Organic Process Research & Development **2010,** *14,* 263–271

Optimisation of Permanganate Oxidation and Suzuki−Miyaura Coupling Steps in the Synthesis of a $Na_v1.8$ Sodium Channel Modulator

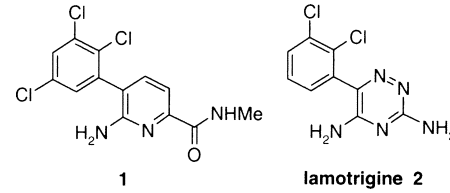
M. Jonathan Fray,* Adam T. Gillmore, Melanie S. Glossop, David J. McManus, Ian B. Moses, Céline F.B. Praquin, Keith A. Reeves, and Lisa R. Thompson

Pfizer Global Research and Development, Sandwich, Kent CT13 9NJ, U.K.

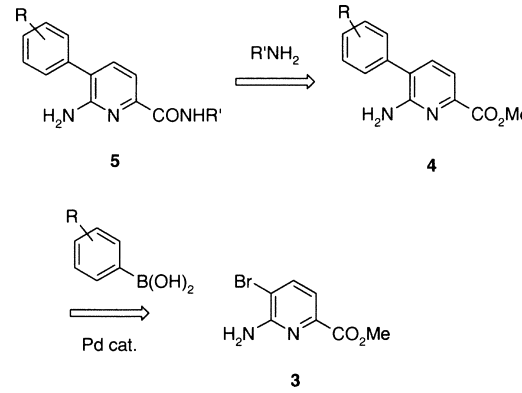
Abstract:

The development is described of a viable kilo-scale synthesis of the $Na_v1.8$ sodium channel modulator, *N*-methyl-6-amino-5-(2,3,5-trichlorophenyl)pyridine-2-carboxamide (PF-1247324) in five steps, starting from 6-amino-5-bromo-2-picoline, in 33% overall yield. Two key steps required significant optimisation to improve yield and reproducibility. Oxidation of 6-acetamido-5-bromo-2-methylpyridine by permanganate to give the corresponding carboxylic acid derivative was improved by adding potassium dihydrogen phosphate, which moderated the reaction mixture pH and doubled the yield. The potassium fluoride-promoted Suzuki−Miyaura coupling between 2,4,5-trichlorophenylboronic acid and methyl 6-amino-5-bromopyridine-2-carboxylate, catalysed by tri(*tert*-butyl)phosphinepalladium (0), proceeded reliably to completion at room temperature in high yield when water was added. Anhydrous reaction mixtures reacted much more slowly, and 'wet' mixtures led to significant proto-deboronation in the absence of sufficient active catalyst. In the final step, amidation of the ester with methylamine gave PF-1247324.

Chart 1



Scheme 1



Introduction

Voltage-gated sodium channels (VGSCs) are transmembrane proteins that are responsible for neuronal excitability in both the central and peripheral nervous system.[1] The VGSCs are a family of nine proteins, among which the sodium channel subsets $Na_v1.3$,[2] $Na_v1.7$,[3] $Na_v1.8$,[4,5] and $Na_v1.9$[6] present the best opportunities for developing pain therapeutics.

The search for sodium channel blockers has led to the discovery of a wide variety of structural classes including mexiletine, lamotrigine, and carbamazepine. During the course of our studies to identify a novel, potent, and selective $Na_v1.8$ inhibitor, we discovered the aryl pyridine derivative PF-1247324 (**1**),[7] which is in a similar structural class to lamotrigine (**2**)[8] (Chart 1).

The retrosynthetic analysis of **1** was relatively straightforward (Scheme 1); however, during our development of the synthetic route into one which was sufficiently practical to provide quantities for preclinical studies, we encountered many challenges. This paper describes the optimisation of the synthesis of **1**, involving significant experimentation on two steps; the permanganate oxidation of a 2-picoline derivative to the corresponding carboxylic acid that was low-yielding, and a hindered Suzuki−Miyaura coupling reaction with poor reproducibility. Identification of the most stable polymorph was also of particular importance.

Results and Discussion

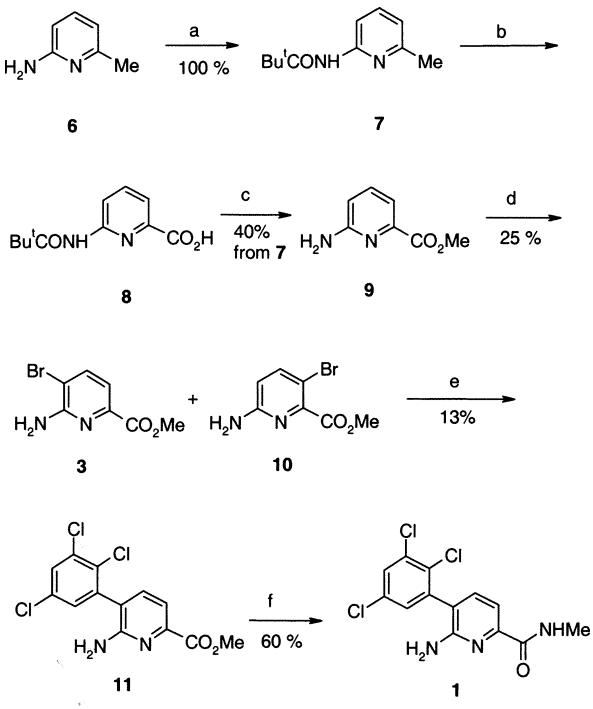
First-Generation Synthesis. The medicinal chemistry route was initially designed to achieve the maximum, late-stage variation of both the aromatic 5-position and the amide substituents. Thus, as shown in Scheme 1, introduction of the

* Author to whom correspondence may be sent. Telephone: +44 (0)1304 649175. Fax: +44 (0)1304 651819. E-mail: jonathan.fray@pfizer.com.

(1) Anger, T.; Madge, D. J.; Mulla, M.; Riddall, D. *J. Med. Chem.* **2001**, *44*, 115.
(2) Lindia, J. A.; Kohler, M. G.; Martin, W. J.; Abbadie, C. *Pain* **2005**, *117*, 145.
(3) Nassar, M. A.; Stirling, L. C.; Forlani, G.; Baker, M. D.; Matthews, E. A.; Dickenson, A. H.; Wood, J. N. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12706.
(4) Akopian, A. N.; Souslova, V.; England, S.; Okuse, K.; Ogata, N.; Ure, J.; Smith, A.; Kerr, B. J.; McMahon, S. B.; Boyce, S.; Hill, R.; Stanfa, L. C.; Dickenson, A. H.; Wood, J. N. *Nat. Neurosci.* **1999**, *2*, 541.
(5) Coggeshall, R. E.; Tate, S.; Carlton, S. M. *Neurosci. Lett.* **2004**, *355*, 45.
(6) Priest, B. T.; Murphy, B. A.; Lindia, J. A.; Diaz, C.; Abbadie, C.; Ritter, A. M.; Liberatore, P.; Iyer, L. M.; Kash, S. F.; Kohler, M. G.; Kaczorowski, G. J.; MacIntyre, D. E.; Martin, W. J. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 9382.
(7) Lane, C. A. L.; Maw, G. N.; Rawson, D. J.; Thompson, L. R. PCT Int. Appl. WO 2006011050, CAN 144:192112, AN 2006:101079, 2006.
(8) Cruccu, G. *Curr. Opin. Neurol.* **2007**, *20*, 531.

10.1021/op900092h CCC: $40.75 © 2010 American Chemical Society
Published on Web 07/24/2009

Scheme 2[a]



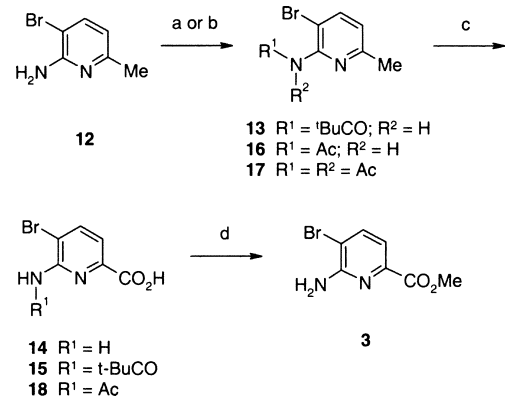
[a] Reagents and conditions: a) pivaloyl chloride, Et_3N, CH_2Cl_2, 20 °C, 24 h; b) $KMnO_4$, H_2O, 75 °C, 4 h; c) $HCl_{(g)}$, MeOH, 20 °C, 18 h; d) Br_2, $CHCl_3$, 20 °C, 40 h; e) 2,3,5-$Cl_3C_6H_2B(OH)_2$ (2 equiv), $Pd(PPh_3)_4$ (10 mol %), Cs_2CO_3, H_2O/dioxane, 80 °C, 16 h; f) $MeNH_2$, EtOH, 20 °C, 18 h.

amide was envisaged from the corresponding methyl ester (**4**) and a variety of aryl groups could be attached *via* Suzuki coupling between the 5-bromopyridine (**3**) and a boronic acid.

The first set of compounds in this series included compound **1**. The original synthesis, performed on small scale and completely unoptimised, is shown in Scheme 2.

In the absence of suitable commercially available pyridine carboxylic acid derivatives, the trifunctionalised pyridine was synthesised according to the method described by Kelly and Lang.[9] Thus, starting with commercial 6-amino-2-picoline (**6**), acylation with pivaloyl chloride gave **7** in quantitative yield. Oxidation of the methyl group with hot aqueous potassium permanganate gave the carboxylic acid **8**, which was treated directly with methanolic hydrogen chloride to form the ester **9** in 40% yield. Bromination of **9** proceeded to give a mixture of isomers (**3** and **10**) from which the desired 5-bromo derivative was isolated in 25% yield (by chromatography). Next, Suzuki−Miyaura coupling of **3** with 2 equiv of 2,3,5-trichlorophenylboronic acid,[10] employing catalytic *tetrakis*(triphenylphosphine)palladium (0) and cesium carbonate in aqueous dioxane gave **11** in only 13% yield. Presumably the hindered nature of the cross-coupling and the sensitivity of the methyl ester to basic hydrolysis contributed to the low yield. Since this reaction was originally performed, modified Suzuki reaction conditions have been described which make difficult cross-couplings much more efficient. The ease with which this coupling may now be performed (*vide infra*) is a measure of the progress made. Finally, treating **11** with an excess of ethanolic methylamine gave **1** in fair yield after recrystallisation.

Scheme 3[a]



[a] Reagents and conditions: a) t-BuCOCl (2.2 equiv), Et_3N (2.2 equiv), CH_2Cl_2, 0−20 °C, 18 h, 81%; b) Ac_2O, dioxane, 50 °C, 75%; c) $KMnO_4$ or $NaMnO_4$, H_2O, various conditions (see text); d) conc. H_2SO_4, MeOH, reflux, 18−48 h.

The deficiencies in the first synthesis are all too apparent. The overall yield was very low (<1%) as a result of three poor steps: the permanganate oxidation, the bromination (poor regioselectivity), and the Suzuki cross-coupling. On the other hand, the synthesis was relatively short (six steps from commercial material), and all the isolated intermediates were crystalline solids. As the compound progressed through the screening sequence, it became necessary to improve the synthesis significantly to provide gram quantities for further screening.

Second-Generation Synthesis. The lack of selectivity in the bromination step, above, was readily circumvented when a commercial source for 6-amino-5-bromo-2-picoline (**12**)[11] was identified; however, this new starting point had a deleterious effect on the subsequent permanganate oxidation (Scheme 3).

Thus, protection of the amino group as the pivalamide (**13**) proceeded as before without problem, but the oxidation gave very poor results. Heating **13** with potassium permanganate (2.4 equiv) in water (11 mL/g) overnight at reflux gave incomplete conversion and only 10% yield of deacylated carboxylic acid **14**, rather than the anticipated product, **15**. If no attempt was made to isolate a product from the oxidation but esterification[12] performed to facilitate product isolation, then only 8−14% of **3** plus an equal amount of recovered starting material was obtained. The perceived problem in the oxidation was that pivalamide **13** was less soluble in water than **7** in the first synthesis. Therefore two changes were made to aid solubility: a switch to the less lipophilic acetamide derivative **16** and addition of pyridine as a cosolvent[13] to the reaction mixture.

(9) Kelly, T. R.; Lang, F. *J. Org. Chem.* **1996**, *61*, 4623.
(10) Cox, B.; Nobbs, M. S.; Shah, G. P.; Edney, D. D.; Loft, M. S. PCT Int. Appl. WO 98/38174, 1998, CAN 129:230741, AN 1998:608606; also commercially available from Alfa Aesar, Heysham, Lancashire, U.K., cat. no. L17511, CAS 212779−19−6.
(11) Dunn, A. D.; Currie, A.; Hayes, L. E. *J. Prakt. Chem. (Leipzig)* **1989**, *331*, 369. CAS registry 126325-46-0. We purchased from Asymchem, Morrisville, NC, U.S.A.
(12) Pomel, V.; Rovera, J. C.; Godard, A.; Marsais, F.; Quéguiner, G. *J. Heterocycl. Chem.* **1996**, *33*, 1995.
(13) Pyridine has been used as solvent in conjunction with permanganate. See: Sala, T.; Sargent, M. V. *J. Chem. Soc. Chem. Commun.* **1978**, 253; Deng, X.; Stefanick, S.; Pippel, M. C. W.; Mani, N. S. *Org. Process Res. Dev.* **2006**, *10*, 1287 (*n*-Bu_4NMnO_4); Erickson, J. L. E.; Dechary, J. M.; Pullig, T. R. *J. Am. Chem. Soc.* **1952**, *74*, 5621 ($KMnO_4$).

Table 1. **Effect of changing reaction conditions of permanganate oxidation of 16**

entry	scale (g/**16**)	oxidant[a] (equiv)	water (mL/g)	additive (amount)	temp. (°C)	yield of **3**[b] (%)
1	4.8	$KMnO_4$ (4)	20	pyridine (0.2% v/v)	75	34[c]
2	20	$KMnO_4$ (3.6)	10	pyridine (2.5% v/v)	60−78	13[d]
3	36	$KMnO_4$ (4.8)	11	pyridine (6% v/v)	80−90	24[e]
4	30	$KMnO_4$ (3.5)	53	none	80	26[d]
5	2	$NaMnO_4$ (3.2)	15	none	85−90	34
6	1	$NaMnO_4$ (3.2)[f]	15	KH_2PO_4 (2 equiv)	85−90	40
7	10	$NaMnO_4$ (2.5)	19	KH_2PO_4 (2 equiv)	83−90	53
8	30	$NaMnO_4$ (2.5)[g]	21	KH_2PO_4 (2 equiv)	85−90	50−52[h]
9	80	$NaMnO_4$ (2.5)	23	KH_2PO_4 (2 equiv)	83−90	50
10	177	$NaMnO_4$ (2.5)[i]	18	KH_2PO_4 (2 equiv)	85−89	47

[a] $KMnO_4$ was added as a solid in portions except entry 4 where it was added as a solution. $NaMnO_4$ was added as a solution (40% w/v in water). [b] Esterification/amide cleavage employed 10% H_2SO_4 in MeOH, reflux, 18−24 h unless noted otherwise. [c] Esterification with 1.3% H_2SO_4, reflux, 2d. [d] Esterification with 4% H_2SO_4, reflux, 18 h. [e] Esterification with 5% H_2SO_4, reflux, 2.5d. [f] Added over 20 min. [g] Added over 75 min. [h] Yield range for three experiments. [i] Added over 180 min.

Treatment of **12** with a 4-fold excess of acetic anhydride in dioxane at 50−60 °C gave **16** in reasonable yield (75%, 50−100 g scale) after trituration with pentane. On closer examination it was discovered that under these reaction conditions a significant proportion of the related imide **17** was also formed. However, if acetylation was conducted at room temperature in excess acetic anhydride containing a little CH_2Cl_2 to aid stirring, imide formation was avoided, and the yield increased accordingly (87%, 300 g scale), although the reaction took 4 days to complete.[14]

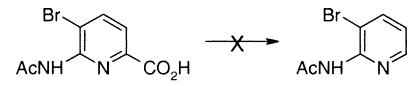
A series of small-scale experiments was conducted with the objective of understanding the cause of the low yield in the oxidation. The reactions were generally performed as follows. A mixture of **16** in water (with pyridine as optional additive) was heated and potassium permanganate added in portions. After the end of the addition, the reaction mixture was heated for a further hour, cooled, and filtered to remove manganese dioxide. The aqueous solution was washed with ethyl acetate or CH_2Cl_2 (to remove any unreacted starting material) and then evaporated to dryness, as attempts to extract the presumed pyridine carboxylic acid **18** (at various pHs) gave a very low recovery of material. Consequently, we decided to treat the crude intermediate **18** with methanolic sulphuric acid at reflux, thereby forming the methyl ester and cleaving the acetamide. After removal of the solvent and neutralising the solution, ester **3** was obtained by solvent extraction with ethyl acetate. These results are summarised in Table 1. They revealed much information, but also posed several puzzling questions.

Thus, following an initially encouraging result at 75 °C (entry 1) which gave 34% of **3**, two larger-scale runs with more pyridine (entries 2 and 3) gave lower yields (13−24%). Other water-soluble cosolvents (acetone, acetic acid, *tert*-butanol) were also examined briefly, but they reduced the stability of the permanganate, which decolourised rapidly and failed to oxidise any of the starting material.

The heterogeneous nature of the oxidation, resulting from the low aqueous solubility of both **16** (~1 g/20 mL at 85 °C) and potassium permanganate (65 g/L at 20 °C, 0.4 M), was a concern. Thus, we performed a reaction where the reagents were dissolved completely (entry 4), but the yield did not improve, and the overall dilution (53 mL/g) was excessive.

(14) Compare Zafar, A.; Geib, S. J.; Hamuro, Y.; Carr, A. J.; Hamilton, A. D. *Tetrahedron* **2000**, *56*, 8419. ; for the *des*-bromo case, but interestingly they isolated the acetate salt, not the free base.

Scheme 4



18 **19**

In the reactions performed with ~10 mL/g water and solid potassium permanganate, we noticed that each addition was accompanied by a sharp increase in temperature. With experience this could be controlled, but as the strongly exothermic nature of the oxidation was a concern, we performed trial reactions in a thermal screening unit (TSu). These experiments confirmed the exothermicity of the reaction and its onset at around 70 °C. Significant gas evolution was noted when the reaction mixture approached 100 °C, and the presence of pyridine in the reaction mixture was associated with even greater exothermicity. Consequently, efforts were focused on strict control of the reaction temperature in the range 80−90 °C, the pyridine was omitted, and the cause of the gas evolution was investigated.

Regardless of the reaction temperature, the dilution or whether aqueous or solid permanganate was used, the yield (following esterification to give **3**) was poor and variable (9−34%), although the quality of the product was excellent. The loss of mass was puzzling, and although excess permanganate was used, variable but small amounts of starting material were recovered. Nevertheless, they did not fully explain the low yield, and so we also questioned the efficiency of the esterification.

Two hypotheses were proposed to explain the low yield but high purity of crude **3**. Since no side products were observed, we concluded that complete destruction of the pyridine ring might be occurring. This could be happening *via* thermal decarboxylation of **18,**[15] as loss of the carboxyl would increase the electron density on the pyridine ring, making it more vulnerable to oxidation (Scheme 4). Furthermore, it might explain the gas evolution. This hypothesis was comprehensively disproved in the following manner. We first isolated the crude carboxylic acid

(15) 5-Bromo-4-chloro-3-methoxypyridine-2-carboxylic acid readily decarboxylates at only 120 °C, see: Looker, J. H.; Prokop, R. J.; Serbousek, W. E.; Clifton, M. D. *J. Org. Chem.* **1979**, *44*, 3408. more typically high temperature (>200 °C) is required, see: de Bie, D. A.; Geurtsen, B.; van de Plas, H. C. *J. Org. Chem.* **1985**, *50*, 484. Stanforth, S. P.; Tarbit, B.; Watson, M. D. *Tetrahedron* **2004**, *60*, 8893.

18 (mixed with inorganic salts). The NMR spectrum clearly showed that **18** was the major component by far (purity ≥96%). The stability of **18** was examined at three pH levels (4.8, 6.6, and 8.4), temperatures (70, 85, and 100 °C), and reaction times (3, 6, and 22 h) and the product composition monitored by flow NMR. These experiments clearly showed the conversion of **18** to a single component, the deacylated derivative **14**, and not to decarboxylated product **19**.

The hydrolysis was more pronounced at low pH, higher temperature, and long reaction times; minimal conversion (13%) was noted at pH 6.6 after 22 h at 70 °C, whereas the highest amount of degradation (only 8% **18** remaining) was observed after 22 h at 100 °C and pH 4.8. The identity of **14** was confirmed from NMR and mass spectroscopic measurements in comparison with a small sample isolated from the oxidation of pivalamide **13**, and its presence was also detected by LC/MS during optimisation of the esterification (*vide infra*).

The gas evolution noted during the TSu experiments was therefore deduced to be from thermal decomposition of the permanganate,[13] as shown in eq 1.

$$4\,MnO_4^- + 2H_2O \rightarrow 4MnO_2 + 3O_2 + 4OH^- \quad (1)$$

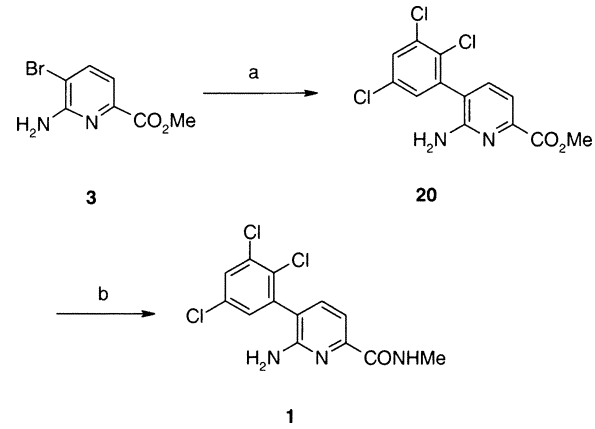
We then sought to develop the second hypothesis, namely that the high pH of the reaction mixture was causing hydrolysis of the *N*-acetyl group, followed by destructive oxidation of **12**. A search of the literature for oxidations of unprotected aminopyridines with permanganate revealed no examples. Indeed, the hydrolysis experiments showed that about 20% conversion to **14** occurred at pH 8.4, 85 °C, in only 3 h, suggesting that the acetyl group of **16** and/or **18** might be quite labile under the oxidation conditions. At this stage we were also concerned to keep the maximum control over the reaction temperature, and therefore made another change, to 40% (2.8 M) aqueous sodium permanganate from solid potassium permanganate. In this way we could add the permanganate in a controlled fashion, whilst keeping the overall dilution to a reasonable level (24 mL/g). The yield was maintained (entry 5).

If one considers the equation for the oxidation, it is evident that the reaction mixture becomes very basic, as 2 equiv of permanganate are consumed, and 1 equiv of hydroxide is formed, in addition to the product carboxylate salt (eq 2).

$$\text{Het-}CH_3 + 2NaMnO_4 \rightarrow \text{Het-}CO_2Na + 2MnO_2 + NaOH + H_2O \quad (2)$$

To counteract the rise in pH during the reaction, we decided to buffer the mixture with 2 equiv of potassium dihydrogen phosphate,[16] which were added at the start to give a thick slurry of initial pH 4. This simple expedient had a significant effect on yield (Table 1, entry 6), which increased further on lowering the excess of permanganate (entry 7). The results for three experiments run on 30 g scale by three different chemists were remarkably consistent and gave us confidence about the robustness of the procedure (entry 8). Further scale-up (entries 9−10) was successful, with only slight diminution of yield.

Scheme 5[a]



[a] Reagents and conditions: a) 2,3,5-$Cl_3C_6H_2B(OH)_2$ (1.2 equiv), $Pd_2(dba)_3$ (2 mol %), t-$Bu_3P{\cdot}HBF_4$ (4 mol %), KF (3.3 equiv), 0.4 M in THF, 20 °C, 16 h, 83%; b) $MeNH_2$ (2 M in THF), 70 °C, autoclave, 48 h, 90%.

The smaller-scale reactions (1−80 g) were performed using oil-bath heating, whereas the largest batch was run using a thermostatically controlled heating mantle. The rate of permanganate addition was primarily determined by the desire to maintain the reaction temperature in the target range, the exothermicity of the reaction, and rate of heat loss from the reaction flask. Thus, the permanganate could be added over 20 min on a gram scale, but 3 h was required on 170 g scale, during which time no heat was required from the isomantle.

As conversion of **16** to **3** comprised two separate reactions, we attempted to measure the yield and conversion for each step. Thus, analysis of the residue by NMR and LC/MS showed **18** (Na^+/K^+ salt) as the main component in 68−71% yield, with only trace impurities (see Experimental Section), with 9% of **16** being recovered from the organic washings. The esterification and acetamide hydrolysis to **3** were monitored by LC/MS. When using 10% methanolic sulphuric acid for 18 h, the conversion was approximately 93%, whereas 5% methanolic sulphuric acid gave about 60% conversion in 24 h, the remainder being **14**.

The final two steps of the synthesis are shown in Scheme 5.

The aryl group had originally been introduced *via* a conventional, 'first-generation' Suzuki coupling (Scheme 2) in poor yield, which could be attributed to a combination of low activity catalyst (palladium *tetrakis*(triphenylphosphine), steric hindrance from two ortho substituents, a partially aqueous solvent and relatively high temperature, which may have caused ester hydrolysis. The discovery by Fu,[17,18] Hartwig,[19−21] and others[22,23] that electron-rich, sterically hindered alkyl phosphines

(16) Addition of phosphate to the permanganate oxidation of aldehydes has been found to be beneficial, see: Takemoto, T.; Yasuda, K.; Ley, S. V. *Synlett* **2001**, 1555. Abiko, A.; Roberts, J. C.; Takemasa, T.; Masumune, S. *Tetrahedron Lett.* **1986**, *27*, 4537.

(17) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **1999**, *37*, 3387.
(18) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020.
(19) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369.
(20) Hartwig, J. F. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley: New York, Chichester, 2002; Vol. 1, p 1051.
(21) Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553.
(22) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413.
(23) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550.

permit more efficient Suzuki couplings to be achieved suggested their modified conditions would be advantageous.[24]

In particular, Fu's conditions employing anhydrous potassium fluoride as promoter would help ensure integrity of the ester group.[25,26] Thus, bromide **3** coupled to the trichlorophenylboronic acid[10] smoothly at room temperature (83% yield) in the presence of 4 mol % palladium dibenzylideneacetone (dba) and tri-*tert*-butylphosphine (40−50 g scale).[27] Surprisingly, on one occasion the coupling was exothermic enough to warrant ice-bath cooling (50 g scale) to moderate the temperature.[28] The rapid reaction initiation was investigated further, as described below.

In the final step, treatment of **20** with an excess of methylamine in THF in an autoclave vessel at 70 °C for 48 h gave **1** in high crude yield (>85%). Longer reaction times were deleterious since they produced more side products. Earlier trial reactions had been conducted at 50 °C, but they took longer (up to four days) and sometimes stalled or required additional methylamine. The product was triturated with ethyl acetate to give about 90% yield (98% purity), followed by recrystallisation from hot toluene. The crystals retained toluene (between 0.33 and 0.5 equiv) that could not be removed by drying, but if the solid was suspended in warm ethanol, the toluene was taken out.

Several key changes in the second-generation synthesis underpinned a large increase in overall yield (from <1% to 30%). Addition of a buffer to the permanganate oxidation almost doubled the yield for this step through suppression of amide hydrolysis. As a comparison, the unbuffered permanganate oxidation of 6-acetamido-2-picoline proceeds in only 26−32% yield[14,29] compared with 51−70% yields, for example 6-methyl-, 6-chloro-, and 6-bromo-2-picolines[30−32] The Suzuki-coupling step was improved significantly by changing to anhydrous conditions and employing a much more active palladium catalyst. Minor improvements to the other steps permitted isolation of all intermediates and final product as solids in high purity without recourse to chromatography. Thus, over 100 g of **1** (in several batches) were prepared to meet preclinical pharmacology and toxicology needs. In the next section, further development of the synthesis is discussed, particularly issues with the Suzuki-coupling step and polymorphism in **1**.

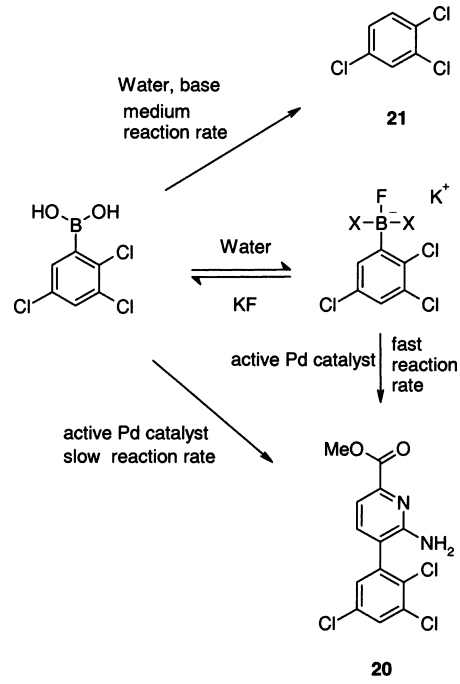


Figure 1

Third-Generation Synthesis. For the provision of clinical API, the first three steps were successfully outsourced leaving the Suzuki coupling and amide formation to be run in-house. Given the earlier success, we expected scale-up to be relatively trivial; however, we discovered some significant robustness issues with the Suzuki−Miyaura coupling.

The procedure (100 g batch) worked well but was not suited to large scale due to final addition of the catalyst and the subsequent exotherm that ensued. Addition of the boronic acid as a THF solution to the other reagents was reliable up to 10 g scale, but the first reaction on 50 g stalled at 65% conversion and gave significant levels (approximately 30%) of the protodeboronation product 1,2,4-trichlorobenzene (**21**) (Figure 1), although addition of more catalyst and boronic acid pushed the reaction to 95% conversion without increasing the level of **21**. Subsequent attempts were similarly unsuccessful, and some reactions had an induction period of between 1and 20 h.

After many unsuccessful attempts to improve the reaction by changing the temperature, speed, and mode of addition, it was found that increasing the catalyst and phosphine loadings to 3 and 6 mol %, respectively, gave complete reaction with no evidence of 1,2,4-trichlorobenzene. Encouraged by this, we repeated the reaction; however, we were surprised to find that the reaction was very slow, taking three days to reach 75% conversion, but no degradation of the boronic acid was observed. Interestingly after workup (by the addition of filter aid and filtration) it was found that the reaction was 90% complete, with the remainder being 1,2,4-trichlorobenzene. This suggested that either oxygen and/or moisture played a key role in pushing the reaction to completion and generation of **21**.

We found that running the reaction in air resulted in only a 60% conversion with the remainder being 1,2,4-trichlorobenzene. This was consistent with the observation that increased catalyst loading had the opposite effect and showed that at low loadings the catalyst is more easily deactivated by oxygen. This did not, however, explain the induction period observed in some

(24) More recently the search for alternatives to phosphine ligands has provided a number of catalyst systems capable of achieving biaryl cross-couplings in good yield; see, for example:Mohanty, S.; Suresh, D.; Balakrishna, M. S.; Mague, J. T. *Tetrahedron* **2008**, *64*, 240, and references therein.
(25) Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095.
(26) Edwards, J. P.; Zhi, L.; Pooley, C. L. F.; Tegley, C. M.; West, S. J.; Wang, M.-W.; Gottardis, M. M.; Palhirana, C.; Schrader, M. T.; Jones, T. K. *J. Med. Chem.* **1998**, *41*, 2779.
(27) Earlier experiments employed 1 mol % Pd_2dba_3 + 1.8 mol % Pd(t-$Bu_3)_2$ and gave 70−75% yield on 10−18 g scale.
(28) This was important as over-reaction was observed if the temperature was allowed to rise unduly with the excess boronic acid coupling to a chloro substituent.
(29) Schmuck, C.; Machon, U. *Chem.−Eur. J.* **2005**, *11*, 1109.
(30) Su, B.; Zhao, J.; Cui, Y.; Liang, Y.; Sun, W. *Synth. Commun.* **2005**, *35*, 2317.
(31) Meier, P.; Legraverant, S.; Mueller, S.; Schaub, J. *Synthesis* **2003**, 551.
(32) Ashimori, A.; Ono, T.; Uchida, T.; Ohtaki, Y.; Fukaya, C.; Watanabe, M.; Yokoyama, K. *Chem. Pharm. Bull.* **1990**, *38*, 2446.

reactions or the fact that degradation of the boronic acid was not always seen, even in the case of stalled reactions. We hypothesized that moisture might be having a detrimental effect on the reaction since potassium fluoride is known to be hygroscopic. However, we were surprised to find that the opposite was true, and a low level of water was *required* to give consistent reaction initiation and complete conversion to the desired product with no evidence of **21**. The addition of one equivalent of water consistently reduced the reaction time from overnight (at best) to just two hours. We attempted to use *in situ* infrared spectroscopy to see whether the addition of water was resulting in a different intermediate being formed, but no such difference was observed, suggesting that either the level of such a catalytic intermediate was below the level of detection or that the water is having an effect on the solubility of the potassium fluoride required to promote the reaction. We propose that the latter is most likely to be the case. A combination of slightly higher catalyst loading and the addition of one equivalent of water gave us a consistently performing reaction (77% yield on 2.9 kg scale) with no significant levels of proto-deboronation.

Whilst these conditions solved the robustness problems, it is interesting to consider how these factors affected the observed results. It has been proposed that arylboronic acids form hydroxyfluoroboronates in the presence of fluoride ion and that these are the active species that transfer the aryl group to palladium.[18,25,33] Whilst it is well documented that arylboronic acids undergo proto-deboronation under basic hydrolytic conditions and that the rate increases for chloro substituents,[34,35] there seem to be no examples or studies of the proto-deboronation of hydroxyfluoroboronates. However, it is known that potassium aryltrifluoroboronate salts hydrolyse to give the corresponding arylboronic acids, presumably *via* hydroxyfluoroboronates, suggesting that proto-deboronation is suffered only by the boronic acid and not the hydroxyfluoroboronate. We therefore propose that there are two key factors (water level and presence of active catalyst) involved in four scenarios as follows (Figure 1).

(i) Adequate water level and catalyst loading give enough solubility for the KF to form an activated fluoroboronate which then reacts quickly to give the desired product.

(ii) Inadequate water level gives poor solubility of the KF, but an active catalyst gives slow or stalled reaction of the boronic acid to the desired product with varying levels of competing proto-deboronation (for very dry KF no proto-deboronation is seen).

(iii) Adequate water level gives enough solubility for the KF to form an activated fluoroboronate; however, a low catalyst loading results in poor conversion to product. Crucially, this intermediate does not appear to be susceptible to degradation.

(iv) Finally, inadequate water level and inactive catalyst result in degradation of the boronic acid to **21** as the major reaction pathway. This outcome is similar to that of (ii).

Other reactions carried out during the course of our development work support this hypothesis; namely

(i) Omitting the KF resulted in low conversion and significant levels of proto-deboronation.

(ii) Substitution of KF by potassium carbonate gave good conversion when higher levels of water are present, but a significant amount of proto-deboronation was seen with only one equivalent of water.

(iii) Attempted generation of the trihydroxyborate salt[36] resulted only in protodeboronation to **21**.

(iv) Reaction with oven-dried KF and higher catalyst levels resulted in slow reaction, but no degradation of boronic acid.

Our findings are consistent with those in recent publications[37−39] where the addition of water to Suzuki reactions was found to be beneficial through increased reaction rate and/or yield.

It is interesting to speculate why the requirement for water only became evident after a number of reactions had been run successfully on small scale. The same batch of potassium fluoride had been used for all the experiments, so it is quite likely that the material at the top of the jar was fairly wet due to its hygroscopic nature. Once we started to run larger-scale reactions, we were probably using drier potassium fluoride from the bottom of the jar, which then was less soluble in the reaction medium.

The final step amide coupling had previously been carried out using methylamine in THF in an autoclave at 70 °C. We subsequently found that this reaction could be carried out at room temperature by the addition of 0.5 equiv of magnesium chloride;[40] however, we were surprised to find that the magnesium chloride was difficult to remove and carried through the filtration, possibly as a soluble etherate complex. We therefore decided to backtrack and find suitable conditions which required neither magnesium chloride nor a sealed vessel. Raising the reaction concentration (7 mL/g, 11-fold excess of methylamine with ethanol as cosolvent) gave complete reaction in 5 h at 25 °C. Prior to the amidation, the residual palladium content was 257 ppm, but a charcoal treatment during the workup of **1** reduced the level to 4 ppm, which was satisfactory for clinical use. After diluting the reaction mixture with THF and carrying out a solvent swap into ethanol/water (which also served to drive off the residual methylamine), the product crystallised. These conditions were then used in two campaigns on 0.6 and 2.8 kg scale, giving the product (form A, mp 200 °C) in 79% yield.

The nature of the solid form of drug substances (e.g., amorphous/crystalline/polymorph/salt) can have a profound effect on solubility, and hence absorption and circulating plasma levels following oral dosing. Compound **1** has relatively low solubility and basicity. We were therefore keen to identify any new polymorphs at an early stage. Thus, after completion of the 0.6 kg scale campaign, solid form assessment studies identified a new, more stable polymorph (form B, mp 118 °C),

(33) Barder, T. E.; Buchwald, S. L. *Org. Lett.* **2004**, *6*, 2649.
(34) Ainley, A. D.; Challenger, F. *J. Chem. Soc.* **1930**, 2171.
(35) Kuivila, H. G.; Reuwer, J. F., Jr.; Mangravite, J. A. *Can. J. Chem.* **1963**, *41*, 3081.
(36) Cammidge, A. N.; Goddard, V. H. M.; Gopee, H.; Harrison, N. L.; Hughes, D. L.; Schubert, C. J.; Sutton, B. M.; Watts, G. L.; Whitehead, A. J. *Org. Lett.* **2006**, *8*, 4071.
(37) Chai, D. I.; Lautens, M. *J. Org. Chem.* **2009**, *74*, 3054.
(38) Ishikawa, S.; Manabe, K. *Chem. Lett.* **2006**, *35*, 164.
(39) Le Drian, C.; Becht, J.-M.; Schweizer, S. PCT Int. Appl. 2008, WO 2008142333, 2008, CAN 149:576721, AN 2008:1426135.
(40) Guo, Z.; Dowdy, E. D.; Li, W.-S.; Polniaszek, R.; Delaney, E. *Tetrahedron Lett.* **2001**, *42*, 1843.

which had been isolated by slurrying form A in ethanol at 40 °C for two weeks. We then converted form A to the new polymorph by simply heating a slurry overnight in the isolation solvents (ethanol/water 2:1), which reliably effected the conversion to form B.

Conclusion

The main challenge in the synthesis of compound **1** was the very poor overall yield, mainly arising from two steps: the permanganate oxidation of the picoline derivative, and the subsequent sterically hindered Suzuki−Miyaura coupling involving a fairly electron-rich pyridine with an electron-deficient boronic acid. Crucial to improving the permanganate oxidation was deducing the likely fate of the amino protecting group, since permanganate oxidations generate hydroxide, which can cause unwanted amide hydrolysis at the temperature employed. By adding potassium dihydrogen phosphate, the pH of the reaction mixture was moderated, and the yield roughly doubled. In the Suzuki−Miyaura coupling step between **3** and 2,4,5-trichlorophenylboronic acid, performed under Fu's room temperature conditions with tri-*tert*-butylphosphine/palladium (0) and potassium fluoride, problems of reproducibility were noted. Under strictly anhydrous and anaerobic conditions (to maintain catalyst viability), the reaction proceeded slowly to completion in high yield, whereas in the presence of water, the reaction was very rapid and exothermic. Under 'wet' conditions with low catalyst loading or in the presence of air, significant decomposition of the boronic acid to 1,2,4-trichlorobenzene was noted. Our results suggest that small amounts of adventitious water might play an important part in determining the outcome of other palladium-catalysed cross-coupling reactions mediated by hygroscopic salts such as potassium fluoride and potassium phosphate. The modified conditions allowed us to prepare over 2 kg of **1** to support toxicology studies.

Experimental Section

General. Melting points were determined using open glass capillary tubes and a Gallenkamp melting point apparatus and are uncorrected. Spectroscopic data were recorded on a ThermoNicolet Avatar 360 FT-IR spectrometer with a Smart Golden Gate accessory using single reflection Attenuated Total Reflectance (ATR), Finnigan Mat. Navigator (LRMS, either positive (ES^+) or negative (ES^-) electrospray mode), and Varian Unity Inova (^1H NMR 300, 400, or 500 MHz) instruments and are consistent with the assigned structures. Combustion analyses were performed by Exeter Analytical (UK) Limited, Uxbridge, Middlesex, U.K., or Warwick Analytical Service, University of Warwick Science Park, The Venture Centre, Sir William Lyons Road, Coventry CV4 7EZ, U.K. Accurate mass determinations for molecular ions were obtained using a commercially available Apex II Fourier Transform mass spectrometer (Bruker Daltonics, Inc. Billerica, MA, USA) equipped with a 4.7 T, passively shielded, superconducting magnet and an electrospray ionisation source (ESI), used in positive ion mode (Analytica of Branford, Branford, CT, USA) and calibrated using sodium trifluoroacetate. Ether refers to diethyl ether; MTBE to methyl *tert*-butyl ether. All reactions were conducted under a positive pressure of dry nitrogen unless stated otherwise. Anhydrous solvents were purchased from Sigma-Aldrich and used directly. Flash chromatography refers to column chromatography on silica gel (Kieselgel 60, 230-400 mesh, from E. Merck, Darmstadt). Kieselgel 60 F_{254} plates from E. Merck were used for TLC, and compounds were visualised using UV light or 0.5% aqueous potassium permanganate solution.

6-Acetamido-5-bromo-2-methylpyridine (16). Acetic anhydride (32.3 kg, 317 mol) was added to a suspension of 6-amino-5-bromopicoline (6.17 kg, 32.99 mol) in CH_2Cl_2 (3.7 L, 0.6 mL/g), maintaining the temperature <15 °C with intermittent external cooling, to give a solution by the end of the addition. After approximately 5 h of further stirring at ambient temperature, precipitation occurred. Additional CH_2Cl_2 (2.2 L, 0.36 mL/g) was added to maintain adequate stirring. The reaction mixture was stirred for 3 days, after which time TLC showed the reaction to be essentially complete. The batch was diluted with MTBE (37 L, 6 mL/g) and cooled to 0 °C. The product was filtered, washed with MTBE (3.7 L, 0.6 mL/g), and dried in air to give a first crop of white solid. The filtrates were evaporated, and the resulting solid was suspended in CH_2Cl_2 (31 L, 5 mL/g). The CH_2Cl_2 was evaporated to give a damp solid which was slurried in MTBE (18.5 L, 3 mL/g) and filtered. The two crops were combined to give **16** as the product as a colourless solid, (7.1 kg, 30.99 mol, 94% yield), mp = 143−144 °C. ^1H NMR (400 MHz, $CDCl_3$) δ 2.43 (s, 3H), 2.44 (s, 3H), 6.80 (d, J = 8.2 Hz, 1H), 7.75 (d, J = 8.2 Hz, 1H), 7.80 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 23.9, 24.6, 107.6, 120.7, 141.6, 147.8, 156.7, 171.0; LC/MS (Phenomenex Luna C_{18}, 0.05% formic acid/MeCN/water, 15 min, gradient 5−95% MeCN, 1 mL/min) R_t = 4.16 min, m/z (ES^+) 228, 230 (MH^+), 187, 189 (MH^+ − Ac). $\nu_{max.}$ (neat) 3244, 3198, 3104, 1669, 1585, 1526, 1437, 1389, 1363, 1279, 1261, 1142, 1047, 1021, 965, 834 cm^{-1}; Anal. Calcd ($C_8H_9BrNO_2$) C, 41.95; H, 3.96; N, 12.23. Actual: C, 41.92; H, 3.91; N, 12.16.

6-Acetamido-5-bromopyridine 2-Carboxylic Acid (Sodium/Potassium Salt) (18). A 5 L 3-necked flask equipped with a mechanical stirrer, pressure-equalising dropping funnel and thermocouple was placed in a 5 L electric heating mantle. The thermocouple was used to measure the internal temperature of the reaction mixture and also control the electrical supply to the heating mantle elements, with heating set to stop if the temperature reached 85 °C. The flask was charged with water (2.5 L) and 6-acetamido-5-bromo-2-methylpyridine **16** (177.4 g, 0.775 mol). Stirring and heating were commenced. When the temperature reached 85 °C, virtually all **16** had dissolved. KH_2PO_4 (211 g, 1.55 mol) was added as a solid over 1 min. A thick white suspension (pH 4.5) formed, presumably the phosphate salt of **16**. An aqueous solution of $NaMnO_4$ (40%, 690 mL, 1.95 mol) was charged to the dropping funnel. Residual permanganate from the measuring cylinder was transferred to the dropping funnel with water (70 mL). The permanganate solution was added over 187 min at such a rate that the reaction temperature stayed in the range 82−90 °C. The mixture was then stirred for 75 min at 85 °C by which time the purple colour had dissipated to be replaced by a dark brown suspension of manganese dioxide. The mixture was allowed to cool slightly, and filtered through a 2 cm thick pad of Celite. The filter cake was washed with water (1 L) and the pale yellow filtrate (pH

8) cooled to 20 °C. The filtrate was washed with CH_2Cl_2 (2 × 500 mL) and concentrated under reduced pressure (55 °C, 25 mmHg). The residue was dried by suspending it in toluene (1 L) and evaporating the solvent. This was repeated with more toluene (1 L) and MeOH (2 × 500 mL) to afford **18** (sodium/potassium salt) as a white solid, 320.1 g (calculated to contain 139.9 g, 70%). The yield was calculated by taking an aliquot of the solid (9.2 mg), dissolving it in D_2O, and adding a known amount of a solution of citric acid in D_2O. NMR was then used to compare the relative molar amounts of **18** and citric acid. The weight of **18** (4.02 mg) in the aliquot was then calculated, and from that, the weight of **18** in the crude product. ^{1}H (400 MHz, D_2O) δ 2.13 (s, 3H), 7.63 (d, J = 8 Hz, 1H), 8.12 (d, J = 8 Hz, 1H). LC/MS (Phenomenex Luna C_{18}, 0.05% formic acid/MeCN/water, 15 min gradient 5−95% MeCN, 1 mL/min) R_t = 3.82 min, 97% purity (UV), *m/z* 258, 260 (M^+), 280, 282 (MNa^+), remainder being starting material, *m/z* 228, 230 (M^+).

Methyl 6-Amino-5-bromopyridine-2-carboxylate (3). Concentrated sulphuric acid (160 mL) was added over 30 min to MeOH (1600 mL) with ice-bath cooling. The resulting solution was added to crude **18** (124.9 g, calculated to contain 0.213 mol), and the resulting suspension heated under reflux for 24 h. LCMS (Phenomenex Luna C_{18}, 0.05% formic acid/MeCN/water, 15 min, gradient 5−95% MeCN, 1 mL/min) showed R_t = 5.23 min, 93% purity (uv), *m/z* 230, 232 (M^+), remainder R_t = 3.23 min, *m/z* 216, 218 (M^+, 6-amino-5-bromopyridine carboxylic acid **14**. The mixture was cooled and concentrated under reduced pressure to give a thick, white slurry, which was poured into a mixture of water (1.5 L) and EtOAc (800 mL). The mixture was cooled in an ice bath whilst concentrated aqueous ammonia (250 mL) was added over 30 min with stirring. The phases were separated and the aqueous phase extracted with EtOAc (800 mL). The combined organic solutions were dried ($MgSO_4$) and concentrated under reduced pressure. The residue (pale yellow solid, 48.3 g) was suspended in MTBE (100 mL) for 1.5 h and the product collected by filtration to give **3**, (43.14 g, 68%; 48% from **16**) as a colourless solid, mp = 143 −145 °C. ^{1}H (400 MHz, $CDCl_3$) δ 3.95 (s, 3H), 7.36 (d, J = 7.8 Hz, 1H), 7.78 (d, J = 7.8 Hz, 1H). ^{13}C (100 MHz, $CDCl_3$) δ 52.9, 109.3, 116.5, 141.1, 145.3, 155.7, 165.5; *m/z* (ES^+) 231, 233 (MH^+); $\nu_{max.}$ (neat) 3463, 3272, 3147, 3009, 1714, 1615, 1578, 1463, 1444, 1335, 1299, 1255, 1195, 1161, 1114, 1018, 839, 777, 742 cm^{-1}; Anal. Calcd ($C_7H_7BrN_2O_2$): C, 36.39; H, 3.05; N, 12.12. Actual: C, 36.22; H, 3.03; N, 12.13.

Methyl 6-Amino-5-(2,3,5-trichlorophenyl) Pyridine-2-carboxylate (20). THF (53.2 L, 19 mL/g) was sparged with nitrogen at 25 °C for 15 min, and then a portion (11.1 L, 4 mL/g) was removed and used to make up a solution of 2,3,5-trichlorophenylboronic acid (2.87 kg, 12.74 mol, 1.05 equiv) in a separate vessel. To the remaining 42.1 L of THF was added **3** (2.80 kg, 12.12 mol) with stirring. Potassium fluoride (2.32 kg, 39.9 mol, 3.3 equiv) and water (218 mL, 12.12 mol, 1.0 equiv) were then added, and the mixture was stirred for 20 min under nitrogen. *Tris*(dibenzylideneacetone)dipalladium (0.33 kg, 0.364 mol, 0.03 equiv) was then added followed by tri-*tert*-butylphosphonium tetrafluoroborate (0.211 kg, 0.727 mol, 0.06 equiv). The reaction mixture was sparged with nitrogen again for 15 min, and then the previously prepared solution of 2,3,5-trichlorophenylboronic acid in THF was added over 1 h, maintaining the temperature below 30 °C. The transfer lines were rinsed with THF (2.8 L, 1 mL/g)), and this was added to the mixture. The reaction mixture was then stirred under nitrogen at 25 °C for 1 h before analysis to confirm reaction completion. Arbocel filter aid (2.64 kg, 0.94 g/g) was added to the reaction mixture and stirred for 45 min before filtering through a bed of Arbocel (0.50 kg, 0.18 g/g). The filter cake was transferred back into the reaction vessel and suspended in THF (42 L, 15 mL/g) with stirring for 45 min and then filtered through a bed of Arbocel (0.50 kg, 0.18 g/g). The filter cake was then suspended in THF and filtered through Arbocel once more using the same procedure. The transfer lines were rinsed with THF (2.8 L, 1 mL/g) and this was added to the filter cake. The combined filtration liquors were clarified through a ceramic filter, and EtOAc (25.2 kg, 28.0 L, 10 mL/g) was added. The reaction mixture was heated to distill the volume down to approximately 28 L, and then a further charge of EtOAc (25.2 kg, 28.0 L, 10 mL/g) was made. The reaction mixture was again heated to distill the volume down to approximately 20 L to crystallise the product. The mixture was then cooled down to 20 °C over 3.5 h and stirred at 20 °C overnight (12 h). The suspension was filtered, and the filter cake was washed with EtOAc (2 × 1.4 L, 0.5 mL/g). The product was then dried under vacuum overnight at 40 °C to give **20** as a crystalline solid (3.08 kg, 9.29 mol, 77%). The product may be purified as follows: **20** (3.07 kg, 9.26 mol) was added to EtOAc (15.3 L, 5 mL/g) and heated to reflux for 1 h to give a slurry. The mixture was then cooled to 20 °C over 3.5 h and stirred at this temperature overnight (13.5 h). The product was then filtered and washed with EtOAc (2 × 1.5 L, 0.5 mL/g) and dried under vacuum overnight at 40 °C to give **20** as a crystalline solid (2.86 kg, 8.63 mol, 93% yield); the residual palladium content was 257 ppm. Mp = 197 °C (from EtOAc); ^{1}H (400 MHz, DMSO-d_6) δ 3.83 (s, 3H), 6.19 (s, 2H), 7.28 (d, J = 7.62, 1H), 7.43 (s, 1H), 7.44 (d, J = 7.81, 1H), 7.89 (d, J = 2.54, 1H); ^{13}C (100 MHz, DMSO-d_6) δ 52.04, 112.87, 120.72, 129.71, 130.01, 130.33, 132.27, 133.32, 138.49, 139.30, 146.11, 156.38, 165.41. HRMS *m/z* Found 330.9815 $[M + H]^+$ $C_{13}H_{10}Cl_3N_2O_2$ requires 330.9802; $\nu_{max.}$ (neat) 3449, 3280, 3171, 2947, 1749, 1734, 1623, 1570, 1548, 1469, 1450, 1320, 1246, 1118, 1026, 827, 787 cm^{-1}.

***N*-Methyl-6-amino-5-(2,3,5-trichlorophenyl)pyridine-2-carboxamide (1).** Compound **20** (2.81 kg, 8.47 mol) was added to THF (8.43 L, 3 mL/g) with stirring at 20 °C under nitrogen. Methylamine (33% in EtOH, 11.2 L, 90.5 mol, 4 mL/g) was then added over 20 min, and the reaction was stirred at 25 °C for 5 h. The reaction mixture was transferred to a larger vessel, and the transfer line was rinsed with THF (8.43 L, 3 mL/g) and added to the reaction. Activated carbon (Darco KB, 2.11 kg, 0.75 g/g) was then added, and the mixture was stirred for 1.5 h. The reaction mixture was then filtered through Arbocel filter aid (2.2 kg, 0.8 g/g), and the filter cake was washed with THF (4.21 L, 1.5 mL/g). The reaction solution was slowly heated to reflux to degas the methylamine. EtOH (denatured with cyclohexane, 8.43 L, 3 mL/g) was then added, and the solution was distilled down to a volume of approximately 11

L. This addition−distillation cycle was repeated a further two times. EtOH (denatured with cyclohexane, 7.59 L, 2.7 mL/g) and water (9.27 L, 3.3 mL/g) were then added to the solution, which was then cooled to 40 °C, whereupon crystallisation initiated. The slurry was seeded with **1** (polymorph B, 5 g) and heated to reflux for 17 h. The slurry was then cooled to 40 °C over 90 min and a sample analysed by PXRD to check the morphology. The slurry was cooled to 20 °C over 30 min, stirred for 2 h, and filtered. The filter cake was washed with EtOH (denatured with cyclohexane, 2 × 1.41 L, 0.5 mL/g) and dried under vacuum overnight at 45 °C to give **1** as a crystalline solid (2.20 kg, 6.65 mol, 79% yield); the residual palladium content was 4 ppm. Mp = 227 °C (from EtOH); ^{1}H (400 MHz, MeOH-d_4) δ 2.95 (s, 3H), 7.35 (d, J = 2.5 Hz, 1H), 7.41 (d, J = 7.4 Hz, 1H), 7.44 (d, J = 7.4 Hz, 1H), 7.70 (d, J = 2.5 Hz, 1H); ^{13}C (100 MHz, MeOH-d_4) δ 26.34, 111.86, 122.27, 131.09, 131.25, 132.21, 134.41, 135.65, 140.29, 140.93, 149.65, 156.96, 167.66. HRMS m/z Found 329.9968 $[M + H]^+$ $C_{13}H_{11}Cl_3N_3O$ requires 329.9962; $\nu_{max.}$ (neat) 3418, 3362, 3324, 3217, 2931, 1658, 1612, 1582, 1532, 1466, 1411, 1382, 1235, 1118, 1032, 830, 759 cm^{-1}.

Measurement of Stability of Compound 16 at Various Temperatures and pH by flow NMR. Three stock solutions (10 mL, 11 mg/mL of crude **18**, sodium/potassium salt) of initial pH 9.5, were treated with solid KH_2PO_4 and K_2HPO_4 to give pH 4.8, 6.6, and 8.4, and each solution was dispensed to nine vials (1 mL per vial). The solutions were stirred and heated in air at 70, 85, or 100 °C for 3, 6, or 22 h. The solutions were cooled, and 100 μL samples were taken and diluted with 400 μL of H_2O and 500 μL of MeOH. NMR spectra were measured with a Varian INOVA 500 spectrometer equipped with a 60 μL flow probe P4774, employing solvent signal suppression for CH_3OH and H_2O. All the NMR spectra showed clean mixtures, in varying proportions, of remaining **18** (δ_H 2.16 (s, 3H), 7.73 (d, 1H), 8.13 (d, 1H)) and a single product **14** (δ_H 7.16 (d, 1H), 7.94 (d, 1H)). A singlet at δ_H 1.95 (s, 3H) was also noted, presumably corresponding to acetate.

Acknowledgment

We gratefully acknowledge the following for their practical contributions: Samantha Dunnage, David Fengas, Marcel Hoogenraad, Charlotte Lane, William Mitchell, Shahid Mohammed, Twana Saleh and Stefania Tabanella. We also thank Torren Peakman for flow NMR experiments.

Received for review April 15, 2009.

OP900092H