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Efficient Synthesis of a $GABA_A$ $\alpha_{2,3}$-Selective Allosteric Modulator via a Sequential Pd-Catalyzed Cross-Coupling Approach

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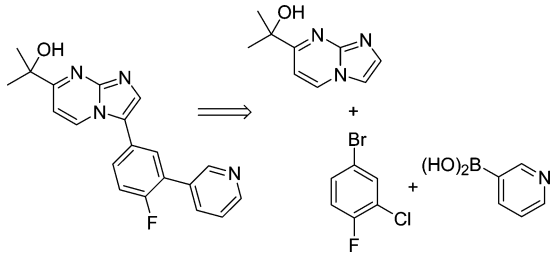
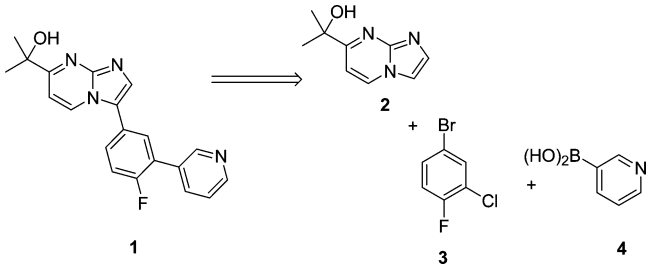


A practical synthesis of 2-[3-(4-fluoro-3-pyridin-3-yl-phenyl)-imidazo[1,2-*a*]pyrimidin-7-yl]-propan-2-ol (**1**), an oral $GABA_A$ $\alpha_{2/3}$-selective agonist, is described. The five-step process, which afforded **1** in 40% overall yield, included imidazopyrimidine **2** and pyridine boronic acid **4** as key fragments. The synthesis is highlighted by consecutive Pd-catalyzed coupling steps to assemble the final free base **1** in high yield and regioselectivity. A novel method for Pd removal in the final step is also described.

Introduction

GABA (γ-aminobutyric acid) is the major inhibitory neurotransmitter in the central nervous system. One of its sites of action is the $GABA_A$ receptor family. Within this family there are various subtypes that, when selectively allosterically modulated, elicit different responses. For example, selective agonists of the α_1 subtype elicit a sedative/muscle relaxation effect, while agonists of the α_2 and α_3 subtypes are believed to mediate anxiety.[2] Benzodiazepines such as diazepam bind nonselectively to the α_1, α_2, α_3, and α_5 subtypes with nanomolar affinity. While the benzodiazepines are widely used in the clinic, this nonselective binding leads to a variety of undesirable side effects.[3] Recently, workers at Merck identified **1**[4] as a potential α_2/α_3-selective agonist, and a synthetic route capable of supplying kilo-scale quantities was needed.[5]



The approach taken for the assembly of this molecule relies on Pd catalysis to form the two aryl−aryl bonds. The key to the success of this approach is the availability

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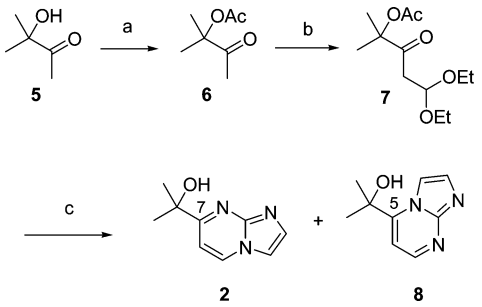
of 4-bromo-2-chloro-1-fluorobenzene (**3**). With the proper ligand choice, a Heck-type reaction of **3** with imidazopyrimidine **2** should be feasible to provide a coupled aryl chloride product. In the final step, another proper ligand choice would enable the coupling of the aryl chloride with 3-pyridine boronic acid (**4**) in a Suzuki reaction to provide the target compound **1**. The major challenges anticipated for this approach were the lack of availability of **4**, difficulty in removing residual Pd from this nitrogen-rich compound, and chemoselectivity in the coupling reactions. Herein we report a scalable, high-yielding process for the preparation of **1**. This work highlights the versatility of Pd-catalyzed coupling and also describes a novel method of removing residual Pd from the process stream.

Results

The required imidazopyrimidine intermediate **2** was prepared in three steps from commercially available starting materials. In particular, the availability of 2-aminoimidazole sulfate in bulk made this strategy, which is based on literature precedent,[6] attractive. The alcohol function of 3-hydroxy-3-methyl-2-butanone (**5**) was protected as an acetate in 96% yield using standard conditions. Attempts to use bulkier protecting groups (trialkyl silyl or benzoate) were less successful. One-carbon homologation of the resulting methyl ketone **6** to provide the β-ketoacetal **7** was accomplished by treating triethyl orthoformate with boron trifluoride etherate at −65 °C. The resulting complex was warmed to 0 °C and again cooled to −65 °C, and the methyl ketone **6** was then introduced followed by the diisopropylethylamine.[7] Following an aqueous workup, **7** was isolated as a crude oil and used directly in the next step. To form the imidazopyrimidine ring system, 2-aminoimidazole sulfate was treated with 2 equiv of NaOMe followed by the β-ketoacetal **7**. It has been previously reported that the regioselectivity of this type of ring formation is strongly influenced by pH.[6a] High pH promotes formation of the 7-substituted isomer (**2**), while low pH promotes formation of the 5-substituted isomer (**8**). This trend held here, and using the excess NaOMe gave a 96:4 mixture of **2** and **8**. The isolation of **2** was key to success here, and a crystallization method was developed. The crude reaction mixture was adjusted to pH 6 with HCl/IPA, and the solvent was switched from ethanol to ethyl acetate. Under these conditions, imidazopyrimidine **2** crystallized and was isolated as a free-flowing solid. The undesired isomer **8** was completely rejected in the crystallization. The overall yield of the three-step process just described was 48−50% and provided **2** as a crystalline compound with excellent purity.

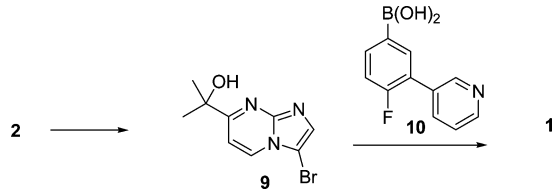
Heck-Type Coupling. The initial approach[4] to couple imidazopyrimidine **2** with the central aryl ring relied on a Suzuki coupling to form the carbon−carbon bond (Scheme 2). To accomplish this, **2** was first brominated with bromine in the presence of sodium acetate, potassium bromide, and methanol to provide the 3-bromo imidazopyrimidine **9** in excellent yield. When arylboronic acid **10** was used as the partner in the Suzuki coupling with **9**, the target compound **1** was the product. While the convergency of this approach was attractive, the preparation of the requisite arylboronic acid **10** was lengthy. In a new strategy (Scheme 3), the coupling reaction between **2** and 4-bromo-2-chloro-1-fluorobenzene (**3**) would directly install the aryl group.[8] The chloride of **11** could then be used as a handle to install the 3-pyridyl

SCHEME 1[a]

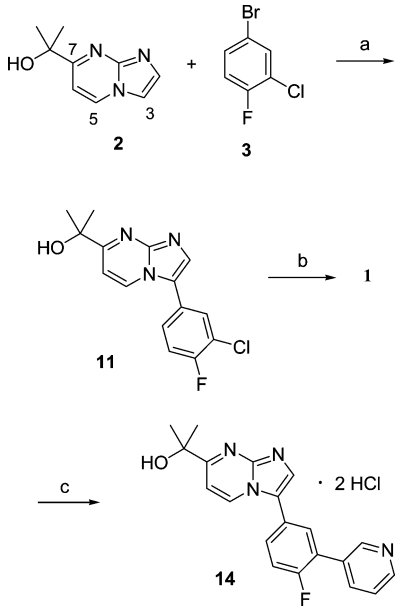


[a] Reagents and conditions: (a) Ac_2O, DMAP, Et_3N, CH_2Cl_2 (96%); (b) $HC(OEt)_3$, $BFOEt_2$, CH_2Cl_2; *i*-Pr_2-NEt (69%); (c) 2-aminoimidazole sulfate, EtOH, NaOMe (74%).

SCHEME 2



SCHEME 3[a]



[a] Reagents and conditions: (a) $Pd(OAc)_2$, Ph_3P, Cs_2CO_3, 1,4-dioxane, 90 °C, 12 h (88%); (b) **4**, $Pd(dba)_2$, *t*-Bu_3P, K_3PO_4, H_2O, 1,4-dioxane, 80 °C, 16 h (96%); (c) HCl, EtOH, Δ, then IPAC (88%).

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moiety. With this two-step approach, the bromination of **2** and the numerous functional group manipulations needed to prepare boronic acid **10** would be eliminated.

In the event, treatment of **2** with **3**, $Pd(OAc)_2$, Ph_3P, and Cs_2CO_3 in 1,4-dioxane at 90 °C gave, after an extractive workup, coupled product **11** as a crystalline compound in 88% isolated yield. No other cross-coupled products were observed. K_2CO_3 could also be used as base in this reaction; however, other bases such as Na_2CO_3, phosphates, and amines failed. Ph_3P proved to be superior to other common ligands, and DMF was an acceptable alternative solvent. The regiochemical outcome of this reaction can be rationalized solely on the electronic nature of **2**.[9] Nucleophiles typically attack the imidazopyrimidine at the 5- and 7-positions, while electrophiles react at the 3-position.

Suzuki Coupling. With **11** in hand, only installation of the 3-pyridyl moiety remained. Recently reported successes in the cross-coupling of aryl chlorides in the Suzuki reaction[10] led us to focus our efforts in that direction.[11] The main drawback to this approach was the lack of access to the requisite 3-pyridyl boronic acid (**4**). While **4** is commercially available, it is quite expensive and supplies are limited. These limitations led to the development of an improved method for preparing **4**.[12] When *n*-BuLi was added over 1 h to a −40 °C solution of 3-bromopyridine, triisopropylborate, toluene, and THF, **4** was the result. Following an extractive workup, **4** was isolated in 91% yield.[13]

Our initial attempts to couple **11** and **4** utilized anhydrous conditions[14] [Pd_2dba_3, P(*t*-Bu)$_3$, KF, THF], but to our surprise, no reaction occurred under these conditions. Anhydrous conditions with other typical solvents (i.e., 1,4-dioxane) and additives (i.e., Cs_2CO_3, CsF, K_3PO_4) also failed. The reaction between aryl chloride **11** and phenyl boronic acid, however, worked well under these conditions, so the 3-pyridyl boronic acid was viewed as the culprit.

Water was essential for the reaction.[11] In the first successful reaction, the coupling partners were subjected to Pd_2dba_3, *t*-Bu_3P, Na_2CO_3, THF, and water at 70 °C for 48 h. While these conditions provided **1**, a new challenge was revealed. Two products were formed. Both had the empirical formula of the desired product, and their ^{1}H and ^{13}C NMR spectra were similar. There was a distinct difference in their UV spectra. The major product exhibited λ_{max} at 230 and 240 nm, while the minor component had λ_{max} at 201, 228, and 312 nm. NOE experiments[15] unambiguously established that the two compounds differed in substitution on the imidazole ring (Figure 1). During the Suzuki reaction, a Dimroth rearrangement[16] had occurred (Scheme 4). Studying the reaction profile using HPLC revealed that the rearrangement occurred both at aryl chloride **11** and the coupled product **1** to yield aryl chloride **13** and coupled product **12**, respectively. The rearranged aryl chloride **13** subsequently underwent a Suzuki coupling to provide **12**. While the Dimroth rearrangement is typically a reversible process, in this system, substitution at the 2-position with an aryl group is thermodynamically favored to substitution at the 3-position. In compounds **13** and **12**, the aryl ring can be coplanar and thus conjugated with the imidazopyrimidine ring system. This is evidenced by the UV data cited above and also supported by molecular modeling calculations. This conjugation is not possible with compounds **11** and **1** due the steric interaction between the ortho hydrogens of the aryl ring and the 5-hydrogen of the pyrimidine ring. In fact, under basic aqueous conditions, **1** can be cleanly and completely converted to **12**. No rearrangement, however, was seen in the arylation reaction of **2** and **3** to produce **11**. This is due to the anhydrous conditions of the reaction. A plausible mechanism for this Dimroth rearrangement is shown in Figure 2.

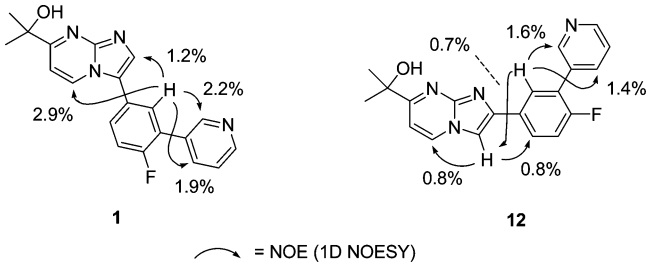
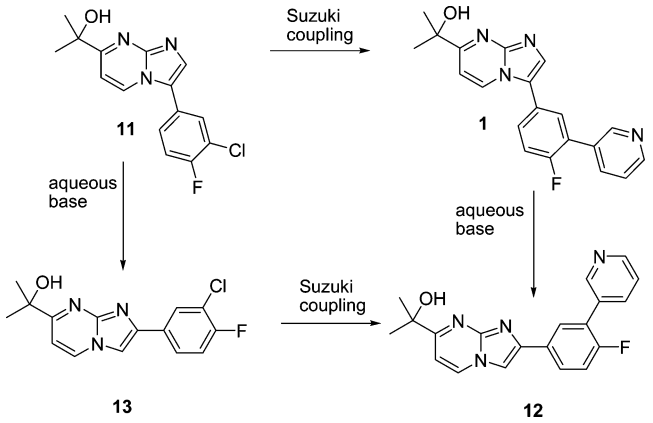


FIGURE 1. NOE studies of **1** and **12**.

SCHEME 4



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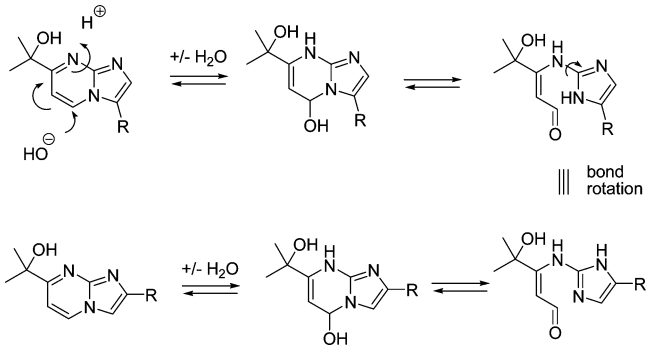

FIGURE 2. Plausible rearrangement mechanism.

Since the Suzuki coupling is the last bond-forming step of this synthesis, the appearance of this impurity presented a significant problem. Impurities introduced at the late stage of a drug synthesis can be difficult to reject, and the yield loss due to their formation should be avoided. A careful study of solvents, bases, reaction temperatures, and amounts of water was undertaken. Stability studies where **1** was warmed in a mixture of aqueous Cs_2CO_3 and an organic solvent indicated that the rearrangement is rapid in dimethylacetamide (DMAC), acetonitrile, and ethanol but much slower in 1,4-dioxane, THF, and 2-Me THF. When the latter solvents were used in the reaction, the product crystallized out of solution as the reaction progressed, presumably protecting the compound from rearrangement. Also, minimizing the amount of water was essential. With 1,4-dioxane, 25 vol % water was optimal. More water increased the rearrangement, and less water gave a sluggish reaction that did not go to completion. Under the optimized reaction conditions, a 102:1 mixture of **1** and **12** was formed. Following an extractive workup, **1** was isolated as a crystalline free base in 96% yield. Free base **1** was then dissolved in a hot solution of HCl and ethanol. Addition of isopropyl acetate (IPAC) and cooling provided crystalline bis-HCl salt **14**. During this sequence, the Dimroth rearrangement product **12** was completely rejected.

Pd Removal. While the current Pd-catalyzed cross-coupling route to **1** is efficient in forming the carbon−carbon bonds, it has a significant drawback. Residual Pd can be challenging to remove late in a synthesis, particularly when the target compound is rich in heteroatoms, as **1** is. Without any treatment to remove Pd, free base **1** was crystallized with ca. 4000 ppm Pd. The salt formation using this material gave bis-HCl salt **14** with ca. 2700 ppm Pd. The target Pd level was <10 ppm. Treatment of an acidic ethanolic solution of **1** with numerous commercially available Pd scavengers, including polymer-bound phosphines, thiols, sulfonates, carboxylates, and isothiouroniums, all failed to significantly lower the Pd levels. Treatment with *n*-Bu_3P[17] also failed. Darco G-60, an activated charcoal, gave good removal of Pd, but 100−200 wt %, based on **1**, was required. While this is a functional solution to the problem, we were concerned with variable product loss to the charcoal. During the workup of the Suzuki reaction, the acidic aqueous solution of **1** was clear yellow, leading us to suspect that the metal was Pd(II). With the hope that reducing the metal to Pd(0) would facilitate its removal, borane−trimethylamine complex was added to the acidic aqueous solution. This was rewarded with the formation of a black precipitate. Filtration through a nylon membrane with a 1 μm pore size removed the precipitated Pd. Addition of NaOH to the now colorless solution gave crystalline free base **1** that contained about 40 ppm Pd. This low-Pd free base was then taken up in HCl and ethanol, polished with Darco-G60, and then crystallized by addition of IPAC to provide **14** with less than 3 ppm Pd.

Conclusion

A new route to the GABA$_A$ $\alpha_{2,3}$-selective agonist **1** has been developed. A known route to the imidazopyrimidines was refined to provide **2** in good yield and excellent purity. A new two-step route from **2** to **1** that relies on Pd catalysis to form both aryl−aryl bonds was identified and developed. In this route, 4-bromo-2-chloro-1-fluorobenzene (**3**) was used, and the ligand choice in the Pd-catalyzed reactions exquisitely controlled the regioselectivity. This work also revealed an improved method for preparing 3-pyridyl boronic acid. Impurity formation via the Dimroth rearrangement was identified and suppressed, and a new method of removing Pd from the process stream was found. The overall yield from commercially available **5** to free base **1** was 40.5% with the longest linear sequence being five steps. The bis-HCl salt **14** was prepared in 35.6% overall yield from **5**.

Experimental Section

Acetic Acid 1,1-Dimethyl-2-oxo-propyl Ester (6). A mechanically stirred 3 L round-bottomed flask under an atmosphere of nitrogen was charged with 3-hydroxy-3-methyl-2-butanone (**5**, 100.0 g, 979 mmol) and CH_2Cl_2 (900 mL). A solution of acetic anhydride (92.4 mL, 979 mmol) and CH_2Cl_2 (50 mL) was added over 10 min, and the resulting solution was cooled to 10 °C. DMAP (5.98 g, 49.0 mmol) was added in one portion followed by Et_3N (205 mL, 1.47 mol) over 50 min while maintaining an internal temperature below 16 °C. After the addition, the mixture was aged for 16 h at room temperature. The resulting solution was poured onto MeOH (200 mL), and after 15 min, 2 N HCl (400 mL) was added. The phases were separated, and the organic phase was washed with water (500 mL) followed by saturated $NaHCO_3$ (500 mL) and then dried over Na_2SO_4. The solvent was removed in vacuo to provide **6** as a golden oil (132.5 g, 96.9 wt % pure, 95.8% isolated yield). The characterization data was identical to that reported previously.[18]

Acetic Acid 4,4-Diethoxy-1,1-dimethyl-2-oxo-butyl Ester (7). A 3 L round-bottomed flask fitted with a mechanical stirrer under an atmosphere of N_2 was charged with triethyl orthoformate (304 mL, 1.83 mol) and CH_2Cl_2 (1.30 L). The solution was cooled to −65 °C, and $BF_3{\cdot}OEt_2$ (255 mL, 2.01 mol) was added over 30 min to provide a yellow solution. After an additional 15 min, the cold bath was removed, and the flask contents were allowed to warm to 0 °C. After aging at 0 °C for 45 min, the mixture was cooled to −65 °C to provide a thin white slurry. A solution of methyl ketone **6** (131.55 g, 0.912 mol) and CH_2Cl_2 (100 mL) was added over 17 min. After the

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mixture was aged for 40 min at −65 °C, diisopropylethylamine (404 mL, 2.32 mol) was added over 30 min maintaining an internal temperature below −63 °C. After an additional 45 min at −65 °C, the mixture was warmed to room temperature over 45 min and aged at that temperature for 5 h. The reaction mixture was poured onto saturated aqueous $NaHCO_3$ (800 mL) and stirred for 15 min. The layers were partitioned, and the organic phase was washed with 1 M H_2SO_4 at 5 °C (2 × 800 mL) and water at 5 °C (2 × 800 mL) and then dried over Na_2SO_4. The solvent was removed in vacuo to provide **7** as an oil (270 g, 57 wt % pure, 69% isolated yield). An analytical sample was prepared by HPLC on a Zorbax C-8 preparative column with gradient elution from 30% ACN, 70% 0.1% H_3PO_4/H_2O to 70% ACN, 30% 0.1% H_3PO_4/H_2O over 20 min: ^{1}H NMR ($CDCl_3$, 400.13 MHz) δ 4.95 (t, J = 5.6 Hz, 1H), 3.69 (m, 2H), 3.53 (m, 2H), 2.79 (d, J = 5.6 Hz, 2H), 2.07 (s, 3H), 1.47 (s, 6H), 1.18 (t, J = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ 205.7, 170.4, 100.8, 83.7, 63.2, 41.4, 22.9, 21.1, 15.1.

2-Imidazo[1,2-*a*]pyrimidin-7-yl-propan-2-ol (2). A 3 L round-bottomed flask equipped with a mechanical stirrer, thermocouple and nitrogen inlet adaptor was charged with aminoimidazole sulfate (84.6 g, 641 mmol) and EtOH (900 mL, absolute). The resulting slurry was stirred at 24 °C, and solid NaOMe (69.2 g, 1.28 mol) was added in two portions over 15 min. After the addition was complete, the reaction temperature was 46 °C. The mixture was warmed to 60 °C and stirred for 45 min. After the aging, the mixture was cooled to 50 °C. A solution of crude acetal **7** (253.5 g of 57 wt % material, 611 mmol) and EtOH (150 mL, absolute) was added over 1 h, maintaining a reaction temperature of about 45 °C. After the addition, the reaction was maintained at 60 °C for 3 h and then cooled to 20 °C. The pH was adjusted to 5.9 by addition of aqueous HCl (5 N, 130 mL) in 10 mL portions. Darco G-60 (9.0 g) was added, and the slurry was stirred for 30 min. The solids were removed by filtration through a pad of Solka-floc, and the cake was rinsed with EtOH (200 mL). The filtrate was concentrated to ca. 200 mL via a rotovap; then, 300 mL of EtOAc was added, and the mixture was concentrated to ca. 300 mL. This was repeated three times, with crystals forming during the process. The final slurry was diluted to 600 mL with EtOAc and then cooled to 5 °C with stirring. The solids were collected on a frit, rinsed with cold EtOAc (50 mL), and dried overnight under vacuum at 22 °C to provide **2** (79 g, 99 wt % pure, 74% isolated yield) as a crystalline solid: mp 150−152 °C; ^{1}H NMR (MeOH-d_6, 400.13 MHz) δ 8.80 (d, J = 7.2 Hz, 1H), 7.77 (d, J = 1.6 Hz, 1H), 7.66 (d, J = 1.6 Hz, 1H), 7.39 (d, J = 7.2 Hz, 1H), 1.60 (s, 6H); ^{13}C NMR (MeOH-d_6, 100.61 MHz) δ 169.7, 147.8, 134.7, 132.8, 111.1, 105.4, 72.8, 28.4. Anal. Calcd for $C_9H_{11}N_3O$: C, 61.00; H, 6.26; N, 23.71. Found: C, 60.79; H, 6.30; N, 23.50.

2-[3-(3-Chloro-4-fluoro-phenyl)-imidazo[1,2-*a*]pyrimidin-7-yl]-propan-2-ol (11). A 500 mL round-bottomed flask equipped with a mechanical stirrer, thermocouple and nitrogen/vacuum inlet was charged with **2** (10.62 g, 60.0 mmol), 4-bromo-2-chloro-1-fluorobenzene (**3**, 8.00 mL, 66.0 mmol), palladium(II) acetate (270 mg, 1.20 mmol), triphenylphosphine (630 mg, 2.40 mmol), cesium carbonate (19.6 g, 60.2 mmol), and anhydrous 1,4-dioxane (120 mL). The slurry was degassed using five vacuum/nitrogen back-fill cycles, heated to 90 °C, and aged for 12 h. The mixture was cooled to 60 °C; then, water (150 mL) and EtOAc (150 mL) were added to the crude reaction mixture, and the slurry was stirred at 45 °C until all of the solids were dissolved. The layers were partitioned, and the aqueous phase was extracted again with EtOAc (50 mL). The organic phases were combined and extracted twice with 2 N HCl (100 mL and then 30 mL). The acidic aqueous phases were combined with EtOAc (250 mL), and NaOH (10.9 g, final pH = 10) was added slowly with stirring; the mixture was warmed to 65 °C to dissolve the solids. The phases were separated, and the organic phase was concentrated to ca. 200 mL to provide a slurry. IPAC (110 mL) was added, and the slurry was concentrated again to ca. 200 mL. The slurry was warmed to 90 °C and then cooled over several hours to 0 °C. The crystalline solids were collected on a frit, rinsed with IPAC/EtOAc (1:1), and air-dried to provide the coupled product **11** (16.19 g, 88%) as a cream-colored crystalline solid: mp 180−182 °C; ^{1}H NMR ($CDCl_3$, 400.25 MHz) δ 8.53 (d, J = 7.2 Hz, 1H), 7.86 (s, 1H), 7.59 (dd, J = 6.8, 2.0 Hz, 1H), 7.42 (m, 1H), 7.34 (m, 1H), 7.14 (d, J = 7.2 Hz, 1H), 1.63 (s, 6H); ^{13}C NMR ($CDCl_3$, 100.64 MHz) δ 167.8, 158.1 (d, J = 252.2 Hz), 148.0, 133.8, 131.4, 130.0, 127.8 (d, J = 7.2 Hz), 125.5 (d, J = 4.0 Hz), 122.4 (d, J = 18.5 Hz), 122.1, 117.8 (d, J = 20.9 Hz), 105.7, 72.5, 29.9. Anal. Calcd for $C_{15}H_{13}ClFN_3O$: C, 58.93; H, 4.29; N, 13.74. Found: C, 58.65; H, 4.11; N, 13.66.

2-[3-(4-Fluoro-3-pyridin-3-yl-phenyl)-imidazo[1,2-*a*]pyrimidin-7-yl]-propan-2-ol (1). A 5 L round-bottomed flask equipped with a mechanical stirrer, thermocouple, nitrogen/vacuum inlet adapter, and septum was charged with aryl chloride **11** (101.59 g, 333 mmol), 3-pyridine boronic acid (**4**, 42.98 g, 350 mmol), K_3PO_4 (111.69 g, 526 mmol), 1,4-dioxane (1.20 L), and water (406 mL). Cycling vacuum and then nitrogen three times degassed the stirred slurry. All solids dissolved on warming to 70 °C.

A 500 mL round-bottomed-flask equipped with a magnetic stir bar, thermocouple, nitrogen/vacuum inlet adapter, and septum was charged with $Pd(dba)_2$ (9.57 g, 16.7 mmol) and 1,4-dioxane (130 mL). The resulting solution was degassed as above, and then t-Bu_3P (49.8 mL of a 10 wt % solution in hexanes, 16.7 mmol) was added by syringe. The solution was degassed again and then warmed to 70 °C. The warm catalyst solution was cannulated to the 5 L flask, and the resulting mixture was stirred at 70 °C for 16 h. At the end of reaction most, of the product had crystallized out to provide a gray slurry. The reaction mixture was partitioned between 2 N HCl (1.8 L) and toluene (0.9 L). The clear yellow aqueous phase was transferred to a stirred 4 L Erlenmeyer flask with a nitrogen sweep, and borane trimethylamine complex (1.87 g) was added. After 90 min, the resulting black solids were removed by filtration through a 1.0 μm nylon filter. The filtrate was transferred to a mechanically stirred 5 L flask equipped with a pH probe. The pH was adjusted to 3.8 by slow addition of 50 wt % NaOH (ca. 130 mL). The mixture self-nucleated to provide a slurry. Additional 50 wt % NaOH (ca. 36 mL) was added over 30 min to pH 7.1 to provide a cream-colored slurry. The solids were collected on a frit, washed with water (250 mL), and air-dried to give the free base **1** as an off-white crystalline solid (117.38 g, 94.5 wt % pure, 95.6% isolated yield, 41 ppm Pd): mp 234−236 °C; ^{1}H NMR (DMSO-d_6, 399.87 MHz) δ 9.00 (d, J = 7.2 Hz, 1H), 8.85 (bs, 1H), 8.60 (dd, J = 4.8, 1.6 Hz, 1H), 8.06 (m, 1H), 7.92 (s, 1H), 7.87 (dd, J = 7.2, 2.4 Hz, 1H), 7.74 (m, 1H), 7.76−7.68 (om, 2H), 7.37 (d, J = 7.2 Hz, 1H), 5.49 (s, 1H), 1.47 (s, 6H); ^{13}C NMR (DMSO-d_6, 100.55 MHz) δ 169.6, 159.3 (d, J = 248.2 Hz), 149.9 (d, J = 3.2 Hz), 149.6, 148.5, 137.0 (d, J = 3.2 Hz), 134.0, 133.5, 130.9, 130.3 (d, J = 3.2 Hz), 130.0 (d, J = 8.0 Hz), 126.6 (d, J = 14.5 Hz), 126.1 (d, J = 4.0 Hz), 124.1, 122.7, 117.7 (d, J = 22.5 Hz), 106.3, 73.0, 30.3. Anal. Calcd for $C_{20}H_{17}FN_4O$: C, 68.95; H, 4.92; N, 16.08. Found: C, 68.55; H, 4.84; N, 15.90.

2-[3-(4-Fluoro-3-pyridin-3-yl-phenyl)-imidazo[1,2-*a*]pyrimidin-7-yl]-propan-2-ol Dihydrogen Chloride Salt (14). A magnetically stirred, 2 L, three-necked, round-bottomed flask equipped with a condenser, thermocouple, and drying tube was charged with free base **1** (25.00 g, 71.8 mmol) and EtOH (950 mL). The suspension was warmed to 75 °C, then HCl (47 mL of a 4.6 M solution in IPA) was added to provide a clear solution. Powdered Darco G-60 (2.50 g) was added and the mixture refluxed for 2 h. The suspension was cooled to 60 °C, and the solids were removed by filtration through a pad of Solka-floc. The resulting clear solution was transferred to a mechanically stirred 3 L round-bottomed flask equipped with a reflux condenser. The solution was warmed to 75 °C, and IPAC (1.00 L) was added. During the IPAC addition, the solution self-nucleated to provide a white suspension, which was cooled over several hours to room temperature. The solids

were collected on a frit, rinsed with 1:1 EtOH/IPAC (100 mL), and then dried in a 60 °C vacuum oven to provide the bis-HCl salt **14** as colorless crystals (26.76 g, 88%, <3 ppm Pd, <30 ppm P, <10 ppm B): mp 241−250 °C; ^{1}H NMR (CD_3OD, 400.13 MHz) δ 9.32 (m, 1H), 9.30 (d, J = 7.2 Hz, 1H), 9.02 (m, 1H), 8.97 (m, 1H), 8.38 (s, 1H), 8.28 (m, 1H), 8.18 (dd, J = 7.2, 2.0 Hz, 1H), 8.03 (d, J = 7.2 Hz, 1H), 7.99 (m, 1H), 7.68 (dd, J = 10.4, 8.4 Hz, 1H), 1.67 (s, 6H); ^{13}C NMR (CD_3OD, 100.61 MHz) δ 178.4, 160.5 (d, J = 254.0 Hz), 146.9 (d, J = 3.4 Hz), 143.5, 141.4 (d, J = 4.0 Hz), 140.7, 135.8, 134.4, 133.3 (d, J = 9.4 Hz), 131.9 (d, J = 2.4 Hz), 127.5, 124.3, 123.1 (d, J = 13.6 Hz), 122.4 (d, J = 3.8 Hz), 120.8, 117.8 (d, J = 23.2 Hz), 110.7, 73.2, 28.5.

2-[2-(4-Fluoro-3-pyridin-3-yl-phenyl)-imidazo[1,2-α]pyrimidin-7-yl]-propan-2-ol (12). ^{1}H NMR (DMSO-d_6, 400.13 MHz) δ 8.91 (d, J = 7.2 Hz, 1H), 8.84 (m, 1H), 8.64 (dd, J = 4.8, 1.6 Hz, 1H), 8.43 (s, 1H), 8.18 (dd, J = 7.6, 2.0 Hz, 1H), 8.09−8.05 (m, 2H), 7.55 (ddd, J = 8.0, 4.8, 0.8 Hz, 1H), 7.46 (dd, J = 10.8, 8.8 Hz, 1H), 7.35 (d, J = 6.8 Hz, 1H), 1.49 (s, 6H); ^{13}C NMR (DMSO-d_6, 100.62 MHz) δ 170.0, 159.3 (d, J = 247.5 Hz), 149.6 (d, J = 3.2 Hz), 149.4, 147.8, 144.1, 136.7 (d, J = 3.2 Hz), 135.4, 131.2$_2$ (d, J = 3.2 Hz), 131.1$_7$ (d, J = 1.6 Hz), 128.1 (d, J = 3.2 Hz), 127.7 (d, J = 8.0 Hz), 125.8 (d, J = 14.4 Hz), 124.1, 117.1 (d, J = 23.2 Hz), 107.8, 105.9, 72.8, 26.6.

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