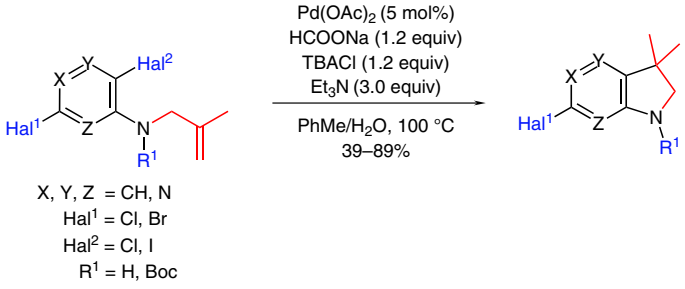
Synlett J. E. Day et al. Letter

The Synthesis of 3,3-Dimethyl Aza- and Diazaindolines Using a Palladium-Catalysed Intramolecular Reductive Cyclisation

James E. H. Day*[a]
Martyn Frederickson[a]
Colin Hogg[b]
Christopher N. Johnson[a]
Alistair Meek[b]
Julian Northern[b]
Michael Reader[a]
Gary Reid[b]

[a] Astex Pharmaceuticals, 436 Cambridge Science Park, Milton Road, Cambridge, CB4 0QA, UK
james.day@astx.com
[b] Onyx Scientific Limited, Silverbriar, Enterprise Park East, Sunderland, Tyne & Wear, SR5 2TQ, UK



Received: 09.07.2015
Accepted after revision: 22.08.2015
Published online: 22.09.2015
DOI: 10.1055/s-0035-1560320; Art ID: st-2015-d0527-l

Abstract A range of azaindolines was prepared in three steps from heterocyclic amines using halogenation, alkylation with 3-bromo-2-methylpropene, and a palladium-catalysed reductive cyclisation. The chemistry proved applicable to a multigram-scale operation.

Key words heterocycles, cyclisation, palladium, ring closure, catalysis

Indolines and azaindolines are well-known motifs in natural products and medicinal chemistry.[1–6] Preparations of 3,3-dimethylindolines and azaindolines include radical cyclisation,[3,7–10] nucleophilic aromatic substitution,[5] palladium-catalysed α-arylation cyclisation and reduction,[11] copper-catalysed intramolecular C–H amination,[12] Fischer indole synthesis with reduction of the initially formed indolenine,[13] alkylation of an oxindole with subsequent reduction,[5,6,14] and an intramolecular palladium-catalysed reductive cyclisation.[15] The work in this paper extends and expands the examples from the seminal work done by Larock on palladium-catalysed reductive cyclisation.[15]

As part of our fragment-based drug-discovery[16] efforts in developing antagonists of inhibitor of apoptosis proteins (IAP) for the treatment of cancer,[17] we required a general and efficient route for the synthesis of 3,3-dimethylindolines and azaindolines bearing a halogen atom **1** (Figure 1), for use as core scaffold intermediates.

We initially focused on the 5-azaindolines (Scheme 1) and our initial synthesis, based on commercially available 6-chloro-1*H*-pyrrolo[3,2-*c*]pyridine, was low yielding and not suitable for large-scale preparation because of a delayed exotherm observed for the zinc reduction (step iii).[17] In addition, the method was only suitable for the preparation of 5-azaindolines **1** (X = N, Y = Z = CH), and we required a general route providing access to 4- and 7-aza, as well as diaza analogues. Methodology from the Larock group makes use of an intramolecular palladium-catalysed reductive cyclisation to synthesise 3,3-dimethylindolines from iodinated aniline starting materials.[15,18] However, there have been very few reports of the application of such methodology to the synthesis of 3,3-dimethylaza- and diazaindolines.[5] Furthermore, we required a method compatible with the presence of a leaving group such as a halogen (as in **1**) that could allow further elaboration. However, such substituents can prove challenging for palladium-mediated chemistry.

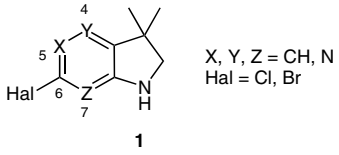


Figure 1

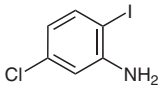
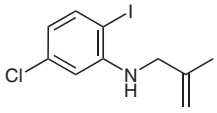
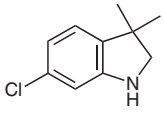
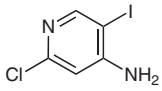
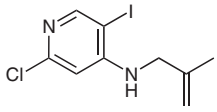
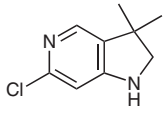
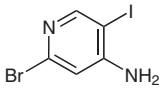
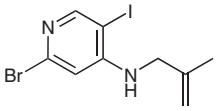
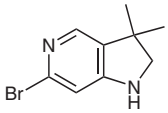
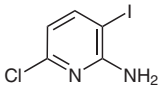
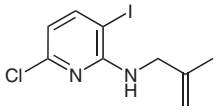
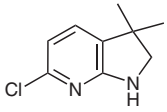
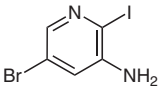
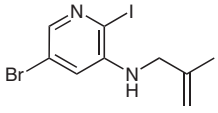
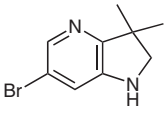
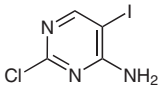
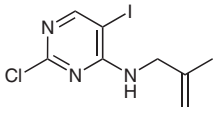
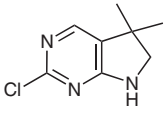
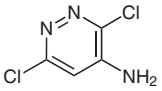
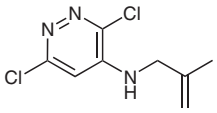
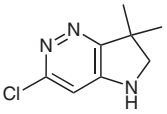
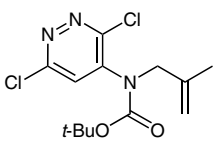
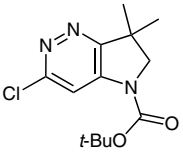
This Letter reports the successful application of this chemistry to synthesise a range of 3,3-dimethylindoline and azaindolines (Scheme 2 and Table 1). Importantly, the method proved compatible with the presence of a halogen substituent allowing subsequent elaboration using palladium-catalysed methods such as Negishi and Suzuki reactions.[17,30]

The required dihalogenated heterocyclic amines were either commercially available (Table 1, entries 1, 4, and 7) or prepared from the monohalogenated derivatives using *N*-iodosuccinimide (NIS) in acetonitrile at reflux or NIS in acetic acid. Iodination of the 2-halo-4-aminopyridines in acetonitrile gave a mixture of regioisomers which could be separated by column chromatography (Table 1, entries 2 and 3). The iodination of 5-bromopyridin-3-ylamine (Table

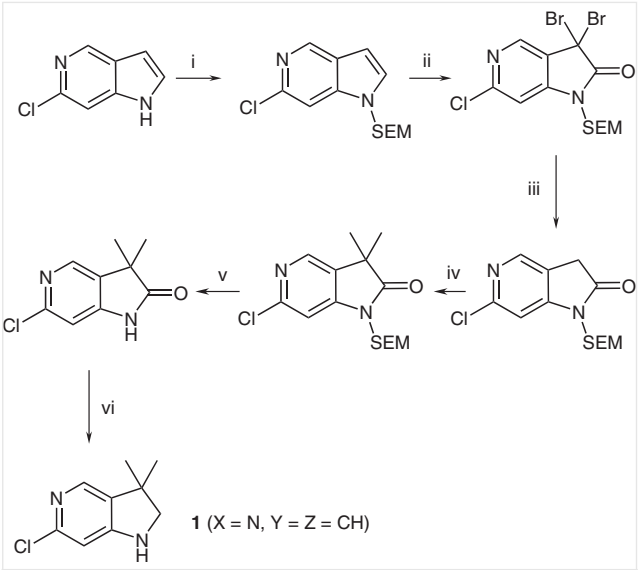
1, entry 5) was done in acetic acid as the solvent and gave a mixture of monoiodinated and a di-iodinated product (42% and 8% isolated yield, respectively) using 0.9 equivalents of NIS.

Initially, we attempted alkylation of 2-chloro-5-iodopyridin-4-ylamine with 3-bromo-2-methylpropene (1.1 equiv) using sodium hydride (1.1 equiv) as base in DMF giving a 53% yield. However, upon scale-up of the reaction, a significant amount of a dialkylated product was observed. By screening different reaction conditions we found the use

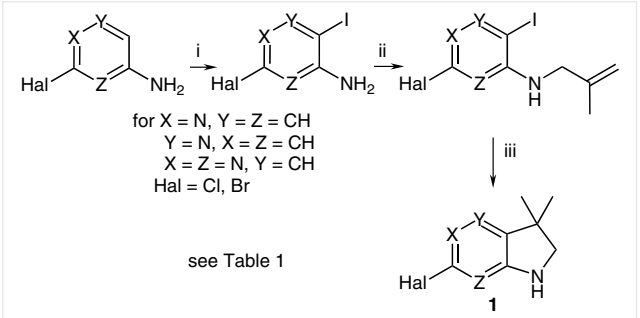
Table 1 Preparation 3,3-Dimethylindolines and Azaindolines[a]

Entry	Aniline	Yield (%)[c]	Alkene precursor	Yield (%)[c,g]	Cyclisation product	Yield (%)[c,i,m]
1		NA[b]		37[h]		60
2		36[d]		76		89
3		33[d]		71		39[j]
4		NA[b]		79		87
5		42[e]		75		44
6		40[f]		57		48
7		NA[b]		52		0[k]
8				84[l]		63

[a] Reactions were done on multigram scale.
[b] NA = not applicable; starting material commercially available.
[c] Yields are isolated yields.
[d] NIS (1.1 equiv), MeCN (0.25 M), 82 °C.[20]
[e] NIS (0.9 equiv), AcOH (0.18 M).
[f] NIS (1.1 equiv), AcOH (0.18 M), r.t.
[g] Alkene precursor (1.0 equiv), $H_2C{=}C(CH_3)CH_2Br$ (1.2 equiv), KO*t*-Bu (1.2 equiv), THF (0.24 M), r.t.[21]
[h] Product contained 25% dialkylated impurity, yield calculated from ^{1}H NMR.
[i] Cyclisation precursor (1.0 equiv), Et_3N (3.0 equiv), HCO_2Na (1.2 equiv), $Pd(OAc)_2$ (5.0 mol%), *n*-Bu_4NCl (1.2 equiv), PhMe (0.13 M), H_2O (2.6 M), N_2, 100 °C.[22]
[j] 8.0 mol% catalyst used.
[k] Dechlorination of starting material observed by mass spectroscopy.
[l] Boc protection: alkylated pyridazine (1.0 equiv, Table 1, entry 7), DMAP (1.0 equiv), Boc_2O (1.0 equiv), THF, 60 °C, 2 h.
[m] Compounds were >95% pure by LC–MS and ^{1}H NMR.[23–29]



Scheme 1 Original Synthesis of 5-aza indoline[17]. *Reagents and conditions*: i) NaH, $TMSCH_2CH_2OCH_2Cl$, DMF, 0 °C (82%); ii) $C_5H_5N{\cdot}HBr{\cdot}Br_2$, dioxane, r.t. (58%);[19] iii) Zn, NH_4Cl (aq), THF, r.t. (75%);[19] iv) LiHMDS, MeI, THF, –78 °C (51%); v) TFA, CH_2Cl_2, r.t. (67%); vi) BH_3–Me_2S, THF, 68 °C



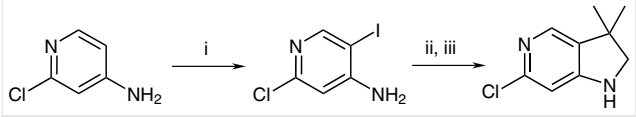
Scheme 2 Preparation 3,3-dimethylindolines and azaindolines. *Reagents and conditions*: i) NIS, MeCN, 82 °C or NIS, AcOH, r.t. (36–48%); ii) $H_2C{=}C(Me)CH_2Br$, KO*t*-Bu, THF, r.t. (37–79%); iii) $Pd(OAc)_2$, HCO_2Na, *n*-Bu_4NCl, Et_3N, PhMe, H_2O, 100 °C (39–89%).

of potassium *tert*-butoxide and 3-bromo-2-methylpropene in THF gave the cyclisation precursors in good yields over a range of substrates with no appreciable dialkylation observed upon scale-up (Table 1). The use of potassium *tert*-butoxide was advantageous because it avoided the generation of flammable gas and the *tert*-butanol solvates the resultant anion.

The reported conditions[15,18] involved use of a polar solvent (DMF) for the palladium-catalysed cyclisation. We found that a toluene–water mixture was a suitable solvent system for this process, with the advantage of more straightforward workup and isolation. Using these modified conditions, we successfully obtained a 3,3-dimethylindoline (Table 1, entry 1) and range of azaindolines with a halogen substituent (Table 1, entries 2–6). In general, the reaction was highly tolerant to changes to the heterocycle and presence of an unprotected nitrogen giving acceptable yields. However, the bromo-5-azaindoline (Table 1, entry 3) was isolated in lower yield than the chloro-5-azaindoline (Table 1, entry 2). Higher catalyst loadings (8 mol%), longer reaction times and repeated addition of aliquots of catalyst, sodium formate, phase-transfer reagent, and base were needed for a complete reaction.

Of all the heterocylic precursors only the chloro pyrazine, (Table 1, entry 7, X = Y = N, Z = CH) failed to undergo palladium-catalysed reductive cyclisation; by mass spectrometric analysis there was evidence for protodehalogenation. It has been reported that aryl chlorides are difficult substrates for such palladium-catalysed cyclisations.[31] *tert*-Butyl carbamate protection of the nitrogen resulted in a successful cyclisation giving the *tert*-butyl carbamate protected diazaindoline (Table 1, entry 8) in 63% yield. The *tert*-butyl carbamate diazaindoline was deprotected using HCl in ethyl acetate to give the the chloropyridazine (Table 1, entry 7, X = Y = N, Z = CH) in quantitative yield.[29]

We were keen to develop this chemistry for use at larger scale (>100 g) to synthesise the 5-azaindoline (Table 1, entry 2). The initial iodination was modified to use iodine monochloride as a replacement for NIS, leading to reduced cost (Scheme 3). The reaction run on 250 g input of 4-amino-2-chloropyridine gave a 1:1 mixture of regioisomers that could be separated by column chromatography to give the desired 5-iodo aniline in 33% isolated yield.[32]



Scheme 3 Synthesis of 5-azaindoline using iodine monochloride. *Reagents and conditions*: i) ICl, AcOH, 80 °C (33%); ii) a. $H_2C{=}C(Me)CH_2Br$, KO*t*-Bu, THF, 0 °C to r.t., b. 5 M HCl (quant.); iii) $Pd(OAc)_2$, HCO_2Na, *n*-Bu_4NCl, Et_3N, PhMe, H_2O, 100 °C (66%).[33]

The alkylation of the iodinated aniline (Table 1, entry 2) using potassium *tert*-butoxide and 3-chloro-2-methylpropene in THF gave a quantitative yield of the cyclisation precursor after isolation as the hydrochloride salt without need for chromatography. This salt was then used directly in the palladium-catalysed reductive cyclisation with addition of an extra equivalent of base. Using toluene as solvent, the reaction gave 75 g of the 5-azaindoline (Table 1, entry 2) in 66% yield and by using an diethyl ether–water partition as workup, we were able to again avoid the need for chromatography.[33]

In summary, we have developed a three-step procedure for the synthesis of 3,3-dimethylaza- and diazaindolines from heterocyclic amines using halogenation, alkylation, and palladium-catalysed reductive cyclisation. The procedure provides key building blocks for the synthesis of IAP

antagonists,[17] and these compounds may be of general utility for medicinal chemistry (e.g., as synthetic intermediates or fragments[16]) and other applications.

Acknowledgment

The authors would like to thank Matt Sanders for analytical support during the course of this work. In addition we would like to acknowledge Manchester Organics for their support in the scale-up synthesis of these compounds and other IAP project team members.

References and Notes

(1) Gribble, G. W. *J. Chem Soc., Perkin Trans. 1* **2000**, 1045.
(2) Song, J. J.; Reeves, J. T.; Gallou, F.; Tan, Z.; Yee, N. K.; Senanayake, C. H. *Chem. Soc. Rev.* **2007**, *36*, 1120.
(3) Wipf, P.; Maciejewski, J. P. *Org. Lett.* **2008**, *10*, 4383.
(4) Gonzalez-Lopez de Turiso, F.; Shin, Y.; Brown, M.; Cardozo, M.; Chen, Y. L.; Fong, D.; Hao, X.; He, X.; Henne, K.; Hu, Y. L. *J. Med. Chem.* **2012**, *55*, 7667.
(5) Qiao, J. X.; Wang, T. C.; Ruel, R.; Thibeault, C.; L'heureux, A.; Schumacher, W. A.; Spronk, S. A.; Hiebert, S.; Bouthillier, G.; Lloyd, J.; Pi, Z.; Schnur, D. M.; Abell, L. M.; Hua, J.; Price, L. A.; Liu, E.; Wu, Q.; Steinbacher, T. E.; Bostwick, J. S.; Chang, M.; Zheng, J.; Gao, Q.; Ma, B.; McDonnell, P. A.; Huang, C. S.; Rehfuss, R.; Wexler, R. R.; Lam, P. Y. S. *J. Med. Chem.* **2013**, *56*, 9275.
(6) Genin, M. J.; Chidester, C. G.; Constance, G.; Rohrer, D. C.; Romero, D. L. *Bioorg Med. Chem. Lett.* **1995**, *5*, 1875.
(7) Leroi, C.; Bertin, D.; Dufils, P. E.; Gigmes, D.; Marque, S.; Tordo, P.; Courturier, J. L.; Guerret, O.; Ciufolini, M. A. *Org. Lett.* **2003**, *5*, 4943.
(8) Johnston, J. N.; Plotkin, M. A.; Viswanathan, R.; Prabhakaran, E. N. *Org. Lett.* **2001**, *3*, 1009.
(9) Mo, D.-L.; Ding, C.-H.; Dai, L.-X.; Hou, X.-L. *Chem. Asian J.* **2011**, *6*, 3200.
(10) Viswanathan, R.; Prabhakaran, E. N.; Plotkin, M. A.; Johnston, J. N. *J. Am. Chem. Soc.* **2003**, *125*, 163.
(11) Pfefferkorn, J. A.; Choi, C. *Tetrahedron Lett.* **2008**, *49*, 4372.
(12) Takamatsu, K.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2015**, *80*, 3242.
(13) Liu, K. G.; Lo, J. R.; Robichaud, A. J. *Tetrahedron* **2010**, *66*, 573.
(14) Vu, A. T.; Cohn, S. T.; Zhang, P.; Kim, C. Y.; Mahaney, P. E.; Bray, J. A.; Johnston, G. H.; Koury, E. J.; Cosmi, S. A.; Deecher, D. C.; Smith, V. A.; Harrison, J. E.; Leventhal, L.; Whiteside, G. T.; Kennedy, J. D.; Trybulski, E. J. *J. Med. Chem.* **2010**, *53*, 2051.
(15) Larock, R. C.; Babu, S. *Tetrahedron Lett.* **1987**, *28*, 5291.
(16) Jhoti, H.; Williams, G.; Rees, D. C.; Murray, C. W. *Nat. Rev. Drug Discovery* **2013**, *12*, 644.
(17) Chessari, G.; Buck, I. M.; Day, J. E. H.; Day, P. J.; Iqbal, A.; Johnson, C. N.; Lewis, E. J.; Martins, V.; Miller, D.; Reader, M.; Rees, D. C.; Rich, S. J.; Tamanini, E.; Vitorino, M.; Ward, G. A.; Williams, P. A.; Williams, G.; Wilsher, N. E.; Woolford, A. J.-A. *J. Med. Chem.* **2015**, *58*, 6574.
(18) $Pd(OAc)_2$ (0.005 mmol, 2 mol%), Et_3N (0.625 mmol), substrate (0.25 mmol), sodium formate (0.06 M), *n*-Bu_4NCl (0.25 mmol), and DMF (0.06 M) at 80 °C.
(19) Bell, I. M.; Gallicchio, S. N.; Wood, M. R.; Quigley, A. G.; Stump, C. A.; Zartman, C. B.; Fay, J. F.; Li, C.-C.; Lynch, J. J.; Moore, E. L.; Mosser, S. D.; Prueksaritanont, T.; Regan, C. P.; Roller, S.; Salvatore, C. A.; Kane, S. A.; Vacca, J. P.; Selnick, H. G. *ACS Med. Chem. Lett.* **2010**, *1*, 24.
(20) **General Iodination Procedure**
NIS (24.75 g, 110.0 mmol) was added to a solution of 2-chloropyridin-4-ylamine (12.85 g, 100.0 mmol) in MeCN (400 mL), and the mixture was stirred and held at reflux overnight. Upon cooling to r.t. the solvent was removed in vacuo and the residue partitioned between EtOAc (250 mL), sat. $Na_2S_2O_3$ (100 mL), and H_2O (250 mL). The organic layer was separated, washed with H_2O (2 × 250 mL), separated, and the solvent removed in vacuo to afford an orange oil that was subjected to column chromatography on silica gel. Elution with 30–50% EtOAc in PE afforded a pale orange solid that was rinsed with 25% EtOAc in PE (80 mL). The solids were collected by filtration and sucked dry to afford 2-chloro-5-iodopyridin-4-ylamine (7.32 g) as an off-white solid. The mother liquors were concentrated to dryness in vacuo and the residues subjected to column chromatography on silica. Elution with 30–50% EtOAc in PE afforded further pure material (1.90 g). Combined yield 9.22 g, 36%. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.20 (s, 1 H), 6.64 (s, 1 H), 6.50 (br s, 2 H). MS: *m/z* = 255, 257 $[M + H]^+$.
(21) **General Alkylation Procedure**
KO*t*-Bu (4.56 g, 40.73 mmol) was added to a stirred solution of 2-chloro-5-iodopyridin-4-ylamine (8.62 g, 33.94 mmol) in anhydrous THF (140 mL), and the mixture was stirred at r.t. for 15 min. 3-Bromo-2-methylpropene (5.51 g, 40.73 mmol) was added, and the mixture was stirred at r.t. overnight. The solvent was removed in vacuo and the residues partitioned between CH_2Cl_2 (100 mL) and H_2O (100 mL). The organic layer was separated, the solvent removed in vacuo, and the residues subjected to column chromatography on silica. Elution with 5–20% EtOAc in PE afforded (2-chloro-5-iodopyridin-4-yl)-(2-methylallyl)amine (7.93 g, 76%) as a pale yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.23 (s, 1 H), 6.49 (t, *J* = 6.4 Hz, 1 H), 6.39 (s, 1 H), 4.84 (s, 1 H), 4.73 (s, 1 H), 3.82 (d, *J* = 5.7 Hz, 2 H), 1.69 (s, 3 H). MS: *m/z* = 309, 311 $[M + H]^+$.
(22) **General Palladium-Catalysed Cyclisation**
$Pd(OAc)_2$ (300 mg, 1.34 mmol), sodium formate (2.40 g, 30.53 mmol), *n*-Bu_4NCl (8.48 g, 30.53 mmol), and Et_3N (10.6 mL, 76.32 mmol) were added to a solution of (2-chloro-5-iodopyridin-4-yl)-(2-methylallyl)amine (7.85 g, 25.44 mmol) in toluene (200 mL) and H_2O (10 mL), and the mixture was stirred and held at 100 °C under a nitrogen atmosphere overnight. The mixture was filtered whilst still hot and the solids rinsed with toluene (50 mL), H_2O (50 mL), and EtOAc (50 mL). The organic solvent was removed in vacuo, the aqueous residues were diluted with H_2O (100 mL), and extracted with EtOAc (2 × 200 mL). The organic layer was separated, the solvent was removed in vacuo, and the residues subjected to column chromatography on silica. Elution with 30–100% EtOAc in PE afforded 6-chloro-3,3-dimethyl-2,3-dihydro-1*H*-pyrrolo[3,2-*c*]pyridine (4.12 g, 89%) as a colourless solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.72 (s, 1 H), 6.75 (br s, 1 H), 6.33 (s, 1 H), 3.32 (s, 2 H,), 1.25 (s, 6 H). MS: *m/z* = 183, 185 $[M + H]^+$.
(23) **Cyclisation Product (Table 1, Entry 1)**
^{1}H NMR (400 MHz, DMSO-d_6): δ = 6.94 (d, *J* = 7.8 Hz, 1 H), 6.57–6.47 (m, 1 H), 6.44 (d, *J* = 2.0 Hz, 1 H), 5.74 (s, 1 H), 3.21 (d, *J* = 1.8 Hz, 1 H), 1.20 (s, 6 H). MS: *m/z* = 182 $[M + H]^+$.
(24) **Cyclisation Product (Table 1, Entry 2)**
^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.72 (s, 1 H), 6.75 (br s, 1 H), 6.33 (s, 1 H), 3.32 (s, 2 H), 1.25 (s, 6 H). MS: *m/z* = 183 $[M + H]^+$.
(25) **Cyclisation Product (Table 1, Entry 3)**
^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.71 (s, 1 H), 6.74 (s, 1 H), 6.48 (s, 1 H), 3.31 (s, 1 H), 1.25 (s, 6 H). MS: *m/z* = 228 $[M + H]^+$.

(26) **Cyclisation Product (Table 1, Entry 4)**
^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.09–7.06 (d, *J* = 8.0 Hz, 1 H), 6.51–6.48 (d, *J* = 8.0 Hz, 1 H), 5.05 (br s, 1 H), 3.37 (s, 2 H), 1.28 (s, 6 H). MS: *m/z* = 183 $[M + H]^+$.

(27) **Cyclisation Product (Table 1, Entry 5)**
^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.72–7.64 (m, 1 H), 6.87 (t, *J* = 2.2 Hz, 1 H), 6.05 (s, 1 H), 3.30 (m, 2 H), 1.20 (s, 6 H). MS: *m/z* = 228 $[M + H]^+$.

(28) **Cyclisation Product (Table 1, Entry 6)**
^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.74 (s, 1 H), 5.79 (br s, 1 H), 3.46 (s, 2 H), 1.35 (s, 6 H). MS: *m/z* = 184 $[M + H]^+$.

(29) **Cyclisation Product from HCl Deprotection (Table 1, Entry 7)**
^{1}H NMR (270 MHz, CD_3OD): δ = 6.92 (s, 1 H), 3.79 (s, 2 H), 1.44 (s, 6 H). MS: *m/z* = 184 $[M + H]^+$.

(30) Negishi, E.-I. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Wiley-Interscience: New York, **2002**.

(31) Liu, P.; Huang, L.; Lu, Y.; Dilmeghani, M.; Baum, J.; Xiang, T.; Adams, J.; Tasker, A.; Larsen, R.; Faul, M. M. *Tetrahedron Lett.* **2007**, *48*, 2307.

(32) 2-Chloro-3-iodopyridin-4-ylamine isolated in 33% yield. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.75 (d, *J* = 5.5 Hz, 1 H), 6.53 (m, 3 H), MS: *m/z* = 255 $[M + H]^+$.

(33) **Larger-Scale Palladium Cyclisation**
To a 10 L flange flask fitted with stirrer bar and nitrogen inlet/outlet was added (2-chloro-5-iodopyridin-4-yl)-(2-methylallyl)amine hydrochloride (217 g, 0.629 mol), $Pd(OAc)_2$ (7 g, 0.031 mol), sodium formate (51.3 g, 0.755 moles), TBACl (210 g, 0.755 mol), Et_3N (350 mL, 2.52 mol), toluene (4.9 L), and H_2O (242 mL). The reaction mixture was heated at 100 °C (oil bath) overnight after which time NMR confirmed no starting material remaining, bulk material worked up. The reaction mixture was cooled to r.t. and stood overnight. To the cooled reaction mixture was added H_2O (500 mL) and Et_2O (2.5 L), organic layer removed and aqueous re-extracted with Et_2O (1.5 L). Organic extracts combined, washed with sat. brine solution (1.5 L), removed, dried over $MgSO_4$, filtered, and evaporated to dryness at 40 °C to give 6-chloro-3,3-dimethyl-2,3-dihydro-1*H*-pyrrolo[3,2-*c*]pyridine (76.2 g, 66%) as a yellow solid, the analytical data matched those from the smaller scale.