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The Synthesis of OSU 6162: Efficient, Large-Scale Implementation of a Suzuki Coupling

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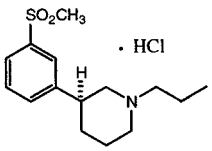
Abstract:

The synthesis of the chiral, nonracemic 3-aryl piperidine, OSU 6162 (1), a potential CNS agent from Pharmacia Corporation, is presented. The key construction in the described synthesis is a palladium-catalyzed aryl cross-coupling reaction between bromosulfone (4) and pyridyl borane (14). Initially developed conditions for this Suzuki reaction, conducted in tetrahydrofuran/aqueous hydroxide, delivered free base (6) or hydrochloride salt (15a) in reproducible 80% yield. However, by changing the solvent to toluene and the base to carbonate, significant decreases in catalyst requirement were realized, and the methane sulfonate salt (15b) of the coupled product could be obtained in reproducible 92−94% yield on 200-kg input. The success of the Suzuki reaction was critically dependent on a bulk source of the pyridyl borane coupling partner. Cryogenic conditions were developed for its generation via lithium−halogen exchange to generate thermally labile 3-lithiopyridine followed by transmetalation with diethylmethoxy borane. This highly exothermic series of transformations yielded crystalline diethyl-3-pyridyl borane in reproducible 75−80% yield on scales ranging up to 200-kg input. Selective reduction of the biaryl, classical resolution and introduction of the propyl group via the Gribble reductive amination procedure completed the synthesis of OSU 6162 free base. This route was employed to deliver over 35 kg of clinical-quality bulk drug in short order.

Introduction

OSU 6162 has been known in the literature since 1994, and two syntheses of this chiral nonracemic 3-aryl piperidine have been reported.[1,2] The chemical structure is depicted below.



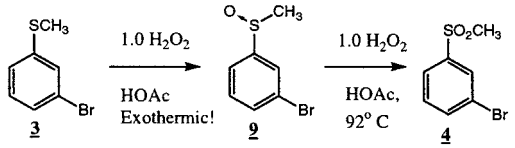
1
OSU 6162

The initially reported synthesis[1] suffered from unserviceable yields for the multistep conversion of a phenol into the requisite methyl sulfone moiety. Despite the known[3] instability of 3-metallopyridines and their general lack of availability, the latter route, depicted in Scheme 1, appeared more promising on paper. This aryl cross-coupling route was therefore explored for viability, and its development is the subject of this report.

Results and Discussion

Reaction of dibromide **2**, in what we believe is simply a nucleophilic displacement, is straightforward. Thus, portionwise addition of an equimolar amount of solid sodium thiomethylate to 1,3-dibromobenzene in warm *N*-methylpyrrolidinone or dimethyl formamide affords the desired thioether in about 86% isolated yield. We found that better results were obtained downstream in the synthesis if the displacement was stopped after about 90% consumption of the starting material. With ca. 10% dibromide remaining, the reaction product competes effectively with the substrate for thiomethoxide, thus generating the bis-thioether. This bis-thioether, after oxidation to the bis-sulfone at the next step, is not efficiently rejected later in the sequence.

Thioether **3**, after an extractive workup, is taken up in acetic acid and oxidized via the *careful, controlled* addition of hydrogen peroxide. Oxidation of the thioether to sulfoxide **9** is *extremely exothermic*, fairly typical for such chemistry, and to control the exotherm, we elected to slowly dose in 1.0 equivalents of hydrogen peroxide. *Only after the exotherm from this oxidation had subsided* did we add the second equivalent of peroxide.



3 **9** **4**

Stirring overnight at elevated temperature consumed all of the sulfoxide, as determined by TLC, since HPLC assay methods proved unreliable in this instance. After a starch iodide paper test to ensure that all of the peroxide had been consumed as well, the acetic acid was removed under vacuum and replaced with 2-propanol to crystallize the product.

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† Pharmacia Corporation.
‡ The Dow Chemical Co.

(1) Sonesson, C.; Lin, C.-H.; Hansson, L.; Svensson, K.; Carlsson, A..; Smith, M. W.; Wikstrom, H. *J. Med. Chem.* **1994**, *37*, 2735.
(2) Sonesson, C.; Lindborg, J. *Tetrahedron Lett.* **1994**, 9063.
(3) Gilman, H.; Spatz, S. M. *J. Org. Chem.* **1951**, *16*, 1485.

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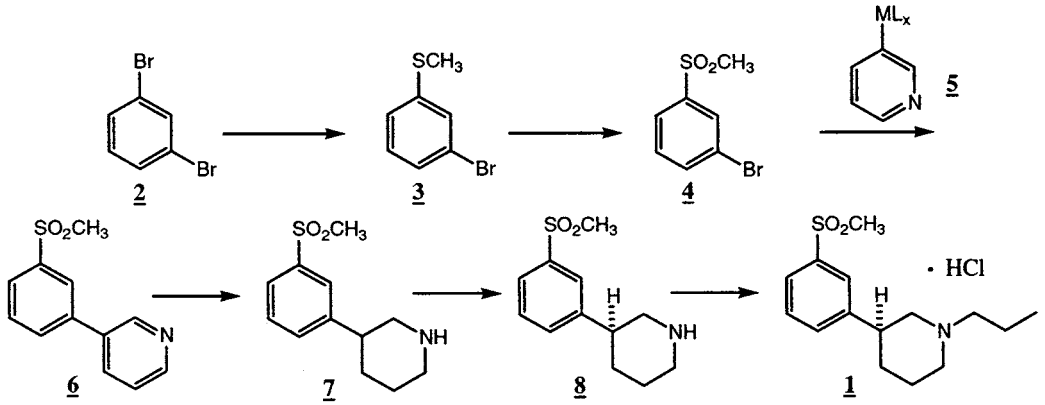
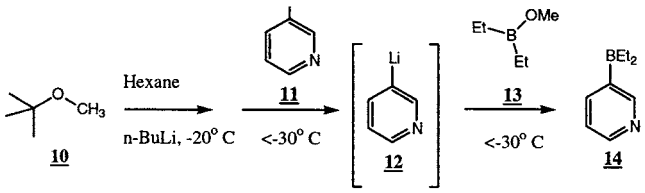
Scheme 1



The isolated yield of crystalline 3-bromomethylphenyl sulfone was 79.8%, corrected, on scale. Although this chemistry was certainly adequate for the preparation of the sulfone in quantity and was in fact used to prepare some 29 kg, it suffered from the extremely high cost of sodium thiomethylate, and this methyl sulfone preparation was supplanted during our second, larger pilot-plant campaign with material made by a commercial supplier using alternative technology.

Much effort went into the development of a scalable procedure for the generation of kilogram quantities of a 3-metallopyridine to be used in a transition metal-catalyzed cross-coupling reaction to produce the desired carbon framework. 3-Pyridyllithium has been known[3] for many years. Gilman had generated it in diethyl ether or petroleum ether by a host of halogen−metal exchange procedures at −20 to 0 °C, but only in modest yield.[3] He suggested that the earlier failures[4] of these methods could be attributed to the higher temperatures at which the reactions were run, which allowed the pyridyllithium as it was formed to react further with reaction byproducts and substrate. Early experiments in the Dow laboratories had demonstrated an apparent method to stabilize 3-pyridyllithium. If the species was generated cold in predominately hydrocarbon solvent with a small amount of diethyl ether present, a thick green-gray slurry could be obtained. Although never characterized, this precipitate is thought to be an ether solvate of an agglomerated anionic pyridine species. It could be converted to diethyl-3-pyridyl borane on reaction with commercially available diethylmethoxy borane (DEMB), but the reaction was somewhat capricious even on modest scale. However, when one substitutes methyl *tert*-butyl ether for diethyl ether at a 1.3−1.7 molar ratio relative to 3-bromopyridine and pays very careful attention to reaction temperature, running cryogenically at −40 to −50 °C, the reaction is very well behaved. In fact, we determined during our development work that the product of the metal−halogen exchange was stable for at least 7 h at −45 °C, and no yield erosion was observed in the generation of the transmetalated product. This was a very significant finding since the initial charge of *n*-butyllithium to the ether-containing hexane solvent is exothermic and both the lithium−halogen exchange and the transmetalation reaction are very energetic. With the generally inefficient cooling that one sees on scale, and our confirmation of Gilman's observation of the thermal lability of 3-pyridyllithium, it was clear that we would require extended reaction times to run the process within these strict temperature requirements. We charged *n*-butyllithium to the hexane/MTBE mixture at −20 °C, cooled the mixture, and slowly added the 3-bromopyridine, maintaining the temperature below −40 °C. Under these conditions, the metalated species is completely insoluble and precipitated as it was formed, thus protecting it from further reaction. The DEMB was then added, keeping the temperature below −30 °C. The still heterogeneous reaction mixture was quenched with acetic acid and MeOH/H_2O. A solution briefly ensued from which the desired product precipitated on stirring. Isolation at this stage is ill-advised, however, since the solid product is contaminated with ca. 20 wt % of salts. Instead, the reaction mixture is distilled to one-half volume under vacuum and then partitioned between methylene chloride and H_2O. Finally, the CH_2Cl_2 is removed in vacuo and replaced with IPA from which the product precipitates as a colorless solid. This process provided reproducible yields in the 85% range on up to 175-kg input. Although suffering from the need for a cryogenic setup, the chemistry is robust, reproducible, and easily carried out on any scale. Our process is depicted in Scheme 2. Recently, the Merck group has reported a similar method.[5,6]

Scheme 2



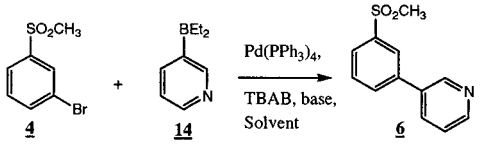
The key Suzuki coupling reaction, shown in Scheme 3 performed well on the pyridyl borane and the bromosulfone from the outset. As had been demonstrated previously, we initially chose to use a polar variant, employing water and THF as solvent, sodium hydroxide as base, and tetrakis-

(4) Banner, I. M.S. Thesis, Iowa State College, Ames, Iowa, 1939.

(5) Cai, D.; Larsen, R. D.; Reider, P. J. *Tetrahedron Lett.* **2002**, 4285.

(6) Li, W.; Nelson, D. P.; Jensen, M. S.; Hoerrner, R. S.; Cai, D.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **2002**, *67*, 5394.

Scheme 3



(triphenylphosphine) palladium (tetrakis) as catalyst.[2] We first examined the use of other palladium sources, but heterogeneuous palladium was ineffective for this reaction. Reactions were conducted at 65−67 °C for 8−12 h. For efficient conversions a phase transfer catalyst was also required; we used tetrabutylammonium bromide (TBAB) at the extremely high loading of 35 mol %, and although this contributed little to the cost, it interfered with the isolation of clean coupled product (vide supra). We initially examined tetrakis loading, as the described procedure used 5 mol % of the palladium catalyst, and reported a yield of 84%. A catalyst turnover rate of only 20 would be unacceptable on scale, given both the high cost of tetrakis and its high molecular weight (1155.6 g/mol). We successfully decreased catalyst loading with no yield erosion to 3.6 mol %, but unfortunately, this was the lower limit for a successful conversion. At this catalyst loading, though, a 1000 mol coupling to produce 240 kg of product would still require some 40 kg of catalyst. Nevertheless, with a robust procedure in hand that was operationally straightforward and provided reproducible yields in the 80% range, the process was readied for eventual scale-up.

As noted, our lab runs were plagued in the early going by product quality issues.

Although the product could be directly crystallized after an aqueous partition, given the high TBAB requirement, product isolated in this fashion tended to be contaminated with varying amounts of the phase-transfer catalyst. This problem, though, was fairly easily solved with a simple acid−base extractive workup, and the clean hydrochloride salt could be precipitated from 10% methanolic ethyl acetate by the addition of 1.0 equiv of concentrated hydrochloric acid. Despite the shortcoming of higher than desirable tetrakis loading, this workup was used together with the previously described reaction conditions on scales ranging up to 225 kg of bromosulfone, affording reproducible yields (typically in the 80% range) of 98+% quality biaryl hydrochloride.

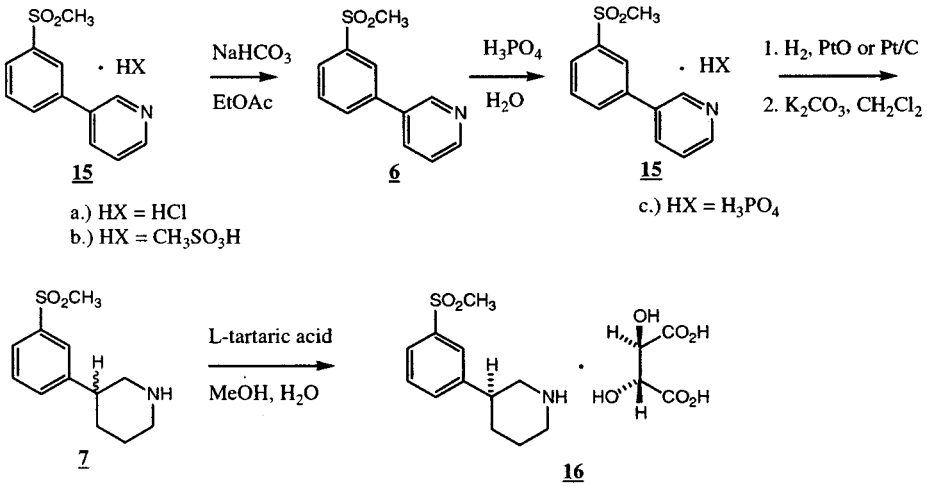
However, we were compelled by cost issues to continue to examine variants of the Suzuki coupling and, in conjunction with another project also featuring a palladium-catalyzed cross-coupling reaction, are pleased to report that the tetrakis catalyst-loading issue has been, for the most part, resolved. Thus, if the cross-coupling reaction is conducted under nonpolar conditions, employing toluene as solvent in a two-phase system with water and employing carbonate as the base, it is possible to significantly reduce catalyst loading, not only of the tetrakis but also of the TBAB. The reactions were run at about 20 °C higher temperature (83−87 °C) than that of the polar procedure, but tetrakis loading was optimized at 0.7 mol % and TBAB at 9 mol %. We believe that these nonpolar conditions offer some protection to the catalyst and the organic reagents, which can be safely sequestered away in the toluene phase. In the THF procedure, doubtless the environment is more hostile with stronger base and the ready miscibility of water with the solvent. A nonpolar Suzuki variant has since been reported.[7] Another significant change that produced this, our optimized final procedure, was to use methane sulfonic acid for the salt formation in the isolation of the product, allowing the precipitation to be conducted under essentially anhydrous conditions. This final process was scaled directly from laboratory glassware to 215 kg input of bromosulfone, providing reproducible yields of 92−96% of +98% quality product.

We had initially hoped that isolation of the methane sulfonate salt would have another operational advantage as well. The next step in the process is a selective catalytic hydrogenation of the pyridine ring under pressure. We knew that stainless steel autoclaves would not be compatible with chloride counterion but thought that methane sulfonate would be acceptable. During development in Paar bottles, initial use of Adam's catalyst (PtO_2) followed by Pt/C cleanly reduced the pyridine ring, activated as a salt; however, relatively high temperatures were required (60−100 °C), depending on the catalyst employed. We examined reduction of the methane sulfonate salt of the biaryl and were quite surprised to determine that methane sulfonic acid, under the somewhat forcing conditions required for this hydrogenation, attacked 316 stainless, as determined by iron content of the product solution from a small autoclave run. *We would therefore strongly advise against the reduction of methane sulfonate salts in stainless steel autoclaves.*

Phosphate counterion is compatible with stainless steel autoclaves, although its use required the addition of several unit operations to the process. Thus, the Suzuki product could be converted to the free base form, extracted into ethyl acetate, and then extracted into a dilute aqueous phosphoric acid solution as feedstock for the reduction. Unfortunately, all attempts to crystallize the phosphate salt of the Suzuki product met with failure, and this somewhat circuitous route had to be employed. In the workup, a dilute phosphoric acid solution of the secondary amine is neutralized and the product extracted into methylene chloride. This extraction is very tedious as the amine shows appreciable water solubility below pH 12. However, at the high pH, di- and tri-basic sodium phosphate begin to precipitate. To avoid the phosphate precipitation problem, it is critically important to neutralize with *potassium, and not sodium* hydroxide. The reduction was then telescoped into the classical resolution, which was run as originally described.[1,2] It provided reasonably good upgrading in acceptable recovery. Thus, without isolation, the secondary amine phosphate was converted to the free base and reacted with L-tartaric acid in aqueous methanol. Crystallization provided directly the desired diastereomeric tartrate salt between 65% and 81% de, as measured by chiral HPLC on the free base. From the lower de's it required two recrystallizations to achieve ca. 95% de, while from the higher initial de's only one recrystallization sufficed; however, either way the yield is 80−85% of the possible 50%, i.e., 40−43% from Suzuki product hydrochloride **6**, as overall recovery and quality appeared

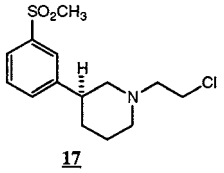
(7) Paetzgold, E.; Oehme, G. *J. Mol. Catal. A: Chem.* **2000**, 69.

Scheme 4



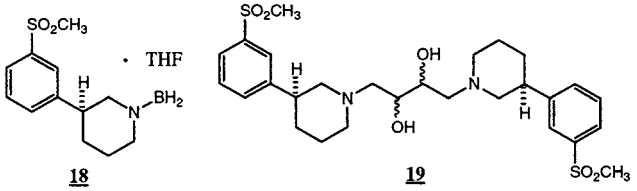
not to be interdependent. The complete series of transformations yielding resolved penultimate secondary amine from Suzuki product is depicted below in Scheme 4.

Although the Sonneson group claimed to have successfully introduced the propyl group via a variant of the procedure first described by Maryanoff,[8] using triacetoxyborohydride and propionaldehyde in ethylene dichloride, on scale we observed under the reaction conditions that significant amounts of chloroethylated product **17** was obtained as well, with the solvent apparently competing effectively with propionaldehyde for substrate.



17

However, in conjunction with some other work, we had occasion to employ the Gribble procedure[9] as a viable option for pilot-scale batch reductive aminations. It is, in fact, an excellent method for this chemistry. Cyanoborohydride procedures are frequently used on lab scale for these transformations, but the resultant cyanide cleanup problems in batch reactors are problematic. The Gribble procedure, which is postulated to generate an aldehyde or aldehyde equivalent in situ by the action of sodium borohydride on a carboxylic acid, is both clean and high-yielding. It may be run both neat, with the carboxylic acid as solvent, or with THF as cosolvent. Thus, our amine free base substrate **8** in THF was treated with an excess of propionic acid, and an excess of sodium borohydride was added portionwise via shot loader at 0 to −10 °C. The mixture is heated to a gentle reflux to complete the reaction. *It is of critical importance to conduct the borohydride addition portionwise.* We isolated and characterized borane adduct **18** as a THF solvate from laboratory runs in which the borohydride addition was conducted too quickly. This impurity proved extremely difficult to separate from final product, and minimization of its formation was tantamount to the success of the project. Likewise, it became again necessary to free the substrate from the tartaric acid counterion prior to conducting the procedure since in the presence of tartaric acid unacceptable quantities of the dimeric structure **19** ensue.



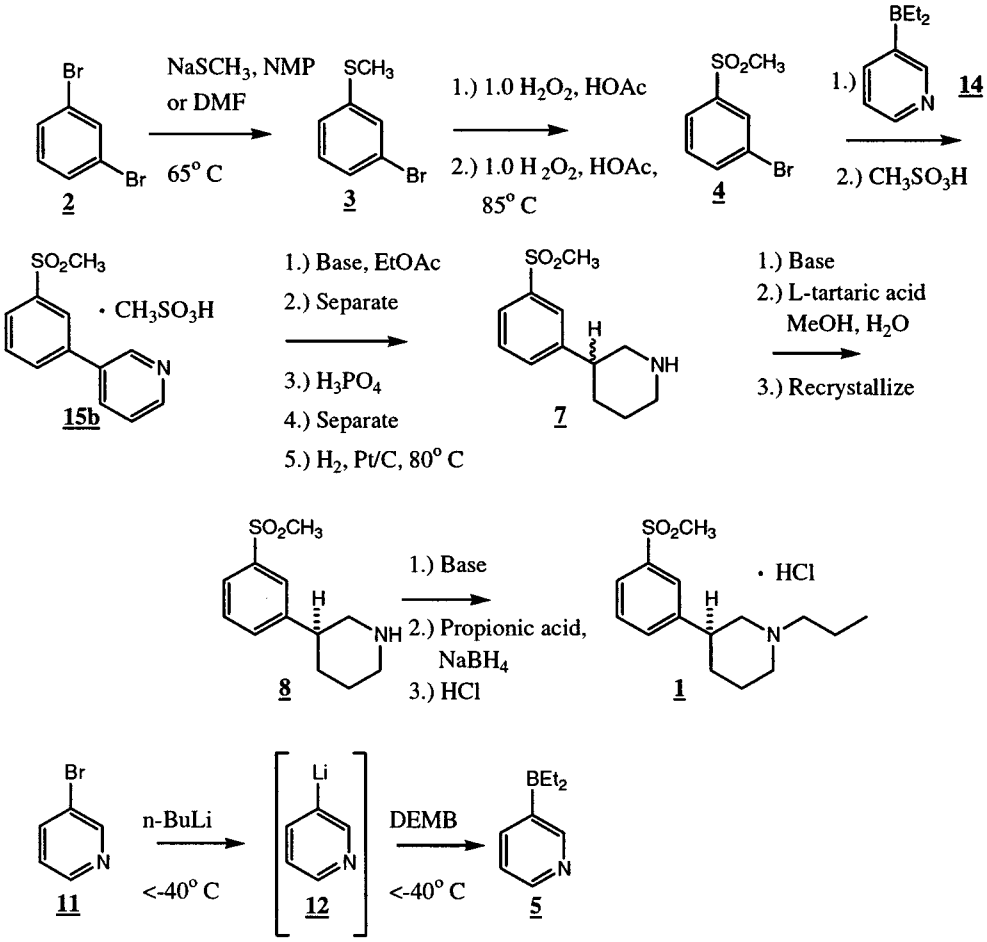
Originally, we had isolated OSU 6162 free base and in a separate step it was converted to the salt. The final procedure that we chose for the pilot-plant runs, however, telescoped the free base generation with the salt formation. Thus, after the propylation workup, which involved simple aqueous partition, the solvent was swapped for an EtOAc/EtOH mixture, and an equivalent of anhydrous HCl in EtOAc was added. The pure HCl salt begins to precipitate midway through the addition. It is interesting to note that secondary amine tartrate of only ca. 93% de could be carried on to final OSU 6162 on the order of 99% ee, demonstrating that enantiomeric enrichment accompanies the final crystallization. It was, however, not possible to obtain usable second crops. The overall yield for this final set of transformations from the secondary amine free base is in the 70−75% range.

Conclusions

A relatively efficient method of preparation of the clinical candidate OSU 6162 has been demonstrated on scale. It involves as the key construction a soluble palladium-catalyzed Suzuki coupling. An efficient method of generating and transmetallating unstable 3-pyridyllithium is also described. The overall final process is shown in Scheme 5. It provides clinical quality OSU 6162 in overall 33−47% yield from 1,3-dibromobenzene, or in its final form, in 46−61% yield, 3-bromomethyl sulfone, taking into account the required classical resolution. Although long in unit operations, the

(8) Abdel-Magid, A. F.; Maryanoff, C. A.; Carson, K. G. *Tetrahedron Lett.* **1990**, 5595.
(9) Gribble, G. W.; Jasinski, J. M.; Pelicone, J. T.; Panetta, J. A. *Synthesis* **1978**, 776.

Scheme 5



process is straightforward and provides workable yields of high-quality material. It supplied over 35 kg of bulk drug in one small and one large pilot-plant campaign in just over a year's elapsed time.

Experimental Section

Reagents were purchased from commercial suppliers and used without purification. ^{1}H NMR spectra were recorded at 300 or 400 MHz on Brucker instruments in $CDCl_3$, D_2O, or DMSO-d_6, and values are reported as parts per million downfield. ^{13}C NMR spectra were recorded at 100 MHz on a Brucker instrument in $CDCl_3$ or D_2O, and values are reported as parts per million downfield.

3-Bromothioanisole (3). A clean, dry, 400-L stainless steel reactor under an inert atmosphere was charged with 40.0 kg (170 mol) of 1,3-dibromobenzene and 54 L of *N*-methylpyrrolidinone (NMP). Solid sodium thiomethylate (12.0 kg, 171 mol) was then added via shot loader in 1.0-kg portions over ca. 2 h, keeping the temperature below 50 °C. The reaction mixture was heated to 64 °C for 2 h, at which time GC analysis (see Table 1) indicated that it was about 90% complete. It was then cooled to 20 °C and quenched by the addition of 4.88 kg (61 mol) of 50% NaOH and 56 L of water. After 10 min of stirring, the reaction mixture was diluted with 66 kg of hexane, and the phases were separated. The organic phase was washed with 50 L of water and concentrated under vacuum to ca. 37 L. GC analysis[1] indicated the product to be of ca. 90% quality. The methyl-3-bromothioanisole was used directly in the next step.

Table 1

GC procedures	Samples are quenched into aqueous NaOH and EtOAc. 1.0 μL of the organic phase is injected.
column:	15 M DB-1
temperature:	50 °C, 10 °C/min program
detection:	FID
retention times:	dibromobenzene - 6.5 min 3-bromothioanisole - 9.1 min 1,3-(thiomethyl)bezene - 11.3 min

Methyl-3-bromophenyl Sulfone (4). A clean, dry, 400-L stainless steel reactor under an inert atmosphere was charged with 37 kg (164 mol corrected) of crude 3- bromothioanisole and 166 kg of glacial acetic acid. The mixture was heated to 32 °C and treated cautiously over 45 min with 19.9 kg (161 mol) of 27.5% hydrogen peroxide. An additional 19.9 kg (161 mol) of 27.5% hydrogen peroxide was then added, and the reaction was heated to 92 °C for 18 h. It was cooled, and a sample was analyzed by TLC (see Table 2) for sulfone and sulfoxide content, and by starch iodide paper for the presence of peroxides (none detected). The reaction mixture was then concentrated under reduced pressure to ca. 60 L and azeotroped with 132 kg of isopropyl alcohol (IPA). An additional 70 kg of IPA was charged, and the reaction mixture was heated to 85 °C to dissolve the solids. It was then cooled to 16 °C and stirred for 8 h, and the product

Table 2

TLC conditions:	reaction mixtures are applied directly to the plate and blown dry under a stream of nitrogen
plate:	EM silica gel 60 F254
solvent system:	1:1 EtOAc:heptane
visualization:	UV
R_f values:	sulfone (**4**) - 0.2 intermediate sulfoxide (**9**) - 0.4 starting material (**3**) - 1.0

Table 3

TLC conditions:	reaction mixtures are applied directly to the plate, solids are dissolved in EtOAc and applied, and then blown dry under a stream of nitrogen
plate:	EM silica gel 60 F254
solvent system:	1:1 EtOAc:heptane
visualization:	UV
R_f values:	Suzuki reagent (**14**) - 0.5

was filtered and washed with fresh IPA. The product was dried under a stream of 40 °C nitrogen to 28.65 kg (122 mol, 71.8% yield for two steps). ^{1}H NMR ($CDCl_3$): 3.07 (3H, s), 7.47 (1H, t), 7.79 (1H, d), 7.89 (1H, d), 8.10 (1H, m) ppm, ^{13}C NMR ($CDCl_3$): 44.49, 123.39, 125.97, 130.45, 130.95, 136.83, 142.41 ppm.

Diethyl-3-pyridyl borane (14). A clean, dry, 4000-L glass steel reactor under an inert atmosphere was charged with 156 kg of methyl-*tert*-butyl ether (MTBE) and 815 kg of hexane. It was then cooled to −28 °C, and 289 kg (1111 mol) of 24.2 mol % *n*-butyllithium in hexane was added. The reaction mixture was further cooled to −44 °C, and 175 kg (1107 mol) of 3-bromopyridine in 97 L of hexane was added over 3 h, keeping the temperature below −40 °C. With continued cooling, 119 kg (1195 mol) of diethylmethoxyborane (DEMB) was added to the thick slurry over 8 h, keeping the temperature below −32 °C. After 0.5 h of stirring, the thick reaction mixture was quenched by the addition of 66.2 kg (1106 mol) of glacial acetic acid, and 97 kg MeOH and 97 L of H_2O were added. The solution was stirred for 2 h at 11−15 °C at which time precipitation was evident. It was then carefully concentrated under reduced pressure to ca. 700 L and diluted with 1706 L of methylene chloride and 1116 L of water. The phases were separated, and the aqueous phase was extracted with an additional 613 L of methylene chloride. The combined organic phase was concentrated under reduced pressure to ca. 500 L. A 677-L portion of IPA was then added and the mixture again concentrated to ca. 500 L under reduced pressure. It was cooled to −25 °C, stirred for 2 h, and filtered. The product solids were washed with fresh, cold IPA and dried at 40 °C under a stream of nitrogen. The yield was 122.4 kg, 75%. Material was single zone by TLC (see Table 3). ^{1}HNMR ($CDCl_3$): 0.51 (6H, t), 0.66 (4H, m), 7.23 (1H, t), 7.58 (1H, s), 7.72 (1H, d), 8.01(1H, d) ppm. ^{13}C NMR ($CDCl_3$): 9.20 (m), 14.45 (bs), 123.44, 140.85, 143.81, 149.13, 155.27 (bs) ppm.

Methyl-3-(3-pyridinyl)benzenesulfone Hydrochloride, Polar Variant (15a). A clean, dry 400-L Hastalloy reactor under an inert atmosphere was charged with 14.5 kg (61.7 mol) of methyl-3-bromophenyl sulfone, 7.26 kg (21.8 mol)

Table 4

TLC conditions:	Reaction mixtures are applied directly to the plate and blown dry under a stream of nitrogen. Solids are dissolved in CH_2Cl_2 and the solution applied to the plate.
plate:	EM silica gel 60 F254
solvent system:	90:9:1 = CH_2Cl_2:MeOH:NH_4OH
visualization:	UV
R_f values:	product (**6**) - 0.5

of tetra-*n*-butylammonium bromide (TBAB), 9.13 kg (62.1 mol) diethyl-3-pyridyl borane, and 103 kg of tetrahydrofuran (THF). The slurry was stirred for 20 min and cooled to 1 °C, and 12.75 kg (159 mol) of 50% NaOH was added. Finally, 2.9 kg (2.47 mol) of tetrakis(triphenylphosphine) palladium was added portionwise, and the reaction mixture was stirred for 1 h at 4 °C. The reaction mixture was heated to 66 °C and stirred for 2 h, at which time TLC analysis (see Table 4) indicated that the reaction was complete. The mixture was cooled to 17 °C and stirred for 14 h, and the THF was distillatively replaced with 110 L of EtOAc. The reaction mixture was carefully acidified to ca. pH = 1 with 80 L of 10% aqueous HCl, and the phases were separated. The organic phase was extracted with an additional 35 kg of 10% HCl. The combined aqueous phase was extracted with 40 L of EtOAc, and the combined organic phase was labeled and reserved for recovery of soluble palladium wastes. The aqueous phase was then treated with 65 L of EtOAc, and the pH was adjusted to 7−8 by the careful addition of 23.5 kg of 50% NaOH. The phases were separated, and the aqueous phase was extracted two more times with 65-L portions of EtOAc. Since some product remained in the aqueous phase, the pH was readjusted to 11−12 by the addition of another 1.0 kg of 50% NaOH, and another extraction with an additional 50 L of EtOAc was conducted. The organic extracts were then concentrated under reduced pressure to ca. 40 L, diluted with an additional 40 L of EtOAc and 8 L of MeOH, cooled to 10 °C, and treated with 6.00 kg (57.5 mol) of 35% HCl. The slurry was then concentrated to 20 L under reduced pressure and stirred a total of 18 h at −4 °C. The product was isolated by filtration. The crystals were washed with cold EtOAc, and the cake was dried under a stream of warm nitrogen. Yield was 11.44 kg (89.6%).

Methyl-3-(3-pyridinyl)benzenesulfone Methanesulfonate, Nonpolar Variant (15b). A clean, dry 4000-L glass-lined steel reactor under an inert atmosphere was charged with 215 kg (915 mol) of methyl-3-bromophenyl sulfone, 26.2 kg (78.8 mol) of tetra-*n*-butylammonium bromide (TBAB), 134 kg (912 mol) of diethyl-3-pyridyl borane, and 1204 L of toluene. The slurry was stirred for 20 min, and 798 kg (2714 mol) of 47% aqueous potassium carbonate diluted with 430 L of water was added. Finally, a slurry of 7.1 kg (6.1 mol) of tetrakis(triphenylphosphine) palladium in 100 L of toluene was added. The reaction mixture was heated to 84 °C and stirred for 12 h at which time HPLC analysis (see Table 5 indicated that the reaction was complete. It was cooled to 21 °C, stirred for 3 h, and filtered. The phases were separated. The organic phase was extracted first with 2200 L of 3.7% aqueous hydrochloric acid and then

Table 5

HPLC conditions:	One drop of reaction mixture is added to 5 mL of acetonitrile.
column:	Luna C-18 (4.6 mm × 250 mm)
injection volume:	10 μL
mobile phase:	60:40 = acetonitrile:0.1 M ammonium acetate
flow rate:	01.0 mL/min
detector:	229 nm
retention times:	sulfone (**4**) - ca. 6.0 min product (**6**) - ca. 3.7 min

Table 6

TLC conditions:	Reaction mixtures are applied directly to the plate and blown dry under a stream of nitrogen. Solids are dissolved in CH_2Cl_2 and the solution applied to the plate.
plate:	EM Silica gel 60 F254
solvent system:	90:9:1= CH_2Cl_2:MeOH:NH_4OH
visualization:	UV and I_2
R_f values:	product (**7**) - 0.2 starting material (**6**) - 0.5

re-extracted with an additional 630 L of 3.7% aqueous hydrochloric acid. The combined aqueous extracts were treated with 860 L of methylene chloride and cooled as the pH was adjusted to 12 with 50% aqueous sodium hydroxide. The phases were separated, and the aqueous phase was extracted with two more 860-L portions of methylene chloride. The combined organic phase was treated with 200 L of ethyl acetate, transferred to a clean, dry 4000-L glass-lined steel tank and concentrated under reduced pressure to 400 L of final volume. Ethyl acetate (1500 L) was added, and the mixture was then concentrated under reduced pressure to 900 L. Methanol (110 L) was added, and the solution was cooled to 7 °C and treated with 87.9 kg (916 mol) of methane sulfonic acid. The slurry was stirred for 17 h at 5 °C and filtered, and the cake was rinsed with 120 L of cold ethyl acetate. Drying with 40 °C nitrogen yielded 278.3 kg (92.5%). ^{13}C NMR ($CDCl_3$): 38.81, 43.65, 126.32, 127.96, 128.77, 131.37, 133.66, 135.52, 138.86, 140.13, 140.57, 140.90, 145.31 ppm.

Methyl-3-(3-piperdinyl)benzenesulfone Tartrate (16). A clean, dry 400-L glass reactor under an inert atmosphere was charged with 160 L of EtOAc and 12.3 kg (37.4 mol) of methyl-3-(3-pyridinyl)benzenesulfone hydrochloride. This was treated with 15.5 kg of sodium bicarbonate dissolved in 161 L of H_2O, and the phases were separated. The aqueous phase was extracted two more times with 80-L portions of EtOAc, and the combined organic phase was then extracted with 4 × 15 kg portions of 16.75% aqueous phosphoric acid. A clean, dry, inert 120-L stainless steel autoclave was charged with 2.91 kg of 5% Pt/C, and the phosphoric acid solution of Suzuki-coupled product from above was rinsed in with 5 L of 16.75% aqueous phosphoric acid. The mixture was hydrogenated at 98 °C under approximately 60 psi of H_2 for 18 h, at which time TLC analysis (see Table 6) indicated that the reaction was complete. The catalyst was filtered off, and the cake was washed with 5 × 20 L portions of warm, dilute phosphoric acid. The hydrogenate was charged to a clean, dry, 400-L glass-lined steel reactor under an inert atmosphere. Methylene chloride (28 L) was added,

Table 7

HPLC conditions:	A 6.2 mg sample of the tartrate is partitioned between 3 mL 1 N NaOH and 3 mL of CH_2Cl_2. The organic phase is concentrated under a stream of nitrogen and taken up in 3 mL of mobile phase for analysis.
column:	Chiracel OD-H (4.6 mm × 250 mm)
injection volume:	10 μL
mobile phase:	800:200:2 = heptane:ethanol:diethylamine
flow rate:	0.8 mL/min
detector:	267 nm
retention times:	desired enantiomer of (**8**) - ca. 13 min undesired enantiomer of (**8**) - ca. 15 min

and the mixture was cooled during the adjustment of the pH to between 12 and 13 with about 50 L of 50% *potassium* hydroxide. The phases were separated, and the aqueous phase was extracted with 2 × 25-L portions of methylene chloride. The combined organic phase was concentrated under reduced pressure to ca. 15 L. Methanol (87 L) was added, and the mixture was reconcentrated to ca. 15 L. This was treated with a solution of 6.05 kg (40.3 mol) of L-tartaric acid in 40 L of methanol. The volume was adjusted to 55 L, and the mixture was heated to 70 °C for 30 min. Water (23 L) was added, and the solution was cooled with stirring to 10 °C to induce crystallization. The slurry was stirred for 8 h, and the solids were isolated by filtration, washed with 10 L of 1:1 H_2O:MeOH, and dried under a steam of nitrogen at 40 °C. The yield was 7.0 kg of material, the free base component of which assayed at 67% ee (see Table 7). This lot was combined with a lot similarly prepared, and the 17.6 kg total of ca. 66% de methyl-3(3-piperdinyl)benzenesulfone tartrate was charged into a clean, dry, inert 400-L Hastalloy reactor. Methanol, (79 kg) and water (46 L) were then added, and the mixture was heated to 66 °C. After 30 min at this temperature, the solution was cooled to 62 °C and seeded. It was further cooled over a 3-h period to 10 °C, and the slurry was stirred for 17 h. The solids were filtered, washed with 15 kg of MeOH, and dried under a stream of warm nitrogen to 12.7 kg of material, the free base component of which assayed at 83.7% ee (see Table 7). The crude methyl-3(3-piperdinyl)benzenesulfone tartrate was recrystallized yet again from 68 kg of MeOH and 40 kg of H_2O, affording 9.73 kg of product, the free base component of which assayed at 93% ee (see Table 7). This material was successfully use-tested in the final propylation/salt formation prior to proceeding.

Methyl-3-(3-*N*-methylpiperdinyl)benzenesulfone, Hydrochloride (OSU 6162, 1). A clean, dry, 1200-L glass reactor under an inert atmosphere was charged with 18.0 kg (46.2 mol) of resolved (97% de by HPLC, see Table 7) methyl-3(3-piperdinyl)benzenesulfone tartrate and 150 L of methylene chloride. The mixture was cooled during the addition of 250 L of 3.3% aqueous NaOH, and the phases were separated. The aqueous phase was extracted with an additional 150 L of methylene chloride, and the combined organic phase was treated with 75 L of THF and concentrated to ca. 40 L. The concentrate was azeotroped in portions with 198 kg of THF to a final volume of ca. 40 L, and the volume was adjusted to 140 L with additional THF. The solution

Table 8

TLC conditions:	Reaction mixtures are quenched into saturated aqueous bicarbonate/EtOAc and the EtOAc phase spotted. Solids are dissolved in CH_2Cl_2, and the solution is applied to the plate.
plate:	EM silica gel 60 F254
solvent system:	90:9:1= CH_2Cl_2:MeOH:NH_4OH
visualization:	UV
R_f values:	starting material (**8**) - 0.3 product (**1**) - 0.6

was cooled to −5 °C and treated with 25.0 kg (338 mol) of propionic acid, and then 5.10 kg (135 mol) of $NaBH_4$ was added portionwise over 2 h via shot loader, keeping the temperature below −5 °C. The reaction mixture was warmed to 25 °C, stirred for 1 h, and heated to 63 °C. The temperature was maintained at 63 °C for 14 h at which time TLC analysis (see Table 8) indicated that the reaction was complete. The mixture was cooled to 20 °C, carefully quenched with 220 L of 8.5% aqueous sodium bicarbonate, after which 200 L of EtOAc was added. The phases were separated, and the organic phase was extracted sequentially with 100 L of 8.5% aqueous sodium bicarbonate, 90 L of water, and 160 L of saturated aqueous sodium chloride. The combined aqueous phase was back-washed with 2 × 120 L portions of EtOAc. The combined organic phase was concentrated to ca. 130 L and then azeotroped with an additional 100 L of EtOAc to a final volume of ca. 130 L. Anhydrous ethanol, 12 L, was added followed by 28.8 kg (50.8 mol) of a 6.9 wt % solution of anhydrous HCl in EtOAc. The resulting slurry was stirred at 10 °C for 1.5 h, and the crystalline product was isolated by filtration. The cake was washed with 10 L of EtOAc and dried under a stream of warm nitrogen, leaving clinical quality OSU 6162 (**1**), 10.45 kg (71.6% yield), which passed all specifications. Chiral HPLC assay (see Table 9) showed it to be >99% single enantiomer. ^{1}H NMR (DMSO-d_6): 0.90 (3H, t), 1.67−1.84 (3H, m), 1.94 (2H, bs), 2.08 (1H, q), 2.89−3.01 (3H, m), 3.17 (1H, q), 3.18 (3H, s), 3.38−3.68 (2H, m), 7.67 (2H, m), 7.85 (2H, m), 11.15 (1H, bs). ^{13}C NMR (DMSO-d_6): 11.40, 16.80, 22.64, 29.33, 39.51, 43.87, 51.39, 55.73, 58.18, 125.82, 126.10, 130.23, 132.87, 141.64, 143.37 ppm.

Table 9

HPLC conditions:	10 mg of the product is dissolved in 2 mL of ethanol, and 8 ml of hexane is added.
column:	CHIRALPACK AS (4.6 mm × 250 mm)
injection volume:	10 μL
mobile phase:	975:25:1 = hexane:methanol:diethylamine
flow rate:	0.6 mL/min
detector:	267 nm
retention times:	PNU-100010 (wrong enantiomer) - ca. 20 min OSU 6162 (**1**) - ca. 22 min

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