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Regioselectivities in deprotonation of 2-(4-chloro-2-pyridyl)benzoic acid and corresponding ester and amide

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Abstract—Upon treatment of ethyl 2-(4-chloro-2-pyridyl)benzoic acid, 2-(4-chloro-2-pyridyl)benzoate, and *N*,*N*-diisopropyl-2-(4-chloro-2-pyridyl)benzamide with LTMP at −75 °C in THF, the lithio derivatives at C5′ are generated regiospecifically, as demonstrated by subsequent quenching with electrophiles. The lithio derivative at C3′ is only evidenced from the benzamide at higher temperature (−50 °C), when treated with LTMP in THF; it instantly cyclizes to 1-chloro-4-azafluorenone. The latter is converted to onychine, an alkaloid endowed with anticandidal activity.

1. Introduction

Directed *ortho*-metallation (DoM) plays an important role in the modern organic synthesis.[1,2] Despite the maturity long since gained by the method, the way a substituent acts in its vicinity remains incompletely understood.

From all the directing groups, the carboxylic acid and derived functions stand out as particularly useful for subsequent elaborations. In the π-deficient aza-aromatic series, lithium pyridinecarboxylates, pyridineoxazolines and pyridinecarboxamides have been deprotonated at ring positions adjacent to the DMG.[2] Moreover, studies concern the deprotonation of a pyridine ring followed by in situ condensation with remote *N*,*N*-dialkylcarboxamide,[3] ester[4] or lithium carboxylate groups.[4b]

We here describe the unprecedented behavior of 2-(4-chloro-2-pyridyl)benzoic acid, its corresponding ethyl ester and *N*,*N*-diisopropyl amide, when compared to their non-chlorinated analogues (Scheme 1).

2. Results and discussion

The starting biaryl substrates were synthesized by cross-coupling reactions. The substituted ethyl 2-(2-pyridyl)-benzoates **1** and **2** were prepared by reactions between ethyl 2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoate[5] and 4-chloro-2-iodopyridine[6] or 2-bromo-4-methylpyridine, respectively, using previously reported conditions.[5] Hydrolyses of the esters allowed the acids **3** and **4** to be obtained (Scheme 2).

The *N*,*N*-diisopropyl-2-(2-pyridyl)benzamides **5** and **6** were synthesized from 2-(diisopropylaminocarbonyl)phenylboronic acid[7] and 4-chloro-2-iodopyridine[6] or 2-chloro-4-methylpyridine, respectively, under Suzuki's conditions[8] (Scheme 3).

Deprotonation of the substrates **1**, **3** and **5** was then considered.

A survey of the literature revealed that LTMP was capable of deprotonate ethyl benzoate at the *ortho* position while LDA was found to react with the function.[5] We thus decided to examine the behavior of ethyl 2-(4-chloro-2-pyridyl)-benzoate (**1**), carrying out the reaction with LTMP.

The ester **1** could be easily deprotonated at C5′ using 2 equiv. of LTMP in THF at −75 °C, and the lithio intermediate trapped with D_2O, *ortho*-tolualdehyde or chlorotrimethylsilane to give the compounds **7a**–**c** in good yields (Scheme 4). Note that the lithio derivative thus obtained does not react intermolecularly with the ester function under the conditions used.

Interestingly, the position 5′ is regioselectively deprotonated.[9] The deprotonation is directed by the chloro group, which acidifies the hydrogens at C3′ and C5′, and exerts a stabilizing effect on the lithio derivative. Studies have shown that coordination of a lithium dialkylamide by an

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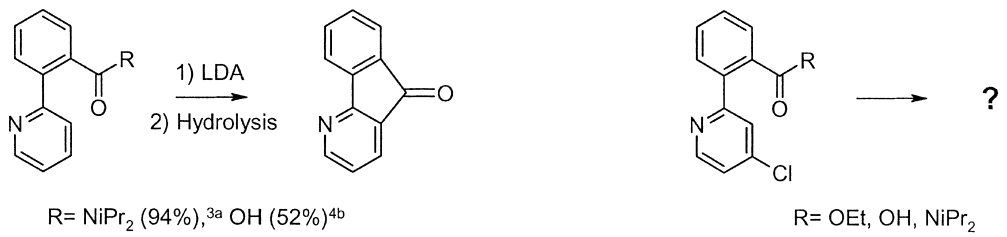
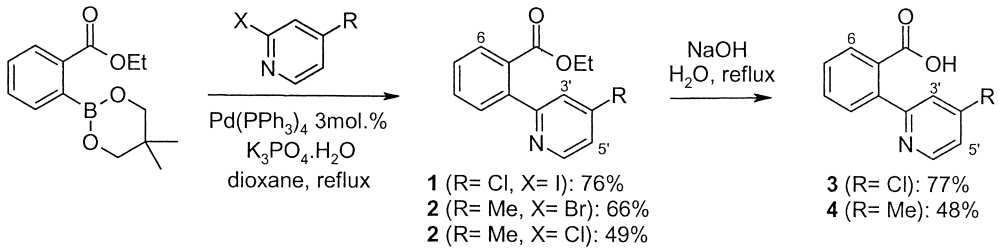
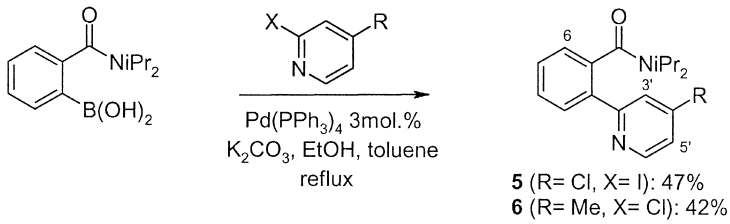


Scheme 1.



Scheme 2.



Scheme 3.

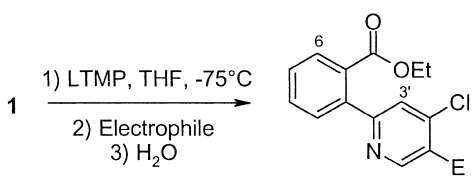
ester function was unlikely.[10] Moreover, one can hardly expect the ester function to stabilize a lithio derivative at C3′ through chelation. A more acidic hydrogen at C5′ (determined by molecular simulations) or/and the steric hindrance encountered by the base to deprotonate at C3′ could be invoked to justify this result.

We recently described pyridine rings metallation examples and subsequent cyclization using a remote lithium carboxylate unit.[4b] 2-(4-Chloro-2-pyridyl)benzoic acid (**3**) was involved in the reaction with LTMP, under the conditions used for the deprotonation of the ester **1**. The reaction also occurred at C5′, as demonstrated by deuteriolysis (Scheme 5). Conducting the reaction at higher temperatures only led to degradation compounds.

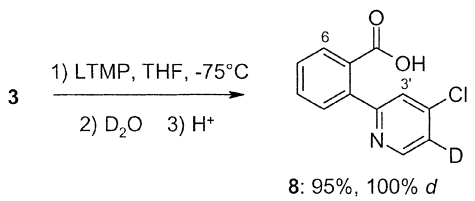
A complex-induced proximity effect (CIPE)[11] is rarely cited to rationalize the regioselectivities of deprotonation reactions using LTMP;[12] a thermodynamic control leading to the most stable (less basic) carbanion (chelation to the carboxylate)[13] could be put forward to explain the results observed in the reported examples. Attempts to detect complexation between the lithium carboxylate of **3** and LTMP in THF using the in situ infrared spectroscopy[14] only suggested that equilibria[15] between different aggregation states (monomers, dimers, tetramers…) were not affected by the addition of the base.

Since various examples[11] demonstrate dominance of a CIPE process in the lithiation reactions with alkyllithiums, the deprotonation of **3** was attempted using BuLi in THF at low temperature (−75 °C): under these metallation non-reversible conditions, butylated products formed were accompanied by a significant amount of **8**, showing the CIPE is not strong enough to counterbalance steric and/or hydrogens acidity-based effects.

We then turned to the metallation of the benzamide **5**. Studies concern the deprotonation of phenylpyridines on the nitrogenous ring, followed by in situ intramolecular condensation with *N*,*N*-dialkylcarboxamide functions



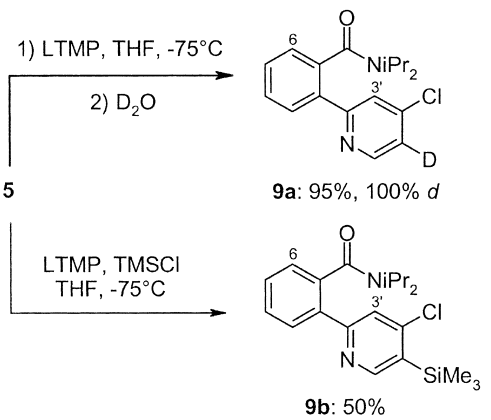
Scheme 4.



Scheme 5.

borne by the phenyl group.[3] We wondered whether *N*,*N*-diisopropyl-2-(4-chloro-2-pyridyl)benzamide (**5**) could be submitted to such a reaction.

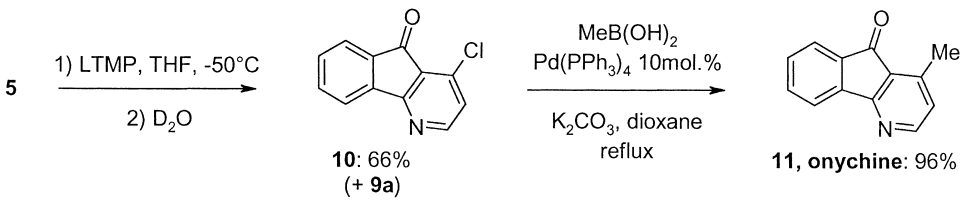
Attempts to detect complexation between the amide function of free *N*,*N*-diisopropylbenzamide and LTMP in THF using the in situ infrared spectroscopy[14] only evidenced a quick deprotonation of the substrate at −75 °C.[16] When the amide **5** was submitted to 4 equiv.[17] of LTMP in THF at −75 °C, deprotonation occurred once again at C5′, as demonstrated by deuteriolysis. Attempts to trap lithio derivatives in other positions, e.g. using in situ quenching with chlorotrimethylsilane,[18] failed: the first lithio derivative formed seems to be at C5′ (Scheme 6).



Scheme 6.

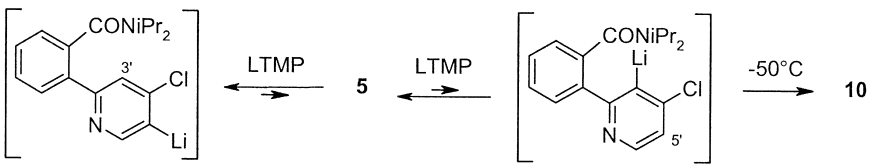
On the other hand, when the amide **5** was added to a solution of LTMP (2 equiv.) in THF at higher temperature (−50 °C), the ketone **10** was obtained in 66% yield, the rest being deuterated compound **9a**.

Cross-coupling[19] of the chloride **10** with methylboronic acid under palladium catalysis further allowed a new synthesis of onychine (**11**), an alkaloid endowed with anticandidal activity[20] (Scheme 7).



Scheme 7.

Thus, at a higher temperature, the remote *N*,*N*-diisopropylcarboxamide group behaves like an in situ trap for the 3-lithiopyridine formed[21] through the following equilibrium (Scheme 8):



Scheme 8.

The ester **1** and the acid **3** either remained unchanged or underwent degradation reactions on exposure to LTMP at higher temperatures. Attempts to shorten the synthesis of onychine (**11**) using the methylated substrates **2**, **4** and **6** in the reaction with LTMP only evidenced deprotonation of the methyl group.[22]

3. Conclusion

At low temperature (−75 °C), LTMP in THF promotes an exclusive regioselective metallation of 2-(4-chloro-2-pyridyl)benzoic acid (**3**), ethyl 2-(4-chloro-2-pyridyl)benzoate (**1**), and *N*,*N*-diisopropyl-2-(4-chloro-2-pyridyl)benzamide (**5**) at C5′, a position close to the chloro group but far from the carbonyl function. This demonstrates that the CIPE, if exists in this case, is not strong enough to counterbalance steric and/or hydrogens acidity-based effects. At higher temperatures, in the case of the amide **5** but also in the previously reported syntheses of azafluorenones,[3] the *N*,*N*-dialkylcarboxamide functions behave like an in situ trap for the remote lithio derivative. The methodology here led to onychine in three steps and 30% overall yield from 4-chloro-2-iodopyridine.[6] Several approaches have been previously developed.[23] As in the Parham cyclization strategy through bromine-lithium exchange,[24] the lithio derivative formed reacts with a remote carbonyl group. Nevertheless, even if the yields are comparable, the lithio derivative results in our case from deprotonation, avoiding the presence of a bromine atom. This short and regioselective method is attractive, when compared with the previously reported syntheses.[23]

4. Experimental

4.1. General

The ^{1}H NMR and ^{13}C NMR spectra were recorded with a 300 MHz spectrometer. THF and dioxane were distilled from benzophenone/Na. The water content of the solvents was estimated to be lower than 45 ppm by the modified Karl Fischer method.[25] Metallation and cross-coupling reactions were carried out under dry argon. Deuterium incorporation was determined from the ^{1}H NMR integration values. After

the reaction, hydrolysis, and neutralization, the aqueous solution was extracted several times with CH_2Cl_2. The organic layer was dried over Na_2SO_4, the solvents were evaporated under reduced pressure, and unless otherwise noted, the crude compound was chromatographed on a silica gel column (the eluent is given in the product description).

Starting materials. $Pd(PPh_3)_4$ was synthesized by a literature method.[26] 4-Chloro-2-iodopyridine,[6] 2-(diisopropylaminocarbonyl)phenylboronic acid[7] and ethyl 2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoate[5] were prepared according to literature procedures.

4.2. Ethyl 2-(4-chloro-2-pyridyl)benzoate (1)

A degassed mixture of 4-chloro-2-iodopyridine (0.29 g, 1.2 mmol), $Pd(PPh_3)_4$ (35 mg, 30 μmol), dioxane (10 mL), ethyl 2-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)benzoate (0.26 g, 1.0 mmol), and $K_3PO_4{\cdot}3H_2O$ (0.53 g, 2.0 mmol) was heated at 100 °C for 18 h. The solvents were removed under reduced pressure and water (10 mL) was added to afford 76% of **1** (eluent: petrol/AcOEt 80:20): pale yellow oil; ^{1}H NMR ($CDCl_3$) δ 1.03 (t, 3H, J=7.2 Hz), 4.09 (q, 2H, J=7.2 Hz), 7.20 (dd, 1H, J=4.9, 1.6 Hz), 7.5 (m, 4H), 7.79 (d, 1H, J=7.5 Hz), 8.46 (d, 1H, J=5.6 Hz); ^{13}C NMR ($CDCl_3$) δ 14.3, 61.5, 122.7, 123.6, 129.2, 130.1, 130.4, 131.6, 132.0, 140.2, 144.5, 150.2, 160.8, 168.7; IR (KBr) ν 3059, 2981, 2936, 1721, 1571, 1549. Anal. calcd for $C_{14}H_{12}ClNO_2$ (261.71): C, 64.25; H, 4.62; N, 5.35. Found: C, 63.95; H, 4.49; N, 5.07%.

4.3. Ethyl 2-(4-methyl-2-pyridyl)benzoate (2)

The procedure described above, using 2-bromo-4-methylpyridine (0.31 g, 1.2 mmol) instead of 4-chloro-2-iodopyridine, gave 66% of **2** (eluent: CH_2Cl_2/Et_2O 90:10): colorless oil; ^{1}H NMR ($CDCl_3$) δ 0.97 (t, 3H, J=7.2 Hz), 2.30 (s, 3H), 4.05 (q, 2H, J=7.2 Hz), 6.98 (d, 1H, J=4.9 Hz), 7.20 (s, 1H), 7.4 (m, 3H), 7.72 (d, 1H, J=7.5 Hz), 8.39 (d, 1H, J=5.2 Hz); ^{13}C NMR ($CDCl_3$) δ 14.2, 21.5, 61.3, 123.4, 124.0, 128.5, 130.0, 130.1, 131.3, 132.3, 141.4, 147.6, 149.2, 159.0, 169.3; IR (KBr) ν 3054, 2981, 2927, 1722, 1604, 1286, 1250, 775, 747, 450. Anal. calcd for $C_{15}H_{15}NO_2$ (241.29): C, 74.67; H, 6.27; N, 5.80. Found: C, 74.37; H, 6.33; N, 6.08%.

4.4. 2-(4-Chloro-2-pyridyl)benzoic acid (3)

A mixture of the ester **1** (0.26 g, 1.0 mmol) and NaOH (0.10 g, 2.5 mmol) in water (1.0 mL) was heated under reflux for 2 h. A 20% aqueous hydrochloric acid solution was added until complete precipitation. The precipitate thus obtained was recovered by filtration and dried under vacuum to give 77% of **3**: mp 134–135 °C (dec.); ^{1}H NMR (DMSO-d_6) δ 7.5 (m, 4H), 7.7 (m, 2H), 8.55 (d, 1H, J=5.3 Hz); ^{13}C NMR (DMSO-d_6) δ 124.2, 124.7, 130.5, 130.7, 131.0, 131.8, 132.7, 139.5, 140.8, 141.0, 143.8, 152.0; IR (KBr) ν 3071, 2777, 2455, 1699, 1581, 1552, 1386, 1275, 1142, 1010, 788, 770, 712. Anal. calcd for $C_{12}H_8ClNO_2$ (233.66): C, 61.69; H, 3.45; N, 5.99. Found: C, 61.38; H, 3.23; N, 5.69%.

4.5. 2-(4-Methyl-2-pyridyl)benzoic acid (4)

The procedure described above, using the ester **2** (0.24 g, 1.0 mmol) instead of the ester **1**, gave 48% of **4**: mp 170–171 °C (dec.); ^{1}H NMR (DMSO-d_6) δ 2.58 (s, 3H), 7.61 (d, 1H, J=7.5 Hz), 7.71 (d, 1H, J=7.5 Hz), 7.8 (m, 2H), 7.87 (s, 1H), 8.06 (d, 1H, J=7.1 Hz), 8.71 (d, 1H, J=5.6 Hz); ^{13}C NMR (DMSO-d_6) δ 21.8, 125.9, 127.3, 130.8, 131.1, 131.2, 131.5, 132.6, 134.4, 134.5, 142.0, 153.8, 167.4; IR (KBr) ν 3386, 3061, 2449, 1954, 1702, 1612, 1315, 1278, 1142, 1048, 1017, 773, 747, 545. Anal. calcd for $C_{13}H_{11}NO_2$ (213.24): C, 73.23; H, 5.20; N, 6.57. Found: C, 72.92; H, 4.90; N, 6.29%.

4.6. *N*,*N*-Diisopropyl-2-(4-chloro-2-pyridyl)benzamide (5)

A degassed mixture of 4-chloro-2-iodopyridine (0.48 g, 2.0 mmol), K_2CO_3 (0.56 g, 4.0 mmol), water (2.0 mL), EtOH (1.0 mL), toluene (20 mL), 2-(diisopropylaminocarbonyl)phenylboronic acid (0.50 g, 2.0 mmol) and $Pd(PPh_3)_4$ (70 mg, 60 μmol) was heated at reflux for 18 h to afford 50% of **5** (eluent: CH_2Cl_2/Et_2O 95:5): mp 100–101 °C; ^{1}H NMR ($CDCl_3$) δ 0.53 (d, 3H, J=6.8 Hz), 0.88 (d, 3H, J=6.8 Hz), 1.38 (d, 3H, J=6.8 Hz), 1.46 (d, 3H, J=6.8 Hz), 3.26 (sept, 1H, J=6.8 Hz), 3.51 (sept, 1H, J=6.8 Hz), 7.16 (dd, 1H, J=5.3, 1.5 Hz), 7.22 (dd, 1H, J=4.9, 3.8 Hz), 7.3 (m, 2H), 7.63 (dd, 1H, J=5.8, 2.8 Hz), 7.70 (d, 1H, J=1.5 Hz), 8.45 (d, 1H, J=5.3 Hz); ^{13}C NMR ($CDCl_3$) δ 19.9, 20.0, 20.9, 21.1, 46.0, 51.2, 122.5, 124.4, 126.7, 129.0, 129.6, 129.7, 135.9, 138.5, 144.7, 150.5, 159.0, 170.5; IR (KBr) ν 2965, 2931, 1619, 1571, 1547, 1452, 1435, 1371, 1340, 783, 710. Anal. calcd for $C_{18}H_{21}ClN_2O$ (316.83): C, 68.24; H, 6.68; N, 8.84. Found: C, 67.93; H, 6.79; N, 8.78%.

4.7. *N*,*N*-Diisopropyl-2-(4-methyl-2-pyridyl)benzamide (6)

The procedure described above, using 2-chloro-4-methylpyridine (0.17 mL, 2.0 mmol) instead of 4-chloro-2-iodopyridine, gave 42% of **6** (eluent: CH_2Cl_2/Et_2O 85:15): mp 98–99 °C; ^{1}H NMR ($CDCl_3$) δ 0.40 (d, 3H, J=6.8 Hz), 0.84 (d, 3H, J=6.8 Hz), 1.27 (d, 3H, J=6.8 Hz), 1.46 (d, 3H, J=6.8 Hz), 2.27 (s, 3H), 3.22 (sept, 1H, J=6.8 Hz), 3.50 (sept, 1H, J=6.8 Hz), 6.98 (d, 1H, J=4.5 Hz), 7.22 (d, 1H, J=6.8 Hz), 7.4 (m, 2H), 7.51 (s, 1H), 7.64 (d, 1H, J=7.5 Hz), 8.44 (d, 1H, J=5.3 Hz); ^{13}C NMR ($CDCl_3$) δ 19.3, 19.5, 20.5, 20.7, 45.3, 50.6, 123.3, 124.6, 126.2, 128.4, 128.6, 129.3, 136.9, 138.0, 147.1, 149.1, 156.9, 170.4; IR (KBr) ν 2968, 2931, 1628, 1604, 1436, 1370, 1339, 1212, 1033, 774, 742. Anal. calcd for $C_{19}H_{24}N_2O$ (296.42): C, 76.99; H, 8.16; N, 9.45. Found: C, 76.70; H, 8.24; N, 9.31%.

4.8. Ethyl 2-(4-chloro-2-(5-D)pyridyl)benzoate (7a)

A solution of the ester **1** (0.10 g, 0.38 mmol) in THF (3 mL) was added to a solution of LTMP (obtained by adding BuLi (0.76 mmol) to a solution of 2,2,6,6-tetramethylpiperidine (0.14 mL, 0.84 mmol) in THF (5 mL) at 0 °C(at −78 °C. The mixture was stirred at −78 °C for 1 h before deuteriolysis with D_2O (0.5 mL) to afford 95% (100% *d*) of **7a** (eluent: petrol/AcOEt 80:20). The ^{1}H and ^{13}C NMR

data of this product showed the replacements of 5′-H by 5′-D, and 5′-CH by 5′-CD, respectively.

4.9. Ethyl 2-(4-chloro-5-(hydroxy(2-methylphenyl)-methyl)-2-pyridyl)benzoate (7b)

A solution of the ester **1** (0.30 g, 1.1 mmol) in THF (15 mL) was added to a solution of LTMP (obtained by adding BuLi (2.3 mmol) to a solution of 2,2,6,6-tetramethylpiperidine (0.43 mL, 2.4 mmol) in THF (20 mL) at 0 °C (at −78 °C. The mixture was stirred at −78 °C for 1 h before trapping with 2-tolualdehyde (0.28 mL, 2.4 mmol), and hydrolysis 18 h later with H_2O (5 mL) to afford 73% of **7b** (eluent: CH_2Cl_2/Et_2O 90:10): yellow oil; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3H, J=7.2 Hz), 2.11 (s, 3H), 3.54 (broad s, 1H), 1.94 (q, 2H, J=7.2 Hz), 6.04 (s, 1H), 7.0 (m, 4H), 7.3 (m, 4H), 7.62 (d, 1H, J=7.1 Hz), 8.42 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.2, 19.5, 61.5, 68.7, 123.8, 126.6, 127.0, 128.4, 129.2, 130.2, 130.4, 131.0, 131.7, 131.9, 135.2, 136.3, 139.6, 139.6, 143.2, 149.5, 159.1, 168.8; IR (KBr) ν 3377, 2981, 1720, 1584, 1286, 1261, 756. Anal. calcd for $C_{22}H_{20}ClNO_3$ (381.86): C, 69.20; H, 5.28; N, 3.67. Found: C, 68.89; H, 5.27; N, 3.58%.

4.10. Ethyl 2-(4-chloro-5-trimethylsilyl-2-pyridyl)-benzoate (7c)

A solution of the ester **1** (0.10 g, 0.38 mmol) in THF (3 mL) was added to a solution of LTMP (obtained by adding BuLi (0.76 mmol) to a solution of 2,2,6,6-tetramethylpiperidine (0.14 mL, 0.80 mmol) in THF (5 mL) at 0 °C(at −78 °C. The mixture was stirred at −78 °C for 1 h before quenching with $ClSiMe_3$ (96 μL, 0.76 mmol) and, 1.5 h later, hydrolysis with water (5 mL) to afford 78% of **7c** (eluent: petrol/AcOEt 90:10): yellow oil; ^{1}H NMR ($CDCl_3$) δ 0.37 (s, 9H), 1.07 (t, 3H, J=7.2 Hz), 4.12 (q, 2H, J=7.2 Hz), 7.38 (s, 1H), 7.5 (m, 3H), 7.79 (d, 1H, J=7.5 Hz), 8.51 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 0.0, 14.8, 62.1, 124.5, 129.8, 130.7, 131.0, 132.3, 132.6, 140.8, 151.8, 155.6, 161.7, 169.4; IR (KBr) ν 2957, 2900, 1725, 1568, 1284, 1252, 1129, 1097, 1056, 844, 763. Anal. calcd for $C_{17}H_{20}ClNO_2Si$ (333.89): C, 61.15; H, 6.04; N, 4.19. Found: C, 61.16; H, 6.11; N, 4.21%.

4.11. 2-(4-Chloro-2-(5-D)pyridyl)benzoic acid (8)

A solution of the acid **3** (0.10 g, 0.43 mmol) in THF (2 mL) was added to a solution of LTMP (obtained by adding BuLi (1.1 mmol) to a solution of 2,2,6,6-tetramethylpiperidine (0.20 mL, 1.2 mmol) in THF (5 mL) at 0 °C (at −78 °C. The mixture was stirred at −78 °C for 1 h before deuteriolysis with D_2O (0.5 mL). After evaporation, a 20% aq. hydrochloric acid solution was added until complete precipitation. The precipitate thus obtained was recovered by filtration and dried under vacuum to afford 95% (100% *d*) of **8**. The ^{1}H and ^{13}C NMR data of this product showed the replacements of 5′-H by 5′-D, and 5′-CH by 5′-CD, respectively.

4.12. *N*,*N*-Diisopropyl-2-(4-chloro-2-(5-D)pyridyl)-benzamide (9a)

A solution of the amide **5** (0.10 g, 0.28 mmol) in THF (3 mL) was added to a solution of LTMP (obtained by adding BuLi (1.1 mmol) to a solution of 2,2,6,6-tetramethylpiperidine (0.20 mL, 1.2 mmol) in THF (5 mL) at 0 °C(at −78 °C. The mixture was stirred at −78 °C for 1.5 h before deuteriolysis with D_2O (0.5 mL) to afford 95% (100% *d*) of **9a** (eluent: CH_2Cl_2/Et_2O 95:5). The ^{1}H and ^{13}C NMR data of this product showed the replacements of 5′-H by 5′-D, and 5′-CH by 5′-CD, respectively.

4.13. *N*,*N*-Diisopropyl-2-(4-chloro-5-trimethylsilyl-2-pyridyl)benzamide (9b)

To a mixture of the amide **5** (0.10 g, 0.28 mmol) and $ClSiMe_3$ (70 μL, 0.56 mmol) in THF (3 mL) at −78 °C was added a solution of LTMP (obtained by adding BuLi (0.56 mmol) to a solution of 2,2,6,6-tetramethylpiperidine (98 μL, 0.59 mmol) in THF (5 mL) at 0 °C(. The mixture was stirred at −78 °C for 1.5 h before hydrolysis with water (5 mL) to afford 50% of **9b** (eluent: CH_2Cl_2/Et_2O 95:5): mp 105–106 °C; ^{1}H NMR ($CDCl_3$) δ 0.34 (s, 9H), 0.58 (d, 3H, J=6.4 Hz), 0.91 (d, 3H, J=6.4 Hz), 1.35 (d, 3H, J=6.4 Hz), 1.47 (d, 3H, J=6.4 Hz), 3.29 (sept, 1H, J=6.4 Hz), 3.54 (sept, 1H, J=6.4 Hz), 7.23 (m, 1H), 7.38 (m, 2H), 7.66 (m, 2H), 8.51 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 0.0, 20.5, 20.8, 21.7, 21.8, 46.7, 51.9, 125.1, 127.5, 129.7, 130.3, 130.4, 132.9, 136.6, 139.2, 152.3, 155.8, 160.0, 171.3; IR (KBr) ν 2968, 2927, 1620, 1571, 1341, 1248, 861, 844, 758. Anal. calcd for $C_{21}H_{29}ClN_2OSi$ (389.02): C, 64.84; H, 7.51; N, 7.20. Found: C, 64.56; H, 7.57; N, 7.24%.

4.14. 1-Chloro-4-azafluorenone (10)

A solution of the amide **5** (0.10 g, 0.28 mmol) in THF (3 mL) was added to a solution of LTMP (obtained by adding BuLi (0.56 mmol) to a solution of 2,2,6,6-tetramethylpiperidine (99 μL, 0.59 mmol) in THF (5 mL) at 0 °C(at −50 °C. The mixture was stirred at −50 °C for 1.5 h before hydrolysis with water (5 mL) to afford 66% of **10** (eluent: CH_2Cl_2): mp 167–168 °C; ^{1}H NMR ($CDCl_3$) δ 7.10 (d, 1H, J=5.6 Hz), 7.42 (t, 1H, J=7.3 Hz), 7.56 (t, 1H, J=7.5 Hz), 7.70 (d, 1H, J=7.1 Hz), 7.80 (d, 1H, J=7.5 Hz), 8.40 (d, 1H, J=5.6 Hz); ^{13}C NMR ($CDCl_3$) δ 106.6, 121.7, 124.8, 125.4, 132.0, 135.8, 139.2, 142.2, 154.4, 155.0, 159.5, 200.2; IR (KBr) ν 2924, 1722, 1606, 1573, 1558, 1449, 1172, 919, 819, 746. Anal. calcd for $C_{12}H_6ClNO$ (215.64): C, 66.84; H, 2.80; N, 6.50. Found: C, 66.52; H, 2.94; N, 6.22%.

4.15. 1-Methyl-4-azafluorenone (11)

A suspension of methylboronic acid (30 mg, 0.50 mmol), K_2CO_3 (0.21 g, 1.5 mmol), $Pd(PPh_3)_4$ (58 mg, 50 μmol), and the azafluorenone **10** (0.12 g, 0.55 mmol) in dioxane (5 mL) was stirred at reflux temperature for 18 h to afford 96% of **11** (eluent: petrol/CH_2Cl_2 80:20): mp 128–129 °C (lit.[23j] mp 127–129 °C). The spectral data of compound **11** are in agreement with those already described.[23j]

References and notes

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