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Flexible and Scalable Route to HDAc Inhibitors Containing an Unusual Trisubstituted Pyridine Core

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ABSTRACT: A scalable route to histone deacetylase inhibitors containing an unusual 2-aryl-3-cyano-5-aminomethylpyridine core has been developed which has the flexibility to deliver a range of compounds on at least a multigram scale. The key step involves a novel Mannich reaction using 3-dimethylaminoacrolein, formaldehyde, and a secondary amine to yield a 2-(alkylaminomethyl)-3-dimethylaminoacrolein. Tuning of this reaction in process development was fundamental to the success of the approach in terms of flexibility and operability on scale-up. This new methodology will also enable access an underutilised family of 3,5-disubstituted pyrid-2-ones and 2,3,5-trisubstituted pyridines.

INTRODUCTION

The substituted pyridine motif is ubiquitous in both naturally occurring and synthetic biologically active molecules. Within this broad family, the 2,3,5-trisubstituted pyridines are a highly desirable template for pharmaceutical research.[1] Despite this, synthetic tractability often limits their exploitation in medicinal chemistry programmes.

As part of a long-standing research programme into the development of potent, orally dosed inhibitors of histone deacetylase (HDAc),[2] we required access to a range of compounds of type **1** (Figure 1),[2h,j] containing the highly unusual 2-aryl-3-cyano-5-aminomethylpyridine motif. Outside of our work,[2h,j] we have identified only one other report of this structural subunit.[3]

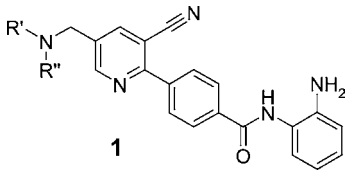

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Figure 1. General target structure for HDAc inhibitors.

Given the potential that several compounds of type **1** would be required on a scale of 10 g to 10 kg for preclinical or clinical studies, any synthetic approach employed should be amenable to scale-up. The route should ideally allow flexibility in the order of steps to facilitate optimisation during scale-up investigations. Furthermore, as a range of structurally similar compounds were to be prepared, the route should allow a variety of alkyl amine functionality to be installed with ease.

RESULTS AND DISCUSSION

With these requirements in mind, we embarked upon a retrosynthetic analysis of the general structure **1** in an effort to define an approach that met these criteria. As depicted in Scheme 1, we conceived a convergent approach that relied upon access to two key intermediates: pyridine **5** and boronate ester **6**. The boronate ester **6** should be readily accessible from **7** and **8**, which are commercially available. Though Scheme 1 shows (in the forward direction) Suzuki coupling followed by introduction of the varying amine moiety, we expected the order of these steps to be interchangeable, affording the desired flexibility in the route design.

As expected, the formation of boronate ester **6** was accomplished *via* coupling of **7** and **8** (Scheme 2). It was quickly identified that *N*-(4,6-dimethoxy-1,3,5-triazin-2-yl)-*N*-methylmorpholinium chloride (DMTMM; **9**), prepared *in situ* from 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT) and *N*-methylmorpholine, was the coupling agent of choice. A simple workup gave boronate ester **6** in excellent purity as a free-flowing white powder, with yield routinely greater than 90%. With boronate ester **6** in hand, our attention moved to the coupling partner, pyridine **5**. Though the proposed chloromethylpyridine **5b** is unknown, there is a single report of the corresponding aldehyde **5a** in the patent literature.[4]

Preliminary investigation of this synthesis (shown in Scheme 3) showed a Knoevenagel condensation between acetaldehyde and malononitrile proceeded efficiently,[5] but subsequent conversion to the pyridine proved to be a low yielding, capricious reaction. Despite several studies into altering the reaction time, temperature, and base, the highest yield observed was 35%. The highest yield was achieved by controlled dropwise addition of the ethylidene nitrile intermediate to preformed Vilsmeier chloroiminium ion at 90 °C. The reaction time proved to be critical, and the yield was shown to diminish if the reaction was heated for more than 1 h. The inherent thermal instability of the product also had a detrimental impact in the subsequent Suzuki reaction. Furthermore, an undesirable exotherm was observed on scale-up of the chloroiminium

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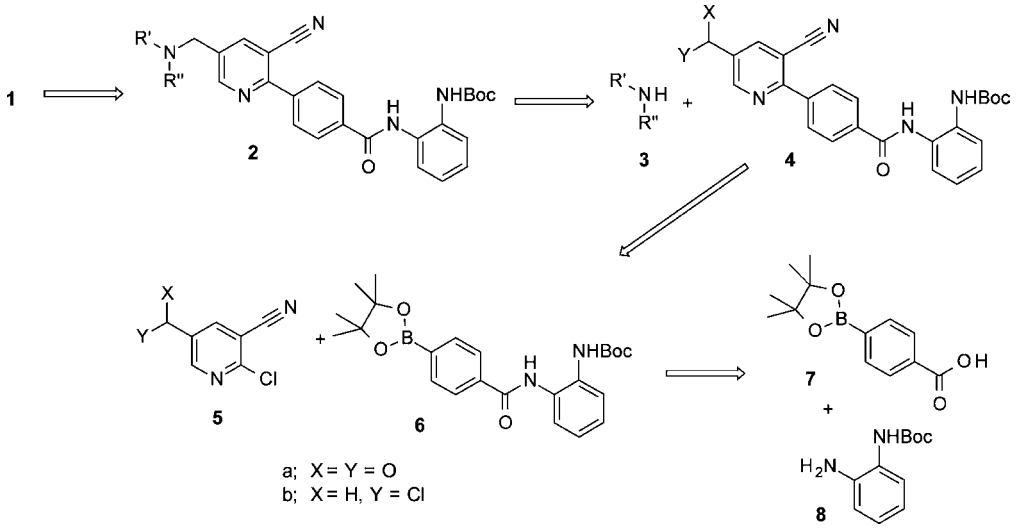
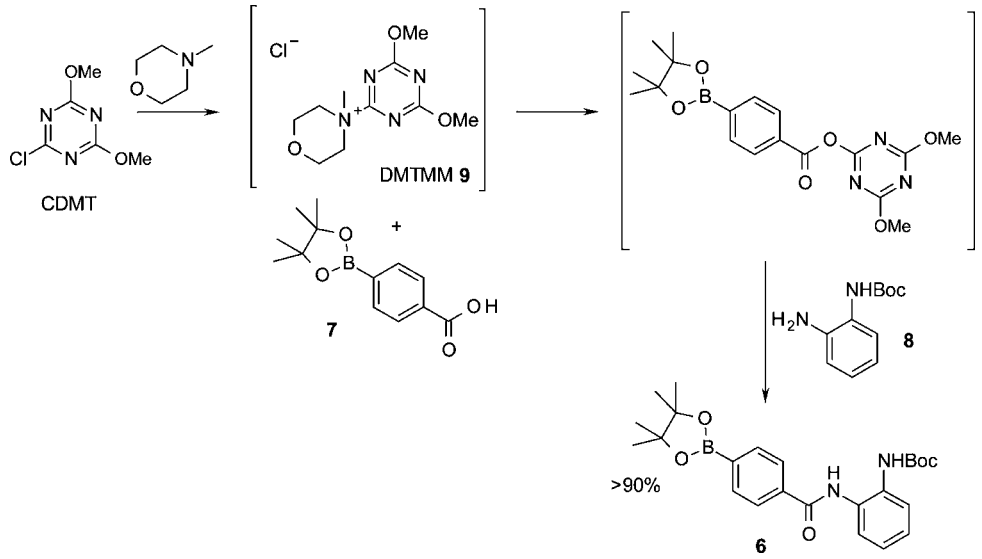
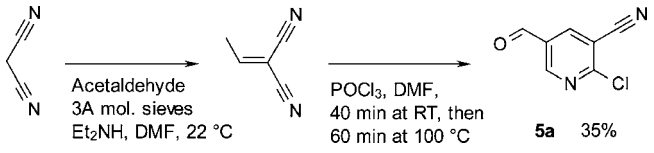
Scheme 1. Retrosynthetic Analysis of General Structure 1



Scheme 2. Formation of Boronate Ester 6



Scheme 3. Literature Synthesis of Pyridine Aldehyde 5a

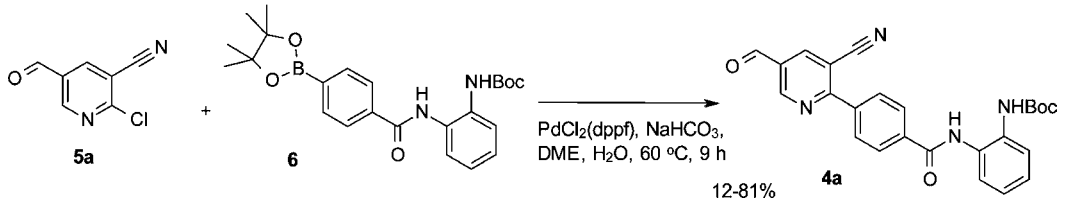


chemistry, and difficult chromatography of the final product would have serious implications for larger scale production.

Concurrent to investigation of the synthesis of pyridine aldehyde **5a**, we went on to study the Suzuki coupling of the two key fragments **5a** and **6** (Scheme 4) leading to the advanced biaryl core **4a** intermediate.

Significant optimisation was carried out on this stage. The reaction, though high-yielding on occasion, again proved to be capricious. The yield and quality of product depended heavily on the temperature-control of the reaction (aldehyde **5a** decomposes above 50 °C to a complex mixture of products), the quality of the catalyst (batches of Strem 1,1′-bis-(diphenylphosphino)ferrocenedichloropalladium(II) having

Scheme 4. Suzuki Coupling To Give the Key Biaryl Core 4a



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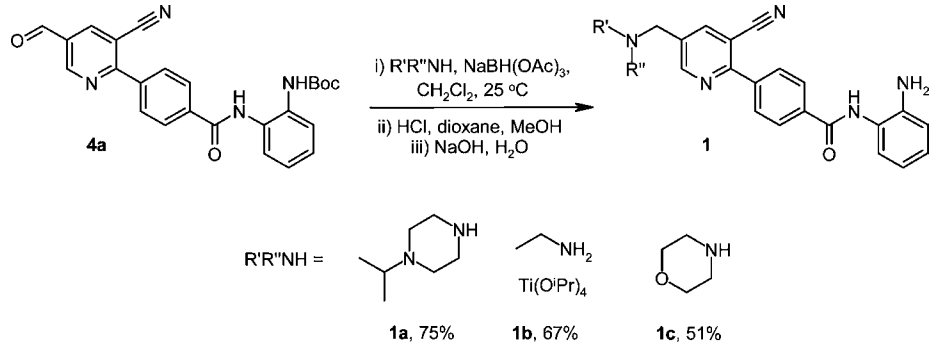
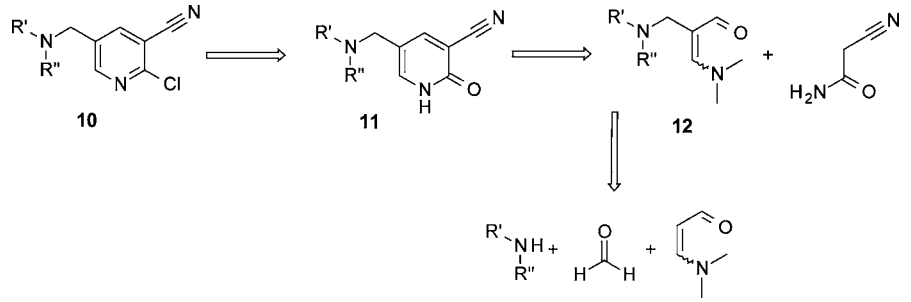
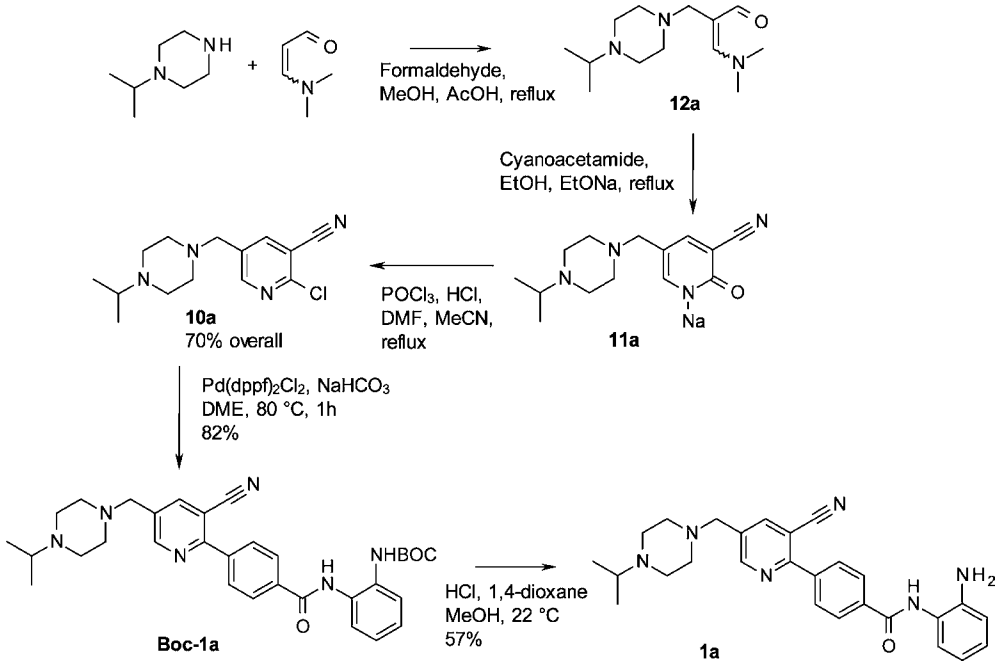
Scheme 5. HDAc Inhibitors 1 from 4a *via* Reductive Amination and Deprotection



Scheme 6. Retrosynthetic Analysis of the Pyridine Fragment



Scheme 7. "Mannich Approach" to 5-Aminomethylpyridines



significantly higher efficacy than others), and the atmosphere (the reaction appeared to require a rigorously inert atmosphere). Nevertheless, we did have access to the key biaryl **4a** in sufficient quantities to prepare over 120 compounds of type **1** (for examples, see Scheme 5) for initial testing.[2h,j]

Though this initial strategy allowed access to many compounds of type **1** on a milligram scale, there were significant issues associated with the approach, as discussed above. In summary: The synthesis of pyridine aldehyde **5a** remained capricious and low-yielding and employed hazardous chemistry, the Suzuki coupling was subject to several limitations, and finally, the use of primary amines in the reductive amination of **4a** proved to be challenging. Primary amines exhibited low reactivity using the standard sodium triacetoxyborohydride conditions,[6] and the addition of titanium(IV) isopropoxide was required to drive the reaction to completion.

The drawbacks outlined above, coupled with demand for increasingly larger amounts of material for continued testing,

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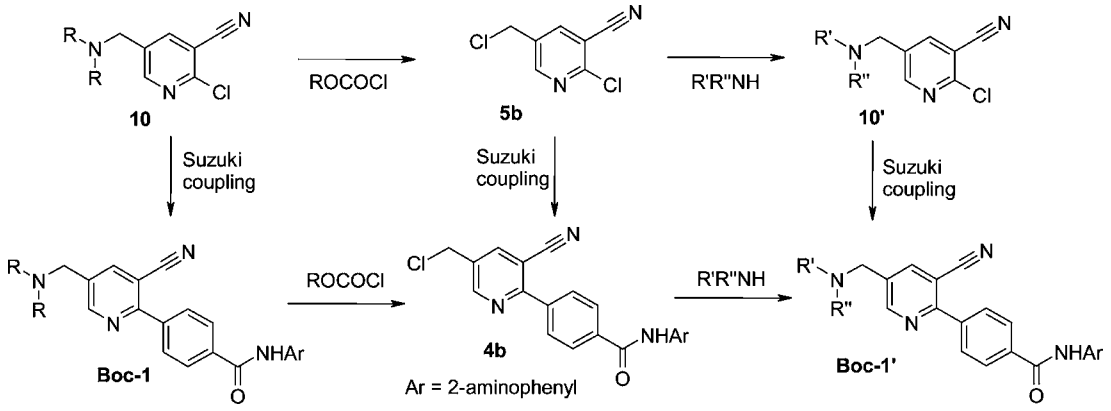
Scheme 8. Flexible "Mannich Approach"



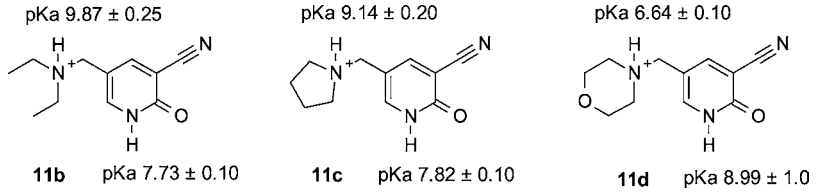


Figure 2. Calculated pK_a values for selected pyridones of type **11**.

led us to reconsider our strategy. Specifically, we required an alternative approach to pyridines of type **5** that avoided the troublesome Vilsmeier-based approach (Scheme 3). We also wanted to entirely avoid the use of the thermally unstable pyridine aldehyde **5a**.

In an effort to address these issues, we conceived of an alternative strategy in which the key biaryl forming Suzuki reaction would be achieved with 2-chloropyridines already containing the amine moiety, thus avoiding pyridine aldehyde **5a** and circumventing the problematic reductive aminations. We therefore subjected the generic structure **10** to a comprehensive retrosynthetic analysis, with the objective of identifying a route which satisfied the initial requirements of scalability and flexibility whilst carrying none of the issues identified above. One attractive approach involved a novel Mannich transformation and is discussed herein.

As shown in Scheme 6, we envisaged 2-chloropyridines of type **10** would be available by chlorination of **11**. Pyridone **11** should be accessible *via* a well-precedented condensation of cyanoacetamide and a 1,3-dicarbonyl or an equivalent such as **12**.[7] The key step of this proposed approach is the novel Mannich-type reaction on commercially available 3-dimethylaminoacrolein to install the desired aminomethyl moiety. Though similar transformations have been carried out on cyclic enaminone-type substrates,[8] to our knowledge such a methodology has thus far not been applied to 3-(dialkylamino)-acroleins.

Preliminary studies, using *N-iso*-propylpiperazine as the amine component, showed this to be a viable approach to pyridines of type **10** (Scheme 7). We were gratified to find the key Mannich-type reaction furnished the functionalised acrolein **12a** with high conversion. This is the first known example of a Mannich reaction using an acyclic enaminal or enaminone. Following condensation and chlorination, the desired chloropyridine **10a** was produced in approximately 70% overall yield. Even more pleasing was the fact that the Suzuki reaction of **10a** and boronic ester **6** proved much more efficient and robust.

However, despite the successes of this "Mannich" approach to **10a** discussed above, it did not meet all of the original criteria, *i.e.* a flexible, scalable route to compounds of type **1**. There were two main drawbacks to the synthesis: First, the pyridone anion **11a** could only be isolated by concentration of the reaction mixture and trituration, operations which are not particularly amenable to scale-up. This is primarily due to the zwitterionic nature of the parent hydroxypyridine of **11a**, which did not allow formation of a neutral species. Second, and more importantly, this approach only gave access to dialkylaminomethyl pyridines, such as **10a**. The use of primary amines, such as ethylamine, or protected analogues, such as *N*-benzylethylamine, in the Mannich reaction with dimethylaminoacrolein resulted only in degradation products, making this route unusable for synthesis of compounds such as **1b**.

Identification of these issues gave us cause to reconsider the "Mannich approach", in an effort to exploit its advantages and avoid the disadvantages, whilst maintaining the desired route flexibility necessary to respond to demands for 50−500 g-scale manufacture of compounds of type **1** as and when required.

It was evident to us that the choice of secondary amine partner would be key to the success of this strategy: First, the functional group interconversion of substituted benzylamines to the corresponding benzylchlorides *via* reaction with alkylchloroformates is well-precedented.[9] If an inexpensive, "disposable" amine could be employed in the Mannich-based synthesis of **10**, then such a transformation would allow access to fragment **5b** *via* simple amination of the intermediate **13** (Scheme 8).

This would therefore give us the desired flexibility in terms of the amine. Furthermore, this modified approach should allow facile reordering of steps should later development work identify the need. The various route options are also outlined in Scheme 8.

Second, judicious choice of amine should also allow us to address the isolation issues surrounding pyridones of type **11**. As shown in Figure 2, the calculated pK_a values[10] for pyridones formed with standard secondary amines, such as diethylamine

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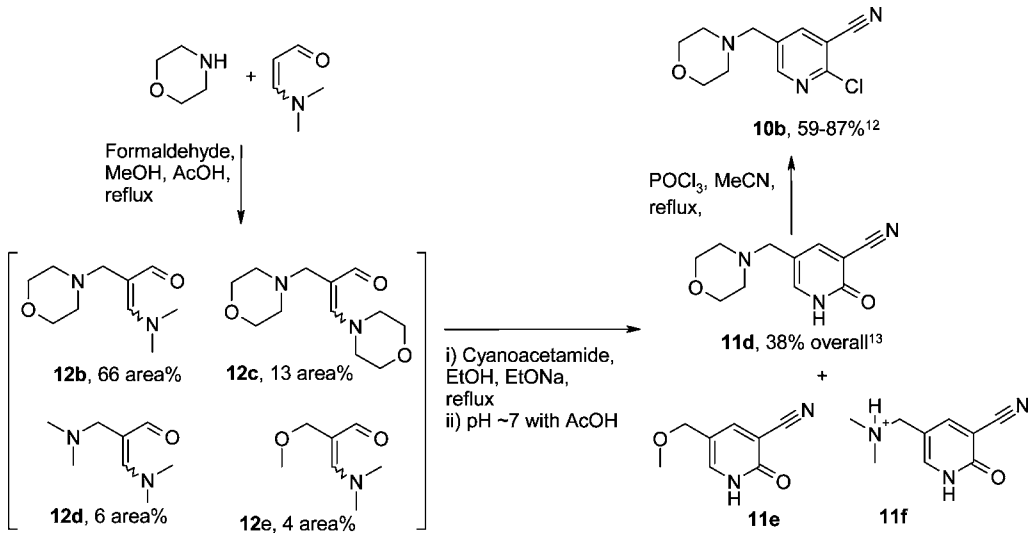
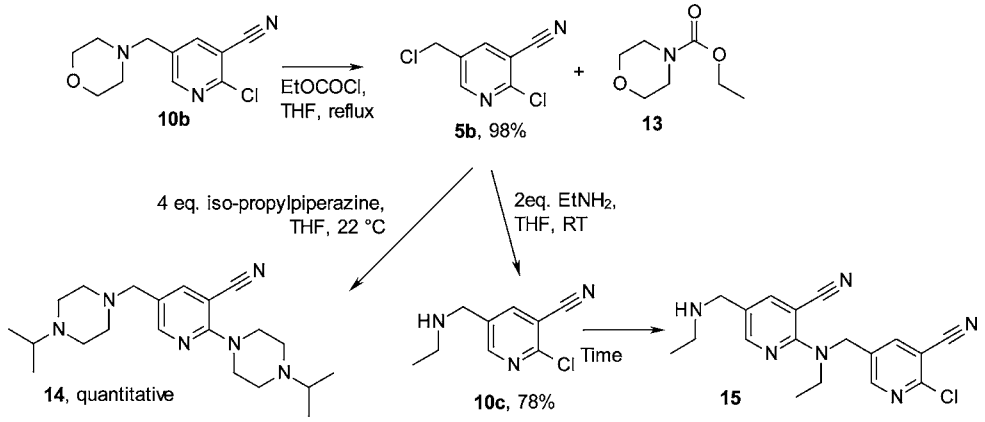
Scheme 9. Morpholine-Based Mannich Approach



Scheme 10. Preliminary Chlorination and Amination Studies



and pyrrolidine (**11b** and **11c**, respectively), indicate zwitterionic character, with the tertiary amine moiety being significantly more basic than the pyridone function. The basicity of morpholine, however, is tempered by the electron-withdrawing nature of the β-oxygen. The calculated pK_a values for the corresponding pyridone **11d** show that the pyridone is indeed more basic than the amine, by a factor of around 2 pK_a units.

Given that morpholine is inexpensive and readily available, we chose this as our amine coupling partner. The Mannich reaction of morpholine with 3-dimethylaminoacrolein gave a complex mixture of products, of which the major components **12b**–**e** were identified by GCMS (Scheme 9). Presumably, **12c** arises from reaction of either 3-dimethylaminoacrolein or product **12b** with morpholine, liberating dimethylamine. A Mannich reaction involving 3-dimethylaminoacrolein and dimethylamine would give **12d**. Lastly, minor byproduct **12e** is formed as methanol solvent forms transient oxonium ions when reacted with formaldehyde under acidic conditions. An isolated example of this process has been reported.[11] Due to the intractable nature of this mixture, no purification was carried out at this stage and the mixture was used directly in the reaction with cyanocetamide. This, in turn, gave the desired pyridone **11d** in acceptable yield after neutralisation with AcOH. This was accompanied by ether **11e** and ammonium species **11f**. These byproducts are, however, efficiently removed in the workup and isolation of **11d**, which crystallises well from MeCN. Finally, reaction of pyridone **11d** with $POCl_3$ in MeCN gives the chloropyridine **10b**.[13] It should be noted that the 2-chloro-3-cyano-5-aminomethyl-pyridine motif exemplified by compounds **10a** and **10b** in itself is also biologically relevant,[12] yet it too remains poorly represented in the literature.

With the key chloropyridine **10b** on hand in sufficient quantities, we moved on to examine the subsequent transformations (Scheme 10). As shown, preliminary studies confirmed that the chlorination of **10b** was an efficient process, affording **5b** in excellent yield. Unfortunately, removal of the byproduct morpholine carbamate **13** *via* nonchromatographic methods proved challenging.

The reactivity of **5b** and its derivatives also proved to be problematic. Primary amines could be selectively reacted at the chloromethyl position with careful monitoring of the reaction conditions, *e.g.* with ethylamine to give **10c**. Secondary amines, however, were nucleophilic enough to also react at the chloropyridine position. So, in the case of *iso*-propylpiperazine, the sole product formed was the disubstituted species **14**. With ethylamine, the product was shown to dimerise on standing to give **15**.

These preliminary observations allowed us to quickly decide upon a final strategy, based on our original plans set out in

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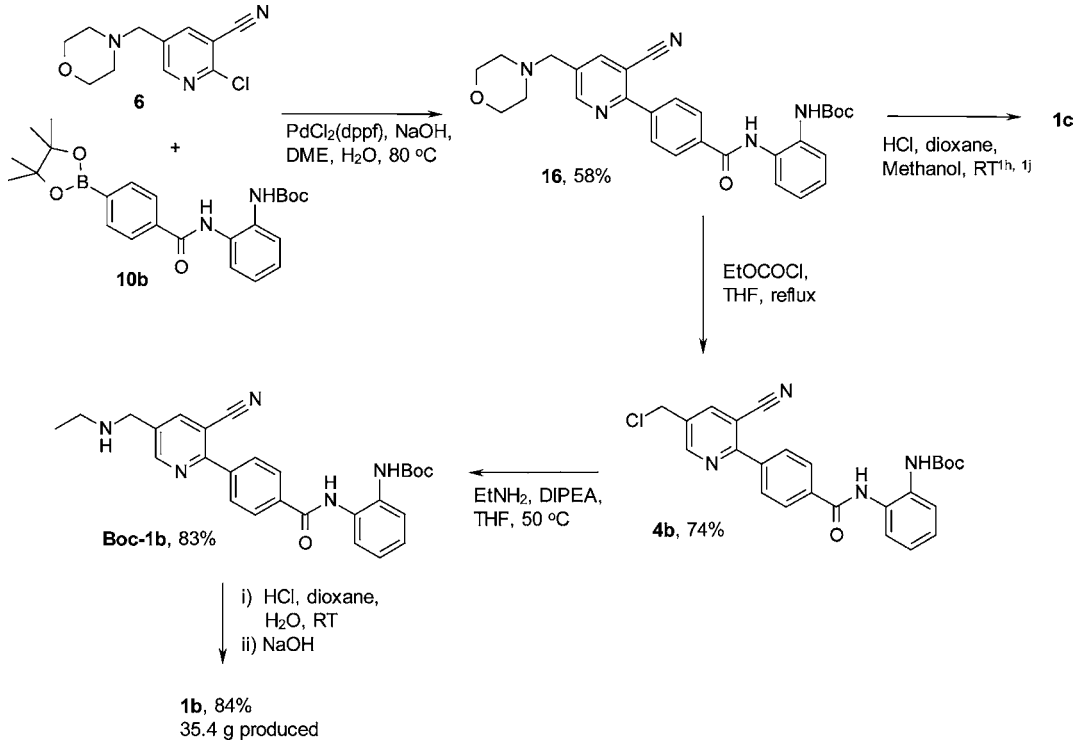
Scheme 11. Synthesis of Target Molecules 1b and 1c



Scheme 8: The issues associated with addition of secondary amines to the chloropyridine position of **5b** ruled out chlorination−substitution−coupling as an approach. We also decided against the possible chlorination−coupling−substitution route, as we felt that, under the Suzuki reaction conditions, there would be significant risk of reaction between **5b** and the product **4b** at the amide function, accompanied by dimerization of **4b** *via* the same mechanism. We therefore moved on to the latter stages of the project, adopting a coupling−chlorination−substitution strategy.

Optimisation and scale-up studies of this strategy allowed its utilisation in the 50 g-scale production of several candidate APIs of type **1** (Scheme 11). As can be seen, the Suzuki reaction of the morpholinomethyl chloropyridine **10b** and the boronate ester **6** proceeded in excellent yield, on scales of up to 45 g. Chlorination of this intermediate also proceeded efficiently, providing **4b** on a 66 g scale.

With **4b** in hand, we were in position to synthesise large amounts of candidate APIs that were required, due to the flexibility inherent in the approach adopted. In the event just one API was required on medium scale, 35 g of **1b** was produced using this approach. Importantly, the substitution reaction proved robust and reliable for the primary amines (e.g., ethylamine), in contrast to the reductive amination outlined in Scheme 5. We also gained access to the morpholine analogue **1c** by deprotection of intermediate **16**.

CONCLUSION

In summary, a scalable route to HDAc inhibitors containing an unusual 2-aryl-3-cyano-5-aminomethylpyridine core has been developed which has the flexibility to deliver a range of API targets on at least a multigram scale. The key step involves a novel Mannich reaction using 3-dimethylaminoacrolein, formaldehyde, and a secondary amine to yield a 2-(alkylaminomethyl)-3-dimethylaminoacrolein. Tuning of this reaction in process development was fundamental to the success of the approach in terms of flexibility and operability on scale-up. This approach has so far enabled the efficient synthesis of one API (**1b**) on a 35 g scale, as well as two more on a smaller scale (**1a** and **1c**). In addition, this new methodology will enable chemists to access an underutilised family of 3,5-disubstituted pyrid-2-ones and 2,3,5-trisubstituted pyridines.

EXPERIMENTAL SECTION

All materials were purchased from commercial suppliers. Unless specified otherwise, all reagents and solvents were used as supplied by manufacturers. Nuclear magnetic resonance spectra were determined using a Jeol JNMEX 400 spectrometer or a Bruker AM300 spectrometer. All ^{1}H NMR assays were performed using maleic acid as an internal standard. LCMS spectra were determined using a Waters Micromass instrument with a XSELECT CSH C18, 5 μm, 2.1 mm × 50 mm column. LCMS peak areas were uncalibrated.

Preparation of *N*-(2-*tert*-Butoxycarbonylaminophenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-benzamide (6). To a solution of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzoic acid (**7**) (6.71 g, 26.3 mmol) in acetontrile (54 mL) was added 2-chloro-4,6-dimethoxy-1,3,5-triazine (4.98 g, 27.5 mmol) and *tert*-butyl (2-aminophenyl)-carbamate (**8**) (5.37 g, 25.0 mmol). The resulting slurry was stirred at ambient temperature, and *N*-methylmorpholine (5.56 g, 6.1 mL, 55.0 mmol) was added dropwise. All the solids rapidly dissolved, and the resulting solution was stirred at ambient temperature until analysis by HPLC showed no **8** remained (~3 h). To this slurry was added water (50 mL), causing further precipitation. The mixture was stirred for a further 45 min, and the solid was then collected by vacuum filtration, washed twice with 50:50 (v/v) acetonitrile/water (2 × 15 mL), and dried *in vacuo* to a constant weight to yield the title compound **6** (9.68 g, 86.2%, purity 97.7% (w/w) by ^{1}H

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NMR assay) as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm) 1.30 (12 H, s), 1.42 (9 H, s), 7.16 (2 H, m), 7.55 (2 H, m), 7.82 (2 H, d, J = 8.2 Hz), 7.97 (2 H, d, J = 8.2 Hz), 8.70 (1 H, s), 9.89 (1 H, s). ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm) 25.6, 28.9, 80.6, 84.9, 124.8, 125.1, 126.6, 127.0, 127.8, 130.6, 132.6, 135.3, 137.6, 154.4, 166.0.[14] LRMS (ESI$^+$) m/z 439 (MH$^+$).

Preparation of *N*-(2-*tert*-Butoxycarbonylaminophenyl)-4-(3-cyano-5-formylpyridin-2-yl)benzamide (4a). 2-Chloro-3-cyano-5-formylpyridine[2] (456 mg, 2.74 mmol), compound **6** (1.2 g, 2.74 mmol), 1,1′-bis(diphenylphosphino)-ferrocene−palladium(II) dichloride dichloromethane complex[15] (112 mg, 0.137 mmol), 1,2-dimethoxyethane (12 mL), and a saturated aqueous solution of sodium hydrogen carbonate (6 mL) were stirred at 60 °C under an atmosphere of nitrogen for 7.5 h. The mixture was allowed to cool before being partitioned between dichloromethane and water. The organics were separated, dried over Na_2SO_4, filtered, and evaporated. The crude product was purified by chromatography on silica, eluting with 40:60 ethyl acetate/isohexane to yield the title compound **4a** (615 mg, 51%, 95% purity by LCMS area) as a cream solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm) 1.46 (9 H, s), 7.20 (2 H, m), 7.58 (2 H, td, J = 1.45, 6.91, 6.01 Hz), 8.11 (2 H, d, J = 8.54 Hz), 8.17 (2 H, d, J = 8.54 Hz), 8.70 (1 H, s), 8.92 (1 H, d, J = 2.01 Hz), 9.40 (1 H, d J = 2.01 Hz), 9.98 (1 H, s), 10.20 (1 H, s). ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm) 24.9, 28.0, 73.5, 79.6, 107.9, 116.8, 123.7, 124.0, 125.8, 126.2, 127.9, 129.3, 129.4, 132.0, 136.3, 139.2, 143.0, 153.4, 162.5, 164.7, 190.6. LRMS (ESI$^+$) m/z M + Na$^+$ 465.

Preparation of (2*E*)-3-(Dimethylamino)-2-[(4-isopropylpiperazin-1-yl)methyl]acrylaldehyde (12a). 1-Isopropylpiperazine (4.4 mL, 30.6 mmol) was added to a solution of 3-(dimethylamino)acrolein (2.82 g, 25.5 mmol) in ethanol (100 mL), followed by formaldehyde (37% solution in water, 2.3 mL, 30.6 mmol) and acetic acid (100 μL). The mixture was stirred at 50 °C for 3.5 h and then room temperature for 15 h. The solution was concentrated *in vacuo* and redissolved in ethanol (25 mL), and then formaldehyde (2.3 mL) and acetic acid (100 μL) were added. The mixture was stirred at 60 °C for 4 h and then concentrated *in vacuo* to yield the title compound **12a** (6.10 g, 90%, purity 99% by LCMS area) as a pale yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 1.03 (6 H, d, J = 6.4 Hz), 2.51 (8 H, m), 2.67 (1 H, m), 3.18 (2 H, s), 3.26 (6 H, s), 6.62 (1 H, s), 8.89 (1 H, s); LRMS (ESI$^+$) m/z 240 (MH$^+$).

Preparation of Sodium 3-Cyano-5-[(4-isopropylpiperazin-1-yl)methyl]pyridin-2-olate (11a). 2-Cyanoacetamide (5.36 g, 63.7 mmol) was added to a solution of **12a** (6.10 g, 25.5 mmol) in ethanol (150 mL), followed by dropwise addition of sodium ethoxide (21% solution in ethanol, 28.6 mL, 76.5 mmol) over 5 min. The solution was heated at reflux for 17 h and then cooled to room temperature. The yellow solid was filtered, and the filtrate was concentrated *in vacuo*. The residue was triturated with diethyl ether, and the solid obtained was dried to yield the title compound **11a** (8.74 g, purity 90% by LCMS area) as a pale yellow solid, which was used without further purification. ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm) 0.92 (6 H, d, J = 6.6 Hz), 2.27 (4 H, m), 2.38 (4 H, m), 2.55 (1 H, m), 3.10 (2 H, s), 7.24 (1H, d, J = 2.8 Hz), 7.74 (1 H, d, J = 2.8 Hz); LRMS (ESI$^+$) m/z 261 (MH − Na$^+$).

Preparation of 2-Chloro-5-[(4-isopropylpiperazin-1-yl)methyl]nicotinonitrile (10a). A 4.0 M solution of hydrogen chloride in dioxane (1.33 mL, 5.31 mmol) was added to a stirred suspension of **11a** (1.5 g, 5.31 mmol) in acetonitrile (15 mL). The mixture was heated to 40 °C, and phosphorous oxychloride (2.48 mL, 26.6 mmol) was added; then the mixture was heated at 80 °C for 18 h. After cooling to room temperature, isopropyl alcohol (8 mL) was added, and the mixture was stirred for 10 min. The mixture was diluted with water (50 mL) and basified with a solution of sodium hydroxide (1 M) to pH 8. The product was extracted with DCM (2 × 100 mL), and the extracts were dried over $MgSO_4$, filtered, and concentrated to yield the title compound **10a** (1.2 g, 81%, purity 95% by LCMS area) as a brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm) 1.05 (6 H, d, J = 6.6 Hz), 2.49 (4 H, m), 2.55 (4 H, m), 2.67 (1 H, m), 3.52 (2 H, s), 8.02 (1 H, d, J = 2.3 Hz), 8.50 (1 H, d, J = 2.3 Hz); LRMS (ESI$^+$) m/z 279/281 (MH$^+$).

Preparation of *tert*-Butyl {2-[(4-{3-Cyano-5-[(4-isopropylpiperazin-1-yl)methyl]pyridin-2-yl}benzoyl)amino]-phenyl}carbamate (Boc-1a). 1,1′-Bis(diphenylphosphino)-ferrocenedichloropalladium(II) chloride[15] (58 mg, 0.072 mmol) was added to a mixture of **6** (626 mg, 1.43 mmol), **10a** (398 mg, 1.43 mmol), saturated aqueous sodium hydrogen carbonate solution (5 mL), and 1,2-dimethoxyethane (10 mL). The mixture was heated at 80 °C for 1 h and then allowed to cool to room temperature and partitioned between dichloromethane (75 mL) and water (50 mL). The aqueous layer was extracted with further dichloromethane (2 × 75 mL). The combined organics were dried over magnesium sulfate, filtered, and then evaporated to dryness. The residue was purified by flash chromatography on silica, eluting with methanol (5−10%) in dichloromethane to yield the title compound **Boc-1a** (652 mg, 82%, purity 100% by LCMS area) as a yellow gum which crystallised on trituration with diethyl ether. ^{1}H NMR (DMSO-d_6, 400 MHz) 1.02 (6 H, d, J = 6.5 Hz), 1.50 (9 H, s), 2.50 (8 H, m), 2.69 (1 H, m), 3.67 (2 H, s), 7.25 (2 H, m), 7.62 (2 H, m), 8.07 (2 H, d, J = 8.5 Hz), 8.18 (2 H, d, J = 8.5 Hz), 8.38 (1 H, d, J = 2 Hz), 8.76 (1 H, s), 8.93 (1 H, d, J = 2 Hz), 10.00 (1 H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm) 18.6, 28.4, 48.3, 53.1, 54.1, 58.2, 80.0, 107.1, 117.9, 124.1, 124.4, 126.1, 126.6, 128.2, 129.3, 129.9, 132.4, 133.8, 135.8, 140.4, 142.5, 153.8, 158.1, 165.2, 165.8; HRMS (ESI$^+$) m/z 555.30786 (MH$^+$).

Preparation of *N*-(2-Aminophenyl)-4-[3-cyano-5-[(4-isopropylpiperazin-1-yl)methyl]-2-pyridyl]benzamide (1a). **Boc-1a** (344 mg, 0.621 mmol) was dissolved in methanol (10 mL), and a 4 M solution of hydrogen chloride in 1,4-dioxan (10 mL) addedm and then the solution was stirred at 22 °C for 2 h. The solvent was evaporated, and then methanol (5 mL) was added and the resulting solution absorbed onto an SCX-2 column, which was then washed with methanol (2 column volumes) and eluted with a 2 M solution of ammonia in methanol (2 column volumes). The ammonia/methanol solution was concentrated *in vacuo* to give a foam. This was treated with diethyl ether (20 mL), stirred, and filtered to yield the title compound **1a** (161 mg, 57%, 96% purity by LCMS area) as a white solid. ^{1}H NMR (DMSO-d_6, 500 MHz) 0.95 (6 H, d, J = 6.4 Hz), 2.44 (8 H, m), 2.60 (1 H, m), 3.60 (2 H, s), 4.94 (2 H, s), 6.60 (1 H, dt, J = 1.4, 7.6 Hz), 6.79 (1 H, dd, J = 1.4, 7.6 Hz), 6.98 (1 H, dt, J = 1.4, 7.6 Hz), 7.20 (1 H, m), 7.98 (2 H, d, J = 8.3 Hz), 8.14 (2 H, J = 8.3 Hz), 8.30 (1 H, J = 2.1 Hz), 8.86 (1 H, d, J = 2.1 Hz), 9.78 (1 H, s); ^{13}C NMR (125 MHz, DMSO) δ 18.2, 47.9, 52.9, 53.5, 57.8, 66.3, 106.6, 116.0, 116.1, 117.6, 123.0, 126.7, 127.9, 128.7, 133.3, 135.7, 139.5, 142.1, 143.2, 153.4, 157.8, 164.7; LRMS (ESI$^+$) m/z 455 (MH$^+$).

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Preparation of 5-(Morpholin-4-ylmethyl)-2-oxo-1,2-dihydropyridine-3-carbonitrile (11d). Aqueous formaldehyde (12.3 M, 29.0 mL, 357.3 mmol) was added to a solution of *N*,*N*-dimethylamino-2-propen-1-al (30.0 mL, 29.70 g, 299.6 mmol) in methanol (150 mL). The stirrer was started, and morpholine (31.0 mL, 30.97 g, 355.5 mmol) was added in three approximately equal portions (CAUTION: a large exotherm is observed over the course of this addition of approximately 30 °C). Once the temperature was stabilised, acetic acid (2.10 mL, 2.20 g, 36.7 mmol) was added. The resulting orange solution was then heated to gentle reflux and stirred until analysis by GC indicated complete consumption of starting material (~2.5 h). The reaction mixture was then cooled to 22 °C and concentrated *in vacuo* to a brown oil. GCMS analysis showed this to comprise the following: **12b**, 66.0 area %; **12c**, 12.9 area %; **12d**, 5.5 area %; **12e**, 3.8 area %. The oil was dissolved in IMS (340 mL) and transferred to a flask containing 2-cyanoacetamide (62.84 g, 747.5 mmol). To the stirred suspension was added 21% (w/w) sodium ethoxide in IMS (335.0 mL, 897.3 mmol). The mixture was warmed to gentle reflux and stirred until analysis by GC showed complete consumption of **12b**−**e** (~4 h). The mixture was then cooled to 40 °C and water (890 mL) was added, causing all solids to dissolve, followed by acetic acid (52.0 mL, 54.5 g, 907.5 mmol). The resulting mixture was transferred to a separating funnel and washed with water (70 mL). This was extracted three times with DCM (3 × 270 mL), and the combined organics was concentrated *in vacuo* to afford an orange solid. This solid was then suspended in acetonitrile (360 mL) and stirred for 1 h. The solid was then collected by vacuum filtration, washed twice with acetonitrile (2 × 100 mL), and dried in vacuo to a constant weight to give the title compound **11d** (26.01 g, 38.1%, purity 96.1% (w/w) by ^{1}H NMR assay), as a red/brown solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm) 2.33 (4 H, m), 3.23 (2 H, s), 3.55 (4 H, m), 7.66 (1 H, d, J = 2.6 Hz), 8.06 (1 H, d, J = 2.6 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm) 52.6, 57.2, 66.1, 103.0, 114.8, 116.4, 140.8, 150.4, 159.8; HRMS (ESI$^+$) m/z 220.10806 (MH$^+$). Calc 220.10805.

Preparation of 2-Chloro-5-(morpholin-4-ylmethyl)-nicotinonitrile (10b). To a stirred suspension of **11d** (24.95 g, 109.4 mmol) in acetonitrile (250 mL) was added phosphoryl chloride (20.5 mL, 33.82 g, 220.6 mmol) over 10 min. The mixture was heated to gentle reflux and stirred for 18 h. The mixture was cooled to 0−5 °C, and a suspension formed. To this mixture was added a 3.0 M NaOH solution (365 mL, 1.10 mol) dropwise over 30 min: **CAUTION:** *this addition is exothermic.* To this slurry was then added DCM (250 mL), and the solid was removed by filtration. The cake was washed with DCM (125 mL). The resulting biphasic mixture was separated and the aqueous layer extracted with further DCM (125 mL). The combined organics were washed sequentially with water (125 mL) and brine (125 mL) and then concentrated *in vacuo* to give a brown solid. This solid was suspended in MTBE (375 mL) and warmed to reflux for 45 min. The solids were removed by hot vacuum filtration, and the residues were washed with hot MTBE (50 mL). The combined MTBE solution was allowed to cool slowly to ambient temperature, and the product crystallised. The solid was collected by vacuum filtration and washed with MTBE (50 mL) and dried *in vacuo* to give the title compound **10b** (15.45 g, 64.8 mmol, 59.3%, purity 99.1% (w/w) by ^{1}H NMR assay), as a yellow crystalline solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm) 2.38 (4 H, m), 3.56 (2 H, s), 3.58 (4 H, m), 8.38 (1 H, d, J = 2.3 Hz), 8.63 (1 H, d, J = 2.3 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm) 52.7, 57.6, 66.0, 109.3, 115.0, 133.8, 143.9, 149.7, 153.6; LRMS (ESI$^+$) m/z 238/240 (MH$^+$).

Preparation of 2-Chloro-5-(chloromethyl)-nicotinonitrile (5b). To a stirred solution of **10b** (8.00 g, 33.56 mmol) in THF (80 mL) was added ethyl chloroformate (4.00 mL, 4.54 g, 41.83 mmol). The solution was heated to reflux for 23 h. HPLC indicated the reaction had gone to approximately 90% completion. A further portion of ethyl chloroformate (2.40 mL, 2.72 g, 25.1 mmol) was added, and the solution was heated to reflux for a further 19 h. The solution was cooled to 25 °C and then poured into a mixture of potassium bicarbonate (56.06 g, 112.0 mmol) and ethyl acetate (120 mL). The flask was rinsed with ethyl acetate (40 mL). The phases were separated, and the organics were then washed with water (2 × 20 mL) and brine (40 mL) and then concentrated *in vacuo*. The residue was triturated with MTBE (30 mL), and the colourless solid was removed by filtration. The organic solution was concentrated *in vacuo* to yield **5b** (13.59 g; 32.84 mmol, 97.9%, purity 45.2% (w/w) by ^{1}H NMR assay) as an orange oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm) 4.86 (2 H, s), 8.60 (1 H, d, J = 2.4 Hz), 8.79 (1 H, d, J = 2.4 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm) 41.0, 109.8, 114.6, 133.7, 144.0, 150.7, 153.4.

Preparation of 2-Chloro-5-[(ethylamino)methyl]-nicotinonitrile (10c). Ethylamine (2.0 M solution in THF, 2.30 mL, 4.60 mmol) was added to **5b** (445 mg, 1.16 mmol), resulting in the formation of a suspension. This was stirred at 22 °C for 2 h. The mixture was poured into water (7 mL) and 2 M hydrochloric acid solution (2 mL, 4 mmol); then it was washed with ethyl acetate (5 mL). The aqueous solution was basified with 2 M sodium hydroxide solution (5 mL, 10 mmol) and then extracted with ethyl acetate (10 mL). The organics were washed sequentially with water (5 mL) and brine (5 mL) and then concentrated *in vacuo*. To the residue was added MTBE (2 mL), and then the solid was removed by filtration and washed with MTBE (1 mL). The combined organics were then concentrated in vacuo to yield **10c** (217 mg, 0.902 mmol, 78.1%, purity 81.4% (w/w) by ^{1}H NMR assay) as a yellow oil. ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm) 1.02 (3 H, t, J = 6.9 Hz), 2.49 (2 H, m), 3.54 (1 H, m), 3.74 (2 H, s), 8.39 (1 H, d, J = 2.4 Hz), 8.64 (1 H, d, J = 2.4 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm) 14.9, 42.7, 48.5, 109.0, 115.1, 136.9, 143.1, 149.0, 152.9. LRMS (ESI$^+$) m/z 196/198 (MH$^+$).

Preparation of *tert*-Butyl [2-({4-[3-Cyano-5-(morpholin-4-ylmethyl)pyridin-2-yl]benzoyl}amino)phenyl]-carbamate (16). To a solution of **10b** (35.0 g, 150 mmol) and **6** (64.7 g, 150 mmol) in 1,2-dimethoxyethane (1000 mL) was added 1,1′-bis(diphenylphosphino)ferrocenedichloropalladium-(II) (5.0 g, 6.83 mmol), followed by saturated sodium bicarbonate solution (23 mL). The reaction mixture was degassed with nitrogen for 5 min and then heated to 80 °C for 4 h. The reaction mixture was diluted with water and extracted with dichloromethane. Dichloromethane extracts were combined, dried over magnesium sulphate, and concentrated. The crude product was purified by flash chromatography (eluting with ethyl acetate/isohexane) to yield **16** (87.6 mmol, 45.0 g, 58%, purity 96% by area LCMS) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.47 (9 H, s), 2.42−2.46 (4 H, m), 3.57−3.62 (4 H, m), 3.64 (2 H, s), 7.16−7.19 (1 H, m), 7.22−7.25 (1 H, m), 7.58−7.61 (2 H, m), 8.03−8.05 (2 H, m), 8.14−8.16 (2 H, m), 8.37 (1 H, d, J = 1.9 Hz), 8.72 (1 H, s), 8.92 (1 H, d, J = 1.9 Hz), 9.97 (1 H, s). ^{13}C NMR (100 MHz, DMSO-

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d_6) δ 29.0, 53.9, 59.1, 67.0, 80.5, 107.7, 118.4, 124.6, 124.9, 126.6, 127.1, 128.7, 129.8, 130.4, 132.9, 134.0, 136.4, 140.8, 143.2, 154.3, 154.4, 158.6, 165.0. LRMS (ESI^-) m/z 514 ($[M - H]^-$).

Preparation of *tert*-Butyl [2-({4-[5-(Chloromethyl)-3-cyanopyridin-2-yl]benzoyl}amino)phenyl]carbamate (4b). To a solution of **16** (26.0 g, 50.6 mmol) in THF (250 mL) was added ethyl chloroformate (14.5 mL, 151.8 mmol) dropwise over 5 min. The reaction was heated at reflux temperature for 18 h. The reaction mixture was cooled to 25 °C and then added to ethyl acetate (500 mL) and saturated sodium bicarbonate solution (350 mL). The layers were partitioned, and then the aqueous layer was extracted with ethyl acetate (2 × 350 mL). Combined organics were dried over magnesium sulfate and then concentrated. The crude product was purified by flash chromatography (eluting with ethyl acetate/isohexane) to yield **4b** (36.7 mmol, 17.3 g, 74%, purity 95% by area LCMS) as a pale brown solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm) (400 MHz, DMSO-d_6) 1.47 (9 H, s), 4.96 (2 H, s), 7.16−7.19 (1 H, m), 7.22−7.25 (1 H, m), 7.57−7.61 (2 H, m), 8.05−8.07 (2 H, m), 8.14−8.16 (2 H, m), 8.59 (1 H, d, J = 2.2 Hz), 8.72 (1 H, s), 9.07 (1 H, d, J = 2.2 Hz), 9.98 (1 H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm) 29.0, 42.6, 80.5, 108.0, 118.0, 124.6, 124.9, 126.7, 127.1, 128.7, 129.9, 130.4, 132.9, 133.9, 136.6, 140.5, 143.2, 154.1, 154.3, 159.5, 165.7; HRMS (ESI^+) m/z 463.15332 (MH^+). Calc 463.15314.

Preparation of *tert*-Butyl {2-[(4-{3-Cyano-5-[(ethylamino)methyl]pyridin-2-yl}benzoyl)amino]-phenyl}carbamate (1b). To a solution of **4b** (66.0 g, 140 mmol) in tetrahydrofuran (1000 mL) was added diisopropylethylamine (52 mL, 290 mmol) and ethylamine (2 M solution in THF, 285 mL). The reaction mixture was stirred at 50 °C for 24 h. The reaction mixture was cooled to room temperature and then added to water, and product was extracted with ethyl acetate. The ethyl acetate extracts were combined, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by flash chromatography (eluting with ethyl acetate/isohexane) to yield **Boc-1b** (116 mmol, 54.8 g, 83%) as a yellow solid. 4 M Hydrogen chloride in dioxane (1300 mL) was added to a stirred suspension of **Boc-1b** (54.0 g, 114.5 mmol) in 1,4-dioxane (800 mL) at 10 °C over 1 h. The reaction mixture was allowed to warm to 22 °C and then stirred for 16 h. The mixture was cooled to 0 °C, and then water (300 mL) and diethyl ether (1000 mL) were added. This mixture was allowed to stir for 30 min, and then the layers were partitioned. The organic phase was washed with water (250 mL). The aqueous extracts were combined and basified to pH 7 with 10 M sodium hydroxide solution. The aqueous solution was extracted with dichloromethane and then dried ($MgSO_4$) and concentrated *in vacuo* to leave a yellow oil. This was dissolved in 2-propanol, and product was allowed to crystallise. The pale yellow solid was isolated by filtration, then washed with isopropanol and diethyl ether, and then dried under vacuum to yield **1b** (35.4 g, 84%, purity 98.9% (w/w) by ^{1}H NMR assay) as a white solid. ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm) 1.07 (3 H, t, J = 7.1 Hz), 2.57 (2 H, q, J = 7.1 Hz), 3.27 (1 H, s), 3.85 (2 H, s), 4.99 (2 H, s), 6.62 (1 H, t, J = 7.6 Hz), 6.80 (1 H, d J = 7.6 Hz), 7.00 (1 H, t, J = 7.6 Hz), 7.21 (1 H, d, J = 7.6 Hz), 7.99 (2 H, d, J = 8.2 Hz), 8.16 (2 H, d, J = 8.2 Hz), 8.39 (1 H, d, J = 1.9 Hz), 8.92 (1 H, d, J = 1.9 Hz), 9.83 (1 H, s); ^{13}C NMR (100 MHz, DMSO-d_6) δ 14.9, 42.8, 48.9, 106.5, 116.0, 116.1, 117.7, 123.0, 126.6, 126.8, 128.0, 128.7, 135.6, 135.7, 139.6, 141.4, 143.3, 152.9, 157.4, 164.8; LRMS (ESI^+) m/z 372 (MH^+).

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Notes

The authors declare no competing financial interest.

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(14) In this ^{13}C spectrum, there should be 16 carbon signals. However, the carbon bonded to boron cannot be seen in this spectrum, so only 15 carbons are published. This can be explained because naturally occurring boron has a $^{11}B/^{12}B$ ratio of 80:20. ^{11}B has a spin of $^3/_2$, and ^{12}B has a spin of 3. This leads to complicated splitting patterns imparted to the carbon bonded to it (80% split into a quartet, 20% split into a heptet). As the carbon is also a weak quaternary signal, this splitting has the effect of diluting the signal into the background. This effect is short-range, so it does not manifest itself in the other signals. In effect, we cannot see the missing carbon in the spectrum.
(15) 1,1′-Bis(diphenylphosphino)ferrocene−palladium(II)dichloride can be readily exchanged with 1,1′-bis(diphenylphosphino)ferrocene−palladium(II)dichloride dichloromethane complex without significant impact on the Suzuki reaction. The catalyst was chosen on the basis of availability at the time of the experiment.