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Regiochemical Switching in Diels−Alder Cycloadditions by Change in Oxidation State of Removable Diene Sulfur Substituents. Synthesis of Carbazoles by Sequential Heteroannulation and Diels−Alder Cycloaddition

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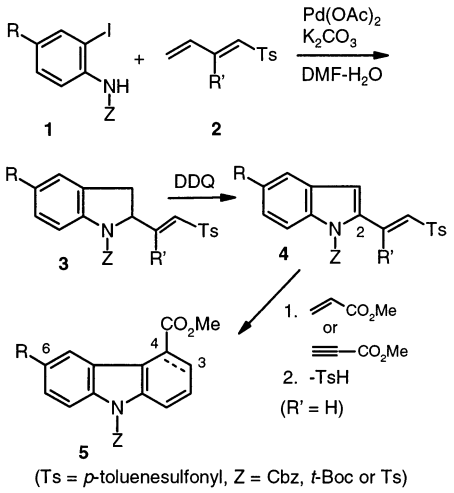
Abstract: The palladium-catalyzed heteroannulation of *N*-carbobenzyloxy-*o*-iodoanilines with 1-phenylthio-1,3-butadiene afforded indolines **7**, which were oxidized with DDQ to produce vinylogous 2-(phenylthio)indoles **8**. The latter compounds underwent highly regioselective Diels−Alder cycloadditions with methyl propiolate in the presence of $MeAlCl_2$ or $AlCl_3$, with simultaneous elimination of benzenethiol, to afford methyl *N*-(carbobenzyloxy)carbazole-3-carboxylates **9** and, in some cases, the N-deprotected derivatives **11**. This is the opposite regiochemistry of that observed previously with the corresponding sulfone analogues of **8**. Thus, the regiochemistry of the cycloaddition can be effectively controlled by appropriate choice of oxidation state of the diene sulfur substituent.

We recently reported[1] that the palladium-catalyzed heteroannulation[2] of *o*-iodoanilines **1** with dienyl sulfones **2**[3] affords the corresponding vinylogous 2-sulfonylindolines **3**, followed by further oxidation to the corresponding indoles **4**. The latter compounds undergo highly regioselective Diels−Alder reactions to afford dihydrocarbazoles or carbazoles **5** after elimination of the sulfone moiety (Scheme 1).[1] This approach provides a convenient route to 4-substituted carbazole derivatives but fails for the corresponding 3-substituted regioisomers. Since many biologically interesting carbazoles[4] are substituted at the 3-position, we were interested in finding a method for switching the regiochemistry of the cycloaddition reaction in order to render the latter isomers accessible.

Since the sulfone substituents in **4** are electron-withdrawing, we reasoned that the corresponding sulfide analogues **8**, where the sulfur moiety is electron-donating, might undergo cycloadditions with the opposite regiochemistry.[5] We now report that the palladium-catalyzed heteroannulations of **1** with dienyl sulfide **6** proceed smoothly, as do the subsequent oxidations of the products **7** with DDQ to afford **8** (Scheme 2). The heteroannulations with dienyl sulfones **2** were typically performed at room temperature in aqueous DMF containing potassium carbonate in the presence of a catalytic amount of palladium(II) acetate.[1] Similar conditions were employed in the preparation of **7**, except that the use of refluxing acetonitrile afforded superior yields to aqueous

SCHEME 1



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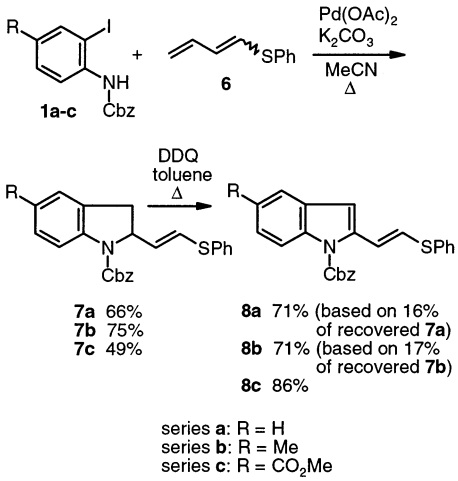

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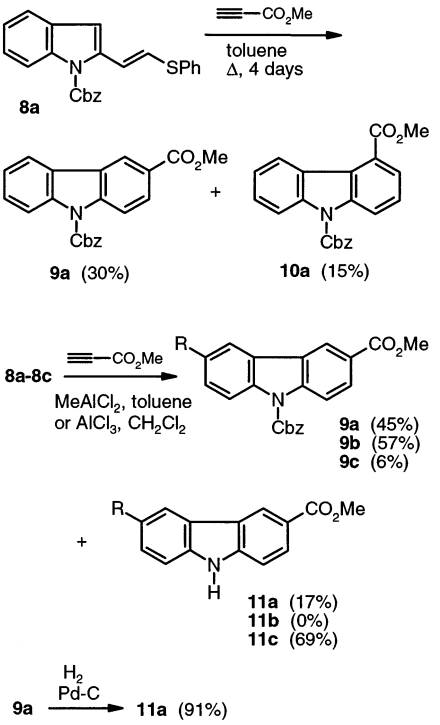
SCHEME 3



DMF. A 2-fold excess of dienyl sulfide **6** was employed to compensate for its partial polymerization during the reaction. The DDQ oxidations[6] of **7** to **8** were performed in refluxing toluene, and slightly higher yields were generally obtained when the reactions were stopped prior to the complete consumption of indolines **7a** and **7b**. The yields of **8a** and **8b** in Scheme 2 are therefore based on the recovery of small amounts of starting materials. These results indicate that the sulfide moiety does not interfere significantly with either the palladium-catalyzed coupling step or the subsequent DDQ oxidation. Moreover, both reactions tolerate electron-donating (series **b**) and -withdrawing (series **c**) groups in the *para* position of the aniline and the 6-position of the resulting indoline.

The Diels−Alder reactions of indoles **8** with methyl propiolate were then investigated. When **8a** was refluxed in toluene with an excess of the dienophile in the absence of a Lewis acid, a slow cycloaddition was observed, along with concomitant elimination of benzenethiol, to afford the two regioisomeric carbazoles **9a** and **10a** in 45% yield in a ratio of 2:1 (Scheme 3). This indicated that replacement of the sulfone moiety in **4** by the sulfide substituent in **8a** had indeed reversed the regioselectivity of the reaction, as desired. Dramatic improvements in the reaction rate and regioselectivity, along with modestly enhanced yields, were observed in the presence of certain Lewis acids, with $AlCl_3$ and $MeAlCl_2$ affording the best results of several studied. Thus, in the presence of 1 equiv of $MeAlCl_2$, **8a** reacted rapidly with excess methyl propiolate in toluene at 0 °C to afford **9a** as the sole regioisomer, along with the deprotected carbazole **11a**, isolated in yields of 45 and 17%, respectively (Scheme 3). The deprotection of **9a** to **11a** was also achieved in excellent yield by hydrogenolysis (Scheme 3). Carbazole **11a** is found in extracts of the roots of the ornamental tree *Clausena lansium*,[7] which are used in Taiwanese folk medicine for the treatment of bronchitis and malaria.

Similar results were obtained with indoles **8b** and **8c**, as shown in Scheme 3. In each case, only the corresponding 3-substituted regioisomers **9b**, **9c**, and **11c** were detected. The 6-methyl derivative **9b** was produced rapidly at 0 °C in the presence of $AlCl_3$ in dichloromethane, with no accompanying formation of the corresponding free carbazole **11b**. On the other hand, the $MeAlCl_2$ catalyst in toluene proved to be more effective for the cyclization of diester **8c**, which required a full day at room temperature for optimum results and afforded chiefly the deprotected carbazole **11c**. Deprotection of benzyl esters and related compounds is known to occur with $AlCl_3$ in anisole,[8] an electron-rich arene. It is therefore not surprising that similar deprotection occurred in the case of **9a** and **9c** in the presence of $MeAlCl_2$ in toluene but was not observed in the case of **9b**, where dichloromethane was employed as the solvent. In general, at least 1 equiv of the Lewis acid was required for optimum results, presumably because of its subsequent reaction with the byproduct benzenethiol. As expected, the more electron-rich indoles **8a** and **8b** reacted more rapidly than the electron-deficient ester derivative **8c**. However, the latter indole afforded a higher cycloaddition yield than **8a** or **8b**.

In conclusion, vinylogous 2-(phenylthio)indoles **8** can be conveniently prepared in two steps by the palladium-catalyzed heteroannulation of *o*-iodoanilines with dienyl sulfide **6**, followed by DDQ oxidation. The Lewis acid-catalyzed Diels−Alder cycloadditions of **8** with methyl propiolate afforded moderate yields of single regioisomers of the corresponding cycloadducts **9** and **11**, in which the propiolate ester moiety is incorporated into the 3-position. The protocol can be applied to carbazoles that are unsubstituted (series **a**) or that contain electron-donating (series **b**) or -withdrawing (series **c**) substituents at C-6. This method is complementary to the previously described cycloadditions of the sulfone analogues of **8**, which result in exclusive formation of the 4-substituted regioisomers. Together, the two methods therefore provide concise routes to a variety of 3,6- and 4,6-disubstituted carbazoles and provide an interesting example of how a complete reversal of regiochemistry can be achieved in Diels−Alder reactions by changing the oxidation state of a sulfur substituent in the diene reactant. This strategy may find broader application in the regiocontrol of other cycloadditions.

Experimental Section

General Methods. All reagents, unless otherwise noted, were obtained from commercial sources and purified by standard methods as necessary. *N*-Cbz-*o*-iodonilines **1a**−**c** were prepared as described previously,[1] and 1-phenylthio-1,3-butadiene (**6**)[9] was prepared by a literature procedure. Chromatography refers to

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flash chromatography on silica gel (230−400 mesh). NMR spectra were recorded in deuteriochloroform unless otherwise indicated.

***N*-(Carbobenzyloxy)-2-[(*E*)-2-(phenylthio)ethenyl]indoline (7a).** *N*-Cbz-2-Iodoaniline (834 mg, 2.35 mmol), 1-phenylthio-1,3-butadiene (773 mg, 4.77 mmol), finely ground K_2CO_3 (328 mg, 2.38 mmol), tetrabutylammonium bromide (766 mg, 2.38 mmol), and 85 mg (0.38 mmol) of $Pd(OAc)_2$ were refluxed in 50 mL of acetonitrile for 24 h. The mixture was diluted with chloroform, filtered through Celite, and concentrated in vacuo. The crude product was chromatographed (hexanes/ethyl acetate, 13:1) to afford 599 mg (66%) of **7a** as a light yellow oil: IR (film) 1706, 1602, 1482 cm^{-1}; ^1H NMR (200 MHz) δ 7.90−7.67 (m, 1 H), 7.49−7.11 (m, 12 H), 7.06−6.91 (m, 1 H), 6.36 (d, J = 14.0 Hz, 1 H), 5.83 (dd, J = 15.1, 7.7 Hz, 1 H), 5.29 (s, 2 H), 5.14−4.97 (m, 1 H), 3.46 (dd, J = 16.5, 9.9 Hz, 1 H), 2.85 (dd, J = 16.3, 2.7 Hz, 1 H); ^{13}C NMR (50 MHz) δ 152.9, 141.5, 136.1, 134.8, 131.2, 129.6, 129.3, 129.0, 128.6, 128.1, 128.1, 127.7, 126.8, 125.4, 124.9, 123.0, 115.3, 67.3, 60.8, 34.9; MS (EI) *m*/*z* (%) 387 (M^+, 3), 278 (33), 142 (86), 91 (72), 89 (100); HRMS calcd for $C_{24}H_{21}NO_2S$ 387.1293, found 387.1304.

***N*-(Carbobenzyloxy)-6-methyl-2-[(*E*)-2-(phenylthio)ethenyl]indoline (7b).** Product **7b** was prepared in 75% yield by the same procedure as **7a**, except that refluxing was continued for 4 days: colorless oil; IR (film) 1700, 1613, 1493 cm^{-1}; ^1H NMR (200 MHz) δ 7.48−7.18 (m, 11 H), 7.00 (m, 2 H), 6.35 (d, J = 15.0 Hz, 1 H), 5.82 (dd, J = 15.0, 7.5 Hz, 1 H), 5.28 (s, 2 H), 5.03 (m, 1 H), 3.43 (dd, J = 16.0, 10.3 Hz, 1 H), 2.80 (dd, J = 16.2, 2.4 Hz, 1 H), 2.30 (s, 3 H, Me); ^{13}C NMR (50 MHz) δ 152.9, 139.2 136.2, 134.8, 132.6, 131.4, 129.6, 129.0, 128.6, 128.1, 128.0, 126.8, 125.6, 125.2, 115.0, 67.3, 60.9, 34.9, 20.9; MS (EI) *m*/*z* (%) 401 (M^+, 2), 292 (16), 156 (100), 130 (73), 91 (48); HRMS calcd for $C_{25}H_{23}NO_2S$ 401.1450, found 401.1463.

Methyl *N*-(Carbobenzyloxy)-2-[(*E*)-2-(phenylthio)ethenyl]indoline-6-carboxylate (7c). Product **7c** was prepared in 49% by the same procedure as **7a**, except that refluxing was continued for 8 days: yellow solid, mp 102−103 °C (from ethanol); IR (film) 1717, 1613, 1487, 1258 cm^{-1}; ^1H NMR (200 MHz) δ 7.99−7.81 (m, 3 H) 7.55−7.26 (m, 10 H), 6.36 (d, J = 15.0 Hz, 1 H), 5.77 (dd, J = 15.0, 7.6 Hz, 1H), 5.29 (s, 2 H), 5.15−5.01 (m, 1 H), 3.89 (s, 3 H), 3.46 (dd, J = 16.2, 10.1 Hz, 1 H), 2.88 (dd, J = 16.4, 2.6 Hz, 1 H); ^{13}C NMR (100 MHz) δ 166.7, 152.7, 135.7, 134.4, 130.3, 130.0, 129.9, 129.6, 129.1, 128.6, 128.3, 128.2, 127.0, 126.4, 126.3, 124.8, 114.6, 67.7, 61.4, 51.9, 34.4; MS (EI) *m*/*z* (%) 445 (M^+, 3), 292 (51), 91 (100); HRMS calcd for $C_{26}H_{23}NO_4S$ 445.1348, found 445.1368. Anal. Calcd for $C_{26}H_{23}NO_4S$: C, 70.09; H, 5.20; N, 3.14. Found: C, 69.90; H, 5.23; N, 2.91.

***N*-(Carbobenzyloxy)-2-[(*E*)-2-(phenylthio)ethenyl]indole (8a).** A solution of DDQ (0.82 g, 3.6 mmol) in 25 mL of toluene was added to indoline **7a** (1.40 g, 3.6 mmol) in 75 mL of toluene, and the solution was refluxed for 24 h. The mixture was concentrated in vacuo, and chromatography of the residue (hexanes/ethyl acetate, 10:1) afforded 226 mg (16%) of unreacted **7a** and 0.82 g (71%, based on recovered **7a**) of **8a** as a beige solid, mp 85.5 °C (from ethyl acetate−hexanes): IR (film) 1733, 1580, 1449, 1323 cm^{-1}; ^1H NMR (200 MHz) δ 8.15−8.06 (m, 1 H), 7.57−7.21 (m, 14 H), 6.88 (d, J = 15.4 Hz, 1 H), 6.71 (s, 1 H), 5.48 (s, 2 H); ^{13}C (50 MHz) δ 151.6, 138.0, 136.6, 134.9, 134.8, 130.1, 129.3, 129.2, 128.8, 128.7, 128.4, 127.1, 126.4, 124.5, 123.3, 122.8, 120.3, 115.8, 107.5, 68.9; MS (EI) *m*/*z* (%) 385 (M^+, 2), 249 (100), 217 (87); HRMS calcd for $C_{24}H_{19}NO_2S$ 385.1137, found 385.1124. Anal. Calcd for $C_{24}H_{19}NO_2S$: C, 74.78; H, 4.97; N, 3.63. Found: C, 74.47; H, 4.91; N, 3.57

***N*-(Carbobenzyloxy)-6-methyl-2-[(*E*)-2-(phenylthio)ethenyl]indole (8b).** Product **8b** was prepared in 71% yield (based on 17% recovery of **7b**) by the same procedure as **8a**, except that refluxing was continued for 8 h: white solid, mp 102 °C (from ethyl acetate/hexanes); IR (film) 1724, 1652, 1397, 1337 cm^{-1}; ^1H NMR (200 MHz) δ 7.96 (d, J = 8.6 Hz, 1 H), 7.57−7.23 (m, 12 H), 7.06 (dd, J = 8.7, 0.5 Hz, 1 H), 6.86 (d, J = 15.2 Hz, 1 H), 6.64 (s, 1 H), 5.46 (s, 2 H), 2.41 (s, 3 H); ^{13}C NMR (100 MHz) δ 151.7, 138.1, 135.0, 134.9, 134.8, 132.8, 130.1, 129.6, 129.2, 128.8, 128.6, 128.4, 127.1, 126.1, 125.9, 123.0, 120.2, 115.5, 107.3, 68.7, 21.2; MS (EI) *m*/*z* (%) 399 (M^+, 2), 248 (58), 230 (83), 186 (100); HRMS calcd for $C_{25}H_{21}NO_2S$ 399.1293, found 399.1264. Anal. Calcd for $C_{25}H_{21}NO_2S$: C, 75.16; H, 5.30; N, 3.51. Found: C, 75.05; H, 5.69; N, 3.65.

Methyl *N*-(Carbobenzyloxy)-2-[(*E*)-2-(phenylthio)ethenyl]indole-6-carboxylate (8c). Product **8c** was prepared in 86% yield by the same procedure as **8a**, except that refluxing was continued for 12 h and 1.1 equiv of DDQ was employed: white solid, mp 94−96 °C (from ethanol); IR (film) 1737, 1713, 1582, 1306 cm^{-1}; ^1H NMR (200 MHz) δ 8.25−8.07 (m, 2 H), 8.01−7.86 m, 1 H), 7.56−7.14 (m, 11 H), 6.92 (d, J = 15.4 Hz, 1 H), 6.74 (s, 1 H), 5.48, (s, 2 H), 3.94, (s, 3 H); ^{13}C NMR (50 MHz) δ 167.2, 151.3, 139.4, 139.2 134.5, 134.3, 130.5, 129.2, 129.1, 128.8, 128.6, 127.9, 127.4, 125.7, 125.3, 122.4, 121.6, 115.5, 107.4, 69.3, 52.0; MS (EI) *m*/*z* (%) 443 (M^+, 4), 248 (100), 91 (53); HRMS calcd for $C_{26}H_{21}NO_4S$ 443.1191, found 443.1183. Anal. Calcd for $C_{26}H_{21}NO_4S$: C, 70.41; H, 4.77; N, 3.16. Found: C, 70.31; H, 4.55; N, 3.14.

Methyl *N*-(Carbobenzyloxy)carbazole-3-carboxylate (9a) and Methyl Carbazole-3-carboxylate (11a). A solution of indole **8a** (100 mg, 0.26 mmol) in 2 mL of toluene was added dropwise over 5 min to a solution of methyl propiolate (0.23 mL, 2.6 mmol) and $MeAlCl_2$ (0.26 mmol) in 5 mL of toluene at 0 °C. The mixture was stirred for 20 min at room temperature. It was then diluted with dichloromethane, washed with 10% HCl solution, dried, and concentrated in vacuo. Chromatography (hexanes/ethyl acetate, 10:1) afforded 42 mg (45%) of **9a** and 10 mg (17%) of **11a**.

Carbazole 9a: white solid, mp 131−134 °C (from ethanol); IR (film) 1733, 1716, 1433, 1245 cm^{-1}; ^1H NMR (200 MHz) δ 8.68 (dd, J = 1.2, 0.6 Hz, 1 H), 8.33 (t, J = 9.4 Hz, 2 H), 8.15 (dd, J = 8.8, 1.8 Hz, 1 H), 8.05 (m, 1 H), 7.60−7.39 (m, 7 H), 5.60 (s, 2 H), 3.99 (s, 3 H); ^{13}C NMR (50 MHz) δ 167.0, 152.0, 141.1, 138.7, 134.8, 128.8, 128.8, 128.6, 127.8, 126.0, 125.4, 125.3, 123.8, 121.5, 119.9, 116.4, 116.0, 69.1, 52.1; MS (EI) *m*/*z* (%) 359 (M^+, 0.6), 315 (17), 164 (82), 91 (100); HRMS calcd for $C_{22}H_{17}NO_4$ 359.1158, found 359.1127. Anal. Calcd for $C_{22}H_{17}NO_4$: C, 73.53; H, 4.77; N, 3.90. Found: C, 73.07; H, 4.43; N 3.76.

Carbazole 11a: mp 175−180 °C (lit.[7] 168−170 °C); ^1H and ^{13}C NMR spectra were in close agreement with those reported in the literature.[7]

When the reaction was performed in refluxing toluene for 4 days in the presence of 10 mol % 2,6-di-*tert*-butyl-4-methylphenol in the absence of the Lewis acid, carbazoles **9a** (see above) and **10a** (identical to an authentic sample[1]) were obtained in yields of 30 and 15%, respectively.

Methyl *N*-(Carbobenzyloxy)-6-methylcarbazole-3-carboxylate (9b). A solution of indole **8b** (51.7 mg, 0.129 mmol) in 2 mL of CH_2Cl_2 was added via cannula to a stirred suspension of methyl propiolate (0.10 mL, 1.1 mmol) and $AlCl_3$ (35 mg, 0.26 mmol) in 1 mL of CH_2Cl_2 at 0 °C. The deep red reaction mixture was stirred for 15 min at 0 °C, filtered through Celite, and concentrated in vacuo. The crude product was immediately chromatographed (hexanes/ethyl acetate, from 20:1 to 9:1) to afford 27.5 mg (57%) of **9b** as a white solid, mp 128−129.5 °C (from ethanol): IR (film) 1732, 1714, 1608, 1387 cm^{-1}; ^1H NMR (200 MHz) δ 8.65 (d, J = 1.7 Hz, 1 H), 8.33 (d, J = 8.7 Hz, 1 H), 8.16 (d, J = 8.7 Hz, 1 H), 8.13 (dd, J = 8.8, 1.7 Hz, 1 H), 7.84 (s, 1 H), 7.62−7.28 (m, 6 H), 5.58 (s, 2 H), 3.99 (s, 3 H), 2.52 (s, 3 H); ^{13}C NMR (100 MHz) δ 167.1, 152.0, 141.3, 136.8, 134.9, 133.5, 129.0, 128.9, 128.8, 128.6, 128.5, 126.0, 125.6, 125.2, 121.5, 120.1, 116.1, 116.0, 69.0, 52.1, 21.3; MS (EI) *m*/*z* (%) 373 (M^+, 0.6), 328 (47), 177 (93), 91 (100); HRMS calcd for $C_{23}H_{19}NO_4$ 373.1314, found 373.1320. Anal. Calcd for $C_{23}H_{19}NO_4$: C, 73.98; H, 5.13; N, 3.75. Found: C, 74.30; H, 5.05; N, 3.80.

Dimethyl *N*-(Carbobenzyloxy)carbazole-3,6-dicarboxylate (9c) and Dimethyl Carbazole-3,6-dicarboxylate (11c). A solution of indole **8d** (100 mg, 0.23 mmol) in 2 mL of toluene was added dropwise over 5 min to a solution of methyl propiolate (0.21 mL, 2.3 mmol) and $MeAlCl_2$ (0.23 mmol) in 5 mL of toluene at 0 °C. The mixture was then warmed to room temperature and stirred for an additional 24 h. It was worked up as in the preparation of **9a** and **11a**. Chromatography (hexanes/ethyl

acetate, 7:1, and then ethyl acetate) yielded 6 mg (6%) of **9c** and 44 mg (69%) of **11c**.

Carbazole 9c: mp 196.5−198 (from ethanol); IR (film) 1733, 1718, 1266 cm^{-1}; ^1H NMR (200 MHz) δ 8.75 (dd, J = 1.8, 0.6 Hz, 2 H), 8.36 (dd, J = 8.8, 0.6 Hz, 2 H), 8.20 (dd, J = 8.8, 1.7 Hz, 2 H), 7.63−7.51 (m, 2 H), 7.50−7.42 (m, 3 H), 5.61 (s, 2 H), 4.00 (s, 6 H); ^{13}C NMR (50 MHz) δ 166.8, 141.5, 129.2, 129.0, 128.9, 128.7, 128.2, 125.8, 125.4, 121.8, 116.1, 69.4, 52.2; MS (EI) m/z (%) 417 (M^+, 0.5), 373 (12), 254 (18), 164 (40), 91 (100); HRMS calcd for $C_{24}H_{19}NO_6$ 417.1212, found 417.1252.

Carbazole 11c:[10] IR (film) 1706, 1692, 1629, 1603, 1587, 1325, 1242, 1105, 767 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 8.93 (dd, J = 1.6, 0.6 Hz, 2 H), 8.12 (dd, J = 8.6, 1.7 Hz, 2 H), 7.64 (dd, J = 8.6, 0.6 Hz, 2 H), 3.93 (s, 6 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 166.8, 143.5, 127.7, 122.9, 122.7, 122.0, 111.1, 51.2; MS (EI) m/z (%) 283 (M^+, 4), 252 (20), 164 (100); HRMS calcd for $C_{16}H_{13}NO_4$ 283.0845, found 283.0833.

Deprotection of Carbazole 9a to Carbazole 11a. Carbazole **9a** (12.6 mg, 0.0351 mmol) was dissolved in 30 mL of methanol/dichloromethane (5:1); 10% Pd on carbon (65 mg) was added, and the mixture was stirred for 2 days under hydrogen (1 atm). The mixture was filtered through Celite, and the filtrate was concentrated in vacuo to provide a beige solid, which was washed with hexanes (4 mL) to afford 7.2 mg (91%) of **11a** as an off-white solid with spectra identical to those of the sample prepared from the cycloaddition of **8a**.

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Supporting Information Available: ^1H and ^{13}C NMR spectra of new compounds and of carbazoles **11a** and **11c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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