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An efficient large-scale synthesis of alkyl 5-hydroxy-pyridin- and pyrimidin-2-yl acetate

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ABSTRACT

The synthesis of methyl 2-(5-hydroxy-3-methoxypyridin-2-yl)acetate and alkyl 2-(5-hydroxypyrimidin-2-yl)acetate is described. Methodology for an efficient access to 5-hydroxy-pyridin- and pyrimidin-2-yl acetate cores has been developed. Based on the difference in halogen reactivity, 5-bromo-2-chloropyridine and its pyrimidine analogue were functionalized judiciously by S_NAr and palladium-catalyzed reactions. The outlined strategy provides a high-yielding route suitable for large-scale synthesis of these compounds as well as paves the way for a potential rapid access to other heterocyclic analogues.

1. Introduction

As part of our continuing interest in C4-heteroaryloxy quinolines as inhibitors of kinases involved in angiogenesis, we required an efficient access to C2-(six-membered heterocyclic ring) acetic acid derivatives of general structure **1** (Fig. 1).

Three general approaches to these systems have been reported in the literature: 1) palladium-catalyzed α-arylation of esters with halogenoarenes has become a convenient route to benzylic esters and is mainly achieved via reaction of the Reformatsky reagent of *tert*-butyl acetate with different halogenoarenes;[1,2] 2) rearrangement of 2-methyl pyridine-*N*-oxides as reported by Golebiewski et al.;[3] 3) displacement of C2-heteroarylhalides with an appropriate nucleophile such as a malonate[4] or a malononitrile carbanion followed by monodecarboxylation.

Even though many natural products, drug candidates, synthetic intermediates, and precursors to emissive polymers possess an aromatic ring attached at the α-position of an acetate, we are not aware of any practical synthetic routes to substrate **2**. Regarding **3**, the established route wasn't suitable for large-scale synthesis. Herein, we report our findings on a general, rapid, and efficient synthesis of such compounds with different substitution patterns and varied electronic properties.

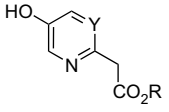
2. Results and discussion

2.1. Synthesis of methyl 2-(5-hydroxy-3-methoxypyridin-2-yl)acetate (2)

2.1.1. *The Golebiewski approach*

The Golebiewski rearrangement[3] involves the transformation of C-2 methyl pyridine-*N*-oxides into the corresponding C-2 methyl-alcohol pyridines by heating in acetic anhydride (Scheme 1). Subsequent displacement of the activated hydroxyl group by a cyanide anion followed by hydrolysis and C-5 benzyloxy deprotection gave the desired compound **1** (Fig. 1).

The preparation of the C-3 methoxypyridine **2** (Fig. 1) was envisaged via three routes based on this rearrangement[3] from commercially available starting materials (Fig. 2). The main potential drawback for route A[5] was the difficulties we anticipated in differentiating the bromine atoms at C-3 and C-5. We also considered building the pyridine core as shown in Route B via an oxazole and



1 Y = C, R = H
2 Y = C-OMe, R = Me
3 Y = N, R = Me, Et or tBu

Figure 1.

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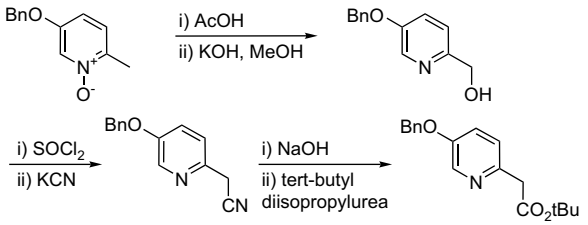


Scheme 1. Golebiewski rearrangement.

a Diels–Alder reaction, followed by a specific rearrangement. However, literature precedent led us to anticipate low yields for this sequence.[6] We then considered route C,[7] involving regioselective lithiation of 3-methoxy-5-formyl-pyridine to introduce the C-2 methyl group developed by Comins et al.,[8] but subsequent transformation to the hydroxyl group by the Bayer–Villiger reaction failed. Moreover all these approaches had the additional drawback of requiring at least 10 steps.

2.1.2. S_NAr approach

We focused, therefore, our efforts on nucleophilic substitution of 2-chloropyridine derivatives bearing two additional different substituents at C-3 and C-5. Pyridine **5**, with the required methoxy already in place at C-3 and a nitro group at C-5, was selected as our starting material. We postulated that **5** would be a suitable intermediate as the nitro function would be a good precursor to the C-5 hydroxyl group and would also facilitate the C-2 chlorine displacement by a malonate anion despite the de-activating mesomeric positive influence of the C-3 methoxy group. The synthesis of this compound has been described in 3 steps (methylation, nitration, chlorination) from commercially available pyridine-2,3-diol albeit in poor yield[9] but we were unable to reproduce the published yield for the methylation step.[10] Therefore, we used the commercially available 3-methoxy-1*H*-pyridin-2-one as our starting material and nitration gave the pyridone **4** in 37% yield. Treatment of **4** with a mixture of $POCl_3$ and PCl_5 afforded the C-2 chloro derivative **5** in 79% yield. S_NAr with the anion of methyl *tert*-butyl propanedioate followed by deprotection and decarboxylation in TFA, gave **7** in 83% yield. Reduction of the nitro function was carried out under hydrogen in the presence of palladium on charcoal, to give **8** in 77% yield (Scheme 2).

Transformation of the amino group of **8** directly into a hydroxyl group to give **2** via a diazotation/oxidation sequence[11,12] failed and Sandmeyer conditions[13] routinely afforded a mixture of the dibromo derivative **10** and the expected product **9** (Scheme 3). Therefore, we decided to add 2 equiv of CuBr to give exclusively **10** with the hope of selectively de-brominating at α-position to the carbonyl function. Indium in acetic acid has been reported for the

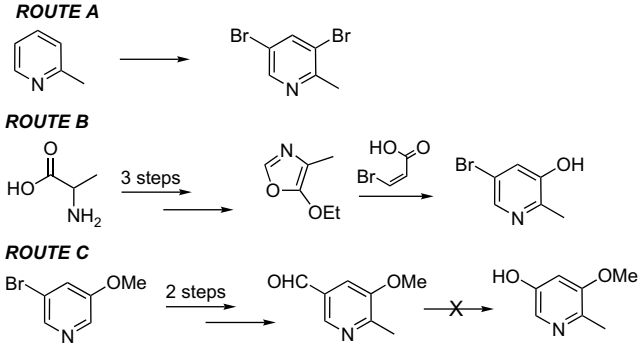
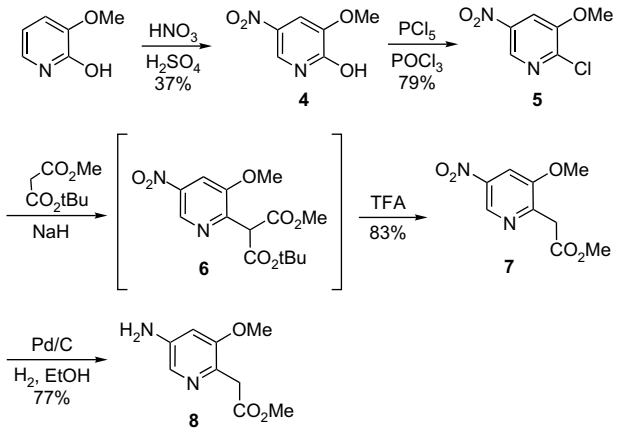
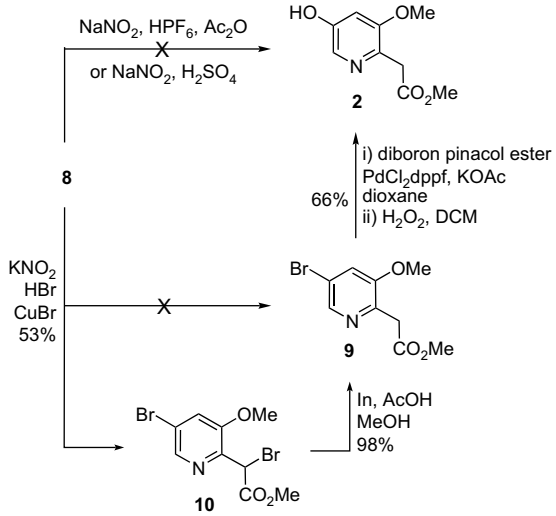


Figure 2. Golebiewski approach: routes envisaged for the syntheses of C-2 methyl substrates.



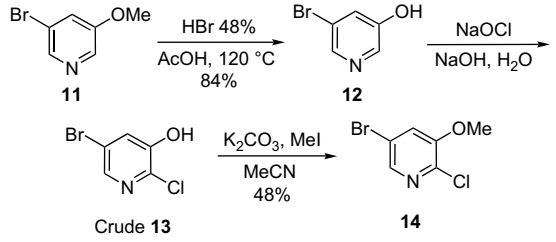
Scheme 2.

debromination of α-bromo phenyl acetic acid derivatives[14] and these conditions gave the desired compound **9** in 52% yield over two steps. Finally, the C-5 bromine atom was subjected to a hydroxydeboronation sequence[15] to introduce the hydroxyl group giving the desired C-5 hydroxypyridines **2** in 77% yield over two steps (Scheme 3). It is worth mentioning that we used the crude boronic ester intermediate in the subsequent mild hydroxydeboronation step.



Scheme 3.

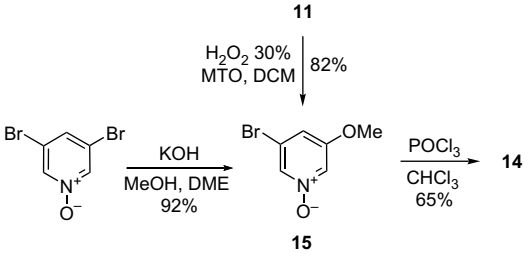
Although we managed to obtain the target product **2** from **9**, the yields were in general only moderate to low, and the overall number of steps was disappointing. Therefore, we turned our attention to molecule **11** as an alternative starting material. This compound was obtained in one step from commercially available 3,5-dibromo-pyridine.[16] Its direct chlorination was unsuccessful.



Scheme 4.

Koch et al.[12] have shown that chlorination of 5-bromopyridin-3-ol (**12**) gives the 5-bromo-2-chloropyridin-3-ol (**13**) as the major product along with the C-6-chloro isomer and C-2,6-dichloro derivative. Unfortunately, this dichloro by-product ran very close to the desired compound **13** by TLC. Isolation of pure material was only possible after methylation of the hydroxyl group and careful chromatography over silica gel. We, thus, obtained 5-bromo-2-chloro-3-methoxypyridine **14** in 48% over two steps (Scheme 4).

In our opinion, this result was not satisfactory in terms of scaling-up feasibility (purification issues) and route efficiency (C-3 demethylation, chlorination, C-3 re-methylation). We therefore devised the shorter route shown in Scheme 5. 5-Bromo-3-methoxypyridine-*N*-oxide (**15**) could easily be obtained either by oxidation of 5-bromo-3-methoxypyridine (**11**) with hydrogen peroxide and MTO (methyltrioxorhenium(VII)) or by selective replacement of one bromine atom of the commercially available 3,5-dibromopyridine 1-oxide[17] by a methoxy group. The crucial Meisenheimer *N*-oxide rearrangement was carried out with phosphorous oxychloride to give 5-bromo-2-chloro-3-methoxypyridine **14** in 65% yield (Scheme 5).



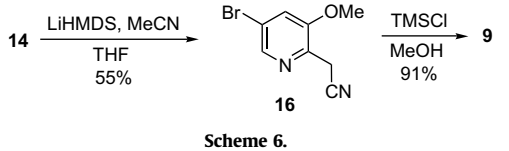
Scheme 5.

However, we were unable to condense **14** with sodium methyl 2-cyanoacetate or methyl *tert*-butyl propanedioate under standard basic or palladium-catalyzed conditions,[18] presumably because of the absence of a suitable activating group in **14**. We assumed harder nucleophiles would be required for a successful displacement but several alkyl acetates failed under standard basic conditions. We rejected the palladium-catalyzed conditions recently described by Hartwig[2] as these conditions seem only effective for electron-poor rather than electron-rich chloroarenes, and may also have given us regioselectivity issues with the C-5 bromine. However, we found that the carbanion of acetonitrile displaces selectively the C-2 chlorine atom of the pyridine **14** at room temperature to give **16** in 55% yield. This reaction could also be carried out on a large scale and is therefore in a practical, short synthesis of the key intermediate **16**. Although the acetonitrile anion has already been used previously in S_NAr displacements on 2-halopyridine,[19] to our knowledge, such a reaction has never been described on an electron-rich chloroheteroarene. Methanolysis of the nitrile function was carried out in methanol in presence of TMSCl to afford **9** in 91% yield (Scheme 6).

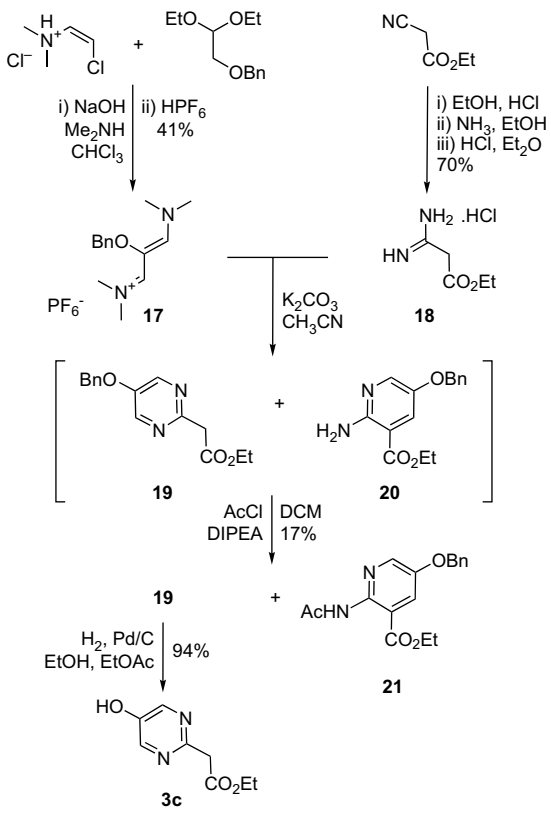
2.2. Synthesis of alkyl 2-(5-hydroxypyrimidin-2-yl)acetate (3)

2.2.1. Pyrimidine ring closure approach

For various pharmacokinetic and physicochemical reasons, 2-alkyl-(5-hydroxypyrimidin-2-yl)acetate **3** became also an interesting intermediate for our exploration. The methodology reported in the literature[20] for its synthesis appeared rather tedious and suffered from the additional drawback of the use of a perchlorate salt unsuitable on large-scale synthesis due to their well documented thermal and shock-sensitivity.[21] Although this issue was solved by replacing the perchlorate counteranion with the PF_6^- anion **17**, we still faced a problem of reproducibility in the preparation of the amidine **18** as well as an issue of non-regioselective cyclization (Scheme 7).



Scheme 6.



Scheme 7.

Indeed, both pyrimidine **19** and pyridine by-product **20** were formed during this reaction in a 3/2 ratio and separation of these two compounds by silica gel chromatography was difficult. Pure pyrimidine **19** could, however, be obtained by silica gel separation of the more lipophilic acetamide derivative **21**. The compound **19** was subsequently debenzylated by hydrogenation in presence of palladium on charcoal, to give the desired product **3c**. Nevertheless, we needed a more robust route, suitable for scale-up.

2.2.2. S_NAr approach

We rapidly rejected the approach consisting of using the pyrimidine N-oxidation[22] (Fig. 3) in a Golebiewski rearrangement, since the desired compound would require a six-step synthesis, starting from the expensive 5-bromo-2-methyl-pyrimidine (Fig. 3).

Finally, pyrimidine derivatives **3** were obtained by an aromatic nucleophilic displacement similar to the one previously described

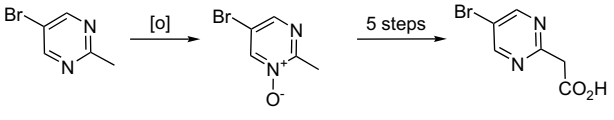
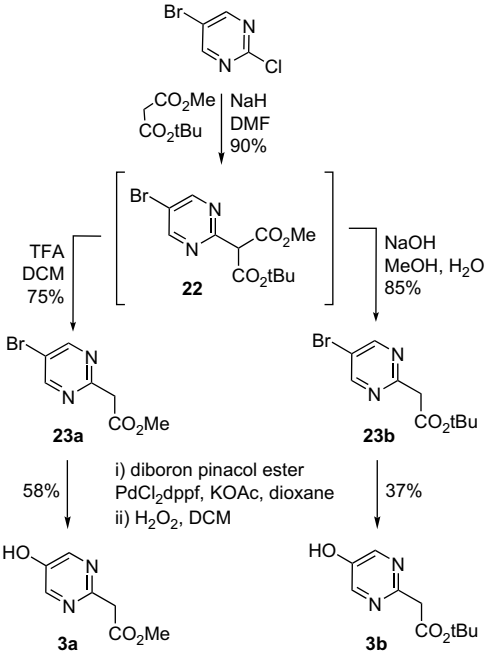


Figure 3.

for pyridine **2**. Treatment of commercially available 5-bromo-2-chloropyrimidine with sodium hydride and *tert*-butyl methyl malonate gave the desired unsymmetrical diester **22** in good yield, which could then be selectively decarboxylated to afford the methyl ester **23a** or *tert*-butyl ester **23b**. Indeed, treatment of the diester **22** under acidic conditions (TFA) gave the methyl ester **23a** whereas basic treatment (aq NaOH) led to the *tert*-butyl ester **23b** as shown in Scheme 8. The diester **22** was a very versatile intermediate and was especially useful for our SAR investigations. The methyl/*tert*-butyl 2-acetate-5-bromopyrimidine derivatives **23** were easily converted to the desired 5-hydroxypyrimidines **3** using the same two-step sequence described in Scheme 3 for the synthesis of **2** from **9** (Scheme 8).



Scheme 8.

3. Conclusion

In this work,[23] we have developed new routes for easy and efficient large-scale access to methyl 2-(5-hydroxy-3-methoxypyridin-2-yl)acetate and its analogue alkyl 2-(5-hydroxypyrimidin-2-yl)acetate, based on aromatic nucleophilic substitution followed by hydroxydeboronation. We believe that this methodology could be rather general and applied to other heterocyclic ring systems.

4. Experimental section

4.1. General

All reagents were purchased from Aldrich, Acros, Fluka or Merck and used without further purification. Flash chromatography was carried out on Merck Kieselgel 50 (Art. 9385) unless otherwise stated. NMR spectra were obtained on a Bruker Avance 500 (500 MHz) spectrometer. Chemical shifts are expressed in δ (ppm) units, and peak multiplicities are expressed as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quadruplet; br s, broad singlet; m, multiplet. Mass spectrometry was carried out on an analytical Waters LC–MS system with positive and negative ion data collected automatically. NMR and mass spectra were run on isolated products and were consistent with the proposed structures and compounds described in the literature. The following abbreviations have been used: AcOH, acetic acid; DCM, dichloromethane; DIPEA, *N*,*N*-diisopropyl-*N*-ethylamine; DMSO, dimethyl sulfoxide; DMF, *N*,*N*-dimethylformamide; dppf, 1,1′-bis (diphenylphosphino) ferrocene; KOAc, potassium acetate; LiHMDS, lithium bis (trimethylsilyl)amide; MTO, methyltrioxorhenium(VII); S_NAr, aromatic nucleophilic substitution; TFA, trifluoroacetic acid; TFAA, (2,2,2-trifluoroacetyl) 2,2,2-trifluoroacetate (trifluoroacetic anhydride); TLC, thin layer chromatography; TMSCl, chlorotrimethylsilane.

4.2. Typical procedure for the hydroxydeboronation reaction

*4.2.1. Methyl 2-(5-hydroxy-3-methoxypyridin-2-yl)acetate **2***

Bis(pinacolato)diboron (43 g, 170 mmol), $PdCl_2$dppf (3.45 g, 4.2 mmol), and potassium acetate (41.5 g, 423 mmol) were added under nitrogen to a stirred solution of **9** (32 g, 141 mmol) in 1,4-dioxane (400 mL). The reaction mixture was heated at 85 °C for 3 h. The black suspension was cooled to room temperature and poured into a 1/1 mixture of water and DCM (2 L). The organic layer was washed with brine, dried over magnesium sulfate and solvent was evaporated to dryness to give 55 g of crude boronic ester intermediate as a black oil, contaminated with pinacol derivatives.

To the crude boronic ester dissolved in DCM (700 mL) was added dropwise a 30% solution of hydrogen peroxide in water (70 mL, 616 mmol) while keeping the internal temperature below 20 °C. The reaction mixture was stirred at room temperature for 3 h. The organic layer was separated, successively washed with brine and an aqueous solution of sodium thiosulfate (10 g in 50 mL of water, until negative peroxide test). The organic layer was dried over magnesium sulfate and solvent was evaporated. The crude mixture was purified by flash chromatography on silica gel eluting with 3% of methanol in DCM. The solid was triturated in diethyl ether, filtered, and dried under high vacuum overnight to give 15.9 g (66% over the two steps) of methyl 2-(5-hydroxy-3-methoxypyridin-2-yl)acetate **2** as a pale beige solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.85 (br s, 1H), 7.63 (d, J=2.3 Hz, 1H), 6.80 (d, J=2.3 Hz, 1H), 3.74 (s, 3H), 3.63 (s, 2H), 3.58 (s, 3H). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (br s, 1H), 6.84 (br s, 1H), 3.84 (s, 2H), 3.82 (s, 3H), 3.69 (s, 3H). MS (ESI) m/z 198 $(MH)^+$.

*4.2.2. Methyl 2-(5-hydroxypyrimidin-2-yl)acetate **3a***

Using the same procedure, 32 g of methyl 2-(5-bromopyrimidin-2-yl)acetate **22a** gave 13.2 g (58% over the two steps) of methyl 2-(5-hydroxypyrimidin-2-yl)acetate **3a**. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.4 (br s, 1H), 8.28 (s, 2H), 3.85 (s, 2H), 3.62 (s, 3H). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.27 (s, 2H), 3.99 (s, 2H), 3.75 (s, 3H). MS (ESI) m/z 169 $(MH)^+$, 167 $(M-H)^-$.

*4.2.3. tert-Butyl 2-(5-hydroxypyrimidin-2-yl)acetate **3b***

Using the same procedure, 1.6 g of *tert*-butyl 2-(5-bromopyrimidin-2-yl)acetate **22b** gave 450 mg (37% over the two steps) of *tert*-butyl 2-(5-hydroxypyrimidin-2-yl)acetate **3b**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.27 (s, 2H), 3.92 (s, 2H), 1.48 (s, 9H). MS (ESI) m/z 155 $(MH-t\text{-}Bu)^+$, 209 $(M-H)^-$.

4.3. Specific procedures

*4.3.1. Ethyl 2-(5-hydroxypyrimidin-2-yl)acetate **3c***

A solution of compound **19** (470 mg, 1.73 mmol) in a 1/1 mixture of ethanol and ethyl acetate (20 mL) was stirred under hydrogen atmosphere (3 atm) in presence of palladium on charcoal 10% (100 mg) for 2 h. The catalyst was removed by filtration through a pad of Celite® and the filtrate was concentrated to give 296 mg (94%) of ethyl 2-(5-hydroxypyrimidin-2-yl)acetate **3c** as an yellow

oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (s, 2H), 4.15 (q, J=7.1 Hz, 2H), 3.89 (s, 2H), 1.25 (t, J=7.1 Hz, 3H). MS (ESI) m/z 183 $(MH)^+$, 181 $(M-H)^-$.

4.3.2. 3-Methoxy-5-nitropyridin-2-ol ***4***

3-Methoxy-1*H*-pyridin-2-one (24 g, 192 mmol) was added to concentrated sulfuric acid (474 mL) under stirring while keeping the temperature below 40 °C. A solution of fuming nitric acid (12 mL, 288 mmol) in concentrated sulfuric acid (12 mL) was dropwise added while keeping the temperature below 50 °C then an additional 15 mL of concentrated sulfuric acid was added to improve stirring. After the addition was complete (3 h), the reaction mixture was stirred at 45 °C for 1 h. The mixture was allowed to cool to room temperature and poured onto ice under stirring. The resulting yellow precipitate was collected by filtration, washed with a 1/1 mixture of ethanol and diethyl ether then dried under vacuum at 45 °C to afford 12 g (37%) of 3-methoxy-5-nitropyridin-2-ol **4** as a yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 12.64 (br s, 1H), 8.33 (d, J=2.8 Hz, 1H), 7.38 (d, J=2.8 Hz, 1H), 3.82 (s, 3H). MS (ESI) m/z 169 $(M-H)^-$.

4.3.3. 2-Chloro-3-methoxy-5-nitropyridine ***5***

3-Methoxy-5-nitropyridin-2-ol **4** (13.9 g, 82 mmol) was added to a mixture of phosphorous pentachloride (8.53 g, 41 mmol) and phosphorous oxychloride (22.5 mL, 246 mmol). The reaction mixture was heated at reflux for 4 h. The resulting solution was allowed to cool to room temperature and poured onto crushed ice under stirring. After 30 min, solid Na_2CO_3 was added portion wise until pH 7 (gas evolution) and the mixture was extracted with diethyl ether (3×). The organic phases were combined, washed with brine, dried over magnesium sulfate, and concentrated. The crude was purified by flash chromatography on silica gel eluting with 0–20% of diethyl ether in DCM to give 12.1 g (79%) of 2-chloro-3-methoxy-5-nitropyridine **5** as an oil, which crystallized in standing. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.85 (d, J=1.8 Hz, 1H), 8.25 (d, J=1.8 Hz, 1H), 4.05 (s, 3H). MS (ESI) m/z 173 and 175 $([M-H]-CH_3)^-$.

4.3.4. Methyl tert-butyl 2-(3-methoxy-5-nitropyridin-2-yl)propanedioate ***6***

NaH, 60% dispersion in mineral oil (5 g, 125 mmol) was washed with pentane under argon then suspended in DMF (150 mL). To the suspension was added dropwise *tert*-butyl methyl malonate (21 mL, 57 mmol) at 5 °C under argon. The yellow solution was stirred for 30 min at room temperature then a solution of 2-chloro-3-methoxy-5-nitropyridine **5** (10.75 g, 57 mmol) in DMF (30 mL) was added dropwise at 5 °C. The resulting dark red solution was stirred at room temperature for 3 h then at 40 °C for 1.5 h. The solution was allowed to cool to room temperature and a saturated aqueous solution of NH_4Cl was added. The pH was adjusted to 6 with a 1 N aqueous solution of citric acid then the total volume adjusted to 750 mL with water. The mixture was extracted with diethyl ether (3×), the organic phases were combined, washed with water, brine, dried over magnesium sulfate, and concentrated to afford 30 g of crude methyl *tert*-butyl 2-(3-methoxy-5-nitropyridin-2-yl)propanedioate **6**, contaminated with starting *tert*-butyl methyl malonate. It was used without any further purification. Extrapolated ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.94 (d, J=2.0 Hz, 1H), 8.19 (d, J=2.0 Hz, 1H), 5.06 (s, 1H), 3.97 (s, 3H), 3.71 (s, 3H), 1.41 (s, 9H). MS (ESI) m/z 327 $(MH)^+$.

4.3.5. Methyl 2-(3-methoxy-5-nitropyridin-2-yl)acetate **7**

To a solution of the crude methyl *tert*-butyl 2-(3-methoxy-5-nitropyridin-2-yl)propanedioate **6** (30 g) in DCM (150 mL) was added TFA (50 mL). The solution was stirred at room temperature for 20 h. Toluene was added (30 mL) and the solution concentrated to dryness. The resulting oil was taken up in diethyl ether (300 mL) and a saturated solution of $NaHCO_3$ was added under stirring then solid $NaHCO_3$ until gas evolution stopped. The two phases were separated, the organic layer was washed with water, brine, dried over magnesium sulfate, and concentrated. The resulting solid was taken up into petroleum ether, collected by filtration and dried to give 11 g (82%) of methyl 2-(3-methoxy-5-nitropyridin-2-yl)acetate **7** as a crystallized orange solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.92 (d, J=2.2 Hz, 1H), 8.13 (d, J=2.2 Hz, 1H), 3.97 (s, 3H), 3.95 (s, 2H), 3.63 (s, 3H). MS (ESI) m/z 227 $(MH)^+$.

4.3.6. Methyl 2-(5-amino-3-methoxypyridin-2-yl)acetate ***8***

A mixture of methyl 2-(3-methoxy-5-nitropyridin-2-yl)acetate **7** (11 g, 48.7 mmol) and platinum on charcoal 10% (50% wet, 500 mg) in a 1/4 mixture of ethyl acetate and ethanol (250 mL) was stirred at room temperature under hydrogen (1.8 atm) for 4 h. The catalyst was removed by filtration through a pad of Celite® and the filtrate concentrated. The resulting oil was taken up into diethyl ether and stirred for 30 min. The resulting solid was collected by filtration and dried to afford 8 g (84%) of methyl 2-(5-amino-3-methoxypyridin-2-yl)acetate **8** as a solid. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.42 (d, J=2.0 Hz, 1H), 6.57 (d, J=2.0 Hz, 1H), 5.25 (s, 2H), 3.69 (s, 3H), 3.57 (s, 3H), 3.55 (s, 2H). MS (ESI) m/z 197 $(MH)^+$.

4.3.7. Methyl 2-(5-bromo-3-methoxypyridin-2-yl)acetate ***9***

Method A: To a solution of compound **10** (130 mg, 0.4 mmol) in methanol (5 mL) in presence of acetic acid (110 μL, 1.9 mmol) was added indium (5 mg, 0.46 mmol) at room temperature. The white suspension was stirred at room temperature for 30 min then concentrated. The residue was taken up into a mixture of diethyl ether and a saturated aqueous solution of $NaHCO_3$. The two phases were separated and the organic phase was dried over magnesium sulfate and concentrated to afford 100 mg (98%) of methyl 2-(5-bromo-3-methoxypyridin-2-yl)acetate **9**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.21 (d, J=1.8 Hz, 1H), 7.30 (d, J=1.8 Hz, 1H), 3.85 (s, 3H), 3.83 (s, 2H), 3.71 (s, 3H). MS (ESI) m/z 260 and 262 $(MH)^+$.

Method B: To a stirred solution of TMSCl (100 mL, 811 mmol) in methanol (300 mL) was added portion wise the pyridine **16** (30 g, 135 mmol). The resulting mixture was heated to 50 °C for 20 h then concentrated under vacuum. The crude product was taken up into diethyl ether (1 L) and a saturated aqueous solution of $NaHCO_3$ was slowly added until gas evolution stopped and pH 8 was obtained. The phases were separated, the aqueous layer was extracted with diethyl ether (250 mL) and the combined organic phases were washed with brine, dried over magnesium sulfate, and concentrated to give 32 g (91%) of methyl 2-(5-bromo-3-methoxypyridin-2-yl)acetate **9** as a crystalline solid.

4.3.8. Methyl 2-bromo-2-(5-bromo-3-methoxypyridin-2-yl)acetate ***10***

To a deep purple solution of aminopyridine **8** (50 mg, 0.26 mmol) and CuBr (73 mg, 0.51 mmol) in HBr 48% (1.2 mL) was added potassium nitrite (29 mg, 0.34 mmol) at 5 °C. The solution was allowed to warm to room temperature and stirred for 1 h. The mixture was cooled to 5 °C and pH adjusted to 5 by slow addition of a 6 N aqueous solution of sodium hydroxide. The resulting light blue aqueous solution was extracted twice with diethyl ether and the combined organic phases were dried over magnesium sulfate then concentrated. The crude was purified by flash chromatography on silica gel eluting with 0–50% of diethyl ether in petroleum ether to give 46 mg (53%) of methyl 2-bromo-2-(5-bromo-3-methoxypyridin-2-yl)acetate **10** as an oil, which crystallized on standing. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.26 (d, J=1.5 Hz, 1H), 7.37 (d, J=1.5 Hz, 1H), 5.86 (s, 1H), 3.92 (s, 3H), 3.81 (s, 3H). MS (ESI) m/z 338, 340, and 342 $(MH)^+$.

4.3.9. 5-Bromopyridin-3-ol ***12***

A solution of 3-bromo-5-methoxypyridine **11**[16] (191 g, 1 mol) in a mixture of AcOH (500 mL) and 48% HBr (700 mL) was stirred at 120 °C for 3 days. The mixture was allowed to cool to 0 °C and a 6 N aqueous solution of sodium hydroxide was added dropwise, while keeping the temperature below 10 °C until pH 5 (a precipitate formed). Ethyl acetate (1.5 L) was added, the phases were separated and the aqueous phase was extracted with ethyl acetate (0.5 L). The combined organic phases were dried over magnesium sulfate and concentrated. The residue was dissolved in DCM, insolubles were removed by filtration and the filtrate was concentrated to give 148 g (84%) of 5-bromopyridin-3-ol **12**. ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.45 (br s, 1H), 8.14 (d, J=2.0 Hz, 1H), 8.13 (d, J=2.2 Hz, 1H), 7.40 (dd, J=2.2 Hz, 2.0 Hz, 1H). MS (ESI) m/z 174 and 176 $(MH)^+$, 172 and 174 $(M-H)^-$.

4.3.10. 5-Bromo-2-chloropyridin-3-ol ***13***

5-Bromopyridin-3-ol **12** (80.7 g, 445 mmol) was dissolved in a 1 N aqueous solution of sodium hydroxide (490 mL, 490 mmol) then a 5% solution of NaOCl (662 mL, 490 mmol) was slowly added. The mixture was stirred at room temperature for 6 h. An additional 5% solution of NaOCl (90 mL, 67 mmol) was added slowly to complete the reaction and the mixture was left to stir for 2 days. The solution was cooled to 5 °C and the pH was adjusted to 4.75 by adding AcOH (approx. 90 mL), keeping the temperature below 15 °C. The resulting precipitate was collected by filtration and washed with water. The solid was dissolved in ethyl acetate (600 mL), washed with a 1 N aqueous solution of HCl (80 mL), brine, dried over magnesium sulfate, and concentrated to give 82 g (88%) of crude 5-bromo-2-chloropyridin-3-ol **13**, contaminated with 9% of starting material, 7% of 5-bromo-6-chloropyridin-3-ol isomer and 12% of 5-bromo-2,6-dichloropyridin-3-ol. It was used in the next step without any further purification. Extrapolated ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.35 (br s, 1H), 8.01 (d, J=2.1 Hz, 1H), 7.50 (d, J=2.1 Hz, 1H). MS (ESI) m/z 208, 210, and 212 $(MH)^+$, 206, 208, and 210 $(M-H)^-$.

4.3.11. 5-Bromo-2-chloro-3-methoxypyridine ***14***

To a suspension of crude **13** (102 g, 490 mmol) in acetonitrile (1.5 L) was added potassium carbonate (101 g, 736 mmol) and the mixture was stirred at room temperature for 15 min under nitrogen. MeI (32 mL, 515 mmol) was then added and the resulting mixture was stirred overnight at room temperature. The insolubles were removed by filtration and the filtrate was concentrated. The residue was taken up into a mixture of water and diethyl ether and stirred for 5 min. The phases were separated and the aqueous phase was washed with diethyl ether. The combined organic phases were washed with brine, dried over magnesium sulfate and concentrated. The crude product was passed through a silica gel column eluting with 8% of ethyl acetate in petroleum ether. The solvents were evaporated to dryness to give 68 g (62%) of 5-bromo-2-chloro-3-methoxypyridine **14**, contaminated with 10% of 3-bromo-2,6-dichloro-5-methoxypyridine. It was used in the next step without any further purification.

Pure material **14** was isolated by chromatography with NOVASEP L.C.80 system, strictly respecting 10 g of crude input per kilogram of silica gel 60 Merk (0.015–0.04 mm) eluting with 5–10% of ethyl acetate in petroleum ether. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07 (d, J=1.9 Hz, 1H), 7.33 (d, J=1.9 Hz, 1H), 3.93 (s, 3H). MS (ESI) m/z 222, 224, and 226 $(MH)^+$.

4.3.12. 3-Bromo-5-methoxypyridine 1-oxide ***15***

Method A: To a solution of 3-bromo-5-methoxypyridine **11**[16] (11.3 g, 60 mmol) in DCM (200 mL) was successively added MTO (74 mg, 0.3 mmol) and a 30% aqueous solution of hydrogen peroxide (6 mL, 120 mmol) under nitrogen at room temperature. The mixture was stirred at 25 °C overnight then MnO_2 (16 mg, 0.018 mmol) was added. After gas evolution stopped, magnesium sulfate was added. The solid was removed by filtration and washed twice with DCM. The organic filtrate was washed with a 1/1 mixture of a 1 N aqueous solution of $Na_2S_2O_5$ and brine, brine, dried over magnesium sulfate, and concentrated, to give 10 g (82%) of 3-bromo-5-methoxypyridine 1-oxide **15** as an off-white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.02 (br s, 1H), 7.91 (br s, 1H), 7.03 (s, 1H), 3.85 (s, 3H). MS (ESI) m/z 204 and 206 $(MH)^+$.

Method B: 3,5-Dibromopyridine 1-oxide (5 g, 20 mmol) was suspended in DME (20 mL). A solution of KOH (1.4 g, 25 mmol) in methanol (20 mL) was added under stirring at room temperature under nitrogen. The resulting mixture was heated at reflux for 4.5 h then allowed to cool to room temperature. NH_4Cl (321 mg, 6 mmol) was added and the mixture stirred for 30 min then diluted with DCM (20 mL). The solid was removed by filtration and washed twice with a 9/1 mixture of DCM and methanol (30 mL). The filtrates were combined and concentrated. The resulting solid was taken up into a 9/1 mixture of DCM and methanol (70 mL) and the mixture stirred for 20 min. The insolubles were removed by filtration and the filtrate concentrated to dryness to give 4.05 g (72%) of 3-bromo-5-methoxypyridine 1-oxide **15**.

4.3.13. 2-(5-Bromo-3-methoxypyridin-2-yl)acetonitrile ***16***

To a solution of 2-choropyridine derivative **14** (43 g, 193.7 mmol) and acetonitrile (10 mL, 193.7 mmol) in THF (500 mL) was added slowly a 1 N solution of LiHMDS in THF (387 mL, 387 mmol) at room temperature under nitrogen. The resulting black solution was stirred at room temperature for 1 h then acetonitrile (10 mL, 193.7 mmol) followed by a 1 N solution of LiHMDS in THF (387 mL, 387 mmol) were added dropwise. The solution was stirred for an additional 2 h then slowly poured into a stirred cold mixture of water (2 L) and diethyl ether (1 L). The phases were separated and the aqueous phase was washed with diethyl ether (500 mL). The combined organic phases were washed with brine, dried over magnesium sulfate and concentrated. The crude was purified by flash chromatography on silica gel eluting with 25% of ethyl acetate in petroleum ether to give 24 g (55%) of 2-(5-bromo-3-methoxypyridin-2-yl)acetonitrile **16**. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (d, J=1.7 Hz, 1H), 7.34 (d, J=1.7 Hz, 1H), 3.91 (s, 3H), 3.85 (s, 2H). MS (ESI) m/z 227 and 229 $(MH)^+$.

4.3.14. [(Z)-3-Dimethylamino-2-phenylmethoxyprop-2-enylidene]-dimethylazanium hexafluorophosphate ***17***

(Chloromethylen)dimethylammonium chloride (196 g, 1.5 mol) was dissolved in $CHCl_3$ (1 L) under nitrogen. The reaction mixture was cooled to 0 °C and benzyloxyacetaldehyde diethyl acetate (100 g, 0.5 mol) was added dropwise. Once completed, the reaction mixture was heated at reflux for 2.5 h then allowed to cool to room temperature. The orange solution was slowly poured into cold water (1 L) at 0 °C and the biphasic mixture was stirred for 15 min. The organic phase was washed with water (500 mL). The combined aqueous layers were added dropwise to a solution of dimethylamine hydrochloride (166 g, 2 mol) in water (500 mL). The pH was adjusted to 8.5 by addition of a 5 N aqueous solution sodium hydroxide while keeping the temperature around 15 °C. The solution was stirred for 1 h and sodium hexafluorophosphate (128.5 g, 0.76 mol) in water (300 mL) was added. The resulting precipitate was collected by filtration, washed with water, diethyl ether, and dried under high vacuum at 45 °C to give 45 g (23%) of [(*Z*)-3-dimethylamino-2-phenylmethoxyprop-2-enylidene]-dimethylazanium hexafluorophosphate **17** as a pale beige solid, which was used in the next step without any further purification. ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.42 (m, 5H), 7.32 (s, 2H), 4.74 (s, 2H), 3.32 (s, 12H).

4.3.15. Ethyl 3-amino-3-iminopropanoate hydrochloride ***18***

To a stirred solution of ethylcyanoacetate (100 mL, 0.94 mol) in $CHCl_3$ (1 L) was added ethanol (65 mL, 1.13 mol). The solution was cooled down to −10 °C and HCl was bubbled through the solution for 1 h. The reaction mixture was then stirred at room temperature for 4 h. To complete the conversion, the solution was cooled down to −10 °C and HCl was bubbled through the solution for another 1 h. The reaction mixture was then stirred at room temperature overnight. The solvent was evaporated, the residue was triturated in diethyl ether and the resulting solid was collected by filtration to give 173 g (94%) of the intermediate ethyl 3-ethoxy-3-iminopropanoate hydrochloride as a white powder. ^{1}H NMR (500 MHz, $CDCl_3$): δ 12.70 (br s, 1H), 12.00 (br s, 1H), 4.73 (q, J=7.1 Hz, 2H), 4.24 (q, J=7.1 Hz, 2H), 3.89 (s, 2H), 1.51 (t, J=7.1 Hz, 3H), 1.29 (t, J=7.1 Hz, 3H).

A solution of ethyl 3-ethoxy-3-iminopropanoate hydrochloride (173 g, 0.88 mol) in ethanol (1 L) was cooled down to −10 °C and NH_3 gas was bubbled through the solution for 1 h. The reaction mixture was then stirred at room temperature overnight. The insolubles were removed by filtration and the solvent was evaporated. The residue was triturated in diethyl ether, filtered and washed with diethyl ether. The resulting solid was taken up into in a 9/1 mixture of DCM and methanol and the solid residue (NH_4Cl) was removed by filtration. The filtrate was evaporated, the resulting oil was diluted with diethyl ether and HCl gas was bubbled through the solution for 10 min to give, after filtration, a mixture of methyl and ethyl ester derivatives. The solid residue was dissolved in ethanol (500 mL) and HCl was bubbled again through the solution for 10 min. The mixture was stirred overnight at room temperature, the solvent was evaporated and the resulting solid was triturated in diethyl ether, collected by filtration and dried to give 75 g (51%) of ethyl 3-amino-3-iminopropanoate hydrochloride **18** as a white powder, which was used without any further purification. ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.22 (s, 2H), 8.94 (s, 2H), 4.15 (q, J=7.1 Hz, 2H), 3.64 (s, 2H), 1.22 (t, J=7.1 Hz, 3H).

4.3.16. Ethyl 2-(5-phenylmethoxypyrimidin-2-yl)acetate ***19***

Method A: To a stirred suspension of **17** (64 g, 274 mmol) and **18** (58 g, 302 mmol) in CH_3CN (1 L) was added K_2CO_3 (114 g, 824 mmol). The reaction mixture was heated at 80 °C for 3 h, cooled to room temperature and insolubles were removed by filtration. The filtrate was concentrated and the residue was taken up into in diethyl ether (800 mL) and a 2 N HCl aqueous solution was added until pH 1. The organic layer was dried over magnesium sulfate and solvent was evaporated. The crude mixture was purified twice by flash chromatography on silica gel eluting with 15% of ethyl acetate in DCM. Solvents were removed under vacuum, the residue was taken up into in diethyl ether and washed again with a 2 N HCl aqueous solution to remove the remaining pyridine residues. The organic layer was dried over magnesium sulfate and solvent was evaporated to give 23 g (31%) of ethyl 2-(5-phenylmethoxypyrimidin-2-yl)acetate **19** as an orange oil. ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.43 (s, 2H), 7.39 (m, 5H), 5.15 (s, 2H), 4.20 (q, J=7.1 Hz, 2H), 3.97 (s, 2H), 1.26 (t, J=7.1 Hz, 3H). MS (ESI) m/z 273 $(MH)^+$.

Method B: *First step*. To a stirred suspension of [(*Z*)-3-dimethylamino-2-phenylmethoxyprop-2-enylidene]-dimethylazanium perchlorate[20] (4.1 g, 12.35 mmol) and **18** (4.3 g, 33.3 mmol) in CH_3CN (50 mL) was added K_2CO_3 (4.3 g, 30.9 mmol). The reaction mixture was heated at 80 °C for 3 h, cooled to room temperature, and the insolubles were removed by filtration. After evaporation, the residue was dissolved in DCM, washed with water, dried over magnesium sulfate, concentrated, and passed through a silica gel column eluting with 0–20% of ethyl acetate in DCM. The solvents were evaporated to dryness to give 1.7 g of a 3/2 mixture of **19** and **20**.

Second step. To a solution of 850 mg of the precedent mixture and DIPEA (1.13 mL, 6.47 mmol) in DCM (10 mL) was added dropwise acetyl chloride (0.35 mL, 4.85 mmol) at 0 °C under nitrogen. The resulting mixture was allowed to warm to room temperature and stirred for 1 h. The mixture was diluted with water and the organic phase was washed with a 1 N HCl aqueous solution, dried over magnesium sulfate, and concentrated. The crude mixture was purified by flash chromatography on silica gel eluting with 0–80% of ethyl acetate in DCM. The solvent was evaporated to dryness to give 470 mg (17%) of ethyl 2-(5-phenylmethoxypyrimidin-2-yl)acetate **19** as an yellow oil.

4.3.17. Ethyl 2-amino-5-phenylmethoxypyridine-3-carboxylate ***20***

Ethyl 2-amino-5-phenylmethoxypyridine-3-carboxylate **20** was characterized from the synthesis of **19** (Method B—First step). Extrapolated ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.05 (d, J=3.1 Hz, 1H), 7.80 (d, J=3.1 Hz, 1H), 7.44–7.32 (m, 5H), 6.11 (br s, 2H), 5.03 (s, 2H), 4.34 (q, J=7.1 Hz, 2H), 1.38 (t, J=7.1 Hz, 3H). MS (ESI) m/z 273 $(MH)^+$.

4.3.18. Ethyl 2-acetamido-5-phenylmethoxypyridine-3-carboxylate ***21***

Ethyl 2-acetamido-5-phenylmethoxypyridine-3-carboxylate **21** was characterized from the synthesis of **19** (Method B—Second step). ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.40 (br s, 1H), 8.45 (d, J=3.1 Hz, 1H), 7.99 (d, J=3.1 Hz, 1H), 7.44–7.36 (m, 5H), 5.19 (s, 2H), 4.34 (q, J=7.3 Hz, 2H), 2.26 (s, 3H), 1.35 (t, J=7.3 Hz, 3H). MS (ESI) m/z 315 $(MH)^+$.

4.3.19. Methyl tert-butyl 2-(5-bromopyrimidin-2-yl)-propanedioate ***22***

NaH, 60% dispersion in mineral oil (42 g, 1 mol) was added portion wise (while keeping the internal temperature around 20 °C) under nitrogen to a stirred solution of *tert*-butyl methyl malonate (175 mL, 1 mol) in DMF (800 mL). The orange solution was stirred at room temperature for 15 min and 5-bromo-2-chloropyrimidine (100 g, 518 mmol) was added. The reaction mixture was heated at 80 °C overnight, then cooled to 10 °C and 250 mL of a saturated aqueous solution of ammonium chloride was added dropwise, followed by 2 L of water. The pH was adjusted to 3 by addition of a 1 N HCl aqueous solution and the aqueous phase was extracted with diethyl ether (3×500 mL). The combined organic layers were washed with water (2×1 L), brine (500 mL), dried over magnesium sulfate, and concentrated to give 250 g of methyl *tert*-butyl 2-(5-bromopyrimidin-2-yl)propanedioate **22** as an orange oil, contaminated with 1 mol of starting *tert*-butyl methyl malonate, which was used in the next step without any further purification. Extrapolated ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.79 (s, 2H), 4.99 (s, 1H), 3.81 (s, 3H), 1.48 (s, 9H). MS (ESI) m/z 331 and 333 $(MH)^+$.

4.3.20. Methyl 2-(5-bromopyrimidin-2-yl)acetate ***23a***

To a cooled solution of crude diester **22** (171 g) in DCM (1.5 L) was added dropwise TFA (1 L) at 0 °C. Once the addition was complete (1 h), the reaction mixture was allowed to warm to room temperature and stirred for 2 h. The solvent was evaporated, the mixture was taken up in toluene and evaporated again. The resulting oil was taken up in ethyl acetate and washed with a saturated aqueous solution of $NaHCO_3$ until pH 7–8. The aqueous layer was extracted with ethyl acetate and the combined organic layers were washed with brine, dried over magnesium sulfate and concentrated. The crude mixture was purified by flash chromatography on silica gel eluting with 30% of ethyl acetate in petroleum ether to give 96 g (80% over the two steps) of methyl 2-(5-bromopyrimidin-2-yl)acetate **23a** as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.77 (s, 2H), 4.00 (s, 2H), 3.75 (s, 3H). MS (ESI) m/z 231 and 233 $(MH)^+$.

4.3.21. tert-Butyl 2-(5-bromopyrimidin-2-yl)acetate ***23b***

A solution of crude diester **22** (2.6 g) and NaOH (600 mg, 15 mmol) in a mixture of water (20 mL) and methanol (50 mL) was stirred at room temperature for 4 h. A 2 N HCl aqueous solution was

added until pH 5 and the mixture was extracted three times with diethyl ether. The combined organic phases were washed with brine, dried over magnesium sulfate, and concentrated to give 1.5 g (73% over the two steps) of *tert*-butyl 2-(5-bromopyrimidin-2-yl)acetate **23b** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.76 (s, 2H), 3.91 (s, 2H), 1.46 (s, 9H). MS (ESI) *m*/*z* 217 and 219 $(MH-t\text{-}Bu)^+$.

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