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Crystallization-Induced Dynamic Resolution of a Diarylmethylamine toward the Synthesis of a Potent TRPM8 Inhibitor

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Supporting Information

ABSTRACT: The development and demonstration of a crystallization-induced dynamic resolution (CIDR) to prepare a chiral diarylmethylamine, a key intermediate toward the synthesis of a potent TRPM8 inhibitor, is described. Essential to the development of this process was the discovery of (1) efficient classical resolution conditions by a high-throughput screening method, (2) formaldehyde as the optimal racemization agent based on comparison of first-order reaction rate constants, and (3) mechanical grinding as a method to improve solid−liquid mass transfer and facilitate reaction progress. Kinetic analysis of the racemization process and identification of the substrate functional group required for racemization provided the foundation for a mechanistic proposal.

Chiral nonracemic amines are integral building blocks for the synthesis of biologically active molecules. Highlighted by the commercial success of cetirizine **1** and solifenacin **3**, diarylmethylamines (e.g., **1**−**3**, Figure 1) represent a privileged

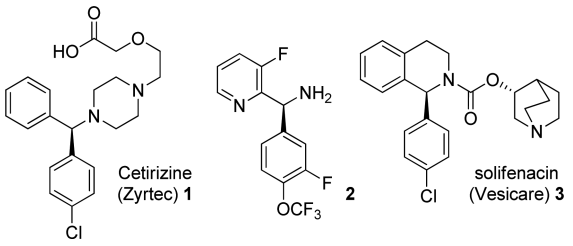

Figure 1. Diarylmethylamine motif in pharmaceutically relevant structures.

structure class, which remain an active area of investigation in drug discovery for a wide range of indications.[1] In the context of cetirizine, numerous stereoselective chemical methods,[2] in addition to approaches utilizing chiral chromatography,[3] have been developed for its large-scale synthesis. Despite these important advances, classical resolution[4,5] remains the preferred method for the commercial manufacture of diarylmethyl amines due to the facile synthesis of racemic amine starting materials, low cost, and ready availability of appropriate resolving agents, straightforward isolation of the crystalline products, and opportunities for enrichment of chiral purity through recrystallization. To surmount the limitation of a 50% theoretical maximum yield inherent to a classical resolution approach, researchers have explored in situ racemization methods to convert the entirety of racemic material to desired product in what is termed a crystallization-induced dynamic resolution (CIDR).[6,7] This manuscript describes the design, development, and application of a CIDR for the preparation of chiral diarylmethylamine **2**, including the unique role of formaldehyde as a facile racemization agent and studies to determine the key elements of **2** that facilitate its epimerization.

A recent project required a practical stereoselective synthesis of amine **2**, an intermediate used in the production of a potent TRPM8 inhibitor. An evaluation of the current technologies available for synthesis of the chiral diarylmethylamine motif identified CIDR as the ideal approach toward this target molecule. Two criteria must be satisfied for the design of a successful CIDR: the development of (1) a crystallization system that resolves the molecule and (2) conditions that allow its simultaneous epimerization. In the course of process development, these two conditions may be developed independently; however, the most critical and challenging design element involves the combination of these individual components such that the two processes can proceed effectively in one-pot with practical efficiency.

We envisioned that classical resolution of amine **2** could be achieved based on the precedence established for related diarylmethylamines in which chiral acids were employed as the stoichiometric resolving agent.[4,8] Toward the development of a resolution method, a panel of chiral acid resolving agents and solvent systems were investigated by a high-throughput screening method;[9,10] these experiments identified L-dibenzoyl tartaric acid (L-DBTA) as the optimal resolving acid in combination with MeCN/water (95:5) as the solvent system. In a representative reaction, a solution of L-DBTA in MeCN/water was added dropwise to a solution of racemic amine **2** in MeCN/water (95:5) at 20 °C (Scheme 1). After aging overnight, the desired (*S*)-amine·L-DBTA **4** was obtained as a white crystalline solid in 39% yield with 90% de in a single crystallization. The resulting product purity aligned with our specifications for amine **2** (≥90% ee) in early development.

Modulating the pK_a of an α-amine stereocenter by formation of the corresponding iminium ion has proven to be an effective strategy for the racemization of amino acids and related α-amino carbonyl compounds.[6a] To identify a suitable iminium

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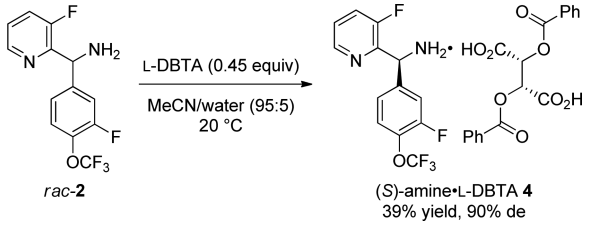
Scheme 1. Classical Resolution of Racemic Amine 2 To Provide (*S*)-Amine·L-DBTA 4



ion in this setting, kinetic studies of the catalytic racemization of optically enriched (*S*)-amine **2** in MeCN/water were performed (Figure 2).[11] Notably, substitution of the resolving

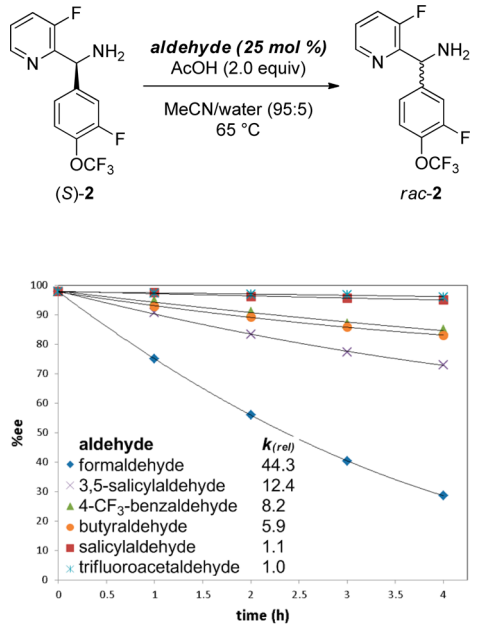
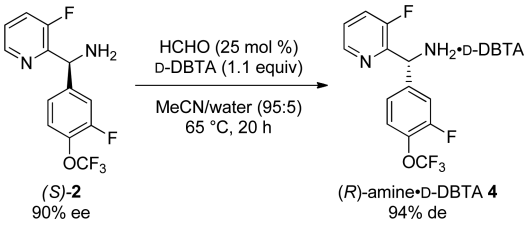


Figure 2. Racemization (% ee) of (*S*)-amine **2** versus time (h) for a range of aldehyde additives.

acid L-DBTA with acetic acid rendered the system homogeneous and allowed an accurate comparison of racemization rates. These data fit well with a kinetic model of a first order reversible reaction.[11] A range of aldehyde catalysts were explored using the same substrate concentrations and catalyst loadings such that reaction rate constants could be extrapolated and directly compared. These experiments identified formaldehyde as the optimal additive to provide appreciable levels of racemization within a reasonable time period. The preponderance of literature evidence illustrates that electron-deficient aryl aldehydes are optimal for the racemization of a stereocenter adjacent to an amine functional group; despite this precedence, a range of aryl aldehydes were less effective for epimerizing (*S*)-amine **2** as compared to formaldehyde. Less sterically encumbered alkyl aldehydes such as butyraldehyde and trifluoroacetaldehyde were also not suitable for this purpose. This study represents the first example of diarylmethylamine epimerization by activation as an iminium ion and the use of formaldehyde in this context.

To verify in this setting that the combination of racemization and chiral resolution could provide a useful platform for CIDR, an experiment was conducted in which (*S*)-amine **2** and mismatched D-DBTA were combined to produce (*R*)-amine·D-DBTA **4** in the presence of formaldehyde. Subjecting (*S*)-amine **2** in MeCN/water (95:5) to D-DBTA and catalytic HCHO at 65 °C resulted in the formation of (*R*)-amine·D-DBTA **4** as a white crystalline solid with 94% de after 20 h (Scheme 2).

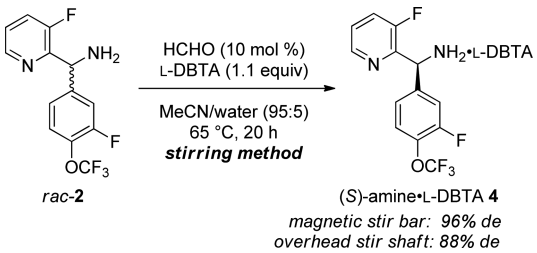
Scheme 2. Conversion of (*S*)-Amine 2 to (*R*)-Amine·D-DBTA via CIDR



Thus, formaldehyde serves as a singular additive to the classical resolution to render the transformation dynamic. In agreement with the racemization studies illustrated in Figure 2, both alkyl and aryl aldehyde additives were ineffective for this transformation,[12] further demonstrating the unique role of formaldehyde in this context.

In the course of process development, inconsistencies were observed during scale-up from exploratory (<1 g) to intermediate scale (1−200 g). The racemization rate proved particularly sensitive to the agitation method, where the use of overhead stirrers equipped with stir paddles resulted in extended reaction times and stalling of the chiral resolution. A direct comparison of reactions performed with a magnetic stir bar versus an overhead stirrer revealed the agitation method to be a critical process parameter for the successful CIDR (Scheme 3). Using otherwise identical conditions, a magnetic

Scheme 3. Impact of Agitation Method on Reaction Progress



stir bar provided (*S*)-amine·L-DBTA **4** as a white crystalline solid with 96% de, whereas an overhead stirrer provided product with only 88% de. The chiral purity of the reaction utilizing an overhead stirrer could not be improved with extended aging of the reaction mixture at 65 °C; only upon inserting a magnetic stir bar to the stalled resolution was an increase to 91% de observed (2 h at 65 °C), thus meeting product specification. We attribute the increased resolution efficiency to attrition-enhanced dissolution, i.e., particle-size reduction by mechanical grinding with a magnetic stir bar.[13]

Wet-milling is a tunable particle−particle collision-based method for reduction in particle size, which serves as a scalable analogy to stir-bar based grinding. Envisioning long-term commercial manufacture of this material, we hypothesized that a high-shear rotor stator wet-milling procedure might allow mass transfer rates necessary to affect an efficient CIDR. A demonstration of the optimized CIDR process utilizing a wet mill was performed to validate this concept (Figure 3). To 197 g of *rac*-amine **2** in MeCN/water (95:5) was charged L-DBTA

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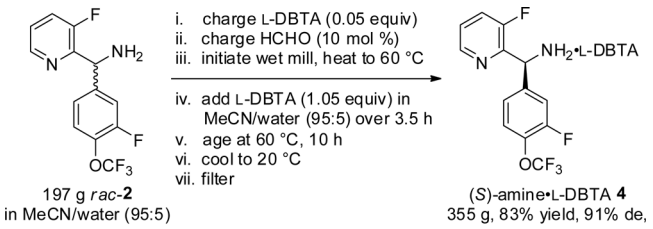


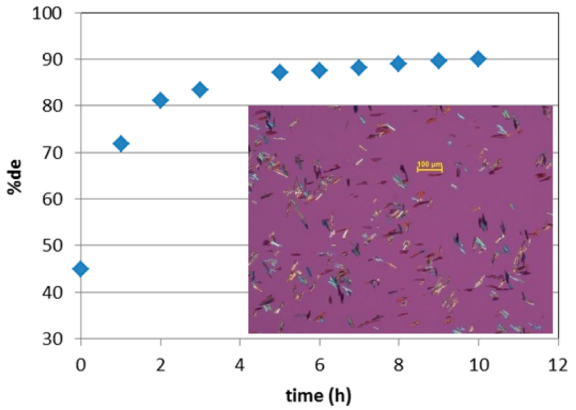


Figure 3. Profiling of the chiral purity of amine **2** versus time (t_0 = end of DBTA addition). Microscope image (100×) illustrates particle size at t = 10 h.[14]

(0.05 equiv) then HCHO (10 mol %) at 20 °C. Upon formation of a white slurry, wet milling was commenced, the reaction temperature was increased to 60 °C, and a solution of L-DBTA (1.05 equiv) in MeCN/water (95:5) was added dropwise over 3.5 h. The slurry was aged for an additional 10 h at 60 °C with continuous wet milling and monitored off-line to track the chiral purity of the resultant white crystalline solid. After 10 h, the reaction mixture was cooled to 20 °C and filtered to provide 355 g (*S*)-amine·L-DBTA **4** (83% yield) with 91% de. In contrast to previous studies using only an overhead stirrer (Scheme 3), utilization of a wet mill enabled isolation of specification quality material in only 10 h.

Efforts to evaluate the scope of this CIDR process provided key insight into the epimerization pathway. As a direct comparison to the racemization studies performed for amine **2** (vide supra, Figure 2), a selection of benzylic amines was subjected to catalytic HCHO in the presence of AcOH at 65 °C (Figure 4). Diarylmethylamine **5**, which differs only by the absence of electron-withdrawing groups on the aryl substituents, underwent rapid racemization in the presence of HCHO in agreement with the results obtained for amine **2**. In contrast, amine **6**, which is isoelectronic with amine **2** but differs only in the position of the pyridine nitrogen, did not racemize under identical conditions. Substrates **7** and **8**, lacking a pyridine ring or aryl substituent, respectively, also did not racemize. These data demonstrate that both the presence and position of the pyridine nitrogen is a critical component of the racemization mechanism.

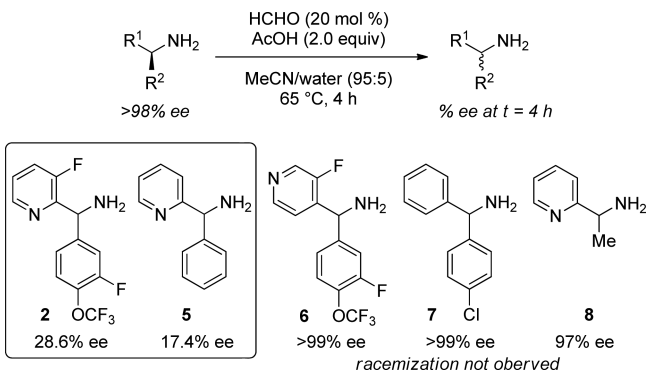
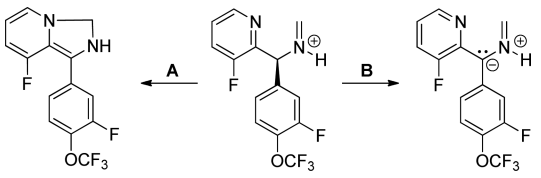


Figure 4. Effect of substrate structure on the extent of racemization.

The geometric requirement of the pyridine nitrogen combined with the unique role of formaldehyde prompted us to consider a different mechanism (Pathway A, Scheme 4) than

Scheme 4. Plausible Pathways for Racemization via Iminium Ion Formation



that traditionally proposed for epimerization of an amine via iminium ion formation (Pathway B, Scheme 4).[15] Both pathways A and B could originate from the iminium ion intermediate **10** formed upon condensation of formaldehyde with amine **2**.[16] In pathway A, we propose that nucleophilic addition of the appropriately positioned pyridine nitrogen could result in aminal formation followed by tautomerization and dearomatization to form intermediate **9**.[17] This pathway accounts for the increased rate of racemization observed with formaldehyde relative to other aldehydes investigated as the iminium ion derived from formaldehyde is 2.58 orders of magnitude more electrophilic than that derived from benzaldehyde.[18] Further, pathway B is expected to be favored as the aldehyde additive becomes more electron-deficient, which is inconsistent with the data described in Figure 2.

An efficient and practical synthesis of (*S*)-amine·L-DBTA **4** could be achieved through the development and implementation of a crystallization-induced dynamic resolution. Upon identifying conditions for a successful classical resolution, formaldehyde was identified as a singular additive to render the system dynamic through rapid epimerization of the racemic diarylmethyl amine. Analysis of the substrate scope and comparison of reaction rates led to the proposal of a distinct epimerization pathway, which relies on both the geometric requirement of an appended pyridine nitrogen and the electrophilic nature of formaldehyde.

EXPERIMENTAL SECTION

General. All reactions were performed under an atmosphere of nitrogen under anhydrous conditions, unless otherwise noted. All solvents and reagents were commercially obtained and used without further purification. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded at ambient temperature at 500 and 125 MHz, respectively, using a Bruker AVANCE-500 spectrometer or at 400 and 100 MHz, respectively, using a Bruker AVANCE-400 spectrometer. The ^{1}H NMR data are reported as follows: chemical shift in parts per million (ppm) from an internal standard of residual $(CH_3)_2SO$ in $(CD_3)_2SO$ (2.50 ppm) or residual $CHCl_3$ in

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$CDCl_3$ (7.27 ppm) on the δ scale, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants in hertz (Hz), and integration (H). Chemical shifts of ^{13}C NMR spectra are reported in ppm from the central peak of $(CD_3)_2SO$ (39.5 ppm) or $CDCl_3$ (77.0 ppm). Infrared (IR) spectra were recorded on a PerkinElmer Spectrum 100 FT-IR spectrometer. High resolution mass spectra (HRMS) were obtained using Agilent 1100 systems. Optical rotations were measured using a Jasco P-2000 polarimeter at 589 nm and calculated using the formula: $[\alpha]_D = \alpha_{obs}/(l(c/1000))$, where c = (g of substrate/100 mL of solvent) and l = 1 dm. Melting points were measured by differential scanning calorimetry (DSC) using a TA Instruments Q200 DSC at 10 °C/min. Enantiomeric excess was determined by high-performance liquid chromatography (HPLC) performed on an Agilent 1200 HPLC system equipped with a spectrophotometric detector; spectra and the details of individual methods are described in the Supporting Information.

(S)-(3-Fluoro-4-(trifluoromethoxy)phenyl)(3-fluoropyridin-2-yl)methanamine ***2***. To a white slurry of (*S*)-(3-fluoro-4-(trifluoromethoxy)phenyl)(3-fluoropyridin-2-yl)methanamine hydrochloride[19] (10.8 g, 31.7 mmol) in 2-MeTHF (108 mL) was added NaOH (79 mL, 1.0 M, 79 mmol), and the reaction mixture was allowed to stir for 1 h at ambient temperature. The biphasic mixture was transferred to a separatory funnel and the layers separated. The organic layer was washed with water (108 mL) and brine (2 × 54 mL) and then concentrated in vacuo. The resultant oil was filtered through a medium-porosity glass-fritted funnel to remove residual inorganic solids, and the filter cake was rinsed with a minimal amount of MeCN. The solution was concentrated in vacuo to afford **2** as a pale yellow oil (9.52 g, 99%): $[\alpha]^{21}_D$ + 48 (*c* 0.80, EtOH); ^1H NMR (500 MHz, $(CD_3)_2SO$) 8.41 (d, *J* = 5.0 Hz, 1H), 7.67 (ddd, *J* = 10.1, 8.5, 1.3 Hz, 1H), 7.52 (dd, *J* = 11.7, 2.2 Hz, 1 H), 7.45 (t, *J* = 7.8 Hz, 1H), 7.37 (dt, *J* = 8.5, 4.3 Hz, 1H), 7.24 (d, *J* = 8.3 Hz, 1H), 5.41 (s, 1H), 2.62 (s, 2H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) 155.9 (d, *J* = 255.1 Hz), 153.4 (d, *J* = 249.6 Hz), 150.6 (d, *J* = 14.7 Hz), 146.9 (d, *J* = 5.4 Hz), 145.2 (d, *J* = 5.5 Hz), 133.7 (dq, *J* = 12.5, 1.6 Hz), 124.1 (d, *J* = 3.8 Hz), 123.6 (m, 3C), 120.0 (q, *J* = 257.8 Hz), 115.6 (d, *J* = 19.1 Hz), 52.9; IR (ATR) 3075, 2973, 1599, 1507, 1443, 1217 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_{13}H_{10}F_5N_2O$ $(M + H)^+$ 305.0708, found 305.0706.

(S)-(3-Fluoro-4-(trifluoromethoxy)phenyl)(3-fluoropyridin-4-yl)methanamine ***6***. To a white slurry of (*S*)-(3-fluoro-4-(trifluoromethoxy)phenyl)(3-fluoropyridin-4-yl)methanamine hydrochloride (0.33 g, 0.98 mmol) in MTBE (13 mL) was added NaOH (2.4 mL, 1.0 M, 2.4 mmol), and the reaction mixture was allowed to stir for 1 h at ambient temperature. The biphasic mixture was transferred to a separatory funnel and the layers separated. The organic layer was washed with water (5 mL) and brine (5 mL), filtered through a medium-porosity glass-fritted funnel to remove residual inorganic solids and then concentrated in vacuo to afford **6** as a pale yellow oil (0.23 g, 76%): $[\alpha]^{21}_D$ − 10 (*c* 0.17, EtOH); ^1H NMR (400 MHz, $CDCl_3$) 8.44 (dd, *J* = 5.1, 0.9 Hz, 1H), 8.40 (d, *J* = 2.0 Hz, 1H), 7.52 (t, *J* = 5.6 Hz, 1H), 7.31 (dd, *J* = 10.8, 1.8 Hz, 1H), 7.26 (m, 1H), 7.20 (m, 1H), 5.52 (s, 1H), 1.78 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) 157.1 (d, *J* = 256.2 Hz), 154.5 (d, *J* = 253.6 Hz), 146.4 (d, *J* = 5.2 Hz), 143.6 (d, *J* = 6.1 Hz), 139.9 (d, *J* = 10.8 Hz), 138.2 (d, *J* = 24.3 Hz), 135.7 (dq, *J* = 12.6, 2.2 Hz), 123.9, 122.9 (d, *J* = 3.0 Hz), 121.7, 120.4 (q, *J* = 258.9 Hz), 115.8 (19.5 Hz), 51.6; IR (ATR) 3043, 2818, 1601, 1514, 1476, 1205 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for $C_{13}H_{10}F_5N_2O$ $(M + H)^+$ 305.0708, found 305.0701.

(S)-(3-Fluoro-4-(trifluoromethoxy)phenyl)(3-fluoropyridin-2-yl)methanamine (2R,3R)-2,3-Bis(benzoyloxy)succinate ***4*** *(Classical Resolution)*. To a solution of *rac*-**2** (17.9 g, 58.7 mmol) in MeCN/water [95:5 v/v] (89.3 mL) was added a prepared solution of L-DBTA in MeCN/water [95:5 v/v] (21.0 mL, 0.10 g/mL, 5.87 mmol) linearly over 30 min, and the reaction mixture, upon self-seeding, was allowed to age with stirring for 30 min at ambient temperature. Additional L-DBTA in MeCN/water [95:5 v/v] (73.6 mL, 0.10 g/mL, 20.6 mmol) was added linearly over 2 h and the white slurry was allowed to age with stirring for 3 d at ambient temperature. The slurry was warmed to 40 °C, aged for 2 h, then cooled linearly to 20 °C over 2 h.[20] The slurry was filtered through a medium-porosity glass-fritted funnel, and the filter cake was washed with MeCN/water [95:5 v/v] (53.6 mL) then MeCN (53.6 mL). The filter cake was dried over vacuum with a nitrogen sweep to provide (*S*)-amine·L-DBTA **4** as a white crystalline solid (15.4 g, 39%). The enantiomeric excess of (*S*)-amine was determined to be 90% by chiral HPLC (Chiralpak AY-H column, 4.6 mm × 100 mm, 5 μm, eluent: heptane/EtOH/diethylamine = 95:5:0.2 (v/v), 1 mL/min, 20 °C, 254 nm. t_r(minor): 3.9 min, t_r(major): 5.1 min): $[\alpha]^{21}_D$ − 17 (*c* 0.35, EtOH); mp (DSC) = 200.16 °C; ^1H NMR (500 MHz, $(CD_3)_2SO$) 8.52 (d, *J* = 4.7 Hz, 1H), 7.94 (m, 4H), 7.78 (t, *J* = 8.8 Hz, 1 H), 7.49−7.66 (m, 9H), 7.35 (d, *J* = 8.4 Hz, 1H), 5.91 (s, 1H), 5.68 (s, 2H); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) 167.7, 164.7, 156.0 (d, *J* = 257.8 Hz), 153.3 (d, *J* = 250.7 Hz), 145.3 (d, *J* = 5.5 Hz), 144.9 (d, *J* = 13.6 Hz), 139.7, 135.0 (d, *J* = 12.0 Hz), 133.5, 129.3, 129.2, 128.7, 125.7 (d, *J* = 3.8 Hz), 125.0 (d, *J* = 3.3 Hz), 124.4 (d, *J* = 16.4 Hz), 124.3, 119.9 (q, *J* = 258.3 Hz), 117.0 (d, *J* = 19.6 Hz), 71.5, 51.4; IR (ATR) 3066, 2950, 1710, 1664, 1518, 1263 cm^{-1}; HRMS (ESI-TOF) *m*/*z* calcd for the freebase $C_{13}H_{10}F_5N_2O$ $(M + H)^+$ 305.0708, found 355.0701.

(S)-(3-Fluoro-4-(trifluoromethoxy)phenyl)(3-fluoropyridin-2-yl)methanamine (2R,3R)-2,3-bis(benzoyloxy)succinate ***4*** *(CIDR Demonstration)*. **Step 1.** To a 5 L jacketed reactor (20 °C) equipped with an overhead stirrer and thermocouple was charged *rac*-(3-fluoro-4-(trifluoromethoxy)phenyl)(3-fluoropyridin-2-yl)methanaminium chloride (250 g, 88.3 wt %, 648 mmol) then MTBE (2500 mL) to generate a yellow slurry. Agitation was initiated, and NaOH (1300 mL, 1.0 M, 1300 mmol) was charged in a single portion by addition funnel. The reaction mixture was allowed to stir for 1 h at ambient temperature. Agitation was stopped, the layers separated, and the organic layer was washed with water (2 × 1250 mL). A constant volume distillative solvent swap to MeCN was initiated: start conditions = jacket temp: 20 °C, vacuum: 200 Torr; end conditions = jacket temp: 50 °C, vacuum: 160 Torr [3000 mL total volume MeCN charged]. The MeCN solution was discharged and then filtered through a medium-porosity glass-fritted funnel to a cleaned 5 L jacketed reactor to remove residual inorganic solids.

Step 2. Agitation was initiated and to the 20 °C solution of *rac*-**2** in MeCN generated from Step 1 was charged water (94 mL) to achieve a 95:5 MeCN/water (v/v) solution. Separately, a solution of L-DBTA (255 g, 713 mmol) in MeCN/water [95:5 v/v] (1104 mL) was prepared. 5% of the prepared L-DBTA solution (65 mL) was added linearly over 10 min via syringe pump and self-seeding was observed. Additional seed [(*S*)-amine·L-DBTA **4**] (8.59 g, 13.0 mmol) was charged and the white slurry allowed to age for 18 h at 20 °C. Formaldehyde

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(4.82 mL, 37 wt % in water, 64.8 mmol) was charged in a single portion, and wet milling was commenced (12800 rpm) using an IKA magic LAB. The reaction mixture was warmed to 60 °C, and the remaining solution of L-DBTA in MeCN/water (95:5 v/v) was charged over 3.5 h. The slurry was aged at 60 °C with continuous wet milling until chiral HPLC analysis indicated the white crystalline solid was >90% de (10 h).[21] The reaction mixture was cooled linearly to 20 °C over 2 h, and wet milling was stopped. The slurry was filtered through a medium-porosity glass-fritted funnel, and the filter cake was washed with MeCN (2 × 662 mL). The filter cake was dried over vacuum with a nitrogen sweep to provide (*S*)-amine·L-DBTA **4** as a white solid (355 g, 83%). The enantiomeric excess of (*S*)-amine was determined to be 91% by chiral HPLC (Chiralpak AY-H column, 4.6 mm × 100 mm, 5 μm, eluent: heptane/EtOH/diethylamine = 95:5:0.2 (v/v), 1 mL/min, 20 °C, 254 nm. t_r(minor): 3.9 min, t_r(major): 5.1 min).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.6b00162.

Complete experimental details, kinetic data and analysis, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(21) The batch was cooled to 20 °C and wet milling stopped for a 16 h period overnight. The % de of the solids improved from 83.4 to 85.6 during this 16 h period, demonstrating the requirement for elevated temperatures and wet milling for an efficient CIDR process.

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