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Synthesis and deprotonation of 2-(pyridyl)phenols and 2-(pyridyl)anilines

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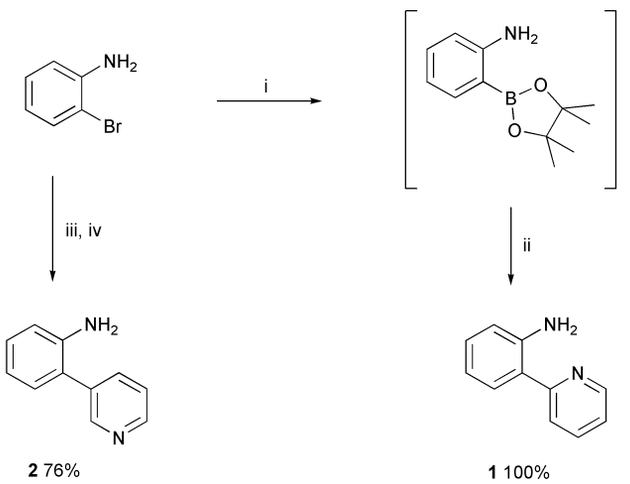
2-(2- and 3-Pyridyl)anilines (**1**, **2**), 2,2-dimethyl-*N*-[2-(2- and 3-pyridyl)phenyl]propanamides (**3**, **4**), and 2-, 3- and 4-(2-methoxyphenyl)pyridines (**7**–**9**) are readily synthesized using cross-coupling reactions. Whereas the amines **1**, **2** undergo side reactions, the corresponding amides **3**, **4** are deprotonated with lithium 2,2,6,6-tetramethylpiperidide (LTMP): the compound **3** at C6′ under *in situ* quenching, and the compound **4** at C4′. When the ether **7** is subjected to the same reagent, lithiation occurs at C6′.

Introduction

Directed *ortho*-metallation (DoM) plays an important role in modern organic synthesis.[1] Despite the maturity long since gained by the method, the way a substituent acts in its vicinity remains incompletely understood. A heteroatom-containing unit (known as the directed metallation group, DMG) coordinates the base and, by amplifying this interaction at the transition state, lowers the energy of activation for the deprotonation process; it also stabilizes the lithio derivative. However, while an electron-withdrawing substituent also acidifies the ring hydrogens in its environment (mostly at the *ortho* position), an electron-donating substituent only facilitates the deprotonation at nearby sites (not necessarily at the *ortho* position) through coordination to the Lewis acidic metal.[2–5] The amino- and hydroxy-based DMGs stand out as particularly useful for subsequent elaborations. In the π-deficient azaaromatic series, *N*-(pyridyl)amides and alkoxypyridines have been deprotonated at ring positions adjacent to the DMG.[6,7] Conversely, to our knowledge, studies concerning the deprotonation of a pyridine ring directed by such groups from a remote position have not been reported.

We therefore decided to synthesize nitrogen- and oxygen-based (2-substituted phenyl)pyridines and study their metallation.



Scheme 1 *Synthesis of 2-(pyridyl)anilines*: (i) pinacolborane, 0.05 equiv. $Pd(OAc)_2$, 0.2 equiv. [1,1′-biphenyl]-2-yldicyclohexylphosphine, Et_3N, dioxane, 80 °C, 1 h; (ii) 2-bromopyridine, $Ba(OH)_2$, H_2O, 100 °C, 4 h; (iii) pinacolborane, 0.05 equiv. $PdCl_2(dppf)$, Et_3N, dioxane, 100 °C, 4 h; (iv) 3-bromopyridine, $Ba(OH)_2$, H_2O, 100 °C, 4 h.

Results and discussion

2-(Pyridyl)anilines

2-(2- and 3-Pyridyl)anilines (**1**, **2**) were easily obtained, using the procedure[8] described by Baudoin and co-workers for the synthesis of 2,2′-disubstituted biphenyls. Thus, borylation of 2-bromoaniline followed by *in situ* cross-coupling with 2- and 3-bromopyridines afforded the amino compounds **1**, **2** in good to excellent yields (Scheme 1).

Lithiation in the 2-phenylaniline series was accomplished by Narasimhan and co-workers.[9–12] They showed that the amino group was capable of directing the deprotonation of 2-phenylaniline at C2′ when BuLi was used.[9,13]

In our case, various attempts to metallate 2-(2- and 3-pyridyl)anilines (**1**, **2**) with BuLi or other alkyllithiums were unsuccessful. The addition products obtained using BuLi are in good agreement with the low LUMO energy values of the substrates. Since the soft character of BuLi favours nucleophilic reactivity, we turned to the harder lithium dialkylamides, which usually leads to preferential protophilic attack.[6] When exposed to lithium dialkylamides such as lithium diisopropylamide (LDA) or lithium 2,2,6,6-tetramethylpiperidide (LTMP) in tetrahydrofuran (THF), the compounds **1**, **2** either remained unchanged or underwent degradation reactions, depending on conditions used. For these reasons, we decided to turn to the corresponding amides.

2,2-Dimethyl-*N*-[2-(pyridyl)phenyl]propanamides

2,2-Dimethyl-*N*-[2-(2- and 3-pyridyl)phenyl]propanamides (**3**, **4**) were prepared by cross-coupling between 2-[(2,2-dimethyl-1-oxopropyl)amino]phenylboronic acid[14] and the required bromopyridines under Suzuki's conditions[15] (Scheme 2).

BuLi, which could allow the lithiation of 2,2-dimethyl-*N*-phenylpropanamide,[16] did not prove to be convenient for the deprotonation of amides **3** and **4**, only addition products being obtained.

LTMP could help to bias the reactions in favour of deprotonation. Metallation of the compound **3** could be effected at C6′ in THF at rt using *in situ* quenching with chlorotrimethylsilane. Under these kinetic control conditions, chelation of the lithium atom of the base by the pyridine nitrogen (or by both the DMG and the pyridine nitrogen) is favoured over an acid–base mechanism, which would have promoted the abstraction of the most acidic H4′ proton[6] (Scheme 3).

The reaction of the compound **3** with an excess of the base, followed by deuteriolysis, gave a mixture of deuterated isomers:

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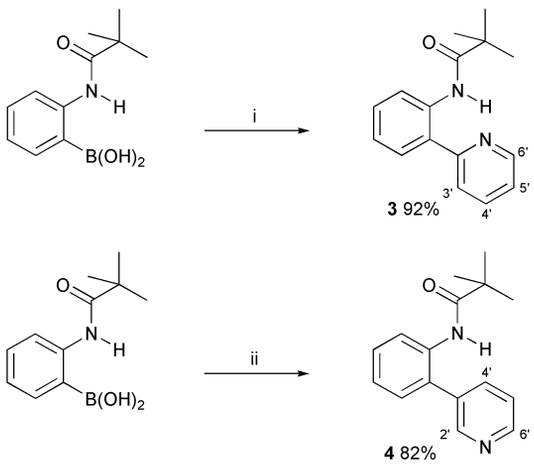
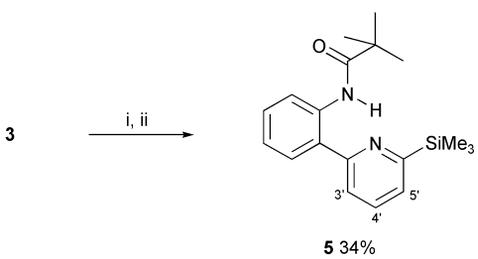


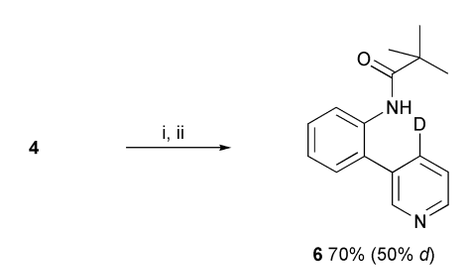
Scheme 2 *Synthesis of 2,2-dimethyl-N-[2-(pyridyl)phenyl]propanamides*: (i) 2-bromopyridine, 0.03 equiv. $Pd(PPh_3)_4$, K_2CO_3, H_2O, EtOH, toluene, reflux, 3 days; (ii) 3-bromopyridine, 0.03 equiv. $Pd(PPh_3)_4$, K_2CO_3, H_2O, EtOH, toluene, reflux, 3 days.



Scheme 3 *Metallation of the amide 3*: (i) 5 equiv. LTMP, 5 equiv. $ClSiMe_3$, THF, rt, 2 h; (ii) hydrolysis.

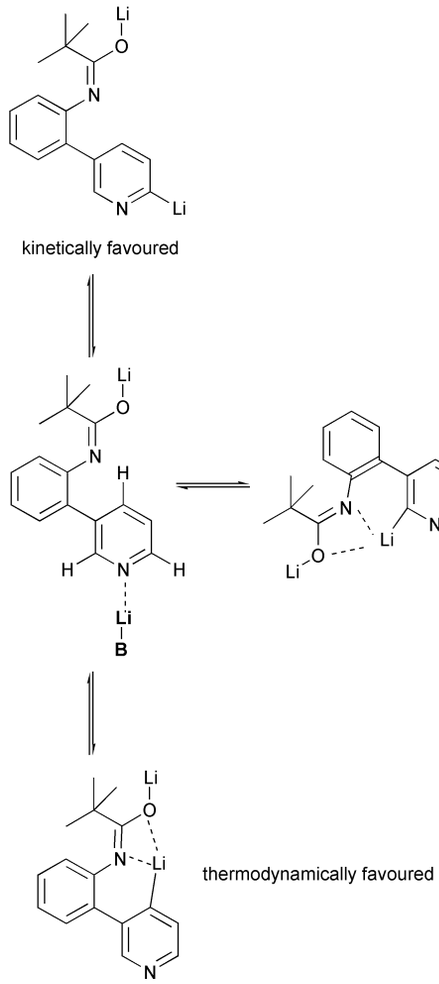
under reversible conditions, isomerization of the initially formed 6-lithiopyridine[17] to more stable derivatives lithiated at C3′ (stabilization through chelation of the metal with the DMG) and at C4′ or C5′ (no more electronic repulsion between the carbanion and the lone pair of the azine nitrogen) could direct the course of the reaction. Attempts to obtain a single lithio derivative by conducting the reaction at higher temperatures or by prolonging the reaction time (thermodynamic control) failed due to degradation reactions.

Metallation of the compound **4** could be effected in THF at 0 °C, using *in situ* quenching with chlorotrimethylsilane. Under these kinetic control conditions, a 66 : 34 mixture of compounds silylated at C6′ and C2′ is produced. In return, when the trapping step (deuteriolysis) was conducted after a 2 h contact between the compound **4** and LTMP at 0 °C (thermodynamic control), the product **6** was isolated (Scheme 4).



Scheme 4 *Metallation of the amide 4*: (i) 5 equiv. LTMP, THF, 0 °C, 2 h; (ii) deuteriolysis.

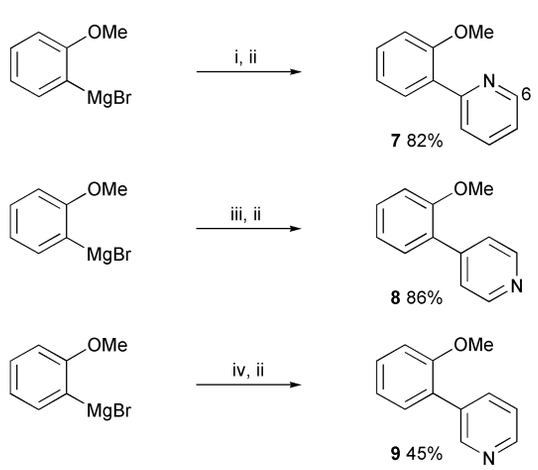
Chelation of the lithium atom of the base by the pyridine nitrogen first results in a deprotonation at C6′ and/or C2′. Next, the 6- and 2-lithiopyridines[17] isomerize to the more stable 4-pyridyllithium (stabilization through chelation of the metal with the DMG, and no more electronic repulsion between the carbanion and the lone pair of the azine nitrogen) (Scheme 5).



Scheme 5

(2-Methoxyphenyl)pyridines

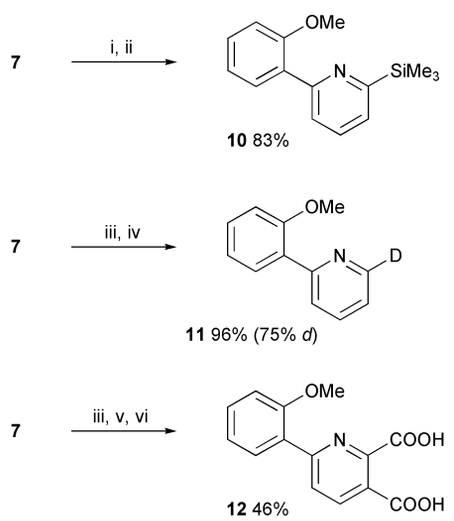
2-, 3- and 4-(2-Methoxyphenyl)pyridines (**7**–**9**) were synthesized by cross-coupling reactions[18] between 2-methoxyphenylmagnesium bromide and the required chloropyridines under nickel catalysis (Scheme 6).



Scheme 6 *Synthesis of (2-methoxyphenyl)pyridines*: (i) 2-chloropyridine, 0.05 equiv. $Ni(acac)_2$, 0.05 equiv. dppp, THF, rt, 18 h; (ii) hydrolysis; (iii) 4-chloropyridinium chloride, 0.05 equiv. $Ni(acac)_2$, 0.05 equiv. dppp, THF, rt, 18 h; (iv) 3-chloropyridine, 0.05 equiv. $Ni(acac)_2$, 0.05 equiv. dppp, THF, rt, 18 h.

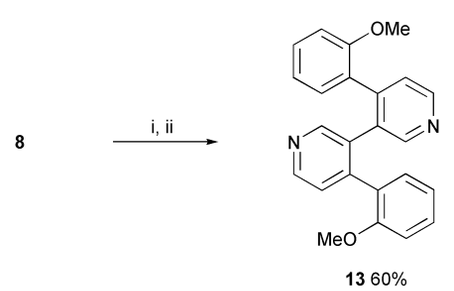
The experiments with the nitrogen-based DMGs led us to attempt the metallation of the ethers **7**–**9** using lithium dialkylamides. As previously described for the compound **3**, metallation of the compound **7** and *in situ* quenching with

chlorotrimethylsilane in THF occurred at C6, leading to the compound **10**. The same lithio derivative was formed when the compound **7** was treated with an excess of LTMP in THF at −15 °C, as demonstrated by deuteriolysis, giving the compound **11**. Nevertheless, intercepting the lithio derivative with dry ice did not afford the corresponding pyridinecarboxylic acid: 6-(2-methoxyphenyl)pyridine-2,3-dicarboxylic acid (**12**) was obtained, probably through deprotonation of the lithium pyridine-2-carboxylate during the trapping step, as we have previously shown [19] (Scheme 7).



Scheme 7 *Metallation of the ether 7*: (i) 3 equiv. LTMP, 3 equiv. $ClSiMe_3$, THF, 0 °C, 2 h; (ii) hydrolysis; (iii) 3 equiv. LTMP, THF, −15 °C, 0.25 h; (iv) deuteriolysis; (v) CO_2 in excess; (vi) acidic hydrolysis.

Conducting the reaction at rt with the ether **8** gave an unexpected result. Under these conditions, the dimer **13** was obtained; the coupling reaction observed could be rationalized by a single electron transfer route, as already mentioned in the pyridine series [6] (Scheme 8).



Scheme 8 *Metallation of the ether 8*: (i) 3 equiv. LTMP, THF, rt, 2 h; (ii) hydrolysis.

Metallation of the compound **9** was not observed using lithium dialkylamides; with BuLi, only nucleophilic addition products at C6 were obtained.

Conclusion

This work describes the remote metallation promoting power of amino- and hydroxy-based groups. For this purpose, various (2-substituted phenyl)pyridines have been synthesized using cross-coupling reactions. As already observed for the *ortho*-metallation,[17] the pivalamido function seems more suitable to stabilize a remote metallated site than the methoxy unit.

Experimental

General

Melting points were measured on a Kofler apparatus. NMR spectra were recorded on a Bruker AM 300 spectrometer (^{1}H at 300 MHz and ^{13}C decoupled spectra at 75 MHz) with residual protic solvent as the internal reference. Chemical shifts are quoted in ppm and coupling constants in Hz. IR spectra were taken on a Perkin-Elmer FT IR 205 spectrometer. Elemental analyses were performed on a Carlo Erba 1106 apparatus.

THF and dioxane were distilled from benzophenone–Na. Reactions were carried out under dry N_2. Silica gel (Geduran Si 60, 0.063–0.200 mm) was purchased from Merck. 2-Methoxyphenylmagnesium bromide (1 mol dm^{-3} in THF) was purchased from Aldrich in Sure/Seal™ bottles. BuLi (2.5 mol dm^{-3} in hexane) was supplied by Aldrich, $PdCl_2$(dppf) and $Ni(acac)_2$ by Avocado, and dppp by Lancaster. Petrol refers to petroleum ether (bp 40–60 °C).

Note: unless otherwise specified 'work-up' refers to extraction with diethyl ether (20 cm^3) and DCM (2 × 20 cm^3), followed by drying ($MgSO_4$) and removal of the solvent *in vacuo*.

Starting materials

$Pd(PPh_3)_4$ [20] and [2-[(2,2-dimethyl-1-oxopropyl)amino]phenyl]-boronic acid [14] were prepared using procedures reported in the literature.

2-(2-Pyridyl)aniline 1. To a solution of 2-bromoaniline (86 mg, 0.50 mmol) in dioxane (1 cm^3) were added triethylamine (0.28 cm^3, 2.0 mmol), $Pd(OAc)_2$ (5.7 mg, 25 μmol), [1,1′-biphenyl]-2-yldicyclohexylphosphine (36 mg, 0.10 mmol), and pinacolborane (0.22 cm^3, 1.5 mmol) dropwise. The mixture was stirred at 80 °C for 1 h and then cooled to rt, and water (0.22 cm^3), $Ba(OH)_2{\cdot}8H_2O$ (0.47 g, 1.5 mmol), and 2-bromopyridine (48 mm^3, 0.50 mmol) were successively added. The mixture was stirred at 100 °C for 4 h before addition of water (5 cm^3) at rt. Column chromatography on silica gel (9 : 1 DCM–Et_2O) afforded **1** (85 mg, 100%), which was identified by comparison of its physical and spectral data with those described [21] (Found: C, 77.6; H, 5.9; N, 16.4. $C_{11}H_{10}N_2$ requires: C, 77.6; H, 5.9; N, 16.5%).

2-(3-Pyridyl)aniline 2. To a solution of 2-bromoaniline (86 mg, 0.50 mmol) in dioxane (1 cm^3) were added triethylamine (0.28 cm^3, 2.0 mmol), $PdCl_2$(dppf) (21 mg, 25 μmol), and pinacolborane (0.22 cm^3, 1.5 mmol) dropwise. The mixture was stirred at 100 °C for 4 h and then cooled to rt, and water (0.22 cm^3), $Ba(OH)_2{\cdot}8H_2O$ (0.47 g, 1.5 mmol), and 3-bromopyridine (48 mm^3, 0.50 mmol) were successively added. The mixture was stirred at 100 °C for 4 h before addition of water (5 cm^3) at rt. Column chromatography on silica gel (7 : 3 DCM–Et_2O) afforded **2** (65 mg, 76%) as a pale yellow oil (Found: C, 77.3; H, 6.2; N, 16.2. $C_{11}H_{10}N_2$ requires: C, 77.6; H, 5.9; N, 16.5%); ν_{max}(KBr)/cm^{-1} 3343, 3215, 1620, 1499, 1474, 1407, 752 and 716; δ_H($CDCl_3$) 3.66 (2 H, br s, NH_2), 6.72 (1 H, dd, *J* 8.3 and 0.8, 6-H), 6.78 (1 H, td, *J* 7.5 and 1.1, 5-H), 7.03 (1 H, dd, *J* 7.5 and 1.7, 3-H), 7.13 (1 H, td, *J* 7.9 and 1.5, 4-H), 7.30 (1 H, ddd, *J* 7.9, 4.9 and 0.8, 5′-H), 7.74 (1 H, dt, *J* 7.9 and 1.9, 4′-H), 8.52 (1 H, dd, *J* 4.9 and 1.5, 6′-H), 8.64 (1 H, d, *J* 1.5, 2′-H); δ_C($CDCl_3$) 116.3 (6-C), 119.3 (4-C), 123.9 (5′-C), 124.1 (2-C), 129.7 (4′-C), 130.9 (3-C), 135.6 (3′-C), 136.9 (5-C), 144.1 (6′-C), 148.8 (2′-C), 150.5 (1-C).

2,2-Dimethyl-*N*-[2-(2-pyridyl)phenyl]propanamide 3. A degassed mixture of 2-bromopyridine (0.48 cm^3, 5.0 mmol), K_2CO_3 (1.4 g, 10 mmol), water (5 cm^3), EtOH (2.5 cm^3), toluene (50 cm^3), 2-[(2,2-dimethyl-1-oxopropyl)amino]phenylboronic acid (1.4 g, 6.5 mmol) and $Pd(PPh_3)_4$ (0.17 g, 0.15 mmol) was heated at reflux for 3 days. Column chromatography on silica gel (1 : 1 petrol–AcOEt) afforded **3** (1.2 g, 92%) as a yellow oil (Found: C, 75.3; H, 7.2; N, 11.1. $C_{16}H_{18}N_2O$ requires: C, 75.6; H, 7.1; N, 11.0%); ν_{max}(KBr)/cm^{-1} 2964, 1676, 1589, 1526, 1476, 1313 and 1166; δ_H($CDCl_3$) 1.24 (9 H, s, Bu^t), 7.08 (1 H, td, *J* 7.5 and 1.3, 4-H), 7.21 (1 H, ddd, *J* 7.5, 5.3 and 1.1, 5′-H), 7.33

(1 H, td, *J* 8.7 and 1.5, 5-H), 7.58 (1 H, dd, *J* 7.5 and 1.5, 6-H), 7.67 (1 H, d, *J* 8.3, 3-H), 7.78 (1 H, td, *J* 8.3 and 1.9, 4′-H), 8.5 (2 H, m, 3′-H and 6′-H), 12.24 (1 H, s, NH); $\delta_C(CDCl_3)$ 28.1 (CMe_3), 40.6 (CMe_3), 122.3 (6-C), 122.4 (5′-C), 123.4 (4-C), 123.6 (5-C), 126.3 (2-C), 129.2 (3′-C), 130.4 (3-C), 138.1 (4′-C), 138.4 (1-C), 147.6 (6′-C), 158.8 (2′-C), 177.9 (CO).

2,2-Dimethyl-*N*-[2-(3-pyridyl)phenyl]propanamide 4. Compound **4** was obtained as described above, using 3-bromopyridine (0.48 cm^3, 5.0 mmol) instead of 2-bromopyridine. Column chromatography on silica gel (4 : 1 petrol–AcOEt) afforded **4** (1.0 g, 82%) as a white powder; mp 111 °C (Found: C, 75.4; H, 7.1; N, 10.7. $C_{16}H_{18}N_2O$ requires: C, 75.6; H, 7.1; N, 11.0%); ν_{max}(KBr)/cm^{-1} 3302, 3056, 2952, 1685, 1518, 1440, 1164 and 756; $\delta_H(CDCl_3)$ 1.06 (9 H, s, Bu^t), 7.15 (2 H, m, 4- and 5′-H), 7.35 (2 H, m, 4′-H and 6-H), 7.64 (1 H, dt, *J* 7.5 and 1.9, 5-H), 8.13 (1 H, d, *J* 7.7, 3-H), 8.59 (1 H, s, 2′-H), 8.60 (1 H, d, *J* 4.9, 6′-H), 11.67 (1 H, s, NH); $\delta_C(CDCl_3)$ 27.8 (CMe_3), 40.0 (CMe_3), 123.4 (6-C), 124.1 (4-C), 125.4 (5′-C), 129.8 (5-C), 130.2 (2-C), 130.5 (3-C), 134.8 (3′-C), 135.4 (1-C), 137.6 (4′-C), 149.1 (6′-C), 150.0 (2′-C), 177.0 (CO).

2,2-Dimethyl-*N*-[2-[6-(trimethylsilyl)-2-pyridyl]phenyl]propanamide 5. To a mixture of **3** (0.10 g, 0.39 mmol) and $ClSiMe_3$ (0.25 cm^3, 2.0 mmol) in THF (3 cm^3) at 0 °C was added a solution of LTMP [obtained by adding BuLi (2.0 mmol) to a solution of 2,2,6,6-tetramethylpiperidine (0.35 cm^3, 2.1 mmol) in THF (2 cm^3) at 0 °C]. The mixture was stirred at rt for 2 h before hydrolysis with water (5 cm^3). Column chromatography on silica gel (9 : 1 petrol–AcOEt) afforded **5** (43 mg, 34%) as a yellow powder; mp 134 °C; ν_{max}(KBr)/cm^{-1} 3306, 2959, 2926, 1681, 1586, 1434, 1248, 1207, 755; $\delta_H(CDCl_3)$ 0.31 (9 H, s, $SiMe_3$), 1.50 (9 H, s, Bu^t), 7.09 (1 H, t, *J* 7.5, 4-H), 7.35 (3 H, m, 3-H, 4′-H and 5′-H), 7.44 (1 H, d, *J* 7.5, 6-H), 7.67 (1 H, t, *J* 7.7, 5-H), 8.23 (1 H, d, *J* 8.3, 3′-H), 10.38 (1 H, s, NH); $\delta_C(CDCl_3)$ 0.0 ($SiMe_3$), 29.0 (CMe_3), 40.8 (CMe_3), 124.3 (6-C), 124.8 (5′-C), 125.1 (4-C), 129.0 (5-C), 130.3 (3′-C), 131.2 (3-C), 131.7 (2-C), 136.8 (4′-C), 137.4 (1-C), 160.2 (2′-C), 168.5 (6′-C), 178.4 (CO); *m*/*z* (EI) 326 (M$^+$), 254 (M − SiC_3H_9).

2,2-Dimethyl-*N*-[2-(4-deuterio-3-pyridyl)phenyl]propanamide 6. To a solution of **4** (0.10 g, 0.39 mmol) in THF (3 cm^3) at 0 °C was added a solution of LTMP [obtained by adding BuLi (2.0 mmol) to a solution of 2,2,6,6-tetramethylpiperidine (0.35 cm^3, 2.1 mmol) in THF (2 cm^3) at 0 °C]. The mixture was stirred at rt for 2 h before addition of D_2O (0.1 cm^3). Column chromatography on silica gel (9 : 1 petrol–AcOEt) afforded **6** (70 mg, 70%, 50% *d*). The characteristics of this product were found to be identical to those described for **4** except for ^{1}H and ^{13}C NMR spectra where the 4′-H and 4′-C signals respectively had disappeared.

2-(2-Methoxyphenyl)pyridine 7. To a mixture of 2-chloropyridine (95 mm^3, 1.0 mmol), $Ni(acac)_2$ (13 mg, 50 μmol) and dppp (21 mg, 50 μmol) in THF (3 cm^3) was added dropwise 2-methoxyphenylmagnesium bromide (1.2 mmol). The mixture was stirred for 18 h at rt before hydrolysis with water (5 cm^3). Column chromatography on silica gel (95 : 5 DCM–Et_2O) afforded **7** (0.15 g, 82%), which was identified by comparison of its physical and spectral data with those described.[22]

4-(2-Methoxyphenyl)pyridine 8. Compound **8** was obtained as described above, using 4-chloropyridinium chloride (0.15 g, 1.0 mmol) instead of 2-chloropyridine, and 2-methoxyphenylmagnesium bromide (2.4 mmol instead of 1.2 mmol). Column chromatography on silica gel (4 : 1 DCM–Et_2O) afforded **8** (0.16 g, 86%), which was identified by comparison of its physical and spectral data with those described[23] (Found: C, 77.9; H, 6.0; N, 7.6. $C_{12}H_{11}NO$ requires: C, 77.8; H, 6.0; N, 7.6%); ν_{max}(KBr)/cm^{-1} 3069, 3016, 2965, 2930, 2836, 1606, 1590, 1484, 1458, 1409, 1271, 1233, 1121, 1024, 1016, 828, 761 and 610; $\delta_C(CDCl_3)$ 55.9 (OMe), 111.8 (3-C), 121.4 (3-C and 5-C), 124.7 (5′-C), 128.1 (1′-C), 130.5 (4′-C), 130.8 (6′-C), 146.7 (4-C), 149.9 (2-C and 6-C), 156.9 (2′-C).

3-(2-Methoxyphenyl)pyridine 9.[24,25] Compound **9** was obtained as described above, using 3-chloropyridine (95 mm^3, 1.0 mmol) instead of 2-chloropyridine. Column chromatography on silica gel (4 : 1 DCM–Et_2O) afforded **9** (83 mg, 45%) as a colourless oil; ν_{max}(KBr)/cm^{-1} 3400, 3029, 2938, 2836, 1600, 1498, 1464, 1408, 1267, 1242, 1027, 756 and 713; $\delta_H(CDCl_3)$ 3.76 (3 H, s, OMe), 7.0 (2 H, m, 5′-H and 6′-H), 7.3 (3 H, m, 3′-H, 4′-H and 5-H), 7.79 (1 H, dt, *J* 7.9 and 1.9, 4-H), 8.48 (1 H, dd, *J* 4.9, 1.5, 6-H), 8.69 (1 H, d, *J* 1.9, 2-H); $\delta_C(CDCl_3)$ 55.9 (OMe), 111.6 (3-C), 121.4 (5′-C), 123.3 (5-C), 129.9 (6′-C), 131.0 (4′-C), 137.2 (4-C), 148.3 (6-C), 150.7 (2-C), quaternary carbons not detected; *m*/*z* (CI) 186 (100%, M + H$^+$).

2-(2-Methoxyphenyl)-6-(trimethylsilyl)pyridine 10. To a mixture of **7** (0.21 g, 1.1 mmol) and $ClSiMe_3$ (0.43 cm^3, 3.4 mmol) in THF (3 cm^3) at 0 °C was added a solution of LTMP [obtained by adding BuLi (3.4 mmol) to a solution of 2,2,6,6-tetramethylpiperidine (0.61 cm^3, 3.6 mmol) in THF (2 cm^3) at 0 °C]. The mixture was stirred at 0 °C for 2 h before hydrolysis with water (5 cm^3) to afford **10** (0.24 g, 83%) as a colourless oil; ν_{max}(KBr)/cm^{-1} 3369, 2955, 1492, 1441, 1259, 1246, 860, 840, 754 and 620; $\delta_H(CDCl_3)$ 0.22 (9 H, s, $SiMe_3$), 3.74 (3 H, s, OMe), 6.87 (1 H, d, *J* 8.3, 3′-H), 6.96 (1 H, td, *J* 7.5 and 0.75, 5′-H), 7.24 (1 H, td, *J* 8.3 and 1.9, 4′-H), 7.27 (1 H, dd, *J* 7.2 and 1.1, 5-H), 7.46 (1 H, t, *J* 7.8, 4-H), 7.65 (1 H, dd, *J* 7.9 and 1.1, 6′-H), 7.79 (1 H, dd, *J* 7.5 and 1.9, 3-H); $\delta_C(CDCl_3)$ 0.0 ($SiMe_3$), 57.3 (OMe), 113.0 (3′-C), 122.7 (3-C), 125.0 (1′-C), 125.7 (5′-C), 128.2 (5-C), 131.3 (4′-C), 133.3 (6′-C), 135.0 (4-C), 136.8 (6-C), 139.9 (2-C), 158.2 (2′-C); *m*/*z* (CI) 258 (M + H$^+$). Compound **10** could not be purified over column chromatography (silica or alumina gel) because of its instability.

6-Deuterio-2-(2-methoxyphenyl)pyridine 11. To a solution of **7** (0.10 g, 0.54 mmol) in THF (3 cm^3) at −15 °C was added a solution of LTMP [obtained by adding BuLi (1.6 mmol) to a solution of 2,2,6,6-tetramethylpiperidine (0.29 cm^3, 1.7 mmol) in THF (2 cm^3) at 0 °C]. The mixture was stirred at −15 °C for 15 min before addition of D_2O (0.1 cm^3). Column chromatography on silica gel (95 : 5 DCM–Et_2O) afforded **11** (96 mg, 96%, 75% *d*). The characteristics of this product were found to be identical to those described for **7** except for ^{1}H and ^{13}C NMR spectra where the 6-H and 6-C signals respectively had disappeared.

6-(2-Methoxyphenyl)pyridine-2,3-dicarboxylic acid 12. To a solution of **7** (0.10 g, 0.54 mmol) in THF (3 cm^3) at −15 °C, was added a solution of LTMP [obtained by adding BuLi (1.6 mmol) to a solution of 2,2,6,6-tetramethylpiperidine (0.29 cm^3, 1.7 mmol) in THF (2 cm^3) at 0 °C]. The mixture was stirred at −15 °C for 15 min and then poured onto an excess of freshly crushed dry ice. After evaporation to dryness, the residue was diluted with water (5 cm^3), the aqueous phase washed with Et_2O and acidified to pH 3. Compound **12** (68 mg, 46%) was recovered by filtration and dried; mp 174 °C (dec.) (Found: C, 61.5; H, 4.1; N, 5.2. $C_{14}H_{11}NO_5$ requires: C, 61.5; H, 4.1; N, 5.1%); ν_{max}(KBr)/cm^{-1} 3436, 3063, 2957, 2360, 1732, 1600, 1471, 1362, 1278, 1247, 1015 and 762; δ_H(DMSO-d_6) 3.93 (3 H, s, OMe), 7.14 (1 H, t, *J* 7.5, 4′-H), 7.24 (1 H, d, *J* 8.3, 5-H), 7.52 (1 H, td, *J* 7.7 and 1.5, 5′-H), 7.82 (1 H, dd, *J* 7.5 and 1.9, 3′-H), 8.09 (1 H, d, *J* 8.3, 4-H), 8.30 (1 H, d, *J* 8.3, 6′-H); δ_C(DMSO-d_6) 56.1 (OMe), 112.4 (3′-C), 121.1 (5′-C), 123.1 (3-C), 125.5 (1′-C), 126.8 (5-C), 131.2 (4′-C), 131.7 (6′-C), 138.1 (4-C), 153.0 (2-C), 157.4 (6-C), 157.4 (2′-C), 166.5 (CO), 168.3 (CO).

4,4′-Bis(2-methoxyphenyl)-3,3′-bipyridine 13. To a solution of **8** (0.10 g, 0.54 mmol) in THF (3 cm^3) at 0 °C was added a solution of LTMP [obtained by adding BuLi (1.6 mmol) to a solution of 2,2,6,6-tetramethylpiperidine (0.29 cm^3, 1.7 mmol) in THF (2 cm^3) at 0 °C]. The mixture was stirred at rt for 2 h before hydrolysis with water (2 cm^3). Column chromatography on silica gel (9 : 1 DCM–Et_2O) afforded **13** (60 mg, 60%) as a pale yellow powder; mp 208 °C (Found: C, 78.1; H, 5.7; N, 7.8. $C_{24}H_{20}N_2O_2$ requires: C, 78.2; H, 5.5; N, 7.6%); ν_{max}(KBr)/cm^{-1} 3017, 2931, 2836, 1733, 1600, 1588, 1540, 1463, 1244, 1126, 1056, 761; δ_H($CDCl_3$) 3.78 (3 H, s, OMe), 6.95 (1 H, d, *J* 8.3, 6′-H), 7.00 (1 H, t, *J* 7.5, 5′-H), 7.33 (1 H, td, *J* 7.9 and 1.5, 4′-H), 7.39 (1 H, dd, *J* 7.5 and 1.5, 3′-H), 7.46 (1 H, d, *J* 4.9, 5-H), 8.50 (1 H, s, 2-H), 8.62 (1 H, d, *J* 4.9, 6-H); δ_C($CDCl_3$) 56.0 (OMe), 111.7 (3′-C), 121.4 (5-C), 122.2 (5′-C), 124.8 (3-C), 128.4 (1′-C), 130.4 (4′-C), 131.1 (6′-C), 147.7 (4-C), 149.2 (2-C), 156.7 (2′-C), 157.0 (6-C); *m*/*z* (CI) 369 (100%, M + H^+).

References

1 The concept emerged from the systematic studies of Gilman, Wittig and Hauser, and found numerous disciples, notably Gschwend, Beak and Snieckus: H. Gilman and R. L. Bebb, *J. Am. Chem. Soc.*, 1939, **61**, 109–112; G. Wittig and G. Fuhrmann, *Chem. Ber.*, 1940, **73B**, 1197–1218; C. R. Hauser and W. H. Puterbaugh, *J. Org. Chem.*, 1964, **29**, 853–856; H. W. Gschwend and H. R. Rodriguez, *Org. React.*, 1979, **26**, 1–360; V. Snieckus, *Chem. Rev.*, 1990, **90**, 879–933; D. R. Anderson, N. C. Faibish and P. Beak, *J. Am. Chem. Soc.*, 1999, **121**, 7553–7558.

2 J. D. Roberts and D. Y. Curtin, *J. Am. Chem. Soc.*, 1946, **68**, 1658–1660.

3 P. Beak and A. I. Meyers, *Acc. Chem. Res.*, 1986, **19**, 356–363.

4 G. W. Klumpp, *Recl. Trav. Chim. Pays-Bas*, 1986, **105**, 1–21.

5 J.-m. Fu, B.-p. Zhao, M. J. Sharp and V. Snieckus, *J. Org. Chem.*, 1991, **56**, 1683–1685.

6 G. Quéguiner, F. Marsais, V. Snieckus and J. Epsztajn, *Adv. Heterocycl. Chem.*, 1991, **52**, 187–304.

7 F. Mongin and G. Quéguiner, *Tetrahedron*, 2001, **57**, 4059–4090.

8 O. Baudoin, D. Guénard and F. Guéritte, *J. Org. Chem.*, 2000, **65**, 9268–9271.

9 N. S. Narasimhan and R. H. Alurkar, *Indian J. Chem.*, 1969, **7**, 1280.

10 N. S. Narasimhan and P. S. Chandrachood, *Synthesis*, 1979, 589–590.

11 N. S. Narasimhan, P. S. Chandrachood and N. R. Shete, *Tetrahedron*, 1981, **37**, 825–827.

12 N. S. Narasimhan and R. S. Mali, *Synthesis*, 1983, 957–986.

13 Note that BuLi could also lithiate 1-aminonaphthalene and various dibenzophenothiazines at the *peri* position of the amino substituent: C. Eaborn, P. Golborn and R. Taylor, *J. Organomet. Chem.*, 1967, **10**, 171–174; D. A. Shirley and J. C. Gilmer, *J. Org. Chem.*, 1962, **27**, 4421–4424.

14 P. Rocca, F. Marsais, A. Godard and G. Quéguiner, *Tetrahedron*, 1993, **49**, 49–64.

15 N. Miyaura, T. Yanagi and A. Suzuki, *Synth. Commun.*, 1981, **11**, 513–519.

16 W. Fuhrer and H. W. Gschwend, *J. Org. Chem.*, 1979, **44**, 1133–1136.

17 P. Gros, S. Choppin and Y. Fort, *J. Org. Chem.*, 2003, **68**, 2243–2247.

18 Concerning Kharasch cross-coupling reactions between arylmagnesium halides and aryl chlorides under nickel catalysis, see: S. Sengupta, M. Leite, D. S. Raslan, C. Quesnelle and V. Snieckus, *J. Org. Chem.*, 1992, **57**, 4066–4068; V. P. W. Böhm, T. Weskamp, C. W. K. Gstöttmayr and W. A. Herrmann, *Angew. Chem., Int. Ed.*, 2000, **39**, 1602–1604; V. Bonnet, F. Mongin, F. Trécourt, G. Breton, F. Marsais, P. Knochel and G. Quéguiner, *Synlett*, 2002, 1008–1010.

19 F. Mongin, F. Trécourt and G. Quéguiner, *Tetrahedron Lett.*, 1999, **40**, 5483–5486.

20 D. R. Coulson, *Inorg. Synth.*, 1972, **13**, 121.

21 P. Molina, A. Lorenzo and E. Aller, *Tetrahedron*, 1992, **48**, 4601–4616.

22 K. Maeyama, M. Kobayashi and N. Yonezawa, *Synth. Commun.*, 2001, **31**, 869–875.

23 E. Le Gall, C. Gosmini, J.-Y. Nédélec and J. Périchon, *Tetrahedron*, 2001, **57**, 1923–1927.

24 M. Ishikura, M. Kamada and M. Terashima, *Heterocycles*, 1984, **22**, 265–268.

25 D. D. Weller, G. R. Luellen and D. L. Weller, *J. Org. Chem.*, 1982, **47**, 4803–4806.