Behaviour of *N*-Pyridylbenzamides versus Benzanilides in the *ortho*-Directed Lithiation of Masked Aromatic Carboxylic Acids[‡]

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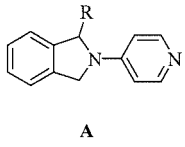
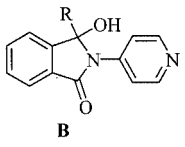
The reaction of *N*-pyridylbenzamides **1**–**3** with *n*-butyllithium or *sec*-butyllithium has been examined. The perfect selectivity that has been observed until now in the lithiation of anilides, a reaction used for *ortho*-functionalisation of masked aromatic carboxylic acids, has been broken; our results indicate that the pyridine ring at the position *ortho* to the directed metallation group is more susceptible to lithiation than the homoaromatic ring itself. This was proved in an intermolecular comparative study of benz-, picolin- and isonicotinanilides **14**–**16**, and *N*-cumylbenzamide (**17**).

Introduction

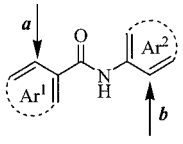
Recently, it has been demonstrated that the 3-hydroxy-*N*-(pyrid-4-yl)-2,3-dihydroisoindol-1-ones **B** could be convenient precursors in the preparation of *N*-(pyridyl)isoindolines **A** and their derivatives. These compounds show activity as selective serotonin reuptake inhibitors.[1,2] This prompted us to seek more insight into the possibility of preparing compounds of structure **B**.



A



B

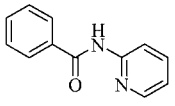


C

The reported methods for the preparation of this skeleton generally require multiple reaction steps, and are unsatisfactory, both in yield and generality.[3,4] The most attractive route reported to date, for the preparation of *N*-aryl-3-hydroxyisoindolin-1-ones is the transformation of secondary aromatic carboxanilides of structure **C**, by *ortho*-lithiation and subsequent reaction of the dilithiated (*C*-*ortho*,*N*-) species with *N*,*N*-dimethylformamide (DMF).[5–9]

Therefore, with the aim of developing a methodology for the synthesis of the required systems, *N*-(pyrid-4-yl)benzamide was subjected to a reaction with *n*-butyllithium (*n*BuLi) in THF, and subsequently with DMF, but this resulted in an intractable mixture. This is astonishing given the known reaction of arylanilides. In general, it is possible to conclude, from the hierarchy of *ortho*-directed metallation groups (*o*-DMGs), that the anilide functionality in **C** could direct the lithiation process at the one of two competitive positions ***a*** and ***b***. However, until now, no examples of lithiation at the ***b*** position of the anilides have been observed.[10–14] The observed behaviour of *N*-(pyrid-4-yl)-benzamide in the reaction with *n*BuLi suggests that in the case of anilides, in which the *N*-aryl ring is replaced by an *N*-pyridyl one, the presence of the *N*-pyridyl moiety could cause a change in the course of the reaction.

While trying to obtain more insight into this process, we investigated the reaction of *N*-pyridylbenzamides **1**–**3** with *n*BuLi or *s*BuLi, and we are reporting the results here. We have determined all the products and their yields.



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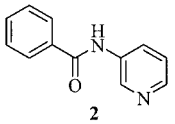

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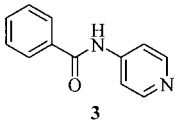

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Results and Discussion

The detailed results of the reaction of *n*BuLi or *s*BuLi with *N*-pyridylbenzamides **1**–**3** are reported in Table 1. All reactions were carried out in THF with 2 equiv. of *n*BuLi or *s*BuLi, and then, before addition of an electrophile, the reaction mixtures were cooled to −78 °C. As a way for determining the reaction of the benzamides **1**–**3** with lithiat-

[‡] Application of Organolithium and Related Reagents in Synthesis, 30. Part 29: A. Bieniek, J. Epsztajn, K. K. Kulikiewicz, *Monatsh. Chem.* **2004**, *135*, 69–77.

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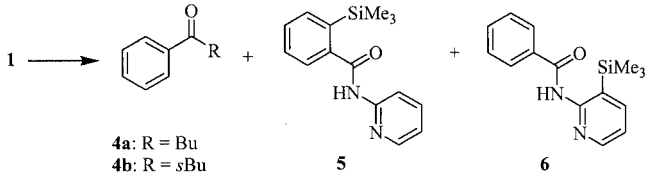
Table 1. Reaction of the *N*-pyridylbenzamides **1**−**3** in the lithiation/silylation process

Benzamides	RLi	Products (yields [%]) Ketones **4** or adduct **10**	Silylated products	Recovered benzamides	Overall yields [%]
1	*n*BuLi	**4a** (50)	**5** (1), **6** (16)	**1** (26)	93
1	*s*BuLi	**4b** (25)	**5** (8), **6** (44)	**1** (16)	93
3	*n*BuLi	**4a** (22)	**7** (14), **8** (14), **9** (32)	**3** (10)	92
3	*s*BuLi	**4b** (16)	**7** (7), **8** (2), **9** (43)	**3** (10)	78
2	*n*BuLi	**10** (12)	**11** (5), **12** (6), **13** (33)	**2** (21)	77

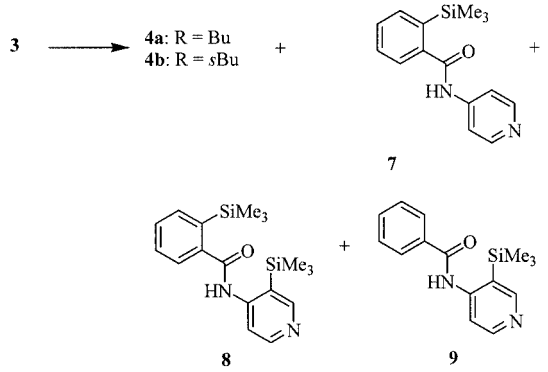
ing agents, the silylation process was selected, since in these cases, the products were readily separated and could be characterised unambiguously. An examination of the data reveals that the reacting benzamides may be divided into two groups. The first group comprises benzamides derived from 2- and 4-aminopyridines **1** and **3**. The second one consists of the benzamide derived from 3-aminopyridine **2**.

N-(Pyrid-2-yl)- and *N*-(Pyrid-4-yl)benzamides 1 and 3

Benzamides **1** and **3** reacted with *n*BuLi or *s*BuLi, and subsequent treatment of the lithiated derivatives with chlorotrimethylsilane (TMSCl) gave the corresponding silylated products **5**−**9**, along with a large amount of valerophenone (**4a**) or *s*-butyl phenyl ketone (**4b**), together with some amount of recovered starting amide (see Table 1). The double *ortho*-lithiation/silylation process gave a considerable amount of the disilylated compound **8** from benzamide **3**, especially in its reaction with *n*BuLi. The results presented in Schemes 1 and 2 show that the cases of the reaction of benzamides **1** and **3** with *n*BuLi or *s*BuLi indicate that the perfect selectivity for path ***a*** in the lithiation of anilides **C** that has been known until now has been broken.[15−20]



Scheme 1



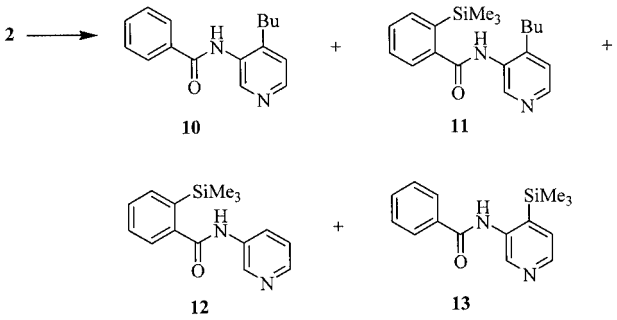
Scheme 2

Independently of which lithiating agent (*n*BuLi or *s*BuLi) was employed for the lithiation/silylation process of amides **1** and **3**, the main products appeared to be compounds **6** or **9**, resulting from substitution at position 3 of the pyridine ring. This suggests that position 3 of the pyridine moiety is more susceptible towards the lithiation process than the homoaromatic ring itself.

The ketones **4a** and **4b** could be simply derived from a nucleophilic acyl substitution reaction of the starting benzamides **1** and **3** with *n*BuLi and *s*BuLi.

N-(Pyrid-3-yl)benzamide (2)

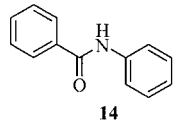
Subjection of benzamide **2** to the lithiation/silylation process resulted in the corresponding silylated products **11**−**13**, accompanied by a considerable amount of compound **10** and some amount of the starting amide (Table 1). One of the silylated products in this mixture (Scheme 3), namely compound **11**, is probably formed as the result of the following reaction sequence: firstly, addition of *n*BuLi across the pyridine ring, and then *ortho*-lithiation of the anilide functionality. However, the reverse sequence cannot be excluded. Compounds **10** and **11** were formed by aromatisation of the unstable 1,4-dihydro adduct of *n*BuLi across the pyridine ring. Formation of adducts **10** and **11** is in agreement with the behaviour of 3-(pivaloylamino)pyridine in its reaction with *n*BuLi.[21−22] The fact that silylated amide **13**, resulting from substitution at C-4 of the pyridine nucleus, appeared to be the main product is additional evidence for the higher susceptibility of heteroaromatic species than homoaromatic ones to the lithiation process.



Scheme 3

Competitive Study of the Lithiation of Anilides 14−16 and *N*-Cumylbenzamide (17)

The suggestion that the pyridine moiety is much more prone to lithiation than the benzene ring itself inspired us to undertake a competitive study of anilides **C** into the susceptibility of the benzene versus the pyridine rings towards lithiation, as well as of the generality of anilides to act as *o*-DMGs. Recently, Snieckus and co-workers have described that the *N*-cumylbenzamide is a very effective *o*-DMG, and suggested that it could play a central role in synthetic aromatic chemistry.[23−24] However, they have not shown any comparative studies, or even discussion, of the *N*-cumyl group relative to the anilide functionality, whose significance as an *o*-DMG is widely documented.[15−20] Therefore, we decided to extend the competitive study of amides **C** to include *N*-cumylbenzamide (**17**), in order to fill this gap.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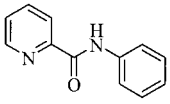
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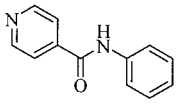
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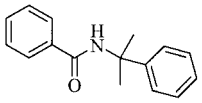
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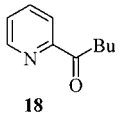
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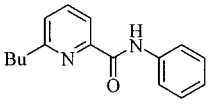
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To this end, benz-, picolin- and isonicotinanilides **14**−**16** and *N*-cumylbenzamide (**17**) were subjected to a reaction with *n*BuLi or *s*BuLi in THF, and quenched with deuterated methanol (MeOD). The detailed results are reported in Table 2. At first, it appeared that treatment of the anilide **14** and the *N*-cumylamide **17** with *n*BuLi at −78 °C for 2 h resulted in no lithiation. If an equimolecular amount of TMEDA relative to the lithiation agent was added, only a small improvement was observed for anilide **14**. Increasing the temperature of the lithiation to 0 °C enhanced the process for amides **14** and **17** to 80% and 73%, respectively. We then found out that the replacement of *n*BuLi by *s*BuLi gave perfect results; complete lithiation was observed in both cases.

On the other hand, picolinanilide (**15**) and isonicotinanilide (**16**) gave a perfect lithiation at position 3 of the pyridine ring when treated with *n*BuLi, irrespective of the reaction conditions. In the case of picolinanilide (**15**), it appeared that if the process was carried out at 0 °C, generation of the lithiated species was accompanied by formation of the ketone **18** (ca. 8%) and a trace amount of the *n*BuLi adduct across the pyridine ring **19**. These compounds were isolated from the testing mixture and characterised by ^{1}H and ^{13}C NMR spectroscopy (Table 2).

In order to gain more insight into the susceptibility of the tested amides **14**−**17** towards the lithiation process, anilide **14** was selected as a reference compound, as it is the most frequently used of the secondary amides as an *o*-DMG.[5−9,15−20] Thus, intermolecular competition reactions were carried out for the following pairs: **14/15**, **14/16**, and **14/17**. Detailed results are reported in Table 3. The data prove that picolinanilide (**15**) and isonicotinanilide (**16**) appear to be the most receptive to lithiation of the amides tested. Moreover, it has been shown that in these cases, the lithiation process is independent of the reaction conditions, as well as the lithiating agents used.

Table 3. Intermolecular competitive lithiation of equimolar mixtures of amides **14/15**, **14/16**, **14/17**

	Extent of the lithiation [%][a,b]	
	*n*BuLi	*s*BuLi
14/15	0:100	0:100
14/16	0:100	0:100
14/17	39:60	45:45

[a] For typical procedures see Exp. Sect. [b] The process was followed by deuteration (MeOD) and reported data were derived from ^{1}H NMR spectra.

Table 2. Lithiation of amides **14**−**17**

Amide	Lithiating reagent[a]	Temp. [°C]	D incorporation for the isolated amide [%][b]
14	*n*BuLi	−78	0
	*n*BuLi[c]	−78	19
	*n*BuLi	0	80
	*s*BuLi[c]	−78	100
15	*n*BuLi	−78	100
	*n*BuLi	0	100[d]
16	*n*BuLi	−78	96
	*n*BuLi	0	94
17	*n*BuLi	−78	0
	*n*BuLi[c]	−78	0
	*n*BuLi	0	73
	*s*BuLi[c]	−78	100

[a] The ratio of amide/lithiated reagents was 1:2 in all cases. [b] Reported data were identified by ^{1}H NMR spectroscopy utilising the peak areas of the hydrogen atoms *ortho* to the carbamoyl group. [c] The lithiation was carried out in the presence of TMEDA. [d] The isolated amide **16** was accompanied by ketone **18** (8%) and a trace of adduct **19**.

The competition reaction between the anilide **14** and *N*-cumylbenzamide (**17**) indicated that there is practically no difference between the activity as *o*-DMGs of their functional groups. Therefore, the similar abilities of these functionalities to act as *o*-DMGs, along with the simplicity of preparation of the anilide group and the ease of its hydrolysis into a carboxylic functionality, mean that the anilide should be considered the group of choice for *ortho*-directed metallation of masked aromatic carboxylic acids.

Conclusion

The results presented here indicate that replacement of the aniline in the benzanilides **C** for aminopyridines caused the breaking of the perfect selectivity of the *ortho*-lithiation reaction for masked aromatic carboxylic acids that has been known until now. In addition, the competitive study of anilides **14**−**16**, and *N*-cumylbenzamide (**17**) showed that position 3 of the pyridine moiety is more susceptible to lithiation than the homoaromatic ring itself. Moreover, the result of the competitive lithiation of the benzanilide (**14**) and *N*-cumylbenzamide (**17**) indicates that the anilide functionality should be recognised as an important *o*-DMG for the *ortho*-lithiation of aromatic carboxylic acids.

Experimental Section

General: Melting points were determined with a Boetius hot stage apparatus and are uncorrected. Yields are given on chromatographically pure products and are not optimised. ^{1}H NMR spectra were recorded at 200 MHz with a Varian Gemini 200 BB or at 500 MHz with a Bruker Avance DRX500 spectrometer. ^{13}C NMR spectra were recorded at 50 MHz with a Varian Gemini 200 BB spectrometer. IR spectra were recorded with a Nexus FT-IR spectrometer (Thermo Nicolet). HRMS data were recorded by using chemical ionisation with a Finnigan MAT 95 spectrometer. TLC was carried out on Merck silica gel plates (Kiselgel 60 F_{254}, layer thickness 0.2 mm) and visualised using a UV lamp at 254 nm and in an iodine chamber. Column chromatography separations and purifications were performed on silica gel 60 (0.063−0.100 mm) from Merck, using 30 g of silica gel per 1 g of the material to be separated or purified. All reagents and commercially available materials were used without purification unless otherwise stated. *n*-Butyllithium (1.6 M solution in hexane) and *sec*-butyllithium (1.4 M solution in cyclohexane) were obtained from Aldrich and were titrated before use. Benzoyl chloride (pure) and 3-aminopyridine (pure) were obtained from POCh. *N*,*N*,*N*′,*N*′-Tetramethylethylenediamine (TMEDA) (99%) from Aldrich was distilled before use and stored over potassium hydroxide pellets. Chlorotrimethylsilane (TMSCl) was obtained from Fluka. [D_1]Methanol (99.8%) was obtained from IBJ Swierk and used as received. Tetrahydrofuran (THF) (pure) was obtained from POCh and freshly distilled from sodium benzophenone ketyl. Pyridine (pure) was obtained from Ubichem Ltd.

Amides 1−3, 14−17: These compounds were obtained according to known procedures. *N*-(Pyrid-2-yl)benzamide (**1**) was obtained from 2-aminopyridine and benzoyl chloride in pyridine according to the procedure given by Pentimalli for *N*-(pyrid-3-yl)benzamide (**2**).[25] Compound **1** was purified by crystallisation from benzene/hexane (3:1) (yield 66%), m.p. 82−84 °C (ref.[26] m.p. 81−83 °C). ^{1}H NMR {200 MHz, [D_6]DMSO, reference TMS (δ = 0 ppm)}: δ = 7.14−7.18 [m, 1 H, Py(5)-H], 7.48−7.62 [m, 3 H, Ph(3,4,5)-H], 7.81−7.86 [m, 1 H, Py(4)-H], 8.01−8.05 [m, 2 H, Ph(2,6)-H], 8.20 (d,1 H, $^3J_{H,H}$ = 7.5 Hz, Py(3)-H], 8.37−8,39 [m, 1 H, Py(6)-H], 10.78 (s, 1 H, NH) ppm. ^{13}C NMR {[D_6]DMSO, reference TMS (δ = 0 ppm)}: δ = 114.9, 120.0, 128.2, 128.6, 132.1, 134.3, 138.3, 148.1, 152.4, 166.2 (CO) ppm.

***N*-(Pyrid-3-yl)benzamide (2):** Amide **2** was prepared from 3-aminopyridine and benzoyl chloride in pyridine.[25] It was purified by recrystallisation from benzene (yield 72%), m.p. 123−124 °C (ref.[25] m.p. 118 °C). ^{1}H NMR {200 MHz, [D_6]DMSO, reference TMS (δ = 0 ppm)}: δ = 7.41 [dd, $^3J_{H,H}$ = 8.3, $^3J_{H,H}$ = 4.6 Hz, 1 H, Py(5)-H], 7.49−7.70 [m, 3 H, Ph(3,4,5)-H], 7.95−8.06 [m, 2 H, Ph(2,6)-H], 8.22 [dd, $^3J_{H,H}$ = 8.4, $^4J_{H,H}$ = 1.6 Hz, 1 H, Py(4)-H], 8.33 [d, $^3J_{H,H}$ = 4.7 Hz, 1 H, Py(6)-H], 8.97 [d, $^4J_{H,H}$ = 1.6 Hz, 1 H, Py(2)-H], 10.49 (s, 1 H, NH; signal disappeared after addition of D_2O) ppm. ^{13}C NMR {[D_6]DMSO, reference TMS (δ = 0 ppm)}: δ = 123.4, 127.2, 127.7, 128.4, 131.8, 134.3, 135.8, 141.9, 144.5, 165.9 (CO) ppm.

***N*-(Pyrid-4-yl)benzamide (3):** Compound **3** was prepared from 4-aminopyridine and benzoyl chloride in the presence of triethylamine.[27] It was purified by crystallisation from ethanol (yield 45%), m.p. 210−211 °C (ref.[25] m.p. 202 °C). ^{1}H NMR {200 MHz, [D_6]DMSO, reference TMS (δ = 0 ppm)}: δ = 7.48−7.72 [m, 3 H, Ph(3,4,5)-H], 7.75−7.85 [m, 2 H, Py(3,5)-H], 7.91−8.04 [m, 2 H, Ph(2,6)-H], 8.43−8.55 [m, 2 H, Py(2,6)-H], 10.61 (s, 1 H, NH) ppm. ^{13}C NMR {[D_6]DMSO, reference TMS (δ = 0 ppm)}: δ = 113.9, 127.8, 128.4, 132.1, 134.2, 145.9, 150.3, 166.5 (CO) ppm.

***N*-Phenylbenzamide (14):** Compound **14** was obtained from benzoyl chloride and aniline according to a known procedure.[28] ^{1}H NMR {500 MHz, [D_6]DMSO, reference [D_6]DMSO (δ = 2.49 ppm)}: δ = 7.09 [t, $^3J_{H,H}$ = 7.3 Hz, 1 H, Ph^2(4)-H], 7.34 [t, $^3J_{H,H}$ = 7.7 Hz, 2 H, Ph^2(3,5)-H], 7.52 [t, $^3J_{H,H}$ = 7.4 Hz, 2 H, Ph^1(3,5)-H], 7.56−7.61 [m, 1 H, Ph^1(4)-H], 7.77 [d, $^3J_{H,H}$ = 8.2 Hz, 2 H, Ph^2(2,6)-H], 7.94 [dd, $^4J_{H,H}$ = 1.2 Hz, $^3J_{H,H}$ = 8.3 Hz, 2 H, Ph^1(2,6)-H], 10.25 (s, 1 H, NH) ppm. ^{13}C NMR {[D_6]DMSO, reference [D_6]DMSO (δ = 39.5 ppm)}: δ = 120.3, 123.6, 127.6, 128.3, 128.5, 131.5, 135.0, 139.1, 165.5 (CO) ppm.

***N*-Phenylpyridine-2-carboxamide (15): 15** was prepared from 2-pyridinecarboxylic acid according to a procedure given by Brunner.[29] Compound **15** was purified by crystallisation from hexane (yield 76%), m.p. 74−76 °C (ref.[29] m.p. 75 °C). ^{1}H NMR {500 MHz, [D_6]DMSO, reference [D_6]DMSO (δ = 2.49 ppm)}: δ = 7.10 [t, $^3J_{H,H}$ = 7.3 Hz, 1 H, Ph(4)-H], 7.32−7.37 [m, 2 H, Ph(3,5)-H], 7.63−7.68 [m, 1 H, Py(5)-H], 7.90 [d, $^3J_{H,H}$ = 7.7 Hz, 2 H, Ph(2,6)-H], 8.06 [dd, $^4J_{H,H}$ = 1.7 Hz, $^3J_{H,H}$ = 7.7 Hz, 1 H, Py(4)-H], 8.09−8.17 [m, 1 H, Py(3)-H], 8.73 [d, $^3J_{H,H}$ = 4.3 Hz, 2 H, Py(6)-H], 10.62 (s, 1 H, NH) ppm. ^{13}C NMR {[D_6]DMSO, reference [D_6]DMSO (δ = 39.5 ppm)}: δ = 120.2, 122.3, 123.8, 126.8, 128.6, 138.0, 138.3, 148.2, 149.8, 162.3 (CO) ppm.

***N*-Phenylpyridine-4-carboxamide (16):** Compound **16** was obtained from 4-pyridinecarbonyl chloride and aniline in pyridine according to a procedure given by Park.[30] ^{1}H NMR {500 MHz, [D_6]DMSO, reference [D_6]DMSO (δ = 2.49 ppm)}: δ = 7.13 [t, $^3J_{H,H}$ = 7.3 Hz, 1 H, Ph(4)-H], 7.37 [t, $^3J_{H,H}$ = 7.7 Hz, 2 H, Ph(3,5)-H], 7.77 [d, $^3J_{H,H}$ = 7.9 Hz, 2 H, Ph(2,6)-H], 7.85 [dd, $^4J_{H,H}$ = 1.4 Hz, $^3J_{H,H}$ = 4.4 Hz, 2 H, Py(3,5)-H], 8.75 [dd, $^4J_{H,H}$ = 1.4 Hz, $^3J_{H,H}$ = 4.4 Hz, 2 H, Py(2,6)-H], 10.49 (s, 1 H, NH) ppm. ^{13}C NMR {[D_6]DMSO, reference [D_6]DMSO (δ = 39.5 ppm)}: δ = 120.4, 121.5, 124.1, 128.7, 138.5, 141.9, 150.2, 163.9 (CO) ppm.

***N*-(1-Methyl-1-phenylethyl)benzamide (17):** Amide **17** was obtained from (1-methyl-1-phenylethyl)amine (this amine was prepared by treatment of 2-bromo-2-phenylpropane with liquid ammonia) and benzoyl chloride in the presence of triethylamine.[31] It was purified by crystallisation from hexane/ethyl acetate (1:2) (yield 66%), m.p. 168−170 °C (ref.[32] m.p. 168−169 °C). ^{1}H NMR {500 MHz, [D$_6$]DMSO, reference [D$_6$]DMSO (δ = 2.49 ppm)}: δ = 1.65 (s, 6 H, Me), 7.15 [t, $^3J_{H,H}$ = 7.5 Hz, 1 H, Ph^2(4)-H], 7.23−7.30 [m, 2 H, Ph^2(3,5)-H], 7.36 [d, $^3J_{H,H}$ = 7.6 Hz, 2 H, Ph^2(2,6)-H], 7.41−7.46 [m, 2 H, Ph^1(3,5)-H], 7.47−7.52 [m, 1 H, Ph^1(4)-H], 7.83 [d, $^3J_{H,H}$ = 7.8 Hz, 2 H, Ph^1(2,6)-H], 8.42 (s, 1 H, NH) ppm. ^{13}C NMR {[D$_6$]DMSO, reference [D$_6$]DMSO (δ = 39.5 ppm)}: δ = 29.6, 55.3, 124.6, 125.6, 127.4, 127.8, 128.0, 130.9, 135.4, 148.0, 165.8 (CO) ppm.

Reaction of *N*-(Pyrid-2-yl)benzamide (1) with *n*-Butyllithium and then with Chlorotrimethylsilane: *n*-Butyllithium (20 mmol) was added to a stirred solution of the amide **1** (1.98 g, 10 mmol) and TMEDA (20 mmol) in THF (100 mL) at −78 °C. The solution was kept at −78 °C for 0.5 h, then warmed up to 0 °C and kept at this temperature for 0.1 h. The mixture was then cooled to −78 °C, and chlorotrimethylsilane (20 mmol) was added. Stirring at −78 °C was continued for another 0.25 h, then the reaction mixture was warmed up to room temperature and water (20 mL) was added. The mixture was adjusted to pH ≈ 5 with hydrochloric acid (2.0 M solution in water) and the organic layer was separated. The water layer was extracted with $CHCl_3$ (3 × 15 mL). The combined organic solutions were dried with magnesium sulfate. Analysis (TLC; $CHCl_3$/acetone, 6:1) of the organic solution indicated the presence of at least four compounds (R_f = 0.88, 0.77, 0.65, 0.40), which were separated by column chromatography. The first eluted fraction (R_f = 0.88) appeared to be valerophenone (**4a**) (0.80 g, yield 49%). It was purified by kugelrohr distillation (oil bath 130 °C/2.0 Torr ; ref.[33] b.p. 82−86 °C/0.5 Torr). ^{1}H NMR [200 MHz, $CDCl_3$, reference TMS (δ = 0 ppm)]: δ = 0.92 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, Me), 1.31−1.49 (m, 2 H, CH_2), 1.62−1.85 (m, 2 H, CH_2), 2.96 (t, $^3J_{H,H}$ = 7.0 Hz, 2 H, CH_2), 7.41−7.59 [m, 3 H, Ph(3,4,5)-H], 7.91−8.01 [m, 2 H, Ph(2,6)-H] ppm. ^{13}C NMR [$CDCl_3$, reference TMS (δ = 0 ppm)]: δ = 13.9, 22.4, 26.4, 38.2, 127.9, 128.5, 132.7, 136.9, 200.4 (CO) ppm. IR (film): $\tilde{\nu}_{max.}$ = 1686 (CO) cm^{-1}. The second eluted fraction (R_f = 0.77) was identified as *N*-(pyrid-2-yl)-2-(trimethylsilyl)benzamide (**5**) (0.22 g, yield 7%). The analytical sample was obtained after recrystallisation from hexane, m.p. 111−114 °C. ^{1}H NMR {200 MHz, [D$_6$]DMSO, reference [D$_6$]DMSO (δ = 2.49 ppm)}: δ = 0.26 (s, 9 H, $SiMe_3$), 7.12−7.18 [m, 1 H, Py(5)-H], 7.42−7.56 (m, 4 H, Ph-H), 7.78−7.92 [m, 1 H, Py(4)-H], 8.19 [d, $^3J_{H,H}$ = 8.3 Hz, 1 H, Py(3)-H], 8.31−8.40 [m, 1 H, Py(6)-H], 10.86 (s, 1 H, NH) ppm. ^{13}C NMR {[D$_6$]DMSO, reference [D$_6$]DMSO (δ = 39.5 ppm)}: δ = 0.0, 114.4, 119.9, 127.4, 128.8, 129.7, 134.9, 139.0, 139.3, 142.0, 148.2 152.3, 169.8 (CO) ppm. IR (KBr): $\tilde{\nu}_{max.}$ = 1683 (CO) cm^{-1}. $C_{15}H_{18}N_2OSi$ (270.41): calcd. C 66.63, H 6.71, N 10.36, O 5.91, Si 10.39; found C 66.9, H 6.8, N 10.4. The third eluted fraction (R_f = 0.65) turned out to be starting amide **1** (0.52 g, yield 26%). The fourth eluted fraction (R_f = 0.40) was identified as *N*-[3-(trimethylsilyl)pyrid-2-yl]benzamide (**6**) (0.43 g, yield 16%). An analytical sample was obtained after recrystallisation from diisopropyl ether, m.p. 105−108 °C. ^{1}H NMR {200 MHz, [D$_6$]DMSO, reference [D$_6$]DMSO (δ = 2.49 ppm)}: δ = 0.23 (s, 9 H, $SiMe_3$), 7.35 [dd, $^3J_{H,H}$ = 7.4, 4.8 Hz, 1 H, Py(5)-H], 7.49−7.61 [m, 3 H, Ph(2,6)-H, Py(4)-H], 7.96−8.01 [m, 3 H, Ph(3,4,5)-H], 8.52 [dd, $^3J_{H,H}$ = 4.6, 1.6 Hz, 1 H, Py(6)-H], 10.50 (s, 1 H, NH) ppm. ^{13}C NMR {[D$_6$]DMSO, reference [D$_6$]DMSO (δ = 39.5 ppm)}: δ = 0.0, 122.3, 127.8, 128.7, 131.9, 132.7, 134.3, 144.7, 149.6, 155.1, 167.0 (CO) ppm. IR (KBr): $\tilde{\nu}_{max.}$ = 1656 (CO) cm^{-1}. $C_{15}H_{18}N_2OSi$ (270.41): calcd. C 66.63, H 6.71, N 10.36, O 5.91, Si 10.39; found C 66.6, H 6.7, N 10.4.

Reaction of *N*-(Pyrid-2-yl)benzamide (1) with *sec*-Butyllithium and then with Chlorotrimethylsilane: *sec*-Butyllithium (20 mmol) was added to a stirred solution of the amide **1** (1.98 g, 10 mmol) and TMEDA (20 mmol) in THF (70 mL) at −78 °C. The solution was kept at −78 °C for 2 h, and chlorotrimethylsilane (20 mmol) was added. Stirring at −78 °C was continued for another 0.5 h, then the reaction mixture was warmed up to room temperature and water (20 mL) was added. The mixture was adjusted to pH ≈ 5 with hydrochloric acid (2.0 M solution in water) and the organic layer was separated. The water layer was extracted with $CHCl_3$ (3 × 15 mL). The combined organic solutions were dried with magnesium sulfate. Analysis (TLC; $CHCl_3$/acetone, 8:1) of the organic solution indicated the presence of at least four compounds (R_f = 0.70, 0.45, 0.32, and 0.11), which were separated by column chromatography. The first eluted fraction (R_f = 0.70) was identified as ketone **4b** (0.41 g, yield 25%). It was purified by kugelrohr distillation (oil bath 130 °C, 5.0 Torr; ref.[34] b.p. 110−112 °C/9.5 Torr). ^{1}H NMR [200 MHz, $CDCl_3$, reference TMS (δ = 0 ppm)]: δ = 0.92 (t, $^3J_{H,H}$ = 7.4 Hz, 3 H, Me), 1.19 (d,$^3J_{H,H}$ = 6.9 Hz, 3 H, Me), 1.39−1.60 (m, 1 H, CH_2), 1.74−1.95 (m, 1 H, CH_2), 3.32−3.49 (m, 1 H, CH), 7.41−7.59 [m, 3 H, Ph(3,4,5)-H], 7.92−7.99 [m, 2 H, Ph(2,6)-H] ppm. ^{13}C NMR [$CDCl_3$, reference TMS (δ = 0 ppm)]: δ = 11.7, 16.7, 26.6, 42.1, 128.1, 128.5, 132.7, 136.7, 204.3 (CO) ppm. IR (film): $\tilde{\nu}_{max.}$ = 1684 (CO) cm^{-1}. The second, third and fourth fractions were identical to those upon the reaction of amide **1** with *n*BuLi and TMSCl (for differences in yield see Table 1).

Reaction of *N*-(Pyrid-4-yl)benzamide (3) with *n*-Butyllithium and then with Chlorotrimethylsilane: *n*-Butyllithium (20 mmol) was added to a stirred solution of the amide **3** (1.98 g, 10 mmol) and TMEDA (20 mmol) in THF (100 mL) at −78 °C under argon. The solution was kept at −78 °C for 0.5 h, then allowed to warm to 0 °C and kept at this temperature for 6 min. The mixture was cooled to −78 °C and chlorotrimethylsilane (20 mmol) was added. After 0.25 h at −78 °C, the reaction mixture was warmed to room temperature, and water (10 mL) was added. The mixture was adjusted to pH ≈ 5 with hydrochloric acid (2.0 M solution in water) and the organic layer was separated. The water layer was extracted with $CHCl_3$/THF (1:1) (3 × 15 mL). The analysis (TLC; ethyl acetate) of the combined organic solutions indicated the presence of at least five compounds (R_f = 0.76, 0.48, 0.35, 0.24 and 0.16), which were separated by the column chromatography. The first eluted fraction (R_f = 0.76) turned out to be valerophenone (**4a**) (0.36 g, yield 22%). The second eluted fraction (R_f = 0.48) was identified as 2-(trimethylsilyl)-*N*-[3-(trimethylsilyl)pyrid-4-yl]benzamide (**8**) (0.48 g; yield 14%). An analytical sample was obtained after recrystallisation from hexane, m.p. 71−72 °C. ^{1}H NMR {200 MHz, [D$_6$]DMSO, reference [D$_6$]DMSO (δ = 2.49 ppm)}: δ = 0.32 and 0.26 ppm (2 overlapping s, 18 H, $SiMe_3$), 7.34 [d, $^3J_{H,H}$ = 5.5 Hz, 1 H, Py(5)-H], 7.42−7.84 (m, 4 H, Ph-H), 8.58 [d,$^3J_{H,H}$ = 5.5 Hz, 1 H, Py(6)-H], 8.66 [s, 1 H, Py(2)-H], 10.00 (s, 1 H, NH) ppm. ^{13}C NMR {[D$_6$]DMSO, reference [D$_6$]DMSO (δ = 39.5 ppm)}: δ = −0.2, 0.6, 120.7, 126.8, 129.0, 129.9, 130.2, 135.3, 140.0, 140.7, 150.1, 150.8, 155.7, 169.1 (CO) ppm. IR (KBr): $\tilde{\nu}_{max.}$ = 1690.3 (CO) cm^{-1}. $C_{18}H_{26}N_2OSi_2$ (342.59): calcd. C 63.10, H 7.65, N 8.18, O 4.67, Si 16.40; found C 63.2, H 7.7, N 8.2. The third eluted fraction (R_f = 0.35) was identified as *N*-[3-(trimethylsilyl)pyrid-4-yl]benzamide (**9**) (0.86 g; yield 32%). An analytical sample was obtained after recrystallisation from diisopropyl ether, m.p. 141−142 °C. ^{1}H NMR {200 MHz, [D$_6$]DMSO, reference [D$_6$]DMSO (δ = 2.49 ppm)}: δ =

0.28 (s, 9 H, $SiMe_3$), 7.32 [d, $^3J_{H,H}$ = 5.2 Hz, 1 H, Py(5)-H], 7.43−7.65 [m, 3 H, Ph(3,4,5)-H], 7.84−8.30 [m, 2 H, Ph(2,6)-H], 8.58 [d, $^3J_{H,H}$ = 5.2 Hz, 1 H, Py(6)-H], 8.66 [s, 1 H, Py(2)-H], 10.08 (s, 1 H, NH) ppm. ^{13}C NMR {[D$_6$]DMSO, reference [D$_6$]DMSO (δ = 39.5 ppm)}: δ = −0.3, 122.1, 127.6, 128.6, 131.1, 132.0, 133.8, 150.3, 150.8, 155.5, 166.0 (CO) ppm. IR (KBr): $\tilde{\nu}_{max.}$ = 1644 (CO) cm^{-1}. $C_{15}H_{18}N_2OSi$ (270.41): calcd. C 66.63, H 6.71, N 10.36, O 5.91, Si 10.39; found C 66.5, H 6.4, N 10.4. The fourth eluted fraction (R_f = 0.24) was identified as *N*-(pyrid-4-yl)-2-(trimethylsilyl)benzamide (**7**) (0.38 g; yield 14%). An analytical sample was obtained after recrystallisation from diisopropyl ether, m.p. 136−137 °C. ^{1}H NMR {200 MHz, [D$_6$]DMSO, reference [D$_6$]DMSO (δ = 2.49 ppm)}: δ = 0.26 (s, 9 H, $SiMe_3$), 7.44−7.86 [m, 6 H, Ph-H, Py(3,5)-H], 8.42−8.56 [m, 2 H, Py(2,6)-H], 10.75 (s, 1 H, NH) ppm. ^{13}C NMR {[D$_6$]DMSO, reference [D$_6$]DMSO δ = 39.5 ppm)}: δ = 0.1, 113.6, 126.9, 128.8, 129.7, 134.9, 138.6, 142.1, 145.8, 150.4, 170.1 (CO) ppm. IR (KBr): $\tilde{\nu}_{max.}$ = 1684 cm^{-1} (CO). $C_{15}H_{18}N_2OSi$ (270.41): calcd. C 66.63, H 6.71, N 10.36, O 5.91, Si 10.39; found C 66.7, H 6.8, N 10.4. The fifth fraction eluted (R_f = 0.16) proved to be starting *N*-(pyrid-4-yl)benzamide (**3**) (0.20 g; 10%).

Reaction of *N*-(Pyrid-4-yl)benzamide (3) with *sec*-Butyllithium and then with Chlorotrimethylsilane: The reaction was carried out according to the procedure given for *N*-(pyrid-2-yl)benzamide (**1**) with *sec*-butyllithium and then chlorotrimethylsilane. The analysis (TLC; ethyl acetate) of the combined organic solution indicated the presence of at least five compounds (R_f = 0.70, 0.48, 0.35, 0.24 and 0.16), which were separated by the column chromatography. The first eluted fraction was identified as ketone **4b** (0.26 g, yield 16%). The second, third, fourth and fifth fractions were identical to those upon the reaction of amide **1** with *n*BuLi and TMSCl (for differences in yield see Table 1).

Reaction of *N*-(Pyrid-3-yl)benzamide (2) with *n*-Butyllithium and then with Chlorotrimethylsilane: *n*-Butyllithium (20.0 mmol) was added to a stirred THF (100 mL) solution of amide **2** (1.98 g, 10.0 mmol) and TMEDA (20.0 mmol) at −78 °C. The resulting solution was stirred at −78 °C for 0.5 h and then allowed to warm up to 0 °C. After subsequent cooling to −78 °C, chlorotrimethylsilane (2.54 mL, 20.0 mmol) was added, and stirring at this temperature was continued for another 0.25 h. The resulting mixture was allowed to reach room temperature and water (10 mL) was added. The mixture was adjusted to pH ≈ 5 with 2.0 M aqueous solution of hydrochloric acid, the layers were separated and the organic layer was dried with anhydrous magnesium sulfate. The analysis (TLC; ethyl acetate) of the organic solution indicated the presence of at least six compounds (R_f = 0.75, 0.54, 0.44, 0.31, 0.27 and 0.20). All volatile materials were distilled off under reduced pressure, and 3.19 g of a brown, very viscous liquid was obtained. This liquid was dissolved in acetone (50 mL) and a saturated solution of potassium permanganate in acetone was added dropwise with stirring at room temperature until a permanent purple colour of the reaction mixture was obtained. The mixture was decolourised with propan-2-ol, the separated manganese(IV) oxide was filtered off and washed with acetone (5 × 5 mL). The TLC plate (ethyl acetate) of the acetone solution looked the same as the TLC plate of the organic solution directly after reaction. Acetone was distilled off under reduced pressure, and a brown, very viscous liquid was obtained, and was separated by the column chromatography, using ethyl acetate/hexane (1:1) as eluent. After chromatography, six fractions were collected. The first and second eluted fractions (R_f = 0.75 and 0.54 in ethyl acetate) were yellow, viscous liquids (0.10 g and 0.31 g), which, according to the ^{1}H NMR and ^{13}C NMR spectra, appeared to be undefined, complex mixtures, and no further attempts of their identification were undertaken. The third eluted fraction (R_f = 0.44 in ethyl acetate) was a yellow, viscous liquid, and was identified as *N*-(4-butylpyrid-3-yl)-2-(trimethylsilyl)benzamide (**11**) (0.15 g, 5%). An analytical sample was obtained as a colourless, viscous liquid after repeated column chromatography on silica gel using ethyl acetate/hexane (1:1) as eluent. ^{1}H NMR {200 MHz, [D$_6$]DMSO, reference [D$_6$]DMSO (δ = 2.49 ppm)}: δ = 0.26 (s, 9 H, $SiMe_3$), 0.87 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, CH_2CH_3), 1.17−1.44 (m, 2 H, CH_2), 1.44−1.67 (m, 2 H, CH_2), 2.65 (t, $^3J_{H,H}$ = 7.5 Hz, 2 H, PyCH_2), 7.32 [d, $^3J_{H,H}$ = 5.0 Hz, 1 H, Py(5)-H], 7.43−7.60 (m, 2 H, Ph-H), 7.60−7.71 (m, 1 H, Ph-H), 7.71−7.83 (m, 1 H, Ph-H), 8.35 [d, 1 H, Py(6)-H], 8.46 [s, 1 H, Py(2)-H], 10.12 (s, 1 H, NH) ppm. ^{13}C NMR {[D$_6$]DMSO, reference [D$_6$]DMSO (δ = 39.5 ppm)}: δ = 0.4 ($SiMe_3$), 13.8, 22.1, 29.8, 30.7 (PyCH_2), 124.2, 127.2, 128.9, 129.9, 132.9, 135.1, 139.5, 141.4, 146.9, 148.0, 169.5 (CO) ppm. IR (film): $\tilde{\nu}_{max.}$ = 1668 (CO) cm^{-1}. HRMS for $C_{19}H_{27}N_2OSi$: calcd. [M + 1]$^+$: 327.189267, found 327.188800. The fourth eluted fraction (R_f = 0.31 in ethyl acetate) was a yellow, viscous liquid, and was identified as *N*-(pyrid-3-yl)-2-(trimethylsilyl)benzamide (**12**) (0.14 g, 5%). An analytical sample was obtained as a colourless solid after repeated column chromatography on silica gel using ethyl acetate/hexane (1:1) as eluent and subsequent recrystallisation from benzene/hexane (1:4); m.p. 88−92 °C. ^{1}H NMR {200 MHz, [D$_6$]DMSO, reference [D$_6$]DMSO (δ = 2.49 ppm)}: δ = 0.25 (s, 9 H, $SiMe_3$), 7.39 [dd, $^3J_{H,H}$ = 4.7, $^3J_{H,H}$ = 8.3 Hz, 1 H, Py(5)-H], 7.45−7.59 (m, 2 H, Ph-H), 7.59−7.73 (m, 2 H, Ph-H), 8.13−8.25 [m, 1 H, Py(4)-H], 8.30 [d, $^3J_{H,H}$ = 3.9 Hz, 1 H, Py(6)-H], 8.88 [s, 1 H, Py(2)-H], 10.60 (s, 1 H, NH) ppm. ^{13}C NMR {[D$_6$]DMSO, reference [D$_6$]DMSO (δ = 39.5 ppm)}: δ = 0.1 ($SiMe_3$), 123.7, 126.6, 126.9, 128.8, 129.6, 134.9, 135.9, 138.6, 141.4, 142.2, 144.5, 169.6 (CO) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max.}$ = 1684 (CO) cm^{-1}. HRMS for $C_{15}H_{19}N_2OSi$: calcd. [M + 1]$^+$: 271.126667, found 271.126500. The fifth eluted fraction (R_f = 0.27 in ethyl acetate) was a tan solid, and was identified as *N*-(pyrid-3-yl)-4-(trimethylsilyl)benzamide (**13**) (0.88 g, 33%). An analytical sample was obtained as a colourless solid after recrystallisation from ethyl acetate/hexane (1:1); m.p. 152−154 °C. ^{1}H NMR {200 MHz, [D$_6$]DMSO, reference [D$_6$]DMSO (δ = 2.49 ppm)}: δ = 0.24 (s, 9 H, $SiMe_3$), 7.45−7.68 [m, 4 H, Ph(3,4,5)-H, Py(5)-H], 7.94−8.07 [m, 2 H, Ph(2,6)-H], 8.39 [s, 1 H, Py(2)-H], 8.48 [d, $^3J_{H,H}$ = 4.8 Hz, 1 H, Py(6)-H], 10.18 (s, 1 H, NH) ppm. ^{13}C NMR {[D$_6$]DMSO, reference [D$_6$]DMSO (δ = 39.5 ppm)]}: δ = −0.9 ($SiMe_3$), 127.6, 128.5, 128.9, 131.8, 133.8, 138.7, 146.7, 147.6, 149.1, 166.7 (CO) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max.}$ = 1680 (CO) cm^{-1}. $C_{15}H_{18}N_2OSi$ (270.41): calcd. C 66.63, H 6.71, N 10.36; found C 66.59, H 6.70, N 10.48. The sixth eluted fraction (R_f = 0.20 in ethyl acetate) was a yellow, viscous liquid, and appeared to be a mixture of *N*-(4-*b*utyl-pyrid-3-yl)benzamide (**10**) and starting *N*-(pyrid-3-yl)benzamide (**2**) (0.41 g) in a 2.18:1.00 molar ratio based on the ^{1}H NMR spectrum. On the basis of this ratio, the yield of product **10** was calculated to be 12% and the yield of recovered starting amide was calculated to be 6%. The mixture was five times heated under reflux with water (5 mL) for 10−15 min, and each time hot water was decanted from the organic liquid. After that, the residual liquid was dissolved in dichloromethane and dried with anhydrous magnesium sulfate. The solvent was distilled off under reduced pressure from the solution, and a yellow, viscous liquid was obtained which, according to the ^{1}H NMR and ^{13}C NMR spectra, appeared to be product **10**, free of the starting amide **2**. An analytical sample of compound **10** was obtained as a colourless, viscous liquid after repeated column chromatography on silica gel, using ethyl acetate/hexane (1:1) as eluent. ^{1}H NMR {200 MHz,

[D_6]DMSO, reference [D_6]DMSO (δ = 2.49 ppm)}: δ = 0.82 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, Me), 1.10−1.38 (m, 2 H, CH_2), 1.40−1.64 (m, 2 H, CH_2), 2.54−2.70 (m, 2 H, PyCH_2), 7.32 [d, $^3J_{H,H}$ = 4.9 Hz, 1 H, Py(5)-H], 7.44−7.68 [m, 3 H, Ph(3,4,5)-H], 7.89−8.06 [m, 2 H, Ph(2,6)-H], 8.36 [d, $^3J_{H,H}$ = 4.8 Hz, 1 H, Py(6)-H], 8.43 [s, 1 H, Py(2)-H], 10.12 (s, 1 H, NH) ppm. ^{13}C NMR {[D_6]DMSO, reference [D_6]DMSO (δ = 39.5 ppm)}: δ = 13.7, 21.9, 29.9, 30.6 (PyCH_2), 124.1, 127.6, 128.5, 131.8, 134.0, 147.2, 147.5, 148.5, 166.1 (CO) ppm. IR ((film): $\tilde{\nu}_{max.}$ = 1651 (CO) cm^{-1}. HRMS for $C_{16}H_{18}N_2O$: calcd. $[M]^+$: 254.141913, found 254.142000.

General Procedure for the Lithiation of the Amides 14−17: *n*BuLi or *s*BuLi (10 mmol) was added to the anilides **14**−**17** (5 mmol) with or without TMEDA (10 mmol) and stirred in THF (50 mL) at −78 °C. In the case when *n*BuLi was used, two procedures were applied. The reaction mixture was kept at −78 °C for 2 h and next was quenched with MeOD; or the solution was kept at −78 °C for 0.25 h, warmed to 0 °C, kept at 0 °C for 0.1 h and again cooled to −78 °C before quenching with MeOD. When *s*BuLi was used, the reaction mixture was kept at −78 °C for 2 h before adding MeOD. The D content was determined by ^{1}H NMR spectroscopy (500 MHz, [D_6]DMSO) using the following peak areas: For Amide **14**: δ = 7.94 [dd, $^4J_{H,H}$ = 1.2 Hz, $^3J_{H,H}$ = 8.3 Hz, 2 H, Ph^1(2,6)-H], 7.61−7.56 [m, 1 H, Ph^1(4)-H] ppm. For Amide **15**: δ = 8.17−8.09 [m, 1 H, Py(3)-H], 8.06 [dd, $^4J_{H,H}$ = 1.7 Hz, $^3J_{H,H}$ = 7.7 Hz, 1 H, Py(4)-H] ppm. For Amide **16**: δ = 8.75 [dd, $^4J_{H,H}$ = 1.4 Hz, $^3J_{H,H}$ = 4.4 Hz, 2 H, Py(2,6)-H], 7.85 [dd, $^4J_{H,H}$ = 1.4 Hz, $^3J_{H,H}$ = 4.4 Hz, 2 H, Py(3,5)-H] ppm. For Amide **17**: δ = 7.83 [d, $^3J_{H,H}$ = 7.8 Hz, 2 H, Ph^1(2,6)-H], 7.15 [t, $^3J_{H,H}$ = 7.5 Hz, 1 H, Ph^2(4)-H] ppm. In the case of the reaction of *N*-phenylpyridine-2-carboxamide (**15**), on increasing the temperature to 0 °C, analysis (TLC; diisopropyl ether) showed anilide **15** (R_f = 0.39) and two additional spots (R_f = 0.48, 0.57). Preparative TLC (diisopropyl ether) resulted in three fractions. The first one (R_f = 0.57) was a yellow, viscous liquid (36 mg), which, according to the ^{1}H and ^{13}C NMR spectra, appeared to be an undefined, complex mixture, and no further attempts at its identification were undertaken. The second fraction (R_f = 0.48) was a mixture of 1-(pyridin-2-yl)pentan-1-one (**18**) and 6-butyl-*N*-phenylpyridine-2-carboxamide (**19**) in a molar ratio of 2:1. Kugelrohr distillation (oil bath 190 °C, 20 Torr, ref.[35] b.p. 60/0.4 Torr) gave the ketone **18** (65 mg, 0.4 mmol) (yield 8%). ^{1}H NMR [200 MHz, $CDCl_3$, reference TMS (δ = 0.0 ppm)]: δ = 0.91−0.99 (m, 3 H, Me), 1.34−1.52 (m, 2 H, CH_2), 1.64−1.81 (m, 2 H, CH_2), 3.17−3.27 (m, 2 H, CH_2), 7.42−7.51 [m, 1 H, Py(5)-H], 7.83 [dd, $^4J_{H,H}$ = 1.7 Hz, $^3J_{H,H}$ = 7.7 Hz, 2 H, Py(4)-H], 8.04 [d, $^3J_{H,H}$ = 7.9 Hz, 1 H, Py(3)-H], 8.68 [d, $^3J_{H,H}$ = 4.8 Hz, 1 H, Py(6)-H] ppm. ^{13}C NMR [$CDCl_3$, reference TMS (δ = 0.0 ppm)]: δ = 13.9, 22.4, 26.1, 37.4, 121.7, 126.9, 136.8, 148.8, 153.5, 202.1 (CO) ppm. IR (film): $\tilde{\nu}_{max.}$ = 1699 (CO) cm^{-1}. The residue from the distillation was initially purified by column chromatography (acetone). The eluate was purified by evaporation of the solvent and kugelrohr distillation (oil bath 180 °C, 5 Torr) to give 6-butyl-*N*-phenylpyridine-2-carboxamide (**19**) (51 mg, 0.2 mmol, yield 4%). ^{1}H NMR [200 MHz, $CDCl_3$, reference TMS (δ = 0.0 ppm)]: δ = 0.91−0.99 (m, 3 H, Me), 1.34−1.52 (m, 2 H, CH_2), 1.64−1.81 (m, 2 H, CH_2), 3.17−3.27 (m, 2 H, CH_2), 7.09−7.19 [m, 1 H, Ph(4)-H], 7.28−7.44 [m, 3 H, Ph(3,5), Py(5)-H], 7.73−7.84 [m, 3 H, Ph(2,6), Py(4)-H], 8.11 [d, $^3J_{H,H}$ = 7.7 Hz, 1 H, Py(3)-H], 10.12 [br. s, 1 H, NH] ppm. ^{13}C NMR [$CDCl_3$, reference TMS (δ = 0.0 ppm)]: δ = 13.9, 22.4, 31.6, 37.6, 119.7, 124.2, 125.6, 129.0, 137.7, 137.8, 149.1, 161.2, 162.3 (CO) ppm. IR (film): $\tilde{\nu}_{max.}$ = 1689 (CO) cm^{-1}. The third fraction (R_f = 0.39) was the anilide **15** (729 mg, 4 mmol, yield 80%).

Competitive Lithiation Tests for Mixture of Amides 14−17: The competitive lithiation tests for the mixtures of amides **14/15**, **14/16** and **14/17** were carried out as follows: *n*BuLi or *s*BuLi (15.5 mmol) was added to the particular equimolecular mixture of amides (10.0 mmol) in THF (100 mL), and the general procedure was used, following the periods of time and the temperature of the reactions.

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