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7-Azaindoles via carbolithiation of vinyl pyridines

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Abstract—The sequential reactions of a pyridine vinylation and alkene carbolithiation constitutes a new route to substituted 7-azaindoles. The methodology involves a reaction sequence of controlled carbolithiation of the vinyl double bond, subsequent trapping of the formal di-anion intermediate with a suitable electrophile, followed by an in situ ring closure and dehydration. The reaction sequence allows for aryl, heteroaryl, alkyl and keto substituents to be included at different positions around the heterocycle.

1. Introduction

The intermolecular carbolithiation of alkenes and alkynes has recently emerged as a profitable approach to target-directed synthesis.[1] The synthetic potential of carbolithiation lies in the fact that both a new carbon–carbon and carbon–lithium bond are generated in tandem. This allows for further in situ transformations to be carried out at the newly created carbon–lithium centre, which can be incorporated into novel synthetic designs. This methodology has been applied to the formation of carbocycles[2] and we have recently developed unique methods for the formation of indoles,[3] quinolines[4] and stereoselective alkene synthesis.[5] As an expansion of this work we have now addressed the 7-azaindole (1*H*-pyrrolo[2,3-*b*]pyridine), as interest in it as a functional heterocyclic scaffold continues to intensify (Fig. 1).[6] 7-Azaindoles can be considered as a one nitrogen analogue of the indole ring system with the substitution of C-7 by a basic nitrogen atom often modifying the pharmacological properties of known indole pharmacophores. This has given rise to the synthesis of an increasing number of such derivatives with the potential to address a spectrum of applications.[7] For example, 7-azaserotonin and 7-azatryptophan are known to impart unique medicinal and biophysical properties when compared to their indole counterparts, tryptophan and serotonin.[8] Additionally, numerous potential pharmaceutical uses such as protein kinase inhibitors, H_1 antagonists and PPAR agonists are being currently being investigated.[9]

Figure 1. 7-Azaindole.

To date, synthetic routes to the 7-azaindole scaffold have primarily focused on modified indole syntheses such as the Fischer,[10] Madelung,[11] or transition metal catalysed cross-coupling/heteroannulation of 2-amino-3-halo-pyridines with alkynes[12] or ketones.[13] Additional approaches have utilised 2-aminobenzyl carbanion intermediates[14] and the regioselective opening of 2-chloro-3-oxiran-2-ylpyridines with amines, followed by nucleophilic aromatic substitution and in situ dehydration.[15]

2. Results and discussion

The synthetic starting point was the commercially available 2-aminopyridines **1a–d**, which were *N*-protected with pivaloyl chloride, using standard procedures, to provide compounds **2a–d** (Scheme 1).[16] Subsequent directed pyridine lithiation at C-3 with *n*-BuLi and in situ reaction with dibromoethane generated the 3-bromo-pyridin-2-ylamines **3a–d** with yields in the range of 81–25%.[17] The low yield of **3b** was due to the competitive formation of the 4-methyl brominated product. The route to *N*-methyl substituted analogue, 3-bromo-5-methyl-pyridin-2-yl-methylamine, **3e** was carried out according to literature procedures (Scheme 1, inset).[18]

The vinylation of **3a–e** was achieved via Suzuki–Miyaura cross-coupling with 0.5 molar ratio of 2,4,6-trivinylcyclotriboroxane–pyridine complex **4** (Table 1). In each case all the starting substrate was consumed and the desired 3-vinyl-pyridin-2-ylamine products **5a–e** were isolated in good to

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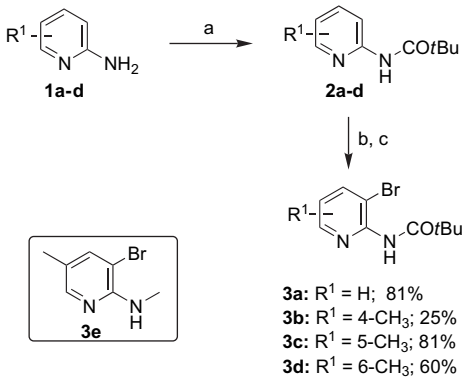
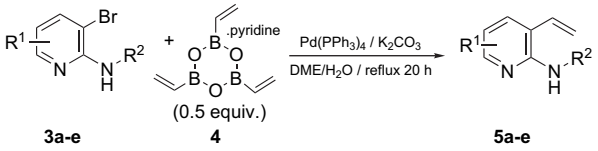


Scheme 1. Reagents and conditions: (a) *t*-BuCOCl, TEA, CH_2Cl_2, 0 °C, 1 h; (b) *n*-BuLi, THF, −30 to 0 °C, 5 h; (c) $Br(CH_2)_2Br$, −78 °C to rt, 1 h.

excellent yields. This versatile vinylation reagent has previously proven an effective substitute for vinyl boronic acid in coupling reactions with arylhalide substrates.[19] This provided a range of starting substrates functionalized on the pyridine ring at C-4, 5 and 6 and on the 2-amino group with pivaloyl (CO*t*-Bu) and alkyl (Me) groups to examine our carbolithiation methods.

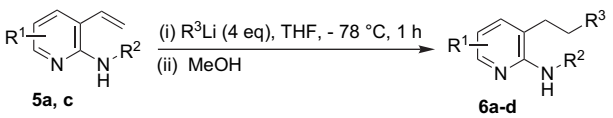
Table 1. Cross-coupling of **3a–e** with a vinyl boronic acid equivalent



Entry	Substrate	R^1	R^2	Product	Yield (%)
1	**3a**	H	CO*t*-Bu	**5a**	85
2	**3b**	4-Me	CO*t*-Bu	**5b**	60
3	**3c**	5-Me	CO*t*-Bu	**5c**	83
4	**3d**	6-Me	CO*t*-Bu	**5d**	75
5	**3e**	5-Me	Me	**5e**	86

To the best of our knowledge, no carbolithiation reaction has previously been described on vinyl-pyridine derivatives. As such, the reaction of **5** with a range of organolithiums, followed by protonation, thereby generating the substituted pyridines **6** was carried out as a precursor study (Table 2). We used **5a** and **5c** as model substrates, with reactions carried out in THF at −78 °C. Our results showed that carbolithiation is highly effective with primary, secondary and

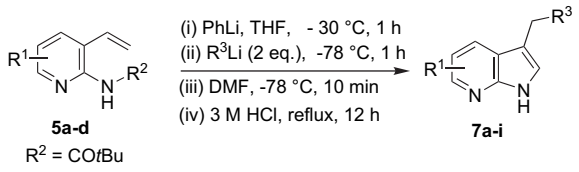
Table 2. Carbolithiation of substituted 3-vinyl-pyridin-2-ylamines



Entry	Substrate	R^1	R^2	R^3	Product	Yield[a] (%)
1	**5a**	H	CO*t*-Bu	*t*-Bu	**6a**	85
2	**5a**	H	CO*t*-Bu	*s*-Bu	**6b**	88
3	**5a**	H	CO*t*-Bu	*n*-Bu	**6c**	70
4	**5c**	5-Me	CO*t*-Bu	*t*-Bu	**6d**	79
5	**5a**	H	CO*t*-Bu	Ph	—	0[b]

[a] Isolated purified yield.
[b] Starting material recovered.

Table 3. Synthesis of 3,4-, 3,5- and 3,6- substituted 7-azaindoles



Entry	Substrate	R^1	R^3	7-Azaindole	Yield[a] (%)
1	**5a**	H	*t*-Bu	**7a**	40[b]
2	**5a**	H	*t*-Bu	**7a**	69
3	**5a**	H	*s*-Bu	**7b**	78
4	**5a**	H	*n*-Bu	**7c**	63
5	**5b**	4-Me	*t*-Bu	**7d**	75
6	**5c**	5-Me	*t*-Bu	**7e**	65
7	**5c**	5-Me	*s*-Bu	**7f**	81
8	**5c**	5-Me	*n*-Bu	**7g**	75
9	**5d**	6-Me	*t*-Bu	**7h**	82
10	**5d**	6-Me	*s*-Bu	**7i**	80

[a] Isolated purified yield.
[b] Conditions: (i) *t*-BuLi (2 equiv), −78 °C, 1 h; (ii) DMF, −78 °C, 10 min; (iii) 3 M HCl, reflux, 12 h.

tertiary alkyllithiums with the alkyl addition products **6a–d** isolated in good yields (Table 2, entries 1–4). Despite the known propensity of the pyridine heterocycle to undergo addition reactions with alkyllithiums, under these conditions no addition of alkyllithium to the pyridine ring was observed.[20] The reaction was also attempted with phenyllithium, but no addition to the vinyl double bond was observed and only starting material was isolated upon reaction work-up (entry 5).

Having identified conditions under which vinyl carbolithiation could be achieved, we proceeded to react the generated intermediate lithiated species with DMF, substituted nitriles or acetic anhydride as electrophile in order to develop our route to 7-azaindoles. The carbolithiation of **5a** with *t*-BuLi and subsequent treatment with DMF was followed by mild acidification. The extracted crude product was heated under reflux with 3 M hydrochloric acid to generate the desired azaindole **7a** in a moderate 40% yield (Table 3, entry 1). Unexpectedly, a byproduct of the pivaloyl-deprotected **6a** was also isolated in significant quantities. A

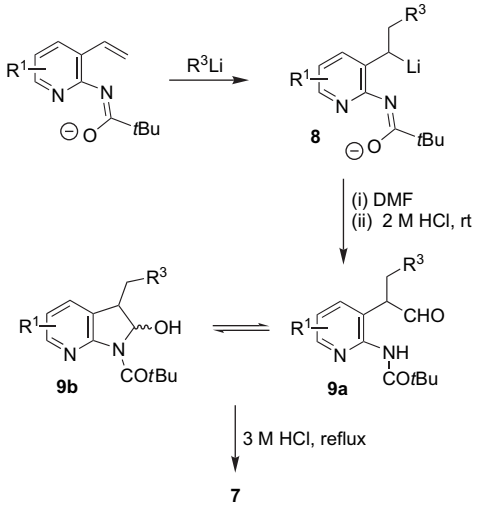
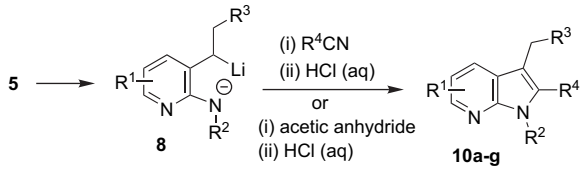
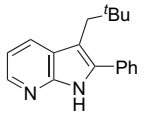
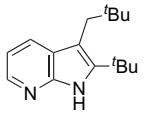
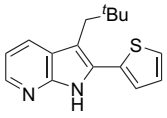
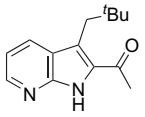
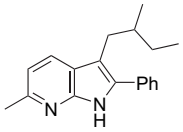
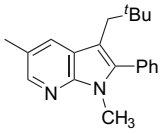
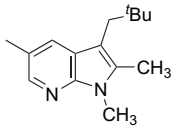


Figure 2. Reaction sequence.

Table 4. Synthesis of 2,3-, 2,3,6-, and 1,2,3,5-substituted 7-azaindoles



Entry	Substrate	Product	Azaindole	Yield[a] (%)
1	**5a**		**10a**[b]	70
2	**5a**		**10b**[b]	58
3	**5a**		**10c**[b]	38
4	**5a**		**10d**[b]	44
5	**5d**		**10e**[b]	65
6	**5e**		**10f**[c]	70
7	**5e**		**10g**[d]	38

[a] Isolated purified yield.
[b] Acidification conditions; 12 M HCl, reflux, 12 h.
[c] Acidification conditions; 2 M HCl, rt, 30 min.
[d] Acidification conditions; 1 M HCl, reflux, 12 h.

possible explanation for this would be incomplete amide NH deprotonation of the starting material prior to initiation of vinyl carbolithiation giving rise to the competing formation of **6a**. This was overcome by a modification of the reaction procedure in which NH deprotonation of **5** was first carried out with phenyllithium prior to treatment with 2 equiv of alkyllithium. This gave rise to an improved 69% yield of the 7-azaindole **7a** (entry 2). While an excess of alkyllithium is not required for reaction it was found to give improved conversions in some examples and was adopted as a standard procedure. This reaction sequence proved tolerant for different alkyllithiums (*tert*, *sec*, or *n*-butyl) with each of the vinylpyridine substrates **5a–d**, leading to the generation of the 7-azaindoles **7b–i** in good to excellent yields (entries 3–10).

The reaction sequence could be envisaged as an initial amide NH deprotonation of **5**, followed by carbolithiation of the vinyl double bond providing the intermediate di-anion **8** (Fig. 2). Subsequent reaction with DMF, generated an aldehyde precursor, which upon treatment with aqueous acid undergoes nitrogen deprotection, ring closure by intramolecular attack of the amine at the aldehyde with subsequent in situ dehydration to the azaindole **7**. If the acidification conditions are sufficiently mild as to not carry out the pivaloyl deprotection (2 M HCl, rt), it is possible to observe, by NMR, an equilibrium mixture between the ring open aldehyde **9a** and the 2-hydroxy-2,3-dihydro-azaindole **9b** in solution (Fig. 2). This was carried out for the specific case of *t*-BuLi as alkyllithium source in reaction with **5a**.

In order to facilitate the introduction of functional group diversity at C-2 of the azaindole scaffold, we exploited substituted nitriles as electrophiles. Thus, treatment of generated organolithium intermediates **8** with either benzo-, 2,2-dimethylpropio- or thiophene-2-carbo-nitrile yielded the desired di- tri- or tetra-substituted products after acidification (Table 4). It was found that improved results were obtained for the reaction of these electrophiles in diethyl ether and so this solvent was used for the carbolithiation step. In each case, the 7-azaindoles **10a–e** were isolated in moderate to good yields and the procedure allowed introduction of various substituents on C-2 position such as aryl, heteroaryl and sterically bulky alkyl groups (Table 4 entries 1–3 and 5). The use of 2,2-diethoxypropionitrile as electrophile was effective for the introduction of a ketone functionality at C-2 of **10d**, as the acetal protected ketone was also deprotected in situ (entry 4). The reaction sequence was also tolerant of the *N*-alkyl substituents of **5e**, as shown by the generation of the *N*-alkylated 1,2,3,5-substituted azaindole **10f** in a 70% yield (entry 6). For these examples the acidification conditions required to effect the cyclisation/dehydration were milder than those necessary for the pivaloyl counterparts (Table 4, entry 1 and 6). The product outcome was confirmed for the reaction sequence by X-ray structural analysis of **10f**, which crystallised in the triclinic space group (*P*-1) (Fig. 3).[21]

The use of the reaction sequence was expanded to include acetic anhydride as electrophile, which facilitated the introduction of a methyl substituent at C-2 (entry 7). For the

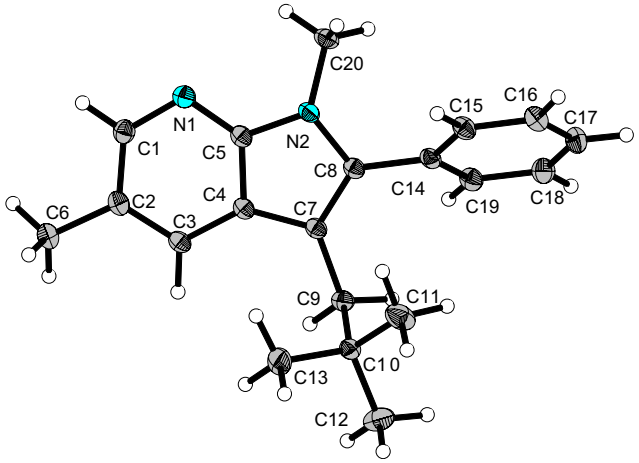
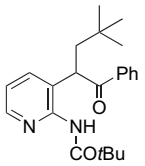


Figure 3. ORTEP plot of **10f**. Thermal ellipsoids drawn at the 50% probability level.



11

Figure 4. Isolated intermediate using benzonitrile as electrophile.

case of the reaction of **5a** with *tert*-butyllithium and benzonitrile as electrophile the ketone intermediate **11** could be isolated confirming the anticipated reaction pathway (Fig. 4).

3. Conclusion

The combination of a robust vinylation procedure using the coupling of 2,4,6-trivinylcyclotriboroxane with 3-bromopyridin-2-ylamines and carbolithiation–electrophile trapping cyclisation methodology provides a new entry into the functionalized 7-azaindole ring system. The methodology is capable of introducing aryl, heteroaryl, alkyl and keto substituents around the azaindole scaffold. The use of carbolithiation as the key synthetic step for the assembly of other reaction sequences is currently under investigation and will be reported in due course.

4. Experimental

4.1. General methods

All commercially available solvents and reagents were used as supplied unless otherwise stated. THF and diethyl ether was distilled from sodium benzophenone ketyl, under nitrogen, immediately before use. TMEDA and nitriles were dried over 4 Å molecular sieves. Reactions were carried out in oven or flame dried glassware. *t*-BuLi was purchased as 1.7 M in pentane, *s*-BuLi as 1.4 M in cyclohexane, *n*-BuLi as 2.5 M in hexanes, phenyllithium as 1.8 M in cyclohexane/ether. Exact concentration of organolithiums was determined by titration in THF with diphenylacetic acid as an indicator prior to use. Low reaction temperatures were obtained with an acetone/solid CO_2 bath. Chromatography was performed on Merck silica gel 60 PF_{254}. ^1H NMR and ^{13}C NMR were recorded on a 300 MHz instrument.

4.1.1. Representative procedure for the synthesis of 5a–e. A stirred solution of **3a–e** (3.87 mmol) in DME (10 mL) under nitrogen was treated with palladium(0) tetrakistriphenylphosphine (0.19 mmol, 5 mol %). The reaction mixture was stirred at room temperature for 20 min and 2,4,6-trivinylcyclotriboroxane **4** (1.94 mmol), potassium carbonate (3.87 mmol) and water (2.3 mL) were added. The reaction mixture was heated under reflux for 20 h, cooled to room temperature, water (20 mL) was added and the solution was extracted with diethyl ether (2&times20 mL). Organic layers were combined, washed with water (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: diethyl ether/cyclohexane, 1:1) to yield the products **5a–e**.

4.1.1.1. 2,2-Dimethyl-*N*-(3-vinyl-pyridin-2-yl)-propionamide (5a). Colourless solid (85%), mp 87–88 °C. IR (KBr plate): 3169, 2967, 1684 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.36 (s, 9H), 5.22 (d, J=11.0 Hz, 1H), 5.38 (d, J=17.6 Hz, 1H), 6.59 (dd, J=11.0, 17.6 Hz, 1H), 7.18 (dd, J=4.8, 7.7 Hz, 1H), 7.69 (br s, 1H), 7.90 (dd, J=1.6, 7.7 Hz, 1H), 8.32 (dd, J=1.6, 4.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.6, 39.9, 116.5, 121.9, 128.0, 132.2, 135.0, 147.5, 148.1, 177.2. ES^+-MS: m/z 205 $(M+H)^+$. HRMS: found $(M+H)^+$ 205.1351. $C_{12}H_{17}N_2O$ requires 205.1341. Anal. Calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71. Found: C, 70.35; H, 8.21; N, 13.61.

4.1.1.2. 2,2-Dimethyl-*N*-(4-methyl-3-vinyl-pyridin-2-yl)-propionamide (5b). Colourless solid (60%). ^1H NMR (300 MHz, $CDCl_3$): δ 1.29 (s, 9H), 2.30 (s, 3H), 5.33 (dd, J=1.8, 18.0 Hz, 1H), 5.50 (dd, J=1.8, 11.7 Hz, 1H), 6.65 (dd, J=11.7, 18.0 Hz, 1H), 6.96 (d, J=4.8 Hz, 1H), 8.10 (br s, 1H), 8.18 (d, J=4.8 Hz, 1H). ES^+-MS: m/z 219 $(M+H)^+$. HRMS: found $(M+H)^+$ 219.1493. $C_{13}H_{19}N_2O$ requires 219.1497. Product contained 20% of an inseparable impurity. It was used in this form for the next step and the impurity removed at that stage.

4.1.1.3. 2,2-Dimethyl-*N*-(5-methyl-3-vinyl-pyridin-2-yl)-propionamide (5c). Colourless solid (83%), mp 101–102 °C. IR (KBr plate): 3193, 2967, 1684 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.35 (s, 9H), 2.34 (s, 3H), 5.36 (d, J=11.0 Hz, 1H), 5.73 (d, J=17.6 Hz, 1H), 6.58 (dd, J=11.0, 17.6 Hz, 1H), 7.71 (m, 2H), 8.14 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.9, 27.6, 39.9, 116.3, 121.7, 125.6, 132.2, 135.2, 147.1, 156.7, 177.2. ES^+-MS: m/z 219 $(M+H)^+$. HRMS: found $(M+H)^+$ 219.1496. $C_{12}H_{19}N_2O$ requires 219.1497. Anal. Calcd for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.23; H, 8.08; N, 12.75.

4.1.1.4. 2,2-Dimethyl-*N*-(6-methyl-3-vinyl-pyridin-2-yl)-propionamide (5d). Colourless solid (75%), mp 117–118 °C. IR (KBr plate): 3169, 2965, 1681 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.35 (s, 9H), 2.43 (s, 3H), 5.31 (d, J=11.0 Hz, 1H), 5.69 (d, J=17.6 Hz, 1H), 6.55 (dd, J=11.0, 17.6 Hz, 1H), 7.03 (d, J=7.9 Hz, 1H), 7.69 (br s, 1H), 7.91 (d, J=7.9 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 23.9, 27.6, 39.5, 115.2, 121.6, 125.6, 132.1, 135.6, 147.9, 157.0, 176.1. ES^+-MS: m/z 219 $(M+H)^+$. HRMS: found $(M+H)^+$ 219.1497. $C_{12}H_{19}N_2O$ requires 219.1497. Anal. Calcd for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.35; H, 8.31; N, 12.83.

4.1.1.5. Methyl-(5-methyl-3-vinyl-pyridin-2-yl)-amine (5e). Colourless oil (86%). IR (NaCl plate): 3331, 2996, 2921, 2871, 1624 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 2.18 (s, 3H), 2.98 (d, J=4.7 Hz, 3H), 4.30 (br s, 1H), 5.31 (d, J=11.0 Hz, 1H), 5.57 (d, J=17.6 Hz, 1H), 6.55 (dd, J=11.0, 17.6, 1H), 7.24 (s, 1H), 7.91 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.3, 29.0, 117.4, 118.9, 121.4, 131.7, 135.7, 146.3, 154.3. ES^+-MS: m/z 149 $(M+H)^+$. HRMS: found $(M+H)^+$ 149.1082. $C_9H_{13}N_2$ requires 149.1079. Anal. Calcd for $C_9H_{12}N_2$: C, 72.94; H, 8.16; N, 18.90. Found: C, 72.74; H, 8.31; N, 18.72.

4.1.2. Representative procedure for the synthesis of 6a–d. A stirred solution of **5** (0.24 mmol) in dry THF (5 mL) at −78 °C under nitrogen was treated dropwise with the alkyllithium (0.98 mmol) over 10 min. The reaction mixture was

stirred at −78 °C for a further 1 h following which it was treated with methanol (1 mL). The mixture was allowed to warm to room temperature, extracted with diethyl ether (2×20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: diethyl ether/cyclohexane, 1:1) to yield the products **6a–d**.

4.1.2.1. *N*-[3-(3,3-Dimethyl-butyl)-pyridin-2-yl]-2,2-dimethyl-propionamide (6a). Colourless solid (85%), mp 102–103 °C. IR (KBr plate): 3220, 3161, 1678, 1594 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.99 (s, 9H), 1.40 (s, 9H), 1.45–1.48 (m, 2H), 2.56–2.62 (m, 2H), 7.18 (dd, *J*=7.6, 4.7 Hz, 1H), 7.63 (dd, *J*=7.6, 1.5 Hz, 1H), 8.04 (br s, 1H), 8.30 (d, *J*=4.7, 1.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.1, 27.9, 29.5, 30.9, 39.7, 44.3, 122.2, 134.4, 138.9, 146.0, 148.1, 177.8. ES^+-MS: *m/z* 263 $(M+H)^+$. HRMS: found $(M+H)^+$ 263.2123. $C_{16}H_{27}N_2O$ requires 263.2123. Anal. Calcd for $C_{16}H_{26}N_2O$: C, 73.24; H, 9.99; N, 10.68. Found: C, 72.88; H, 9.65; N, 10.81.

4.1.2.2. 2,2-Dimethyl-*N*-[3-(3-methyl-pentyl)-pyridin-2-yl]-propionamide (6b). Colourless solid (88%), mp 42–43 °C. IR (KBr plate): 3222, 3161, 2956, 1678, 1579 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.84–0.91 (m, 6H), 1.10–1.45 (m, 5H), 1.35 (s, 9H), 2.47–2.64 (m, 2H), 7.12 (dd, *J*=7.5, 4.7 Hz, 1H), 7.58 (dd, *J*=7.5, 1.2 Hz, 1H), 8.20–8.30 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.4, 19.1, 27.7, 29.1, 29.4, 36.4, 39.4, 39.8, 122.1, 134.2, 138.6, 145.7, 149.3, 177.3. ES^+-MS: *m/z* 263 $(M+H)^+$. HRMS: found $(M+H)^+$ 263.2133. $C_{16}H_{27}N_2O$ requires 263.2123. Anal. Calcd for $C_{16}H_{26}N_2O$: C, 73.24; H, 9.99; N, 10.68. Found: C, 72.94; H, 10.01; N, 10.71.

4.1.2.3. *N*-(3-Hexyl-pyridin-2-yl)-2,2-dimethyl-propionamide (6c). Colourless oil (70%). IR (NaCl plate): 3245, 2957, 2928, 2858, 1658, 1591 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.74–089 (m, 3H), 1.19–1.43 (m, 6H), 1.33 (s, 9H), 1.54–1.60 (m, 2H), 2.57 (t, *J*=2.6 Hz, 2H), 7.12 (dd, *J*=4.7, 7.6 Hz, 1H), 7.58 (dd, *J*=1.6, 7.6 Hz, 1H), 8.24 (br s, 1H), 8.25 (dd, *J*=1.6, 4.7 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.0, 22.6, 27.6, 29.2, 29.3, 31.4, 31.6, 39.6, 122.0, 133.9, 138.5, 145.9, 149.0, 177.3. ES^+-MS: *m/z* 263 $(M+H)^+$. HRMS: found $(M+H)^+$ 263.2129. $C_{16}H_{27}N_2O$ requires 263.2123. Anal. Calcd for $C_{16}H_{26}N_2O$: C, 73.24; H, 9.99; N, 10.68. Found: C, 73.12; H, 10.06; N, 10.55.

4.1.2.4. *N*-[3-(3,3-Dimethyl-butyl)-5-methyl-pyridin-2-yl]-2,2-dimethyl-propionamide (6d). Colourless solid (79%), mp 90–91 °C. IR (KBr plate): 3210, 3141, 2977, 1680 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.99 (s, 9H), 1.40 (s, 9H), 1.44–1.50 (m, 2H), 2.34 (s, 3H), 2.51–2.57 (m, 2H), 7.43 (s, 1H), 8.03 (br s, 1H), 8.11 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.8, 26.6, 27.7, 29.3, 30.6, 39.4, 44.4, 131.8, 134.1, 139.4, 145.9, 146.7, 177.4. ES^+-MS: *m/z* 277 $(M+H)^+$. HRMS: found $(M+H)^+$ 277.2292. $C_{17}H_{29}N_2O$ requires 277.2280. Anal. Calcd for $C_{17}H_{28}N_2O$: C, 73.87; H, 10.21; N, 10.13. Found: C, 73.67; H, 10.05; N, 10.45.

4.1.3. Representative procedure for the synthesis of 7a–i. A stirred solution of **5** (0.23 mmol) in dry THF (5 mL) at −78 °C under nitrogen was treated dropwise with phenyllithium (0.34 mmol) over 10 min. The reaction mixture was warmed to −30 °C, stirred at this temperature for 1 h and cooled to −78 °C. Alkyllithium (0.46 mmol) was added over 5 min and the reaction mixture was stirred at −78 °C for a further 1 h. DMF (2.3 mmol) was added and the temperature maintained for 20 min at −78 °C. Aqueous HCl (2 M, 3 mL) was added and the reaction mixture warmed to room temperature and added carefully over 10 min to a saturated potassium carbonate solution (20 mL). The solution was extracted with diethyl ether (2×20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was treated with 3 M aqueous HCl (10 mL) and the solution was heated under reflux for 12 h. The reaction mixture was cooled to room temperature, slowly added to a saturated potassium carbonate solution (20 mL) and extracted with diethyl ether (2×20 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel column chromatography (eluent: diethyl/cyclohexane, 1:1) yielded the product **7a–i**.

4.1.3.1. 3-(2,2-Dimethyl-propyl)-1*H*-pyrrolo[2,3-*b*]-pyridine (7a). Colourless solid (69%), mp 151–152 °C. IR (KBr plate): 3143, 3089, 2947, 2896, 2864, 1581 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.95 (s, 9H), 2.61 (s, 2H), 7.06 (dd, *J*=4.8, 7.9 Hz, 1H), 7.12 (s, 1H), 7.91 (d, *J*=7.9 Hz, 1H), 8.29 (d, *J*=4.8 Hz, 1H), 10.8 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.7, 32.2, 39.4, 112.4, 115.2, 121.7, 124.0, 128.1, 141.9, 148.7. ES^+-MS: *m/z* 189 $(M+H)^+$. HRMS: found $(M+H)^+$ 189.1384. $C_{12}H_{17}N_2$ requires 189.1392. Anal. Calcd for $C_{12}H_{16}N_2$: C, 76.55; H, 8.57; N, 14.88. Found: C, 76.23; H, 8.64; N, 14.73.

4.1.3.2. 3-(2-Methyl-butyl)-1*H*-pyrrolo[2,3-*b*]pyridine (7b). Colourless solid (78%), mp 61–62 °C. IR (KBr plate): 3151, 3098, 2957, 2927, 1581 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.90–0.96 (m, 6H), 1.15–1.25 (m, 1H), 1.39–1.54 (m, 1H), 1.65–1.82 (m, 1H), 2.52 (dd, *J*=14.3, 7.8 Hz, 1H), 2.76 (dd, *J*=14.3, 6.1 Hz, 1H), 7.06 (dd, *J*=4.8, 7.9 Hz, 1H), 7.12 (s, 1H), 7.91 (d, *J*=7.9 Hz, 1H), 8.30 (d, *J*=4.8 Hz, 1H), 10.5 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.6, 19.4, 29.4, 32.6, 35.8, 114.1, 115.7, 120.8, 122.7, 127.5, 142.3, 149.1. ES^+-MS: *m/z* 189 $(M+H)^+$. HRMS: found $(M+H)^+$ 189.1386. $C_{12}H_{17}N_2$ requires 189.1392. Anal. Calcd for $C_{12}H_{16}N_2$: C, 76.55; H, 8.57; N, 14.88. Found: C, 76.29; H, 8.67; N, 14.95.

4.1.3.3. 3-Pentyl-1*H*-pyrrolo[2,3-*b*]pyridine (7c). Colourless solid (63%), mp 60–61 °C. IR (KBr plate): 3157, 3034, 2959, 2855, 1580 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.87–0.93 (m, 3H), 1.35–1.42 (m, 4H), 1.66–1.76 (m, 2H), 2.74 (t, *J*=7.6 Hz, 2H), 7.06 (dd, *J*=4.8, 7.8 Hz, 1H), 7.13 (s, 1H), 7.91 (dd, *J*=7.8, 1.5 Hz, 1H), 8.31 (d, *J*=4.8, 1.5 Hz, 1H), 10.9 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 22.6, 25.3, 29.8, 31.8, 115.2, 116.0, 120.9, 121.5, 127.3, 142.8, 149.0. ES^+-MS: *m/z* 189 $(M+H)^+$. HRMS: found $(M+H)^+$ 189.1385. $C_{12}H_{17}N_2$ requires 189.1392. Anal. Calcd for $C_{12}H_{16}N_2$: C, 76.55; H, 8.57; N, 14.88. Found: C, 76.29; H, 8.67; N, 14.95.

4.1.3.4. 3-(2,2-Dimethyl-propyl)-4-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (7d). Colourless solid (75%), mp 134–135 °C. IR (KBr plate): 3131, 3082, 2947, 2864,

1581 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.96 (s, 9H), 2.71 (s, 3H), 2.79 (s, 2H), 6.80 (d, J=4.9 Hz, 1H), 7.08 (s, 1H), 8.14 (d, J=4.9 Hz, 1H), 11.3 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.5, 29.6, 32.1, 39.8, 112.7, 117.9, 120.0, 123.7, 140.5, 142.2, 148.6. ES^+-MS: m/z 203 $(M+H)^+$. HRMS: found $(M+H)^+$ 203.1558. $C_{13}H_{19}N_2$ requires 203.1548. Anal. Calcd for $C_{13}H_{18}N_2$: C, 77.18; H, 8.97; N, 13.85. Found: C, 77.43; H, 8.69; N, 14.13.

4.1.3.5. 3-(2,2-Dimethyl-propyl)-5-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (7e). Colourless solid (65%), mp 126–127 °C. IR (KBr plate): 3141, 3082, 2952, 2894, 1581 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.99 (s, 9H), 2.50 (s, 3H), 2.64 (s, 2H), 7.12 (s, 1H), 7.74 (s, 1H), 8.19 (s, 1H), 10.5 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.7, 29.7, 32.2, 39.4, 111.9, 121.5, 124.0, 128.0, 143.0, 147.4. ES^+-MS: m/z 203 $(M+H)^+$. HRMS: found $(M+H)^+$ 203.1551. $C_{13}H_{19}N_2$ requires 203.1548. Anal. Calcd for $C_{13}H_{18}N_2$: C, 77.18; H, 8.97; N, 13.85. Found: C, 76.82; H, 8.99; N, 13.87.

4.1.3.6. 5-Methyl-3-(2-methyl-butyl)-1*H*-pyrrolo[2,3-*b*]pyridine (7f). Colourless solid (81%), mp 67–68 °C. IR (KBr plate): 3131, 3029, 2960, 2896, 1583 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.88–0.99 (m, 6H), 1.15–1.25 (m, 1H), 1.39–1.55 (m, 1H), 1.50–1.82 (m, 1H), 2.44 (s, 3H), 2.48 (dd, J=14.2, 7.8 Hz, 1H), 2.71 (1H, dd, J=14.2, 6.1 Hz, 1H), 7.06 (s, 1H), 7.69 (s, 1H), 8.14 (s, 1H), 10.2 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.6, 18.7, 19.4, 29.5, 32.7, 35.7, 113.4, 120.5, 122.8, 123.9, 127.5, 143.2, 147.8. ES^+-MS: m/z 203 $(M+H)^+$. HRMS: found $(M+H)^+$ 203.1551. $C_{13}H_{19}N_2$ requires 203.1548. Anal. Calcd for $C_{13}H_{18}N_2$: C, 77.18; H, 8.97; N, 13.85. Found: C, 76.83; H, 8.97; N, 13.92.

4.1.3.7. 5-Methyl-3-pentyl-1*H*-pyrrolo[2,3-*b*]pyridine (7g). Colourless solid (75%), mp 58–59 °C. IR (KBr plate): 3121, 3034, 2955, 2921, 1580 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.88–0.93 (m, 3H), 1.33–1.39 (m, 4H), 1.66–1.72 (m, 2H), 2.44 (s, 3H), 2.70 (t, J=7.6 Hz, 2H), 7.05 (s, 1H), 7.70 (s, 1H), 8.13 (s, 1H), 9.8 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.1, 18.6, 22.6, 25.3, 29.9, 31.8, 114.9, 120.1, 121.8, 124.0, 127.4, 143.5, 147.7. ES^+-MS: m/z 203 $(M+H)^+$. HRMS: found $(M+H)^+$ 203.1539. $C_{13}H_{19}N_2$ requires 203.1548.

4.1.3.8. 3-(2,2-Dimethyl-propyl)-6-methyl-1*H*-pyrrolo[2,3-*b*]pyridine (7h). Colourless solid (82%), mp 132–133 °C. IR (KBr plate): 3146, 3080, 2948, 2905, 1583 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.95 (s, 9H), 2.60 (s, 2H), 2.68 (s, 3H), 6.93 (d, J=7.9 Hz, 1H), 7.04 (s, 1H), 7.80 (d, J=7.9 Hz, 1H), 11.35 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.1, 29.7, 32.2, 39.5, 112.3, 115.1, 119.3, 122.7, 128.4, 148.6, 150.6. ES^+-MS: m/z 203 $(M+H)^+$. HRMS: found $(M+H)^+$ 203.1553. $C_{13}H_{19}N_2$ requires 203.1548. Anal. Calcd for $C_{13}H_{18}N_2$: C, 77.18; H, 8.97; N, 13.85. Found: C, 77.50; H, 8.87; N, 13.49.

4.1.3.9. 6-Methyl-3-(2-methyl-butyl)-1*H*-pyrrolo[2,3-*b*]pyridine (7i). Colourless solid (80%), mp 70–71 °C. IR (KBr plate): 3131, 3085, 2947, 2870, 1581 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.82–0.99 (m, 6H), 1.15–1.23 (m, 1H), 1.36–1.55 (m, 1H), 1.62–1.81 (m, 1H), 2.50 (dd, J=14.2, 7.8 Hz, 1H), 2.68 (s, 3H), 2.73 (dd, J=14.2, 6.2 Hz, 1H), 6.93 (d, J=7.9 Hz, 1H), 7.04 (s, 1H), 7.80 (d, J=7.9 Hz, 1H), 11.2 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.7, 19.4, 24.1, 29.5, 32.8, 35.9, 113.8, 115.0, 118.4, 121.5, 127.9, 149.0, 150.9. ES^+-MS: m/z 203 $(M+H)^+$. HRMS: found $(M+H)^+$ 203.1558. $C_{13}H_{19}N_2$ requires 203.1548. Anal. Calcd for $C_{13}H_{18}N_2$: C, 77.18; H, 8.97; N, 13.85. Found: C, 76.80; H, 8.97; N, 13.75.

4.1.4. *N*-[3-(1-Formyl-3,3-dimethylbutyl)-pyridin-2-yl]-2,2-dimethyl-propionamide/1-[3-(2,2-dimethylpropyl)-2-hydroxy-2,3-dihydro-pyrrolo[2,3-*b*]pyridin-1-yl]-2,2-dimethylpropan-1-one (9a/9b). A stirred solution of **5a** (0.1 g, 0.49 mmol) in dry THF (10 mL) at −78 °C under nitrogen was treated dropwise with phenyllithium (0.49 mL of a 2.0 M solution, 0.98 mmol). The reaction mixture was warmed to −30 °C, stirred at this temperature for 1 h and cooled to −78 °C. *tert*-Butyllithium (0.69 mL of a 1.6 M solution, 0.98 mmol) was added and the reaction mixture was stirred at −78 °C for 1 h. DMF (0.4 mL, 4.9 mmol) was added and the reaction mixture was stirred for 20 min at −78 °C. Aqueous HCl (2 M, 3 mL) was added and the reaction mixture was warmed to room temperature, stirred for 20 min and added carefully over 10 min to a saturated potassium carbonate solution (30 mL). The solution was extracted with diethyl ether (2×25 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: diethyl ether/cyclohexane, 3:7) yielded **9a/9b** as a colourless solid (70%), mp 150–155 °C. IR (KBr plate): 3168, 2963, 2911, 2870, 1721, 1679, 1588 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.80 (s), 1.04 (s), 1.06 (s), 1.37 (s), 1.40–1.65 (m), 1.49 (s), 2.09–2.13 (m), 2.20 (dd, J=5.4, 14.1 Hz), 3.04 (d, J=9.9 Hz), 3.15–3.20 (m), 5.77 (d, J=0.6 Hz), 5.95 (d, J=6.6 Hz), 6.91 (dd, J=5.1, 7.2 Hz), 7.20 (dd, J=4.8, 7.5 Hz), 7.35 (d, J=5.1 Hz), 7.41 (d, J=7.2 Hz), 7.57 (dd, J=8.2, 1.2 Hz), 8.06–8.25 (m), 8.33 (d, J=3.3 Hz), 9.81 (s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 26.4, 26.5, 27.8, 29.6, 29.7, 30.9, 41.7, 43.9, 48.8, 49.8, 91.0, 118.5, 122.1, 129.7, 129.9, 131.6, 133.0, 138.6, 145.7, 147.1, 201.3 (not all signals are observed due to mixture). ES^+-MS: m/z 291 $(M+H)^+$. HRMS: found $(M+H)^+$ 291.2063. $C_{17}H_{27}N_2O$ requires 291.2073. Anal. Calcd for $C_{17}H_{26}N_2O$: C, 70.31; H, 9.02; N, 9.65. Found: C, 70.08; H, 9.06; N, 9.52.

4.1.5. Representative procedure for the synthesis of 10a–e. A stirred solution of **5** (0.39 mmol) in dry diethyl ether (8 mL) at −78 °C under nitrogen was treated dropwise with phenyllithium (0.58 mmol) over 10 min. The reaction mixture was warmed to −30 °C, stirred at this temperature for 1 h and cooled to −78 °C. Alkyllithium (0.78 mmol) was added over 10 min and the reaction mixture was stirred at −78 °C for a further 1 h. Nitrile (19.5 mmol) was added and the reaction mixture was stirred for 1 h at 0 °C. Aqueous HCl (2 M, 3 mL) was added and the reaction mixture was warmed to room temperature and added to a saturated potassium carbonate solution (20 mL). The solution was extracted with diethyl ether (2×20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was passed through a short bed of silica eluting with diethyl ether/pentane (7:3; 100 mL) and the organic solvent was removed under reduced pressure. The residue was treated with 12 M

HCl (10 mL) and the solution was heated under reflux for 12 h. The reaction mixture was cooled to room temperature, carefully added over 10 min to a saturated potassium carbonate solution (30 mL) and extracted with diethyl ether (2×20 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel column chromatography (eluent: diethyl ether/cyclohexane, 6:4) yielded **10a–e**.

4.1.5.1. 3-(2,2-Dimethyl-propyl)-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (10a). Colourless solid (70%), mp 175–176 °C. IR (KBr plate): 3134, 3081, 3035, 2955, 1600 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.76 (s, 9H), 2.91 (s, 2H), 7.06 (dd, J=4.8, 7.9 Hz, 1H), 7.38–7.43 (m, 1H), 7.49–7.54 (m, 2H), 7.73 (d, J=7.0 Hz, 1H), 7.92 (d, J=7.9 Hz, 1H), 8.03 (d, J=4.8, 1H), 12.7 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.0, 34.2, 37.4, 109.0, 115.1, 123.5, 128.4, 128.7, 129.1, 134.6, 134.6, 137.2, 141.6, 148.8. ES^+-MS: m/z 265 $(M+H)^+$. HRMS: found $(M+H)^+$ 265.1701. $C_{18}H_{21}N_2$ requires 265.1705. Anal. Calcd for $C_{18}H_{20}N_2$: C, 81.78; H, 7.63; N, 10.60. Found: C, 81.35; H, 7.65; N, 10.47.

4.1.5.2. 2-*tert*-Butyl-3-(2,2-dimethyl-propyl)-1*H*-pyrrolo[2,3-*b*]pyridine (10b). Colourless solid (58%), mp 173–174 °C. IR (KBr plate): 3214, 3153, 3091, 2957, 1605 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.01 (s, 9H), 1.57 (s, 9H), 2.88 (s, 2H), 7.01 (br s, 1H), 7.92 (d, J=7.8 Hz, 1H), 8.03 (br s, 1H), 12.9 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 31.1, 31.5, 33.4, 34.6, 37.3, 107.2, 114.5, 123.8, 128.8, 140.6, 144.4, 147.4. ES^+-MS: m/z 245 $(M+H)^+$. HRMS: found $(M+H)^+$ 245.2016. $C_{16}H_{25}N_2$ requires 245.2018. Anal. Calcd for $C_{16}H_{24}N_2$: C, 78.64; H, 9.90; N, 11.46. Found: C, 78.46; H, 9.96; N, 11.35.

4.1.5.3. 3-(2,2-Dimethyl-propyl)-2-thiophen-2-yl-1*H*-pyrrolo[2,3-*b*]pyridine (10c). Colourless solid (38%), mp 132–133 °C. IR (KBr plate): 3215, 3154, 3086, 2947, 1601 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.91 (s, 9H), 2.95 (s, 2H), 7.05 (dd, J=7.9, 4.7 Hz, 1H), 7.18 (dd, J=5.1, 3.6 Hz, 1H), 7.41 (dd, J=5.1, 1.1 Hz, 1H), 7.45 (dd, J=3.6, 1.1 Hz, 1H), 7.90 (dd, J=7.9, 1.5 Hz, 1H), 8.21 (dd, J=4.7, 1.5 Hz, 1H), 11.7 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 30.1, 34.2, 37.9, 110.6, 115.6, 123.4, 125.8, 126.4, 127.4, 128.6, 130.6, 135.3, 142.6, 148.7. ES^+-MS: m/z 271 $(M+H)^+$. HRMS: found $(M+H)^+$ 271.1266. $C_{16}H_{19}N_2S$ requires 271.1269.

4.1.5.4. 1-[3-(2,2-Dimethyl-propyl)-1*H*-pyrrolo[2,3-*b*]pyridin-2-yl]-ethanone (10d). Colourless solid (44%), mp 144–145 °C. IR (KBr plate): 3187, 3142, 3082, 2946, 1672 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.00 (s, 9H), 2.73 (s, 3H), 3.10 (s, 2H), 7.13 (dd, J=8.1, 4.7 Hz, 1H), 8.07 (dd, J=8.1, 1.6 Hz, 1H), 8.62 (dd, J=4.7, 1.6 Hz, 1H), 11.5 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 29.3, 30.2, 33.9, 37.9, 116.2, 119.9, 122.2, 131.7, 133.1, 147.5, 147.7, 181.8. ES^+-MS: m/z 231 $(M+H)^+$. HRMS: found $(M+H)^+$ 231.1488. $C_{14}H_{19}N_2O$ requires 231.1497. Anal. Calcd for $C_{14}H_{18}N_2O$: C, 73.01; H, 7.88; N, 12.16. Found: C, 72.84; H, 7.98; N, 12.35.

4.1.5.5. 6-Methyl-3-(2-methyl-butyl)-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (10e). Colourless solid (65%), mp 64–65 °C. IR (KBr plate): 3152, 3139, 3051, 2961, 1600 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.82–0.90 (m, 6H), 1.10–1.27 (m, 1H), 1.35–1.46 (m, 1H), 1.72–1.84 (m, 1H), 2.35 (s, 3H), 2.64 (dd, J=14.2, 8.2 Hz, 1H), 2.87 (dd, J=14.2, 6.3 Hz, 1H), 6.89 (d, J=7.9 Hz, 1H), 7.32–7.38 (m, 1H), 7.42–7.47 (m, 2H), 7.55–7.59 (m, 2H), 7.80 (d, J=7.9 Hz, 1H), 10.4 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.7, 19.6, 23.9, 29.7, 31.8, 36.4, 111.3, 115.5, 119.9, 127.6, 128.1, 128.5, 128.7, 134.6, 135.5, 148.7, 151.7. ES^+-MS: m/z 279 $(M+H)^+$. HRMS: found $(M+H)^+$ 279.1862. $C_{19}H_{23}N_2$ requires 279.1861. Anal. Calcd for $C_{19}H_{22}N_2$: C, 81.97; H, 7.97; N, 10.06. Found: C, 81.75; H, 8.10; N, 9.73.

4.1.5.6. 3-(2,2-Dimethyl-propyl)-1,5-dimethyl-2-phenyl-1*H*-pyrrolo[2,3-*b*]pyridine (10f). A stirred solution of **5e** (0.045 g, 0.3 mmol) in dry diethyl ether (5 mL) at −78 °C under nitrogen was treated dropwise over 10 min with phenyllithium (0.45 mmol). The reaction mixture was warmed to −30 °C, stirred at this temperature for 1 h and cooled to −78 °C. *tert*-Butyllithium (0.6 mmol) was added and the reaction mixture was stirred at −78 °C for a further 1 h. Benzonitrile (0.155 mL, 1.5 mmol) was added and the reaction mixture was stirred for 1 h at 0 °C. Aqueous HCl (2 M, 3 mL) was added and the reaction mixture was stirred for 30 min at room temperature and carefully added over 10 min to a saturated potassium carbonate solution (20 mL). The solution was extracted with diethyl ether (2×20 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel column chromatography (eluent: pentane/Et_2O, 95:5) yielded **10f** as a colourless solid (70%), mp 68–69 °C. IR (KBr plate): 3058, 3007, 2950, 1600 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.72 (s, 9H), 2.45 (s, 3H), 2.65 (s, 2H), 3.64 (s, 3H), 7.38–7.69 (m, 5H), 7.69 (s, 1H), 8.15 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.7, 29.4, 30.0, 33.8, 37.6, 108.8, 121.6, 124.1, 128.1, 128.3, 128.4, 130.9, 132.6, 139.7, 143.2, 143.8. ES^+-MS: m/z 293 $(M+H)^+$. HRMS: found $(M+H)^+$ 293.2027. $C_{20}H_{25}N_2$ requires 293.2018. Suitable crystals for X-ray crystallographic analysis were grown by slow evaporation of an ethanol solution.

4.1.5.7. 3-(2,2-Dimethyl-propyl)-1,2,5-trimethyl-1*H*-pyrrolo[2,3-*b*]pyridine (10g). A stirred solution of **5e** (0.04 g, 0.27 mmol) in dry diethyl ether (5 mL) at −78 °C under nitrogen was treated dropwise over 5 min with phenyllithium (0.4 mmol). The reaction mixture was warmed to −30 °C, stirred at this temperature for 1 h and cooled to −78 °C. *tert*-Butyllithium (0.54 mmol) was added and the reaction mixture was stirred at −78 °C for a further 1 h. The reaction mixture was warmed to 0 °C, acetic anhydride (1 Ml, 0.01 mol) added and the reaction mixture was stirred for 15 min. Water (20 mL) was added and the mixture extracted with diethyl ether (2×20 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was treated with 1 M HCl (10 mL) and the solution was heated under reflux for 12 h. The reaction mixture was cooled to room temperature, carefully added over 10 min to a saturated potassium carbonate solution (20 mL) and extracted with diethyl ether (2×20 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel column chromatography (eluent: Et_2O/pentane, 7:3) yielded **10g** as a colourless solid (38%), mp 85–86 °C. IR (KBr

plate): 2951, 2937, 2903, 1606 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.94 (s, 9H), 2.34 (s, 3H), 2.40 (s, 3H), 2.54 (s, 2H), 3.75 (s, 3H), 7.54 (s, 1H), 8.03 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 11.3, 18.8, 28.2, 30.1, 34.1, 38.3, 107.5, 121.9, 123.8, 127.1, 135.5, 142.0, 146.4. ES^+-MS: *m/z* 231 $(M+H)^+$. HRMS: found $(M+H)^+$ 231.1853. $C_{15}H_{23}N_2$ requires 231.1861. Anal. Calcd for $C_{15}H_{22}N_2$: C, 78.21; H, 9.63; N, 12.16. Found: C, 78.20; H, 9.88; N, 11.99.

4.1.6. *N*-[3-(1-Benzoyl-3,3-dimethyl-butyl)-pyridin-2-yl]-2,2-dimethyl-propionamide 11. A stirred solution of **5a** (0.05 g, 0.24 mmol) in dry diethyl ether (5 mL) at −78 °C under nitrogen was treated dropwise with phenyllithium (0.27 mL of a 1.35 M solution, 0.37 mmol). The reaction mixture was warmed to −30 °C, stirred at this temperature for 1 h and cooled to −78 °C. *tert*-Butyllithium (0.32 mL of a 1.15 M solution, 0.37 mmol) was added over 10 min and the reaction mixture was stirred at −78 °C for a further 1 h. Benzonitrile (0.06 mL, 0.61 mmol) was added and the reaction mixture was warmed to 0 °C and stirred for 1 h. Aqueous HCl (2 M, 3 mL) was added and the reaction mixture was warmed to room temperature, stirred for 20 min and slowly added over 10 min to a saturated potassium carbonate solution (20 mL). The solution was extracted with diethyl ether (2×25 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography with diethyl ether/cyclohexane (7:3) as eluent yielding **11** as a colourless solid (80%), mp 68–69 °C. IR (KBr plate): 3218, 3168, 3062, 2958, 1680 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 0.87 (s, 9H), 1.41 (s, 9H), 1.80 (dd, *J*=5.1, 13.9 Hz, 1H), 2.39 (dd, *J*=7.5, 13.9 Hz, 1H), 4.87 (dd, *J*=5.1, 7.5 Hz, 1H), 7.14 (dd, *J*=4.8, 7.8 Hz, 1H), 7.45–7.50 (m, 2H), 7.56–7.61 (m, 1H), 7.88 (dd, *J*=1.5, 7.8 Hz, 1H), 8.04–8.08 (m, 2H), 8.29 (dd, *J*=1.5, 4.8 Hz, 1H), 8.6 (br s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 27.6, 30.0, 31.6, 39.8, 45.0, 46.1, 121.8, 128.68, 128.70, 131.5, 133.3, 136.3, 146.8, 148.8, 178.9, 200.8. ES^+-MS: *m/z* 367 $(M+H)^+$. HRMS: found $(M+H)^+$ 367.2402. $C_{23}H_{31}N_2O_2$ requires 367.2386. Anal. Calcd for $C_{23}H_{30}N_2O_2$: C, 75.37; H, 8.25; N, 7.64. Found: C, 75.12; H, 8.31; N, 7.53.

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