

Novel synthetic strategy of carbolines *via* palladium-catalyzed amination and arylation reaction

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Four parent carbolines and the corresponding 5- or 9-methylsulfonyl derivatives were synthesized by the palladium-catalyzed intramolecular arylation reaction of *ortho*-bromo-substituted anilinopyridines which were prepared by the palladium-catalyzed amination reaction of iodobenzenes with aminopyridines. Carbazole and its 9-methylsulfonyl derivative were also synthesized by the same method.

Introduction

Carbolines (pyrido[*x,y-b*]indoles) are known as the skeletons of naturally occurring compounds, and, particularly, β -carboline (9*H*-pyrido[3,4-*b*]indole) is known as the skeleton of numerous alkaloids. Although many synthetic methods for producing carboline ring systems have been studied,¹ most of them are applications of the Fischer indole cyclization reaction to cyclohexanone pyridinylhydrazones or piperidinone phenylhydrazones and isoquinoline cyclization reactions (e.g., Bischler–Napieralsky or Pictet–Spengler reaction) to indole derivatives. These methods are suitable for partially hydrogenated carbolines, but not very effective for fully aromatic derivatives. In addition, the Fischer cyclization reaction sometimes affords isomers and the synthesis of α - and δ -carbolines is not possible using isoquinoline cyclization reactions. Simple, general, and efficient synthetic methods for the four parent carbolines are scarcely known (to our knowledge) except for Quéguiner's method to be discussed later.

One of the simple and general synthetic methods for fully aromatic carbolines is considered to be the pyrrole-ring construction from benzene and pyridine building blocks. One of the two routes known up to now is the Type 1 route shown in Scheme 1, which is the cyclization reaction of anilinopyridine equivalent derivatives or the ring-transformation reaction of benzo- or pyridotriazoles, and the other one (Type 2 route) is the cyclization reaction of phenylpyridine derivatives which have a nitrogen substituent at an *ortho*-position.

Examples of the Type 1 synthesis are the thermolysis

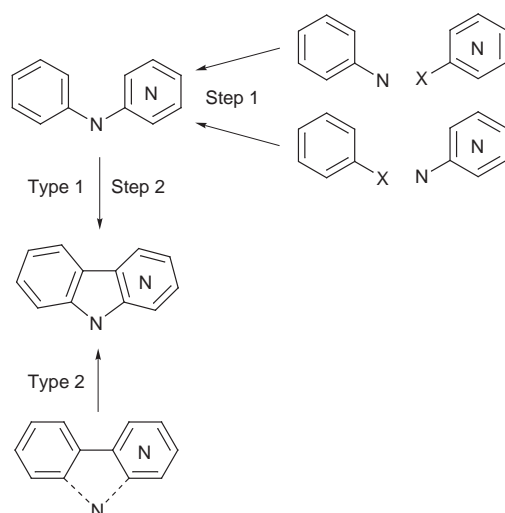
reaction of 1-pyridinylbenzotriazoles^{2a-c} or phenylpyridotriazoles,^{2d} and the radical cyclization reaction of the aryl radicals generated from the *o*-diazonium derivatives,^{2e,f} but these methods have no generality for the synthesis of all carboline skeletons and sometimes gave a mixture of isomers. The Type 2 synthetic methods involve the thermolysis reaction of *o*-pyridinylphenyl azides^{3a} or *o*-phenylpyridinyl azides^{3b} and the insertion reaction of the aryl nitrenes generated from the corresponding nitroso^{3c} or nitro derivatives.^{3d,e} These methods also have no generality for the synthesis of the four carbolines and sometimes gave the products in low yields. Recently, a general Type 2 method giving high yields was developed by Quéguiner *et al.*^{4a-d} who applied their method to the synthesis of natural products. Their method consists of the combination of the palladium-catalyzed cross-coupling reaction of iodo-fluoropyridines with aminophenylboronic acid derivatives and the intramolecular nucleophilic substitution reaction of the amino group on the benzene ring to the fluoro group of the pyridine ring.

On the basis of the background described above, we designed a new strategy for the Type 1 synthesis of the four parent carbolines. This strategy consists of the combination of two palladium-catalyzed reactions, namely the amination reaction of iodobenzenes with aminopyridines and the intramolecular arylation reaction of *ortho*-bromo-substituted anilinopyridines.

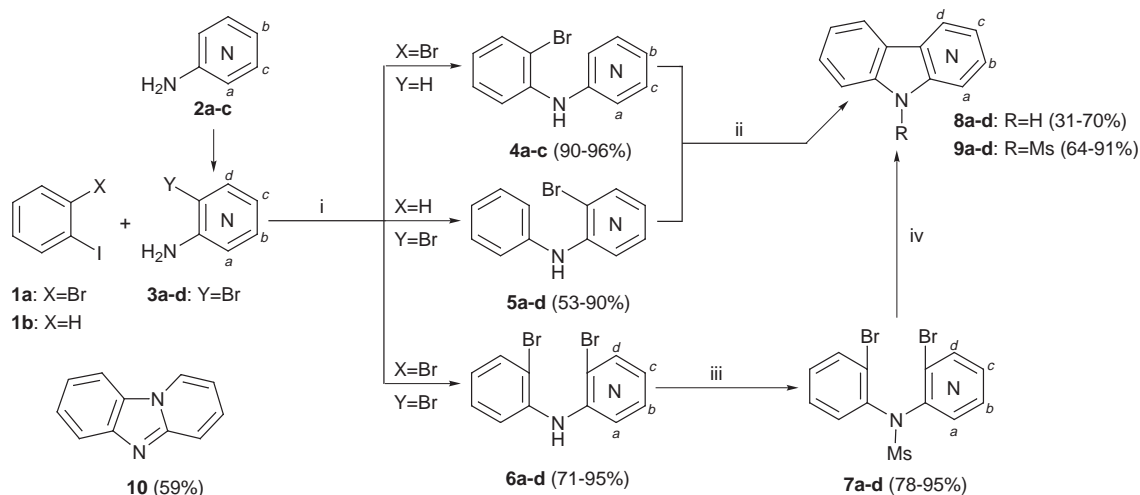
There are two possible strategies to synthesize *ortho*-bromo-substituted anilinopyridines using the method reported by Buchwald *et al.*⁵ (Step 1). These are the palladium-catalyzed reactions of halogenopyridines with aniline derivatives, and of halogenobenzenes with aminopyridines. We chose the latter route, because of the easy availability of the starting compounds and the selectivity of the palladium-catalyzed reaction. As the cyclization reaction to carbolines (Step 2), the palladium-catalyzed intramolecular arylation reactions^{6,7} of *ortho*-monohalogenoanilinopyridines and of *ortho,ortho'*-dihalogenoanilinopyridines were selected.

Results and discussion

The palladium-catalyzed cross-coupling reaction of 2-bromoiodobenzene **1a** with 2-aminopyridine **2a** under the reported conditions^{5a} gave 2-(2-bromoanilino)pyridine **4a** in 95% yield. Analogously, 4- **4b** and 3-(2-bromoanilino)pyridine **4c** were also obtained from the reaction of **1a** with **2b,c** in 96 and 90% yield, respectively. Although the cyclization by the intramolecular palladium-catalyzed arylation reaction of **4b,c** in the presence of palladium diacetate and sodium carbonate in DMF under reflux conditions gave the corresponding γ -(5*H*-pyrido[4,3-*b*]indole) **8c** and δ -carboline (5*H*-pyrido-



Scheme 1



Scheme 2 Reagents and conditions: i, $\text{Pd}_2(\text{dba})_3$, DPPF, *t*-BuONa, toluene, 100 °C; ii, $\text{Pd}(\text{OAc})_2$, Na_2CO_3 , DMF, reflux; iii, NaH, MsCl, THF, rt; iv, $\text{PdCl}_2(\text{PPh}_3)_2$, $(\text{SnBu}_3)_2$, Li_2CO_3 , Et_4NI , toluene (DMF), reflux. **a** N replaces CH at *a*; **b** N replaces CH at *b*; **c** N replaces CH at *c*; **d** N replaces CH at *d*.

[3,2-*b*]indole) **8d** in 70 and 51% yield, respectively, the cyclization reaction of **4a** gave no α -carboline (9*H*-pyrido[2,3-*b*]indole) **8a** but, gave instead, the pyrido[1,2-*a*]benzimidazole **10** in 59% yield, which resulted from the cyclization reaction at the pyridine ring nitrogen of **4a** (Scheme 2). Although the yields of **4a-c** were satisfactory, this route has some weak points, such as the fact that the starting (2-bromoanilino)pyridines necessary to synthesize all four carbolines were not available, the palladium-catalyzed cyclization reaction of **4a** gave no α -carboline, and the yield of δ -carboline was unsatisfactory.

In order to overcome these weak points, we next examined an alternative route which consists of the cross-coupling reaction of iodobenzene **1b** with *o*-aminobromopyridines **3a-d**. This route is suitable for the synthesis of the starting materials for all carbolines and cannot yield the unexpected pyrido[1,2-*a*]benzimidazole **10**. Moreover, the palladium-catalyzed cyclization reaction of the relatively π -deficient bromopyridine moieties with the relatively π -excessive aniline moiety is expected to proceed smoothly, because the palladium-catalyzed cross-coupling reactions of π -deficient heteroaryl halides with π -excessive heterocycles have been reported.⁸

o-Aminobromopyridines **3a-c**, but not 3-amino-2-bromopyridine **3d**, were synthesized by the alkaline hydrolysis reaction of *o*-bromo-(2,2-dimethylpropanoylamino)pyridines which were prepared by the *ortho*-directed lithiation reaction of (2,2-dimethylpropanoylamino)pyridines⁹ and subsequent bromination with 1,2-dibromoethane. The palladium-catalyzed cross-coupling reaction of iodobenzene **1b** with 2-amino-3-bromopyridine **3a** under the above mentioned reaction conditions gave 2-anilino-3-bromopyridine **5a** in 90% yield. The analogous cross-coupling reaction of **1b** with 3-amino-2-bromo- **3b**, 4-amino-3-bromo- **3c**, and 3-amino-2-bromopyridine **3d** gave the corresponding anilinobromopyridines **5b-d** in 53–88% yield, respectively. The four *o*-anilinobromopyridines **5a-d** were subjected to the same conditions as the cyclization reaction of isomers **4a-c** to give the corresponding carbolines **8a-d** in yields of 31–61%.

As a result, this general route can synthesize all parent carbolines, but the yields of the cyclization reactions were unsatisfactory. In order to improve the yields of the cyclization step, we examined the aforementioned third method. The palladium-catalyzed cross-coupling reaction of 2-bromoiodobenzene **1a** with *o*-aminobromopyridines **3a-d** gave *o,o'*-dibromoanilinopyridines **6a-d** in 71–93% yield. The cyclization reaction to carbolines **9a-d** via the intermediary tributylstannyl derivatives by reaction with hexabutyldistannane in the presence of dichlorobis(triphenylphosphine)palladium, lithium

carbonate, and tetraethylammonium iodide in toluene under reflux conditions⁶ did not proceed. Then **6a-d** were converted to the corresponding *N*-methylsulfonyl derivatives **7a-d** under conventional conditions in yields of 78–95%, and **7a-d** were cyclized under the conditions mentioned above to give *N*-methylsulfonyl- α - **9a** and - δ -carboline **9d** in 91 and 84% yield, respectively. However, the β - **9b** and γ -carboline **9c** were hardly formed under these conditions, because of the low solubilities of **7b,c** in toluene. Improvements in the yields were achieved using toluene–DMF (10:1) as the solvent, and **9b,c** were obtained in 64 and 74% yield, respectively.

Finally, we applied the successful carboline synthesis method to carbazole synthesis. Namely, the palladium-catalyzed reaction of **1a,b** with 2-bromoaniline **11b** gave 2-bromo- **12a** and 2,2'-dibromodiphenylamine **12b** in 46 and 96% yield, respectively (Scheme 3). Although the yields (41–47%) of the cyclization reaction were unsatisfactory, carbazole **14a** and 9-(methylsulfonyl)carbazole **14b** were obtained.

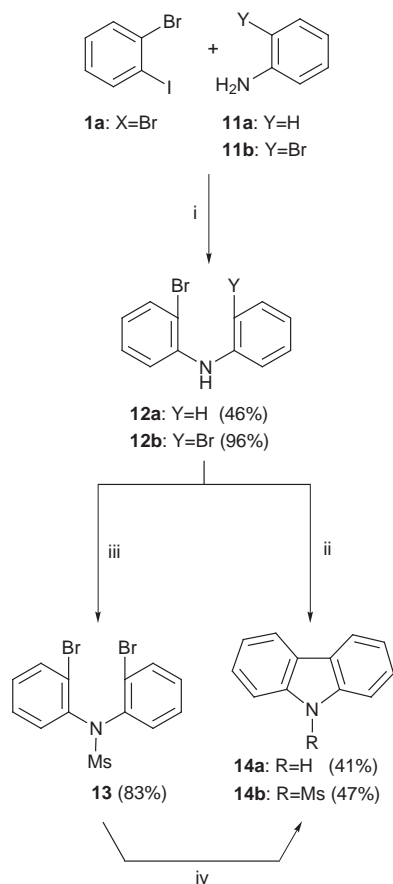
Conclusions

A simple and general method for the synthesis of four parent carbolines and carbazoles was achieved by the combination of two palladium-catalyzed reactions, which are the amination reaction of iodobenzenes with aminopyridines or anilines and the intramolecular biaryl coupling reaction of *ortho*-bromo- and *ortho,ortho'*-dibromo-substituted anilinoarenes.

Experimental

General comments

THF and Et_2O were distilled from sodium/benzophenone ketyl before use. *n*-BuLi was titrated using 2,5-dimethoxybenzyl alcohol before use. All mps (recorded on a YAZAWA micro melting point BY-2 apparatus) and bps are uncorrected. IR spectra were taken on a JASCO IR-810 spectrophotometer. ^1H NMR spectra were recorded on Varian Gemini 2000 (300 MHz) and Hitachi R-300 (300 MHz) spectrometers. Chemical shifts are expressed in δ (ppm) values with tetramethylsilane (TMS) as internal reference, and coupling constants (*J*) are expressed in Hz. The following abbreviations are used: s = singlet, d = doublet, t = triplet, m = multiplet, dd = double doublet, dt = double triplet, br = broad, and br s = broad singlet. Mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded on JMS-DX303 and JMS-AX500 instruments. 3-Amino-2-bromopyridine **3d** was prepared according to the literature method.¹⁰



Scheme 3 Reagents and conditions: i, $\text{Pd}_2(\text{dba})_3$, DPPF, *t*-BuONa, toluene, 100 °C; ii, $\text{Pd}(\text{OAc})_2$, Na_2CO_3 , DMF, reflux; iii, NaH, MsCl, THF, rt; iv, $\text{PdCl}_2(\text{PPh}_3)_2$, $(\text{SnBu}_3)_2$, Li_2CO_3 , Et_4NI , toluene (DMF), reflux.

3-Bromo-2-(2,2-dimethylpropanoylamino)pyridine; typical procedure for *ortho*-directed lithiation-bromination reaction of (2,2-dimethylpropanoylamino)pyridine

n-BuLi (1.94 ml, 2.62 mmol) was slowly added to a solution of 2-(2,2-dimethylpropanoylamino)pyridine (186.2 mg, 1.04 mmol) and TMEDA (0.39 ml, 2.62 mmol) in THF (5 ml) at -70°C . The resulting solution was stirred at -70°C for 15 min and at -10°C for 2 h. Then the mixture was cooled to -70°C , and 1,2-dibromoethane (0.23 ml, 2.62 mmol) was added. The resulting solution was stirred at -70°C for 15 min and at -10°C for 2 h. After evaporation of the THF, the residue was taken up into Et_2O , and the Et_2O phase was washed successively with water and brine, dried over MgSO_4 , and evaporated. The residue was purified by silica gel column chromatography using *n*-hexane–AcOEt (1:1) as eluent. The product was recrystallized from Et_2O –*n*-hexane to give 3-bromo-2-(2,2-dimethylpropanoylamino)pyridine as needles (132.6 mg, 50%), mp 140 – 141°C (Found: C, 46.73; H, 5.04; Br, 31.18; N, 11.14. $\text{C}_{10}\text{H}_{13}\text{BrN}_2\text{O}$ requires C, 46.71; H, 5.10; Br, 31.08; N, 10.89%; $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3290 and 1650; δ_{H} 1.37 (9 H, s), 6.99 (1 H, dd, J 4.67, 7.97), 7.89 (1 H, dd, J 1.64, 7.97), 8.05 (1 H, br s), 8.46 (1 H, dd, J 1.37, 4.67); m/z 256 (M^+) (Found: M^+ , 256.0209. Calc. for $\text{C}_{10}\text{H}_{13}^{79}\text{BrN}_2\text{O}$: M , 256.0211).

4-Bromo-3-(2,2-dimethylpropanoylamino)pyridine. According to the typical procedure, 4-bromo-3-(2,2-dimethylpropanoylamino)pyridine was obtained from the reaction using 3-(2,2-dimethylpropanoylamino)pyridine (340.1 mg, 1.91 mmol). Recrystallization from *i*-Pr₂O–*n*-hexane gave needles (204.2 mg, 45%), mp 98 – 99°C (Found: C, 46.82; H, 5.09; Br, 30.84; N, 10.95%; $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3410 and 1705; δ_{H} 1.37 (9 H, s), 7.50 (1 H, d, J 5.22), 7.84 (1 H, br s), 8.18 (1 H, d, J 5.22), 9.54 (1 H, s); m/z 256 (M^+) (Found: M^+ , 256.0250).

3-Bromo-4-(2,2-dimethylpropanoylamino)pyridine. According to the typical procedure, 3-bromo-4-(2,2-dimethylpropanoylamino)pyridine was obtained from the reaction using 4-(2,2-dimethylpropanoylamino)pyridine (1.38 g, 7.75 mmol). Recrystallization from *i*-Pr₂O–*n*-hexane gave prisms (1.64 g, 83%), mp 70 – 72°C (Found: C, 46.51; H, 5.15; Br, 30.99; N, 10.70. $\text{C}_{10}\text{H}_{13}\text{BrN}_2\text{O}$ requires C, 46.71; H, 5.10; Br, 31.08; N, 10.89%; $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3275 and 1660; δ_{H} 1.36 (9 H, s), 8.17 (1 H, br s), 8.42 (1 H, d, J 0.82), 8.64 (1 H, s); m/z 256 (M^+) (Found: M^+ , 256.0246. Calc. for $\text{C}_{10}\text{H}_{13}^{79}\text{BrN}_2\text{O}$: M , 256.0211).

2-Amino-3-bromopyridine 3a; typical procedure for alkaline hydrolysis reaction of *o*-bromo-(2,2-dimethylpropanoylamino)pyridine

A mixture of 3-bromo-2-(2,2-dimethylpropanoylamino)pyridine (8.35 g, 32.7 mmol) and 3 M KOH (15 ml) in MeOH (35 ml) was refluxed for 4 h. After removal of the solvent, the residue was diluted with Et_2O and the Et_2O phase was washed with brine, dried over MgSO_4 , and evaporated. The residue was purified by silica gel column chromatography using *n*-hexane–AcOEt (1:1) as eluent. The product was recrystallized from Et_2O –*n*-hexane to give needles (2.78 mg, 95%), mp 64 – 65°C (Found: C, 34.78; H, 3.11; Br, 45.90; N, 16.34. $\text{C}_5\text{H}_5\text{BrN}_2$ requires C, 34.71; H, 2.91; Br, 46.18; N, 16.19%; $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3425; δ_{H} 4.92 (2 H, br s), 6.53–6.58 (1 H, m), 7.66 (1 H, dd, J 1.37, 6.59), 8.02 (1 H, dd, J 1.37, 4.95); m/z 172 (M^+) (Found: M^+ , 171.9623. Calc. for $\text{C}_5\text{H}_5^{79}\text{BrN}_2$: M , 171.9636).

3-Amino-4-bromopyridine 3b. According to the typical procedure, 3b was obtained from the reaction using 4-bromo-3-(2,2-dimethylpropanoylamino)pyridine (1.66 g, 6.5 mmol), as an oil (848.6 mg, 76%); bp 46 – $49^\circ\text{C}/3$ mmHg; $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ 3448; δ_{H} 4.14 (2 H, br s), 7.35 (1 H, dd, J 1.37, 4.95), 7.81 (1 H, d, J 4.67), 8.12 (1 H, s); m/z 172 (M^+) (Found: M^+ , 171.9628).

4-Amino-3-bromopyridine 3c. According to the typical procedure, 3c was obtained from the reaction 3-bromo-4-(2,2-dimethylpropanoylamino)pyridine (1.85 g, 7.25 mmol). Recrystallization from Et_2O –*n*-hexane gave needles (1.21 g, 97%), mp 70 – 71°C (Found: C, 34.78; H, 3.14; Br, 45.98; N, 16.41%; $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3365; δ_{H} 4.65 (1 H, br s), 6.61 (2 H, d, J 5.49), 8.12 (1 H, d, J 5.49), 8.41 (1 H, s); m/z 172 (M^+) (Found: M^+ , 171.9641).

2-(2-Bromoanilino)pyridine 4a; typical procedure for the palladium-catalyzed reaction of iodobenzenes with arylamines

A mixture of 2-aminopyridine 2a (343.6 mg, 3.65 mmol), 2-bromoiodobenzene 1a (0.56 ml, 4.38 mmol), *t*-BuONa (475.7 mg, 5.11 mmol), $\text{Pd}_2(\text{dba})_3$ † (174.2 mg, 0.19 mmol), and DPPF‡ (204.9 mg, 0.37 mmol) in toluene (18 ml) was stirred at 100°C for 14 h. After cooling, the mixture was diluted with Et_2O and filtered through a Celite® pad. The filtrate was evaporated, and purified by silica gel column chromatography using *n*-hexane–AcOEt (7:3) as eluent to give a pale yellow oil (853.9 mg, 94%); bp 140 – $143^\circ\text{C}/3$ mmHg; $\nu_{\text{max}}(\text{neat})/\text{cm}^{-1}$ 3410; δ_{H} 6.09 (1 H, br s), 6.98–6.84 (1 H, m), 7.16–7.27 (3 H, m), 7.45–7.49 (1 H, m), 7.55 (1 H, dd, J 1.10, 7.97), 8.27 (1 H, dd, J 1.10, 4.67), 8.47 (1 H, d, J 2.47); m/z 248 (M^+) (Found: M^+ , 247.9940. Calc. for $\text{C}_{11}\text{H}_9^{79}\text{BrN}_2$: M , 247.9949).

4-(2-Bromoanilino)pyridine 4b. According to the typical procedure, 4b was obtained from the reaction using 4-amino-pyridine 2b (222.1 mg, 2.36 mmol). Recrystallization from *i*-Pr₂O–*n*-hexane gave needles (555.9 mg, 96%), mp 94 – 95°C (Found: C, 53.06; H, 3.62; Br, 32.07; N, 11.14. $\text{C}_{11}\text{H}_9\text{BrN}_2$ requires C, 53.04; H, 3.64; Br, 32.08; N, 11.25%; $\nu_{\text{max}}(\text{KBr})/\text{cm}^{-1}$ 3207; δ_{H} 6.23 (1 H, br s), 6.89 (2 H, d, J 6.32), 6.98 (1 H,

† dba = dibenzylideneacetone.

‡ DPPF = 1,1'-bis(diphenylphosphino)ferrocene.

dt, J 1.37, 7.97), 7.31 (1 H, dt, J 1.37, 7.97), 7.46 (1 H, dd, J 1.37, 7.97), 7.62 (1 H, dd, J 1.37, 7.97), 8.36 (2 H, d, J 6.32); m/z 248 (M^+) (Found: M^+ , 247.9935).

3-(2-Bromoanilino)pyridine 4c. According to the typical procedure, **4c** was obtained from the reaction using 3-amino-pyridine **2c** (95.8 mg, 1.02 mmol), as a pale yellow oil (222.4 mg, 90%), bp 150–153 °C/3 mmHg; $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 3380; δ_{H} 6.07 (1 H, br s), 6.98–6.84 (1 H, m), 7.16–7.27 (3 H, m), 7.45–7.49 (1 H, m), 7.55 (1 H, dd, J 1.10, 7.97), 8.27 (1 H, dd, J 1.10, 4.67), 8.47 (1 H, d, J 2.75); m/z 248 (M^+) (Found: M^+ , 247.9941).

2-Anilino-3-bromopyridine 5a. According to the typical procedure, **5a** was obtained from the reaction for 17 h using 2-amino-3-bromopyridine **3a** (638.0 mg, 3.68 mmol) and iodobenzene (0.90 ml, 4.43 mmol), as a pale yellow oil (817.4 mg, 90%), bp 153–156 °C/3 mmHg (Found: C, 52.98; H, 3.86; Br, 31.77; N, 11.13%); $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 3400; δ_{H} 6.63 (1 H, dd, J 4.95, 7.69), 7.01 (1 H, br s), 7.03–7.13 (1 H, m), 7.32–7.37 (2 H, m), 7.62 (2 H, d, J 7.69), 7.73 (1 H, dd, J 1.65, 7.69), 8.15 (1 H, dd, J 1.65, 4.67); m/z 248 (M^+) (Found: M^+ , 247.9949).

3-Anilino-4-bromopyridine 5b. According to the typical procedure, **5b** was obtained from the reaction for 17 h using 3-amino-4-bromopyridine **3b** (824.3 mg, 4.79 mmol) and iodobenzene (0.64 ml, 5.75 mmol). Recrystallization from *i*-Pr₂O–*n*-hexane gave needles (628.3 mg, 53%), mp 109–110 °C (Found: C, 53.04; H, 3.69; Br, 32.08; N, 11.18%); $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$ 3220; δ_{H} 5.96 (1 H, br s), 7.11 (1 H, t, J 7.42), 7.19 (1 H, d, J 7.69), 7.36 (1 H, dt, J 1.92, 7.42), 7.46 (1 H, d, J 5.22), 7.93 (1 H, d, J 4.95), 8.51 (1 H, s); m/z 248 (M^+) (Found: M^+ , 247.9928).

4-Anilino-3-bromopyridine 5c. According to the typical procedure, **5c** was obtained from the reaction for 17 h using 4-amino-3-bromopyridine **3c** (342.7 mg, 1.99 mmol) and iodobenzene (0.27 ml, 2.39 mmol). Recrystallization from *i*-Pr₂O–*n*-hexane gave plates (436.4 mg, 88%), mp 66–68 °C (Found: C, 53.09; H, 3.66; Br, 31.99; N, 11.08%); $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$ 3380; δ_{H} 6.50 (1 H, br s), 6.92 (1 H, d, J 5.77), 7.20–7.27 (3 H, m), 7.39–7.44 (2 H, m), 8.14 (1 H, d, J 5.49), 8.49 (1 H, s); m/z 248 (M^+) (Found: M^+ , 247.9919).

3-Anilino-2-bromopyridine 5d. According to the typical procedure, **5d** was obtained from the reaction for 17 h using 3-amino-2-bromopyridine **3d** (142.9 mg, 0.90 mmol) and iodobenzene (0.12 ml, 1.08 mmol). Recrystallization from *i*-Pr₂O–*n*-hexane gave needles (142.5 mg, 64%), mp 85–86 °C (Found: C, 53.03; H, 3.83; Br, 32.13; N, 11.44. C₁₁H₉BrN₂ requires C, 53.04; H, 3.64; Br, 32.08; N, 11.25%); $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$ 3400; δ_{H} 6.16 (1 H, br s), 7.06–7.18 (4 H, m), 7.30–7.40 (2 H, m), 7.43 (1 H, dd, J 1.65, 7.97), 7.85 (1 H, dd, J 1.65, 4.67); m/z 248 (M^+) (Found: M^+ , 247.9949).

3-Bromo-2-(2-bromoanilino)pyridine 6a. According to the typical procedure, **6a** was obtained from the reaction for 18 h using 2-amino-3-bromopyridine **3a** (188.7 mg, 1.10 mmol) and 2-bromiodobenzene **1a** (0.17 ml, 1.32 mmol). Recrystallization from *n*-hexane gave prisms (333.8 mg, 93%), mp 73–74 °C (Found: C, 40.12; H, 2.49; Br, 48.70; N, 8.48. C₁₁H₈Br₂N₂ requires C, 40.28; H, 2.46; Br, 48.72; N, 8.54%); $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$ 3355; δ_{H} 6.71 (1 H, dd, J 4.95, 7.69), 6.90 (1 H, dt, J 1.37, 7.69), 7.33 (1 H, dt, J 1.37, 8.24), 7.57 (1 H, dd, J 1.37, 7.96), 7.73 (1 H, br s), 7.80 (1 H, dd, J 1.65, 7.96), 8.19 (1 H, dd, J 1.65, 4.65), 8.59 (1 H, dd, J 1.65, 8.24); m/z 326 (M^+) (Found: M^+ , 325.9032. Calc. for C₁₁H₈⁷⁹Br₂N₂: M , 325.9055).

4-Bromo-3-(2-bromoanilino)pyridine 6b. According to the typical procedure, **6b** was obtained from the reaction for 18 h using 3-amino-4-bromopyridine **3b** (909.2 mg, 5.29 mmol) and 2-bromiodobenzene **1a** (0.81 ml, 6.34 mmol). Recrystal-

lization from *n*-hexane gave needles (1.49 g, 86%), mp 89–91 °C (Found: C, 40.51; H, 2.59; Br, 48.69; N, 8.52%); $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$ 3380; δ_{H} 6.30 (1 H, br s), 6.89–6.94 (1 H, m), 7.23–7.33 (2 H, m), 7.52 (1 H, d, J 5.22), 7.62 (1 H, dd, J 1.10, 7.96), 8.02 (1 H, d, J 5.22), 8.54 (1 H, s); m/z 326 (M^+) (Found: M^+ , 325.9009).

3-Bromo-4-(2-bromoanilino)pyridine 6c. According to the typical procedure, **6c** was obtained from the reaction for 18 h using 4-amino-3-bromopyridine **3c** (946.8 mg, 5.50 mmol) and 2-bromiodobenzene **1a** (0.85 ml, 6.61 mmol). Recrystallization from CHCl₃–*n*-hexane gave needles (1.67 g, 90%), mp 125–127 °C (Found: C, 40.38; H, 2.54; Br, 48.81; N, 8.47%); $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$ 3380; δ_{H} 6.74 (1 H, br s), 6.93 (1 H, d, J 5.77), 7.08 (1 H, dt, J 1.65, 7.69), 7.36 (1 H, dt, J 1.37, 8.24), 7.45 (1 H, dd, J 1.65, 8.24), 7.68 (1 H, dd, J 1.37, 8.24), 8.19 (1 H, d, J 5.77), 8.55 (1 H, s); m/z 326 (M^+) (Found: M^+ , 325.9034).

2-Bromo-3-(2-bromoanilino)pyridine 6d. According to the typical procedure, **6d** was obtained from the reaction for 18 h using 3-amino-2-bromopyridine **3d** (554.8 mg, 3.23 mmol) and 2-bromiodobenzene **1a** (0.50 ml, 3.87 mmol). Recrystallization from *n*-hexane gave needles (751.7 mg, 71%), mp 49–51 °C (Found: C, 40.45; H, 2.64; Br, 48.67; N, 8.52%); $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$ 3375; δ_{H} 6.49 (1 H, br s), 6.92–6.98 (1 H, m), 7.15 (1 H, dd, J 4.67, 8.24), 7.27–7.32 (2 H, m), 7.47 (1 H, dd, J 1.65, 7.96), 7.63 (1 H, d, J 8.79), 7.94 (1 H, dd, J 1.37, 4.67); m/z 326 (M^+) (Found: M^+ , 325.9019).

2-Bromodiphenylamine 12a. According to the typical procedure, **12a** was obtained from the reaction for 12 h using aniline **11a** (94.9 mg, 1.02 mmol) and **1a** (0.16 ml, 1.22 mmol), as a pale yellow oil (116.2 mg, 46%), bp 138–141 °C/3 mmHg; $\nu_{\max}(\text{neat})/\text{cm}^{-1}$ 3390; δ_{H} 6.08 (1 H, br s), 6.73 (1 H, dt, J 1.65, 7.96), 7.01–7.07 (1 H, m), 7.13–7.19 (3 H, m), 7.25 (1 H, dd, J 1.37, 5.77), 7.29–7.35 (2 H, m), 7.52 (1 H, dd, J 1.65, 7.96); m/z 247 (M^+) (Found: M^+ , 246.9984. Calc. for C₁₂H₁₀⁷⁹BrN: M , 246.9996).

2,2'-Dibromodiphenylamine 12b. According to the typical procedure, **12b** was obtained from the reaction for 12 h using 2-bromoaniline **11b** (821.9 mg, 4.78 mmol) and **1a** (0.74 ml, 5.73 mmol), as an oil (1.50 g, 96%), bp 154–158 °C/3 mmHg; $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$ 3370; δ_{H} 6.44 (1 H, br s), 6.84 (2 H, dt, J 1.65, 7.96), 7.22 (2 H, dd, J 1.37, 8.24), 7.29 (2 H, dt, J 1.65, 8.24), 7.58 (2 H, dd, J 1.37, 7.96); m/z 325 (M^+) (Found: M^+ , 324.9092. Calc. for C₁₂H₉⁷⁹Br₂N: M , 324.9102).

9H-Pyrido[2,3-*b*]indole or α -carboline **8a**; typical procedure for the palladium-catalyzed reaction of *ortho*-anilinobromoarenes

A mixture of **5a** (204.5 mg, 0.82 mmol), Pd(OAc)₂ (18.5 mg, 0.08 mmol), and Na₂CO₃ (143.1 mg, 1.15 mmol) in DMF (7 ml) was refluxed for 67 h. After cooling, the mixture was diluted with AcOEt and filtered through a Celite® pad. The filtrate was washed successively with water and brine, dried over MgSO₄, and evaporated. The residue was purified by silica gel column chromatography using *n*-hexane–AcOEt (1:1) as eluent. The product was recrystallized from toluene to give needles (43.3 mg, 31%), mp 210–211 °C (lit.,^{4a} 212 °C); $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$ 3400; $\delta_{\text{H}}(\text{CDCl}_3\text{--}d_6\text{--DMSO})$ 7.19 (1 H, dd, J 4.95, 7.49), 7.25–7.30 (1 H, m), 7.45–7.55 (2 H, m), 8.07 (1 H, d, J 7.69), 8.34 (1 H, dd, J 1.65, 7.69), 8.47 (1 H, d, J 7.69).

9H-Pyrido[3,4-*b*]indole or β -carboline **8b. According to the typical procedure, **8b** was obtained from the reaction using **5b** (132.5 mg, 0.53 mmol). Recrystallization from toluene gave needles (54.1 mg, 61%), mp 199–200 °C (lit.,^{4a} mp 198–200 °C); $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$ 3400; $\delta_{\text{H}}(\text{CDCl}_3\text{--}d_6\text{--DMSO})$ 7.19 (1 H, dd, J 2.74, 5.22), 7.42–7.47 (2 H, m), 7.88 (1 H, d, J 5.22), 8.05 (1 H, d, J 7.69), 8.34 (1 H, dd, J 5.22), 8.84 (1 H, s), 10.14 (1 H, br s).**

5H-Pyrido[4,3-*b*]indole or γ -carboline 8c. According to the typical procedure, **8c** was obtained from the reaction using **5c** (151.2 mg, 0.61 mmol). Yield 48 mg (47%).

According to the typical procedure, **8c** was obtained from the reaction after 10 h using **4b** (257.1 mg, 1.04 mmol). Yield 123.0 mg (70%). Recrystallization from toluene gave needles, mp 216–218 °C (lit.,^{4a} 218 °C); $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$ 3400; $\delta_{\text{H}}(\text{CDCl}_3-d_6\text{-DMSO})$ 6.98 (1 H, dt, J 1.37, 7.69), 7.08–7.24 (3 H, m), 7.82 (1 H, d, J 7.69), 8.16 (1 H, d, J 8.24), 8.99 (1 H, s), 10.54 (1 H, br s).

5H-Pyrido[3,2-*b*]indole or δ -carboline 8d. According to the typical procedure, **8d** was obtained from the reaction using **5d** (142.5 mg, 0.57 mmol). Yield 49.0 mg (51%).

According to the typical procedure, **8c** was obtained from the reaction after 14 h using **4b** (117.2 mg, 0.47 mmol). Yield 40.1 mg (51%). Recrystallization from toluene gave needles, mp 205–207 °C (lit.,^{4a} 206 °C); $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$ 3400; $\delta_{\text{H}}(\text{CDCl}_3-d_6\text{-DMSO})$ 6.97–7.07 (2 H, m), 7.19–7.25 (2 H, m), 7.52 (1 H, dd, J 1.37, 8.24), 8.05 (1 H, d, J 7.69), 8.24 (1 H, d, J 4.67), 10.29 (1 H, br s).

Pyrido[1,2-*a*]benzimidazole 10. According to the typical procedure, **10** was obtained from the reaction using **4a** (672.1 mg, 2.71 mmol). Recrystallization from acetone–*n*-hexane gave needles (269.8 mg, 59%), mp 179–182 °C (lit.,¹¹ 180 °C); δ_{H} 6.87 (1 H, t, J 6.87), 7.36–7.47 (2 H, m), 7.55 (1 H, dt, J 1.10, 8.24), 7.71 (1 H, d, J 9.34), 7.91 (1 H, d, J 8.24), 7.95 (1 H, d, J 8.24), 8.47 (1 H, d, J 6.87); m/z 168 (M^+) (Found: M^+ , 168.0683. Calc. for $C_{11}H_8N_2$: M , 168.0687).

Carbazole 14a. According to the typical procedure, **14** was obtained from the reaction for 15 h using **12a** (219.1 mg, 0.89 mmol). Recrystallization from acetone–*n*-hexane gave needles (60.5 mg, 41%), mp 242–247 °C (lit.,¹² 246 °C); $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$ 3415; $\delta_{\text{H}}(\text{CDCl}_3-d_6\text{-DMSO})$ 7.22 (2 H, dt, J 1.37, 7.69), 7.38–7.44 (4 H, m), 8.08 (2 H, d, J 7.69), 9.03 (1 H, br s).

3-Bromo-2-[2-bromo-*N*-(methylsulfonyl)anilino]pyridine 7a; typical procedure for the preparation of 2,2'-dibromo-*N*-(methylsulfonyl)diarylamines

A THF (5 ml) solution of **6a** (353.4 mg, 1.08 mmol) was added dropwise to a THF (5 ml) suspension of 60% NaH (130.1 mg, 3.25 mmol), and the mixture was stirred at room temperature (rt) for 1 h. To this mixture was added methanesulfonyl chloride (0.17 ml, 2.16 mmol), and the whole mixture was stirred at rt for 4 h. After evaporation of the THF, the residue was taken up into AcOEt. The AcOEt phase was washed successively with water and brine, dried over MgSO_4 , and evaporated. The residue was purified by silica gel column chromatography with *n*-hexane–AcOEt (4:1) as eluent. The product was recrystallized from acetone–*n*-hexane to give needles (340.6 mg, 78%), mp 120–122 °C (Found: C, 35.55; H, 2.50; Br, 39.54; N, 6.83; S, 7.87. $C_{12}H_{10}Br_2N_2O_2S$ requires C, 35.49; H, 2.48; Br, 39.35; N, 6.90; S, 7.89%); $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$ 1350 and 1150; δ_{H} 3.55 (3 H, s), 7.09 (1 H, dd, J 4.95, 7.69), 7.24 (1 H, dt, J 1.37, 7.69), 7.40 (1 H, dt, J 1.37, 8.29), 7.58 (1 H, dd, J 1.37, 7.96), 7.88 (1 H, dd, J 1.65, 7.96), 7.93 (1 H, dd, J 1.65, 8.24), 8.47 (1 H, dd, J 1.65, 4.65); m/z 404 (M^+) (Found: M^+ , 403.8830. Calc. for $C_{12}H_{10}^{79}Br_2N_2O_2S$: M , 403.8830).

4-Bromo-3-[2-bromo-*N*-(methylsulfonyl)anilino]pyridine 7b. According to the typical procedure, **7b** was obtained from the reaction using **6b** (408.3 mg, 1.25 mmol). Recrystallization from acetone–*n*-hexane gave needles (420.8 mg, 83%), mp 159–160 °C (Found: C, 35.58; H, 2.52; Br, 39.44; N, 6.80; S, 7.82%); $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$ 1350 and 1130; δ_{H} 3.31 (3 H, s), 7.27 (1 H, dt, J 1.65, 8.24), 7.43 (1 H, dt, J 1.65, 8.24), 7.59 (1 H, d, J 5.22), 7.65 (1 H, dd, J 1.65, 7.96), 8.16 (1 H, dd, J 1.65, 8.24), 8.32

(1 H, d, J 5.22), 9.14 (1 H, s); m/z 404 (M^+) (Found: M^+ , 403.8832).

3-Bromo-4-[2-bromo-*N*-(methylsulfonyl)anilino]pyridine 7c. According to the typical procedure, **7c** was obtained from the reaction using **6c** (570.4 mg, 1.75 mmol). Recrystallization from MeOH gave needles (579.7 mg, 82%), mp 199–201 °C (Found: C, 35.51; H, 2.54; Br, 39.60; N, 6.88; S, 7.92%); $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$ 1350 and 1120; δ_{H} 3.32 (3 H, s), 7.29 (1 H, dt, J 1.65, 7.69), 7.45 (1 H, dt, J 1.65, 7.96), 7.64–7.69 (2 H, m), 8.06 (1 H, dd, J 1.65, 8.24), 8.53 (1 H, d, J 5.94), 8.79 (1 H, s); m/z 404 (M^+) (Found: M^+ , 403.8826).

2-Bromo-3-[2-bromo-*N*-(methylsulfonyl)anilino]pyridine 7d. According to the typical procedure, **7d** was obtained from the reaction using **6d** (275.4 mg, 0.85 mmol). Recrystallization from acetone–*n*-hexane gave needles (327.5 mg, 95%), mp 142–143 °C (Found: C, 35.57; H, 2.49; Br, 39.46; N, 6.91; S, 7.86%); $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$ 1350 and 1120; δ_{H} 3.31 (3 H, s), 7.23–7.28 (1 H, m), 7.36–7.46 (2 H, m), 7.65 (1 H, dd, J 1.65, 7.96), 8.09 (1 H, dd, J 1.37, 8.24), 8.35 (1 H, dd, J 1.65, 4.77), 8.42 (1 H, dd, J 1.37, 7.96); m/z 404 (M^+) (Found: M^+ , 403.8839).

2,2'-Dibromo-*N*-(methylsulfonyl)diphenylamine 13. According to the typical procedure, **13** was obtained from the reaction using **12b** (670.1 mg, 2.05 mmol). Recrystallization from acetone–*n*-hexane gave needles (692.7 mg, 83%), mp 163–165 °C (Found: C, 38.49; H, 2.81; Br, 39.66; N, 3.52; S, 7.87. $C_{13}H_{11}Br_2NO_2S$ requires C, 38.54; H, 2.74; Br, 39.45; N, 3.46; S, 7.91%); $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$ 3220; δ_{H} 3.30 (3 H, s), 7.21 (2 H, dt, J 1.65, 7.96), 7.38 (2 H, dt, J 1.65, 7.96), 7.65 (2 H, dd, J 1.65, 7.96), 8.08 (2 H, dd, J 1.37, 7.96); m/z 403 (M^+) (Found: M^+ , 402.8901. Calc. for $C_{13}H_{11}^{79}Br_2NO_2S$: M , 402.8878).

9-Methylsulfonyl- α -carboline 9a; typical procedure for the palladium-catalyzed cyclization reaction of *ortho,ortho'*-dibromoarylamines 7a–d, 13

A mixture of **7a** (131.9 mg, 0.32 mmol), $(\text{Bu}_3\text{Sn})_2$ (0.19 ml, 0.38 mmol), Et_4NI (115.2 mg, 0.45 mmol), Li_2CO_3 (33.1 mg, 0.45 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (22.8 mg, 0.03 mol), and toluene (5 ml) was refluxed for 6 h. After cooling, the mixture was diluted with Et_2O and filtered through a Celite® pad. The filtrate was evaporated, and the residue was purified by silica gel column chromatography using *n*-hexane–AcOEt (7:3) as eluent. The product was recrystallized from acetone–*n*-hexane to give needles (71.4 mg, 91%), mp 109–110 °C (Found: C, 58.49; H, 4.10; N, 11.40; S, 13.01. $C_{12}H_{10}N_2O_2S$ requires C, 58.52; H, 4.09; N, 11.37; S, 13.02%); $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$ 1355 and 1120; δ_{H} 3.61 (3 H, s), 7.38 (1 H, dd, J 4.95, 7.69), 7.43 (1 H, dt, J 1.10, 7.42), 7.55 (1 H, dt, J 1.37, 7.42), 8.01 (1 H, d, J 7.69), 8.32 (1 H, dd, J 1.65, 7.69), 8.33 (1 H, d, J 8.52), 8.61 (1 H, dd, J 1.65, 4.94); m/z 246 (M^+) (Found: M^+ , 246.0436. Calc. for $C_{12}H_{10}N_2O_2S$: M , 246.0462).

9-Methylsulfonyl- β -carboline 9b. According to the typical procedure, **9b** was obtained from the reaction using **7b** (131.9 mg, 0.33 mmol) and toluene–DMF (10:1; 5 ml) as solvent. Recrystallization from acetone–*n*-hexane gave needles (51.5 mg, 64%), mp 163–165 °C (Found: C, 58.48; H, 3.82; N, 11.35; S, 13.04%); $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$ 1355 and 1115; δ_{H} 3.08 (3 H, s), 7.51 (1 H, dt, J 1.10, 9.96), 7.68 (1 H, dt, J 1.37, 8.24), 7.93 (1 H, d, J 5.22), 8.11 (1 H, d, J 7.96), 8.21 (1 H, d, J 8.24), 8.69 (1 H, d, J 5.22), 9.50 (1 H, s); m/z 246 (M^+) (Found: M^+ , 246.0450).

5-Methylsulfonyl- γ -carboline 9c. According to the typical procedure, **9c** was obtained from the reaction using **7c** (464.6 mg, 1.15 mmol) and toluene–DMF (10:1; 5 ml) as solvent. Recrystallization from CHCl_3 –*n*-hexane gave needles (210.3 mg, 74%), mp 165–166 °C (Found: C, 58.19; H, 3.94; N, 11.29;

S, 13.11%); $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$ 1350 and 1125; δ_{H} 3.12 (3 H, s), 7.64–7.71 (2 H, m), 8.06 (1 H, d, J 6.04), 8.12 (1 H, d, J 7.42), 8.17 (1 H, d, J 8.24), 8.68 (1 H, d, J 6.04), 9.33 (1 H, s); m/z 246 (M^+). (Found: M^+ , 246.0442).

5-Methylsulfonyl- δ -carboline 9d. According to the typical procedure, **9d** was obtained from the reaction using **7d** (237.9 mg, 0.58 mmol). Recrystallization from acetone–n-hexane gave needles (119.3 mg, 84%), mp 153–154 °C; $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$ 1358 and 1115 (Found: C, 58.55; H, 4.12; N, 11.29; S, 13.21%); δ_{H} 3.03 (3 H, s), 7.43 (1 H, dd, J 4.67, 8.52), 7.51–7.56 (1 H, m), 7.64 (1 H, dt, J 1.37, 8.24), 8.19 (1 H, d, J 8.52), 8.35 (1 H, d, J 7.69), 8.45 (1 H, dd, J 1.37, 8.52), 8.71 (1 H, dd, J 1.37, 4.95); m/z 246 (Found: M^+ , 246.0465).

9-(Methylsulfonyl)carbazole 14b. According to the typical procedure, **14b** was obtained from the reaction using **13** (137.2 mg, 0.34 mmol). Recrystallization from n-hexane gave needles (39.2 mg, 47%), mp 108–109 °C (Found: C, 63.70; H, 4.49; N, 5.74; S, 13.10. $\text{C}_{13}\text{H}_{11}\text{NO}_2\text{S}$ requires C, 63.66; H, 4.52; N, 5.71; S, 13.07%); $\nu_{\max}(\text{KBr})/\text{cm}^{-1}$ 1350 and 1120; δ_{H} 2.99 (3 H, s), 7.41–7.54 (4 H, m), 8.03 (2 H, d, J 7.69), 8.18 (2 H, d, J 8.24); m/z 245 (M^+) (Found: M^+ , 245.0506. Calc. for $\text{C}_{13}\text{H}_{11}\text{NO}_2\text{S}$: M , 245.0510).

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