# SYNTHESIS OF β-SUBSTITUTED AND α,β-DISUBSTITUTED δ-CARBOLINES USING A HALOGEN-DANCE REACTION

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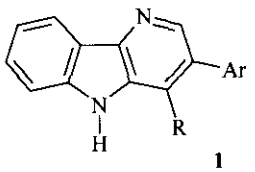
***Abstract-*** The paper describes the first total syntheses of β-substituted δ-carbolines and α,β-disubstituted δ-carbolines starting from benzene and pyridine blocks using a halogen-dance reaction.

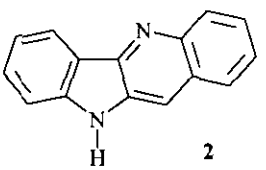
## INTRODUCTION

Up to 1992 all the known iodo-directed metalation of aromatics affected the α-lithiation of iodothiophenes[1] or iodoisothiazoles.[2] In 1993 and 1995, we established that ortho metalation of iodopyridines by LDA at low temperature was feasible if the pyridine nucleus bears a second halo (chloro or fluoro) substituent[3] or a carboxamide group.[4] In most cases, lithiation of haloiodopyridines was regioselectively directed by the iodo group which subsequently ortho migrates to afford the most stable lithio derivative. Following our investigations in this field, we wish to report here an application of this reaction to the syntheses of β-substituted δ-carbolines and α,β-disubstituted δ-carbolines of general structures (**1**). It should be noted that δ-carbolines are very rare compounds and only benzo-δ-carbolines are well depicted in nature (quindoline (**2**) and its derivatives[5]).




**1**

R= H, Me, Ph
*Ar= aryl, hetaryl*




**2**

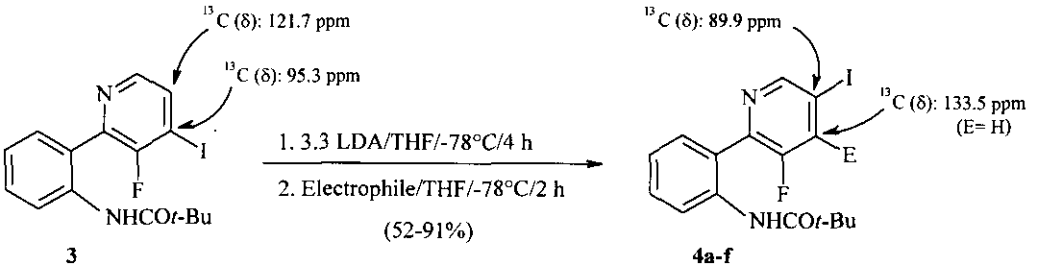
Quindoline

**Scheme 1**

## RESULTS AND DISCUSSION

### 1. Halogen-dance

The synthesis of 2,2-dimethyl-*N*-[2-(3-fluoro-4-iodo-2-pyridyl)phenyl]propanamide (**3**) was previously described as a precursor for α-substituted δ-carbolines.[6] Compound (**3**) was readily prepared in a high yield from 2,2-dimethyl-*N*-[2-(3-fluoro-2-pyridyl)phenyl]propanamide[7] by a metalation-iodination sequence. Treatment of iodopyridine (**3**) with 3.3 equivalents of LDA at –75°C for 4 h followed by quenching with various electrophiles led to the expected 4-substituted 5-iodo derivatives (**4a-f**) in good to high yields (Scheme 2 and Table 1). Migration of iodine is due to a halogen-dance reaction[3] affording the most stable lithio intermediate.




**Scheme 2**

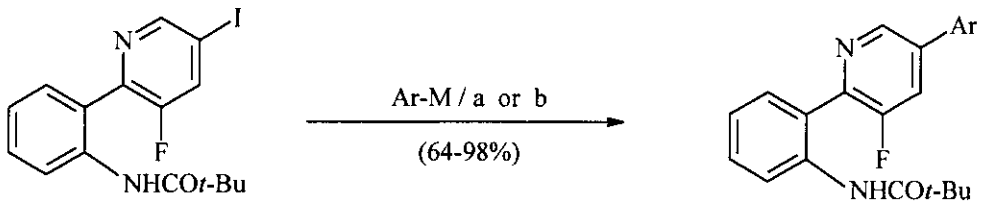
**Table 1**

| Electrophile | E | Product | Yield (%) |
|---|---|---|---|
| $H_2O$ | H | **4a** | 91 |
| $I_2$ | I | **4b** | 80 |
| $C_2Cl_6$ | Cl | **4c** | 82 |
| MeCHO | MeCH(OH) | **4d** | 80 |
| PhCHO | PhCH(OH) | **4e** | 52 |
| HCOOEt | CHO | **4f** | 80 |

It should be pointed out that any alkylated compound at the C-4 position of the pyridinic ring was obtained, probably due to steric hindrance. Metalation of **3** seems to be regioselectively directed by the iodine atom. Indeed, when **3** was metalated by the mixture LDA/TMSCl, the silylated compound at the C-5 position was recovered, thus proving the first step of the mechanism of this halogen-dance reaction. Moreover, no reaction can be observed at the C-6 position. It can also be noted that no reaction occurred on the benzene ring which could be induced by the ortho-directing effect of the pivaloylamino moiety. Identification of these derivatives were inferred from the $^1$H and $^{13}$C NMR spectra: a strong shielding of the carbon bearing the iodo atom could be observed[8] (Scheme 2).

## 2. Cross-coupling reactions

A palladium catalyzed cross-coupling reaction[9] between iodo compounds (**4a**) and various arylboronic acids (**5a-c**)[10] and stannanes (**6a-c**)[10] led to the corresponding polyaromatic structures (**7a-f**) in fairly good yields (Scheme 3 and Table 2).




**4a** **7a-f**

a. M= $B(OH)_2$: $Pd(PPh_3)_4$/Toluene/2M $K_2CO_3$/reflux, 48 h
b. M= $SnMe_3$: $Pd(PPh_3)_4$/Toluene/reflux, 48 h

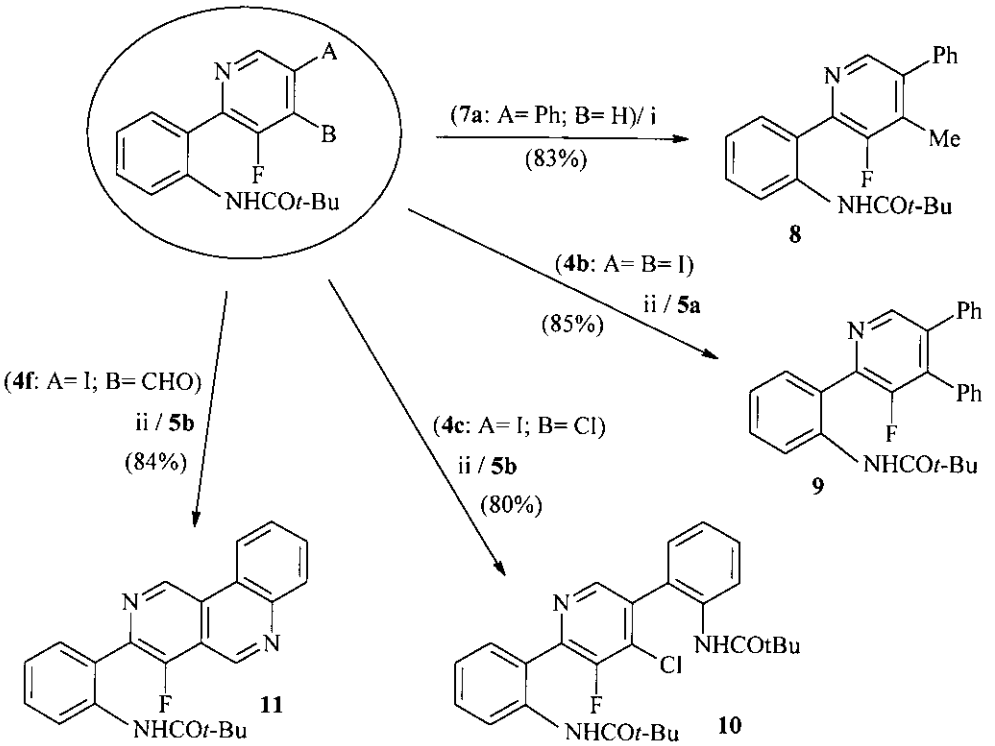
**Scheme 3**

**Table 2**

| Reagent (Ar-M) | Ar | Product | Yield (%) |
|---|---|---|---|
| $PhB(OH)_2$ (**5a**) | Ph | **7a** | 85 |
| 2-NHPiv-$C_6H_4B(OH)_2$ (**5b**) | 2-NHPiv-$C_6H_4$ | **7b** | 78 |
| 2-NHPiv-4-OMe-$C_6H_3B(OH)_2$ (**5c**) | 2-NHPiv-4-OMe-$C_6H_3$ | **7c** | 98 |
| 2-Pyridyl-$SnMe_3$ (**6a**) | 2-Pyridyl | **7d** | 77 |
| 2-Quinolyl-$SnMe_3$ (**6b**) | 2-Quinolyl | **7e** | 64 |
| 2-Thienyl-$SnMe_3$ (**6c**) | 2-Thienyl | **7f** | 75 |

Further functionnalization of the pyridine ring could then be achieved. Alkylation at the C-4 position on the pyridinic ring became possible after cross-coupling. For instance, treatment of diphenylpyridine (**7a**) with 2.8 equivalents of nBuLi at –75°C followed by quenching with methyl iodide led to the corresponding 4-methyl-5-phenylpyridine (**8**) in a very good yield (Scheme 4).

No selectivity between the two iodine atoms has been observed when reacting diiodopyridine (**4b**) with phenylboronic to give the triarylpyridine (**9**). Reaction between **4f** and **5b** using the Suzuki conditions resulted in heteroring cross-coupling and subsequent cyclization to the diazaphenanthrene (**11**). Reaction between **4c** and **5b** using the Suzuki conditions resulted in heteroring cross-coupling to give the tetra-substituted pyridine (**10**) (Scheme 4).



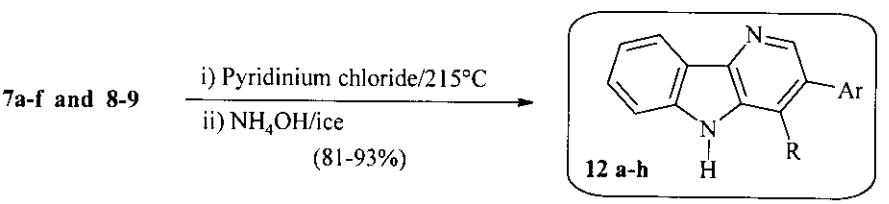

i: 1) 2.8 BuLi/THF/-78°C/3 h. 2) MeI/-78°C/2 h. 3) $H_2O$
ii: $Pd(PPh_3)_4$/2M $K_2CO_3$ /toluene/reflux, 48 h

**Scheme 4**

Compounds (**7**) to (**10**) are precursors for the synthesis of new α,β-disubstituted δ-carbolines with original structures.

### 3. Substituted δ-carbolines

Arylpyridines (**7a-f**) and (**8-9**) were cyclized by treatment in boiling pyridinium chloride[11] at 215°C. Hydrolysis and basic workup yielded the corresponding substituted δ-carbolines (**12a-h**) in very good yields (Scheme 5 and Table 3).



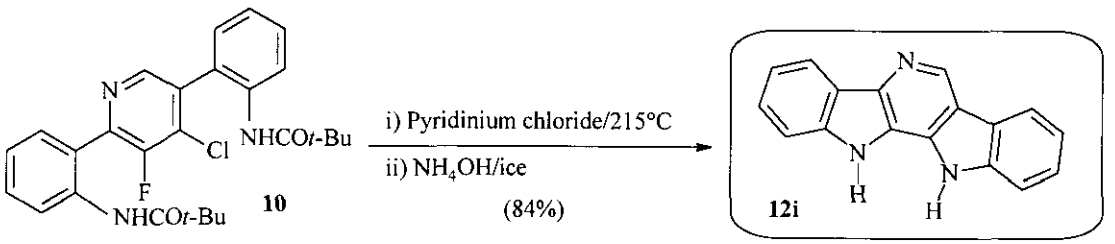

**Scheme 5**

**Table 3**

| Reagent | R | Ar | Product | Yield (%) |
|---|---|---|---|---|
| **7a** | H | Ph | **12a** | 89 |
| **7b**[#] | H | 2-$NH_2$-$C_6H_4$ | **12b** | 93 |
| **7c**[#] | H | 2-$NH_2$-4-OH-$C_6H_3$ | **12c** | 86 |
| **7d** | H | 2-Pyridyl | **12d** | 64 |
| **7e** | H | 2-Quinolyl | **12e** | 81 |
| **7f** | H | 2-Thienyl | **12f** | 78 |
| **8** | Me | Ph | **12g** | 90 |
| **9** | Ph | Ph | **12h** | 86 |

[#]: cyclization carried out on the deprotected material (hydrolysis of the pivaloylamino group[6]).

A similar procedure applied to **10** gave the γ,δ-biscarboline[12] (**12i**) which is an aza-analogue of the biologically active indolo[3,2-*c*]carbazole[13] (Scheme 6).




**Scheme 6**

## CONCLUSION

The first synthesis of β-substituted δ-carbolines and α,β-disubstituted δ-carbolines using a halogen-dance reaction has been described starting from benzene and pyridine blocks. The strategy is fully convergent, regioselective and allows 41 to 67% overall yields in 3 steps. It shows that the halogen-dance reaction is a powerful method to functionalize aromatic structures leading to highly convergent syntheses. The present work is currently being extended to the preparation of biologically active polysubstituted benzo δ-carbolines starting from quinoline derivatives.

## AKNOWLEDGEMENTS

We thank Isabelle Salliot for NMR discussions.

## EXPERIMENTAL

**General data.** The $^1H$ NMR spectra were obtained on a 200 MHz Brücker spectrometer (400 MHz for **12i**) using $CDCl_3$ or deuteriated sulfoxide as solvent with chemical shifts being reported as δ (ppm), respectively, from tetramethylsilane or from hexamethyldisiloxane. $^{13}C$ NMR spectra were obtained on a 100 MHz Brücker spectrometer. The IR spectra were taken on a Perkin Elmer Paragon 500 FT-IR spectrometer, main absorption frequencies (NH, CH, C=O, C=C, C=N) are given in $cm^{-1}$. Elemental analyses were performed on a CE instrument apparatus EA 1110 CHNS-O.

THF was distilled from benzophenone/sodium. The water content of the solvent was estimated lower than 45 ppm by the Karl-Fischer method.[14] Commercial diisopropylamine was distilled from calcium hydride under a dry argon atmosphere. Commercial 2.5 M solution of n-butyllithium in hexane used and all reactions involving organometallic compounds were carried out under a dry argon atmosphere.

**General procedure A : metallation-isomerisation of 2,2-dimethyl-*N*-[2-(3-fluoro-4-iodo-2-pyridyl)-phenyl]propanamide (3).** n-Butyllithium (1.32 mL, 3.30 mmol, 2.5 M) was added to diisopropylamine (0.460 mL, 3.30 mmol) in THF (2.0 mL) at –78°C. After 20 min, 398 mg (1.0 mmol) of **3** in 5.0 mL of THF were added to the solution of LDA. The resulting mixture was stirred for 4 h at –78°C, and the electrophile (3.40 mmol) in 2.0 mL of THF was slowly added. Stirring was continued for 2 h at –78° before hydrolysis at 0°C by 5.0 mL of THF/$H_2O$ 4/1. Extraction with ethyl acetate, drying over $MgSO_4$ and solvant removal afforded a crude product which was purified by flash chromatography on silica gel (light petroleum/ethyl acetate: 9/1).

**2,2-Dimethyl-*N*-[2-(3-fluoro-5-iodo-2-pyridyl)phenyl]propanamide (4a).** General procedure A, using water as electrophile, gave 362 mg (91%) of **4a** as a white powder, mp 146°C; $^1H$ NMR ($CDCl_3$): 10.74 (s, 1H, NH), 8.70 (comp, 1H, H-6'), 8.44 (dd, *J*=1.2 and 7.9 Hz, 1H, H-6), 7.96 (dd, *J*=1.7 and 9.9 Hz, 1H, H-4'), 7.65 (ddd, *J*=1.5/4.4 and 7.6 Hz, 1H, H-3), 7.45 (td, *J*=1.5 and 7.9 Hz, 1H, H-5), 7.17 (td, *J*=1.2 and 7.6 Hz, 1H, H-4), 1.26 (s, 9H, *t*-Bu); IR (KBr): 3236, 2956, 1663, 1583, 1433, 1385, 1158, 883, 747. Anal. Calcd for $C_{16}H_{16}N_2OFI$: C, 48.26; H, 4.05; N, 7.09. Found: C, 48.45; H, 4.03; N, 6.82.

**2,2-Dimethyl-*N*-[2-(3-fluoro-4,5-diiodo-2-pyridyl)phenyl]propanamide (4b).** General procedure A, using iodide as electrophile, gave 420 mg (80%) of **4b**, mp 138°C; $^1H$ NMR ($CDCl_3$): 10.48 (s, 1H, NH), 8.72 (s, 1H, H-6'), 8.41 (d, *J*=8.2 Hz, 1H, H-6), 7.60 (ddd, *J*=1.5/4.9 and 7.7 Hz, 1H, H-3), 7.45 (td, *J*=1.5 and 7.9 Hz, 1H, H-5), 7.16 (td, *J*=1.0 and 7.7 Hz, 1H, H-4), 1.25 (s, 9H, *t*-Bu); IR (KBr): 3250, 2961, 1664, 1364, 748. Anal. Calcd for $C_{16}H_{15}N_2OFI_2$: C, 36.66; H, 2.88; N, 5.35. Found: C, 36.38; H, 2.92; N, 5.42.

**2,2-Dimethyl-*N*-[2-(4-chloro-3-fluoro-5-iodo-2-pyridyl)phenyl]propanamide (4c).** General procedure A, using hexachloroethane as electrophile, gave 354 mg (82%) of **4c** as a white solid, mp 128°C; $^1H$ NMR ($CDCl_3$): 10.52 (s, 1H, NH), 8.78 (s, 1H, H-6'), 8.44 (d, *J*=8.2 Hz, 1H, H-6), 7.63 (ddd, *J*=1.5/4.7

and 7.8 Hz, 1H, H-3), 7.46 (td, *J*=1.5 and 7.7 Hz, 1H, H-5), 7.17 (td, *J*=1.1 and 7.6 Hz, 1H, H-4), 1.22 (s, 9H, *t*-Bu); IR (KBr): 3239, 2959, 1667, 1451, 1427, 749. Anal. Calcd for $C_{16}H_{15}N_2OClFI$: C, 44.42; H, 3.49; N, 6.47. Found: C, 44.63; H, 3.32; N, 6.26.

**2,2-Dimethyl-*N*-{2-[3-fluoro-4-(1-hydroxyethyl)-5-iodo-2-pyridyl]phenyl}propanamide (4d).** General procedure A, using acetaldehyde as electrophile, gave 352 mg (80%) of **4d** as a white powder, mp 160°C; $^1$H NMR, ($CDCl_3$): 10.52 (s, 1H, NH), 8.73 (s, 1H, H-6'), 8.38 (dd, *J*=1.2 and 8.4 Hz, 1H, H-6), 7.60 (ddd, *J*=1.5/4.8 and 7.8 Hz, 1H, H-3), 7.41 (td, *J*=1.5 and 7.9 Hz, 1H, H-5), 7.13 (td, *J*=1.2 and 7.9 Hz, 1H, H-4), 5.20 (qt, *J*=7.0 Hz, 1H, C<u>H</u>(OH)), 3.13 (dd, *J*=3.7 and 7.0 Hz, 1H, OH), 1.63 (dd, *J*=0.6 and 7.0 Hz, 3H, $CH_3$), 1.22 (s, 9H, *t*-Bu); IR (KBr): 3330, 2961, 2925, 2849, 1664, 1584, 1522, 1452, 1391, 1164, 874, 754. Anal. Calcd for $C_{18}H_{20}N_2O_2FI$: C, 48.88; H, 4.56; N, 6.33. Found: C, 48.75; H, 4.51; N, 6.41.

**2,2-Dimethyl-*N*-{2-[3-fluoro-4-(1-hydroxybenzyl)-5-iodo-2-pyridyl]phenyl}propanamide (4e).** General procedure A, using benzaldehyde as electrophile, gave 260 mg (52%) of **4e** as a white solid, mp 168°C; $^1$H NMR ($CDCl_3$): 10.43 (s, 1H, NH), 8.66 (s, 1H, H-6'), 8.22 (d, *J*=8.3 Hz, 1H arom), 7.46-7.20 (m, 7H arom), 6.97 (t, *J*=7.6 Hz, 1H arom), 6.18 (d, *J*=5.3 Hz, 1H, C<u>H</u>(OH)), 3.98 (s, 1H, OH), 1.11 (s, 9H, *t*-Bu); IR (KBr): 3326, 2964, 1652, 1520, 1393, 874, 756, 702, 678. Anal. Calcd for $C_{23}H_{22}N_2O_2FI$: C, 54.75; H, 4.39; N, 5.55. Found: C, 55.02; H, 4.83; N, 5.64.

**2,2-Dimethyl-*N*-[2-(3-fluoro-4-formyl-5-iodo-2-pyridyl)phenyl]propanamide (4f).** General procedure A, using ethyl formate as electrophile, gave the unpurified product (**4f**) in 80% yield (oil); $^1$H NMR ($CDCl_3$): 10.41 (s, 1H, NH), 10.22 (s, 1H, CHO), 8.97 (s, 1H, H-6'), 8.42 (d, *J*=8.0 Hz, 1H, H-6), 7.66 (ddd, *J*=1.4/4.8 and 7.8 Hz, 1H, H-3), 7.49 (dd, *J*=1.4 and 7.8 Hz, 1H, H-5), 7.24 (td, *J*=1.1 and 7.8 Hz, 1H, H-4), 1.27 (s, 9H, *t*-Bu); IR (KBr): 3263, 2961, 1716, 1664, 1583, 1529, 752.

**General procedure B : cross-coupling of iodo compounds (4a-c and 4f) with various boronic acids.** The required boronic acid ($\chi$ mmol) and iodo compound ($\chi$ mmol) were added to an aqueous solution of 2.0 M $K_2CO_3$ ($\chi$ mL) and ethanol ($\chi$/2 mL) in deoxygenated toluene (10$\chi$ mL). The resulting mixture was stirred for 30 min under an argon atmosphere. Tetrakis(triphenylphosphine)palladium(0) (35$\chi$ mg, 0.03$\chi$ mmol) was added, and the mixture was refluxed for 48 h. Cooling, filtration, extraction with toluene, drying over $MgSO_4$, and solvent removal afforded to a crude product which was purified by flash chromatography on silica gel (light petroleum/ethyl acetate: 9/1).

**2,2-Dimethyl-*N*-[2-(3-fluoro-5-phenyl-2-pyridyl)phenyl]propanamide (7a).** The foregoing procedure ($\chi$= 1.0), with phenylboronic acid and iodo compound (**4a**), gave 295 mg (85%) of **7a** as a white solid, mp 164°C; $^1$H NMR ($CDCl_3$): 11.04 (s, 1H, NH), 8.74 (s, 1H, H-6'), 8.50 (d, *J*=8.0 Hz, 1H, H-6), 7.84-7.41 (m, 8H arom), 7.19 (t, *J*=7.7 Hz, 1H, H-4), 1.27 (s, 9H, *t*-Bu); IR (KBr): 3263, 2961, 1669, 1437, 756, 693. Anal. Calcd for $C_{22}H_{21}N_2OF$: C, 75.82; H, 6.08; N, 8.04. Found: C, 75.88; H, 6.19; N, 7.91.

**2,2-Dimethyl-*N*-{2-[3-fluoro-5-(2-pivaloylamino)phenyl-2-pyridyl]phenyl}propanamide (7b).** The foregoing procedure ($\chi$= 1.0), with 2-pivaloylaminophenylboronic acid and iodo compound (**4a**), gave 349 mg (78%) of **7b** as a yellow solid, mp 183°C; $^1$H NMR ($CDCl_3$): 11.13 (s, 1H, NH), 8.54 (d, *J*=1.5 Hz, 1H, H-6'), 8.51 (d, *J*=8.0 Hz, 1H arom), 8.05 (d, *J*=8.0 Hz, 1H arom), 7.75 (ddd, *J*=1.3/4.2 and 7.8 Hz, 1H, H-3), 7.67 (dd, *J*=1.7 and 11.5 Hz, 1H, H-4'), 7.53-7.43 (m, 2H arom), 7.36-7.16 (m, 3H arom and NH), 1.27 (s, 9H, *t*-Bu), 1.18 (s, 9H, *t*-Bu); IR (KBr): 3281, 2959, 1682, 1648, 1434, 1153, 927, 757. Anal. Calcd for $C_{27}H_{30}N_3O_2F$: C, 72.44; H, 6.76; N, 9.39. Found: C, 72.72; H, 6.65; N, 9.20.

**2,2-Dimethyl-*N*-{2-[3-fluoro-5-(5-methoxy-2-pivaloylamino)phenyl-2-pyridyl]phenyl}propanamide (7c).** The foregoing procedure ($\chi$= 1.0), with 4-methoxy-2-pivaloylaminophenylboronic acid and iodo compound (**4a**), gave 467 mg (98%) of **7c** as a red solid, mp 180°C; $^1$H NMR ($CDCl_3$): 11.14 (s, 1H, NH), 8.52 (d, J=1.9 Hz, 1H, H-6'), 8.49 (comp, 1H arom), 7.73 (d, *J*=8.8 Hz, 1H arom), 7.72 (comp, 1H arom), 7.65 (dd, *J*=1.9 and 11.5 Hz, 1H, H-4'), 7.46 (td, *J*=1.6 and 8.0 Hz, 1H, H-5), 7.19 (td, *J*=1.4 and 8.0 Hz, 1H, H-4), 7.08 (s, 1H, NH), 7.00 (dd, *J*=2.9 and 8.8 Hz, 1H arom), 6.88 (d, *J*=2.9 Hz, 1H arom), 3.86 (s, 3H, $CH_3$), 1.26 (s, 9H, *t*-Bu), 1.17 (s, 9H, *t*-Bu); IR (KBr): 3339, 3055, 2958, 2869, 1654, 1508, 751. Anal. Calcd for $C_{28}H_{32}N_3O_3F$: C, 70.40; H, 6.76; N, 9.39. Found: C, 70.82; H, 6.69; N, 9.24.

**2,2-Dimethyl-*N*-[2-(3-fluoro-4,5-diphenyl-2-pyridyl)phenyl]propanamide (9).** The foregoing procedure ($\chi$= 4.0), with phenylboronic acid and iodo compound (**4b**), gave 721 mg (85%) of **9** as a white solid, mp 184°C; $^1$H NMR ($CDCl_3$): 11.10 (s, 1H, NH), 8.56 (s, 1H, H-6'), 8.51 (d, *J*=8.0 Hz, 1H, H-6), 7.73 (ddd, *J*=1.1/4.4 and 7.8 Hz, 1H, H-3), 7.44 (td, *J*=1.1 and 8.0 Hz, 1H, H-5), 7.35-7.13 (m, 11H arom), 1.28 (s, 9H, *t*-Bu); IR (KBr): 3272, 3062, 2963, 1677, 1529, 1439, 756, 698. Anal. Calcd for $C_{28}H_{25}N_2OF$: C, 79.22; H, 5.93; N, 6.60. Found: C, 78.92; H, 6.05; N, 6.43.

**2,2-Dimethyl-*N*-{2-[4-chloro-3-fluoro-5-(2-pivaloylamino)phenyl]phenyl}propanamide (10).** The fore-going procedure ($\chi$= 2.0), with 2-pivaloylaminophenylboronic acid and iodo compound (**4c**), gave 771.0 mg (80%) of **10** as a yellow solid, mp 200°C; $^1$H NMR ($CDCl_3$): 10.86 (s, 1H, NH), 8.50-8.45 (m, 2H arom), 7.96 (d, *J*=8.0 Hz, 1H arom), 7.68 (ddd, *J*=1.4/4.6 and 7.8 Hz, 1H arom), 7.58-7.42 (m, 2H arom), 7.38-7.14 (m, 3H arom and NH), 1.26 (s, 9H, *t*-Bu), 1.09 (s, 9H, *t*-Bu); IR (KBr): 3316, 2961, 1868, 1677, 1655, 1586, 1512, 1432, 1389, 1165, 756. Anal. Calcd for $C_{27}H_{29}N_3O_2ClF$: C, 67.28; H, 6.06. N, 8.72. Found: C, 67.66; H, 6.30; N, 8.34.

**2,2-Dimethyl-*N*-[2-(2,6-diaza-4-fluorophenanthrene)phenyl]propanamide (11).** The foregoing procedure ($\chi$= 2.0), with 2-pivaloylaminophenylboronic acid and iodo compound (**4f**), gave 626.0 mg (84%) of **11** as an orange solid, mp 184°C; $^1$H NMR ($CDCl_3$): 10.85 (s, 1H, NH), 9.89 (s, 1H phenan), 9.72 (s, 1H phenan), 8.74 (dd, *J*=1.4 and 7.4 Hz, 1H arom), 8.50 (dd, *J*=1.1 and 7.8 Hz, 1H arom), 8.33 (dd, *J*=2.1 and 7.4 Hz, 1H arom), 7.95-7.76 (m, 2H arom and H-3), 7.49 (td, *J*=1.5 and 7.8 Hz, 1H arom), 7.24 (td, *J*= 1.1 and 7.7 Hz, 1H arom), 1.27 (s, 9H, *t*-Bu); IR (KBr): 3271, 2920, 1673, 1520, 1460, 743. Anal.

Calcd for $C_{23}H_{20}N_3OF$: C,73.98; H, 5.40; N, 11.25. Found: C, 73.86; H, 5.53; N, 11.07.

**General procedure C : cross-coupling of 2,2-dimethyl-*N*-[2-(3-fluoro-5-iodo-2-pyridyl)phenyl]-propanamide (4a) with various arylstannanes.** The required arylstannane (1.0 mmol) is added to a solution of 2,2-dimethyl-*N*-[2-(3-fluoro-5-iodo-2-pyridyl)phenyl]propanamide (**4a**) (398.0 mg, 1.0 mmol) in deoxygenated toluene (10.0 mL). The resulting mixture was stirred 30 min under argon atmosphere before the addition of tetrakis(triphenylphosphine)palladium(0) (35.0 mg, 0.03 mmol). The mixture was refluxed for 48 h. Cooling, filtration, washing with an $NH_4OH$ solution (10%), drying over $MgSO_4$ and solvent removal afforded a crude product which was purified by flash chromatography on silica gel (light petroleum/ethyl acetate: 9/1).

**2,2-Dimethyl-*N*-{2-[3-fluoro-5-(2-pyridyl)-2-pyridyl]phenyl}propanamide (7d).** The foregoing procedure, with 2-trimethylstannylpyridine, gave 269 mg (77%) of **7d** as a white solid, mp 150°C; $^1$H NMR ($CDCl_3$): 11.15 (s, 1H, NH), 9.11 (t, *J*= 1.3 Hz, 1H, H-6'), 8.76 (comp, 1H pyr), 8.51 (dd, *J*=0.6 and 8.3 Hz, 1H arom), 8.27 (dd, *J*= 1.3 and 12.0 Hz, 1H, H-4'), 7.87-7.83 (m, 2H arom), 7.76 (ddd, *J*= 1.5/4.3 and 7.6 Hz, 1H, H-3), 7.49-7.23 (m, 2H arom), 7.19 (td, *J*= 1.3 and 7.6 Hz, 1H, H-4), 1.28 (s, 9H, *t*-Bu); IR (KBr): 3321, 2964, 1673, 1584, 1154, 783, 757. Anal. Calcd for $C_{21}H_{20}N_3OF$: C, 72.17; H, 5.77; N, 12.03. Found: C, 72.31; H, 5.73; N, 11.92.

**2,2-Dimethyl-*N*-{2-[3-fluoro-5-(2-quinolyl)-2-pyridyl]phenyl}propanamide (7e).** The foregoing proce-dure, with 2-trimethylstannylquinoline, gave 255 mg (64%) of **7e** as a green solid, mp 152°C; $^1$H NMR ($CDCl_3$): 11.21 (s, 1H, NH), 9.25 (t, *J*=1.5 Hz, 1H, H-6'), 8.45-8.55 (m, 2H arom), 8.34 (d, *J*= 8.5 Hz, 1H arom), 8.21 (d, *J*= 8.0 Hz, 1H arom), 7.96 (d, *J*= 8.6 Hz, 1H arom), 7.87 (dd, *J*=1.0 and 8.2 Hz, 1H arom), 7.85-7.74 (m, 2H arom) 7.61 (td, *J*= 1.2 and 7.5 Hz, 1H arom), 7.46 (td, *J*=1.5 and 7.8 Hz, 1H arom), 7.20 (td, *J*=1.3 and 7.8 Hz, 1H arom), 1.29 (s, 9H, *t*-Bu); IR (KBr): 3225, 3060, 2961, 1669, 1583, 1426, 1163, 835, 754. Anal. Calcd for $C_{25}H_{22}N_3OF$: C, 75.17; H, 5.55; N, 10.52. Found: C, 75.05; H, 5.42; N, 10.51.

**2,2-Dimethyl-*N*-{2-[3-fluoro-2-pyridyl-5-(2-thienyl)]phenyl}propanamide (7f).** The foregoing procedure, with 2-trimethylstannylthiophene, gave 251 mg (75%) of **7f** as a white solid, mp 153°C; $^1$H NMR ($CDCl_3$): 11.04 (s, 1H, NH), 8.74 (dd, *J*=1.5 and 2.0 Hz, 1H, H-6'), 8.49 (dd, *J*=1.1 and 8.3 Hz, 1H, H-6), 7.78 (dd, *J*=2.0 and 11.7 Hz, 1H, H-4'), 7.70 (ddd, *J*=1.5/4.3 and 7.8 Hz, 1H, H-3), 7.49-7.39 (m, 3H arom), 7.21-7.13 (m, 2H arom), 1.29 (s, 9H, *t*-Bu); IR (KBr): 3287, 3048, 2960, 1671, 1581, 1161, 842, 754, 697. Anal. Calcd for $C_{20}H_{19}N_2OFS$: C, 67.77; H, 5.40; N, 7.90; S, 9.05. Found: C, 68.02; H, 5.62; N, 8.21; S, 9.41.

**2,2-Dimethyl-*N*-[2-(3-fluoro-4-methyl-5-phenyl-2-pyridyl)phenyl]propanamide (8).** n-Butyllithium (2.24 mL, 5.6 mmol, 2.5 M) was slowly added to a solution of **7a** (696 mg, 2.0 mmol) in 50.0 mL of anhydrous THF at –78°C. The resulting mixture was stirred during 3 h before the addition of methyl

iodide (856 mg, 6.0 mmol) in 10.0 mL of anhydrous THF. The solution was stirred at –78°C during 2 h before hydrolysis with 5.0 mL of water. Extraction with AcOEt, drying over $MgSO_4$ and solvent removal afforded a crude product which was purified by flash chromatography on silica gel (light petroleum/ethyl acetate: 95/5). The yield was 301 mg (83%) of **8** as a white solid, mp 104°C; $^1$H NMR ($CDCl_3$): 11.14 (s, 1H, NH), 8.46 (d, *J*=8.0 Hz, 1H, H-6), 8.37 (s, 1H, H-6'), 7.72 (comp, 1H arom), 7.56-7.38 (m, 6H arom), 7.18 (comp, 1H arom), 2.34 (d, *J*=2.3 Hz, 3H, $CH_3$), 1.26 (s, 9H, *t*-Bu); IR (KBr): 3246, 3060, 2962, 2867, 1681, 1585, 1439, 753, 705. Anal. Calcd for $C_{23}H_{23}N_2OF$: C, 76.22; H, 6.40; N, 7.73. Found: C, 75.95; H, 6.52; N, 7.71.

**General procedure D : synthesis of 3-substituted and 3,4-disubstituted 5*H*-pyrido[3,2-*b*]indole or β-substituted and α,β-disubstituted δ-carbolines (12a-i).** Anhydrous pyridinium chloride (10.0 g) at the boiling point (215°C) was added to the corresponding phenylpyridine (**7a-f**) and (**8-10**) (1.0 mmol) and the mixture was refluxed for 15 min (12 h for **10**). The resulting hot solution was poured onto a mixture of ice (10.0 mL) and concentrated ammonia (10.0 mL). Extraction of the aqueous layer with ethyl acetate, drying over $MgSO_4$, solvent removal and flash chromatography on silica gel (light petroleum/ethyl acetate: 7/3) afforded a pure product.

**3-Phenyl-5*H*-pyrido[3,2-*b*]indole or β-phenyl-δ-carboline (12a).** General procedure D, using **7a**, gave 206 mg (89%) of **12a** as a white solid, mp 255°C; $^1$H NMR (DMSO-$d_6$): 11.39 (s, 1H, NH), 8.75 (d, *J*=1.9 Hz, 1H, H-2), 8.19 (d, *J*=7.8 Hz, 1H, H-6), 8.07 (d, *J*=1.9 Hz, 1H, H-4), 7.83-7.78 (m, 2H arom), 7.59-7.38 (m, 5H arom), 7.25 (td, *J*=1.0 and 7.5 Hz, 1H arom); IR (KBr): 3060, 2952, 2871, 2769, 1458, 764, 744, 702. Anal. Calcd for $C_{17}H_{12}N_2$: C, 83.58; H, 4.95; N, 11.47. Found: C, 85.29; H, 4.71; N, 11.57.

**3-(2-Aminophenyl)-5*H*-pyrido[3,2-*b*]indole or β-(2-aminophenyl)-δ-carboline (12b).** General procedure D, using **7b**, gave 241 mg (93%) of **12b** as a white solid, mp 224°C; $^1$H NMR (DMSO-$d_6$): 11.42 (s, 1H, NH), 8.46 (d, *J*=1.8 Hz, 1H, H-2), 8.18 (d, *J*=7.7 Hz, 1H arom), 7.88 (d, *J*= 1.8 Hz, 1H, H-4), 7.59-7.45 (m, 2H arom), 7.24 (td, *J*=1.1 and 7.9 Hz, 1H arom), 7.12-7.05 (m, 2H arom), 6.80 (dd, *J*=1.0 and 7.8 Hz, 1H arom), 6.67 (t, *J*=8.0 Hz, 1H arom), 4.98 (s, 2H, $NH_2$); IR (KBr): 3388, 3060, 2976, 1610, 1227, 749. Anal. Calcd for $C_{17}H_{13}N_3$: C, 78.74; H, 5.05; N, 16.20. Found: C, 78.51; H, 5.29; N, 15.97.

**3-(2-Amino-4-hydroxyphenyl)-5*H*-pyrido[3,2-*b*]indole or β-(2-amino-4-hydroxyphenyl)-δ-carboline (12c).** General procedure D, using **7c**, gave 236 mg (86%) of **12c** as a white solid, mp >260°C; $^1$H NMR (DMSO-$d_6$): 11.43 (s, 1H, NH), 8.64 (s, 1H, OH), 8.45 (d, *J*=1.4 Hz, 1H, H-2), 8.18 (d, *J*=7.7 Hz, 1H arom), 7.88(d, *J*=1.4 Hz, 1H, H-4), 7.58-7.44 (m, 2H arom), 7.23 (td, *J*=0.9 and 7.7 Hz, 1H arom), 6.69-6.56 (m, 3H arom), 4.36 (s, 2H, $NH_2$); IR (KBr): 3333, 2931, 2660, 2578, 1458, 1222, 732. Anal. Calcd for $C_{17}H_{13}N_3O$: C, 74.17; H, 4.76; N, 15.26. Found: C, 74.05; H, 5.02; N, 15.08.

**3-(2-Pyridyl)-5*H*-pyrido[3,2-*b*]indole or β-(2-pyridyl)-δ-carboline (12d).** General procedure D, using

**7d**, gave 157 mg (64 %) of **12d** as a white solid, mp >260°C; $^1$H NMR (DMSO-$d_6$): 11.34 (s, 1H, NH), 9.15 (d, *J*=1.8 Hz, 1H, H-2), 8.72 (comp, 1H pyr), 8.49 (d, *J*=1.8 Hz, 1H, H-4), 8.20 (d, *J*=7.8 Hz, 1H, H-6), 8.14 (dd, *J*=0.8 and 8.0 Hz, 1H pyr), 7.93 (td, *J*=1.6 and 7.9 Hz, 1H arom), 7.67-7.48 (m, 2H arom), 7.37 (comp, 1H pyr), 7.25 (comp, 1H arom); IR (KBr): 3048, 2965, 2878, 2777, 1587, 1394, 777, 736. Anal. Calcd for $C_{16}H_{11}N_3$: C, 78.35; H, 4.52; N, 17.13. Found: C, 78.21; H, 4.49; N, 16.82.

**3-(2-Quinolyl)-5*H*-pyrido[3,2-*b*]indole or β-(2-quinolyl)-δ-carboline (12e).** General procedure D, using **7e**, gave 239 mg (81%) of **12e** as a white solid, mp >260°C; $^1$H NMR (DMSO-$d_6$): 11.29 (s, 1H, NH), 9.36 (d, *J*=1.8 Hz, 1H, H-2), 8.71 (d, *J*=1.8 Hz, 1H, H-4), 8.53 (d, *J*=8.5 Hz, 1H arom), 8.34 (d, *J*=8.7 Hz, 1H arom), 8.24 (d, *J*=7.8 Hz, 1H arom), 8.13 (d, *J*=8.2 Hz, 1H arom), 8.04 (d, *J*=8.0 Hz, 1H arom), 7.82 (td, *J*=1.4 and 7.8 Hz, 1H arom), 7.68-7.50 (m, 3H arom), 7.28 (td, *J*=1.2 and 7.8 Hz, 1H arom); IR (KBr): 3058, 2961, 2870, 2764, 1596, 1233, 824, 754. Anal. Calcd for $C_{20}H_{13}N_3$: C, 81.34; H, 4.43; N, 14.23. Found: C, 81.51; H, 4.40; N, 14.08.

**3-(2-Thienyl)-5*H*-pyrido[3,2-*b*]indole or β-(2-thienyl)-δ-carboline (12f).** General procedure D, using **7f**, gave 195 mg (78%) of **12f** as a white solid, mp 260°C; $^1$H NMR (DMSO-$d_6$): 11.41 (s, 1H, NH), 8.78 (d, *J*=1.8 Hz, 1H, H-2), 8.16 (d, *J*=7.7 Hz, 1H, H-6), 8.04 (d, *J*=1.8 Hz, 1H, H-4), 7.68-7.45 (m, 4H arom), 7.27-7.17 (m, 2H arom); IR (KBr): 3059, 2964, 2868, 2755, 1225, 744, 686. Anal. Calcd for $C_{15}H_{10}N_2S$: C, 71.97; H, 4.03; N, 11.19; S, 12.79. Found: C, 71.78; H, 4.36; N, 10.90; S, 12.61.

**4-Methyl-3-phenyl-5*H*-pyrido[3,2-*b*]indole or α-methyl-β-phenyl-δ-carboline (12g).** General procedure D, using **8**, gave 232 mg (90%) of **12g** as a white solid, mp >260°C. $^1$H NMR (DMSO-$d_6$): 11.50 (s, 1H, NH), 8.29 (s, 1H, H-2), 8.17 (d, *J*=7.7 Hz, 1H, H-6), 7.61-7.39 (m, 7H arom), 7.24 (t, *J*=7.8 Hz, 1H arom), 2.51 (s, 3H, $CH_3$); IR (KBr): 3056, 2961, 2854, 2781, 1624, 1458, 1320, 1232, 752, 701. Anal. calcd for $C_{18}H_{14}N_2$: C, 83.69; H, 5.46; N, 10.84. Found: C, 83.61; H, 5.64; N, 10.54.

**3,4-Diphenyl-5*H*-pyrido[3,2-*b*]indole or α,β-diphenyl-δ-carboline (12h).** General procedure D, using **9**, gave 275 mg (86%) of **12h** as a white solid, mp >260°C; $^1$H NMR (DMSO-$d_6$): 11.06 (s, 1H, NH), 8.47 (s, 1H, H-2), 8.21 (d, *J*=7.4 Hz, 1H, H-6), 7.57-7.14 (m, 13H arom); IR (KBr): 3047, 2957, 2849, 2778, 2661, 1459, 1225, 750, 695. Anal. Calcd for $C_{23}H_{16}N_2$: C, 86.22; H, 5.03; N, 8.75. Found: C, 85.91; H, 5.27; N, 8.54.

**11*H*, 12*H*-Pyrido[3,2-*b*; 4,5-*b*']diindole or γ,δ-biscarboline (12i).** General procedure, using **10**, gave 216 mg (84%) of **12i** as a green solid, mp >260°C; $^1$H NMR (400 MHz, DMSO-$d_6$): 11.51 (s, 1H, NH-11), 11.20 (s, 1H, NH-12), 9.27 (s, 1H, H-6), 8.28 (d, *J*= 7.5 Hz, 1H, H-10), 8.20 (d, *J*= 7.9 Hz, 1H, H-1), 7.74 (d, *J*= 8.1 Hz, 1H, H-4 or H-7), 7.72 (d, *J*= 8.1 Hz, 1H, H-7 or H-4), 7.46 (m, 2H, H-3 and H-8), 7.29 (comp, 1H, H-9), 7.24 (comp, 1H, H-2). $^{13}$C NMR (100 MHz, DMSO-$d_6$): 139.42 (C-10a), 139.35 (C-1a), 137.18 (C-5a), 136.11 (C-6), 130.31 (C-11a), 126.13 (C-12a), 125.88 (C-3 or C-8), 123.30 (C-8 or C-3), 122.59 (C-7a), 120.56 (C-4a), 120.52 (C-9), 119.83 (C-10), 119.80 (C-1), 119.78 (C-2), 117.17 (C-6a),

112.52 (C-4 or C-7), 112.37 (C-7 or C-4); IR (KBr): 3442, 2694, 1655, 1549, 1363, 1324, 1234, 741, 593. Anal. Calcd for $C_{17}H_{11}N_3$: C, 79.36; H, 4.31; N, 16.33. Found: C, 79.41; H, 4.42; N, 16.02.

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Received, 22nd June, 1998