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Preparation of a Corticotropin-Releasing Factor Antagonist by Nucleophilic Aromatic Substitution and Copper-Mediated Ether Formation†

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Abstract:

Several synthetic approaches to a corticotropin-releasing factor (CRF) antagonist containing a tetrasubstituted pyridine were evaluated. In particular, nucleophilic aromatic substitutions on 2,4-dichloropyridine derivatives were attempted using 2,6-dimethyl-4-chlorophenol (4), (*S*)-2-aminobutanol (7), and several sulfur nucleophiles. It was found that a copper-mediated coupling of a phenoxymesylate (26) was preferred for preparation of the diarylether followed by nucleophilic aromatic substitution to introduce the amine side chain, affording the desired drug candidate (1) in two steps from the commercially available methyl 2,4-dichloro-6-methylnicotinate (2).

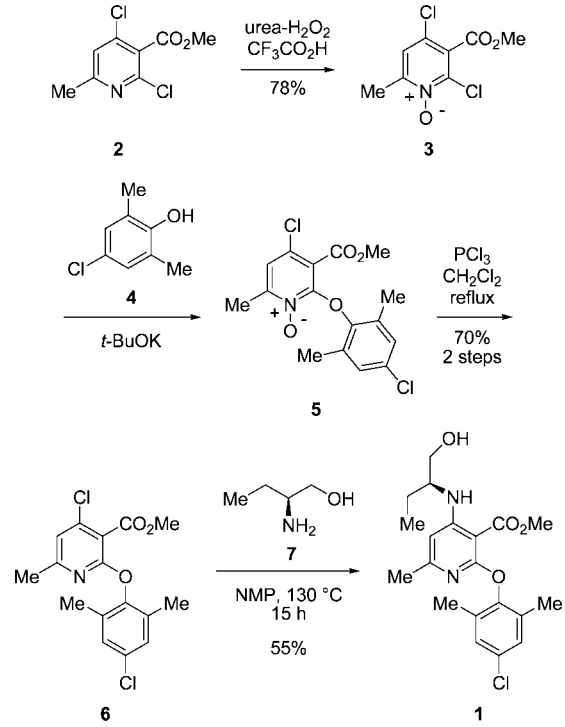
Introduction

Corticotropin-releasing factor (CRF) antagonists are part of a class of central nervous system agents that have demonstrated preclinical activity in anxiety and depression animal models. As a result, they have been postulated as potential novel therapies in neuroscience and have generated several research programs across the pharmaceutical industry.[1] As part of a Discovery effort, Pfizer identified a number of potential drug candidates based on a pyrimidine[2] or pyridine[3,4] framework. Compound **1** was identified and selected as a candidate for further development. This tetrasubstituted pyridine was prepared in Medicinal Chemistry starting from methyl 2,4-dichloro-6-methylnicotinate **2**, which was activated as the *N*-oxide (**3**) followed by a selective nucleophilic aromatic substitution at the 2-position with 2,6-dimethyl-4-chlorophenol (**4**, Scheme 1). The *N*-oxide (**5**) was reduced, and the (*S*)-2-aminobutanol (**7**) side chain was introduced on chloropyridine **6** using a second nucleophilic aromatic substitution under more forcing conditions to afford the desired target **1**.

Discussion

Evaluation of the Discovery route showed that the *N*-oxide (**3**) formation was slow and had only proceeded in 80% conversion after 24 h. The use of trifluoroacetic acid as the solvent in the reaction made the workup and product isolation difficult. A number of alternative reagents were evaluated for this oxidation,[5] and it was found that the use of the urea/hydrogen peroxide complex (UHP) with trifluoroacetic anhydride (TFAA) in dichloromethane provided >95% conversion after only 5 h[6] and compound **3** was isolated in 97% yield (Scheme 2). After a base and solvent evaluation (Cs_2CO_3, K_2CO_3, *t*-BuOK with THF, NMP, MeCN, toluene, DMSO, DMAc, DME), it was concluded that the first nucleophilic aromatic substitution could be best carried out using 2 equiv of Cs_2CO_3 in THF at reflux to provide a 67% yield of adduct **5**. Reduction of the *N*-oxide without the use of PCl_3 was accomplished by adding acetic acid and Fe(0) to the crude toluene extracts from the previous step and heating to 50 °C which afforded the desired aryl ether (**6**) in 85% yield. Process safety evaluation of the thermal stability of **3** (806 J/g with a 98 °C onset temperature) suggested that it should be handled in solution. Therefore, the dichloromethane was exchanged to THF for the following step without isolation of **3**, and the THF

Scheme 1. **Medicinal Chemistry Synthesis of 1**



† This manuscript is dedicated to the memory of Dr. Christopher R. Schmid.

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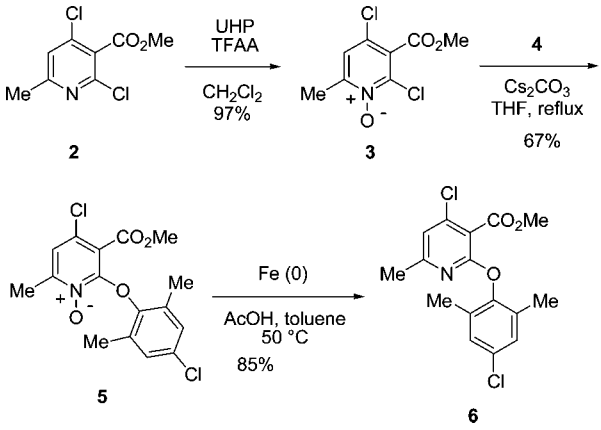
Scheme 2. **Enabled synthesis of diaryl ether 6**



was displaced by toluene for the final step. The telescoped process provided the desired intermediate in about 60% overall yield after recrystallization from methanol. This enabled route provided superior processing conditions to intermediate **6**, but concerns about the stability and processability of *N*-oxides **3** and **5** (655 J/g with a 101 °C onset temperature) suggested that alternative routes should be investigated.

To avoid the use of an *N*-oxide,[7] an attractive alternative approach would be the direct nucleophilic aromatic substitution on a 2-halopyridine. This strategy was studied by coupling ethyl ester **8**[8] with either phenol **4** or aminoalcohol **7**. With phenol **4**, the nucleophilic substitution in NMP using Cs_2CO_3 led to a slow but fairly selective reaction favoring the undesired 4-isomer (entry 1, table 1). It was expected that this problem could be circumvented by changing the order of introduction of the nucleophiles. Unfortunately, while addition of amine **7** provided some selectivity for the 4-position, bis-addition proceeded at a competitive rate (entry 2). A selective nucleophilic aromatic substitution at the 2-position of 2,4-dichloro-3,6-dimethylpyridine had been demonstrated at Pfizer with mesitol.[9] This protocol was evaluated, and although it provided good selectivity, it led to only 29% of the desired product (entry 3). The low yield was attributed to the instability of phenol **4** as it completely degraded under the reaction conditions within 90 min. A short evaluation of palladium-mediated catalysis[10−12] indicated that the 4-position was slightly preferred for addition of **4** (entry 4) and that no regioselectivity was obtained with **7** (entries 5).

In further attempts to achieve the desired regioselectivity, alternative nucleophiles were evaluated. Sulfur nucleophiles were an attractive choice since the resulting thioether could be oxidized to the sulfone, which could then serve as a leaving group.[13] As shown in Scheme 3, high regioselectivity was obtained for the nucleophilic aromatic substitution with thiophenol, and the reaction proceeded under mild conditions to generate thioether **14**. While the chloride in the 2-position could be displaced without the aid of a copper catalyst to afford arylether **15**, generation of sulfone **16** proved to be difficult. With Oxone, a fairly rapid oxidation to the sulfoxide was achieved followed by slow and incomplete conversion to **16**. In contrast, the oxidation of **14** to **17** with Oxone proved to work effectively in 97% yield. Alternatively, **17** could be accessed by the reaction of **2** with $PhSO_2Na$, which also proved to be regioselective. Unfortunately, displacement of the 2-chloro substituent and formation of arylether **16** failed. Another approach to prepare **16** relied on the reaction of the sulfone with arylether **6** (which was becoming available through an alternative route *vide infra*) and provided sufficient quantities of material to test the key nucleophilic aromatic substitution. Unfortunately, nucleophilic aromatic substitution with amine **7** proved to be very slow, which led to the speculation that the phenyl group would need to be modified into a superior leaving group to improve the rate of substitution.

Several phenylsulfone derivatives were prepared, and promising results were observed with the 4-chlorophenyl derivative. (Scheme 4) Using 4-chlorophenyl sodium sulfinate as the first nucleophile, sulfone **18** could be obtained in a single step. While displacement of the chlorosulfone with amine **7** generated the desired 4-aminopyridine derivative (**19**), it also produced significant amounts of carboxylic acid **20** and bis-addition product **21** in an equivalent ratio. Once again, nucleophilic aromatic substitution on chloride **6** was possible using a sulfinate to provide penultimate intermediate **22**. Displacement of the chlorosulfone with amine **7** was achieved to afford **1** in 42% yield.

Suspecting that the ester moiety could be the culprit for some of the side reactions observed, a more stable and less sterically demanding nitrile was studied as a potential ester surrogate. Aminobutanol **7** was added regioselectively to the known dichloronitrile **23**[14] under mild conditions to afford **24** in 76% yield (Scheme 5). The second nucleophilic aromatic substitution proceeded equally well and provided aryl ether **25** in 75% yield. While this substrate could be accessed easily by two successive nucleophilic aromatic substitutions, attempts to hydrolyze the nitrile to an ester or a carboxylic acid proved to be unsuccessful. Nitrile **25** also proved to be resistant to reduction by Dibal-H, and so this approach was abandoned to refocus on ester substrates.

The copper-mediated regioselective formation of the aryl ether from ester **2** was revisited within the context of developing conditions to avoid the decomposition of chlorophenol **4**. The mesylate and acetate were prepared and evaluated as protected forms of the phenol that could generate the desired phenoxide under the reaction conditions.[15] Mesylate **26** was prepared in high yields and proved to be the superior substrate (Scheme 6). After reaction optimization, it was found that addition of a tetrahydrofuran solution of potassium *tert*-butoxide to a mixture of **2** and **26** and one equivalent of copper(I) iodide in

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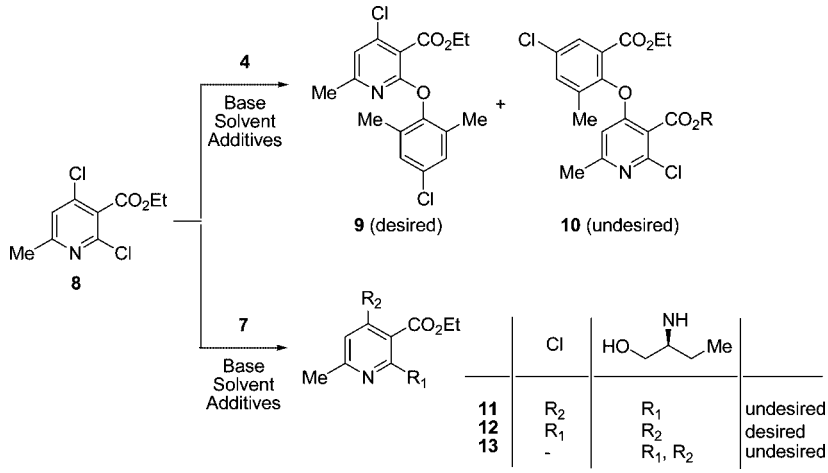
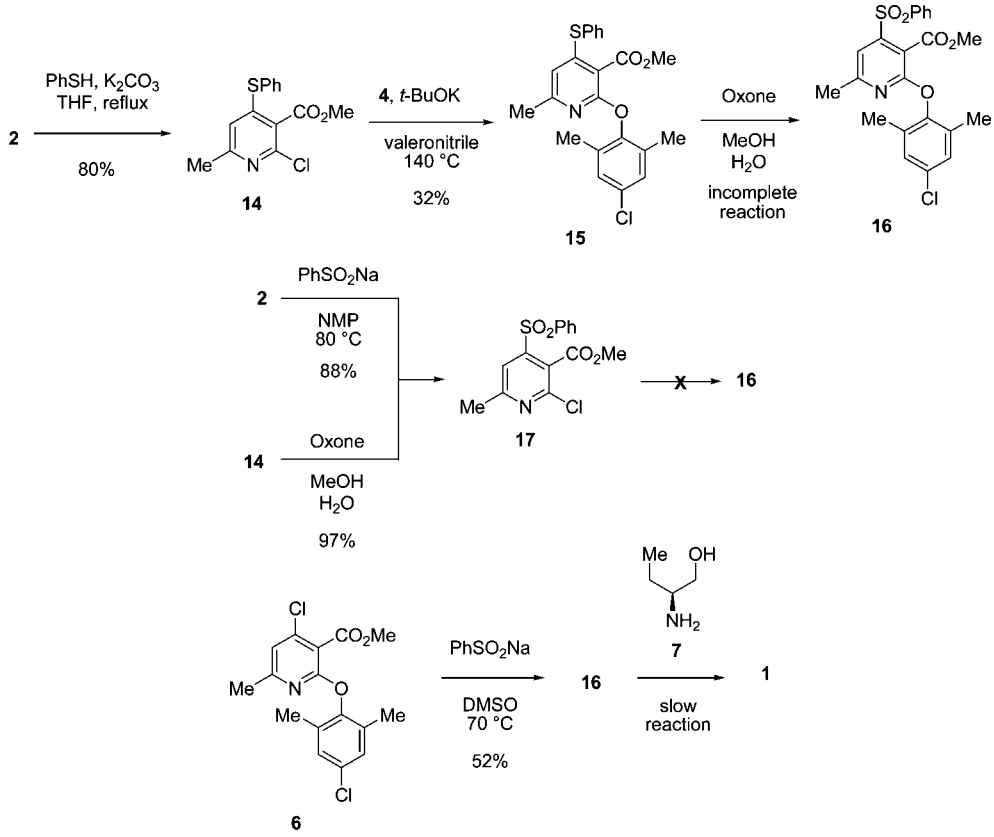
Table 1. **Nucleophilic aromatic substitutions of dichloropyridine 8**



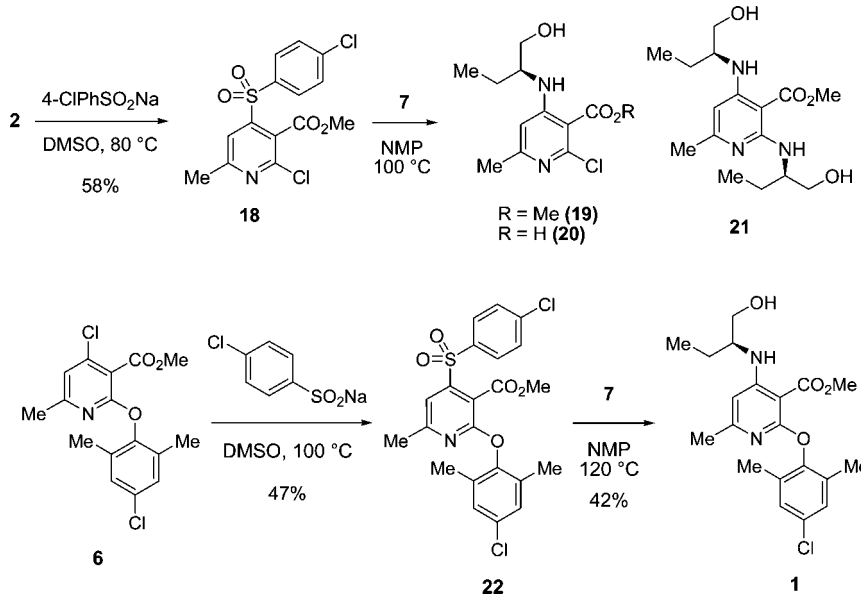
entry	reagent	base	solvent	*T* (°C)	additive	product ratio (yield)
1	**4**	Cs_2CO_3	NMP	95	–	1:8 (n/a) (**9:10**)
2	**7**	Cs_2CO_3	NMP	100	–	1:5.4:6.5 (n/a) (**11:12:13**)
3	**4**	*t*-BuOK	pyridine	100	CuBr·Me_2S	1:0 (29%) (**9:10**)
4	**4**	K_3PO_4	toluene	110	$Pd(PPh_3)_4$ (*R*)-BINAP	1:3.4(n/a) (**11:12**)
5	**7**	K_2CO_3	toluene	110	$Pd(PPh_3)_4$ (*R*)-BINAP	1:1(n/a) (**11:12**)

Scheme 3. **Sulfur nucleophiles**

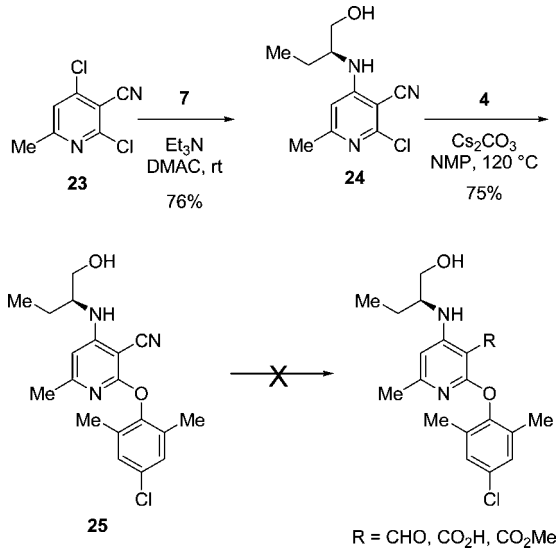


tetrahydrofuran at 60 °C allowed for conversion to diaryl ether **6** with approximately 5:1 regioselectivity. In this case, the source of Cu(I) did not affect the reaction, but utilization of a Cu(II) reagent or addition of other Lewis acids proved to be detrimental. The reaction mixture was treated with aqueous sodium thiosulfate, and the majority of the copper salts were removed by a filtration. A second filtration through a small pad of silica gel, followed by a crystallization, provided the product in laboratory yields of 41%. Upon scale-up, due to the extended length of the difficult filtration of the copper salts on scale, compound **6** was isolated in only 34%. It was postulated that a long filtration in the presence of aqueous media led to hydrolysis of the methyl ester. A nonaqueous quench was developed that simply involved the addition of an acidic resin, Amberlite 15, with a small amount of silica gel. Filtration of the mixture proceeded rapidly, and the aryl ether was isolated in 47% yield

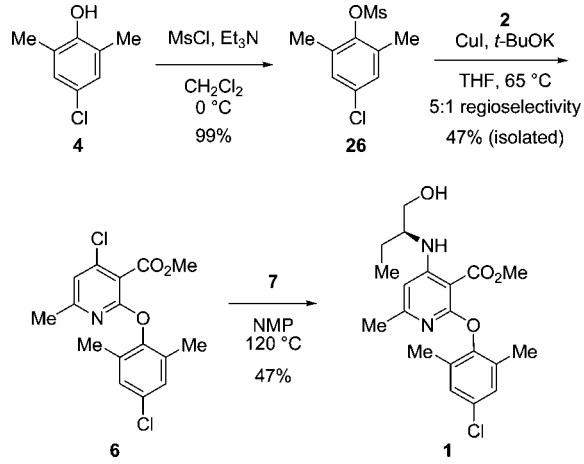
Scheme 4. **4-Chlorophenylsulfone as a leaving group**



Scheme 5. **Nitrile approach**



Scheme 6. **Scaled synthesis of compound 1**



on a >20 kg scale (41% on 50 kg after crystallization from *i*-PrOH). For the completion of the synthesis, the original Discovery conditions were utilized, and reaction of an excess of amine **7** in NMP at 125 °C provided a 47% yield of the desired drug candidate **1** after crystallization from cyclohexane. It was confirmed that the stereochemical integrity of (*S*)-aminoalcohol **7** was preserved in the final product.

Three major impurities were observed during the final step (Figure 1). The first impurity was carboxylic acid **27**, which represented about 40% of the crude mass balance at reaction completion. This carboxylic acid was easily removed as part of the reaction workup since it was soluble in the aqueous layer at basic pH. While it is easy to imagine that hydrolysis of the ester was the result of the presence of water in the reaction, efforts to strictly avoid moisture in the reaction did not significantly minimize the level of this impurity. We speculated that the chloride generated in the nucleophilic aromatic substitution acted as a nucleophile on the methyl group and generated the carboxylate and methyl chloride, which distilled at the high temperature of the reaction.[16] Efforts to identify reaction conditions that avoided the polar aprotic solvents, that usually favor this type of demethylation, did not positively affect the overall yield of the reaction because of the poor conversion, although the formation of the carboxylate was reduced. The second impurity was amide **28**, resulting from a second addition of **7** to the methyl ester. This impurity was present at 3−5% in the crude reaction mixture and was purged to 0.3% after Darco treatment and crystallization of the API. The final impurity was the *N*-methyl derivative (**29**) of the API which was observed at about 2% at the end of the reaction and below 0.6% in the API. This impurity can be generated by methylation of either

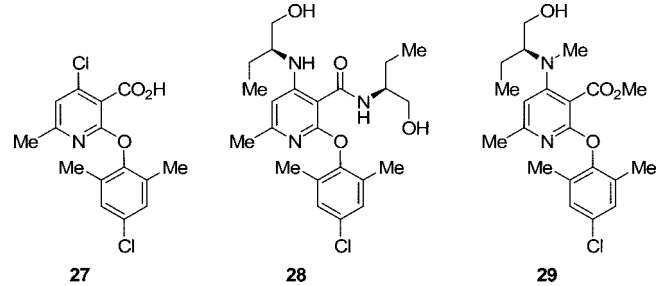


Figure 1. **Observed impurities.**

the API itself or aminoalcohol **7**. Analysis of the reaction showed the presence of *N*-methylaminobutanol which was not present in the starting material. This impurity confirmed the hypothesis that generation of the carboxylic acid proceeded through nucleophilic cleavage. The final API also contained only 4.6 ppm of copper, and the chiral purity of amine **7** was preserved in the final API (97.8% ee).

In conclusion, several synthetic approaches involving nucleophilic aromatic substitutions of 2,4-dichloropyridine derivatives were studied for the preparation of a CRF drug candidate (**1**). It was noted that changing the 3-position of the substrate from a methyl group[9] to a methyl ester drastically changed the reaction conditions required for the introduction of the aryl ether. While the approach utilizing the pyridine *N*-oxide provided high levels of regioselectivity in the formation of the aryl ether, it was avoided for safety reasons due to the low onset temperature of both *N*-oxides. Approaches utilizing sulfur nucleophiles as a latent leaving group provided high regioselectivity for the 4-position but poor reactivity for the final introduction of the aminoalcohol side chain. It was ultimately found that a copper(I)-mediated coupling of dichloropyridine (**2**) and mesylate **26**, a phenoxide surrogate, allowed for acceptable regioselectivity and yield. Completion of the synthesis with a second nucleophilic aromatic substitution provide the desired target in about 20% overall yield on a 20 kg scale.

Experimental Section

General. Starting materials were obtained from commercial suppliers and used without further purification. Reactions were performed under a dry N_2 atmosphere and monitored using HPLC. Melting points were measured in open capillary tubes and are uncorrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were obtained in $CDCl_3$ unless otherwise indicated. IR spectra were recorded neat on a Thermo Nicolet Avatar 360 FTIR. High-resolution mass spectrometry was conducted at Pfizer on a Thermo LTQFT Ultra mass spectrometer.

Methyl 2,4-Dichloro-6-methylnicotinate *N*-Oxide (3). To a solution of methyl 2,4-dichloro-6-methylnicotinate (**2**) (16.46 g, 74.80 mmol) in CH_2Cl_2 (20 mL) was added H_2O_2·urea (UHP) (14.55 g, 154.7 mmol). The reaction mixture was cooled to 0 °C, and a solution of TFAA (21.0 mL, 149 mmol) in CH_2Cl_2 (10 mL) was added dropwise. The mixture was allowed to warm to room temperature overnight. Saturated aqueous $Na_2S_2O_3$ (30 mL) was added, and the mixture was stirred 30 min, poured into H_2O (40 mL), and extracted with CH_2Cl_2 (2 × 30 mL). The organic extracts were washed with 1 N NaOH (60 mL), dried over $MgSO_4$, and concentrated to a solid to afford methyl 2,4-dichloro-6-methylnicotinate *N*-oxide (**3**) (17.12 g, 97%). Analysis of the material was in accordance with the previously reported data.[3]

Methyl 4-Chloro-2-(4-chloro-2,6-dimethylphenoxy)-6-methylnicotinate *N*-Oxide (5). To a solution of 4-chloro-2,6-dimethylphenol (**4**) (6.14 g, 39.2 mmol) in THF (20 mL) was added Cs_2CO_3 (24.3 g, 74.6 mmol). The mixture was heated to reflux, and methyl 2,4-dichloro-6-methylnicotinate *N*-oxide (**3**) (8.81 g, 37.3 mmol) in THF (140 mL) was added via an addition funnel. The mixture was heated for 15 h, cooled to rt, filtered through Celite, and washed with EtOAc (2 × 100 mL). The filtrate was washed with 1 N HCl (2 × 50 mL), and the organic layer was concentrated to a crude oil. The oil was dissolved in 1:1 THF/toluene (200 mL), washed with 1 N NaOH (100 mL) and brine (50 mL), and concentrated. The crude product was dissolved in EtOAc (100 mL) and then treated with Darco at reflux for 3 h. The mixture was cooled to rt, filtered, and washed with EtOAc. The solvent was removed under reduced pressure to afford the desired product as a thick oil (8.91 g, 67%). Analysis of the material was in accordance with the previously reported data.[3]

Methyl 4-Chloro-2-(4-chloro-2,6-dimethylphenoxy)-6-methylnicotinate (6).[4] A solution of methyl 4-chloro-2-(4-chloro-2,6-dimethylphenoxy)-6-methylnicotinate *N*-oxide (**5**) (4.25 g, 11.9 mmol) in toluene (25 mL) was added to a suspension of Fe(0) (2.68 g, 55.9 mmol) in AcOH (25 mL) at 50 °C. The mixture was stirred for 3.5 h and cooled to rt. Toluene (30 mL) and H_2O (30 mL) were added, and the mixture was filtered through Celite. The layers of the filtrate were separated, and the aqueous layer was extracted with toluene (30 mL). The organic extracts were combined, washed with brine (30 mL), dried over Na_2SO_4, and filtered. The solvent was removed under reduced pressure to afford methyl 4-chloro-2-(4-chloro-2,6-dimethylphenoxy)-6-methylnicotinate (**6**) (3.44 g, 85%). Mp = 130−134 °C. ^{1}H NMR δ 2.06 (s, 6), 2.26 (s, 3), 3.96 (s, 3), 6.86 (s, 1), 7.04 (s, 2). ^{13}C NMR δ 16.70, 24.29, 53.09, 114.33, 118.23, 128.31, 130.24, 133.12, 143.32, 148.86, 159.10, 165.04. IR υ 1740, 1589, 1559, 1364, 1284, 1184, 1159, 1088, 869, 577 cm^{-1}.

Methyl 2-Chloro-6-methyl-4-(phenylthio)nicotinate (14). To a solution of methyl 2,4-dichloro-6-methylnicotinate (**2**) (8.85 g, 40.2 mmol) in THF (40 mL) was added K_2CO_3 (6.15 g, 44.5 mmol) followed by addition of thiophenol (4.50 mL, 44.2 mmol). The reaction was heated to reflux and stirred overnight. The mixture was cooled to rt and poured into a mixture of MTBE (50 mL) and H_2O (50 mL). The layers were separated, and the organic layer was washed with brine (20 mL). The organic extracts were dried over Na_2SO_4, filtered, and concentrated to off-white solids. The solids were triturated in hexanes (50 mL) at reflux for 2.5 h, cooled to rt, and filtered to afford methyl 2-chloro-6-methyl-4-(phenylthio)nicotinate (**14**) as a white solid (9.47 g, 80%). Mp = 81−83 °C. ^{1}H NMR δ 2.31 (s, 3), 3.96 (s, 3), 6.43 (s, 1), 7.41−7.52 (m, 5). ^{13}C NMR δ 24.41, 53.10, 119.53, 124.19, 129.35, 130.31, 135.46, 147.52, 152.25, 159.57, 165.68. IR υ 2952, 1732, 1569, 1517, 1439, 1276, 1218, 1155, 1065, 807, 752, 691 cm^{-1}. HREIMS *m*/*z* 294.03488 (calcd *m*/*z* 294.03500 for $C_{14}H_{12}O_2N^{35}Cl^{32}S$ + H). Analysis calculated for $C_{14}H_{12}ClNO_2S$: C, 57.24; H, 4.12; N, 4.77; Cl, 12.07. Found: C, 57.17; H, 4.14; N, 4.74; Cl, 12.33.

Methyl 2-(4-Chloro-2,6-dimethylphenoxy)-6-methyl-4-(phenylthio)nicotinate (15). To a solution of 2,6-dimethyl-4-chlorophenol (**4**) (2.76 g, 17.6 mmol) and methyl 2-chloro-6-methyl-4-(phenylthio)nicotinate (**14**) (2.59 g, 8.82 mmol) in valeronitrile (9.0 mL) was added *t*-BuOK (1.28 g, 11.5 mmol). The reaction mixture was heated to 120 °C for 24 h. The reaction was cooled to rt and poured into MTBE (100 mL) in a separatory funnel. The mixture was washed with water (2 ×

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50 mL) and brine (50 mL), and the organic extracts were dried over Na_2SO_4 and concentrated. The brown residue was purified by chromatography on silica gel (20% EtOAc/hexanes) to afford methyl 2-(4-chloro-2,6-dimethylphenoxy)-6-methyl-4-(phenylthio)nicotinate (**15**) (1.15 g, 32%). Mp = 136−137 °C. ^{1}H NMR δ 2.06 (s, 3), 2.07 (s, 6), 3.96 (s, 3), 6.17 (s, 1), 7.02 (s, 2), 7.42−7.46 (m, 3), 7.54−7.57 (m, 2). ^{13}C NMR δ 16.82, 24.52, 52.74, 110.61, 114.94, 128.19, 129.87, 130.01, 130.10, 130.18, 133.21, 135.67, 149.22, 153.25, 158.14, 159.30, 166.46. IR υ 1732, 1579, 1357, 1187. 861, 587 cm^{-1}. HREIMS *m*/*z* 414.09269 (calcd *m*/*z* 414.09252 for $C_{22}H_{20}O_3N^{35}Cl^{32}S$ + H).

Methyl 2-(4-Chloro-2,6-dimethylphenoxy)-6-methyl-4-(phenylsulfonyl)nicotinate (16). A solution of methyl 4-chloro-2-(4-chloro-2,6-dimethylphenoxy)-6-methylnicotinate (**6**) (2.23 g, 6.55 mmol) and $PhSO_2Na$ (1.09 g, 6.64 mmol) in DMSO (22 mL) was heated to 70 °C. After 5 h, additional $PhSO_2Na$ (2.10 g, 13.0 mmol) was added, and heating was continued. After another 5 h, additional $PhSO_2Na$ (2.10 g, 13.0 mmol) was added, and the reaction was heated overnight. The mixture was poured into H_2O (30 mL) and extracted with MTBE (2 × 40 mL). The organic extracts were washed with brine (30 mL), dried over $MgSO_4$, filtered, and concentrated to afford methyl 2-(4-chloro-2,6-dimethylphenoxy)-6-methyl-4-(phenylsulfonyl)nicotinate (**16**) (1.50 g, 52%). Mp = 150−154 °C. ^{1}H NMR δ 2.02 (s, 6), 2.32 (s, 3), 4.03 (s, 3), 7.03 (s, 2), 7.26 (s, 1), 7.56−7.59 (m, 2), 7.63−7.67 (m, 1), 8.04−8.06 (m, 2). ^{13}C NMR δ 16.71, 24.61, 53.54, 113.18, 115.44, 128.04, 128.77, 129.66, 130.50, 133.03, 134.47, 140.02, 148.74, 149.51, 159.07, 160.24, 165.46. IR υ 2953, 1739, 1584, 1363, 1283, 1181, 1152, 1093, 729, 580 cm^{-1}. HREIMS *m*/*z* 446.08259 (calcd *m*/*z* 446.08235 for $C_{22}H_{20}O_5N^{35}Cl^{32}S$ + H).

Methyl 2-Chloro-6-methyl-4-(phenylsulfonyl)nicotinate (17). *Procedure A.* To a solution of methyl 2-chloro-6-methyl-4-(phenylthio)nicotinate (14) (795 mg, 2.42 mmol) in MeOH (8.0 mL) and H_2O (1.5 mL) was added Oxone (3.64 g). The mixture was stirred at rt for 6 h, and an additional portion of Oxone was added (2.50 g). The reaction mixture was stirred overnight, poured into H_2O (10 mL), and extracted with CH_2Cl_2 (2 × 15 mL). The organic extracts were dried over $MgSO_4$, filtered, and concentrated to afford methyl 2-chloro-4-(4-chlorophenylsulfonyl)-6-methylnicotinate (17) (846 mg, 97%).

Procedure B. To a solution of methyl 2,4-dichloro-6-methylnicotinate (**2**) (2.30 g, 10.4 mmol) in NMP (11 mL) was added $PhSO_2Na$ (3.46 g, 164 mmol). The mixture was heated to 80 °C overnight and cooled to rt, and H_2O (30 mL) was added. Solids precipitated, and the mixture was stirred for 10 min and filtered. The solids were washed with additional H_2O and hexanes and dried under vacuum to afford methyl 2-chloro-6-methyl-4-(phenylsulfonyl)nicotinate (**17**) (3.01 g, 88%). Mp = 142−146 °C. ^{1}H NMR δ 2.58 (s, 3), 4.03 (s, 3), 7.50−7.63 (m, 4), 7.97 (d, 2, *J* = 7.5). ^{13}C NMR δ 24.60, 53.91, 120.75, 124.96, 128.74, 129.79, 134.79, 139.48, 148.72, 149.46, 162.13, 164.98. IR υ 1738, 1577, 1447, 1333, 1280, 1232, 1150, 1088, 1065, 911, 820, 718, 686, 609, 580 cm^{-1}. HREIMS *m*/*z* 326.02495 (calcd *m*/*z* 326.02483 for $C_{14}H_{12}O_4N^{35}Cl^{32}S$ + H).

Methyl 2-Chloro-4-(4-chlorophenylsulfonyl)-6-methylnicotinate (18). To a solution of methyl 2,4-dichloro-6-methylnicotinate (**2**) (1.06 g, 4.84 mmol) in NMP (5.0 mL) was added 4-$ClPhSO_2Na$ (2.01 g, 10.1 mmol). The mixture was heated to 80 °C overnight and cooled to rt, and H_2O (15 mL) and *i*-PrOH (10 mL) were added. Solids precipitated, and the mixture was stirred overnight and filtered. The solids were washed with H_2O, dried under vacuum to afford methyl 2-chloro-4-(4-chlorophenylsulfonyl)-6-methylnicotinate (**18**) (1.01 g, 58%). Mp = 121−124 °C. ^{1}H NMR δ 2.61 (s, 3), 4.04 (s, 3), 7.52 (d, 2, *J* = 8.7), 7.58 (s, 1), 7.92 (d, 2, *J* = 8.7). ^{13}C NMR δ 24.63, 53.97, 120.56, 124.99, 130.13, 130.27, 137.94, 141.79, 148.89, 149.10, 162.24, 165.03. IR υ 2954, 1739, 1578, 1339, 1283, 1151, 1091, 911, 818, 755, 636, 579 cm^{-1}. HREIMS *m*/*z* 359.98607 (calcd *m*/*z* 359.98586 for $C_{14}H_{11}O_4N^{35}Cl_2{}^{32}S$ + H).

Methyl 2-(4-Chloro-2,6-dimethylphenoxy)-4-(4-chlorophenylsulfonyl)-6-methylnicotinate (22). A slurry of methyl 4-chloro-2-(4-chloro-2,6-dimethylphenoxy)-6-methylnicotinate (**6**) (1.01 g, 2.97 mmol) and 4-$ClPhSO_2Na$ (3.056 g, 15.39 mmol) in DMSO (10 mL) was heated 100 °C for 24 h. The reaction mixture was cooled to room temperature and poured into MTBE (15 mL) and H_2O (15 mL). The layers were separated, and the organic layer was washed with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated to afford an amorphous solid. The product was purified by chromatography (EtOAc/heptane) to provide methyl 2-(4-chloro-2,6-dimethylphenoxy)-4-(4-chlorophenylsulfonyl)-6-methylnicotinate (**22**) (672 mg, 47%). ^{1}H NMR δ 1.16 (s, 3), 2.01 (s, 6), 4.03 (s, 3), 7.02 (s, 2), 7.25 (s, 1), 7.53 (d, 2, *J* = 8.7), 7.98 (d, 2, *J* = 8.7). ^{13}C NMR δ 16.71, 24.61, 53.54, 113.21, 115.27, 128.41, 129.97, 130.26, 130.58, 132.97, 138.61, 141.35, 148.72, 149.22, 159.16, 160.37, 165.41. IR υ 1739, 1582, 1363, 1179, 1151, 1089, 753, 642, 583 cm^{-1}. HREIMS *m*/*z* 480.04296 (calcd *m*/*z* 480.04338 for $C_{22}H_{19}O_5N^{35}Cl_2{}^{32}S$ + H).

(*S*)-Methyl 2-(4-Chloro-2,6-dimethylphenoxy)-4-(1-hydroxybutan-2-ylamino)-6-methylnicotinate (1).[4] To a solution of methyl 2-(4-chloro-2,6-dimethylphenoxy)-4-(4-chlorophenylsulfonyl)-6-methylnicotinate (**22**) (1.499 g, 3.120 mmol) in NMP (7.0 mL) was added (*S*)-2-aminobutanol (**7**) (0.90 mL, 9.5 mmol). The mixture was heated to 120 °C overnight and cooled to room temperature. MTBE (15 mL) and water (15 mL) were added. The layers were separated, and the organic layer was extracted with MTBE (15 mL). The organic extracts were combined, washed with water (15 mL) and brine (10 mL), and dried over $MgSO_4$. The solvent was removed under vacuum, and the crude oil was purified by chromatography (EtOAc/Hexanes) to afford (*S*)-methyl 2-(4-chloro-2,6-dimethylphenoxy)-4-(1-hydroxybutan-2-ylamino)-6-methylnicotinate (**1**) (0.506 g, 42%). Analysis of the product was in accordance with the data provided in the last experimental of this manuscript.

(*R*)-2-Chloro-4-(1-hydroxybutan-2-ylamino)-6-methylnicotinonitrile (24). To a solution of 2,4-dichloro-6-methylnicotinonitrile (**23**) (4.871 g, 26.04 mmol) in DMAc (48 mL) was added Et_3N (3.70 mL, 26.5 mmol). The reaction mixture was stirred overnight. Hexanes (50 mL) was added, and the orange mixture was added to H_2O (300 mL). Solids appeared, and the mixture was triturated and filtered. The solids were washed with hexanes and dried to afford (*R*)-2-chloro-4-(1-hydroxybutan-2-ylamino)-6-methylnicotinonitrile (**24**) (4.78 g,

77%). Mp = 122−125 °C. ^{1}H NMR δ 0.96 (t, 3, J = 7.5), 1.51−1.62 (m, 1), 1.65−1.75 (m, 1), 2.37 (s, 3), 2.64 (bs, 1), 3.40−3.57 (m, 1), 3.39 (ABdq, 2), 5.23 (d, 1, J = 8.3), 6.38 (s, 1). ^{13}C NMR δ 10.66, 24.52, 25.11, 56.44, 63.76, 91.30, 103.78, 114.73, 152.94, 156.94, 162.25. IR υ 3339, 2967, 2935, 2878, 2218, 1596, 1560, 1434, 1055, 730 cm^{-1}. HREIMS m/z 240.08988 (calcd m/z 240.08982 for $C_{11}H_{14}ON_3{}^{35}Cl$ + H).

(*R*)-2-(4-Chloro-2,6-dimethylphenoxy)-4-(1-hydroxybutan-2-ylamino)-6-methylnicotinonitrile (25). To a solution of (*R*)-2-chloro-4-(1-hydroxybutan-2-ylamino)-6-methylnicotinonitrile (**24**) (1.87 g, 7.80 mmol) and 4-chloro-2,6-dimethylphenol (**4**) (1.25 g, 7.95 mmol) in NMP (18 mL) was added Cs_2CO_3 (2.56 g, 7.86 mmol). The reaction mixture was heated to 100 °C overnight. The reaction was cooled to rt, and 1 N HCl (20 mL) was added followed by MTBE (30 mL). The layers were separated, and the organic extracts were washed with 1 N HCl (20 mL) and brine (15 mL). The organic extracts were concentrated under reduced pressure, and the crude product was recrystallized from EtOAc/hexanes to afford (*R*)-2-(4-chloro-2,6-dimethylphenoxy)-4-(1-hydroxybutan-2-ylamino)-6-methylnicotinonitrile (**25**) (2.10 g, 75%). Mp = 124−126 °C. ^{1}H NMR δ 1.00 (t, 3, J = 7.5), 1.53−1.64 (m, 1), 1.67−1.79 (m, 1), 2.07 (s, 6), 2.15 (s, 3), 3.50−3.58 (m, 1), 3.70 (ABdq, 2), 5.07 (d, 1, J = 9.7), 6.16 (s, 1), 7.01 (s, 2). ^{13}C NMR δ 10.69, 16.78, 24.75, 25.38, 56.22, 64.08, 76.68, 100.35, 115.28, 128.25, 130.16, 133.04, 148.86, 157.78, 161.63, 163.79. IR υ 3387, 3346, 2966, 2931, 2878, 2213, 1602, 1571, 1447, 1377, 1183, 732 cm^{-1}. HREIMS m/z 360.14755 (calcd m/z 360.14733 for $C_{19}H_{22}O_2N_3{}^{35}Cl$ + H).

4-Chloro-2,6-dimethylphenyl Methanesulfonate (26). To a solution of 4-chloro-2,6-dimethylphenol (**4**) (20.01 g, 127.8 mmol) in CH_2Cl_2 (200 mL) at 0 °C was added Et_3N (19.6 mL, 141 mmol) and MsCl (10.9 mL, 141 mmol). The reaction was allowed to warm to rt overnight and was quenched with sat. aq $NaHCO_3$ (40 mL). The layers were separated, and the organic layer was washed with brine (40 mL), dried over Na_2SO_4, filtered, and concentrated to a solid, affording 4-chloro-2,6-dimethylphenyl methanesulfonate (**26**) (29.63 g, 99%). Mp = 150−154 °C. ^{1}H NMR δ 2.34 (s, 6), 3.28 (s, 3), 7.06 (s, 2). ^{13}C NMR δ 17.71, 39.45, 129.24, 132.26, 134.04, 145.52. IR υ 3025, 2940, 1578, 1470, 1344, 1187, 1138, 975, 828, 540 cm^{-1}. Analysis calculated for $C_9H_{11}ClO_3S$: C, 46.06; H, 4.72; Cl, 15.11. Found: C, 45.96; H, 4.61; Cl, 15.31.

Methyl 4-Chloro-2-(4-chloro-2,6-dimethylphenoxy)-6-methylnicotinate (6). To a solution of methyl 2,4-dichloro-6-methylnicotinate (**2**) (10.33 g, 46.94 mmol) and 4-chloro-2,6-dimethylphenyl methanesulfonate (**26**) (10.16 g, 43.29 mmol) in THF (100 mL) was added CuI (8.31 g, 43.61 mmol). The mixture was stirred 10 min and heated to 45 °C. *t*-BuOK (14.88 g, 132.6 mmol) in THF (115 mL) was slowly added. The mixture was heated to 80 °C and stirred 6 h. $Na_2S_2O_3 \cdot 5H_2O$ was added, and the mixture was stirred 30 min. Toluene (150 mL) and H_2O (100 mL) were added, and the mixture was stirred overnight and filtered through Celite. The layers of the filtrate were separated, and the organic layer was washed with sat. aq $Na_2S_2O_3$ (50 mL) and brine (50 mL) and was dried over Na_2SO_4. The mixture was filtered and concentrated to a thick oil which was crystallized with MeOH to afford methyl 4-chloro-2-(4-chloro-2,6-dimethylphenoxy)-6-methylnicotinate (**6**) (6.70 g, 45%). At 20 kg scale, the workup was modified to a nonaqueous system were the reaction was quenched with an acidic resin (Amberlite 15), followed by a filtration on silica pad. (47% yield). Analysis of the product was in accordance with the previously available data from the reduction of *N*-oxide **5**.[4]

(*S*)-Methyl 2-(4-chloro-2,6-dimethylphenoxy)-4-(1-hydroxybutan-2-ylamino)-6-methylnicotinate (1).[4] A mixture of methyl 4-chloro-2-(4-chloro-2,6-dimethylphenoxy)-6-methylnicotinate (**6**) (50.0 g, 147 mmol) and (*S*)-2-aminobutanol (**7**) (42.0 mL, 445 mmol) in NMP (300 mL) was heated to 120 °C for 14 h. At this point the starting material had been reduced to less than 2% (HPLC). The reaction mixture was cooled to 20 °C and diluted with 500 mL of water. The mixture was extracted with 500 mL of IPE and the organic extracts were washed with 500 mL of water, 400 mL of 0.5 N HCl, and another 400 mL of water. The organic phase was dried over $MgSO_4$ in the presence of 2.5 g of Darco G-60 and filtered. The solvent was displaced with cyclohexane, by an atmospheric distillation, to a final volume of 175 mL. The mixture was allowed to cool and granulate overnight. The solids were filtered, washed with 50 mL of cyclohexane, and recrystallized from 145 mL of cyclohexane to give (*S*)-methyl 2-(4-chloro-2,6-dimethylphenoxy)-4-(1-hydroxybutan-2-ylamino)-6-methylnicotinate (**1**) (23.6 g, 41%). Mp = 124−125 °C. $[\alpha]^{25}$ = −21.58 (CH_2Cl_2, c = 2.28). Chiral HPLC (CHIRALPAK AD; 4.6 mm × 250 mm, 35 °C, 1960:400:2 (v/v/v) hexanes/*i*-PrOH/Et_2NH, 1.0 mL/min, @315 nm: 97.8% ee. ^{1}H NMR δ 0.99 (t, 3, J = 7.5), 1.58 (m, 1), 1.73 (m, 1), 1.76 (br s, 1), 2.06 (s, 6), 2.09 (s, 3), 3.54 (m, 1), 3.66 (m, 1), 3.70 (m, 1), 3.86 (s, 3), 6.18 (s, 1), 7.01 (s, 2), 8.13 (br d, 1). ^{13}C NMR δ 10.48, 16.73, 24.70, 24.81, 51.74, 55.76, 64.39, 100.71, 127.76, 129.05, 132.95, 149.58, 158.08, 159.48, 162.29, 169.69. IR υ 3557, 3365, 1670, 1564, 1186, 1092 cm^{-1}. Analysis calculated for $C_{20}H_{25}ClN_2O_4$: C, 61.14; H, 6.41; N, 7.13; Cl, 9.02. Found: C, 60.98; H, 6.06; N, 6.80; Cl, 8.91. Cu level: 4.6 ppm (ICP).

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