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Palladium-catalysed tandem alkenyl- and aryl-C–N bond formation: a cascade *N*-annulation route to 1-functionalised 7-azaindoles

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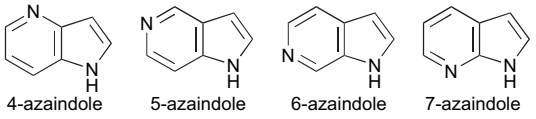
ABSTRACT

A series of 3-(2-haloalkenyl)-2-pyridyl-halides undergo consecutive palladium-catalysed inter- and intramolecular amination reactions to deliver a series of 1-functionalised 7-azaindoles. Anilines and amines can be readily employed as the *N*-nucleophile and incorporation of both electron-donating and electron withdrawing substituents on the pyridine core is possible.

1. Introduction

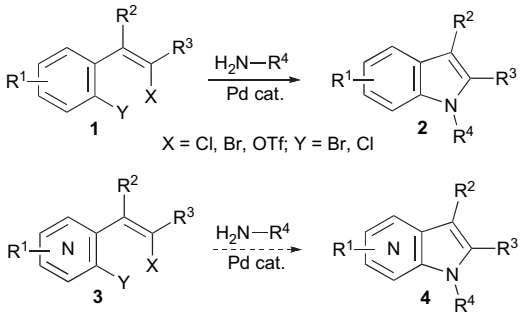
Azaindole's bioisoteric relationship with indoles has resulted in their evaluation in a host of medicinal chemistry applications.[1] Despite their widespread use, the synthesis of these core units is not always straightforward; the electron-deficient nature of the pyridine ring, combined with their strong metal-binding ability can present difficulties in adapting existing indole syntheses to the required aza-variant.[2] Azaindole synthesis is further complicated, with respect to the parent indole, in that four possible *N*-isomers exist (Scheme 1).



Scheme 1. The four azaindole isomers.

Palladium catalysis has enjoyed considerable success when applied to heterocycle synthesis;[3] azaindoles are no exception and a number of approaches to these important molecules based on key palladium- and copper-catalysed bond constructions have been reported.[4,5] The majority of these methods are centred on alkyne-based approaches,[6] but Heck,[7] Suzuki[8] and Buchwald–Hartwig[9] chemistries also feature. A recent report from the Lautens group demonstrated an elegant tandem process, in which intramolecular palladium-catalysed amination reactions were combined with intermolecular Suzuki couplings to efficiently access all four isomers of the azaindole core.[10]

We have recently demonstrated that tandem palladium catalysed amination reactions—one intermolecular, one intramolecular—can be used to access 1-functionalised indoles from acyclic non-nitrogen containing precursors (**1**→**2**, Scheme 2).[11,12] Variation of the 1-substituent was achieved by choice of the *N*-nucleophile coupling partner, and includes the successful use of amines, anilines, amides, sulfonamides and hydrazines. Given the broad utility of azaindoles in medicinal chemistry, we were interested in developing a related approach, commencing with pyridine-based substrates, which would allow access to the corresponding 1-functionalised azaindoles (**3**→**4**, Scheme 2).[13] In this account we detail the successful realisation of this goal with an efficient synthesis of 7-azaindoles.



Scheme 2. Tandem palladium-catalysed amination routes to 1-functionalised indoles and azaindoles.

2. Results and discussion

In analogy to the corresponding indole chemistry we planned to prepare the required (2-haloalkenyl)-pyridylhalide substrates using simple Wittig chemistry.[11b] Given the ready availability of a number

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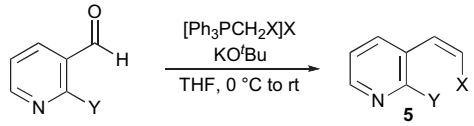
of 2-halonicotinaldehydes, we began our investigation by targeting the 7-azaindole core. Accordingly, the four substrates **5a**–**d**, featuring all combinations of Br- and Cl-activating groups, were prepared (Table 1).

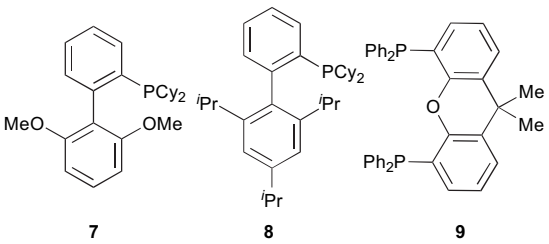
Table 1
Preparation of 3-(2-haloalkenyl)-2-halopyridine substrates



Entry	Compound	X	Y	*E*/*Z*	Yield[a] (%)
1	**5a**	Br	Br	>1:20	80
2	**5b**	Cl	Br	1:3	75
3	**5c**	Br	Cl	1:13	70
4	**5d**	Cl	Cl	1:4	70

[a] Isolated yields.

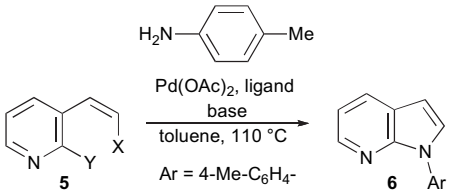
With the required substrates in hand, we set about evaluating reaction conditions and the catalyst choice needed to achieve azaindole formation (Table 2). We began with the coupling between dibromo-substrate **5a** and *p*-toluidine to deliver 7-azaindole **6**. Guided by our previous indole chemistry, we selected phosphine ligands **7**, **8** and **9** as the starting point of our investigation.[14,15] As can be seen from the first five entries, the use of biphenyl ligand **7** in combination with Cs_2CO_3 as base delivered 76% of azaindole **6** after 6 h reaction in toluene at 110 °C. If the reaction temperature was reduced to 80 °C, a 16 h reaction provided 61% of the expected product (entry 6). We next evaluated the same three ligands against the alternative substrates, **5b**–**d**, featuring the remaining combinations of Br- and Cl-activating substituents. For the vinyl chloride/aryl bromide substrate, **5b**, the use of ligand **9** was optimal, providing an 80% yield of azaindole **6**. For the vinyl bromide/aryl chloride substrate, **5c**, ligand **8** was preferred and delivered azaindole **6** in 90% yield. Finally, for the dichloride substrate (**5d**), ligand **9** was again optimal; however, a 42% yield of azaindole **6** was the maximum that could be achieved using this substrate.



As shown in Table 1, the alkenyl halide substrates were produced with varying ratios of *E*/*Z* isomers. Although we had previously established for the related indole substrates that both the *E*- and *Z*-alkene isomers delivered the expected indole product,[11b] we needed to confirm this for the pyridine-based substrates. Accordingly, *E*-configured dibromo-substrate *E*-**5a** was prepared using Hayes' modified Hirao reduction procedure (Scheme 3).[16] Pleasingly, the *E*-dibromo-substrate was converted to azaindole **6** using identical conditions to those employed for the *Z*-substrate. As with the indole chemistry, the successful use of the *E*-configured substrate is attributed to initial coupling at the alkenyl bromide to generate an enamine intermediate that undergoes isomerisation under the reaction conditions. This was a synthetically useful observation as it allowed mixtures of alkene isomers to be used directly in the azaindole forming reactions, without the need to isolate the separate geometrical isomers.

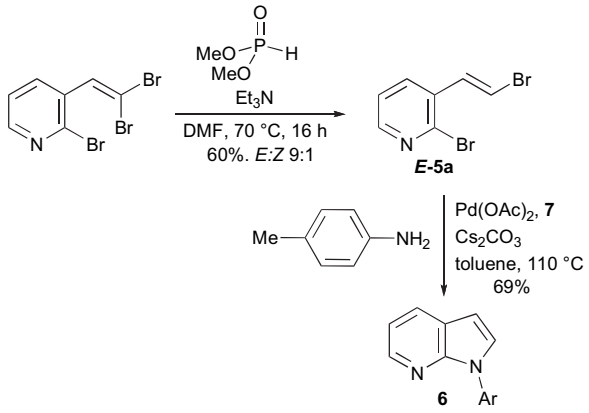
Having established that both *Z*- and *E*-isomers of the dibromide substrates deliver the desired azaindole, and that reasonable yields could also be achieved using all combinations of Br- and Cl-activating groups, we next embarked on exploring the scope of the *N*-nucleophile (Table 3). The dibromo-substrate, **5a**, was used throughout. A range of anilines was successfully incorporated, including those featuring both electron-withdrawing and electron-donating substituents (entries 1–4). The use of 6-chloropyridin-3-amine as the nucleophile (entry 5) is particularly notable, given the possibility of oxidative addition to the pyridyl-chloride. All of the anilines were reacted employing a catalyst system incorporating biphenyl ligand **7**. However, when pentylamine was reacted under identical conditions none of the expected azaindole was obtained (entry 6). A brief survey of alternative ligands revealed that the use of dppf, **10**, allowed the azaindole to be isolated in 64% yield (entry 7). Reactions incorporating ligands **8** and **9** as well as PCy_3 all failed to deliver any product. The dppf system allowed a range of alkyl amines to be incorporated in good yields (entries 7–11). The final entry demonstrates that the use of ligand **8** allowed ^{t}Bu-carbamate to be successfully employed as the *N*-coupling partner.

Table 2
Initial catalyst evaluation[a]



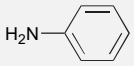
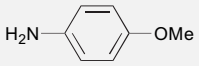
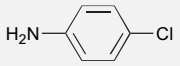
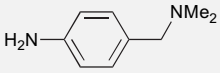
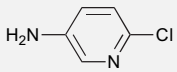
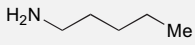
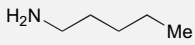
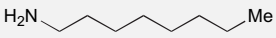
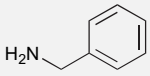
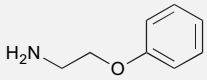
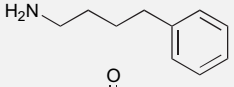
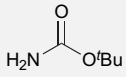
Entry	Substrate (X, Y)	Ligand	Base	Yield[b] (%)
1	**5a** (Br, Br)	**7**	NaO^{t}Bu	35
2	**5a** (Br, Br)	**8**	NaO^{t}Bu	0
3	**5a** (Br, Br)	**9**	NaO^{t}Bu	0
4	**5a** (Br, Br)	**7**	Cs_2CO_3	76
5	**5a** (Br, Br)	**7**	K_3PO_4	0
6[c]	**5a** (Br, Br)	**7**	Cs_2CO_3	61
7	**5b** (Cl, Br)	**7**	Cs_2CO_3	52
8	**5b** (Cl, Br)	**8**	Cs_2CO_3	0
9	**5b** (Cl, Br)	**9**	Cs_2CO_3	80
10	**5c** (Br, Cl)	**7**	Cs_2CO_3	0
11	**5c** (Br, Cl)	**8**	Cs_2CO_3	90
12	**5c** (Br, Cl)	**9**	Cs_2CO_3	<5
13	**5d** (Cl, Cl)	**7**	Cs_2CO_3	0
14	**5d** (Cl, Cl)	**8**	Cs_2CO_3	0
15	**5d** (Cl, Cl)	**9**	Cs_2CO_3	42

[a] Conditions: Substrate (1.0 equiv), *p*-toluidine (2.0 equiv), $Pd(OAc)_2$ (5 mol %), ligand (12 mol %), base (2.5 equiv), toluene, 110 °C.
[b] Isolated yields.
[c] Reaction performed at 80 °C.

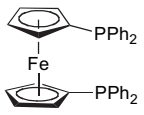


Scheme 3. Synthesis of azaindole **6** from *E*-configured substrate **5a**. Ar=4-Me-C_6H_4.

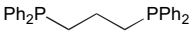
Table 3
Scope of the *N*-nucleophile coupling partner in combination with dibromide substrate **5a**[a]

Entry	Nucleophile	Ligand	Yield[b] (%)
1		**7**	96
2		**7**	79
3		**7**	86
4		**7**	91
5		**7**	70
6		**7**	0
7		**10**	64
8		**10**	60
9		**10**	73
10		**10**	74
11		**10**	53
12		**8**	68

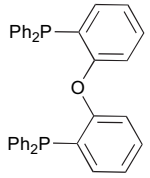
[a] Conditions: **5a** (1.0 equiv), amine (2.0 equiv), $Pd(OAc)_2$ (5 mol %), ligand (12 mol %), Cs_2CO_3 (2.2 equiv), toluene, 110 °C, 6 h. Substrate **5a** was used as a >20:1 mixture of *Z*/*E* isomers.
[b] Isolated yields.



10 (dppf)



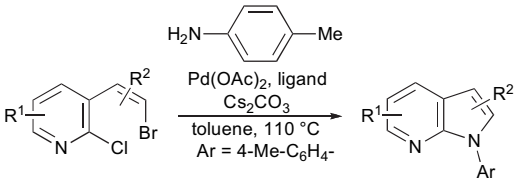
11 (dppp)

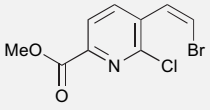
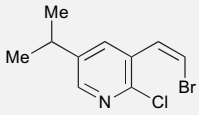
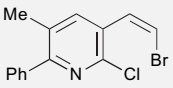
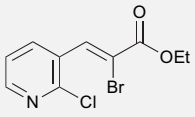
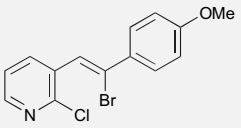
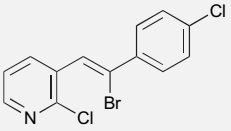
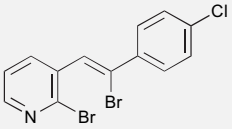
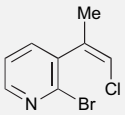


12 (DPEphos)

We next explored variation of the azaindole backbone; suitable functionalised aldehydes were either commercially available or prepared using the Vilsmeier-based chemistry of Rao.[17] This allowed ready access to 2-Cl-nicotinaldehydes. Wittig chemistry was then used as before to deliver the dihalogenated heterocycle precursors. *p*-Toluidine was employed as the standard *N*-nucleophile throughout (Table 4). Initially, we employed the conditions developed for the basic alkenyl bromide/pyridyl-chloride substrate, **5c**, which used ligand **8** (see Table 2). Using these conditions the Me-ester substituted backbone delivered the expected *N*-aryl-7-azaindole in 61% yield (entry 1). However, application of the same conditions to the *iso*-propyl-substituted substrate used in

Table 4
Variation of the substrate backbone in the preparation of *N*-aryl-7-azaindoles[a]



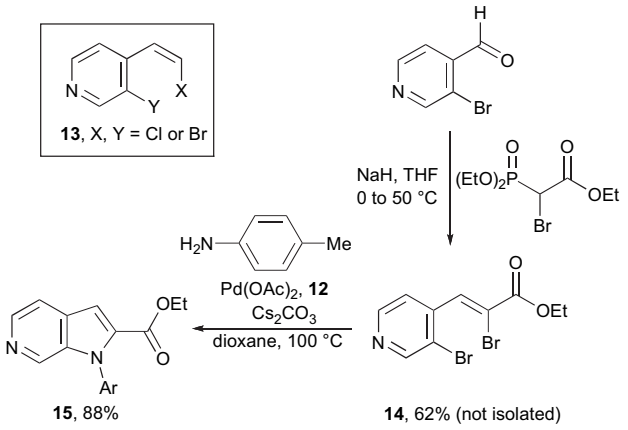
Entry	Substrate	*E*/*Z*	Ligand	Yield[b] (%)
1		1:4	**8**	61
2		1:20	**8**	20
3			**7**	18
4			**9**	41
5			**11**	48
6[c]			**11**	71
7		1:3	**8**	60
8		1:8	**8**	0
9			**9**	42
10			**11**	36
11			**12**	50
12[c]			**12**	83
13		1:>20	**8**	71
14		1:>20	**8**	0
15		1:>20	**7**	95
16		1:2	**8**	0
17			**9**	0
18			**12**	50
19[d]			**12**	73

[a] Conditions: substrate (1.0 equiv), toluidine (2.0 equiv), $Pd(OAc)_2$ (5 mol %), ligand (12 mol %), Cs_2CO_3 (2.2 equiv), toluene, 110 °C, 6 h.
[b] Isolated yields.
[c] Dioxane used as solvent.
[d] KO^{t}Bu used as base.

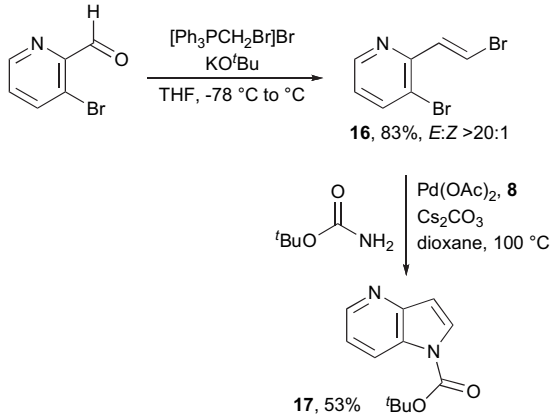
entry 2 only delivered a 20% yield of the azaindole. For substrates such as this, in which the original conditions were not optimal, a brief survey of alternative ligands was undertaken. In the event, employing dppp (**11**) as the ligand and using dioxane as solvent allowed a 70% yield of the desired azaindole to be achieved (see entries 2–6). The Me,Ph-disubstituted substrate shown in entry 7 was converted to the corresponding azaindole using the original conditions, however, the next substrate examined, bearing a 2-Et-ester substituent (azaindole numbering), required optimisation

before an 83% yield was achieved (entries 8–12). Two 2-aryl substituted substrates were next examined. The first, featuring a 2-(4-MeO-phenyl)-substituent, performed well under the standard conditions (entry 13), however, the corresponding substrate incorporating a 2-(4-Cl-phenyl)-substituent delivered a complex mixture of products. The difficulty with this substrate was attributed to competitive reaction at the arylchloride position. This was remedied by employing the corresponding 2-bromopyridine substrate; the use of ligand **8** then allowed a 95% yield of the expected azaindole to be achieved (entries 14 and 15). The final substrate examined featured a 3-methyl substituent; brief optimisation allowed a 66% yield 73 of the desired product to be achieved.

Having established reasonable variation of both the *N*-nucleophile and the substrate backbones in an approach towards 7-azaindoles, we next began to investigate the synthesis of the remaining azaindole isomers. It was soon apparent that the stability of the required dihalogenated precursors was an issue with 4-, 5- and 6-azaindoles. For 6-azaindoles it was not possible to isolate any of the substrates corresponding to structures **13** (Scheme 4), with decomposition being observed upon isolation in every case. Introduction of an electron-withdrawing ethyl ester to the alkene side-chain did confer some stability, and allowed dibromide **14** to be prepared and used directly in an azaindole forming process (Scheme 4). Initial experiments established that dibromide **14** underwent coupling with toluidine to deliver the required 6-azaindole (**15**) in 88% yield. However, further exploration of this substrate was limited due to its poor stability and subsequent decomposition. Unfortunately, preparation and isolation of substrates suitable for the synthesis of 5-azaindoles were similarly unsuccessful.



Scheme 4. Synthesis of 6-azaindole **15**. Ar=4-Me-C_6H_4.



Scheme 5. Synthesis of 4-azaindole **17**.

It was possible to prepare dibromide **16**, required for access to 4-azaindoles (Scheme 5). Initial experiments employing substrate **16** established that it displayed significantly reduced reactivity relative to the 7-azaindole system. A similar observation was made by Lautens,[10] and was attributed to potential coordination of the pyridine nitrogen to palladium. Nevertheless, a 53% yield could be achieved in the coupling of dibromide **16** with ^{t}Bu-carbamate. Lautens was able to remedy the poor reactivity of similar substrates by preparation of the corresponding *N*-oxides. However, although the *N*-oxide corresponding to pyridine **16** could be prepared, it was unreactive under a variety of coupling conditions.

3. Conclusion

We have established that a cascade palladium-catalysed inter/intramolecular amination process can be applied to appropriate 3-(2-haloalkenyl)-2-halopyridine substrates to deliver a series of *N*-functionalised 7-azaindoles. Anilines and amines can be readily employed as the *N*-nucleophile and incorporation of both electron-donating and electron-withdrawing substituents on the pyridine core is possible, delivering the expected azaindoles in good to excellent yields. Unfortunately, it was not possible to identify a single effective catalyst for all of the azaindoles produced; however, variation between a small group of ligands allowed efficient reactions to be achieved. Preliminary experiments have shown that the general method is far more limited when applied to 4-, 5- and 6-azaindoles, with the stability of the dihalogenated precursors being problematic.

4. Experimental section

4.1. General information

All reactions were performed under an inert atmosphere of nitrogen, in oven or flame dried glassware. Palladium catalysts and ligands were purchased from Aldrich Chemical Company or Strem Chemical.

4.2. General procedure for Wittig reactions using [Ph_3PCH_2X]X; preparation of (*Z*)-2-bromo-3-(2-bromovinyl)pyridine (5a, Table 1, entry 1)

Potassium *tert*-butoxide (1.45 g, 0.13 mol) was added portionwise to a stirred solution of (bromomethyl)triphenylphosphonium bromide (5.63 g, 0.13 mol) in anhydrous THF (100 mL) at −78 °C under nitrogen. The resulting mixture was stirred for 1.5 h to give a bright yellow suspension, which was treated dropwise with 2-bromonicotinaldehyde (2.00 g, 0.11 mol). This was allowed to warm to 0 °C and stirred for 5 h. The resulting mixture was purified by adding silica and evaporating to dryness. Column chromatography (diethyl ether) removed the triphenyl phosphine oxide. A second column chromatography (DCM) yielded the *vinyl bromide* **5a** (2.26 g, *E*/*Z* >1:20, 80%) as a yellow oil. ν_{max} (film)/cm^{-1} 3291, 3073, 2922, 1721, 1682, 1616, 1572, 1550, 1444, 1319, 1252, 1120, 1052, 878; δ_H (400 MHz, $CDCl_3$) *Z* isomer: 6.70 (1H, d, *J*=8), 7.17 (1H, d, *J*=8), 7.30–7.36 (1H, m), 8.10 (1H, dd, *J*=4 and 2), 8.33 (1H, dd, *J*=4 and 2); δ_C (100 MHz, $CDCl_3$) 111.3, 122.3, 130.6, 138.6, 143.1, 144.5, 149.3; LRMS (Cl$^+$) 263.9 (^{79}Br−^{81}Br−[M+H]$^+$, 100%), 261.9 (58), 265.9 (53); HRMS (Cl$^+$): 260.8786 ([M]$^+$ $C_7H_5N^{79}Br_2$ requires 260.8789).

4.3. 2-Bromo-3-(2-chlorovinyl)pyridine (5b, Table 1, entry 2)

Prepared using (chloromethyl)triphenylphosphonium chloride (1.67 g, 0.05 mol) and 2-bromonicotinaldehyde (750 mg, 0.04 mol) at 0 °C for 5 h. The reaction mixture was absorbed onto silica and separated by column chromatography (DCM) to yield the *vinyl chloride* **5b** (656 mg, *E*/*Z* 1:3, 75%) as a yellow oil. ν_{max} (film)/

cm^{-1} 3293, 3069, 1623, 1572, 1551, 1444, 1386, 1179, 1120, 1052, 930, 857; δ_H (400 MHz, acetone-d_6) *Z*-isomer: 6.72 (1H, d, *J*=8), 6.88 (1H, d), 7.45 (1H, dd, *J*=8), 8.13 (1H, dd, *J*=6 and 2), 8.33 (1H, dd, *J*=6 and 2); *E* isomer: 7.04 (1H, d, *J*=12), 7.08 (1H, d, *J*=12), 7.38 (1H, dd, *J*=8 and 4), 7.96 (1H, dd, *J*=6 and 2), 8.30 (1H, dd, *J*=6 and 2); δ_C (100 MHz, acetone-d_6) 122.4, 123.3, 124.0, 127.7, 132.4, 139.2, 143.3, 149.8; LRMS (ESI$^+$) 220.0 (^{35}Cl–^{81}Br–[M+H]$^+$, 100%), 218.0 (79), 221.0 (17%); HRMS (ESI$^+$): 217.9369 ([M+H]$^+$ $C_7H_6N^{79}Br^{35}Cl$ requires: 217.9372).

4.4. 3-(Bromovinyl)-2-chloropyridine (5c, Table 1, entry 3)

Prepared using (bromomethyl)triphenylphosphonium bromide (4.48 g, 0.13 mol) and 2-chloronicotinaldehyde (2.00 g, 0.11 mol). The product was purified by column chromatography (DCM) to yield the *vinyl bromide* **5c** (1.65 g, *E*/*Z* 1:13, 70%) as a yellow oil. ν_{max} (film)/cm^{-1} 3294, 3074, 1619, 1572, 1446, 1392, 1319, 1190, 1068, 943; δ_H (400 MHz, $CDCl_3$) *Z* isomer: 6.70 (1H, d, *J*=8), 7.21 (1H, d, *J*=8), 7.29 (1H, dd, *J*=8 and 4), 8.18 (1H, dd, *J*=6), 8.36 (1H, d, *J*=6); *E* isomer: 6.88 (1H, d, *J*=14), 7.40 (1H, d, *J*=14), 7.59 (1H, dd, *J*=8 and 4), 7.73 (1H, d, *J*=6), 8.35 (1H, d, *J*=6); δ_C (100 MHz, $CDCl_3$) 111.4, 121.8, 128.4, 130.0, 138.8, 148.9, 155.4; HRMS (ESI$^+$): 217.9368 ([M+H]$^+$ $C_7H_4N^{79}Br_2$ requires 217.9372).

4.5. 2-Chloro-3-(2-chlorovinyl)pyridine (5d, Table 1, entry 4)

Prepared using (chloromethyl)triphenylphosphonium chloride (2.22 g, 0.06 mol) and 2-chloronicotinaldehyde (750 mg, 0.05 mol) at 0 °C for 5 h. The reaction mixture was absorbed onto silica and was separated by column chromatography (DCM) to yield the *vinyl chloride* **5d** (645 mg, *E*/*Z* 1:4, 70%) as a yellow oil. ν_{max} (film)/cm^{-1} 3296, 3071, 1608, 1575, 1556, 1447, 1364, 1341, 1280, 1255, 1187, 1130, 932, 859; δ_H (400 MHz, acetone-d_6) *Z* isomer: 6.75 (1H, d, *J*=8), 6.94 (1H, d, *J*=8), 7.45 (1H, dd, *J*=8 and 4), 8.23 (1H, dd, *J*=8 and 4), 8.37 (1H, dd, *J*=8 and 4); *E* isomer: 7.11 (2H, s), 7.45 (1H, dd, *J*=8 and 4), 8.04 (1H, dd, *J*=6 and 2), 8.34 (1H, dd, *J*=6 and 2); δ_C (100 MHz, acetone-d_6) 122.5, 123.0, 125.7, 129.3, 139.5, 149.5, 150.3; LRMS (ES$^+$) 174.0 (^{35}Cl–^{35}Cl–[M+H]$^+$, 100%), 176.0 (63); HRMS (ESI$^+$): 173.9874 ([M−H]$^+$ $C_7H_6N^{35}Cl_2$ requires 173.9877).

4.6. 2-Bromo-3-(2,2-dibromovinyl)pyridine

A solution of carbon tetrabromide (2.14 g, 0.06 mol) in DCM (25 mL) was added dropwise to a stirred solution of PPh_3 (3.40 g, 0.12 mol) in DCM (50 mL) at −78 °C under nitrogen. The resulting mixture was stirred for 30 min to give a pale orange solution, which was then treated dropwise with 2-bromonicotinaldehyde (600 mg, 0.03 mol), at −78 °C. The resulting reaction mixture was stirred for 2 h and then allowed to warm to room temperature and stirred for a further 16 h. The reaction mixture was poured into hexane (100 mL), filtered and concentrated in vacuo to give a yellow oil. The crude product was purified via absorbing onto silica and column chromatography (diethyl ether), to produce the *gem-dibromide* (580 mg, 53%) as a pale yellow oil. ν_{max} (film)/cm^{-1} 3023, 1579, 1568, 1552, 1437, 1385, 1273, 1182, 1119, 1054, 945, 873, 804, 732; δ_H (400 MHz, acetone-d_6) 7.54 (1H, dd, *J*=8 and 4), 7.61 (1H, s), 8.03 (1H, dd, *J*=8 and 4), 8.41 (1H, dd, *J*=8 and 4); δ_C (100 MHz, acetone-d_6) 94.8, 123.5, 134.2, 135.7, 139.4, 141.9, 150.3; LRMS (CI$^+$) 341.81 (^{79}Br$_2$-^{81}Br-[M+H]$^{+\cdot}$, 100%), 343.8 (97), 339.8 (34), 345.8 (24); HRMS (CI$^+$): 339.7983 ([M]$^+$ $C_7H_4{}^{79}Br_3N$ requires: 339.7972).

4.7. (*E*)-2-Bromo-3-(2-bromovinyl)pyridine, *E*-5a

Triethylamine (8.15 g, 11.10 mL, 0.08 mmol) was added to a solution of 2-bromo-3-(2,2-bromovinyl)pyridine (500 mg, 0.02 mol) and dimethyl phosphite (660 mg, 0.6 mL, 0.06 mol) in DMF (60 mL). The reaction mixture was stirred at 70 °C for 16 h, then cooled to room temperature, diluted with water (10 mL) and washed with ethyl acetate (3×30 mL). The layers were separated and the organic fractions were washed with brine (3×30 mL), dried ($MgSO_4$) and concentrated under reduced pressure. The product was purified by absorption onto silica and column chromatography (diethyl ether) to yield the *vinyl bromide* (236 mg, *E*/*Z* 9:1, 60%) as a yellow oil; δ_H (400 MHz, $CDCl_3$) *E* isomer: 6.83 (1H, d, *J*=16), 7.24–7.27 (1H, m), 7.38 (1H, d, *J*=16), 7.67 (1H, dd, *J*=8 and 1.6), 8.32 (1H, dd, *J*=8 and 1.6).

4.8. General procedure for the synthesis of 7-azaindoles; preparation of 1-*p*-tolyl-7-azaindole, 6

Caesium carbonate (161 mg, 0.84 mmol) was added to an oven dried flask charged with palladium(II) acetate (4 mg, 0.02 mmol) and ligand **7** (19 mg, 0.05 mmol) under nitrogen. The sealed tube was flushed with nitrogen and the reagents suspended in anhydrous toluene (1.5 mL). 2-Bromo-3-(2-bromovinyl)pyridine **5a** (100 mg, 0.38 mmol) and *p*-toluidine (82 mg, 0.76 mmol) were added and the reaction mixture heated to 110 °C for 6 h in a sealed tube. After cooling, the reaction mixture was diluted with DCM (10 mL) and filtered through a Celite pad, washing with DCM (2×25 mL). The filtrate was reduced in vacuo. The product was purfied via column chromatography (DCM) to yield the *azaindole* **6** (60 mg, 76%) as a yellow oil. ν_{max} (film)/cm^{-1} 2922, 1593, 1520, 1424, 1359, 1323, 1270, 1235, 1147, 893, 817, 796, 773, 720; δ_H (400 MHz, $CDCl_3$) 2.43 (3H, s), 6.63 (1H, d, *J*=4), 7.13 (1H, dd, *J*=5 and 3), 7.34 (2H, d, *J*=8), 7.50 (1H, d, *J*=4), 7.62–7.64 (2H, m), 7.98 (1H, dd, *J*=6 and 2), 8.39 (1H, dd, *J*=6 and 2); δ_C (100 MHz, $CDCl_3$) 21.1, 101.2, 116.2, 121.4, 124.1 (2C), 128.0, 129.0 (2C), 129.9, 135.9, 136.2, 143.5, 147.5; HRMS (ESI$^+$): 209.1073 ([M+H]$^+$ $C_{14}H_{13}N_2$ requires: 209.1079).

4.9. 1-Phenyl-7-azaindole (Table 3, entry 1)

Prepared using 2-bromo-3-(2-bromovinyl)pyridine (100 mg, 0.38 mmol) and aniline (76 mg, 0.76 mmol). Isolation via column chromatography (DCM) yielded the *azaindole* (79 mg, 96%) as a yellow oil. ν_{max} (film)/cm^{-1} 3047, 2925, 1591, 1516, 1476, 1456, 1423, 1365, 1324, 1270, 1236, 1210, 1147, 893, 797, 753; δ_H (400 MHz, $CDCl_3$) 6.61 (1H, d, *J*=4), 7.12 (1H, dd, *J*=8 and 4), 7.30–7.34 (1H, m), 7.49–7.53 (3H, m), 7.75 (2H, d, *J*=7), 7.95 (1H, d, *J*=4), 8.39 (1H, d, *J*=7); δ_C (100 MHz, $CDCl_3$) 101.6, 116.7, 121.5, 124.2, 124.3, 126.3, 127.8, 128.7, 129.0, 129.6, 138.5, 143.6, 147.4; HRMS (ESI$^+$): 195.0917 ([M]$^+$ $C_{13}H_{10}N_2$ requires: 195.0922).

4.10. 1-*p*-Ansidyl-7-azaindole (Table 3, entry 2)

Prepared using 2-bromo-3-(2-bromovinyl)pyridine (100 mg, 0.38 mmol) and *p*-anisidine (94 mg, 0.76 mmol). Isolation via column chromatography (DCM) yielded the *azaindole* (67 mg, 79%) as a yellow oil. ν_{max} (film)/cm^{-1} 2932, 1593, 1519, 1463, 1424, 1358, 1324, 1298, 1272, 1247, 1181, 1147, 1034, 894; δ_H (400 MHz, $CDCl_3$) 3.86 (3H, s), 6.60 (1H, d, *J*=4), 7.04–7.06 (2H, m), 7.12 (1H, dd, *J*=8 and 4), 7.45 (1H, d, *J*=4), 7.60–7.62 (2H, m), 7.97 (1H, dd, *J*=6 and 4), 8.36 (1H, dd, *J*=6 and 4); δ_C (100 MHz, $CDCl_3$) 55.6, 100.9, 114.6 (2C), 116.4, 121.2, 125.7 (2C), 128.3, 128.9, 131.5, 143.5, 147.6, 158.1; HRMS (ESI$^+$): 225.1022 ([M+H]$^+$ $C_{14}H_{13}N_2O$ requires: 225.1028).

4.11. 1-(4-Chlorophenyl)-7-azaindole (Table 3, entry 3)

Prepared using 2-bromo-3-(2-bromovinyl)pyridine (100 mg, 0.38 mmol) and 4-chloroaniline (97 mg, 0.76 mmol). Isolation

via column chromatography (DCM) yielded the *azaindole* (75 mg, 86%) as a yellow solid; mp 165–168 °C. ν_{max} (film)/cm^{-1} 2922, 1592, 1521, 1495, 1420, 1359, 1325, 1278, 1266, 1236, 1147, 1095, 893, 821; δ_H (400 MHz, $CDCl_3$) 6.64 (1H, d, J=4), 7.15 (1H, dd, J=8 and 5), 7.48–7.51 (3H, m), 7.72–7.75 (2H, m), 7.97 (1H, dd, J=8 and 2), 8.36 (1H, dd, J=8 and 2); δ_C (100 MHz, $CDCl_3$) 102.1, 116.9, 121.6, 125.0 (2C), 127.4, 129.2, 129.5 (2C), 131.7, 137.0, 143.7, 147.4. Anal. Calcd for $C_{13}H_9N_2Cl$: C: 68.33; H, 3.90; N, 12.29. Found: C, 68.37; H, 3.97; N, 12.36.

4.12. 1-(4-(*N*,*N*-Dimethyl)methyl)phenyl-7-azaindole (Table 3, entry 4)

Prepared using 2-bromo-3-(2-bromovinyl)pyridine (100 mg, 0.38 mmol) and 4-(dimethylaminomethyl)aniline (114 mg, 0.76 mmol). Isolation via column chromatography (DCM) yielded the *azaindole* (87 mg, 91%) as a yellow oil. ν_{max} (film)/cm^{-1} 2934, 2815, 2772, 1593, 1427, 1423, 1361, 1323, 1269, 1147, 1111, 1018, 893, 838; δ_H (400 MHz, $CDCl_3$) 2.28 (6H, s), 3.48 (2H, s), 6.62 (1H, d, J=4), 7.13 (1H, dd, J=8 and 4), 7.46 (2H, d, J=6), 7.51 (1H, d, J=4), 7.71 (2H, d, J=6), 7.96 (1H, d, J=4), 8.36 (1H, d, J=4); δ_C (100 MHz, $CDCl_3$) 45.5 (2C), 63.9, 101.9, 116.6, 121.6, 121.6, 123.7, 127.9, 129.0, 129.2, 129.9, 137.1, 137.4, 143.6, 147.5; HRMS (ESI$^+$): 252.1495 ([M+H]$^+$ $C_{16}H_{18}N_3$ requires: 252.1511).

4.13. 1-(6-Chloropyridin-3-yl)-7-azaindole (Table 3, entry 5)

Prepared using 2-bromo-3-(2-bromovinyl)pyridine (100 mg, 0.38 mmol) and 5-amino-2-chloropyridine (98 mg, 0.76 mmol). Isolation via column chromatography (DCM) yielded the *azaindole* (61 mg, 70%) as a yellow solid; mp 169–172 °C. ν_{max} (film)/cm^{-1} 3029, 2922, 2857, 1596, 1571, 1517, 1490, 1457, 1416, 1399, 1312, 1246, 1179, 1091, 1013, 961; δ_H (400 MHz, $CDCl_3$) 6.70 (1H, d, J=4), 7.18 (1H, dd, J=8 and 5), 7.47 (1H, s), 7.49–7.51 (1H, m), 7.98 (1H, dd, J=8 and 2), 8.32–8.38 (2H, m), 8.77 (1H, d, J=3); δ_C (100 MHz, $CDCl_3$) 103.3, 117.5, 121.7, 124.5, 126.4, 129.5, 133.6, 134.3, 143.7, 143.9, 147.4. 148.0; HRMS (ESI$^+$): 230.0479 ([M+H]$^+$ $C_{12}H_9{}^{35}ClN_3$ requires: 230.0485).

4.14. 1-Pentyl-7-azaindole (Table 3, entry 7)[18]

Prepared using 2-bromo-3-(2-bromovinyl)pyridine (100 mg, 0.38), dppf **10** (28 mg, 0.05 mmol) and pentylamine (66 mg, 88 μL, 0.76 mmol). Isolation via column chromatography (DCM) yielded the *azaindole* (46 mg, 64%) as a tan oil. ν_{max} (film)/cm^{-1} 2957, 2930, 2860, 1594, 1569, 1509, 1426, 1306, 1205, 1096, 894, 796, 773, 717; δ_H (500 MHz, $CDCl_3$) 0.85–0.92 (3H, m), 1.25–1.40 (4H, m), 1.80–1.95 (2H, m), 4.30 (2H, t, J=7), 6.46 (1H, d, J=3), 7.05 (1H, dd, J=8 and 4), 7.23 (1H, d, J=3), 7.92 (1H, dd, J=6 and 2), 8.33 (1H, dd, J=6 and 2); δ_C (125 MHz, $CDCl_3$) 14.0, 22.4, 28.1, 29.1, 44.5, 99.1, 115.5, 120.5, 127.7, 128.0, 142.6, 147.3.

4.15. 1-Octyl-7-azaindole (Table 3, entry 8)

Prepared using 2-bromo-3-(2-bromovinyl)pyridine (100 mg, 0.38 mmol), dppf **10** (28 mg, 0.05 mmol) and octylamine (98 mg, 126 μL, 0.76 mmol). Isolation via column chromatography (DCM) yielded the *azaindole* (53 mg, 60%) as a tan oil. ν_{max} (film)/cm^{-1} 3424, 3051, 2925, 2855, 1593, 1509, 1464, 1426, 1403, 1307, 1205, 1111, 958, 894; δ_H (400 MHz, acetone-d_6) 0.81–0.93 (3H, m), 1.23–1.35 (10H, m), 1.82–1.92 (2H, m), 4.32 (2H, t, J=7), 6.45 (1H, d, J=3), 7.05 (1H, dd, J=8 and 4), 7.46 (1H, d, J=3), 7.93 (1H, dd, J=6 and 2), 8.26 (1H, dd, J=6 and 2); δ_C (100 MHz, $CDCl_3$) 14.1, 22.6, 26.9, 29.2 (2C), 30.4, 31.2, 44.6, 99.1, 115.4, 120.6, 127.9, 128.7, 142.6, 147.4; LRMS (FI$^+$) 230.2 (M$^+$, 100%), 231.2 (14); HRMS (FI$^+$): 230.1781 ([M]$^+$ $C_{15}H_{22}N_2$ requires: 230.1783).

4.16. 1-Benzyl-7-azaindole (Table 3, entry 9)[19]

Prepared using 2-bromo-3-(2-bromovinyl)pyridine (100 mg, 0.38 mmol), dppf **10** (28 mg, 0.05 mmol) and benzylamine (81 mg, 83 μL, 0.76 mmol). Isolation via column chromatography (DCM) yielded the *azaindole* (58 mg, 73%) as a tan oil. ν_{max} (film)/cm^{-1} 3120, 3060, 2916, 1961, 1873, 1716, 1658, 1592, 1492, 1434, 1349, 1314, 1253, 1183, 1120, 1075, 1031, 965, 890; δ_H (400 MHz, $CDCl_3$) 5.55 (2H, s), 6.51 (1H, d, J=4), 7.09 (1H, dd, J=8 and 5), 7.22–7.34 (5H, m), 7.49 (1H, d, J=4), 7.97 (1H, dd, J=6 and 2), 8.30 (1H, dd, J=6 and 2); δ_C (100 MHz, $CDCl_3$) 47.7, 100.0, 116.1, 120.8, 127.8, 127.9 (2C), 128.8, 128.8, 128.9 (2C), 139.2, 143.1, 148.2.

4.17. 1-(2-Phenoxyethyl)-7-azaindole (Table 3, entry 10)

Prepared using 2-bromo-3-(2-bromovinyl)pyridine (100 mg, 0.38 mmol), dppf **10** (28 mg, 0.05 mmol) and 2-phenoxyethanamine (104 mg, 99 μL, 0.76 mmol). Isolation via column chromatography (DCM) yielded the *azaindole* (67 mg, 74%) as a tan oil. ν_{max} (film)/cm^{-1} 3053, 2933, 2874, 1927, 1851, 1721, 1597, 1496, 1427, 1347, 1318, 1244, 1207, 1172, 1107, 1080, 1062, 962, 906; δ_H (400 MHz, $CDCl_3$) 4.34 (2H, t, J=6), 4.72 (2H, t, J=6), 6.47 (1H, d, J=4), 6.86–6.90 (2H, m), 6.92–6.97 (1H, m), 7.09 (1H, dd, J=8 and 4), 7.24–7.29 (2H, m), 7.42 (1H, dd, J=4), 7.93 (1H, dd, J=6 and 4), 8.34 (1H, dd, J=6 and 4); δ_C (100 MHz, $CDCl_3$) 44.0, 66.9, 99.6, 114.5 (2C), 115.8, 120.8, 121.1, 128.9, 129.2, 129.5 (2C), 142.7, 147.3, 158.4; LRMS (ES$^+$) 239.1 ([M+H]$^+$, 100%), 240.1 (10); HRMS (ESI$^+$): 239.1179 ([M+H]$^+$ $C_{15}H_{15}N_2O$ requires: 239.1184).

4.18. 1-(4-Phenylbutyl)-7-azaindole (Table 3, entry 11)

Prepared using 2-bromo-3-(2-bromovinyl)pyridine (100 mg, 0.38 mmol), dppf **10** (28 mg, 0.05 mmol) and 4-phenylbutyl-1-amine (113 mg, 120 μL, 0.76 mmol). Isolation via column chromatography (DCM) yielded the *azaindole* (50 mg, 53%) as a tan oil. ν_{max} (film)/cm^{-1} 3052, 3025, 2935, 2858, 1593, 1569, 1509, 1453, 1426, 1402, 1346, 1307, 1205, 1087, 1030, 894; δ_H (400 MHz, $CDCl_3$) 1.63–1.75 (2H, m), 1.89–1.94 (2H, m), 2.65 (2H, t, J=8), 4.33 (2H, t, J=8), 6.45 (1H, d, J=4), 7.06 (1H, dd, J=8 and 5), 7.11–7.12 (4H, m), 7.23–7.29 (2H, m), 7.91 (1H, dd, J=6 and 1), 8.33 (1H, dd, J=6 and 1); δ_C ($CDCl_3$) 100 MHz 28.7, 30.0, 35.5, 44.4, 99.3, 115.5, 120.6, 125.8 (2C), 127.9, 128.3 (2C), 128.4 (2C), 128.7, 142.1, 142.7; LRMS (FI$^+$) 250.1 (M$^+$, 100%), 251.2 (10); HRMS (FI$^+$): 250.1470 ([M]$^+$ $C_{17}H_{18}N_2$ requires: 250.1470).

4.19. *tert*-Butyl-7-azaindole-1-carboxylate (Table 3, entry 12)[20]

Prepared using 2-bromo-3-(2-bromovinyl)pyridine (100 mg, 0.38 mmol), X-Phos **8** (24 mg, 0.05 mmol) and *tert*-butyl carbamate (87 mg, 0.76) in anhydrous dioxane (1.5 mL). Isolation via column chromatography (10%→20% EtOAc/Petrol) yielded the *azaindole* (52 mg, 63%) as a yellow oil. ν_{max} (film)/cm^{-1} 2981, 1730, 1530, 1411, 1321, 1256, 1158, 1114, 1089, 773; δ_H (400 MHz, $CDCl_3$) 1.68 (9H, s), 6.51 (1H, d, J=4), 7.20 (1H, dd, J=8 and 6), 7.65 (1H, d, J=4), 7.89 (1H, dd, J=8 and 2), 8.52 (1H, dd, J=6 and 2); δ_C (125 MHz, $CDCl_3$) 28.3 (3C), 84.1, 104.5, 118.6, 123.0, 126.6, 129.2, 145.2, 148.0, 148.4.

4.20. (*Z*)-Methyl-5-(2-bromovinyl)-6-chloropicolinate (Table 4, entry 1 substrate)

Prepared using (bromomethyl)triphenylphosphonium bromide (1.31 g, 0.03 mol) and methyl-6-chloro-5-formylpicolinate[17] (500 mg, 0.03 mol). The product was purified by flash chromatography (DCM) to yield the *vinyl bromide* (138 mg, *E*/*Z* 1:4, 20%) as an oil. ν_{max}

(film)/cm^{-1} 3075, 2957, 2925, 1744, 1727, 1555, 1445, 1358, 1317, 1222, 1138, 1067, 819; δ_H (500 MHz, $CDCl_3$) *Z*-isomer: 4.00 (3H, s), 6.81 (1H, d, *J*=10), 7.26 (1H, d, *J*=10), 8.10 (1H, d, *J*=5), 8.35 (1H, d, *J*=5); *E*-isomer: 3.99 (3H, s), 7.04 (1H, d, *J*=15), 7.45 (1H, d, *J*=15), 7.87 (1H, d, *J*=8), 7.97 (1H, d, *J*=8); δ_C (125 MHz, $CDCl_3$) 53.2, 113.2, 123.4, 127.9, 133.6, 135.7, 143.0, 146.9, 164.3; LRMS (ES$^+$) 278.0 (^{35}Cl−^{81}Br−[M+H]$^+$, 100%), 276.0 (81), 280.0 (19); HRMS (ESI$^+$): 275.9413 ([M−H]$^+$ $C_9H_8{}^{79}Br^{35}ClNO_2$ requires: 275.9421).

4.21. (*Z*)-3-(2-Bromo)-2-chloro–5-*iso*-propylpyridine (Table 4, entry 2 substrate)

Prepared using (bromomethyl)triphenylphosphonium bromide (2.85 g, 0.07 mol) and 2-chloro-5-*iso*-propyl nicotinaldehyde[17] (1.00 g, 0.05 mol). The product was purified by flash chromatography (DCM) to yield the *vinyl bromide* (0.92 g, *E*/*Z* ≥1:20, 65%) as a tan oil. ν_{max} (film)/cm^{-1} 3299, 3076, 3028, 2964, 2929, 2872, 1619, 1607, 1585, 1553, 1463, 1423, 1398, 1366, 1338, 1317, 1280, 1224, 1177, 1163, 1149, 1086, 1020, 924, 909, 864, 833; δ_H (400 MHz) 1.28 (3H, s), 1.30 (3H, s), 2.88–3.03 (1H, m), 6.68 (1H, d, *J*=8), 7.21 (1H, d, *J*=8), 8.07 (1H,d, *J*=4), 8.21 (1H, d, *J*=4); δ_C (100 MHz, $CDCl_3$) 23.6 (2C), 31.1, 111.0, 123.9, 128.6, 129.3, 137.0, 140.2, 142.4; LRMS (CI$^+$) 261.0 (^{35}Cl−^{81}Br−[M+H]$^+$, 100%), 260.0 (80), 264.0 (20); HRMS (CI$^+$): 258.9771 ([M]$^+$ $C_{10}H_{11}N^{35}Cl^{79}Br$ requires: 258.9763).

4.22. (*Z*)-3-(2-Bromovinyl)-2-chloro-5-methyl-6-phenylpyridine (Table 4, entry 7 substrate)

Prepared using (bromomethyl)triphenylphosphonium bromide (567 mg, 0.01 mol) and 2-chloro-5-methyl-6-phenylnicotinaldehyde[17] (250 mg, 0.01 mol). The product was purified by flash chromatography (DCM) to yield the *vinyl bromide* (1.05 g, *E*/*Z* 1:3, 95%) as a tan oil. ν_{max} (film)/cm^{-1} 3060, 2960, 2926, 1614, 1577, 1535, 1494, 1444, 1386, 1316, 1263, 1194, 1144, 1002, 937; δ_H (500 MHz, MeOH-d_4) *Z*-isomer: 2.33 (3H, s), 6.85 (1H, d, *J*=10), 7.24 (1H, d, *J*=10), 7.42–7.48 (5H, m), 8.12 (1H, s); *E*-isomer: 2.28 (3H, s), 7.22 (1H, d, *J*=15), 7.36 (1H, d, *J*=15), 7.42–7.48 (5H, m), 7.86 (1H, s); δ_C (125 MHz, MeOH-d_4) 19.7, 112.6, 112.9, 124.4, 129.4 (2C), 129.9, 130.1, 131.4, 139.5, 140.0, 142.9, 147.8, 160.3; LRMS (FI$^+$) 309.0 (^{35}Cl−^{81}Br−M$^+$, 100%), 307.0 (76), 311.0 (23); HRMS (FI$^+$): 306.9769, ([M]$^+$ $C_{14}H_{11}{}^{79}Br^{35}ClN$ requires: 306.9763).

4.23. (*Z*)-Ethyl-2-bromo-3-(2-chloropyridin-3-yl)acrylate (Table 4, entry 9 substrate)

A solution of sodium hydride (60% dispersion in mineral oil, 236 mg, 0.08 mol) in THF (30 mL) was added to ethyl-2-bromo-2-(diethoxyphosphoryl)acetate[21] (4.24 g, 0.14 mol) at room temperature. The solution was stirred for 1 h and then 2-chloronicotinaldehyde (1.00 g, 0.07 mol) was added at room temperature then the reaction mixture was heated to 50 °C for 12 h. The reaction mixture was cooled to room temperature and water (20 mL) was added and extracted with DCM (3×50 mL). The layers were separated and the organic portions dried over $MgSO_4$, filtered and concentrated in vacuo. The crude material was purified by column chromatography (DCM) to yield the *acrylate* (1.26 g, 62%) as a white solid; mp 36–38 °C; ν_{max} (film)/cm^{-1} 2982, 2937, 1726, 1616, 1574, 1557, 1447, 1369, 1219, 1154, 1029, 838; δ_H (400 MHz, acetone-d_6) *Z*-isomer: 1.38 (3H, t, *J*=7), 4.38 (2H, q, *J*=8), 7.56 (1H, dd, *J*=8), 8.28 (1H, s), 8.29 (1H, dd, *J*=8 and 4), 8.48 (1H, dd, *J*=8 and 4); *E*-isomer: 1.08 (3H, t, *J*=7 and 2, Me), 4.14 (2H, q, *J*=7 and 4), 7.45 (1H, dd, *J*=8), 7.64 (1H, s), 7.84 (1H, d, *J*=6), 8.42 (1H, d, *J*=6); δ_C (100 MHz, acetone-d_6) 13.9, 63.3, 119.0, 123.1, 130.2, 136.9, 139.8, 150.7, 162.2; LRMS (CI$^+$) 292.0 (^{35}Cl−^{81}Br−[M+H]$^+$, 100%), 290.0 (79), 294.0 (25); HRMS (CI$^+$): 289.9588 ([M]$^+$ $C_{10}H_9{}^{79}Br^{35}ClNO_2$ requires: 289.9583).

4.24. 2-Chloro-3-(2,2-dibromovinyl)pyridine

A solution of carbon tetrabromide (4.71 g, 0.14 mol) in DCM (50 mL) was added dropwise to a stirred solution of PPh_3 (7.45 g, 0.28) in DCM (100 mL) at −78 °C under nitrogen. The resulting mixture was stirred for 30 min to give a pale orange solution, which was then treated dropwise with 2-chloronicotinaldehyde (1.00 g, 0.07 mol), at −78 °C. The resulting reaction mixture was stirred for 2 h and then allowed to warm to room temperature and stirred for a further 16 h. The reaction mixture was poured into hexane (200 mL), filtered and concentrated in vacuo. The crude product was purified via absorbing onto silica and column chromatography (diethyl ether), to produce the *gem-dibromide* (158 g, 75%) as a white solid; mp 57–59 °C. ν_{max} (film)/cm^{-1} 3026, 2201, 1599, 1571, 1391, 1187, 1131, 1071, 978, 945; δ_H (400 MHz, acetone-d_6) 7.51 (1H, dd, *J*=8 and 4), 7.67 (1H, s), 8.10 (1H, dd, *J*=8 and 4), 8.43 (1H, dd, *J*=8 and 4); δ_C (125 MHz, acetone-d_6) 95.2, 123.8, 131.9 134.4, 140.1, 149.9, 150.0; LRMS (FI$^+$) 296.8 (^{35}Cl−^{81}Br$_2$−M$^+$, 100%), 298.8 (69), 294.8 (44); HRMS (FI$^+$): 294.8409 ([M]$^+$ $C_7H_4{}^{79}Br_2{}^{35}ClN$ requires: 294.8399).

4.25. (*Z*)-3-(2-Bromo-2-(4-methoxyphenyl)vinyl)-2-chloropyridine (Table 4, entry 13 substrate)

p-Methoxyphenylboronic acid (86 mg, 0.6 mmol) was added to a flask charged with $Pd(OAc)_2$ (2 mg, 0.01 mmol) and P(2-fur)$_3$ (19 mg, 0.08 mmol). The flask was flushed with argon and the reagents suspended in degassed dioxane (2.0 mL). To this suspension a degassed 1 M solution of $NaHCO_3$ (1.0 mL) and 2-chloro-3-(2,2-dibromovinyl)pyridine (150 mg, 0.5 mmol) were added and the reaction mixture heated to 70 °C for 4 h. After cooling to room temperature the reaction mixture was partitioned with water (10 mL), extracted with DCM (3×20 mL) and the organic fractions dried ($MgSO_4$), filtered and concentrated in vacuo. The crude material was purified by column chromatography (DCM) to yield the *pyridine* (131 mg, 81%) as an off-white solid; mp 112–114 °C. ν_{max} (film)/cm^{-1} 3039, 3004, 2931, 1723, 1651, 16.03, 1571, 1551, 1461, 1415, 1385, 1304, 1273, 1228, 1117, 1030, 943; δ_H (400 MHz, $CDCl_3$) 3.88 (3H, s), 7.04 (2H, d, *J*=8), 7.25 (1H, s), 7.54 (1H, dd, *J*=8 and 4), 7.74 (2H, d, *J*=8), 8.11 (1H, dd, *J*=8 and 4), 8.36 (1H, dd, *J*=8 and 4); δ_C (125 MHz, acetone-d_6) 55.4, 114.3, 123.2, 126.2, 128.6, 128.7, 129.6, 132.0, 133.6, 135.4, 139.9, 143.2, 149.5, 161.4; LRMS (FI$^+$) 325.0 (^{35}Cl−^{81}Br−M$^+$, 100%), 323.0 (78), 327.0 (28); HRMS (FI$^+$): 322.9712 ([M]$^+$ $C_{14}H_{11}{}^{79}Br^{35}ClNO$ requires: 322.9713). Anal. Calcd for $C_{14}H_{11}N$: C, 52.87; H, 3.31; N, 4.26. Found: C, 52.92; H, 3.37; N, 4.26.

4.26. (*Z*)-3-(2-Bromo-2-(4-chlorophenyl))-2-chloropyridine (Table 4, entry 14 substrate)

p-Chlorophenylboronic acid (289 mg, 1.85 mmol) was added to a flask charged with $Pd(OAc)_2$ (6.7 mg, 0.03 mmol) and P(2-fur)$_3$ (55 mg, 0.24 mmol). The flask was flushed with argon and the reagents suspended in degassed dioxane (5.0 mL). To this suspension a degassed 1 M solution of $NaHCO_3$ (3.0 mL) and 2-chloro-3-(2,2-dibromovinyl)pyridine (500 mg, 1.68 mmol) were added and the reaction mixture heated to 70 °C for 4 h. After cooling to room temperature the reaction mixture was partitioned with water (10 mL), extracted with DCM (3×20 mL) and the organic fractions dried ($MgSO_4$), filtered and concentrated in vacuo. The crude material was purified by column chromatography (DCM) to yield the *pyridine* (473 mg, 86%) as a white solid; mp 61–63 °C. ν_{max} (film)/cm^{-1} 3047, 1612, 1590, 1574, 1556, 1487, 1447, 1301, 1264, 1225, 1180,

1126, 1093, 1070, 1012, 977; δ_H (400 MHz, acetone-d_6) 7.46 (1H, s), 7.51–7.55 (3H, m), 7.79–7.83 (2H, m), 8.20 (1H, ddd, J=8, 2 and 1), 8.43 (1H, dd, J=5 and 2); δ_C (100 MHz, acetone-d_6) 123.0, 127.0, 129.0, 129.1, 129.5, 129.9, 132.5, 133.6, 135.4, 138.5, 140.1, 148.6, 149.6; LRMS (FI$^+$) 328.9 ($^{35}Cl_2-^{81}Br-M^+$, 100%), 326.9 (63), 330.9 (47); HRMS (FI$^+$): 326.9216 ([M]$^+$ $C_{13}H_8{}^{79}Br^{35}Cl_2N$ requires: 326.9217).

4.27. (*Z*)-2-Bromo-3-(2-bromo-2-(4-chlorophenyl))pyridine (Table 4, entry 15 substrate)

p-Chlorophenylboronic acid (200 mg, 1.29 mmol) was added to a flask charged with $Pd(OAc)_2$ (4.7 mg, 0.02 mmol) and P(2-fur)$_3$ (38 mg, 0.17 mmol). The flask was flushed with argon and the reagents suspended in degassed dioxane (3.5 mL). To this suspension a degassed 1 M solution of $NaHCO_3$ (2.0 mL) and 2-bromo-3-(2,2-dibromovinyl)pyridine (400 mg, 1.17 mmol) were added and the reaction mixture heated to 70 °C for 4 h. After cooling to room temperature the reaction mixture was partitioned with water (10 mL), extracted with DCM (3×20 mL) and the organic fractions dried ($MgSO_4$), filtered and concentrated in vacuo. The crude material was purified by column chromatography (DCM) to yield the *pyridine* (327 mg, 85%) as a white solid; mp 76–78 °C. ν_{max} (film)/cm^{-1} 3052, 1630, 1590, 1566, 1522, 1486, 1445, 1397, 1385, 1264, 1226, 1175, 1118, 1092, 1052, 1013, 979, 947, 905; δ_H (400 MHz, acetone-d_6) 7.41 (1H, s), 7.53–7.57 (3H, m), 7.81–7.83 (2H, m), 8.11–8.13 (1H, m), 8.40 (1H, d, J=4); δ_C (100 MHz, acetone-d_6) 123.3, 127.3, 128.8, 129.2 (2C), 129.8 (2C), 135.0, 135.4, 138.5, 139.8, 143.0, 149.9; LRMS (FI$^+$) 372.9 ($^{35}Cl-^{81}Br_2-M^+$, 100%), 374.9 (78), 370.9 (50); HRMS (FI$^+$): 370.8708 ([M]$^+$ $C_{13}H_8{}^{79}Br_2{}^{35}ClN$ requires: 370.8712). Anal. Calcd for $C_{13}H_8Br_2ClN$: C, 41.81; H, 2.16; N, 3.75. Found: C, 41.91; H, 2.09; N, 3.65.

4.28. 2-Bromo-3-(1-chloroprop-1-en-2-yl)pyridine (Table 4, entry 16 substrate)

Prepared using (chloromethyl)triphenylphosphonium chloride (6.25 g, 0.18 mol) and 1-(2-bromopyridin-3-yl)ethanone[22] (1.00 g, 5.02 mmol). The product was purified by flash chromatography (DCM) to yield the *vinyl chloride* (2.58 g, *E*/*Z* 2:1, 74%) as colourless crystalline solid; mp 69–71 °C. ν_{max} (film)/cm^{-1} 3067, 2973, 2913, 2849, 1679, 1634, 1574, 1551, 1443, 1387, 1324, 1255, 1232, 1193, 1105, 1013, 987, 840; δ_H (500 MHz, MeOH-d_4) *Z*-isomer: 2.15 (3H, d, J=2), 6.28 (1H, q, J=4 and 2), 7.43 (1H, dd, J=8 and 4), 7.67 (1H, dd, J=6 and 2), 8.31 (1H, dd, J=6 and 2); *E*-isomer: 2.10 (3H, d, J=2), 6.39 (1H, q, J=4 and 2), 7.47 (1H, dd, J=8 and 4), 7.64 (1H, dd, J=6 and 2), 8.32 (1H, dd, J=6 and 2); δ_C (125 MHz, MeOH-d_4) 21.0, 116.9, 123.7, 137.5, 138.4, 139.3, 139.8, 141.0, 149.2; LRMS (CI$^+$) 233.9 ($^{35}Cl-^{81}Br-[M+H]^+$, 100%), 231.9 (85), 235.9 (21); HRMS (CI$^+$): 230.9458, ([M]$^+$ $C_8H_7{}^{79}Br^{35}ClN$ requires:230.9450). Anal. Calcd for C_8H_7BrClN: C, 41.33; H, 3.03; N, 6.02. Found: C, 41.40; H, 2.90; N, 5.99.

4.29. Methyl 1-*p*-tolyl-7-azaindole-6-carboxylate (Table 4, entry 1)

Prepared using (*Z*)-methyl-5-(2-bromovinyl)-6-chloropicolinate (100 mg, 0.36 mmol), X-Phos **8** (19 mg, 0.04) and *p*-toluidine (77 mg, 0.72 mmol). Isolation via column chromatography (DCM) yielded the *azaindole* (47 mg, 61%) as a yellow oil. ν_{max} (film)/cm^{-1} 3036, 2950, 2922, 1716, 1612, 1590, 1425, 1374, 1310, 1288, 1242, 1192, 1121, 1021, 1002, 958, 913; δ_H (400 MHz, $CDCl_3$) 2.43 (3H, s), 3.99 (3H, s), 6.70 (1H, d, J=4), 7.34 (2H, d, J=8), 7.72 (1H, d, J=4), 7.71 (2H, d, J=8), 8.03 (1H, d, J=8), 8.07 (1H, d, J=8); δ_C (100 MHz, $CDCl_3$) 21.1, 52.6, 101.6, 118.1, 123.5, 124.4, 128.5, 128.6, 130.0, 131.5, 132.1, 135.6, 136.3, 141.3, 146.6, 166.8; LRMS (CI$^+$) 267.1 ([M+H]$^+$, 100%), 268.1 (14); HRMS (CI$^+$): 267.1142 ([M+H]$^+$ $C_{16}H_{15}N_2O_2$ requires: 267.1134).

4.30. 5-*iso*-Propyl-1-*p*-tolyl-7-azaindole (Table 4, entry 6)

Prepared using (*Z*)-3-(2-bromovinyl)-2-chloro5-*iso*-propylpyridine (100 mg, 0.38 mmol), dppp **11** (21 mg, 0.05 mmol) and *p*-toluidine (46 mg, 0.43 mmol). Isolation via column chromatography (DCM) yielded the *azaindole* (49 mg, 71%) as a yellow oil. ν_{max} (film)/cm^{-1} 3104, 3036, 3009, 2959, 2868, 1603, 1583, 1567, 1481, 1407, 1384, 1362, 1262, 1209, 1179, 1121, 1068, 1020, 965, 921; δ_H (500 MHz, $CDCl_3$) 1.34 (3H, s), 1.35 (3H, s), 2.42 (3H, s), 3.07 (1H, spt, J=8), 6.57 (1H, d, J=3), 7.32 (2H, d, J=10), 7.46 (1H, d, J=3), 7.61–7.63 (2H, m), 7.82 (1H, d, J=2), 8.27 (1H, d, J=2); δ_C (125 MHz, $CDCl_3$) 21.0, 24.5, 31.9, 100.9, 121.3, 123.8 (2C), 126.1, 128.0, 129.9 (2C), 135.9, 136.1, 136.7, 143.2, 146.5, 153.5; LRMS (CI$^+$) 251.1 ([M+H]$^+$, 100%), 252.2 (16); HRMS (ES$^+$): 251.1550 ([M+H]$^+$ $C_{17}H_{19}N_2$ requires: 251.1548).

4.31. 5-Methyl-6-phenyl-1-*p*-tolyl-7-azaindole (Table 4, entry 7)

Prepared using (*Z*)-3-(2-bromovinyl)-2-chloro-5-methyl-6-phenylpyridine (100 mg, 0.32 mmol), X-Phos **8** (19 mg, 0.04 mmol) and *p*-toluidine (69 mg, 0.64 mmol). Isolation via column chromatography (DCM) yielded the *azaindole* (60 mg, 60%) as a yellow solid; mp 90–92 °.; ν_{max} (film)/cm^{-1} 3105, 3082, 3034, 2953, 2924, 2855, 1722, 1609, 1583, 1555, 1466, 1439, 1381, 1360, 1289, 1175, 1122, 1072, 1020, 995, 935; δ_H (500 MHz, acetone-d_6) 2.38 (3H, s), 2.46 (3H, s), 6.66 (1H, d, J=4), 7.31 (2H, d, J=10), 7.39–7.49 (1H, m), 7.49–7.46 (2H, m), 7.62–7.64 (2H, m), 7.79 (1H, d, J=4), 7.84–7.87 (2H, m), 7.94 (1H, s); δ_C (125 MHz, acetone-d_6) 20.6, 21.0, 101.7, 121.7 (2C), 123.8 (2C), 124.3, 128.2, 128.7 (2C), 129.1 (2C), 130.3 (2C), 130.4 (2C), 131.7, 136.0, 137.5, 142.8, 147.1, 153.5; LRMS (CI$^+$) 298.1 (M$^+$, 100%), 299.2 (86); HRMS (CI$^+$): 298.1479 ([M]$^+$ $C_{21}H_{18}N_2$ requires: 298.1470).

4.32. Ethyl 1-*p*-tolyl-7-azaindole-2-carboxylate (Table 4, entry 12)

Prepared using (*Z*)-ethyl-2-bromo-3-(2-chloropyridin-3-yl) acrylate (100 mg, 0.34 mmol), DPE-Phos (22 mg, 0.04 mmol) and *p*-toluidine (73 mg, 0.68 mmol) in anhydrous dioxane (1.5 mL). Isolation via column chromatography (DCM) yielded the *azaindole* (79 mg, 83%) as a off-white solid; mp 93–95 °C. ν_{max} (film)/cm^{-1} 3041, 2981, 2925, 1722, 1594, 1567, 1475, 1427, 1377, 1319, 1250, 1206, 1185, 1114, 1041, 1025, 983; δ_H (400 MHz, $CDCl_3$) 1.26 (3H, t, J=8), 2.45 (3H, s), 4.26 (2H, q, J=8), 7.17 (1H, dd, J=4), 7.26–7.29 (2H), 7.33–7.36 (2H, m), 7.39 (1H, s), 8.06 (1H, dd, J=6 and 2), 8.47 (1H, dd, J=6 and 2); δ_C (125 MHz, $CDCl_3$) 14.1, 21.3, 60.8, 109.0, 117.5, 118.7, 127.9 (2C), 129.4, 129.6 (2C), 130.8, 134.6, 138.1, 147.5, 150.5, 161.0; LRMS (CI$^+$) 281.1 ([M+H]$^+$, 100%), 252.1 (21); HRMS (CI$^+$): 281.1291 ([M+H]$^+$ $C_{17}H_{17}N_2O_2$ requires: 281.1290).

4.33. 2-(4-Methoxyphenyl)-1-*p*-tolyl-7-azaindole (Table 4, entry 13)

Prepared using (*Z*)-3-(2-bromo-2-(4-methoxy phenyl)vinyl)-2-chloropyridine (70 mg, 0.22 mmol), X-Phos **8** (14 mg, 0.03 mmol) and *p*-toluidine (46 mg, 0.43 mmol). Isolation via column chromatography (DCM) yielded the *azaindole* (49 mg, 71%) as a yellow solid; Mp 117–119 °C. ν_{max} (film)/cm^{-1} 3039, 2957, 2835, 1610, 1592, 1568, 1514, 1499, 1440, 1370, 1315, 1299, 1249, 1110, 1030, 918; δ_H (400 MHz, acetone-d_6) 2.38 (3H, s), 3.79 (3H, s), 6.72 (1H, s), 6.86–6.90 (2H, m), 7.15 (1H, dd, J=8 and 4), 7.19–7.30 (6H, m), 7.99 (1H, dd, J=6 and 4), 8.19 (1H, dd, J=6 and 4); δ_C (100 MHz, acetone-d_6) 20.7, 55.1, 100.7, 114.2 (2C), 117.4, 121.3, 125.0, 128.2, 128.8 (2C), 129.6 (2C), 130.6 (2C), 135.3, 137.1, 141.5, 143.2, 150.2, 158.0; LRMS (ES$^+$) 315.2 ([M+H]$^+$, 100%), 316.2 (17); HRMS (ESI$^+$): 315.1485 ([M+H]$^+$ $C_{21}H_{19}N_2O$ requires: 315.1497).

4.34. 2-(4-Chlorophenyl)-1-*p*-tolyl-7-azaindole (Table 4, entry 15)

Prepared using (*Z*)-3-(2-bromo-2-(4-chlorophenyl)vinyl)-2-chloropyridine (100 mg, 0.30 mmol), S-Phos **7** (16 mg, 0.04 mmol) and *p*-toluidine (64 mg, 0.60 mmol). Isolation via column chromatography (DCM) yielded the *azaindole* (91 mg, 95%) as a yellow oil. ν_{max} (film)/cm^{-1} 3029, 2922, 2857, 1596, 1517, 1490, 1457, 1416, 1399, 1337, 1312, 1246, 1179, 1091, 1013, 961, 908; δ_H (500 MHz, acetone-d_6) 2.30 (3H, s), 6.82 (1H, dd, *J*=10 and 5), 7.13 (2H, d, *J*=10), 7.49–7.51 (2H, m), 7.66–7.70 (4H, m), 7.79 (1H, dd, *J*=7 and 2), 7.83 (1H, br s), 8.20 (1H, dd, *J*=7 and 2); δ_C (125 MHz, acetone-d_6) 20.8, 86.0, 96.1, 104.9, 114.8, 121.0, 121.2, 122.4, 129.7 (2C), 129.8 (2C), 132.2, 134.0, 134.3, 135.2, 139.0, 141.2, 148.6, 156.6; LRMS (ES$^+$) 319.1 ([M+H]$^+$, 100%), 320.1 (10); HRMS (FI$^+$): 319.0990 ([M−H]$^+$ $C_{20}H_{16}{}^{35}ClN_2$ requires: 319.1002).

4.35. 1-*p*-Tolyl-3-methyl-7-azaindole (Table 4, entry 19)

Prepared using 1-(2-bromopyridin-3-yl)ethanone (100 mg, 0.43), DPE-Phos **12** (16 mg, 0.03 mmol), potassium *tert*-butoxide (107 mg, 0.95 mmol) and *p*-toluidine (92 mg, 0.86 mmol). Isolation via column chromatography (DCM) yielded the *azaindole* (70 mg, 73%) as a yellow oil. ν_{max} (film)/cm^{-1} 2918, 1602, 1548, 1429, 1361, 1335, 1285, 1268, 1232, 1260, 1125, 1070, 1037, 818; δ_H (400 MHz, acetone-d_6) 2.37 (3H, d, *J*=1), 2.39 (3H, s), 7.16 (1H, dd, *J*=8 and 4), 7.32–7.34 (2H, m), 7.58 (1H, s), 7.79–7.83 (2H, m), 8.00 (1H, dd, *J*=6 and 2), 8.31 (1H, dd, *J*=6 and 2); δ_C (100 MHz, acetone-d_6) 9.2, 20.4, 111.0, 116.4 (2C), 122.6, 123.2 (2C), 125.5, 127.3, 129.9, 135.2, 136.9, 143.4, 148.0; LRMS (ES$^+$) 223.2 ([M+H]$^+$, 100%), 224.1 (11); HRMS (ESI$^+$): 223.1230 ([M+H]$^+$ $C_{15}H_{15}N_2$ requires: 223.1235).

4.36. (*Z*)-Ethyl-2-bromo-3-(3-bromopyridin-4-yl)acrylate, 14

A solution of sodium hydride (60% dispersion in mineral oil, 259 mg, 0.07 mol) in THF (30 mL) was added to ethyl 2-bromo-2-(diethoxyphosphoryl)acetate (3.27 g, 0.11 mol) at room temperature. This solution was stirred for 1 h at room temperature, and then 3-bromonicotinaldehdye (1.00 g, 0.05 mol) was added and the reaction mixture heated to 50 °C and stirred for 12 h. The reaction mixture was cooled to room temperature, water (20 mL) was added, extracted with DCM (3×50 mL), dried over $MgSO_4$ and concentrated in vacuo. Crude material was purified by column chromatography (DCM) to produce the *ester* (1.26 g, 62%) as a white solid. The compound was used immediately, due to decomposition. Characterisation not possible.

4.37. Ethyl 1-*p*-tolyl-6-azaindole-2-carboxylate, 15

Prepared using (*Z*)-ethyl-2-bromo-3-(2-chloropyridin-4-yl) acrylate **14** (100 mg, 0.30 mmol), DPE-Phos **12** (11 mg, 0.02 mmol) and *p*-toluidine (64 mg, 0.60 mmol) in anhydrous dioxane (1.5 mL). Isolation via column chromatography (DCM) yielded the *azaindole* (84 mg, 88%) as a yellow oil. ν_{max} (film)/cm^{-1} 2982, 1726, 1557, 1515, 1441, 1403, 1334, 1262, 1220, 1185, 1117, 1025, 833; δ_H (400 MHz, acetone-d_6) 1.20 (3H, t, *J*=6), 2.47 (3H, s), 4.22 (2H, q, *J*=8), 7.33–7.35 (2H, m), 7.39–7.41 (2H, m), 7.42 (1H, s), 7.69 (1H, d, *J*=8), 8.30 (1H, d, *J*=8), 8.49 (1H, s); δ_C (125 MHz, $CDCl_3$) 13.8, 20.8, 61.1, 109.6, 116.3, 127.9 (2C), 130.1 (2C), 130.8, 132.1, 132.5, 135.5, 135.8, 138.8140.1, 160.6; LRMS (ES$^+$) 281.1 ([M+H]$^+$, 100%), 282.2 (17); HRMS (ESI$^+$): 281.1287 ([M+H]$^+$ $C_{17}H_{17}N_2O_2$ requires: 281.1290).

4.38. (*E*)-3-Bromo-2-(2-bromovinyl)pyridine, 16

Prepared using (bromomethyl)triphenylphosphonium bromide (5.63 g, 0.13 mol) and 3-bromo-2-formyl pyridine (2.00 g, 0.11 mol). The product was purified by flash chromatography (DCM) to yield the *vinyl bromide* as a single isomer (2.36 g, 83%) as a yellow oil. ν_{max} (film)/cm^{-1} 3081, 3048, 1602, 1566, 1435, 1414, 1224, 1198, 1122, 1067, 1046, 1016, 934; δ_H (400 MHz, $CDCl_3$) 7.08 (1H, dd, *J*=8 and 4), 7.57 (1H, d, *J*=16), 7.61 (1H, d, *J*=16), 7.48 (1H, dd, *J*=6 and 2), 8.47 (1H, dd, *J*=6 and 2); δ_C (100 MHz, $CDCl_3$) 116.6, 119.6, 123.8, 133.8, 140.8, 148.1, 152.0; LRMS (FI$^+$) 262.9 (^{79}Br−^{81}Br−M$^+$, 100%), 260.9 (49), 264.9 (46); HRMS (FI$^+$): 260.8784 ([M]$^+$ $C_7H_5N^{79}Br_2$ requires 260.8789).

4.39. *tert*-Butyl-4-azaindole-1-carboxylate, 17

Prepared using 3-bromo-2-(2-bromovinyl)pyridine **16** (100 mg, 0.38 mmol), DPE-Phos **12** (27 mg, 0.05 mmol) and *tert*-butyl carbamate (87 mg, 0.76) in anhydrous dioxane (1.5 mL). Isolation via column chromatography (DCM) yielded the *4-azaindole* **17** (44 mg, 53%) as a yellow oil. ν_{max} (film)/cm^{-1} 2979, 1736, 1597, 1567, 1530, 1477, 1410, 1370, 1352, 1317, 1253, 1156, 1129, 1076, 1021, 850, 782, 737; δ_H (500 MHz, $CDCl_3$) 1.71 (9H, s), 6.82 (1H, d, *J*=4), 7.26 (1H, dd, *J*=4 and 5), 7.86 (1H, d, *J*=4), 8.41 (1H, d, *J*=6) 8.53 (1H, d, *J*=6); δ_C (125 MHz, $CDCl_3$) 28.2 (3C), 85.3, 108.9, 119.1, 122.4, 129.1, 129.3, 146.3, 146.5, 170.9; LRMS (ES$^+$) 219.1 ([M+H]$^+$, 100%), 220.1 (10); HRMS (ESI$^+$): 219.1124 ([M+H]$^+$ $C_{12}H_{15}N_2O_2$ requires: 219.1134).

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