One-Pot Reaction between N -Tosylhydrazones and 2-Nitrobenzyl Bromide: Route to NH-Free C2-Arylindoles

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One-pot Reaction between *N*-tosylhydrazones and 2-Nitrobenzyl Bromide: Efficient Route to NH-free C2-Arylindoles

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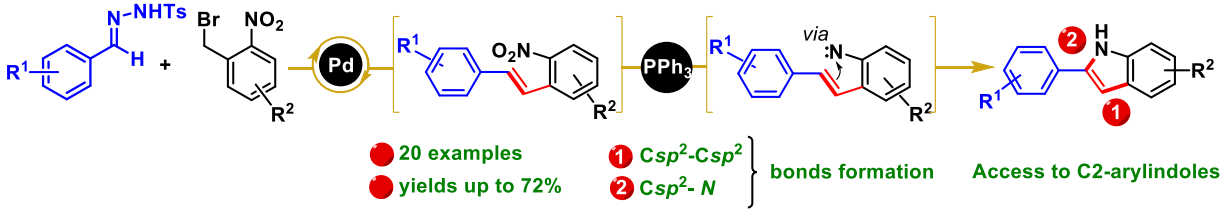


Abstract:

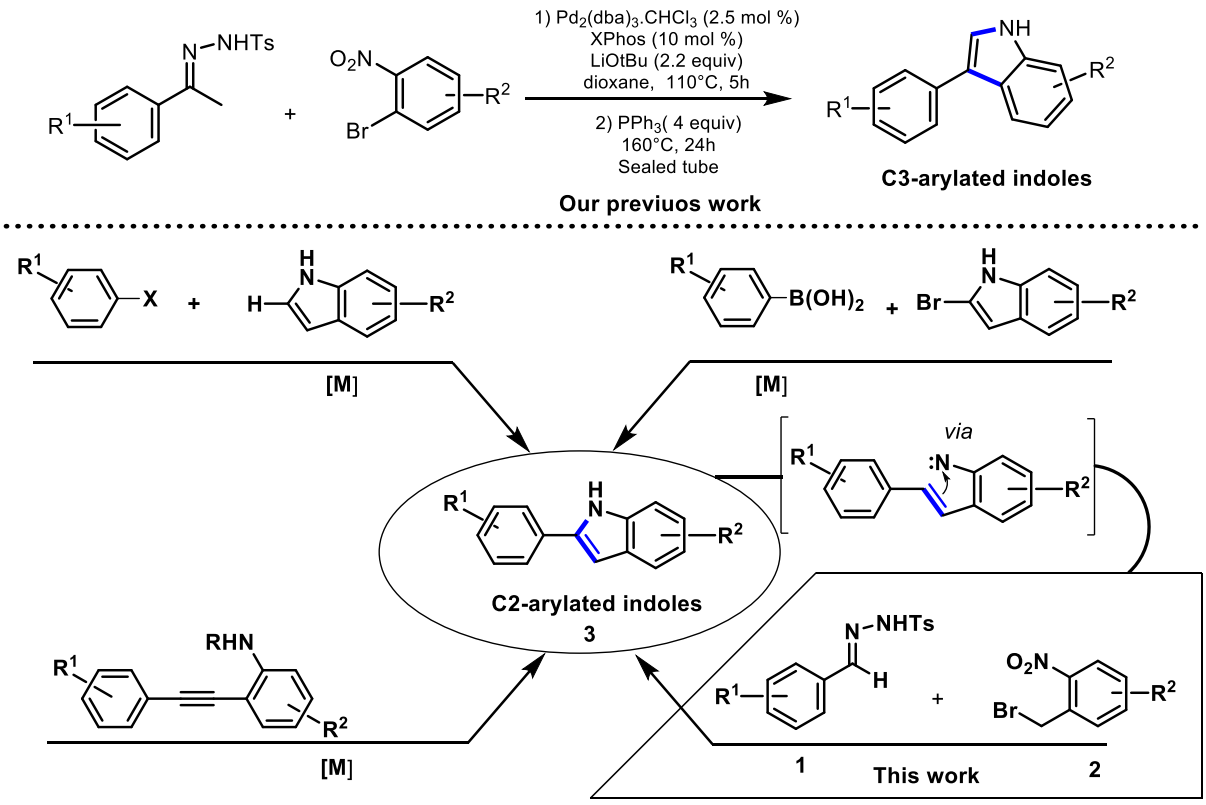
A one-pot Barluenga coupling between *N*-tosylhydrazones and nitro-benzylbromide, followed by deoxygenation of *ortho*-nitrostyrenes, and subsequent cyclization has been developed providing an efficient way to synthesize various C2-arylindoles. This method exhibits a good substrate scope and functional group tolerance, and it allows an access to NH-free indoles, which can present a potential utility in medicinal chemistry applications.

Introduction

N-Tosylhydrazones (NTH) have been emerged recently as a carbene precursors and have been one of the most important achievements in the search for a new type of cross-coupling partners in transition-metal catalysis.[1] They serve as a versatile and powerful synthetic tool for the formation of C-C,[1] C-X (N,[2] O,[3] S[4]) bonds with a remarkable range of applications in medicinal chemistry.[5] NTH are solid and stable reagents and are readily accessible from ketones, and aldehydes. In comparison to classical cross-coupling reactions, which employ stoichiometric organometallic reagents (such as boronic reagents, Grignard reagents, organozinc reagents, organolithium) as a nucleophilic component, the use of NTH represents an attractive alternative for metal-catalyzed cross-coupling processes that does not involve the use of a stoichiometric organometallic species (R-MgX, $RSnBu_3$, RLi).

Indoles constitute a privileged structure that can be found in a large number of drugs approved for various diseases including cancer, cardiovascular diseases, and neurologic disorders.[6] In the framework of our medicinal chemistry-screening program to discover new anticancer compounds,[5c,7] recently, we developed a novel strategy for the effective synthesis of 3-aryl-indoles from NTH, as antitubulin agents (Scheme 1),[8] this approach has already proven useful in the synthesis of potent antiproliferative agents compounds. Over the previous decade, the access to molecular diversity has increased impressive enthusiasm within the community of synthetic chemists because of its vital role in drug discovery.[9] In connection with the above and in order to use the NTH as a versatile building block in organic synthesis, which enables further transformations of the carbene coupling product, we decided to explore the reactivity of NTH derived from aldehydes in the cross-coupling reaction with 2-nitrobenzyl bromide to form C2-arylated indoles in a one-pot reaction. This transformation consists firstly on the formation of a Csp^2-Csp^2 bond between NTH and the benzyl bromide, then in situ reduction of the nitroalkene to nitrene derivative, followed by annulation leading to the formation of C2-arylated indoles.

Over the past decades, many synthetic strategies have been developed to obtain C2 arylated indoles.[10] Among them, great efforts have been devoted to transition metal catalyzed direct C2-H arylations,[11] Suzuki-Miyaura coupling (Scheme 1),[12] and predominant metal-catalyzed preparation of indoles starting from 2-alkynylanilines.[13] However, many of these methods require activated indoles and arenes, some work better with *N*-methylated or protected indoles,[14] and others suffer from regioselectivity issue (C2:C3).[15] Hence, the development of straightforward and efficient methodologies for synthesizing 2-aryl indoles remains highly desirable. Highlighted features of this strategy are (a) the divergent synthesis of 2-arylindoles can be achieved by changing the coupling partners; (b) functional-group tolerance; (c) formation of NH-free arylindoles which can be interesting for biological activity.

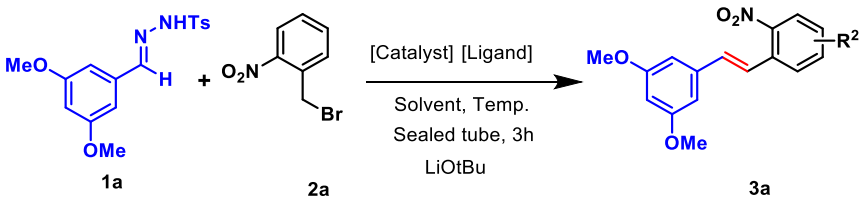


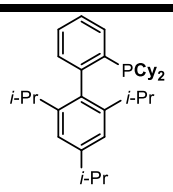
Scheme 1. Different strategies for the access of C2-arylated indoles derivatives

Results and discussion

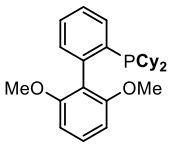
Initially, the reaction of NTH **1a** with 2-nitrobenzylbromide **2a** under previously reported conditions (Pd_2dba_3/Xphos)[16] or (Pd_2dba_3/ P(2-furyl)$_3$)[17] provided **3a** in a low 25% and 50% yields respectively (entries 1-2, Table 1). The low reactivity of 2-nitrobenzylbromide derivative led to inefficient coupling and resulted in the concomitant formation of sulfone derivative resulted from decomposition of NTH.[18] Performing the coupling by using a combination of Pd_2dba_3/ P(2-furyl)$_3$ in dioxane instead of toluene led to a slight increase in the yield (cf. entry 2 and 3). We also tested other solvents such as THF and CPME but no improvement in the yield was observed in comparison to dioxane. Surprisingly, the reduction of the amount of ligand from 20 mol% (entry 3) to 10 mol% (entry 6) led to a significant increase in the yield of the desired product **3a**. Then, we turned toward the study of the temperature parameter, and we found that the optimal range is at 110°C (entry 7). We examined other palladium sources such as $Pd(OAc)_2$ which was also effective, albeit affording **3a** with slightly reduced yield (entry 8). Switching the P(2-furyl)$_3$ by Sphos ligand led to dramatically decrease in the yield (cf. entry 7 and 9). Finally, other inorganic bases were tested such as NaOtBu and Cs_2CO_3 and we found them less efficient than LiOtBu in this coupling (entries 10-11). As a result, the combination of $Pd_2dba_3.CHCl_3$ (2.5 mol%), P(2-furyl)$_3$ (10 mol%), LiO*t*Bu (2.2 equiv), dioxane in a sealed tube at 110 °C was fixed as optimal condition.

Table 1. Optimization of Coupling Reaction of *N*-Tosylhydrazones **1a** with 2-Nitrobenzyl bromide **2a** under Various Conditions.[a]

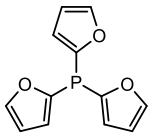




XPhos



SPhos



P(2-furyl)$_3$

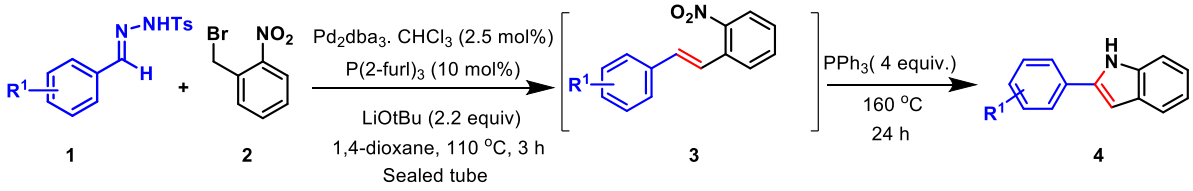
entry	[Pd] X mol%	L mol%	solvent	base	Temp (°C)	yield (%)[b]
1	$Pd_2dba_3.CHCl_3$ (2.5)	XPhos (10)	dioxane	LiO*t*Bu	90	25
2	$Pd_2dba_3.CHCl_3$ (2.5)	P(2-furyl)$_3$ (20)	PhMe	LiO*t*Bu	90	50
3	$Pd_2dba_3.CHCl_3$ (2.5)	P(2-furyl)$_3$ (20)	dioxane	LiO*t*Bu	90	55
4	$Pd_2dba_3.CHCl_3$ (2.5)	P(2-furyl)$_3$ (20)	THF	LiO*t*Bu	90	15
5	$Pd_2dba_3.CHCl_3$ (2.5)	P(2-furyl)$_3$ (20)	CPME	LiO*t*Bu	90	35
6	$Pd_2dba_3.CHCl_3$ (2.5)	P(2-furyl)$_3$ (10)	dioxane	LiO*t*Bu	90	64
7	**$Pd_2dba_3.CHCl_3$ (2.5)**	**P(2-furyl)$_3$ (10)**	**dioxane**	**LiO*t*Bu**	**110**	**85**
8	$Pd(OAc)_2$ (5)	P(2-furyl)$_3$ (10)	dioxane	LiO*t*Bu	110	65
9	$Pd_2dba_3.CHCl_3$ (2.5)	Sphos (10)	dioxane	LiO*t*Bu	110	15
10	$Pd_2dba_3.CHCl_3$ (2.5)	P(2-furyl)$_3$ (10)	dioxane	NaO*t*Bu	110	18
11	$Pd_2dba_3.CHCl_3$ (2.5)	P(2-furyl)$_3$ (10)	dioxane	Cs_2CO_3	110	30

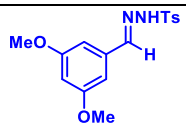
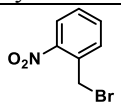
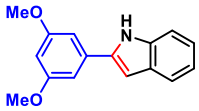
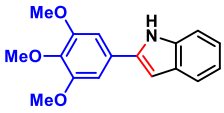
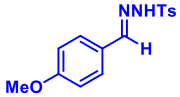
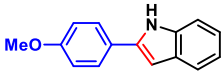
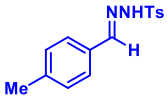
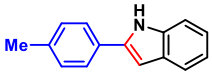
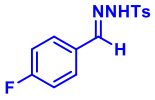
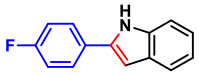
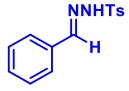
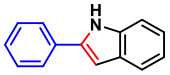
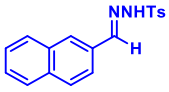
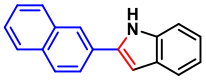
[a] The reactions were carried out in a sealed tube with **1a** (1 mmol), **2a** (1 mmol), [Pd] (X mol %), Ligand (Y mol %), base (2.2 equiv) in 2.5 mL of solvent. [b] Isolated yield of **3a**.

With the optimal conditions for the first step in hand, we subsequently investigated the one-pot reaction in order to perform reduction of the nitro function to nitrenes, and then spontaneous annulation led to C2-aryl indole **4**. To our delight, we found that the optimal conditions were compatible with the one-pot reaction and when the first coupling was achieved (3 hours), PPh_3 was added allowing the formation of C2-aryl indole **4a** in 70% isolated yield (Table 2, entry 1). This yield represents an average of 84% for each step. Next, we examined the scope of NTH partner in this one-pot sequence. Most of these NTH were prepared from the corresponding aldehydes and used without further purification. Both electron-donating and

electron-withdrawing groups on the phenyl ring of NTH were compatible, affording the desired C2-aryl indole derivatives with moderate to good yields (Table 2, entry 1-7). Different substituents at various positions on the arenes, including 3,4,5-trimethoxy group did not hamper the coupling. Also, the reaction was successfully carried out with *N*-tosylhydrazones derived from 2-naphthaldehyde (compound **4g**, entry 7).

Table 2. Substrate scope of NTH, synthesis of C2-aryl indoles.



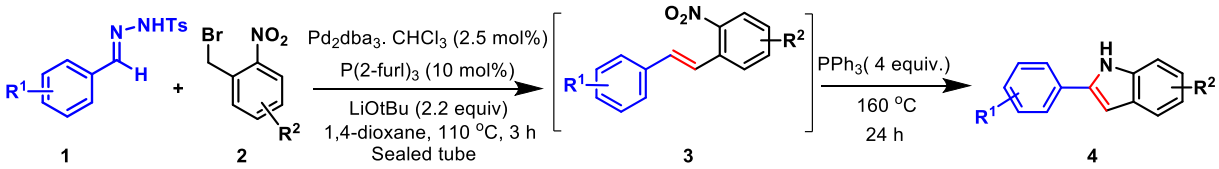
entry	NTH **1**	Benzyl bromides **2**	product	yield (%)[a]
1	 **1a**	 **2a**	 **4a**	70
2	 **1b**	**2a**	 **4b**	65
3	 **1c**	**2a**	 **4c**	73
4	 **1d**	**2a**	 **4d**	70
5	 **1e**	**2a**	 **4e**	55
6	 **1f**	**2a**	 **4f**	68
7	 **1g**	**2a**	 **4g**	62

[a] Yield of isolated products.

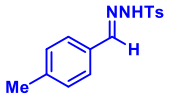
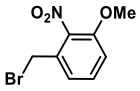
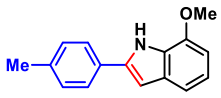
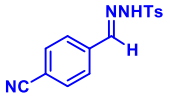
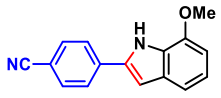
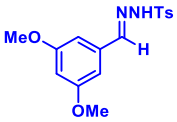
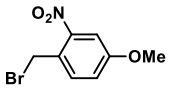
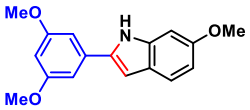
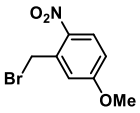
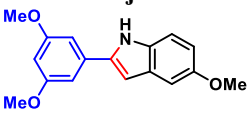
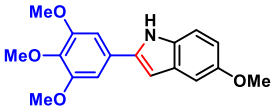
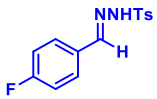
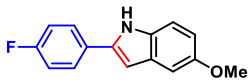
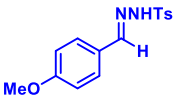
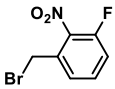
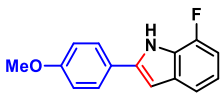
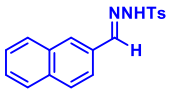
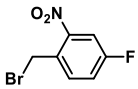
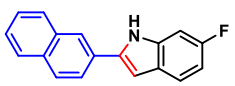
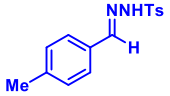
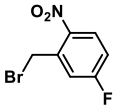
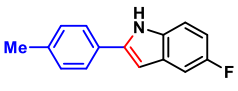
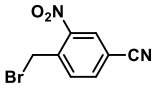
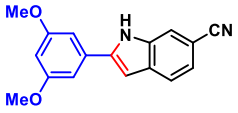
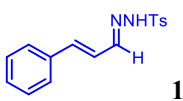
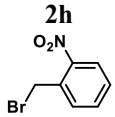
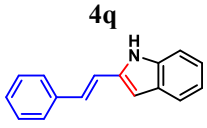
In order to gauge the performance of this one-pot procedure, the substrate scope has been investigated with respect to the substituted *ortho*-nitro-benzylbromide **2** (Table 3). These aryl halides derivatives were prepared easily by bromination of the corresponding 1-methyl-2-nitroaryls in the presence of AIBN/NBS.[19]

Under the optimized reactions conditions, the electrophilic coupling partner *ortho*-nitro-benzylbromide having an EDG (OMe), in *ortho* (**2b**), *meta* (**2c**), and *para* (**2d**) positions to NO_2 were coupled to a diverse range of *N*-tosylhydrazones **1**, and the corresponding 2-aryl indole derivatives were obtained in satisfactory yields (Table 3, entries 1-6). Also, the coupling was successful in the presence of EWG (F) on the benzylbromide partner (entries 7-10). Remarkably, functional groups, such as fluoro (compounds **4m**-**p**), and cyano (**4i** and **4q**) were tolerated, providing the possibility for further transformations. Finally, under our standard conditions, we were able to realize the coupling between hydrazones derivated from cinnamaldehyde and benzylbromide **2a**, which lead to the corresponding (*E*)-2-styryl-1*H*-indole in a 32% isolated yield.

Table 3. Substrate scope of NTH and nitro-benzylbromide.

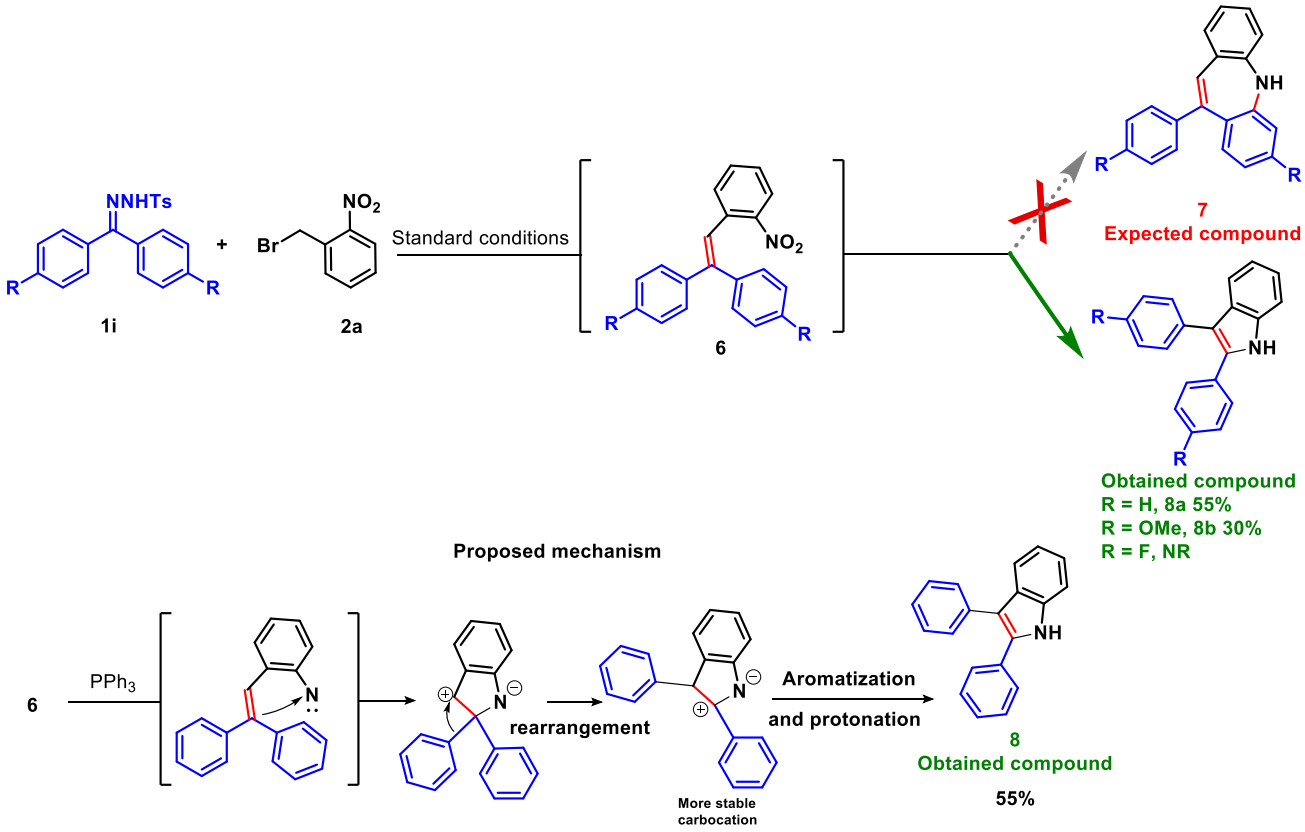


1 2 3 4

entry	NTH **1**	Benzyl bromides **2**	product	yield (%)[a]
1	 **1d**	 **2b**	 **4h**	58
2	 **1h**	**2b**	 **4i**	56
3	 **1a**	 **2c**	 **4j**	66
4	**1a**	 **2d**	 **4k**	71
5	 **1b**	**2d**	 **4l**	63
6	 **1e**	**2d**	 **4m**	68
7	 **1c**	 **2e**	 **4n**	52
8	 **1g**	 **2f**	 **4o**	72
9	 **1d**	 **2g**	 **4p**	65
10	**1a**	 **2h**	 **4q**	55
11	 **1i**	 **2a**	 **4r**	32

[a] Yield of isolated products.

After the success in the coupling of NTH derived from aldehydes, we finally intended to perform the one-pot reaction between NTH derived from benzophenone **1i** (R = H) (Scheme 2) and nitrobenzyl bromide **2a** which would lead to the intermediate **6i** and then the reductive cyclization normally would give rise to a compound with seven-member azepin heterocycle **7i** (Scheme 2). When the reaction has performed, a new compound was obtained in 55% yield and was expected to be the desired 7-member ring compound. Even if we obtained the desired pic of mass for this product **7**: HRMS (ESI): for $C_{20}H_{16}N$ $(M + H)^+$: *m/z* calcd 270.1283, found 270.1274, however the ^1H and ^{13}C NMR analysis did not fit with this already known compound **7**.[20] After careful analysis (MS, ^1H, and ^{13}C NMR), we deduced that the obtained compound corresponds to 2,3-diphenyl-1*H*-indole **8a** (Scheme 2).[21] To validate this observation, we studied the same reaction with another NTH derived from benzophenone (R = OMe), again no traces of 7-member ring compound was observed and we isolated compound **8b** in a 30% yield. However, NTH having EWG (R = F) was not suitable for this transformation, in this case the corresponding intermediate **6** was not obtained. This coupling with NTH derived from benzophenone is currently under investigation by our laboratory.



Scheme 2. Unexpected 2,3 diphenyl indoles formation from NTH derived from acetophenone and nitrobenzyl bromide

Conclusion

In summary, we have developed an efficient one-pot method for the synthesis of C2-aryl indoles. This method implies the formation of *ortho*-nitrostyrenes intermediates from *N*-tosylhydrazones and nitro-benzylbromides. Then, nitrenes derivatives were generated in situ after deoxygenation of nitrostyrenes, followed by annulation leading to the formation of C2-arylated indoles. We anticipate that his method may quickly find use in medicinal chemistry programmes as it allows the synthesis of NH-free indoles libraries for direct biological tests, and which can be alkylated thereafter in order to increase the molecular diversity and enables drug discovery.

EXPERIMENTAL SECTION

General Methods. Solvent peaks were used as reference values, with $CDCl_3$ at 7.26 ppm for ^1H NMR and 77.16 ppm for ^{13}C NMR. Chemical shifts δ are given in ppm, and the following abbreviations are used: singlet (s), doublet (d), doublet of doublet (dd), triplet (t), multiplet (m) and broad singlet (bs). Reaction courses and product mixtures were routinely monitored by TLC on silica gel, and compounds were visualized with under a UVP Mineralight UVGL-58 lamp (254 nm) and with phosphomolybdic acid/Δ, anisaldehyde/Δ, or vanillin/Δ. Flash chromatography was performed using silica gel 60 (40–63 mm, 230–400 mesh) at medium pressure (200 mbar). Fluorobenzene was used as received, dioxane, dichloromethane, cyclohexane and tetrahydrofuran were dried using the procedures described in D. Perrin Purification of Laboratory Chemicals.[22] Organic extracts were, in general, dried over $MgSO_4$ or Na_2SO_4. All products reported showed ^1H and ^{13}C NMR spectra in agreement with the assigned structures.

General procedure for preparation of hydrazone[23]

To a rapidly stirred suspension of *p*-toluenesulphonohydrazide (5 mmol) in dry methanol (10 mL) at 60 °C, the ketone (5 mmol) was added dropwise. Within 5-60 min the *N*-tosylhydrazone began to precipitate. The mixture was cooled to 0 °C and the product was collected on a Büchner funnel, washed by petroleum ether then was dried *in vacuo* to afford the pure product.

General procedure for the synthesis of *2*-arylated NH-free indole derivatives

A 5 ml sealed tube under argon atmosphere was charged with *N*-tosylhydrazone (0.6 mmol, 1.0 eq), 2-nitrobenzylbromide (0.6 mmol, 1.0 eq), $Pd_2dba_3 \cdot CHCl_3$ (2.5 mol%), and P(2-furyl)$_3$ (10 mol%). Then dioxane (2.5 mL) was added via syringe and the mixture was stirred at room temperature for 1 min before the addition of Li*O*t*Bu* (1.32 mmol, 2.2 eq). Then the flask was put into a preheated oil bath (110 °C) and stirred. After 3 h, PPh_3 (2.4 mmol, 4 eq) was added to the same reaction mixture which was stirred at 160 °C for 24 h. The crude reaction mixture

was allowed to cool to room temperature. EtOAc was added to the mixture, which was filtered through Celite®. The solvents were evaporated under reduced pressure, and the crude residue was purified by column chromatography on silica gel.

2-(3,5-Dimethoxyphenyl)-1*H*-indole (4a).[24] Column chromatography on silica gel afforded 106 mg of the desired compound (0.42 mmol, yield 70%), white solid, m.p.= 129-130 ˚C. TLC: R_f = 0.4 (Cyclohexane/ Ethyl acetate 8/2). IR (film, cm^{-1}): 3388, 2994, 2937, 1611, 1592, 1546, 1455, 1428, 1359, 1280, 1204, 1151, 1081. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.36 (s, 1H), 7.67 (d, *J* = 7.7 Hz, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.24 (t, *J* = 7.7 Hz, 1H), 7.17 (t, *J* = 7.8 Hz, 1H), 6.84 (s, 1H), 6.83 (d, *J* = 2.1 Hz, 2H), 6.48 (t, *J* = 2.1 Hz, 1H), 3.87 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 161.3 (2C), 137.9 (C), 136.8 (C), 134.4 (C), 129.2 (C), 122.5 (CH), 120.8 (CH), 120.4 (CH), 111.1 (CH), 103.7 (2CH), 100.4 (CH), 99.7 (CH), 55.5 ($2OCH_3$). HRMS (ESI): for $C_{16}H_{16}NO_2$ $(M + H)^+$: *m/z* calcd 254.1181, found 254.1182.

2-(3,4,5-Trimethoxyphenyl)-1*H*-indole (4b).[25] Column chromatography on silica gel afforded 109 mg of the desired compound (0.39 mmol, yield 65%), brown solid, m.p.= 178-180˚C. TLC: R_f= 0.27 (Cyclohexane/ Ethyl acetate 8/2). IR (film, cm^{-1}): 3332, 2923, 1591, 1501, 1462, 1363, 1285, 1261, 1239, 1184, 1127, 1077. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.37 (s, 1H), 7.63 (d, *J* = 7.7 Hz, 1H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.20 (td, *J* = 7.7, 1.2 Hz, 1H), 7.13 (td, *J* = 7.8, 1.1 Hz, 1H), 6.87 (s, 2H), 6.76 (d, *J* = 2.0 Hz, 1H), 3.95 (s, 6H), 3.90 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 153.9 (2C), 138.3 (C), 138.2 (C), 136.9 (C), 129.4 (C), 128.5 (C), 122.5 (CH), 120.7 (CH), 120.5 (CH), 111.0 (CH), 102.9 (2CH), 100.1 (CH), 61.2 (OCH_3), 56.4 ($2OCH_3$). HRMS (ESI): for $C_{17}H_{18}NO_3$ $(M+ H)^+$: *m/z* calcd 284.1287, found 284.1280.

2-(4-Methoxyphenyl)-1*H*-indole (4c).[26] Column chromatography on silica gel afforded 98 mg of the desired compound (0.44 mmol, yield 73%), yellow solid, m.p.= 228-230˚C. TLC: R_f = 0.51 (Cyclohexane/ Ethyl acetate 8/2). IR (film, cm^{-1}): 3431, 3054, 2361, 2340, 1607, 1545, 1502, 1486, 1454, 1432, 1398, 1351, 1287, 1256, 1182, 1115. ^{1}H NMR (300 MHz, Acetone-

d_6) δ (ppm): 10.54 (s, 1H), 7.79 (d, *J* = 8.6 Hz, 2H), 7.53 (d, *J* = 7.7 Hz, 1H), 7.38 (d, *J* = 7.8 Hz, 1H), 7.07 (t, *J* = 7.7 Hz, 1H), 7.02 (d, *J* = 8.7 Hz, 2H), 7.01 – 6.97 (m, 1H), 6.76 (d, *J* = 2.1 Hz, 1H), 3.84 (s, 3H). ^{13}C NMR (75 MHz, Acetone-d_6) δ (ppm): 160.3 (C), 139.0 (C), 138.2 (C), 130.4 (C), 127.3 (2CH), 126.3 (C), 122.1 (CH), 120.8 (CH), 120.3 (CH), 115.2 (2CH), 111.8 (CH), 98.7 (CH), 55.6 (OCH_3). HRMS (ESI): for $C_{15}H_{14}NO$ $(M + H)^+$: *m/z* calcd 224.1075, found 224.1086.

2-(*p*-Tolyl)-1*H*-indole (4d).[27] Column chromatography on silica gel afforded 87 mg of the desired compound (0.42 mmol, yield 70%), yellow solid, m.p.= 214-216˚C. TLC: R_f = 0.6 (Cyclohexane/ Ethyl acetate 8/2). IR (film, cm^{-1}): 3441, 1595, 1546, 1501, 1454, 1426, 1351, 1298, 1264, 1205, 1155. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.30 (s, 1H), 7.67 (d, *J* = 7.7 Hz, 1H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.42 (d, *J* = 7.7 Hz, 1H), 7.29 (d, *J* = 7.9 Hz, 2H), 7.23 (t, *J* = 7.7 Hz, 1H), 7.17 (t, *J* = 7.8 Hz, 1H), 6.83 (d, *J* = 1.5 Hz, 1H), 2.44 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 138.2 (C), 137.8 (2C), 136.8 (C), 129.8 (2CH), 129.5 (C), 125.2 (2CH), 122.2 (CH), 120.7 (CH), 120.3 (CH), 110.9 (CH), 99.5 (CH), 21.4 (CH_3). HRMS (ESI): for $C_{15}H_{14}N$ $(M + H)^+$: *m/z* calcd 208.1126, found 208.1130.

2-(4-Fluorophenyl)-1*H*-indole (4e).[26] Column chromatography on silica gel afforded 70 mg of the desired compound (0.33 mmol, yield 55%), white solid, m.p.= 189-191˚C. TLC: R_f= 0.6 (Cyclohexane/ Ethyl acetate 8/2). IR (film, cm^{-1}): 3413, 1606, 1545, 1498, 1484, 1453, 1428, 1347, 1298, 1233, 1160, 1100, 1011. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.25 (s, 1H), 7.65 – 7.60 (m, 3H), 7.40 (d, *J* = 7.7 Hz, 1H), 7.21 (td, *J* = 7.7, 1.3 Hz, 1H), 7.18 – 7.15 (m, 1H), 7.14 (t, *J* = 7.9 Hz, 2H), 6.77 (d, *J* = 2.0 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 162.5 (d, *J* = 247.4 Hz, C), 137.2 (C), 137.0 (C), 129.4 (C), 128.9 (d, *J* = 3.0 Hz, C), 127.0 (d, *J* = 8.0 Hz, 2CH), 122.6 (CH), 120.8 (CH), 120.5 (CH), 116.2 (d, *J* = 21.8 Hz, 2CH), 111.0 (CH), 100.1 (CH). ^{19}F NMR (188 MHz, $CDCl_3$) δ (ppm): -110.7 (s). HRMS (ESI): for $C_{14}H_{11}NF$ $(M + H)^+$: *m/z* calcd 212.0876, found 212.0878.

2-Phenyl-1*H*-indole (4f).[28] Column chromatography on silica gel afforded 80 mg of the desired compound (0.41 mmol, yield 68%), white solid, m.p.= 188-190˚C. TLC: R_f= 0.6 (Cyclohexane/ Ethyl acetate 8/2). IR (film, cm^{-1}): 3446, 1603, 1480, 1458, 1446, 1403, 1352, 1299. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.33 (s, 1H), 7.68 (d, *J* = 7.7 Hz, 1H), 7.66 (d, *J* = 7.2 Hz, 2H), 7.47 (d, *J* = 7.7 Hz, 1H), 7.42 (t, *J* = 7.2 Hz, 2H), 7.37 – 7.31 (m, 1H), 7.22 (t, *J* = 7.7 Hz, 1H), 7.15 (t, *J* = 7.8 Hz, 1H), 6.85 (d, *J* = 1.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 138.0 (C), 136.9 (C), 132.5 (C), 129.4 (C), 129.2 (2CH), 127.8 (CH), 125.3 (2CH), 122.5 (CH), 120.8 (CH), 120.4 (CH), 111.0 (CH), 100.1 (CH). HRMS (ESI): for $C_{14}H_{12}N$ $(M + H)^+$: *m/z* calcd 194.0970, found 194.0970.

2-(Naphthalen-2-yl)-1*H*-indole (4g).[29] Column chromatography on silica gel afforded 91 mg of the desired compound (0.37 mmol, yield 62%), white solid, m.p.= 196-197˚C. TLC: R_f = 0.63 (Cyclohexane/ Ethyl acetate 8/2). IR (film, cm^{-1}): 3054, 1603, 1454, 1422, 1345, 1296, 1264. ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 8.47 (s, 1H), 8.05 (s, 1H), 7.92 – 7.81 (m, 4H), 7.68 (d, *J* = 7.7 Hz, 1H), 7.56 – 7.46 (m, 2H), 7.44 (d, *J* = 7.8 Hz, 1H), 7.24 (t, *J* = 7.7 Hz, 1H), 7.16 (t, *J* = 7.7 Hz, 1H), 6.97 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 138.0 (C), 137.2 (C), 133.7 (C), 133.0 (C), 129.8 (C), 129.5 (C), 129.0 (CH), 128.1 (CH), 127.9 (CH), 126.8 (CH), 126.3 (CH), 123.9 (CH), 123.2 (CH), 122.7 (CH), 120.9 (CH), 120.5 (CH), 111.0 (CH), 100.8 (CH). HRMS (ESI): for $C_{18}H_{14}N$ $(M + H)^+$: *m/z* calcd 244.1126, found 244.1124.

7-Methoxy-2-(p-tolyl)-1*H*-indole (4h). Column chromatography on silica gel afforded 83 mg of the desired compound (0.35 mmol, yield 58%), brown solid, m.p.= 107 ˚C. TLC: R_f = 0.6 (Cyclohexane/ Ethyl acetate 8/2). IR (film, cm^{-1}): 3783, 3451, 2925, 2375, 2061, 1634, 1420, 1332, 1255, 1097. ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 8.55 (s, 1H), 7.59 (d, *J* = 8.0 Hz, 2H), 7.25 (d, *J* = 8.0 Hz, 2H), 7.23 (d, *J* = 7.8 Hz, 1H), 7.05 (t, *J* = 7.8 Hz, 1H), 6.78 (d, *J* = 2.4 Hz, 1H), 6.66 (d, *J* = 7.8 Hz, 1H), 4.00 (s, 3H), 2.40 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm:

146.1 (C), 137.9 (C), 137.7 (C), 130.8 (C), 130.7 (C), 129.8 (2CH), 127.3 (C), 125.2 (2CH), 120.6 (CH), 113.4 (CH), 102.2 (CH), 99.8 (CH), 55.5 (OCH_3), 21.4 (CH_3). HRMS (ESI): for $C_{16}H_{16}NO$ $(M + H)^+$: *m/z* calcd 238.1232, found 238.1240.

4-(7-Methoxy-1*H*-indol-2-yl)benzonitrile (4i). Column chromatography on silica gel afforded 84 mg of the desired compound (0.34 mmol, yield 56%), yellow solid, m.p.= 135 ˚C. TLC: R_f = 0.34 (Cyclohexane/ Ethyl acetate 8/2). IR (film, cm^{-1}): 3781, 3449, 2925, 2853, 2223, 1634, 1425, 1335, 1257, 1173, 1094. ^1H NMR (300 MHz, Acetone-d_6) δ ppm: 10.73 (s, 1H), 8.14 (d, *J* = 8.7 Hz, 2H), 7.81 (d, *J* = 8.7 Hz, 2H), 7.20 (d, *J* = 7.9 Hz, 1H), 7.09 (d, *J* = 2.0 Hz, 1H), 6.98 (t, *J* = 7.9 Hz, 1H), 6.72 (d, *J* = 7.8 Hz, 1H), 3.96 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 147.5 (C), 137.9 (C), 136.7 (C), 133.5 (2CH), 131.2 (C), 129.4 (C), 126.6 (2CH), 121.6 (CH), 119.5 (C), 114.3 (CH), 111.0 (C), 103.8 (CH), 103.3 (CH), 55.7 (OCH_3). HRMS (ESI): for $C_{16}H_{13}N_2O$ $(M + H)^+$: *m/z* calcd 249.1028, found 249.1026.

2-(3,5-Dimethoxyphenyl)-6-methoxy-1*H*-indole (4j). Column chromatography on silica gel afforded 113 mg of the desired compound (0.40 mmol, yield 66%), yellow oil. TLC: R_f= 0.29 (Cyclohexane/ Ethyl acetate 8/2). IR (film, cm^{-1}): 3853, 3779, 3415.31, 2925, 2851, 2372, 2051, 1727, 1618, 1439, 1356, 1236, 1201, 1155, 1063. ^1H NMR (300 MHz, acetone-d6) δ ppm: 10.63 (s, 1H), 7.42 (d, *J* = 8.6 Hz, 1H), 6.99 (d, *J* = 2.2 Hz, 2H), 6.94 (d, *J* = 2.2 Hz, 1H), 6.83 (d, *J* = 2.2 Hz, 1H), 6.70 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.42 (t, *J* = 2.2 Hz, 1H), 3.84 (s, 6H), 3.79 (s, 3H). ^{13}C NMR (75 MHz, acetone-d6) δ ppm: 162.3 (2C), 157.6 (C), 139.1 (C), 137.7 (C), 135.7 (C), 124.3 (C), 121.7(CH), 110.7 (CH), 103.6 (2CH), 100.3 (CH), 99.9 (CH), 95.2 (CH), 55.7 (2OCH3), 55.6 (OCH3). HRMS (ESI): for $C_{17}H_{18}NO_3$ $(M + H)^+$: *m/z* calcd 284.1287, found 284.1280.

2-(3,5-Dimethoxyphenyl)-5-methoxy-1*H*-indole (4k).[30] Column chromatography on silica gel afforded 121 mg of the desired compound (0.43 mmol, yield 71%), yellow oil. TLC: R_f =

0.32 (Cyclohexane/ Ethyl acetate 8/2). IR (film, cm^{-1}): 3854, 3779 3414, 2925, 2852, 2376, 2051, 1726, 1616, 1459, 1355, 1295, 1205, 1153, 1064. ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 8.24 (s, 1H), 7.24 (d, *J* = 8.8 Hz, 1H), 7.05 (d, *J* = 2.2 Hz, 1H), 6.83 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.76 (d, *J* = 2.2 Hz, 2H), 6.71 (d, *J* = 2.3 Hz, 1H), 6.41 (t, *J* = 2.2 Hz, 1H), 3.83 (s, 3H), 3.82 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 161.4 (2C), 154.6 (C), 138.7 (C), 134.6 (C), 132.1 (C), 129.7 (C), 112.9 (CH), 111.8 (CH), 103.6 (2CH), 102.4 (CH), 100.3 (CH), 99.8 (CH), 56.0 (OCH_3), 55.6 ($2OCH_3$). HRMS (ESI): for $C_{17}H_{18}NO_3$ $(M + H)^+$: *m/z* calcd 284.1287, found 284.1281.

5-Methoxy-2-(3,4,5-trimethoxyphenyl)-1*H*-indole (4l).[25] Column chromatography on silica gel afforded 119 mg of the desired compound (0.38 mmol, yield 63%), brown solid, m.p.= 151-152 ˚C. TLC: R_f = 0.26 (Cyclohexane/ Ethyl acetate 7/3). IR (film, cm^{-1}): 3783, 3417, 2926, 2851, 2378, 2054, 1727, 1624, 1460, 1353, 1231, 1127, 1033, 1001. ^1H NMR (300 MHz, $CDCl_3$) δ ppm: 8.23 (s, 1H), 7.29 (d, *J* = 8.6 Hz, 1H), 7.08 (d, *J* = 2.2 Hz, 1H), 6.87 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.85 (s, 2H), 6.68 (d, *J* = 2.1 Hz, 1H), 3.94 (s, 6H), 3.89 (s, 3H), 3.87 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 154.7 (C), 153.9 (2C), 139.0 (C), 138.1 (C), 132.1 (C), 129.9 (C), 128.6 (C), 112.6 (CH), 111.7 (CH), 102.8 (2CH), 102.4 (CH), 99.9 (CH), 61.2 (OCH_3), 56.4 ($2OCH_3$), 56.0 (OCH_3). HRMS (ESI): for $C_{18}H_{20}NO_4$ $(M + H)^+$: *m/z* calcd 314.1392, found 314.1390.

2-(4-Fluorophenyl)-5-methoxy-1*H*-indole (4m).[31] Column chromatography on silica gel afforded 98 mg of the desired compound (0.41 mmol, yield 68%), yellow oil. TLC: R_f = 0.47 (Cyclohexane/ Ethyl acetate 8/2). IR (film, cm^{-1}): 3853, 3781, 3415, 2925, 2854, 2378, 2037, 1885, 1728, 1620, 1448, 1381, 1221, 1156, 1112, 1028. ^1H NMR (300 MHz, Acetone-d_6) δ ppm: 9.70 (s, 1H), 7.85 (dd, *J* = 8.9, 5.3 Hz, 2H), 7.42 (d, *J* = 8.8 Hz, 1H), 7.30 (t, *J* = 8.9 Hz, 2H), 7.16 (d, *J* = 2.4 Hz, 1H), 6.90 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.82 (d, *J* = 1.6 Hz, 1H), 3.91 (s,

3H). ^{13}C NMR (75 MHz, Acetone-d_6) δ ppm: 162.7 (d, *J* = 244.8 Hz, C-F), 154.9 (C), 138.2 (C), 132.9 (C), 130.2 (C), 129.6 (C), 129.6 (d, *J* = 3.3 Hz, C), 127.5 (d, *J* = 8.2 Hz, 2CH), 116.3 (d, *J* = 21.9 Hz, 2CH), 112.8 (CH), 112.4 (CH), 102.3 (CH), 99.4 (CH), 55.7 (OCH_3). ^{19}F NMR (188 MHz, $CDCl_3$) δ (ppm): -110.7 (s). HRMS (ESI): for $C_{15}H_{13}NOF$ $(M + H)^+$: *m/z* calcd 242.0981, found 242.0984.

7-Fluoro-2-(4-methoxyphenyl)-1*H*-indole (4n). Column chromatography on silica gel afforded 75 mg of the desired compound (0.31 mmol, yield 52%), brown solid, m.p.= 120 ˚C. TLC: R_f = 0.47 (Cyclohexane/ Ethyl acetate 8/2). IR (film, cm^{-1}): 3782, 3419, 2925, 2854, 2376, 2037, 1634, 1438, 1334, 1240, 1179, 1111, 1025. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.41 (s, 1H), 7.61 (d, *J* = 8.8 Hz, 2H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.03 – 7.01 (m, 1H), 7.00 (d, *J* = 8.8 Hz, 2H), 6.88 (dd, *J* = 11.1, 7.8 Hz, 1H), 6.74 – 6.71 (m, 1H), 3.87 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 159.8 (C), 149.5 (d, *J* = 242.9 Hz, C-F), 139.0 (d, *J* = 0.9 Hz, C), 133.1 (d, *J* = 5.3 Hz, C), 126.8 (2CH), 125.0 (d, *J* = 13.0 Hz, C), 124.8 (C), 120.5 (d, *J* = 6.2 Hz, CH), 116.2 (d, *J* = 3.4 Hz, CH), 114.7 (2CH), 106.9 (d, *J* = 16.2 Hz, CH), 99.5 (d, *J* = 2.4 Hz, CH), 55.5 (OCH_3). ^{19}F NMR (188 MHz, $CDCl_3$) δ (ppm): -135.7 (s). HRMS (ESI): for $C_{15}H_{13}NOF$ $(M + H)^+$: *m/z* calcd 242.0981, found 242.0982.

6-Fluoro-2-(naphthalen-2-yl)-1*H*-indole (4o). Column chromatography on silica gel afforded 113 mg of the desired compound (0.43 mmol, yield 72%), white solid, m.p.= 180 ˚C. TLC: R_f = 0.47 (Cyclohexane/ Ethyl acetate 8/2). IR (film, cm^{-1}): 3781, 3441, 2924, 2854, 2375, 2035, 1625, 1498, 1442, 1393, 1348, 1249, 1141, 1107. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.49 (s, 1H), 8.02 (d, *J* = 1.3 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.85 – 7.77 (m, 2H), 7.59 – 7.54 (m, 1H), 7.53 – 7.45 (m, 2H), 7.11 (dd, *J* = 8.5, 2.2 Hz, 1H), 6.95 – 6.88 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 160.3 (d, *J* = 238.5 Hz, C-F), 138.5 (d, *J* = 3.7 Hz, C), 137.1 (d, *J* = 12.5 Hz, C), 133.7 (C), 133.0 (C), 129.6 (C), 129.0 (CH), 128.1 (CH), 128.0

(CH), 126.9 (CH), 126.3 (CH), 126.0 (d, J = 0.7 Hz, C), 123.7 (CH), 123.0 (CH), 121.6 (d, J = 12.2 Hz, CH), 109.2 (d, J = 24.5 Hz, CH), 100.7 (d, J = 0.7 Hz, CH), 97.5 (d, J = 24.8 Hz, CH). ^{19}F NMR (188 MHz, $CDCl_3$) δ (ppm): -120.0 (s). HRMS (ESI): for $C_{18}H_{13}NF$ $(M + H)^+$: *m/z* calcd 262.1032, found 262.1037.

5-Fluoro-2-(*p*-tolyl)-1*H*-indole (4p). Column chromatography on silica gel afforded 88 mg of the desired compound (0.39 mmol, yield 65%), yellow solid. TLC: R_f = 0.47 (Cyclohexane/ Ethyl acetate 8/2). IR (film, cm^{-1}): 3781, 3437, 2924, 2854, 2375, 2053, 1635, 1447, 1262, 1200, 1111. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.30 (s, 1H), 7.54 (d, J = 7.8 Hz, 2H), 7.29 (d, J = 4.4 Hz, 1H), 7.29 – 7.25 (m, 1H), 7.25 (d, J = 7.8 Hz, 2H), 6.91 (td, J = 8.6, 2.5 Hz, 1H), 6.73 (d, J = 2.2 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ ppm: 158.3 (d, J = 234.4 Hz, C-F), 140.0 (C), 138.1 (C), 133.4 (C), 129.9 (2CH), 129.8 (C), 129.4 (C), 125.3 (2CH), 111.5 (d, J = 9.7 Hz, CH), 110.5 (d, J = 25.4 Hz, CH), 105.4 (d, J = 24.6 Hz, CH), 99.6 (d, J = 4.6 Hz, CH), 29.9 (CH_3). ^{19}F NMR (188 MHz, $CDCl_3$) δ (ppm): -124.3 (s). HRMS (ESI): for $C_{15}H_{13}NF$ $(M + H)^+$: *m/z* calcd 226.1032, found 226.1040.

2-(3,5-Dimethoxyphenyl)-1*H*-indole-6-carbonitrile (4q). Column chromatography on silica gel afforded 92 mg of the desired compound (0.33 mmol, yield 55%), white solid, m.p.= 189-191 ˚C. TLC: R_f = 0.22 (Cyclohexane/ Ethyl acetate 8/2). IR (film, cm^{-1}): 3852, 3780, 3428, 2925, 2854, 2373, 2050, 1728, 1625, 1439, 1356, 1240, 1201, 1162. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.80 (s, 1H), 7.72 (d, J = 8.2 Hz, 1H), 7.32 (dd, J = 8.2, 1.3 Hz, 1H), 7.08 (d, J = 2.2 Hz, 2H), 7.07 (d, J = 1.5 Hz, 1H), 6.54 (t, J = 2.2 Hz, 1H), 3.87 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 162.4 (2C), 143.0 (C), 137.0 (C), 134.2 (C), 133.1 (C), 123.6 (CH), 122.0 (CH), 121.1 (C), 116.6 (CH), 104.7 (C), 104.6 (2CH), 101.4 (CH), 101.0 (CH), 55.8 ($2OCH_3$). HRMS (ESI): for $C_{17}H_{15}N_2O_2$ $(M + H)^+$: *m/z* calcd 279.1134, found 279.1132.

(*E*)-2-Styryl-1*H*-indole (4r).[32] Column chromatography on silica gel afforded 42 mg of the desired compound (yield 32%), white solid, m.p.= 188-190 ˚C. TLC: R_f = 0.4 (Cyclohexane/ Ethyl acetate 8/2). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.26 (bs, 1H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.51 (d, *J* = 7.6 Hz, 2H), 7.40 – 7.34 (m, 3H), 7.28 (d, *J* = 7.6 Hz, 1H), 7.22-7.15 (m, 2H), 7.11 (t, *J* = 7.6 Hz, 2H), 6.92 (d, *J* = 16.6 Hz, 1H), 6.63 (s, 1H). HRMS (ESI): for $C_{16}H_{13}N$ $(M + H)^+$: *m/z* calcd 220.1126, found 220.1125.

2,3-Diphenyl-1*H*-indole (8a).[21a] Column chromatography on silica gel afforded 90 mg of the unknown compound (0.33 mmol, yield 55%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.25 (s, 1H), 7.71 (d, *J* = 7.9 Hz, 1H), 7.48-7.43 (m, 5H), 7.40-7.34 (m, 2H), 7.35 – 7.24 (m, 5H), 7.23 – 7.12 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 136.0 (C), 135.2 (C), 134.2 (C), 132.9 (C), 130.3 (2CH), 128.9 (C), 128.8 (2CH), 128.7 (2CH), 128.3 (2CH), 127.8 (CH), 126.4 (CH), 122.8 (CH), 120.6 (CH), 119.8 (CH), 115.2 (C), 111.0 (CH). HRMS (ESI): for $C_{20}H_{16}N$ $(M + H)^+$: *m/z* calcd 270.1283, found 270.1274.

2,3-bis(4-Methoxyphenyl)-1*H*-indole (8b).[32] Column chromatography on silica gel afforded 119 mg of the desired compound (yield 30%), slight yellow solid, m.p.= 151-152 ˚C. TLC: R_f = 0.4 (Cyclohexane/ Ethyl acetate 8/2). IR (film, cm^{-1}): 3376, 3333, 2835, 1610, 1555, 1517, 1242, 1231, 1175, 1033, 906, 727. ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 8.23 (bs, 1H), 7.68 (d, *J* = 7.7 Hz, 1H), 7.49 – 7.28 (m, 5H), 7.25-7.14 (m, 2H), 6.96 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 3.85 (s, 3H), 3.79 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 159.1(C), 158.1 (C), 135.8 (C), 133.9 (C), 131.2 (2CH), 129.4 (2CH), 129.1 (C), 127.7 (C), 125.4 (C), 122.3 (CH), 120.2(CH), 119.4 (CH), 114.2 (2CH), 114.1 (2CH), 113.7 (C), 110.9 (CH), 55.3 ($2OCH_3$). HRMS (ESI): for $C_{22}H_{20}NO_2$ $(M + H)^+$: *m/z* calcd 330.1494, found 330.1495.

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Supporting Information

Details for experiments conditions, copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org

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