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Copper-Mediated Cyclization−Halogenation and Cyclization−Cyanation Reactions of β-Hydroxyalkynes and *o*-Alkynylphenols and Anilines

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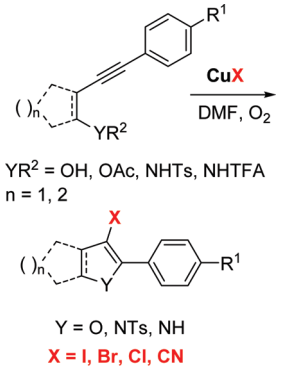

The CuX (X = I, Br, Cl, CN)-mediated cyclization−halogenation and cyclization−cyanation reactions of β-hydroxyalkynes and *o*-alkynylphenol and -aniline derivatives give rise to 3-halo- and 3-cyanofuro-[3,2-*b*]pyrroles, 3-iodo-, 3-bromo-, and 3-cyanobenzofurans, and 3-cyanoindoles, respectively.

Introduction

The benzofuran and indole ring structures are common to many bioactive and natural product molecules, and therefore efficient methods for the synthesis of substituted derivatives are highly desirable.[1,2] The less common furo[3,2-*b*]pyrrole heterocyclic system is a key structural feature of the bioactive fungal metabolite lucilactaene and related alkaloids.[3] We recently reported an efficient synthesis of this latter heterocyclic class of compounds, for example, **2** (R = H, Ph, Scheme 1), via metal-catalyzed cycloisomerization of 4,5-*cis*-hydroxyalkynylpyrrolidin-2-ones **1** using Ag^+, Au^+, or Pd^{2+}/Cu^+ as catalyst.[4] Related cycloisomerization reactions have been developed to prepare benzofurans and indoles.[5] This type of transformation would be made more valuable if the initially formed cyclized organometallic intermediate **A** could be utilized to introduce further useful functional groups into the cyclized products and provide, for example, 3-functionalized furo[3,2-*b*]pyrroles, like **3** (Scheme 1). Such useful functional groups could include halogen and cyano that have well-documented utility in organic synthesis for the formation of new C−Y bonds (Y = C, N, S and O) and the preparation of other key functional groups (e.g., keto, formyl, CH_2NH_2, and CH_2OH groups), respectively.[6]

The organometallic intermediates formed in the cycloisomerization reactions of related *o*-alkynylphenols and anilines have been shown to undergo further metal-mediated

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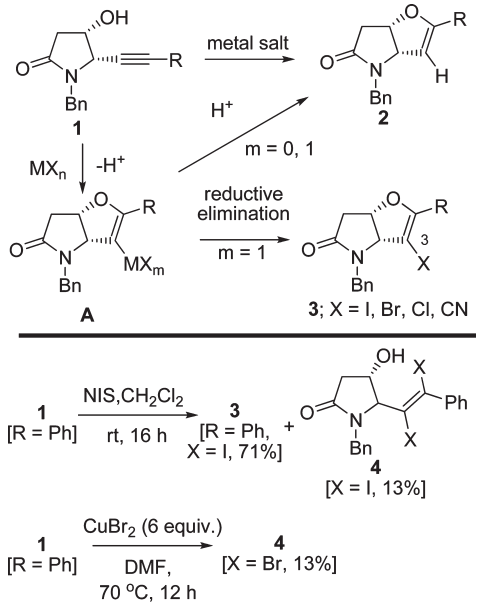
SCHEME 1. Synthesis of Furo[3,2-*b*]pyrroles 2 and 3



reactions with alkenes or CO/MeOH, or reductive elimination when the cyclization catalyst is RPd(II), to provide 3-substituted benzofurans and indoles through subsequent C−C bond-forming reactions.[5] Further, methods that involve migration of the initial *O*- or *N*-substituent of the phenol and aniline precursors, respectively, to the C-3 position during the cyclization process have also been reported.[7] Metal-catalyzed procedures for the direct cyclization−cyanation reaction of these and related substrates, however, have not been reported.[8]

While the synthesis of 2-substituted 3-iodobenzofurans and indoles has been achieved from the cyclization reactions of *o*-alkynylphenols[9] (or their *O*-protected derivatives)[10] and anilines[11] with electrophilic iodine reagents, the synthesis of the valuable nitrile products in a direct process requires a different synthetic strategy. Further, these iodonium ion induced cyclization reactions are sometimes complicated due to competing 1,2-addition reactions to the triple bond of the starting substrates.[11b] Indeed, treatment of **1** (R = Ph) with $I_2/NaHCO_3/CH_2Cl_2$ gave a complex mixture of products while the reaction of **1** (R = Ph) with NIS/CH_2Cl_2 resulted in an 81:19 mixture of **3** (R = Ph, X = I, 71% isolated yield) and the 1,2-diiodo addition product **4** (X = I, 13% isolated yield), Scheme 1.

In principle, compounds **3** could be prepared from reductive elimination of the cyclization intermediate **A** (X = halogen or CN) (Scheme 1). In fact, Ma has demonstrated that $CuCl_2$ and $CuBr_2$ are effective reagents for the halolactonization of 2,3-allenoic acids.[12] Presumably, these reactions occur via a reductive elimination pathway of a RCu(II)X (X = Cl or Br) intermediate. This type of reaction has been further developed employing Pd/Cu catalysis, using PdX_2 (5 mol %) and CuX_2 (3 equiv) [X = Cl, Br or I], for the cyclization-halogenation reactions of *o*-alkynylphenols and *N*-acetyl-*o*-alkynylanilines to give 3-halo-2-substituted benzofurans and indoles, respectively.[13] These reactions, however, often gave mixtures of 3-unsubstituted-2-substituted benzofurans and indoles (cycloisomerization products) and 3-halo-2-substituted benzofurans and indoles (cyclization−halogenation products). We report here a novel and direct method for the synthesis of 3-halo- and 3-cyanofuro[3,2-*b*]pyrroles, 3-iodo, 3-bromo-, and 3-cyanobenzofurans, and 3-cyanoindoles from the CuX (X = I, Br, Cl, CN)-promoted sequential cyclization−reductive elimination reactions of the *cis*-4-hydroxy-5-phenylethynylpyrrolidinones **1** (R = Ph, *n*-Pent) and *O*- and *N*-protected *o*-alkynylphenols and -anilines, respectively.

Results and Discussion

Under the Ma conditions,[12] the reaction of **1** (R = Ph) with $CuBr_2$ (2 equiv) in acetone/water at 70 °C resulted in only recovered **1**, while the same reaction with 6 equiv of $CuBr_2$ in DMF with heating at 70 °C for 12 h gave the 1,2-dibromo derivative **4** (X = Br) in 67% yield (Scheme 1). When **1** (R = Ph) was treated with CuI (1.5 equiv) in DMF at rt, no reaction occurred; however, when the mixture was heated at 80 °C under a nitrogen atmosphere for 16 h, a 68:32 mixture of **3** and **2** (R = Ph) was obtained from which **3** (R = Ph, X = I) could be isolated after column chromatography in 46% yield (Table 1, entry 1). We assumed that intermediate **A** (M = Cu(I), *m* = 0) was formed initially and underwent oxidation by a redox reaction with CuI to the corresponding Cu(II), or possibly Cu(III),[14] intermediate **A** (M = Cu(II), *m* = 1), which then gave the desired product **3** (R = Ph). Consistent with this hypothesis was the fact that increasing the amount of CuI to 3 and 6 equiv gave higher ratios of **3**:**2**, the latter modification giving only **3** (R = Ph, X = I) in 71% isolated yield (Table 1, entries 2 and 3, respectively). The addition of base (Et_3N) resulted in formation of only the cyclized product **2** (R = Ph). The amount of CuI could be reduced to 1.1 equiv if the reaction was performed under an oxygen atmosphere (balloon) providing iodide **3** (R = Ph, X = I) in 85% yield (Table 1, entry 4). The reactions under an oxygen atmosphere required heating at 100 °C to ensure complete conversion in 16 h. Similar results were obtained using **1** (R = Ph) and 1.1 equiv of CuBr or CuCl under an oxygen atmosphere (Table 1, entries 5 and 6) providing the corresponding 3-bromo- and 3-chloro-cyclized products. The cyano derivative **3** (R = Ph, X = CN) was obtained in 76% yield when the amount of CuCN was increased

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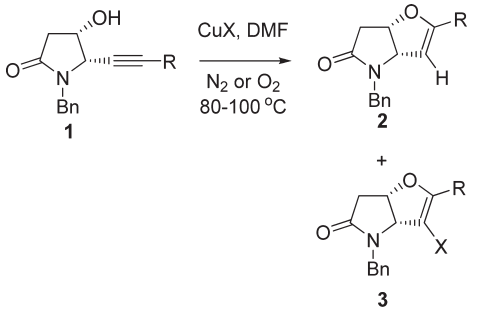
TABLE 1. Synthesis of Furo[3,2-*b*]pyrroles 3[a,b]



entry	**1** (R)	CuX (equiv)	atm	ratio **2**:**3**	yield (%) of **3**
1	Ph	CuI (1.5)	N_2	32:68	46
2	Ph	CuI (3.0)	N_2	25:75	50
3	Ph	CuI (6.0)	N_2	0:100	71
4	Ph	CuI (1.1)	O_2	0:100	85
5	Ph	CuBr (1.1)	O_2	0:100	87
6	Ph	CuCl (1.1)	O_2	0:100	77[c]
7	Ph	CuCN (2.2)[d]	O_2	7:93	76
8	*n*-Pent	CuI (1.1)	O_2	0:100	72
9	*n*-Pent	CuCN (2.2)	O_2	0:100	79

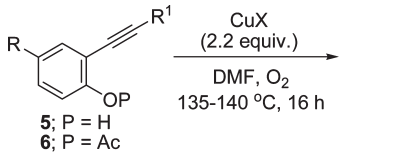
[a]Reactions under N_2 were performed in DMF at 80 °C for 16 h. [b]Reactions under O_2 were performed in DMF at 100 °C for 16 h. [c]This product was obtained in approximately 90% purity. [d]When 1.1 equiv was used the ratio of **2**:**3** was 28:72 and the yield of **3** was 50%.

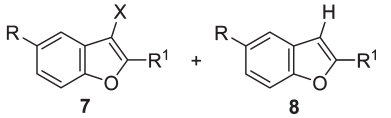
to 2.2 equiv (Table 1, entry 7). Quenching of the CuCl reaction mixture with water after 2 h at 80 °C afforded only the product **2** (R = Ph). This result suggested that cyclization of **1** (R = Ph) to a Cu(I) intermediate **A** (M = Cu(I), m = 0) was relatively fast and that its further oxidation by O_2 to **A** (M = Cu(II), m = 1) and/or reductive elimination to give **3** was a much slower process. The nonaromatic substrate **1** (R = n-Pent) reacted with CuI and CuCN to provide the iodinated and cyanated derivatives **3** (R = *n*-Pent, X = I or CN) in respective yields of 72% and 79% (Table 1, entries 8 and 9).

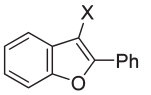
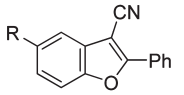
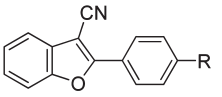
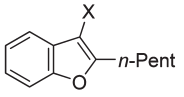
In order to further examine the scope of these CuX-mediated reactions, the related *o*-alkynylphenols and -anilines were examined as substrates. The *o*-alkynylphenol **5** (R = H, R^1 = Ph) underwent similar CuI- and CuCN-mediated reactions to provide mixtures of **7a** or **7c** and the cycloisomerization product **8** (R = H, R^1 = Ph). Often, the products **7** and **8** were difficult to separate. For example, treatment of **5** (R = H, R^1 = Ph) with CuI (1.1 equiv) under an oxygen atmosphere as described above gave an inseparable 86:14 mixture of **7a** and the benzofuran **8** (R = H, R^1 = Ph) in a combined yield of 82%. The starting *o*-alkynylphenol **5** (R = H, R^1 = Ph) was, as previously noted,[10a] an unstable substrate and underwent cyclization to benzofuran **8** (R = H, R^1 = Ph) on storage and had to be prepared or purified fresh before each reaction.

Because of these difficulties, attention was focused on the more stable *O*-acetyl derivatives **6**. These substrates required higher reaction temperatures (135−140 °C) than **5** in their reactions with CuX but provided much higher ratios of **7**:**8** (usually **7**:**8** = 100:0, see Table 2, footnote a) and allowed for the isolation of pure products **7** (Table 2). We found that 2.2 equiv of CuX was required in these cases to ensure good conversions to **7** in 16 h. The parent compound **6** (R = H, R^1 = Ph) gave the desired 3-substituted benzofurans **7a**−**c** exclusively and in good yields (Table 2, entries 1−3), while its reaction with CuCl gave a complex mixtures of

TABLE 2. Synthesis of 3-Substituted Benzofurans 7[a]





Entry		Entry	
			
1	**7a**; X = I, 70%,	6[b]	**7f**; R = OMe, 0%
2	**7b**; X = Br, 62%	7[c]	**7g**; CN, 80%
3	**7c**; X = CN, 78%		
			
4	**7d**; R = OMe, 67%	8	**7h**; X = I, 76%
5	**7e**; R = F, 74%	9	**7i**; X = CN, 69%

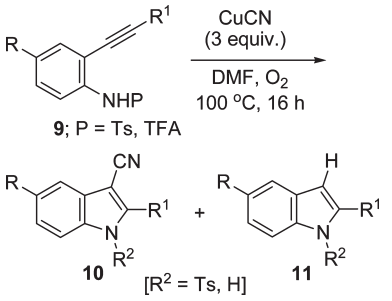
[a]Reactions were performed under O_2 in DMF at 135−140 °C for 16 h. The ratio of **7**:**8** was 100:0, except entry 4 (93:7) and entry 9 (92:8). [b]A complex mixture of products was obtained that included **7f**, which could not be obtained pure. [c]Reaction performed at 100 °C for 16 h.

products. The reactions of substrates **6** having electron-withdrawing (Table 2, entries 5 and 7) and electron-donating (Table 2, entry 4) substituents work equally well in their reactions with CuCN as did the parent compound **6** (R = H, R^1 = Ph). The methoxy derivative **6** (R = OMe, R^1 = Ph), however, produced a complex mixture of products. The 1-alkylalkynyl substrate **6** (R = H, R^1 = *n*-Pent) also reacted efficiently with CuI and CuCN to give the respective benzofuran products **7h** and **7i** in 76% and 69% yields, respectively (Table 2, entries 8 and 9).

An attempt to perform the cyclization−iodination reaction on **6** (R = H, R^1 = Ph) using CuI in a catalytic amount (0.1 equiv) in the presence of LiI (3 equiv) and TMEDA (1 equiv) under an oxygen atmosphere gave an inseparable 49:51 mixture of **7a** and **8** (R = H, R^1 = Ph) in a combined yield of 73%.

The N-Ts and N-TFA *o*-alkynylanilines **9** (R = H, R^1 = Ph) underwent CuCN-mediated cyclization−cyanation reactions upon heating at 100 °C for 16 h to provide the 3-cyano, N-Ts, and N-unsubstituted indoles **10a** and **10b** in yields of 74% and 80%, respectively (Table 3, entries 1 and 2) when 3.0 equiv.of CuCN was used. The aforementioned reaction also produced a small amount (3%) of the less substituted indole **11** (R = H, R^1 = Ph, R^2 = Ts), while the reaction of the latter substrate resulted in clean formation of the N-unprotected indole product **10b** with efficient loss of the N-TFA group. Attempts to cyclize the N-unprotected compound **9** (P = H, R = H, R^1 = Ph) resulted in a complex mixture of products, while the reaction of its N-Cbz analogue **9** (P = Cbz, R = H, R^1 = Ph) returned only unreacted starting material. These results may suggest that only the

TABLE 3. Synthesis of 3-Cyanoindoles 10[a]



Entry		Entry	
1[b]	**10a**; R = Ts, 74%,	5[c]	**10e**; R = OMe, R^1 = H, 78%
2	**10b**; R = H, 80%	6[d]	**10f**; R = CN, R^1 = Ts, 22%
		7	**10g**; R = CN, R = H, 60%
3	**10c**; R = OMe, 77%	8	**10h**; R = H, 73%
4	**10d**; R = F, 65%	9[e]	**10i**; R = Ts, 55%

[a]Reactions were performed under O_2 in DMF at 100 °C for 16 h. The ratio of **7**:**8** was 100:0, except entry 1 (98:2), entry 6 (30:70), and entry 9 (70:30). [b]Compound **11** was also isolated in 3% yield. [c]At 130 °C for 16 h. [d]Compound **11** was also isolated in 38% yield. [e]Compound **11** was also isolated in 24% yield.

softer amine nucleophiles (NHTFA and NHTS compared to NH_2) were suitable for cyclization with the relatively soft electrophilic Cu−alkyne complex intermediate.[15] In contrast, the reactions of **9** (P = Ts R = H, R^1 = Ph) with CuX (X = I, Br, Cl) were unsuccessful and resulted in the return of unreacted starting material. The reactions of substrates **9** having electron-withdrawing (Table 3, entries 4, 6, and 7) and electron-donating (Table 2, entry 3) substituents work equally well as **9** (P = Ts or TFA, R = H, R^1 = Ph) with CuCN. The methoxy-substituted substrate **9** (P = TFA, R = OMe, R^1 = Ph), however, required heating at 130 °C to obtain 100% consumption of **9** in 16 h, resulting in a 78% isolated yield of indole **10e** (Table 3, entry 5). The N-TFA protected, 1-alkylalkynyl substrate **9** (P = TFA, R = H, R^1 = *n*-Pent) reacted efficiently with CuCN to give the 3-cyanated indole product **10i** in 73% yield (Table 3, entry 8), while its N-Ts analogue **9** (P = Ts R = H, R^1 = *n*-Pent) gave a mixture of **10i** (55% isolated yield) and **11** (R = Ts R = H, R^1 = *n*-Pent, 24% isolated yield) (Table 3, entry 9).

Conclusions

In conclusion, we have developed a direct and convenient method for the cyclization−halogenation and cyclization−cyanation reactions of *cis*-4-hydroxy-5-phenylethynylpyrrolidinones **1** and *O*- and *N*-protected *o*-alkynylphenols **6** and -anilines **9**, respectively. Although cyclization−halogenation reactions of similar substrates have been reported using electrophilic halogenation reagents,[10,11] the CuX (X = I, Br, Cl) method reported here will be useful in cases where the aforementioned reagents give poor yields of cyclized products due to competing intermolecular addition reactions of the alkyne moiety or halogenation of the aromatic ring. While the cyanation reactions of alkynes are known,[16] the sequential cyclization−cyanation reactions of these substrates has not been reported. Furthermore, this method allows for the synthesis of 3-cyanobenzofurans and indoles in a one-step process that otherwise would require two sequential steps from the same starting substrates, that is, iodonium ion induced cyclization followed by a classical Rosenmund−von Braun reaction with CuCN[17] or its more recent and milder Pd-catalyzed versions,[18] on the resulting 3-iodobenzofurans or 3-iodoindoles.[10,11] As a comparison, the 3-cyanobenzofuran **7c** was obtained in 65% overall yield from the two-step method, which employed in the second step a Pd-catalyzed Rosenmund−von Braun reaction which required heating at 120 °C for 36 h,[13a] while this compound was obtained in 78% yield using this new method at a similar reaction temperature (135 °C) in 16 h. The majority of reactions that provided the 3-cyanoindoles **10**, using this new one-step process, however, proceeded efficiently under much milder conditions at 100 °C. Further, this new method is also more cost-effective when one compares the relatively higher costs per mole of iodine and NIS with the less expensive CuCN.

While the exact mechanism of these reactions is not known, the difference in the results of the reaction of **1** (R = Ph) with $CuBr_2$ (alkyne dibromination) and CuBr (cyclization−bromination) (Scheme 1) suggests that a Cu(II) species is not involved in the initial cyclization reaction. We suggest that, in the reactions of CuX with **1** under an oxygen atmosphere, the intermediate **A** (M = Cu(I), *m* = 0) in Scheme 1 is formed initially via cyclization of an electrophilic Cu(I)−alkyne complex intermediate[5] which then undergoes oxidation by molecular oxygen to the corresponding Cu(II) or Cu(III) species before reductive elimination to give products **3**.

Experimental Section

General Details. See the Supporting Information. Safety Note. While we have experienced no problems, care must be taken when heating DMF above its flash point (58 °C) under an oxygen atmosphere.

Cyclization−Iodination Reaction of 1 (R = Ph) Using *N*-Iodosuccinimide. (3a*R*,6a*S*)-4-Benzyl-3-iodo-2-phenyl-6,6a-dihydro-3a*H*-furo[3,2-*b*]pyrrol-5(4*H*)-one (3, R = Ph, X = I) and (4*S*,5*R*)-1-Benzyl-5-((*E*)-1,2-diiodo-2-phenylvinyl)-4-hydroxypyrrolidin-2-one (4, X = I). To a solution of **1** (R = Ph)[4] (25 mg, 0.085 mmol) and NIS (57 mg, 0.25 mmol) in CH_2Cl_2 (3 mL) was added $NaHCO_3$ (21 mg, 0.25 mmol), and stirring was continued

(15) A reviewer has suggested that the NTs or NTFA aniline substrates may undergo initial deprotonation prior to cyclization, and hence, they are more reactive than their N-unsubstituted aniline counterparts. While this may be a possibility, the absence of a base in these reactions would suggest that this is less likely.

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at rt for 16 h under a N_2 atmosphere. The reaction mixture was diluted with water (8 mL), quenched with saturated sodium thiosulfate solution (1 mL), and extracted with EtOAc (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed in vacuo. The crude product was chromatographed on silica gel (1:2 EtOAc/petroleum ether) to give **3** (R = Ph, X = I) as a white crystalline solid (26 mg, 71%) and **4** (X = I) as a white solid (6 mg, 13%).

3 (R = Ph, X = I): mp 140−142 °C; R_f = 0.71 (1:1 EtOAc/petroleum ether); $[\alpha]^{24}_D$ +6.1 (*c* 1.8, $CHCl_3$); IR (neat, ν_{max}/cm^{-1}) 1672, 1406, 1218, 916, 862, 756; δ_H 7.82−7.29 (10H, m, *H*), 5.18 (1H, m, HC-6a), 5.15 (1H, d, *J* = 15.2 Hz, C*H*HPh), 4.70 (1H, dd, *J* = 7.8, 0.7 Hz, HC-3a), 4.54 (1H, d, *J* = 15.2 Hz, C*H*HPh), 2.96−2.86 (2H, m, H_2C-6). δ_C 172.34 (CO), 159.2 (2-C), 136.2 (C), 130.2 (CH), 129.3 (CH), 128.6 (CH), 128.4 (CH), 128.3 (CH), 128.1 (CH), 127.6 (C), 77.4 (6a-C), 71.1 (3a-C), 52.3 (3-C), 44.8 (CH_2Ph), 37.6 (6-C); EIMS *m*/*z* 417 [(M^+) 50]; HREIMS calcd for $C_{19}H_{16}NO_2I$ (M^+) 417.0225, found 417.0211.

4 (X = I): mp 166−168 °C; R_f = 0.75 (1:1 EtOAc/petroleum ether); $[\alpha]^{24}_D$ −0.9 (*c* 1.28, $CHCl_3$); IR (neat, ν_{max}/cm^{-1}) 3232, 1675, 1408, 1261, 1045, 744 and 703; δ_H 7.88−7.31 (10H, m, *H*), 5.40 (1H, d, *J* = 15.0 Hz, C*H*HPh), 4.83 (1H, m, HC-4), 4.61 (1H, d, *J* = 8.1 Hz, HC-5), 4.30 (1H, d, *J* = 15.0 Hz, C*H*HPh), 3.47 (1H, s, OH), 2.93 (1H, dd, *J* = 18.0, 9.3 Hz, HC-3), 2.80 (1H, dd, *J* = 18.0, 5.3 Hz, HC-3). δ_C 173.3 (CO), 139.0 (C), 135.3 (C), 129.9 (CH), 128.9 (CH), 128.8 (CH), 127.9 (CH), 127.8 (CH), 127.6 (CH), 107.2 (I*C*=CI), 75.1 (IC=*C*I and 5-C), 72.1 (4-C), 45.0 (CH_2Ph), 37.5 (3-C); ESIMS *m*/*z* 562 [($M + NH_3$)$^+$ 100]; HRESIMS calc. for $C_{19}H_{20}N_2O_2I_2$ ($M + NH_3$)$^+$ 561.9459, found 561.9503.

Reaction of 1 (R = Ph) with $CuBr_2$. (4*S*,5*R*)-1-Benzyl-5-((*E*)-1,2-dibromo-2-phenylvinyl)-4-hydroxypyrrolidin-2-one (4, X = Br). A mixture of **1** (R = Ph) (20 mg, 0.068 mmol) and $CuBr_2$ (90 mg, 0.4 mmol) in anhydrous DMF (2 mL, Aldrich) was stirred at 70 °C for 12 h under a N_2 atmosphere. The reaction mixture was cooled to rt, diluted with water (10 mL), and extracted with EtOAc (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed under vacuo. The crude product was chromatographed on silica gel (1:2 EtOAc/petroleum ether) to give the title compound as a white powder (20 mg, 67%): mp 178−180 °C; R_f = 0.75 (1:1 EtOAc/petroleum ether); $[\alpha]^{24}_D$ −17.7 (*c* 1.69, $CHCl_3$); IR (neat, ν_{max}/cm^{-1}) 3230, 1669, 1428, 1215, 1044, 1017 and 754; δ_H 7.80−7.32 (10H, m, *H*), 5.36 (1H, d, *J* = 14.9 Hz, C*H*HPh), 4.85−4.84 (1H, m, HC-4), 4.80 (1H, d, *J* = 8.3 Hz, HC-5), 4.15 (1H, d, *J* = 14.9 Hz, CH*H*Ph), 3.70 (1H, s, OH), 2.84 (1H, dd, *J* = 17.9, 8.6 Hz, HC-3), 2.76 (1H, dd, *J* = 17.9, 5.2 Hz, HC-3); δ_C 173.0 (CO), 137.3 (C), 135.3 (C), 129.9 (CH), 128.9 (CH), 128.7 (CH), 128.0 (CH), 127.7 (CH), 127.5 (CH), 107.7, 73.2 (BrC=CBr), 72.3, 71.5 (5-C, 4-C), 45.0 (CH_2Ph), 37.1 (3-C); ESIMS *m*/*z* 450 [(MH^+), ^{79}Br, 10%]; HRESIMS calcd for $C_{19}H_{18}NO_2{}^{79}Br_2$ (MH^+) 449.9642, found 449.9704.

General Procedure (A) for the Cyclization−halogenation and Cyclization−cyanation Reactions. The preparation of **3** (R = Ph, X = I) is representative. To a solution of **1** (R = Ph) (50 mg, 0.17 mmol) in anhydrous DMF (2 mL, Aldrich) under an O_2 atmosphere (balloon) was added CuI (36 mg, 0.19 mmol), and the reaction flask was inserted into a preheated oil bath at 100 °C (see the safety note above). Stirring was continued for 16 h at the same temperature, until the reaction was complete as determined by TLC. The reaction mixture was cooled to rt, diluted with water (15 mL), and extracted with ethyl acetate (2 × 30 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed in vacuo. The crude product was chromatographed on silica gel (1:2 EtOAc/petroleum ether) to give compound **3** (R = Ph, X = I) as a white crystalline solid (61 mg, 85%). The spectroscopic data and physical properties of **3** (R = Ph, X = I) were the same as those described above.

(3a*R*,6a*S*)-4-Benzyl-3-bromo-2-phenyl-6,6a-dihydro-3a*H*-furo-[3,2-*b*]pyrrol-5(4*H*)-one (3, R = Ph, X = Br). Prepared from **1** (R = Ph) (50 mg, 0.17 mmol) and CuBr (27 mg, 0.19 mmol) according to the general procedure **A** described above. Purification via flash chromatography (1:1 EtOAc/petroleum ether) provided the title compound as a colorless gum (55.3 mg, 87%): R_f = 0.72 (1:1 EtOAc/petroleum ether); $[\alpha]^{24}_D$ +2.6 (*c* 0.87, $CHCl_3$); IR (neat, ν_{max}/cm^{-1}) 1674, 1438, 1226, 1068, 922 and 753; δ_H 7.86−7.29 (10H, m, Ar*H*), 5.18 (1H, d, *J* = 15.0 Hz, C*H*HPh), 5.16 (1H, m, HC-6a), 4.73 (1H, d, *J* = 7.9 Hz, HC-3a), 4.43 (1H, d, *J* = 15.0 Hz, CH*H*Ph), 2.97−2.87 (2H, m, H_2C-6). δ_C 172.1 (CO), 154.9 (2-C), 136.1 (C), 130.1 (CH), 128.8 (CH), 128.7 (CH), 128.6 (C), 128.4 (CH), 128.2 (CH), 127.7 (CH), 87.9 (3-C), 76.3 (6a-C), 68.7 (3a-C), 44.8 (CH_2Ph), 37.9 (6-C); ESIMS *m*/*z* 370 [(MH^+), ^{79}Br, 100], 372 [(MH^+), ^{81}Br, 100]; HREIMS calcd. for $C_{19}H_{16}NO_2{}^{79}Br$ (M^+) 369.0365, found 369.0364.

(3a*R*,6a*S*)-4-Benzyl-3-chloro-2-phenyl-6,6a-dihydro-3a*H*-furo-[3,2-*b*]pyrrol-5(4*H*)-one (3, R = Ph, X = Cl). Prepared from **1** (R = Ph) (50 mg, 0.17 mmol) and CuCl (19 mg, 0.19 mmol) according to the general procedure **A** described above. Purification via flash chromatography (1:1 EtOAc/petroleum ether) provided the title compound as an off white solid (43 mg, 77%). This compound was approximately 90% pure from NMR analysis: mp 158−160 °C; R_f = 0.74 (1:1 EtOAc/petroleum ether); $[\alpha]^{25}_D$ +21.2 (*c* 0.80, $CHCl_3$); IR (neat, ν_{max}/cm^{-1}): 1692, 1485, 1398, 1227, 1028, 937 and 768; δ_H 7.83−7.81 (2H, m, Ar*H*), 7.41−7.25 (8H, m, Ar*H*), 5.20 (1H, d, *J*=15.0 Hz, C*H*HPh), 5.15−5.12 (1H, m, HC-6a), 4.68 (1H, d, *J* = 7.5 Hz, HC-3a), 4.34 (1H, d, *J* = 15.0 Hz, CH*H*Ph), 2.95−2.88 (2H, m, H_2C-6). δ_C 172.0 (CO), 152.6 (2-C), 136.0 (C), 130.0 (CH), 128.7 (CH), 128.4 (CH), 128.3 (CH), 128.2 (CH), 127.7 (C), 127.2 (CH), 102.5 (3-C), 75.5 (6a-C), 67.4 (3a-C), 44.8 (CH_2Ph), 37.9 (6-C); ESIMS *m*/*z* 326 [(MH^+), ^{35}Cl, 100]; HREIMS calcd. for $C_{19}H_{16}NO_2{}^{35}Cl$ (M^+) 325.0872, found 325.0869.

(3a*R*,6a*S*)-4-Benzyl-3-iodo-2-pentyl-6,6a-dihydro-3a*H*-furo-[3,2-*b*]pyrrol-5(4*H*) one (3, R = *n*-Pent, X = I). Prepared from **1** (R = *n*-Pent) (50 mg, 0.21 mmol) and CuI (44 mg, 0.23 mmol) according to the general procedure **A** described above. Purification via flash chromatography (1:2 EtOAc/petroleum ether) provided the title compound **3** (R = Pent, X = I) as a light yellow gum (52 mg, 72%): R_f = 0.82 (1:2 EtOAc/petroleum ether); $[\alpha]^{25}_D$ −25.2 (*c* 4.0, $CHCl_3$); IR (neat, ν_{max}/cm^{-1}) 2945, 2924, 1681, 1408, 1219, 1040, 958, 860 and 702; δ_H 7.36−7.26 (5H, m, Ar*H*), 5.12 (1H, d, *J* = 15.0 Hz, C*H*HPh), 5.02−4.98 (1H, td, *J* = 1.5, 8.0 Hz, HC-6a), 4.52 (1H, d, *J* = 8.0 Hz, HC-3a), 4.40 (1H, d, *J* = 15.0 Hz, C*H*HPh), 2.90−2.84 (1H, dd, *J* = 7.5, 18.5 Hz, *H*HC-3), 2.75 (1H, d, *J* = 18.5 Hz, *H*HC-3), 2.27(2H, t, *J* = 7.5 Hz, H_2C-pent), 1.53−1.47 (2H, m, H_2C-pent), 1.35−1.25 (4H, m, -H_2C−H_2C-pent), 0.90 (3H, t, J=7.0 Hz, H_3C-pent). δ_C 172.2 (CO), 164.6 (2-C), 136.1 (C), 128.6 (CH), 128.3 (CH), 127.6 (CH), 77.5 (3-C), 68.8 (6a-C), 53.6 (3a-C), 44.7 (CH_2Ph), 37.8 (6-C), 31.1, 28.0, 25.8, 22.3, and 13.9 (pent-C); EIMS *m*/*z* 411 [(M^+, 30]; HRESIMS calcd for $C_{18}H_{23}NO_2I$ (MH^+) 412.0761, found 412.0774.

(3a*S*,6a*S*)-4-Benzyl-5-oxo-2-phenyl-4,5,6,6a-tetrahydro-3a*H*-furo[3,2-*b*]pyrrole-3-carbonitrile (3, R = Ph, X = CN). Prepared from **1** (R = Ph) (25 mg, 0.085 mmol) and CuCN (17 mg, 0.19 mmol) and anhydrous DMF (1.5 mL), according to the general procedure **A** described above. The crude product (93: 07 ratio of **3** (R = Ph, X = CN):**2** (R = Ph) was chromatographed on silica gel (1:1 EtOAc/petroleum ether) to give the title compound as a colorless gum (20.4 mg, 76%) and **2** (R = Ph)[4] (1.6 mg, 6%). Data for **3** (R = Ph, X = CN): R_f = 0.65 (1:2 EtOAc/petroleum ether); $[\alpha]^{24}_D$ +26.1 (*c* 0.42, $CHCl_3$); IR (neat, ν_{max}/cm^{-1}) 2194, 1692, 1618, 1233, 1019 and 750; δ_H 7.96−7.32 (10H, m, Ar*H*), 5.30−5.29 (1H, m, HC-6a), 5.23 (1H, d, *J* = 15.0 Hz, C*H*HPh),

4.87 (1H, d, J = 7.5 Hz, HC-3a), 4.18 (1H, d, J = 15.0 Hz, C*H*HPh), 3.01−2.92 (2H, m, H_2C-6). δ_C 171.0 (CO), 170.5 (2-C), 135.2 (C), 132.6 (CH), 128.9 (CH), 128.85 (CH), 128.7 (CH), 128.0 (CH), 127.6 (CH), 126.8 (C), 80.9 (CN), 79.3 (6a-C), 64,5 (3a-C), 44.3 (CH_2Ph), 37.1 (6-C); ESIMS m/z 317 [(MH^+) 100]; HREIMS calcd for $C_{20}H_{16}N_2O_2$, (M^+) 316.1220, found 316.1211.

(3a*R*,6a*S*)-4-Benzyl-5-oxo-2-pentyl-4,5,6,6a-tetrahydro-3a*H*-furo[3,2-*b*]pyrrole-3-carbonitrile (3, R = *n*-Pent, X = CN). Prepared from **1** (R = Pent) (60 mg, 0.21 mmol) and CuCN (41 mg, 0.46 mmol) according to the general procedure **A** described above. Purification via flash chromatography (1:2 EtOAc/petroleum ether) provided the title compound as a light yellow gum (52 mg, 79%): R_f = 0.63 (1:2 EtOAc/petroleum ether); $[\alpha]^{25}_D$−42.8 (c 4.5, $CHCl_3$); IR (neat, ν_{max}/cm^{-1}) 2960, 2924, 2207, 1692, 1632, 1239, 994, 772, and 731. δ_H 7.35−7.26 (5H, m, Ar*H*), 5.20 (1H, d, J = 15.0 Hz, C*H*HPh), 5.15 (1H, t, J = 7.5 Hz, HC-6a), 4.68 (1H, d, J = 7.5 Hz, HC-3a), 4.05 (1H, d, J = 15.0 Hz, C*H*HPh), 2.94−2.88 (1H, dd, J = 7.5, 18.5 Hz, *H*HC-3), 2.81 (1H, d, J = 18.5 Hz, *H*HC-3), 2.43−2.40 (2H, m, H_2C-pent), 1.61−1.56 (2H, m, H_2C-pent), 1.35−1.30 (4H, m, -H_2C−H_2C-pent), 0.90 (3H, t, J = 6.5 Hz, H_3C-pent). δ_C 179.3 (CO), 170.4 (2-C), 135.2 (C), 128.9 (CH), 128.7 (CH), 128.1 (CH), 115.9 (3-C), 83.8 (CN), 80.1 (6a-C), 63.3 (3a-C), 44.3 (CH_2Ph), 37.1 (6-C), 31.0, 28.0, 25.7, 22.1, and 13.8 (pent-C). EIMS m/z 310 [(M^+) 40]; HREIMS calcd for $C_{19}H_{22}N_2O_2$ (M^+) 310.1687, found 310.1681.

General Procedure (B) for the Synthesis of Substituted 3-Halo- and 3-Cyanobenzo[*b*]furans. The preparation of 3-iodo-2-phenylbenzofuran is representative. To a mixture of **6** (R = H, R^1 = Ph) (50 mg, 0.21 mmol) in anhydrous DMF (2 mL) under an O_2 atmosphere (balloon) was added CuI (88 mg, 0.46 mmol), and the reaction flask was inserted in to a preheated oil bath at 135−140 °C (see the safety note above). Stirring was continued for 16 h at the same temperature until complete consumption of starting material as determined by TLC. The reaction mixture was cooled to rt, diluted with water (8 mL), and extracted with EtOAc (2 × 10 mL). The combined organic extracts were dried ($MgSO_4$), and the solvent was removed in vacuo. The crude product was chromatographed on silica gel (petroleum ether) to give the product **7a** as a yellow oil (47 mg, 70%): R_f = 0.82 (1:4 EtOAc/petroleum ether); δ_H 8.19 (2H, d, J = 8.0 Hz), 7.28 −7.51 (7H, m); EIMS m/z 320 [(M^+) 100]. The analytical and spectroscopic data matched with those reported in the literature.[10a]

3-Bromo-2-phenylbenzofuran (7b). Prepared from **6** (R = H, R^1 = Ph) (50 mg, 0.21 mmol) and CuBr (66 mg, 0.46 mmol) according to the general procedure **B** described above. The crude product was chromatographed on silica gel (petroleum ether) to give the title compound **7b** as a colorless solid (35 mg, 62%): mp 62−64 °C (lit.[7] mp 62−63 °C); R_f = 0.83 (1:4 EtOAc/petroleum ether); δ_H 8.17 (2H, d, J = 7.5 Hz), 7.58−7.31 (7H, m); EIMS m/z 272 [(M^+), ^{79}Br, 100], 274 [(M^+), ^{81}Br, 98]. The analytical and spectroscopic data matched with those reported in the literature.[13a]

2-Phenylbenzofuran-3-carbonitrile (7c). Prepared from **6** (R = H, R^1 = Ph) (50 mg, 0.21 mmol) and CuCN (41 mg, 0.46 mmol) according to the general procedure **B** described above. The crude product was chromatographed on silica gel (9:1, petroleum ether/EtOAc) to give **7c** as a colorless solid (36 mg, 78%): mp 58−60 °C (lit.[8] mp 57.5−59.4 °C); R_f = 0.69 (1:4 EtOAc/petroleum ether); δ_H 8.19 (2H, d, J = 7.5 Hz), 7.70 (1H, d, J = 7.5 Hz), 7.57−7.36 (6H, m); EIMS m/z 219 [(M^+) 100]. The analytical and spectroscopic data matched with those reported in the literature.[10b]

2-(4-Methoxyphenyl)benzofuran-3-carbonitrile (7d) and 2-(4-Methoxyphenyl)benzofuran (8d). Prepared from **6** (R = H, R^1 = *p*-MeOPh) (50 mg, 0.18 mmol) and CuCN (37 mg, 0.41 mmol) according to the general procedure **B** described above. The crude product (ratio of **7d**:**8d** was 93:7) was chromatographed on silica gel (1:8, EtOAc/petroleum ether) to give **7d** as a white solid (31.3 mg, 67%) and 2-(4-methoxyphenyl)benzofuran (**8d**) as a white solid (1 mg, 3%).

7d: mp 138−140 °C; R_f = 0.65 (1:4 EtOAc/petroleum ether); IR (neat, ν_{max}/cm^{-1}) 2225, 1608, 1506, 1266, 1024, 831 and 738; δ_H 8.14 (2H, d, J = 9.0 Hz), 7.66 (1H, dd, J = 2.5, 6.5 Hz), 7.52 (1H, dd, J = 2.5, 6.5 Hz), 7.37 − 7.34 (2H, m), 7.03 (2H, d, J = 9.0 Hz), 3.88 (3H, s, OMe); δ_C 162.0 (2-C), 161.8 (C), 153.0 (C), 128.3 (CH), 127.4 (C), 125.8 (CH), 124.5 (CH), 120.4 (C), 119.6 (CH), 114.7 (C), 114.5 (CH), 111.5 (CH), 86.2 (CN), 55.4 (OMe); EIMS m/z 249 [(M^+) 100]; HREIMS calcd for $C_{16}H_{11}NO_2$ (M^+) 249.0784, found 249.0789.

8d: colorless solid; mp 142−144 °C (lit.[19] mp 143 °C); δ_H 7.81 (2H, d, J = 8.5 Hz), 7.56 (1H, d, J = 7.0 Hz), 7.50 (1H, d, J = 8.0 Hz), 7.26−7.20 (3H, m), 6.99 (2H, d, J = 8.9 Hz), 6.89 (1H, s), 3.87 (3H, s, OMe); EIMS m/z 224 [(M^+) 80]. The analytical and spectroscopic data matched with those reported in the literature.[19]

2-(4-Fluorophenyl)benzofuran-3-carbonitrile (7e). Prepared from **6** (R = H, R^1 = *p*-FPh) (50 mg, 0.19 mmol) and CuCN (39 mg, 0.43 mmol) according to the general procedure (**B**) described above. The crude product was chromatographed on silica gel (9:1, petrol/EtOAc) to give **7e** as a colorless solid (34.5 mg, 74%): mp 124−126 °C; R_f = 0.68 (1:4 EtOAc/petroleum ether); IR (neat, ν_{max}/cm^{-1}) 2226, 1606, 1503, 1236, 1040, 835 and 748; δ_H 8.19−8.16 (2H, dd, J = 5.5, 9.0 Hz), 7.69 (1H, d, J = 7.5 Hz), 7.55 (1H, d, J = 8.5 Hz), 7.42−7.35 (2H, m), 7.21 (2H, t, J = 8.5 Hz); δ_C 164.2 (C, d, J = 251.7 Hz), 160.7 (C), 153.2 (C), 128.7 (CH, d, J = 9.2 Hz), 127.0 (C), 126.4 (CH), 124.7 (CH), 124.1 (C, d, J = 3.7 Hz), 120.0 (CH), 116.4 (CH, d, J = 22.2 Hz), 114.2 (C), 111.6 (CH), 87.8 (CN); EIMS m/z 237 [(M^+) 100%]; HREIMS calcd. for $C_{15}H_8FNO$ (M^+) 237.0589, found 237.0589.

2-Phenylbenzofuran-3,5-dicarbonitrile (7g). To a solution of **6** (R = CN, R^1 = Ph) (50 mg, 0.19 mmol) in anhydrous DMF (2 mL) under an O_2 atmosphere (balloon) was added CuCN (39 mg, 0.42 mmol), and the reaction flask was inserted into a preheated oil bath at 100 °C. Stirring was continued for 16 h at the same temperature, until complete consumption of starting material as determined by TLC. Workup was according to the general procedure **B** described above. The crude product was chromatographed on silica gel (5:1 petrol/EtOAc) to give **7g** as a colorless solid (37.3 mg, 80%): mp 168−170 °C; R_f = 0.51 (1:4 EtOAc/petroleum ether); IR (neat, ν_{max}/cm^{-1}) 2230, 1562, 1465, 1448, 1169, 897, 817 and 770; δ_H 8.18 (2H, dd, J = 1.5, 5.5 Hz), 8.02 (1H, s), 7.69 (2H, s), 7.58−7.57 (3H, m); δ_C 163.8 (2-C), 154.6 (C), 132.2 (CH), 129.9 (CH), 129.3 (CH), 128.0 (C), 126.8 (CH), 126.7 (C), 124.6 (CH), 118.2 (C), 113.0 (CH), 112.9 (C), 109.0 (CN), 87.8 (CN); EIMS m/z 244 [(M^+) 100]; HREIMS calcd. for $C_{16}H_8N_2O$ (M^+) 244.0640, found 244.0636.

3-Iodo-2-pentylbenzofuran (7h). Prepared from **6** (R = H, R^1 = n-Pent) (50 mg, 0.21 mmol) and CuI (90 mg, 0.47 mmol) according to the general procedure **B** described above. The crude product was chromatographed on silica gel (petroleum ether) to give **7h** as a pale yellow gum (51 mg, 76%): R_f = 0.75 (1:4 EtOAc/petroleum ether); IR (neat, ν_{max}/cm^{-1}) 2955, 2919, 1582, 1449, 1014 and 742; δ_H 7.38−7.24 (4H, m), 2.84 (2H, t, J = 7.5 Hz), 1.75−1.72 (2H, m), 1.36−1.33 (4H, m), 0.90 (3H, t, J = 7.5 Hz); δ_C 159.1 (2-C), 154.2 (C), 131.0 (C), 124.4 (CH), 123.0 (CH), 120.7 (CH), 110.9 (CH), 62.5 (3-C), 31.1, 28.0, 27.5, 22.3, and 13.9 (pent-C); EIMS m/z 314 [(M^+) 40]; HREIMS calcd for $C_{13}H_{15}OI$ (M^+) 314.0166, found 314.0167.

2-Pentylbenzofuran-3-carbonitrile (7i) and 2-Pentylbenzofuran (8i). Prepared from **6** (R = H, R^1 = *n*-Pent) (50 mg, 0.21 mmol)

(19) Razler, T. M.; Hsiao, Y.; Qian, F.; Fu, R.; Khan, R. K.; Doubleday, W. *J. Org. Chem.* **2009**, *74*, 1381–1384.

and CuCN (43 mg, 0.47 mmol) according to the general procedure **B** described above. The crude product (ratio of **7i**:**8i** was 92:8) was chromatographed on silica gel (1:8, EtOAc/petroleum ether) to give **7i** as a pale yellow gum (51 mg, 76%) and 2-pentylbenzofuran (**8i**) as a colorless oil (2 mg, 5%).

7i: R_f = 0.69 (1:4 EtOAc/petroleum ether); IR (neat, ν_{max}/cm^{-1}) 2960, 2924, 2233, 1593, 1454, 1178 and 747; δ_H 7.62−7.33 (4H, m), 2.96 (2H, t, J = 7.5 Hz), 1.83 (2H, t, J = 7.5 Hz), 1.39−1.37 (4H, m), 0.91 (3H, t, J = 7.5 Hz); δ_C 168.7 (2-C), 153.6 (C), 126.0 (C), 125.4 (CH), 124.2 (CH), 119.5 (CH), 113.4 (3-C), 111.5 (CH), 90.6 (CN), 31.1, 28.1, 27.1, 22.3, and 13.8 (pent-C); EIMS m/z 213 [(M$^+$) 40]; HREIMS calcd for $C_{14}H_{15}NO$ (M$^+$) 213.1154, found 213.1153.

8i: δ_H 7.47(1H, d, J = 7.0 Hz), 7.40 (d, J = 8.0 Hz, 1H), 7.20−7.16 (2H, m), 6.36 (s, 1H), 2.75 (2H, t, J = 7.0 Hz), 1.76−1.73 (2H, m), 1.39−1.36 (4H, m), 0.90 (3H, t, J = 7.0 Hz); EIMS m/z 188 [(M$^+$) 90]. The analytical and spectroscopic data matched with those reported in the literature.[20]

General Procedure (C) for the Synthesis of 3-Cyanoindoles. To a solution of the 2-ethynylaniline derivative (0.30 mmol) in anhydrous DMF (4 mL) under an oxygen atmosphere (balloon) was added CuCN (0.90 mmol), and the reaction vessel was inserted into a preheated oil bath at 100 °C (see the safety note above). The reaction mixture was stirred at this temperature for 16 h. Two different workup procedures were followed. Workup procedure A: Water (5 mL) was added and the aqueous layer was extracted with EtOAc (3 × 5 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude product was purified by column chromatography. Workup procedure B: The solvent was removed in vacuo at 60 °C. The crude residue was purified by column chromatography.

2-Phenyl-1-(4-methylbenzenesulfonyl)-1*H*-indole-3-carbonitrile (10a) and 2-Phenyl-1-(4-methylbenzenesulfonyl)-1*H*-indole (11; R = H, R^1 = Ph, R^2 = Ts). Using the general indole preparation procedure **C** above, a mixture of **9** (R = H, R^1 = Ph, P = Ts) (0.100 g, 0.288 mmol), DMF (4 mL), and CuCN (0.080 g,0.86 mmol) was stirred at 100 °C for 16 h. Workup procedure A was applied. The crude product was purified by column chromatography (silica gel, 1:5 EtOAc/petroleum ether) to give the compound **10a** (0.080 g, 74%) as a white solid and compound **11** (R = H, R^1 = Ph, R^2 = Ts) (0.003 g, 3%) as a colorless solid.

10a: R_f = 0.35 (1:5 EtOAc/petroleum ether); mp 148−150 °C; IR (neat, ν_{max}/cm^{-1}) 2361, 1342, 2230, 1451, 1375, 1197, 1178; δ_H 8.36 (1H, d, J = 8.5 Hz, ArH), 7.65 (1H, d, J = 7.5 Hz, ArH), 7.55−754 (1H, m, ArH), 7.51−7.46 (5H, m, ArH), 7.42 (1H, t, J = 7.5 Hz, ArH), 7.28 (2H, d, J = 8.0 Hz, ArH), 7.10 (2H, d, J = 8.0 Hz, ArH), 2.33 (3H, s, CH_3); δ_C 148.6 (C),145.8 (C), 136.4 (C), 134.6 (C), 130.9 (CH), 130.5 (CH), 129.7 (CH), 128.3 (C), 127.9 (CH), 127.8 (C), 126.9 (CH), 126.6 (CH), 125.3 (CH), 119.6 (CH), 116.3 (CH), 113.9 (C), 96.7 (CN), 21.6 (CH_3); EIMS m/z 372 [(M)$^+$, 65]; HREIMS calcd for $C_{22}H_{16}N_2O_2S$ (M)$^+$ 372.0935, found 372.0932.

11 (R = H, R^1 = Ph, R^2 = Ts): R_f = 0.52 (1:3 EtOAc/petroleum ether); mp 144−146 °C (lit.[11] mp 146−148 °C); IR (neat, ν_{max}/cm^{-1}) 1598, 1449, 1367, 1306, 1167, 1060, 978, 809; δ_H 8.31 (1H, d, J = 8.5 Hz, ArH), 7.50−7.48 (2H, m, ArH), 7.43 (4H, m, ArH), 7.35 (1H, t, J = 7.5 Hz, ArH), 7.27−7.24 (3H, m, ArH), 7.03 (2H, d, J = 8.5 Hz, ArH), 6.54 (1H, s, ArH), 2.28 (3H, s, CH_3); EIMS m/z 348 [(M)$^+$, 100]; HREIMS calcd. for $C_{21}H_{18}NO_2S$ (M)$^+$ 348.1042, found 348.1058.

2-Phenyl-1*H*-indole-3-carbonitrile (10b). Using the general indole preparation procedure **C** above, a mixture of **9** (R = H, R^1 = Ph, P = TFA) (0.100 g, 0.34 mmol), DMF (4 mL), and CuCN (0.093 g, 1.02 mmol) was stirred at 100 °C for 16 h. Workup procedure A was applied. The crude product was purified by column chromatography (silica gel, 1:3 EtOAc/petroleum ether) to give the title compound (0.059 g, 80%) as a white solid: R_f = 0.22 (1:3 EtOAc/petroleum ether); mp 224−226 °C; IR (neat, ν_{max}/cm^{-1}) 3221, 2361, 2335, 2217, 1654, 1490, 1451, 1424, 1250, 732; δ_H (acetone-d_6) 11.5 (1H, br s, NH), 8.05−8.02 (2H, m, ArH), 7.71−7.68 (1H, m, ArH), 7.61−7.56 (4H, m, ArH), 7.35−7.26 (2H, m, ArH); δ_C (acetone-d_6) 145.5 (C), 136.6 (C), 130.7 (C), 130.6 (CH), 130.1 (CH), 129.7 (C), 127.8 (CH), 124.8 (CH), 122.9 (CH), 119.4 (CH), 117.1 (C), 113.2 (CH), 83.7 (CN), ESIMS m/z 218 [(MH)$^+$, 100]; HRESIMS calcd for $C_{15}H_{10}N_2$ (MH)$^+$ 218.0846, found 218.0843.

2-(4-Methoxyphenyl)-1*H*-indole-3-carbonitrile (10c). Using the general indole preparation procedure **C** above, a mixture of **9** (R = H, R^1 = 4-MeOC$_6$H$_4$-, P = TFA) (0.100 g, 0.32 mmol), DMF (4 mL), and CuCN (0.086 g, 0.95 mmol) was stirred at 100 °C for 16 h. Workup procedure B was applied. The crude product was purified by column chromatography (silica gel, EtOAc) to give the title compound (0.061 g, 77%) as a white solid: R_f = 0.15 (3:1 EtOAc/petroleum ether); mp 99−101 °C; IR (neat, ν_{max}/cm^{-1}) 3257, 2212, 1613, 1499, 1446, 1255, 1245, 1173, 1040, 836; δ_H (acetone-d_6) 11.4 (1H, br s, NH), 7.99 (2H, d, J = 8.5 Hz, ArH), 7.67 (1H, d, J = 7.5 Hz, ArH), 7.53 (1H, d, J = 7.5 Hz, ArH), 7.30−7.24 (2H, m, ArH), 7.15 (2H, d, J = 8.5 Hz, ArH), 3.89 (3H, s, CH_3O); δ_C (acetone-d_6) 161.3 (C), 145.1 (C), 135.8 (C), 129.1 (C), 128.7 (CH) 123.8 (CH), 122.4 (C), 122.1 (CH), 118.6 (CH), 116.8 (C), 114.9 (CH), 112.3 (CH), 81.9 (CN), 55.2 (CH_3O); EIMS m/z 248 [(M)$^+$, 80]; HREIMS calcd for $C_{16}H_{12}N_2O$ (M)$^+$ 248.0943, found 248.0949.

2-(4-Fluorophenyl)-1*H*-indole-3-carbonitrile (10d). Using the general indole preparation procedure **C** above, a mixture of **9** (R = H, R^1 = 4-FC$_6$H$_4$-, P = TFA) (0.080 g, 0.26 mmol), DMF (3 mL), and CuCN (0.072 g, 0.79 mmol) was stirred at 100 °C for 16 h. Workup procedure B was applied. The crude product was purified by column chromatography (silica gel, 1:3 EtOAc/petroleum ether) to give the title compound (0.041 g, 65%) as a white solid: R_f = 0.26 (1:3 EtOAc/petroleum ether); mp 239−241 °C; (neat, ν_{max}/cm^{-1}) 3257, 2213, 1675, 1613, 1498, 1448, 1241, 1173, 830; δ_H (acetone-d_6) 11.5 (1H, br s, NH), 8.08−8.06 (2H, m, ArH), 7.69 (1H, d, J = 7.5 Hz, ArH), 7.56 (1H, d, J = 7.5 Hz, ArH), 7.39−7.34 (2H, m. ArH), 7.32−7.27 (2H, m, ArH); δ_C (acetone-d_6) 164.2 (C, d, J = 247.6 Hz), 144.5 (C), 136.6 (C), 130.2 (CH, d, J = 8.5 Hz), 129.5 (C), 127.3 (C), 124.9 (CH), 122.9 (CH), 119.4 (CH), 116.9 (CH, d, J = 7.1 Hz), 116.5 (C, d, J = 3.1 Hz), 113.1 (CH), 83.7 (CN); EIMS m/z 236 [(M)$^+$, 100]; HREIMS calcd for $C_{15}H_9N_2F$ (M)$^+$ 236.0760, found 236.0749.

5-Methoxy-2-phenyl-1*H*-indole-3-carbonitrile (10e). Using the general indole preparation procedure **C** above, a mixture of **9** (R = OMe, R^1 = Ph, P = TFA) (0.100 g, 0.32 mmol), DMF (4 mL), and CuCN (0.086 g, 0.95 mmol) was stirred at 100 °C for 16 h at 130 °C. Workup procedure B was applied. The crude product was purified by column chromatography (silica gel, 1:3 EtOAc/petroleum ether) to give the title compound (0.062 g, 78%) as a white solid: R_f = 0.35 (1:3 EtOAc/petroleum ether); mp 120−122 °C; IR (neat, ν_{max}/cm^{-1}) 3216, 2965, 2909, 2358, 2341, 2217, 1685, 1652, 1558, 1540, 1456, 1055, 752; δ_H (acetone-d_6) 11.4 (1H, br s, NH), 8.01 (2H, d, J = 7.0 Hz, ArH), 5.95 (2H, t, J = 7.0 Hz, ArH), 7.53 (1H, d, J = 7.0 Hz, ArH), 7.46 (1H, d, J = 8.5 Hz, ArH), 7.16 (1H, s, ArH), 6.94 (1H, d, J = 8.5 Hz, ArH), 3.90 (3H, s, CH_3O); δ_C (acetone-d_6) 156.7 (C), 145.1 (C), 131.2 (C), 130.5 (C), 130.3 (CH), 130.2 (CH), 129.8 (CH), 127.3 (CH), 117.1 (C), 115.1 (CH), 113.8 (C), 100.4 (CH), 83.2 (CN), 55.6 (CH_3O); EIMS m/z 248 [(M)$^+$, 100]; HREIMS calcd for $C_{16}H_{12}N_2O$ (M)$^+$ 248.0938, found 248.0949.

2-Phenyl-1-(4-methylbenzenesulfonyl)-1*H*-indole-3,5-dicarbonitrile (10f) and 2-Phenyl-1-(4-methylbenzenesulfonyl)-1*H*-indole-5-carbonitrile (11; R = CN, R^1 = Ph, R^2 = Ts). Using the general indole preparation procedure above, a mixture of **9**

(20) Furstner, A.; Davies, P. W. *J. Am. Chem. Soc.* **2005**, *127*, 15024–15025.

(R = CN, R^1 = Ph, P = Ts) (0.100 g, 0.26 mmol), DMF (4 mL), and CuCN (0.072 g, 0.78 mmol) was stirred at 100 °C for 16 h. Workup procedure A was applied. The crude product was purified by column chromatography (silica gel, 1:4 EtOAc/petroleum ether) to give the compound **11** (R = CN, R^1 = Ph, R^2 = Ts) (0.037 g, 38%) and compound **10f** (0.023 g, 22%) both as a white solid.

10f: R_f = 0.32 (1:4 EtOAc/petroleum ether); mp 131−133 °C; IR (neat, ν_{max}/cm^{-1}) 2228, 1598, 1465, 1378, 1260, 1378, 1260, 1175, 1091, 819; δ_H 8.50 (1H, d, J = 8.5 Hz, ArH), 7.99 (1H, s, ArH), 7.59 (1H, t, J = 7.0 Hz, ArH), 7.74 (1H, d, J = 8.5 Hz, ArH), 7.49 (2H, t, J = 7.0 Hz, ArH), 7.42 (2H, d, J = 7.0 Hz, ArH), 7.25 (2H, d, J = 8.0 Hz, ArH), 7.14 (2H, d, J = 8.0 Hz, ArH), 2.36 (3H, s, CH_3); δ_C 150.6 (C), 146.6 (C), 138.0 (C), 134.1 (C), 131.3 (CH), 130.2 (CH), 129.6 (CH), 128.3 (CH), 127.7 (C), 127.3 (CH), 124.4 (CH), 118.2 (C), 117.4 (CH), 112.7 (C), 109.1 (CN), 96.0 (CN), 21.6 (CH_3); ESIMS m/z 398 [$(MH)^+$, 100]; HRESIMS calcd for $C_{23}H_{16}N_3O_2S$ $(MH)^+$ 398.0944, found 398.0963.

11 (R = CN, R^1 = Ph, R^2 = Ts): R_f = 0.34 (1:4 EtOAc/petroleum ether); mp 78−80 °C; IR (neat, ν_{max}/cm^{-1}) 2970, 2361, 1340, 2223, 1654, 1375, 1173, 1091, 1081, 756; δ_H 8.42 (1H, d, J = 8.0 Hz, ArH), 7.70 (1H, s, ArH), 7.60 (1H, dd, J = 1.5, 8.0 Hz, ArH), 7.45−7.42 (5H, m, ArH), 7.24 (2H, d, J = 7.0 Hz, ArH), 7.07 (2H, d, J = 7.0 Hz, ArH), 6.56 (1H, s, ArH), 2.31 (3H, s, CH_3); δ_C 145.3 (C), 144.1 (C), 139.8 (C), 134.5 (C), 130.5 (CH), 129.5 (CH), 129.2 (CH), 127.7 (CH), 127.5 (CH), 126.9 (CH), 125.3 (CH), 123.5 (C), 119.2 (C), 117.0 (CH), 111.9 (CH), 107.6 (CN), 21.6 (CH_3); ESIMS m/z 373 [$(MH)^+$, 100]; HRESIMS calcd for $C_{22}H_{17}N_2O_2S$ $(MH)^+$ 373.1018, found 373.1011.

Phenyl-1*H*-indole-3,5-dicarbonitrile (10g). Using the general indole preparation procedure **C** above, a mixture of **9** (R = CN, R^1 = Ph, P = TFA) (0.070 g, 0.21 mmol), DMF (3 mL), and CuCN (0.059 g, 0.64 mmol) was stirred at 100 °C for 16 h. Workup procedure B was applied. The crude product was purified by column chromatography (silica gel, 2:1 EtOAc/petroleum ether) to give the title compound (0.031 g, 60%) as a white solid: R_f = 0.64 (EtOAc); mp 265−267 °C; IR (neat, ν_{max}/cm^{-1}) 3231, 2360, 2335, 2224, 1685, 1654, 1475, 1449, 1367, 1255, 1070, 906; δ_H (acetone-d_6) 12.1 (1H, br s, NH), 8.13 (1H, d, J = 1.5 Hz, ArH), 8.06 (2H, dd, J = 1.5, 7.0 Hz, ArH), 7.76 (1H, d, J = 7.0 Hz, ArH), 7.68−7.59 (4H, m, ArH); δ_C (acetone-d_6) 147.8 (C), 138.0 (C), 131.1 (CH), 130.0 (CH), 129.4 (C), 129.0 (C), 127.8 (CH), 127.4 (CH), 124.3 (CH), 119.7 (C), 115.7 (C), 114.2 (CH), 106.0 (CN), 84.1 (CN); EIMS m/z 243 [$(M)^+$, 100]; HREIMS calcd for $C_{16}H_9N_3$ $(M)^+$ 243.0813, found 243.0796.

2-Pentyl-1*H*-indole-3-carbonitrile (10h). Using the general indole preparation procedure **C** above, a mixture of **9** (R = H, R^1 = *n*-Pentyl, P = TFA) (0.100 g, 0.32 mmol), DMF (4 mL), and CuCN (0.088 g, 0.96 mmol) was stirred at 100 °C for 16 h. Workup procedure A was applied. The crude product was purified by column chromatography (silica gel, 1:3 EtOAc/petroleum ether) to give the title compound (0.050 g, 73%) as a white solid: R_f = 0.31 (1:3 EtOAc/petroleum ether); mp 49−51 °C; IR (neat, ν_{max}/cm^{-1}) 3262, 2955, 2929, 2858, 2208, 1557, 1490, 1452, 1332, 1239, 742; δ_H 8.70 (1H, br s, NH), 7.65 (1H, d, J = 8.5 Hz, ArH), 7.38 (1H, d, J = 8.5 Hz, ArH), 7.25−7.22 (2H, m, ArH), 2.94 (2H, t, J = 7.0 Hz, CH_2), 1.80−1.78 (2H, m, CH_2), 1.38−1.35 (4H, m, 2 × CH_2), 0.90 (3H, t, J = 7.0 Hz, CH_3); δ_C 149.3 (C), 134.5 (C), 127.6 (C), 123.3 (CH), 121.9 (CH), 118.9 (CH), 116.4 (C), 111.3 (CH), 84.7 (CN), 31.1 (CH_2), 28.7 (CH_2), 27.5 (CH_2), 22.2 (CH_2), 13.8 (CH_3); ESIMS m/z 213 [$(MH)^+$, 100]; HREIMS calcd for $C_{14}H_{17}N_2$ $(MH)^+$ 213.1360, found 213.1392.

2-Pentyl-1-(4-methylbenzenesulfonyl)-1*H*-indole-3-carbonitrile (10i) and 2-Pentyl-1-(4-methylbenzenesulfonyl)-1*H*-indole (11; R = H, R^1 = *n*-Pent, R^2 = Ts). Using the general indole preparation procedure **C** above, a mixture of **9** (R = H, R^1 = *n*-Pentyl, R^2 = Ts) (0.0.080 g, 0.23 mmol), DMF (3 mL), and CuCN (0.063 g, 0.69 mmol) was stirred at 100 °C for 16 h. Workup procedure A was applied. The crude product was purified by column chromatography (silica gel, 1:5 EtOAc/petroleum ether) to give the compound **10i** (0.046 g, 55%) as a colorless oil and compound **11** (R = H, R^1 = Pent, R^2 = Ts) (0.019 g, 24%) as a white solid. **10i**: R_f = 0.42 (1:5 EtOAc/petroleum ether); (neat, ν_{max}/cm^{-1}) 2955, 2924, 2863, 2228, 1598, 1451, 1384, 1191, 1178, 1155, 1098, 969; δ_H 8.17 (1H, d, J = 8.5 Hz, ArH), 7.65 (1H, d, J = 8.5 Hz, ArH), 7.58 (1H, d, J = 8.0 Hz, ArH) 7.39−7.33 (2H, m, ArH), 7.25 (3H, d, J = 8.0 Hz, ArH), 3.20 (2H, t, J = 7.5 Hz, CH_2), 2.37 (3H, s, CH_3), 1.82−1.77 (2H, m, CH_2), 1.43−1.35 (4H, m, 2 × CH_2), 0.91 (3H, t, J = 7.5 Hz, CH_3); δ_C 151.4 (C), 145.9 (C), 135.6 (C), 135.3 (C), 130.2 (CH), 127.2 (C), 126.4 (CH), 125.7 (CH), 124.8 (CH), 119.1 (CH), 115.1 (CH), 114.1 (C), 94.5 (CN), 31.4 (CH_2), 30.4 (CH_2), 28.5 (CH_2), 22.2 (CH_2), 21.6 (CH_3), 13.9 (CH_3); ESIMS m/z 367 [$(MH)^+$, 100]; HRESIMS calcd for $C_{21}H_{23}N_2O_2S$ $(MH)^+$ 367.1470, found 367.1480.

11 (R = H, R^1 = Pent, R^2 = Ts): R_f = 0.55 (1:5 EtOAc/petroleum ether); mp 57−59 °C; IR (neat, ν_{max}/cm^{-1}) 2955, 2924, 2356, 2330, 1444, 1369, 1224, 1170, 1139, 1092, 1060, 804; δ_H 8.16 (1H, d, J = 8.0 Hz, ArH), 7.61 (2H, d, J = 8.0 Hz, ArH), 7.39 (1H, d, J = 8.0 Hz, ArH), 7.25−7.16 (4H, m, ArH), 6.37 (1H, s, ArH), 2.97 (2H, t, J = 7.5 Hz, CH_2), 2.32 (3H, s, CH_3), 1.75−1.72 (2H, m, CH_2), 1.39−1.35 (4H, m, 2 × CH_2), 0.91 (3H, t, J = 7.5 Hz, CH_3); δ_C 144.2 (C), 142.5 (C), 137.1 (C), 136.2 (C), 129.7 (CH), 126.6 (CH), 126.2 (C), 123.7 (CH), 123.4 (CH), 119.9 (CH), 114.7 (CH), 108.5 (CH), 31.5 (CH_2), 28.9 (CH_2), 28.5 (CH_2), 22.4 (CH_2), 21.5 (CH_3), 14.0 (CH_3); EIMS m/z 341 [$(M)^+$, 50]; HREIMS calcd for $C_{20}H_{23}NO_2S$ $(M)^+$ 341.1451, found 341.1449.

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Supporting Information Available: Full experimental and spectroscopic details for the synthesis of the substrates **1** (R = *n*-Pentyl), **5**, **6**, and **9** and copies of the ^1H and ^{13}C NMR spectra of all new compounds. This information is available free of charge via the Internet at http://pubs.acs.org.