Control of Site of Lithiation of 3-(Aminomethyl)pyridine Derivatives

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Abstract: Lithiation of *N*-(pyridin-3-ylmethyl)pivalamide, *tert*-butyl *N*-(pyridin-3-ylmethyl)carbamate, and *N*,*N*-dimethyl-*N*′-(pyridin-3-ylmethyl)urea with *tert*-butyllithium (3 equiv) in anhydrous tetrahydrofuran at –78 °C takes place on the nitrogen and on the ring at the 4-position. The dilithium reagents thus obtained react with various electrophiles to give the corresponding substituted derivatives in high yields. On the other hand, regioselective side-chain lithiation occurs with lithium diisopropylamide (3.3 equiv) at –20 to 0 °C. A mixture of ring and side-chain substitution products is obtained with *n*-butyllithium as the lithium reagent. Treatment of one of the ring-substituted products with trifluoroacetic anhydride in dichloromethane under reflux conditions led to formation of the corresponding 1*H*-pyrrolo[3,4-*c*]pyridine in high yield.

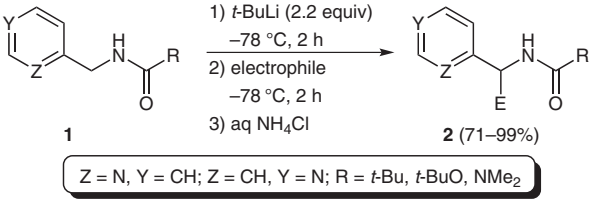
Key words: directed lithiation, side-chain lithiation, *N*-(pyridin-3-ylmethyl)pivalamide, *N*,*N*-dimethyl-*N*′-(pyridin-3-ylmethyl)urea, *tert*-butyl *N*-(pyridin-3-ylmethyl)carbamate

Lithiation of aromatic compounds is an important approach for modification of such systems.[3–5] In our own studies[6] we have investigated selective lithiation of various benzyl- and phenylethylamine derivatives and shown that the site of lithiation depends on any substituent groups, the nature of the lithium reagent, and the reaction conditions.[7–12] We have applied such processes in the preparation of substituted heterocycles.[13–15]

Heterocyclic compounds are of great importance since they represent the core unit of numerous important products.[16] However, regioselective lithiation of substituted pyridines is not always practical due to nucleophilic addition of alkyllithiums to the azomethine bond, although success has sometimes been achieved by the use of less nucleophilic lithium reagents such as lithium diisopropylamide[17–22] and lithium 2,2,6,6-tetramethylpiperidide.[23–27]

The literature records several protocols for α-lithiation and directed *ortho*-metalation (DoM) of pyridines and related heterocycles, depending on the solvent, temperature, or lithium reagent,[28–30] or by the use of additives[31] to control the level of aggregation of the organolithium reagent.[32] Regioselective lithiation of pyridines containing directing metalating groups (DMGs) mostly relies on the position of the DMG. Pyridines containing various DMGs directly attached to the ring at the C2[28] or C4[29] position, with various lithium reagents invariably takes place at C3 to give the corresponding 3-substituted derivatives after reactions of the lithium reagents produced with electrophiles.[29,30]

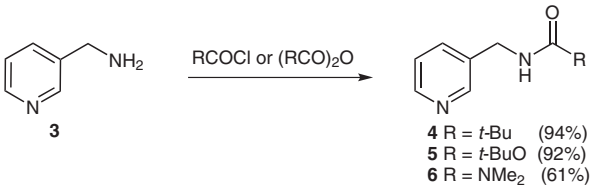
Very recently, we have investigated the effect of an extra CH_2 group between the DMG and the pyridine ring.[33] It was found that lithiation and substitution of derivatives of *N*-(pyridin-2-ylmethyl)amine **1** (Z = N, Y = CH_2) or *N*-(pyridin-4-ylmethyl)amine **1** (Z = CH_2, Y = N) provided easy access to various side chain (methylene) substituted derivatives **2** in high yields (Scheme 1).[33]



Scheme 1 Lithiation of substituted *N*-(pyridinylmethyl)amines **1**

The high selectivity in the lithiation of compounds **1** is helped by the significant acidity of the CH_2 protons as a result of the ring nitrogen, which enhances side-chain lithiation over ring lithiation to a greater extent than for the simple benzyl analogues.[33] However, the acidity of the CH_2 group would not be enhanced to the same extent for the pyridin-3-ylmethylamine derivatives. Therefore, it was of interest to investigate lithiation of *N*-(pyridin-3-ylmethyl)pivalamide, *N*,*N*-dimethyl-*N*′-(pyridin-3-ylmethyl)urea, and *tert*-butyl *N*-(pyridin-3-ylmethyl)carbamate. We now report that lithiation can be controlled to give either ring or side-chain substitution, depending on the protocol used.

3-Substituted pyridines **4**–**6** were synthesized, based on a literature procedure for analogous compounds,[9,10] by reaction of 3-(aminomethyl)pyridine (**3**) with pivaloyl chlo-



Scheme 2 Synthesis of *N*-(pyridin-3-ylmethyl) derivatives **4**–**6**

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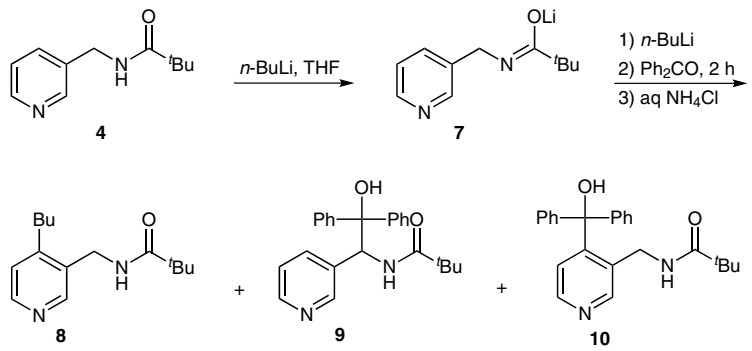


Scheme 3 Lithiation of **4** followed by reaction with benzophenone

ride, di-*tert*-butyl dicarbonate or dimethylcarbamoyl chloride, respectively (Scheme 2).

Initially, *N*-(pyridin-3-ylmethyl)pivalamide (**4**) was treated with *n*-butyllithium (2.2 equiv) in anhydrous tetrahydrofuran at –78 °C for two hours to form first the monolithium compound **7** (Scheme 3) and then perhaps one or more dilithium species. The mixture was then treated with benzophenone (2.2 equiv) at –78 °C for two hours. The crude product was separated by column chromatography to give **8** (6%), **9** (27%), and **10** (44%) along with residual starting material **4** (10%, Scheme 3).

N-[(4-Butylpyridin-3-yl)methyl]pivalamide (**8**) presumably results from nucleophilic addition of *n*-butyllithium at the 4-position of the pyridine ring to give reagent **11** (Figure 1), followed by aromatization. Substitution products **9** and **10** are produced from reaction of benzophenone with dilithium intermediates **12** and **13** (Figure 1), respectively. The modest selectivity for the ring-substituted product, arising from dilithium reagent **13**, can be compared with the previously reported highly selective lithiation of *N*-(pyridin-3-yl)pivalamide at C4 using *n*-butyllithium/*N*,*N*,*N*′,*N*′-tetramethylethylenediamine.[28a]

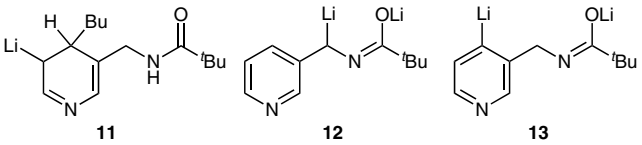


Figure 1 Structures of lithium intermediates **11**–**13**

Several experiments were conducted in which alkyllithium, temperature, and reaction time were varied in an attempt to optimize the yield of **10** (Table 1). The use of *n*-butyllithium invariably provided a mixture of **9** (30–9%)

Table 1 Yields of Compounds **8**–**10** and **14** Formed by Lithiation of **4** under Different Reaction Conditions (Scheme 3)

Entry	RLi (equiv)	Temp (°C)	Time (h)	Yield[a] (%)			
				4	**8** or **14**	**9**	**10**
1	*n*-BuLi (2.2)	–78	2	13 (10)[b]	8 (6)[b]	30 (27)[b]	49 (44)[b]
2	*n*-BuLi (3.3)	–78	2	–	–	59	41
3	*n*-BuLi (3.3)	–50	2	–	24	48	25
4	*n*-BuLi (3.3)	–20 to 0	2	–	36	37	22
5	*t*-BuLi (3.3)	–78	2	– (8)[b]	–	–	96 (88)[b]
6	*t*-BuLi (3.3)	–50	2	–	22 (20)[b]	–	64 (63)[b]
7	*t*-BuLi (3.3)	–20 to 0	2	–	53	–	32
8	LDA(3.3)	–78	2	96	–	–	–
9	LDA (3.3)	–78	4	86	–	11[b]	–
10	LDA (3.3)	–78 to 0	4	61	–	34	–
11	LDA (3.3)	–20 to 0	4	28	–	68	–
12	LDA (3.3)	–20 to 0	6	21	–	72	–
13	LDA (3.3)	0	4	31	–	63	–

[a] Yield by ^{1}H NMR unless otherwise indicated.
[b] Yield of isolated material after purification by column chromatography.

and **10** (22–49%) along with **8** (0–36%) in most cases (Table 1, entries 1–4), based on the ^{1}H NMR spectra of the crude product mixtures. At higher temperatures nucleophilic addition of *n*-butyllithium competed with lithiation to a greater extent, but lithiation remained relatively unselective, giving both side-chain substitution product **9** (37–48%) and ring-substitution product **10** (22–25%) in significant amounts.

The more hindered and less aggregated *tert*-butyllithium was more selective than *n*-butyllithium, resulting in product mixtures containing only the addition–aromatization product **14** (Figure 2) and the ring-substituted product **10** (Table 1, entries 5–7). As with *n*-butyllithium, nucleophilic addition competed more effectively at higher temperatures, but at –78 °C the only product was **10**, which could be isolated in 88% yield (entry 5). Presumably, dilithium reagent **13** (Figure 1) is the kinetic product at low temperature because the aromatic proton is more appropriately positioned for directed metalation than those of the CH_2 group. If so, use of a reagent that does not lend itself so readily to complexation by the pivaloylamino group might favour side-chain lithiation to a greater extent. Indeed, reaction with lithium diisopropylamide (entries 8–13) was highly regioselective towards formation of side-chain substitution product **9**, with no evidence for the formation of any other products, and a reasonable yield up to 72% could be obtained following lithiation at –20 to 0 °C for a relatively long time.

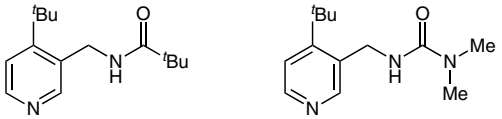
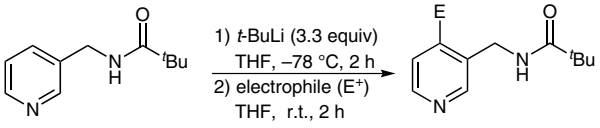


Figure 2 Structures of compounds **14** and **25**

It was of interest to see if the reactions of the dilithium intermediates **13** (prepared as in entry 5) and **12** (entry 12) with other electrophiles would be useful and general. Reactions with various electrophiles [acetone, 4-methoxybenzaldehyde, 4-(dimethylamino)benzaldehyde, and iodoethane] were carried out (Table 2) under conditions identical to those in Table 1, entry 5 and the products were purified by column chromatography (silica gel, EtOAc–hexane, 1:3) to give the corresponding substituted derivatives **15**–**18** in excellent yields (Table 2). The ^{1}H NMR spectra of compounds **16** and **17** showed that the signals of the CH_2 protons appeared separately, verifying that the protons are diastereotopic.

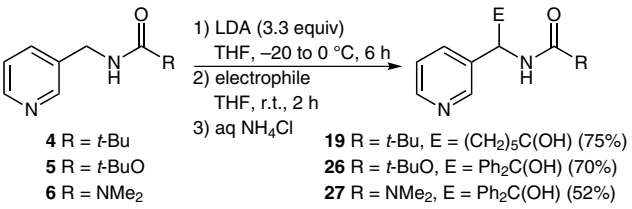
To test the generality of the side-chain substitution process, cyclohexanone was used as an electrophile. It was found that lithiation of **4** with lithium diisopropylamide under the conditions used with benzophenone (Table 1, entry 12) followed by reaction with cyclohexanone gave **19** (Scheme 4) in 75% yield. The two sides of the cyclohexane ring appeared as separated signals in the ^{13}C NMR spectrum confirming that they are diastereotopic, and in the same way the two phenyl groups of compound **9** showed separated signals.

Table 2 Synthesis of Substituted *N*-(Pyridin-3-ylmethyl)pivalamides **10** and **15**–**18**



Entry	Product	Electrophile	E	Yield[a] (%)
1	**10**	Ph_2CO	$Ph_2C(OH)$	88
2	**15**	Me_2CO	$Me_2C(OH)$	91
3	**16**	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	89
4	**17**	4-$Me_2NC_6H_4CHO$	4-$Me_2NC_6H_4CH(OH)$	85
5	**18**	EtI	Et	90

[a] Yield of the pure isolated product.

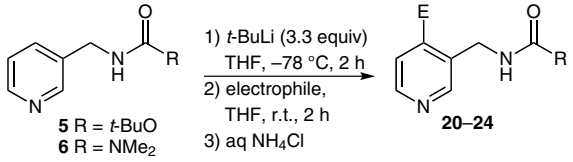


Scheme 4 Lithiation of **4**–**6** using lithium diisopropylamide followed by reaction with cyclohexanone or benzophenone

In the light of the success at controlling lithiation of **4** to give either ring or side-chain substituted products, attention was turned to lithiation of *tert*-butyl *N*-(pyridin-3-ylmethyl)carbamate (**5**) and *N*,*N*-dimethyl-*N*′-(pyridin-3-ylmethyl)urea (**6**). Lithiations of both **5** and **6** with *tert*-butyllithium (3.3 equiv) under identical conditions to those used for the ring substitution of **4** (entry 5) also gave mainly ring-substituted products. Reactions with several electrophiles (benzophenone, acetophenone, cyclohexanone, and benzaldehyde) were carried out and the products were purified by column chromatography (silica gel, EtOAc–hexane, 1:3) to give the corresponding substituted derivatives **20**–**24** (Table 3). Yields were very high with the carbamate **5**, but the yield of product from the single reaction conducted with the urea **6** was significantly lower (66% of compound **24**, Table 3), at least in part because of competition from nucleophilic addition, since around 5% of compound **25** (Figure 2) was isolated from the reaction mixture. The reason for the increased proportion of side product with the urea is not clear, but it is likely that the urea is better at complexing *tert*-butyllithium than either the pivalamide or the carbamate.

Finally, lithiations of **5** and **6** were attempted with lithium diisopropylamide as the lithium reagent under similar

Table 3 Synthesis of **20**–**24** via Lithiation and Substitution of **5** and **6**



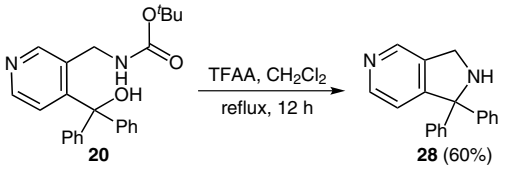
Entry	Products	R	Electrophile	E	Yield[a] (%)
1	**20**	*t*-BuO	Ph_2CO	$Ph_2C(OH)$	88
2	**21**	*t*-BuO	PhCOMe	PhC(OH)Me	81
3	**22**	*t*-BuO	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	80
4	**23**	*t*-BuO	PhCHO	PhCH(OH)	84
5	**24**	NMe_2	Ph_2CO	$Ph_2C(OH)$	66[b]

[a] Yield of the pure isolated product.
[b] Compound **25** (Figure 2), due to the addition of *t*-BuLi at C4 of **6** followed by aromatization, was isolated in 5% yield.

conditions to those used for the side-chain lithiation of **4** (Table 1, entry 12) in an attempt to produce analogous side-chain substitution products. Indeed, lithiations of **5** and **6** with lithium diisopropylamide followed by reactions with benzophenone as a representative electrophile gave the corresponding side-chain substitution products **26** and **27** in 70% and 52% yields, respectively (Scheme 4) along with recovered starting materials **5** (23%) and **6** (38%). There was no evidence for the production of a significant amount of ring-substituted product and the modest yields of side-chain substituted products, particularly from the urea, presumably reflect either slow deprotonation or less favourable equilibrium concentrations of the corresponding organolithium species. Among the pivalamide, carbamate, and urea derivatives, it would be expected that the urea would provide least stabilization of a negative charge on the side chain.

We have previously shown that *ortho*-(hydroxyalkyl)benzylamine derivatives can be cyclized to isoindolines on treatment with trifluoroacetic anhydride[13]and it was of interest to know whether the same reaction would be effective with these aza analogues. Therefore, **20** was treated with trifluoroacetic anhydride under reflux for 12 hours and gave **28** in 60% yield (Scheme 5) after purification by column chromatography. Clearly, cyclization of **20** via dehydration had taken place, along with hydrolysis of the carbamate group, to produce 1,1-diphenyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine (**28**).

In conclusion, two independent, convenient, and simple experimental procedures have been developed for the production of ring and side-chain substitution products of various 3-(acylaminomethyl)pyridines. Ring lithiation has been achieved by the use of *tert*-butyllithium (3.3 equiv) at –78 °C. The dilithium reagents produced in situ were allowed to react with various electrophiles to give



Scheme 5 Synthesis of 1,1-diphenyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine (**28**)

the corresponding 4-substituted products in high yields. On the other hand, the reaction was regioselective towards the side-chin when lithium diisopropylamide (3.3 equiv) was used as the lithium reagent at –20 to 0 °C. A mixture of ring and side-chain substitution products, and also some product resulting from addition–oxidation, was obtained when *n*-butyllithium was the lithium reagent.

In one case a product involving a hydroxyalkyl group on a ring position adjacent to the acylaminomethyl group has been shown to cyclize to a pyrrolopyridine derivative under the influence of trifluoroacetic anhydride.

Melting point determinations were performed by the open capillary method using a Gallenkamp melting point apparatus and are reported uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV500 spectrometer operating at 500 MHz (^{1}H) and 125 MHz (^{13}C) relative to TMS; ^{13}C multiplicities were revealed by DEPT signals. Assignments of signals are based on integration values, coupling patterns and expected chemical shift values and have not been rigorously confirmed. Signals with similar characteristics might be interchanged. LR-MS were recorded on a Waters GCT Premier spectrometer and accurate mass data were recorded on a Waters LCT Premier XE instrument. IR spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrophotometer as thin films (liquids) or KBr discs (solids). Microanalysis was performed by Warwick analytical service at the University of Warwick. Column chromatography was carried out using Fischer Scientific silica 60A (35–70 μm). Alkyllithiums were obtained from Aldrich Chemical Company and were estimated prior to use by the method of Watson and Eastham.[34] Other chemicals were obtained from Aldrich Chemical Company and used without further purification.

***N*-(Pyridin-3-ylmethyl)pivalamide (4)**

To a cooled solution (0 °C) of 3-(aminomethyl)pyridine (**3**, 4.32 g, 40.0 mmol) and Et_3N (6.10 g, 60.0 mmol) in CH_2Cl_2 (50 mL), pivaloyl chloride (5.80 g, 48.0 mmol) was slowly added in a dropwise manner over 30 min. The mixture was stirred at 0 °C for 1 h and poured into H_2O (50 mL). The organic layer was separated, washed with H_2O (2 × 50 mL), and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude product was separated by column chromatography (silica gel, EtOAc–hexane; 1:3) to give pure **4**; (7.22 g, 37.6 mmol, 94%) as a colourless oil.

FT-IR: 3340, 2966, 1651, 1593, 1481, 1324, 1259, 1207, 1121 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.41–8.39 (m, 2 H, H2, H6), 7.52 (d, *J* = 8 Hz, 1 H, H4), 7.17 (dd, *J* = 5, 8 Hz, 1 H, H5), 6.37 (br, exch., 1 H, NH), 4.36 (d, *J* = 6 Hz, 2 H, CH_2), 1.15 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.6 (s, C=O), 148.9 (d, C2), 148.7 (d, C6), 135.3 (s, C3), 134.5 (d, C4), 123.6 (d, C5), 40.9 (t, CH_2), 38.7 [s, $C(CH_3)_3$], 27.6 [q, $C(CH_3)_3$].

MS (APCI): *m*/*z* (%) = 193 (100, $[M + H]^+$).

HRMS (APCI): *m*/*z* $[M + H]^+$ calcd for $C_{11}H_{17}N_2O$: 193.1341; found: 193.1332.

***tert*-Butyl *N*-(Pyridin-3-ylmethyl)carbamate (5)**
To a cooled solution (0 °C) of 3-(aminomethyl)pyridine (**3**, 4.32 g, 40.0 mmol) and Et_3N (6.10 g, 60.0 mmol) in CH_2Cl_2 (50 mL), $(Boc)_2O$ (10.50 g, 48.0 mmol) was slowly added in a dropwise manner over 30 min. The mixture was stirred at 0 °C for 1 h and poured into H_2O (100 mL). The organic layer was separated, washed with H_2O (2 × 50 mL), and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude product was separated by column chromatography (silica gel, EtOAc–hexane; 1:3) to give pure **5** (7.70 g, 37.0 mmol, 92%) as a colourless oil.

FT-IR: 3352, 2980, 1707, 1579, 1431, 1367, 1249, 1218, 1165 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.19 (s, 1 H, H2), 8.13 (d, *J* = 5 Hz, 1 H, H6), 7.34 (d, *J* = 8 Hz, 1 H, H4), 6.93 (dd, *J* = 5, 8 Hz, 1 H, H5), 6.45 (br, exch., 1 H, NH), 4.01 (d, *J* = 6 Hz, 2 H, CH_2), 1.16 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.2 (s, C=O), 148.5 (d, C2), 148.0 (d, C6), 135.0 (s, C3), 134.9 (d, C4), 123.2 (d, C5), 79.0 [s, $C(CH_3)_3$], 41.8 (t, CH_2), 28.2 [q, $C(CH_3)_3$].

MS (EI): *m*/*z* (%) = 208 (5, $[M]^+$), 152 (30), 135 (20), 107 (68), 80 (100).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{11}H_{16}N_2O_2$: 208.1212; found: 208.1207.

***N*,*N*-Dimethyl-*N*′-(pyridin-3-ylmethyl)urea (6)**
To a cooled solution (0 °C) of 3-(aminomethyl)pyridine (**3**, 4.32 g, 40.0 mmol) and Et_3N (6.10 g, 60.0 mmol) in CH_2Cl_2 (50 mL), dimethylcarbamoyl chloride (5.20 g, 48.0 mmol) was slowly added in a dropwise manner over 30 min. The mixture was stirred at r.t. for 1 h and poured into H_2O (100 mL). The organic layer was separated, washed with H_2O (2 × 50 mL), and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The crude product was separated by column chromatography (silica gel, EtOAc–hexane; 1:3) to give **6** (4.37 g, 24.4 mmol, 61%) as a reddish oil.

FT-IR: 3335, 2929, 1633, 1537, 1427, 1378, 1234, 1033 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.48–8.42 (m, 2 H, H2, H6), 7.70 (d, *J* = 8 Hz, 1 H, H4), 7.21 (dd, *J* = 5, 8 Hz, 1 H, H5), 5.07 (br, exch., 1 H, NH), 4.36 (d, *J* = 6 Hz, 2 H, CH_2), 2.85 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.3 (s, C=O), 148.7 (d, C2), 148.0 (d, C6), 136.1 (s, C3), 136.0 (d, C4), 123.7 (d, C5), 42.4 (t, CH_2), 36.3 [q, $N(CH_3)_2$].

MS (EI): *m*/*z* (%) = 179 (100, $[M]^+$), 135 (40), 107 (45).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_9H_{13}N_3O$: 179.1059; found: 179.1057.

Lithiation and Substitution of 4–6; General Procedure
A 1.6 M solution of *n*-BuLi in hexane (2.75 mL, 4.4 mmol), 1.9 M *t*-BuLi in pentane (3.47 mL, 6.6 mmol), or 2.0 M LDA in a mixture of THF, heptane, and ethylbenzene (3.30 mL, 6.6 mmol) was added to a cold (–78 °C), stirred solution of **4**, **5**, or **6** (2.0 mmol) in anhyd THF (15 mL) under N_2. The mixture was stirred at –78 °C for 2 h with *n*-BuLi or *t*-BuLi, or at –20 to 0 °C for 6 h with LDA, to ensure the complete formation of the appropriate dilithium reagent(s) after which an electrophile (4.4 mmol) [in anhyd THF (3 mL) if solid, otherwise neat] was added. The mixture was stirred for 2 h and allowed to warm up to r.t. It was then quenched with sat. aq NH_4Cl (10 mL). The organic layer was separated, washed with H_2O (2 × 10 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The crude mixture obtained was separated by column chromatography (silica gel, EtOAc–hexane, 1:3) to give pure products.

***N*-[(4-Butylpyridin-3-yl)methyl]pivalamide (8)**
Table 1, entry 1; colourless oil; yield: 0.030 g (0.12 mmol, 6%).

FT-IR: 3339, 2958, 1642, 1597, 1412, 1208, 1010 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.37 (d, *J* = 5 Hz, 1 H, H6), 8.36 (s, 1 H, H2), 7.06 (d, *J* = 5 Hz, 1 H, H5), 5.72 (br, exch., 1 H, NH), 4.42 (d, *J* = 5 Hz, 2 H, CH_2NH), 2.56 (t, *J* = 7 Hz, 2 H, $CH_3CH_2CH_2CH_2$), 1.51 (m, 2 H, $CH_3CH_2CH_2$), 1.33 (m, 2 H, CH_3CH_2), 1.15 [s, 9 H, $C(CH_3)_3$], 0.87 (t, *J* = 7 Hz, 3 H, CH_3).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.0 (s, C=O), 149.6 (d, C2), 148.9 (d, C6), 140.6 (s, C4), 131.8 (s, C3), 124.2 (d, C5), 38.8 (t, CH_2NH), 38.7 [s, $C(CH_3)_3$], 32.3 [t, $CH_3CH_2CH_2$], 31.5 (t, $CH_3CH_2CH_2CH_2$), 27.6 [q, $C(CH_3)_3$], 22.6 (t, CH_3CH_2), 13.8 (q, CH_3).

MS (EI): *m*/*z* (%) = 248 (53, $[M]^+$), 206 (25), 149 (29), 106 (23), 85 (100), 57 (24).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{24}N_2O$: 248.1889; found: 248.1894.

***N*-[2-Hydroxy-2,2-diphenyl-1-(pyridine-3-yl)ethyl]pivalamide (9)**
Table 1, entry 12; reagents: LDA, benzophenone; white solid; yield: 0.54 g (1.44 mmol, 72%); mp 222–224 °C.

FT-IR: 3434, 2932, 1652, 1558, 1423, 1336, 1213, 1025 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.47 (s, 1 H, H2), 7.88 (d, *J* = 5 Hz, 1 H, H6), 7.57 (d, *J* = 8 Hz, 1 H, H4), 7.38–6.99 (m, 10 H, 10 H_{Ph}), 6.90 (dd, *J* = 5, 8 Hz, 1 H, H5), 5.96 (d, *J* = 6 Hz, 1 H, CH), 5.22 (br, exch., 1 H, OH), 4.43 (d, *J* = 6 Hz, 1 H, NH), 0.99 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.7 (s, C=O), 149.4 (d, C2), 147.4 (d, C6), 144.6, 144.1 (2 s, $C1_{Ph}$), 137.2 (d, C4), 135.0 (s, C3), 128.4, 128.1 (2 d, $C3_{Ph}$/$C5_{Ph}$), 127.4, 127.2 (2 d, $C4_{Ph}$), 126.2, 125.9 (2 d, $C2_{Ph}$/$C6_{Ph}$), 122.5 (d, C5), 80.8 (s, COH), 57.7 (d, CH), 38.6 [s, $C(CH_3)_3$], 27.2 [q, $C(CH_3)_3$].

MS (APCI): *m*/*z* (%) = 416 (40, $[M + MeCN + H]^+$), 375 (100, $[M + H]^+$), 234 (30), 193 (35), 126 (30).

HRMS (APCI): *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{27}N_2O_2$: 375.2073; found: 375.2079.

Anal. Calcd for $C_{24}H_{26}N_2O_2$: C, 76.98; H, 7.00. Found: C, 76.8; H, 7.0.

***N*-{[4-(Hydroxydiphenylmethyl)pyridin-3-yl]methyl}pivalamide (10)**
Table 1, entry 5; reagents: *t*-BuLi, benzophenone; white solid; yield: 0.72 g (1.92 mmol, 96%); mp 211–213 °C.

FT-IR: 3381, 2984, 1640, 1546, 1425, 1240, 1017 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.68 (s, 1 H, H2), 8.32 (d, *J* = 5 Hz, 1 H, H6), 7.38–7.28 (m, 11 H, 10 H_{Ph}, OH), 6.72 (br t, *J* = 6 Hz, exch., 1 H, NH), 6.68 (d, *J* = 5 Hz, 1 H, H5), 4.20 (d, *J* = 6 Hz, 2 H, CH_2), 1.13 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.0 (s, C=O), 151.2 (d, C2), 147.1 (d, C6), 146.8 (s, C4), 146.0 (s, 2 $C1_{Ph}$), 134.4 (s, C3), 128.3 (d, 2 $C3_{Ph}$/$C5_{Ph}$), 127.6 (d, 2 $C4_{Ph}$), 127.5 (d, 2 $C2_{Ph}$/$C6_{Ph}$), 124.1 (d, C5), 81.7 (s, COH), 39.9 (t, CH_2), 38.5 [s, $C(CH_3)_3$], 27.4 [q, $C(CH_3)_3$].

MS (EI): *m*/*z* (%) = 374 (10, $[M]^+$), 358 (50), 255 (100), 179 (95).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{24}H_{26}N_2O_2$: 374.1994; found: 374.1989.

***N*-[(4-*tert*-Butylpyridin-3-yl)methyl]pivalamide (14)**
Table 1, entry 6; colourless oil; yield: 0.10 g (0.40 mmol, 20%).

FT-IR: 3337, 2988, 1639, 1539, 1419, 1239, 1013 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.43 (s, 1 H, H2), 8.36 (d, *J* = 5 Hz, 1 H, H6), 7.25 (d, *J* = 5 Hz, 1 H, H5), 5.91 (br, exch., 1 H, NH), 4.61 (d, *J* = 5 Hz, 2 H, CH_2), 1.36 [s, 9 H, $C(CH_3)_3$], 1.09 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.2 (s, C=O), 158.0 (s, C4), 151.0 (d, C2), 148.2 (d, C6), 132.6 (s, C3), 121.2 (d, C5), 40.5 (t, CH_2), 38.7 [s, *C*(CH_3)$_3$], 35.9 [s, *C*(CH_3)], 30.7 [q, C(*C*H_3)$_3$], 27.5 [q, C(*C*H_3)$_3$].

MS (EI): *m*/*z* (%) = 248 (25, $[M]^+$), 191 (33), 148 (15), 117 (15), 101 (84), 83 (100), 68 (68), 57 (96).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{24}N_2O$: 248.1889; found: 248.1891.

***N*-{[4-(2-Hydroxypropan-2-yl)pyridin-3-yl]methyl}pivalamide (15)**
Reagents: *t*-BuLi, acetone; colourless oil; yield: 0.45 g (1.8 mmol, 91%).

FT-IR: 3351, 2989, 1648, 1542, 1427, 1233, 1018 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.47 (s, 1 H, H2), 8.37 (d, *J* = 5 Hz, 1 H, H6), 7.10 (d, *J* = 5 Hz, 1 H, H5), 6.48 (br, exch., 1 H, NH), 4.69 (d, *J* = 5 Hz, 2 H, CH_2), 3.36 (s, exch., 1 H, OH), 1.59 [s, 6 H, C(C*H*$_3$)$_2$], 1.09 [s, 9 H, C(CH_3)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.8 (s, C=O), 152.9 (s, C4), 150.6 (d, C2), 148.9 (d, C6), 136.4 (s, C3), 125.1 (d, C5), 73.9 (s, C–OH), 40.3 (t, CH_2), 38.6 [s, *C*(CH_3)$_3$], 32.1 [q, C(*C*H_3)$_2$], 27.5 [q, C(*C*H_3)$_3$].

MS (EI): *m*/*z* (%) = 232 (50, $[M - H_2O]^+$), 217 (73), 192 (100), 174 (94), 147 (97), 118 (99), 107 (88), 92 (98), 83 (65), 65 (67).

HRMS (EI): *m*/*z* $[M - H_2O]^+$ calcd for $C_{14}H_{20}N_2O$: 232.1576; found: 232.1581.

***N*-({4-[Hydroxy(4-methoxyphenyl)methyl]pyridin-3-yl}methyl)pivalamide (16)**
Reagents: *t*-BuLi, 4-methoxybenzaldehyde; colourless oil; yield: 0.58 g (1.8 mmol, 89%).

FT-IR: 3331, 2986, 1644, 1542, 1424, 1243, 1011 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.45–8.41 (m, 2 H, H2, H6), 7.40 (d, *J* = 5 Hz, 1 H, H5), 7.17 (d, *J* = 9 Hz, 2 H, H2$_{Ar}$, H6$_{Ar}$), 6.81 (d, *J* = 9 Hz, 2 H, H3$_{Ar}$, H5$_{Ar}$), 7.87 (app. t, exch., *J* = 6 Hz, 1 H, NH), 5.96 (br, 1 H, C*H*OH), 4.48 (dd, *J* = 6, 15 Hz, 1 H, CH_2), 4.38 (d, *J* = 6 Hz, 1 H, OH), 4.13 (dd, *J* = 6, 15 Hz, 1 H, CH_2), 3.73 (s, 3 H, OCH_3), 1.03 [s, 9 H, C(CH_3)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.5 (s, C=O), 159.6 (s, C4$_{Ar}$), 150.0 (d, C2), 147.6 (d, C6), 146.0 (s, C4), 133.8 (s, C1$_{Ar}$), 131.6 (s, C3), 128.4 (d, C2$_{Ar}$/C6$_{Ar}$), 122.4 (d, C5), 114.3 (d, C2$_{Ar}$/C6$_{Ar}$), 72.1 (d, CHOH), 55.3 (q, OCH_3), 38.6 [s, *C*(CH_3)$_3$], 38.4 (t, CH_2), 27.4 [q, C(*C*H_3)$_3$].

MS (EI): *m*/*z* (%) = 327 (10, $[M - H]^+$), 267 (7), 223 (100), 118 (98), 77 (94).

HRMS (EI): *m*/*z* $[M - H]^+$ calcd for $C_{19}H_{23}N_2O_3$: 327.1709; found: 327.1707.

***N*-[(4-{[4-(Dimethylamino)phenyl](hydroxy)methyl}pyridin-3-yl)methyl]pivalamide (17)**
Reagents: *t*-BuLi, 4-(dimethylamino)benzaldehyde; colourless oil; yield: 0.58 g (1.7 mmol, 85%).

FT-IR: 3328, 2977, 1640, 1589, 1429, 1248, 1015 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.37 (d, *J* = 5 Hz, 1 H, H6), 8.31 (s, 1 H, H2), 7.43 (d, *J* = 5 Hz, 1 H, H5), 7.06 (d, *J* = 9 Hz, 2 H, H2$_{Ar}$, H6$_{Ar}$), 6.59 (d, *J* = 9 Hz, 2 H, H3$_{Ar}$, H5$_{Ar}$), 5.84 (app. t, exch., *J* = 6 Hz, 1 H, NH), 5.83 (s, 1 H, C*H*OH), 4.45 (dd, *J* = 6, 15 Hz, 1 H, CH_2), 4.37 (br, 1 H, OH), 4.02 (dd, *J* = 6, 15 Hz, 1 H, CH_2), 2.84 [s, 6 H, N(CH_3)$_2$], 0.95 [s, 9 H, C(CH_3)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.2 (s, C=O), 150.6 (d, C2), 150.4 (s, C4$_{Ar}$), 149.0 (d, C6), 135.5 (s, C3), 131.2 (s, C1$_{Ar}$), 128.2 (d, C2$_{Ar}$/C6$_{Ar}$), 121.5 (d, C5), 112.6 (d, C3$_{Ar}$/C5$_{Ar}$), 72.2 (d, CHOH), 40.4 [q, N(CH_3)$_2$], 38.5 [s, *C*(CH_3)$_3$], 38.4 (t, CH_2), 27.4 [q, C(*C*H_3)$_3$].

MS (ES$^+$): *m*/*z* (%) = 341 (100, $[M]^+$), 329 (58), 193 (10).

HRMS (ES$^+$): *m*/*z* $[M]^+$ calcd for $C_{20}H_{27}N_3O_2$: 341.2103; found: 341.2107.

***N*-[(4-Ethylpyridin-3-yl)methyl]pivalamide (18)**
Reagents: *t*-BuLi, EtI; colourless oil; yield: 0.40 g (1.8 mmol, 90%).

FT-IR: 3338, 2967, 1642, 1529, 1208, 1010 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.38–8.28 (m, 2 H, H2, H6), 7.11 (d, *J* = 5 Hz, 1 H, H5), 5.86 (br, exch., 1 H, NH), 4.43 (d, *J* = 6 Hz, 2 H, CH_2), 2.62 (q, *J* = 7 Hz, 2 H, CH_3CH_2), 1.18 (t, *J* = 7 Hz, 3 H, CH_3CH_2), 1.15 [s, 9 H, C(CH_3)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.1 (s, C=O), 152.1 (s, C4), 149.2 (d, C2), 148.8 (d, C6), 131.9 (s, C3), 123.5 (d, C5), 38.79 [s, *C*(CH_3)$_3$], 38.77 (t, CH_2), 27.6 [q, C(*C*H_3)$_3$], 24.7 (t, CH_3CH_2), 14.0 (q, CH_3CH_2).

MS (EI): *m*/*z* (%) = 220 (42, $[M]^+$), 163 (14), 135 (15), 120 (59), 107 (20), 83 (100), 77 (10), 57 (41).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{20}N_2O$: 220.1576; found: 220.1574.

***N*-[(1-Hydroxycyclohexyl)(pyridin-3-yl)methyl]pivalamide (19)**
Reagents: LDA, cyclohexanone; colourless oil; yield: 0.44 g (1.5 mmol, 75%).

FT-IR: 3351, 2962, 1642, 1560, 1421, 1333, 1209, 1019 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.55 (s, 1 H, H2), 8.40 (br, 1 H, H6), 7.60 (d, *J* = 8 Hz, 1 H, H4), 7.21 (br, exch., 1 H, OH), 6.75 (d, *J* = 8 Hz, 1 H, H5), 6.58 (br, exch., 1 H, NH), 4.77 (d, *J* = 8 Hz, 1 H, CH), 1.80–1.50 (m, 10 H, 10 H$_{Cy}$), 1.14 [s, 9 H, C(CH_3)$_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.5 (s, C=O), 149.2 (d, C2), 148.3 (d, C6), 136.3 (s, C3), 133.1 (d, C4), 123.3 (d, C5), 73.2 (s, C1$_{Cy}$), 63.4 (d, CH), 40.8 [s, *C*(CH_3)$_3$], 35.9, 35.4 (2 t, C2$_{Cy}$/C6$_{Cy}$), 27.5 [q, C(*C*H_3)$_3$], 25.3 (t, C4$_{Cy}$), 21.9, 21.5 (2 t, C3$_{Cy}$/C5$_{Cy}$).

MS (EI): *m*/*z* (%) = 290 (33, $[M]^+$), 217 (55), 192 (100), 171 (91), 150 (55), 107 (99), 93 (96), 83 (98).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{17}H_{26}N_2O_2$: 290.1994; found: 290.1993.

***tert*-Butyl *N*-{[4-(Hydroxydiphenylmethyl)pyridin-3-yl]methyl}carbamate (20)**
Reagents: *t*-BuLi, benzophenone; white solid; yield: 0.69 g (1.77 mmol, 88%); mp 215–217 °C.

FT-IR: 3447, 2980, 1692, 1591, 1445, 1369, 1214, 1076 cm^{-1}.

^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.45 (s, 1 H, H2), 8.34 (d, *J* = 5 Hz, 1 H, H6), 7.38 (s, exch., 1 H, OH), 7.36 (app. t, *J* = 8 Hz, 4 H, H3$_{Ph}$/H5$_{Ph}$), 7.31 (t, *J* = 8 Hz, 2 H, H4$_{Ph}$), 7.19 (d, *J* = 8 Hz, 4 H, H2$_{Ph}$/H6$_{Ph}$), 6.89 (br, exch., 1 H, NH), 6.54 (d, *J* = 5 Hz, 1 H, H5), 4.07 (d, *J* = 6 Hz, 2 H, CH_2), 1.38 [s, 9 H, C(CH_3)$_3$].

^{13}C NMR (125 MHz, DMSO-d_6): δ = 156.2 (s, C=O), 152.9 (s, C1$_{Ph}$), 150.0 (d, C2), 148.1 (d, C6), 146.2 (s, C4), 134.4 (s, C3), 128.4 (d, 2 C3$_{Ph}$/C5$_{Ph}$), 127.9 (d, 2 C2$_{Ph}$/C6$_{Ph}$), 127.7 (d, 2 C4$_{Ph}$), 123.4 (d, C5), 81.7 (s, COH), 78.5 [s, *C*(CH_3)$_3$], 40.6 (t, CH_2), 28.7 [q, C(*C*H_3)$_3$].

MS (APCI): *m*/*z* (%) = 432 (5, $[M + MeCN + H]^+$), 391 (100, $[M + H]^+$), 115 (8).

HRMS (APCI): *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{27}N_2O_3$: 391.2022; found: 391.2017.

Anal. Calcd for $C_{24}H_{26}N_2O_3$: C, 73.82; H, 6.71. Found: C, 73.7; H, 6.8.

***tert*-Butyl *N*-{[4-(1-Hydroxy-1-phenylethyl)pyridin-3-yl]methyl}carbamate (21)**
Reagents: *t*-BuLi, acetophenone; colourless oil; yield: 0.53 g (1.62 mmol, 81%).

FT-IR: 3352, 2979, 1686, 1581, 1449, 1391, 1267, 1166 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.36 (s, 1 H, H2), 8.30 (d, *J* = 5 Hz, 1 H, H6), 7.79 (d, *J* = 8 Hz, 2 H, $H2_{Ph}/H6_{Ph}$), 7.49–7.27 (m, 4 H, $H3_{Ph}/H5_{Ph}/H4_{Ph}$, OH), 7.07 (d, *J* = 5 Hz, 1 H, H5), 6.20 (br, exch., 1 H, NH), 4.17 (app. d, *J* = 6 Hz, 2 H, CH_2), 2.42 (s, 3 H, CH_3), 1.31 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.1 (s, C=O), 148.7 (d, C2), 148.1 (d, C6), 136.9 (s, C4), 135.1 (s, $C1_{Ph}$), 134.9 (s, C3), 132.9 (d, $C4_{Ph}$), 128.4 (d, $C3_{Ph}/C5_{Ph}$), 128.1 (d, $C2_{Ph}/C6_{Ph}$), 123.3 (d, C5), 79.1 (s, COH), 77.4 [s, $C(CH_3)_3$], 41.9 (t, CH_2), 28.2 [q, $C(CH_3)_3$], 26.3 (q, CH_3).

MS (EI): *m*/*z* (%) = 313 (5, $[M - CH_3]^+$), 271 (10), 210 (60), 195 (100), 180 (60), 133 (85), 83 (95).

HRMS: *m*/*z* $[M - CH_3]^+$ calcd for $C_{18}H_{21}N_2O_3$: 313.1552; found: 313.1555.

tert-Butyl _N_-{[4-(1-Hydroxycyclohexyl)pyridin-3-yl]methyl}carbamate (22)

Reagents: *t*-BuLi, cyclohexanone; colourless oil; yield: 0.49 g (1.6 mmol, 80%).

FT-IR: 3347, 2979, 1700, 1579, 1449, 1367, 1280, 1252, 1167 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.36 (s, 1 H, H2), 8.32 (d, *J* = 5 Hz, 1 H, H6), 7.50 (d, *J* = 5 Hz, 1 H, H5), 7.11 (br, exch., 1 H, OH), 5.98 (br, exch., 1 H, NH), 4.18 (d, *J* = 6 Hz, 2 H, CH_2), 2.25–1.44 (m, 10 H, 10 H_{Cy}), 1.32 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.1 (s, C=O), 148.7 (d, C2), 148.2 (d, C6), 135.2 (s, C4), 134.9 (s, C3), 123.4 (d, C5), 79.4 [s, $C(CH_3)_3$], 71.9 (s, $C1_{Cy}$), 43.7 (t, CH_2), 38.0 (t, $C2_{Cy}/C6_{Cy}$), 28.2 [q, $C(CH_3)_3$], 25.8 (t, $C4_{Cy}$), 21.5 (t, $C3_{Cy}/C5_{Cy}$).

MS (ES): *m*/*z* (%) = 307 (100, $[M + H]^+$), 250 (43), 209 (68), 194 (35), 153 (20).

HRMS: *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{27}N_2O_3$: 307.2022; found: 307.2014.

tert-Butyl _N_-({4-[Hydroxy(phenyl)methyl]pyridin-3-yl}methyl}carbamate (23)

Reagents: *t*-BuLi, benzaldehyde; colourless oil; yield: 0.53 g (1.69 mmol, 84%).

FT-IR: 3344, 2969, 1688, 1580, 1454, 1388, 1265, 1161 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.36 (d, *J* = 5 Hz, 1 H, H6), 8.33 (s, 1 H, H2), 7.29–7.19 (m, 7 H, H5, H_{Ph}, OH), 5.96 (s, 1 H, C*H*OH), 4.97 (br, exch., 1 H, NH), 4.27 (br d, *J* = 14 Hz, 1 H, CH_2), 4.06 (dd, *J* = 5, 14 Hz, 1 H, CH_2), 1.33 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.8 (s, C=O), 150.5 (d, C2), 149.1 (d, C6), 150.3 (s, C4), 141.7 (s, $C1_{Ph}$), 131.6 (s, C3), 128.8 (d, $C3_{Ph}/C5_{Ph}$), 128.0 (d, $C4_{Ph}$), 127.0 (d, $C2_{Ph}/C6_{Ph}$), 122.0 (d, C5), 80.0 [s, $C(CH_3)_3$], 72.2 (d, CHOH), 39.6 (t, CH_2), 28.4 [q, $C(CH_3)_3$].

MS (APCI): *m*/*z* (%) = 315 (100, $[M + H]^+$), 259 (22), 209 (9), 153 (7).

HRMS (APCI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{23}N_2O_3$: 315.1709; found: 315.1702.

_N′_-{[4-(Hydroxydiphenylmethyl)pyridin-3-yl]methyl}-_N_,_N_-dimethylurea (24)

Reagents: *t*-BuLi, benzophenone; white solid; yield: 0.48 g (1.32 mmol, 66%); mp 219–221 °C.

FT-IR: 3583, 2965, 1638, 1524, 1476, 1376, 1218, 1028 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.58 (s, 1 H, H2), 8.26 (d, *J* = 5 Hz, 1 H, H6), 7.33–7.28 (m, 11 H, 10 H_{Ph}, OH), 6.59 (d, *J* = 5 Hz, 1 H, H5), 5.38 (t, *J* = 6 Hz, exch., 1 H, NH), 4.12 (d, *J* = 6 Hz, 2 H, CH_2), 2.82 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.6 (s, C=O), 153.6 (s, C4), 152.1 (d, C2), 147.8 (d, C6), 146.7 (s, $C1_{Ph}$), 134.6 (s, C3), 128.1 (d, $C3_{Ph}/C5_{Ph}$), 127.6 (d, $C2_{Ph}/C6_{Ph}$), 127.2 (d, $C4_{Ph}$), 124.0 (d, C5), 81.3 (s, COH), 41.1 (t, CH_2), 36.2 [q, $N(CH_3)_2$].

MS (EI): *m*/*z* (%) = 361 (10, $[M]^+$), 343 (70).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{22}H_{23}N_3O_2$: 361.1790; found: 361.1790.

_N′_-[(4-_tert_-Butylpyridin-3-yl)methyl]-_N_,_N_-dimethylurea (25)

Byproduct from the preparation of **24**; colourless oil; yield: 0.024 g (0.10 mmol, 5%).

FT-IR: 3341, 2972, 1632, 1521, 1469, 1230, 1023 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.56 (s, 1 H, H2), 8.33 (d, *J* = 5 Hz, 1 H, H6), 7.28 (d, *J* = 5 Hz, 1 H, H5), 4.85 (br, exch., 1 H, NH), 4.62 (d, *J* = 5 Hz, 2 H, CH_2), 2.85 [s, 6 H, $N(CH_3)_2$] 1.38 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.4 (s, C4), 156.7 (s, C=O), 150.2 (d, C2), 147.0 (d, C6), 128.5 (s, C3), 121.4 (d, C5), 41.7 (t, CH_2), 36.5 [q, $N(CH_3)_2$], 36.1 [s, $C(CH_3)_3$], 30.7 [q, $C(CH_3)_3$].

MS (ES^+): *m*/*z* (%) = 493 (21, $[2 M + Na]^+$), 299 (49, $[M + MeCN + Na]^+$), 236 (100, $[M + H]^+$), 191 (5).

HRMS (ES^+): *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{22}N_3O$: 236.1763; found: 236.1765.

tert-Butyl _N_-[2-Hydroxy-2,2-diphenyl-1-(pyridin-3-yl)ethyl]carbamate (26)

Reagents: LDA, benzophenone; colourless oil; yield: 0.55 g (1.4 mmol, 70%).

FT-IR: 3357, 2931, 1693, 1541, 1423, 1374, 1224, 1061 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.21 (br, 2 H, H2/H6), 7.48 (d, *J* = 8 Hz, 2 H, $H2_{Ph}/H6_{Ph}$), 7.30 (t, *J* = 8 Hz, 2 H, $H3_{Ph}/H5_{Ph}$), 7.26–7.20 (m, 3 H, H4, $H2_{Ph}/H6_{Ph}$), 7.07–7.00 (m, 5 H, H5, $H3_{Ph}/H5_{Ph}$, 2 $H4_{Ph}$), 6.94 (br, exch., 1 H, OH), 5.66 (d, *J* = 8 Hz, 1 H, CH), 5.59 (br, exch., 1 H, NH), 1.27 [s, 9 H, $C(CH_3)_3$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.9 (s, C=O), 149.9 (d, C2), 148.1 (d, C6), 144.3, 144.0 (2 s, 2 $C1_{Ph}$), 141.3 (s, C3), 138.0 (d, C4), 128.5, 128.1 (2 d, 2 $C3_{Ph}/C5_{Ph}$), 127.5, 127.2 (2 d, 2 $C4_{Ph}$), 126.3, 125.7 (2 d, 2 $C2_{Ph}/C6_{Ph}$), 122.0 (d, C5), 90.4 (s, COH), 81.4 [s, $C(CH_3)_3$], 58.5 (d, CH), 28.3 [q, $C(CH_3)_3$].

MS (APCI): *m*/*z* (%) = 391 (8, $[M + H]^+$), 193 (8), 124 (28), 83 (100).

HRMS (APCI): *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{27}N_2O_3$: 391.2022; found: 391.2016.

_N′_-[2-Hydroxy-2,2-diphenyl-1-(pyridin-3-yl)ethyl]-_N_,_N_-dimethylurea (27)

Reagents: LDA, benzophenone; white solid; yield: 0.38 g (1.05 mmol, 52%); mp 203–205 °C.

FT-IR: 3366, 2927, 1623, 1522, 1448, 1380, 1214, 1064 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.54 (s, 1 H, H2), 7.96 (d, *J* = 5 Hz, 1 H, H6), 7.52 (d, *J* = 8 Hz, 1 H, H4), 7.31–6.86 (m, 11 H, 10 H_{Ph}, OH), 7.01 (dd, *J* = 5, 8 Hz, 1 H, H5), 5.82 (br, exch., 1 H, NH), 5.76 (d, *J* = 6 Hz, 1 H, CH), 2.64 [s, 6 H, $N(CH_3)_2$].

^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.4 (s, C=O), 149.2 (d, C2), 146.6 (d, C6), 144.7, 144.4 (2 s, 2 $C1_{Ph}$), 137.8 (s, C3), 136.4 (d, C4), 128.5, 128.0 (2 d, 2 $C3_{Ph}/C5_{Ph}$), 127.3, 127.1 (2 d, 2 $C4_{Ph}$), 126.5, 125.8 (2 d, 2 $C2_{Ph}/C6_{Ph}$), 122.6 (d, C5), 80.9 (s, COH), 59.4 (d, CH), 36.1 [q, $N(CH_3)_2$].

MS (APCI): *m*/*z* (%) = 362 (100, $[M + H]^+$), 120 (65).

HRMS (APCI): *m*/*z* $[M + H]^+$ calcd for $C_{22}H_{24}N_3O_2$: 362.1869; found: 362.1874.

1,1-Diphenyl-2,3-dihydro-1*H*-pyrrolo[3,4-*c*]pyridine (28)

A mixture of TFAA (0.50 mL, 3.60 mmol), **20** (0.50 g, 1.28 mmol), and CH_2Cl_2 (10 mL) was heated under reflux for 12 h. The mixture was quenched with H_2O (10 mL). The organic layer was separated,

washed with aq sat. $NaHCO_3$ (10 mL) and H_2O (2 × 10 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The crude product was purified by flash column chromatography (silica gel, EtOAc–hexane, 1:3) to give **28** (0.21 g, 0.77 mmol, 60%) as a white solid; mp 206–208 °C.

FT-IR: 3054, 2985, 1589, 1422, 1265 cm^{-1}.

^1H NMR (500 MHz, DMSO-d_6): δ = 8.48 (s, 1 H, H4), 8.39 (d, J = 5 Hz, 1 H, H6), 7.36–7.18 (m, 10 H, 10 H_{Ph}), 6.47 (d, J = 5 Hz, 1 H, H7), 5.25 (br, exch., 1 H, NH), 3.43 (d, J = 6 Hz, 2 H, CH_2).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 156.1 (s, C7a), 152.7 (d, C4), 149.5 (d, C6), 146.7 (s, C3a), 134.2 (s, 2 $C1_{Ph}$), 128.4 (d, 2 $C3_{Ph}$/$C5_{Ph}$), 127.8 (d, 2 $C2_{Ph}$/$C6_{Ph}$), 127.5 (d, 2 $C4_{Ph}$), 123.7 (d, C7), 81.5 (s, C1), 41.9 (t, CH_2).

MS (APCI): m/z (%) = 314 (25, $[M + MeCN + H]^+$), 273 (100, $[M + H]^+$), 256 (13).

HRMS (APCI): m/z $[M + H]^+$ calcd for $C_{19}H_{17}N_2$: 273.1392; found: 273.1393.

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