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Nonracemic Synthesis of GK–GKRP Disruptor AMG-3969

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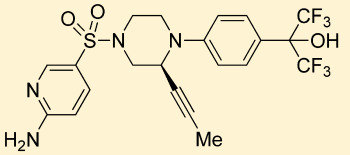
Supporting Information

ABSTRACT: A nonracemic synthesis of the glucokinase–glucokinase regulatory protein disruptor AMG-3969 (**5**) is reported. Key features of the synthetic approach are an asymmetric synthesis of the 2-alkynyl piperazine core via a base-promoted isomerization and a revised approach to the synthesis of the aminopyridinesulfonamide with an improved safety profile.



We recently reported the development of a series of disruptors of the glucokinase (GK)–glucokinase regulatory protein (GKRP) protein–protein interaction. Animals dosed with these compounds show improved metabolic profiles, and thus these compounds may hold potential for the treatment of diabetes in humans.[1−3] As part of our research program, a significant quantity of compound AMG-3969 (**5**) was required for in vivo efficacy and toxicology studies. This material demand caused us to re-evaluate our synthetic approach to **5** with an eye toward improving efficiency and safety. The original synthetic approach to **5** began from protected piperazanone **1** (prepared in 81% yield from 2-piperazinone), which was treated with propynyl Grignard to afford alkynone **2** (Scheme 1).[1] Boc cleavage promoted by TFA and reduction of the resulting imine afforded racemic 2-alkynyl piperazine **3** that was further elaborated to chloropyridine **4**. Displacement of the chloride with ammonia at elevated temperature, followed by chiral supercritical fluid chromatography (SFC), afforded **5** in 99% ee. When we considered how to improve on our original approach to the synthesis of **5**, there were two particular aspects that we focused on. The first was the synthesis of the 2-alkynyl piperazine core. We hoped to develop an asymmetric method to install the propynyl group, obviating the need for a large-scale, late-stage enantiomer separation. To the best of our knowledge, there are no prior examples in the literature of the asymmetric synthesis of 2-alkynyl piperazines. Second, we sought to develop an alternative method for the installation of the aminopyridine functional group. Aminolysis of chloropyridine **4** required forcing conditions which resulted in significant pressurization of the reaction vessel (∼110 psi). Differential scanning calorimetry analysis of this reaction also showed a large exotherm at 140 °C. For an exotherm of this magnitude, we would prefer to run the reaction 100 °C cooler than the exotherm temperature, which in this case would be significantly below the temperature required for conversion. Thus, an alternative method to install the aminopyridine was required for large-scale preparations of **5**.

Our revised retrosynthetic analysis of **5** led us to protected sulfonyl chloride **6** and 2-propynylpiperazine **7** (Figure 1). Compound **7** was expected to be synthesized by palladium-catalyzed cross-coupling of aryl bromide **8** with piperazine **9**. It was postulated that **9** could be prepared by base-promoted isomerization of terminal alkyne **10**. While there is good precedence for KO*t*Bu-mediated isomerization of terminal alkynes, we were uncertain whether such a transformation would potentially erode the enantiopurity of the product.[4] Compound **10** could be readily prepared from chiral diketopiperazine **11**, itself the product of commercially available glycine and propargylglycine derivatives **12** and **13**.

The synthesis began with 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxide hexafluorophosphate-mediated amide coupling of ethyl 2-(benzylamino)-acetate (**14**) and (2*S*)-2-((*tert*-butoxycarbonyl)amino)-4-pentynoic acid (propargyl glycine, **15**, purchased from Matrix Scientific; Scheme 2). Boc cleavage and treatment with ammonia in methanol resulted in the formation of piperazinedione **16** in good yield.[5] Treatment of **16** with $LiAlH_4$ resulted in reduction to the corresponding piperazine, setting the stage for the planned alkyne isomerization. The crude reduction product was treated with KO*t*Bu in THF for 30 min at room temperature, resulting in complete isomerization to the alkynyl piperazine **17**. Compound **17** then underwent palladium-mediated cross-coupling with **8**[6] utilizing Buchwald's RuPhos first-generation precatalyst to afford aryl piperazine **18** in quantitative yield.[7] Benzyl group cleavage promoted by 1-chloroethyl chloroformate afforded piperazine **7**, also in quantitative yield.[8] To eliminate the need for the late-stage, high-pressure aminolysis used in the first-generation synthesis,

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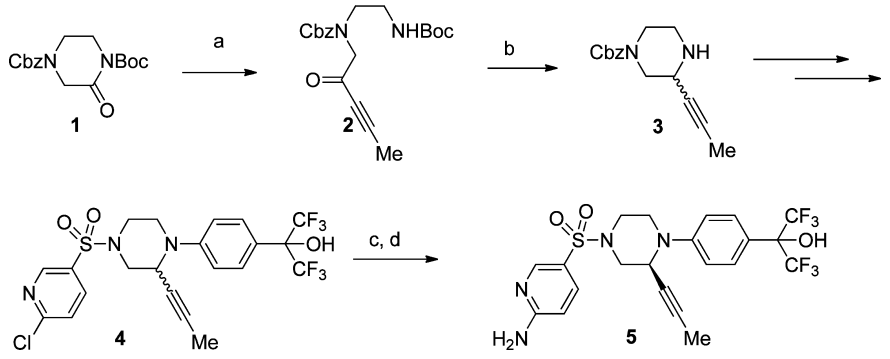
Scheme 1[a]



[a]Reagents and conditions: (a) 1-propynylmagnesium bromide, THF, 0 °C, 99%; (b) TFA, DCM, then $NaBH(OAc)_3$ 77%; (c) NH_4OH, EtOH, 120 °C, 88%; (d) chiral SFC, 38%.

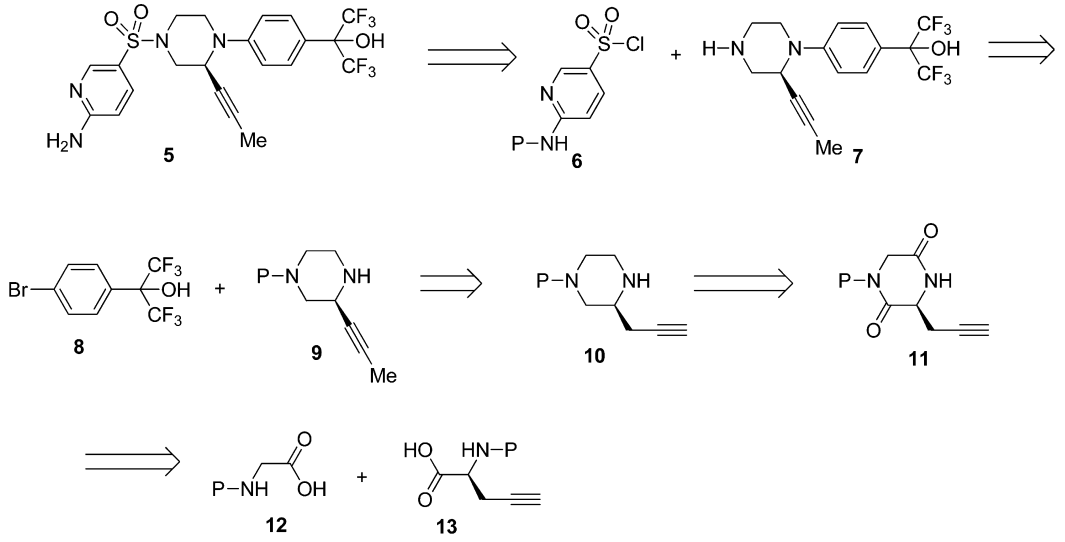
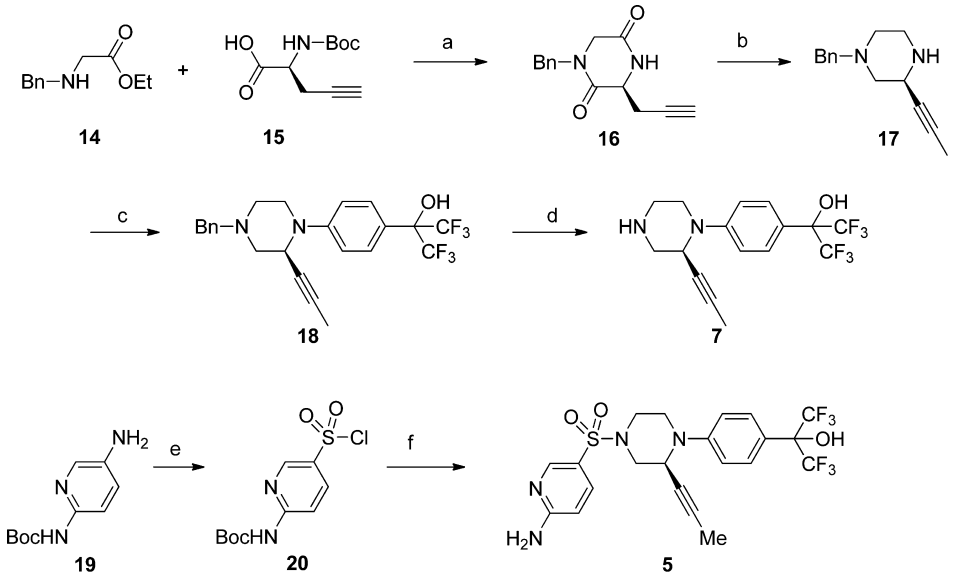


Figure 1. Second-generation retrosynthetic analysis of **5**.

Scheme 2[a]



[a]Reagents and conditions: (a) HATU, DIPEA, DMF then TFA, DCM, then NH_3, MeOH, 78%; (b) $LiAlH_4$, THF, 0 °C to reflux, then KO*t*Bu, 67%; (c) **8**, RuPhos first-generation precatalyst, NaO*t*Bu, 80 °C, 100%; (d) 1-chloroethyl chloroformate, K_2CO_3, 100%; (e) $NaNO_2$, HCl, then AcOH, CuCl, $CuCl_2$, SO_2, 64%; (f) **18**, Et_3N, then TFA, 49%.

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Boc-protected aminopyridyl sulfonyl choride **20** (purchased from Green Chempharm, Inc.) was utilized, which was synthesized from commercially available aniline **19**.[9] Finally, piperazine **7** was coupled with sulfonyl chloride **20**, followed by TFA deprotection of the Boc group to deliver compound **5** in good yield. HPLC characterization of compound **5** prepared via the second-generation approach showed the resulting product to be >99% ee, indicating that the alkyne isomerization had occurred with complete retention of configuration. This protocol has been utilized to prepare >60 g lots of compound **5**. Compared to the original route, this new approach resulted in a significantly higher overall yield of **5** (original route from 2-piperazinone: 7 steps longest linear sequence, 14% yield; new route from Boc-(*S*)-propargylglycine: 5 steps longest linear sequence, 26% yield).

In summary, we have developed an improved synthesis of the GK−GKRP disruptor **5** featuring a novel asymmetric route to the 2-alkynyl piperazine core and a safer, more easily scalable route to the aminopyridine sulfonamide. In particular, the alkyne isomerization used to generate the chirally pure alkynyl piperazine **17** may offer a potentially useful method for the synthesis of other 2-alkynyl piperazines.

EXPERIMENTAL SECTION

General Considerations. Unless otherwise noted, all reagents were commercially available and used as received. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 MHz (101 MHz for ^{13}C) NMR spectrometer at ambient temperature. Data are reported as follows: chemical shift (ppm, δ units) from an internal standard, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad), coupling constant (Hz), and integration. Silica gel chromatography was performed using a medium-pressure liquid chromatography system, and melting point data were generated using a melting point apparatus.

(3*S*)-1-Benzyl-3-(2-propyn-1-yl)-2,5-piperazinedione (16). A 1 L round-bottomed flask was charged with (2*S*)-2-((*tert*-butoxycarbonyl)amino)-4-pentynoic acid **15** (42.0 g, 197 mmol, purchased from Matrix Scientific), ethyl 2-(benzylamino)acetate **14** (40.0 g, 207 mmol), 1-[bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]-pyridinium 3-oxide hexafluorophosphate (90 g, 240 mmol), and 200 mL of DMF. To this was added *N*,*N*-diisoproylethylamine (38.2 g, 51.5 mL, 296 mmol). After 15 min at room temperature, the mixture was diluted with water (300 mL) and extracted with a mixture of 20% EtOAc in diethyl ether (1 L). The layers were separated, and the organic extracts were washed with 2 M aqueous HCl, water, saturated aqueous $NaHCO_3$, and then brine. The organics were dried ($MgSO_4$), filtered, and concentrated to give an off-white solid. To this was added 200 mL of CH_2Cl_2 and trifluoroacetic acid (227 g, 152 mL, 1.97 mol). After being stirred at room temperature for 30 min, the mixture was concentrated. Residual TFA was then removed via two sequential azeotropic distillations using toluene (100 mL each). To the resulting oil was added ammonia (2 M in MeOH, 394 mL, 788 mmol). After the mixture was stirred at room temperature for 30 min, the reaction was concentrated, dissolved in EtOAc (1 L), and washed with water. The organics were dried ($MgSO_4$), filtered, and concentrated to give the crude product. This material was then slurried with diethyl ether (500 mL) to give (3*S*)-1-benzyl-3-(2-propyn-1-yl)-2,5-piperazinedione **16** (37.3 g, 78%) as a white amorphous solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.15 (m, 5 H), 6.53 (br s, 1 H), 4.75 (d, J = 14.7 Hz, 1 H), 4.49 (d, J = 14.5 Hz, 1 H), 4.20 (br s, 1 H), 3.96 (d, J = 17.8 Hz, 1 H), 3.83 (d, J = 18.0 Hz, 1 H), 2.94−2.73 (m, 2 H), 2.05 (br s, 1 H); ^{13}C NMR (101 MHz, CD_3OD) δ 168.0, 167.2, 136.7, 129.9, 129.5, 129.2, 79.8, 73.7, 55.3, 50.6, 50.1, 25.9; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{14}H_{15}N_2O_2$ 243.1134, found 243.1135; mp 136−144 °C; $[\alpha]_D^{20}$ = +33 (c = 2.8, MeOH).

(3*S*)-1-Benzyl-3-(1-propyn-1-yl)piperazine (17). A 1 L round-bottomed flask was charged with (3*S*)-1-benzyl-3-(2-propyn-1-yl)-2,5-piperazinedione **16** (37.3 g, 154 mmol) and 150 mL of THF. The suspension was cooled to 0 °C, then lithium aluminum hydride (1 M in THF, 539 mL, 539 mmol) was slowly added. After the addition was complete, the mixture was heated at 80 °C for 12 h. The mixture was then cooled to 0 °C, and solid sodium sulfate decahydrate was added until effervescence ceased. The mixture was then filtered, and the filtrate was concentrated to give (3*S*)-1-benzyl-3-(2-propyn-1-yl)-piperazine (18.1 g) as a yellow oil. This material was combined with an additional 20.7 g of crude amine synthesized in a similar manner. The combined lots were used directly in the next step without purification.

To a solution of (3*S*)-1-benzyl-3-(2-propyn-1-yl)piperazine (38.8 g, 181 mmol) in THF (200 mL) was added potassium *t*-butoxide (40.6 g, 362 mmol) portionwise. After the addition was complete, the reaction mixture was stirred at room temperature for 30 min and then quenched with water (500 mL) and diluted with EtOAc (1 L). The organic phase was dried (Na_2SO_4), filtered, and concentrated to give a solid. Purification via silica gel chromatography (0−7% MeOH in CH_2Cl_2) followed by recrystallization from 100% hexanes provided (3*S*)-1-benzyl-3-(1-propyn-1-yl)piperazine **17** (26.0 g, 67%) as tan crystalline solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.18 (m, 5 H), 3.59 (br d, J = 8.8 Hz, 1 H), 3.51 (s, 2 H), 2.98 (d, J = 11.9 Hz, 1 H), 2.88−2.76 (m, 2 H), 2.65 (d, J = 11.0 Hz, 1 H), 2.22−2.05 (m, 2 H), 1.84−1.76 (s, 3 H), 1.73 (br s, 1 H); ^{13}C NMR (101 MHz, CD_3OD) δ 138.5, 130.7, 129.5, 128.5, 80.3, 78.9, 64.0, 59.8, 53.8, 48.0, 45.5, 3.2; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{14}H_{19}N_2$ 215.1548, found 215.1551; mp 65−68 °C, $[\alpha]_D^{20}$ = −55.4 (c = 2.9, MeOH).

(*S*)-2-(4-(4-((6-Aminopyridin-3-yl)sulfonyl)-2-(prop-1-yn-1-yl)piperazin-1-yl)phenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol, AMG-3969 (5). A 2 L round-bottomed flask was charged with (*S*)-1-benzyl-3-(prop-1-yn-1-yl)piperazine **17** (50.0 g, 233 mmol), 2-(4-bromophenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (98.0 g, 303 mmol), 300 mL of dioxane, and sodium *tert*-butoxide (56.1 g, 583 mmol). After nitrogen gas was bubbled through the solution for 5 min, chloro(2-dicyclohexylphosphino-2′,6′-diisopropoxy-1,1′-biphenyl)[2-(2-aminoethylphenyl)]palladium(II),methyl-*tert*-butylether adduct (6.80 g, 9.33 mmol) was added, and the mixture was then heated to 70 °C under an inert atmosphere. After 12 h at 80 °C, the mixture was allowed to cool to room temperature, concentrated, and partitioned between water and EtOAc. The organic extracts were separated, washed with brine, dried ($MgSO_4$), filtered, and concentrated to give a brown solid. This solid was dissolved in CH_2Cl_2 and passed through a plug of silica gel (approx 1 kg) to give (*S*)-2-(4-(4-benzyl-2-(prop-1-yn-1-yl)piperazin-1-yl)phenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol **18** (110 g) as a brown oil. The product was carried on without additional purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.6 Hz, 2 H), 7.44−7.39 (m, 2 H), 7.38−7.32 (m, J = 7.3, 7.3 Hz, 2 H), 7.30−7.27 (m, J = 7.2 Hz, 1 H), 7.06−6.95 (m, J = 9.2 Hz, 2 H), 4.47−4.38 (m, 1 H), 3.73 (d, J = 13.5 Hz, 1 H), 3.54 (d, J = 13.5 Hz, 1 H), 3.50−3.44 (m, 1 H), 3.40−3.30 (m, 1 H), 3.07−2.94 (m, 2 H), 2.41−2.31 (m, 2 H), 1.82 (d, J = 2.2 Hz, 3 H); ^{13}C NMR (101 MHz, CD_3OD) δ 150.9, 137.4, 128.9, 127.9, 127.4, 126.9, 123.4 (q), 121.9, 115.5, 79.5, 77.1 (sep), 76.0, 62.0, 57.0, 52.9, 48.2, 44.2, 1.7; HRMS (ESI-TOF) m/z [M + H]$^+$ calcd for $C_{23}H_{23}F_6N_2O$ 457.1715, found 457.1718; $[\alpha]_D^{20}$ = +100 (c = 2.4, MeOH).

(*S*)-2-(4-(4-benzyl-2-(prop-1-yn-1-yl)piperazin-1-yl)phenyl)-1,1,-1,3,3,3-hexafluoropropan-2-ol **18** (106 g, 232 mmol) was dissolved in 1 L of CH_2Cl_2. To this was added 1-chloroethyl chloroformate (74.7 g, 523 mmol) and K_2CO_3 (64.2 g, 464 mmol). After 20 min at room temperature, the mixture was filtered and the filtrate was concentrated to give an oil. Then, 500 mL of MeOH was added, and the resulting solution was heated at 70 °C for 12 h. The solution was allowed to cool to room temperature and then concentrated to provide the crude product. This solid was then slurried with diethyl ether (≈500 mL) to give (*S*)-1,1,1,3,3,3-hexafluoro-2-(4-(2-(prop-1-yn-1-yl)piperazin-1-yl)phenyl)propan-2-ol **7** (92 g) as an off-white solid. The product was carried on without additional purification: ^{1}H NMR (400 MHz, CD_3OD) δ 7.63 (d, J = 8.2 Hz, 2 H), 7.14 (d, J = 8.4 Hz, 2 H), 4.94 (br. s., 1 H), 3.73 (d, J = 13.3 Hz, 1 H), 3.59−3.40 (m, 4 H), 3.33−3.23 (m, 1 H), 1.83 (s, 3 H); ^{13}C NMR (101 MHz, CD_3OD) δ 151.4, 129.2, 125.0, 124.7 (q), 117.9, 86.5, 78.4 (sep), 73.1, 49.4, 48.2, 45.0,

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42.6, 3.4; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{17}F_6N_2O$ 367.1245, found 367.1249; mp >178 °C (decomp), $[\alpha]_D^{20}$ = +160 (c = 2.3, MeOH).

A 2 L round-bottomed flask was charged with (*S*)-1,1,1,3,3,3-hexafluoro-2-(4-(2-(prop-1-yn-1-yl)piperazin-1-yl)phenyl)propan-2-ol **7** (92 g, 251 mmol), 500 mL of CH_2Cl_2, and triethylamine (52.5 mL, 377 mmol). To this was added *tert*-butyl (5-(chlorosulfonyl)pyridin-2-yl)carbamate **20** (73.5 g, 251 mmol). After 2 h at room temperature, the mixture was diluted with water and the organics were separated, dried ($MgSO_4$), filtered, and concentrated. The resulting oil was purified via silica gel chromatography (1.5 kg of silica, 0−50% ethyl acetate in hexanes) to give the Boc-protected intermediate. To this was added 500 mL of CH_2Cl_2 and trifluoroacetic acid (289 g, 194 mL, 2.51 mol). After being stirred at room temperature for 4 h, the mixture was concentrated, diluted with EtOAc (500 mL), and carefully quenched with saturated aqueous $NaHCO_3$. The organics were then separated, dried ($MgSO_4$), filtered, and concentrated to provide a brown foam. Purification via silica gel chromatography (1.5 kg of silica, 15−100% ethyl acetate in hexanes) gave (*S*)-2-(4-(4-((6-aminopyridin-3-yl)-sulfonyl)-2-(prop-1-yn-1-yl)piperazin-1-yl)phenyl)-1,1,1,3,3,3-hexafluoropropan-2-ol (**5**) (64.0 g, 49% yield) as white solid. The enanatiomeric excess was found to be >99.5% by chiral SFC (see Supporting Information): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1 H), 7.79 (d, J = 8.6 Hz, 1 H), 7.59 (d, J = 8.2 Hz, 2 H), 6.97 (d, J = 8.6 Hz, 2 H), 6.55 (d, J = 8.8 Hz, 1 H), 5.06 (br s, 2 H), 4.45 (br s, 1 H), 3.96 (br s, 1 H), 3.77 (t, J = 12.1 Hz, 2 H), 3.50−3.35 (m, 2 H), 2.82 (d, J = 11.0 Hz, 1 H), 2.68 (t, J = 10.9 Hz, 1 H), 1.79 (s, 3 H); ^{13}C NMR (101 MHz, CD_3OD) δ 163.8, 152.0, 150.1, 138.2, 129.0, 124.7 (q), 123.9, 121.1, 117.5, 109.3, 82.8, 78.3 (m), 75.5, 52.0, 47.2, 44.9, 3.2; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{21}H_{21}F_6N_4O_3S$ 523.1239, found 523.1229; mp 113−123 °C; $[\alpha]_D^{20}$ = +75.1 (c = 2.2, MeOH).

***tert*-Butyl (5-(chlorosulfonyl)-2-pyridinyl)carbamate (20).** To a 5 L three-necked round-bottomed flask equipped with a mechanical stirrer, N_2 inlet, a 6 N NaOH scrubber, and a temperature probe were charged concentrated hydrochloric acid (348 mL, 11.5 mol) and acetonitrile (1000 mL). The solution was cooled to 0 °C, and sodium nitrite (39.6 g, 573 mmol) in water (400 mL) was added slowly over 5 min. The resulting solution was stirred at 0 °C for 10 min. *tert*-Butyl 5-aminopyridin-2-ylcarbamate **19** (100 g, 478 mmol, purchased from Green Chempharm, Inc.) in acetonitrile (200 mL) was added to the above solution at 0 °C. The resulting reaction mixture was stirred for 1 h at 0 °C. The mixture was then cooled to −10 °C, and acetic acid (497 mL, 8.60 mol), copper(II) chloride (32.1 g, 239 mmol), and copper(I) chloride (0.946 g, 9.56 mmol) were added sequentially. Sulfur dioxide (153 g, 2390 mmol) gas was then bubbled through the mixture for 10 min at −10 to −15 °C. The resulting reaction mixture was stirred at −10 to −5 °C for 1 h. The reaction mixture was diluted with ice cold water (1000 mL) at which time a solid precipitated. The solid was quickly filtered, washed with cold water (500 mL), and dried in the filter funnel under vacuum (with N_2 over the filter funnel) for 24 h to afford *tert*-butyl (5-(chlorosulfonyl)pyridin-2-yl)carbamate **20** (89.4 g, 64% yield) as an off white solid: ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.67 (s, 1 H), 8.44 (s., 1 H), 8.36 (d, J = 8.8 Hz, 1 H), 7.54 (d, J = 8.8 Hz, 1 H), 1.55 (s, 9 H); ^{13}C NMR (101 MHz, DMSO-d_6) δ 152.3, 148.8, 142.5, 139.1, 136.0, 115.2, 83.2, 27.8; mp >300 °C (decomp).

■ ASSOCIATED CONTENT

Supporting Information

Reaction pressure monitoring and differential scanning calorimetry data for the transformation of **4** to **5**, copies of the ^{1}H and ^{13}C spectra for all new compounds, and the chromatogram for the ee determination of **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare the following competing financial interest(s): The authors are employees of Amgen, Inc.

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