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Catalytic, Enantioselective Synthesis of Taranabant, a Novel, Acyclic Cannabinoid-1 Receptor Inverse Agonist for the Treatment of Obesity

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Abstract:

Chiral amide 1 (MK-0364, taranabant) is a potent, selective, and orally bioavailable cannabinoid-1 receptor (CB-1R) inverse agonist indicated for the treatment of obesity. An asymmetric synthesis featuring a dynamic kinetic resolution via hydrogenation for the preparation of the bromo alcohol 5 is disclosed. Conversion of the alcohol intermediate to the chiral amide 1 is accomplished in good overall yield.

Introduction

Obesity is a serious and chronic medical condition that continues to spread rapidly throughout the world. It is estimated that obesity affects about 30% of the adult population in the Western world, and many people who are afflicted with obesity also suffer from subsequent co-morbidities, including diabetes, hypertension, cardiovascular disease, cancer, and arthritis.[1] Although modifications of lifestyle may be the preferred approach for the management of obesity, these modifications often prove to be insufficient or unsustainable. Currently, there are a few drugs available in the market for the treatment of obesity, each of which only has modest efficacy at tolerable doses. Therefore, novel anti-obesity therapeutics with improved efficacy and safety profiles are actively pursued. The appetite enhancement of a cannabinoid agonist together with the positive weight loss attributed to SR141716 (rimonabant)[2] suggest the use of cannabinoid-1 receptor (CB-1R) inverse agonists for the treatment of obesity. Recently, rimonabant has been approved in the EU for the treatment of obesity. Discovery efforts in our laboratories identified **1** (MK-0364, taranabant) as a selective, acyclic cannabinoid-1 receptor inverse agonist for the suppression of food intake and reduction of body weight.[3] With continuing efforts to develop this compound, we needed to define an efficient process for the compound that was amenable to scale-up. Our objective was to design and develop an elegant, practical, efficient, environmentally responsible, and economically viable chemical synthesis and to subsequently demonstrate the process on scale. We report herein our efforts to design and develop a route to **1** that meets all of these objectives. A chromatography-free, practical asymmetric synthesis of **1**, which features novel methodology for the stereoselective synthesis of bromoalcohol **5** using an asymmetric hydrogenation of racemic ketone via dynamic kinetic resolution is disclosed.

As shown in Scheme 1, the initial route to amide **1** was a multistep, racemic synthesis based on a resolution of acid **2** to set the benzylic stereogenic center. The chiral acid **3** was converted to chiral ketone **4** which upon diastereoselective reduction using L-Selectride at −78 °C afforded bromo alcohol **5** in 98% dr. The bromo alcohol was converted to cyano amine **6** via a cyanation, mesylation, displacement, and reduction sequence. Finally, the coupling of the acid **7** with amine **6** produced chiral amide **1**.[3] This route allowed us to quickly make small amounts of the drug; however, further scale-up represented a challenge as the resolution step was quite inefficient and an ee upgrade of amine **6** by chiral HPLC was not feasible for large scale. In addition, this approach featured setting the stereogenic centers in a stepwise fashion where the first stereogenic center was obtained through resolution while the introduction of the second center relied on substrate-controlled diastereoselective reduction. We envisioned that the key intermediate, the chiral bromo alcohol, could be derived from the racemic ketone if each enantiomer of the ketone (**4** and **ent-4** in Scheme 2) underwent fast equilibrium, but only one of the enantiomers got reduced to the alcohol enantioselectively using a suitable chiral catalyst. Racemization occurring concurrently with the kinetic resolution, known as dynamic kinetic resolution, would allow 100% of the racemic mixture to be converted to one diastereoisomer.[4] Namely, the enantioselective reduction of ketone (**4** and **ent-4**) would only afford one enantio-

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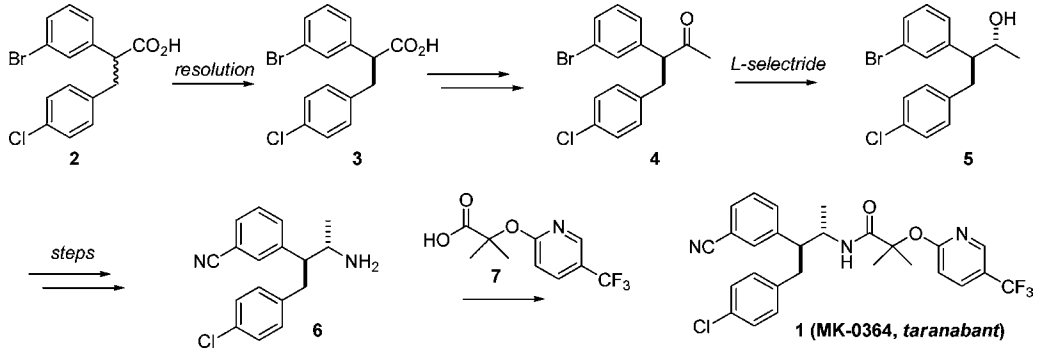
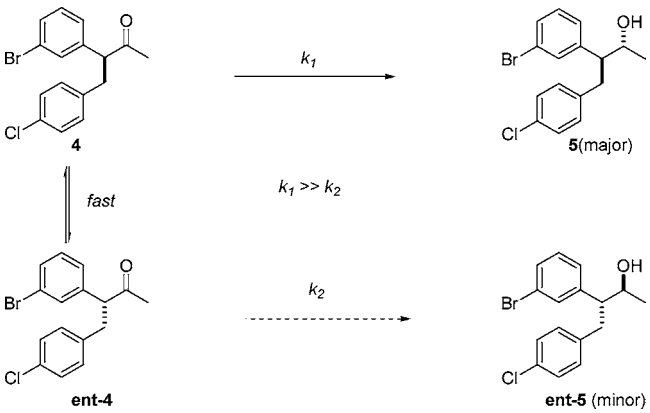
Scheme 1. **Synthesis of amide 1 (MK-0364, taranabant) via resolution**



Scheme 2. **Dynamic kinetic resolution of bromoketone 4**

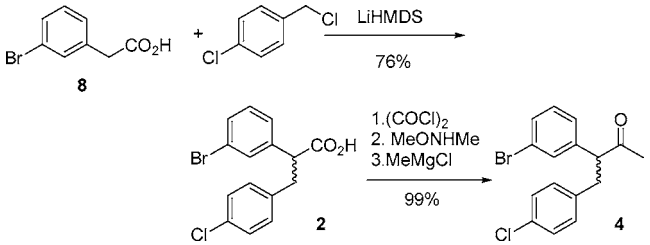


mer of the alcohol if $k_1 > k_2$. This innovative process would set two stereogenic centers simultaneously in one step, taking advantage of the labile stereogenic center of the ketone.

Results and Discussion

We began our synthesis with the preparation of bromoketone **4** in a straightforward manner via alkylation of 3-bromophenyl acetic acid followed by methylation (Scheme 3).

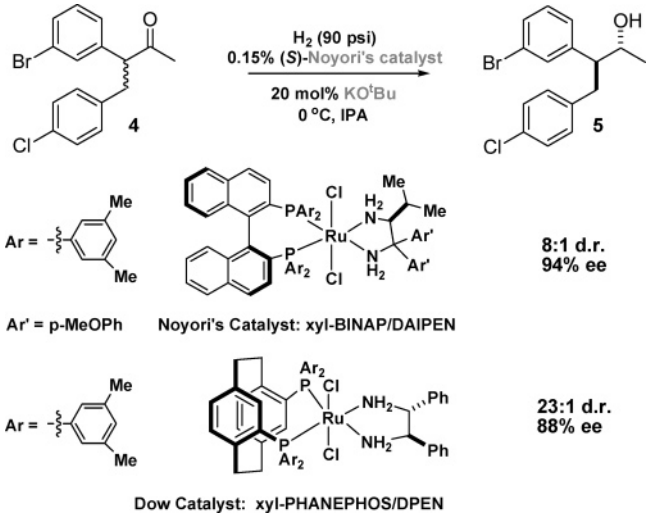
Scheme 3. **Preparation of bromoketone 4**



Thus, treatment of the dianion generated from 3-bromophenylacetic acid (**8**) and LiHMDS with *p*-chlorobenzyl chloride afforded the alkylated acid **2** in 76% yield. Keeping the reaction temperature between −10 and −15 °C during the LiHMDS addition minimized the formation of the bis-alkylated byproduct to <5%. Crystallization of the crude material from toluene/heptane afforded acid **2** as a white crystalline solid. The methyl ketone **4** was prepared in almost quantitative yield from alkylated acid **2** via the acid chloride and Weinreb amide in a through process in toluene. The acid chloride generated from the reaction of the free acid with oxalyl chloride catalyzed by DMF was added to a solution of potassium carbonate and *N*,*O*-dimethyl hydroxylamine HCl in water. After workup and azeotropic drying, the resulting Weinreb amide was treated with MeMgCl to produce the desired methyl ketone **4** in 99% yield.

The viability of the dynamic kinetic resolution to produce one diastereomer was dependent on the catalyst not only to differentiate between the enantiotopic faces of the ketone but also to discriminate between the two enantiomers at the α position. Bearing this concept in mind, we first set out to explore the racemization of the ketone under basic conditions. As expected, ketone **4** was readily epimerized upon treatment with 20 mol % of KO*t*-Bu in IPA at 0 °C to ambient temperature (Scheme 4). The chiral catalyst was next introduced for the asymmetric hydrogenation of the ketone. We were very delighted when the ketone was hydrogenated at room temperature under basic conditions in the presence of the (xyl-BINAP)(DAIPEN)$RuCl_2$ catalyst to give the desired diastereoisomer **5** in 89% ee and 5:1 dr (*vide infra*).[5] This exciting lead validated our proposal and allowed us to consolidate our efforts toward development of a practical process to prepare **1** using the asymmetric hydrogenation protocol. The resulting chromatography-free process featured

Scheme 4. **Enantioselective reduction of ketone 4 via dynamic kinetic resolution**



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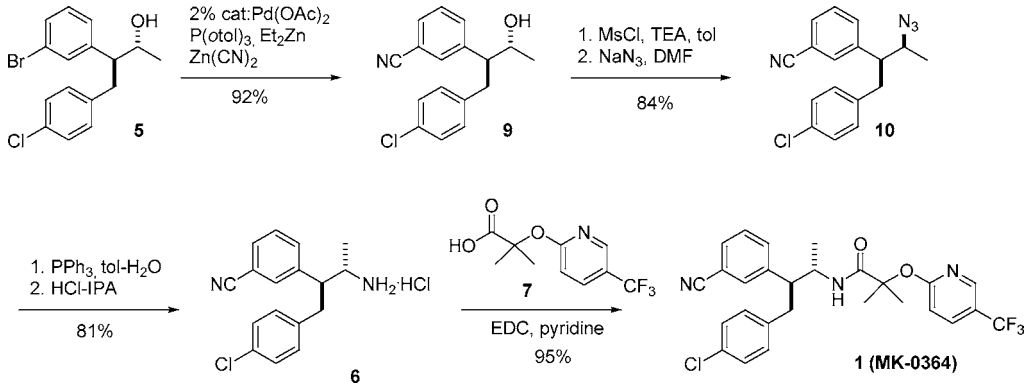
Scheme 5. **Synthesis of amide 1 (MK-0364, taranabant) from bromo alcohol 5**



an efficient synthesis of racemic ketone **4**, a highly enantioselective reduction of ketone **4** under dynamic kinetic resolution conditions, and a streamlined process for the downstream chemistry.

As mentioned above, dynamic kinetic resolution under hydrogenation conditions using ((*S*)-xyl-BINAP)(*S*)-DAIPEN)$RuCl_2$ was implemented to set both stereogenic centers in a single step from racemic ketone **4**, giving bromo alcohol **5** directly. The stereoselectivity was improved from the initial lead to 93−94% ee and a 9:1 ratio of diastereomers after further optimization.

A number of different reaction variables were explored in order to gain a more thorough understanding of the reaction. We found that isopropanol and 2-butanol were the best solvents with respect to catalyst stability, rate, and selectivity. Under otherwise identical conditions, 2-butanol gave ∼2% better ee, but IPA gave better diastereomeric purity. Decreasing the temperature from 20 °C to 0 °C resulted in higher ee and dr. Running the reaction at higher temperatures resulted in lower selectivity. Hydrogen pressure (15−90 psig) was found to affect only the rate of the reaction, and only under conditions where the racemization was very slow would there be a deleterious effect on selectivity. The KO*t*-Bu charge was screened at 5, 10, 20, and 30 mol %, and no effect on selectivity was observed under the conditions tested. The base charge did affect the rate, however, with more base giving rise to a higher rate of hydrogenation. We believe that at least part of this rate increase is due to catalyst activation. Subsequent to our initial studies Noyori reported that the active form of the catalyst is the dihydride complex [(phosphine)(diamine)RuH_2] and that the rate of its formation from (phosphine)(diamine)Ru(H) η^1-BH_4 is enhanced by the presence of alkoxide base.[5f] We mixed (xyl-BINAP)(DAIPEN)$RuCl_2$ with excess KO*t*-Bu in wet 2-propanol-d_8 and observed two new resonances in the hydride region of the ^{1}H spectrum (δ 9.1 (m), −14.6 (m)). Additionally, a >5-fold increase in initial hydrogenation rate was observed when we aged the whole hydrogenation batch for 3 h (vs 0.25 h) prior to cooling to 0 °C and pressurization with H_2. In practice, a 2−3 h whole batch age (30 mol % KO*t*-Bu, 100% ketone) at 25 °C will fully activate 0.15 mol % catalyst. To date, we have not investigated other modes of catalyst activation on scale (in the absence of ketone for example). Noyori does note an inherent acceleration of the catalytic cycle from increasing the concentration of alkoxide base reaching a maximum at 10−15 mM; however, the concentration of KO*t*-Bu in our optimized conditions (450 mM) is outside the range tested by Noyori. An overall lower rate of hydrogenation was observed at a high KF (3500 ppm, water content). Optimal and reproducible results were obtained at a KF of ≤500.

A S/C of 667 (0.15 mol % Ru) was determined to be optimal for both rate and selectivity. The rate of hydrogenation does increase with higher catalyst loadings, but this was accompanied by some loss of selectivity under some conditions tested. The catalyst ((*R*)-xyl-Phanephos)((*S*,*S*)-DPEN)-$RuCl_2$ is potentially a suitable backup in this chemistry.[6] At 0 °C this catalyst gives a dr of 23:1 and 88% ee at ∼0.1 mol % loading in 24 h.

It was determined that an aqueous workup of the hydrogenation solution was necessary in order for the cyanation reaction to occur. After switching the IPA solution into toluene, the batch was washed with pH 7 buffer, dilute brine, and water. The toluene layer was azeotropically dried and switched into DMF in preparation for the cyanation step.

As shown in Scheme 5, the cyano group was next introduced to the molecule via a Pd-catalyzed cyanation. The cyanation of bromoarenes is a common transformation in organic chemistry, and numerous variants for the reaction conditions were reported in literature.[7] We initially carried out the cyanation of bromide **5** to nitrile **9** under the following conditions: $Pd_2(dba)_3$ as catalyst and dppf as ligand, Zn-$(CN)_2$, 115 °C, DMF. Because the ligand dppf was difficult to remove in the downstream process, we explored a number of phosphine ligands and found that Pd[P(*o*-tol)$_3$]$_4$, formed

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in situ by adding Et_2Zn to a mixture of $Pd(OAc)_2$ and P(*o*-tol)$_3$ in DMF, was the most successful catalyst for this transformation. This catalyst allowed for a smooth cyanation under mild conditions with the advantage that the phosphine residues were readily removed. Experimentally, the catalyst thus prepared was transferred to a slurry of $Zn(CN)_2$ and bromo alcohol **5** in DMF. The reaction was typically complete within 12 h at 55 °C to give cyano alcohol **9** in 92% yield.

A few observations are worth noting. The efficiency of the reaction was highly dependent on the quality of the cyanide. As little as 0.6 equiv of $Zn(CN)_2$ was enough for full conversion, but more reagent was required with certain batches of cyanide. As expected, the reaction was highly sensitive to oxygen; as a result, the reaction solution in DMF was degassed using a subsurface nitrogen sparge prior to the introduction of the catalyst. The reaction was demonstrated with as little as 0.5 mol % catalyst, though to ensure complete conversion, 2 mol % catalyst was used. The reaction can be run in a temperature range of 55−80 °C, and it tolerates a small amount of water. However, we discovered that excess inorganic salts in the solution were detrimental to the success of the reaction as they led to increased levels of soluble cyanide. A full account of the investigation into the causes and effects of high cyanide levels in the Pd-catalyzed cyanation has been disclosed.[8]

Precaution in the workup was also taken to ensure that free CN ions were completely sequestered by the addition of concentrated NH_4OH. The resulting slurry was filtered over solka floc, and the waste cake was washed with toluene. The toluene layer was washed with aq NH_4OH and water sequentially to remove all of the cyanide. The toluene solution was azeotropically dried and carried forward into the mesylation step.

The cyano alcohol **9** was next converted to azide **10** via a mesylation and azide displacement sequence. Mesylation of the alcohol using MsCl in the presence of triethylamine afforded the mesylate in 96% yield. Displacement of the mesylate using sodium azide in DMF afforded azide **10** in 88% yield. During the displacement reaction, we envisioned that hydrazoic acid (HN_3, a hazardous species) could be generated in small amounts due to the formation of an elimination impurity produced by the reaction. To evaluate the potential safety hazard associated with HN_3 for process scale-up, we applied online FTIR to investigate the existence of hydrazoic acid in the headspace.[9] Results revealed that HN_3 was indeed formed and was present in the headspace during this reaction. We also observed that the amount of HN_3 in the headspace could be completely suppressed with the addition of an organic base such as diisopropylethyl amine to the reaction. The use of inorganic bases such as K_2CO_3 was less effective, as a small amount of HN_3 was still detected in the headspace.

Conversion of azide to amine was next explored. Hydrogenation[10] and transfer hydrogenation conditions for reduction of the azide **10** to amine **6** were attempted but generated several impurities. In addition, the reproducibility upon scale-up represented quite a challenge. More success was seen using the Staudinger conditions.[11] Treatment of azide **10** with PPh_3 (1.1 equiv) in toluene/water provided a reliable route to amine **6**. Addition of PPh_3 in one portion to the solution of azide in toluene was exothermic and generated significant N_2 off-gassing. Thus, the toluene/water solution of azide was heated to 50 °C, and the PPh_3 was added in portions over 40 min. The reaction exothermed to 65 °C without external heating, at which point steam heating was applied to hold the reaction at 70 °C for several hours to afford amine **6** in >90% assayed yield. Following this protocol, the challenge was to remove the triphenylphosphine oxide byproduct that was generated in the reaction. Because this byproduct typically crystallized with the amine salt during isolation, an extractive workup was explored. Extraction of the amine into aq HCl, citric acid, or phosphoric acid resulted mainly in oiling, but good results were seen when the amine was extracted into 10% acetic acid. Three extractions with aq acetic acid were necessary to recover >98% of the amine, leaving much of the color and many of the impurities in the organic layer. After neutralization and re-extraction into the organic layer, isolation of the amine as the HCl salt in 85% yield allowed for further purification and an upgrade in diastereomeric purity.

Coupling of amine HCl salt **6** with acid chloride derived from acid **7**[3] gave amide **1** smoothly with a good impurity profile. The reaction was hampered by formation of yellow color which was not readily removed by treatment with Ecosorb. The color issues prompted us to investigate an alternative coupling procedure using EDC.[12] Initially the coupling reaction for amine and acid was run with HOBT and EDC with triethylamine in acetonitrile, and the reaction also resulted in dark yellow/orange solutions. A screen of reaction conditions demonstrated that HOBT was not necessary, and switching from triethylamine to pyridine drastically reduced the color produced in the reaction. However, EDC was expensive to use on scale, and further literature searching led us to an attractive coupling procedure using inexpensive and readily available cyanuric chloride. Much has been published on the use of this reagent to prepare amides and esters, and there is some debate as to whether the reaction proceeds via an acid chloride[13] or an acylated triazine

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(activated ester).[14] Typically, literature procedures describe preforming the activated ester by reacting the acid with cyanuric chloride and base. On our substrate, this order of addition was not successful. Better results were obtained when the base was added slowly to a slurry of the acid, amine salt, and cyanuric chloride in acetonitrile. It could be that acid **7**[3] was too hindered to form a stable, activated ester intermediate and thus benefited from rapid reaction with each drop of base added to the mixture. Less than one equivalent of cyanuric chloride has been shown to be successful for complete conversion of an acid to an amide,[15] and on our substrate 0.6 equiv of cyanuric chloride was sufficient for complete reaction. Presumably, more than one of the aryl chloride reactive sites on the cyanuric chloride was involved in the reaction. Using these optimized conditions, the amide was isolated as a white solid. The ee of the crude amide remained the same at 94%, and thus an ee upgrade was required to deliver quality API. Direct crystallization of amide **1** was expected to give good ee upgrade (to >98%), but front runs of the large-scale batch indicated that the material was not upgrading as expected. We then chose to explore dissolution of high ee material such that the solid of low ee was removed and the majority of the batch was recovered in the filtrate. A number of solvent combinations were explored using the crude amide. Slurrying the crude solid in MTBE/cyclohexane, MTBE/heptane, or IPAc/cyclohexane, the supernant ee only increased from 94% to 96−97%. However, when the material was slurried in 2:1 EtOH/water, we were pleased to observe an upgrade to approximately 99% ee in the supernatant (the solid represented approximately 5% of the material at 31% ee). The low ee solid was filtered off, and crystallization of the product from the filtrate afforded amide **1** in 90% recovery and excellent quality.

In conclusion, we have developed an efficient and chromatography-free process for the preparation of amide **1** (MK-0364, taranabant), a CB1 inverse agonist targeted for the treatment of obesity. The process was developed and demonstrated on multikilogram scale. In the process, the chirality of the molecule was elegantly introduced via the dynamic kinetic resolution of the racemic bromo ketone **4**, rather than resolution of acid **2** followed by L-Selectride reduction of chiral ketone **4**. The process reduced the losses incurred in the original resolution and several process improvements were implemented; in particular the reaction conditions for the cyanation and azide reduction were defined with regards to scaleability and safety concerns. The dynamic kinetic resolution process described here represents an innovative improvement to the conventional stereoselective synthesis, and we believe such a protocol should find wider application in the future.

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(15) Rayle, H. L.; Fellmeth, L. *Org. Process Res. Dev.* **1999**, *3*, 172.

Experimental Section

General. All commercially available reagents and solvents were used as received. All manipulations were carried out under a positive atmosphere of dry nitrogen. Dry solvents were used (KF < 300 μg/mL). NMR data was obtained in $CDCl_3$ or in DMSO-d_6 using a Bruker AM400 spectrometer. Coupling constants are reported in Hertz. All chemicals were purchased from Aldrich Chemical Co. unless otherwise noted and were used without further purification.

2-(3-Bromophenyl)-3-(4-chlorophenyl)propionic Acid (2). To a solution of *p*-chlorobenzyl chloride (48.4 mol, 7.8 kg) and *m*-bromophenylacetic acid (46.0 mol, 9.9 kg) in THF (165 kg) at −15 °C was added LHMDS (1.4 M THF, 92.0 mol, 65.7 L) over 2 h, and the reaction mixture was aged for an additional 2 h. HCl (2.5 N , 57.7 L) was added, the reaction temperature was adjusted to 20−25 °C, and the layers were separated. The organic layer was washed with 2.5 N HCl (25.0 L), and the solvent was switched to toluene. The batch volume was adjusted to ~103 L by adding toluene. The reaction mixture was heated to 55 °C to dissolve the material and was then cooled to 30−35 °C. *n*-Heptane (139 L) was charged over 3 h, and the slurry was cooled to −5 °C to 0 °C and aged overnight. The slurry was filtered, the cake was washed with *n*-heptane (41.1 L), and the solid was dried at 40 °C to afford 12.0 kg of acid **2** (77% yield) as white solid: ^{1}H NMR (400 MHz, CD_3OD): δ 7.45 (t, 1 H, J = 1.69 Hz), 7.35 (m, 1H), 7.23 (d, 1 H, J = 7.78 Hz), 7.16 (m, 3H), 7.07 (d, 2 H, J = 8.44 Hz), 3.81 (t, 1 H, J = 7.84 Hz), 3.29 (dd, 1 H, J = 8.40, 13.68 Hz), 2.93 (dd, 1 H, J = 7.41, 13.78 Hz). ^{13}C NMR ($CDCl_3$): δ 174.7, 141.3, 137.6, 131.9, 130.8, 130.3, 130.1, 130.0, 128.0, 126.8, 122.1, 52.9, 38.5. Anal. Calcd for $C_{15}H_{12}BrClO_2$: C 53.05; H 3.56. Found: C 52.88; H 3.42.

(3*S*)-3-(3-Bromophenyl)-4-(4-chlorophenyl)butan-2-one (4). To a solution of acid **2** (34.5 mol, 11.7 kg) in toluene (86 L) was added catalytic DMF (117 g). Oxalyl chloride (41.0 mol, 3.6 L) was added over 30 min, and the reaction was aged an additional 1 h. In a separate flask a solution of potassium carbonate (141.1 mol, 19.5 kg) and *N*,*O*-dimethylhydroxylamine hydrochloride (55.4 mol, 5.4 kg) in water (85 L) was prepared. The acid chloride was transferred to the basic aqueous Weinreb amine solution over 30 min while maintaining the temperature below 30 °C. After a 45 min age, toluene (71 L) and water (35 L) were added, and the layers were separated. The organic layer was washed with water (70 L) and then vacuum concentrated (azeotropically dried) to 82 L. To this solution was added THF (40 L), and the mixture was cooled to 0 °C. Methylmagnesium chloride (3 M in THF, 14.0 L) was added over 30 min, and the reaction was aged an additional 1 h. HCl (1 N, 71 L) was added, and the layers were separated. The organic layer contained 11.5 kg (99% yield) of methyl ketone **4**. The ketone was directly used in the next reaction. An analytical sample was obtained by silica gel chromatography: ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.96−7.45 (8H), 3.83 (1H pseudo t, $^3J_{HH}$ = 7.4 Hz), 3.36 (dd, 1H, $^2J_{HH}$ = 13.9 Hz, $^3J_{HH}$ = 7.4 Hz), 2.84 (dd, 1H, $^2J_{HH}$ = 13.9 Hz, $^3J_{HH}$ = 7.4 Hz), 2.04 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 206.3, 140.5, 137.8, 132.1, 131.1,

130.8, 130.6, 130.5, 128.5, 127.1, 123.1, 60.7, 37.7, 29.6. HRMS Calcd for $C_{15}H_{12}BrClO_2$ [M + Ag]: 442.8967. Found: 442.8976.

(2*R*,3*S*)-3-(3-Bromophenyl)-4-(4-chlorophenyl)butan-2-ol (5). In an argon atmosphere glovebox, ((*S*)-xyl-BINAP)-((*S*)-DAIPEN)$RuCl_2$ (20 g, 0.016 mol) was dissolved in toluene (0.2 L, N_2 degassed) in a 250-mL round-bottom flask to give a dark orange solution. This solution was added to a 1-L stainless steel vessel (see Figure 1 below) followed by additional toluene rinses (2 × 0.15 L). An additional 0.13 L of toluene was added to a 0.15-L stainless steel vessel. These two vessels were connected with a ball-valve separating the two vessels (see Figure 1 below).

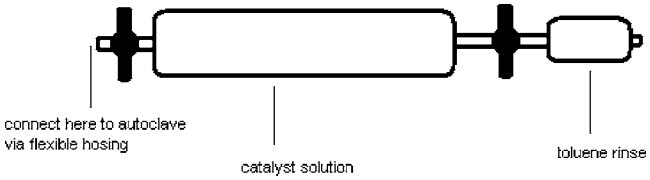

Figure 1. **Diagram of the equipment.**

IPA (7.0 L) and KO*t*-Bu (370 g) were charged to a 50-L round-bottom flask containing ketone **4** (6.6 kg, 56.0 wt %, in isopropanol, 10.9 mol) with overhead agitation. The solution became yellow, and the temperature rose from 18 to 25 °C. The KO*t*-Bu took ~30 min to dissolve completely. This solution was transferred via vacuum to a glass carboy (18-L capacity) followed by an isopropanol rinse (1 L). The ketone solution was drawn into a 10-gal-stirred autoclave via vacuum followed by an isopropanol (1.3 L) rinse of the glass carboy. The solution was then degassed with nitrogen three times. The stainless steel vessels containing the catalyst solution were connected to the autoclave via flexible tubing. The autoclave was placed under partial vacuum, and the catalyst solution was drawn into the autoclave followed by the toluene rinse. The autoclave was placed under nitrogen atmosphere at 25 °C and aged for 2 h. The vessel was cooled to 0 °C over 4−5 h, the solution was degassed with H_2 (90 psig) three times, and the reaction mixture was agitated (700 rpm). The reaction progress was monitored by hydrogen uptake from a reservoir. Reaction end was determined by HPLC analysis. The hydrogen was vented, and the reaction was drained into a 20-L poly drum when residual ketone was typically observed to be <0.2 A%. The vessel was rinsed with toluene (18 L).

The IPA solution from the hydrogenation was concentrated to a very low volume (5 L) and diluted with the toluene vessel rinse (18 L). The solution was again concentrated to a low volume (5 L). At this point, it was diluted to 18 L with toluene. Aqueous buffer solution (11 L, pH = 7) was added with vigorous stirring. The layers were separated, and the toluene layer was then washed with water (11 L).

The resulting slight emulsion was reduced with a dilute brine wash (11 L), followed by a final water wash (11 L). The toluene was then distilled to a very low volume (5 L) to remove water and diluted with toluene (10 L). After subsequent concentration it was diluted with DMF (18 L) for the next reaction. Distillation was continued until residual toluene specification was met.

Chiral analysis of L-055 bromo chiral alcohol intermediate: Instrument: HP1100. Column: Chiralpak AD-H, 25 cm × 4.6 mm, 5 μm, at 20 °C. Detection: UV 220 nm. Injection: 5 μL. Flow rate: 0.7 mL/min. Mobile phase: heptane/EtOH = 96:4. Run time: 25 min, isocratic. Sample concentration: 50 XD in ethanol.

ID	RT (min)
(*S*)-ketone **4**	8.65
(*R*)-ketone **4**	9.18
(2*R*,3*R*)-**5**	12.97
(2*R*,3*S*)-**5** (desired)	15.30
(2*S*,3*S*)-**5**	16.95
(2*S*,3*R*)-**2**	18.99

Analytical Data for a Chromatographed Sample of 5. *Major diastereomer*: ^{1}H NMR (DMSO-d_6): δ 7.39 (m, 1H), 7.29−7.26 (m, 1H), 7.19−7.07 (m, 6H), 4.67 (d, 1H, J = 4.02 Hz), 3.83−3.76 (m, 1H), 3.02 (dd, 1H, J = 5.62, 13.25 Hz), 2.89−2.78 (m, 2H), 0.89 (d, 3H, J = 6.02 Hz). ^{13}C NMR (DMSO-d_6): δ 144.8, 140.0, 132.4, 131.3, 130.7, 130.1, 129.3, 129.0, 128.4, 121.5, 68.2, 53.8, 37.3, 21.9.

Minor diastereomer: ^{1}H NMR (DMSO-d_6): δ 7.37−7.28 (m, 2 H), 7.19−7.12 (m, 3 H), 7.10−7.07 (m, 1 H), 6.99 (d, 2 H, J = 8.43 Hz), 4.84 (d, 1 H, J = 5.22 Hz), 3.81−3.73 (m, 1 H), 3.34−3.26 (m, 1 H), 2.83−2.75 (m, 1 H) 0.89 (d, 3 H, J = 6.42 Hz). ^{13}C NMR (DMSO-d_6): δ 145.5, 140.1, 131.7, 131.1, 130.5, 130.4, 129.4, 128.3, 128.1, 121.8, 69.7, 55.3, 36.9, 22.0.

3-[(1*S*,2*R*)-1-(4-Chlorobenzyl)-2-hydroxypropyl]benzonitrile (9). $Zn(CN)_2$ (778 g, 6.62 mol) was added to a solution of bromo alcohol **5** (3.75 kg, 11.04 mol) and DMF (15 L). The mixture was then degassed with a subsurface nitrogen sparge for 20 min, and the batch was heated to 56 °C. In a separate flask, DMF (11.3 L) was charged and degassed with subsurface nitrogen sparge. $Pd(OAc)_2$ (49.2 g, 0.219 mol) and P(*o*-tol)$_3$ (267 g, 0.876 mol) were charged to this flask, and the degassing continued while the red-orange solution was heated to 56 °C over 40 min and held for an additional 15 min. $ZnEt_2$ (301 mL, 0.331 mol) was then added to the catalyst solution over 15 min, and the resulting slurry was aged at 56 °C for 1 h. The $Zn(CN)_2$ mixture was transferred to the catalyst slurry over 1 h at 56 °C, and the mixture was aged an additional 2 h. The reaction was cooled with an ice bath to 5−10 °C. Concentrated NH_4-OH (3.75 L) was added, keeping the batch temperature at <30 °C, and the batch was aged for 1 h. The slurry was then filtered over a pad of solka floc that was wetted with toluene. The cake was washed with 20 L of toluene. To the filtrate was added 26 L of 20% aq NH_4OH and toluene (17.5 L). After mixing well, the layers were separated, and the organic layer was washed with 26 L each of 15% aq NaCl solution and water. This solution (HPLC assay 2.90 kg, a 92.0% yield) was carried forward to the mesylation reaction.

Analytical Data for a Chromatographed Sample of 9. *Major diastereomer*: ^{1}H NMR (DMSO-d_6): δ 7.67 (s, 1H), 7.59 (d, 1 H, J = 7.63 Hz), 7.52 (d, 1 H, J = 7.63 Hz), 7.40 (app t, 1 H, J = 7.63 Hz), 7.21 (d, 2 H, J = 8.03 Hz), 7.11 (d, 2 H, J = 8.03 Hz), 4.72 (d, 1 H, J = 4.02 Hz), 3.90−

3.81 (m, 1 H), 3.11−3.06 (m, 1 H), 3.03−2.89 (m, 2 H), 0.92, (d, 3 H, J = 6.42 Hz) ppm. ^{13}C NMR (DMSO-d_6): δ 143.5, 139.8, 135.0, 133.2, 131.2, 130.7, 130.3, 129.2, 128.4, 119.6, 111.0, 68.1, 53.6, 37.2, 22.0. HRMS Calcd for $C_{17}H_{16}ClNO$ [M + Ag]: 391.9971. Found: 391.9970.

Minor diastereomer: ^{1}H NMR (DMSO-d_6): δ 7.57 (s, 1 H), 7.54 (d, 1 H, J = 7.23 Hz), 7.41−7.33 (m, 2 H), 7.14 (d, 2 H, J = 8.43 Hz), 6.97 (d, 2 H, J = 8.43 Hz), 4.85 (d, 1H, J = 5.22 Hz), 3.82−3.72 (m, 1 H), 3.32−3.23 (m, 1 H), 2.89−2.78 (m, 2 H), 0.86 (d, 3 H, J = 6.42 Hz). ^{13}C NMR (DMSO-d_6): δ 144.3, 140.0, 134.3, 132.6, 131.1, 130.6, 130.5, 129.5, 128.4, 119.5, 111.4, 69.5, 55.1, 36.6, 21.9.

3-[(1*S*,2*R*)-1-(4-Chlorobenzyl)-2-methanesulfonylhydroxypropyl]benzonitrile. A toluene solution of alcohol **9** (2.85 kg, 9.99 mol) was azeotropically dried and then diluted to 28.5 L with toluene. The batch was cooled to between −5 and 0 °C. Triethylamine (1.81 L, 13.0 mol) was added, followed by slow addition (35 min) of methanesulfonyl chloride (929 mL, 12.0 mol), maintaining batch temperature at <20 °C. The batch was aged 10 min, and then 50% saturated aq $NaHCO_3$ (22.6 L) was added. After separating the layers, the organic layer was washed with water (14.8 L). The batch was assayed to give 3.53 kg (97% yield) of mesylate. The batch was azeotropically dried and switched into DMF in preparation for the mesylate displacement.

Analytical Data for a Chromatographed Sample. *9:1 mixture of diastereomers (m is minor diastereomer, b is both diastereomers):* ^{1}H NMR ($CDCl_3$): δ 7.57−7.52 (m, 1.1 H), 7.47−7.38 (m, 3.2 H), 7.35−7.32 (m, 0.1 H), 7.17 (d, 2 H, J = 8.43 Hz), 7.14 (d, 0.2 H, J = 8.43 Hz), 6.97 (d, 2 H, J = 8.43 Hz), 6.88 (d, 0.2 H, J = 8.43 Hz), 5.10−5.04 (m, 1 H), 5.02−4.98 (m, 0.1 H), 3.31 (dd, 0.1 H, J = 4.82, 13.65 Hz), 3.20 (dd, 1 H, J = 5.62, 13.65 Hz), 3.20−3.15 (m, 0.1 H), 3.10−3.05 (m, 1 H), 3.02 (s, 0.3 H), 2.97 (dd, 1 H, J = 10.56, 13.65 Hz), 2.91 (s, 3 H), 2.87 (dd, 0.1 H, J = 10.56, 13.65 Hz), 1.35 (d, 3 H, J = 6.42 Hz), 1.30 (d, 0.3 H, J = 6.42 Hz). ^{13}C NMR (DMSO-d_6): δ 141.1m, 140.9, 138.5b, 135.0, 134.7m, 133.3, 133.0m, 131.2, 131.1m, 131.0, 131.0m, 129.8m, 129.6, 128.5b, 119.3, 119.2m, 111.7m, 111.5, 81.6m, 81.6, 51.7m, 51.4, 38.3, 38.2m, 36.3, 35.7m, 19.9, 19.1m.

3-[(1*S*,2*S*)-2-Azido-1-(4-chlorobenzyl)propyl]benzonitrile (10). To the DMF solution of mesylate (3.53 kg, 9.70 mol) was added DIEA (2.03 L, 11.64 mol) followed by NaN_3 (757 g, 11.64 mol). The reaction temperature was slowly increased to 70 °C, and the batch was aged for 8−11 h. **Caution! The reaction vessel should be behind a blast shield due to the use of sodium azide.** The batch was cooled to 25 °C, and 5% aq $NaHCO_3$ (34.4 L) and toluene (13.6 L) were added. The layers were separated; the organic layer was washed with water (15.4 L) and then with 1 N HCl (15.4 L) and used directly in the next step (HPLC assay 2.62 kg, 87% yield).

Analytical Data for a Chromatographed Sample of 10. *9:1 mixture of diastereomers (m is minor diastereomer, b is both diastereomers):* ^{1}H NMR (DMSO-d_6): δ 7.71 (s, 0.1 H), 7.68 (s, 1 H), 7.59 (d, 1.1 H, J = 7.63 Hz), 7.53 (d, 0.1 H, J = 8.03 Hz), 7.48 (d, 1 H, J = 8.03 Hz), 7.43−7.38 (m, 1.1 H), 7.18 (d, 0.2 H, J = 8.43 Hz), 7.15 (d, 2 H, J = 8.43 Hz), 7.08 (d, 0.2 H, J = 8.43 Hz), 7.00 (d, 2 H, J = 8.43 Hz), 3.91−3.83 (m, 1.1 H), 3.19 (dd, J = 4.02, 13.65 Hz), 3.14−3.04 (m, 1.2 H), 2.99−2.90 (m, 1.1 H), 1.15 (d, 0.3 H, J = 6.42 Hz), 1.04 (d, 3 H, J = 6.42 Hz). ^{13}C NMR (DMSO-d_6): δ 142.5, 142.1m, 138.9, 138.8m, 134.6m, 134.4, 133.0m, 132.7, 131.3m, 131.2, 131.1, 131.0m, 129.8, 129.6m, 128.5m, 128.5, 119.4m, 119.3, 111.7, 111.5m, 61.3, 60.7m, 52.0, 51.5m, 37.2m, 36.7, 17.8m, 17.3. HRMS Calcd for $C_{17}H_{15}N_4Cl$ [M + Ag]: 417.0036. Found: 417.0038.

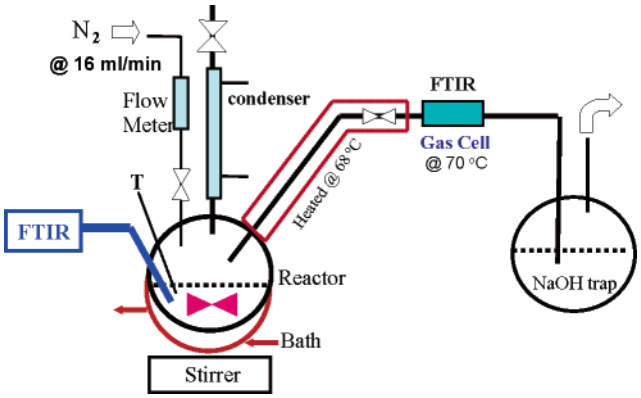

Figure 2. **Schematic of the experimental setup.**

Experimental Section for Hydrozoic Acid Assay by FTIR

An FTIR analyzer (ReactIR4000) equipped with an online gas cell (30 mL) was connected to a 250-mL jacketed resin kettle. The gas phase during the reaction was examined continuously by purging dry nitrogen gas through the headspace at a rate of 16 mL/min. The tubing connecting the headspace of the reactor to the IR gas-cell was heat-traced with a set temperature at 68 °C, thus preventing the condensation of HN_3 (bp 37 °C) in the tubing (see Figure 2 for a schematic of the setup).

Reaction Procedures. To a 250-mL, multineck round-bottom flask equipped with a magnetic stirrer, thermocouple probe, and nitrogen inlet was charged mesylate (33 mmol) in DMF (40 mL). NaN_3 (39.6 mmol) and/or DIPEA or Na_2CO_3 was added, and the suspension was stirred for 5 min at room temperature. The mixture was then heated to 80 °C and stirred until reaction was complete.

Results

The typical absorption bands of HN_3 in the vapour of the reactor are indicated in Figure 3 which includes two spectra, one of carbon dioxide and the other of hydrazoic acid. Peaks at 2127 and 2153 cm^{-1} are the strong absorption bands, stretches of linear HN_3. It is the most visual band used for tracing the presence of HN_3.

DIPEA appears to be an effective reagent to suppress the appearance of HN_3 in the reaction headspace; however, it could affect the yield if used in large quantity. Therefore, the amount of DIPEA was reduced to 0.3 equiv to provide a reasonable yield but still significantly suppress the level of HN_3 in the headspace during the reaction, allowing the process to be scaled up successfully.

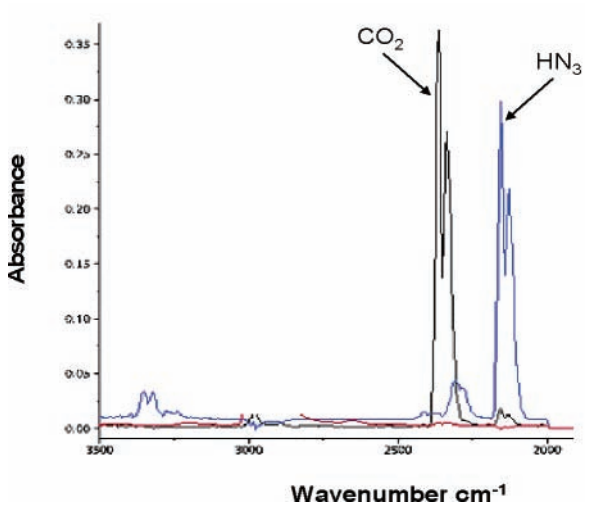

Figure 3. **Spectra of hydrazoic acid (HN_3) and carbon dioxide around 2000−2500 cm^{-1}.**

3-[(1*S*,2*S*)-2-Amino-1-(4-chlorobenzyl)propyl]benzonitrile (6). To the toluene solution of azide **10** (2.62 kg, 8.43 mol) from the previous step was added water (455 mL), and the batch was heated to 70 °C. A solution of PPh_3 (2.45 kg, 9.35 mol) in toluene (4.0 L) was added to the batch over 1 h (slowly in order to control nitrogen evolution). The batch was aged an additional 7 h and then cooled to ambient temperature. Acetic acid (10 vol %, 28.9 L) was added, and the layers were mixed well and then separated. The toluene layer was washed with 24.0 L of 10% aq AcOH. The toluene layer contained 3% amine **6** and was discarded. The AcOH layers were combined, and toluene (15.2 L) was added. After cooling to 10 °C, NaOH (50% w/v) was added to adjust the pH to 10−12. The layers were separated, and the organic layer was washed with water (5.0 L). The toluene (HPLC assay 2.31 kg amine, 96% yield) was azeotropically dried and diluted with toluene to a volume of 34.7 L.

Analytical Data for a Chromatographed Sample. *Free base major diastereomer:* ^{1}H NMR (CD_3OD): δ 7.43 (m, 2H), 7.35 (m, 2H), 7.07 (d, J = 8.41 Hz, 2H), 6.94 (d, J = 8.40 Hz, 2H), 3.28 (m, 1H), 3.17 (m, 1H), 2.82 (m, 2H), 0.91 (d, J = 6.50 Hz, 3H). ^{13}C NMR (CD_3OD): δ 143.3, 138.7, 133.6, 132.2, 131.4, 130.4, 130.2, 129.1, 128.0, 118.8, 111.9, 55.3, 50.6, 37.4, 19.8.

Free base minor diastereomer: ^{1}H NMR (CD_3OD): δ 7.52 (m, 2H), 7.43 (m, 2H), 7.11 (d, J = 8.38 Hz, 2H), 6.97 (d, J = 8.38 Hz, 2H), 3.18 (m, 2H), 2.85 (m, 2H), 1.20 (d, J = 6.42 Hz, 3H). ^{13}C NMR (CD_3OD): δ 143.1, 138.6, 133.6, 132.2, 131.3, 130.2, 130.1, 129.0, 127.8, 118.4, 111.9, 55.2, 50.1, 37.0, 19.9. HRMS calcd for $C_{17}H_{17}ClN_2$ (M^+) m/z 285.1157, found m/z 285.1159.

3-[(1*S*,2*S*)-2-Amino-1-(4-chlorobenzyl)propyl]benzonitrile Hydrochloride (6). HCl/IPA (5.0−6.0 N, 1.39 L) was added dropwise over 2 h. After an overnight age, the amine salt was filtered and washed with toluene (19.4 L). After drying at 40 °C, the solid (2.19 kg, 81% yield from azide **10**) contained 1.3% minor diastereomer and was 94.2% ee.

Analytical Data for a Chromatographed Sample of 6. *Major diastereomer:* ^{1}H NMR (CD_3OD): δ 7.57 (m, 2H), 7.46 (m, 2H), 7.12 (d, J = 8.41 Hz, 2H), 6.99 (d, J = 8.44 Hz, 2H), 3.68 (m, 1H), 3.26 (m, 2H), 2.95 (dd, J = 12.21, 14.63 Hz, 1H), 1.60 (d, J = 6.74 Hz, 3H). ^{13}C NMR (CD_3OD): δ 140.3, 137.1, 133.7, 132.4, 131.9, 131.1, 130.4, 129.6, 128.1, 118.3, 112.4, 51.0 (2C), 37.1, 15.7.

Minor diastereomer: ^{1}H NMR (CD_3OD): δ 7.57 (m, 2H), 7.49 (m, 1H), 7.44 (t, J = 7.68 Hz, 1H), 7.09 (d, J = 8.45 Hz, 2H), 6.96 (d, J = 8.42 Hz, 2H), 3.71 (m, 1H), 3.23 (m, 2H), 2.91 (m, 1H), 1.51 (d, J = 6.57 Hz, 3H). ^{13}C NMR (CD_3OD): δ 140.2, 137.0, 133.6, 132.3, 131.8, 131.3, 130.4, 129.8, 128.0, 118.2, 112.6, 51.5, 51.2, 36.3, 16.1. Anal. Calcd for $C_{17}H_{18}Cl_2N_2$: C 63.56; H 5.65; N 8.72. Found: C 63.65; H 5.52; N 8.71.

***N*-[(1*S*,2*S*)-3-(4-Chlorophenyl)-2-(3-cyanophenyl)-1-methylpropyl]-2-methyl-2-{[5-(trifluoromethyl)pyridin-2-yl]oxy}propanamide (1, MK-0364).** To a solution of pyridine acid **7** (598 g, 2.40 mol) in acetonitrile (8.04 L) was added amine salt **6** (700 g, 2.18 mol) and then cyanuric chloride (1.31 mol, 242 g). The mixture was heated to 50 °C, and NMM (719 mL, 6.54 mol) was added over 4 h. The reaction mixture was cooled to RT; MTBE (9.5 L) and 1 N HCl (9.5 L) were added, and the layers were separated. The organic layer was washed with aq K_2CO_3 (9.5 wt %, 9.5 L) then with aq NH_4Cl (1.5 wt %, 9.5 L). The organic layer was diluted with MTBE (9.3 L) and washed with water (9.5 L). The final organic layer was dried and concentrated to 4.4 L total volume. The batch was cooled to 20−25 °C and seeded with 5 g of hemisolvate. After aging for 30 min a slurry developed, and heptane (17.6 L) was added over 3 h. After a 1-h age, the slurry was cooled to 0−10 °C and aged for another 30 min. The batch was filtered and washed with heptane (2.3 L). The dry solid was 1.13 kg of hemisolvate (approximately 94 wt %, 94% isolated yield from amine salt). ^{1}H NMR ($CDCl_3$): δ 8.35 (s, 1H), 7.83 (dd, J = 2.38, 8.70 Hz, 1H), 7.45 (d, J = 7.57 Hz, 1H), 7.31 (t, J = 7.99 Hz, 1H), 7.24 (m, 2H), 7.07 (d, J = 8.34 Hz, 2H), 6.88 (d, J = 8.63 Hz, 1H), 6.72 (d, J = 8.33 Hz, 2H), 5.88 (d, J = 8.95 Hz, 1H), 4.34 (m, 1H), 3.13 (dd, J = 3.04, 12.72 Hz, 1H), 2.82 (m, 2H), 1.76 (s, 3H), 1.72 (s, 3H), 0.87 (d, J = 6.72 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 173.4, 163.9, 144.5 (q, J = 4.30 Hz), 142.4, 137.5, 136.3 (q, J = 3.02 Hz), 133.0, 132.2, 132.0, 130.7, 130.0, 129.3, 128.5, 123.7 (q, J = 271.45 Hz), 121.1 (q, J = 33.32 Hz), 118.6, 112.7, 112.6, 82.1, 53.6, 48.6, 38.2, 25.4, 25.1, 18.4. Anal. Calcd for $C_{27}H_{25}ClF_3N_3O_2$: C 62.85; H 4.88; N 8.14. Found: C 62.95; H 4.74; N 8.00.

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