JOC The Journal of Organic Chemistry

Note

Synthesis of Functionalized Indoles via Palladium-Catalyzed Aerobic Cycloisomerization of o-Allylanilines Using Organic Redox Cocatalyst

Xiao-Shan Ning, Mei-Mei Wang, Jian-Ping Qu, and Yan-Biao Kang

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b01999 • Publication Date (Web): 08 Oct 2018

ACS Publications

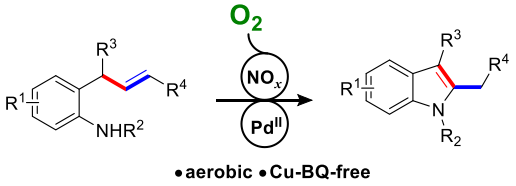
is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Synthesis of Functionalized Indoles via Palladium-Catalyzed Aerobic Cycloisomerization of *o*-Allylanilines Using Organic Redox Cocatalyst

Xiao-Shan Ning,[†‡] Mei-Mei Wang,[‡] Jian-Ping Qu,*[†] and Yan-Biao Kang*[‡]

[†]Institute of Advanced Synthesis, School of Chemistry and Molecular Engineering, Jiangsu National Synergetic Innovation Center for Advanced Materials, Nanjing Tech University, Nanjing 211816, China

[‡]Department of Chemistry, University of Science and Technology of China, Hefei, Anhui 230026, China



ABSTRACT: A scalable and practical synthesis of functionalized indoles via Pd-^{t}BuONO cocatalyzed aerobic cycloisomerization of o-allylanilines is reported. Using molecular oxygen as a terminal oxidant, a series of substituted indoles were prepared in moderate to good yields. The avoidance of hazardous oxidants, heavy metal-cocatalysts as well as high boiling point solvents like DMF and DMSO enables this method to be applied in the pharmaceutical synthesis. A practical gram-scale synthesis of indomethacin demonstrates its application potential.

Substituted indoles are among the most studied heterocycles because numerous biologically active molecules as well as medicinal agents are based on the indole skeleton (Figure 1).[1] The synthesis of this class of compounds thus attracts tremendous research interests. Starting with the seminal studies by Fischer et. al.,[2] a large number of methods toward the synthesis of substituted indoles have been developed.[3-5] On the other hand, molecular oxygen is undoubtedly a clean terminal oxidant whereas the hazardous transition metal redox cocatalysts normally cannot be avoided in such aerobic processes. Several modifications to avoid the hazardous oxidants in indole synthesis have been developed recently.[6-7]

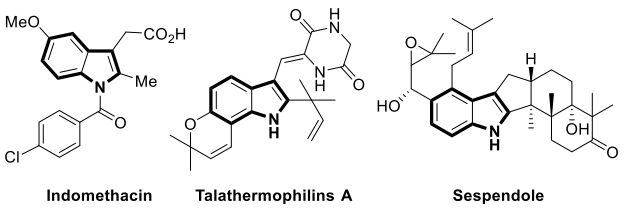
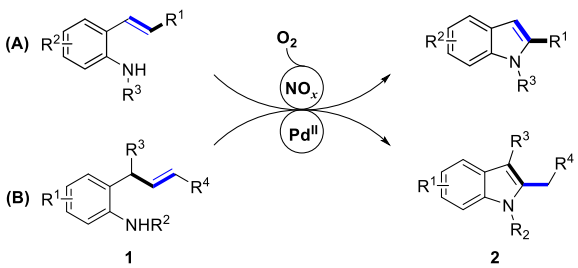


Figure 1. Representative molecules based on indole skeleton.

Hegedus indole synthesis, an intramolecular oxidative *N*-heterocyclization of *o*-alkenyl anilines or *o*-allylanilines, has evolved as an efficient method to construct indole skeleton.[3a,4,5] Traditionally, stoichiometric or catalytic palladium salts have been used in the presence of oxidants such as $Cu(OAc)_2$, AgOAc, $PhI(OAc)_2$, benzoquinone, etc. Using molecular oxygen as the terminal oxidant to replace the hazardous oxidant is an attractive choice. Several examples have been reported but with limited success.[4d,7]

On the basis of our previous work on Pd-^{t}BuONO cocatalyzed aerobic oxygenations of alkenes,[8] we have recently developed a general synthetically practical approach from 2-vinylanilines through regioselective C-H amination.[9] It provides an efficient method for accessing substituted indoles bearing C2, C4-C7 functional groups in one step. This method is aslo practical in pharmaceutical synthesis as it employs molecular O_2 as the sole terminal oxidant avoiding the use of hazardous oxidants, metal cocatalysts (Scheme 1A). During our further investigation, we found that using the same Pd-^{t}BuONO system[9] cycloisomerization of *o*-allylanilines underwent smoothly (Scheme 1B) as well. And this could also afford functionalized indoles in a practical manner. Here we report this in details.

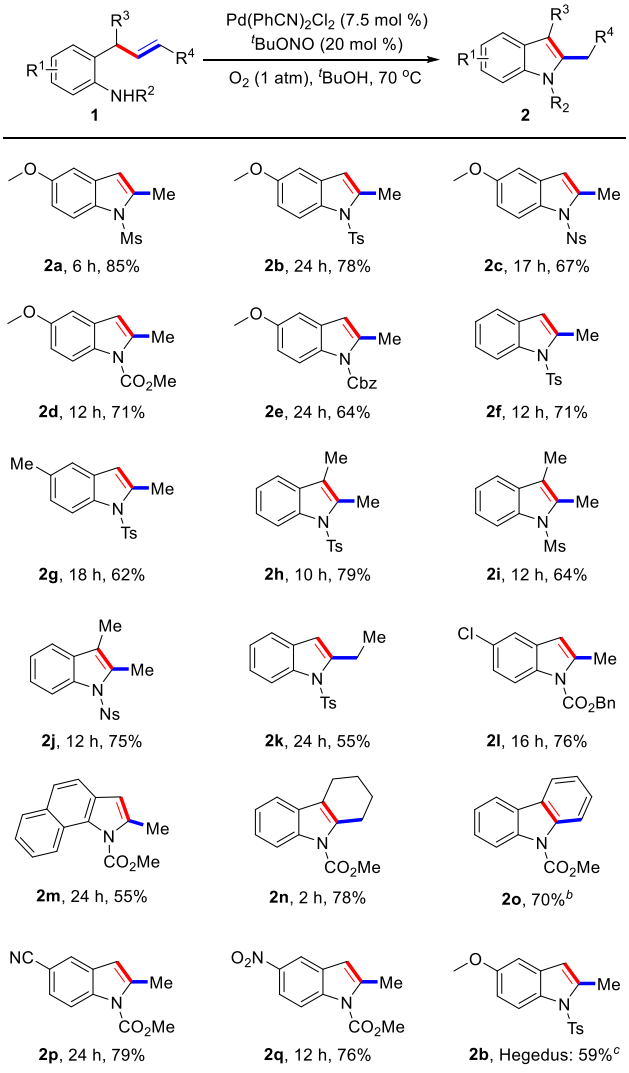
Scheme 1. Pd-^{t}BuONO-Catalyzed Aerobic C-H amination of *o*-Vinylanilines (A) and Cycloisomerization of *o*-Allylanilines (B)



The reaction conditions have been investigated in previous work.[9] The optimized reaction conditions for 2-vinyl anilines were applied directly into the cyclization of 2-allyl anilines. The scope of substituted indoles were investigated using $Pd(PhCN)_2Cl_2$ as catalyst,

^{t}BuONO as cocatalyst and ^{t}BuOH as solvent in the presence of 1 atm O_2 atmosphere at 70 °C (Scheme 2). Various *N*-protecting groups are applicable (Ms, Ns, Ts, Cbz, CO_2Me). Indoles with different *N*-protecting groups were investigated. Indoles bearing *N*-Ms (2a), *N*-Ts (2b), *N*-Ns (2c), *N*-CO_2Me (2d), and *N*-Cbz (2e) were achieved in 64-85% yields. Either 2-methyl or 2-ethyl indoles could be readily obtained (2f, 2k). C2,C3-dimethyl indole is also avaible by this method (2h-2j). Benzyl 5-chloro-2-methyl-1*H*-indole-1-carboxylate (2l) and methyl 2-methyl-1*H*-benzo[*g*]indole-1-carboxylate (2m) were all synthesized in good yields. Methyl 1,2,3,4-tetrahydro-9*H*-carbazole-9-carboxylate (2n) could be obtained in 78% yield, while methyl 9*H*-carbazole-9-carboxylate (2o) could be obtained in 70% yield after treatment with DDQ when the amination was completed.

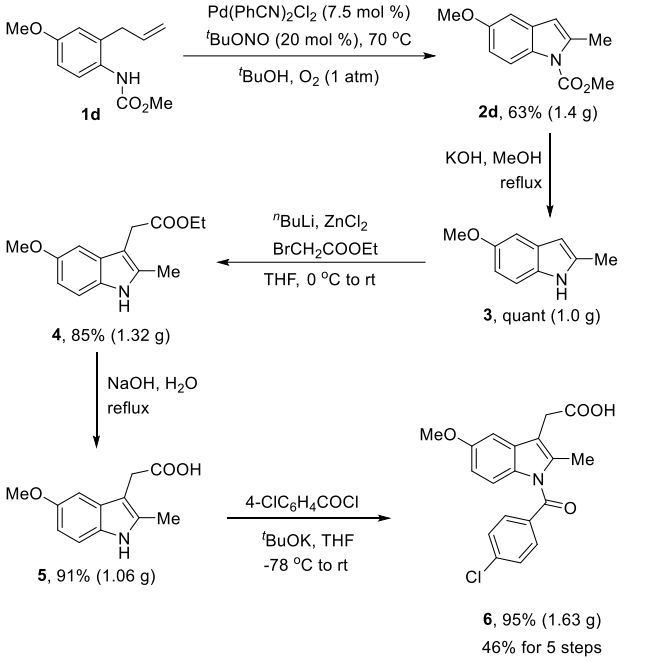
Scheme 2. Reaction Scope[a]



[a] Reaction conditions: 1 (0.25 mmol), ^{t}BuOH (2 mL), isolated yields. [b] Treated by DDQ (2.0 equiv) after amination. [c] Under Hegedus conditions: $Pd(PhCN)_2Cl_2$ (10 mol%), benzoquinone (2 equiv), LiCl (10 equiv), THF, 75 °C, 24 h.

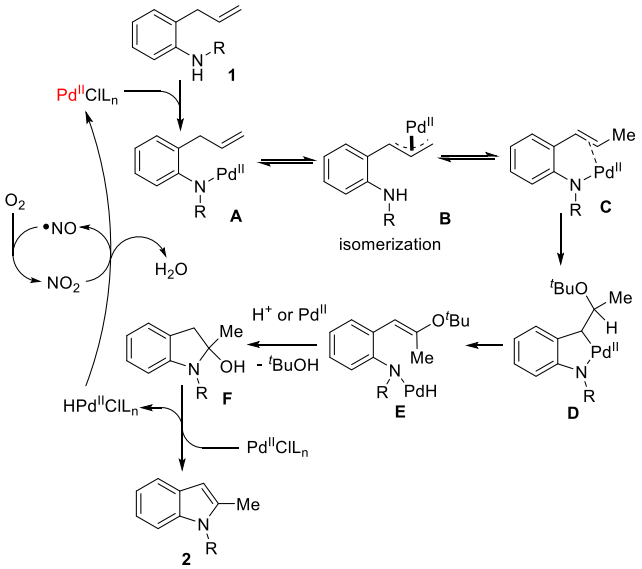
To evaluate the effectiveness and practical utility of this reaction in organic synthesis, a gram scale preparation of 2d from 1d using the standard condition was performed giving the desired product in 63% isolated yield (Scheme 3). Compound 2d was then applied in the gram scale synthesis of indomethacin 6, a nonsteroidal *anti*-inflammatory drug which is commonly used as a prescription medication to reduce fever, pain, stiffness, and swelling from inflammation, to demonstrate the application potential in pharmaceutical synthesis. By using present method, 1.63 grams of indomethacin 6 was synthesized via a Pd-^{t}BuONO cocatalyzed aerobic cycloisomerization of *o*-allylanilines 1d through 5 steps in overall 46% of yield.

Scheme 3. Gram-Scale Synthesis of Indomethacin



The reaction mechanism is proposed in Scheme 4 on the bases of previous report.[9] The isomerization transforms allyl aniline to propenyl aniline isomer C, which passes through a Wacker process to produce the final indoles. The pathway from C to 2 has been discussed with experimental evidence.[9]

Scheme 4. Proposed Mechanism



In conclusion, we have developed a general and practical synthesis of functionalized indoles via a Pd-^{t}BuONO cocatalyzed aerobic cycloisomerization of *o*-allylanilines. Using molecular oxygen as terminal oxidant, a series of substituted indoles were prepared in moderate to good yields under mild conditions. The non-involvement of hazardous oxidants, heavy metal cocatalysts as well as high boiling point solvents such as DMF and DMSO facilitates the application of this method in pharmaceutical synthesis. A gram scale synthesis of indomethacin was performed to demonstrate its application potential.

EXPERIMENTAL SECTION

General Information. Solvents were pre-dried over activated MS 4Å and heated to reflux over sodium (for toluene and THF) or calcium hydride (for CH_2Cl_2) under a nitrogen atmosphere and collected by distillation. ^{1}H NMR (400 MHz) and ^{13}C{^{1}H} NMR (100 MHz) spectra were recorded on a Bruker spectrometer. Chemical shifts are reported in δ units relative to (TMS, ^{1}H δ = 0; $CDCl_3$, ^{1}H δ = 7.26, ^{13}C δ = 77.36).

General procedure for Pd-^{t}BuONO Cocatalyzed Aerobic Cycloisomerization of o-Allylanilines. $Pd(PhCN)_2Cl_2$ (7.2 mg, 0.019 mmol) was weighed directly into a 25 mL Schlenk tube and dried under high vacuum for 15 min, purged oxygen 3 times. Under an atmosphere of oxygen (1 atm, ballon), ^{t}BuOH (2 mL) and ^{t}BuONO (5.2 mg, 0.05 mmol) were added and stirred. 2-allylaniline (0.25 mmol) was then added and the resulting reaction mixture was heated at 70 ℃ until the starting material disappeared (monitored by TLC) and cooled to room temperature, filtered through a thin silica gel pad and washed with EtOAc. The filtrate was concentrated and the residue was purified by chromatography on silica gel to afford the corresponding products.

5-Methoxy-2-methyl-1-(methylsulfonyl)-1H-indole (2a). This compound was This compound was prepared according to the general procedure and purified by flash column chromatography (PE/Et_2O = 40/1); colorless oil (6 h, 50.8 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.8 Hz, 1 H), 6.94 (d, *J* = 2.4 Hz, 1 H), 6.86 (dd, *J* = 9.2, 2.4 Hz, 1 H), 6.36 (s, 1 H), 3.84 (s, 3 H), 2.98 (s, 3 H), 2.55 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 156.9, 138.4, 131.5, 131.0, 115.1, 112.6, 109.9, 103.2, 56.0, 40.7, 15.9. HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for $C_{11}H_{13}NO_3SNa$ 262.0514; found 262.0512.

5-Methoxy-2-methyl-1-tosyl-1H-indole (2b).[10] This compound was prepared according to the general procedure and purified by flash column chromatography (PE/Et_2O = 200/1); colorless oil (24 h, 61.2 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 10.0 Hz, 1 H), 7.62 (d, *J* = 8.4 Hz, 2 H), 7.18 (d, *J* = 8.0 Hz, 2 H), 6.87-6.84 (m, 2 H), 6.26 (s, 1 H), 3.80 (s, 3 H), 2.57 (d, *J* = 0.4 Hz, 3 H), 2.33 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 156.7, 144.9, 138.4, 136.5, 131.9, 131.0, 130.1, 126.6, 115.7, 112.5, 110.1, 103.0, 55.9, 21.9, 16.1.

5-Methoxy-2-methyl-1-((4-nitrophenyl)sulfonyl)-1H-indole (2c). This compound was prepared according to the general procedure and purified by flash column chromatography (PE/Et_2O = 40/1); yellow oil (17 h, 58.1 mg, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24-8.21 (m, 2 H), 7.98 (d, *J* = 8.8 Hz, 1 H), 7.89-7.86 (m, 2 H),6.88-6.86 (m, 2 H), 6.32 (s, 1 H), 3.80 (s, 3 H), 2.57 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.3, 150.7, 144.4, 138.2, 131.5, 131.3, 127.8, 124.8, 115.6, 113.0, 111.6, 103.5, 55.9, 16.2. HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for $C_{16}H_{14}N_2O_5SNa$ 369.0521; found 369.0514.

Methyl 5-methoxy-2-methyl-1H-indole-1-carboxylate (2d).[9] This compound was prepared according to the general procedure and purified by flash column chromatography (PE/Et_2O = 50/1); white solid, mp 69-70 °C (12 h, 39.1 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 9.2 Hz, 1 H), 6.91 (s, 1 H), 6.84 (d, *J* = 9.2 Hz, 1 H), 6.27 (s, 1 H), 4.02 (s, 3 H), 3.84 (s, 3 H), 2.58 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 156.3, 152.9, 138.8, 131.3, 130.7, 116.5, 111.9, 108.8, 102.8, 55.9, 53.6, 17.1. For gram scale reaction in Scheme 3, $Pd(PhCN)_2Cl_2$ (287.7 mg, 0.75 mmol) was weighed directly into a 500 mL round bottom and dried under high vacuum for 15 min, purged oxygen 3 times. Under an atmosphere of oxygen (1 atm, ballon), ^{t}BuOH (80 mL) and ^{t}BuONO (206.2 mg, 2 mmol) were added and stirred methyl (2-allyl-4-methoxyphenyl)carbamate (1d) (2.21 g, 10 mmol) was then added and the resulting reaction mixture was heated at 70 ℃ until the starting material disappeared and cooled to room temperature, filtered through a thin silica gel pad and washed with EtOAc. The filtrate was concentrated and the residue was purified by chromatography on silica gel (PE/Et_2O 50/1 to PE/EA 10/1) to afford the corresponding product 2d as a white solid (1.39 g, 63%).

Benzyl 5-methoxy-2-methyl-1H-indole-1-carboxylate (2e). This compound was prepared according to the general procedure and purified by flash column chromatography (PE/Et_2O = 100/1); yellow oil (24 h, 47.6 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 9.2 Hz, 1 H), 7.46 (d, *J* = 6.8 Hz, 2 H), 7.41-7.34 (m, 3 H), 6.89 (d, *J* = 2.8 Hz, 1 H), 6.80 (dd, *J* = 9.0, 2.2 Hz, 1 H), 6.24 (s, 1 H), 5.42 (s, 2 H), 3.81 (s, 3 H), 2.55 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 156.3, 152.2, 138.9, 135.5, 131.4, 130.8, 129.1, 129.0, 128.9, 116.7, 111.9, 108.9, 102.9, 68.8, 55.9, 17.3. HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for $C_{18}H_{17}NO_3Na$ 318.1106; found 318.1102.

2-Methyl-1-tosyl-1H-indole (2f).[12] This compound was prepared according to the general procedure and purified by flash column chromatography (PE/Et_2O = 200/1); colorless oil (12 h, 50.5 mg, 71%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.0 Hz, 1 H), 7.66 (d, *J* = 8.4 Hz, 2 H), 7.39 (d, *J* = 7.2 Hz, 1 H), 7.23-7.19 (m, 4 H), 6.34 (s, 1 H), 2.60 (s, 3 H), 2.34 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 145.0, 137.6, 137.3, 136.6, 130.2, 130.0, 126.6, 124.0, 123.7, 120.3, 114.8, 109.9, 21.8, 16.1.

2,5-Dimethyl-1-tosyl-1H-indole (2g). This compound was prepared according to the general procedure and purified by flash column chromatography (PE/Et_2O = 200/1); yellow oil (18 h, 46.2 mg, 62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.4 Hz, 1 H), 7.63 (d, *J* = 8.0 Hz, 2 H), 7.17 (d, *J* = 6.4 Hz, 3 H), 7.06 (d, *J* = 8.4 Hz, 1 H), 6.25 (s, 1 H), 2.57 (s, 3 H), 2.38 (s, 3 H), 2.31 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 144.9, 137.7, 136.7, 135.5, 133.3, 130.2, 130.1, 126.6, 125.4, 120.3, 114.5, 109.8, 21.8, 21.5, 16.1. HRMS (ESI-TOF) m/z: [M+Na]$^+$ Calcd for $C_{17}H_{17}NO_2SNa$ 322.0872; found 322.0876.

2,3-Dimethyl-1-tosyl-1H-indole (2h).[11] This compound was prepared according to the general procedure and purified by flash column chromatography (PE/Et_2O = 50/1); colorless oil (10 h, 59.1 mg, 79%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.0 Hz, 1 H), 7.62 (d, *J* = 8.0 Hz, 2 H), 7.36 (d, *J* = 7.6 Hz, 1 H), 7.28-7.21 (m, 2 H), 7.17 (d, *J* = 8.0 Hz, 2 H), 2.51 (s, 3 H), 2.32 (s, 3 H), 2.12 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 144.8, 136.7, 136.6, 132.6, 131.6, 130.1, 126.6, 124.2, 123.5, 118.6, 116.3, 114.9, 21.9, 13.1, 9.2.

2,3-Dimethyl-1-(methylsulfonyl)-1H-indole (2i).[11] This compound was prepared according to the general procedure and purified by flash column chromatography (PE/Et_2O = 100/1), yellow oil (12 h, 35.8 mg, 64%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00-7.97 (m, 1 H), 7.46-7.44 (m, 1 H), 7.29-7.25 (m, 2 H), 2.95 (s, 3 H), 2.51 (s, 3 H), 2.20 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 136.3, 132.7, 131.6, 124.4, 123.8, 118.8, 116.3, 114.4, 40.5, 12.9, 9.2.

2,3-Dimethyl-1-((4-nitrophenyl)sulfonyl)-1H-indole (2j). This compound was prepared according to the general procedure and purified by flash column chromatography (PE/Et_2O = 100/1); yellow solid, mp 168-170 °C (12 h, 62.1 mg, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 9.2 Hz, 2 H), 8.13 (d, *J* = 7.6 Hz, 1 H), 7.88 (d, *J* = 9.2 Hz, 2 H),

7.37 (d, J = 7.2 Hz, 1 H), 7.32-7.25 (m, 2 H), 2.53 (s, 3 H), 2.13 (s, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 150.7, 144.6, 136.4, 132.3, 131.9, 127.9, 124.9, 124.8, 124.4, 119.1, 118.1, 114.8, 13.2, 9.3. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{14}N_2O_4SNa$ 353.0572; found 353.0574.

2-Ethyl-1-tosyl-1H-indole (2k).[12] This compound was prepared according to the general procedure and purified by flash column chromatography (PE/Et_2O = 200/1); yellow solid (24 h, 41.5 mg, 55%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 8.4 Hz, 1 H), 7.62 (d, J = 8.4 Hz, 2 H), 7.41 (d, J = 8.0 Hz, 1 H), 7.27-7.16 (m, 4 H), 6.38 (s, 1 H), 3.02 (qd, J = 7.6, 0.8 Hz, 2 H), 2.32 (s, 3 H), 1.33 (t, J = 7.6 Hz, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 144.9, 144.2, 137.6, 136.6, 130.1, 126.6, 124.1, 123.7, 120.4, 115.0, 108.0, 22.6, 21.9, 13.2.

Benzyl 5-chloro-2-methyl-1H-indole-1-carboxylate (2l). This compound was prepared according to the general procedure and purified by flash column chromatography (PE/Et_2O = 200/1); yellow solid (16 h, 57.0 mg, 76%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8.8 Hz, 1 H), 7.47 (d, J = 7.6 Hz, 2 H), 7.43-7.37 (m, 4 H), 7.14 (d, J = 8.8 Hz, 1 H), 6.25 (s, 1 H), 5.44 (s, 2 H), 2.56 (s, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 152.0, 139.6, 135.2, 135.1, 131.1, 129.2, 129.0, 128.8, 123.8, 119.5, 116.9, 108.3, 69.2, 17.3. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{14}ClNO_2Na$ 322.0611; found 322.0606.

Methyl 2-methyl-1H-benzo[g]indole-1-carboxylate (2m). This compound was prepared according to the general procedure and purified by flash column chromatography (PE/Et_2O = 100/1); white solid, mp 129-130 °C (24 h, 32.9 mg, 55%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.4 Hz, 1 H), 7.90 (d, J = 8.0 Hz, 1 H), 7.63 (d, J = 8.4 Hz, 1 H), 7.54 (d, J = 8.4 Hz, 1 H), 7.48 (t, J = 8.4 Hz, 1 H), 7.40 (t, J = 7.0 Hz, 1 H), 6.43 (s, 1 H), 4.08 (s, 3 H), 2.58 (s, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 154.2, 137.7, 131.9, 131.1, 129.4, 127.9, 125.6, 125.1, 124.0, 123.3, 122.7, 119.7, 108.2, 54.4, 15.9. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{13}NO_2Na$ 262.0844; found 262.0837.

Methyl 1,2,3,4-tetrahydro-9H-carbazole-9-carboxylate (2n). This compound was prepared according to the general procedure and purified by flash column chromatography (PE/Et_2O = 200/1); yellow oil (2 h, 44.6 mg, 78%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (dd, J = 7.2, 1.6 Hz, 1 H), 7.40-7.38 (m, 1 H), 7.27-7.20 (m, 2 H), 4.01 (s, 3 H), 3.01-2.98 (m, 2 H), 2.66-2.62 (m, 2 H), 1.92-1.80 (m, 4 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 153.0, 136.0, 130.4, 123.9, 123.0, 117.9, 117.5, 115.7, 53.5, 25.8, 23.8, 22.5, 21.4. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{14}H_{15}NO_2Na$ 252.1000; found 252.0991.

Methyl 9H-carbazole-9-carboxylate (2o). This compound was prepared according to the general procedure and treated with DDQ (2.0 equiv), purified by flash column chromatography (PE/Et_2O = 200/1); brown solid, mp 72-73 °C (4 h, 39.2 mg, 70%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 8.4 Hz, 2 H), 7.96 (d, J = 7.6 Hz, 2 H), 7.46 (t, J = 7.6 Hz, 2 H), 7.35 (t, J = 7.6 Hz, 2 H), 4.12 (s, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 153.3, 138.5, 127.5, 126.2, 123.7, 120.0, 116.6, 53.9. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{14}H_{11}NO_2Na$ 248.0687; found 248.0679.

Methyl 5-cyano-2-methyl-1H-indole-1-carboxylate (2p). Prepared according to the general procedure, purified by flash column chromatography (PE/Et_2O = 40/1), as a white solid, mp: 138-139 °C (24 h, 42.4 mg, 79%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 8.7 Hz, 1 H), 7.75 (s, 1 H), 7.49 (dd, J = 8.7, 1.6 Hz, 1 H), 6.40 (s, 1 H), 4.08 (s, 3 H), 2.63 (s, 3 H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2, 140.4, 138.4, 129.7, 126.7, 124.3, 120.0, 116.4, 108.1, 106.4, 54.1, 16.9. HRMS (ESI) calcd for $C_{12}H_{11}N_2O_2$ $[M+H]^+$ 215.0821, found 215.0820.

Methyl 2-methyl-5-nitro-1H-indole-1-carboxylate (2q). Prepared according to the general procedure, purified by flash column chromatography (PE/Et_2O = 20/1), as a yellow solid, mp: 147-148 °C (12 h, 44.5 mg, 76%). ^1H NMR (400 MHz, $CDCl_3$) δ. 8.33 (d, J = 2.2 Hz, 1 H), 8.18 (d, J = 9.2 Hz, 1 H), 8.12 (dd, J = 9.2, 2.3 Hz, 1 H), 6.48 (br, 1 H), 4.10 (s, 3 H), 2.64 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ152.1, 144.0, 141.2, 139.7, 129.5, 118.7, 115.8, 115.7, 108.9, 54.2, 16.9. HRMS (ESI) calcd for $C_{11}H_{11}N_2O_4$ $[M+H]^+$ 235.0719, found 235.0715.

5-Methoxy-2-methyl-indole (3).[9] To a solution of 2d (1.39 g, 6.3 mmol) in MeOH (30 mL) was added 3N KOH (3.20 mL), and the mixture was refluxed for 1 h. After completed, the reaction mixture was cooled to room temperature, the mixture was concentrated under reduced pressure and the residue was added H_2O (10 mL), the organic compounds were extracted with ethyl acetate, then the combined organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The corresponding product 3 was obtained without further purification, yellow oil (1.02 g, quant). ^1H NMR (400 MHz, $CDCl_3$) δ 7.73 (br s, 1 H), 7.14 (d, J = 8.8 Hz, 1 H), 6.99 (s, 1 H), 6.76 (d, J = 8.4 Hz, 1 H), 6.14 (s, 1 H), 3.83 (s, 3 H), 2.40 (s, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 154.4, 136.3, 131.5, 129.8, 111.1, 111.0, 102.2, 100.6, 56.2, 14.1.

Ethyl 2-(5-methoxy-2-methyl-indol-3-yl)acetate (4).[9] To a solution of 3 (1.02 g, 6.3 mmol) in dry THF (60 mL) was added a solution of ^{n}BuLi in hexane (1.6 M, 7.56 mmol, 4.73 mL) dropwise at 0 ℃. The reaction mixture was stirred at 0 ℃ for 30 min, and to the mixture was added $ZnCl_2$ (0.86 g, 6.3 mmol) at room temperature. The mixture was continuously stirred for 30 min, then a solution of ethyl bromoacetate (1.26 g, 7.56 mmol) in THF (20 mL) was added, and the mixture was stirred for further 24 h. The reaction was quenched with saturated aqueous NH_4Cl, the organic layer was separated and the aqueous layer was extracted with ethyl acetate, then the combined organic phase was washed with brine, dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The mixture was purified by column chromatography on silica gel (PE/EA 20/1 to 5/1) to afford the corresponding product 4 as a brown oil (1.32 g, 85%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.78 (br s, 1 H), 7.13 (d, J = 8.8 Hz, 1 H), 7.00 (d, J = 2.4 Hz, 1 H), 6.77 (dd, J = 8.8, 2.4 Hz, 1 H), 4.13 (q, J = 7.2 Hz, 2 H), 3.85 (s, 3 H), 3.64 (s, 2 H), 2.37 (s, 3 H), 1.24 (t, J = 7.2 Hz, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 172.5, 154.4, 133.8, 130.5, 129.3, 111.3, 104.8, 100.7, 61.0, 56.2, 30.9. 14.6, 12.1.

2-(5-Methoxy-2-methyl-indol-3-yl)acetic acid (5).[9] To a 100 mL round bottom were added 4 (1.32 g, 5.3 mmol) and 1 M NaOH (30 mL) at 100 ℃, then the mixture was stirred for 6 h. After completed, the reaction mixture was cooled to room temperature, addition of 12 N HCl resulted in precipitation of the product which was filtered off and washed with water, and dried under infrared drying lamps for 1 h to afford the corresponding product 5 as a brown solid, mp 161-162 °C (1.06 g, 91%). ^1H NMR (400 MHz, DMSO-d_6) δ 12.13 (br s, 1 H), 10.67 (br s, 1 H), 7.14 (d, J = 8.4 Hz, 1 H), 6.90 (d, J = 2.0 Hz, 1 H), 6.64 (dd, J = 8.8, 2.4 Hz, 1 H), 3.74 (s, 3 H), 3.53 (s, 2 H), 2.30 (s, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 173.5, 153.1, 133.9, 130.2, 128.9, 111.0, 109.6, 104.0, 100.2, 55.4, 30.1, 11.5.

Indomethacin (6).[9] To a solution of 5 (1.06 g, 4.8 mmol) in dry THF (40 mL) was added a solution of ^{t}BuOK (1.08 g, 9.6 mmol) in THF (40 mL) dropwise at -78 ℃, and the mixture was stirred for 1 h. To the mixture was added a solution of 4-chlorobenzoyl chloride (1.01 g, 5.76 mmol) in THF (5 mL), and the whole mixture was allowed up to room temperature for 16 h. Addition of 12 N HCl resulted in precipitation of the product which was filtered off and washed with water, and dried under infrared drying lamps for 1 h to afford 6 as a yellow solid, mp 155-157 °C (1.63 g, 95%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 8.0 Hz, 2 H), 7.46 (d, J = 8.4 Hz, 2 H), 6.94 (d, J = 1.6 Hz, 1 H), 6.85 (d, J = 8.8 Hz, 1 H), 6.67 (dd, J = 8.8, 1.6 Hz, 1 H), 3.82 (s, 3 H), 3.69 (s, 2 H), 2.38 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 168.4, 156.2, 139.5,

136.4, 133.9, 131.3, 130.9, 130.6, 129.3, 115.2, 111.9, 111.8, 101.3, 55.9, 30.1, 13.5.

General Procedure 1 for the Preparation of 2-allyl anilines. To a solution of 2-allyl anilines (1.0 equiv) in CH_2Cl_2 (15 mL) were added pyridine (1.4 equiv) and RCl (MsCl, TsCl, Ns, Cbz, MeOCOCl, etc) (1.2 equiv) at 0 ℃. After being stirred at 25 ℃ for overnight, the reaction mixture was poured into water and then the product was extracted with CH_2Cl_2 (3 times), dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude mixture was purified by column chromatography on silica gel to afford the corresponding product 1.

N-(2-allyl-4-methoxyphenyl)methanesulfonamide (1a).[13] This compound was prepared according to the general procedure 1 with 2-allyl-4-methoxyaniline (2.3 mmol), MsCl (2.8 mmol), pyridine (2.8 mmol), and CH_2Cl_2 (20 mL); column chromatography with PE/EA (5/1), white solid, mp 94.5-95 °C, 0.50 g, 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.4 Hz, 1 H), 6.80 (d, *J* = 8.0 Hz, 2 H), 6.18 (br s, 1 H), 5.99-5.89 (m, 1 H), 5.17 (d, *J* = 9.6 Hz, 1 H), 5.07 (d, *J* = 17.2 Hz, 1 H), 3.80 (s, 3 H), 3.44 (d, *J* = 6.0 Hz, 2 H), 2.98 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.6, 136.1, 135.8, 127.3 (two peaks), 117.2, 116.3, 112.7, 55.6, 39.9, 36.6.

N-(2-allyl-4-methoxyphenyl)-4-methylbenzenesulfonamide (1b).[14] This compound was prepared according to the general procedure 1 with 2-allyl-4-methoxyaniline (3.6 mmol), tosyl chloride (4.3 mmol), pyridine (4.3 mmol), CH_2Cl_2 (20 mL); column chromatography with PE/EA (5/1), yellow oil, 0.93 g, 82%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 8.0 Hz, 2 H), 7.24-7.21 (m, 3 H), 6.72 (dd, *J* = 8.8, 2.0 Hz, 1 H), 6.62 (s, 1 H), 6.24 (br s, 1 H), 5.79-5.69 (m, 1 H), 5.09 (d, *J* = 10.0 Hz, 1 H), 4.92 (d, *J* = 16.8 Hz, 1 H), 3.77 (s, 3 H), 2.92 (d, *J* = 6.4 Hz, 2 H), 2.41 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.5, 143.8, 136.9, 136.1, 135.7, 129.7, 128.4, 127.4, 127.3, 117.0, 115.9, 112.5, 55.5, 36.3, 21.7.

N-(2-allyl-4-methoxyphenyl)-4-nitrobenzenesulfonamide (1c). This compound was prepared according to the general procedure 1 with 2-allyl-4-methoxyaniline (2.3 mmol), NsCl (2.8 mmol), pyridine (2.8 mmol), CH_2Cl_2 (20 mL); column chromatography with PE/EA (20/1), amorphous solid, 0.55 g, 68%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.8 Hz, 2 H), 7.87 (d, *J* = 8.8 Hz, 2 H), 7.18 (d, *J* = 8.8 Hz, 1 H), 6.74 (dd, *J* = 9.0, 2.6 Hz, 1 H), 6.66 (d, *J* = 2.0 Hz, 1 H), 6.48 (br s, 1 H), 5.80-5.71 (m, 1 H), 5.10 (d, *J* = 10.0 Hz, 1 H), 4.92 (d, *J* = 17.2 Hz, 1 H), 3.78 (s, 3 H), 2.96 (d, *J* = 6.0 Hz, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.0, 150.3, 145.5, 136.6, 135.4, 128.5 (two peaks), 126.1, 124.3, 117.2, 116.1, 112.8, 55.5, 36.3. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{16}N_2O_5SNa$ 371.0672; found 371.0675.

Methyl (2-allyl-4-methoxyphenyl)carbamate (1d). This compound was prepared according to the general procedure 1with 2-allyl-4-methoxyaniline (3.0 mmol), methyl chloroformate (3.6 mmol), pyridine (3.6 mmol), CH_2Cl_2 (20 mL); column chromatography with PE/EA (1/1), yellow solid, mp 65-66 °C, 0.53 g, 79%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (br s, 1 H), 6.78 (dd, *J* = 8.8, 2.0 Hz, 1 H), 6.72 (s, 1 H), 6.41 (br s, 1 H), 5.97-5.88 (m, 1 H), 5.13 (d, *J* = 10.0 Hz, 1 H), 5.05 (d, *J* = 17.2 Hz, 1 H), 3.78 (s, 3 H), 3.74 (s, 3 H), 3.32 (d, *J* = 6.0 Hz, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.0, 155.2, 135.9, 132.6, 128.9, 124.9, 116.7, 115.6, 112.3, 55.5, 52.4, 36.7. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{12}H_{15}NO_3Na$ 244.0950; found 244.0948.

Benzyl (2-allyl-4-methoxyphenyl)carbamate (1e). This compound was prepared according to the general procedure 1 with 2-allyl-4-methoxyaniline (2.5 mmol), CbzCl (3.0 mmol), pyridine (3.5 mmol), CH_2Cl_2 (10 mL); column chromatography with PE/EA (10/1), white solid, mp 80-81 °C, 0.64 g, 86%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (s, 1 H), 7.38-7.35 (m, 5 H), 6.78 (d, *J* = 8.8 Hz, 1 H), 6.72 (s, 1 H), 6.44 (br s, 1 H), 5.96-5.86 (m, 1 H), 5.18 (s, 2 H), 5.11 (d, *J* = 10.0 Hz, 1 H), 5.01 (d, *J* = 17.2 Hz, 1 H), 3.77 (s, 3 H), 3.31 (d, *J* = 6.0 Hz, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.0, 154.6, 136.4, 135.8, 132.8, 128.7, 128.6, 128.3, 125.1, 116.7, 115.6, 112.2, 67.0, 55.5, 36.5. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{18}H_{19}NO_3Na$ 320.1263; found 320.1260.

N-(2-allylphenyl)-4-methylbenzenesulfonamide (1f).[14] This compound was prepared according to the general procedure 1 with 2-allylaniline (0.79 g, 5.9 mmol), CH_2Cl_2 (30 mL), pyridine (1.40 g, 17.7 mmol), tosyl chloride (1.21 g, 7.1 mmol) at 0 ℃; column chromatography with PE/EA (10/1), yellow oil, 1.44 g, 85%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.0 Hz, 2 H), 7.40 (d, *J* = 8.0 Hz, 1 H), 7.23-7.18 (m, 3 H), 7.11 (t, *J* = 7.2 Hz, 1 H), 7.07 (d, *J* = 7.2 Hz, 1 H), 6.55 (br s, 1 H), 5.83-5.73 (m, 1 H), 5.11 (d, *J* = 10.0 Hz, 1 H), 4.94 (d, *J* = 17.2 Hz, 1 H), 3.02 (d, *J* = 5.6 Hz, 2 H), 2.39 (s, 3 H).

N-(2-allyl-4-methylphenyl)-4-methylbenzenesulfonamide (1g). This compound was prepared according to the general procedure 1 with 2-allyl-4-methylaniline (3.0 mmol), TsCl (3.6 mmol), pyridine (3.6 mmol), CH_2Cl_2 (20 mL); column chromatography with PE/EA (10/1), yellow oil, 0.86 g, 95%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (d, *J* = 8.4 Hz, 2 H), 7.23 (t, *J* = 8.4 Hz, 3 H), 7.00 (dd, *J* = 8.0, 1.2 Hz, 1 H), 6.88 (s, 1 H), 6.45 (br s, 1 H), 5.81-5.71 (m, 1 H), 5.09 (dd, *J* = 10.0, 1.2 Hz, 1 H), 4.92 (dd, *J* = 17.2, 1.6 Hz, 1 H), 2.95 (d, *J* = 6.0 Hz, 2 H), 2.39 (s, 3 H), 2.27 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 143.8, 137.0, 136.5, 135.9, 132.7, 132.3, 131.2, 129.7, 128.4, 127.2, 125.4, 116.9, 36.2, 21.7, 21.0. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{19}NO_2SNa$ 324.1029; found 324.1032.

N-(2-(but-3-en-2-yl)phenyl)-4-methylbenzenesulfonamide (1h). This compound was prepared according to the general procedure 1 with 2-(but-3-en-2-yl)aniline (2.0 mmol), tosyl chloride (2.4 mmol), pyridine (2.4 mmol), CH_2Cl_2 (30 mL); column chromatography with PE/EA (10/1), yellow oil, 0.55 g, 91%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.0 Hz, 2 H), 7.37-7.35 (m, 1 H), 7.23 (d, *J* = 8.0 Hz, 2 H), 7.18-7.14 (m, 3 H), 6.54 (br s, 1 H), 5.77-5.69 (m, 1 H), 5.06 (d, *J* = 10.0 Hz, 1 H), 4.92 (d, *J* = 17.6 Hz, 1 H), 3.25-3.19 (m, 1 H), 2.39 (s, 3 H), 1.14 (d, *J* = 7.2 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 143.9, 141.9, 137.5, 136.8, 134.3, 129.7, 127.5, 127.4, 127.3, 126.6, 125.0, 114.7, 37.8, 21.7, 19.3. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{19}NO_2SNa$ 324.1034; found 324.1029.

N-(2-(but-3-en-2-yl)phenyl)methanesulfonamide (1i). This compound was prepared according to the general procedure 1 with 2-(but-3-en-2-yl)aniline (2.5 mmol), MsCl (3.0 mmol), pyridine (3.0 mmol), CH_2Cl_2 (20 mL); column chromatography with PE/EA (5/1), yellow oil, 0.44 g, 78%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 7.6 Hz, 1 H), 7.30-7.21 (m, 3 H), 6.50 (br s, 1 H), 5.99-5.91 (m, 1 H), 5.16 (dd, *J* = 10.4, 0.8 Hz, 1 H), 5.06 (d, *J* = 1.2 Hz, 1 H), 3.68 (s, 1 H), 3.02 (s, 3 H), 1.42 (d, *J* = 6.8 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 141.9, 136.7, 134.5, 128.1, 127.7, 126.5, 123.4, 115.0, 40.2, 38.3, 19.6. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{11}H_{15}NO_2SNa$ 248.0721; found 248.0717.

N-(2-(but-3-en-2-yl)phenyl)-4-nitrobenzenesulfonamide (1j). This compound was prepared according to the general procedure 1 with 2-(but-3-en-2-yl)aniline (2.5 mmol), NsCl (3.0 mmol), pyridine (3.0 mmol), CH_2Cl_2 (20 mL); column chromatography with PE/EA (10/1), amorphous yellow solid, 0.74 g, 88%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.8 Hz, 2 H), 7.92 (d, *J* = 8.8 Hz, 2 H), 7.34-7.31 (m, 1 H), 7.26-7.17 (m, 3 H), 6.75 (br s, 1 H), 5.79-5.71 (m, 1 H), 5.08 (d, *J* = 10.4 Hz, 1 H), 4.93 (d, *J* = 17.2 Hz, 1 H), 3.29-3.22 (m, 1 H), 1.17 (d, *J* = 7.2 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 150.2, 145.4, 141.7, 138.2, 133.1, 128.6, 128.0, 127.6 (two peaks), 125.2, 124.4, 114.9, 37.9, 19.5. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{16}H_{16}N_2O_4SNa$ 355.0728; found 355.0727.

Benzyl (2-allyl-4-chlorophenyl)carbamate (1l). This compound was prepared according to the general procedure 1 with 2-allyl-4-chloroaniline (1.1 mmol), CbzCl (1..3 mmol), pyridine (1.5 mmol), CH_2Cl_2 (20 mL); column chromatography with PE/EA (10/1), white solid, mp 90-91 °C, 0.30 g, 94%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (s, 1 H), 7.38-7.33 (m, 5 H), 7.20 (dd, *J* = 8.8, 2.4 Hz), 7.12 (d, *J* = 2.4 Hz, 1 H), 6.63 (br s, 1 H), 5.94-5.84 (m, 1 H), 5.18-5.14 (m, 3 H), 5.03 (dd, *J* = 17.2, 1.6 Hz, 1 H), 3.29 (d, *J* = 6.0 Hz, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 153.8, 136.0, 134.9, 134.7, 131.1, 129.9, 129.5, 128.7, 128.4 (two peaks), 127.5, 123.4, 117.5, 67.2, 36.1. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{17}H_{16}ClNO_2Na$ 324.0767; found 324.0760.

Methyl (2-allylnaphthalen-1-yl)carbamate (1m). This compound was prepared according to the general procedure 1 with 2-allylnaphthalen-1-amine (4 mmol), methyl chloroformate (4.8 mmol), pyridine (5.6 mmol), CH_2Cl_2 (20 mL); column chromatography with PE/EA (10/1), yellow solid, mp 120-123 °C, 0.70 g, 72%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93-7.92 (m, 1 H), 7.80 (d, *J* = 8.0 Hz, 1 H), 7.74 (d, *J* = 8.0 Hz, 1 H), 7.51-7.42 (m, 2 H), 7.34 (d, *J* = 8.4 Hz, 1 H), 6.55 (br s, 1 H), 5.96-5.94 (m, 1 H), 5.09-5.02 (m, 2 H), 3.80 (s, 3 H), 3.53 (d, *J* = 6.0 Hz, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 155.8, 136.3, 134.8, 133.2, 131.3, 130.0, 128.2, 128.0, 127.9, 126.8, 125.7, 122.8, 116.2, 52.8, 36.7. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{15}NO_2Na$ 264.1000; found 264.0995.

Methyl (1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2-yl)carbamate (1n). This compound was prepared according to the general procedure 1 with 1',2',3',4'-tetrahydro-[1,1'-biphenyl]-2-amine (0.35 g, 2.0 mmol), CH_2Cl_2 (20 mL), pyridine (0.22 g, 2.8 mmol), chloroformate (0.23 g, 2.4 mmol) at 0 ℃, column chromatography with PE/EA (10/1), yellow oil, 0.46 g, 99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (br s, 1 H), 7.25-7.20 (m, 1 H), 7.18 (dd, *J* = 7.6, 1.6 Hz, 1 H), 7.07 (t, *J* = 7.2 Hz, 1 H), 6.86 (br s, 1 H), 6.03-5.99 (m, 1 H), 5.70 (dd, *J* = 10.0, 2.0 Hz, 1 H), 3.77 (s, 3 H), 3.52-3.49 (m, 1 H), 2.13-2.12 (m, 2 H), 1.97-1.95 (m, 1 H), 1.81-1.75 (m, 1 H), 1.69-1.58 (m, 2 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 154.7, 135.4, 130.0, 129.5, 129.3, 127.2, 124.5, 122.5, 52.5, 38.9, 29.9, 24.9, 21.5. HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{14}H_{17}NO_2Na$ 254.1157; found 254.1150.

Methyl (2-allyl-4-cyanophenyl)carbamate (1p). This compound was prepared according to the general procedure 1 with 2-allyl-4-cyanocyaniline (5.8 mmol), methyl chloroformate (7.0 mmol), pyridine (7.0 mmol), CH_2Cl_2 (40 mL); column chromatography with PE/EA (15/1), white solid, mp 116-117 °C, 1.1 g, 88%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, *J* = 6.7 Hz, 1 H), 7.55–7.53 (m, 1 H), 7.44 (s, 1 H), 6.93 (br, 1 H), 5.97–5.87 (m, 1 H), 5.26 (d, *J* = 10.1 Hz, 1 H), 5.12 (d, *J* = 17.2 Hz, 1 H), 3.80–3.78 (m, 3 H), 3.39 (d, *J* = 5.8 Hz, 2 H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 140.8, 134.1, 133.9, 131.9, 128.1, 120.3, 119.0, 118.3, 106.6, 52.8, 36.1. HRMS (ESI) calcd for $C_{12}H_{13}N_2O_2$ $[M+H]^+$ 217.0977, found 217.0980.

Methyl (2-allyl-4-nitrophenyl)carbamate (1q). This compound was prepared according to the general procedure 1 with 2-allyl-4-nitroaniline (2.1 mmol), methyl chloroformate (2.5 mmol), pyridine (2.5 mmol), CH_2Cl_2 (14 mL); column chromatography with PE/EA (15/1), white solid, mp 105-106 °C, 0.45 g, 90%. ^{1}H NMR (400 MHz, $CDCl_3$) δ. 8.21 (d, *J* = 9.1 Hz, 1 H), 8.15–8.13 (m, 1 H), 8.07 (s, 1 H), 7.02 (br, 1 H), 6.01–5.91 (m, 1 H), 5.29 (d, *J* = 10.2 Hz, 1 H), 5.16 (d, *J* = 17.2 Hz, 1 H), 3.81 (s, 3 H), 3.46 (d, *J* = 6.0 Hz, 2 H), ^{13}C NMR (100 MHz, $CDCl_3$) δ153.5, 143.1, 142.6, 134.0, 127.7, 125.7, 123.7, 119.6, 118.5, 52.9, 36.4. HRMS (ESI) calcd for $C_{11}H_{13}N_2O_4$ $[M+H]^+$ 237.0875, found 237.0875.

ASSOCIATED CONTENT

SUPPORTING INFORMATION

This material is available free of charge *via* the Internet at http://pubs.acs.org.

NMR Spectra (PDF).

AUTHOR INFORMATION

Corresponding Author

ybkang@ustc.edu.cn

ias_jpqu@njtech.edu.cn

ORCID

Yan-Biao Kang: 0000-0002-7537-4627

Jian-Ping Qu: 0000-0002-5002-5594

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

We thank the National Natural Science Foundation of China (21602001, 21672196, 21404096, U1463202), and the Fundamental Research Funds for the Central Universities of China (WK2060190086) for financial support.

REFERENCES

(1) (a) Sundberg, R. J. *Indoles*; 2nd ed.; Academic Press: London, 1996. (b) Kawasaki, T.; Higuchi, K. Simple Indole Alkaloids and Those with a Nonrearranged Monoterpenoid Unit. *Nat. Prod. Rep.* 2005, *22*, 761-793. (c) Kochanowska-Karamyan, A. J.; Hamann, M. T. Marine Indole Alkaloids: Potential New Drug Leads for the Control of Depression and Anxiety. *Chem. Rev.* 2010, *110*, 4489-4497. (d) Kaushik, N. K.; Kaushik, N.; Attri, P.; Kumar,N.; Kim, C. H.; Verma, A. K.; Choi, E. H. Biomedical Importance of Indoles. *Molecules* 2013, *18*, 6620-6662.

(2) (a) Fischer, E.; Jourdan, F. Ueber die Hydrazine der Brenztraubensäure. *Ber. Dtsch. Chem. Ges.* 1883, *16*, 2241-2245. (b) Robinson, B. The Fischer Indole Synthesis. *Chem. Rev.* 1963, *63*, 373-401.

(3) Selected reviews on synthesis of substituted indoles: (a) Hegedus, L. S. Transition Metals in the Synthesis and Functionalization of Indoles [New Synthesis Methods (72)]. *Angew. Chem., Int. Ed.* 1988, 27, 1113-1226. (b) Humphrey, G. R.; Kuethe, J. T. Practical Methodologies for the Synthesis of Indoles. *Chem. Rev.* 2006, *106*, 2875-2911. (c) Taber, D. F.; Tirunahari, P. K. Indole Synthesis: a Review and Proposed Classification. *Tetrahedron* 2011, *67*, 7195-7210. (d) Cacchi, S.; Fabrizi, G. Update 1 of: Synthesis and Functionalization of Indoles Through Palladium-Catalyzed Reactions. *Chem. Rev.* 2011, *111*, PR215-PR283. (e) Vicente, R. Recent Advances in Indole Syntheses: New Routes for a Classic Target. *Org. Biomol. Chem.* 2011, *9*, 6469–6480. (f) Kochanowska-Karamyan, A. J.; Hamann, M. T. Marine Indole Alkaloids: Potential New Drug Leads for the Control of Depression and Anxiety. *Chem. Rev.* 2010, *110*, 4489–4497. (g) Shiri, M. Indoles in Multicomponent Processes (MCPs). *Chem. Rev.* 2012, *112*, 3508-3549. (h) *Indole Ring Synthesis: From Natural Products to Drug Discovery*; Gribble, G. W., Ed.; John Wiley & Sons: Chichester, West Sussex, 2016. (i) Leitch, J. A.; Bhonoah, Y.; Frost, C. G. Beyond C2 and C3: Transition-Metal-Catalyzed C–H Functionalization of Indole. *ACS Catal.* 2017, *7*, 5618-5627.

(4) From 2-allylanilines: with stoichiometric Pd, (a) Hegedus, L. S.; Allen, G. F.; Waterman, E. I. Palladium Assisted Intramolecular Amination of Olefins. A New Synthesis of Indoles. *J. Am. Chem. Soc.* 1976, *98*, 2674-2676. (b) Hegedus, L. S.; Allen, G. F.; Bozell, J. J.; Waterman, E. L. Palladium-Assisted Intramolecular Amination of Olefins. Synthesis of Nitrogen Heterocycles. *J. Am. Chem. Soc.* 1978, *100*, 5800-5807. With Pd-cat.: (c) Hegedus, L. S. Palladium-Catalyzed Synthesis of Heterocycles. *J. Mol. Catal.* 1983, *19*, 201-211. (d) Kasahara, A.; Izumi, T.; Murakami, S.; Miyamoto, K.; Hino, T. A Regiocontrolled Synthesis of Substituted Indoles by Palladium-Catalyzed coupling of 2-Bromonitrobenzenes and 2-Bromoacetanilides. *J. Heterocycl.*

Chem. 1989, *26*, 1405-1413. (e) Gowan, M.; Caillé, A. S.; Lau, C. K. Synthesis of 3-Alkoxyindoles via Palladium-Catalyzed Intramolecular Cyclization of N-Alkyl ortho-Siloxyallylanilines. *Synlett* 1997, 1312-1314. (f) Zakrzewski, P.; Gowan, M.; Trimble, L. A.; Lau, C. K. *ortho*-Hydroxyalkylation of Aminopyridines: A Novel Approach to Heterocycles. *Synthesis* 1999, 1893. (g) Fix, S. R.; Brice, J. L.; Stahl, S. S. Efficient Intramolecular Oxidative Amination of Olefins through Direct Dioxygen-Coupled Palladium Catalysis. *Angew. Chem., Int. Ed.* 2002, *41*, 164-166. (h) Nallagonda, R.; Rehan, M.; Ghorai, P. Synthesis of Functionalized Indoles via Palladium-Catalyzed Aerobic Oxidative Cycloisomerization of *o*-Allylanilines. *Org. Lett.* 2014, *16*, 4786-4789.

(5) From 2-vinylanilines, Pd-cat with BQ as oxidant: (a) Harrington, P. J.; Hegedus, L. S. Palladium-Catalyzed Reactions in the Synthesis of 3- and 4-Substituted Indoles. Approaches to Ergot Alkaloids. *J. Org. Chem.* 1984, *49*, 2657-2662. (b) Krolski, M. E.; Renaldo, A. F.; Rudisill, D. E.; Still, J. K. Palladium-Catalyzed Coupling of 2-Bromoanilines with Vinylstannanes. A Regiocontrolled Synthesis of Substituted Indoles. *J. Org. Chem.* 1988, *53*, 1170-1176.

(6) (a) Larock, R. C.; Yum, E. K. Synthesis of Indoles via Palladium-Catalyzed Heteroannulation of Internal Alkynes. *J. Am. Chem. Soc.* 1991, *113*, 6689-6690. (b) Stokes, B. J.; Liu, S.; Driver, T. G. Rh2(II)-Catalyzed Nitro-Group Migration Reactions: Selective Synthesis of 3-Nitroindoles from β-Nitro Styryl Azides. *J. Am. Chem. Soc.* 2011, *133*, 4702–4705. (c) Yang, Q.-Q.; Xiao, C.; Lu, L.-Q.; An, J.; Tan, F.; Li, B.-J.; Xiao, W.-J. Synthesis of Indoles through Highly Efficient Cascade Reactions of Sulfur Ylides and *N*-(*ortho*-Chloromethyl)aryl Amides. *Angew. Chem., Int. Ed.* 2012, *51*, 9137-9140. (d) Watanabe, T.; Mutoh, Y.; Saito, S. Ruthenium-Catalyzed Cycloisomerization of 2-Alkynylanilides: Synthesis of 3-Substituted Indoles by 1,2-Carbon Migration. *J. Am. Chem. Soc.* 2017, *139*, 7749-7752. Metal free C-H amination: (e) Fra, L.; Millá, A.; Souto, J. A.; Muñiz, K. Indole Synthesis Based On A Modified Koser Reagent. *Angew. Chem., Int. Ed.* 2014, *53*, 7349-7353. (f) Liu, Y.; Yao, B.; Deng, C.-L.; Tang, R.-Y.; Zhang, X.-G.; Li, J.-H. Palladium-Catalyzed Selective Heck-type Diarylation of Allylic Esters with aryl Halides Involving a β-OAc Elimination Process, *Org. Lett.* 2011, *13*, 1126–1129. (g) Gong, T.-J.; Cheng, W.-M.; Su, W., Xiao, B.; Fu, Y. Synthesis of Indoles through Rh(III)-catalyzed C-H Cross-Coupling with Allyl Carbonates, *Tetrahydron Lett* 2014, *55*, 1859-1862.

(7) (a) Shi, Z.; Zhang, C.; Li, S.; Pan, D.; Ding, S.; Cui, Y.; Jiao, N. Indoles from Simple Anilines and Alkynes: Palladium-Catalyzed C-H Activation Using Dioxygen as the Oxidant. *Angew. Chem., Int. Ed.* 2009, *48*, 4572-4576. (b) Wei, Y.; Deb, I.; Yoshikai, N. Palladium-Catalyzed Aerobic Oxidative Cyclization of *N*-Aryl Imines: Indole Synthesis from Anilines and Ketones. *J. Am. Chem. Soc.* 2012, *134*, 9098–9101.

(8) (a) Ning, X.-S.; Wang, M.-M.; Yao, C.-Z.; Chen, X.-M.; Kang, Y.-B. *tert*-Butyl Nitrite: Organic Redox Cocatalyst for Aerobic Aldehyde-Selective Wacker–Tsuji Oxidation. *Org. Lett.* 2016, *18*, 2700-2703. (b) Wang, M.-M.; Ning, X.-S.; Qu, J.-P.; Kang, Y.-B. Dehydrogenative Synthesis of Linear α,β-Unsaturated Aldehydes with Oxygen at Room Temperature Enabled by tBuONO. *ACS Catal.* 2017, *7*, 4000-4003. (c) Chen, X.-M.; Ning, X.-S., Kang, Y.-B. Aerobic Acetoxyhydroxylation of Alkenes Co-catalyzed by Organic Nitrite and Palladium. *Org. Lett.* 2016, *18*, 5368-5371. (d) Liu, J.; Zheng, H.-X.; Yao, C.-Z.; Sun, B.-F.; Kang, Y.-B. Pharmaceutical-Oriented Selective Synthesis of Mononitriles and Dinitriles Directly from Methyl(hetero)arenes: Access to Chiral Nitriles and Citalopram. *J. Am. Chem. Soc.* 2016, *138*, 3294-3297. (e) Ge, J.-J.; Yao, C.-Z.; Wang, M.-M.; Zheng, H.-X.; Kang, Y.-B.; Li, Y. Transition-Metal-Free Deacylative Cleavage of Unstrained C(sp3)–C(sp2) Bonds: Cyanide-Free Access to Aryl and Aliphatic Nitriles from Ketones and Aldehydes. *Org. Lett.* 2016, *18*, 228-231.

(9) Ning, X.-S.; Liang, X.; Hu, K.-F.; Yao, C.-Z.; Qu, J.-P.; Kang, Y.-B. Pd-^{t}BuONO Cocatalyzed Aerobic Indole Synthesis. *Adv. Synth. Catal.* 2018, *360*, 1590–1594.

(10) Kasaya, Y.; Hoshi, K.; Terada, Y.; Nishida,A.; Shuto, S.; Arisawa, M. Aromatic Enamide/Ene Metathesis toward Substituted Indoles and Its Application to the Synthesis of Indomethacins. *Eur. J. Chem.* 2009, *27*, 4606-4613.

(11) Zhu, C.; Ma, S. Coupling and cyclization of o-iodoanilines and propargylic bromides via allenes: an efficient entry to indomethacin. *Org. Lett.* 2013, *15*, 2782-2785.

(12) Zhang, X.; Guo, R.; Zhao, X. Organoselenium-catalyzed synthesis of indoles through intramolecular C–H amination. *Org. Chem. Front.* 2015, *2*, 1334-1337.

(13) Theodorou, A.; Kokotos, C. G. Green organocatalytic synthesis of indolines and pyrrolidines from alkenes. *Adv. Synth. Catal.* 2017, *359*, 1577-1581.

(14) Yu, S.-N.; Li, Y.-L.; Deng, J. Enantioselective synthesis of 2-bromomethyl indolines via BINAP(S)-catalyzed bromoaminocyclization of allyl aniline. *Adv. Synth. Catal.* 2017, *359*, 2499-2508.