Pd(II)/Bu_4NBr/DMSO Catalytic System for Practical Synthesis of Indoles and Pyrroles from Imines through Aerobic Dehydrogenative Cyclization

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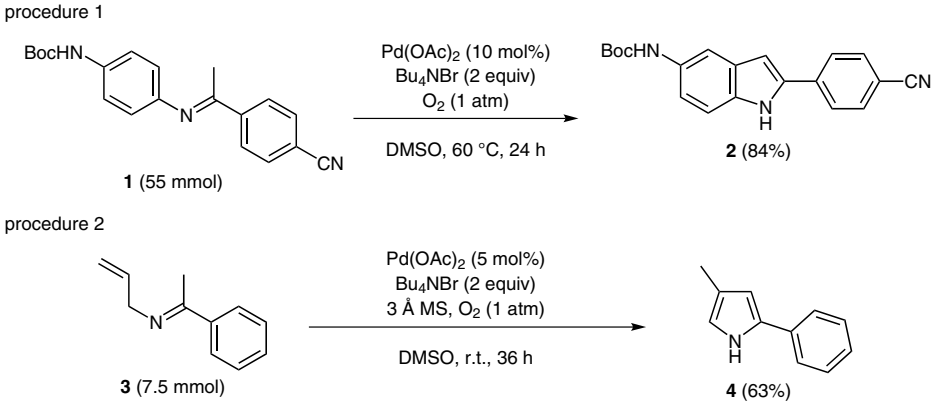
Abstract: *N*-Aryl- and *N*-allylimines derived typically from substituted acetophenones undergo palladium(II)-catalyzed dehydrogenative cyclization reactions in the presence of tetrabutylammonium bromide and molecular oxygen in DMSO to afford indole and pyrrole derivatives, respectively, in moderate to good yields. The reactions are operationally simple and can be readily performed on multigram scales (up to 55 mmol).

Key words: palladium, imines, indoles, pyrroles, C–H activation, Heck reaction



Scheme 1 Aerobic dehydrogenative synthesis of indoles and pyrroles from imines under palladium catalysis

Introduction

Indole and pyrrole structural motifs are ubiquitously present in biologically active natural and unnatural compounds as well as in other functional molecules such as dyes and pigments.[1] The development of synthetic methods for these privileged heterocycles has therefore been an important subject in organic synthesis.[2] While classical synthetic methods, such as the Fischer indole synthesis and the Paal–Knorr pyrrole synthesis have played pivotal roles for more than a hundred years, transition metal-catalyzed reactions have emerged and evolved into practical alternatives over the past several decades – the Larock indole synthesis from 2-haloanilines and alkynes using a palladium catalyst being one of the most successful examples.

A common drawback in many of the existing synthetic methods for indoles and pyrroles concerns the toxicity, cost, and availability of the starting materials. For example, the Fischer indole synthesis uses carcinogenic arylhydrazines, while the Larock's method typically requires expensive 2-iodoanilines. Furthermore, the range of commercially available arylhydrazines and 2-haloanilines is relatively limited. Thus, the development of indole/pyrrole synthesis from inexpensive and readily available starting materials (e.g., simple anilines) through C–H functionalization has gained increasing attention from the synthetic community.[3–5]

Building on pioneering works of Åkermark and Knölker on carbazole synthesis from diarylamines[6] and of Glorius on indole synthesis from *N*-arylenamines,[7] we recently developed a palladium(II)-catalyzed indole synthesis via aerobic dehydrogenative cyclization of an *N*-arylimine using Bu_4NBr and DMSO as the key additive and solvent, respectively (Scheme 1, Procedure 1).[8–10] The reaction features ready availability of the starting material, mild conditions, and the use of molecular oxygen as the sole

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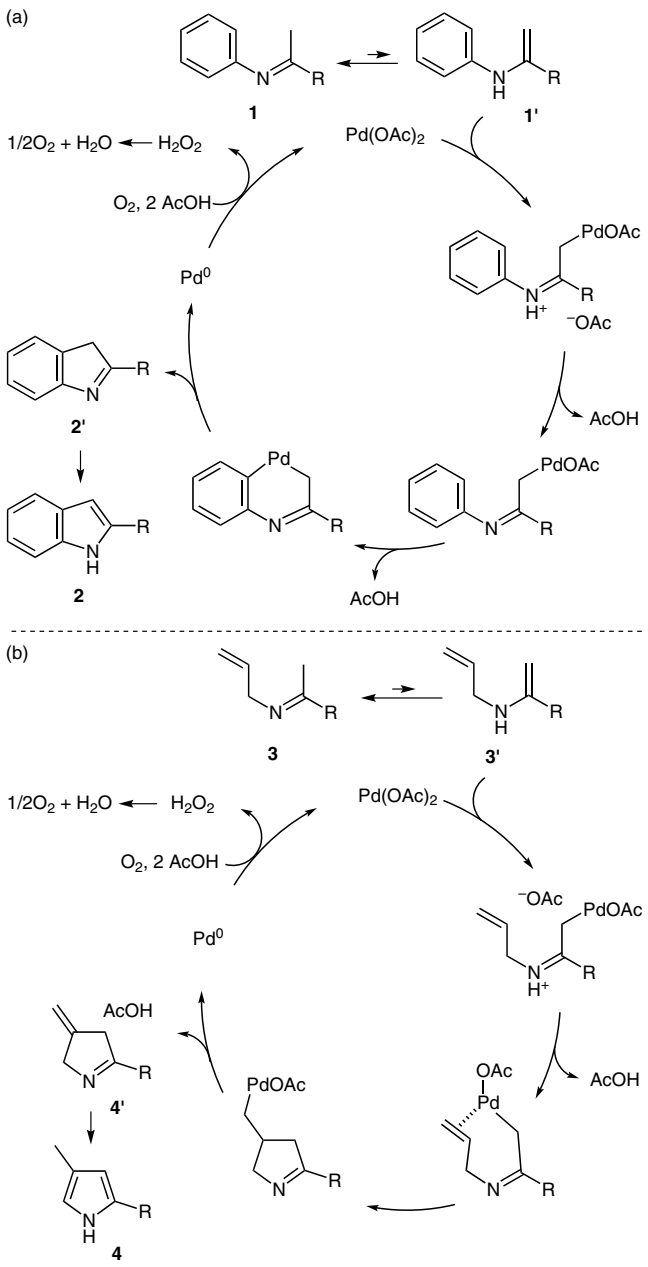


Scheme 2 Proposed catalytic cycles for dehydrogenative cyclization to indole and pyrrole

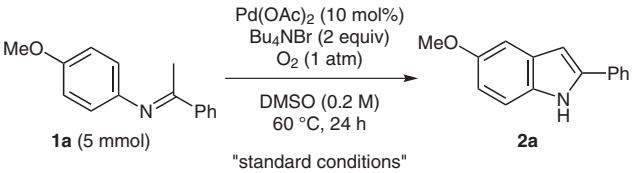
oxidant. A proposed catalytic cycle for this reaction involves α-palladation of the imine through imine–enamine tautomerization, intramolecular aromatic C–H activation, and reductive elimination (Scheme 2, a). This mechanistic consideration guided us and the groups of Glorius and Lei to independently develop pyrrole synthesis from an *N*-allylimine under a similar catalytic system (Scheme 1, Procedure 2), which likely involves α-palladation, intramolecular alkene insertion, and β-hydride elimination (Scheme 2, b).[11,12] In both of the catalytic cycles, the palladium(II) catalyst is regenerated by reoxidation of Pd(0) with molecular oxygen.[13] The versatility of these protocols has been demonstrated on small scales (0.2–0.4 mmol). Herein we wish to describe our procedures for the indole/pyrrole syntheses to demonstrate their utility on preparatively useful scales (5–55 mmol).

Scope and Limitations

As reported previously, a broad range of *N*-arylimines derived from substituted anilines and acetophenones can be converted into the corresponding 2-arylindoles in the presence of $Pd(OAc)_2$ (10 mol%), Bu_4NBr (2 equiv), and molecular oxygen (1 atm) in DMSO at 60 °C. Both the additive and the solvent are crucial for the reaction, because the yield significantly drops either in the absence of Bu_4NBr or in other solvent. *N*-Aryl imines derived from 2-arylacetophenones also undergo the dehydrogenative cyclization to afford 2,3-diarylindoles, while the use of $Cu(OAc)_2$ instead of Bu_4NBr and O_2 is necessary to avoid undesirable competing oxygenation of the benzylic position. On the other hand, *N*-arylimines containing β-hydrogens, for example, those prepared from propiophenone and tetralone, fail to give 2,3-disubstituted indoles but undergo α,β-dehydrogenation presumably through β-hydride elimination of α-palladated imine intermediates.[14,15] A few alkyl methyl ketones, such as cyclopropyl methyl ketone and pinacolone, can also be used to prepare the corresponding 2-alkylindoles.

To examine the scalability of our indole synthesis, we first examined the reaction of a benchmark substrate, that is, imine **1a** prepared from *p*-anisidine and acetophenone on a 5 mmol scale (Table 1). The reaction under the standard conditions for 24 hours afforded the desired indole **2a** in an excellent GC yield of 93% (Table 1, entry 1). The catalyst loading could be reduced to 5 mol% without an apparent problem (entry 2), while lowering the reaction temperature to 40 °C led to a slight decrease in the product yield (entry 3). Increase of the reaction concentration to 0.4 M did not have a positive influence (entry 4).

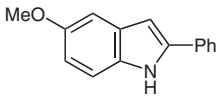
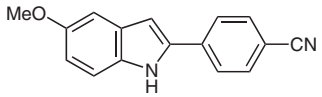
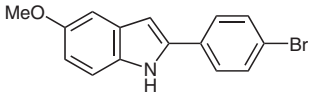
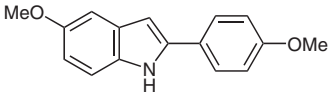
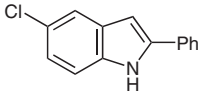
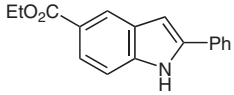
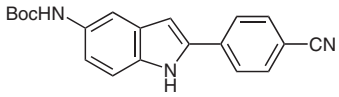
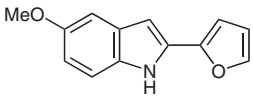
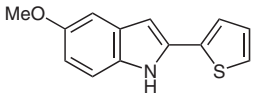
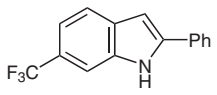
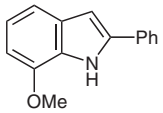
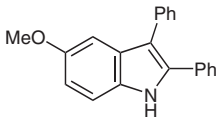
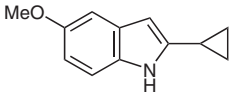
Table 1 Cyclization of Imine **1a** to Indole **2a**



Entry	Variation from the 'standard conditions'	Yield (%)[a]
1	none	93
2	loading of $Pd(OAc)_2$: 5 mol%	90
3	temperature: 40 °C	79
4	concentration: 0.4 M	84

[a] Determined by GC using *n*-tridecane as an internal standard.

Table 2 Indole Synthesis from *N*-Arylimines[a]

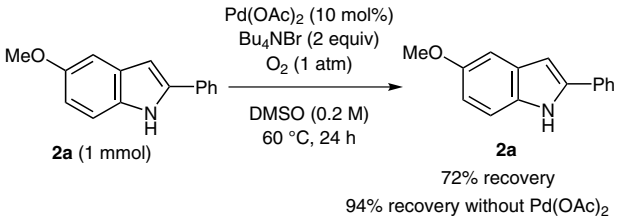
Entry	Product		Small-scale yield (%)[b,c]	Large-scale yield (%)[b,d]
1	**2a**		89	84[e,f]
2	**2b**		91	91[e]
3	**2c**		77	78[e]
4	**2d**		82	76
5	**2e**		88	76
6	**2f**		82	72
7	**2g**		–	84[g]
8	**2h**		76	64
9	**2i**		–	32
10	**2j**		72	80
11	**2k**		67	33
12[h]	**2l**		86	84
13	**2m**		84	81

[a] Reaction conditions: imine **1**, $Pd(OAc)_2$ (10 mol%), Bu_4NBr (2 equiv), O_2 (1 atm), DMSO (0.2 M), 60 °C, 24 h.
[b] Yield of isolated product.
[c] Reaction was conducted on a 0.2 mmol scale.
[d] Reaction was conducted on a 5 mmol scale, unless otherwise noted.
[e] Reaction was conducted on a 10 mmol scale.
[f] Average of three runs (84%, 84%, and 83%).
[g] Reaction was conducted on a 55 mmol scale.
[h] $Cu(OAc)_2$ (3 equiv) was used instead of Bu_4NBr and O_2.

Having confirmed the applicability of the original catalytic system to a preparative scale reaction, the reaction of representative *N*-arylimines was next examined. The latter and a few others have been used previously by us on a 0.2 mmol scale (Table 2). Cyclization of imine **1a** took place smoothly on a 10 mmol scale to produce the indole **2a** in an average yield of 84% for three runs, which was comparable to the yield obtained by the small-scale reaction (Table 2, entry 1). The yields of the individual runs were uniform (84%, 84%, and 83%), demonstrating high reproducibility of the reaction. Electron-withdrawing and -donating groups on the acetophenone moiety could be tolerated, as demonstrated by the preparation of indoles **2b**–**d** in good yields (entries 2–4). Electronic perturbations on the aniline moiety did not interfere with the reaction (entries 5–7). Notably, cyclization of imine bearing cyano and Boc-protected amino groups was achieved on a 55 mmol scale (entry 7). The corresponding indole product **2g** could be isolated in an analytically pure form in 84% yield just by washing the crude solid with ethyl acetate. Imine derived from 2-acetylfuran was efficiently converted into the corresponding indole **2h** in 64% yield (entry 8). By contrast, the reaction of imine derived from 2-acetylthiophene was rather sluggish, affording the desired product **2i** in only 32% yield (entry 9).

Imine derived from *m*-trifluoromethylaniline underwent cyclization exclusively onto the less hindered position, affording 7-trifluoromethylindole **2j** in 80% yield (entry 10). The reaction of imine derived from *o*-anisidine on a 0.2 mmol scale afforded the desired indole **2k** in 67% yield, demonstrating the tolerance of the present reaction to the blockage of one of the *ortho*-positions of the *N*-aryl group (entry 11). However, unlike other cases, the yield of this reaction dropped significantly (33%) on a 5 mmol scale. Cyclization of imine derived from 2-phenylacetophenone could be achieved using $Cu(OAc)_2$ (3 equiv) as an oxidant instead of Bu_4NBr and molecular oxygen, affording the corresponding 2,3-diphenylindole **2l** in 84% yield (entry 12). The reaction of imine derived from cyclopropyl methyl ketone was also amenable to the scale-up to 5 mmol, affording the product **2m** in 81% yield (entry 13).

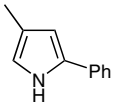
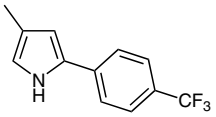
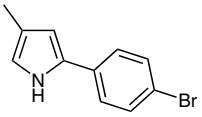
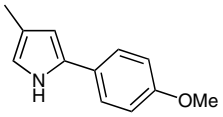
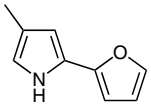
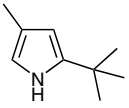
We briefly examined the stability of the isolated indole product **2a** to oxidation (Scheme 3). A prolonged (24 h) exposure of **2a** to the standard reaction conditions caused its gradual decomposition, leading to the recovery of **2a** in 72% yield. The palladium catalyst appears to play a crucial role in this decomposition process, because the degree of decomposition was much smaller in its absence (94% recovery). Thus, in order to achieve the highest yield, practitioners of the present indole synthesis are advised to carefully monitor the progress of the reaction. Note that we did not observe any apparent decomposition of **2a** and other indole products during purification on silica gel.



Scheme 3 Stability of indole **2a** to aerobic conditions

With slight modification, the $Pd(OAc)_2/Bu_4NBr$/DMSO system allows aerobic dehydrogenative cyclization of *N*-allylimines to pyrroles. Thus, imine derived from acetophenone and allylamine (0.4 mmol) was converted into 2-phenyl-4-methylpyrrole (**4a**) in 76% yield in the presence of $Pd(OAc)_2$ (5 mol%), Bu_4NBr (2 equiv), and 3 Å MS (400 mg) under 1 atm of O_2 in DMSO at room temperature (Table 3, entry 1). The same reaction could be achieved on a 7.5 mmol scale in an average yield of 63%

Table 3 Pyrrole Synthesis from *N*-Allylimines[a]

Entry	Product		Small-scale yield (%)[b,c]	Large-scale yield (%)[b,d]
1	**4a**		76	63[e]
2	**4b**		75	70
3	**4c**		57	69
4	**4d**		57	38
5	**4e**		49	41
6[f]	**4f**		61	33

[a] Reaction conditions: imine **3**, $Pd(OAc)_2$ (5 mol%), Bu_4NBr (2 equiv), 3 Å MS (100 mg per 0.1 mmol of **3**), O_2 (1 atm), DMSO (0.2 M), r.t., 24–36 h.
[b] Yield of isolated product.
[c] Reaction was conducted on a 0.4 mmol scale.
[d] Reaction was conducted on a 5 mmol scale, unless otherwise noted.
[e] Reaction was conducted on a 7.5 mmol scale. Average of two runs (67% and 59%).
[f] Powdered 4 Å MS was used instead of 3 Å MS.

(two runs), while the degree of the fluctuation of the yields (67% and 59%) was greater compared with the case of the indole synthesis (vide supra). This fluctuation is not due to product decomposition, because, unlike the indole **2a**, the isolated product **4a** did not undergo noticeable decomposition upon exposure to the catalytic conditions for 24 hours (96% recovery). Like the indole cyclization reaction, this catalytic system was applicable to *N*-allylimines derived from aryl and heteroaryl methyl ketones (entries 2–5) and pinacolone (entry 6). The reaction could be performed on a 5 mmol scale, while some cases led to a significant decrease in the product yield (entries 4 and 6). Unfortunately, *N*-allylimine prepared from 2-phenylacetophenone failed to give the desired pyrrole. Not unexpectedly, tetralone-derived imine also failed to participate in the reaction because of α,β-dehydrogenation. Note that besides imines bearing parent allyl group, those bearing α-branched allyl groups have also been reported to participate in the dehydrogenative cyclization.[11,12]

In summary, palladium(II)-catalyzed aerobic dehydrogenative cyclization reactions of *N*-arylimines and *N*-allylimines to indole and pyrrole derivatives, respectively, have been developed. The catalytic systems employ Bu_4NBr and DMSO as the key additive and solvent, respectively, and feature operational simplicity and mild conditions. With successful demonstration of a series of gram-scale experiments, the present protocols are now ready for practical synthesis of some classes of indole and pyrrole derivatives.

Analytical TLC was performed on Merck 60 F254 silica gel plates. ^1H and ^{13}C NMR spectra were recorded on Bruker AV-400 (400 MHz) NMR spectrometers. ^1H and ^{13}C NMR spectra are reported in parts per million (ppm) downfield from an internal standard, TMS (0 ppm) or DMSO (2.50 ppm) and $CHCl_3$ (77.0 ppm) or DMSO (39.5 ppm), respectively. Gas chromatographic analysis was performed on a Shimadzu GC-2010 system equipped with an FID detector and a capillary column DB-5 (Agilent J & W, 0.25 mm i.d. × 30 m). High-resolution mass spectra (HRMS) were obtained with a Waters Q-Tof Premier LC HR mass spectrometer. Melting points were determined using a capillary melting point apparatus and are uncorrected. $Pd(OAc)_2$ was purchased from Strem (min 98%, 99.9+% Pd) or Alfa Aesar (Pd 45.9–48.4%) and was used as received. No apparent difference in the performance of the Pd catalysts from these suppliers was observed during the present study. Bu_4NBr (98+%) was purchased from Alfa Aesar and was used as received. O_2 cylinder (99.7%) was purchased from National Oxygen and was used as received. Unless otherwise noted, all other materials were purchased from commercial suppliers and were used as received. Anhydrous DMSO was distilled over CaH_2 and stored under N_2 or purchased from Aldrich and used without further purification. Imines were prepared from the corresponding amines and ketones. Except for **1g** and **1i**, their analytical data can be found in the appropriate reference.[8,11]

N-Arylimines; General Procedure

A 100 mL round-bottomed flask equipped with a stirrer bar was charged with activated molecular sieves 4Å (9.0 g), the respective ketone (10 mmol), and the appropriate aniline (12 mmol). Toluene (10 mL) was added, and the reaction mixture was stirred for 24 h. The reaction mixture was then diluted with EtOAc (40 mL), followed by filtration through a pad of Celite, and concentration under reduced pressure. The crude product was purified by recrystallization from a hexane–EtOAc mixture to afford the desired *N*-arylimine.

(*E*)-*tert*-Butyl (4-{[1-(4-Cyanophenyl)ethylidene]amino}phenyl)carbamate (1g)

Yield: 17.5 g (87%; 60 mmol scale); yellow solid; mp 189–191 °C.

^1H NMR (400 MHz, DMSO-d_6): δ = 9.31 (s, 1 H), 8.12 (d, J = 8.5 Hz, 2 H), 7.94 (d, J = 8.5 Hz, 2 H), 7.46 (d, J = 8.6 Hz, 2 H), 6.75 (d, J = 8.7 Hz, 2 H), 2.25 (s, 3 H), 1.48 (s, 9 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.1, 152.9, 144.9, 143.1, 135.6, 132.3 (2 C), 127.8 (2 C), 119.9 (2 C), 118.8 (2 C), 118.6, 112.6, 78.9, 28.1 (3 C), 17.1.

HRMS (ESI): *m*/*z* calcd for $C_{20}H_{21}N_3O_2$ $[M + H]^+$: 336.1712; found: 336.1718.

(*E*)-4-Methoxy-*N*-[1-(thiophen-2-yl)ethylidene]aniline (1i)

Yield: 1.66 g (72%; 10 mmol scale); yellow solid; mp 81–83 °C.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.43 (m, 2 H), 7.08 (dd, J = 5.1, 3.7 Hz, 1 H), 6.89 (d, J = 8.8 Hz, 2 H), 6.78 (d, J = 8.8 Hz, 2 H), 3.81 (s, 3 H), 2.25 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.7, 159.4, 147.0, 143.9, 129.9, 128.5, 127.7, 121.6 (2 C), 114.4 (2 C), 55.7, 17.6.

HRMS (ESI): *m*/*z* calcd for $C_{13}H_{13}NOS$ $[M + H]^+$: 232.0792; found: 232.0788.

Preparative Scale Indole Synthesis (5 mmol Scale); General Procedure

A 100 mL 2-necked round-bottomed flask equipped with a stirrer bar was charged with the appropriate *N*-arylimine (5 mmol), $Pd(OAc)_2$ (112 mg, 0.50 mmol, 10 mol%), and Bu_4NBr (3.2 g, 10 mmol, 2 equiv), followed by the addition of DMSO (25 mL). The flask was quickly evacuated and then refilled three times with O_2 using an O_2 balloon (3 L). The resulting mixture was stirred at a stirring rate of 600 rpm at 60 °C for 24 h. Upon cooling to r.t., the reaction mixture was diluted with EtOAc (30 mL), followed by filtration through a pad of silica gel using EtOAc (150 mL) as an eluent. The filtrate was washed with H_2O (3 × 30 mL), dried (Na_2SO_4), and then concentrated under reduced pressure. Purification of the residue by flash chromatography on silica gel afforded the indole product.

Analytical data for representative and/or new indole products **2a**, **2g**, **2i**, and **2m** are provided below. Data for other products can be found in the appropriate reference.[8]

5-Methoxy-2-phenyl-1*H*-indole (2a)

The reaction of (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline (**1a**; 2.25 g, 10 mmol) was performed in a 100 mL 2-necked round-bottomed flask following the general procedure, proportionally scaling up the quantities of other reagents and solvents except for the size of the O_2 balloon. After the workup according to the general procedure, the crude product was purified by flash chromatography on silica gel (eluent: hexane–EtOAc, 90:10) to afford the title compound as an off-white solid; yield: 1.87 g (84%); R_f = 0.21 (hexane–EtOAc, 90:10); mp 169–170 °C (EtOAc).

^1H NMR (400 MHz, $CDCl_3$): δ = 8.26 (br s, 1 H), 7.66–7.64 (m, 2 H), 7.44 (t, J = 7.2 Hz, 2 H), 7.35 (t, J = 7.4 Hz, 1 H), 7.27 (d, J = 8.6 Hz, 1 H), 7.12 (d, J = 2.3 Hz, 1 H), 6.90 (dd, J = 8.7, 2.4 Hz, 1 H), 6.77 (d, J = 1.9 Hz, 1 H), 3.89 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.5, 138.6, 132.4, 132.0, 129.7, 129.0, 127.7, 125.1, 112.6, 111.6, 102.3, 99.8, 55.8.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{13}NO$ $[M + H]^+$: 224.1075; found: 224.1069.

tert-Butyl [2-(4-Cyanophenyl)-1*H*-indol-5-yl]carbamate (2g)

The reaction of **1g** (18.4 g, 55 mmol) was performed in a 500 mL 3-necked round-bottomed flask following the general procedure, proportionally scaling up the quantities of other reagents and solvents

except for the size of the O_2 balloon. Upon cooling to r.t., the reaction mixture was diluted with EtOAc (150 mL), followed by filtration through a pad of silica gel with EtOAc (250 mL) as an eluent. The treatment of the filtrate with H_2O (200 mL) resulted in poorly soluble brown precipitates, which were extracted with EtOAc (5 × 400 mL). The combined organic layers were washed with H_2O (600 mL) and brine (300 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The solid residue was treated with EtOAc (50 mL), filtered through a Büchner funnel, and washed with additional EtOAc (50 mL) to afford the title compound as a brown solid in an analytically pure form; yield: 15.5 g (84%); R_f = 0.21 (hexane–EtOAc, 70:30). Further purification could be performed by recrystallization from hot EtOAc affording yellow crystals; mp 213–215 °C.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 11.58 (s, 1 H), 9.11 (s, 1 H), 8.01 (d, J = 7.7 Hz, 2 H), 7.89 (d, J = 7.6 Hz, 2 H), 7.72 (s, 1 H), 7.30 (d, J = 8.3 Hz, 1 H), 7.20 (d, J = 8.2 Hz, 1 H), 7.05 (s, 1 H), 1.49 (s, 9 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 153.1, 136.6, 135.9, 134.0, 132.8 (2 C), 132.3, 128.3, 125.2 (2 C), 119.0, 116.2, 111.4, 109.5, 109.0, 101.4, 78.4, 28.2 (3 C).

HRMS (ESI): m/z calcd for $C_{20}H_{19}N_3O_2$ $[M + H]^+$: 334.1556; found: 334.1553.

5-Methoxy-2-(thiophen-2-yl)-1*H*-indole (2i)
The reaction of **1i** (1.16 g, 5 mmol) was performed according to the general procedure. The crude product was purified on silica gel (eluent: hexane–EtOAc, 90:10) to afford the title compound as a grey solid; yield: 0.37 g (32%); R_f = 0.18 (hexane–EtOAc, 90:10); mp 137–139 °C (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09 (s, 1 H), 7.29–7.22 (m, 3 H), 7.08 (dd, J = 5.0, 3.6 Hz, 1 H), 7.04 (d, J = 2.4 Hz, 1 H), 6.85 (dd, J = 8.8, 2.5 Hz, 1 H), 6.65 (d, J = 1.4 Hz, 1 H), 3.85 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.9, 136.0, 133.3, 131.9, 129.9, 128.1, 124.7, 123.0, 113.0, 111.7, 102.5, 100.6, 56.1.

HRMS (ESI): m/z calcd for $C_{13}H_{11}NOS$ $[M + H]^+$: 230.0640; found: 230.0632.

2-Cyclopropyl-5-methoxy-1*H*-indole (2m)
The reaction of (*E*)-*N*-(1-cyclopropylethylidene)-4-methoxyaniline (**1m**; 0.95 g, 5 mmol) was performed according to the general procedure. The crude product was purified on silica gel (eluent: hexane–EtOAc, 92:8) to afford the title compound as a yellow oil; yield: 0.76 g (81%); R_f = 0.24 (hexane–EtOAc, 90:10).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.85 (br s, 1 H), 7.15 (d, J = 8.7 Hz, 1 H), 7.00 (d, J = 2.4 Hz, 1 H), 6.78 (dd, J = 8.8, 2.5 Hz, 1 H), 6.09 (d, J = 2.0 Hz, 1 H), 3.85 (s, 3 H), 1.97–1.90 (m, 1 H), 0.99–0.94 (m, 2 H), 0.80–0.75 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.2, 142.6, 130.9, 129.2, 110.9, 110.8, 101.9, 97.6, 55.9, 9.0, 7.4.

HRMS (ESI): m/z calcd for $C_{12}H_{13}NO$ $[M + H]^+$: 188.1075; found: 188.1082.

***N*-Allylimines; General Procedure**
A 100 mL round-bottomed flask equipped with a stirrer bar was charged with the respective ketone (10 mmol), the corresponding allylamine (50 mmol), and anhydrous toluene or Et_2O (20 mL). To this mixture was added a solution of $TiCl_4$ in CH_2Cl_2 (1.0 M, 6.4 mL, 6.4 mmol) at 0 °C in a dropwise manner over a period of 40 min. The reaction mixture was allowed to stir at r.t. for 2 h, followed by filtration through a pad of Celite with EtOAc (40 mL) as an eluent. The filtrate was washed with brine (2 × 25 mL), dried (Na_2SO_4), and concentrated under reduced pressure. The yellow residue was purified by Kugelrohr distillation or used as such.

Preparative Scale Pyrrole Synthesis (5 mmol Scale); General Procedure
A 100 mL 2-necked round-bottomed flask equipped with a stirrer bar was charged with activated molecular sieves 3Å (5.0 g), $Pd(OAc)_2$ (56 mg, 0.25 mmol, 5 mol%), and Bu_4NBr (3.2 g, 10 mmol, 2 equiv). The flask was evacuated and refilled three times with O_2 using a balloon, followed by the addition of the requisite *N*-allylimine (5.0 mmol) and anhydrous DMSO (25 mL). The resulting mixture was stirred at r.t. for 36 h. The reaction mixture was diluted with EtOAc (30 mL), followed by filtration through a short pad of silica gel with EtOAc (150 mL) as an additional eluent. The filtrate was washed with sat. aq $NaHCO_3$ (3 × 50 mL) and brine (40 mL), and then concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel to afford the desired pyrrole product.

Analytical data for representative pyrrole products **4b** and **4e** are provided below. Data for other products can be found in the appropriate reference.[10]

4-Methyl-2-[4-(trifluoromethyl)phenyl]-1*H*-pyrrole (4b)
The reaction of (*E*)-*N*-{1-[4-(trifluoromethyl)phenyl]ethylidene}prop-2-en-1-amine (**3b**; 1.14 g, 5 mmol) was performed according to the general procedure. The crude product was purified by flash chromatography on silica gel (eluent: hexane–EtOAc, 90:10) to afford the title compound as a light red solid; yield: 0.79 g (70%); R_f = 0.34 (hexane–EtOAc, 90:10); mp 169–171 °C (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (br s, 1 H), 7.57 (d, J = 8.4 Hz, 2 H), 7.48 (d, J = 8.0 Hz, 2 H), 6.66 (s, 1 H), 6.46 (s, 1 H), 2.15 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.0, 130.4, 127.8 (q, $^2J_{C,F}$ = 33.0 Hz), 127.1, 125.8 (q, $^3J_{C,F}$ = 3.0 Hz), 124.3 (q, $^1J_{C,F}$ = 270.0 Hz), 123.3, 118.1, 109.1, 11.8.

HRMS (ESI): m/z calcd for $C_{12}H_{11}F_3N$ $[M + H]^+$: 226.0844; found: 226.0846.

2-(Furan-2-yl)-4-methyl-1*H*-pyrrole (4e)
The reaction of (*E*)-*N*-[1-(furan-2-yl)ethylidene]prop-2-en-1-amine (**3e**; 0.75 g, 5 mmol) was performed according to the general procedure. The crude product was purified by flash chromatography on silica gel (eluent: hexane–EtOAc, 90:10) to afford the title compound as a green solid; yield: 0.30 g (41%); R_f = 0.36 (hexane–EtOAc, 90:10); mp 40–42 °C (EtOAc).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 (br s, 1 H), 7.32 (d, J = 1.2 Hz, 1 H), 6.54 (s, 1 H), 6.40 (dd, J = 3.2, 2.0 Hz, 1 H), 6.29 (d, J = 3.2 Hz, 1 H), 6.26 (s, 1 H), 2.12 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.4, 140.2, 123.9, 120.3, 116.0, 111.4, 106.8, 101.9, 11.8.

HRMS (ESI): m/z calcd for $C_9H_{10}NO$ $[M + H]^+$: 148.0762; found: 148.0764.

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