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SIDE-CHAIN LITHIATION OF 2- AND 4-SUBSTITUTED PYRIDINES: SYNTHESIS OF MORE COMPLEX SUBSTITUTED PYRIDINES

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Abstract — Lithiation of pyridines substituted in the 2- and 4-positions by acylaminomethyl groups, namely of the corresponding *N*-(pyridinylmethyl)pivalamides, *N*′-(pyridinylmethyl)-*N*,*N*-dimethylureas and *tert*-butyl *N*-pyridinylmethylcarbamates, with two mole equivalents of *t*-BuLi in anhydrous THF at -78 °C takes place on the nitrogen and on the methylene group of the side-chain. The lithium reagents thus obtained react with a variety of electrophiles to give the corresponding side-chain substituted derivatives in high yields.

INTRODUCTION

Simple electrophilic aromatic substitution reactions often lead to various isomers and require the use of stoichiometric quantities of non-reusable activators under forcing conditions.[1] It is well recognized that organolithium reagents can play an important role in development of more regioselective processes for production of specific products.[2,3] Indeed, lithiation of aromatics or heterocycles followed by reaction of the lithium reagent thus obtained with an electrophile is one of the most efficient approaches for synthesis of substituted and/or modified derivatives.[4-6]

We have developed several efficient lithiation procedures for preparation of various substituted aromatics and heteroaromatics that might be difficult to prepare by other means.[7] As part of such studies we have successfully lithiated and substituted various *N*-(substituted benzyl)pivalamides and *N*′-(substituted benzyl)-*N*-*N*-dimethylureas selectively using *n*-BuLi or *t*-BuLi in THF[8-10] and with appropriate modifications these processes enable the production of substituted isoindoline and isoquinoline

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Dedicated to Professor Ei-ichi Negishi on the occasion of his 77th birthday.

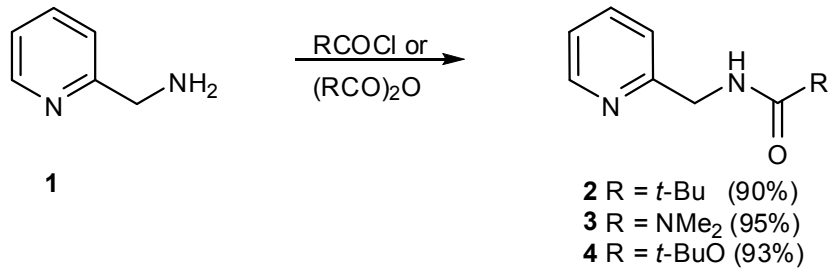
derivatives.[11-13] During the course of these investigations we have found that the site of lithiation depends on a number of factors, including the lithium reagent, the nature of the aromatic substituent(s) and the temperature.[8-10] For example, lithiation of *N*-benzylpivalamide with *t*-BuLi at 0 or -78 °C took place competitively on the ring (2-position) and on the CH_2 of the side-chain,[9] while for *N*′-benzyl-*N,N*-dimethylurea lithiation took place only on the 2-position using *t*-BuLi at -78 °C.[9] Others showed that lithiation of *tert*-butyl *N*-benzylcarbamate using *sec*-BuLi at -78 °C in the presence of tetramethylethylenediamine (TMEDA) took place selectively on the side-chain.[14]

Presumably, *ortho*-lithiation is encouraged by complexation of the organolithium reagent to the deprotonated benzylaminocarbonyl compound, which brings the organolithium reagent into close proximity with the *ortho*-proton to be removed. This would be favoured by a strongly nucleophilic carbonyl oxygen atom. By contrast, removal of the side-chain proton, which is adjacent to the benzylamino nitrogen, would be encouraged by a more strongly electron-withdrawn carbonyl group, which would in turn result in lower nucleophilicity of the carbonyl oxygen atom. The trend in carbonyl oxygen nucleophilicity, as judged by carbonyl group stretching frequencies (typically *ca*. <1609-1646 cm^{-1} for ureas, 1635-1670 cm^{-1} for amides and 1698-1725 cm^{-1} for carbamates, with lower frequencies arising from a greater contribution of the dipolar carbonyl group resonance structure, C^{+}—O^{-}), is indeed consistent with a shift from *ortho*-lithiation for the urea to side-chain lithiation for the carbamate.

It was of interest to see whether lithiation of analogous heteroaromatics would take place in a similar manner. Therefore, we decided to attempt lithiation and substitution of *N*-(pyridinylmethyl)pivalamides, *N*′-(pyridinylmethyl)-*N*,*N*-dimethylureas and *tert*-butyl *N*-pyridinylmethylcarbamates. We now report the successful side-chain lithiation and substitution of the 2- and 4-substituted pyridine derivatives.

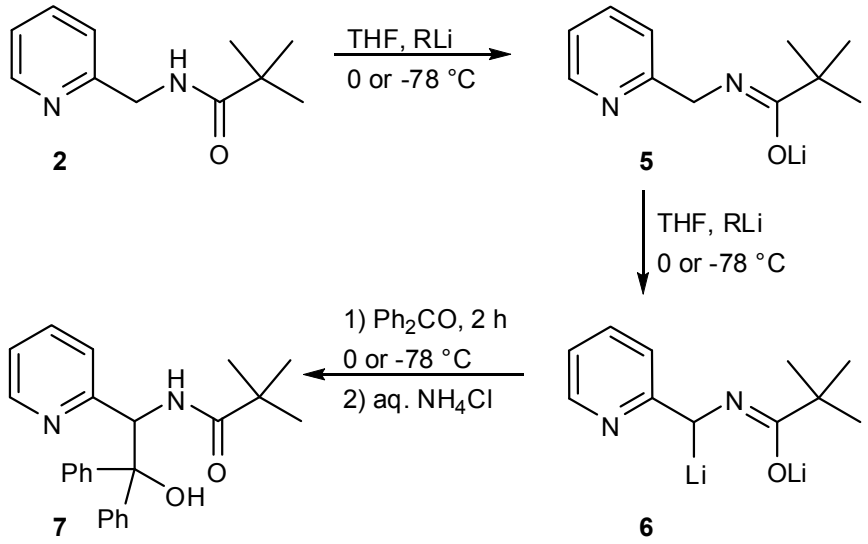
RESULTS AND DISCUSSION

The first stage of this study required the synthesis of various 2-substituted pyridines **2-4** (Scheme 1), based on literature procedures for analogous compounds.[7n,10] Reaction of 2-aminomethylpyridine (**1**; Scheme 1) with pivaloyl chloride in dichloromethane (DCM) in the presence of triethylamine (TEA) at 0 °C for 1 h gave *N*-(pyridin-2-ylmethyl)pivalamide (**2**) in 90% yield. Similarly, reaction of **1** (Scheme 1) with dimethylcarbamoyl chloride in DCM in the presence of TEA at 0 °C for 1 h gave *N*′-(pyridin-2-ylmethyl)-*N*,*N*-dimethylurea (**3**) in 95% yield. Also, reaction of **1** with di-*tert*-butyl dicarbonate in the presence of $InCl_3$ at room temperature gave *tert*-butyl *N*-(pyridin-2-ylmethyl)carbamate (**4**) in 93% yield.



Scheme 1. Synthesis of 2-substituted pyridines **2-4**.

Treatment of *N*-(pyridin-2-ylmethyl)pivalamide (**2**) with *n*-butyllithium (*n*-BuLi; 2.2 mole equivalents) in anhydrous THF at -78 °C for 2 h, followed by addition of benzophenone and stirring at -78 °C for a further 2 h, gave **7** (Scheme 2), which was isolated by column chromatography in 79% yield. This implies that **2** underwent lithiation on nitrogen to form the monolithium reagent **5** followed by lithiation on the CH_2 of the side chain to produce the dilithium reagent **6** (Scheme 2).



Scheme 2. Synthesis of **7** under different reaction conditions

Several experiments were conducted in which the reaction conditions and the lithium reagent were varied in an attempt to optimise the yield of **7** or to see what effect the lithium reagent would have on the site of lithiation (Table 1). Compound **7** (79-87%) was the only product identified under any of the reaction conditions tried. Although the differences were not great, the yield of **7** was highest (87%) when *t*-BuLi was used at -78 °C (Table 1; Entry 2).

Table 1. Yields of **7** formed by lithiation of **2** using 2.2 equivalents of RLi according to Scheme 2

Entry	RLi	Temperature (ºC)	Yield (%)[a]
1	*n*-BuLi	-78	79
2	*t*-BuLi	-78	87
3	*t*-BuLi	0	84
4	LDA	-78	81

[a] Yield of isolated product after purification by column chromatography.

The results showed that with a variety of reagents and under different conditions lithiation occurred selectively on the side chain, which is in contrast to the case of *N*-benzylpivalamide, where side-chain lithiation and ring lithiation were competitive.[9] It was therefore of interest to compare the lithiation reactions of **3** (the dimethylurea analogue) and **4** (the *tert*-butyl carbamate analogue).

Treatment of urea derivative **3** under the conditions that were found to be optimal for the pivalamide **2**, first with *t*-BuLi and then with benzophenone, gave the side-chain substituted product **8** in 90% isolated yield. There was no evidence for production of the ring-substituted product and most of the remainder of the material was recovered **3**. This is therefore an even sharper contrast with the *N*-benzyl analogue.

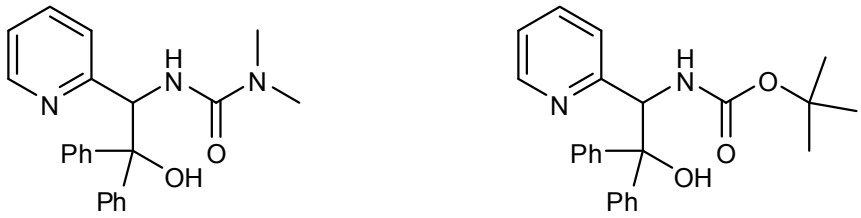
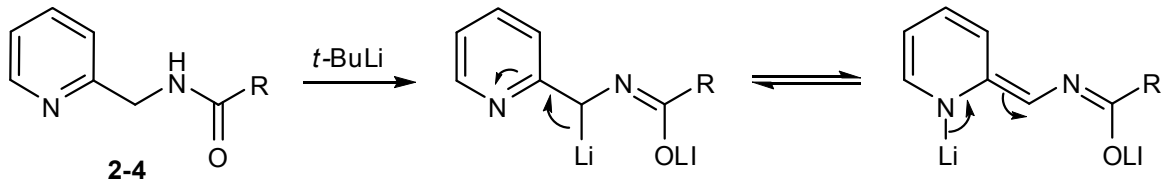


Figure 1. Structures of compounds **8** and **9**.

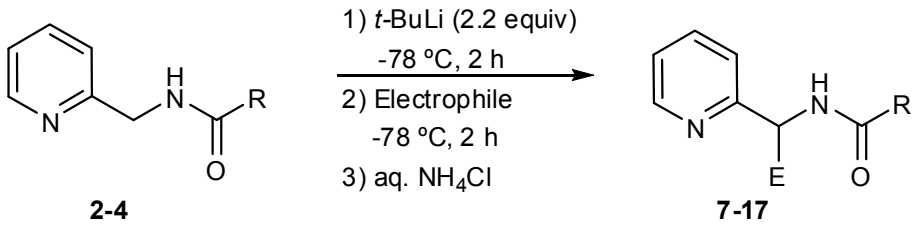
Corresponding treatment of the carbamate derivative **4** also gave side-chain substituted product **9**, isolated in 85% yield. Therefore, all three derivatives (pivalamide, urea and carbamate) gave side-chain substitution products.

Presumably, the highly selective side-chain lithiation of compounds **2-4** arises because of higher acidity of the CH_2 protons as a result of the ring nitrogen. The dilithium intermediates resulting from lithiation at the CH_2 group would be stabilised by the ring nitrogen (Scheme 3), while the nucleophilicity of the carbonyl oxygen would be reduced. As a result, lithiation on the CH_2 group in the 2-substiuted pyridines **2-4** would be favoured over ring lithiation to a greater extent than for the simple benzyl analogues. The 4-substituted derivatives would be expected to behave similarly.



Scheme 3. Resonance forms obtained from **2-4** on reaction with *t*-BuLi.

It was of interest to see whether the intermediate organolithium species could be trapped successfully with other electrophiles. We therefore conducted a series of reactions in which lithiation of 2-substituted pyridines **2-4** with *t*-BuLi at -78 °C for 2 h was followed by reactions with various electrophiles at -78 °C for 2 h to give the corresponding substituted derivatives **7-17** (Scheme 4). The yields (Table 2) of pure products were high and the process was general to produce various side-chain substituted derivatives.



Scheme 4. Synthesis of **7-17** *via* lithiation and substitution of **2-4**.

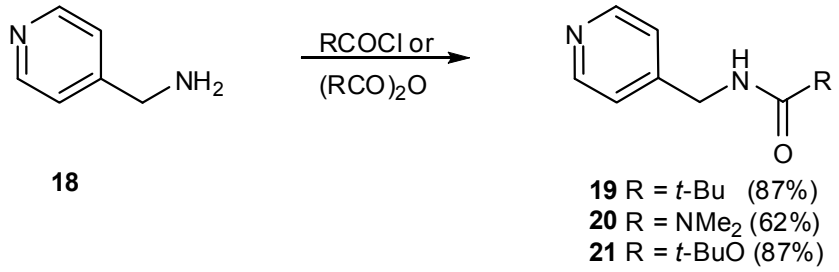
Table 2. Synthesis of **7-17** according to Scheme 4

Product	R	Electrophile	E	Yield (%)[a]
7	*t*-Bu	Ph_2CO	$Ph_2C(OH)$	87
8	NMe_2	Ph_2CO	$Ph_2C(OH)$	90
9	*t*-BuO	Ph_2CO	$Ph_2C(OH)$	85
10	*t*-Bu	Me_2CO	$Me_2C(OH)$	84
11	*t*-BuO	Me_2CO	$Me_2C(OH)$	79
12	*t*-Bu	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	86
13	*t*-BuO	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	80
14	*t*-Bu	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	75
15	*t*-BuO	4-$MeOC_6H_4CHO$	4-$MeOC_6H_4CH(OH)$	71
16	*t*-Bu	EtI	Et	86
17	NMe_2	EtI	Et	99

[a] Yield of isolated product after purification by column chromatography.

The structures of the products were verified by their spectroscopic properties. The ^{13}C NMR signals of compounds **7-9** showed that the two phenyl groups originating from the benzophenone used as electrophile appeared separately, verifying that they were diastereotopic. Similarly, the two methyl groups originating from acetone in compounds **10** and **11** appeared separately in their ^{13}C NMR spectra. Also, the ^{1}H NMR signals of compounds **16** and **17** showed that the signals of the two hydrogens of the CH_2 unit of the ethyl group appeared separately. The NMR spectra of compounds **14** and **15** showed that they were mixtures of two diastereoisomers in the ratios of *ca*. 4:5 and 5:6, respectively.

It was of interest to know whether selectivity for side chain lithiation would be as marked for the *N*-pyridin-4-ylmethyl analogues **19-21** as it was for the *N*-pyridin-2-ylmethyl compounds. Therefore, *N*-(pyridin-4-ylmethyl)pivalamide (**19**), *N'*-(pyridin-4-ylmethyl)-*N*,*N*-dimethylurea (**20**) and *tert*-butyl *N*-(pyridin-4-ylmethyl)carbamate (**21**) were synthesised from 4-aminomethylpyridine (**18**) as shown in Scheme 5, based mostly on the same general literature procedures used for syntheses of **2-4**.[10]

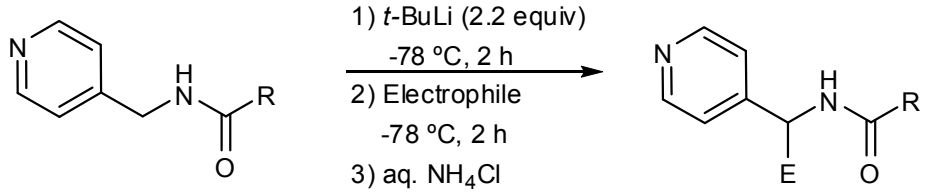


18

19 R = *t*-Bu (87%)
20 R = NMe_2 (62%)
21 R = *t*-BuO (87%)

Scheme 5. Synthesis of 4-substituted pyridines **19-21**.

Lithiation of 4-substituted pyridines **19-21** using in *t*-BuLi under conditions similar to those used for the lithiation of 2-substituted pyridines **2-4**, followed by reactions with various electrophiles, gave the corresponding substituted derivatives **22-29** (Scheme 6) in good yields (Table 2). Table 2 showed that the process represented in Scheme 6 was general to produce various substituted derivatives.



19-21 **22-29**

Scheme 6. Synthesis of **22-29** *via* lithiation and substitution of **19-21**.

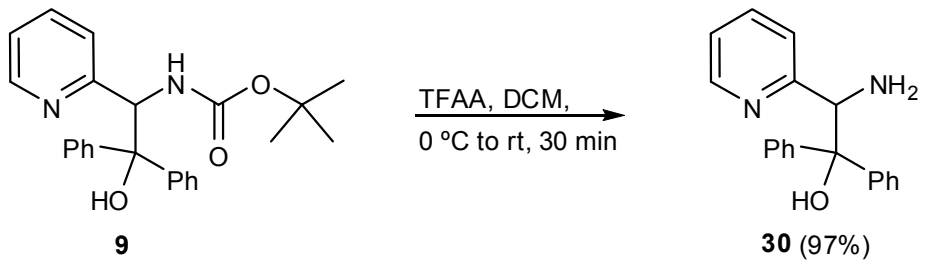
Table 3. Synthesis of **22-29** according to Scheme 6

Product	R	Electrophile	E	Yield (%)[a]
22	*t*-Bu	Ph_2CO	$Ph_2C(OH)$	76
23	NMe_2	Ph_2CO	$Ph_2C(OH)$	77
24	*t*-BuO	Ph_2CO	$Ph_2C(OH)$	77
25	*t*-Bu	EtI	Et	80
26	NMe_2	EtI	Et	80
27	*t*-BuO	EtI	Et	74
28	*t*-Bu	PhCHO	PhCH(OH)	79
29	*t*-BuO	$(CH_2)_5CO$	$(CH_2)_5C(OH)$	74

[a] Yield of isolated product after purification by column chromatography.

Again, the structures were confirmed by spectra, which showed features similar to those of the 2-substituted analogues. The NMR spectra showed that compound **28** was a mixture of two diastereoisomers in the ratio of *ca*. 5:7.

In order to render the synthetic approach described in this report even more valuable, it would be useful if the directed metalating group could be removed to reveal a free amino group available for further reaction without the ring system itself being damaged. Hydrolysis of such groups is known in the literature and can be carried out under acidic or basic conditions.[7a,15] Indeed, hydrolysis of compound **7**, as an example, took place smoothly on treatment with trifluoroacetic acid (TFAA) at room temperature in DCM for 30 minutes to produce the corresponding amino derivative **30** in 97% yield (Scheme 7).



9 **30** (97%)

Scheme 7. Synthesis of 2-(1-amino-2-hydroxy-2,2-diphenylethyl)pyridine (**30**).

CONCLUSION

A simple, efficient and general procedure that allows side-chain lithiation and substitution of 2- and 4-substituted *N*-(pyridinylmethyl)pivalamides, *N*′-(pyridinylmethyl)-*N*,*N*-dimethylureas and *tert*-butyl *N*-pyridinylmethylcarbamates provides easy access to various side-chain (methylene) substituted derivatives in high yields. The results show a significant change in site of lithiation compared to the

corresponding benzyl products, where ring lithiation is the norm for the urea derivative and competitive lithiation on both the side chain and the ring occurs for the pivalamide derivative. We continue to explore the facets of such lithiation reactions.

EXPERIMENTAL

GENERAL METHODS: 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 for ^{1}H and 125 MHz for ^{13}C measurements. Chemical shifts δ are reported in parts per million (ppm) relative to TMS and coupling constants J are in Hz and have been rounded to the nearest whole number (s = singlet, d = doublet, t = triplet, m = multiplet, br. = broad, app. = apparent (*i.e*. appears as a signal with the specified multiplicity even though not all coupled protons are equivalent), exch. = exchangeable with D_2O). ^{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. Low-resolution mass spectra 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 spectrometer and were measured either as thin films (for liquids) or as KBr discs (for 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 micron). Alkyllithiums were obtained from Aldrich Chemical Company and alkyllithiums were estimated prior to use by the method of Watson and Eastham.[16] Other chemicals were obtained from Aldrich Chemical Company and used without further purification. THF was distilled from sodium benzophenone ketyl. Other solvents were purified by standard procedures.[17,18]

Synthesis of *N*-(pyridin-2-ylmethyl)pivalamide (2): To a cooled solution (0 °C) of 2-(aminomethyl)pyridine (**1**; 4.33 g, 40.0 mmol) and TEA (8.0 mL) in dichloromethane (DCM, 100 mL) pivaloyl chloride (5.43 g, 45.0 mmol) was slowly added in a drop-wise manner over 30 min. The reaction mixture was stirred at 0 °C for 1 h and then poured onto H_2O (100 mL). The organic layer was separated, washed with H_2O (2 x 50 mL), dried ($MgSO_4$) and the solvent was removed under reduced pressure to give pure product **2 (**6.89 g, 35.8 mmol, 90%) as oil (Lit.,[19] oil). IR (FT): 3347, 2965, 1652, 1531, 1479, 1253, 1226, 1149 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.45 (d, J = 5 Hz, 1 H, H-6), 7.58 (m, 1 H, H-4), 7.16 (d, J = 8 Hz, 1H, H-3), 7.11 (m, 1 H, H-5), 7.04 (br., exch., 1 H, NH), 4.45 (d, J = 6 Hz, 2 H, CH_2), 1.18 [s, 9 H, $C(CH_3)_3$]. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.5 (s, C=O), 156.7 (s, C-2), 148.9 (d, C-6),

136.7 (d, C-4), 122.2 (d, C-3), 122.0 (d, C-5), 44.4 (t, CH_2), 38.7 [s, *C*$(CH_3)_3$], 27.6 [q, C(*C*$H_3)_3$]. MS (EI): *m/z* (%) = 192 (10, $[M]^+$), 135 (100), 107 (30), 92 (85), 79 (13), 65 (20), 57 (13). HRMS (EI): *m/z* $[M^+]$ calcd for $C_{11}H_{16}N_2O$: 192.1263; found: 192.1256.

Synthesis of *N'*-(pyridin-2-ylmethyl)-*N*,*N*-dimethylurea (3): A stirred mixture of **1** (5.00 g, 46.3 mmol), dimethylcarbamoyl chloride (5.40 g, 50.3 mmol) and TEA (8 mL) in DCM (20 mL) was stirred at room temperature for 1 h. The mixture was poured onto H_2O (50 mL) and extracted with DCM (2 x 50 mL). The organic layer was separated, washed with H_2O (2 x 25 mL) and dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the residue obtained was purified by column chromatography (Et_2O) to give pure product **3** (7.87 g, 44.0 mmol, 95%) as oil. IR (FT): 3343, 2925, 1635, 1534, 1474, 1232, 1049 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.41 (d, *J* = 5 Hz, 1 H, H-6), 7.55 (app. t, *J* = 8 Hz, 1 H, H-4), 7.20 (d, *J* = 8 Hz, 1 H, H-3), 7.06 (dd, *J* = 5, 8 Hz, 1 H, H-5), 5.96 (t, *J* = 5 Hz, exch., 1 H, NH), 4.42 (d, *J* = 5 Hz, 2 H, CH_2), 2.85 [s, 6 H, N$(CH_3)_2$]. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.5 (s, C=O), 158.0 (s, C-2), 148.0 (d, C-6), 137.5 (d, C-4), 122.6 (d, C-3), 122.3 (d, C-5), 45.6 (t, CH_2), 36.2 [q, N$(CH_3)_2$]. MS (APCI): *m/z* (%) = 180 (100, $[MH]^+$), 135 (85). HRMS (APCI): *m/z* $[MH]^+$ calcd for $C_9H_{14}N_3O$: 180.1137; found: 180.1139.

Syntheses of *tert*-butyl pyridin-2-ylmethylcarbamate (4): Di-*tert*-butyl dicarbonate (8.74 g, 40.0 mmol) was slowly added to a stirred mixture of **1** (4.33 g, 40.0 mmol) and $InCl_3$ (0.110 g, 0.050 mmol) at r.t. and the reaction was monitored by TLC until completion. The mixture was diluted in EtOAc (20 mL) and washed with H_2O (2 × 10 mL), aq. $NaHCO_3$ (2 ×10 mL) and H_2O (2 ×10 mL), respectively. The organic layer was dried ($MgSO_4$) and the solvent was removed under reduced pressure to give pure product **4** (7.74 g, 37.2 mmol, 93%) as oil (Lit.,[20] oil). IR (FT): 3343, 2977, 1712, 1571, 1477, 1275, 1249, 1171 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.48 (d, *J* = 5 Hz, 1 H, H-6), 7.59 (m, 1 H, H-4), 7.23 (d, *J* = 8 Hz, 1 H, H-3), 7.11 (m, 1 H, H-5), 5.82 (br., exch., 1 H, NH), 4.40 (d, *J* = 5 Hz, 2 H, CH_2), 1.41 [s, 9 H, C$(CH_3)_3$]. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.6 (s, C=O), 156.0 (s, C-2), 149.0 (d, C-6), 136.6 (d, C-4), 122.1 (d, C-3), 121.6 (d, C-5), 79.3 [s, *C*$(CH_3)_3$], 45.7 (t, CH_2), 28.4 [q, C(*C*$H_3)_3$]. MS (CI): *m/z* (%) = 209 (5, $[MH]^+$), 153 (100), 135 (95), 109 (98), 92 (95), 80 (83), 57 (93). HRMS (CI): *m/z* $[MH]^+$ calcd for $C_{11}H_{17}N_2O_2$: 209.1290; found: 209.1293.

Substituted pyridines 7-17; General Procedure: A solution of *t*-BuLi in pentane (2.60 mL, 1.7 M, 4.42 mmol) was added to a cold (-78 °C), stirred solution of **2-4** (2.00 mmol) in anhydrous THF (20 mL) under N_2. The mixture was stirred at -78 °C for 2 h to ensure the complete formation of the dilithium reagent, after which electrophile (2.20 mmol), in anhydrous THF (8 ml) if solid, otherwise neat, was added. The mixture was stirred for 2 h at -78 °C, then the cooling bath was removed and the mixture allowed to warm

to r.t. It was then diluted with Et_2O (10 mL) and quenched with sat. aq. NH_4Cl (10 mL). The organic layer was separated, washed with H_2O (2 x 10 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The crude product obtained was purified by column chromatography (silica gel; EtOAc–hexane; 1:3) to give pure product (**7-17**, Table 2).

***N*-(2-Hydroxy-2,2-diphenyl-1-(pyridin-2-yl)ethyl)pivalamide (7):** 0.65 g (1.74 mmol, 87%). Mp 183-185 ºC. IR (FT): 3447, 2967, 1650, 1573, 1423, 1366, 1215, 1061 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.27 (d, *J* = 5 Hz, 1 H, H-6), 7.73 (br., exch., 1 H, OH), 7.55 (d, *J* = 8 Hz, 4 H, H-2/H-6 of 2 Ph), 7.50 (m, 1 H, H-4), 7.37 (d, *J* = 8 Hz, 1 H, H-3), 7.22 (t, *J* = 8 Hz, 2 H, H-4 of 2 Ph), 7.05 (appt. t, *J* = 8 Hz, 4 H, H-3/H-5 of 2 Ph), 6.92 (m, 1 H, H-5), 6.77 (d, *J* = 8 Hz, exch., 1 H, NH), 6.00 (d, *J* = 8 Hz, 1 H, CH), 1.28 [s, 9 H, $C(CH_3)_3$]. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.8 (s, C=O), 159.8 (s, C-2), 147.9 (d, C-6), 145.7, 144.5 (2 s, C-1 of Ph), 137.5 (d, C-4), 128.2, 128.0 (2 d, C-3/C-5 of Ph), 126.8 (d, C-3), 126.4 (d, C-5), 125.5, 125.3 (2 d, C-2/C-6 of Ph), 122.66, 122.65 (2 d, C-4 of Ph), 80.8 (s, COH), 56.7 (d, CH), 38.5 [s, $C(CH_3)_3$], 27.1 [q, $C(CH_3)_3$]. MS (APCI): *m/z* (%) = 375 (100, $[MH]^+$), 357 (50). HRMS (APCI): *m/z* $[MH]^+$ calcd for $C_{24}H_{27}N_2O_2$: 375.2073; found: 375.2062.

***N'*-(2-Hydroxy-2,2-diphenyl-1-(pyridin-2-yl)ethyl)-*N*,*N*-dimethylurea (8):** 0.65 g (1.80 mmol, 90%). Mp 197-199 ºC. IR (FT): 3459, 2924, 1652, 1569, 1450, 1371, 1267, 1094 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.37 (d, *J* = 5 Hz, 1 H, H-6), 7.67-6.99 (m, 14 H, 2 Ph, H-4/H-3/H-5 and OH), 5.98 (d, *J* = 8 Hz, 1 H, CH), 5.79 (d, *J* = 8 Hz, exch., 1 H, NH), 2.74 [s, 6 H, $N(CH_3)_2$]. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.5 (s, C=O), 157.6 (s, C-2), 147.6 (d, C-6), 145.8, 144.7 (2 s, C-1 of Ph), 137.5 (d, C-4), 128.2, 127.9 (2 d, C-3/C-5 of Ph), 126.7 (d, C-3), 126.28, 126.31 (2 d, C-4 of Ph), 125.6, 125.5 (2 d, C-2/C-6 of Ph), 122.5 (d, C-5), 80.9 (s, COH), 58.4 (d, CH), 36.0 [q, $N(CH_3)_2$]. MS (APCI): *m/z* (%) = 362 (100, $[MH]^+$), 344 (50). HRMS (APCI): *m/z* $[MH]^+$ calcd for $C_{22}H_{24}N_3O_2$: 362.1869; found: 362.1879.

***tert*-Butyl 2-hydroxy-2,2-diphenyl-1-(pyridin-2-yl)ethylcarbamate (9):** 0.66 g (1.69 mmol, 85%). Mp 155-157 ºC. IR (FT): 3273, 2981, 1701, 1573, 1449, 1304, 1216, 1160 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.23 (d, *J* = 5 Hz, 1 H, H-6), 7.58 (d, *J* = 8 Hz, 2 H, H-2/H-6 of Ph), 7.40 (m, 1 H, H-4), 7.31 (d, *J* = 8 Hz, 2 H, H-2/H-6 of other Ph), 7.24 (appt. t, *J* = 8 Hz, 2 H, H-3/H-5 of Ph), 7.18 (d, *J* = 5 Hz, 1 H, H-3), 7.09 (t, *J* = 8 Hz, 1 H, H-4 of Ph), 6.99 appt. (t, *J* = 8 Hz, 2 H, H-3/H-5 of other Ph), 6.95 (m, 1 H, H-5), 6.88 (t, *J* = 8 Hz, 1 H, H-4 of other Ph), 5.75 (br., exch., 1 H, NH), 5.72 (s, 1 H, CH), 5.70 (br., exch., 1 H, OH), 1.19 [s, 9 H, $C(CH_3)_3$]. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.0 (s, C-2), 155.5 (s, C=O), 148.0 (d, C-6), 145.9, 144.5 (2 s, C-1 of Ph), 137.3 (d, C-4), 128.1, 127.9 (2 d, C-3/C-5 of Ph), 126.7, 126.3 (2 d, C-4 of Ph), 125.7, 125.5 (2 d, C-2/C-6 of Ph), 125.1 (d, C-3), 122.6 (d, C-5), 80.9 (s, COH), 79.5 [s, $C(CH_3)_3$], 58.1 (d, CH), 28.2 [q, $C(CH_3)_3$]. MS (APCI): *m/z* (%) = 391 (100, $[MH]^+$). HRMS (APCI): *m/z*

$[MH]^+$ calcd for $C_{24}H_{27}N_2O_3$: 391.2022; found: 391.2032.

***N*-(2-Hydroxy-2-methyl-1-(pyridin-2-yl)propyl)pivalamide (10):** 0.42 g (1.68 mmol, 84%). Mp 112-114 ºC. IR (FT): 3446, 2982, 1648, 1572, 1438, 1278, 1212, 1145 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.52 (d, *J* = 5 Hz, 1 H, H-6), 7.68 (m, 1 H, H-4), 7.37 (d, *J* = 8 Hz, 1H, H-3), 7.24 (m, 1 H, H-5), 6.91 (d, *J* = 6 Hz, exch., 1 H, NH), 5.42 (br., exch., 1 H, OH), 4.85 (d, *J* = 6 Hz, 1 H, CH), 1.28 (s, 3 H, CH_3), 1.18 [s, 9 H, $C(CH_3)_3$], 1.05 (s, 3 H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.2 (s, C=O), 159.8 (s, C-2), 148.7 (d, C-6), 137.2 (d, C-4), 124.7 (d, C-3), 122.8 (d, C-5), 73.0 (s, COH), 59.2 (d, CH), 38.8 [s, $C(CH_3)_3$], 27.8 (q, CH_3), 27.5 [q, $C(CH_3)_3$], 26.7 (q, CH_3). MS (APCI): *m/z* (%) = 251 (100, $[MH]^+$), 233 (20). HRMS (APCI): *m/z* $[MH]^+$ calcd for $C_{14}H_{23}N_2O_2$: 251.1760; found: 251.1762.

***tert*-Butyl 2-hydroxy-2-methyl-1-(pyridin-2-yl)propylcarbamate (11):** 0.42 g (1.58 mmol, 79%). Mp 156-158 ºC. IR (FT): 3437, 2981, 1704, 1570, 1367, 1274, 1216, 1164 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.44 (d, *J* = 5 Hz, 1 H, H-6), 7.61 (m, 1 H, H-4), 7.27 (d, *J* = 8 Hz, 1 H, H-3), 7.15 (m, 1 H, H-5), 5.67 (d, *J* = 8 Hz, exch., 1 H, NH), 5.25 (br., exch., 1 H, OH), 4.47 (d, *J* = 8 Hz, 1 H, CH), 1.33 [s, 9 H, $C(CH_3)_3$], 1.25 (s, 3 H, CH_3), 0.96 (s, 3 H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.2 (s, C-2), 155.8 (s, C=O), 148.8 (d, C-6), 137.2 (d, C-4), 124.4 (d, C-3), 122.8 (d, C-5), 79.4 [s, $C(CH_3)_3$], 73.0 (s, COH), 60.7 (d, CH), 28.4 [q, $C(CH_3)_3$], 27.9 (q, CH_3), 26.5 (q, CH_3). MS (APCI): *m/z* (%) = 267 (100, $[MH]^+$), 211 (65), 193 (17). HRMS (APCI): *m/z* $[MH]^+$ calcd for $C_{14}H_{23}N_2O_3$: 267.1709; found: 267.1696.

***N*-((1-Hydroxycyclohexyl)(pyridin-2-yl)methyl)pivalamide (12):** 0.50 g (1.72 mmol, 86%). Mp 170-172 ºC. IR (FT): 3447, 2938, 1652, 1572, 1458, 1366, 1215, 1105 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.51 (d, *J* = 5 Hz, 1 H, H-6), 7.67 (m, 1 H, H-4), 7.38 (d, *J* = 8 Hz, 1H, H-3), 7.22 (m, 1 H, H-5), 6.85 (d, *J* = 8 Hz, exch., 1 H, NH), 5.27 (br., exch., 1 H, OH), 4.94 (d, *J* = 8 Hz, 1 H, CH), 1.86-1.38 (m, 10 H, cyclohexyl), 1.17 [s, 9 H, $C(CH_3)_3$]. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.1 (s, C=O), 159.8 (s, C-2), 148.8 (d, C-6), 137.2 (d, C-4), 124.8 (d, C-3), 122.7 (d, C-5), 73.8 (s, C-1 of cyclohexyl), 57.8 (d, CH), 38.8 [s, $C(CH_3)_3$], 38.7, 36.2 (2 t, C-2/C-6 of cyclohexyl), 27.5 [q, $C(CH_3)_3$], 25.6 (t, C-4 of cyclohexyl), 21.82, 21.77 (2 t, C-3/C-5 of cyclohexyl). MS (EI): *m/z* (%) = 290 (10, $[M]^+$), 272 (35), 239 (55), 205 (25), 192 (100), 159 (100), 107 (95), 92 (93), 57 (50). HRMS: *m/z* $[M]^+$ calcd for $C_{17}H_{26}N_2O_2$: 290.1994; found: 290.1995.

***tert*-Butyl (1-hydroxycyclohexyl)(pyridin-2-yl)methylcarbamate (13):** 0.49 g (1.60 mmol, 80%). Mp 178-180 ºC. IR (FT): 3438, 2981, 1704, 1572, 1440, 1309, 1214, 1166 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.54 (d, *J* = 5 Hz, 1 H, H-6), 7.67 (m, 1 H, H-4), 7.34 (d, *J* = 8 Hz, 1 H, H-3), 7.24 (m, 1 H, H-5), 5.72 (d, *J* = 8 Hz, exch., 1 H, NH), 5.18 (s, exch., 1 H, OH), 4.64 (d, *J* = 8 Hz, 1 H, CH), 1.83-1.31 (m, 10 H,

cyclohexyl), 1.40 [s, 9 H, $C(CH_3)_3$]. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 160.2 (s, C-2), 155.8 (s, C=O), 148.9 (d, C-6), 137.2 (d, C-4), 124.5 (d, C-3), 122.7 (d, C-5), 79.3 [s, *C*$(CH_3)_3$], 73.9 (s, C-1 of cyclohexyl), 59.3 (d, CH), 36.2, 34.5 (2 t, C-2/C-6 of cyclohexyl), 28.4 [q, C(*C*$H_3)_3$], 25.7 (t, C-4 of cyclohexyl), 21.83, 21.81 (2 t, C-3/C-5 of cyclohexyl). MS (APCI): *m/z* (%) = 307 (100, $[MH]^+$), 251 (20). HRMS: *m/z* $[MH]^+$ calcd for $C_{17}H_{27}N_2O_3$: 307.2022; found: 307.2025. Anal. Calcd for $C_{17}H_{26}N_2O_3$: C, 66.64; H, 8.55; N, 9.14. Found: C, 66.4; H, 8.5; N, 9.1.

***N*-(2-Hydroxy-2-(4-methoxyphenyl)-1-(pyridin-2-yl)ethyl)pivalamide (14):** 0.49 g (1.49 mmol, 75%). Mp 149-151 ºC. The product was a mixture of diastereoisomers, which were not separated; however, many individual NMR signals could be identified, allowing the ratio to be determined; **14a**/**14b** = 4:5. IR (FT): 3370, 2965, 1651, 1571, 1473, 1248, 1215, 1173 cm^{-1}. MS (APCI): *m/z* (%) = 329 (100, $[MH]^+$), 311 (95), 115 (8). HRMS (APCI): *m/z* $[MH]^+$ calcd for $C_{19}H_{25}N_2O_3$: 329.1865; found: 329.1857. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.54 (d, *J* = 5 Hz, H-6 of **14a**), 8.48 (d, *J* = 5 Hz, H-6 of **14b**), 7.66-7.62 (m, H-4 of both), 7.40 (br., exch., NH of both), 7.25-7.23 (m, H-3 of both), 7.20-7.18 (m, H-5 of both), 6.93 (d, *J* = 9 Hz, H-2/H-6 of 4-methoxyphenyl for **14b**), 6.85 (d, *J* = 9 Hz, H-2/H-6 of 4-methoxyphenyl of **14a**), 6.74-6.72 (m, H-3/H-5 of 4-methoxyphenyl of both), 5.22-5.21 (m, C*H*OH of both), 5.20-5.19 (m, C*H*NH of both), 5.14 (br., exch., OH of both), 3.80 (s, OCH_3 of **14a**), 3.76 (s, OCH_3 of **14b**), 1.21 [s, $C(CH_3)_3$ of **14b**], 1.12 [s, $C(CH_3)_3$ of **14a**]. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 179.4 (s, C=O of **14b**), 178.9 (s, C=O of **14a**), 159.2 (s, C-4 of 4-methoxyphenyl of **14b**), 159.0 (s, C-4 of 4-methoxyphenyl of **14a**), 158.8 (s, C-2 of **14a**), 156.9 (s, C-2 of **14b**), 148.4 (d, C-6 of **14a**), 148.2 (d, C-6 of **14b**), 137.1 (d, C-4 of **14a**), 137.0 (d, C-4 of **14b**), 132.8 (s, C-1 of 4-methoxyphenyl of **14a**), 132.5 (s, C-1 of 4-methoxyphenyl of **14b**), 127.3 (d, C-2/C-6 of 4-methoxyphenyl of **14a**), 127.2 (d, C-2/C-6 of 4-methoxyphenyl of **14b**), 124.1 (d, C-3 of **14a**), 123.9 (d, C-3 of **14b**), 122.9 (d, C-5 of **14a**), 122.8 (d, C-5 of **14b**), 113.5 (d, C-3/C-5 of 4-methoxyphenyl of **14a**), 113.2 (d, C-3/C-5 of 4-methoxyphenyl of **14b**), 77.8 (d, CHOH of **14b**), 75.4 (d, CHOH of **14a**), 58.7 (d, CHNH of **14b**), 58.1 (d, CHNH of **14a**), 55.3 (s, OCH_3 of **14a**), 55.2 (s, OCH_3 of **14b**), 38.8 [s, *C*$(CH_3)_3$ of **14b**], 38.7 [s, *C*$(CH_3)_3$ of **14a**], 27.5 [q, C(*C*$H_3)_3$ of **14b**], 27.4 [q, C(*C*$H_3)_3$ of **14a**].

***tert*-Butyl 2-hydroxy-2-(4-methoxyphenyl)-1-(pyridin-2-yl)ethylcarbamate (15):** 0.49 g (1.42 mmol, 71%). Mp 99-101 ºC. The product was a mixture of diastereoisomers, which were not separated; however, many individual NMR signals could be identified, allowing the ratio to be calculated; **15a**/**15b** = 5:6. IR (FT): 3436, 2981, 1704, 1572, 1438, 1365, 1216, 1171 cm^{-1}. MS (APCI): *m/z* (%) = 345 (100, $[MH]^+$), 289 (10), 271 (10). HRMS (APCI): *m/z* $[MH]^+$ calcd for $C_{19}H_{25}N_2O_4$: 345.1814; found: 345.1809. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.56 (d, *J* = 5 Hz, H-6 of **15b**), 8.50 (d, *J* = 5 Hz, H-6 of **15a**), 7.64-7.60 (m, H-4 of both), 7.25-7.23 (m, H-3 of both), 7.20-7.18 (m, H-5 of both), 7.04-7.01 (m, H-2/H-6 of

4-methoxyphenyl of both), 6.86 (d, *J* = 8 Hz, H-3/H-5 of 4-methoxyphenyl of **15a**), 6.75 (d, *J* = 8 Hz, H-3/H-5 of 4-methoxyphenyl of **15b**), 6.00 (br., exch., NH of both), 5.79-5.77 (m, C*H*OH of both), 5.16-5.12 (m, C*H*NH of both), 4.92 (br., exch., OH of both), 3.80 (s, OCH_3 of **15b**), 3.76 (s, OCH_3 of **15a**), 1.44 [s, $C(CH_3)_3$ of **15a**], 1.37 [s, $C(CH_3)_3$ of **15b**]. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 159.5 (s, C-4 of 4-methoxyphenyl of **15a**), 159.0 (s, C-4 of 4-methoxyphenyl of **15b**), 157.8 (s, C-2 of both), 156.1 (s, C=O of **15b**), 155.8 (s, C=O of **15a**), 148.7 (d, C-6 of **15b**), 148.3 (d, C-6 of **15a**), 137.0 (d, C-4 of **15a**), 136.9 (d, C-4 of **15b**), 133.1 (s, C-1 of 4-methoxyphenyl of **15a**), 132.8 (s, C-1 of 4-methoxyphenyl of **15b**), 127.5 (d, C-2/C-6 of 4-methoxyphenyl of **15b**), 127.2 (d, C-2/C-6 of 4-methoxyphenyl of **15a**), 124.1 (d, C-3 of **15a**), 123.6 (d, C-3 of **15b**), 122.8 (d, C-5 of both), 113.6 (d, C-3/C-5 of 4-methoxyphenyl of **15b**), 113.4 (d, C-3/C-5 of 4-methoxyphenyl of **15a**), 79.8 (d, CHOH of **15a**), 79.7 (d, CHOH of **15b**), 75.5 [s, *C*$(CH_3)_3$ of both], 59.6 (d, CHNH of **15a**), 59.2 (d, CHNH of **15b**), 55.3 (s, OCH_3 of **15b**), 55.2 (s, OCH_3 of **15a**), 28.34 [q, C(*C*$H_3)_3$ of **15a**], 28.29 [q, C(*C*$H_3)_3$ of **15b**].

***N*-(1-(Pyridin-2-yl)propyl)pivalamide (16):** 0.38 g (1.72 mmol, 86%). Mp 58-60 ºC. IR (FT): 3433, 2968, 1649, 1571, 1507, 1304, 1215, 1150 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.48 (d, *J* = 5 Hz, 1 H, H-6), 7.56 (m, 1 H, H-4), 7.14 (d, *J* = 8 Hz, 1 H, H-3), 7.11 (m, 1 H, H-5), 6.99 (br., exch., 1 H, NH), 4.90 (m, 1 H, CH), 1.81 (m, 1 H, C$H_a$$CH_b$), 1.72 (m, 1 H, CH_aCH_b), 1.16 [s, 9 H, $C(CH_3)_3$], 0.74 (appt. t, *J* = 7 Hz, 3 H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.9 (s, C=O), 160.1 (s, C-2), 149.1 (d, C-6), 136.5 (d, C-4), 122.4 (d, C-3), 122.2 (d, C-5), 54.7 (d, CH), 38.8 [s, *C*$(CH_3)_3$], 29.4 (t, CH_2), 27.6 [q, C(*C*$H_3)_3$], 9.8 (q, CH_3). MS (EI): *m/z* (%) = 220 (12, $[M]^+$), 191 (30), 163 (65), 135 (20), 120 (100), 107 (43), 92 (20), 57 (35). HRMS (EI): *m/z* $[M]^+$ calcd for $C_{13}H_{20}N_2O$: 220.1576; found: 220.1574.

***N'*-(1-(Pyridin-2-yl)propyl)-*N*,*N*-dimethylurea (17):** 0.41 g (1.98 mmol, 99%) as oil. IR (FT): 3419, 2986, 1642, 1594, 1472, 1381, 1265, 1150 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.26 (d, *J* = 5 Hz, 1 H, H-6), 7.35 (m, 1 H, H-4), 6.96 (d, *J* = 8 Hz, 1 H, H-3), 6.87 (m, 1 H, H-5), 5.50 (br., exch., 1 H, NH), 4.64 (m, 1 H, CH), 2.66 [s, 6 H, $N(CH_3)_2$], 1.58 (m, 1 H, C$H_a$$CH_b$), 1.42 (m, 1 H, CH_aCH_b), 0.57 (appt. t, *J* = 7 Hz, 3 H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 161.1 (s, C=O), 158.0 (s, C-2), 149.0 (d, C-6), 136.4 (d, C-4), 122.4 (d, C-3), 122.0 (d, C-5), 56.3 (d, CH), 36.1 [q, $N(CH_3)_2$], 29.9 (t, CH_2), 9.9 (q, CH_3). MS (APCI): *m/z* (%) = 208 (100, $[MH]^+$), 163 (60). HRMS (APCI): *m/z* $[MH]^+$ calcd for $C_{11}H_{18}N_3O$: 208.1450; found: 208.1455.

***N*-(Pyridin-4-ylmethyl)pivalamide (19):** The procedure was identical to that described for the synthesis of **2** but 4-aminomethylpyridine (**18**) was used instead of **1** to produce **19** (6.70 g, 34.9 mmol, 87%). Mp 88-90 ºC (Lit.,[19] Mp 63 ºC). IR (FT): 3370, 2968, 1660, 1563, 1480, 1366, 1216, 1068 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.38 (d, *J* = 5 Hz, 2 H, H-2 and H-6), 7.03 (d, *J* = 5, 2 H, H-3 and H-5), 6.91 (br.,

exch., 1 H, NH), 4.30 (d, J = 6 Hz, 2 H, CH_2), 1.14 [s, 9 H, $C(CH_3)_3$]. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.9 (s, C=O), 149.6 (d, C-2/C-6), 148.4 (s, C-4), 122.0 (d, C-3/C-5), 42.1 (t, CH_2), 38.7 [s, $C(CH_3)_3$], 27.5 [q, $C(CH_3)_3$]. MS (EI): *m/z* (%) = 192 (100, $[M]^+$), 150 (20), 93 (55). HRMS (EI): *m/z* $[M]^+$ calcd for $C_{11}H_{16}N_2O$: 192.1263; found: 192.1254.

***N'*-(Pyridin-4-ylmethyl)-*N*,*N*-dimethylurea (20):** A stirred mixture of **18** (4.33 g, 40.0 mmol), dimethylcarbamoyl chloride (4.84 g, 45.0 mmol) and TEA (8 mL) in methanol (20 mL) was heated under reflux for 1 h. The mixture was poured onto H_2O (50 mL) and extracted with DCM (2 x 50 mL). The organic layer was separated, washed with H_2O (2 x 25 mL) and dried ($MgSO_4$). The solvent was evaporated under reduced pressure and the residue obtained was purified by column chromatography (DCM) to give **20** (4.45 g, 42.8 mmol, 62%) as oil. IR (FT): 3337, 2929, 1635, 1537, 1417, 1359, 1233, 1066 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.45 (d, J = 5 Hz, 2 H, H-2 and H-6), 7.16 (d, J = 5 Hz, 2 H, H-3 and H-5), 4.80 (br., exch., 1 H, NH), 4.38 (d, J = 6 Hz, 2 H, CH_2), 2.89 [s, 6 H, $N(CH_3)_2$]. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.2 (s, C=O), 149.8 (d, C-2/C-6), 149.1 (s, C-4), 122.2 (d, C-3/C-5), 43.8 (t, CH_2), 36.3 [q, $N(CH_3)_2$]. APCI–MS: *m/z* (%) = 180 (100, $[MH]^+$), 131 (20). HRMS: *m/z* $[M]^+$ calcd for $C_9H_{14}N_3O$: 180.1137; found: 180.1145.

***tert*-Butyl pyridin-4-ylmethylcarbamate (21):** The procedure was identical to that described for the synthesis of **4** but **18** was used instead of **1** to produce **21** (7.24 g, 34.8 mmol, 87%). Mp 89-91 (Lit.,[21] Mp 89-90 ºC). IR (FT): 3219, 2971, 1707, 1565, 1454, 1278, 1217, 1167 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.50 (d, J = 5 Hz, 2 H, H-2 and H-6), 7.18 (d, J = 5 Hz, 2 H, H-3 and H-5), 5.44 (br., exch., 1 H, NH), 4.30 (d, J = 6 Hz, 2 H, CH_2), 1.45 [s, 9 H, $C(CH_3)_3$]. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 156.0 (s, C=O), 149.8 (d, C-2/C-6), 148.4 (s, C-4), 122.0 (d, C-3/C-5), 79.9 [s, $C(CH_3)_3$], 43.4 (t, CH_2), 28.3 [q, $C(CH_3)_3$]. MS (EI): *m/z* (%) = 208 (10, $[M]^+$), 152 (90), 134 (70), 107 (85), 92 (38), 80 (100), 57 (90). HRMS: *m/z* $[M]^+$ calcd for $C_{11}H_{16}N_2O_2$: 208.1212; found: 208.1209.

Substituted pyridines 22-29; General Procedure: The procedure was identical to that described for the lithiation and substitution of 2-substituted pyridines **2-4** except that **19-21** (2.00 mmol) were used instead. The crude product obtained was purified by column chromatography (silica gel; EtOAc–hexane; 1:3) to give pure products **22-29** (Table 3).

***N*-(2-Hydroxy-2,2-diphenyl-1-(pyridin-4-yl)ethyl)pivalamide (22):** 0.57 g (1.52 mmol, 76%). Mp 218-220 ºC. IR (FT): 3455, 2967, 1658, 1510, 1419, 1367, 1214, 1059 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.17 (d, J = 5 Hz, 2 H, H-2 and H-6), 7.53 (d, J = 8 Hz, 2 H, H-2/H-6 of Ph), 7.37 (appt. t, J = 8 Hz, 2 H, H-3/H-5 of Ph), 7.30-7.17 (m, 6 H, H-2/H-3/H-5/H-6 of other Ph and H-4 of both Ph), 6.95 (d, J = 5

Hz, 2 H, H-3 and H-5), 6.76 (d, *J* = 8 Hz, exch., 1 H, NH), 5.93 (d, *J* = 8 Hz, 1 H, CH), 3.96 (br., exch., 1 H, OH), 1.00 [s, 9 H, $C(CH_3)_3$]. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 177.6 (s, C=O), 148.8 (d, C-2 and C-6), 147.8 (s, C-4), 144.1, 143.7 (2 s, C-1 of Ph), 128.5, 128.2 (2 d, C-3/C-5 of Ph), 127.5, 127.4 (2 d, C-4 of Ph), 125.9, 125.7 (2 d, C-2/C-6 of Ph), 124.0 (d, C-3 and C-5), 80.9 (s, COH), 58.4 (d, CH), 38.6 [s, $C(CH_3)_3$], 27.1 [q, $C(CH_3)_3$]. MS (APCI): *m/z* (%) = 438 (20, $[M + MeCNNa]^+$), 375 (40, $[M + MeCNH]^+$), 375 (100, $[MH]^+$), 357 (5), 234 (60), 193 (94). HRMS (APCI): *m/z* $[MH]^+$ calcd for $C_{24}H_{27}N_2O_2$: 375.2073; found: 375.2075.

***N'*-(2-Hydroxy-2,2-diphenyl-1-(pyridin-4-yl)ethyl)-*N*,*N*-dimethylurea (23):** 0.55 g (1.54 mmol, 77%). Mp 204-206 ºC. IR (FT): 3329, 2917, 1630, 1510, 1419, 1367, 1275, 1059 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 8.22 (d, *J* = 6 Hz, 2 H, H-2 and H-6), 7.56 (d, *J* = 7.5 Hz, 2 H, H-2 and H-6 of Ph), 7.35 (appt. t, *J* = 7.5 Hz, 2 H, H-3 and H-5 of Ph), 7.23 (t, *J* = 7.5 Hz, 1 H, H-4 of Ph), 7.20 (d, *J* = 7.5 Hz, 2 H, H-2 and H-6 of other Ph), 7.11 (appt. t, *J* = 7.5 Hz, 2 H, H-3 and H-5 of other Ph), 7.05 (t, *J* = 7.5 Hz, 1 H, H-4 of other Ph), 6.90 (d, *J* = 6 Hz, 2 H, H-3 and H-5), 6.45 (d, *J* = 8.5 Hz, exch., 1 H, NH), 6.33 (s, exch., 1 H, OH), 5.77 (d, *J* = 8.5 Hz, 1 H, CH), 2.70 [s, 6 H, $N(CH_3)_2$]. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 157.5 (s, C=O), 150.1 (s, C-4), 148.5 (d, C-2 and C-6), 147.0, 145.4 (2 s, C-1 of Ph), 128.4, 127.9 (2 d, C-3/C-5 of Ph), 127.7, 126.7 (2 d, C-4 of Ph), 126.8, 126.2 (2 d, C-2/C-6 of Ph), (124.8 (d, C-3 and C-5), 80.0 (s, COH), 60.6 (d, CH), 36.4 [q, $N(CH_3)_2$]. MS (APCI): *m/z* (%) = 362 (20, $[MH]^+$), 344 (50), 262 (60), 180 (100). HRMS (APCI): *m/z* $[MH]^+$ calcd for $C_{22}H_{24}N_3O_2$: 362.1869; found: 362.1875.

***tert*-Butyl 2-hydroxy-2,2-diphenyl-1-(pyridin-4-yl)ethylcarbamate (24):** 0.60 g (1.54 mmol, 77%). Mp 178-180 ºC. IR (FT): 3583, 2939, 1709, 1523, 1475, 1363, 1212, 1063 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 8.25 (d, *J* = 5 Hz, 2 H, H-2 and H-6), 7.60-7.06 (m, 11 H, 2 Ph and OH), 7.06 (d, *J* = 5 Hz, 2 H, H-3 and H-5), 6.00 (br., exch., 1 H, NH), 5.61 (d, *J* = 8 Hz, 1 H, CH), 1.32 [s, 9 H, $C(CH_3)_3$]. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 155.4 (s, C=O), 149.1 (s, C-4), 148.6 (d, C-2 and C-6), 146.8, 144.8 (2 s, C-1 of Ph), 128.5, 128.0 (2 d, C-3/C-5 of Ph), 127.3, 126.8 (2 d, C-4 of Ph), 126.7, 126.1 (2 d, C-2/C-6 of Ph), 124.7 (d, C-3 and C-5), 80.2 (s, COH), 79.0 [s, $C(CH_3)_3$], 60.6 (d, CH), 28.6 [q, $C(CH_3)_3$]. MS (ES^+): *m/z* (%) = 432 (13, $[M + MeCNH]^+$), 391 (100, $[MH]^+$), 250 (40), 209 (60), 153 (10). HRMS (ES^+): *m/z* $[MH]^+$ calcd for $C_{24}H_{27}N_2O_3$: 391.2022; found: 391.2034.

***N*-(1-(Pyridin-4-yl)propyl))pivalamide (25):** 0.35 g (1.59 mmol, 80%). Mp 111-113 ºC. IR (FT): 3458, 2969, 1663, 1601, 1475, 1367, 1214, 1022 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.41 (d, *J* = 5 Hz, 2 H, H-2 and H-6), 7.03 (d, *J* = 5 Hz, 2 H, H-3 and H-5), 5.78 (d, *J* = 7 Hz, exch., 1 H, NH), 4.70 (m, 1 H, CH), 1.70 (m, 1 H, C*Ha*CHb), 1.61 (m, 1 H, CHaC*Hb*), 1.08 [s, 9 H, $C(CH_3)_3$], 0.80 (appt. t, *J* = 7 Hz, 3 H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.0 (s, C=O), 151.7 (s, C-4), 149.9 (d, C-2 and C-6), 121.5 (d,

C-3 and C-5), 53.7 (d, CH), 38.7 [s, *C*$(CH_3)_3$], 28.7 (t, CH_2), 27.6 [q, C(*C*$H_3)_3$], 10.5 (q, CH_3). MS (EI): *m/z* (%) = 220 (35, $[M]^+$), 191 (80), 120 (100), 106 (65), 65 (15). HRMS (EI): *m/z* $[M]^+$ calcd for $C_{13}H_{20}N_2O$: 220.1576; found: 220.1577.

***N'*-(1-(Pyridin-4-yl)propyl)-*N*,*N*-dimethylurea (26):** 0.33 g (1.60 mmol, 80%) as oil. IR (FT): 3333, 2965, 1636, 1529, 1462, 1383, 1251, 1066 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.46 (d, *J* = 6 Hz, 2 H, H-2 and H-6), 7.15 (d, *J* = 6 Hz, 2 H, H-3 and H-5), 4.67 (m, 1 H, CH), 4.61 (d, *J* = 7 Hz, exch., 1 H, NH), 2.86 [s, 6 H, N$(CH_3)_2$], 1.76–1.65 (m, 2 H, CH_2), 0.86 (appt. t, *J* = 7.5 Hz, 2 H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 157.6 (s, C=O), 153.0 (s, C-4), 149.7 (d, C-2 and C-6), 121.7 (d, C-3 and C-5), 55.4 (d, CH), 36.2 [q, N$(CH_3)_2$], 29.4 (t, CH_2), 10.6 (q, CH_3). MS (EI): *m/z* (%) = 207 (15, $[M]^+$), 178 (50), 162 (100), 147 (5), 133 (98), 118 (20), 105 (65), 92 (22), 78 (96), 72 (53), 65 (10). HRMS (EI): *m/z* $[M]^+$ calcd for $C_{11}H_{17}N_3O$: 207.1372; found: 207.1369.

***tert*-Butyl 1-(pyridin-4-yl)propylcarbamate (27):** 0.35 g (1.48 mmol, 74%). Mp 124-126 ºC. IR (FT): 3447, 2977, 1710, 1563, 1417, 1367, 1216, 1167 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.55 (d, *J* = 5 Hz, 2 H, H-2 and H-6), 7.20 (d, *J* = 5 Hz, 2 H, H-3 and H-5), 5.13 (d, *J* = 6 Hz, exch., 1 H, NH), 4.55 (m, 1 H, CH), 1.74 (m, 1 H, CH_aCH_b), 1.46 (m, 1 H, CH_aCH_b), 1.43 [s, 9 H, C$(CH_3)_3$], 0.92 (appt. t, *J* = 7 Hz, 3 H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.3 (s, C=O), 152.1 (s, C-4), 149.9 (d, C-2 and C-6), 121.5 (d, C-3 and C-5), 79.8 [s, *C*$(CH_3)_3$], 55.5 (d, CH), 29.3 (t, CH_2), 28.3 [q, C(*C*$H_3)_3$], 10.4 (q, CH_3). MS (CI): *m/z* (%) = 237 (5, $[MH]^+$), 207 (100), 163 (80), 151 (92), 133 (96), 120 (50), 107 (90), 78 (90), 57 (35). HRMS (CI): *m/z* $[MH]^+$ calcd for $C_{13}H_{21}N_2O_2$: 237.1603; found: 237.1614.

***N*-(2-Hydroxy-2-phenyl-1-(pyridin-4-yl)ethyl)pivalamide (28):** 0.47 g (1.58 mmol, 79%). Mp 133-135 ºC. The product was a mixture of diastereoisomers, which were not separated; however, many individual NMR signals could be identified, allowing the ratio to be determined; **28a**/**28b** = 5:7. IR (FT): 3451, 2967, 1657, 1562, 1417, 1365, 1214, 1061 cm^{-1}. MS (EI): *m/z* (%) = 280 (15, $[M - H_2O]^+$), 192 (100), 174 (90), 107 (90). HRMS (EI): *m/z* $[M - H_2O]^+$ calcd for $C_{18}H_{20}N_2O$: 280.1576; found: 280.1569. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.40 (d, *J* = 5 Hz, H-2 and H-6 of both diastereoisomers), 8.26 (d, *J* = 5 Hz, H-3 and H-5 of both), 7.36-7.10 (m, Ph of both), 6.72 (br., exch., NH of both), 5.11-5.08 (m, C*H*OH of both), 5.09-5.07 (m, C*H*NH of both), 5.02 (br., exch., OH of both), 1.18 [s, C$(CH_3)_3$ of **28a**], 1.09 [s, C$(CH_3)_3$ of **28b**]. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 178.4 (s, C=O of **28a**), 178.2 (s, C=O of **28b**), 150.4 (s, C-4 of **28a**), 150.2 (s, C-4 of **28b**), 148.8 (d, C-2 and C-6 of **28b**), 147.5 (d, C-2 and C-6 of **28a**), 140.9 (s, C-1 of Ph of **28a**), 139.8 (s, C-1 of Ph of **28b**), 128.4 (d, C-3/C-5 of Ph of **28a**), 128.3 (d, C-3/C-5 of Ph of **28b**), 128.1 (d, C-4 of Ph of **28b**), 127.9 (d, C-4 of Ph of **28a**), 126.2 (d, C-2/C-6 of Ph of **28b**), 125.8 (d, C-2/C-6 of Ph of **28a**), 123.2 (d, C-3 and C-5 of **28b**), 122.2 (d, C-3 and C-5 of **28a**), 75.6 (d, CHOH of

28b), 75.2 (d, CHOH of **28a**), 58.3 (d, CHNH of **28a**), 58.1 (d, CHNH of **28b**), 38.8 [s, *C*$(CH_3)_3$ of both], 27.41 [q, C(*C*$H_3)_3$ of **28b**], 27.37 [q, C(*C*$H_3)_3$ of **28a**].

***tert*-Butyl (1-hydroxycyclohexyl)(pyridin-4-yl)methylcarbamate (29):** 0.45 g (1.47 mmol, 74%) as oil. IR (FT): 3438, 2979, 1699, 1560, 1449, 1321, 1274, 1216, 1166 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.36 (d, *J* = 5 Hz, 2 H, H-2 and H-6), 7.19 (d, *J* = 5 Hz, 2 H, H-3 and H-5), 5.79 (d, *J* = 6 Hz, exch., 1 H, NH), 4.44 (d, *J* = 6 Hz, 1 H, CH), 3.14 (br., exch., 1H, OH), 1.82-1.07 (m, 10 H, cyclohexyl), 1.31 [s, 9 H, $C(CH_3)_3$]. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 155.6 (s, C=O), 149.3 (s, C-4), 149.0 (d, C-2 and C-6), 123.8 (d, C-3 and C-5), 79.7 [s, *C*$(CH_3)_3$], 72.8 (s, C-1 of cyclohexyl), 61.3 (d, CH), 35.5, 35.3 (2 t, C-2/C-6 of cyclohexyl), 28.3 [q, C(*C*$H_3)_3$], 25.4 (t, C-4 of cyclohexyl), 21.8, 21.5 (2 t, C-3/C-5 of cyclohexyl). MS (APCI): *m/z* (%) = 348 (40, $[M + MeCNH]^+$), 307 (100, $[MH]^+$), 209 (5). HRMS (APCI): *m/z* $[MH]^+$ calcd for $C_{17}H_{27}N_2O_3$: 307.2022; found: 307.2027.

Synthesis of 2-(1-amino-2-hydroxy-2,2-diphenylethyl)pyridine (30): Trifluoroacetic acid (1.5 mL) was added to a stirred cold (0 °C) solution of **7** (0.10 g, 0.25 mmol) in DCM (5 mL). The cooling bath was removed and the mixture was stirred for 30 min. The reaction mixture was quenched with H_2O (10 mL) and DCM (10 mL) was added. The organic layer was separated, washed with aq. Na_2CO_3 (10 mL, 1 M) and H_2O (10 mL), dried ($MgSO_4$), and evaporated under reduced pressure. The residue obtained was subjected to flash column chromatography (silica gel; Et_2O–hexane, 1:1) to give pure **30** (0.07 g, 0.24 mmol, 97%). Mp 139-141 ºC. IR (FT): 3432, 2917, 1570, 1423, 1360, 1056 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 5 Hz, 1 H, H-6), 7.62–6.92 (m, 14 H, H-3, H-4, H-5, OH and 2 Ph), 4.79 (s, 1 H, CH), 1.72 (br., 2 H, NH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ = 162.0 (s, C-2), 148.1 (d, C-6), 146.7, 145.1 (2 s, C-1 of 2 Ph), 137.1 (d, C-4), 128.4, 127.8 (2 d, C-3/C-5 of 2 Ph), 126.7 (d, C-3), 126.1 (d, C-4 of Ph), 126.0, 125.7 (2 d, C-2/C-6 of 2 Ph), 124.6 (d, C-4 of other Ph), 122.3 (d, C-5), 80.9 (s, COH), 61.2 (d, CH). MS (APCI): *m/z* (%) = 291 (100, $[M + H]^+$), 273 (79), 224 (3), 183 (8). HRMS (APCI): *m/z* $[MH]^+$ calcd for $C_{19}H_{19}N_2O$: 291.1497; found: 291.1507.

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