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Rapid Access to Amino-Substituted Quinoline, (Di)Benzofuran, and Carbazole Heterocycles through an Aminobenzannulation Reaction

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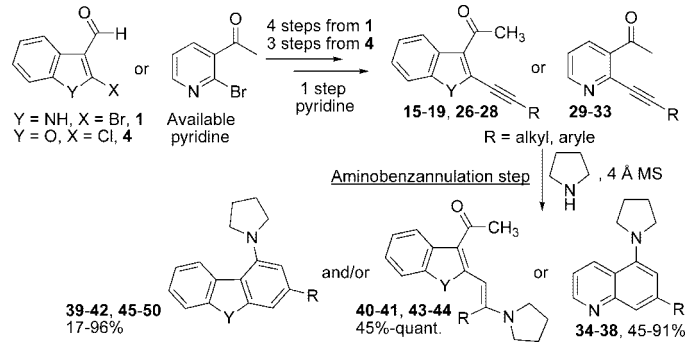

The use of a powerful aminobenzannulation reaction has been applied for the synthesis of amino-substituted quinolines, dibenzofurans, and carbazoles. The precursors are heterocycles bearing a methyl ketone group *ortho* to an internal alkyne. They are commercially available or can be obtained in three to four classical and efficient reactions: Vilsmeier−Haack, Sonogashira (diversity point), Grignard, and Ley's oxidation. Upon aminobenzannulation reaction—classical conditions being pyrrolidine neat or in a solvent and 4 Å MS—an interesting range of disubstituted quinolines, dibenzofurans, and carbazoles are obtained along with enamine formation in some cases. The reaction is useful since *meta*-substituted heterocycles are produced and also differs from classical heterocyclic methods which go through closure at the heteroatom-containing ring instead of benzene ring formation.

Introduction

Since the pioneering work of Berthelot,[1] protocols for the de novo construction of functionalized benzenoid rings (benzannulations) have emerged.[2] Metal-mediated benzannulations are very useful reactions.[3] The chromium-templated [3 + 2 + 1] cycloaddition, based on the reactivity of chromium Fisher carbenes,[4] was first reported by Dötz in 1975.[5] Cobalt-mediated [2 + 2 + 2] cyclotrimerization of alkynes led to many developments,[6] also chemo- and regioselective benzannulation has been illustrated.[6a] The palladium-catalyzed [4 + 2] or [2 + 2 + 2] benzannulation has been well studied[2a,7] along with other transition or Lewis acidic metals.[3a,8] Recently, we developed a method for acridine derivatives using a rhodium catalysis[9]

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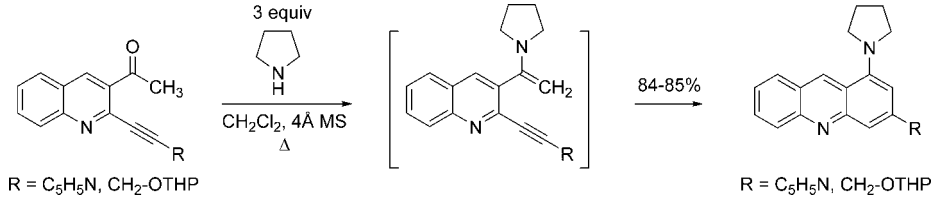
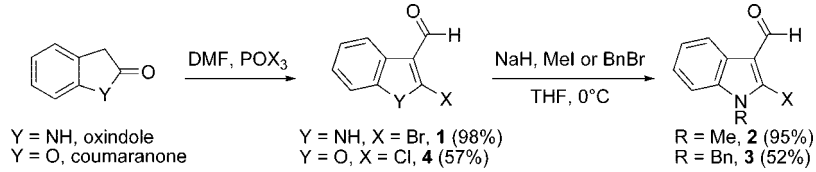
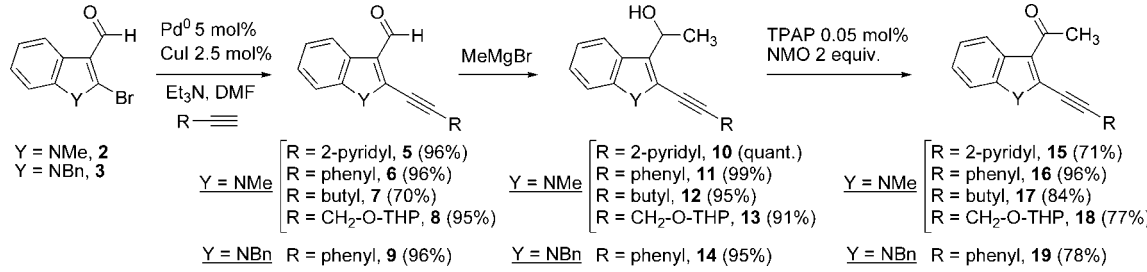
SCHEME 1. Previous Work[21]



SCHEME 2. Starting Materials



SCHEME 3. Precursor Synthesis in the Indole Series



inspired from a naphthalene synthesis reported previously.[8q,10] Also, a metal-free iodocyclization using ICl[11] or $I(py)_2BF_4$[12] led to functionalized benzene and heterocyclic nuclei. Upon irradiation (Hanovia mercury lamp, Pyrex filter)[13] or thermal conditions,[14] the synthesis of highly substituted benzenoid derivatives has been nicely achieved. Benzannulation can be also completed with acid (camphorsulfonic acid)[15] or various basic conditions.[16]

Aminobenzannulation arose some years ago as a benzannulation method with the participation of an external nitrogen unit. Thus Merlic's group[17] developed an aminobenzannulation method with chromium dienylcarbene complex (Dötz reaction), and the use of simple isonitriles as the nitrogen unit, to generate *o*-alkoxy aromatic amine derivatives upon thermal activation. This group reported also a photoinduced cyclization of *tert*-butoxycarbonyl-coordinated tetracarbonyl complexes yielding *o*-amino aromatic alcohols.[17c] Würthwein's group[18] designed an aminobenzannulation method based on the deprotonation of 2-(1-alkynyl)benzaldimines through a multistep rearrangement cascade. This method was also used to construct decahydronaphthalen-1-ylamines, 7-aminobenzofurans, and more recently polysubstituted aminobenzannulated heterocycles.[19] Herndon's group[20] reported in 2001 a powerful method allowing access to aminonaphthalenes taking advantage of the dual role of a palladium catalyst. Inspired from Herndon's results, we built up a metal-free pyrrolidine-triggered aminobenzannulation reaction[21] where the enamine formation and the aminobenzan-

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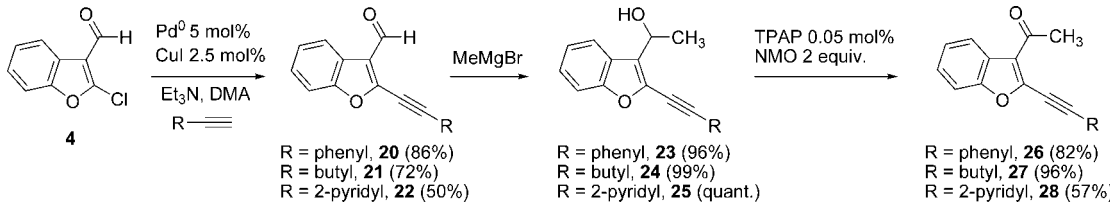
SCHEME 4. Precursor Synthesis in the Benzofuran Series



nulation step took place subsequently. The scope of this method was limited to the construction of 1-aminoacridine derivatives (Scheme 1).

We thus became interested in widening the field of application of our method and also extend the nature of the substitution pattern on the newly formed heterocycles. Therefore, starting from commercially available pyridine or easily accessible indole and benzofuran, we wish to report in this paper a new and efficient access to amino-substituted quinoline, carbazole, and dibenzofuran rings. Also, these heterocycles are of interest for their broad biological or physical properties. Indeed, quinoline nucleus is incorporated in numerous alkaloids and displays many biological activities.[22] Dibenzofuran rings display interesting physical and biological properties.[23] Finally, carbazole units are found in many bioactive molecules, particularly in antitumor derivatives.[24]

Results and Discussion

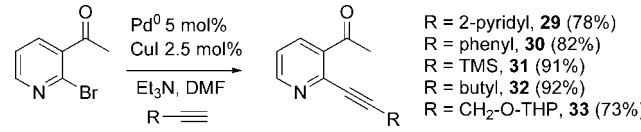
For the synthesis of the starting materials, we followed a classical Vilsmeier−Haack bromoformylation reaction[25] to get efficiently 2-bromo-1*H*-indole-3-carbaldehyde **1** (98%) from commercial oxindole (Scheme 2). The nitrogen of indole **1** was then protected either by methylation or by benzylation to get, respectively, in high to fair yield, compound **2** (95%) or **3** (52%). In the carbazole series, 2-chlorobenzofuran-3-carbaldehyde **4** (Scheme 2) was obtained from commercial coumaranone as previously reported (57%).[26]

The first diversity point was introduced thanks to a Sonogashira reaction[27] on the halogen derivatives **2**, **3**, and **4**. Therefore, from methylindole **2** (Scheme 3), following Toyota-Ihara's conditions,[28] we obtained efficiently four different alkynyl compounds bearing a 2-pyridyl unit **5** (96%), a phenyl unit **6** (96%), a butyl unit **7** (70%), or a tetrahydropyranyl unit **8** (95%). Also, benzyl-protected indole **3** (Scheme 3) was coupled with phenylethynyl reagent to produce compound **9** (96%). The coupling products **5**−**9** were then submitted to a Grignard reaction with methyl magnesium bromide, yielding, respectively, secondary alcohol derivatives **10**−**14** in high yields (91% quant.). Upon oxidation of alcohols **10**−**14** with Ley's conditions (TPAP/NMO),[29] the desired methyl ketone derivatives **15**−**19** were produced in good yields (71−96%).

Using the same reaction sequence (Sonogashira, Grignard, Ley's oxidation), the benzofuran derivative **4** was transformed at first in coupling compounds **20**−**22** (Scheme 4), respectively, with a phenyl (86%), butyl (72%), or 2-pyridine (50%) substituent on the alkynyl group.[30] Further Grignard reaction on **20**−**22** afforded secondary alcohols **23**−**25** in high yields (96% quant.) and, upon oxidation, the needed methyl ketones **26**−**28** in fair to high yield (57−96%).

For the quinoline series, we began with commercially available 1-(2-bromopyridin-3-yl)ethanone[31] that underwent several efficient Sonogashira reactions to obtain directly the desired methyl ketone derivatives (Scheme 5) bearing on the alkynyl group either a 2-pyridine **29** (78%), a phenyl **30** (82%), a trimethylsilyl **31** (91%), a butyl **32** (92%), or a tetrahydropyranyl moiety **33** (73%).

SCHEME 5. Precursor Synthesis in the Quinoline Series



Having in hand the requisite heteroaryl substrates **15**−**19** and **26**−**33**, bearing a methyl ketone group and *ortho*-functionalized with an alkynyl group, we could then test their reactivity toward our pyrrolidine-triggered aminobenzannulation (Tables 1–3). Using pyridine **29** in simple reaction conditions (3 equiv of pyrrolidine, 6 weight equiv powdered 4 Å molecular sieves in CH_2Cl_2), quinoline **34** was obtained in very good yield (87%) at room temperature (Method A, Table 1). With the other pyridine derivatives **30**−**33**, following Method A conditions, only starting material was recovered. Heating the reaction mixture (Method B, in $Cl(CH_2)_2Cl$) led only to the formation of traces of the desired products. Finally, performing the reaction in the amine as the solvent and at reflux (Method C) gave successfully quinoline **35** (91%), **36** (85%), **37** (45%), and **38** (53%). It is worth noting that having an alkyl substituent (**37** and **38**) diminishes the efficiency of the 6-*endo*-dig cyclization/aromatization reaction. Activation of the triple bond seems to play an important role since smooth conditions are needed to build quinoline **34**, bearing an electron-deficient pyridine ring, whereas heating in pyrrolidine neat is required to get phenyl-substituted quinoline **36**. Interestingly, trimethylsilyl quinoline intermediate **31** cyclized nicely to give quinoline **35** with concomitant loss of the TMS group.[32]

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(30) In this case, dimethylacetamide (DMA) was used instead of DMF to avoid partial reduction of the triple bond.
(31) Otherwise, this compound can be easily made from commercially available 2-bromopyridine-3-carbaldehyde by standard procedure (Grignard and oxidation).
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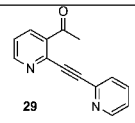
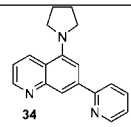
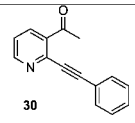
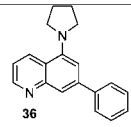
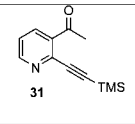
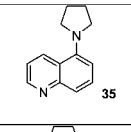
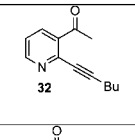
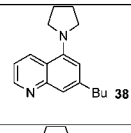
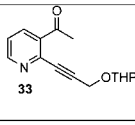
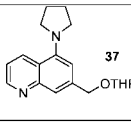
TABLE 1. Aminobenzannulation Products: Quinolines from Pyridines

Starting materials	Products	Method[a]	Yield
 29	 34	A	87%
 30	 36	C	85%
 31 TMS	 35	C	91%
 32 Bu	 Bu 38	C	53%
 33 OTHP	 37 OTHP	C	45%

[a] Method A: 1 mmol starting material in dry dichloromethane (5 mL) under argon, 4 Å molecular sieves (6 weight equiv) and amine (3 equiv), at room temperature. Method C: 1 mmol starting material in pyrrolidine (5 mL), with 4 Å molecular sieves (6 weight equiv), at reflux.

On the other hand, reactions performed with benzofuran derivatives **26**−**28** led surprisingly to undesired compounds or even mixtures (Table 2). In the case of phenylbenzofuran **26**, following Method B (heating in $Cl(CH_2)_2Cl$) was necessary to run the reaction, and the desired dibenzofuran derivative **39** (55%) was accompanied by another compound **40** (45%) formed through direct attack on the alkynyl function.

The structure of this enamino-benzofuran derivative **40** (45%), along with its stereo- and regiochemistry, has been confirmed by NMR data and X-ray analysis.[33] It is interesting to see that in the case of pyridine benzofuran **28** (Table 2) the same reaction led only to the formation of enamino-benzofuran **41** (quant.). The reactivity pattern between these two benzofurans recalls what was observed earlier in the case of quinoline synthesis, attesting the higher reactivity of the triple bond when linked to a pyridine instead of a phenyl moiety.[34] Hence, the benzofuran nucleus is obviously more electrophilic than the quinoline one since direct pyrrolidine addition onto the alkynyl function is preferred toward the aminobenzannulation reaction.[35] We can thus propose a *pseudo* 1,6-addition leading to the enamine derivatives, whereas the aminobenzannulation products are obtained through a 6-*endo*-dig cyclization driven by the aromatization (see more details in ref 35). For the same reasons as earlier, reaction of alkyl-substituted benzofuran such as **27** is less effective and only 17% of the desired dibenzofuran **42** is isolated. The compound of direct addition **43** is also observed but was hard to characterize due to the instability of the butyl enamino group compared to the aromatic enamino group present in **40** and **41**.

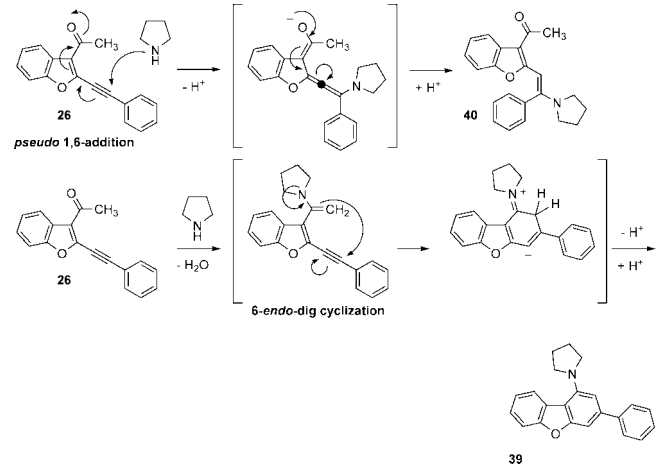
In the indole series, activation of the triple bond for compound **15** (Table 3), due to the indole and pyridine moieties, led as before only to direct addition of pyrrolidine onto the alkynyl bond (**44**, quant.), even at room temperature (Method A). For the other indole precursors **16**−**18**, an efficient synthesis of disubstituted carbazoles was made possible with a phenyl (**45**, 96%), a butyl (**46**, 65%), or a tetrahydropyranyl (**47**, 65%) substitution (Method B). Changing the nitrogen protecting group for a benzyl group, as seen in phenylindole **19**, had no impact on cyclization since we observed, in the same reaction condition (Method B), an efficient aminobenzannulation yielding carbazole **48** (80%). We used this last transformation as a test reaction in order to show that no remaining palladium traces from previous Sonogashira reaction could participate in the aminobenzannulation step. Indeed, based on recent studies[36] applied in our case, palladium traces do not appear to be involved, and thus we are confident in our metal-free aminobenzannulation reaction.

Also, the amine moiety can be changed for benzylamine or diethylamine producing, respectively, carbazoles **49** (73%) or **50** (70%) from indole **16**, showing that cyclic secondary amine was not compulsory. Indeed, carbazole **49** is interesting since it opens the way to further substitution or deprotection reactions.

(33) Crystallographic information concerning compound **40** can be found in the Supporting Information.

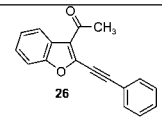
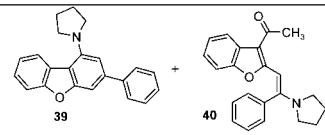
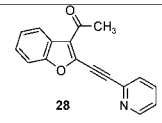
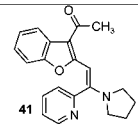
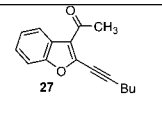
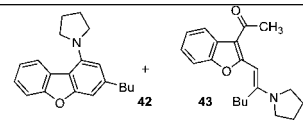
(34) Indeed, in the quinoline series, synthesis of compound **34** from the pyridyl-substituted derivative **29** was performed at room temperature and does not require heating as for other substituent (e.g., phenyl-substituted derivative **30**). Pyridine is known as a π-deficient nitrogen heterocycle, and position-2 which bears here the alkynyl group is electronically deficient which may explain the higher reactivity of the alkyne group in the 2-pyridine-substituted compounds compared with that of the phenyl group. Therefore, this could explain the different reactivity pattern of **26** versus **28** leading to exclusive formation of compound **41** in the case of pyridine substitution. More data on pyridine properties can be viewed in the following: *The Chemistry of Heterocycles*, 2nd ed.; Eicher, T., Hauptmann, S., Eds.; Wiley-VCH: Weinheim, Germany, 2003; Chapter 6.

(35) The C-2/C-3 double bond in benzo[*b*]furans is known to behave like a localized double bond. See: *The Chemistry of Heterocycles*, 2nd ed.; Eicher, T., Hauptmann, S., Eds.; Wiley-VCH: Weinheim, Germany, 2003; Chapter 5. Therefore, compared to reactions operated with quinoline and indole moieties, the alkynyl bond in benzofuran systems is more prone to a pseudo 1,6-addition competing with the 6-*endo*-dig cyclization leading to aminobenzannulation reaction, as shown in the following scheme



(36) This point was further investigated following one reviewer's useful comment. For a review, see: (a) Garret, C. E.; Prasad, K. *Adv. Synth. Catal* **2004**, *346*, 889. (b) Urawa, Y.; Miyazawa, M.; Ozeki, N.; Ogura, K. *Org. Process Res. Dev* **2003**, *7*, 191. (c) Following ref 36b, compound **19**, previously recrystallized, was treated with a polymer-bound tris(2-aminoethyl)amine in order to complex the remaining traces of Pd(0) and Pd(II) and then subjected to the aminobenzannulation reaction. After purification, we obtained carbazole **48bis** in 84% yield; therefore, the reaction is reproducible and in the same range of yield and time than without treatment, which strengthens our belief that no palladium residue is involved (see Supporting Information for more details on the procedure and copy of the ^1H NMR for carbazole **48bis**).

TABLE 2. Dibenzofurans and Enamino-benzofuran Synthesis

Starting materials	Products	Method[a]	Yield
 26	 39 + 40	B	55% + 45%
 28	 41	B	quant.
 27	 42 + 43	B	17% + N/A

[a] Method B: 1 mmol starting material in dry dichloroethane (5 mL) under argon, 4 Å molecular sieves (6 weight equiv) and pyrrolidine (3−6 equiv), at reflux.

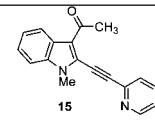
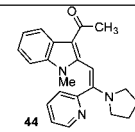
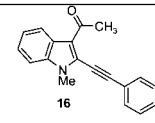
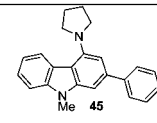
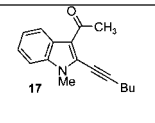
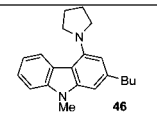
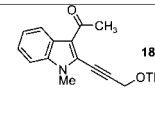
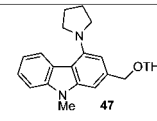
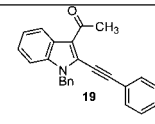
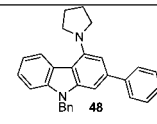
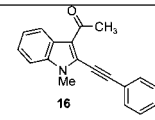
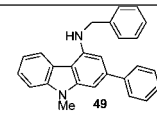
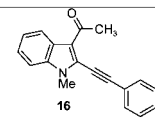
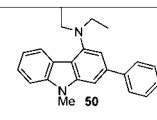
Overall, the development of an aminobenzannulation reaction onto pyridine, benzofuran, and indole heterocycles is powerful since it leads to the synthesis of attractive amino-substituted quinoline, dibenzofuran, and carbazole structures with moderate to excellent yield. Our methodology allows all the substituents to be in the *meta* position in the newly formed ring. Also, an interesting reactivity is observed with benzofuran nuclei where a competition occurs between aminobenzannulation reaction versus regio- and stereoselective enamine formation. Finally, the most important point is to note that this methodology brings some novelty in these heterocycle's synthesis since the key step is the benzene ring formation instead of the usual heteroatom-containing ring formation. Improvements are still sought after in term of nitrogen source for the aminobenzannulation reaction and will be published in due course.

Experimental Section

General Information: Unless otherwise noted, all commercial materials were used without further purification. TLC analysis of reaction mixtures was performed on silica gel F254 TLC plates. Flash chromatography was carried out on silica gel (32−63 μm). ^{1}H and ^{13}C NMR spectra were recorded with 300 MHz spectrometers and referenced to $CDCl_3$ unless otherwise noted. High-resolution mass spectra (*m*/*z*) and crystallographic data were obtained thanks to the facilities operated by the Université Claude Bernard, Lyon 1. For all the general methods, see Supporting Information.

2-Bromo-1*H*-indole-3-carbaldehyde (1). To a solution of dimethylformamide (3.6 mL, 46 mmol) in dichloromethane (12 mL) was added dropwise a solution of phosphorus oxybromide (11.1g, 36.6 mmol) in dichloromethane (20 mL) at 0 °C. The white thick mixture was refluxed during 15 min, and then oxindole (2.053 g, 15.42 mmol) was added portionwise. The mixture was stirred at reflux during 1 h. The reaction was quenched by addition of crushed ice to the media. The mixture was stirred for 20 min, then the two layers were separated. The aqueous layer was neutralized with solid potassium carbonate. The pale yellow precipitate which appeared was washed with cold water and cold dichloromethane then was triturated with acetone. After evaporation of solvent, pure 2-bromo-1*H*-indole-3-carbaldehyde was obtained as 3.44 g (15.35 mmol) of pale yellow solid (98%): mp 186 °C (lit. 196−198 °C[37]); ^{1}H NMR (300 MHz, $CDCl_3$, δ) 13.05 (br s, 1H), 9.98 (s, 1H), 8.49 (dd, J = 8.6, 1.9 Hz, 1H), 7.43 (dd, J = 8.6, 1.9 Hz, 1H), 7.30−7.20 (m, 2H).

TABLE 3. Aminobenzannulation Products: Carbazoles from Indoles

Starting materials	Products	Method[a]	Yield
 15	 44	A	quant.
 16	 45	B	96%
 17	 46	B	65%
 18	 47	B	65%
 19	 48	B	80%
 16	 49	B	73%
 16	 50	B	70%

[a] Method A: 1 mmol starting material in dry dichloromethane (5 mL) under argon, 4 Å molecular sieves (6 weight equiv) and pyrrolidine (3 equiv), at room temperature. Method B: 1 mmol starting material in dry dichloroethane (5 mL) under argon, 4 Å molecular sieves (6 weight equiv) and the appropriate amine (3−6 equiv), at reflux.

2-Bromo-1-methyl-1*H*-indole-3-carbaldehyde (2). To a solution of 2-bromo-1*H*-indole-3-carbaldehyde (4.52 g, 20 mmol) in dry THF was added at 0 °C sodium hydride (60% weight in mineral oil, 994 mg, 24 mmol). The mixture was stirred for 15 min, then MeI (1.5 mL, 24 mmol) was added dropwise. The mixture was stirred 20 min at 0 °C, then water was added. Extraction with dichloromethane and evaporation of solvents afforded 4.52 g (19 mmol, 95%) of the pure desired product: mp 106−107 °C (lit. 110−111 °C[38]); ^{1}H NMR (300 MHz, $CDCl_3$, δ) 9.97 (s, 1H), 8.19 (d, J = 7.0 Hz, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.34−7.23 (m, 2H), 3.86 (s, 3H).

1-Benzyl-2-bromo-1*H*-indole-3-carbaldehyde (3). To a solution of 2-bromo-1*H*-indole-3-carbaldehyde (440 mg, 1.96 mmol) in dry THF was added at 0 °C sodium hydride (60% weight in mineral oil, 100 mg, 2.5 mmol). The mixture was stirred for 15 min, then benzyl bromide (0.3 mL, 2.5 mmol) was added dropwise. The mixture was stirred 8 h, then water was added. Extraction with dichloromethane and evaporation of solvents and purification by flash chromatography on silica gel using ethyl acetate/cyclohexane (1:1) as eluent afforded 317 mg of a white solid (52%): mp 122−125 °C (lit. 125 °C[39]); ^{1}H NMR (300 MHz, $CDCl_3$, δ) 9.89 (s, 1H), 8.17 (d, J = 7.1 Hz, 1H), 7.13−7.08 (m, 6H), 6.95−6.92 (m, 2H), 5.27 (s, 2H).

2-Chlorobenzofuran-3-carbaldehyde (4). To a solution of dimethylformamide (2 g) in chloroform (10 mL) was added dropwise phosphorus oxychloride (3.1 g) at 0 °C. After stirring at 0−5 °C for 5 min, a solution of coumaranone (1.1 g, 8.12 mmol) in chloroform (7.5 mL) was added dropwise under ice cooling and then refluxed for 18 h. The chloroform was removed under reduced pressure, and water was added to the residue. Potasssium acetate was added until pH 5 then 2 N sodium hydroxide was added until pH 7 was reached. The mixture was extracted with dichloromethane, dried over sodium sulfate, and the solvent was removed under reduced pressure. The residue was chromatographed on a column of silica gel using chloroform as eluent, and 643 mg of pale yellow solid was obtained (4.68 mmol, 57%): mp 87 °C (lit.[26] 83−86 °C); ^{1}H NMR (300 MHz, $CDCl_3$, δ) 10.13 (s, 1H), 8.19−8.12 (m, 1H), 7.47−7.42 (m, 1H), 7.37−7.33 (m, 2H).

1-Methyl-2-pyridin-2-ylethynyl-1*H*-indole-3-carbaldehyde (5): Pale yellow solid, 96%; mp 144−145 °C; IR (neat) 3048, 2781, 2737, 2208, 1656; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 10.32 (s, 1H), 8.70 (ddd, J = 4.8, 1.5, 0.9 Hz, 1H), 8.34 (ddd, J = 7.4, 1.2, 1.2 Hz, 1H), 7.79 (ddd, J = 7.7, 7.7, 1.7 Hz, 1H), 7.68−7.64 (m, 1H), 7.42−7.32 (m, 4H), 3.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 185.0, 150.4, 141.7, 137.7, 136.6, 130.6, 127.9, 125.4, 124.4, 124.0, 123.7, 122.3, 120.7, 109.9, 99.7, 76.9, 31.4; HRMS-EI (*m*/*z*) for $[C_{17}H_{12}N_2O]^{+\bullet}$ calcd 260.0950, found 260.0954.

1-Methyl-2-phenylethynyl-1*H*-indole-3-carbaldehyde (6): Yellow solid, 96%; mp 113−114 °C (lit. 120−121 °C[40]); ^{1}H NMR (300 MHz, $CDCl_3$, δ) 10.33 (s, 1H), 8.40 (d, J = 7.2 Hz, 1H), 7.71−7.68 (m, 2H), 7.53−7.34 (m, 6H), 3.91 (s, 3H).

2-Hex-1-ynyl-1-methyl-1*H*-indole-3-carbaldehyde (7): Yellow thick oil, 70%; IR (neat) 3057, 2953, 2936, 2871, 1703, 1641; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 10.08 (s, 1H), 8.28−8.25 (m, 1H), 7.27−7.24 (m, 2H), 7.15−7.12 (m, 1H), 3.62 (s, 3H), 2.55 (t, J = 6.9 Hz, 2H), 1.71−1.61 (m, 2H), 1.57−1.45 (m, 2H), 0.98 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 185.0, 136.8, 133.1, 124.4, 124.1, 123.0, 121.6, 119.1, 109.5, 103.5, 69.0, 30.7, 30.2, 22.0, 19.4, 13.5; HRMS-EI (*m*/*z*) for $[C_{16}H_{17}NO]^{+\bullet}$ calcd 239.1310, found 239.1310.

1-Methyl-2-[3-(tetrahydropyran-2-yloxy)prop-1-ynyl]-1*H*-indole-3-carbaldehyde (8): Orange thick oil, 95%; IR (neat) 3055, 2944, 2852, 2360, 1728, 1651; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 10.03 (s, 1H), 8.18 (d, J = 7.2 Hz, 1H), 7.24−7.13 (m, 3H), 4.83−4.80 (m, 1H), 4.53 (s, 2H), 3.84−3.77 (m, 1H), 3.66 (s, 3H), 3.53−3.47 (m, 1H), 1.77−1.49 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 185.1, 137.2, 131.2, 125.0, 124.1, 123.5, 122.0, 120.1, 109.8, 97.8, 97.4, 74.0, 62.2, 54.6, 31.1, 30.2, 25.3, 19.0; HRMS-EI (*m*/*z*) for $[C_{18}H_{19}NO_3]^{+\bullet}$ calcd 297.1365, found 297.1367.

1-Benzyl-2-phenylethynyl-1*H*-indole-3-carbaldehyde (9): Pale brown solid, 96%; mp 110−112 °C (lit.[32]119−120 °C); ^{1}H NMR (300 MHz, $CDCl_3$, δ) 10.42 (s, 1H), 8.48−8.46 (m, 1H), 7.62−7.60 (m, 2H), 7.45−7.28 (m, 11H), 5.52 (s, 2H); HRMS-CI (*m*/*z*) for $[C_{24}H_{17}NO+H]^+$ calcd 336.1388, found 336.1385.

1-(1-Methyl-2-pyridin-2-ylethynyl-1*H*-indol-3-yl)ethanol (10): Pale brown solid, quant.; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.61 (d, J = 4.8 Hz, 1H), 7.89 (d, J = 8.1 Hz, 1H), 7.69 (ddd, J = 7.7, 7.7, 1.7 Hz, 1H), 7.54 (d, J = 7.7 Hz, 1H), 7.32−7.22 (m, 3H), 7.15−7.10 (m, 1H), 5.47 (q, J = 6.6 Hz, 1H), 3.84 (s, 3H), 2.32 (br s, 1H), 1.74 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 150.1, 142.9, 137.8, 136.3, 127.1, 126.2, 124.8, 123.9, 123.0, 121.0, 120.0, 118.1, 109.7, 97.8, 80.1, 64.8, 30.7, 24.0; HRMS-ESI (*m*/*z*) for $[C_{18}H_{16}N_2O + H - H_2O]^+$ calcd 259.1235, found 259.1238.

1-(1-Methyl-2-phenylethynyl-1*H*-indol-3-yl)ethanol (11): Orange oil, 99%; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.91 (d, J = 8.0 Hz, 1H), 7.61−7.57 (m, 2H), 7.42−7.37 (m, 3H), 7.31−7.26 (m, 2H), 7.16 (ddd, J = 8.0 Hz, J = 5.8 Hz, J = 2.2 Hz, 1H), 5.47 (q, J = 6.6 Hz, 1H), 3.82 (s, 3H), 2.27 (br s, 1H), 1.78 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 137.5, 131.4 (2C), 128.8, 128.6 (2C), 124.8, 124.3, 123.4, 122.6, 120.7, 119.9, 119.1, 109.5, 98.7, 79.8, 65.0, 30.5, 23.8; HRMS-EI (*m*/*z*) for $[C_{19}H_{17}NO]^{+\bullet}$ calcd 275.1310, found 275.1309.

1-(2-Hex-1-ynyl-1-methyl-1*H*-indol-3-yl)ethanol (12): Red oil, 95%; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.85 (d, J = 8.0 Hz, 1H), 7.27−7.23 (m, 2H), 7.15−7.10 (m, 1H), 5.36 (q, J = 5.6 Hz, 1H), 3.73 (s, 3H), 2.57 (t, J = 6.9 Hz, 2H), 2.26 (br s, 1H), 1.74−1.64 (m, 5H), 1.62−1.50 (m, 2H), 1.02 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 137.0, 124.8, 122.9, 122.8, 120.3, 119.9, 119.6, 109.3, 100.1, 71.1, 65.0, 30.7, 30.3, 23.7, 22.1, 19.5, 13.6; HRMS-EI (*m*/*z*) for $[C_{17}H_{21}NO]^{+\bullet}$ calcd 255.1623, found 255.1624.

1-{1-Methyl-2-[3-(tetrahydropyran-2-yloxy)prop-1-ynyl]-1*H*-indol-3-yl}ethanol (13): Brown oil, 91%; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.88 (d, J = 8.0 Hz, 1H), 7.28−7.20 (m, 2H), 7.15−7.10 (m, 1H), 5.37 (q, J = 6.6 Hz, 1H), 4.94−4.92 (m, 1H), 4.61 (s, 2H), 3.96−3.88 (m, 1H), 3.76 (s, 3H), 3.63−3.58 (m, 1H), 2.58 (br s, 1H), 1.91−1.56 (m, 6H), 1.71 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 137.3, 124.8, 124.6, 123.4, 120.7, 119.8, 118.4, 109.5, 97.1, 94.8, 76.4, 64.8, 62.1, 54.9, 30.5, 30.3, 25.3, 23.8, 19.0; HRMS-ESI (*m*/*z*) for $[C_{19}H_{23}NO_3 + Na]^+$ calcd 336.1576, found 336.1578.

1-(1-Benzyl-2-phenylethynyl-1*H*-indol-3-yl)ethanol (14): Yellow oil, 95%; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.94 (d, J = 7.9 Hz, 1H), 7.52−7.48 (m, 2H), 7.37−7.33 (m, 3H), 7.29−7.20 (m, 7H), 7.17−7.12 (m, 1H), 5.51 (q, J = 6.6 Hz, 1H), 5.45 (s, 2H), 2.34 (br s, 1H), 1.81 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 137.6, 137.1, 131.3, 128.8, 128.7, 128.5, 127.5, 126.9, 125.1, 124.7, 123.5, 122.4, 120.8, 120.1, 118.8, 110.1, 98.8, 79.9, 65.1, 47.9, 23.8; HRMS-ESI (*m*/*z*) for $[C_{25}H_{21}NO + Na]^+$ calcd 374.1521, found 374.1521.

1-(1-Methyl-2-pyridin-2-ylethynyl-1*H*-indol-3-yl)ethanone (15): Pale brown solid, 71%; mp 116−118 °C; IR (neat) 3053, 2925, 2851, 2210, 1726, 1641; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.60 (br s, 1H), 8.38−8−35 (m, 1H), 7.66 (ddd, J = 7.7, 7.7, 1.5 Hz, 1H), 7.52 (d, J = 7.6 Hz, 1H), 7.29−7.19 (m, 4H), 3.83 (s, 3H), 2.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 193.7, 150.5, 142.1, 137.3, 136.6, 127.5, 125.9, 125.6, 125.0, 123.9, 123.3, 123.3, 120.6, 109.6, 100.7, 80.1, 31.4, 30.1; HRMS-ESI (*m*/*z*) for $[C_{18}H_{14}N_2O + H]^+$ calcd 275.1184, found 275.1186.

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1-(1-Methyl-2-phenylethynyl-1*H*-indol-3-yl)ethanone (16): Pale yellow solid, 96%; mp 113−115 °C; IR (neat) 3053, 2927, 2861, 1679; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.38 (d, J = 6.8 Hz, 1H), 7.53−7.50 (m, 2H), 7.35−7.32 (m, 3H), 7.26−7.16 (m, 3H), 3.78 (s, 3H), 2.72 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 193.8, 137.2, 131.5, 129.8, 128.8, 126.9, 126.1, 124.7, 123.2, 123.2, 121.8, 119.8, 109.5, 102.2, 80.8, 31.3, 30.0; HRMS-CI (*m*/*z*) for $[C_{19}H_{15}NO + H]^+$ calcd 274.1232, found 274.1235.

1-(2-Hex-1-ynyl-1-methyl-1*H*-indol-3-yl)ethanone (17): Pale green oil, 84%; IR (neat): 3053, 2958, 2932, 2230, 1713, 1643; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.44−8.41 (m, 1H), 7.30−7.16 (m, 3H), 3.73 (s, 3H), 2.69 (s, 3H), 2.59 (t, J = 6.9 Hz, 2H), 1.72−1.63 (m, 2H), 1.58−1.46 (m, 2H), 0.97 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 191.8, 134.6, 125.9, 123.8, 122.1, 120.9, 120.8, 116.8, 107.3, 102.8, 70.4, 28.9, 28.3, 27.7, 20.2, 17.6, 11.6; HRMS-EI (*m*/*z*) for $[C_{17}H_{19}NO]^{+\bullet}$ calcd 253.1466, found 253.1464.

1-{1-Methyl-2-[3-(tetrahydropyran-2-yloxy)prop-1-ynyl]-1*H*-indol-3-yl}ethanone (18): Brown oil, 77%; IR (neat) 2942, 1728, 1640; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.46−8.43 (m, 1H), 7.37−7.25 (m, 3H), 4.95 (m, 1H), 4.67 (s, 2H), 3.94−3.88 (m, 1H), 3.82 (s, 3H), 3.63−3.56 (m, 1H), 2.73 (s, 3H), 1.89−1.57 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 193.8, 136.9, 126.1, 125.8, 124.6, 123.2, 123.2, 120.0, 109.5, 99.0, 97.4, 77.1, 62.3, 54.8, 31.2, 30.3, 29.9, 25.4, 19.1; HRMS-ESI (*m*/*z*) for $[C_{19}H_{21}NO_3 + Na]^+$ calcd 334.1419, found 334.1417.

1-(1-Benzyl-2-phenylethynyl-1*H*-indol-3-yl)ethanone (19): White solid, 78%; mp 138−139 °C; IR (neat) 3063, 3028, 2916, 2208, 1632; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.56−8.53 (m, 1H), 7.56−7.53 (m, 2H), 7.44−7.41 (m, 2H), 7.34−7.22 (9H), 5.59 (s, 2H), 2.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 194.0, 136.8, 136.5, 131.6, 129.8, 129.0 (2C), 128.8 (2C), 128.0, 126.9, 126.7, 126.4, 124.9, 123.4, 123.4, 121.7, 120.3, 110.1, 102.3, 81.0, 48.6, 30.1; HRMS-ESI (*m*/*z*) for $[C_{25}H_{19}NO + H]^+$ calcd 350.1545, found 350.1546.

2-Phenylethynylbenzofuran-3-carbaldehyde (20): Yellow solid, 86%; mp 86 °C; IR (neat) 3060, 2209, 1673; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 10.36 (s, 1H), 8.21−8.18 (m, 1H), 7.67−7.63 (m, 2H), 7.53−7.36 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 185.5, 154.7, 148.0, 132.2 (2C), 130.4, 128.8 (2C), 127.2, 125.3, 123.9, 123.4, 122.5, 120.5, 111.3, 101.0, 77.2; HRMS-EI (*m*/*z*) for $[C_{17}H_{10}O_2]^{+\bullet}$ calcd 246.0681, found 246.0678.

2-Hex-1-ynylbenzofuran-3-carbaldehyde (21): Orange oil, 72%; IR (neat) 2972, 2958, 2932, 2230,1672, 1721; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 10.22 (s, 1H), 8.15−8.13 (m, 1H), 7.47−7.32 (m, 3H), 2.59 (t, J = 6.9 Hz, 2H), 1.73−1.63 (m, 2H), 1.58−1.46 (m, 2H), 0.98 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 185.8, 154.3, 148.8, 126.8, 125.1, 123.4, 123.3, 122.3, 111.2, 103.9, 69.3, 30.0, 22.1, 19.6, 13.6; HRMS-EI (*m*/*z*) for $[C_{15}H_{14}O_2]^{+\bullet}$ calcd 226.0994, found 226.0994.

2-Pyridin-2-ylethynylbenzofuran-3-carbaldehyde (22): Brown solid, 50%; mp 89−92 °C; IR (neat) 3055, 2216, 1681; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 10.37 (s, 1H), 8.67 (d, J = 4.8 Hz, 1H), 8.17 (d, J = 7.1 Hz, 1H), 7.74 (ddd, J = 7.7, 7.7, 1.8 Hz, 1H), 7.64 (d, J = 7.7 Hz, 1H), 7.49 (d, J = 7.7 Hz, 1H), 7.43 (ddd, J = 7.1, 7.1, 1.5 Hz, 1H), 7.40−7.31 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 185.3, 154.9, 150.6, 146.8, 141.1, 136.5, 128.1, 127.5, 125.3, 125.0, 124.4, 123.2, 122.6, 111.4, 99.1, 76.2; HRMS-EI (*m*/*z*) for $[C_{16}H_9NO_2]^{+\bullet}$ calcd 247.0633, found 247.0632.

1-(2-Phenylethynylbenzofuran-3-yl)ethanol (23): Yellow oil, 96%; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.78 (d, J = 7.6 Hz, 1H), 7.56−7.53 (m, 2H), 7.42 (d, J = 8.2 Hz, 1H), 7.36−7.29 (m, 4H), 7.22 (ddd, J = 7.0, 7.0, 1.0 Hz, 1H), 5.31 (q, J = 6.6 Hz, 1H), 2.37 (br s, 1H), 1.69 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 154.9, 134.6, 131.6, 129.3, 128.6, 128.4, 126.0, 125.9, 123.1, 121.8, 121.3, 111.4, 98.3, 78.6, 63.9, 23.1; HRMS-EI (*m*/*z*) for $[C_{18}H_{14}O_2]^{+\bullet}$ calcd 262.0994, found 262.0992.

1-(2-Hex-1-ynylbenzofuran-3-yl)ethanol (24): Yellow oil, 99%; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.76 (d, J = 7.6 Hz, 1H), 7.40 (d, J = 8.1 Hz, 1H), 7.33−7.27 (m, 1H), 7.25−7.19 (m, 1H), 5.23 (q, J = 6.6 Hz, 1H), 2.52 (t, J = 7.1 Hz, 2H), 2.18 (br s, 1H), 1.67−1.59 (m, 5H), 1.56−1.44 (m, 2H), 0.97 (t, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 154.5, 135.3, 126.9, 126.1, 125.4, 123.0, 121.0, 111.3, 100.4, 70.2, 63.9, 30.4, 23.1, 22.1, 19.5, 13.7; HRMS-EI (*m*/*z*) for $[C_{16}H_{18}O_2]^{+\bullet}$ calcd 242.1307, found 242.1307.

1-(2-Pyridin-2-ylethynylbenzofuran-3-yl)ethanol (25): Brown oil, quant.; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.52 (d, J = 4.8 Hz, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.67 (ddd, J = 7.8, 7.8, 1.8 Hz, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.42 (d, J = 8.2 Hz, 1H), 7.35 (ddd, J = 7.0, 7.0, 1.3 Hz, 1H), 7.27−7.20 (m, 2H), 5.42 (q, J = 6.6 Hz, 4H), 1.72 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 155.5, 150.4, 142.5, 136.8, 134.1, 131.2, 127.6, 126.6, 126.3, 123.8, 123.5, 122.0, 111.8, 97.2, 79.0, 63.8, 23.7; HRMS-EI (*m*/*z*) for $[C_{17}H_{13}NO_2]^{+\bullet}$ calcd 263.0946, found 263.0941.

1-(2-Phenylethynylbenzofuran-3-yl)ethanone (26): Yellow solid, 82%; mp 89−92 °C; IR (neat) 3055, 2987, 2214, 1665; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.30−8.27 (m, 1H), 7.63−7.60 (m, 2H), 7.48−7.33 (m, 6H), 2.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 194.0, 154.8, 143.2, 132.2, 130.7, 129.2, 127.1, 125.6, 125.3, 124.2, 123.9, 121.3, 111.3, 102.2, 80.3, 30.4; HRMS-EI (*m*/*z*) for $[C_{18}H_{12}O_2]^{+\bullet}$ calcd 260.0837, found 260.0838.

1-(2-Hex-1-ynylbenzofuran-3-yl)ethanone (27): Yellow oil, 96%; IR (neat) 2959, 2933, 2873, 2226, 1664; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.26−8.22 (m, 1H), 7.44−7.30 (m, 3H), 2.72 (s, 3H), 2.60 (t, J = 7.0 Hz, 2H), 1.74−1.46 (m, 2H), 1.58−1.46 (m, 2H), 0.98 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 194.0, 154.0, 143.5, 126.4, 125.3, 124.8, 123.4, 123.0, 110.9, 104.9, 71.9, 30.0, 29.9, 22.2, 19.7, 13.7 HRMS-EI (*m*/*z*) for $[C_{16}H_{16}O_2]^{+\bullet}$ calcd 240.1150, found 240.1149.

1-(2-Pyridin-2-ylethynylbenzofuran-3-yl)ethanone (28): Brown solid, 57%; mp 129−130 °C; IR (neat) 3053, 2921, 2850, 1656; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.67 (ddd, J = 4.9, 1.4, 0.8 Hz, 1H), 8.28−8.24 (m, 1H), 7.73 (ddd, J = 7.8, 7.8, 1.8 Hz, 1H), 7.61 (ddd, J = 7.8, 1.1, 1.1 Hz, 1H), 7.48−7.31 (m, 4H), 2.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 193.6, 154.7, 150.7, 141.8, 141.5, 136.4, 127.8, 127.1, 125.1, 125.0, 125.0, 124.3, 123.6, 114.6, 111.1, 100.1, 78.7, 30.2; HRMS-CI (*m*/*z*) for $[C_{17}H_{11}NO_2 + H]^+$ calcd 262.0868, found 262.0869.

1-(2-Pyridin-2-ylethynylpyridin-3-yl)ethanone (29): Orange solid, 78%; mp 86−89 °C; IR (neat) 3058, 2994, 2925, 2851, 1724, 1666; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.66 (dd, J = 4.7, 1.6 Hz, 1H), 8.57 (d, J = 4.6 Hz, 1H), 8.01 (dd, J = 8.0, 1.6 Hz, 1H), 7.67−7.54 (m, 2H), 7.32 (dd, J = 8.0, 4.8 Hz, 1H), 7.22 (ddd, J = 7.3, 6.0, 1.2 Hz, 1H), 2.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 198.7, 152.2, 150.3, 142.2, 140.1, 137.1, 136.5, 136.2, 127.7, 123.7, 123.3, 96.2, 86.8, 30.1 ; HRMS-EI (*m*/*z*) for $[C_{14}H_{10}N_2O]^{+\bullet}$ calcd 222.0793, found 222.0791.

1-(2-Phenylethynylpyridin-3-yl)ethanone (30): Colorless oil, 82%; IR (neat) 3059, 2924, 2851, 2220, 1682; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.72 (d, J = 3.3 Hz, 1H), 8.05 (dd, J = 8.0, 1.7 Hz, 1H), 7.62−7.59 (m, 2H), 7.40−7.31 (m, 4H), 2.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 199.1, 152.3, 141.0, 136.8, 136.6, 132.0 (2C), 129.7, 128.6 (2C), 122.8, 121.8, 95.0, 88.1, 30.1; HRMS-EI (*m*/*z*) for $[C_{15}H_{11}NO]^{+\bullet}$ calcd 221.0841, found 221.0842.

1-(2-Trimethylsilanylethynylpyridin-3-yl)ethanone (31): Colorless oil, 91%; IR (neat) 2961, 2896, 2168, 1686; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.67 (dd, J = 1.7, 4.7 Hz, 1H), 8.00 (dd, J = 8.0, 4.7 Hz, 1H), 7.33 (dd, J = 8.0, 4.7 Hz, 1H), 2.80 (s, 3H), 0.28 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 199.5, 152.2, 140.5, 137.4, 136.6, 123.2, 102.8, 102.2, 30.3, −0.5; HRMS-EI (*m*/*z*) for $[C_{12}H_{15}NOSi + H]^+$ calcd 218.1001, found 218.1003.

1-(2-Hex-1-ynylpyridin-3-yl)ethanone (32): Colorless oil, 90%; IR (neat) 2959, 2932, 2872, 1694, 1715; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.59 (dd, J = 4.7, 1.7 Hz, 1H), 7.91 (dd, J = 7.9, 1.7 Hz, 1H), 7.23 (dd, J = 7.9, 4.7 Hz, 1H), 2.72 (s, 3H), 2.46 (t, J = 7.2 Hz, 2H), 1.64−1.54 (m, 2H), 1.50−1.37 (m, 2H), 0.89 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 199.6, 152.0, 141.3, 136.7, 136.3, 122.3, 97.7, 79.9, 30.1 (2C), 22.1, 19.3, 13.6; HRMS-EI (*m*/*z*) for $[C_{13}H_{15}NO]^{+\bullet}$ calcd 201.1154, found 201.1155.

1-{2-[3-(Tetrahydropyran-2-yloxy)prop-1-ynyl]pyridin-3-yl}ethanone (33): Brown oil, 73%; IR (neat) 2941, 2861, 1726, 1686; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.60 (d, J = 4.8 Hz, 1H), 7.94 (d, J = 7.7 Hz, 1H), 7.28 (dd, J = 7.7, 4.8 Hz, 1H), 4.84 (br s, 1H), 4.49 (s, 2H), 3.82−3.75 (m, 1H), 3.51−3−45 (m, 1H), 2.70 (s, 3H), 1.77−1.47 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 198.9, 152.0, 140.2, 136.8, 136.3, 122.9, 97.0, 91.5, 84.2, 61.9, 54.4, 30.1, 29.9, 25.2, 18.9; HRMS-EI (*m*/*z*) for $[C_{15}H_{17}NO_3]^{+\bullet}$ calcd 259.1208, found 259.1207.

7-Pyridin-2-yl-5-pyrrolidin-1-ylquinoline (34): Brown oil, Method A: 87%; IR (neat) 2964, 1870, 1607, 1586, 1560; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.88 (dd, J = 4.1, 1.4 Hz, 1H), 8.75 (d, J = 4.8 Hz, 1H), 8.55 (d, J = 8.6 Hz, 1H), 8.15 (s, 1H), 7.94 (d, J = 8.0 Hz, 1H), 7.83−7.77 (m, 2H), 7.34−7.26 (m, 2H), 3.54−3.50 (m, 4H), 2.07−2.03 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 157.5, 150.2, 150.0, 149.7, 148.4, 140.4, 136.9, 133.4, 123.0, 122.5, 121.4, 119.8, 119.2, 109.8, 53.0 (2C), 25.3 (2C); HRMS-ESI (*m*/*z*) for $[C_{18}H_{17}N_3 + H]^+$ calcd 276.1501, found 276.1502.

5-Pyrrolidin-1-ylquinoline (35): Pale yellow oil, Method A: 0%, Method B: traces, Method C: 91%; IR (neat) 2865, 2871, 2825, 1585, 1571; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.83 (dd, J = 4.1, 1.6 Hz, 1H), 8.53 (d, J = 8.6 Hz, 1H), 7.65 (d, J = 8.3 Hz, 1H),7.56 (m, 1H), 7.29 (dd, J = 8.6 Hz, 4.2 Hz, 1H), 6.92 (d, J = 7.6 Hz, 1H), 3.41−3.37 (m, 4H), 2.04−1.99 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 149.8 (2C), 147.9, 133.4, 129.5, 122.8, 121.6, 118.8, 110.9, 52.9 (2C), 25.2 (2C); HRMS-CI (*m*/*z*) for $[C_{13}H_{14}N_2 + H]^+$ calcd 199.1235, found 199.1235.

7-Phenyl-5-pyrrolidin-1-ylquinoline (36): Pale brown oil, Method C: 85%; IR (neat) 2970, 2870, 2830, 1683, 1595, 1579, 1557; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.74 (dd, J = 4.1, 1.6 Hz, 1H), 8.41 (d, J = 8.4 Hz, 1H), 7.71 (br s, 1H), 7.66−7.63 (m, 2H), 7.40−7.35 (m, 2H), 7.31−7.25 (m, 1H), 7.16 (dd, J = 8.4, 4.1 Hz, 1H), 7.04 (d, 1.5 Hz, 1H), 3.37−3.33 (m, 4H), 1.94−1.89 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 150.2, 150.1, 148.1, 142.3, 141.3, 133.4, 129.0, 127.7, 127.5, 121.7, 119.4, 118.6, 110.4, 52.9, 25.2; HRMS-ESI (*m*/*z*) for $[C_{19}H_{18}N_2 + H]^+$ calcd 275.1548, found 275.1546.

5-Pyrrolidin-1-yl-7-(tetrahydropyran-2-yloxymethyl)quinoline (37): Brown oil, Method C: 45%; IR (neat) 2942, 2870, 1614, 1589, 1569; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.81 (dd, J = 4.2, 1.5 Hz, 1H), 8.52 (d, J = 8.6 Hz, 1H), 7.65 (s, 1H), 7.27 (dd, J = 8.4, 4.1 Hz, 1H), 6.91 (s, 1H), 4.92 (d, J = 12.6 Hz, 1H), 4.77 (t, J = 3.85 Hz, 1H) 4.66 (d, J = 12.6 Hz, 1H), 4.00−3.92 (m, 1H), 3.60−3.53 (m, 1H), 3.44−3.40 (m, 4H), 2.04−2.00 (m, 4H), 1.81−1.52 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 149.5, 149.3, 148.0, 140.5, 134.0, 122.1, 119.2, 118.6, 110.4, 98.1, 69.0, 62.4, 52.9 (2C), 30.7, 25.6, 25.3 (2C), 19.5; HRMS-ESI (*m*/*z*) for $[C_{19}H_{24}N_2O_2 + H]^+$ calcd 313.1916, found 313.1917.

7-Butyl-5-pyrrolidin-1-ylquinoline (38): Brown oil, Method C: 53%; IR (neat) 2955, 2924, 2854, 1737, 1612, 1589, 1567; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.79 (d, J = 3.6 Hz, 1H), 8.59 (d, J = 8.5 Hz, 1H), 7.53 (s, 1H), 7.30−7.26 (m, 1H), 6.77 (s, 1H), 3.46−3.41 (m, 4H), 2.76 (t, J = 7.7 Hz, 2H), 2.06−2.02 (m, 4H), 1.75−1.65 (m, 2H), 1.47−1.37 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 147.9, 147.7, 147.5, 147.4, 136.4, 121.5, 117.6 (2C), 112.9, 53.3 (2C), 36.9, 33.6, 25.7 (2C), 22.9, 14.4; HRMS-ESI (*m*/*z*) for $[C_{17}H_{22}N_2 + H]^+$ calcd 255.1861, found 255.1863.

1-(3-Phenyldibenzofuran-1-yl)pyrrolidine (39): Brown oil, Method B: 55%; IR (neat) 2923, 2853, 1627, 1598, 1572; ^{1}H MNR (300 MHz, $CDCl_3$, δ) 7.79 (d, J = 7.2 Hz, 1H), 7.59−7.57 (m, 2H), 7.47−7.45 (m, 1H), 7.39−7.34 (m, 2H), 7.31−7.23 (m, 4H) 6.97 (s, 1H), 3.30 (br s, 4H), 1.96 (br s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 158.3, 156.2, 146.4, 141.8, 141.5, 128.9 (2C), 127.6 (2C), 127.5, 125.8, 124.0, 123.0, 122.7, 115.2, 111.2, 109.3, 103.2, 51.2 (2C), 24.5 (2C); HRMS-ESI (*m*/*z*) for $[C_{22}H_{19}NO + H]^+$ calcd 314.1545, found 314.1544.

1-[2-(2-Phenyl-2-pyrrolidin-1-ylvinyl)benzofuran-3-yl]ethanone (40): Yellow/brown solid, Method B: 45%; mp 140−142 °C; IR (neat) 3041, 2964, 2860, 1634; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.59 (d, J = 7.7 Hz, 1H), 7.43−7.40 (m, 3H), 7.31−7.26 (m, 2H), 7.10 (dd, J = 7.6, 7.7 Hz, 1H), 6.95 (dd, J = 7.7, 7.7 Hz, 1H), 6.63 (d, J = 7.8 Hz, 1H), 6.49 (s, 1H), 3.31 (br s, 4H), 2.61 (s, 3H), 1.9 (br s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 193.2, 164.5, 162.4 (2C), 157.1, 152.4, 138.3, 128.3, 128.3 (2C), 127.3, 123.1, 122.2, 119.6, 109.9, 109.7, 87.5 (2C), 49.6, 31.6 (2C), 25.5; HRMS-ESI (*m*/*z*) for $[C_{22}H_{21}NO_2 + Na]^+$ calcd 354.1470, found 354.1469.

1-[2-(2-Pyridin-2-yl-2-pyrrolidin-1-ylvinyl)benzofuran-3-yl]-ethanone (41): Yellow/brown solid, Method B: quant.; mp 145−148 °C; IR (neat) 3052, 2976, 2871, 1640; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.71 (s, 1H), 7.75−7.70 (m, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.37−7.33 (m, 2H), 7.08 (dd, J = 7.7, 7.7 Hz, 1H), 6.93 (dd, J = 7.7, 7.7 Hz, 1H), 6.58 (d, J = 8.3 Hz, 1H), 6.45 (s, 1H), 3.35 (br s, 4H), 2.58 (s, 3H), 1.94 (br s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 193.1, 163.7, 156.6, 154.4, 152.3, 149.4, 136.4, 127.1, 124.1, 123.1 (2C), 122.2, 119.7, 110.0, 109.7, 87.6, 49.1 (2C), 31.5, 25.3 (2C); HRMS-EI (*m*/*z*) for $[C_{21}H_{20}N_2O_2]^{+\bullet}$ calcd 332.1525, found 332.1525.

1-(3-Butyldibenzofuran-1-yl)pyrrolidine (42): Brown oil, Method B: 17%; IR (neat) 2955, 2928, 2857, 2810, 1628, 1599, 1579; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.88−7.85 (m, 1H), 7.56−7.53 (m, 1H), 7.42−7.31 (m, 2H), 7.03 (s, 1H), 6.71 (s, 1H), 3.36 (br s, 4H), 2.79−2.73 (m, 2H), 2.09−2.05 (m, 4H), 1.76−1.66 (m, 2H), 1.49−1.37 (m, 2H), 0.98 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 158.1, 155.8, 146.0, 143.6, 125.3, 124.2, 122.7, 122.5, 113.9, 111.0, 110.4, 104.2, 51.1 (2C), 36.5, 34.0, 24.4 (2C), 22.6, 14.1; HRMS-EI (*m*/*z*) for $[C_{20}H_{23}NO]^{+\bullet}$ calcd 293.1780, found 293.1781.

1-[2-(2-Pyrrolidin-1-ylhex-1-enyl)benzofuran-3-yl]ethanone (43): Yellow slurry solid, Method B; HRMS-ESI (*m*/*z*) for $[C_{20}H_{25}NO_2 + H]^+$ calcd 312.1964, found 312.1963.

1-[1-Methyl-2-(2-pyridin-2-yl-2-pyrrolidin-1-ylvinyl)-1*H*-indol-3-yl]ethanone (44): Yellow solid, Method A: quant.; mp 200 °C; IR (neat) 3048, 2966, 2873, 1623, 1584, 1563; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.61 (d, J = 4.3 Hz, 1H), 8.19 (d, J = 7.9 Hz, 1H), 7.35−7.32 (m, 1H), 7.18 (dd, J = 7.4, 7.4 Hz, 1H), 7.14−7.08 (m, 2H), 7.01 (d, J = 8.0 Hz, 1H), 6.88 (d, J = 7.9 Hz, 1H), 5.59 (s, 1H), 3.33−3.30 (m, 4H), 3.18 (s, 3H), 2.70 (s, 3H), 2.01−1.99 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 194.1, 155.6, 151.5, 149.5, 146.7, 137.0, 136.6, 127.3, 125.1, 123.2, 122.1, 122.0, 121.5, 114.8, 109.3, 89.0, 49.3 (2C), 31.2, 31.0, 25.4 (2C); HRMS-CI (*m*/*z*) for $[C_{22}H_{23}N_3O + H]^+$ calcd 346.1919, found 346.1917.

9-Methyl-2-phenyl-4-pyrrolidin-1-yl-9*H*-carbazole (45): White solid, Method A: 0%, Method B: 96%; mp 126−127 °C; IR (neat) 3050, 2924, 2853, 2804, 1593, 1563; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.07 (d, J = 7.8 Hz, 1H), 7.76−7.73 (m, 2H), 7.52−7.35 (m, 5H), 7.31−7.26 (m, 2H), 7.10 (s, 1H), 3.89 (s, 3H), 3.43−3.39 (m, 4H), 2.14−2.09 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 146.6, 143.2, 142.7, 141.2, 140.0, 128.8 (2C), 127.8 (2C), 127.1, 124.6, 123.1, 122.2, 119.1, 114.8, 108.0, 107.1, 101.5, 51.3 (2C), 29.3, 24.1 (2C); HRMS-ESI (*m*/*z*) for $[C_{23}H_{22}N_2 + H]^+$ calcd 327.1861, found 327.1864.

2-Butyl-9-methyl-4-pyrrolidin-1-yl-9*H*-carbazole (46): Brown oil, Method B: 65%; mp = 59−61 °C; IR (neat) 2955, 2926, 2855, 1598, 1570; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.01 (d, J = 7.6 Hz, 1H), 7.44−7.33 (m, 2H), 7.24 (dd, J = 7.6, 7.6 Hz, 1H), 6.89 (s, 1H), 6.72 (s, 1H), 3.79 (s, 3H), 3.33 (br s, 4H), 2.80 (t, J = 7.7 Hz, 2H), 2.08 (br s, 4H), 1.78−1.67 (m, 2H), 1.50−1.38 (m, 2H), 0.98 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 142.9 (2C), 141.9 (2C), 140.7 (2C), 124.0, 122.7 (3C), 118.8, 107.8, 51.2 (2C), 36.8, 34.3, 29.2, 24.0 (2C), 22.7, 14.2; HRMS-ESI (*m*/*z*) for $[C_{21}H_{26}N_2 + H]^+$ calcd 307.2174, found 307.2175.

9-Methyl-4-pyrrolidin-1-yl-2-(tetrahydropyran-2-yloxymethyl)-9*H*-carbazole (47): Brown oil, Method B: 65%; IR (neat) 2970, 2870, 2831, 1683, 1595, 1579, 1557; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.02 (d, J = 7.9 Hz, 1H), 7.45−7.36 (m, 2H), 7.27−7.21 (m, 1H), 7.09 (s, 1H), 6.84 (s, 1H), 4.96 (d, J = 12.0 Hz, 1H), 4.78−4.75 (m, 1H), 4.68 (d, J = 12.0 Hz, 1H), 4.03−3.95 (m, 1H), 3.83 (s, 3H), 3.61−3.54 (m, 1H), 3.33−3.30 (m, 4H),

2.08−2.04 (m, 4H), 1.77−1.52 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 142.8, 140.9, 136.7, 124.5, 123.0, 122.1, 119.0, 114.9, 108.0, 107.5, 102.5, 97.8, 97.0, 69.8, 62.5, 51.3, 30.8, 30.3, 29.3, 27.0, 25.6, 24.0, 19.7; HRMS-CI (*m*/*z*) for $[C_{23}H_{28}N_2O_3 + H]^+$ calcd 365.2229, found 365.2226.

9-Benzyl-2-phenyl-4-pyrrolidin-1-yl-9*H*-carbazole (48): Pale brown solid, Method B: 80%; mp 130−131 °C; IR (neat) 3048, 3028, 2965, 2922, 2810, 1596, 1563; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.10 (d, J = 7.6 Hz, 1H), 7.67−7.65 (m, 2H), 7.45−7.11 (m, 13H), 5.50 (s, 2H), 3.40 (br s, 4H), 2.09 (br s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 146.7, 142.9, 142.6, 140.8, 140.1, 137.3, 128.8 (2C), 128.8 (2C), 127.7 (2C), 127.4, 127.1, 126.5 (2C), 124.8, 123.2, 122.5, 119.5, 115.0, 108.5, 107.4, 101.8, 51.3 (2C), 46.6, 24.1 (2C); HRMS-ESI (*m*/*z*) for $[C_{29}H_{26}N_2 + H]^+$ calcd 403.2174, found 403.2175.

Benzyl-(9-methyl-2-phenyl-9*H*-carbazol-4-yl)amine (49): Pale brown solid, Method B: 73%; mp 142−145 °C; IR (neat) 3049, 3023, 2924, 2854, 1732, 1585, 1567; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 7.89 (d, J = 7.8 Hz, 1H), 7.65 (d, J = 7.3 Hz, 2H), 7.50 (d, J = 7.2 Hz, 2H), 7.44−7.30 (m, 8H), 7.21−7.17 (m, 1H), 7.02 (s, 1H), 4.91 (br s, 1H), 4.64 (s, 2H), 3.83 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 149.9, 144.7, 143.0, 142.8, 140.8, 139.5, 128.9 (2C), 128.7 (2C), 127.8 (4C), 127.5, 127.1, 124.2, 122.3, 120.4, 119.1, 108.6, 108.3, 101.0, 97.8, 48.6, 29.3; HRMS-ESI (*m*/*z*) for $[C_{26}H_{22}N_2 + H]^+$ calcd 363.1861, found 363.1862.

Diethyl-(9-methyl-2-phenyl-9*H*-carbazol-4-yl)amine (50): White solid, Method B: 70%; mp 146−150 °C; IR (neat) 3053, 2967, 2925, 2852, 1596, 1562; ^{1}H NMR (300 MHz, $CDCl_3$, δ) 8.30 (d, J = 7.8 Hz, 1H), 7.72−7.69 (m, 2H), 7.49−7.41 (m, 3H), 7.39−7.31 (m, 2H), 7.26−7.21 (m, 2H), 7.10 (d, J = 1.1 Hz, 1H), 3.84 (s, 3H), 3.40 (q, J = 7.1 Hz, 4H), 1.10 (t, J = 7.1 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$, δ) 147.4, 143.2, 142.8, 141.2, 139.4, 128.8 (2C), 127.8 (2C), 127.1, 124.9, 123.4, 122.3, 119.1, 116.9, 111.6, 107.9, 102.0, 45.9 (2C), 29.3, 11.9 (2C); HRMS-ESI (*m*/*z*) for $[C_{23}H_{24}N_2 + H]^+$ calcd 329.2018, found 329.2016.

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Supporting Information Available: General synthetic methods and copies of ^{1}H NMR and ^{13}C NMR spectra for compounds **5**, **7**, **8**, **10**−**42**, and **44**−**50**. This material is available free of charge via the Internet at http://pubs.acs.org.

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