation, which accounts for the offgassing of CO_2,

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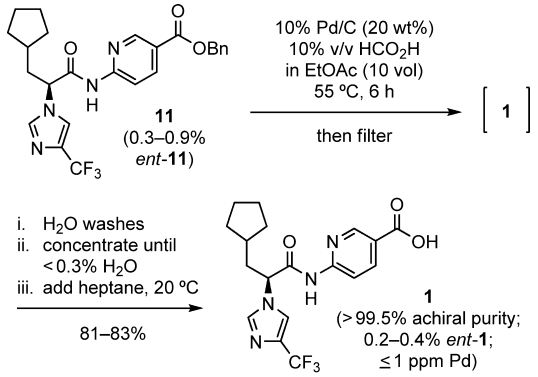
excess H_2, and CO (detected but not quantified). Interestingly, HPLC analysis of the reaction mixture over the course of hydrogenation showed a near-constant 9:1 v/v solvent ratio of EtOAc to HCO_2H, which suggests that HCO_2H consumption is offset by EtOAc evaporation from heating a vented mixture. Upon reaction completion, the mixture was cooled and filtered to provide a colorless solution of API in HCO_2H and EtOAc. After extracting the formic acid into aqueous washes,[41] the resulting solution of **1** was concentrated to low volume and azeotropically dried via constant-volume distillation from EtOAc until <0.3% H_2O. This drying was necessary to prevent the oiling of API on subsequent heptane addition, which led to the crystallization of **1** as the desired polymorph[35] with excellent purity (>99.5% with 0.2−0.4% *ent*-**1**; no detection of byproducts **26** or **27**) (Scheme 11). Of particular note, very low levels of Pd

Scheme 11. Transfer Hydrogenation of Benzyl Ester 11 to API 1



(≤1 ppm) were retained in the API without metal-scavenger treatment. This process was executed five times above 20 kg scale with consistent 81−83% yields to synthesize over 110 kg of glucokinase activator **1**.

CONCLUSIONS

In this work, we have described the early-stage process development of a robust and scalable synthesis of a hepatoselective glucokinase activator for clinical activities. In addition to solving typical process-related issues, this project uncovered difficult obstacles associated with particularly racemization-prone intermediates and an unusually hydrolytically-labile amide in the API. In solving these issues, improved and general conditions were developed for the coupling of racemization-prone carboxylic acids with relatively non-nucleophilic amines,[30] and specific challenges associated with regioselective imidazole alkylation and the hydrogenation of nicotinic acid-containing amides were addressed.

EXPERIMENTAL SECTION

All achiral HPLC data were obtained using an Agilent Zorbax SB-CN column (4.6 × 150 mm) with a 10-min method (10:90 MeCN/0.1% aq $HClO_4$, 0.5 min isocratic, 2.5 min ramp to 50:50 MeCN/aqueous, 5.0 min ramp to 90:10 MeCN/aqueous, 2.0 min isocratic at 90:10) at 25 °C and 2.0 mL/min flow rate. Chiral HPLC data for **9** were obtained using a Chiralpak AD-RH column (4.6 × 150 mm) with an isocratic 60:40 water/MeCN method at 40 °C and 0.8 mL/min flow rate. Chiral SFC data for **2** were obtained using a Chiralpak AD-H column (4.6 × 250 mm) with an isocratic 85:15 CO_2/MeOH method at 40 °C, 150 bar outlet pressure, and 2.5 mL/min flow rate. Chiral HPLC data for **11** were obtained using a Chiralpak OD-RH column (4.6 × 150 mm) with an isocratic 70:30 MeCN/water method at 40 °C and 0.8 mL/min flow rate. Chiral SFC data for **1** were obtained using a Chiralpak IC column (4.6 × 250 mm) with an isocratic 80:20 CO_2/phase B method at 40 °C, 150 bar outlet pressure, and 4.0 mL/min flow rate (phase B = 0.3% *i*-$PrNH_2$ and 0.3% HCO_2H in 75:25 MeOH/MeCN).

(*R*)-Methyl 3-Cyclopentyl-2-(trifluoromethylsulfonyloxy)-propanoate (7). A stirred solution of alcohol **6** (15.0 kg, 87.1 mol), hexanes (130 L), toluene (30 L), and 2,6-lutidine (11.7 kg, 109 mol, 1.25 equiv) was held at −15 °C as triflic anhydride (29.6 kg, 105 mol, 1.20 equiv) was added over 2 h at < −5 °C. The resulting mixture was held at −10 °C for 30 min and then warmed to 0 °C. A solution of 0.1 M aqueous HCl (150 L) was added over 20 min at <10 °C, and the resulting biphasic mixture was warmed to 20 °C and stirred for 30 min. The organic layer was separated and passed through a filter preloaded with silica gel (10 kg) with the aid of 4:1 v/v hexanes/toluene (60 L). The filtrate was concentrated under vacuum (<30 °C, 0.1 bar) to provide 25.0 kg of triflate **7** (94% yield). An analytical sample of **7** was purified by silica gel chromatography (3% EtOAc/hexanes) as a clear oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.14 (dd, J = 3.6, 8.4 Hz, 1H), 3.85 (s, 3H), 2.04−2.14 (m, 1H), 1.81−2.02 (m, 4H), 1.53−1.71 (m, 4H), 1.10−1.20 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.8, 118.4 (q, J_{CF} = 317 Hz), 83.3, 53.0, 38.1, 35.5, 32.6, 31.9, 25.0, 24.9; ^{19}F NMR (376 MHz, $CDCl_3$) δ −74.9. HRMS-ESI m/z: $[M+H]^+$ calcd for $C_{10}H_{15}F_3O_5S$, 305.0665; found, 305.0670.

(*S*)-Methyl 3-Cyclopentyl-2-(4-(trifluoromethyl)-1*H*-imidazol-1-yl)propanoate (9). *Alkylation with K_2CO_3.* A stirred solution of triflate **7** (5.99 kg, 19.7 mol) and imidazole **8** (2.68 kg, 19.7 mol, 1.0 equiv) in EtOAc (51 L) was charged with K_2CO_3 (8.16 kg, 59.1 mol, 3.0 equiv) in one portion at 25−30 °C. The resulting slurry was held at 25 °C for 2 h, diluted with MTBE (15 L), and held for 1 h before passing through a Celite-packed Nutsche filter. The filter cake was rinsed with MTBE (45 L), and the combined filtrates were washed three times with water (60 L per wash). The organic layer was concentrated to 8 L (30 °C, 0.1 bar), diluted with toluene (10 L), and distilled at 30−40 °C (0.1 bar) at constant volume with the continuous addition of toluene (60 L). The solution was concentrated to 8 L and diluted again with toluene (5 L) to obtain 5.62 kg of imidazolyl ester **9** (containing 4% regioisomer **10**; 98% combined yield) as a 50 wt% solution in toluene (11.25 kg total solution) that was telescoped directly into ester hydrolysis. An analytical sample of **9** was purified by silica gel chromatography (25% EtOAc/hexanes) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.41 (s, 1H), 4.74 (dd, J = 6.0, 9.2 Hz, 1H), 3.78 (s, 3H), 2.04−2.16 (m, 2H), 1.45−1.82 (m, 7H), 1.06−1.21 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 137.7, 132.4 (q, J_{CF} = 39 Hz), 121.4 (q, J_{CF} = 265 Hz), 118.4 (q, J_{CF} = 4 Hz), 59.6, 52.8, 39.0, 36.0, 32.2, 31.6, 24.8, 24.7; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.8. HRMS-ESI m/z: $[M+H]^+$ calcd for $C_{13}H_{17}F_3N_2O_2$, 291.1315; found, 291.1319. Achiral HPLC: rt 4.9 min (**9**), 4.7 min (**10**). Chiral HPLC: rt 14.4 min (**9**), 10.8 min (*ent*-**9**).

Alkylation with K_3PO_4. A stirred solution of triflate **7** (24.0 kg, 78.9 mol) and imidazole **8** (10.8 kg, 79.4 mol, 1.0 equiv) in EtOAc (240 L) was charged with K_3PO_4 (33.6 kg, 158 mol, 2.0 equiv) in

five equal portions at −10 to 0 °C. The resulting slurry was held at 0 °C for 7 h, diluted with MTBE (74 L), and held for 1 h before passing through a Celite-packed Nutsche filter. The filter cake was washed four times with MTBE (30 L per wash), and the combined filtrates were washed three times with water (240 L per wash). The organic layer was separated, concentrated to 30−40 L (30 °C, 0.2 bar), and diluted with toluene (48 L) to obtain 20.6 kg of imidazolyl ester **9** (containing 4% regioisomer **10**; 90% combined yield) as a ∼30 wt% solution in toluene (75.9 kg total solution) that was telescoped directly into ester hydrolysis. An analytical sample of **9** was purified by silica gel chromatography (25% EtOAc/hexanes) as a pale yellow oil with physical and analytical data matching those reported above.

(*S*)-3-Cyclopentyl-2-(4-(trifluoromethyl)-1*H*-imidazol-1-yl)propanoic Acid (2). *Acid-Catalyzed Hydrolysis.* A stirred, biphasic mixture of ester **9** (5.62 kg of **9** + **10**, 18.6 mol of **9** corrected for 4% **10**) in toluene (6 L) and 6 M aqueous HCl (34 L) was heated at 90 °C for 5 h and cooled to 20 °C. The phases were separated, and the aqueous layer was held at <40 °C while charging with 50% aqueous NaOH (10 L). The mixture was adjusted to pH 3 with the addition of 6 M aq HCl or 6 M aq NaOH as necessary at <30 °C. The resulting suspension was mixed at 5 °C for 12 h while readjusting to pH 3 as necessary. The solids were extracted into EtOAc (56 L), and the organic layer was dried over Na_2SO_4 (11 kg) and passed through a Celite-packed Nutsche filter. The filter cake was rinsed with EtOAc (56 L), and the combined filtrates were concentrated to 12 L (50 °C, 0.1 bar). The solution was diluted with EtOAc (11 L) and distilled at 78 °C at constant volume with the continuous addition of EtOAc (45 L). The solution was concentrated to 18 L, cooled to 25 °C, and diluted with heptane (39 L) to precipitate solids. The mixture was heated at 65 °C for 1 h to redissolve the solids and cooled to 15 °C over 2 h. The recrystallized solids were mixed at 15 °C for 12 h, collected on a Nutsche filter, rinsed with heptane (10 L), and dried at 45 °C under vacuum with N_2 sweep to obtain 3.53 kg of acid **2** (69% yield) as a white solid: mp 160−161 °C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 13.42 (br s, 1H), 7.95−7.97 (m, 2H), 5.06 (dd, J = 4.4, 11.2 Hz, 1H), 2.20 (ddd, J = 5.2, 11.2, 14.0 Hz, 1H), 2.02 (ddd, J = 4.4, 9.2, 14.0 Hz, 1H), 1.69−1.76 (m, 1H), 1.49−1.61 (m, 3H), 1.36−1.47 (m, 3H), 1.09−1.18 (m, 1H), 1.01−1.08 (m, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 171.3, 139.2, 129.9 (q, J_{CF} = 37 Hz), 122.1 (q, J_{CF} = 265 Hz), 120.2 (q, J_{CF} = 4 Hz), 59.0, 37.4, 36.4, 31.9, 31.3, 24.6, 24.3; ^{19}F NMR (376 MHz, d_6-DMSO) δ −60.7. HRMS-ESI m/z: [M + H]$^+$ calcd for $C_{12}H_{15}F_3N_2O_2$, 277.1158; found, 277.1160. Achiral HPLC: rt 4.4 min. Chiral SFC: rt 4.6 min (**2**), 2.0 min (*ent*-**2**).

Base-Catalyzed Hydrolysis. A solution of ester **9** (58.9 kg of **9** + **10**, 195 mol of **9** corrected for 4% **10**) in toluene (140 L) was added to a stirred solution of NaOH (24.4 kg, 610 mol, 3.1 equiv) in water (790 L) over 4 h at 15−20 °C. The biphasic mixture was held at 20 °C for 2 h and adjusted to pH 3 with conc HCl (45 L) at 15−20 °C. The resulting suspension was mixed at 20 °C for 30 min and passed through a Nutsche filter, and the filter cake was rinsed sequentially with toluene (90 L) and 0.01 M aqueous HCl (40 L). The filtered solids were dried under vacuum at 45 °C, dissolved in MTBE (510 L) and acetone (55 L), and charged with a solution of (*R*)-(+)-α-methylbenzylamine (25.9 kg, 214 mol, 1.1 equiv) in MTBE (68 L) at 15−25 °C. The resulting suspension was mixed at 20 °C for 3 h and passed through a Nutsche filter, and the filter cake was rinsed with MTBE (290 L). The filtered solids were redissolved in MTBE (320 L) and water (450 L) and held at 15−20 °C while adjusting to pH 3 with the addition of 12% aqueous HCl (56.4 kg). The mixture was held at 20 °C for 30 min, and the organic layer was washed twice with 0.01 M aqueous HCl (84 L per wash). The organic layer was concentrated to 120−150 L (40 °C, 0.2 bar), diluted with heptane (310 L), and re-concentrated to 300−350 L (40 °C, 0.2 bar). The mixture was cooled to 20 °C and passed through a Nutsche filter. The filter cake was rinsed with heptane (42 L) and dried under vacuum at 40 °C to provide 42.2 kg of acid **2** (78% yield) as a white solid with physical and analytical data matching those reported above.

(*S*)-Benzyl 6-(3-cyclopentyl-2-(4-(trifluoromethyl)-1*H*-imidazol-1-yl)propanamido)nicotinate (11). A stirred mixture of acid **2** (22.00 kg, 79.64 mol), amine **3** (20.00 kg, 87.62 mol, 1.1 equiv), pyridine (22 L, 270 mol, 1.0 vol), MeCN (110 L), and EtOAc (57 L) was charged with T3P solution (50 wt% MeCN, 101 kg, 104 L, 159 mol, 2.0 equiv) at −5 °C. The resulting homogeneous solution was held at 0 °C for 20 h as fine solids precipitated. A solution of 0.5 M aqueous HCl (67 L) was added over 30 min at <10 °C, and the resulting suspension was mixed at 20 °C for 16 h and passed through a filter drier. The cake was rinsed under continuous agitation with three charges of water (110 L per charge) and dried at 50 °C with N_2 sweep to obtain 34.08 kg of amide **11** (88% yield) as a white solid: mp 170−171 °C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 11.55 (s, 1H); 8.91 (dd, J = 0.4, 2.4 Hz, 1H), 8.34 (dd, J = 2.4, 8.8 Hz, 1H), 8.16 (d, J = 8.8 Hz, 1H), 7.97−7.99 (m, 2H), 7.46−7.50 (m, 2H), 7.34−7.44 (m, 3H), 5.36 (s, 2H), 5.26 (dd, J = 5.2, 10.4 Hz, 1H), 2.20 (ddd, J = 6.0, 10.4, 14.0 Hz, 1H), 2.10 (ddd, J = 5.2, 8.8, 14.0 Hz, 1H), 1.27−1.69 (m, 8H), 1.02−1.12 (m, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 168.9, 164.1, 154.7, 149.6, 139.7, 138.9, 135.9, 130.0 (q, J_{CF} = 38 Hz), 128.5, 128.2, 128.1, 122.1 (q, J_{CF} = 265 Hz), 121.5, 120.1 (q, J_{CF} = 4 Hz), 113.0, 66.3, 60.0, 37.5, 36.2, 32.0, 30.8, 24.6, 24.4; ^{19}F NMR (376 MHz, d_6-DMSO) δ −60.7. HRMS-ESI m/z: [M + H]$^+$ calcd for $C_{25}H_{25}F_3N_4O_3$, 487.1952; found, 487.1955. Achiral HPLC: rt 5.9 min. Chiral HPLC: rt 6.0 min (**11**), 7.0 min (*ent*-**11**).

(*S*)-6-(3-Cyclopentyl-2-(4-(trifluoromethyl)-1*H*-imidazol-1-yl)propanamido)nicotinic Acid (1). *Pressure Hydrogenation.* A stirred mixture of benzyl ester **11** (4.28 kg, 8.80 mol), 10% Pd/C (0.22 kg, 5 wt% relative to **11**), and IPA (26 L) under 50 psig of H_2 was held in a pressure reactor at 25 °C for 24 h. The reactor was vented and purged with N_2, and the reactor contents were passed through a Celite-packed Nutsche filter and rinsed with IPA (8 L). The filtrate was diluted with heptane (40 L), held at 25 °C for 30 min, and passed through another Celite-packed Nutsche filter with 1:1 v/v IPA/heptane rinse (6 L). The filtrates were stirred over Si-Thiol (0.35 kg) at 25 °C for 4 h, passed through a speck-free filter, and concentrated to 9 L (35−45 °C; 0.1 bar). The solution was diluted with heptane (8 L), cooled to 20 °C over 2 h, and held at 20 °C for 12 h. The mixture was diluted with additional heptane (40 L) over 1 h, cooled to 15 °C, and held at 15 °C for 12 h. The suspension was passed through a Nutsche filter, and the filter cake was rinsed with 9:1 v/v heptane/IPA (8 L) and dried at 45 °C under vacuum with N_2 sweep to obtain 3.12 kg of **1** (89% yield) as a white solid: mp 187−189 °C; ^{1}H NMR (400 MHz, d_6-DMSO) δ 13.23 (s, 1H), 11.49 (s, 1H), 8.86 (dd, J = 0.4, 2.4 Hz, 1H), 8.27 (dd, J = 2.4, 8.8 Hz, 1H), 8.13 (d, J = 8.8 Hz, 1H), 7.97−7.99 (m, 2H), 5.27 (dd, J = 5.6, 10.0 Hz, 1H), 2.20 (ddd, J = 6.0, 10.0, 14.0, 1H), 2.10 (ddd, J = 5.6, 8.4, 14.0, 1H), 1.27−1.69 (m, 8H), 1.03−1.12 (m, 1H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 168.8, 165.7, 154.3, 149.7, 139.6, 138.8, 129.9 (q, J_{CF} = 38 Hz), 122.6, 122.0 (q, J_{CF} = 265 Hz), 120.0 (q, J_{CF} = 4 Hz),

112.8, 60.0, 37.6, 36.2, 32.0, 30.8, 24.6, 24.4; ^{19}F NMR (376 MHz, d_6-DMSO) δ −60.7. HRMS-ESI m/z: $[M + H]^+$ calcd for $C_{18}H_{19}F_3N_4O_3$, 397.1482; found, 397.1481. Achiral HPLC: rt 4.6 min. Chiral SFC: rt 4.1 min (**1**), 3.1 min (*ent*-**1**).

Transfer Hydrogenation. A stirred solution of benzyl ester **11** (41.28 kg, 84.85 mol) in EtOAc (230 L) was charged with a slurry of 10% Pd/C (8.26 kg, 20 wt% relative to **11**) in EtOAc (145 L). Formic acid (41 L, 13 equiv) was added, and the mixture was warmed to 55 °C over 1.5 h and held at 55 °C for 6 h. After cooling to 20 °C, the mixture was charged with Arbocel (6 kg) and filtered through an Arbocel-packed Nutsche filter, rinsing with EtOAc (290 L). The filtrate was washed three times with water (620 L per wash), and the organic layer was passed through a speck-free filter and concentrated to 130 L (20 °C, 0.1 bar). The solution was diluted with EtOAc (210 L) and reconcentrated to 130 L (20 °C, 0.1 bar). Again, the solution was diluted with EtOAc (210 L) and reconcentrated to 130 L (20 °C, 0.1 bar), at which point the solution contained <0.3% water. Heptane (210 L) was added over 2 h at 20 °C, and the resulting suspension was mixed at 20 °C for 20 h. The solids were collected on a filter drier and rinsed under continuous agitation with heptane (66 L). The solids were dried at 50 °C with N_2 sweep to obtain 27.22 kg of **1** (81% yield) as a white solid with physical and analytical data matching those reported above.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for **7**, **9**, **2**, **11**, and **1** and a PXRD pattern of **1** (Form A). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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