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One Pot Synthesis of 2-Styrylindoles from Ortho-Substituted Chloroenynes

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KEYWORDS: 2-Styrylindole, palladium, Suzuki, coupling, cyclization.

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ABSTRACT: A facile one pot synthesis of 2-styrylindoles, through Suzuki-arylation of *ortho*-substituted chloroenynes followed by *N*-cyclization and *N*-demethylation has been developed. A variety of 2-styrylindoles were obtained in good to excellent yields and were evaluated for their anticancer properties.

1. INTRODUCTION

Combretastatin A-4 (CA-4, Fig. 1) is a (*Z*)-stilbene isolated in 1989 by Pettit from the South African willow tree *Combretum caffrum*.[1]

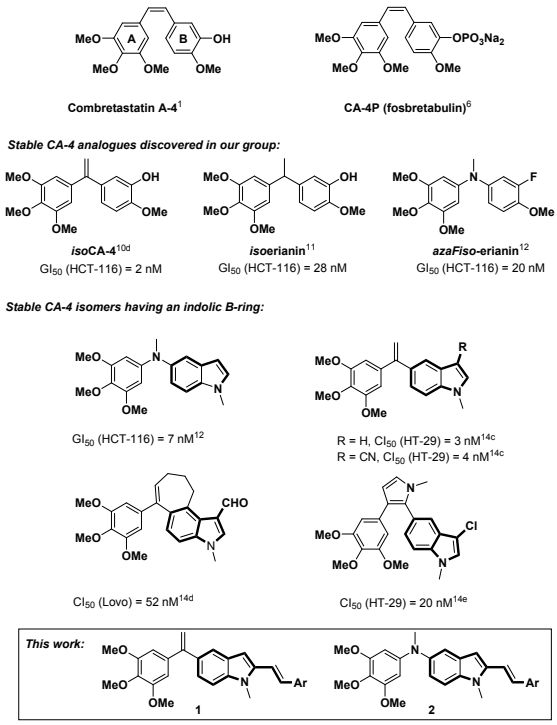


FIGURE 1. CA-4 and structural analogues

This natural compound exhibited strong antitumor properties as for example, a nanomolar level of cytotoxicity against a variety of cancer cell lines including multi-drugs resistant cells.[2] Moreover at very low doses, CA-4 inhibited tubulin assembly by binding at the colchicine binding-site,[3] induced apoptosis[4] and caused *in vivo* spectacular vascular shutdown in established tumors.[5] In 2016, CA-4P (fosbretabulin), a phosphate water-soluble prodrug of the natural product has received the status of orphan drug in USA and Europe for the treatment of ovarian cancers, neuroendocrine tumours, certain thyroid cancers and multiform glioma.[6] Despite these excellent antitumor properties, CA-4 has some drawbacks as a poor water-solubility and a chemical instability due to the isomerization of the *Z*-double bond to its less active *E*-form during storage, administration[7] and metabolism.[8] Due to the simplicity of its chemical structure, CA-4 has been extensively studied to find more stable analogues and to establish structure-activity relationships (SARs).[9] As a part of our research program dedicated to novel stable vascular disrupting agents (VDAs)[10] having a non-isomerizable spacer between A- and B-rings, we found that *iso*CA-4,[10d] *iso*erianin[11] and azaF*iso*-erianin[12] derivatives were as potent as CA-4 with comparable anticancer activities (Fig. 1). Moreover, if the replacement of the 3,4,5-trimethoxyphenyl A-ring of CA-4 has received little attention,[13] the B-ring of CA-4 has been subject to numerous modifications and can be replaced for example, by a variety of indole nuclei with

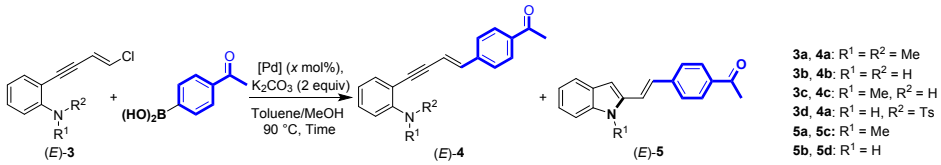
no loss of biological properties.[14] For examples, it was recently showed that non-substituted *N*-methylindoles[12] and 3-substituted indoles[14] replaced with a certain success the traditional phenolic B-ring of CA-4. To our knowledge, introduction of styryl substituents on the C-2 position of the indole B-ring and their effects on biological activity was not reported in the CA-4 and *iso*CA-4 series.

Due to the synthetic and biological interest for 2-alkenylindoles,[15] their preparations have been well studied[16] and often, involve the alkenylation of pre-formed indoles by C-H functionalization[17] or by Suzuki-Miyaura coupling reactions.[18] Otherwise, 2-styrylindoles have also been prepared from 5-*endo*-*dig*-cyclizations of 2-alkynylanilines having a free NH_2 function by electrochemistry or using various metal catalysts.[19] Herein, we would like to present a novel and rapid access to 2-alkenylindoles from an efficient "one pot" Suzuki arylation–heterocyclization-*N*-demethylation process. *N*,*N*-Dimethylanilines having on *ortho*-position a conjugated chloroenyne moiety were firstly arylated using different boronic acids in the presence of a catalytic amount of $Pd(PPh_3)_4$ which was re-used for the cyclization-step to furnish a small library of 2-styryl indoles after *N*-demethylation. After optimization of this "one pot" three-step process, the cytotoxicity of novel 2-styrylindoles **1** and **2** having a trimethoxyphenyl A-ring will be discussed.

2. RESULTS AND DISCUSSION

The required starting material, (*E*)-2-(4-chlorobut-3-en-1-yn-1-yl)-*N*,*N*-dimethylaniline **3a**, used as a model substrate, was readily prepared by the Sonogashira coupling of 2-ethynyl-*N*,*N*-dimethylaniline with (*E*)-1,2-dichloroethylene in 78 %. Since the treatment of chloroenyne **3** with boronic acids in the presence of suitable Pd-catalysts would lead to diarylated enynes[20] **4** intermediates, we anticipated that the Pd species might activated the alkyne triple bond of intermediates **4** to provide 2-styrylindoles **5** after *N*-cyclization and ammonium demethylation. To identify suitable conditions for this transformation, we evaluated the Suzuki arylation / cyclization / *N*-demethylation reaction with (*E*)-chloroenyne **3a** in the presence of (4-acetyl) phenylboronic acid and a variety of Pd-catalysts. The result of this study is reported in Table 1.

TABLE 1: Optimization of the tandem Suzuki-Miyaura cyclization reaction between (*E*)-**3** and (4-acetylphenyl) boronic acid[a]



Entry	[Pd]	**3**	*x*	Time (h)	**4**	Yield of (*E*)-**4** (%)[b]	**5**	Yield of (*E*)-**5** (%)[b]
1	$Pd(PPh_3)_4$	**3a**	5	15	**4a**	46	**5a**	43
2	$Pd(dba)_2$		5	15		nd[c]		nd[c]
3	$PdCl_2(PhCN)_2$		5	15		nd[c]		nd[c]
4	$PdCl_2(dppf)$		5	15		nd[c]		nd[c]
5	XantPhos Pd G3		5	15		nd[c]		nd[c]
6	$Pd(PPh_3)_4$		8	15		32		55
7	$Pd(PPh_3)_4$		8	30		21		67
8	**$Pd(PPh_3)_4$**		**8**	**48**		**0**		**90**
9	$Pd(PPh_3)_4$	**3b**	8	48	**4b**	nd[c]	**5b**	nd[c]
10	$Pd(PPh_3)_4$	**3c**	8	48	**4c**	nd[c]	**5c**	nd[c]
11	$Pd(PPh_3)_4$	**3d**	8	48	**4d**	nd[c]	**5d**	nd[c]

[a]Conditions: (*E*)-**3** (0.5 mmol), (4-acetyl)boronic acid (0.65 mmol), [Pd] (x mmol), K_2CO_3 (2 equiv) and toluene/MeOH (2:1) (9 mL) were heated in a sealed tube at 90 °C for time indicated in Table 1 under an argon atmosphere. [b]Yield of isolated product. [c] Complex mixture of compounds.

Initially, we have tested the conditions developed in our laboratory for the coupling of boronic acids with chloroenynes[20] using $Pd(PPh_3)_4$ (5 mol %) as the catalyst, K_2CO_3 (2 equiv) as the base, and toluene/MeOH (2:1) as the solvent combination at 90 °C in a sealed tube (entry 1). After 15 h of stirring and disappearance of chloroenyne (*E*)-**3a**, we isolated the desired indole (*E*)-**5a** together with diarylenyne (*E*)-**4a** in almost similar yields. This promising first result, confirming our initial hypothesis, led us to evaluate other Pd-catalysts to improve the cyclization reaction of the (*E*)-**4a** intermediate. Unfortunately, as depicted in entries 2-5, none of the Pd(0), Pd(II) catalysts as well as the third generation (G3) Buchwald pre-catalyst were able to transform (*E*)-**3a** into indole (*E*)-**5a** which was not detected in crude mixtures after 15 h of reaction. It is likely that under these conditions, the Suzuki-arylation reaction leading to **4a** did not occur and that (*E*)-**3a** was completely degraded. We then decided to increase the amount of $Pd(PPh_3)_4$ quantity from 5 to 8 mol %, and we were pleased to observe the formation of indole (*E*)-**5a**, as the main product (90 %) after 48 h of reaction (entry 8). Further screening of solvents, solvent combinations and bases associated to $Pd(PPh_3)_4$ were less effective for 2-styrylindole (*E*)-**5a** generation. We also examine the efficiency of this process, under our optimized conditions, with arylated chloroenynes **3b-d** (entries 9-11) having on *ortho*-position a free-NH_2 (**3b**), a secondary amine (NHMe, **3c**) or a NH-tosylamine (**3d**). In contrast to (*E*)-**3a**, none of chloroenynes **3b-d** were able to provide the desired corresponding indole derivatives which were not detected in the crude complex mixtures. Using 8 mol% of $Pd(PPh_3)_4$ in the presence of 2 equiv of K_2CO_3 in hot toluene/MeOH mixture,

chloroenyne (*E*)-**3a** reacted with various boronic acids to generate a number of 2-styrylindoles **5a-l**. As depicted in Figure 2, the reaction exhibits excellent scope: both electron-deficient and electron-rich arylboronic acids reacted efficiently to provide the desired 2-styryl indoles with high to excellent yields for this three-step "one-pot" reaction (from 71 to 92%).

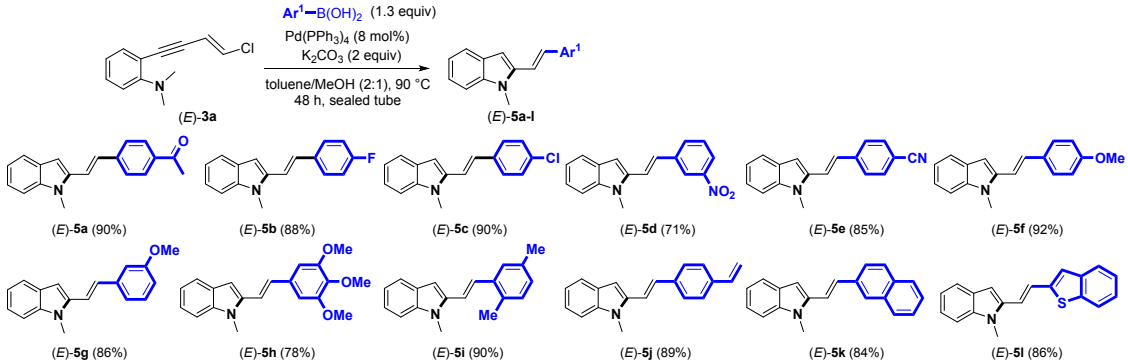
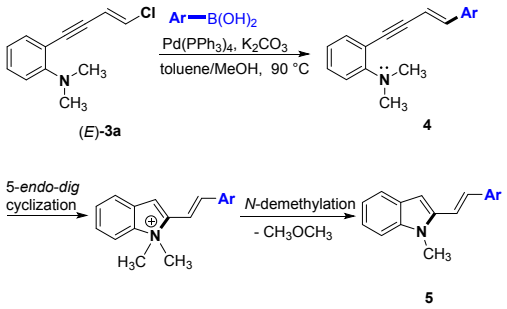


FIGURE 2. Tandem Suzuki-Miyaura cyclization reaction of (*E*)-chloroenyne **3a** using a variety of arylboronic acids.

Substitutions are readily tolerated at all positions of the arylboronic acid substrates to provide the 2-styrylindoles in similar yields (**5f-h**). Introduction of heterocycles on the double bond is also permitted with this protocol since **5l** was obtained in a good yield of 86 % using 2-benzothiophene boronic acid as the nucleophile. The following mechanism depicted in Scheme 1 can be considered.

SCHEME 1. Plausible mechanism for the synthesis of styrylindoles **5** from chloroenyne (*E*)-**3a**.

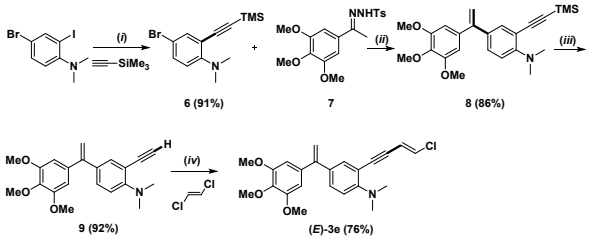


A plausible mechanism is depicted in Scheme 1 involving the formation of an indolinium salt according to a 5-*endo-dig* cyclization of diarylenyne **4**.[21] Then, a *N*-demethylation step of the indolinium by MeOH leads to styrylindole **5** and dimethylether.[22]

Next, as part of our medicinal chemistry project, we next have synthesized *N*,*N*-dimethylaniline (*E*)-**3e** having a chloroenyne group on *ortho*-position and on *para*-position a 1-(3,4,5-trimethoxyphenyl)vinyl moiety as the future A-ring (Scheme 2).

A Pd-catalyzed reaction of trimethylsilylacetylene with 4-bromo-2-iodo-*N*,*N*-dimethylaniline afforded trimethyl silylated (TMS)-alkyne **6** according to a Sonogashira coupling reaction (91%).

SCHEME 2. Synthesis of (*E*)-**3e**.[a]



[a]Conditions: (*i*) ArI (20 mmol), alkyne (22 mmol), $PdCl_2(PPh_3)_2$ (5 mol %), CuI (10 mol %), Et_3N, rt. (*ii*) **7** (12 mmol), **6** (10 mmol), Pd_2dba_3 (5 mol %), Xphos (10 mol %), LiO*t*Bu (2.2 equiv), dioxane, 70 °C. (*iii*) K_2CO_3, MeOH, rt. (*iv*) (*E*)-1,2-dichloroethylene (10 equiv), $PdCl_2(PPh_3)_2$ (5 mo%), CuI (10 mol %), piperidine (2 equiv), Et_2O, rt.

Then, by using a recent methodology developed by Barluenga and co-workers,[23] diarylethylene derivative **8** was synthesized in a good yield of 86% through the palladium coupling reaction of *N*-tosylhydrazone **7** with **6** using Pd_2dba_3 as the catalyst, Xphos as the ligand and LiO*t*Bu as the base in hot dioxane. Under these basic conditions, we were surprised to observe that the TMS group of **8** remained unchanged and was finally deprotected under classical conditions using K_2CO_3 in MeOH to give **9** (92%). A further Sonogashira-Linstrumelle coupling reaction with (*E*)-1,2-dichloroethylene furnished (*E*)-**3e** (76%) as a useful platform to introduce a variety of styryl groups on the C-2 position of novel substituted indole derivatives after Pd-catalyzed arylation-cyclization reactions (Figure 3). By applying our optimized protocol developed for the tandem arylation-cyclization of chloroenyne (*E*)-**3** with boronic acids, we prepared the desired indole derivatives (*E*)-**1a-g** in moderate yields due to difficulties encountered during the purification step.

Next, to synthesize a series of aza*iso*erianin analogues (*E*)-**2a-d** of biological interest, 3,4,5-trimethoxy-*N*-methylaniline was coupled with alkyne **6** under Pd-catalysis to give tertiary amine **10** (83%). After a desilylation step of the alkyne function of **10**, the resulting terminal alkyne **11** (90%) was then coupled with (*E*)-1,2-dichloroethylene to give (*E*)-**3f** in an acceptable yield of 66%. This later was then transformed into the desired indoles **2a-d** using this novel Suzuki-cyclization-*N*-demethylation process with good yields (from 74% to 82%) for the three steps (Scheme 3).

In vitro cytotoxicity of the newly synthesized indole derivatives **1** and **2** was investigated against HCT116, a human colon carcinoma cell line. A colorimetric-based assay was used to determine the drug concentration required to inhibit cell growth by 50% (GI_{50}) after incubation in the culture medium for 72 h. *Iso*CA-4 was included as the reference for comparisons. The screening revealed that all newly synthesized indole derivatives **1** and **2** evaluated against HCT cancer cell lines displayed an average level of cytotoxicity when compared with *iso*CA-4 (Table 2). The comparison of the GI_{50} values obtained for compounds **1** and **2** clearly revealed that 1,1-diarylethylenes derivatives **1a-g** displayed a promising sub-micromolar level of cytotoxicity (0.18 μM < GI_{50} < 0.74 μM) whereas their *N*-Methyl analogues **2a-d** displayed a lower level of cytotoxicity with GI_{50} values ranging from 1.32 to 4.08μM. The cytotoxic of promising derivatives **1c** and **1e** having respectively a *p*-methoxy and a *m*-NO_2 group on their aromatic rings displayed encouraging GI_{50} values (0.26 μM for **1c** and 0.18 μM for**1e**.) will be furthermore modified in our lab in view of possible improvements of cytotoxicity against a range human cancer cell lines.

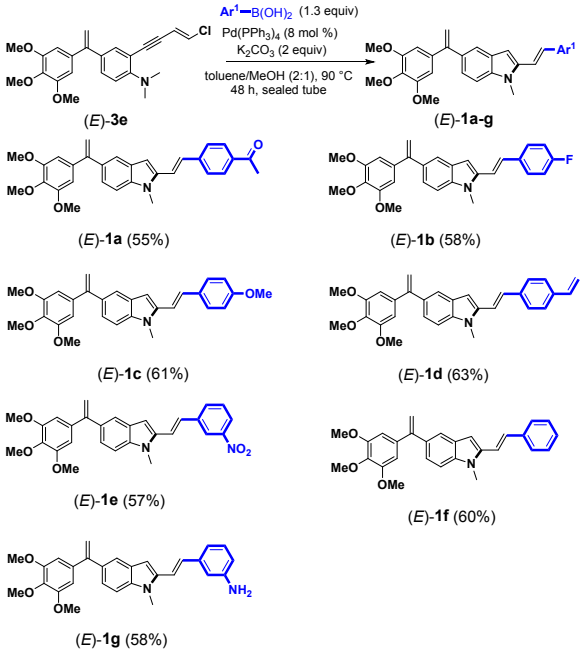
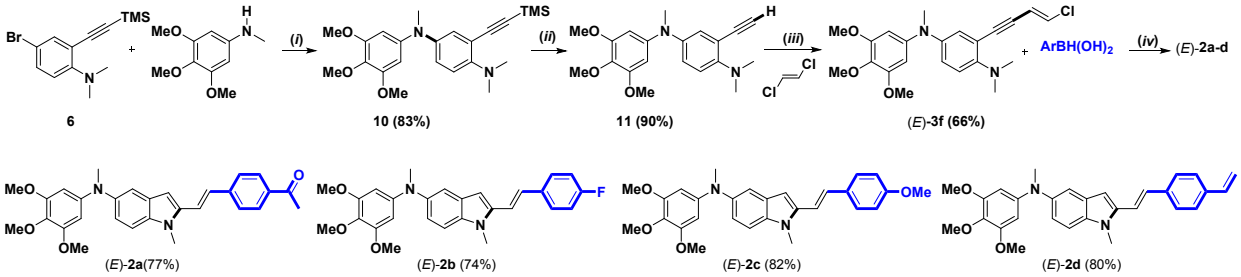


FIGURE 3. Tandem Suzuki-cyclization reaction of (*E*)-chloroenyne **3e** using a variety of arylboronic acids.

SCHEME 3. Synthesis of (*E*)-**2a-d**.



[a]Conditions: (*i*) ArBr (1 mmol), 3,4,5-trimethoxy-*N*-methylaniline (1.2 mmol), Pd_2dba_3 (5 mol %), Xphos (10 mol %), NaO*t*Bu (2.2 equiv), toluene, 70 °C. (*ii*) K_2CO_3, MeOH, rt. (*iii*) (*E*)-1,2-dichloroethylene (10 equiv), $PdCl_2(PPh_3)_2$ (5 mo%), CuI (10 mol %), piperidine (5 equiv), Et_2O, rt. (*iv*) (*E*)-**3f** (0.5 mmol), boronic acid (0.65 mmol), $Pd(PPh_3)_4$ (8 mol%), K_2CO_3 (2 equiv) were diluted in in toluene/MeOH (2:1) (9 mL) and placed in a sealed tube and heated at 90 °C.

TABLE 2. Cytotoxicity against HCT116 cells[a] and ITP of indoles **1a-g** and **2a-d**.

Compound	**(*E*)-1a**	**(*E*)-1b**	**(*E*)-1c**	**(*E*)-1d**	**(*E*)-1e**	**(*E*)-1f**
Cytotoxicity GI_{50}[b] [μM]	0.74 ± 0.17	0.43 ± 0.21	0.26 ± 0.02	0.37 ± 0.04	0.18 ± 0.06	0.52 ± 0.07
% of inhibition at 100 μM	21	31	23	37	26	56
Compound	**(*E*)-1g**	**(*E*)-2a**	**(*E*)-2b**	**(*E*)-2c**	**(*E*)-2d**	***iso*CA-4**
Cytotoxicity GI_{50}[b] [μM]	0.54 ± 0.03	1.90 ± 0.67	1.32 ± 0.32	1.84 ± 0.27	4.08 ± 0.41	0.002
% of inhibition at 100 μM	40	35	36	83	19	1.0 ± 0.1[c]

[a]HCT-116 Human colon carcinoma. [b]GI_{50} is the concentration of compound needed to reduce cell growth by 50% following 72 h cell treatment with the tested drug (average of three experiments). [c]GI_{50} is the concentration of *iso*CA-4 required to inhibit 50% of the rate of microtubule assembly (average of three experiments).

To examine if the cytotoxicity of compounds **1** and **2** was related to an interaction with the microtubule system, indoles **1** and **2** were next evaluated in tubulin assembly assays in parallel with *iso*CA-4 (Table 2). However, **1c** and **1e** which displayed the best cytotoxicity level against HCT116 cells inhibited tubulin assembly with modest GI_{50} values comparable to the GI_{50} of all other indole derivatives **1** and **2**. Currently, we are working to improve the cytotoxicity of derivatives **1** through the introduction of more suitable substituents.

3. CONCLUSION

In summary, we have discovered a novel 3-steps Suzuki-Miyaura arylation / cyclization / *N*-demethylation of (*E*)-2-(4-chlorobut-3-en-1-yn-1-yl)-*N*,*N*-dimethylanilines, giving an efficient and rapid access to 2-styrylindoles with good to excellent yields. Using this strategy, we have rapidly achieved the synthesis of a series of 1,1-diarylethylenes **1** and diarylmethylamines **2** bearing a 3,4,5-trimethoxyphenyl core and various functionalized 2-styrylindoles as *iso*CA-4 and aza*iso*erianin analogues. From the preliminary biological results, indoles **1c** and **1e** were the most promising compounds with nanomolar GI_{50} values. Structural modifications on the indole nucleus are currently under study in our laboratory and will be published later.

4. EXPERIMENTAL SECTION

General Information and Method. All glasswares were oven-dried at 140 °C and all reactions were conducted under an argon atmosphere. Solvents: cyclohexane, ethyl acetate (EtOAc), for chromatography, were technical grade. The ^{1}H NMR and ^{13}C NMR and ^{19}F spectra were recorded in $CDCl_3$, acetone-d6 or DMSO-d6 on Bruker Avance 300 spectrometer. The chemical shifts of ^{1}H are reported in ppm relative to the solvent residual peak in $CDCl_3$ (δ 7.26), acetone-d6 (δ 2.05), DMSO-d6 (δ 2.50) for ^{1}H NMR. For the ^{13}C NMR spectra, the solvent signals of $CDCl_3$ (δ 77.14), acetone-d6 (δ 206.26), DMSO-d6 (δ 39.52) were used as the internal standards. The following abreviation are used: m (multiplet), s (singlet), d (doublet), t (triplet), dd (doublet of doublet), td (triplet of doublet), ddd (doublet of doublet of doublet). IR spectra were measured on a Bruker Vector 22 spectrophotometer (neat, cm^{-1}). High-resolution mass spectra were recorded on a Bruker Daltonics micrOTOF-Q instrument. Analytical TLC was performed on Merck precoated silica gel 60 F-254 plates. Merck silica gel 60 (230-400 mesh) was used for column chromatography. The plates were visualized by either UV light (254 nm), or by a solution of phosphomolybdic acid in ethanol.

General procedure for the synthesis of (*E*)-chloroenynes 3a, 3b, 3e, 3f.

To a solution of alkyne (5 mmol) in Et_2O (30 mL) was added successively (*E*)-1,2-dichloroethylene (4 mL, 50 mmol), $PdCl_2(PPh_3)_2$ (175 mg, 0.25 mmol), piperidine (1 mL, 10 mmol) and CuI (95 mg, 0.5 mmol). After complete disappearance of starting material monitored by TLC, the solution was filtered through a pad of celite using EtOAc. The organic layer was washed successively with sat. NH_4Cl, sat. $NaHCO_3$ and HCl (1 M) solutions. After drying over $MgSO_4$ and evaporation *in vacuo*, the crude residue was purified by silica gel column chromatography (0 to 30% AcOEt in cyclohexane) (the crude of **3g** was purified on neutral Al_2O_3).

(*E*)-2-(4-Chlorobut-3-en-1-yn-1-yl)-*N*,*N*-dimethyl aniline (3a)

Brown solid, mp 36.8 – 37.0 °C, yield 78%, 802 mg.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.52 (dd, *J* = 7.5 Hz, *J* = 1.2 Hz, 1H), 7.28 (td, *J* = 7.5 Hz, *J* = 1.2 Hz, 1H), 6.97 – 6.86 (m, 2H), 6.63 (d, *J* = 13.5 Hz, 1H), 6.25 (d, *J* = 13.5 Hz, 1H), 2.95 (s, 6H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ = 154.9 (Cq), 134.3 (CH), 129.7 (CH), 129.2 (CH), 120.7 (CH), 117.1 (CH), 114.6 (Cq), 114.4 (CH), 91.5 (Cq), 89.7 (Cq), 43.6 (2 CH_3). IR (neat): 2945, 2197, 1595, 1325, 1049, 1011 cm^{-1}. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{12}H_{13}N^{35}Cl$: 206.0737; found: 206.0735.

(*E*)-2-(4-Chlorobut-3-en-1-yn-1-yl)aniline (3b)

Brown oil, yield 79%, 702 mg.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.16 (d, *J* = 7.5 Hz, 1H), 7.01 (t, *J* = 8.1 Hz, 1H), 6.61 – 6.45 (m, 3H), 6.08 (d, *J* = 13.5 Hz, 1H), 4.01 (br, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ = 147.9 (Cq), 132.1 (CH), 130.1 (CH), 129.6 (CH), 118.0 (CH), 114.4 (CH), 113.8 (CH), 107.2 (Cq), 89.6 (Cq), 88.7 (Cq). IR (neat): 3479, 3384, 2194, 1699, 1488, 1314 cm^{-1}. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{10}H_9N^{35}Cl$: 178.0424; found: 178.0424.

(*E*)-2-(4-Chlorobut-3-en-1-yn-1-yl)-*N*,*N*-dimethyl-4-(1-(3,4,5-trimethoxyphenyl)vinyl)-aniline (3e)

Brown oil, yield 76%, 1.51 g.

^{1}H NMR (300 MHz, acetone-d6) δ = 7.36 (d, *J* = 2.1 Hz, 1H), 7.26 (dd, *J* = 8.7 Hz, *J* = 2.1 Hz, 1H), 6.91 (d, *J* = 8.7 Hz, 1H), 6.82 (d, *J* = 13.5 Hz, 1H), 6.62 (s, 2H), 6.33 (d, *J* = 13.5 Hz, 1H), 5.38 (s, 1H), 5.35 (s, 1H), 3.79 (s, 6H), 3.77 (s, 3H), 2.97 (s, 6H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ = 159.1 (Cq), 157.9 (2 Cq), 153.1 (Cq), 142.6 (Cq), 141.7 (Cq), 138.3 (CH), 137.1 (Cq), 135.2 (CH), 134.6 (CH), 121.9 (CH), 119.4 (CH), 118.3 (CH_2), 117.3 (Cq), 110.8 (2 CH), 96.7 (Cq), 94.8 (Cq), 65.2 (CH_3), 61.1 (2 CH_3), 47.9 (2 CH_3). IR (neat): 2937, 2196, 1579, 1502, 1347, 1235 cm^{-1}. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{23}H_{25}NO_3{}^{35}Cl$: 398.1523; found: 398.1523.

(*E*)-2-(4-Chlorobut-3-en-1-yn-1-yl)-*N*^{1},*N*^{1},*N*^{4}-trimethyl-*N*^{4}-(3,4,5-trimethoxyphenyl)-benzene-1,4-diamine (3f)

Brown oil, yield 66%, 1.32 g.

^{1}H NMR (300 MHz, acetone-d6) δ = 7.09 – 6.90 (m, 3H), 6.83 (d, *J* = 13.5 Hz, 1H), 6.34 (d, *J* = 13.5 Hz, 1H), 6.25 (s, 2H), 3.75 (s, 6H), 3.69 (s, 3H), 3.23 (s, 3H), 2.86 (s, 6H). ^{13}C{1H} NMR (75 MHz, acetone-d6) δ = 154.8 (2 Cq), 150.8 (Cq), 146.6 (Cq), 143.8 (Cq), 134.2 (Cq), 130.1 (CH), 127.0 (CH), 124.1 (CH), 119.1 (CH), 116.2 (Cq), 115.2 (CH), 98.9 (2 CH), 92.4 (Cq), 89.9 (Cq), 60.6 (CH_3), 56.4 (2 CH_3), 43.9 (2 CH_3), 40.9 (CH_3). IR (neat): 2937, 2197, 1585, 1496, 1235, 1128 cm^{-1}. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{22}H_{26}N_2O_3{}^{35}Cl$: 401.1632; found: 401.1639.

Procedure for the synthesis of (*E*)-chloroenynes 3c.

To a solution of **3b** (5 mmol, 888 mg) in DMF (30 mL) was added K_2CO_3 (1.5 equiv) and iodomethane (1.1 equiv). The reaction was stirred at room temperature for 3 h then quenched with water (30 mL). The aqueous layer was extracted with CH_2Cl_2 three times and the combined organic extracts were dried with anhydrous $MgSO_4$, filtered and concentrated. The crude mixture was purified by silica gel column chromatography (0 to 30% AcOEt in cyclohexane)**.**

(*E*)-2-(4-Chlorobut-3-en-1-yn-1-yl)-*N*-methylaniline (3c)

Brown oil, yield 48%, 460 mg.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.22 – 7.10 (m, 2H), 6.63 – 6.44 (m, 3H), 6.11 (d, *J* = 13.8 Hz, 1H), 4.46 (br, 1H), 2.80 (s, 3H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ = 149.9 (Cq), 132.2 (CH), 130.5 (CH), 129.5 (CH), 116.4 (CH), 114.0 (CH), 109.2 (CH), 106.7 (Cq), 89.9 (Cq), 88.9 (Cq), 30.3 (CH_3). IR (neat): 3421, 3071, 2191, 1510, 1320 cm^{-1}. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{11}H_{11}N^{35}Cl$: 192.0580; found: 192.0570.

Procedure for the synthesis of (*E*)-chloroenynes 3d.

A solution of 4-methylbenzene-1-sulfonyl chloride (1 equiv) in THF (20 mL) was added dropwise over 0.5 h to

a solution of **3b** (5 mmol) and pyridine (1.1 equiv) in THF (30 mL) under argon. The solution was stirred at r.t. for 12 h. The resulting mixture was evaporated under vacuum and the residue was purified by silica gel column chromatography (0 to 30% AcOEt in cyclohexane)**.**

(*E*)-*N*-(2-(4-Chlorobut-3-en-1-yn-1-yl)phenyl)-4-methylbenzenesulfonamide (3d)

White solid, mp 125.6 – 125.9 °C, yield 63%, 1.05 g.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.68 (d, *J* = 8.4 Hz, 2H), 7.59 (d, *J* = 8.4 Hz, 1H), 7.33 – 7.22 (m, 4H), 7.10 – 7.01 (m, 2H), 6.63 (d, *J* = 13.8 Hz, 1H), 6.13 (d, *J* = 13.8 Hz, 1H), 2.39 (s, 3H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ = 144.2 (Cq), 137.7 (Cq), 136.2 (Cq), 132.2 (CH), 131.8 (CH), 130.1 (CH), 129.7 (2 CH), 127.3 (2 CH), 124.7 (CH), 120.4 (CH), 114.0 (Cq), 113.0 (CH), 90.9 (Cq), 86.4 (Cq), 21.7 (CH_3). IR (neat): 3074, 1489, 1396, 1159 cm^{-1}. HRMS (ESI): m/z $[M+Na]^+$ calcd for $C_{17}H_{14}NO_2NaS^{35}Cl$: 354.0331; found: 354.0332.

General procedure for the synthesis of 2-styrylindole 5, 1, 2.

Under argon, chloroenyne (0.5 mmol), the desired boronic acid (1.3 equiv), K_2CO_3 (2 equiv), and $Pd(PPh_3)_4$ (8 mol%) were mixed in toluene (6 mL) and MeOH (3 mL). The reaction mixture was stirred at 90°C in 30 mL sealed tube monitored by TLC (48 h). After the mixture were allowed to cool to room temperature and filtrated through a pad of celite washed by CH_2Cl_2. Solvent was removed under reduced pressure and the crude material was purified by silica gel column chromatography (0 to 30% AcOEt in cyclohexane).

(*E*)-1-(4-(2-(1-Methyl-1*H*-indol-2-yl)vinyl)phenyl) ethan-1-one (5a)

Yellow solid, mp 188.5 – 188.9 °C, yield 90%, 123.9 mg.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.99 (d, *J* = 8.4 Hz, 2H), 7.65 – 7.60 (m, 3H), 7.36 – 7.11 (m, 5H), 6.90 (s, 1H), 3.86 (s, 3H), 2.64 (s, 3H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ = 197.5 (Cq), 141.9 (Cq), 138.5 (Cq), 137.8 (Cq), 136.1 (Cq), 129.3 (CH), 129.1 (2 CH), 128.0 (Cq), 126.5 (2 CH), 122.4 (CH), 120.8 (CH), 120.2 (CH), 119.7 (CH), 109.4 (CH), 100.2 (CH), 30.1 (CH_3), 26.7 (CH_3). IR (neat): 3054, 1675, 1597, 1348, 1274 cm^{-1}. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{19}H_{18}NO$: 276.1388; found: 276.1378.

(*E*)-2-(4-Fluorostyryl)-1-methyl-1*H*-indole (5b)

Yellow solid, mp 155.5 – 155.8 °C, yield 88%, 110.6 mg.

^{1}H NMR (300 MHz, DMSO-d6) δ = 7.77 – 7.71 (m, 2H), 7.54 – 6.99 (m, 8H), 6.86 (s, 1H), 3.85 (s, 3H). ^{13}C{1H} NMR (75 MHz, DMSO-d6) δ = 161.7 (d, *J* = 243.5 Hz, Cq), 138.2 (Cq), 137.7 (Cq), 133.6 (d, *J* = 2.0 Hz, Cq), 129.0 (CH), 128.4 (d, *J* = 8.0 Hz, 2 CH), 127.4 (Cq), 121.3 (CH), 119.8 (CH), 119.5 (CH), 117.2 (CH), 115.6 (d, *J* = 21.4 Hz, 2 CH), 109.7 (CH), 98.1 (CH), 29.7 (CH_3). ^{19}F NMR (188 MHz, DMSO-d6): δ = - 114.1. IR (neat): 1531, 1470, 1349, 1247, 1157 cm^{-1}. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{17}H_{15}NF$: 252.1189; found: 252.1190.

(*E*)-2-(4-Chlorostyryl)-1-methyl-1*H*-indole (5c)

Yellow solid, mp 127.6 – 127.9 °C, yield 90%, 120.5 mg.

^{1}H NMR (300 MHz, DMSO-d6) δ = 7.72 (d, *J* = 8.4 Hz, 2H), 7.55 – 7.41 (m, 5H), 7.29 (d, *J* = 16.2 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 6.89 (s, 1H), 3.86 (s, 3H). ^{13}C{1H} NMR (75 MHz, DMSO-d6) δ = 138.0 (Cq), 137.8 (Cq), 136.0 (Cq), 131.9 (Cq), 128.8 (CH), 128.6 (2 CH), 128.2 (2 CH), 127.4 (Cq), 121.4 (CH), 119.9 (CH), 119.6 (CH), 118.2 (CH), 109.7 (CH), 98.5 (CH), 29.7 (CH_3). IR (neat): 1532, 1443, 1320, 1248 cm^{-1}. HRMS (APCI): m/z $[M+H]^+$ calcd for $C_{17}H_{15}N^{35}Cl$: 268.0888; found: 268.0891.

(*E*)-1-Methyl-2-(3-nitrostyryl)-1*H*-indole (5d)

Yellow solid, mp 136.9 – 137.2 °C, yield 71%, 98.8 mg.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.26 (s, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.42 (t, *J* = 7.8 Hz, 1H), 7.23 – 7.01 (m, 5H), 6.77 (s, 1H), 3.73 (s, 3H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ = 148.9 (Cq), 139.0 (Cq), 138.5 (Cq), 137.3 (Cq), 132.3 (CH), 129.7 (CH), 127.9 (Cq), 127.8 (CH), 122.5 (CH), 122.1 (CH), 120.8 (CH), 120.6 (CH), 120.3 (CH), 120.1 (CH), 109.4 (CH), 100.4 (CH), 30.1 (CH_3). IR (neat): 1520, 1463, 1347, 1321 cm^{-1}. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{17}H_{15}N_2O_2$: 279.1134; found: 279.1125.

(*E*)-4-(2-(1-Methyl-1*H*-indol-2-yl)vinyl)benzonitrile (5e)

Yellow solid, mp 177.4 – 177.7 °C, yield 85%, 109.8 mg.

^{1}H NMR (300 MHz, DMSO-d6) δ = 7.95 – 7.77 (m, 4H), 7.66 (d, *J* = 16.2 Hz, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 1H), 7.38 (d, *J* = 16.2 Hz, 1H), 7.16 (t, *J* = 7.5 Hz, 1H), 7.04 (t, *J* = 7.5 Hz, 1H), 6.98 (s, 1H), 3.88 (s, 3H). ^{13}C{1H} NMR (75 MHz, DMSO-d6) δ = 141.8 (Cq), 138.0 (Cq), 137.5 (Cq), 132.5 (2 CH), 128.1 (CH), 127.3 (Cq), 127.1 (2 CH), 121.9 (CH), 121.0 (CH), 120.2 (CH), 119.7 (CH), 119.1 (Cq), 109.9 (CH), 109.3 (Cq), 99.6 (CH), 29.7 (CH_3). IR (neat): 2223, 1599, 1463, 1346, 1322 cm^{-1}. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{18}H_{15}N_2$: 259.1235; found: 259.1246.

(*E*)-2-(4-Methoxystyryl)-1-methyl-1*H*-indole (5f)

Yellow solid, mp 141.4 – 141.8 °C, yield 92%, 121.1 mg.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.63 (d, *J* = 7.5 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.34 – 7.12 (m, 4H), 7.05 (d, *J* = 15.9 Hz, 1H), 6.96 (d, *J* = 8.4 Hz, 2H), 6.80 (s, 1H), 3.87 (s, 3H), 3.83 (s, 3H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ = 159.5 (Cq), 138.8 (Cq), 138.1 (Cq), 130.6 (CH), 130.0 (Cq), 128.1 (Cq), 127.7 (2 CH), 121.5 (CH), 120.3 (CH), 119.8 (CH), 114.9 (CH), 114.2 (2 CH), 109.1 (CH), 98.4 (CH), 55.4 (CH_3), 29.9 (CH_3). IR (neat): 1573, 1463, 1395, 1247 cm^{-1}. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{18}H_{18}NO$: 264.1388; found: 264.1387.

(*E*)-2-(3-Methoxystyryl)-1-methyl-1*H*-indole (5g)

Yellow solid, mp 94.1 – 94.5 °C, yield 86%, 102.7 mg.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.65 (d, *J* = 8.1 Hz, 1H), 7.43 – 7.06 (m, 8H), 6.94 – 6.82 (m, 2H), 3.91 (s, 3H), 3.84 (s, 3H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ = 160.0 (Cq), 138.7 (Cq), 138.4 (Cq), 138.2 (Cq), 130.8 (CH), 129.8 (CH), 128.0 (Cq), 121.9 (CH), 120.5 (CH), 120.0 (CH), 119.2 (CH), 117.5 (CH), 113.4 (CH), 111.9 (CH), 109.2 (CH), 99.2 (CH), 55.4 (CH_3), 30.0 (CH_3). IR (neat): 2936, 1597, 1577, 1433, 1319, 1284, 1157, 1010, 952 cm^{-1}. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{18}H_{18}NO$: 264.1388; found: 264.1390.

(*E*)-1-Methyl-2-(3,4,5-trimethoxystyryl)-1*H*-indole (5h)

Yellow solid, mp 180.2 – 180.3 °C, yield 78%, 126.1 mg.

^{1}H NMR (300 MHz, DMSO-d6) δ = 7.63 – 7.30 (m, 3H), 7.23 (d, *J* = 16.2 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.05 - 6.95 (m, 3H), 6.83 (s, 1H), 3.87 (s, 3H), 3.86 (s, 6H), 3.69 (s, 3H). ^{13}C{1H} NMR (75 MHz, DMSO-d6) δ = 153.0 (2 Cq), 138.4 (Cq), 137.7 (Cq), 137.4 (Cq), 132.7 (Cq), 130.6 (CH), 127.5 (Cq), 121.2 (CH), 119.8 (CH),

119.5 (CH), 116.6 (CH), 109.6 (CH), 104.1 (2 CH), 97.9 (CH), 60.1 (CH_3), 55.9 (2 CH_3), 29.8 (CH_3). IR (neat): 2925, 1581, 1504, 1465, 1366 cm^{-1}. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{20}H_{22}NO_3$: 324.1600; found: 324.1600.

(*E*)-2-(2,5-Dimethylstyryl)-1-methyl-1*H*-indole (5i)

Yellow solid, mp 121.1 – 121.2 °C, yield 90%, 117.6 mg.

^{1}H NMR (300 MHz, DMSO-d6) δ = 7.63 (s, 1H), 7.56 – 7.37 (m, 3H), 7.29 (d, *J* = 15.9 Hz, 1H), 7.16 – 7.08 (m, 2H), 7.05 – 6.99 (m, 2H), 6.90 (s, 1H), 3.86 (s, 3H), 2.37 (s, 3H), 2.33 (s, 3H). ^{13}C{1H} NMR (75 MHz, DMSO-d6) δ = 138.6 (Cq), 137.7 (Cq), 135.3 (Cq), 135.0 (Cq), 132.4 (Cq), 130.3 (CH), 128.4 (CH), 127.8 (CH), 127.4 (Cq), 125.5 (CH), 121.2 (CH), 119.8 (CH), 119.5 (CH), 117.9 (CH), 109.7 (CH), 98.3 (CH), 29.7 (CH_3), 20.7 (CH_3), 19.0 (CH_3). IR (neat): 2921, 1463, 1319, 1236, 1104, 954 cm^{-1}. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{19}H_{20}N$: 262.1596; found: 262.1597.

(*E*)-1-Methyl-2-(4-vinylstyryl)-1*H*-indole (5j)

Yellow solid, mp 157.6 – 157.8 °C, yield 89%, 115.4 mg.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.50 (d, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 8.1 Hz, 2H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.21 – 6.99 (m, 5H), 6.72 (s, 1H), 6.63 (dd, *J* = 17.4 Hz, *J* = 10.8 Hz, 1H), 5.69 (d, *J* = 17.6 Hz, 1H), 5.18 (d, *J* = 10.8 Hz, 1H), 3.70 (s, 3H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ = 138.5 (Cq), 138.3 (Cq), 137.2 (Cq), 136.8 (Cq), 136.5 (CH), 130.5 (CH), 128.1 (Cq), 126.7 (4 CH), 121.9 (CH), 120.5 (CH), 120.0 (CH), 117.0 (CH), 114.0 (CH_2), 109.2 (CH), 99.2 (CH), 30.0 (CH_3). IR (neat): 1530, 1462, 1346, 1320, 907 cm^{-1}. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{19}H_{18}N$: 260.1439; found: 260.1445.

(*E*)-1-Methyl-2-(2-(naphthalen-2-yl)vinyl)-1*H*-indole (5k)

Yellow solid, mp 198.3 – 198.5 °C, yield 84%, 119.0 mg.

^{1}H NMR (300 MHz, DMSO-d6) δ = 8.20 – 7.80 (m, 5H), 7.63 – 7.43 (m, 6H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.94 (s, 1H), 3.90 (s, 3H). ^{13}C{1H} NMR (75 MHz, DMSO-d6) δ = 138.3 (Cq), 137.8 (Cq), 134.6 (Cq), 133.3 (Cq), 132.6 (Cq), 130.2 (CH), 128.1 (CH), 127.8 (CH), 127.6 (CH), 127.5 (Cq), 126.5 (CH), 126.4 (CH), 126.0 (CH), 123.7 (CH), 121.4 (CH), 119.9 (CH), 119.6 (CH), 117.8 (CH), 109.7 (CH), 98.4 (CH), 29.7 (CH_3). IR (neat): 2923, 1463, 1342, 1320 cm^{-1}. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{21}H_{18}N$: 284.1439; found: 284.1438.

(*E*)-2-(2-(Benzo[b]thiophen-2-yl)vinyl)-1-methyl-1*H*-indole (5l)

Yellow solid, mp 203.7 – 203.8 °C, yield 86%, 124.4 mg.

^{1}H NMR (300 MHz, DMSO-d6) δ = 7.96 – 7.78 (m, 2H), 7.64 – 7.34 (m, 6H), 7.21 – 7.11 (m, 2H), 7.03 (t, *J* = 7.2 Hz, 1H), 6.96 (s, 1H), 3.86 (s, 3H). ^{13}C{1H} NMR (75 MHz, DMSO-d6) δ = 142.3 (Cq), 139.9 (Cq), 138.2 (Cq), 137.9 (Cq), 137.2 (Cq), 127.4 (Cq), 125.0 (CH), 124.8 (CH), 123.8 (CH), 123.7 (CH), 123.6 (CH), 122.3 (CH), 121.7 (CH), 120.0 (CH), 119.7 (CH), 119.0 (CH), 109.8 (CH), 99.4 (CH), 29.7 (CH_3). IR (neat): 2928, 1531, 1469, 1347, 1154 cm^{-1}. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{19}H_{16}NS$: 290.1003; found: 290.1003.

(*E*)-1-(4-(2-(1-Methyl-5-(1-(3,4,5-trimethoxyphenyl) vinyl)-1*H*-indol-2-yl)vinyl)phenyl)-ethan-1-one (1a)

Yellow solid, mp 170.1 – 170.5 °C, yield 55%, 128.6 mg.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.90 (d, *J* = 8.2 Hz, 2H), 7.55 – 7.52 (m, 3H), 7.25 – 7.10 (m, 4H), 6.78 (s, 1H), 6.55 (s, 2H), 5.38 (s, 1H), 5.31 (s, 1H), 3.82 (s, 3H), 3.79 (s, 3H), 3.73 (s, 6H), 2.55 (s, 3H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ = 197.5 (Cq), 152.9 (2 Cq), 151.0 (Cq), 141.8 (Cq), 138.4 (Cq), 138.3 (Cq), 138.2 (Cq), 137.9 (Cq), 136.2 (Cq), 133.7 (Cq), 129.5 (CH), 129.1 (2 CH), 127.8 (Cq), 126.5 (2 CH), 123.4 (CH), 120.7 (CH), 119.6 (CH), 112.7 (CH_2), 109.0 (CH), 105.9 (2 CH), 100.5 (CH), 61.1 (CH_3), 56.3 (2 CH_3), 30.3 (CH_3), 26.7 (CH_3). IR (neat): 2936, 1678, 1598, 1579, 1504, 1392 cm^{-1}. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{30}H_{30}NO_4$: 468.2175; found: 468.2192.

(*E*)-2-(4-Fluorostyryl)-1-methyl-5-(1-(3,4,5-trimethoxy phenyl)vinyl)-1*H*-indole (1b)

Yellow solid, mp 151.6 – 151.8 °C, yield 58%, 128.6 mg.

^{1}H NMR (300 MHz, acetone-d6) δ = 7.74 – 7.69 (m, 2H), 7.54 (s, 1H), 7.44 – 7.26 (m, 3H), 7.26 – 7.06 (m, 3H), 6.86 (s, 1H), 6.67 (s, 2H), 5.42 (s, 1H), 5.40 (s, 1H), 3.92 (s, 3H), 3.78 (s, 3H), 3.77 (s, 6H). ^{13}C{1H} NMR (75 MHz, acetone-d6) δ = 163.2 (d, *J* = 244.1 Hz, Cq), 154.0 (2 Cq), 152.2 (Cq), 140.0 (Cq), 139.1 (Cq), 139.0 (Cq), 138.9 (Cq), 134.8 (d, *J* = 3.2 Hz, Cq), 134.0 (Cq), 130.3 (CH), 129.2 (d, *J* = 7.9 Hz, 2 CH), 128.9 (Cq), 123.2 (CH), 120.8 (CH), 118.0 (CH), 116.3 (d, *J* = 21.7 Hz, 2 CH), 112.5 (CH_2), 109.9 (CH), 106.9 (2 CH), 99.8 (CH), 60.6 (CH_3), 56.4 (2 CH_3), 30.2 (CH_3). ^{19}F NMR (188 MHz, acetone-d6): δ = -113.558. IR (neat): 2937, 1631, 1505, 1462, 1391, 1277, 1260, 1235 cm^{-1}. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{28}H_{27}NO_3F$: 444.1975; found: 444.1973.

(*E*)-2-(4-Methoxystyryl)-1-methyl-5-(1-(3,4,5-trimetho xyphenyl)vinyl)-1*H*-indole (1c)

Yellow solid, mp 159.7 – 159.9 °C, yield 61%, 136.7 mg.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.61 (s, 1H), 7.50 (d, *J* = 8.4 Hz, 2H), 7.30 – 7.14 (m, 3H), 7.10 – 6.89 (m, 3H), 6.77 (s, 1H), 6.67 (s, 2H), 5.48 (s, 1H), 5.41 (s, 1H), 3.93 (s, 3H), 3.87 – 3.83 (m, 12H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ = 159.7 (Cq), 152.9 (2 Cq), 151.2 (Cq), 139.6 (Cq), 138.4 (Cq), 138.0 (Cq), 137.8 (Cq), 133.3 (Cq), 130.9 (CH), 130.0 (Cq), 128.0 (Cq), 127.8 (2 CH), 122.5 (CH), 120.3 (CH), 114.8 (CH), 114.3 (2 CH), 112.5 (CH_2), 108.7 (CH), 105.9 (2 CH), 98.7 (CH), 61.0 (CH_3), 56.2 (2 CH_3), 55.4 (CH_3), 30.1 (CH_3). IR (neat): 2935, 1766, 1604, 1578, 1508, 1464, 1348, 1252 cm^{-1}. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{29}H_{30}NO_4$: 456.2175; found: 456.2189.

(*E*)-1-Methyl-5-(1-(3,4,5-trimethoxyphenyl)vinyl)-2-(4-vinylstyryl)-1*H*-indole (1d)

Yellow solid, mp 139.4 – 139.8 °C, yield 63%, 142.2 mg.

^{1}H NMR (300 MHz, acetone-d6) δ = 7.64 (d, *J* = 8.1 Hz, 2H), 7.56 – 7.26 (m, 6H), 7.19 (dd, *J* = 8.4 Hz, *J* = 1.5 Hz, 1H), 6.88 (s, 1H), 6.78 (dd, *J* = 17.7 Hz, *J* = 11.1 Hz, 1H), 6.68 (s, 2H), 5.85 (d, *J* = 17.7 Hz, 1H), 5.41 (d, *J* = 4.8 Hz, 2H), 5.26 (d, *J* = 11.1 Hz, 1H), 3.91 (s, 3H), 3.78 (s, 3H), 3.77 (s, 6H). ^{13}C{1H} NMR (75 MHz, acetone-d6) δ = 154.0 (2 Cq), 152.2 (Cq), 140.1 (Cq), 139.1 (Cq), 139.0 (Cq), 138.9 (Cq), 137.9 (2 Cq), 137.4 (CH), 134.0 (Cq), 131.1 (CH), 128.9 (Cq), 127.6 (2 CH), 127.4 (2 CH), 123.3 (CH), 120.8 (CH), 118.0 (CH), 114.1 (CH_2), 112.5 (CH_2), 109.9 (CH), 106.9 (2 CH), 99.9 (CH), 60.6 (CH_3), 56.4 (2 CH_3), 30.2 (CH_3). IR (neat): 2935, 1579, 1504, 1463, 1449, 1348 cm^{-1}. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{30}H_{30}NO_3$: 452.2226; found: 452.2223.

(*E*)-1-Methyl-2-(3-nitrostyryl)-5-(1-(3,4,5-trimethoxy phenyl)vinyl)-1*H*-indole (1e)

Yellow solid, mp 191.9 – 192.1 °C, yield 57%, 134.1 mg.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 8.32 (s, 1H), 8.04 (d, *J* = 8.1 Hz, 1H), 7.72 (d, *J* = 8.1 Hz, 1H), 7.58 – 7.42 (m, 2H), 7.28 – 7.08 (m, 4H), 6.78 (s, 1H), 6.55 (s, 2H), 5.38 (s, 1H), 5.32 (s, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.73 (s, 6H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ = 152.9 (2 Cq), 151.0 (Cq), 148.9 (Cq), 139.0 (Cq), 138.4 (Cq), 138.2 (Cq), 137.9 (2 Cq), 133.7 (Cq), 132.5 (CH), 129.8 (CH), 128.1 (CH), 127.7 (Cq), 123.5 (CH), 122.3 (CH), 120.7 (CH), 120.6 (CH), 119.9 (CH), 112.7 (CH_2), 109.0 (CH), 105.9 (2 CH), 100.7 (CH), 61.1 (CH_3), 56.3 (2 CH_3), 30.3 (CH_3). IR (neat): 2936, 1630, 1578, 1529, 1504, 1465, 1349 cm^{-1}. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{28}H_{27}N_2O_5$: 471.1920; found: 471.1924.

(*E*)-1-Methyl-2-styryl-5-(1-(3,4,5-trimethoxy phenyl)vinyl)-1*H*-indole (1f)

Yellow solid, mp 121.0 – 121.3 °C, yield 60%, 127.6 mg.

^{1}H NMR (300 MHz, acetone-d6) δ = 7.67 (d, *J* = 7.2 Hz, 2H), 7.54 – 7.29 (m, 7H), 7.19 (d, *J* = 8.7 Hz, 1H), 6.88 (s, 1H), 6.67 (s, 2H), 5.41 (s, 1H), 5.39 (s, 1H), 3.93 (s, 3H), 3.78 (s, 9H). ^{13}C{1H} NMR (75 MHz, acetone-d6) δ = 153.1 (2 Cq), 151.3 (Cq), 139.2 (Cq), 138.2 (Cq), 138.1 (Cq), 138.0 (Cq), 137.4 (Cq), 133.1 (Cq), 130.6 (CH), 128.7 (2 CH), 128.0 (Cq), 127.7 (CH), 126.5 (2 CH), 122.3 (CH), 119.9 (CH), 117.1 (CH), 111.6 (CH_2), 108.9 (CH), 106.0 (2 CH), 98.9 (CH), 59.7 (CH_3), 55.5 (2 CH_3), 29.3 (CH_3). IR (neat): 1579, 1503, 1463, 1449, 1411, 1348, 1236 cm^{-1}. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{28}H_{28}NO_3$: 426.2069; found: 426.2065.

(*E*)-3-(2-(1-Methyl-5-(1-(3,4,5-trimethoxyphenyl)vinyl)-1*H*-indol-2-yl)vinyl)aniline (1g)

Yellow solid, mp 95.6 – 95.8 °C, yield 58%, 127.8 mg.

^{1}H NMR (300 MHz, acetone-d6) δ = 7.52 (s, 1H), 7.39 – 7.05 (m, 5H), 6.96 – 6.83 (m, 3H), 6.71 – 6.58 (m, 3H), 5.41 (s, 1H), 5.39 (s, 1H), 4.68 (br, 2H), 3.90 (s, 3H), 3.78 (s, 9H). ^{13}C{1H} NMR (75 MHz, acetone-d6) δ = 153.1 (2 Cq), 151.3 (Cq), 148.7 (Cq), 139.4 (Cq), 139.1 (Cq), 138.2 (Cq), 138.0 (Cq), 137.9 (Cq), 133.0 (Cq), 131.6 (CH), 129.2 (CH), 128.0 (Cq), 122.1 (CH), 119.8 (CH), 116.2 (CH), 115.5 (CH), 114.2 (CH), 112.2 (CH), 111.5 (CH_2), 108.9 (CH), 106.0 (2 CH), 98.6 (CH), 59.7 (CH_3), 55.5 (2 CH_3), one CH_3 peak was buried in the solvent signals. IR (neat): 3450, 2396, 1599, 1579, 1503, 1463, 1412, 1348 cm^{-1}. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{28}H_{29}N_2O_3$: 441.2178; found: 441.2180.

(*E*)-1-(4-(2-(1-Methyl-5-(methyl(3,4,5-trimethoxy phenyl)amino)-1*H*-indol-2-yl)vinyl)phenyl)ethan-1-one (2a)

Yellow solid, mp 212.8 – 213.0 °C, yield 77%, 181.2 mg.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.99 (d, *J* = 8.4 Hz, 2H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.39 (d, *J* = 1.8 Hz, 1H), 7.33 – 7.20 (m, 3H), 7.07 (dd, *J* = 8.4 Hz, *J* = 1.8 Hz, 1H), 6.85 (s, 1H), 6.08 (s, 2H), 3.87 (s, 3H), 3.82 (s, 3H), 3.76 (s, 6H), 3.35 (s, 3H), 2.64 (s, 3H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ = 197.5 (Cq), 153.6 (2 Cq), 147.2 (Cq), 143.3 (Cq), 142.5 (Cq), 141.8 (Cq), 138.5 (Cq), 136.2 (Cq), 135.9 (Cq), 129.4 (CH), 129.1 (2 CH), 128.7 (Cq), 126.5 (2 CH), 121.2 (CH), 119.6 (CH), 116.3 (CH), 110.2 (CH), 100.0 (CH), 94.2 (2 CH), 61.2 (CH_3), 56.2 (2 CH_3), 41.5 (CH_3), 30.3 (CH_3), 26.7 (CH_3). IR (neat): 2958, 1678, 1598, 1507, 1307, 1263 cm^{-1}. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{29}H_{31}N_2O_4$: 471.2284; found: 471.2286.

(*E*)-2-(4-Fluorostyryl)-*N*,1-dimethyl-*N*-(3,4,5-trimetho xyphenyl)-1*H*-indol-5-amine (2b)

Yellow solid, mp 180.1 – 180.4 °C, yield 74%, 165.2 mg.

^{1}H NMR (300 MHz, acetone-d6) δ = 7.76 – 7.70 (m, 2H), 7.46 – 7.28 (m, 4H), 7.21 -7.14 (m, 2H), 7.00 (d, *J* = 8.7 Hz, 1H), 6.84 (s, 1H), 6.09 (s, 2H), 3.92 (s, 3H), 3.69 (s, 6H), 3.66 (s, 3H), 3.31 (s, 3H). ^{13}C{1H} NMR (75 MHz, acetone-d6) δ = 163.2 (d, *J* = 244.6 Hz, Cq), 154.6 (2 Cq), 148.1 (Cq), 143.2 (Cq), 139.9 (Cq), 136.6 (Cq), 134.9 (d, *J* = 3.2 Hz, Cq), 132.2 (Cq), 130.1 (CH), 129.7 (Cq), 129.2 (d, *J* = 7.8 Hz, 2 CH), 121.1 (CH), 118.1 (CH), 116.6 (d, *J* = 22.8 Hz, 2 CH), 116.2 (CH), 111.0 (CH), 99.4 (CH), 95.2 (2 CH), 60.6 (CH_3), 56.3 (2 CH_3), 41.6 (CH_3), one CH_3 peak was buried in the solvent signals. ^{19}F NMR (188 MHz, acetone-d6): δ = -115.708. IR (neat): 2934, 1603, 1583, 1506, 1258, 1233 cm^{-1}. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{27}H_{28}N_2O_3F$: 447.2084; found: 447.2085.

(*E*)-2-(4-Methoxystyryl)-*N*,1-dimethyl-*N*-(3,4,5-trimethoxyphenyl)-1*H*-indol-5-amine (2c)

Yellow solid, mp 110.1 – 110.3 °C, yield 82%, 188.0 mg.

^{1}H NMR (300 MHz, acetone-d6) δ = 7.61 (d, *J* = 8.7 Hz, 2H), 7.42 – 7.23 (m, 4H), 7.07 – 6.86 (m, 3H), 6.78 (s, 1H), 6.09 (s, 2H), 3.89 (s, 3H), 3.84 (s, 3H), 3.68 (s, 6H), 3.66 (s, 3H), 3.30 (s, 3H). ^{13}C{1H} NMR (75 MHz, acetone-d6) δ = 160.6 (Cq), 154.5 (2 Cq), 148.1 (Cq), 143.1 (Cq), 140.5 (Cq), 136.6 (Cq), 132.1 (Cq), 131.2 (CH), 131.0 (Cq), 129.8 (Cq), 128.7 (2 CH), 120.9 (CH), 116.8 (CH), 115.8 (CH), 115.0 (2 CH), 110.9 (CH), 98.7 (CH), 95.1 (2 CH), 60.6 (CH_3), 56.2 (2 CH_3), 55.6 (CH_3), 41.6 (CH_3). one CH_3 peak was buried in the solvent signals. IR (neat): 2958, 1604, 1582, 1507, 1483, 1465, 1247 cm^{-1}. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{28}H_{31}N_2O_4$: 459.2284; found: 459.2291.

(*E*)-*N*,1-Dimethyl-*N*-(3,4,5-trimethoxyphenyl)-2-(4-vinylstyryl)-1*H*-indol-5-amine (2d)

Yellow solid, mp 133.2 – 133.6 °C, yield 80%, 181.8 mg.

^{1}H NMR (300 MHz, acetone-d6) δ = 7.64 (d, *J* = 8.4 Hz, 2H), 7.56 – 7.24 (m, 6H), 6.99 (dd, *J* = 8.7 Hz, *J* = 2.1 Hz, 1H), 6.93 – 6.62 (m, 2H), 6.10 (s, 2H), 5.85 (d, *J* = 18.3 Hz, 1H), 5.26 (d, *J* = 10.8 Hz, 1H), 3.91 (s, 3H), 3.69 (s, 6H), 3.67 (s, 3H), 3.31 (s, 3H). ^{13}C{1H} NMR (75 MHz, acetone-d6) δ = 154.6 (2 Cq), 148.1 (Cq), 143.2 (Cq), 140.1 (Cq), 138.0 (Cq), 137.9 (Cq), 137.4 (CH), 136.7 (Cq), 132.2 (Cq), 130.9 (CH), 129.8 (Cq), 127.6 (2 CH), 127.4 (2 CH), 121.2 (CH), 118.1 (CH), 116.8 (CH), 114.1 (CH_2), 111.0 (CH), 99.5 (CH), 95.3 (2 CH), 60.6 (CH_3), 56.3 (2 CH_3), 41.6 (CH_3), 30.2 (CH_3). IR (neat): 2935, 1603, 1582, 1506, 1482, 1465, 1450, 1258 cm^{-1}. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{29}H_{31}N_2O_3$: 455.2335; found: 455.2336.

Procedure for the synthesis of 4-bromo-*N*,*N*-dimethyl-2-((trimethylsilyl)ethynyl)aniline 6.

To a stirred mixture of 4-bromo-2-iodo-*N*,*N*-dimethylaniline (20 mmol), $PdCl_2(PPh_3)_2$ (0.05 equiv) and CuI (0.1 equiv) in Et_3N (50 mL), trimethylsilylacetylene (1.1 equiv, 3.3 mL) was added dropwise at 0 °C. The mixture was then stirred at room temperature. When the starting material was disappeared (TLC monitoring), the mixture was passed through a pad of Celite to remove the insoluble materials. The filtrate was concentrated in vacuo and the residue was purified by silica gel column chromatography (0 to 10% AcOEt in cyclohexane).

4-bromo-*N*,*N*-dimethyl-2-((trimethylsilyl)ethynyl) aniline (6)

Colorless oil, yield 91%, 5.33 g.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.29 (d, *J* = 2.4 Hz, 1H), 7.06 (dd, *J* = 9.0 Hz, *J* = 2.5 Hz, 1H), 6.48 (d, J = 9.0 Hz, 1H), 2.70 (s, 6H), 0.03 (s, 9H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ = 154.2 (Cq), 137.0 (CH), 132.3 (CH), 118.3 (CH), 116.4 (Cq), 111.8 (Cq), 103.2 (Cq), 101.2 (Cq), 43.3 (2 CH_3), 0 (3 CH_3). IR (neat): 2958, 2838, 2151, 1488, 1386, 838 cm^{-1}. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{13}H_{19}N^{79}BrSi$: 296.0470; found: 296.0469.

Procedure for the synthesis of 8.

A 50 mL flask was charged with aryl halide **6** (10 mmol), Xphos (10 mol%), Pd_2dba_3 (5 mol%), Li*O*t*Bu (2.2 equiv), the tosylhydrazone **7** (1.2 equiv) and dioxane (25 mL). The system was stirred at 70º with monitored by TLC analysis. When the reaction was completed, the crude reaction mixture was allowed to cool to room temperature and filtered through celite washed by CH_2Cl_2. The solvents were evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (0 to 20% AcOEt in cyclohexane).

***N*,*N*-Dimethyl-4-(1-(3,4,5-trimethoxyphenyl)vinyl)-2-((trimethylsilyl)ethynyl)aniline (8)**

Brown oil, yield 86%, 3.52 g.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.47 (d, *J* = 1.8 Hz, 1H), 7.17 (dd, *J* = 8.7 Hz, *J* = 1.8 Hz, 1H), 6.79 (d, *J* = 8.4 Hz, 1H), 6.55 (s, 2H), 5.36 (s, 1H), 5.30 (s, 1H), 3.88 (s, 3H), 3.81 (s, 6H), 2.99 (s, 6H), 0.26 (s, 9H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ = 154.8 (Cq), 153.0 (2 Cq), 149.1 (Cq), 137.9 (Cq), 137.4 (Cq), 134.6 (CH), 132.9 (Cq), 129.6 (CH), 116.3 (CH), 114.8 (Cq), 113.9 (Cq), 112.6 (CH_2), 105.8 (2 CH), 104.7 (Cq), 61.0 (CH_3), 56.3 (2 CH_3), 43.3 (2 CH_3), 0.1 (3 CH_3). IR (neat): 2999, 2957, 2835, 2786, 2148, 1598, 1503, 1465, 1347 842 cm^{-1}. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{24}H_{32}NO_3Si$: 410.2151; found: 410.2149.

Procedure for the synthesis of 10.

Aryl bromine **6** (1 mmol) (note: the yiled will drastically decrease when increasing the quantity of starting material), Xphos (10 mol%), Pd_2dba_3 (5 mol%), NaO*t*Bu (2.2 equiv), 3,4,5-trimethoxy-N-methylaniline (1.2 equiv) were mixed in 8 mL of toluene. The system was stirred at 70º in a 30 mL sealed tube with monitored by TLC analysis. When the reaction was completed, the crude reaction mixture was allowed to cool to room temperature and filtered through celite washed by CH_2Cl_2. The solvents were evaporated under reduced pressure, and the residue was purified by silica gel column chromatography (0 to 20% AcOEt in cyclohexane).

***N*^{1},*N*^{1},*N*^{4}-Trimethyl-*N*^{4}-(3,4,5-trimethoxyphenyl)-2-((trimethylsilyl)ethynyl)benzene-1,4-diamine (10)**

Brown oil, yield 83%, 342.5 mg.

^{1}H NMR (300 MHz, acetone-d6) δ = 7.06 – 6.87 (m, 3H), 6.21 (s, 2H), 3.73 (s, 6H), 3.67 (s, 3H), 3.21 (s, 3H), 2.88 (s, 6H), 0.22 (s, 9H). ^{13}C{1H} NMR (75 MHz, acetone-d6) δ = 154.9 (2 Cq), 154.1 (Cq), 151.6 (Cq), 146.9 (Cq), 143.6 (Cq), 128.2 (CH), 124.7 (CH), 119.0 (CH), 116.7 (Cq), 105.9 (Cq), 99.6 (Cq), 98.6 (2 CH), 60.8 (CH_3), 56.5 (2 CH_3), 43.9 (2 CH_3), 41.1 (CH_3), 0.2 (3 CH_3). IR (neat): 2958, 2783, 2149, 1715, 1611, 1496, 1247, 841 cm^{-1}. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{23}H_{33}N_2O_3Si$: 413.2260; found: 413.2266.

Procedure for the Synthesis of terminal alkyne 9, 11.

To an oven dried 100 mL round-bottomed flask was added 2-((trimethylsilyl)ethynyl)aniline (5 mmol), MeOH (30 mL), and oven dried K_2CO_3 (1 equiv). The flask was stirred under argon atmosphere at room temperature. When TLC show the disappearance of starting material, H_2O (30 mL) was added to the flask. After extracted with CH_2Cl_2 (3 × 30 mL), the organic layer was dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude oil was then purified by column chromatography on silica gel (0 to 20% AcOEt in cyclohexane).

2-Ethynyl-*N*,*N*-dimethyl-4-(1-(3,4,5-trimethoxy phenyl)vinyl)aniline (9)

Brown oil, yield 92%, 1.55 g.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.41 (d, *J* = 2.1 Hz, 1H), 7.18 – 7.14 (m, 1H), 6.79 (d, *J* = 8.7 Hz, 1H), 6.47 (s, 2H), 5.30 (s, 1H), 5.24 (s, 1H), 3.81 (s, 3H), 3.75 (s, 6H), 3.32 (s, 1H), 2.90 (s, 6H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ = 155.2 (Cq), 153.0 (2 Cq), 149.0 (Cq), 137.3 (Cq), 134.8 (CH), 133.4 (Cq), 129.7 (CH), 116.7 (CH), 113.7 (Cq), 112.9 (CH_2), 112.8 (Cq), 105.8 (2 CH), 83.1 (Cq), 82.5 (CH), 61.0 (CH_3), 56.3 (2 CH_3), 43.6 (2 CH_3). IR (neat): 3276, 2957, 2836, 1599, 1579, 1464, 1451, 1347, 1266 cm^{-1}. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{21}H_{24}NO_3$: 338.1756; found: 338.1755.

2-Ethynyl-*N*^{1},*N*^{1},*N*^{4}-trimethyl-*N*^{4}-(3,4,5-trimethoxy phenyl)benzene-1,4-diamine (11)

Brown oil, yield 90%, 1.53 g.

^{1}H NMR (300 MHz, $CDCl_3$) δ = 7.15 (d, *J* = 2.7 Hz, 1H), 6.96 (dd, *J* = 8.7 Hz, *J* = 2.7 Hz, 1H), 6.87 (d, *J* = 8.7 Hz, 1H), 6.15 (s, 2H), 3.81 (s, 3H), 3.77 (s, 6H), 3.38 (s, 1H), 3.23 (s, 3H), 2.89 (s, 6H). ^{13}C{1H} NMR (75 MHz, $CDCl_3$) δ = 153.7 (2 Cq), 150.6 (Cq), 145.7 (Cq), 142.9 (Cq), 132.8 (Cq), 127.5 (CH), 123.3 (CH), 118.3 (CH), 115.8 (Cq), 97.5 (2 CH), 82.7 (Cq), 82.3 (CH), 61.1 (CH_3), 56.2 (2 CH_3), 44.2 (2 CH_3), 40.8 (CH_3). IR (neat): 2937, 2826, 1612, 1495, 1450, 1309, 1236 cm^{-1}. HRMS (ESI): m/z $[M+H]^+$ calcd for $C_{20}H_{25}N_2O_3$: 341.1865; found: 341.1870.

Supporting Information:

Supporting Information contains copies of ^{1}H, ^{13}C and ^{19}F NMR spectra of new compounds.

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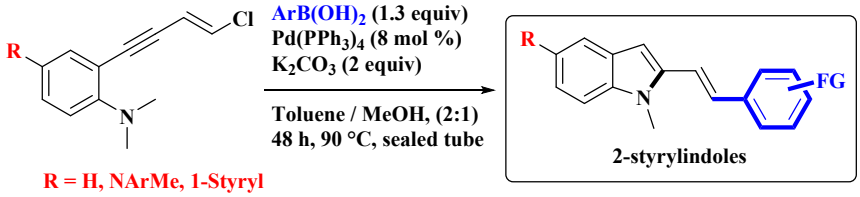

R = H, NArMe, 1-Styryl

FG = NO_2, CN, F, Cl, H, Me, OMe, vinyl, naphthyl, benzothiophenyl

- 3 steps "one pot" rapid access to functionalized 2-styrylindoles
- 21 examples (55 to 92 %)
- Good to excellent functional group tolerance