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Connection Between Metalation and Cross-Coupling Strategies. A New Convergent Route to Azacarbazoles.

Patrick ROCCA, Francis MARSAIS, Alain GODARD and Guy QUEGUINER*

Laboratoire de Chimie Organique Fine et Hétérocyclique de l'IRCOF, URA CNRS 1429, Institut National des Sciences Appliquées de Rouen, BP08 76131 Mont-Saint-Aignan Cédex, France.

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Key Words: Azacarbazoles, Alkaloid, Boron, Carbolines, Cross-Coupling, Halopyridines, Metalation, Palladium.

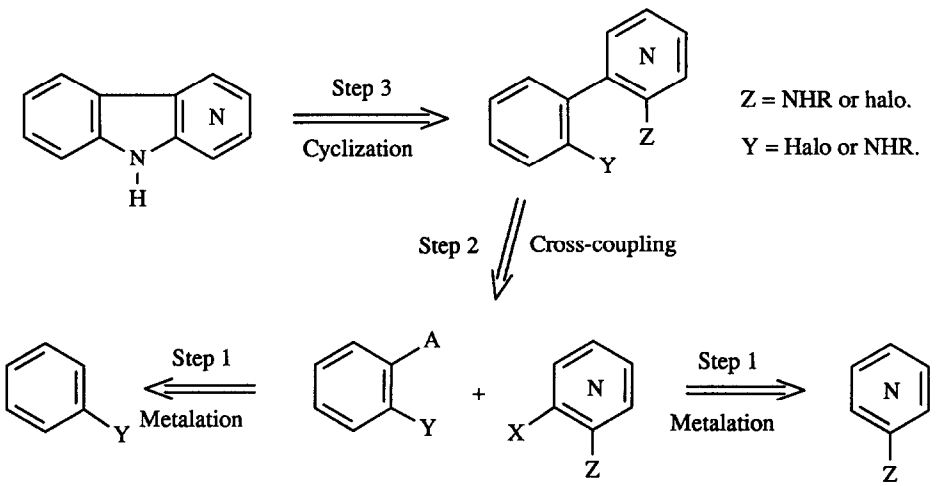
Abstract: New convergent synthesis of azacarbazoles through metalation, cross-coupling reaction and intramolecular substitution via (2-aminobenzene)boronic acid and ortho-fluoroiodopyridines .

INTRODUCTION

Numerous natural alkaloids belong to the carboline series[1] (mainly β-carboline) and display interesting biological properties (Harman derivatives,[2] Eudistomins,[3] Lavendamycine,[4] Picrasma Javanica alkaloids[5]). Until now most syntheses[6a] have used indole or a derivative as the starting material. This limits the scope of these methods to the β-carboline. Some other reactions[6b] are based on the construction of the pyrrole ring by cyclization of amino derivatives. They are not general and often lead to mixtures of isomers as it is the case with the Clark's photocyclisation of anilinopyridines[6c]. Therefore, a new general and convergent route to the four parent carbolines from benzene and pyridine building blocks was sought. This method should be adaptable for substituted carbolines.

RETROSYNTHETIC ANALYSIS

From a retrosynthetic analysis (scheme 1), all four azacarbazoles could be prepared by cyclization of a phenylpyridine (step 3) to form the pyrrole ring. The cyclization of *o,o'*-disubstituted biaryls (step 3) under acid conditions has so far been successfully used to prepare various polycondensed heteroaromatics (xanthones, coumarones, acridones).[9] The requisite phenylpyridines could be prepared through a palladium coupling reaction[8] of the appropriately substituted benzene and pyridine building blocks (step 2). The introduction of suitable substituents (iodine, borane or boronic acid) (step 1) for a transition metal coupling reaction (step 2) on the benzene and pyridine rings could be obtained by a metalation strategy.[7] A similar methodology has been already disclosed by us for a benzocarboline analog.[10]



X = I, BR_2; Y = F, OCH_3, NHR; Z = F, Cl, NHR; A = BR_2, SnR_3, I.

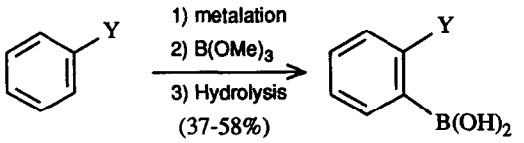
Scheme 1.

The last cyclization step can be distinguished by two variants for the synthesis of carbolines depending on attachment of the amino group to the pyridine or benzene ring.

RESULTS and DISCUSSION

Synthesis of boronic acids and boranes

Metalation of pivaloylamino[13], fluoro[14] and methoxybenzene[15] was achieved with n-butyllithium in THF. The resulting lithio derivatives were then treated with trimethylborate[16] to give the corresponding boronic acids **(4-6)** in moderate yields after hydrolysis and acidification (scheme 2).



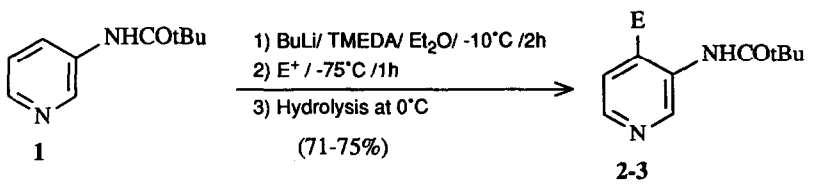
4-6

Y = F; OCH_3; NHCOtBu.

Scheme 2.

Nevertheless, it was demonstrated that the individual metalation and boronation steps of the pivaloylaminobenzene were almost quantitative respectively after 6 and 2 hours (monitoring of these two steps was achieved by quenching metalation and boronation mixtures samples respectively with D_2O and H_2O followed by ^1H NMR analysis of the resulting crude solutions). We suspect a protodeboronation reaction, which cannot be avoided during the boronic acid precipitation upon acid treatment of the reaction mixture, leads to a 58% reduced yield.

To our knowledge, 4-pyridineboronic acids (as well as the 2-isomers) were never obtained, so it was decided to prepare a 4-pyridylborane. 3-Aminopyridine activated as the pivaloylamino derivative (**1**) was subjected to lithiation.[11] The resulting 4-lithio derivative was then reacted with 9-methoxy-9-BBN (9-BBN = 9-borabicyclo[3.3.1]nonane) to give the corresponding borane (**3**) in good yield (scheme 3).



1 **2-3**

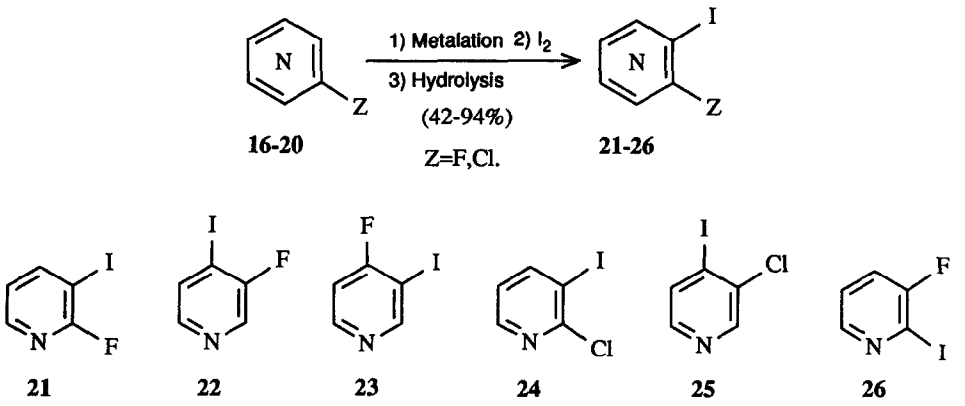
Scheme 3.

2: E = I.
3: E = 9-BBN.

Synthesis of iodopyridines.

4-Iodo-3-pivaloylaminopyridine (**2**) was obtained by metalation-iodination as previously described (scheme 3).

The metalation[17,24] of 2-, 3- and 4-fluoropyridines (**16-18**), by LDA in THF at low temperature and reaction of the resulting lithio derivatives with iodine afforded the corresponding 3-, 4- and 3-iodopyridines (**21-23**) in good yields (scheme 4).



Scheme 4.

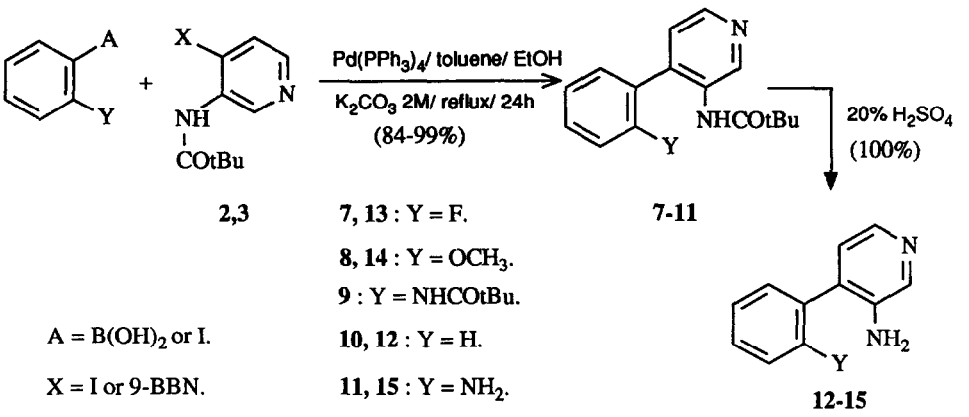
Similarly, the ortho-chloroiodo compounds (**24**) and (**25**) were obtained from 2- and 3-chloropyridines (**19** and **20**). 3-Fluoro-2-iodopyridine (**26**) was synthesized from 3-fluoropyridine (**17**) following a similar strategy, but under modified metalation conditions[18] (n-butyllithium/DABCO in diethylether).

Palladium coupling reaction

The palladium catalyzed cross-coupling reaction between 4-iodo-3-pivaloylaminopyridine (**2**) and ortho-substituted benzeneboronic acids (**4-6**), was achieved by the Suzuki procedure[8] to give the 4-phenyl-3-pivaloylaminopyridines (**7-9**) in high yields (scheme 5).

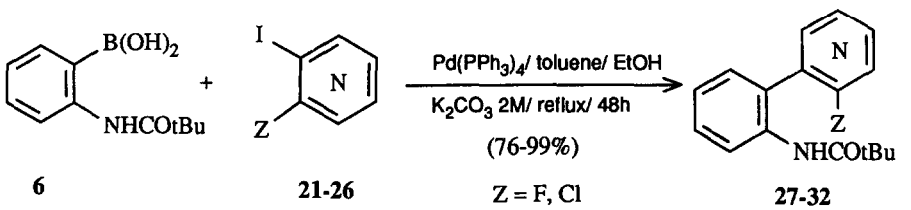
Conversely, the (3-pivaloylamino-4-pyridyl)borane (**3**) was coupled with various commercial iodobenzenes to give the corresponding 4-phenyl-3-pivaloylaminopyridines (**7**), (**8**), (**10**) and (**11**) (scheme 5). Indeed, this coupling reaction could not be achieved in good yields either by using Terashima's[12] or Suzuki's[8] procedure as respectively described for arylboranes or arylboronic acids. Suzuki's procedure was conveniently improved by using greater amounts of base (four equivalents of potassium carbonate instead of two).

Hydrolysis of the 4-phenyl-3-pivaloylaminopyridines (**7**), (**8**), (**10**) and (**11**) with hot diluted sulfuric acid quantitatively led to the corresponding amino derivatives (**12-15**) (scheme 5).



Scheme 5.

Coupling the (2-pivaloylamino)benzeneboronic acid (**6**) and the previously prepared ortho-fluoroiodopyridines (**21**), (**22**), (**23**) and (**26**) (or ortho-chloroiodo (**24**) and (**25**)) gave the corresponding heterobiaryls (**27-32**) in high yields (scheme 6).



Scheme 6.

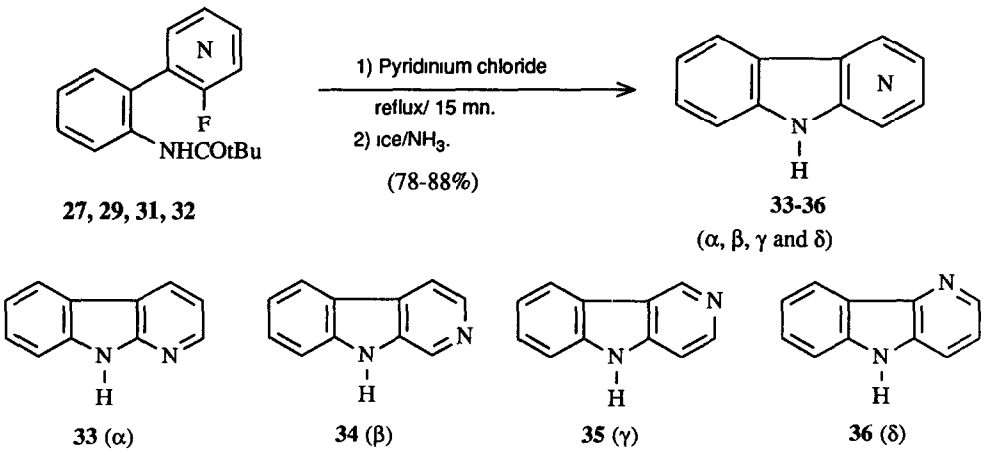
Cyclization of o-substituted phenyl-o'-amino (or pivaloylamino) pyridines - Route A.

The cyclization of the protected or unprotected 4-(2-substituted phenyl)-3-aminopyridines (**13-15**) to β-carboline under various acid conditions was unsuccessful. Nevertheless, low and variable yields of β-carboline were obtained when the 2-methoxyphenyl derivative (**8**) was treated with boiling pyridinium chloride.

Among the cyclization methods of *o,o'*-disubstituted biphenyls into carbazoles, Sako's procedure gives good results with diamino compounds. This reaction was checked for the cyclization of monoprotected *o,o'*-diamino-4-phenylpyridine (**11**) into β-carboline. Diazotation of the amine at 0°C and reaction at 20°C overnight only led to small amounts (less than 10%) of the expected carboline together with numerous by-products.

Cyclization of o-pivaloylaminophenyl-o'-halopyridines - Route B.

With the fluorine displacement on the pyridine ring, cyclization of the (o-pivaloylamino)phenyl-o'-fluoropyridines **(27)**, **(29)**, **(31)** and **(32)** with boiling pyridinium chloride gave the four parent carbolines **(33-36)** in good to high yields after basic workup (scheme 7). The ^{1}H and ^{13}C NMR spectra of the four isomers were found to be identical with those reported.



Scheme 7.

The same acid treatment of the chloro derivatives only succeeded in the case of the more activated 2-chloropyridine **(28)** to give α-carboline **(33)** in a good yield.

The advantage of an acid catalyzed cyclization is taken for combining activation of the pyridine ring (as pyridinium) with the cleavage of the pivaloyl group. This is particularly true with the 3-fluoropyridines **(29)** and **(32)** which could not be cyclized under neutral or basic conditions.

CONCLUSION

In conclusion, the link between the metalation and the cross-coupling provides a new convenient and simple way to carbolines. The parent α-, β-, γ- and δ-carbolines were prepared in three steps from (2-pivaloylaminobenzene)boronic acid and fluoropyridines, with respectively 72%, 79%, 49% and 26 % overall yield respectively. The strategy is fully convergent and highly regioselective. The most important natural β-carboline (Norharman) can be thus prepared in three steps in 79% overall yield. The same β-carboline has been obtained by the Snyder's method[25] in six steps starting from indole with tryptophan[26] as intermediate. Moreover, the Snyder's synthesis cannot be applied to other carbolines whereas our method is quite general and gives the four parent compounds. The total synthesis of natural carboline alkaloids is currently being studied using this method.

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EXPERIMENTAL

General data. The ^1H NMR spectra were obtained on a Varian T60 spectrometer and were recorded in ppm downfield from an internal standard, TMS in $CDCl_3$ or HMDS in DMSO-d_6. ^1H-^1H coupling constants are in good agreement with the common values of pyridines (J_{2-3} = 5 Hz; J_{3-4} = 8 Hz; J_{2-4} = 2 Hz) and are not given. ^1H NMR and ^{13}C NMR spectra of carbolines were recorded on a 200 MHz Brücker spectrometer. IR spectra were taken on a Beckman IR 4250 spectrometer, and main absorption frequencies (NH, CH, C=O, C=C, C=N) are given in cm^{-1}. Mass spectra were obtained on a JEOL D700 instrument, and elemental analyses were performed on a Carlo Erba CHN apparatus.

Solvents. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from benzophenone/sodium and stored over 3Å molecular sieves. The water content of the solvents was estimated by the modified Karl-Fischer method[21] : Et_2O < 10 ppm, THF < 45 ppm.

Starting materials. Commercial TMEDA, diisopropylamine, 2-fluoropyridine (**16**), 2- and 3-chloropyridine (**19**) and (**20**) were distilled from CaH_2 and stored over CaH_2 under a dry argon atmosphere. 3-(Pivaloylamino)pyridine (**1**) was prepared from commercial 3-aminopyridine[11]. 2,2-Dimethyl-N-(4-iodo-3-pyridyl)propanamide (**2**) was prepared by metalation of 3-(pivaloylamino)pyridine[22]. 3-Fluoropyridine (**17**) and 4-fluoropyridine (**18**) were prepared by diazotation of the corresponding aminopyridines[23,24]. 4-Fluoropyridine (**18**) was stored and used in dilute cold etheral solution (1g/10mL). Commercial 2.5 M solutions of n-butyllithium in hexane were stored and transfered under a deoxygenated and dehydrated argon atmosphere.

2,2-Dimethyl-N-(4-(9-bora-bicyclo[3.3.1]nonan-9-yl)-3-pyridyl)propanamide (3).

n-Butyllithium (48 mL, 0.120 mol) was slowly added to a cold (-75°C) suspension of 3-pivaloylaminopyridine (8.91 g, 0.050 mol) in a mixture of Et_2O (200 mL) and TMEDA (18.1 mL, 0.120 mol). The resulting solution was reacted for 15 min. at -75°C, before being stirred for 2h at -10°C. A white precipitate slowly appeared, the mixture was cooled to -75°C and a solution of 9-methoxy-9-BBN (1M in hexane) was added. Stirring was continued for 1h at -75°C and 1h at -10°C, before hydrolysis at 0°C by a 6N hydrochloric acid solution and further stirring for 1h to room temperature. The yellow precipitate was filtrated, dried and crystallized from ethanol to give 66-71% of **3** : mp > 260°C; ^1H NMR (DMSO-d_6) δ 0.65 (m, 2H, 2CH of 9-BBN), 1.10 (s, 9H, tBu), 1.75 (m, 12H, CH_2 of 9-BBN), 7.40 (d, 1H, H_5), 8.10 (d, 1H, H_6), 8.25 (d, 1H, H_2), 10.9 (s, 1H, NH); IR (KBr) 3400, 3040, 2970, 2920, 2880, 2840, 1630, 1560, 1470; mass calcd for $C_{18}H_{27}BN_2O$ 298.24, found (MS) 298. Anal. Calcd

for $C_{18}H_{27}BN_2O$ (298.24): C, 72.49; H, 9.13; N, 9.39. Found: C, 72.31; H, 9.20; N, 9.35.

(2-Fluorobenzene)boronic acid (4). n-Butyllithium (42 mL, 0.105 mol) was slowly added to a cold (-75°C) solution of fluorobenzene (9.61 g, 0.100 mol) in dry THF (200 mL). The resulting solution was reacted for 6h at -75°C and a precipitate appeared. Trimethylborate (11.9 mL, 0.105 mol) was slowly added and stirring was continued for 2h at -75°C, before hydrolysis at 0°C. After decantation and extraction by CH_2Cl_2, the aqueous layer was acidified by 2M HCl and a white precipitate appeared. Filtration, washing with water and drying, yielded 2.57 g (37%) of **4** : mp 224°C; ^{1}H NMR ($CDCl_3$) δ 6.75 to 7.60 (m, 5H, H_3 + H_4 + H_5 + 2 OH), 7.90 (c, 1H, H_6); IR (KBr) 3400, 3080, 1615, 1450, 1360. Anal. Calcd for $C_6H_6BFO_2$ (139.92): C, 51.51; H, 4.32. Found: C, 51.50; H, 4.30.

(2-Methoxybenzene)boronic acid (5). n-Butyllithium (22.4 mL, 0.055 mol) was added to a cold (0°C) solution of anisole (5 mL, 0.0464 mol) in dry Et_2O (80 mL). The resulting solution was refluxed for 24h and a white precipitate appeared. The mixture was cooled to 0°C and trimethylborate (6.3 mL, 0.055 mol) was slowly added. Stirring was continued for 4h at room temperature, before hydrolysis at 0°C. After decantation, the aqueous layer was acidified by HCl 1/5. Extraction by CH_2Cl_2, drying over $MgSO_4$ and solvent removal afforded a crude oil, which was purified by crystallization from hexane to yield 3.53 g (50%) of **5** : mp 106°C; ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3H, OCH_3), 6.60 (c, 2H, $B(OH)_2$), 6.75 to 7.65 (c, 3H, H_3 + H_4 + H_5), 7.85 (dd, 1H, H_6); IR (KBr) 3400, 3070, 3010, 2950, 2840, 1600, 1480, 1465, 1400. Anal. Calcd for $C_7H_9BO_3$ (151.96): C, 55.33; H, 5.97. Found: C, 55.34; H, 6.07.

(2-Pivaloylaminobenzene)boronic acid (6). n-Butyllithium (240 mL, 0.60 mol) was slowly added to a cold (-10°C) solution of pivaloylaminobenzene (35.4 g, 0.20 mol) in dry THF (400 mL). The resulting solution was stirred 6h at room temperature and a white precipitate appeared. The mixture was cooled to -20°C, and trimethylborate (68.0 mL, 0.60 mol) was slowly added. Stirring was continued for 2h at -10°C before hydrolysis at 0°C. After decantation and extraction by CH_2Cl_2, the aqueous layer was acidified by HCl 1/5. Filtration of the white precipitate appeared, washing with water and drying, yielded 15.6 g of **6** . Extraction of the aqueous layer by CH_2Cl_2, drying over $MgSO_4$, solvent removal, dissolving in acetone and addition of water gave a white solid which was filtrated and dried to give additional 10.04 g of **6** (58% total yield) : mp > 260°C; ^{1}H NMR (DMSO-d_6) δ 1.10 (s, 9H, tBU), 3.30 (s, 2H, $B(OH)_2$), 7.10 (c, 2H, H_5 + Ar), 7.60 (c, 2H, Ar), 11.05 (s, 1H, NH); IR (KBr) 3320, 2970, 1620, 1580, 1550, 1450. Anal. Calcd for $C_{11}H_{16}BNO_3$ (221.07): C, 59.77; H, 7.30; N, 6.34. Found: C, 59.96; H, 7.19; N, 6.28.

Monitoring of the synthesis of (2-pivaloylaminobenzene)boronic acid (6).

a) Metalation of pivaloylaminobenzene. Metalation of pivaloylaminobenzene was achieved according to the previous procedure and cold samples (O.5 mL) of the reaction mixture were

added to a cold mixture of a D_2O/THF (1/1) (1mL) solution. The ^1H NMR spectra of the crude resulting THF solutions gave the relative intensities of the protons ortho to the pivaloylamino group compared to the four other aromatic protons. Proton removal ortho to the pivaloylamino group was thus calculated depending on the reaction time (1 h : 60%; 2h : 75%; 3h : 85%; 4h : 90%; 5h : 95%). The optimal metalation time was estimated to be 6 h at 20°C.

b) Reaction with trimethylborate. Pure trimethylborate was added to the previous metalation mixture (6 hours) at -10°C, as previously described, and cold samples (0.5 mL) of the reaction mixture were added to a cold mixture of a H_2O/THF (1/1) (1.5 mL). The ^1H NMR spectra of the crude resulting THF solutions gave the relative intensities of the protons ortho to the pivaloylamino group compared to the four other aromatic protons. The rate of reaction of the dilithio intermediate was thus calculated depending on the reaction time (0.5 h : 60%; 1h : 80%; 1.5h : 95%). The optimal boronation time was estimated to be 2 h at -10°C.

General procedure for the cross-coupling reaction between halopyridines and ortho-functionalized benzeneboronic acids. The required iodopyridine (2.0 mmol) and benzeneboronic acid (2.0 mmol) were added to a solution of potassium carbonate (2M, 2.0 mL) and ethanol (1.0 mL) in deoxygenated toluene (20 mL). The resulting mixture was stirred for 0.5h under an argon atmosphere. Terakis-(triphenylphosphine)palladium(0) (70 mg, 0.06 mmol) was added and this mixture was refluxed for 48h. Cooling, filtration, extraction with toluene, drying over $MgSO_4$, and solvent removal afforded a crude oil which was purified by preparative flash chromatography on silica (ethyl acetate).

2,2-Dimethyl-N-(4-(2-fluorophenyl)-3-pyridyl)propanamide (7). The foregoing procedure, applied to **2** and **4**, gave 96% of **7** : mp 168°C; ^1H NMR ($CDCl_3$) δ 1.10 (s, 9H, tBu), 7.25 (m, 6H, H_5 + NH + C_6H_4), 8.45 (d, 1H, H_6), 9.30 (s, 1H, H_2); IR (KBr) 3400, 3160, 2960, 1680, 1560, 1520, 1480, 1415. Anal. Calcd for $C_{16}H_{17}FN_2O$ (272.325): C, 70.57; H, 6.29; N, 10.29. Found: C, 70.75; H, 6.30; N, 10.32.

2,2-Dimethyl-N-(4-(2-methoxyphenyl)-3-pyridyl)propanamide (8). The foregoing procedure, applied to **2** and **5** gave 93% of **8** (oil): ^1H NMR ($CDCl_3$) δ 1.10 (s, 9H, tBu), 3.80 (s, 3H, OCH_3), 7.10 (m, 5H, H_5 + C_6H_4), 7.85 (s, 1H, NH), 8.35 (d, 1H, H_6), 9.25 (s, 1H, H_2); IR (film) 3340, 3130, 2970, 2835, 1675. Anal. Calcd for $C_{17}H_{20}N_2O_2$ (284.36): C, 71.81; H,7.09; N, 9.85. Found: C, 71.62; H, 6.93; N, 9.91.

2,2-Dimethyl-N-(4-(2-pivaloylaminophenyl)-3-pyridyl)propan amide (9). The foregoing procedure, applied to **2** and **6** gave 86% of **9** : mp 164°C: $_1H$ NMR ($CDCl_3$) δ 1.00 (s, 18H, tBu), 6.95 (d, 1H, H_5), 7.05 to 7.75 (m, 4H, C_6H_4), 8.00 (s, 2H, 2NH), 8.35 (d, 1H, H_6), 8.95 (s, 1H, H_2); IR (KBr) 3300, 2960, 2870, 1660, 1505, 1425. Anal. Calcd for $C_{21}H_{27}N_3O_2$ (353.47). C, 71.36; H, 7.70; N, 11.89. Found: C, 71.24; H, 7.70; N, 11.76.

General Procedure for the cross-coupling reaction between 2,2-dimethyl-N-(4-(9-bora-bicyclo[3.3.1]nonan-9-yl)-3-pyridyl) propanamide and iodobenzene. The required iodobenzene (2.0 mmol) was added to a solution of potassium carbonate (2M, 4.0 mL) and ethanol (2.0 mL) in deoxygenated toluene (20 mL). The resulting mixture was stirred for 1/2h under argon atmosphere. The 4-pyridylborane (3) (597 mg, 2.0 mmol) and tetrakis(triphenylphosphine)palladium(0) (70 mg, 0.06 mmol) were added and refluxed for 60h. Cooling, filtration, decantation, extraction with toluene, drying over $MgSO_4$ and solvent removal afforded a crude oil, which was purified by preparative flash chromatography on silica (ethyl acetate).

2,2-Dimethyl-N-(4-phenyl-3-pyridyl)propanamide (10). The foregoing procedure, applied to iodobenzene, gave 99% of **10** : mp 154°C; ^1H NMR ($CDCl_3$) δ 1.05 (s, 9H, tBu), 7.05 (d, 1H, H_5), 7.30 (m, 6H, C_6H_5 + NH), 8.25 (d, 1H, H_6), 9.30 (s, 1H, H_2); IR (KBr) 3400, 2960, 1670, 1515, 1410. Anal. Calcd for $C_{16}H_{18}N_2O$ (254.33): C, 75.56; H, 7.13; N, 11.01. Found: C, 75.50; H, 7.10; N, 11.05.

2,2-Dimethyl-N-(4-(2-aminophenyl)-3-pyridyl)propanamide (11). The foregoing procedure, applied to 2-iodoaniline, gave 89% of **11** : mp 108°C; ^1H NMR ($CDCl_3$) δ 1.15 (s, 9H, tBu), 4.15 (s, 2H, NH_2), 6.85 (m, 2H, Ar), 7.15 (d, 1H, H_5), 7.45 (m, 2H, Ar), 8.25 (d, 1H, H_6), 8.40 (s, 1H, NH), 9.15 (s, 1H, H_2); IR (KBr) 3330, 3220, 3060, 2970, 2870, 1680, 1555, 1520, 1420. Mass calcd for $C_{16}H_{19}N_3O$ (269.35), found (MS) 269. Anal. Calcd dor $C_{16}H_{19}N_3O$ (269,35): C, 71.35; H, 7.11; N, 15.60. Found: C, 71.52; H, 7.15; N, 15,51.

2,2-Dimethyl-N-(4-(2-fluorophenyl)-3-pyridyl)propanamide (7). The foregoing procedure, applied to 2-fluoroiodobenzene gave 86% of **7**. The physical characteristics of this product were found to be identical to those given for material described above.

2,2-Dimethyl-N-(4-(2-methoxyphenyl)-3-pyridyl)propanamide (8). The foregoing procedure, applied to 2-methoxyiodobenzene, gave 89% of **8**. The physical characteristics of this product were found to be identical to those given for material described above.

General procedure for the hydrolysis of pivalamides (7), (8), (10) and (11). The required pivaloylamino compound (1.0 mmol) was added to a 20% solution of sulfuric acid (10 mL) and refluxed for 1h. The resulting cold solution was poured into a mixture of ice and concentrated ammonia. Extraction with ethyl acetate, drying over $MgSO_4$ and solvent removal afforded crude oil which was purified by preparative flash chromatography on silica (ethyl acetate). The yields are quantitative. The resulting purified amines are moderately stable and fast turned brown. For this reason they were characterized by their mass spectra.

3-Amino-4-phenylpyridine (12). This compound was obtained from **10** as an oil: ^1H NMR ($CDCl_3$) δ 4.15 (s, 2H, NH_2), 6.90 (d, 1H, H_5), 7.40 (m, 5H, C_6H_5), 7.95 (d, 1H, H_6), 8.10 (s,

1H, H_2); IR (film) 3320, 3200, 3060, 1630, 1550, 1485, 1420. Mass calcd for $C_{11}H_{10}N_2$ 170.0844, found (HRMS) 170.0833.

3-Amino-4-(2-fluorophenyl)pyridine (13). This compound was obtained from **7** as a white solid: mp 100-102°C; ^1H NMR ($CDCl_3$) δ 4.00 (s, 2H, NH_2), 7.00 (d, 1H, H_5), 7.30 (m, 5H, C_6H_4 + NH), 8.05 (d, 1H, H_6), 8.15 (s, 1H, H_2); IR (KBr) 3460, 3360, 3220, 3040, 1625, 1550, 1480, 1450, 1420. Anal. Calcd for $C_{11}H_9FN_2$ (188.21): C, 70.20; H, 4.82; N, 14.88. Found: C, 70.03; H, 4.80; N, 14.81.

3-Amino-4-(2-methoxyphenyl)pyridine (14). This compound was obtained from **8** as an oil: ^1H NMR ($CDCl_3$) δ 3.70 (s, 3H, OCH_3), 4.05 (s, 2H, NH_2), 6.80 to 7.50 (m, 5H, H_5 + C_6H_4), 7.95 (d, 1H, H_6), 8.05 (s, 1H, H_2); IR (film) 3340, 3220, 3060, 2940, 2840, 1630, 1480, 1425. Mass calcd for $C_{12}H_{12}N_2O$ 200.0950, found (HRMS) 200.0962.

3-Amino-4-(2-aminophenyl)pyridine (15). This compound was obtained from **11** as an oil: ^1H NMR ($CDCl_3$) δ 3.90 (s, 2H, NH_2), 4.60 (s, 2H, NH_2), 6.55 (d, 1H, H_5), 6.60 to 7.25 (m, 4H, C_6H_4), 8.00 (s, 1H, H_2), 8.10 (d, 1H, H_6); IR (film) 3340, 3200, 3030, 1625, 1490, 1455, 1415. Mass calcd for $C_{11}H_{11}N_3$ 185.0953, found (HRMS) 185.0971.

General procedure for the synthesis of fluoroiodopyridines (21), (22), (23), and chloroiodopyridines (24) and (25). The required fluoropyridine (4.85 g, 0.050 mol), or chloropyridine (5,68 g, O.O50 mol), in THF solution, was slowly added to a cold (-75°C) solution of lithium diisopropylamide in THF (previously prepared by reaction of diisopropylamine (7.0 mL, 0.050 mol) in THF (200 mL) and n-butyllithium (20 mL, 2.5M, 0.050 mol) at -20°C for 1/2h). The resulting yellow mixture was stirred for 4h at -75°C, before addition of iodine (12.7 g, 0.050 mol) in THF (40 mL) solution. Stirring was continued for 1h at -75°C, before hydrolysis by a mixture of H_2O/THF (10 mL/ 50 mL) at -75°C, further addition of water (50 mL) at 0°C and reductive workup with solid sodium thiosulfate. Extraction by Et_2O, drying over $MgSO_4$ and solvent removal afforded a crude solid, wich was purified by sublimation (60°C / 2mmHg).

2-Fluoro-3-iodopyridine (21).[22] The foregoing procedure gave 85% of **21** : mp 42°C; ^1H NMR ($CDCl_3$) δ 6.95 (dd, 1H, H_5); 8.15 (m, 2H, H_4 + H_6); IR (KBr) 3060, 1590, 1580, 1450, 1430, 1410. Anal. Calcd. for C_5H_3FIN (222.99): C, 26.93; H, 1.36; N, 6.28. Found: C, 26.88; H, 1.23; N, 6.14.

3-Fluoro-4-iodopyridine (22).[17a] The foregoing procedure gave 94% of **22** : mp 96°C; ^1H NMR ($CDCl_3$) δ 7.75 (dd, 1H, H_5), 8.10 (d, 1H, H_6), 8.35 (s, 1H, H_2); IR (KBr) 3060, 1570, 1550, 1475, 1415. Anal. Calcd for C_5H_3FIN (222.99): C, 26.93; H, 1.36; N, 6.28. Found: C, 26.87; H, 1.30; N, 6.31.

4-Fluoro-3-iodopyridine (23). The foregoing procedure gave 57% of **23** : mp 68°C; ^{1}H NMR ($CDCl_3$) δ 7.05 (dd, 1H, H_5), 8.50 (dd, 1H, H_6), 8.85 (d, 1H, H_2); IR (KBr) 3070, 1570, 1485, 1395. Anal. Calcd for C_5H_3FIN (222.99): C, 26.93; H, 1.36; N, 6.28. Found: C, 27.02; H, 1.40; N, 6.30.

2-Chloro-3-iodopyridine (24).[17c] The foregoing procedure gave 60% of **24** : mp 90°C; ^{1}H NMR ($CDCl_3$) δ 7.00 (dd, 1H, H_5), 8.15 (dd, 1H, H_4), 8.35 (dd, 1H, H_6); IR (KBr) 3040, 1550, 1390. Anal. Calcd for C_5H_3ClIN (239.44): C, 25.08; H, 1.26; N, 5.85. Found: C, 25.30; H, 1.20; N, 5.80.

3-Chloro-4-iodopyridine (25). The foregoing procedure gave 88% of **25** : mp 103°C; ^{1}H NMR ($CDCl_3$) δ 7.80 (d, 1H, H_5), 8.10 (dd, 1H, H_6), 8.55 (s, 1H, H_2); IR (KBr) 3040, 1550, 1455, 1390. Anal. Calcd for C_5H_3ClIN (239.44): C, 25.08; H, 1.26; N, 5.85. Found: C, 24.95; H, 1.30; N, 5.92.

3-Fluoro-2-iodopyridine (26). 3-Fluoropyridine (4.85 g, 0.050 mol) was slowly added to a cold (-75°C) suspension of the n-butyllithium/DABCO chelate in Et_2O, which had been previously prepared by reaction of DABCO (5.9 g, 0.050 mol) in Et_2O (200 mL) and n-butyllithium (20 mL, 0.050 mol) at -20°C for 1h. The resulting white mixture was stirred for 2h at -60°C before addition of iodine (12.7 g, 0.050 mol) in THF (40 mL) solution. Stirring was continued for 1h at -60°C, before hydrolysis by mixture of H_2O/THF (10 mL/50 mL) at -75°C, further addition of water (50 mL) at 0°C and reductive workup with solid sodium thiosulfate. Extraction by Et_2O, drying over $MgSO_4$, solvent removal, and vaccuum distillation of the crude oil yielded 4.69 g (42%) of **26** : bp 98°C-100°C (20 mmHg); ^{1}H NMR ($CDCl_3$) δ 7.20 (m, 2H, H_4 + H_5), 8.15 (c, 1H, H_6); IR (film) 3060, 1580, 1445, 1415. Anal. Calcd for C_5H_3FIN (222.99): C, 26.93; H, 1.36; N, 6.28. Found: C, 26.90; H, 1.34; N, 6.29.

General procedure for the cross-coupling reaction between ortho-haloiodopyridines and (2-pivaloylaminobenzene)boronic acid (6). This procedure was identical to the previously described cross-coupling procedure, between halopyridines and benzeneboronic acids.

2,2-Dimethyl-N-(2-(2-fluoro-3-pyridyl)phenyl)propanamide (27). The foregoing procedure, applied to **21**, gave 99% of **27** : mp 82°C; ^{1}H NMR ($CDCl_3$) δ 1.10 (s, 9H, tBu), 7.15 to 7.65 (m, 5H, H_5 + NH + Ar), 7.75 (m, 2H, H_4 + Ar), 8.25 (c, 1H, H_6); IR (KBr) 3320, 3050, 2960, 2870, 1670, 1515, 1495, 1460, 1430, 1400. Anal. Calcd for $C_{16}H_{17}FN_2O$ (272.325): C, 70.57; H, 6.29; N, 10.29. Found: C, 70.69; H, 6.40; N, 10.25.

2,2-Dimethyl-N-(2-(2-chloro-3-pyridyl)phenyl)propanamide (28). The foregoing procedure, applied to **24**, gave 96% of **28** : mp 96°C; ^{1}H NMR ($CDCl_3$) δ 1.05 (s, 9H, tBu), 7.10 to 7.95 (m, 6H, H_5 + C_6H_4 + NH), 8.35 (m, 2H, H_4 + H_6); IR (KBr) 3300, 3040, 2960,

2860, 1670, 1515, 1490, 1455, 1395. Anal. Calcd for $C_{16}H_{17}ClN_2O$ (288.78): C, 66.55; H, 5.93; N, 9.70. Found: C, 66.36; H, 5.99; N, 9.64.

2,2-Dimethyl-N-(2-(3-fluoro-4-pyridyl)phenyl)propanamide (29). The foregoing procedure, applied to **22**, gave 98% of **29** : mp 98°C; ^1H NMR ($CDCl_3$) δ 1.10 (s, 9H, tBu), 7.25 (m, 4H, H_5 + Ar), 7.70 (m, 2H, NH + Ar), 8.40 (d, 1H, H_6), 8.50 (s, 1H, H_2); IR (KBr) 3310, 3060, 2960, 2910, 2870, 1670, 1515, 1490, 1440. Anal. Calcd for $C_{16}H_{17}FN_2O$ (272.325): C, 70.57; H, 6.29; N, 10.29. Found: C, 70.38; H, 6.37; N, 10.42.

2,2-Dimethyl-N-(2-(3-chloro-4-pyridyl)phenyl)propanamide (30). The foregoing procedure, applied to **25**, gave 95°% of **30** : mp 104°C; ^1H NMR ($CDCl_3$) δ 1.05 (s, 9H, tBu), 7.20 to 7.45 (m, 5H, NH + H_5 + Ar), 8.00 (c, 1H, Ar), 8.55 (d, 1H, H_6), 8.70 (s, 1H, H_2); IR (KBr) 3320, 3060, 2960, 2860, 1670, 1580, 1515, 1490, 1480, 1465, 1440, 1400. Anal. Calcd for $C_{16}H_{17}ClN_2O$ (288.78): C, 66.55; H, 5.93; N, 9.70. Found: C, 66.68; H, 5.86; N, 9.64.

2,2-Dimethyl-N-(2-(4-fluoro-3-pyridyl)phenyl)propanamide (31). the foregoing procedure, applied to **23**, gave 94% of **31** : mp 97°C; ^1H NMR ($CDCl_3$) δ 1.10 (s, 9H, tBu), 7.00 to 7.55 (m, 5H, C_6H_4 + NH), 8.00 (d, 1H, H_5), 8.55 (d, 1H, H_6), 8.65 (s, 1H, H_2); IR (KBr) 3310, 3060, 2960, 2870, 1670, 1570, 1520, 1500, 1480, 1450, 1400. Anal. Calcd for $C_{16}H_{17}FN_2O$ (272.325): C, 70.57; 6.29; N, 10.29. Found: C, 70.71; H, 6.40; N, 10.25.

2,2-Dimethyl-N-(2-(3-fluoro-2-pyridyl)phenyl)propanamide (32). The foregoing procedure, applied to **26**, gave 76% of **32** : mp 92°C; ^1H NMR ($CDCl_3$) δ 1.15 (s, 9H, tBu), 6.75 to 7.70 (m, 6H, H_5 + NH + C_6H_4), 8.20 to 8.50 (m, 2H, H_4 + H_6); IR (KBr) 3310, 3070, 2970, 2910, 2870, 1680, 1590, 1525, 1460, 1440. Anal. Calcd for $C_{16}H_{17}FN_2O$ (272.325): C, 70.57; H, 6.29; N, 10.29. Found: C, 70.42; H, 6.40; N, 10.40.

General procedure for the synthesis of carbolines. Anhydrous pyridinium chloride (10 g) at the boiling point was added to 2,2-Dimethyl-N-(2-(ortho-fluoropyridyl or ortho-chloropyridyl) phenyl)propanamide (2.0 mmol) and the mixture was refluxed for 15 min. The resulting hot solution was poured into a mixture of ice and concentrated ammonia. Filtration of the precipitate, washing with water and drying gave a first crop of the corresponding carbolines. Extraction of the aqueous layer by ethyl acetate, drying over $MgSO_4$, solvent removal and crystallization from toluene gave an additional product.

9H-Pyrido[2,3-b]indole or α-carboline (33). The foregoing procedure, applied to **27** or **28**, gave 82% of **33** : mp 212°C; ^1H NMR (DMSO-d_6) δ 7.20 (dd, 1H, H_3), 7.24 (dt, 1H, H_6), 7.48 (dt, 1H, H_7), 7.57 (d, 1H, H_8), 7.74 (d, 1H, H_5), 8.46 (dd, 1H, H_2), 8.48 (dd, 1H, H_4), 11.75 (s, 1H, NH), J_{2-3} = 4.86 Hz, J_{3-4} = 7.66 Hz, J_{2-4} = 1.62 Hz, J_{5-6} = 7.1 Hz, J_{6-7} = 7.5 Hz, J_{7-8} = 8.1 Hz; ^{13}C NMR (DMSO-d_6) δ 111.47, 115.19, 115.43, 119.55, 120.63, 121.36, 126.80, 128.63, 139.07, 146.20, 152.17 ppm; IR (KBr) 3400, 3130, 3070, 2980, 2910, 2850,

2830, 2770, 2690, 1605, 1460, 1420. Anal. Calcd for $C_{11}H_8N_2$ (168.20): C, 78.55; H, 4.79; N, 16.65. Found: C, 78.34; H, 4.78; N, 16.58.

9H-Pyrido[3,4-b]indole or β-carboline (34). The foregoing procedure, applied to **29**, gave 86% of **34** : mp 200°C; ^{1}H NMR (DMSO-d_6) δ 7.26 (dt, 1H, H_6), 7.57 (dt, 1H, H_7), 7.64 (d, 1H, H_8), 8.11 (d, 1H, H_4), 8.25 (d, 1H, H_5), 8.38 (d, 1H, H_3), 8.97 (s, 1H, H_1), 11.35 (s, 1H, NH), J_{3-4} = 5.2 Hz, J_{5-6} = 7.9 Hz, J_{6-7} = 7.1 Hz, J_{7-8} = 8.2 Hz; ^{13}C NMR (DMSO-d_6) δ 112.18, 114.91, 119.45, 120.84, 121.98, 127.69, 128.30, 134.25, 136.23, 138.21, 140.78 ppm; IR (KBr) 3400, 3120, 3050, 2960, 2840, 2750, 2640, 1625, 1445. Anal. Calcd for $C_{11}H_8N_2$ (168.20): C, 78.55; H, 4.79; N, 16.65. Found: C, 78.61; H, 4.82; N, 16.70.

5H-Pyrido[4,3-b]indole or γ-carboline (35). The foregoing procedure, applied to **31**, gave 88% of **35** : mp 218°C; ^{1}H NMR (DMSO-d_6) δ 7.29 (t, 1H, H_8), 7.49 (m, 2H, H_4 + H_7), 7.59 (d, 1H, H_6), 8.25 (d, 1H, H_9), 8.45 (d, 1H, H_3), 9.37 (s, 1H, H_1), 11.77 (s, 1H, NH), J_{3-4} = 5.5 Hz, J_{8-9} = 7.7 Hz, J_{7-8} = 7.3 Hz, J_{6-7} = 8.1 Hz; ^{13}C NMR (DMSO-d_6) δ 106.58, 111.68, 119.61, 120.20, 120.82, 120.94, 126.81, 139.45, 142.81, 143.76, 144.55 ppm; IR (KBr) 3400, 3120, 3060, 2950, 2800, 2730, 2680, 1610, 1580, 1465, 1440. Anal. Calcd for $C_{11}H_8N_2$ (168.20): C, 78.55; H, 4.79; N, 16.65. Found: C, 78.39; H, 4.85; N, 16.60.

5H-Pyrido[3,2-b]indole or δ-carboline (36). The foregoing procedure, applied to **32**, gave 78% of **36** : mp 206°C; ^{1}H NMR (DMSO-d_6) δ 7.28 (t, 1H, H_8), 7.41 (dd, 1H, H_3), 7.53 (t, 1H, H_7), 7.62 (d, 1H, H_6), 7.93 (d, 1H, H_4), 8.27 (d, 1H, H_9), 8.51 (d, 1H, H_2), 11.35 (s, 1H, NH), J_{3-4} = 8.2 Hz, J_{2-3} = 4.6 Hz, J_{2-4} = 1.35 Hz, J_{8-9} = 7.8 Hz, J_{7-8} = 7.3 Hz, J_{6-7} = 8.0 Hz; ^{13}C NMR (DMSO-d_6) δ 111.93, 118.17, 119.53, 120.34, 121.79, 127.79, 133.12, 140.73, 141.14, 141.40, 141.54 ppm; IR (KBr) 3400, 3120, 3060, 2980, 2920, 2850, 2760, 2690, 1630, 1610, 1560, 1505, 1460, 1400. Anal. Calcd for $C_{11}H_8N_2$ (168.20): C, 78.55; H, 4.79; N, 16.65. Found: C, 78.42; H, 4.90; N, 16.59.

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