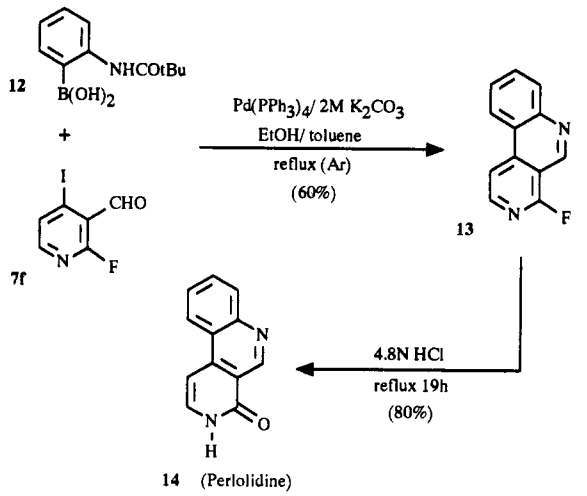
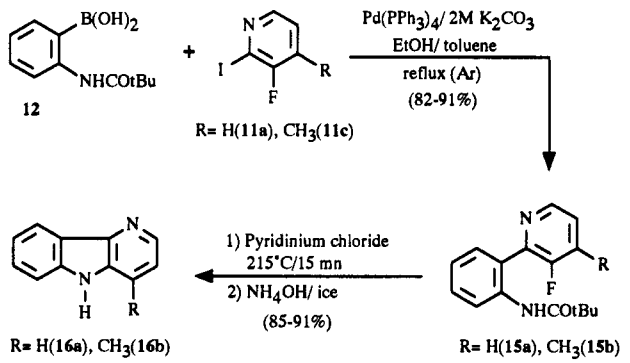
Scheme V



Scheme VI

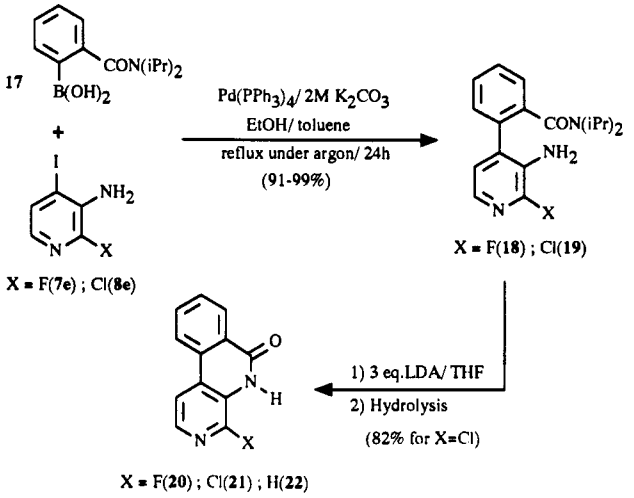


(14) (an alkaloid of the New Zealand perennial rye grass "*Lolium perenne L*" which is effective on plant growth[17a]) (Scheme V).

(b) Synthesis of δ-Carboline and 4-Methyl-δ-carboline. Reaction between 3-fluoro-2-iodopyridine (**11a**) or 3-fluoro-2-iodo-4-methylpyridine (**11c**) and the N-protected (2-aminophenyl)boronic acid[14] **12** as previously described (see IIIa) led to the expected polysubstituted 4-phenylpyridines **15a** and **15b**, respectively. These compounds were readily cyclized by boiling pyridinium chloride to δ-carboline (**16a**) or 4-methyl-δ-carboline (**16b**) (Scheme VI).

(c) Synthesis of 2,10-Diazaphenanthrenes. Little has been done in the field of 2,10-diazaphenanthrenes[20] which is an isomeric structure of th 2,9-diaza skeleton found in numerous alkaloids of the "Marine sponge" family.[24] Heteroring cross-coupling between the 3-amino-4-iodopyrdines **7e** and **8e** and (2-((diisopropylamino)carbonyl)-phenyl)boronic acid[21] (**17**) using a Pd(0) catalyst gave the 4-phenyl-3-aminopyridines **18** and **19** in excellent yield. Cyclization of fluoro and chloro compounds **18** and **19** to the corresponding halonaphthiridinones **20** and **21** was achieved by treatment with LDA.[22] The base-catalyzed cyclization of the (fluorophenyl)pyridine **18** yielded 28% of fluorophenanthrenone **20** with unavoidable side formation of tarry products. Cyclization of the chloro isomer

Scheme VII



19 gave better results, but it was demonstrated that long reaction times induced competitive dechlorination of the chloro product **21** to diazaphenanthrenone **22** (thus a 6 h reaction time led to 68% of **21** and 28% of **22**). However, treatment of **19** by a 3-fold excess of LDA at room temperature for 4 h gave the expected halonaphthiridinone **21** in very good yields (82% of **21** and 15% of unreacted **19**) (Scheme VII).

Discussion

In a general way, metalation of iodopyridines proved to be feasible at the very condition that the pyridine nucleus bears a second halo (chloro or fluoro) substituent. It should be pointed out that this is the first iodo-directed metalation of aromatics leading to stable *o*-iodolithiopyridines. In most cases, lithiation of haloiodopyridines is regioselectivity directed by the iodo group which subsequently migrates to a position ortho to its initial one. All these results are very similar to those previously obtained in the bromopyridines series.[8] However, metalation yields are almost quantitative, and halo migration is fully selective in the iodo unlike the bromo series.

Thus, lithiation of 2-halo-3-iodopyridines (chloro or fluoro) gives the corresponding 2-halo-4-iodo-3-lithiopyridines. It is likely that the reaction mechanism first proceeds from the abstraction of the 4-proton and subsequent isomerization of the resulting 3-iodo-4-lithiopyridines to the stabilized 4-iodo-3-lithiopyridines (stabilization can be explained by the strong additional withdrawing effect of the 2-fluoro or chloro substituent). It has been proposed in various bromoaromatics series that "halogen-dance" is due to the reaction between bromolithio intermediaries and catalytic amounts of dibromo derivatives.[11,26] In all our experiments, no 3-iodo-4-lithio derivative could be trapped whatever the reaction conditions (lower temperature, shorter reaction times, or the in situ quenching with trimethylsilyl chloride). Moreover, any diiodopyridines could be detected in the reaction mixtures. These results do not help us choose between the two following isomerization mechanisms: (1) very fast reaction between free 4-lithio species and traces of diiodo intermediates or (2) fast intramolecular iodo scrambling

(20) Petrow, V. A. *J. Chem. Soc.* **1946**, 200. Kessar, S. V.; Joshi, G. S. *Tetrahedron* **1973**, *29*, 419.
(21) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.
(22) Zhao, B.; Snieckus, V. *Tetrahedron Lett.* **1991**, *32*, 5277.
(23) Bizot, J. *Bull. Soc. Chim. Fr.* **1967**, *1*, 151.
(24) Alvarez, M.; Joule, J. A. *Heterocycles* **1992**, *34*, 2385.
(25) Rocca, P.; Marsais, F.; Godard, A.; Quéguiner, G. *Tetrahedron* **1993**, *49*, 3325.
(26) Den Hertog, H. J.; Burrman, D. J. *Rec. Trav. Chim. Pays-Bas* **1973**, *92*, 304. Guilford, A. J.; Tometski, M. A.; Turner, M. W. *Synthesis* **1983**, 987.

occurring in the solvent cage, thus preventing the formation of free 4-lithio species.

2-Chloro-3-fluoro-4-iodopyridine (4) reacts with LDA in the same way as 2-halo-3-iodopyridines. The iodo-directed lithiation of the 5-position followed by iodo scrambling gives the corresponding 5-iodo-4-lithiopyridine. Lithiation of 3-fluoro-4-iodopyridine (4) very likely results from the fluoro-directed metalation of the more acidic 2-position under kinetic control, followed by the fast isomerization to the more stable 4-lithiopyridine.[27]

Synthesis of perlolidine was readily achieved by taking advantage of the one-pot cross-coupling and cyclization of phenylboronic acid (12) and iodopyridinecarboxaldehyde (7f). This constitutes a convenient route to perlolidine (simple reagents, few steps, and good yields) compared to the few known syntheses. δ-Carbolines 16 were prepared in a very efficient way (high convergence and good overall yields) in five steps from 3-fluoropyridine and N-protected aniline. A further utility of iodopyridine metalation was demonstrated in the synthesis of 2,10-diazaphenanthrenes with sequential heteroring cross-coupling and base-catalyzed cyclization. In this last step, it has been shown that reductive dechlorination (likely due to LDA) can be avoided by optimization of the reaction time.

Conclusion

For the first time, iodo-directed metalation of aromatics was successfully achieved with iodopyridines using LDA at low temperature. In most examples, lithiation is ortho directed by the iodo group which subsequently ortho-migrates very fast to give stabilized iodolithiopyridines. The resulting lithiopyridines were obtained in high yields, are stable, and can be reacted with electrophiles leading to polysubstituted pyridines. This is a very convenient two-step route to 3-substituted 4-iodopyridines starting from commercial 2-halopyridines. Some of these iodopyridines were used as key molecules for the synthesis of fused polyaromatic alkaloids (perlolidine, δ-carbolines, and 2,10-diazaphenanthrenes). The metalation–isomerization mechanism seems to be either much faster or quite different from that described for the lithiation of bromo aromatics. This study is currently being extended to the lithiation of other iodo aromatics as well as the application of this strategy to the synthesis of more complex alkaloids.

Experimental Section

General Data. The ^1H NMR spectra were obtained on a Varian T60 (60 MHz) spectrometer (and were recorded in ppm downfield from internal standard, TMS in $CDCl_3$, or HMDS in DMSO-d_6) or on a 200-MHz Brücker spectrometer. ^{13}C NMR spectra 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.

Solvent. Tetrahydrofuran (THF) was distilled from benzophenone/sodium. The water content of the solvent was estimated lower than 45 ppm by the modified Karl-Fischer method.[23]

Starting Materials. Commercial 2-fluoropyridine, 2-chloropyridine, TMEDA, and diisopropylamine were distilled froom CaH_2 and stored over CaH_2 under a dry argon atmosphere. Arylboronic acids 12 and 17 were prepared by metalation and boronation[14,22] of the corresponding aromatic compounds. 2-Fluoro-3-iodopyridine (1), 2-chloro-3-iodopyridine (2), 2-chloro-3-fluoro-4-iodopyridine (3), and 3-fluoro-4-iodopyridine (4) were prepared by metalation and iodination of the corresponding halopyridines.[14] 2-Fluoro-4-methylpyridine (5) was prepared by diazotation of the commercial 2-amino-5-methylpyridine according to Talik's procedure.[24] Commercial 2.5 M solutions of *n*-butyllithium in hexane and 1.4 M solutions of *sec*-butyllithium in pentane were stored and transferred under a dehydrated and deoxygenated argon atmosphere. Lithium diisopropylamide (LDA) was prepared by reaction of diisopropylamine (7.0 mL, 0.050 mol) in THF (100 mL) and *n*-butyllithium (20 mL, 2.5 M, 0.050 mol) at −75 °C for 15 min. Phenyllithium (PhLi) was prepared by reaction of iodobenzene (10.2 g, 0.050 mol) in THF (100 mL) and *n*-butyllithium (40 mL, 0.10 mol) at −30 °C for 30 min.

2-Fluoro-3-iodo-5-methylpyridine (6). 2-Fluoro-5-methylpyridine (5) (5.55 g, 0.050 mol) in THF solution (20 mL) was slowly added to a cold (−75 °C) solution of LDA (0.050 mol) in dry THF (100 mL). The resulting mixture was stirred for 4 h at −75 °C, before addition of iodine (12.7 g, 0.050 mol) in THF (40 mL). Stirring was continued for 2 h at −75 °C, before hydrolysis by water (20 mL) and further addition of water (150 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, which was purified by flash chromatography on silica (diethyl ether/cyclohexane (2/8)). The yield was 80%: mp <50 °C; ^1H NMR ($CDCl_3$) δ 2.30 (s, 3H, CH_3), 8.10 (m, 2H, $H_4 + H_6$); ^{13}C NMR ($CDCl_3$) δ 16.82 (CH_3), 75.19 (d, C_3, J_{3-F} = 44.0 Hz), 132.64 (C_5), 146.72 (d, C_6, J_{6-F} = 12.9 Hz), 150.28 (d, C_4, J_{4-F} = 2.6 Hz), 160.33 (d, C_2, J_{2-F} = 232.6 Hz); IR (KBr) 3410, 2920, 1585, 1445, 1380, 1255, 1050. Anal. Calcd for C_6H_5FIN (237.02): C, 30.40; H, 2.12; N, 5.91. Found: C, 30.21; H, 2.11; N, 5.67.

General Procedure A: Synthesis of 3-Substituted 2-Fluoro(or 2-chloro)-4-iodopyridine by Metalation–Isomerization of 2-Fluoro(or 2-chloro)-3-iodopyridine. 2-Fluoro(or 2-chloro)-3-iodopyridine (1 or 2) (0.050 mol) in THF solution (20 mL) was slowly added to a cold (−75 °C) solution of LDA (0.050 mol) in THF (100 mL). The resulting mixture was stirred for 1 h (fluoro compound) or 3 h (chloro compound) at −75 °C before addition of the required electrophile (0.050 mol) in THF solution (20 mL). Stirring was continued for 2 h at the same temperature before hydrolysis at −75 °C by water (50 mL) and further addition of water (100 mL) at room temperature. Extraction by Et_2O, drying over $MgSO_4$ and solvent removal afforded a crude product, which was purified by sublimation, distillation, crystallization, or flash chromatography on silica gel.

2-Fluoro-4-iodopyridine (7a). The general procedure A, applied to 1 using water, gave 96% (sublimation: 45 °C/1 mmHg) of **7a**: mp 60 °C; ^1H NMR ($CDCl_3$) δ 7.35 (dd, 1H, H_3, J_{3-5} = 1.0 Hz, J_{H_3-F} = 2.9 Hz), 7.53 (ddd, 1H, H_5, J_{5-6} = 5.2 Hz, J_{3-5} = 1.0 Hz, J_{H_5-F} = 1.0 Hz), 7.90 (d, 1H, H_6, J_{5-6} = 5.2 Hz); ^{13}C NMR ($CDCl_3$) δ 107.82 (d, C_4, J_{4-F} = 7.5 Hz), 119.09 (d, C_3, J_{3-F} = 39.3 Hz), 130.41 (d, C_5, J_{5-F} = 4.4 Hz), 147.73 (d, C_6, J_{6-F} = 15.5 Hz), 162.82 (d, C_2, J_{2-F} = 243.7 Hz); IR (KBr) 3060, 1575, 1530, 1450, 1380. Anal. Calcd for C_5H_3FIN (222.99): C, 26.93; H, 1.36; N, 6.28. Found: C, 26.89; H, 1.40; N, 6.32.

3-Deuterio-2-fluoro-4-iodopyridine (7b). The general procedure A, applied to 1 using deuterium oxide, gave 96% (sublimation: 45 °C/1 mmHg) of **7b**. The physical characteristics of this product were found to be identical to those described for **7a** excepted for the ^1H NMR spectrum where the H_3 signal has disappeared.

2-Fluoro-4-iodo-3-methylpyridine (7c). The general procedure A, applied to 1 using methyl iodide, gave 93% (sublimation: 60 °C/1 mmHg) of **7c**: mp 92 °C; ^1H NMR ($CDCl_3$) δ 2.43 (s, 3H, CH_3), 7.66 (m, 2H, $H_5 + H_6$); IR (KBr) 1575, 1530, 1400. Anal. Calcd for C_6H_5FIN (237.02): C, 30.40; H, 2.12; N, 5.91. Found: C, 30.63; H, 2.11; N, 5.89.

(2-Fluoro-4-iodo-3-pyridylphenyl)methanol (7d). The general procedure A, applied to 1 using benzaldehyde, gave 61% (crystallization from hexane) of **7d**: mp 100 °C; ^1H NMR ($CDCl_3$) δ 3.40 (s, 1H, OH), 6.33 (s, 1H, CH), 7.40 (m, 5H, phenyl), 7.80

(27) Abramovitch, R. A.; Singer, G. M.; Vinutha, A. R. *J. Chem. Soc., Chem. Commun.* **1967**, 55. Zoltewicz, J. A.; Smith, C. L. *Tetrahedron* **1969**, *25*, 4331.

(m, 2H, $H_5 + H_6$); IR (KBr) 1580, 1540, 1490, 1440. Anal. Calcd for $C_{12}H_9FINO$ (329.11): C, 43.80; H, 2.76; N, 4.26. Found: C, 43.49; H, 2.61; N, 4.07.

2-Fluoro-4-iodo-3-pyridinecarboxaldehyde (7f). The general procedure A, applied to 1 using ethylformate, gave 75% (sublimation: 60 °C/1 mmHg) of **7f**: mp 78 °C; ^{1}H NMR ($CDCl_3$) δ 7.95 (m, 2H, $H_5 + H_6$), 10.20 (s, 1H, CHO); IR (KBr) 1700, 1575, 1530, 1435. Anal. Calcd for C_6H_3FINO (251.00): C, 28.71; H, 1.20; N, 5.58. Found: C, 28.69; H, 1.24; N, 5.24.

2-Fluoro-3,4-diiodopyridine (7g). The general procedure A, applied to 1 using iodine, gave 54% (crystallization from acetone) of **7g**: mp 114 °C; ^{1}H NMR ($CDCl_3$) δ 7.73 (d, 1H, H_5), 7.93 (d, 1H, H_6), J_{5-6} = 5.0 Hz; IR (KBr) 1560, 1520, 1425. Anal. Calcd for $C_5H_2FI_2N$ (348.89): C, 17.21; H, 0.58; N, 4.01. Found: C, 17.12; H, 0.50; N, 4.07.

3-Azido-2-fluoro-4-iodopyridine (7h). The general procedure A, applied to 1 using tosyl azide, gave 85% of **7h** as a crude oil: ^{1}H NMR ($CDCl_3$) δ 7.76 (m, 2H, $H_5 + H_6$); IR (film) 3300, 2200, 2120, 1570, 1540, 1445, 1420.

3-Amino-2-fluoro-4-iodopyridine (7e). Hydrogen sulfide was bubbled into a stirred solution of 3-azido-2-fluoro-4-iodopyridine (0.010 mol) in methanol (100 mL) containing a few drops of piperidine during 30 min, while the temperature was kept between 10 and 20 °C. The precipitated elementary sulfur was filtered, and solvent removal afforded a crude product which was purified by flash chromatography on silica (diethyl ether/cyclohexane (2.5/7.5)). The yield was 81%: mp 62–64 °C; ^{1}H NMR ($CDCl_3$) δ 4.30 (s, 2H, NH_2), 7.20 (dd, 1H, H_5), 7.40 (d, H1, H_6), J_{5-6} = 5.0 Hz, J_{H_5-F} = 5.0 Hz; IR (KBr) 3400, 2860, 2820, 1810, 1740, 1620, 1580, 1545, 1425, 1200. Anal. Calcd for $C_5H_4FIN_2$ (238.00): C, 25.23; H, 1.69; N, 11.77. Found: C, 25.13; H, 1.69; N, 11.45.

2-Chloro-4-iodopyridine (8a). The general procedure A, applied to 2 using water, gave 73% (sublimation: 40 °C/1 mmHg) of **8a**: mp <50 °C; ^{1}H NMR ($CDCl_3$) δ 7.60 (dd, 1H, H_5, J = 1.3, 5.2 Hz), 7.75 (d, 1H, H_3, J = 1.3 Hz), 8.07 (d, 1H, H_6, J = 5.2 Hz); ^{13}C NMR ($CDCl_3$) δ 106.49 (C_4), 131.42 (C_3), 132.92 (C_5), 149.54 (C_6), 151.58 (C_2); IR (KBr) 1535, 1406, 1331, 1179. Anal. Calcd for C_5H_3ClIN (239.44): C, 25.08; H, 1.26; N, 5.85. Found: C, 25.27; H, 1.37; N, 5.82.

2-Chloro-3-deuterio-4-iodopyridine (8b). The general procedure A, applied to 2 using deuterium oxide, gave 75% (sublimation: 40 °C/1 mmHg) of **8b**. The physical characteristics of this product were found to be identical to those described for **8b** except for the ^{1}H NMR spectrum where the H_3 signal has disappeared.

2-Chloro-4-iodo-3-methylpyridine (8c). The general procedure A, applied to 2 using methyl iodide, gave 69% (crystallization from acetone) of **8c**: mp 108 °C; ^{1}H NMR ($CDCl_3$) δ 2.66 (s, 3H, CH_3), 7.70 (d, 1H, H_5), 7.86 (d, 1H, H_6), J_{5-6} = 5.0 Hz); IR (KBr) 1550, 1525. Anal. Calcd for C_6H_5ClIN (253.47): C, 28.43; H, 1.99; N, 5.52. Found: C, 28.31; H, 1.83; N, 5.33.

(2-Chloro-4-iodo-3-pyridylphenyl)methanol (8d). The general procedure A, applied to 2 using benzaldehyde, gave 64% (crystallization from chloroform) of **8d**: mp 132 °C; ^{1}H NMR (DMSO-d_6) δ 3.60 (s, 1H, OH), 6.53 (s, 1H, CH), 7.33 (m, 5H, phenyl), 7.83 (d, 1H, H_5), 7.96 (d, 1H, H_6), J_{5-6} = 5.0 Hz; IR (KBr) 3050, 2980, 1550, 1490, 1450, 1430. Anal. Calcd for $C_{12}H_9ClINO$ (345.57): C, 41.71; H, 2.62; N, 4.05. Found: C, 41.56; H, 2.41; N, 3.96.

2-Chloro-4-iodo-3-pyridinecarboxaldehyde (8f). The general procedure A, applied to 2 using ethyl formate, gave 64% (flash chromatography on silica, diethyl ether/hexane (25/75)) of **8f**: mp 91–92 °C; ^{1}H NMR ($CDCl_3$) δ 7.93 (dd, 1H, H_5, J = 5.2 and 0.4 Hz); 8.06 (d, 1H, H_6, J = 5.2 Hz); 10.18 (d, 1H, CHO, J = 0.4 Hz); IR (KBr) 3049, 1700, 1550, 1515, 1430, 1344, 1245, 1205. Anal. Calcd for C_6H_3ClINO (267.45): C, 26.95; H, 1.13; N, 5.24. Found: C, 27.23; H, 0.98; N, 5.45.

2-Chloro-3,4-diiodopyridine (8g). The general procedure A, applied to 2 using iodine, gave 71% (crystallization from hexane) of **8g**: mp 163–164 °C; ^{1}H NMR ($CDCl_3$) δ 7.70 (d, 1H, H_5), 7.99 (d, 1H, H_6), J_{5-6} = 5.0 Hz; IR (KBr) 1535, 1406, 1331, 1179. Anal. Calcd for $C_5H_2ClI_2N$ (365.34): C, 16.44; H, 0.55; N, 3.83. Found: C, 16.32; H, 0.62; N, 3.95.

3-Azido-2-chloro-4-iodopyridine (8h). The general procedure A, applied to 2 using tosyl azide, gave 75% of **8f** as a crude oil: ^{1}H NMR ($CDCl_3$) δ 7.10 to 8.10 (m, 2H, $H_5 + H_6$); IR (KBr) 3500, 2980, 2140, 1600, 1540, 1530, 1450, 1435, 1410.

3-Amino-2-chloro-4-iodopyridine (8e). Reduction of **8f** was achieved as previously described for the synthesis of **7e**. A 57% yield of **8e** was obtained after purification by flash chromatography on silica (diethyl ether/cyclohexane (2/8)): mp 96–98 °C; ^{1}H NMR ($CDCl_3$) δ 4.60 (s, 2H, NH_2), 7.50 (m, 2H, $H_5 + H_6$); IR (KBr) 3380, 3270, 1605, 1540, 1440, 1400, 1280, 1220, 1090, 1075. Anal. Calcd for $C_5H_4ClIN_2$ (254.46): C, 23.60; H, 1.58; N, 11.01. Found: C, 23.83; H, 1.44; N, 11.15.

2-Fluoro-4-iodo-5-methylpyridine (9a). The general procedure A, applied to 5 using water, gave 88% (flash chromatography on silica, diethyl ether/cyclohexane (2/8)) of **9a**: mp <50 °C; ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 1H, CH_3), 7.50 (d, 1H, H_3, J_{3-F} = 2.0 Hz), 8.10 (s, 1H, H_6); ^{13}C NMR ($CDCl_3$) δ 23.52 (CH_3), 114.40 (d, C_4, J_{4-F} = 7.7 Hz), 119.15 (d, C_3, J_{3-F} = 39.3 Hz), 134.83 (d, C_5, J_{5-F} = 4.8 Hz), 145.01 (d, C_6, J_{6-F} = 15.0 Hz), 161.02 (d, C_2, J_{2-F} = 241.0 Hz); IR (KBr) 3450, 2920, 1655, 1575, 1470, 1385, 1340. Anal. Calcd for C_6H_5FIN (237.02): C, 30.40; H, 2.12; N, 5.91. Found: C, 30.36; H, 2.01; N, 5.83.

3-Deuterio-2-fluoro-4-iodo-5-methylpyridine (9b). The general procedure A, applied to 5 using deuterium oxide, gave 90% (flash chromatography on silica, diethyl ether/cyclohexane (2/8)) of **9b**. The physical characteristics of this product were found to be identical to those described for **9a** except for the ^{1}H NMR spectrum where the H_3 signal has disappeared.

2-Fluoro-4-iodo-5-methyl-3-pyridinecarboxaldehyde (9d). The general procedure A, applied to 5 using ethyl formate, gave 84% of **9d** (flash chromatography on silica, cyclohexane/diethyl ether (75/25)): mp 108–110 °C; ^{1}H NMR ($CDCl_3$) δ 2.21 (s, 3H, CH_3), 8.11 (s, 1H, H_6), 10.14 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$) δ 24.45 (CH_3), 117.62 (C_4), 119.18 (d, C_3, J_{3-F} = 80.7 Hz), 137.75 (C_5), 149.30 (d, C_6, J_{6-F} = 15.4 Hz), 160.40 (d, C_2, J_{2-F} = 253.0 Hz), 189.6 (CHO); IR (KBr) 3400, 1705, 1570, 1550, 1445, 1405, 1390, 1330, 1250, 1180. Anal. Calcd for C_7H_5FINO (265.03): C, 31.72; H, 1.90; N, 5.28. Found: C, 31.84; H, 1.70; N, 5.28.

3-Azido-2-fluoro-4-iodo-5-methylpyridine (9e). The general procedure A, applied to 5 using tosyl azide, gave 88% of **9e** (flash chromatography on silica, diethyl ether/hexane (1/9)): mp 70 °C; ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 3H, CH_3), 7.70 (s, 1H, H_6); IR (KBr) 3400, 2120, 1560, 1435, 1390, 1280, 1130. Anal. Calcd for $C_6H_4FIN_4$ (278.03): C, 25.92; H, 1.45; N, 20.15. Found: C, 26.14; H, 1.40; N, 20.07.

3-Amino-2-fluoro-4-iodo-5-methylpyridine (9c). Reduction of **9e** was achieved as previously described for the synthesis of **7e**. A 85% yield of **9c** was obtained after purification by flash chromatography on silica (diethyl ether/cyclohexane (25/75)): mp 78–80 °C; ^{1}H NMR ($CDCl_3$) δ 2.30 (s, 3H, CH_3), 4.40 (s, 2H, NH_2), 7.35 (s, 1H, H_6); IR (KBr) 3400, 1620, 1575, 1450, 1415, 1200. Anal. Calcd for $C_6H_6FIN_2$ (252.03): C, 28.59; H, 2.40; N, 11.12. Found: C, 28.60; H, 2.27; N, 11.04.

General Procedure B: Synthesis of 4-Substituted 2-Chloro-3-fluoro-5-iodopyridines by Metalation–Isomerization of 2-Chloro-3-fluoro-4-iodopyridine (3). Procedure B identical to procedure A except that a metalation time of 4 h is required. The crude products were purified by preparative flash chromatography on silica gel (cyclohexane/ethyl acetate (95/5)).

2-Chloro-3-fluoro-5-iodopyridine (10a). The general procedure B, applied to 3 using water, gave 78% of **10a**: mp 66 °C; ^{1}H NMR ($CDCl_3$) δ 7.80 (dd, 1H, H_4, J_{4-6} = 2.0 Hz, J_{H_4-F} = 7.5 Hz), 8.40 (d, 1H, H_6, J_{6-4} = 2.0 Hz); ^{13}C NMR ($CDCl_3$) δ 89.66 (s, C_5), 132.61 (d, C_4, J_{4-F} = 20.2 Hz), 138.81 (d, C_2, J_{2-F} = 19.0 Hz), 150.62 (d, C_6, J_{6-F} = 5.7 Hz), 154.21 (d, C_3, J_{3-F} = 268.3 Hz); IR (KBr) 3020, 1555, 1425, 1395, 1210, 1100, 1070. Anal. Calcd for C_5H_2ClFIN (257.43): C, 23.33; H, 0.73; N, 5.44. Found: C, 23.38; H, 0.74; N, 5.38.

2-Chloro-4-deuterio-3-fluoro-5-iodopyridine (10b). The general procedure B, applied to 3 using deuterium oxide, gave 78% of **10b**: ^{1}H NMR ($CDCl_3$) δ 8.35 (s, 1H, H_6). The other physical characteristics of this product were found to be identical to those described above for 2-chloro-3-fluoro-5-iodopyridine.

2-Chloro-3-fluoro-5-iodo-4-methylpyridine (10c). The general procedure B, applied to 3 using methyl iodide, gave 70% of **10c**: η_D = 1.6125; ^{1}H NMR ($CDCl_3$) δ 2.45 (d, 3H, CH_3, J_{CH_3-F} = 2.0 Hz), 8.50 (s, 1H, H_6); ^{13}C NMR ($CDCl_3$) δ 19.85 (d, CH_3, J_{C-F} = 2.8 Hz), 98.35 (s, C_5), 138.69 (d, C_2 or C_4, J_{C-F} = 21.0 Hz), 139.48

(d, C_4 or C_2, J_{C-F} = 15.6 Hz), 150.53 (d, C_6, J_{6-F} = 6.6 Hz), 152.60 (d, C_3, J_{3-F} = 263.4 Hz); IR (film) 3050, 2920, 1570, 1540, 1430, 1400, 1375, 1195, 1180, 1010. Anal. Calcd for C_6H_4ClFIN (271.46): C, 26.55; H, 1.49; N, 5.16. Found: C, 26.34; H, 1.33; N, 5.31.

2-Chloro-3-fluoro-4,5-diiodopyridine (10d). The general procedure B, applied to **3** using iodine, gave 64% (sublimation: 110 °C/1 mmHg) of **10d**: mp 146 °C; ^1H NMR ($CDCl_3$) δ 8.45 (s, 1H, H_6); ^{13}C NMR ($CDCl_3$) δ 106.16 (d, C_5, J_{5-F} = 4.7 Hz), 108.35 (d, C_4, J_{4-F} = 24.3 Hz), 137.03 (d, C_2, J_{2-F} = 23.0 Hz), 150.26 (d, C_6, J_{6-F} = 6.5 Hz), 154.97 (d, C_3, J_{3-F} = 262.7 Hz); IR (KBr) 3020, 1535, 1410, 1375, 1220. Anal. Calcd for C_5HClFI_2N (383.33): C, 15.67; H, 0.26; N, 3.65. Found: C, 15.74; N, 0.23; N, 3.69.

(2-Chloro-3-fluoro-5-iodo-4-pyridylphenyl)methanol (10e). The general procedure B, applied to **3** using benzaldehyde, gave 77% of **10e**: mp 94 °C; ^1H NMR ($CDCl_3$) δ 3.80 (d, 1H, OH, J_{CH-OH} = 8.0 Hz), 6.15 (d, 1H, CH, J = 8.0 Hz), 7.30 (s, 5H, phenyl), 8.40 (s, 1H, H_6); ^{13}C NMR ($CDCl_3$) δ 76.83 (s, CH(OH)), 95.25 (s, C_5), 125.74, 128.30, 128.61, 139.29, 140.29 (d, C_2 or C_4, J_{C-F} = 21.0 Hz), 142.99 (d, C_4 or C_2, J_{C-F} = 10.7 Hz), 151.85 (d, C_6, J_{6-F} = 6.7 Hz), 152.79 (d, C_3, J_{3-F} = 269.5 Hz); IR (KBr) 3350, 3050, 2920, 1560, 1530, 1495, 1420, 1395, 1225, 1170. Anal. Calcd for $C_{12}H_8ClFINO$ (363.56): C, 39.65; H, 2.22; N, 3.85. Found: C, 39.91; H, 2.29; N, 3.74.

General Procedure C: Synthesis of 4-Substituted 3-Fluoro-2-iodopyridines by Metalation–Isomerization of 3-Fluoro-4-iodopyridine (4). Procedure C is identical to procedure A except that a metalation time of 1.5 h is required.

3-Fluoro-2-iodopyridine[14] (11a). The general procedure C, applied to **4** using water, gave 95% of **11a**. This molecule was purified by distillation under reduced pressure: bp 98–100 °C (20 mmHg); η_D = 1.6211; ^1H NMR ($CDCl_3$) δ 7.20 (m, 2H, H_4 + H_5), 8.15 (s, 1H, H_6); IR (film) 3060, 1580, 1445, 1415, 1265, 1205, 1060, 1045; ^{13}C NMR ($CDCl_3$) δ 106.60 (d, C_2, J_{2-F} = 28.4 Hz), 122.13 (d, C_4, J_{4-F} = 20.7 Hz), 124.00 (d, C_5, J_{5-F} = 3.2 Hz), 146.44 (d, C_6, J_{6-F} = 5.0), 158.74 (d, C_3, J_{3-F} = 258.5). Anal. Calcd for C_5H_3FIN (222.99): C, 26.93; H, 1.36; N, 6.28. Found: C, 26.82; H, 1.38; N, 6.22.

4-Deuterio-3-fluoro-2-iodopyridine (11b). The general procedure C, applied to **4** using deuterium oxide, quantitatively gave **11b** (^1H NMR integration >99%). The physical characteristics of this product were found to be identical to those described for **11a** except for the ^1H NMR spectrum where the H_4 signal has disappeared.

3-Fluoro-2-iodo-4-methylpyridine (11c). The general procedure C, applied to **4** using methyl iodide, gave 70% (crystallization from hexane) of **11c**: mp 69–70 °C; ^1H NMR ($CDCl_3$) δ 2.30 (d, 3H, CH_3), 7.05 (dd, 1H, H_5), 8.00 (d, 1H, H_6), J_{5-6} = 5.0 Hz; J_{CH_3-F} = 2.0 Hz, J_{H_5-F} = 5.0 Hz; ^{13}C NMR ($CDCl_3$) δ 14.61 (d, CH_3, J_{C-F} = 2.7 Hz), 106.24 (d, C_2, J_{2-F} = 29.5 Hz), 126.03 (d, C_5, J_{5-F} = 1.7 Hz), 133.78 (d, C_4, J_{4-F} = 17.3 Hz), 145.99 (d, C_6, J_{6-F} = 6.0 Hz), 157.66 (d, C_3, J_{3-F} = 255.5 Hz); IR (KBr) 3060, 2960, 2920, 1595, 1400, 1375, 1215, 1170. Anal. Calcd for C_6H_5FIN (237.02): C, 30.41; H, 2.13; N, 5.91. Found: C, 30.22; H, 2.11; N, 5.84.

3-Fluoro-2,4-diiodopyridine (11d). The general procedure C, applied to **4** using iodine, gave 73% (flash chromatography on silica, hexane) of **11d**: mp 102 °C; ^1H NMR ($CDCl_3$) δ 7.75 (m, 2H, H_5 + H_6); ^{13}C NMR ($CDCl_3$) δ 90.97 (d, C_4, J_{4-F} = 26.1 Hz), 105.24 (d, C_2, J_{2-F} = 31.7 Hz), 133.82 (s, C_5), 146.73 (d, C_6, J_{6-F} = 6.2 Hz), 158.33 (d, C_3, J_{3-F} = 255.5 Hz); IR (KBr) 3040, 1550, 1380, 1245, 1195, 1070. Anal. Calcd for $C_5H_2FI_2N$ (348.89): C, 17.21; H, 0.58; N, 4.01. Found: C, 17.09; H, 0.54; N, 4.03.

(3-Fluoro-2-iodo-4-pyridylphenyl)methanol (11e). The general procedure C, applied to **4** using benzaldehyde, gave 75% of **11e** which was obtained as an oil after flash chromatography on silica gel (methylene chloride/ethyl acetate (7/3)): ^1H NMR ($CDCl_3$) δ 4.85 (s, 1H, OH), 4.95 (s, 1H, CH), 7.25 (m, 5H, phenyl), 7.50 (dd, 1H, H_5), 7.95 (d, 1H, H_6), J_{5-6} = 5.0 Hz; J_{H_5-F} = 5.0 Hz; ^{13}C NMR ($CDCl_3$) δ 69.08 (d, CH(OH), J_{C-F} = 1.1 Hz), 106.26 (d, C_2, J_{2-F} = 29.6 Hz), 121.56 (s), 126.41 (d, J_{C-F} = 0.6 Hz), 128.44 (d, J_{C-F} = 5.7 Hz), 128.72 (s), 140.19 (d, C_4, J_{4-F} = 13.6 Hz), 140.81 (s, C_5), 146.66 (d, C_6, J_{6-F} = 5.8 Hz), 155.52 (d, C_3, J_{3-F} = 257.1 Hz); IR (film) 3340, 3060, 2960, 2860, 1590, 1545, 1495, 1455, 1400, 1210, 1150, 1050. Anal. Calcd for $C_{12}H_9FINO$ (329.11): C, 43.80; H, 2.76; N, 4.26. Found: C, 43.85; H, 3.03; N, 4.12.

1-(3-Fluoro-2-iodo-4-pyridyl)-1-(3,4-dimethoxyphenyl)methanol (11f). The general procedure C, applied to **4** using 3,4-dimethoxybenzaldehyde, gave 80% of **11f** (flash chromatography on silica, methylene chloride/ethyl acetate (7/3)): mp 108–110 °C; ^1H NMR ($CDCl_3$) δ 3.80 (s, 6H, $2OCH_3$), 4.75 (s, 1H, OH), 5.95 (s, 1H, CH), 6.30–6.95 (m, 3H, phenyl), 7.55 (dd, 1H, H_5), 8.10 (d, 1H, H_6), J_{5-6} = 5.0 Hz, J_{H_5-F} = 5.0 Hz; ^{13}C NMR ($CDCl_3$) δ 55.77 (OMe), 68.63 (OMe), 106.22 (d, C_2, J_{2-F} = 29.7 Hz), 109.56, 111.12, 118.86, 121.50, 133.55, 140.57 (d, C_4, J_{4-F} = 13.5 Hz), 146.57 (d, C_5 or C_6, J_{C-F} = 5.8 Hz), 148.78 (d, C_6 or C_5, J_{C-F} = 7.4 Hz), 155.44 (d, C_3, J_{3-F} = 256.8 Hz); IR (KBr) 3470, 3020, 2970, 2940, 1590, 1505, 1465, 1385, 1260, 1145. Anal. Calcd for $C_{14}H_{13}FINO_3$ (389.17): C, 43.21; H, 3.37; N, 3.60. Found: C, 42.94; H, 3.23; H, 3.41.

3-Fluoro-2-iodo-4-pyridinecarboxylic Acid (11g). The general procedure C, applied to **4** using carbon dioxide, gave 72% of **11g** (sublimation: 140 °C/1 mmHg): mp 220 °C (sublimation); ^1H NMR (DMSO) δ 7.65 (dd, 1H, H_5), 8.35 (d, 1H, H_6), 13.40 (s, 1H, COOH), J_{5-6} = 5.0 Hz, J_{H_5-F} = 5.0 Hz; ^{13}C NMR (DMSO) δ 110.49 (d, C_2, J_{2-F} = 30.3 Hz), 124.79 (s, C_5), 126.77 (d, C_4, J_{4-F} = 11.7 Hz), 147.90 (d, C_6, J_{6-F} = 6.6 Hz), 156.04 (d, C_3, J_{3-F} = 265.4 Hz), 163.28 (d, COOH, J_{C-F} = 3.1 Hz); IR (KBr) 3400, 3090, 1700, 1540, 1390, 1275, 1210, 1070. Anal. Calcd for $C_6H_3FINO_2$ (267.00): C, 26.99; H, 1.13; N, 5.25. Found: C, 27.19; H, 1.06; N, 5.17.

General Procedure D: Cross-Coupling Reaction between Haloiodopyridines and Benzeneboronic Acids. The required haloiodopyridines (1.0 mL) and arylboronic acid (1.0 mmol) were added to a solution of potassium carbonate (2M, 1.0 mL) and ethanol (1.0 mL) in deoxygenated toluene (10 mL). The resulting mixture was stirred for 0.5 h under an argon atmosphere. Tetrakis(triphenylphosphine)palladium(0) (35 mg, 0.030 mmol) was added, and the reaction mixture was refluxed for 24 h. Cooling, filtration, extraction with toluene, drying over $MgSO_4$, and solvent removal afforded a crude oil which was purified by flash chromatography.

8-Fluoro-2,9-diazaphenanthrene (13). The general procedure D, applied to **7f** and (2-(pivaloylamino)phenyl)boronic acid (**12**), gave 60% of **13** (flash chromatography on silica, diethyl ether/hexane (25/75): mp 152 °C; ^1H NMR ($CDCl_3$) δ 7.79 (dt, 1H, phenyl, J = 1.3 and 6.9 Hz), 7.92 (dt, 1H, phenyl, J = 1.4 and 7.0 Hz), 8.25 (d, 1H, phenyl, J = 6.9 Hz), 8.30 (d, 1H, H_5, J_{5-6} = 5.0 Hz), 8.50 (d, 1H, H_6, J_{5-6} = 5.0 Hz), 8.53 (d, 1H, phenyl, J = 7.0 Hz), 9.58 (s, 1H, imine); IR (KBr) 3400, 1620, 1580, 1420. Anal. Calcd for $C_{12}H_7FN_2$ (198.20): C, 72.72; H, 3.56; N, 14.13. Found: C, 72.84; H, 3.51; N, 14.02.

2,2-Dimethyl-*N*-(2-(3-fluoro-2-pyridyl)phenyl)propanamide (15a).[14] The general procedure D, applied to **11a** and (2-(pivaloylamino)phenyl)boronic acid (**12**), gave 82% of **15a** (flash chromatography on silica, ethyl acetate): mp 91–92 °C; ^1H NMR ($CDCl_3$) δ 1.15 (s, 9H, tBu), 6.75 to 7.70 (m, 5H, H_5 + C_6H_4), 8.20 to 8.50 (m, 2H, H_4 + H_6), 10.95 (s, 1H, NH); IR (KBr) 3310, 3070, 2970, 2910, 2870, 1680, 1590, 1525, 1460, 1440. Anal. Calcd for $C_{16}H_{17}FN_2O$ (272.33): C, 70.57; H, 6.29; N, 10.29. Found: C, 70.38; H, 6.52; N, 10.35.

2,2-Dimethyl-*N*-(2-(3-fluoro-4-methyl-2-pyridyl)phenyl)propanamide (15b). The general procedure D, applied to **11c** and (2-(pivaloylamino)phenyl)boronic acid (**12**), gave 91% of **15b** (flash chromatography on silica, hexane/ethyl acetate (1/1)) as an oil: ^1H NMR ($CDCl_3$) δ 1.20 (s, 9H, tBu), 2.30 (d, 3H, CH_3), 6.85 to 8.00 (m, 4H, phenyl), 8.25 (d, 1H, H_5), 8.45 (dd, 1H, H_6), 11.00 (s, 1H, NH), J_{5-6} = 5.0 Hz, J_{CH_3-F} = 2.0 Hz; IR (KBr) 3300, 3060, 2960, 2900, 1680, 1610, 1585, 1525, 1460, 1445, 1315. Anal. Calcd for $C_{17}H_{19}FN_2O$ (286.35): C, 71.31; H, 6.69; N, 9.78. Found: C, 71.06; H, 6.63; N, 9.58.

***N,N*-Diisopropyl-2-(3-amino-2-fluoro-4-pyridyl)benzamide (18).** The general procedure D, applied to **7e** and boronic acid **17**, gave 99% of **18** (flash chromatography on silica, Et_2O/hexane (8/2)): mp; ^1H NMR (DMSO) δ 0.80 (d, 3H, CH_3, J = 6.6 Hz), 1.03 (d, 3H, CH_3, J = 6.6 Hz), 1.16 (d, 3H, CH_3, J = 6.8 Hz), 1.49 (d, 3H, CH_3, J = 6.8 Hz), 3.31 (mult, 1H, CH, J = 6.6 Hz), 3.56 (mult, 1H, CH, J = 6.6 Hz), 4.18 (s, 2H, NH_2), 6.95 (s, 1H), 7.25–7.35 (m, 2H), 7.43–7.55 (m, 3H); IR (KBr) 3484, 3345, 2970,

2928, 1612, 1443, 1342. Anal. Calcd for $C_{18}H_{22}FN_3O$ (315.39): C, 68.55; H, 7.03; N, 13.32. Found: C, 68.75; H, 7.10; N, 13.25.

***N,N*-Diisopropyl-2-(3-amino-2-chloro-4-pyridyl)benzamide (19).** The general procedure D, applied to **8e** and boronic acid **17**, gave 91% of **19** (flash chromatography on silica, Et_2O): mp 174–175 °C; ^1H NMR (DMSO) δ 0.80 (m, 3H, CH_3), 1.03 (d, 3H, CH_3, J = 5.9 Hz), 1.14 (d, 3H, CH_3, J = 6.7 Hz), 1.48 (d, 3H, CH_3, J = 6.7 Hz), 3.30 (mult, 1H, CH, J = 6.7 Hz), 3.56 (m, 1H, CH), 4.50 (m, 2H, NH_2), 6.86 (s, 1H), 7.25–7.35 (m, 2H), 7.40–7.50 (m, 2H), 7.77 (d, 1H, J = 4.7 Hz); IR (KBr) 3443, 3294, 3180, 2965, 2931, 1597, 1469, 1415, 1369, 1345. Anal. Calcd for $C_{18}H_{22}ClN_3O$ (331.85): C, 65.15; H, 6.68; N, 12.66. Found: C, 65.47; H, 6.82; N, 12.79.

2,9-Diazaphenanthren-1(2*H*)-one (Perlolidine) (14). 8-Fluoro-2,9-diazaphenanthrene (**13**) (1.0 mmol) was refluxed in 4.8 M aqueous hydrochloric acid (12 mL) under vigourous stirring for 19 h. Cooling and addition of diethyl ether afforded a crude product which was purified by crystallization from ethanol. The yield was 80% of **14**: mp >250 °C (lit.[17d] mp 336–340 °C); ^1H NMR (DMSO) δ 7.58 (d, 1H, H_5, J = 7.0 Hz), 7.90 to 8.15 (m, $2H_{arom}$ + H_6), 8.33 (d, 1H, J = 8.2 Hz), 8.82 (d, 1H, J = 8.2 Hz), 9.52 (s, 1H, imine), 12.73 (s, 1H, NH); IR (KBr) 3480, 3420, 3140, 3090, 3070, 3050, 3020, 1700, 1630, 1600, 1570, 1440, 1400, 1300, 1230, 1210; mass calcd for $C_{12}H_8N_2O$ 196.21, found (MS) 196 ($M^{\bullet+}$, base peak), 168 (M – CO), 140 (168 – H_2CN). Anal. Calcd for $C_{12}H_8N_2O$ (196.21): C, 73.46; H, 4.11; N, 14.28. Found: C, 73.21; H, 4.20; N, 14.09.

General Procedure E: Synthesis of δ-Carbolines. Anhydrous boiling (215 °C) pyridinium chloride (10 g) was added to the required phenylpyridines **15a** or **15b** (2.0 mmol), and the resulting 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 carboline. Extraction of the aqueous layer by ethyl acetate, drying over $MgSO_4$, solvent removal, and crystallization from toluene (or acetone) gave an additional crop.

5*H*-Pyrido[3,2-*b*]indole (δ-Carboline) (16a). The general procedure E, applied to **15a**, gave 85% of **16a**: mp 207–208 °C (lit.[14] mp 206 °C); ^1H NMR (DMSO-d_6) δ 7.28 (dd, 1H, H_8), 7.41 (dd, 1H, H_3), 7.53 (dd, 1H, H_7), 7.62 (d, 1H, H_6), 7.93 (dd, 1H, H_4), 8.27 (d, 1H, H_9), 8.51 (dd, 1H, H_2), 11.35 (s, 1H, NH), J_{2-3} = 4.6 Hz, J_{3-4} = 8.2 Hz, J_{2-4} = 1.4 Hz, J_{6-7} = 8.0 Hz, J_{7-8} = 7.3 Hz, J_{8-9} = 7.8 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; 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, 78.45; H, 4.72; N, 16.78.

4-Methyl-5*H*-pyrido[3,2-*b*]indole (4-Methyl-δ-carboline) (16b). The general procedure E, applied to **15b**, gave 91% of **16b**: mp > 250 °C (lit.[19b] mp 264–265 °C); ^1H NMR (DMSO) δ 2.58 (s, 3H, CH_3), 7.22 (m, 2H, H_3 + H_8), 7.48 (t, 1H, H_7), 7.54 (t, 1H, H_6), 8.14 (d, 1H, H_9), 8.32 (d, 1H, H_2), 11.35 (s, 1H, NH), J_{2-3} = 4.7 Hz, J_{6-7} = 8.1 Hz, J_{8-9} = 7.7 Hz; ^{13}C NMR (DMSO) δ 16.77, 112.01, 116.98, 119.58, 120.43, 121.34, 127.45, 128.93, 133.21, 140.65, 141.66, 140.88; IR (KBr) 3120, 3050, 2960, 2900, 2820, 2760, 2680, 1620, 1610, 1460, 1380. Anal. Calcd for $C_{12}H_{10}N_2$ (182.23): C, 79.09; H, 5.53; N, 16.37. Found: C, 78.88; H, 5.52; N, 15.06.

General Procedure F: Synthesis of 1-Halo-2,10-diazaphenanthren-9(10*H*)-one. Compound **18** or **19** (0.50 mmol) in THF solution (2.5 mL) was slowly added to a cold (−50 °C) solution of LDA (1.65 mmol) in THF (10 mL). The resulting mixture was stirred for 1 h at 0 °C and 4 h at room temperature before hydrolysis at 0 °C by water (12.5 mL). Extraction by CH_2Cl_2, drying over $MgSO_4$, and solvent removal afforded a crude product, which was purified by flash chromatography.

1-Fluoro-2,10-diazaphenanthren-9(10*H*)-one (20). The general procedure F applied to **18** gave 25% of **20** (flash chromatography on silica, diethyl ether): mp > 260 °C; ^1H NMR (DMSO) δ 7.81–8.00 (m, 3H), 8.27 (d, 1H, J = 5.2 Hz), 8.38 (d, 1H, J = 7.4 Hz), 8.59 (d, 1H, J = 7.8 Hz), 11.89 (s, 1H, NH); IR (KBr) 2918, 2850, 1654, 1405, 1352. Anal. Calcd for $C_{12}H_7FN_2O$ (214.20): C, 67.29; H, 3.29; N, 13.08. Found: C, 67.42; H, 3.05; N, 12.84.

1-Chloro-2,10-diazaphenanthren-9(10*H*)-one (21). The general procedure F applied to **19** gave 15% of **19** and 82% of **21** (flash chromatography on silica, diethyl ether): mp 238 °C; ^1H NMR (DMSO) δ 7.69 (m, 1H), 7.83 (dd, 1H, J = 7.5 Hz), 7.96 (dd, 1H, J = 7.2 and 1.1 Hz), 8.24 (d, 1H, J = 5.2 Hz), 8.39 (d, 2H, J = 5.5 Hz), 8.62 (d, 1H, J = 8.1 Hz), 11.15 (s, 1H, NH); IR (KBr) 3190, 3087, 2925, 1700, 1655, 1479, 1313; mass calcd for $C_{12}H_7ClN_2O$ 230.66, found (MS) 230/232 ($^{35}Cl/^{37}Cl$). Anal. Calcd for $C_{12}H_7ClN_2O$ (230.66): C, 62.49; H, 3.06; N, 12.14. Found: C, 62.34; H, 2.98; N, 12.29.

2,10-Diazaphenanthren-9(10*H*)-one (22). When the foregoing cyclization of **19** was performed during 6 h, the same workup led to 21% of **21** and 28% of **22**: mp 220–221 °C; ^1H NMR (DMSO) δ 7.79 (dd, 1H, J = 6.3 Hz), 7.93 (dd, 1H, J = 5.4 Hz), 8.24–8.42 (m, 3H), 8.61 (dd, 1H, J = 5.4 and 6.3 Hz), 8.68 9s, 1H), 11.90 (s, 1H, NH); IR (KBr) 3027, 1663, 1608, 1364; mass calcd for $C_{12}H_8N_2O$ 196.21, found (MS) 196. Anal. Calcd for $C_{12}H_8N_2O$ (196.21): C, 73.46; H, 4.11; N, 14.28. Found: C, 73.67; H, 4.22; N, 14.12.

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Sensitized Photooxygenations of 3-Vinylindole Derivatives

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A series of 1-methyl- and 1-(phenylsulfonyl)-substituted 3-vinylindoles with different electronic and steric features has been synthesized and their sensitized photooxygenation in aprotic solvents investigated. 1-Methyl-3-vinyl- (**1a**), 1,2-dimethyl-3-vinyl- (**1b**), 1-methyl-3-(β-methoxyvinyl)- (**4-Z** and **4-E**), 1-(phenylsulfonyl)-3-vinyl- (**8a**), 1-(phenylsulfonyl)-3-(α-methylvinyl) (**8b**), 1-(phenylsulfonyl)-3-(β-methoxyvinyl)- (**8c** and **8d**), and *cis*-1-(phenylsulfonyl)-3-(α-methyl-β-methoxyvinyl) indoles (**15-Z**) react with $^1O_2$ predominantly to give endoperoxides via [4 + 2] cycloaddition. However, 1,2-dimethyl-3-(β-methoxyvinyl)indole (**1c**) gives [2 + 2] cycloaddition with the 3-double bond to give 1,2-dimethyl-3-formylindole (**3c**); *trans*-1-(phenylsulfonyl)-3-(α-methyl-β-methoxyvinyl)indole (**15-E**) gives the 3-indolyl allylic hydroperoxide (**17**) via ene reaction, along with a small amount of isomerization of the 3-vinyl double bond. A zwitterionic intermediate in the isomerization is proposed. Most of the resulting dioxacarbazole endoperoxides are isolable and inert to reduction by trimethyl phosphite and thiourea except for *N*-methyldioxacarbazole **5**, which undergoes clean rearrangement to indolin-2-one epoxide **7** at −20 °C.

Introduction

The three major modes of reaction of $^1O_2$ with alkenes are ene reaction with alkenes with abstractable allylic hydrogens to give allylic hydroperoxides,[1-3] [2 + 2] cycloaddition with activated alkenes to give dioxetanes,[4] and Diels–Alder [4 + 2] cycloaddition with dienes to give endoperoxides.[5,6] The mechanism of the ene reaction has been extensively studied, and a stepwise mechanism is believed to be involved.[7-11] [2 + 2] Cycloaddition and the decomposition of 1,2-dioxetanes have also been extensively studied.[12-14] Only recently has the [4 + 2] cycloaddition of $^1O_2$ received comparable mechanistic attention.[15-19]

Indole derivatives have provided important tests of the scope and variability of the reaction of $^1O_2$ with organic molecules of biological significance.[20-22] Most electron-rich *N*-alkylindoles undergo C_2–C_3 cleavage upon photooxygenation to give dicarbonyl fragments via [2 + 2] addition.[23,24] Intermediate 1,2-dioxetanes have been produced and characterized spectroscopically in a few cases.[22,25-27] Some *N*-acyl-2,3-disubstituted indoles give ene reaction with $^1O_2$ in aprotic solvents to give 3-hydroperoxyindolines exclusively.[22] On the other hand, 3-vinylindole derivatives react with $^1O_2$ to afford dioxacarbazole endoperoxides.[28,29]

Recently, methods for synthesis of functionalized 2- and 3-vinylindole derivatives which could act as 4π components in the Diels–Alder reaction have been greatly improved.[30-34] Diels–Alder reaction of these compounds with a variety of dienophiles has been intensively studied and is preparatively useful for regio- and stereocontrolled construction of annelated indoles and carbazole alkaloids.[31,35] We decided to take advantage of these new approaches to 3-vinylindole derivatives in order to understand $^1O_2$ chemistry in these systems better. We describe here a detailed study of the effects of stereochemical and electronic features of 3-vinylindoles on the photooxygen-

† X-ray structure data may be obtained from this author.

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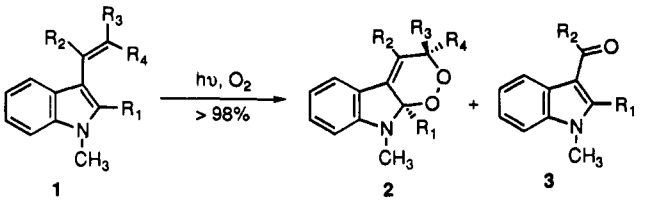
(1) Frimer, A. A.; Stephenson, L. M. In *Singlet O₂*; Frimer, A. A., Ed.; CRC Press, Boca Raton, FL, 1985; pp 68–87.
(2) Gollnick, K.; Kuhn, H. J. In *Singlet Oxygen*; Wasserman, H. H., Murray, R. W., Eds.; Academic Press: New York, 1979; p 287.
(3) Schenck, G. O.; Eggert, H.; Denk, W. *Liebigs Ann. Chem.* **1953**, *584*, 177.
(4) Bartlett, P. D.; Landis, M. E. In *Singlet Oxygen*; Wasserman, H. H., Murray, R. W., Eds.; Academic Press: New York, 1979; pp 244–286.
(5) Gollnick, K.; Schenck, G. O. In *1,4 Cycloaddition Reactions*; Hamer, J., Ed.; Academic Press: New York, 1967; pp 255–345.
(6) Balci, M. *Chem. Rev.* **1981**, *81*, 91–108.
(7) Clennan, E. L.; Chen, X.; Koola, J. J. *J. Am. Chem. Soc.* **1990**, *112*, 5193–5199.
(8) Elemes, Y.; Foote, C. S. *J. Am. Chem. Soc.* **1992**, *114*, 6044–6050.
(9) Orfanopoulos, M.; Foote, C. S. *J. Am. Chem. Soc.* **1988**, *110*, 6583–6584.
(10) Gorman, A. A.; Gould, I. R.; Hamblett, I. *J. Am. Chem. Soc.* **1982**, *104*, 7098–7104.
(11) Gorman, A. A.; Hamblett, I.; Lambert, C.; Spencer, B.; Standen, M. C. *J. Am. Chem. Soc.* **1988**, *110*, 8053–8059.
(12) Baumstark, A. L. In *Singlet O₂*; Frimer, A. A., Ed.; CRC Press: Boca Raton, FL, 1985; pp 1–37.
(13) Schaap, A. P.; Zaklika, K. A. In *Singlet Oxygen*; Wasserman, H. H., Murray, R. W., Eds.; Academic Press: New York, 1979; pp 174–243.
(14) Wilson, T. In *Singlet O₂*; Frimer, A. A., Ed.; CRC Press: Boca Raton, FL, 1985; pp 37–66.
(15) Clennan, E. L.; L'Esperance, R. P. *Tetrahedron Lett.* **1983**, *24*, 4291–4294.
(16) Clennan, E. L.; Mehrsheikh-Mohammadi, M. E. *J. Am. Chem. Soc.* **1983**, *105*, 5932–5933.
(17) Clennan, E. L.; Mehrsheikh-Mohammadi, M. E. *J. Org. Chem.* **1984**, *49*, 1321–1322.
(18) Gollnick, K.; Griesbeck, A. *Tetrahedron Lett.* **1983**, *24*, 3303–3306.
(19) O'Shea, K. E.; Foote, C. S. *J. Am. Chem. Soc.* **1988**, *110*, 7167–7170.
(20) Zhang, X.; Foote, C. S. *J. Org. Chem.* **1993**, *58*, 5524–5527.
(21) Saito, I.; Matsuura, T.; Nakagawa, M.; Hino, T. *Acc. Chem. Res.* **1977**, *10*, 346–352.
(22) Zhang, X.; Foote, C. S.; Khan, S. I. *J. Org. Chem.* **1993**, *58*, 47–51.
(23) Saito, I.; Matsugo, S.; Matsuura, T. *J. Am. Chem. Soc.* **1979**, *101*, 7332–7338.
(24) Saito, I.; Imuta, M.; Matsugo, S.; Yamamoto, H.; Matsuura, T. *Synthesis* **1976**, *4*, 255–256.
(25) Saito, I.; Matsugo, S.; Matsuura, T. *J. Am. Chem. Soc.* **1979**, *101*, 4757–4759.
(26) Zhang, X.; Foote, C. S. *J. Am. Chem. Soc.* **1993**, *115*, 8867–8868.
(27) Adam, W.; Ahrweiler, M.; Sauter, M.; Schmiedeskamp, B. *Tetrahedron Lett.* **1993**, *34*, 5247–5250.
(28) Adam, W.; Takayama, K. *J. Org. Chem.* **1980**, *45*, 447–452.
(29) Matsumoto, M.; Kondo, K. *J. Am. Chem. Soc.* **1979**, *99*, 2393–2394.
(30) Kusurkar, R. S.; Patil, U. G. *Indian J. Chem.* **1986**, *25B*, 1038.
(31) Pindur, U. *Heterocycles* **1988**, *27*, 1253–1268.
(32) Saroja, B.; Srinivasan, P. C. *Synthesis* **1986**, 748–749.
(33) Pfeuffer, L.; Pindur, U. *Chimia* **1987**, *41*, 125–128.
(34) Gotz, P. H.; Bats, J. W.; Fritz, H. *Liebigs. Ann. Chem.* **1986**, 2065–2080.
(35) Pindur, U.; Kim, M.-H. *J. Org. Chem.* **1992**, *57*, 910–915.

0022-3263/93/1958-7839$04.00/0

Scheme I



1a: $R_1 = R_2 = R_3 = R_4 = H$;	> 98%	-
1b: $R_1 = CH_3$, $R_2 = R_3 = R_4 = H$;	93%	7%
1c: $R_1 = CH_3$, $R_2 = R_3 = H$, $R_4 = OCH_3$ or $R_1 = CH_3$, $R_2 = R_4 = H$, $R_3 = OCH_3$	0%	> 90%

ation rate and products and propose some tentative explanations.

Results

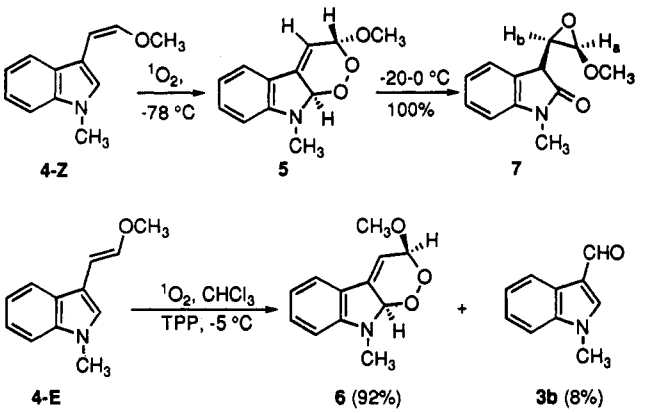
Photooxygenation of *N*-Methyl-Substituted 3-Vinylindoles. We first reinvestigated the photooxygenation of 1-methyl-3-vinylindole (**1a**) in CH_2Cl_2 at −78 °C with tetraphenylporphyrin (TPP) as sensitizer (Scheme I). In accord with previous results,[29] the production of dioxacarbazole endoperoxide **2a** is almost quantitative. No other products could be observed in the reaction mixture by ^1H NMR.

Similarly, 1,2-dimethyl-3-vinylindole (**1b**) reacted with $^1O_2$ in $CDCl_3$ to give mainly endoperoxide **2b**. ^1H NMR indicated that 7% of cleavage product **3b** was produced. Endoperoxide **2b** was isolated by crystallization from ether/pentane (5:1). The ^1H NMR spectrum of **2b** shows two sets of triplets and two sets of doublets between 6.51–7.24 ppm, typical for the indole aromatic protons. The olefinic hydrogen (H_2) appears as a triplet (J = 2.67 Hz) at 5.79 ppm, and the methylene hydrogens give an AB pattern at 4.94 and 4.59 ppm, respectively, further split by H_2 (J = 2.61 Hz). The ^{13}C NMR shows chemical shifts similar to those of endoperoxide **2a**, with two peroxy carbons at 105.4 and 70.6 ppm, respectively.

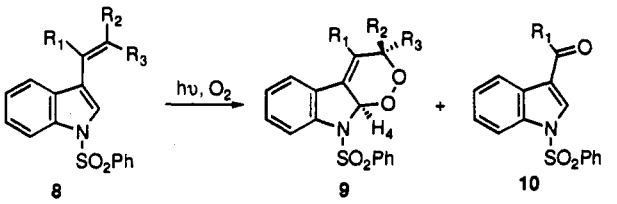
In contrast, photooxygenation of 1,2-dimethyl-3-(β-methoxyvinyl)indole (**1c**) gave no endoperoxide in acetone or CH_2Cl_2 even at −78 °C; cleaved aldehyde **3c** (the synthetic precursor of **1c**!) was the only identifiable product by ^1H NMR (>90%). Failure of **1c** to undergo 1,4-cycloaddition with $^1O_2$ may result from the fact that the 2-methyl (R_1) hinders the ***1c-s-cis*** conformation and thereby prevents [4 + 2] cycloaddition.[28] It is known that 1,2-dimethyl-3-vinylindole **1b** reacts with dienophiles to form a cyclobutane ring with a 3-vinyl double bond instead of undergoing Diels–Alder reaction.[36]

If the 2-methyl hinders the ***1c-s-cis*** conformation, its removal should permit [4 + 2] cycloaddition to proceed efficiently. For this reason, 1-methyl-3-(β-methoxyvinyl)-indoles (**4-*Z*** and **4-*E***) were prepared. As expected, both undergo [4 + 2] cycloaddition with $^1O_2$ to give endoperoxides **5** and **6**, respectively (Scheme II). The stereochemistry of the adducts was assigned based on the assumption that, since there was complete stereospecificity, the addition was *cis*, as expected and shown by X-ray crystal structure in a related compound (see below). However, the stability of these compounds is surprisingly different. Endoperoxide **5** could only be identified by ^1H and ^{13}C NMR spectroscopy at −40 °C. ^1H NMR showed two doublets and two triplets in the range of 6.65–7.33

Scheme II



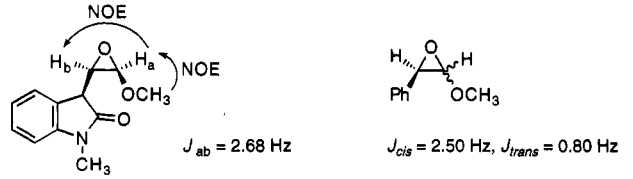
Scheme III



8a: $R_1 = R_2 = R_3 = H$;	> 98%	-
8b: $R_1 = CH_3$, $R_2 = R_3 = H$;	85%	15%
8c: $R_1 = R_2 = H$, $R_3 = OCH_3$;	> 98%	-
8d: $R_1 = R_3 = H$, $R_2 = OCH_3$	93%	7%

ppm, two methyls at 3.53 and 2.89 ppm, and three sets of triplets (J = 2.20 Hz) for the methine protons at 5.83, 5.80, and 5.77 ppm, respectively. ^{13}C NMR and DEPT showed three different CH groups at 109.22, 101.82, and 98.11 ppm, besides aromatic and methyl carbons. Endoperoxide **5** starts to rearrange at −20 °C to give the indolin-2-one epoxide **7**; rearrangement is complete in 10 min between −20 and 0 °C.

The *cis* relationship of the a and b hydrogens in epoxide **7** was established by comparision of the J value with that in methoxystyrene oxide[37] and confirmed by observation of NOE effects (shown below). In contrast, the stereoisomeric endoperoxide **6** was isolated in good yield and was stable at 0 °C. Three methine triplets (J = 2.30 Hz) appeared at 5.79, 5.77, and 5.34 ppm and three CH carbons at 108.6, 99.5,, and 97.5 ppm, respectively. Trimethyl phosphite did not reduce the peroxide in chloroform.



Photooxygenation of *N*-(Phenylsulfonyl)-3-vinylindoles. 1-(Phenylsulfonyl)-3-vinylindole (**8a**) was photooxygenated in $CHCl_3$ at −5 °C to give endoperoxide **9a** exclusively in 40–50 min (Scheme III). **9a** was isolated by TLC and showed similar ^1H and ^{13}C NMR patterns to its 1-methyl counterpart **2a**. Besides nine aromatic protons between 8.00–7.09 ppm, two quartets (J = 2.60 Hz) at 6.35 (H_1) and 6.18 ppm (H_4) and two sets of doublets of triplets (J = 17.4, 2.80 Hz) at 5.00 and 4.25 ppm (H_2 and H_3) were assigned to the remaining protons. COSY showed that H_1, H_2, H_3, and H_4 are all coupled; J_{12}, J_{13}, and J_{14} are

(36) Bergamasco, R.; Porter, Q. N.; Yap, C. *Aust. J. Chem.* **1977**, *30*, 1531–1544.

(37) Riehl, J. J.; Thil, L. *Tetrahedron Lett.* **1969**, 1913–1916.