JOC Article

Enantioselective Pd-Catalyzed α-Arylation of *N*-Boc-Pyrrolidine: The Key to an Efficient and Practical Synthesis of a Glucokinase Activator

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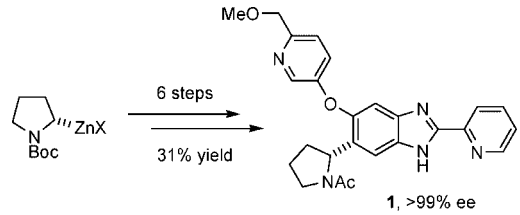
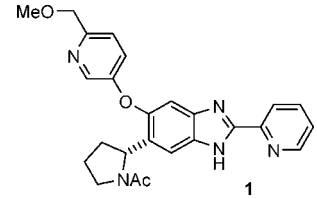


A short and practical synthesis of glucokinase activator **1** was achieved utilizing a convergent strategy involving S_NAr coupling of activated aryl fluoride **11** with hydroxypyridine **9**. The key to the success of the synthesis was the development of a novel method for enantioselective formation of α-arylpyrrolidines during the course of the project. In this method, (−)-sparteine-mediated enantioselective lithiation of *N*-Boc-pyrrolidine was followed by in situ transmetalation to zinc and Pd-catalyzed coupling with aryl bromide **3**, proceeding in 92% ee. This transformation allowed the preparation of compound **1** in a 31% overall yield over six steps.

Introduction

Advances in the development of highly selective and efficacious pharmaceuticals have been accompanied by a steady rise in the molecular complexity of the lead structures. The increasing complexity of chiral drug molecules has greatly fostered the development of new catalytic asymmetric processes that are amenable to industrial environment, such as the catalytic enantioselective hydrogenation of unsaturated bonds.[1] However, there remains an urgent need for new asymmetric methods that would allow practical access to a wider range of structures on a kilogram scale. We encountered the limitations of existing synthetic methodologies during the development of compound **1**, a glucokinase activator recently discovered in our laboratories.[2] Among the synthetic challenges presented by compound **1** are a densely functionalized benzimidazole ring, a hindered biaryl ether, and, most importantly, a chiral α-arylpyrrolidine. Herein we report an efficient, practical, and scalable process for the asymmetric synthesis of **1**, which was made possible by the discovery of the enantioselective Pd-catalyzed α-arylation of *N*-Boc-pyrrolidine.[3]



Results and Discussion

The drug discovery route to compound **1** started out with the expensive boronic acid **2**, which was coupled with aryl bromide **3** (Scheme 1). Hydrogenation of pyrrole **4** provided the racemic pyrrolidine **5**. After protecting group manipulation, the bis-trifluoroacetyl derivative **6** was selectively nitrated, the pyrrolidine protecting group was exchanged to *N*-Boc, the remaining trifluoroacetyl group was cleaved, and finally the aniline was acylated with picolinyl chloride. The resulting aryl fluoride **8** underwent a smooth and convergent coupling with

(1) Blaser, H.-U.; Malan, C.; Pugin, B.; Spindler, F.; Steiner, H.; Studer, M. *Adv. Synth. Catal.* **2003**, *345*, 103.

(2) Nonoshita, K.; Ogino, Y.; Ishikawa, M.; Sakai, F.; Nakashima, H.; Nagae, Y.; Tsukahara, D.; Arakawa, K.; Nishimura, T.; Eiki, J. Patent Application WO 2005063738.

(3) Campos, K. R.; Klapars, A.; Waldman, J. H.; Dormer, P. G.; Chen, C.-y. *J. Am. Chem. Soc.* **2006**, *128*, 3538.

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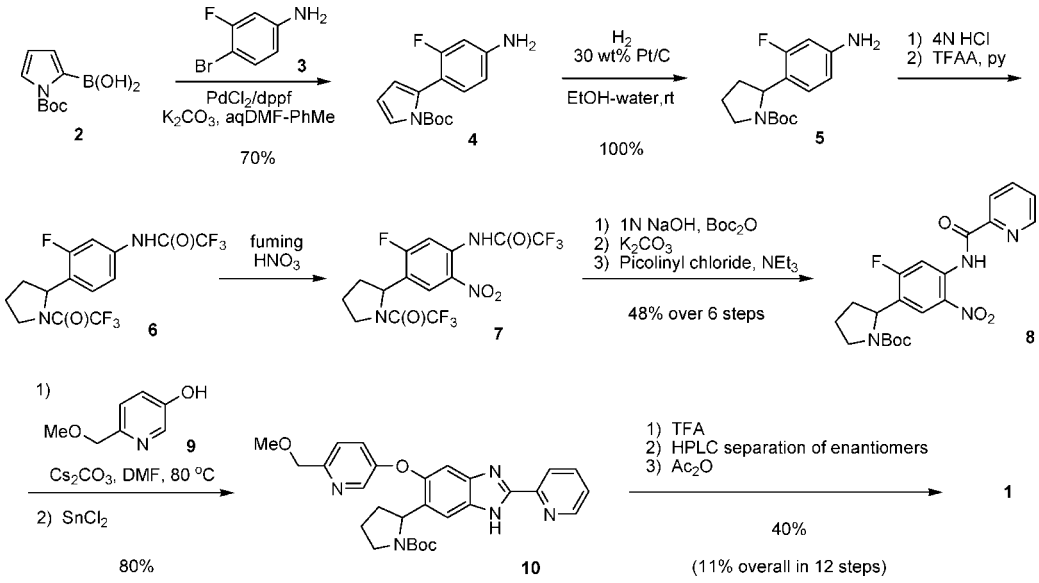
SCHEME 1. Drug Discovery Route to 1[2]

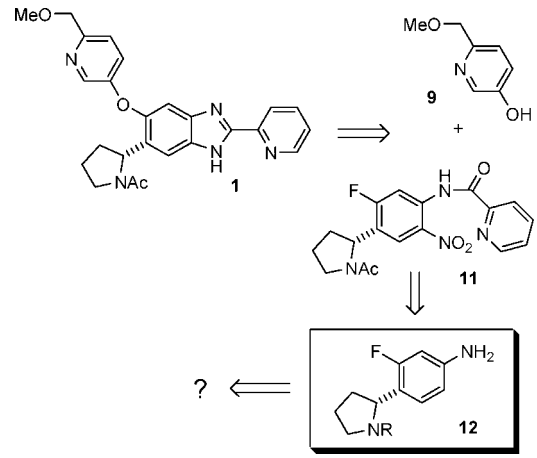


hydroxypyridine **9** via nucleophilic aromatic substitution (S_NAr). The nitro group in compound **8** served a dual role of activating the aryl fluoride and also providing a building block for the benzimidazole ring **10** after reduction with $SnCl_2$ and cyclization. The synthesis was completed by deprotection of the *N*-Boc group, HPLC separation on a chiral stationary phase, and acetylation to provide **1** in 12 steps and 11% overall yield.

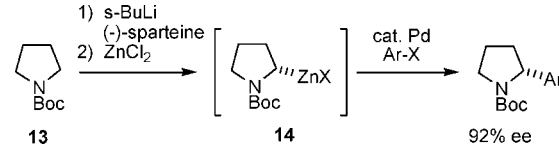
The drug discovery route, referred to earlier in Scheme 1, suffered from several shortcomings that prohibited implementation on a kilogram scale while meeting the project timeline requirements. The cost of the starting material **2**, the multiple protecting group manipulations, and environmental issues associated with the use of $SnCl_2$ were highly undesirable. Moreover, the inefficiency of the HPLC separation of the enantiomers in the penultimate step was detrimental to the speed and throughput required for the project. Nevertheless, several features of the drug discovery route were attractive. The highly selective nitration of **6** set the stage for the installation of the benzimidazole as well as solved the problem of the biaryl ether formation, which would have been a challenge for existing transition-metal-catalyzed technologies. Coupling of aryl fluoride **8** and hydroxypyridine **9** was a highly convergent strategy that allowed parallel preparation of the two fragments. With these considerations, a retrosynthetic analysis of **1** identified the key challenge, enantioselective preparation of the α-arylpyrrolidine **12** (Scheme 2).

At the outset of our studies, very few methods for enantioselective preparation of α-arylpyrrolidines were known.[4] Asymmetric hydrosilylation of cyclic imines was precedented but required an expensive catalyst, and the synthesis of the prerequisite imine was difficult to apply in our case.[5] We became interested in a disconnection between the pyrrolidine ring and

SCHEME 2. Retrosynthetic Analysis of 1



SCHEME 3



the aryl group as the most convergent method for the construction of **12**. Although enantioselective deprotonation of *N*-Boc-pyrrolidine is well-established,[6] arylation of the resulting chiral 2-pyrrolidinolithium was only known to provide racemic product in the presence of a Pd/Cu catalyst system.[7] We decided to investigate the related organozinc reagent **14** (Scheme 3) because of the documented configurational integrity of secondary alkylzinc reagents[8] and the precedent for Pd-catalyzed coupling of achiral secondary alkylzincs with aryl halides.[9] Moreover, the chiral organozinc reagent **14** could be readily prepared by simply adding a solution of $ZnCl_2$ to the in situ generated chiral

(4) Brinner, K. M.; Ellman, J. A. *Org. Biomol. Chem* **2005**, *3*, 2109, and references therein.

(5) Willoughby, C. A.; Buchwald, S. L. *J. Am. Chem. Soc.* **1992**, *114*, 7562.

(6) (a) Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 9708. (b) O'Brien, P.; McGrath, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 16378. (c) Coldham, I.; Dufour, S.; Haxell, T. F. N.; Patel, J. J.; Sanchez-Jimenez, G. *J. Am. Chem. Soc.* **2006**, *128*, 10943. For an alternative approach to the undesired enantiomer of 2-aryl-*N*-Boc-pyrrolidines involving asymmetric deprotonation/intramolecular alkylation of *N*-(arylmethyl)-*N*-(3-chloropropyl)-*N*-Boc-amines, see: (d) Wu, S.; Lee, S.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 715.

(7) Dieter, R. K.; Li, S. *J. Org. Chem.* **1997**, *62*, 7726.

(8) Boudier, A.; Flachsmann, F.; Knochel, P. *Synlett* **1998**, 1438.

(9) Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 158.

(10) Transmetalation with $ZnCl_2$ on a chiral lithiated alkyl carbamate: Papillon, J. P. N.; Taylor, J. K. *Org. Lett.* **2002**, *4*, 119.

SCHEME 4

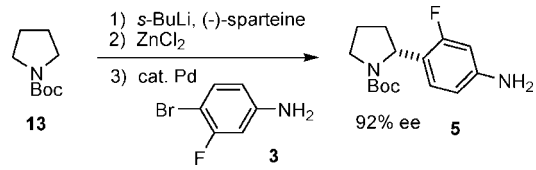
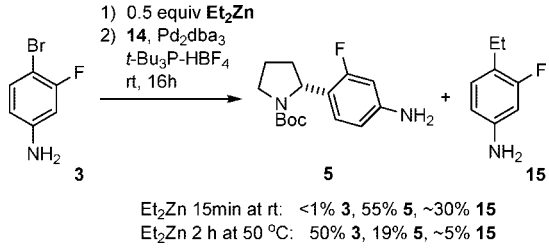


TABLE 1. Catalyst Optimization for the Coupling of 13 and 3[a]

entry	Pd source	amount of *t*-Bu_3P·HBF_4, %	conv. of **3**, %	yield of **5**, %
1	2.5% Pd_2dba_3	5	65	48
2	5% Pd(*t*-Bu_3P)$_2$		20	5
3	2.5% [PdBr(*t*-Bu_3P)]$_2$		53	24
4	5% $PdCl_2$	5	64	49
5	**5% Pd(OAc)$_2$**	**5**	**90**	**74**
6	3% Pd(OAc)$_2$	3	95	72
7	1% Pd(OAc)$_2$	1	42	27

[a] With 1.2 equiv of the chiral organozinc reagent **14**.

SCHEME 5



2-pyrrolidinolithium.[10] Gratifyingly, the Negishi-type coupling of **14** with aryl bromides was indeed feasible using Pd catalysts comprising hindered electron-rich phosphine ligands such as *t*-Bu_3P providing 2-arylpyrrolidines in 92% ee with retention of stereointegrity throughout the process (Scheme 3). We have recently communicated the application of this novel methodology to a wider range of substrates.[3]

Aryl halide **3** presented an additional challenge for the cross-coupling due to the presence of the acidic NH_2 group (Scheme 4). Initial experiments using Pd_2dba_3 and *t*-Bu_3P-HBF_4 provided incomplete conversion of aryl halide and a significantly lower yield of the product **5** (Table 1, entry 1) than was observed in the cases of simpler aryl halides, such as bromobenzene (typically 82% yield, 92% ee).[3] It was speculated that the NH_2 group in aryl bromide **3** or the product **5** underwent competitive deprotonation during the Negishi coupling step, and therefore an extra equivalent of the organozinc reagent was consumed. To verify this hypothesis, two experiments were performed in which the aniline NH_2 group was deprotonated with Et_2Zn prior to the addition of the chiral organozinc reagent and catalyst (Scheme 5). When aryl bromide **3** was premixed with 0.5 equiv of Et_2Zn at room temperature for 15 min and then subjected to the Negishi coupling conditions, product **15** resulting from coupling of the ethyl group in Et_2Zn was detected in ~30% yield. This result indicated that deprotonation of the NH_2 group in **3** with an organozinc reagent was relatively slow at room temperature and was competing with the coupling reaction. In the second experiment, Et_2Zn was heated with **3** at 50 °C prior to addition of the Pd catalyst and **14**, to facilitate the deprotonation of **3**. Interestingly, the subsequent Negishi coupling with the deprotonated **3** was quite sluggish, indicating that either the deprotonated bromoaniline **3** underwent a slower oxidative addition due to increased electron density or alternatively the deprotonated anilines were binding to the Pd catalyst, thus inhibiting the catalytic cycle for the Negishi coupling.

TABLE 2. Optimization of the Stoichiometry of $ZnCl_2$[a]

entry	$ZnCl_2$, equiv[b]	R:Zn ratio[c]	conv. of **3**, %	yield of **5**, %
1	1.2	1:1	91	75
2	0.85	1.4:1	96	76
3	0.43	2.8:1	31	16

[a] Coupling reaction performed with 1.2 equiv of **13**, 1.2 equiv of sparteine, 1.2 equiv of *s*-BuLi, 1.0 equiv of **3**, 5 mol % of Pd(OAc)$_2$, and 5 mol % of *t*-Bu_3P·HBF_4 in MTBE at rt for 18 h. [b] Equivalents of $ZnCl_2$ with respect to the limiting reagent, aryl bromide **3**. [c] Molar ratio of lithiated **13** to $ZnCl_2$.

Since it was determined that competitive deprotonation of the NH_2 group in **3** had an adverse effect on the Negishi coupling, a more active catalyst was sought in order to increase the rate of Negishi coupling with respect to the rate of deprotonation of aryl bromide **3** (Table 1). The two commercially available Pd complexes of *t*-Bu_3P (entries 2 and 3)[11] provided inferior results to the in situ formed catalyst (entry 1). In contrast, Pd(OAc)$_2$ provided a significantly faster reaction rate and an improved 74% yield of the coupled product (entry 5).[12] It is possible that the acetate ion stabilizes the active catalyst (or a catalyst resting state) and prevents formation of inactive Pd black.[13] The catalyst loading could be reduced to 3 mol % (entry 6) without a significant decrease in the product yield; however, only 27% yield was obtained with 1 mol % of catalyst (entry 7). Eventually, 4% Pd(OAc)$_2$ and 5% *t*-Bu_3P·HBF_4[14] were chosen to ensure robustness of the process.

The stoichiometry of $ZnCl_2$ was found to have a pronounced effect on the coupling reaction (Table 2). Depending on the amount of $ZnCl_2$ added, either RZnCl, R_2Zn, or R_3ZnLi species or their aggregates could theoretically be produced in the reaction mixture. It was found that the stoichiometry favoring the more basic "R_3ZnLi" species gave a poor yield of the coupled product **5** (Table 2, entry 3), presumably due to competitive deprotonation of the NH_2 group, while those favoring the "R_2Zn" and "RZnCl" species provided optimal results (Table 2, entries 1 and 2). Several stress tests were also performed. If the asymmetric deprotonation of **13** was carried out at −55 to −45 °C instead of −70 °C, product **5** from the coupling reaction was obtained in a significantly lower 85% ee although the yield was not affected (83%). A 0.5 M solution of $ZnCl_2$ in THF could be used instead of a solution of $ZnCl_2$ in diethyl ether (91% ee, 81% yield). An overcharge of (−)-sparteine provided only a marginal improvement in the ee of product **5**; for example, 1.1 equiv of sparteine provided a 93% ee, while 0.90 equiv of sparteine gave a slightly eroded 89% ee. With the optimized conditions (Table 2, entry 2), the coupling reaction was demonstrated in two 6.0 mol batches to provide a total of 2.13 kg of the coupled product **5** in 78−79% assay yield, 61−64% isolated yield, 91−93% ee, and 99.1 wt % purity.

Although impurities generated in the coupling reaction were cleanly rejected during crystallization of **5** and therefore did

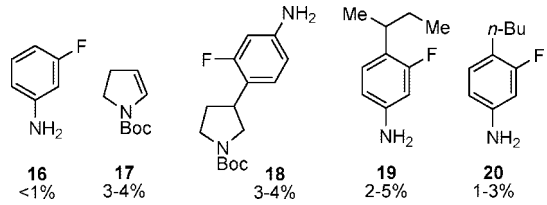
(11) (a) Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 2719. (b) Stambuli, J. P.; Kuwano, R.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2002**, *41*, 4746.

(12) The color of the reactions utilizing Pd(OAc)$_2$ was clean yellow and so was quite different from the reactions using either Pd_2dba_3 (entry 1) or $PdCl_2$ (entry 4) which both turned grayish black.

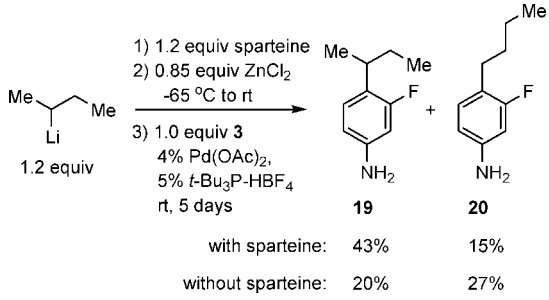
(13) Formation of a palladacycle from Pd(OAc)$_2$ and *t*-Bu_3P has been proposed in a Negishi-type coupling reaction. See: Wu, L.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 15824.

(14) Netherton, M. R.; Fu, G. C. *Org. Lett.* **2001**, *3*, 4292.

CHART 1. Impurities in the Coupling Reaction of 14 and 3



SCHEME 6. Coupling of *s*-BuLi with 3



not affect the quality of the product, we decided to isolate and identify these impurities for better understanding of the coupling reaction (Chart 1). The debrominated aniline **16** was observed at a very low level (<1%). The impurity **17** (3−4%) seemed to arise from β-hydride elimination, and impurity **18** (3−4%) probably resulted from a subsequent reductive Heck reaction of **17** with **3**. It is possible that impurities **17** and **18** were only generated during the activation of $Pd(OAc)_2$ to form the reactive Pd(0) catalyst. Since a slight excess of *s*-BuLi was utilized in the lithiation step, the *s*-Bu-coupled product **19** (2−5%) was observed. Unexpectedly, the *n*-Bu impurity **20** (1−3%) was also isolated, which prompted a further investigation into the coupling of *s*-BuLi with aryl bromide **3** under the same conditions that were optimized for the preparation of **5** (Scheme 6). The coupling of *s*-BuLi turned out to be significantly less efficient than the coupling of metalated *N*-Boc-pyrrolidine **14**, which suggests that the *N*-Boc group plays an important role in the Pd-catalyzed coupling reaction. Furthermore, a high level of *n*-Bu/*s*-Bu scrambling was observed, suggesting extensive β-hydride elimination/hydropalladation,[15] not seen with metalated *N*-Boc-pyrrolidine **14**. If the coupling of *s*-BuLi was performed in the absence of sparteine, even higher levels of the *n*-Bu product **20** were obtained and the Pd catalyst rapidly decomposed. These observations indicate that both sparteine and the *N*-Boc group in the substrate exert a significant effect on the Pd-catalyzed coupling reaction.

The protecting group issues in the synthesis of **1** were addressed next. The drug discovery route (Scheme 1) resorted to multiple protecting group switches, primarily in order to ensure compatibility of the substrate with the relatively harsh nitration step, which was performed in fuming HNO_3. We speculated that the *N*-picolinyl group, containing an extremely electron-poor heteroaromatic ring, as well as the robust *N*-acetyl group should be compatible with the nitration reaction conditions. Thus, the use of protecting groups would be avoided altogether by strategically employing the *N*-picolinyl and *N*-acetyl groups not only as building blocks for the final structure **1** but also as protecting group equivalents. To test this hypothesis, the picolinamide **21** was prepared using in situ activated picolinic acid (Scheme 7).[16] Compound **21** could be isolated in 87% yield by crystallization from aq *i*-PrOH, which also resulted in an ee upgrade from 92 to 99.3%. Deprotection of the *N*-Boc group was performed by dissolving **21** in 5 M aq HCl. It was found that the subsequent N-acetylation of the revealed amine could be performed in the same pot under Schotten−Baumann conditions by simply adding 10 M aq NaOH and Ac_2O. After extraction with CH_2Cl_2, the organic phase was concentrated and used in the nitration step without any further purification.

The nitration step was the ultimate test of our decision to pursue a protecting-group-free strategy. We were very pleased to find that the desired nitro compound **11** was formed in 94% assay yield using a mixture of 90% HNO_3 and concd H_2SO_4 as the nitrating reagent. Only two impurities were detected in the nitration reaction (Chart 2). The isomer **23** was formed in a 4% yield and could be partially rejected during crystallization of **11**. More interestingly, the product of an apparent *ipso*-nitration **24**[17] was also observed at a 1% level. With the nitro group successfully introduced, the aromatic fluoride substituent in **11** was ready to undergo the nucleophilic aromatic substitution with the hydroxypyridine **9**.

Hydroxypyridine **9** was prepared from the known alcohol **25**[18] (Scheme 8): a straightforward methylation of **25** followed by deprotection of the benzyl ether via catalytic hydrogenation gave the hydroxypyridine **9**. The key S_NAr coupling of **9** and **11** (Scheme 7) proceeded smoothly in DMF at 55 °C using an equimolar amount of cesium carbonate as a base and provided a 90% isolated yield of **22** after crystallization.

With compound **22** in hand, only the reduction of the nitro group and cyclization to form the benzimidazole ring remained unsolved. To avoid the use of the toxic $SnCl_2$ reagent, several alternatives for the reduction of the nitro group were explored. Catalytic hydrogenation of **22** suffered from catalyst poisoning, resulting in incomplete conversion. Fortunately, it was found that iron powder in a mixture of acetic acid and DME effected clean reduction of the nitro group as well as in situ cyclization directly to the desired product **1** in a 90% assay yield. Compound **1** was isolated as a phosphate salt (1:1 molar ratio) via slow addition of H_3PO_4 to a solution of the free base of **1** in a 73% yield, 99.4% purity, and >99.8% ee.

In summary, a short and practical synthesis of glucokinase activator **1** was developed utilizing a convergent strategy involving an S_NAr coupling of the activated aryl fluoride **11** with hydroxypyridine **9**. The key to the success of the synthesis was the development of a novel method for enantioselective formation of α-arylpyrrolidines. In this method, (−)-sparteine-mediated, enantioselective lithiation of *N*-Boc-pyrrolidine **13** was followed by an in situ transmetalation to zinc and Pd-catalyzed coupling reaction with aryl bromide **3**, which

(15) Luo, X.; Zhang, H.; Duan, H.; Liu, Q.; Zhu, L.; Zhang, T.; Lei, A. *Org. Lett.* **2007**, *9*, 4571.

(16) The activation of picolinic acid was not straightforward. The best results were obtained by adding 1.4 equiv of thionyl chloride to a solution of 1.4 equiv of picolinic acid in acetonitrile followed by addition of triethylamine. As soon as the addition of triethylamine was complete, aniline **5** was introduced immediately because the activated picolinic acid was unstable in the presence of triethylamine. For example, the assay yield of **21** decreased from 98 to 49% if the activated picolinic acid was aged for 16 h in the presence of NEt_3 before the addition of aniline **5**.

(17) For precedents of *ipso*-nitration, see: (a) Moodie, R. B.; Schofield, K. *Acc. Chem. Res.* **1976**, 287. (b) Malecki, N.; Carato, P.; Houssin, P. C.; Hénichart, J.-P. *Monatsh. Chem.* **2005**, *136*, 1601.

(18) (a) Takeda, Y.; Uoto, K.; Chiba, J.; Horiuchi, T.; Iwahana, M.; Atsumi, R.; Ono, C.; Terasawa, H.; Soga, T. *Bioorg. Med. Chem.* **2003**, *11*, 4431. (b) Akita, H.; Takano, Y.; Nedu, K.; Kato, K. *Tetrahedron: Asymmetry* **2006**, *17*, 1705.

SCHEME 7. Synthesis of 1

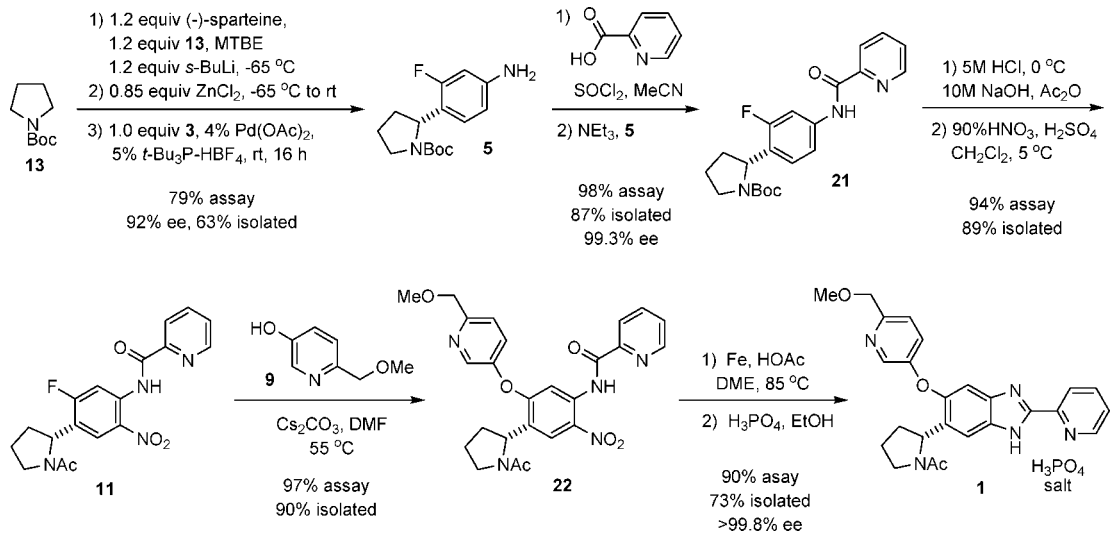
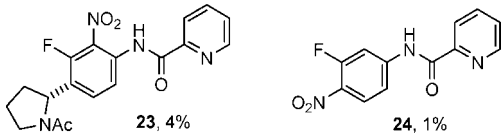
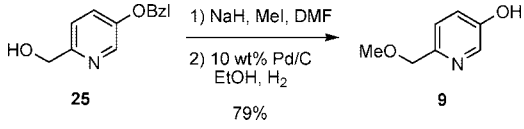


CHART 2. Impurities in the Nitration Reaction



SCHEME 8. Preparation of Hydroxypyridine 9



afforded 2-arylpyrrolidine in 63% isolated yield and 92% ee. Notably, the acidic aniline NH_2 group was tolerated under the coupling reaction conditions. The use of protecting groups in the synthesis was minimized by utilizing the *N*-picolinyl and *N*-acetyl groups not only as structural components of **1** but also to tune the reactivity of the intermediates. Overall, 1.4 kg of compound **1** was prepared in excellent purity (>99% ee) and 31% yield over six steps. We believe that this synthesis highlights the benefits of problem-driven approach toward the development of new synthetic methodology.

Experimental Section

General Information. Unless indicated otherwise, the reaction temperatures refer to internal reaction temperatures. LCAP stands for liquid chromatography area percent. Purity of compounds (wt %) and assay yields were measured using reverse phase HPLC. A 1 M solution of $ZnCl_2$ in Et_2O and (−)-sparteine were purchased from Aldrich. These and other commercial reagents were used without any additional drying or purification.

(*R*)-2-(4-Amino-2-fluorophenyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (5). A 75 L four-neck round-bottom flask was equipped with an overhead stirrer, nitrogen inlet, thermocouple, and an addition funnel, purged with nitrogen overnight, and then charged with MTBE (15 L), *N*-Boc-pyrrolidine (1.30 L, 7.20 mol), and (−)-sparteine (1.67 L, 7.20 mol). The reaction mixture was cooled to −68 °C in a dry ice/acetone bath. A 1.25 M solution of *sec*-BuLi (5.76 L, 7.20 mol) was added to the reaction mixture over 4 h, while the internal temperature was maintained below −68 °C. The reaction mixture was stirred at −72 °C for 2.5 h to give a pale brown solution. A 1.05 M solution of $ZnCl_2$ in Et_2O (4.80 L, 5.04 mol) was added over 2.5 h. The cooling bath was immediately drained once the addition was complete, while the reaction temperature remained below −65 °C for another 30 min. An off-white suspension formed. Over 1 h, the reaction temperature was brought to +13 °C by exchanging the cooling liquid to warm acetone−water and then water. A cloudy, off-white solution formed. Solid 4-bromo-3-fluoroaniline (1.16 kg, 6.00 mol) was added followed by a mixture of solid *t*-$Bu_3P\cdot HBF_4$ (87.0 g, 0.300 mol) and $Pd(OAc)_2$ (53.8 g, 0.240 mol). An orange, cloudy solution formed immediately. Over 30 min, the reaction temperature was brought to +19 °C. A mild exotherm started, and the reaction mixture gradually turned into a pale yellow suspension. After 1.5 h, the reaction temperature peaked at 26 °C. The pale yellow reaction mixture was stirred to 20 °C for 15 h (93% conversion by HPLC). The reaction was quenched with aq ammonium hydroxide (0.36 L), resulting in a very mild exotherm and an increase of temperature from +19 to +21 °C. The white, slightly grayish suspension was stirred for 1 h and then filtered through about 2 cm layer of Solka Floc filter aid in a 5 L fritted glass filter funnel. The filter cake was rinsed with MTBE (3 × 2 L). The filtrate was transferred into a 100 L cylindrical extractor and washed with 2.0 M aq NH_4Cl (2 × 20 L) and water (2 × 20 L). Assay of the organic phase: 78% (1.31 kg), combined aq losses: 0.21% (the aq NH_4Cl wash removes most of the (−)-sparteine from the organic phase). The dark brown organic phase was concentrated to 4.5 L volume in a 50 L round-bottom flask with a batch concentrator at 20−30 °C over 2 h. At the end of the concentration, a small amount of crystals formed in the solution and the internal temperature reached 35 °C. Heptane (18 L) was added using an addition funnel over 40 min; the end temperature was 27 °C. After the addition was complete, the flask was cooled in a water bath to 19 °C and stirred for 3 h. The brown suspension was filtered, the filter cake was rinsed with heptane (3 × 2 L) and dried on the filter under a stream of nitrogen overnight. Mother liquor loss: 9.1%. The product was obtained as 1.094 kg of tan, sandy crystals (64% yield); 99.1 wt %, 98.7% LCAP by HPLC; 91% ee as an *N*-Ac derivative (chiral HPLC on AD-H column; 150 × 4.60 mm, 5 μm; 1.00 mL/min; 5.0 μL; 30 °C; isocratic 90% *n*-heptane and 10% IPA; major (*R*)-**3**: 4.4 min; minor (*S*)-**3**: 5.8 min): mp 149−151 °C; $[\alpha]^{20}_D$ +88.4 (*c* 1.90, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (m, 1H), 6.22 (m, 2H), 4.96−4.78 (br m, 1H), 3.61 (m, 2H), 3.50−3.29 (br m, 2H), 2.18−2.03 (br m, 1H), 1.81−1.64 (br m, 3H), 1.70 (br s, 3H), 1.08 (br s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2 (d, J = 242 Hz), 154.3, 146.7, 147.6, 127.5,127.1, 121.0, 120.9 110.2, 101.8, 101.6, 78.9, 54.8, 46.9, 46.6, 34.5, 33.4, 28.3, 28.0, 23.1; ^{19}F NMR (377 MHz, $CDCl_3$) δ −118.9, −120.1. The compound exhibited two amide rotamers in the NMR spectra. Anal. Calcd for $C_{15}H_{21}FN_2O_2$: C, 64.27; H, 7.55; N, 9.99. Found: C, 64.43; H, 7.60; N, 9.96.

Impurities Generated in the Coupling Reaction (Chart 1). A portion of the mother liquors from the crystallization of compound **5** (see above) was concentrated and separated by flash chromatography on silica gel (hexane/EtOAc 4:1 to neat EtOAc) followed by mass-directed reverse phase preparative HPLC in the case of **18**, **19**, and **20** to provide the following compounds: 2,3-dihydropyrrole-1-carboxylic acid *tert*-butyl ester (**17**): ^{1}H NMR spectrum matched the reported data.[19] 3-(4-Amino-2-fluorophenyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (**18**), a viscous oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.99 (br t, J = 8.1 Hz, 1H), 6.43 (br d, J = 8.1 Hz, 1H) 6.39 (dd, J = 12.2, 2.3 Hz, 1H), 3.85−3.19 (m, 7 H), 2.25−2.13 (m, 1H), 2.04−1.92 (m, 1H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8 (d, J = 244 Hz), 154.6, 146.9, 146.8, 128.3, 117.3, 110.77, 110.75, 102.4, 102.1, 79.1, 51.4, 50.7, 45.7, 45.4, 37.1, 36.3, 32.2, 31.2, 28.6; ^{19}F NMR (377 MHz, $CDCl_3$) δ −117.1, −117.3; the compound exhibited two amide rotamers in the NMR spectra; the structure of **18** was further confirmed by HMBC and NOE experiments (see Supporting Information); HRMS (ESI+) $[MNa]^+$ calcd for $C_{15}H_{21}FNaN_2O_2^+$ 303.14793; found 303.1488. 4-*sec*-Butyl-3-fluoroaniline (**19**), an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00 (t, J = 8.3 Hz, 1H), 6.46 (dd, J = 8.3, 2.4 Hz, 1H), 6.39 (dd, J = 12.1, 2.4 Hz, 1H), 3.65 (br s, 2H), 2.91 (sextet, J = 7.0 Hz, 1H), 1.62 (pent, J = 7.4 Hz, 2H), 1.26 (d, J = 6.8 Hz, 3H), 0.88 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5 (d, J = 242 Hz), 145.6 (d, J = 12 Hz), 128.5 (d, J = 7 Hz), 123.7 (d, J = 16 Hz), 110.9 (d, J = 2 Hz), 102.3 (d, J = 26 Hz), 33.7, 30.16, 20.78, 12.15; ^{19}F NMR (377 MHz, $CDCl_3$) δ −118.8; HRMS (ESI+) $[MH]^+$ calcd for $C_{10}H_{15}FN^+$ 168.11830; found 168.1189. 4-*n*-Butyl-3-fluoroaniline (**20**), an oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.94 (t, J = 8.3 Hz, 1H), 6.42−6.35 (m, 2H), 3.65 (br s, 2H), 2.53 (t, J = 7.8 Hz, 2H), 1.60−1.52 (m, 2H), 1.42−1.33 (m, 2H), 0.94 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8 (d, J = 243 Hz), 145.9 (d, J = 11 Hz), 131.1 (d, J = 7 Hz), 119.3 (d, J = 17 Hz), 110.7 (d, J = 3 Hz), 102.3 (d, J = 26 Hz), 32.7, 28.0, 22.4, 14.0; ^{19}F NMR (377 MHz, $CDCl_3$) δ −119.1; HRMS (ESI+) $[MH]^+$ calcd for $C_{10}H_{15}FN^+$ 168.11830; found 168.1188.

(*R*)-2-{2-Fluoro-4-[(pyridine-2-carbonyl)amino]phenyl}pyrrolidine-1-carboxylic acid *tert*-butyl ester (21). A 75 L round-bottom flask equipped with a thermocouple, mechanical stirrer, and nitrogen inlet was charged with CH_3CN (20 L) and picolinic acid (1.28 kg, 10.28 mol). Thionyl chloride (750 mL, 10.28 mol) was added to the suspension while maintaining the internal temperature at 20 °C over 30 min. The resulting thick suspension was stirred at 20 °C for 1 h during which time it turned from white to pale green to light yellow, and SO_2 gas evolved. The reaction was cooled to 0 °C by adding dry ice to the acetone bath. NEt_3 (4.12 L, 29.38 mol) was added over 45 min while maintaining the internal temperature at 0 °C. Immediately upon completion of the NEt_3 charge, addition of aniline **5** was started in portions over 20 min while maintaining the internal temperature between 10 and 16 °C. The thick, brown suspension was stirred for an additional 90 min at 15 °C after which time HPLC analysis showed complete conversion of **5**. The reaction was quenched by careful addition of 2 M aq NH_4Cl (8 L) and dilution with MTBE (8 L). The organic layer turned dark red in color and all suspended solids dissolved. The biphasic mixture was pumped into a 100 L cylindrical extractor, and the flask was rinsed with an additional 2 M NH_4Cl (8 L) and MTBE (8 L). The layers were separated, and the organic phase was washed with water (2 × 14 L). Combined aqueous losses: 1.3%, assay yield: 98%. The organic phase was transferred into a 75 L flask. A total of 33 L of *i*-PrOH was used to remove the residual MTBE as determined by ^{1}H NMR, and the batch was concentrated to a volume of 17 L at a vacuum of 28 in Hg and an internal temperature of 28 °C. To this was added water (22 L) over 80 min at 27 °C. Ice/H_2O was added to the bath to cool the suspension to 20 °C after which time it was stirred for 1 h. The brown suspension was filtered, and the filter cake was washed with 2:1 H_2O:*i*-PrOH (7 L). The cake was dried under a stream of nitrogen overnight and in a 35 °C vacuum oven at 65 mmHg with nitrogen flow for an additional night. Mother liquor loss: 8.3%. The product was obtained as 2.45 kg of a light brown dusty solid (87%); 99.1 wt %; 99.7% LCAP; 99.3% ee (Chiralpak AD-H; 250 × 4.6 mm; 1.5 mL/min; 210 nm; isocratic 30% MeOH/ 70% CO_2; major (*R*)-**21**: 3.6 min; minor (*S*)-**21**: 5.4 min); 63 ppm Pd: mp 140−142 °C; $[\alpha]^{20}_D$ +97.6 (*c* 1.48, MeOH); IR (film) 2054.5, 2894.3, 1688.9, 1528.0, 1400.3, 1265.6, 1166.4, 743.1, 704.8 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.03 (br s, 1H), 8.60 (d, 1H, J = 4.3 Hz), 8.27 (d, 1H, J = 7.8 Hz), 7.90 (t, 1H, J = 7.4 Hz), 7.80 - 7.62 (m, 1H), 7.48 (m, 1H), 7.33 (d, 1H, J = 7.8 Hz), 7.19 (m, 1H), 5.15 (br s, 0.3H), 5.03 (br s, 0.7H), 3.70−3.50 (m, 2H), 2.30 (br s, 1H), 1.88 (br s, 3H), 1.46 (br s, 3H), 1.22 (br s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 162.1, 159.8 (d, J = 244.5 Hz), 159.7 (d, J = 244.3 Hz), 154.6, 154.5, 149.3, 149.2, 148.1, 148.1, 138.0, 138.0, 137.6 (d, J = 11.0 Hz), 137.4 (d, J = 11.2 Hz), 127.5 (d, J = 13.9 Hz), 127.2 (d, J = 5.9 Hz), 127.0, 126.9, 126.8 (d, J = 5.9 Hz), 126.6 (d, J = 14.0 Hz), 122.5, 122.5, 114.9 (d, J = 2.8 Hz), 114.7 (d, J = 2.7 Hz), 107.4 (d, J = 26.5 Hz), 106.8 (d, J = 27.1 Hz), 79.7, 79.6, 55.3, 55.0, 47.2, 46.9, 34.5, 33.4, 28.6, 28.3, 27.1, 23.6, 23.4; ^{19}F NMR (377 MHz, $CDCl_3$) δ −116.90, −117.96; the compound exhibited two amide rotamers in the NMR spectra. Anal. Calcd for $C_{21}H_{24}FN_3O_3$: C, 65.44; H, 6.28; N, 10.90. Found: C, 65.33; H, 6.10; N, 10.84.

Pyridine-2-carboxylic acid [4-((*R*)-1-acetylpyrrolidin-2-yl)-3-fluorophenyl]amide. A 75 L four-neck round-bottom flask equipped with a thermocouple, mechanical stirrer, and nitrogen inlet was charged with 5 M aq HCl (12.4 L, 61.9 mol) and cooled to 0 °C. Compound **21** (2.39 kg, 6.19 mol) was added in portions over 25 min while maintaining the internal temperature at 0 °C. The reaction was stirred for 2 h at an internal temperature range of 5−10 °C and then at 20 °C for 2 h. Upon completion of the reaction (HPLC), the reaction was cooled again to 0 °C. CH_2Cl_2 (12 L) was added, and the pH was raised to 14 with 10 M NaOH (6.31, 63.1 mol) solution while maintaining the temperature at 0 °C. All suspended solids dissolved at this point. Acetic anhydride (717 mL, 7.43 mol) was added over 10 min, and the pH was adjusted to 14 with additional 10 M NaOH solution (1 L). The reaction was allowed to warm to room temperature and was stirred overnight. The reaction mixture was pumped into a 100 L extractor, and the reaction flask was washed with H_2O (16 L) and CH_2Cl_2 (4 L). The layers were allowed to separate, and the organic phase was removed. The aq phase was extracted with CH_2Cl_2 (12 + 12 L). Total aqueous losses were <0.01%. The organic phase was transferred into a 75 L four-neck round-bottom flask and concentrated to a volume of 6 L (2 mL/g) using a batch concentrator at a vacuum of 14 in Hg and an internal temperature of 25 °C. The resulting solution was used directly in the next step. For analytical purposes, the compound could be isolated by flash chromatography as a white amorphous solid: $[\alpha]^{20}_D$ +100.4 (*c* 1.30, MeOH); IR (film) 3054.2, 2986.6, 1422.0, 1265.8, 747.0, 705.4 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.95 (br s, 0.7H), 9.88 (br s, 0.3H), 8.45 (m, 1H), 8.12 (m, 1H), 7.76 (td, 1H, J = 7.8, 1.7 Hz), 7.72 (dd, 0.7H, J = 12.3, 2.0 Hz), 7.56 (dd, 0.3H, J = 12.4, 2.0 Hz), 7.34 (m, 1H), 7.15 (td, 1H, J = 8.6, 1.9 Hz), 6.93 (t, 0.7H, J = 8.4 Hz), 6.84 (t, 0.3H, J = 8.4 Hz), 5.20 (m, 0.3H), 5.00 (d, 0.7H, J = 6.5 Hz), 3.65−3.40 (m, 2H), 2.30−2.08 (m, 2H), 1.98 (s, 1H), 1.85−1.65 (m, 3H), 1.72 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 168.9, 162.0, 161.8, 159.7 (d, J = 245.0 Hz), 159.4 (d, J = 244.9 Hz), 169.3, 149.1, 147.9, 147.8, 138.4 (d, J = 11.2 Hz), 137.6, 137.6 (d, J = 11.2 Hz), 137.5, 127.0 (d, J = 6.4 Hz), 126.8 (d, J = 5.6 Hz), 126.6, 126.4, 125.5 (d, J = 13.7 Hz), 125.5 (d, J = 13.7 Hz), 122.3, 122.3, 115.1 (d, J = 3.2 Hz), 114.6 (d, J = 3.2 Hz), 107.4 (d, J = 26.5 Hz), 107.3 (d, J = 26.5 Hz), 56.1 (d, J = 2.3 Hz), 55.2 (d, J = 2.3 Hz), 48.2, 46.6, 34.6, 32.7, 23.8, 22.6, 22.2, 21.9; ^{19}F NMR (377 MHz, $CDCl_3$) δ −116.19, −116.78; the compound exhibited two amide rotamers

(19) Oliveira, D. F.; Miranda, P. C. M. L.; Correia, C. R. D. *J. Org. Chem.* **1999**, *64*, 6646.

in the NMR spectra; HRMS (ESI+) $[MH]^+$ calcd for $C_{18}H_{19}FN_3O_2^+$ 328.1461; found 328.1461.

Pyridine-2-carboxylic acid [4-((*R*)-1-acetylpyrrolidin-2-yl)-5-fluoro-2-nitrophenyl]amide (11). The 75 L four-neck round-bottom flask containing the solution of the compound prepared above was equipped with a mechanical stirrer, thermocouple, addition funnel, and a nitrogen inlet that was connected to a trap and scrubber half-filled with a 10% aqueous urea solution to scavenge nitrogen oxides. The reaction flask was cooled to 0 °C and 90% HNO_3 (2.80 L, 59.3 mol) was added over 45 min; 95% H_2SO_4 (1.39 L, 23.7 mol) was then added to the reaction mixture over 3 h while maintaining the internal temperature below 5 °C. The reaction was allowed to warm and was stirred overnight, reaching an internal temperature of 16.5 °C. Upon completion (HPLC), the reaction mixture was cooled to 0 °C and water (4.2 L) was added over 90 min followed by CH_2Cl_2 (8 L) and then 1 M aqueous K_3PO_4 (32 L) over 2 h at 10 °C. The biphasic mixture was pumped into a 170 L cylindrical extractor, CH_2Cl_2 (20 L) and K_3PO_4 (16 L) were added (pH of the aqueous phase = 7), the layers were separated, and the organic phase was collected. The aqueous phase was washed with additional CH_2Cl_2 (2 × 8 L). Total aqueous losses were <0.1%. Total assay yield in the organic layers was 94.4%. The combined organic phases were transferred into a 75 L four-neck round-bottom flask, and solvent was switched to 10% residual CH_2Cl_2 (by NMR) with a total of 71 L of MTBE. The resulting slurry was stirred overnight under nitrogen and filtered, and the filter cake was washed with 2:1 heptane:MTBE (5 L). The product was dried on the filter under a stream of nitrogen for 4 h followed by treatment in a 35 °C vacuum oven with nitrogen flow at 135 mmHg. Mother liquor losses were 6.5%. The product was obtained as 1.97 kg of a yellow powdery solid (89%); 98.0 wt %, 98.8% LCAP by HPLC; 99.6% ee ((*R*,*R*)-Whelko; 250 × 4.6 mm; 1.5 mL/min; 200 bar; 270 nm; isocratic 10% of 25 mM *i*-$BuNH_2$ in MeOH)/ 90% CO_2 for 10 min; major (*R*)-**11**: 5.4 min; minor (*S*)-**11**: 4.1 min); 35 ppm Pd. Residual **23** was 1.1 LCAP and all of **24** was rejected: mp 199−201 °C; $[\alpha]^{20}_D$ +145 (*c* 1.52, CH_2Cl_2); IR (film) 3054.4, 2986.6, 1510.5, 1422.0, 1264.8, 749.7 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 12.78 (m, 1H), 8.84 (d, 0.3H, J = 12.7 Hz), 8.75 (d, 0.7H, J = 12.8 Hz), 8.63 (m, 1H), 8.17 (d, 1H, J = 10.2 Hz), 8.01 (d, 0.3H, J = 7.7 Hz), 7.92 (d, 0.7H, J = 7.7 Hz), 7.88 (m, 1H), 7.48 (m, 1H), 5.26 (dd, 0.7H, J = 8.2, 3.0 Hz), 5.15 (d, 0.3H, J = 7.1 Hz), 3.70 (m, 1H), 3.60 (m, 1H), 2.40−2.30 (m, 1H), 2.17 (s, 2H), 2.00−1.80 (m, 3H), 1.90 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 169.5, 163.5 (d, J = 257.0 Hz), 163.5, 163.4, 162.9 (d, J = 256.2 Hz), 148.8, 148.6, 148.6, 137.7, 137.7, 136.5 (d, J = 14.5 Hz), 135.5 (d, J = 14.5 Hz), 133.1 (d, J = 2.4 Hz), 132.8 (d, J = 2.4 Hz), 127.3, 127.1, 126.2 (d, J = 16.1 Hz), 126.1 (d, J = 16.9 Hz), 125.1 (d, J = 8.0 Hz), 124.8 (d, J = 7.2 Hz), 122.8, 122.7, 109.1 (d, J = 30.2 Hz), 109.0 (d, J = 30.4 Hz), 77.4, 55.9, 54.9, 48.3, 46.7, 34.5, 32.6, 24.0, 22.7, 22.4, 22.0; ^{19}F NMR (377 MHz, $CDCl_3$) δ −103.06, −103.79; the compound exhibited two amide rotamers in the NMR spectra. Anal. Calcd for $C_{18}H_{17}FN_4O_4$: C, 58.06; H, 4.60; N, 15.05. Found: C, 57.82; H, 4.35; N, 14.90.

Impurities Generated in the Nitration Reaction: Pyridine-2-carboxylic acid [4-((*R*)-1-acetylpyrrolidin-2-yl)-3-fluoro-2-nitrophenyl]amide (23). Yellow amorphous solid; $[\alpha]^{20}_D$ +81.5 (*c* 1.16, MeOH); IR (film) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 11.3 (m, 1H), 8.55 (m, 1H), 8.36 (dd, 0.4H, J = 8.9, 1.6 Hz), 8.27 (dd, 0.6H, J = 8.9, 1.6 Hz), 8.12 (t, 1H, J = 7.5 Hz), 7.79 (m, 1H), 7.40 (m, 1H), 7.24 (t, 0.4H, J = 8.3 Hz), 7.14 (t, 0.6H, J = 8.3 Hz), 5.22 (dd, 0.6H, J = 8.6, 3.5 Hz), 5.09 (d, 0.4H, J = 7.5 Hz), 3.70−3.50 (m, 2H), 2.40−2.20 (m, 1H), 2.03 (s, 2H), 1.95−1.80 (m, 3H), 1.77 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 169.2, 162.8, 162.8, 162.8 (d, J = 6.7 Hz), 152.4 (d, J = 260.3 Hz), 151.9 (d, J = 260.2 Hz), 148.6, 148.4, 148.4, 148.4, 137.7, 137.5, 132.4, 131.7, 130.8 (d, J = 6.5 Hz), 130.6 (br s), 130.5 (br s), 130.4 (d, J = 6.1 Hz), 127.1, 126.9, 126.9 (d, J = 12.9 Hz), 126.8 (d, J = 13.0 Hz), 122.6, 122.5, 117.6 (d, J = 4.2 Hz), 117.1 (d, J = 4.1 Hz), 55.9 (d, J = 3.2 Hz), 55.0 (d, J = 2.6 Hz), 48.2, 46.7, 34.6, 32.7, 26.5, 22.6, 22.3, 21.9; ^{19}F NMR (377 MHz, $CDCl_3$) δ −124.26, −124.60; the compound exhibited two amide rotamers in the NMR spectra; HRMS (ESI+) $[MH]^+$ calcd for $C_{18}H_{18}FN_4O_4^+$ 373.13066; found 373.1307. **Pyridine-2-carboxylic acid (3-fluoro-4-nitrophenyl)amide (24).** White crystalline solid, mp 208−210 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 11.22 (br s, 1H), 8.63 (d, 1H, J = 4.6 Hz), 8.15 - 8.00 (m, 3H), 7.96 (td, 1H, J = 7.6, 1.6 Hz), 7.87 (dd, 1H, J = 9.1, 1.6 Hz), 7.58 (ddd, 1H, J = 7.5, 4.8, 1.1 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ 164.0, 157.0, 154.5, 149.3, 148.9, 146.0, 145.9, 138.6, 132.0, 131.9, 127.9, 127.6, 127.6, 123.3, 116.2, 116.2, 108.8, 108.5; ^{19}F NMR (377 MHz, DMSO-d_6) δ −116.31.

5-Hydroxy-2-methoxymethylpyridine (9). A 1 L three-neck round-bottom flask with a magnetic stirbar, internal temperature probe, and addition funnel was charged with NaH (15.03 g, 60% in mineral oil, 0.376 mol) and DMF (100 mL) and cooled to an internal temperature of <10 °C with an ice bath. Compound **25**[13] (40.45 g, 0.188 mol) was dissolved in DMF (100 mL) and charged to the addition funnel. Maintaining the temperature below 10 °C, the solution of **25** was added dropwise over 45 min. The reaction was stirred at 0 °C for 30 min. MeI (15.2 mL, 0.244 mol) was added dropwise over 30 min, maintaining the internal temperature below 15 °C. The reaction mixture became very thick due to the precipitate of NaBr. The reaction mixture was stirred overnight and allowed to warm to room temperature. Water (200 mL) was added slowly to quench excess NaH, and then additional water (300 mL) and MTBE (500 mL) were added. The aqueous layer was washed with MTBE (2 × 250 mL), and the combined organic layers were washed with water (4 × 200 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated to afford 43.7 g of a dark red oil. A 34.0 g aliquot of the compound (0.148 mol) was dissolved in ethanol (170 mL), combined with 50% wet 20 wt % $Pd(OH)_2$ on carbon (5.10 g, ∼3.65 mmol Pd), and hydrogenated at 30 psi H_2 at room temperature for 2 h. The catalyst was filtered off through a pad of Solka Floc eluting with EtOAc (500 mL). The resulting orange solution was concentrated to dryness. The damp brown crystals were washed with 5:1 hexanes:EtOAc (225 mL) followed by hexanes (100 mL). The resulting solid was dried in a 40 °C oven at 25 in Hg vacuum with nitrogen gas flowing through the chamber for 30 min. The product was isolated as 19.3 g of a light brown solid (91% yield over two steps accounting for 97.7 wt % purity by HPLC). This procedure describes a small scale run, which is slightly different from the kilo scale synthesis of **9** that will be published separately. A small sample of crude **9** was purified by flash chromatography on silica gel (hexanes:EtOAc 2:1) to provide analytically pure **9** as white crystals: mp 92−93 °C; ^1H NMR (400 MHz, DMSO) δ 10.86 (br s, 1H), 8.19 (d, 1H, J = 2.7 Hz), 7.34 (d, 1H, J = 8.5 Hz), 7.29 (dd, 1H, J = 8.5, 2.7 Hz), 4.53 (s, 2H), 3.42 (s, 3H); ^{13}C NMR (100 MHz, DMSO) δ 154.1, 148.3, 136.0, 125.5, 123.8, 74.2, 58.6. Anal. Calcd for $C_7H_9NO_2$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.21; H, 6.49; N, 10.00.

(*R*)-2-{2-(6-Methoxymethylpyridin-3-yloxy)-5-nitro-4-[(pyridine-2-carbonyl)amino]phenyl}pyrrolidine-1-carboxylic acid *tert*-butyl ester (22). To a solution of aryl fluoride **11** (800 g, 2.1 mol) in DMF (6 L) in a 22 L round-bottom flask equipped with an overhead stirrer, a heating mantle, and a thermocouple, was added hydroxypyridine **9** (320 g, 2.3 mol, 1.1 equiv) and additional DMF (2 L) used as a rinse. Cs_2CO_3 (684 g, 2.1 mol, 1 equiv) was added, and the slurry was aged at 55 °C over 2 h. When conversion reached 98% (by HPLC), the reaction mixture was cooled to 5 °C using an ice bath and quenched with water (4 L) over 20 min keeping temperature below 20 °C. The yellow slurry was diluted with EtOAc (12 L), the layers were separated, and aqueous layer was extracted with additional EtOAc (2 × 3 L). Combined organic layer was washed with brine (10 L). Assay in the organic phase: 96−97%. The organic layer was concentrated to a 5 L mark, allowed to cool to rt, and *n*-heptane (4 L) was added slowly over 1 h. The slurry was aged at 35 °C over 2 h and overnight at rt. The slurry was

filtered, and the filter cake was washed with *n*-heptane (2 L). The solid was dried overnight in a vacuum oven at 40 °C to provide 941.2 g (90%) of **22** (95.4 wt % and 99.8A% by HPLC): mp 163−164 °C; $[\alpha]^{20}_D$ +99.7 (*c* 1.50, MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.88 (br s, 0.3H), 12.84 (br s, 0.7H), 8.72−8.68 (m, 1H), 8.57 (s, 0.3H), 8.51−8.47 (m, 1.4H), 8.43 (d, J = 2.5 Hz, 0.3H), 8.16−8.10 (m, 1.3H), 8.02 (s, 0.7H), 7.91−7.85 (m, 1H), 7.59−7.47 (m, 3H), 5.46 (dd, J = 7.9, 2.7 Hz, 0.7H), 5.32 (dd, J = 8.0, 2.1 Hz, 0.3H), 4.66 (s, 0.6H), 4.63, (s, 1.4H), 3.84−3.61 (m, 2H), 3.53 (s, 0.9H), 3.50 (s, 2.1H), 2.45−2.32 (m, 1H), 2.18 (s, 2.1H), 2.09−1.90 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.9, 169.5, 163.6, 163.5, 159.7, 159.2, 155.9, 155.2, 150.8, 150.2, 149.1, 148.9, 148.8, 148.7, 141.7, 141.6, 137.7, 137.6, 136.0, 135.5, 132.2, 129.0, 128.5, 128.0, 127.9, 127.2, 127.1, 124.7, 124.6, 122.75, 122.72, 122.50, 122.47, 108.9, 108.4, 75.1, 75.0, 58.9, 58.8, 56.8, 55.7, 48.6, 46.9, 34.5, 32.7, 24.1, 22.9, 22.6, 22.1; the compound exhibited two amide rotamers in the NMR spectra. Anal. Calcd for $C_{25}H_{25}N_5O_6$: C, 61.09; H, 5.13; N, 14.25. Found: C, 61.01; H, 5.01; N, 14.09.

(*R*)-2-[6-(6-Methoxymethylpyridin-3-yloxy)-2-pyridin-2-yl-1*H*-benzoimidazol-5-yl]pyrrolidine-1-carboxylic acid *tert*-butyl ester phosphate salt (1). To a 22 L round-bottom flask equipped with an overhead stirrer, a thermocouple, and an addition funnel, were charged **22** (900 g, 1.83 mol) and DME (6.8 L). The slurry was cooled to 10 °C, and glacial acetic acid (3.4 L) was added over 30 min. To the resulting cloudy solution was charged iron powder (251 g, 4.5 mol, 2.5 equiv). The heterogeneous mixture was allowed to warm to 50 °C over 1 h, aged at 50 °C for 1 h, and then heated to 84 °C over 1 h. When conversion reached 98% (HPLC), reaction mixture was cooled to rt, and filtered over Celite eluting with DME (4 L). A 100 L extraction vessel was charged with 2.5 M aq $(NH_4)_2HPO_4$ (45 L) and cooled to 8 °C. The red to purple colored reaction filtrate was transferred into the extraction vessel and aged with stirring at rt overnight. Layers were separated, and the aqueous layer was extracted with EtOAc (6 L). Combined organic layer was treated with DARCO (160 g, 20 wt %) and aged at 55 °C over 2 h and then overnight at rt. The batch was filtered, and the filter cake was washed with EtOAc (2 L) (90% assay of **1** in filtrate by HPLC). The filtrate was solvent switched to 10 volumes of EtOH and transferred into a 22 L round-bottom flask equipped with an overhead stirrer, heating mantle, a thermocouple, and an addition funnel. A 1 M solution of H_3PO_4 in EtOH (2.2 L, 1.9 mol, 1.2 equiv) was added slowly over 2 h at rt (addition rate was kept at ∼3 mL/min until a seed bed was formed and then increased to ∼20 mL/min). The white slurry was aged at 55 °C over 2 h and at rt overnight. The slurry was filtered, and the wet solid was dried in a vacuum oven at 45 °C over the weekend to provide 697 g of phosphate salt of **1** as a dry white solid (70% yield, 99.4% LCAP, >99.8% ee): mp 248−250 °C (decomp); $[\alpha]^{20}_D$ +73.8 (*c* 1.72, MeOH); ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.6 (br s, 3H), 8.69−8.65 (m, 1H), 8.35−8.31 (m, 1H), 8.26−8.20 (m, 1H), 7.97−7.92 (m, 1H), 7.48−7.32 (m, 4H), 7.13 (br s, 0.5H), 7.04 (br s, 0.5H), 5.21−5.17 (m, 1H), 4.44 (s, 1H), 4.43 (s, 1H), 3.80−3.72 (m, 0.5H), 3.67−3.43 (m, 1.5H), 3.32 (s, 1.5H), 3.31 (s, 1.5H), 2.31−2.09 (m, 1H), 1.98 (s, 1.5H), 1.90−1.68 (m, 4.5H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 169.1, 168.6, 154.0, 153.7, 153.1, 152.8, 152.4, 152.0, 149.93, 149.90, 149.7, 149.3, 148.7, 148.6, 139.8, 139.7, 138.06, 138.04, 131.4, 130.9, 125.7, 125.3, 125.2, 123.0, 122.9, 121.8, 121.7, 74.82, 74.79, 58.44, 58.43, 57.7, 56.5, 48.3, 46.9, 34.8, 33.3, 23.8, 23.1, 22.7, 21.9; the compound exhibited two amide rotamers in the NMR spectra; ^{31}P NMR (162 MHz, DMSO-d_6) δ 0.8. Anal. Calcd for $C_{25}H_{28}N_5O_7P$: C, 55.45; H, 5.21; N, 12.93. Found: C, 54.95; H, 5.02; N, 12.88.

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Supporting Information Available: Copies of ^{1}H, ^{19}F, and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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