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Intramolecular Pd(II)-Catalyzed Oxidative Biaryl Synthesis Under Air: Reaction Development and Scope

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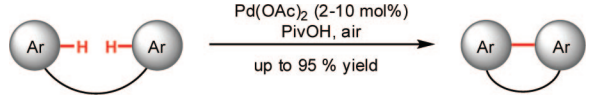
Received March 16, 2008



New reaction conditions for intramolecular palladium(II)-catalyzed oxidative carbon−carbon bond formation under air are described. The use of pivalic acid as the reaction solvent, instead of acetic acid, results in greater reproducibility, higher yields, and broader scope. This includes the use of electron-rich diarylamines as illustrated in the synthesis of three naturally occurring carbazole products: Murrayafoline A, Mukonine, and Clausenine. A variety of side products have also been isolated, casting light on competing reaction pathways and revealing new reactivity with palladium(II) catalysis.

Introduction

Chemists continue to develop increasingly efficient methods for the construction of biaryl molecules. Emerging alternatives to the frontline of palladium-catalyzed cross-coupling reactions[1] include direct arylation and related processes in which one of the preactivated arenes is replaced by a simple arene.[2,3] Recently, methods that avoid arene preactivation have appeared, enabling the coupling of two unactivated aromatic compounds directly.[4] As part of our work in this area, we conducted studies in the area of intramolecular oxidative biaryl coupling reactions (Scheme 1).[5–8] These processes have recognized value in synthesis, particularly in the preparation of the carbazole motif.[9,10] Despite their potential, the evolution of these reactions from stoichiometric processes, described over 30 years ago[5] to catalytic processes[7] is only quite recent. Furthermore, the scope of these transformations remains limited; electron-rich arenes, for example, remain problematic in carbazole synthesis and are

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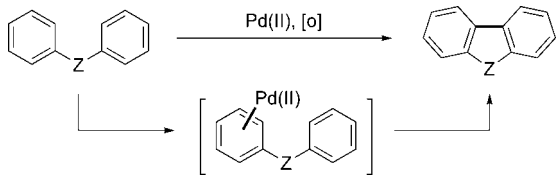
(8) For the use of catalytic palladium in various intramolecular biaryl coupling, see: Wang, J.; Rosingana, M.; Watson, D. J.; Dowdy, E. D.; Discordia, R. P.; Soundarajan, N.; Li, W.-S. *Tetrahedron Lett.* **2001**, *42*, 8935. See also refs 6h and 7e.

(9) For recent reviews on carbazoles, see: (a) Knölker, H.-J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303. (b) Knölker, H.-J. *Curr. Org. Synth.* **2004**, *1*, 309. (c) Knölker, H.-J. *Top. Curr. Chem.* **2005**, *244*, 115.

10.1021/jo800596m CCC: $40.75
Published on Web 06/11/2008

SCHEME 1. Palladium(II)-Catalyzed Oxidative Biaryl Synthesis

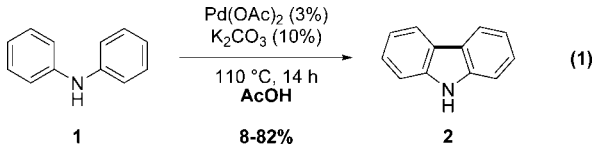


associated with extensive substrate and/or product decomposition reducing the yield and utility.[5i] With these limitations in mind, and with the desire to learn more about the challenges associated with palladium-catalyzed oxidative arene cross-coupling, we initiated studies aimed at elucidating competing and deleterious side reactions and at minimizing their occurrence.

Herein, we describe our findings in this area by defining several competing palladium-catalyzed oxidative reaction pathways as well as the development of new reaction conditions that minimize their formation. These conditions permit the use of otherwise problematic electron-rich substrates and have been applied to the synthesis of several naturally occurring carbazoles.[9,15] Importantly, these reactions employ an air atmosphere at ambient pressure as the terminal oxidant, obviating the need for stoichiometric metal oxidants as is frequently the case. In addition to explaining the low mass balance in challenging reactions, the isolation and structural characterization of oxidative byproducts also sheds light on new catalytic possibilities for palladium complexes and should serve as a source of inspiration in the development of other novel palladium-catalyzed transformations.

Results and Discussion

Initial investigations were performed with diphenylamine **1** and catalytic $Pd(OAc)_2$ in acetic acid at 110 °C under an air atmosphere. During early reaction development efforts, it was discovered that the addition of small amounts of potassium carbonate resulted in enhanced yields; consequently, its use was applied in these studies. Despite the widespread use of conditions very similar to these, they were found to provide inconsistent yields of the carbazole **2** ranging from 8% to 82% (eq 1).



(1)

Even more problematic were reactions with electron-rich diarylamines that are known to be challenging substrates for these transformations.[5i] When acetic acid was employed as the solvent with diarylamines **3**−**6**, complete consumption of the starting materials was observed, but with very low yields of the desired carbazole products **7**−**10** (Table 1, entries 1, 3, 5, and 7). To improve the yield of the desired carbazole products, a variety of solvents, solvent mixtures, catalyst precursors, and additives were evaluated. To maximize the ultimate efficiency and technical simplicity of the overall reaction, only conditions employing an air atmosphere at ambient pressure as the terminal oxidant were considered. From these studies, we were pleased to find that substituting the use of acetic acid with 2,2-dimethylpropionic acid (pivalic acid, PivOH) not only increases the reactivity but drastically improves the selectivity for the formation of the carbazole products. For example, when mono- and disubstituted electron-rich diphenylamines **3**−**6** are reacted in the presence of palladium acetate (3−5 mol %) and potassium carbonate (10 mol %) in pivalic acid (1 M), good isolated yields (up to 78%) are obtained for the preparation of carbazole products **7**−**10** (Table 1, entries 2, 4, 6, and 8). Previous work in our group has shown that pivalic acid can play an important role as a cocatalyst in Pd(0)-catalyzed benzene arylation.[11] Sigman and co-workers have also demonstrated the efficiency of the pivaloyl moiety for palladium-catalyzed aerobic oxidation of alcohols.[12] In both of these cases, the pivalate ligand is proposed to play a key role in a C−H bond cleaving event. While it is speculative, a similar effect may be operating here.

In contrast to many reactions performed in AcOH, very little secondary oxidative byproduct is detected in the crude reaction mixtures with PivOH; only the carbazole products and unreacted starting materials are observed by ^{1}H NMR analysis of the crude reaction mixtures (Figure 1). To elucidate the mechanism of this oxidative byproduct formation, major side products were isolated whenever possible. These efforts led to the discovery not only of known reactions accounting for lost mass balance, but also to the discovery of new reactivity as well.

Since byproduct formation may occur from both the starting material and the products, both were subjected to the reaction conditions to determine if unwanted processes might occur. It is important to note that several competing processes may be at play in each case, and that the isolated compounds likely comprise only one of the possible undesired outcomes. Informative results dealing with competitive diarylamine side reactions are illustrated in eqs 2−4 and Figure 1.

While submission of **11** to conditions employing acetic acid as the solvent leads to extensive decomposition, the use of pivalic acid results in the formation of the desired product in 91% yield (Scheme 2). Potentially problematic reactivity was revealed by the isolation of a major side product **12** involving the catalytic formation of a new carbon−oxygen bond (eq 2). Such a C−O bond-forming process may also occur with acetic acid as the solvent; however, the arylacetoxy products may be unstable under the reaction conditions, undergoing acetate deprotection. The resulting aryloxyphenylamines would be highly sensitive to further oxidative degradation and lead to complex mixtures and further loss of material. While palladium-catalyzed carbon−oxygen bond-forming reactions have been recently described at aromatic C−H bonds, all have required the use of stoichiometric iodine(III) oxidants.[13] The fact that this side process can occur with air as an oxidant is interesting from a reaction development perspective.

Another interesting side reaction is observed with diarylamine **4** (eq 3). Instead of undergoing the desired oxidative biaryl

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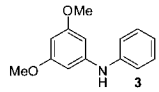
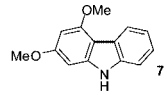
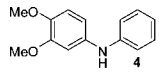
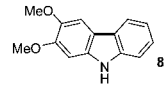
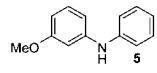
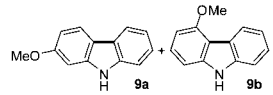
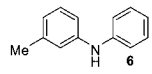
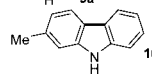
TABLE 1. Effect of Solvent on the Palladium(II)-Catalyzed Oxidative Ring Closure of Electron-Rich Diarylamines[a]

Entry	Starting Material	Product	Mol% Pd	Solvent	Yield (%)[b]
1			3	AcOH	9[c]
2			3	PivOH	58[c]
3			3	AcOH	trace[d]
4			3	PivOH	70[d]
5			5	AcOH	9, 2[e]
6			5	PivOH	72, 5[e]
7			3	AcOH	26[d]
8			3	PivOH	78[d]

[a] Conditions: Diarylamine (0.5 mmol), $Pd(OAc)_2$ (3−5 mol %), K_2CO_3 (10 mol %), solvent (0.5 mL), 110 °C, 14 h under air at ambient pressure; see the Supporting Information for details; [b] Isolated yield. [c] See also Figure 1 for crude ^1H NMR spectra. [d] Only one isomer detected by GC-MS and ^1H NMR. [e] Isolated yields of the major and the minor regioisomers, respectively.

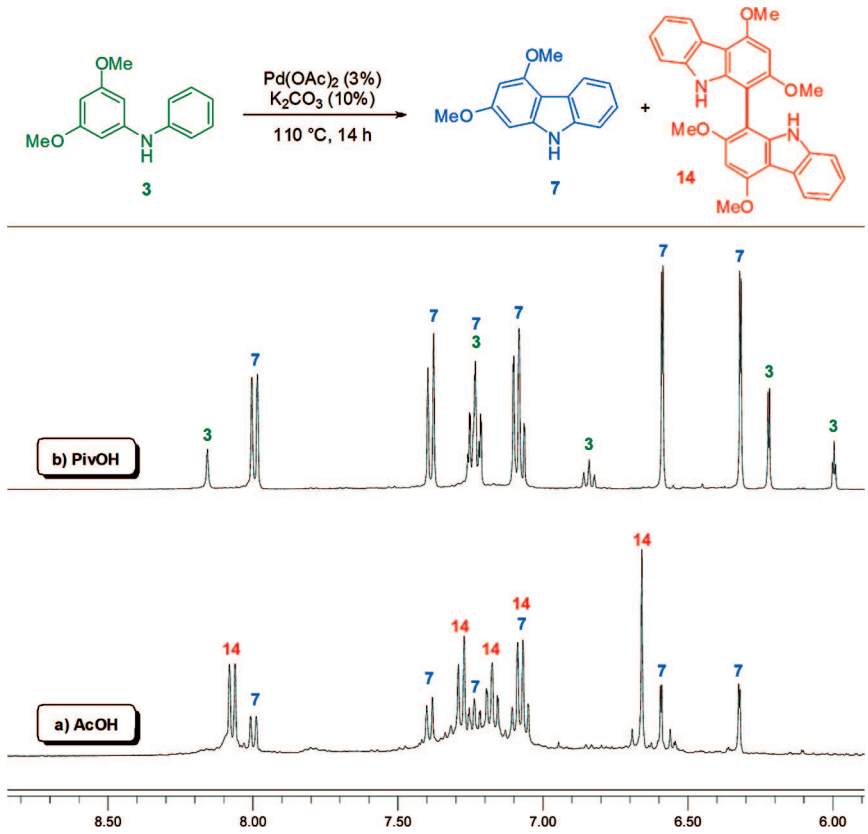
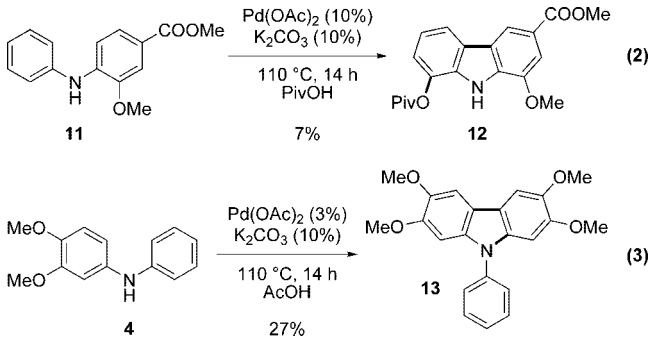


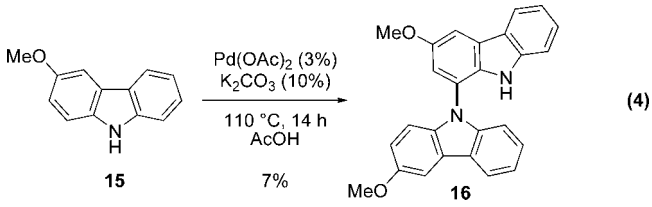
FIGURE 1. Crude ^1H NMR spectra (in DMSO-d_6) of the intramolecular coupling of diarylamine **3**: (a) reaction conducted in AcOH and (b) reaction conducted in PivOH.

coupling, as is observed in pivalic acid, carbazole **13** is formed in 27% yield when performed in acetic acid. This could arise from the fragmentation of a molecule of **4** and subsequent recombination with a second starting diarylamine **4**. While the mechanism has not yet been elucidated, the relatively high yield of this interesting process may warrant further attention and reaction development.

We have also found that the carbazole products may undergo further oxidative transformations under the reaction conditions, and that the presence of these secondary oxidation events is highly solvent dependent. For example, treatment of diarylamine **3** under the standard conditions with acetic acid provides a mixture of products and very low yield of **7** (Table 1, entry 1; Figure 1). We have determined that a major side reaction is the formation of dimer **14**, which could be isolated in 14% yield when the product carbazole **7** is subjected to the acetic acid reaction conditions. Dimer **14** is not observed in reactions employing pivalic acid. In fact, even when isolated carbazole **7** is placed under standard conditions in pivalic acid, no reaction is observed, underlining the low propensity for unwanted byproduct formation in this solvent.



Also noteworthy is the outcome with carbazole **15** that does not undergo further reaction when subjected to the standard reaction conditions in pivalic acid. In contrast, when reacted in acetic acid, 39% consumption of **15** is observed and product **16** arising from oxidative C−N bond formation is isolated in 7% yield (eq 4). Given the importance of nitrogen-containing compounds in medicinal chemistry, and the potential efficiency that an oxidative C−N bond-forming process could provide,[14] this reaction may also warrant further investigation.



To further evaluate the improved reactivity and yields that can be achieved with pivalic acid as the reaction solvent, a concise approach to the synthesis of three naturally occurring electron-rich tricyclic carbazoles was undertaken including Murrayafoline A (**17**), Clausenine (**18**) and Mukonine (**19**).[9,15,16] All three syntheses commenced with arene **20**, which was either reduced to the corresponding aniline **21** in near quantitative yield[17] or first oxidized to the benzoic acid **22**, esterified to **23**, and reduced to give aniline **24** in a three-step sequence.[18] These compounds were then subjected to Buchwald−Hartwig amination[19] to furnish the key diarylamines **11**, **25**, and **26**. The coupling of **21** with bromobenzene was found to best proceed when reacted in the presence of $Pd_2(dba)_3$, DavePhos (**27**),[20] and sodium *tert*-butoxide in dioxane at 80 °C,[21] giving diarylamine **25** in 96% yield. These same conditions were employed to couple **21** with 4-bromoanisole to provide **26** in 89% yield. On the other hand, the optimal conditions for the coupling of the more electron-deficient aniline **24** with bromobenzene required the use of the more sterically encumbered X-Phos ligand **28**[22] instead of DavePhos. Under these conditions, diarylamine **11** could be generated in 76% isolated yield. With the three diarylamine precursors **11**, **25**, and **26** in hand, we were pleased to find that the intramolecular Pd(II)-catalyzed oxidative coupling reaction under the standard conditions in pivalic acid provided the three target molecules **17**, **18**, and **19** in 50%, 79%, and 91% yields, respectively. In each case, when pivalic acid was substituted with acetic acid, significantly lower yields (12%, 8%, and 19%, respectively) and complex product mixtures were produced, again illustrating the benefits associated with the use of pivalic acid.

In addition to electron-rich diarylamines, the new reaction conditions are compatible with a wide range of other substrates, including those bearing electron-withdrawing groups (Table 2, entries 2−4 and 7). 2-Anilinonaphthoquinone (**35**) is also a good substrate for the reaction, providing **36** in 77% isolated yield (entry 5), as are diaryl ethers as exemplified by the formation of dibenzofurans **38** and **40** in good yields (entries 6 and 7).[23]

SCHEME 2. Synthesis of Naturally Occurring Carbazoles 17, 18, and 19

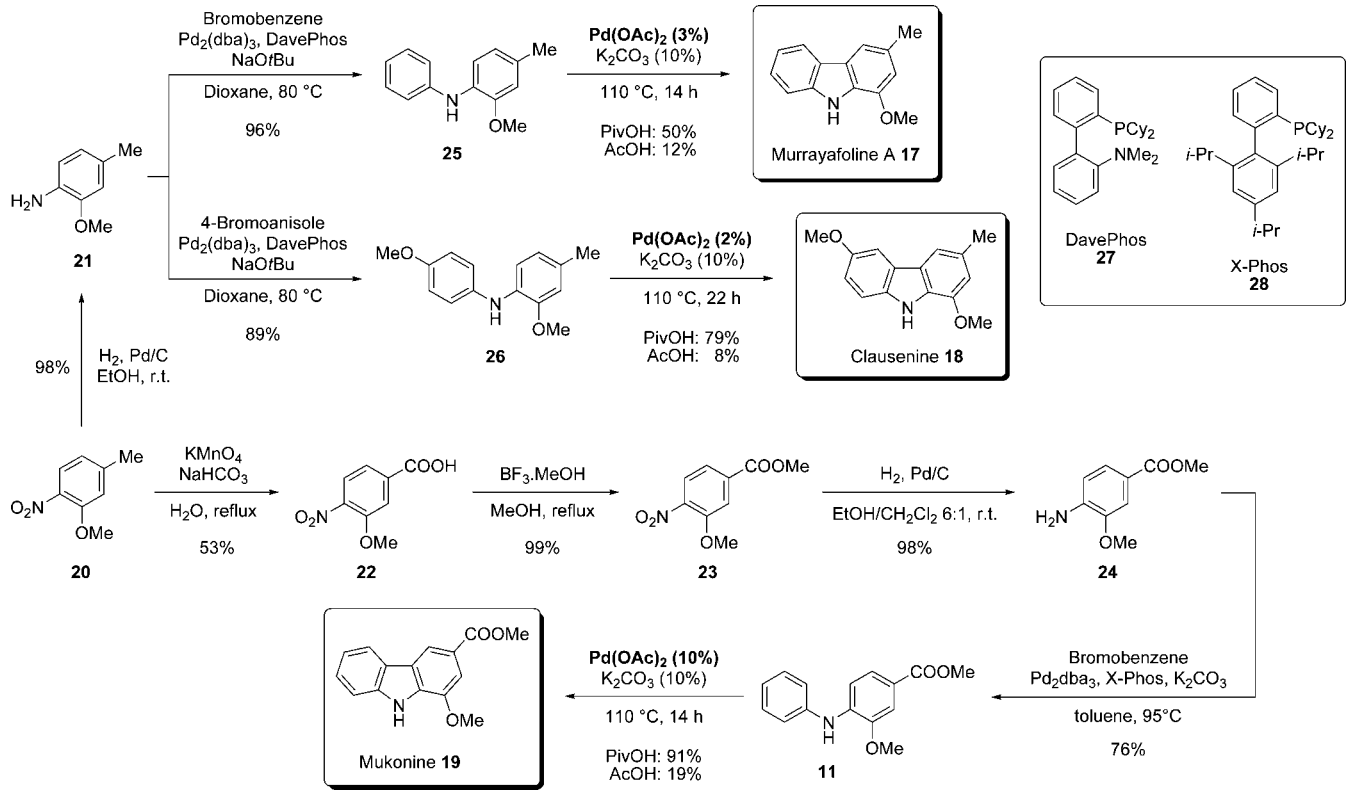
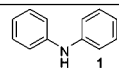
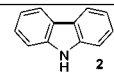
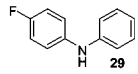
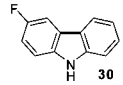
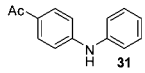
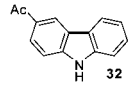
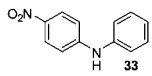
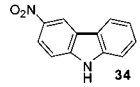
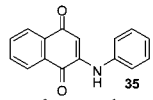
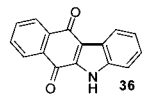
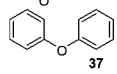
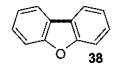
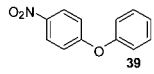
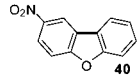
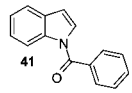
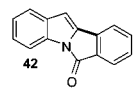
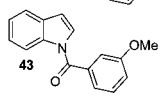
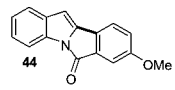


TABLE 2. Scope of the Palladium-Catalyzed Oxidative Ring Closure Reaction[a]

Entry	Starting Material	Product	Mol% Pd	T (°C)	Time (h)	Yield (%)[b]
1	 1	 2	3	110	14	95
2	 29	 30	3	110	14	76
3	 31	 32	3	110	14	74
4	 33	 34	5	110	14	76
5	 35	 36	10	120	14	77
6	 37	 38	5	120	42	75
7	 39	 40	5	120	48	78
8	 41	 42	5	120	24	72
9	 43	 44	5	110	14	73[c]

[a] Conditions: starting material (0.5 mmol), $Pd(OAc)_2$ (3−10 mol %), K_2CO_3 (10 mol %), PivOH (0.5 mL), air at ambient pressure; see the Supporting Information for details; [b] Isolated yield. [c] Only one isomer detected by GC-MS and ^1H NMR.

N-Benzoylindoles **41** and **43** are also good substrates, giving rise to the corresponding cyclized products **42** and **44** (entries 8 and 9). As noticed by DeBoef and co-workers,[4b] compound **43**, with a methoxy group on the benzoyl moiety, proved to be more reactive than compound **41**, which required a higher temperature and a longer reaction time (120 °C vs 110 °C, 24 h vs 14 h).

Conclusion

In summary, these studies should not only enable a broadening of the applicability of the palladium-catalyzed oxidative biaryl coupling in intramolecular processes, but also should cast light on the challenges associated with achieving more challenging intermolecular processes. Furthermore, the isolation and characterization of several oxidative byproducts not only begins to account for the poor mass balance associated with the use of challenging substrates, but also hints at new reaction development opportunities.

Experimental Section

General Procedure of the Intramolecular Pd(II)-Catalyzed Biaryl Coupling Reaction. Biaryl compound (0.5 mmol), $Pd(OAc)_2$ (2−10 mol %), K_2CO_3 (10 mol %), and pivalic acid (450 mg) are weighed to air and transferred into a test tube (1.2 × 10 cm^2). The uncapped test tube is placed in an oil bath and the mixture is stirred under air at the indicated temperature and time. The solution is then cooled to rt, diluted with CH_2Cl_2, washed with a saturated aqueous solution of Na_2CO_3, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product is purified by silica gel column chromatography to afford the corresponding coupling product.

3,5-Dimethoxydiphenylamine, 3. Synthesized according to a literature procedure.[21] Light brown solid; mp 72−73 °C; R_f 0.4 (petroleum ether/ethyl acetate 90/10); ^1H NMR (400 MHz, $CDCl_3$) δ 7.26 (dd, J = 8.5 and 7.3 Hz, 2H), 7.09 (dd, J = 8.5 and 1.1 Hz, 2H), 6.94 (t, J = 7.3 Hz, 1H), 6.23 (d, J = 2.1 Hz, 2H), 6.06 (t, J = 2.1 Hz, 1H), 5.72 (br s, NH), 3.74 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6, 145.2, 142.5, 129.3, 121.5, 118.8, 95.8, 93.0, 55.3; IR (ν_{max}) 3387, 2941, 2842, 1593, 1495, 1256, 1203, 1151, 1065, 815, 754, 687 cm^{-1}; HRMS calcd for $C_{14}H_{15}NO_2$ (M^+) 229.1103, found 229.1090.

3,4-Dimethoxydiphenylamine, 4. Synthesized according to a literature procedure.[21] Light brown solid; mp 102−103 °C; R_f 0.2 (petroleum ether/ethyl acetate 90/10); ^1H NMR (400 MHz, $CDCl_3$) δ 7.23 (dd, J = 8.5 and 7.4 Hz, 2H), 6.95 (d, J = 7.6 Hz, 2H), 6.85 (t, J = 7.3 Hz, 1H), 6.81 (d, J = 8.5 Hz, 1H), 6.72 (d, J = 2.4 Hz, 1H), 6.67 (dd, J = 8.4 and 2.1 Hz, 1H), 5.63 (br s, NH), 3.86 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6, 144.8, 144.7, 136.2, 129.3, 119.9, 116.1, 112.2, 112.2, 105.3, 56.3, 55.9; IR (ν_{max}) 3370, 2935, 2837, 1598, 1513, 1495, 1230, 1025, 691 cm^{-1}; HRMS calcd for $C_{14}H_{15}NO_2$ (M^+) 229.1103, found 229.1108.

3-Methyldiphenylamine, 6. Synthesized according to a literature procedure.[21] Black oil; R_f 0.5 (petroleum ether/ethyl acetate 90/10); ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (t, J = 7.4 Hz, 2H), 7.14 (t, J = 8.1 Hz, 1H), 7.04 (t, J = 8.5 Hz, 2H), 6.90 (td, J = 7.4 and 1.1 Hz, 1H), 6.88−6.85 (m, 2H), 6.74 (d, J = 7.4 Hz, 1H), 5.61 (br s, NH), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.2, 143.0, 139.2, 129.3, 129.1, 121.8, 120.8, 118.5, 117.8, 114.9, 21.5; IR (ν_{max}) 3393, 3036, 2919, 1590, 1495, 1316, 1166, 744, 690 cm^{-1}; HRMS calcd for $C_{13}H_{13}N$ (M^+) 183.1048, found 183.1035.

2,4-Dimethoxycarbazole, 7. Synthesized according to the general procedure. Light brown solid; mp 114−115 °C; R_f 0.3 (petroleum ether/ethyl acetate 80/20); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.13 (s, NH), 7.99 (d, J = 7.7 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.23 (ddd, J = 8.1, 7.1, and 1.1 Hz, 1H), 7.08 (ddd, J = 7.8 , 7.1, and 0.6 Hz, 1H), 6.59 (d, J = 1.8 Hz, 1H), 6.32 (d, J = 1.8 Hz, 1H), 3.97 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.6, 155.9, 141.6, 138.7, 123.1, 121.9, 120.9, 118.5, 110.0, 105.4, 90.4, 86.9, 55.3, 55.3; IR (ν_{max}) 3407, 2940, 2840, 1632, 1610, 1457, 1323, 1209, 1150, 1123, 750, 727 cm^{-1}; HRMS calcd for $C_{14}H_{13}NO_2$ (M^+) 227.0946, found 227.0939.

2,3-Dimethoxycarbazole, 8. Synthesized according to the general procedure. Mauve solid; mp 184−186 °C; R_f 0.15 (petroleum ether/ethyl acetate 80/20); ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.94 (s, NH), 7.98 (d, J = 7.6 Hz, 1H), 7.65 (s, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.25 (t, J = 7.4 Hz, 1H), 7.07 (d, J = 7.4 Hz, 1H), 7.02 (s, H), 3.85 (s, 3H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 149.0, 143.6, 139.4, 134.5, 123.5, 122.8, 119.1, 117.9, 114.2, 110.5, 103.3, 94.5, 56.1, 55.5; IR (ν_{max}) 3396, 3022, 1497, 1455, 1312, 1204, 1148, 1027, 747 cm^{-1}; HRMS calcd for $C_{17}H_{13}NO_2$ (M^+) 227.0946, found 227.0924.

Methyl 1-Methoxy-8-(pivaloyloxy)carbazole-3-carboxylate, 12. Synthesized according to the general procedure. Colorless oil; R_f 0.4 (petroleum ether/ethyl acetate 80/20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (dd, J = 1.2 and 0.6 Hz, 1H), 8.23 (br s, 1H), 7.95 (ddd, J = 7.3, 1.3, and 0.6 Hz, 1H), 7.61 (d, J = 1.2 Hz, 1H), 7.28−7.21 (m, 2H), 4.07 (s, 3H), 3.98 (s, 3H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 167.9, 145.4, 136.6, 133.1, 131.9, 126.7, 124.0, 122.7, 120.7, 118.6, 118.3, 116.4, 107.3, 55.9, 52.2, 39.7, 27.5; IR (ν_{max}) 3325, 2962, 2932, 1749, 1709, 1346, 1242, 1215, 1118, 758 cm^{-1}; HRMS calcd for $C_{20}H_{21}NO_5$ (M^+) 355.1420, found 355.1416.

2,2′,4,4′-Tetramethoxy-1,1′-bicarbazole, 14. Synthesized according to the general procedure. Mauve solid; mp 206−209 °C; R_f 0.2 (petroleum ether/ethyl acetate 80/20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (dd, J = 7.7 and 0.5 Hz, 2H), 7.71 (br s, 2H), 7.29−7.25 (m, 2H), 7.22−7.18 (m, 4H), 6.56 (s, 2H), 4.16 (s, 6H), 3.84 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.2, 156.3, 141.0, 138.9, 123.9, 123.2, 122.2, 119.6, 109.8, 107.2, 97.9, 88.8, 57.1, 55.6; IR (ν_{max}) 3422, 2937, 2835, 1608, 1452, 1322, 1197, 1127, 982, 745 cm^{-1}; HRMS calcd for $C_{28}H_{24}N_2O_4$ (M^+) 452.1736, found 452.1755.

3-Methoxycarbazole, 15. Synthesized according to the general procedure. Light brown solid; mp 152−153 °C; R_f 0.2 (petroleum ether/ethyl acetate 90/10); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.03 (s, NH), 8.09 (d, J = 7.8 Hz, 1H), 7.67 (d, J = 2.5 Hz, 1H), 7.44 (br d, J = 8.1 Hz, 1H), 7.39 (br d, J = 8.7 Hz, 1H), 7.34 (ddd, J = 8.2, 7.0, and 1.1 Hz, 1H), 7.11 (ddd, J = 7.9, 7.0, and 1.0 Hz, 1H), 7.02 (dd, J = 8.7 and 2.5 Hz, 1H), 3.84 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 152.8, 140.2, 134.4, 125.2, 122.6, 122.3, 120.1, 117.8, 114.6, 111.5, 110.8, 102.8, 55.5; IR (ν_{max}) 3404, 1460, 1170, 1132, 817, 748 cm^{-1}; HRMS calcd for $C_{13}H_{11}NO$ (M^+) 197.0841, found 197.0834.

3,3′-Dimethoxy-1,9′-bicarbazole, 16. Synthesized according to the general procedure. Brown oil; R_f 0.45 (petroleum ether/ethyl acetate 80/20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 7.4 Hz, 1H), 8.11 (d, J = 7.8 Hz, 1H), 7.70 (d, J = 2.3 Hz, 1H), 7.68 (d, J = 2.4 Hz, 1H), 7.61 (br s, 1H), 7.41−7.37 (m, 2H), 7.30 (ddd, J = 8.0 , 7.0, and 1.0 Hz, 1H), 7.28−7.22 (m, 4H), 7.16 (d, J = 8.8 Hz, 1H), 7.03 (dd, J = 8.8 and 2.5 Hz, 1H), 3.98 (s, 3H), 3.96 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 154.2, 141.0, 140.0, 135.5, 130.8, 126.5, 126.2, 125.8, 124.0, 123.4, 123.3, 121.2, 120.5, 120.4, 119.8, 119.5, 115.1, 113.3, 111.1, 110.9, 110.2, 103.5, 103.5, 56.3, 56.2; IR (ν_{max}) 3406, 3323, 3005, 2933, 2854, 1594, 1490, 1461, 1432, 1321, 1286, 1203, 1035, 745 cm^{-1}; HRMS calcd for $C_{26}H_{20}N_2O_2$ (M^+) 392.1525, found 392.1549.

3-Fluorocarbazole, 30. Synthesized according to the general procedure. Light brown solid; mp 209−211 °C; R_f 0.45 (petroleum ether/ethyl acetate 80/20); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.30 (s, NH), 8.13 (d, J = 7.8 Hz, 1H), 7.95 (dd, J = 9.4 and 2.6 Hz, 1H), 7.51−7.47 (m, 2H), 7.41 (ddd, J = 8.2, 7.0, and 1.2 Hz, 1H), 7.23 (td, J = 9.2 and 2.4 Hz, 1H), 7.15 (dd, J = 7.9, 7.0, and 1.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.3 (d, $^1J_{CF}$ = 232 Hz), 140.7, 136.1, 126.0, 122.7 (d, $^3J_{CF}$ = 10 Hz), 122.0 (d, $^4J_{CF}$ = 4 Hz), 120.5, 118.3, 113.0 (d, $^2J_{CF}$ = 25 Hz), 111.6, (d, $^3J_{CF}$ = 9 Hz), 111.1, 105.6 (d, $^2J_{CF}$ = 24 Hz); IR (ν_{max}) 3420, 1585, 1456, 1167, 865, 807, 746, 724, 598, 570 cm^{-1}; HRMS calcd for $C_{12}H_8NF$ (M^+) 185.0641, found 185.0648.

3-Acetylcarbazole, 32. Synthesized according to the general procedure. Light brown solid; mp 165−167 °C; R_f 0.45 (petroleum ether/ethyl acetate 70/30); ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.71 (s, NH), 8.85 (d, J = 1.6 Hz, 1H), 8.27 (d, J = 7.8 Hz, 1H), 8.04 (dd, J = 8.6 and 1.7 Hz, 1H), 7.56 (br d, J = 8.6 Hz, 2H), 7.46 (ddd, J = 8.2, 7.1, and 1.1 Hz, 1H), 7.25 (ddd, J = 7.9, 7.0, and 0.9 Hz, 1H), 2.58 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 196.9, 142.5, 140.3, 128.2, 126.2, 125.8, 122.6, 122.0, 122.0, 120.5, 119.4, 111.3, 110.6, 26.5; IR (ν_{max}) 3405, 3283, 1658, 1601, 1331, 1247, 737 cm^{-1}; HRMS calcd for $C_{14}H_{11}NO$ (M^+) 209.0841, found 209.0870.

3-Nitrocarbazole, 34. Synthesized according to the general procedure. Dark yellow solid; mp 212−213 °C; R_f 0.2 (petroleum ether/ethyl acetate 80/20); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.08 (s, NH), 9.17 (d, J = 2.2 Hz, 1H), 8.38 (br d, J = 7.8 Hz, 1H), 8.31 (dd, J = 9.0 and 2.3 Hz, 1H), 7.65 (d, J = 9.1 Hz, 1H), 7.61 (d, J = 8.1 Hz, 1H), 7.53 (ddd, J = 8.2, 7.1, and 1.1 Hz, 1H), 7.30 (ddd, J = 8.0, 7.0, and 1.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 143.2, 140.9, 139.7, 127.2, 122.4, 122.1, 121.2, 121.1, 120.2, 117.3, 111.8, 111.0; IR (ν_{max}) 3414, 3332, 3236, 3067, 1643, 1459, 1311, 1084, 814, 751, 724 cm^{-1}; HRMS calcd for $C_{12}H_8N_2O_2$ (M^+) 212.0586, found 212.0605.

2-Anilinonaphthoquinone, 35. To a solution of naphthaquinone (10 mmol, 1.58 g) in H_2O/AcOH 1:1 (10 mL) at 0 °C is added aniline (10 mmol, 0.91 mL) dropwise. The mixture is stirred under reflux over 3 h, cooled, and allowed to reach pH ∼ 7 by adding saturated aqueous solution of Na_2CO_3. CH_2Cl_2 is then added and the organic phase is dried over $MgSO_4$, filtered on silica, and evaporated under reduced pressure. The residue is washed with diethyl ether and dried under vacuum to afford 198 mg of **35** as a dark red solid in 32% yield. Mp 198−199 °C; R_f 0.35 (CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13−8.10 (m, 2H), 7.76 (td, J = 7.6 and 1.2 Hz, 1H), 7.66 (td, J = 7.6 and 1.2 Hz, 1H), 7.58 (br s, NH), 7.42 (t, J = 7.9 Hz, 2H), 7.28 (d, J = 7.7 Hz, 2H), 7.22 (t, J = 7.4 Hz, 1H), 6.42 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.9, 182.0, 144.7, 137.4, 134.9, 133.2, 132.3, 130.4, 129.7, 126.5, 126.2, 125.6, 122.6, 103.4; IR (ν_{max}) 3317, 1667, 1638, 1608, 1595, 1571, 1527, 1447, 1294, 775, 723 cm^{-1}; HRMS calcd for $C_{16}H_{11}NO_2$ (M^+) 249.0790, found 249.0800.

Benzo[*b*]carbazole-6,11-dione, 36. Synthesized according to the general procedure. Bright orange solid, mp 312−314 °C; R_f 0.3 (CH_2Cl_2); ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.08 (s, NH), 8.21 (d, J = 7.9 Hz, 1H), 8.13−8.09 (m, 2H), 7.86 (td, J = 7.4 and 1.6 Hz, 1H), 7.81 (td, J = 7.4 and 1.6 Hz, 1H), 7.6 (d, J = 8.3 Hz, 1H), 7.45 (ddd, J = 8.3, 7.0, and 1.2 Hz, 1H), 7.37 (ddd, J = 8.0, 7.0, and 1.0 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 180.3, 177.5, 138.1, 137.1, 134.1, 134.0, 133.1, 132.5, 126.9, 126.0, 125.9, 123.9, 123.8, 122.3, 117.3, 113.8; IR (ν_{max}) 3255, 2920, 2852, 1643, 1008, 753, 708, 659 cm^{-1}; HRMS calcd for $C_{16}H_9NO_2$ (M^+) 247.0633, found 247.0619.

2-Nitrodibenzofuran, 40. Synthesized according to the general procedure. Light brown solid; mp 151−152 °C; R_f 0.3 (petroleum ether/diethyl ether 98/2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (dd, J = 2.4 and 0.4 Hz, 1H), 8.40 (dd, J = 9.0 and 2.4 Hz, 1H), 8.04 (ddd, J = 7.7, 1.3, and 0.7 Hz, 1H), 7.66 (dd, J = 9.0 and 0.5 Hz, 1H), 7.65 (ddd, J = 8.3, 1.0, and 0.7 Hz, 1H), 7.58 (ddd, J = 8.5, 7.1, and 1.3 Hz, 1H), 7.45 (ddd, J = 7.7, 7.2, and 1.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 157.5, 128.9, 125.0, 123.9, 123.1,

123.0, 121.3, 117.1, 112.3, 112.0; IR (ν_{max}) 2916, 2847, 1525, 1339, 1182, 745 cm^{-1}; HRMS calcd for $C_{12}H_7NO_3$ (M^+) 213.0426, found 213.0434.

***N*-Benzoylindole, 41.** Indole (16.9 mmol, 1.98 g) and DMAP (2.3 mmol, 279 mg) are weighed to air and transferred to a round-bottomed flask. The flask is then capped with a rubber septum and purged with argon, then CH_2Cl_2 (36 mL) is added. The solution is cooled to 0 °C, and triethylamine (25.6 mmol, 3.6 mL) and benzoyl chloride (17 mmol, 2.0 mL) are successively added dropwise. The solution is then stirred at room temperature overnight, diluted with CH_2Cl_2, washed with a saturated aqueous solution of Na_2CO_3, dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product is purified by silica gel column chromatography with petroleum ether/Et_2O to afford 2.72 g of **41** as a light pink solid in 73% yield, which exhibited identical spectral data to that previously reported.[24] R_f 0.5 (petroleum ether/ethyl acetate 90/10); ^1H NMR (400 MHz, $CDCl_3$) δ 8.41 (d, J = 8.3 Hz, 1H), 7.74−7.72 (m, 2H), 7.62−7.57 (m, 2H), 7.52 (t, J = 7.4 Hz, 2H), 7.38 (m, 1H), 7.33−7.28 (m, 2H), 6.61 (dd, J = 3.8 and 0.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 136.0, 134.6, 131.9, 130.8, 129.1, 128.6, 127.6, 124.9, 123.9, 120.9, 116.4, 108.5.

***N*-(3-Methoxybenzoyl)indole, 43.** NaH (60%, 15 mmol, 600 mg) is weighed to air and transferred to a round-bottomed flask. The flask is then capped with a rubber septum and purged with argon, then DMF (20 mL) is added. The solution is cooled to 0 °C, and indole (10 mmol, 1.17 g) is added portionwise. After 15 min at 0 °C, 3-methoxybenzoyl chloride (12 mmol, 1.6 mL) is added dropwise. The solution is then stirred at room temperature overnight, quenched carefully by addition of water, diluted with CH_2Cl_2, washed with H_2O (3 times), dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The crude product is purified by silica gel column chromatography with petroleum ether/AcOEt, and by Kugelrohr distillation, to afford 1.99 g of **43** as a light pink oil in 79% yield, which exhibited identical spectral data to that previously reported.[4b] R_f 0.2 (petroleum ether/ethyl acetate 95/5); ^1H NMR (400 MHz, $CDCl_3$) δ 8.40 (dd, J = 8.3 and 0.8 Hz, 1H), 7.60 (d, J = 7.5 Hz, 1H), 7.44−7.36 (m, 2H), 7.33−7.26 (m, 4H), 7.13 (ddd, J = 8.3, 2.6, and 1.0 Hz, 1H), 6.60 (dd, J = 3.8 and 0.6 Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.5, 159.6, 136.0, 135.8, 130.8, 129.6, 127.6, 124.9, 124.0, 121.4, 120.9, 118.0, 116.4, 114.1, 108.6, 55.5.

Acknowledgment. We thank NSERC, CFI, OIT, the University of Ottawa, the Research Corporation, Merck Frosst Canada, Boehringer Ingelheim (Laval), and AstraZeneca for financial support of this work.

Supporting Information Available: Copies of NMR spectra for intramolecular coupling products and all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO800596M

(15) For Clausenine, see: Chakraborty, A.; Chowdhury, B. K.; Bhattacharyya, P. *Phytochemistry* **1995**, *40*, 295. See also ref 5j.

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