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Synthesis of Polysubstituted 3-Amino Pyrroles via Palladium-Catalyzed Multicomponent Reaction

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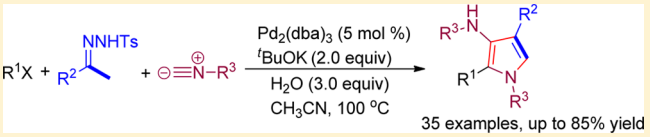
Supporting Information

ABSTRACT: A novel approach for the synthesis of polysubstituted 3-amino pyrroles via palladium-catalyzed three-component tandem reaction was developed. The procedure constructs various polysubstituted 3-amino pyrroles with moderate to excellent yields under mild reaction conditions with assembly efficiency, readily available starting materials, and good functional group tolerance. Furthermore, this process was successfully applied to the synthesis of different 3-phenyl-1,4-dihydropyrrolo[3,2-*b*]indole derivatives via an intramolecular Buchwald−Hartwig cross-coupling reaction in two steps.



INTRODUCTION

Development of a general and efficient method to construct valuable heterocycles[1] from simple starting materials is highly important in modern organic synthesis. 3-Amino pyrrole derivatives are key structural units in numerous natural products[2] and drug molecules[3] (Figure 1) and are also valuable building blocks[4] in synthetic chemistry. Despite its great importance, methods to obtain such scaffolds are relatively rare. In 2015, Tang[5] reported a procedure for the synthesis of polysubstituted 3-amino pyrroles via Rh(II)-catalyzed [3 + 2] cycloaddition of 1-tosyl-1,2,3-triazoles with 2*H*-azirines. Subsequently, You[6] reported that polysubstituted 3-amino pyrroles were synthesized by the cascade oxidative coupling/cyclization of α-amino ketones with enamines under the Fe(III)/DTBP catalytic system. Nevertheless, there is still a demand for easy and efficient protocols to construct these potent bioactivity molecules, especially with readily available starting materials. Therefore, we consider it necessary to develop a novel three-component tandem reaction to construct the 3-amino pyrrole structure from halobenzene, isocyanides, and *N*-tosylhydrazones, which are the fundamental materials in organic synthesis.

Isocyanides have been proven to be powerful and versatile C1 building blocks in organic synthesis due to unique properties which can act as both nucleophiles and electrophiles.[7] Recently, isocyanides have been extensively explored in multicomponent reactions to form multiple bonds in a one-pot manner with remarkable versatility in the construction of various structurally appealing heterocycles.[8] Most of these methods involved the generation of aryl- or alkenyl-palladium intermediates followed by ligand exchange and reductive elimination to afford *N*-heterocycles[9] (Scheme 1, eq 1). Although significant progress has been made in this field, the discovery of different nucleophilic partners to capture the active palladium species could be an interesting project.

N-Tosylhydrazones, which can in situ generate diazo compounds in the presence of base and further form metal−carbene species,[10] have found extensive applications and provided a novel type of cross-coupling reaction in organic synthesis.[11] We envisaged that the active imino palladium species formed with isocyanide insertion of aryl palladium could be trapped by the diazo compounds, and a new multicomponent cascade reaction based on the isocyanide insertion and palladium carbeen formation could be developed. Herein, we present our recent progress in palladium-catalyzed MCRs of halobenzene, isocyanides, and diazo compounds to construct polysubstituted 3-amino pyrroles (Scheme 1, eq 2). This new method included imino group migration and cyclization, leading to the formation of 3-amino polysubstituted pyrroles. Moreover, this transformation accomplished C(sp^3)-H amination as well.

RESULTS AND DISCUSSION

Our initial investigations of this Pd-catalyzed reaction commenced with iodobenzene (**1a**), *N*-tosylhydrazone (**2a**), and *tert*-butyl isocyanide (**3a**) as model substrates in the presence of $Pd(PPh_3)_4$ and Cs_2CO_3 in CH_3CN at 80 °C, and the results are summarized in Table 1. To our delight, the desired product (**4a**) was obtained in 47% GC yield (Table 1, entry 1). Among the palladium catalysts tested, $Pd_2(dba)_3$ exhibited the highest catalytic reactivity, giving 58% yield (entries 1−5). Apart from CH_3CN, other solvents such as toluene, DMF, and 1,4-dioxane were proven to be ineffective for this reaction (entries 6−8). Next, different bases such as K_2CO_3 and CsF were tested, and ^{t}BuOK gave the best result with 85% yield (entries 9−11). Screening the temperature, the

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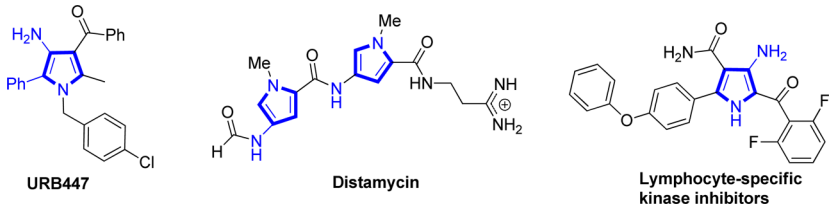


Figure 1. Pharmaceutical and biological molecules containing polysubstituted 3-amino pyrroles.

Scheme 1. Palladium-Catalyzed Isocyanide Insertion Reactions

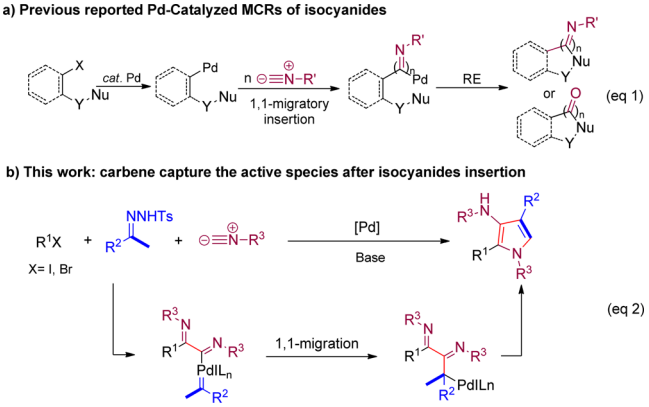
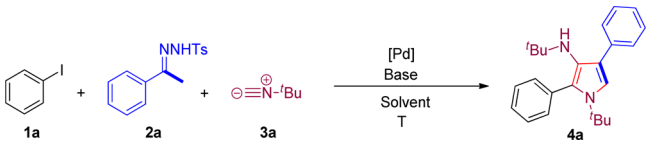


Table 1. Optimization of Reaction Conditions[a]



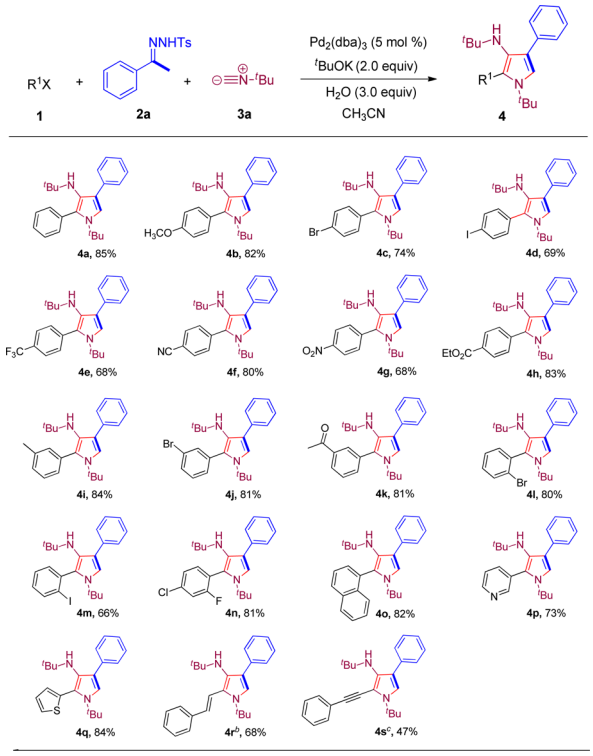
	catalyst	base	solvent	T/°C	yield/%[b]
1	$Pd(PPh_3)_4$	Cs_2CO_3	CH_3CN	80	47
2	$PdCl_2$	Cs_2CO_3	CH_3CN	80	41
3	$Pd(PPh_3)_2Cl_2$	Cs_2CO_3	CH_3CN	80	42
4	$Pd(TFA)_2$	Cs_2CO_3	CH_3CN	80	50
5	$Pd_2(dba)_3$	Cs_2CO_3	CH_3CN	80	58
6	$Pd_2(dba)_3$	Cs_2CO_3	toluene	80	trace
7	$Pd_2(dba)_3$	Cs_2CO_3	DMF	80	trace
8	$Pd_2(dba)_3$	Cs_2CO_3	1,4-dioxane	80	trace
9	$Pd_2(dba)_3$	K_2CO_3	CH_3CN	80	40
10	$Pd_2(dba)_3$	CsF	CH_3CN	80	15
11	$Pd_2(dba)_3$	^{t}BuOK	CH_3CN	80	85
12	**$Pd_2(dba)_3$**	**^{t}BuOK**	**CH_3CN**	**100**	**89 (85)**
13	$Pd_2(dba)_3$		CH_3CN	100	nd
14	$Pd_2(dba)_3$	^{t}BuOK	dry CH_3CN	100	nd

[a]Unless otherwise noted, reactions were performed with **1a** (0.20 mmol), **2a** (0.25 mmol), **3a** (0.45 mmol), catalyst (5 mol %), base (2.0 equiv), and H_2O (3.0 equiv) in the indicated solvent (2.0 mL) for 3 h. [b]Determined by GC using dodecane as the internal standard. Data in parentheses was isolated yield. nd = no data.

yield further improved to 89% when the temperature was increased to 100 °C (entry 12). A control experiment revealed that no product was obtained in the absence of the base, which demonstrated that the base played a vital role in this transformation (entry 13). It was worth noting that the reactions did not proceed at all in the absence of H_2O (entry 14).

After establishment of the optimal reaction conditions, we evaluated the generality of the palladium-catalyzed tandem cyclization reaction. Besides iodobenzene (**1a**), bromobenzene could be also transformed into the desired product albeit in a slightly lower yield (52%). However, chlorobenzene did not afford **4a** even after prolonging the reaction time and elevating the reaction temperature due to low reactivity. As shown in Table 2, with a variety of *para*-substituted iodobenzenes as the

Table 2. Substrate Scope of Aryl Halides[a]



[a]Reaction conditions: Unless otherwise noted, all reactions were performed with **1** (0.20 mmol), **2a** (0.25 mmol), **3a** (0.45 mmol), $Pd_2(dba)_3$ (5 mol %), ^{t}BuOK (2.0 equiv), and H_2O (3.0 equiv) in 2.0 mL CH_3CN at 100 °C for 3 h; isolated yields were given. [b]β-Bromostyrene as substrate. [c]Phenylethynyl bromide as substrate.

substrates, we were pleased to find that iodobenzenes with functional groups, including both electron-donating and electron-withdrawing groups, could react smoothly with *N*-tosylhydrazones and *tert*-butyl isocyanides, and the polysubstituted 3-amino pyrroles (**4b**-**4h**) were obtained in good to excellent yields. Halo-substituents such as Br and I were well-tolerated, which provided the possibility for further functionalization. The structure of **4g** was further confirmed by X-ray crystallographic analysis (see the Supporting Information for details). Furthermore, *ortho*- and *meta*-substituted aromatic rings could be also effectively generated in good yields (**4i**–**4n**).

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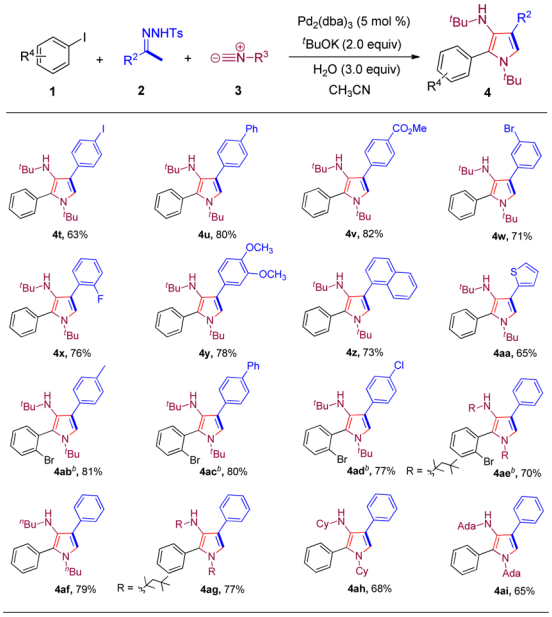
In the transformation, the electronic effect and steric effect of substrates were found to have no impact on the yields. In addition, 1-iodonaphthalen was found to be a suitable reaction partner for this reaction, and **4o** was isolated in 82% yield. To our delight, heterocyclic compounds such as 3-iodo-pyridine and 2-iodo-thiophene were successfully transformed into the desired products with **4p** and **4q** in 73 and 84% yields, respectively. It was noteworthy that β-bromostyrene could also undergo the cascade reaction to give the corresponding product in 68% yield with high (*E*)-stereoselectivity. Furthermore, the method could be extended to phenylethynyl bromide as well, although in 47% yield, which was attributed to the fact that **1s** showed high reactivity in the reaction system and side reactions could not be avoided under standard conditions.

To further explore the synthetic potential of this method, a variety of *N*-tosylhydrazones were investigated, and the results are summarized in Table 3. Functional groups, including

Table 3. Substrate Scope of *N*-Tosylhydrazones and Isocyanides[a]



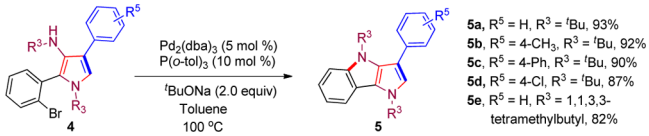
[a]Reaction conditions: Unless otherwise noted, all reactions were performed with **1** (0.20 mmol), **2** (0.25 mmol), **3** (0.45 mmol), $Pd_2(dba)_3$ (5 mol %), ^{t}BuOK (2.0 equiv), and H_2O (3.0 equiv) in 2.0 mL CH_3CN at 100 °C for 3 h; isolated yields were given. [b]*o*-Bromoiodobenzene as substrate.

electron-donating and electron-withdrawing groups such as I, Ph, CO_2Me on the aryl ring, were tolerated in this transformation and gave pyrrole derivatives in 63−82% yields (**4t**−**4v**). Furthermore, substituents at the *meta*- and *ortho*-positions of the aromatic ring had no significant effect, and the desired products could be obtained effectively in good yields (**4w** and **4x**). When polysubstituted *N*-tosylhydrazones were used for this transformation, the corresponding products could be obtained in good yield (**4y**). The electronic properties of the substituents on *N*-tosylhydrazones did not have a significant influence on the reaction efficiency. To our delight, substrates with naphthalene or heterocyclic rings were also tolerated in the system, which expanded the scope of this kind of reaction (**4z** and **4aa**). Then, *o*-bromoiodobenzene was applied to react with different *N*-tosylhydrazones and isocyanides, and the desired products (**4ab**−**4ae**) were obtained to further transformation. Unfortunately, when *N*-tosylhydrazones deriving from alkyl ketones were applied to this system, no desired products were detected. The probable reason was that the aryl group with a conjugated structure had a stronger stabilization effect on the Pd-carbene species compared to that of the alkyl group, which was easily decomposed and would not promote the reaction successfully.[12]

We then turned our attention to evaluate the reactivity of different isocyanides. Alkyl isocyanides such as *n*-butyl isocyanide, 1,1,3,3-tetramethylbutyl isocyanide, cyclohexyl isocyanide, and adamantyl isocyanide were all compatible in this reaction with good yields ranging from 65 to 79%. However, when 2,6-dimethylphenyl isocyanide was employed as substrate, no desired product was obtained.

The pyrrolo[2,3-*b*]indole framework has been widely applied in optoelectronics[13] and is expected to exhibit potential biological activities.[14] The exploration of simple and general methods for the synthesis of these scaffolds from readily available starting materials and convenient operation is of great significance.[14,15] Having successfully established the method for the synthesis of various 2-(2-bromophenyl)-4-phenyl-1*H*-pyrrol-3-amine derivatives, we envisioned that those products could easily afford different 3-phenyl-1,4-dihydropyrrolo[3,2-*b*]indoles through an intramolecular Buch−Hartwig[7e,16] cross-coupling reaction. As expected, the desired products **5a**−**5e** (Scheme 2) were conveniently obtained in good yields through a two-step process which implied the potential applicability of the present method to the synthesis of valuable products.

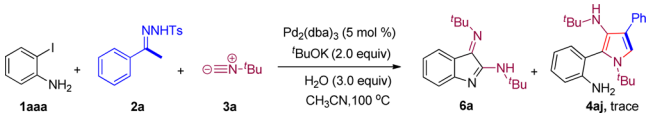
Scheme 2. Synthesis of Various 3-Phenyl-1,4-dihydropyrrolo[3,2-*b*]indoles[a]



[a]Reaction conditions: **4** (0.1 mmol), $Pd_2(dba)_3$ (5 mol %), P(*o*-tol)$_3$ (10 mol %), and ^{t}BuONa (2.0 equiv) in 2.0 mL of toluene at 100 °C for 12 h.

We then turned our attention to gain insight into the mechanism of three-component tandem reaction (Scheme 3).

Scheme 3. Reaction between 2-Iodoaniline, *N*-Tosylhydrazone, and *tert*-Butyl Isocyanide



2-Iodoaniline was then tested under the standard conditions; **6a** was obtained and isolated in 65% yield, while the desired product **4aj** could only be detected by GC analysis (Scheme 3). The reason was that the oxidative addition of Pd(0) catalyst with **1aaa** afforded the Pd(II) intermediate, followed by double isocyanide insertions which were captured by strong nucleophile NH_2 and then reductive elimination and tautomerization to generate **6a**.[9b] The process mentioned above was faster than the migratory insertion of diazo compound, which was generated in situ from **2a**.

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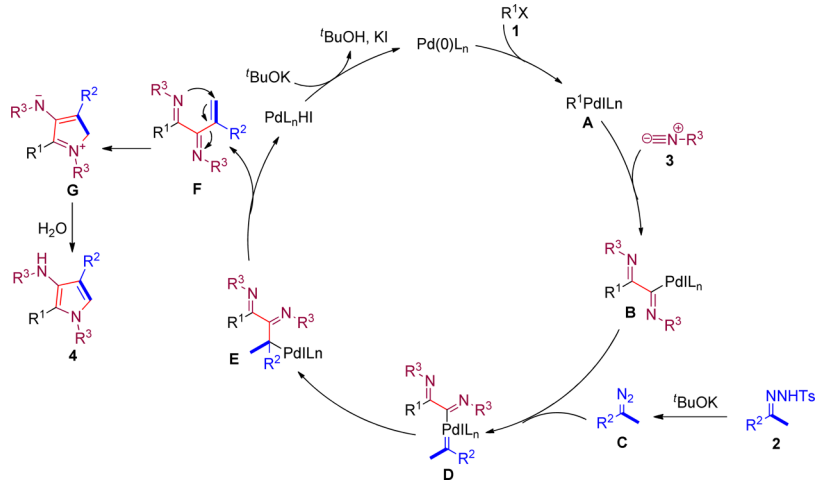
Scheme 4. Plausible Mechanism



On the basis of our previous work on isocyanides,[9,17] a possible reaction pathway for this transformation is depicted in Scheme 4. The reaction was initiated by oxidative addition of Pd(0) to the aryl halides **1** to generate Pd(II) intermediate **A**, which followed by double isocyanide insertions to afford palladium complex **B**.[9b] Then, the complex **B** was trapped by diazo compound **C** (generated by the base-mediated decomposition of the *N*-tosylhydrazone **2**) to produce Pd−carbene complex **D**.[10,11] Migratory insertion of the imino group in palladium−carbene gave intermediate **E**, which then went through *β*-hydrogen elimination to produce intermediate **F**. The imine nitrogen atom attacked the carbon−carbon double bond followed by cyclization and aromatization to produce the final product **4**. Finally, the active Pd(II) species was regenerated with the aid of base and finished the catalytic cycle.

CONCLUSION

In conclusion, we successfully accomplished a novel palladium-catalyzed tandem cyclization with three-component coupling reaction of aryl halides, *N*-tosylhydrazones, and isocyanides. This reaction provides a new method to construct various 3-amino polysubstituted pyrroles with simple reaction conditions, assembly efficiency, readily available starting materials, and wide functional group tolerance. The accomplishment of C(sp^3)-H amination has also made this method particularly attractive. Furthermore, this reaction was applied to construct 3-phenyl-1,4-dihydropyrrolo[3,2-*b*]indoles which show potential applications in the synthesis of more complex compounds.

EXPERIMENTAL SECTION

General Methods. Melting points were measured using a melting point instrument and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded at 400 MHz, and the chemical shifts (d) were referenced to TMS. IR spectra were obtained with an infrared spectrometer on either potassium bromide pellets or liquid films between two potassium bromide pellets. HRMS was carried out on a high-resolution mass spectrometer (LCMS-IT-TOF). TLC was performed using commercially available 100−400 mesh silica gel plates (GF_{254}). Unless otherwise noted, purchased chemicals were used without further purification.

General Procedure for *N*-Tosylhydrazones. A solution of pure $TsNHNH_2$ (5 mmol) in methanol (5 mL) was stirred and heated to 60 °C until the $TsNHNH_2$ was completely dissolved. Then, carbonyl compounds (6.0 mmol) were dropped into the mixture slowly. After approximately 2 h, the crude products were obtained as precipitates. The reaction mixture was washed and filtered with petroleum ether twice and dried under vacuum to provide the corresponding *N*-tosylhydrazones.

General Procedure for Polysubstituted 3-Amino Pyrroles. Aryl halides (0.20 mmol), *N*-tosylhydrazones (0.25 mmol), $Pd_2(dba)_3$ (5 mol %), ^{t}BuOK (2.0 equiv), H_2O (3.0 equiv), and 2 mL of CH_3CN were added to a tube equipped with magnetic stirrer bar. Then, isocyanide (0.45 mmol) were successively added. The reaction mixture was stirred at 100 °C for 3 h and quenched by the addition of aqueous NaCl. The resulting mixture was extracted with ethyl acetate, dried over anhydrous sodium sulfate, filtered, and evaporated under vacuum. Then, the crude product was purified by column chromatography on silica gel with light petroleum ether/ethyl acetate as eluent to afford the desired product.

General Procedure for 3-Phenyl-1,4-dihydropyrrolo[3,2-*b*]-indole. A mixture of 2-(2-bromophenyl)-4-phenyl-1*H*-pyrrol-3-amine (0.10 mmol), $Pd_2(dba)_3$ (5 mol %), P(*o*-tol)$_3$ (10 mol %), ^{t}BuONa (2.0 equiv), and 2.0 mL of toluene were added in a tube equipped with a stir bar and stirred at 100 °C for 12 h. Then, the reaction was quenched by aqueous NaCl and extracted ethyl acetate, dried over anhydrous sodium sulfate, filtered, and evaporated under vacuum. The crude product was purified by column chromatography on silica gel with light petroleum ether/ethyl acetate as eluent to afford the desired product.

*N,1-Di-tert-butyl-2,4-diphenyl-1H-pyrrol-3-amine (**4a**).* Eluent: petroleum ether/ethyl acetate 20/1; yield: 85% (59 mg) as a white solid; mp: 149−152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 7.9 Hz, 2H), 7.40−7.35 (m, 5H), 7.31 (t, J = 7.2 Hz, 2H), 7.17−7.11 (m, 1H), 6.85 (s, 1H), 2.26 (s, 1H), 1.40 (s, 9H), 0.66 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 135.5, 133.4, 128.2, 127.9, 127.8, 127.7, 127.7, 124.9, 119.5, 116.0, 57.2, 53.8, 31.7, 30.2 ppm; ν_{max}(KBr)/cm^{-1} 3393, 2922, 1660, 1457, 1363, 1208, 1021, 702; HRMS-ESI (m/z): calcd for $C_{24}H_{31}N_2$, [M + H]$^+$: 347.2482, found 347.2483.

*N,1-Di-tert-butyl-2-(4-methoxyphenyl)-4-phenyl-1H-pyrrol-3-amine (**4b**).* Eluent: petroleum ether/ethyl acetate 15/1; yield: 82% (62 mg) as a yellow solid; mp: 138−140 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 7.6 Hz, 2H), 7.30 (dd, J = 13.3, 7.3 Hz, 4H), 7.14 (t, J = 7.3 Hz, 1H), 6.93 (d, J = 8.0 Hz, 2H), 6.84 (s, 1H), 3.86 (s, 3H), 1.40 (s, 9H), 0.69 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 138.1, 134.6, 127.9, 127.8, 127.7, 127.3, 124.8, 119.2, 115.8, 113.1, 57.0, 55.2, 53.7, 31.6, 30.3 ppm; ν_{max}(KBr)/cm^{-1} 3526, 2964, 1660, 1506, 1367, 1245, 1027, 840; HRMS-ESI (m/z): calcd for $C_{25}H_{33}N_2O$, [M + H]$^+$: 377.2587, found 377.2591.

*2-(4-Bromophenyl)-N,1-di-tert-butyl-4-phenyl-1H-pyrrol-3-amine (**4c**).* Eluent: petroleum ether/ethyl acetate 20/1; yield: 74% (63 mg) as a brown solid; mp: 154−156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 7.6 Hz, 2H), 7.53 (d, J = 7.8 Hz, 2H), 7.31 (t, J = 7.5 Hz, 2H), 7.26 (d, J = 7.1 Hz, 2H), 7.15 (t, J = 7.3 Hz, 1H), 6.85 (s, 1H),

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2.35 (s, 1H), 1.40 (s, 9H), 0.66 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 135.0, 134.6, 130.9, 127.9, 127.8, 126.9, 125.0, 121.9, 119.8, 116.5, 57.3, 53.9, 31.7, 30.2 ppm; ν_{max}(KBr)/cm^{-1} 3437, 2968, 1664, 1558,1469, 1360, 1209, 1001, 899; HRMS-ESI (m/z): calcd for $C_{24}H_{30}BrN_2$, [M + H] $^+$: 425.1587, found 425.1583.

N,1-Di-tert-butyl-2-(4-iodophenyl)-4-phenyl-1H-pyrrol-3-amine (**4d**). Eluent: petroleum ether/ethyl acetate 20/1; yield: 69% (65 mg) as a yellow solid; mp: 129−131 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 7.9 Hz, 2H), 7.68 (d, J = 7.7 Hz, 2H), 7.31 (t, J = 7.5 Hz, 2H), 7.15 (dd, J = 14.6, 7.6 Hz, 3H), 6.85 (s, 1H), 2.20 (s, 1H), 1.40 (s, 9H), 0.67 (s, 9H);^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 136.9, 135.2, 127.9, 127.8, 126.9, 125.0, 119.8, 116.5, 93.5, 57.3, 53.8, 31.7, 30.2 ppm; ν_{max}(KBr)/cm^{-1} 2967, 1670, 1601, 1479, 1361, 1210, 1002, 836 ppm; HRMS-ESI (m/z): calcd for $C_{24}H_{30}IN_2$, [M + H]$^+$: 473.1448, found 473.1453.

N,1-Di-tert-butyl-4-phenyl-2-(4-(trifluoromethyl)phenyl)-1H-pyrrol-3-amine (**4e**). Eluent: petroleum ether/ethyl acetate 20/1; yield: 68% (56 mg) as a yellow solid; mp: 104−106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (dd, J = 7.7, 2.7 Hz, 4H), 7.52 (d, J = 7.9 Hz, 2H), 7.32 (t, J = 7.6 Hz, 2H), 7.17 (t, J = 7.3 Hz, 1H), 6.89 (s, 1H), 2.08 (s, 1H), 1.40 (s, 9H), 0.63 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.8, 137.6, 133.6, 129.7, 128.0, 127.9, 126.9, 125.5, 125.2, 124.6 (J_{C-F} = 3.3 Hz), 122.8, 120.1, 117.0, 57.5 54.0, 31.8, 30.2 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.42; ν_{max}(KBr)/cm^{-1} 3431, 2964, 1667, 1463, 1324, 1125, 1067, 854; HRMS-ESI (m/z): calcd for $C_{25}H_{30}F_3N_2$, [M + H]$^+$: 415.2356, found 415.2362.

4-(1-(tert-Butyl)-3-(tert-butylamino)-4-phenyl-1H-pyrrol-2-yl)-benzonitrile (**4f**). Eluent: petroleum ether/ethyl acetate 15/1; yield: 80% (59 mg) as a brown solid; mp: 154−156 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 8.0 Hz, 2H), 7.64 (d, J = 7.6 Hz, 2H), 7.52 (d, J = 7.8 Hz, 2H), 7.33 (t, J = 7.5 Hz, 2H), 7.18 (t, J = 7.3 Hz, 1H), 6.89 (s, 1H), 2.30 (s, 1H), 1.40 (s, 9H), 0.61 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.2, 137.3, 133.9, 131.4, 128.1, 127.9, 126.7, 125.3, 120.6, 118.8, 117.5, 111.2, 57.6, 54.1, 31.9, 30.2 ppm; ν_{max}(KBr)/cm^{-1} 3449, 2925, 2228, 1666, 1607, 1464, 1208, 1028, 852; HRMS-ESI (m/z): calcd for $C_{25}H_{30}N_3$, [M + H]$^+$: 372.2434, found 372.2439.

N,1-Di-tert-butyl-2-(4-nitrophenyl)-4-phenyl-1H-pyrrol-3-amine (**4g**). Eluent: petroleum ether/ethyl acetate 15/1; yield: 68% (53 mg) as a red solid; mp: 184−186 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (d, J = 8.5 Hz, 2H), 7.63 (d, J = 7.5 Hz, 2H), 7.58 (d, J = 8.3 Hz, 2H), 7.34 (t, J = 7.5 Hz, 2H), 7.19 (t, J = 7.3 Hz, 1H), 6.92 (s, 1H), 2.07 (s, 1H), 1.42 (s, 9H), 0.61 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.0, 143.4, 137.3, 133.8, 128.4, 128.1, 128.0, 126.5, 125.3, 122.8, 120.8, 117.9, 57.7, 54.2, 31.9, 30.2 ppm; ν_{max}(KBr)/cm^{-1} 3611, 2922, 2856, 1648, 1521, 1461, 1345, 1016, 751; HRMS-ESI (m/z): calcd for $C_{24}H_{30}N_3O_2$, [M + H]$^+$: 392.2333, found 392.2341.

Ethyl 4-(1-(tert-Butyl)-3-(tert-butylamino)-4-phenyl-1H-pyrrol-2-yl)benzoate (**4h**). Eluent: petroleum ether/ethyl acetate 15/1; yield: 83% (69 mg) as a yellow solid; mp: 173−175 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 7.6 Hz, 2H), 7.69 (d, J = 7.5 Hz, 2H), 7.48 (d, J = 7.6 Hz, 2H), 7.31 (t, J = 7.3 Hz, 2H), 7.16 (t, J = 7.1 Hz, 1H), 6.88 (s, 1H), 4.41 (q, J = 6.9 Hz, 2H), 2.42 (s, 1H), 1.44 (d, J = 7.0 Hz, 3H), 1.40 (s, 9H), 0.63 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 140.8, 137.7, 133.2, 129.5, 128.9, 127.9, 127.9, 127.8, 127.4, 125.0, 120.0, 116.9, 61.1, 57.4, 54.0, 31.7, 30.2, 14.3 ppm; ν_{max}(KBr)/cm^{-1} 2969, 1716, 1606, 1461, 1364, 1272, 1209, 1020, 865; HRMS-ESI (m/z): calcd for $C_{27}H_{35}N_2O_2$, [M + H]$^+$: 419.2693, found 419.2705.

N,1-Di-tert-butyl-4-phenyl-2-(m-tolyl)-1H-pyrrol-3-amine (**4i**). Eluent: petroleum ether/ethyl acetate 20/1; yield: 84% (60 mg) as a yellow solid; mp: 133−135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 7.5 Hz, 2H), 7.35−7.23 (m, 4H), 7.15 (dd, J = 17.1, 9.7 Hz, 4H), 6.84 (s, 1H), 2.38 (s, 3H), 1.40 (s, 9H), 0.67 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 137.2, 135.3, 134.1, 130.6, 128.3, 128.3, 127.9, 127.8, 127.5, 124.8, 119.3, 115.9, 57.2, 53.8, 31.6, 30.2, 21.4 ppm; ν_{max}(KBr)/cm^{-1} 3414, 2963, 1664, 1458, 1367, 1207, 1018, 751; HRMS-ESI (m/z): calcd for $C_{25}H_{33}N_2$, [M + H]$^+$: 361.2638, found 361.2647.

2-(3-Bromophenyl)-N,1-di-tert-butyl-4-phenyl-1H-pyrrol-3-amine (**4j**). Eluent: petroleum ether/ethyl acetate 20/1; yield: 81% (69 mg) as a white solid; mp: 140−142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, J = 6.9 Hz, 2H), 7.56 (s, 1H), 7.50 (d, J = 7.7 Hz, 1H), 7.34−7.30 (m, 2H), 7.28 (d, J = 3.5 Hz, 1H), 7.24 (dd, J = 6.8, 5.1 Hz, 1H), 7.15 (t, J = 6.7 Hz, 1H), 6.85 (s, 1H), 2.41 (s, 1H), 1.40 (s, 9H), 0.67 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.8, 137.7, 136.2, 132.0, 130.7, 129.1, 128.1, 127.9, 127.9, 126.7, 125.1, 121.6, 119.8, 116.6, 57.4, 53.9, 31.7, 30.2 ppm; ν_{max}(KBr)/cm^{-1} 2968, 1665, 1598, 1467, 1360, 1209, 1007, 899; HRMS-ESI (m/z): calcd for $C_{24}H_{30}BrN_2$, [M + H]$^+$: 425.1587, found 425.1593.

1-(3-(1-(tert-Butyl)-3-(tert-butylamino)-4-phenyl-1H-pyrrol-2-yl)-phenyl)ethanone (**4k**). Eluent: petroleum ether/ethyl acetate 10/1; yield: 81% (63 mg) as a yellow solid; mp: 120−122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 10.4 Hz, 2H), 7.69 (d, J = 7.4 Hz, 2H), 7.61 (d, J = 7.3 Hz, 1H), 7.51 (t, J = 7.5 Hz, 1H), 7.32 (t, J = 7.3 Hz, 2H), 7.17 (t, J = 7.2 Hz, 1H), 6.88 (s, 1H), 2.63 (s, 3H), 1.40 (s, 9H), 0.64 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.9, 138.0, 137.7, 136.6, 136.2, 133.3, 128.1, 128.0, 127.9, 127.5, 127.2, 125.1, 119.9, 116.6, 57.4, 53.9, 31.8, 30.2, 26.8 ppm; ν_{max}(KBr)/cm^{-1} 2965, 1683, 1601, 1480, 1360, 1212, 1019, 752; HRMS-ESI (m/z): calcd for $C_{26}H_{32}N_2NaO$, [M + Na]$^+$: 411.2407, found 411.2412.

2-(2-Bromophenyl)-N,1-di-tert-butyl-4-phenyl-1H-pyrrol-3-amine (**4l**). Eluent: petroleum ether/ethyl acetate 20/1; yield: 80% (68 mg) as a yellow solid; mp: 108−109 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 7.2 Hz, 2H), 7.67 (dd, J = 8.0, 0.8 Hz, 1H), 7.47 (dd, J = 7.6, 1.3 Hz, 1H), 7.31 (q, J = 7.7 Hz, 3H), 7.25−7.22 (m, 1H), 7.14 (t, J = 7.3 Hz, 1H), 6.90 (s, 1H), 1.99 (s, 1H), 1.41 (s, 9H), 0.69 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.9, 136.6, 136.0, 132.6, 129.5, 128.0, 127.9, 127.8, 126.8, 126.1, 124.9, 120.3, 116.9, 57.3, 53.6, 31.4, 30.4 ppm; ν_{max}(KBr)/cm^{-1} 2966, 1601, 1559, 1469, 1359, 1208, 1024, 748; HRMS-ESI (m/z): calcd for $C_{24}H_{30}BrN_2$, [M + H]$^+$: 425.1587, found 425.1591.

N,1-Di-tert-butyl-2-(2-iodophenyl)-4-phenyl-1H-pyrrol-3-amine (**4m**). Eluent: petroleum ether/ethyl acetate 30/1; yield: 66% (62 mg) as a yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 7.9 Hz, 1H), 7.74 (d, J = 7.7 Hz, 2H), 7.48 (d, J = 7.6 Hz, 1H), 7.36 (t, J = 7.5 Hz, 1H), 7.31 (t, J = 7.5 Hz, 2H), 7.15 (t, J = 7.2 Hz, 1H), 7.05 (t, J = 7.6 Hz, 1H), 6.89 (s, 1H), 1.89 (s, 1H), 1.42 (s, 9H), 0.70 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.6, 138.9, 137.9, 135.3, 130.4, 129.4, 127.9, 127.8, 127.5, 126.8, 124.9, 120.4, 116.5, 106.1, 57.3, 53.6, 31.6, 30.0 ppm; ν_{max}(KBr)/cm $^{-1}$ 2963, 1700, 1555, 1465, 1360, 1208, 1015, 751; HRMS-ESI (m/z): calcd for $C_{24}H_{30}IN_2$, [M + H] $^+$: 473.1448, found 473.1456.

N,1-Di-tert-butyl-2-(4-chloro-2-fluorophenyl)-4-phenyl-1H-pyrrol-3-amine (**4n**). Eluent: petroleum ether/ethyl acetate 20/1; yield: 81% (64 mg) as a yellow solid; mp: 125−127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 7.6 Hz, 2H), 7.31 (t, J = 7.6 Hz, 3H), 7.22−7.13 (m, 3H), 6.92 (s, 1H), 2.23 (s, 1H), 1.40 (s, 9H), 0.68 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.3 (J_{C-F} = 247.5 Hz), 137.6, 135.6 (J_{C-F} = 3.2 Hz), 135.1 (J_{C-F} = 10.1 Hz), 128.8, 128.0, 127.9, 125.1, 124.1 (J_{C-F} = 3.6 Hz), 122.5 (J_{C-F} = 16.1 Hz), 120.5, 120.0, 117.7, 116.5 (J_{C-F} = 26.3 Hz), 57.3, 53.8, 31.1, 30.0 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −104.35; ν_{max}(KBr)/cm^{-1} 3435, 2970, 1605, 1563, 1481, 1361, 1212, 1077, 991; HRMS-ESI (m/z): calcd for $C_{24}H_{29}ClFN_2$, [M + H]$^+$: 399.1998, found 399.1995.

N,1-Di-tert-butyl-2-(naphthalen-1-yl)-4-phenyl-1H-pyrrol-3-amine (**4o**). Eluent: petroleum ether/ethyl acetate 25/1; yield: 82% (65 mg) as a yellow solid; mp: 122−125 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, J = 8.4, 3.5 Hz, 2H), 7.72 (d, J = 7.7 Hz, 2H), 7.62−7.56 (m, 1H), 7.51 (d, J = 7.0 Hz, 1H), 7.44−7.35 (m, 3H), 7.24 (t, J = 7.5 Hz, 2H), 7.07 (t, J = 7.3 Hz, 1H), 6.91 (s, 1H), 1.89 (s, 1H), 1.21 (s, 9H), 0.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 134.7, 133.5, 132.9, 132.0, 128.9, 128.5, 128.2, 127.9, 127.9, 126.7, 126.5, 125.8, 125.0, 124.9, 124.6, 119.8, 117.0, 57.3, 53.5, 31.4, 30.3 ppm; ν_{max}(KBr)/cm^{-1} 3052, 2968, 1663, 1601, 1462, 1363, 1211, 1017; HRMS-ESI (m/z): calcd for $C_{28}H_{33}N_2$, [M + H]$^+$: 397.2638, found 397.2643.

N,1-Di-tert-butyl-4-phenyl-2-(pyridin-3-yl)-1H-pyrrol-3-amine (**4p**). Eluent: petroleum ether/ethyl acetate 4/1; yield: 73% (51 mg) as

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a brown solid; mp: 156−157 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, J = 1.5 Hz, 1H), 8.60 (dd, J = 4.8, 1.6 Hz, 1H), 7.72 (dt, J = 7.8, 1.8 Hz, 1H), 7.69−7.64 (m, 2H), 7.37−7.30 (m, 3H), 7.17 (t, J = 7.4 Hz, 1H), 6.91 (s, 1H), 2.30 (s, 1H), 1.41 (s, 9H), 0.65 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 148.6, 140.6, 137.5, 131.8, 128.7, 128.0, 127.9, 125.1, 124.7, 122.6, 120.3, 117.1, 57.3, 53.9, 31.8, 30.2 ppm; ν_{max}(KBr)/cm^{-1} 2966, 1558, 1471, 1359, 1208, 1023, 748; HRMS-ESI (m/z): calcd for $C_{23}H_{30}N_3$, [M + H]$^+$: 348.2434, found 348.2433.

N,1-Di-tert-butyl-4-phenyl-2-(thiophen-2-yl)-1H-pyrrol-3-amine ***(4q)***. Eluent: petroleum ether/ethyl acetate 20/1; yield: 84% (59 mg) as a brown solid; mp: 114−115 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 7.7 Hz, 2H), 7.42 (d, J = 5.2 Hz, 1H), 7.30 (t, J = 7.6 Hz, 2H), 7.15 (t, J = 7.3 Hz, 1H), 7.10−7.06 (m, 1H), 7.04 (d, J = 3.3 Hz, 1H), 6.90 (s, 1H), 2.46 (s, 1H), 1.48 (s, 9H), 0.74 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7, 136.1, 131.6, 130.9, 127.9, 127.9, 127.4, 126.6, 125.1, 119.4, 118.3, 117.5, 57.3, 53.6, 31.4, 30.3 ppm; ν_{max}(KBr)/cm^{-1} 2965, 1663, 1564, 1463, 1363, 1209, 1019, 929; HRMS-ESI (m/z): calcd for $C_{22}H_{29}N_2S$, [M + H]$^+$: 353.2046, found 353.2051.

(E)-N,1-Di-tert-butyl-4-phenyl-2-styryl-1H-pyrrol-3-amine ***(4r)***. Eluent: petroleum ether/ethyl acetate 20/1; yield: 68% (51 mg) as a yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 7.6 Hz, 2H), 7.47 (d, J = 7.6 Hz, 2H), 7.37 (t, J = 7.5 Hz, 2H), 7.32 (t, J = 7.5 Hz, 2H), 7.26 (t, J = 5.7 Hz, 1H), 7.19−7.14 (m, 1H), 7.12 (d, J = 15.9 Hz, 1H), 6.89 (d, J = 16.1 Hz, 1H), 6.83 (s, 1H), 3.05 (s, 1H), 1.63 (s, 9H), 0.85 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 137.6, 130.2, 128.7, 128.0, 127.9, 127.8, 127.1, 126.9, 125.9, 125.0, 122.0, 120.8, 116.2, 56.3, 55.0, 30.9, 29.9 ppm; ν_{max}(KBr)/cm $^{-1}$ 2922, 1702, 1553, 1466, 1363, 1209, 964, 749; HRMS-ESI (m/z): calcd for $C_{26}H_{33}N_2$, [M + H] $^+$: 373.2638, found 373.2643.

N,1-Di-tert-butyl-4-phenyl-2-(phenylethynyl)-1H-pyrrol-3-amine ***(4s)***. Eluent: petroleum ether/ethyl acetate 25/1; yield: 47% (35 mg) as a yellow solid; mp: 131−133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 7.3 Hz, 2H), 7.47 (d, J = 6.8 Hz, 2H), 7.37−7.33 (m, 3H), 7.30 (d, J = 4.8 Hz, 2H), 7.18 (t, J = 7.4 Hz, 1H), 6.83 (s, 1H), 2.15 (s, 1H), 1.75 (s, 9H), 1.04 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.8, 136.5, 130.1, 128.4, 128.1, 127.8, 127.5, 125.4, 124.3, 119.4, 117.8, 110.1, 97.4, 84.6, 56.9, 55.4, 30.2, 29.9 ppm; ν_{max}(KBr)/cm^{-1} 3315, 2924, 2190, 1703, 1599, 1466, 1367, 1213, 1018; HRMS-ESI (m/z): calcd for $C_{26}H_{31}N_2$, [M + H]$^+$: 371.2482, found 371.2486.

N,1-Di-tert-butyl-4-(4-iodophenyl)-2-phenyl-1H-pyrrol-3-amine ***(4t)***. Eluent: petroleum ether/ethyl acetate 20/1; yield: 63% (59 mg) as a yellow solid; mp: 139−142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, J = 8.2 Hz, 2H), 7.51 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 3.8 Hz, 5H), 6.84 (s, 1H), 1.78 (s, 1H), 1.40 (s, 9H), 0.66 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6, 136.9, 135.2, 133.4, 129.7, 128.6, 128.3, 127.8, 127.6, 118.3, 116.0, 89.6, 57.4, 53.9, 31.6, 30.3 ppm; ν_{max}(KBr)/cm^{-1} 2923, 1672, 1561, 1471, 1365, 1209, 1003, 762; HRMS-ESI (m/z): calcd for $C_{24}H_{30}IN_2$, [M + H]$^+$: 473.1448, found 473.1444.

4-([1,1′-Biphenyl]-4-yl)-N,1-di-tert-butyl-2-phenyl-1H-pyrrol-3-amine ***(4u)***. Eluent: petroleum ether/ethyl acetate 20/1; yield: 80% (68 mg) as a yellow solid; mp: 140−142 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.3 Hz, 2H), 7.64 (d, J = 7.2 Hz, 2H), 7.57 (d, J = 8.3 Hz, 2H), 7.41 (dd, J = 13.7, 5.8 Hz, 7H), 7.29 (t, J = 7.3 Hz, 1H), 6.91 (s, 1H), 2.44 (s, 1H), 1.41 (s, 9H), 0.70 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 137.4, 137.2, 135.5, 133.4, 128.6, 128.4, 128.0, 127.8, 127.7, 127.6, 126.8, 126.7, 126.5, 119.0, 116.1, 57.3, 53.8, 31.7, 30.3 ppm; ν_{max}(KBr)/cm^{-1} 2967, 1664, 1607, 1486, 1365, 1209, 1011, 843; HRMS-ESI (m/z): calcd for $C_{30}H_{35}N_2$, [M + H]$^+$: 423.2795, found 423.2800.

Methyl 4-(1-(tert-Butyl)-4-(tert-butylamino)-5-phenyl-1H-pyrrol-3-yl)benzoate ***(4v)***. Eluent: petroleum ether/ethyl acetate 15/1; yield: 82% (66 mg) as a yellow solid; mp: 169−171 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 8.1 Hz, 2H), 7.86 (d, J = 8.1 Hz, 2H), 7.38 (s, 5H), 6.94 (s, 1H), 3.89 (s, 3H), 2.42 (s, 1H), 1.41 (s, 9H), 0.67 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 143.1, 135.1, 133.3, 129.4, 128.8, 127.8, 127.8, 127.1, 126.1, 118.5, 116.7, 57.5, 53.9, 51.7, 31.6, 30.2 ppm; ν_{max}(KBr)/cm^{-1} 2967, 1717, 1605, 1562, 1441, 1366, 1276, 1206, 1107; HRMS-ESI (m/z): calcd for $C_{26}H_{33}N_2O_2$, [M + H]$^+$: 405.2537, found 405.2544.

4-(3-Bromophenyl)-N,1-di-tert-butyl-2-phenyl-1H-pyrrol-3-amine ***(4w)***. Eluent: petroleum ether/ethyl acetate 20/1; yield: 71% (60 mg) as a yellow solid; mp: 121−123 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.68 (d, J = 7.5 Hz, 1H), 7.37 (d, J = 4.3 Hz, 6H), 7.25 (s, 1H), 7.16 (t, J = 7.8 Hz, 1H), 6.86 (s, 1H), 2.13 (s, 1H), 1.40 (s, 9H), 0.68 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.2, 135.2, 133.4, 130.4, 129.4, 128.6, 127.8, 127.8, 127.7, 127.6, 126.0, 122.1, 117.9, 116.2, 57.4, 53.8, 31.6, 30.3 ppm; ν_{max}(KBr)/cm^{-1} 3450, 2962, 1659, 1592, 1465, 1361, 1209, 1028; HRMS-ESI (m/z): calcd for $C_{24}H_{30}BrN_2$, [M + H]$^+$: 425.1587, found 425.1580.

N,1-Di-tert-butyl-4-(2-fluorophenyl)-2-phenyl-1H-pyrrol-3-amine ***(4x)***. Eluent: petroleum ether/ethyl acetate 20/1; yield: 76% (55 mg) as a yellow solid; mp: 97−99 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (dd, J = 11.2, 4.4 Hz, 1H), 7.42−7.35 (m, 5H), 7.14−7.05 (m, 3H), 6.98 (s, 1H), 2.27 (s, 1H), 1.41 (s, 9H), 0.65 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6 (J_{C-F} = 242.4 Hz), 135.5, 133.5, 131.9 (J_{C-F} = 4.1 Hz),128.1, 127.6, 126.3 (J_{C-F} = 8.1 Hz), 125.3 (J_{C-F} = 14.7 Hz), 123.4 (J_{C-F} = 3.2 Hz), 117.5 (J_{C-F} = 5.6 Hz), 115.4, 115.2, 112.3, 57.3, 53.5, 31.6, 30.1 ppm; ^{19}F NMR (376 MHz, $CDCl_3$) δ −116.35; ν_{max}(KBr)/cm^{-1} 2969, 1671, 1566, 1478, 1361, 1212, 1104, 1026, 930; HRMS-ESI (m/z): calcd for $C_{24}H_{30}FN_2$, [M + H]$^+$: 365.2388, found 365.2396.

N,1-Di-tert-butyl-4-(3,4-dimethoxyphenyl)-2-phenyl-1H-pyrrol-3-amine ***(4y)***. Eluent: petroleum ether/ethyl acetate 5/1; yield: 78% (63 mg) as a black solid; mp: 107−108 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.38 (s, 5H), 7.13 (d, J = 8.1 Hz, 1H), 6.84 (d, J = 8.2 Hz, 2H), 3.91 (d, J = 16.4 Hz, 6H), 2.28 (s, 1H), 1.40 (s, 9H), 0.67 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.3, 146.6, 135.5, 133.4, 131.1, 128.2, 127.7, 127.6, 119.2, 119.2, 115.4, 111.9, 110.9, 57.2, 55.8, 55.7, 53.7, 31.7, 30.2 ppm; ν_{max}(KBr)/cm^{-1} 2962, 1663, 1570, 1509, 1458, 1359, 1216, 1027; HRMS-ESI (m/z): calcd for $C_{26}H_{35}N_2O_2$, [M + H]$^+$: 407.2693, found 407.2695.

N,1-Di-tert-butyl-4-(naphthalen-1-yl)-2-phenyl-1H-pyrrol-3-amine ***(4z)***. Eluent: petroleum ether/ethyl acetate 20/1; yield: 73% (58 mg) as a brown solid; mp: 163−165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.98 (d, J = 8.5 Hz, 1H), 7.81 (dd, J = 12.1, 8.6 Hz, 3H), 7.45−7.35 (m, 7H), 6.98 (s, 1H), 2.27 (s, 1H), 1.43 (s, 9H), 0.68 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.7, 135.4, 133.9, 133.4, 131.7, 128.8, 128.4, 127.9, 127.7, 127.6, 127.5, 127.5, 127.1, 125.5, 124.9, 124.5, 119.2, 116.4, 57.3, 53.8, 31.7, 30.3 ppm; ν_{max}(KBr)/cm^{-1} 3054, 2966, 1724, 1668, 1561, 1462, 1364, 1209, 1028; HRMS-ESI (m/z): calcd for $C_{28}H_{33}N_2$, [M + H]$^+$: 397.2638, found 397.2647.

N,1-Di-tert-butyl-2-phenyl-4-(thiophen-2-yl)-1H-pyrrol-3-amine ***(4aa)***. Eluent: petroleum ether/ethyl acetate 20/1; yield: 65% (46 mg) as a brown solid; mp: 110−112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 5H), 7.19 (s, 1H), 7.12 (d, J = 5.0 Hz, 1H), 7.02−6.97 (m, 1H), 6.91 (s, 1H), 1.40 (s, 9H), 0.73 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.6, 135.3, 133.4, 128.8, 127.8, 127.7, 126.7, 122.9, 122.1, 115.9, 114.0, 57.4, 53.9, 31.6, 30.0 ppm; ν_{max}(KBr)/cm^{-1} 2924, 1688, 1580, 1462, 1365, 1211, 753; HRMS-ESI (m/z): calcd for $C_{22}H_{29}N_2S$, [M + H]$^+$: 353.2046, found 353.2053.

2-(2-Bromophenyl)-N,1-di-tert-butyl-4-(p-tolyl)-1H-pyrrol-3-amine ***(4ab)***. Eluent: petroleum ether/ethyl acetate 20/1; yield: 81% (71 mg) as a yellow solid; mp: 125−126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, J = 13.7, 5.6 Hz, 3H), 7.55 (dd, J = 13.7, 5.6 Hz, 3H), 7.45−7.33 (m, 1H), 7.41−7.35 (m, 1H), 7.22 (t, J = 7.5 Hz, 1H), 7.12 (dd, J = 10.4, 4.9 Hz, 1H), 7.03 (d, J = 6.6 Hz, 2H), 6.80−6.77 (m, 1H), 2.24 (s, 3H), 2.24 (s, 3H), 2.01 (s, 1H), 2.01 (s, 1H), 1.31 (s, 8H), 1.31 (s, 9H), 0.62 (s, 9H), 0.62 (s, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136. 7, 136.0, 134.9, 134.3, 132.6, 129.4, 128.5, 128.0, 127.9, 127.7, 126.6, 126.1, 120.3, 116.7, 57.2, 53.6, 31.4, 30.5, 21.1 ppm; ν_{max}(KBr)/cm^{-1} 2969, 1567, 1469, 1360, 1209, 1025, 824; HRMS-ESI (m/z): calcd for $C_{25}H_{32}BrN_2$, [M + H]$^+$: 439.1743, found 439.1745.

4-([1,1′-Biphenyl]-4-yl)-2-(2-bromophenyl)-N,1-di-tert-butyl-1H-pyrrol-3-amine ***(4ac)***. Eluent: petroleum ether/ethyl acetate 20/1; yield: 80% (80 mg) as a yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89−7.83 (m, 2H), 7.65 (dd, J = 9.3, 8.4 Hz, 3H), 7.59−7.54 (m, 2H), 7.48 (d, J = 7.5 Hz, 1H), 7.41 (t, J = 7.7 Hz, 2H), 7.30 (ddd, J = 9.3, 8.7, 4.5 Hz, 2H), 7.21 (ddd, J = 7.6, 6.1, 1.5 Hz, 1H), 6.96 (d, J =

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0.9 Hz, 1H), 2.15 (s, 1H), 1.41 (s, 9H), 0.74 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 137.5, 137.0, 136.5, 136.0, 132.6, 129.5, 128.6, 128.0, 127.9, 126.9, 126.8, 126.7, 126.5, 126.1, 119.8, 117.0, 57.4, 53.7, 31.4, 30.5 ppm; ν_{max}(KBr)/cm^{-1} 2968, 1669, 1565, 1475, 1361, 1207, 1023 844; HRMS-ESI (m/z): calcd for $C_{30}H_{34}BrN_2$, [M + H]$^+$: 501.1900, found 501.1907.

*2-(2-Bromophenyl)-N,1-di-tert-butyl-4-(4-chlorophenyl)-1H-pyrrol-3-amine (**4ad**).* Eluent: petroleum ether/ethyl acetate 20/1; yield: 77% (71 mg) as a yellow solid; mp: 100−102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65−7.61 (m, 2H), 7.57 (dd, J = 8.0, 1.1 Hz, 1H), 7.37 (dd, J = 7.6, 1.7 Hz, 1H), 7.22 (td, J = 7.5, 1.2 Hz, 1H), 7.19−7.15 (m, 2H), 7.15−7.10 (m, 1H), 6.80 (s, 1H), 2.03 (s, 1H), 1.31 (s, 9H), 0.60 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.4, 136.3, 135.9, 132.6, 130.4, 129.6, 129.0, 128.5, 127.9, 127.8, 127.0, 126.2, 119.1, 116.7, 57.4, 53.7, 31.4, 30.4 ppm; ν_{max}(KBr)/cm^{-1} 2967, 1670, 1561, 1474, 1363, 1207, 1090, 1018, 831; HRMS-ESI (m/z): calcd for $C_{24}H_{29}BrClN_2$, [M + H]$^+$: 459.1197, found 459.1205.

*2-(2-Bromophenyl)-4-phenyl-N,1-bis(2,4,4-trimethylpentan-2-yl)-1H-pyrrol-3-amine (**4ae**).* Eluent: petroleum ether/ethyl acetate 20/1; yield: 70% (75 mg) as a yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 1.2 Hz, 1H), 7.68−7.63 (m, 2H), 7.57 (dd, J = 7.6, 1.5 Hz, 1H), 7.34−7.27 (m, 3H), 7.24−7.20 (m, 1H), 7.14 (t, J = 7.4 Hz, 1H), 6.88 (s, 1H), 2.11 (s, 1H), 1.94−1.89 (m, 1H), 1.62 (d, J = 7.2 Hz, 1H), 1.59 (s, 3H), 1.26 (s, 1H), 1.21 (s, 3H), 1.05 (d, J = 14.4 Hz, 1H), 0.91 (s, 9H), 0.80 (s, 9H), 0.68 (s, 3H), 0.65 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.2, 137.2, 135.6, 132.7, 129.5, 128.9, 128.3, 127.9, 127.8, 126.5, 126.0, 124.9, 120.7, 117.7, 60.8, 57.5, 56.8, 55.5, 31.7, 31.7, 31.4, 31.2, 31.0, 30.7, 29.6, 29.2 ppm; ν_{max}(KBr)/cm^{-1} 2951, 1684, 1602, 1563, 1469, 1361, 1214, 1151, 1023; HRMS-ESI (m/z): calcd for $C_{32}H_{46}BrN_2$, [M + H]$^+$: 537.2839, found 537.2843.

*N,1-Dibutyl-2,4-diphenyl-1H-pyrrol-3-amine (**4af**).* Eluent: petroleum ether/ethyl acetate 20/1; yield: 79% (55 mg) as a yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 7.3 Hz, 2H), 7.43 (d, J = 7.4 Hz, 2H), 7.38−7.31 (m, 5H), 7.17 (t, J = 7.3 Hz, 1H), 6.74 (s, 1H), 3.76 (t, J = 7.3 Hz, 2H), 2.83 (s, 1H), 2.66 (t, J = 6.9 Hz, 2H), 1.55 (dd, J = 14.7, 7.3 Hz, 2H), 1.22 (d, J = 7.7 Hz, 2H), 1.20−1.15 (m, 2H), 1.11−1.05 (m, 2H), 0.79 (t, J = 7.3 Hz, 3H), 0.70 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.0, 132.3, 130.4, 129.8, 128.6, 128.4, 127.1, 126.7, 125.1, 123.4, 117.9, 116.8, 49.6, 47.1, 33.2, 32.3, 19.9, 19.8, 13.8, 13.6 ppm; ν_{max}(KBr)/cm^{-1} 3326, 3063, 2930, 2865, 1658, 1541, 1377, 1267, 1024; HRMS-ESI (m/z): calcd for $C_{24}H_{31}N_2$, [M + H]$^+$: 347.2482, found 347.2480.

*2,4-Diphenyl-N,1-bis(2,4,4-trimethylpentan-2-yl)-1H-pyrrol-3-amine (**4ag**).* Eluent: petroleum ether/ethyl acetate 25/1; yield: 77% (71 mg) as a yellow solid; mp: 82−84 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 7.6 Hz, 2H), 7.34 (d, J = 7.1 Hz, 2H), 7.29 (dd, J = 13.8, 6.5 Hz, 3H), 7.22 (t, J = 7.5 Hz, 2H), 7.06 (t, J = 7.2 Hz, 1H), 6.76 (s, 1H), 2.33 (s, 1H), 1.61 (s, 2H), 1.35 (s, 6H), 1.02 (s, 2H), 0.79 (s, 9H), 0.70 (s, 9H), 0.56 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 136.0, 133.6, 128.2, 127.8, 127.8, 127.7, 127.6, 124.9, 119.8, 117.0, 60.6, 57.7, 56.6, 54.2, 32.0, 31.7, 31.6, 31.4, 30.7, 29.1 ppm; ν_{max}(KBr)/cm^{-1} 2954, 1667, 1603, 1562, 1474, 1363, 1214, 1147; HRMS-ESI (m/z): calcd for $C_{32}H_{46}N_2Na$, [M + Na]$^+$: 481.3553, found 481.3547.

*N,1-Dicyclohexyl-2,4-diphenyl-1H-pyrrol-3-amine (**4ah**).* Eluent: petroleum ether/ethyl acetate 25/1; yield: 68% (54 mg) as a yellow solid; mp: 86−88 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, J = 7.8 Hz, 2H), 7.36 (t, J = 7.3 Hz, 2H), 7.24 (d, J = 7.2 Hz, 5H), 7.07 (t, J = 7.3 Hz, 1H), 6.76 (s, 1H), 3.63 (t, J = 11.8 Hz, 1H), 2.42 (t, J = 9.9 Hz, 1H), 1.89 (d, J = 12.4 Hz, 2H), 1.69 (d, J = 8.8 Hz, 2H), 1.62 (d, J = 12.3 Hz, 2H), 1.53 (s, 2H), 1.33 (s, 2H), 1.20 (d, J = 9.7 Hz, 2H), 1.08 (d, J = 8.9 Hz, 2H), 0.82 (dd, J = 14.3, 7.8 Hz, 4H), 0.67−0.57 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.5, 132.6, 130.6, 128.5, 128.2, 127.8, 127.0, 126.4, 124.9, 123.9, 116.9, 114.4, 56.2, 55.3, 34.5, 33.9, 25.9, 25.8, 25.5, 24.9 ppm; ν_{max}(KBr)/cm^{-1} 3447, 2927, 2854, 1637, 1449, 1376, 1264, 753; HRMS-ESI (m/z): calcd for $C_{28}H_{35}N_2$, [M + H]$^+$: 399.2795, found 399.2767.

*N,1-Diadamantyl-2,4-diphenyl-1H-pyrrol-3-amine (**4ai**).* Eluent: petroleum ether/ethyl acetate 20/1; yield: 65% (65 mg) as a white solid; mp: 220−223 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, J = 6.4 Hz, 2H), 7.38 (s, 5H), 7.30 (t, J = 7.2 Hz, 2H), 7.13 (t, J = 6.9 Hz, 1H), 6.90 (s, 1H), 2.34 (s, 1H), 2.05 (s, 6H), 2.02 (s, 3H), 1.74 (s, 3H), 1.59 (d, J = 11.9 Hz, 3H), 1.50 (d, J = 11.8 Hz, 3H), 1.39 (d, J = 11.7 Hz, 3H), 1.30 (d, J = 11.5 Hz, 3H), 1.17 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.0, 135.9, 133.5, 127.9, 127.8, 127.6, 126.5, 124.8, 119.5, 115.1, 58.4, 53.7, 43.7, 36.4, 36.0, 29.9, 29.7 ppm; ν_{max}(KBr)/cm^{-1} 3450, 2908, 2851, 1654, 1448, 1357, 1214, 741; HRMS-ESI (m/z): calcd for $C_{36}H_{43}N_2$, [M + H]$^+$: 503.3421, found 503.3420.

*1,4-Di-tert-butyl-3-phenyl-1,4-dihydropyrrolo[3,2-b]indole (**5a**).* Eluent: petroleum ether/ethyl acetate 40/:1; yield: 93% (32 mg) as a yellow solid; mp: 178−179 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03−7.97 (m, 1H), 7.87−7.81 (m, 1H), 7.57−7.52 (m, 2H), 7.46 (dd, J = 10.1, 4.7 Hz, 2H), 7.41−7.35 (m, 1H), 7.23 (pd, J = 7.1, 3.4 Hz, 2H), 6.94 (s, 1H), 1.89 (s, 9H), 1.69 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 140.2, 133.0, 130.7, 127.9, 126.0, 122.4, 121.4, 119.5, 118.5, 117.7, 117.2, 114.9, 108.8, 57.2, 55.0, 31.5, 29.6 ppm; ν_{max}(KBr)/cm^{-1} 3468, 2972, 2925, 1760, 1666, 1545, 1448, 1395, 1208, 1064; HRMS-ESI (m/z): calcd for $C_{24}H_{29}N_2$, [M + H]$^+$: 345.2325, found 345.2327.

*1,4-Di-tert-butyl-3-(p-tolyl)-1,4-dihydropyrrolo[3,2-b]indole (**5b**).* Eluent: petroleum ether/ethyl acetate 40/1; yield: 92% (33 mg) as a yellow solid; mp: 169−171 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89−7.85 (m, 1H), 7.73 (dd, J = 7.0, 2.2 Hz, 1H), 7.31 (d, J = 7.9 Hz, 2H), 7.23 (s, 1H), 7.16 (d, J = 7.8 Hz, 2H), 7.11 (t, J = 2.7 Hz, 1H), 6.81 (s, 1H), 2.39 (s, 3H), 1.77 (s, 9H), 1.58 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.3, 137.2, 135.6, 133.1, 130.6, 128.6, 122.5, 121.4, 119.4, 118.5, 117.6, 117.2, 114.8, 108.6, 57.2, 55.0, 31.5, 29.7, 21.2 ppm; ν_{max}(KBr)/cm^{-1} 2967, 2923, 1678, 1550, 1455, 1394, 1207, 1025; HRMS-ESI (m/z): calcd for $C_{25}H_{31}N_2$, [M + H]$^+$: 359.2482, found 359.2483.

*3-([1,1′-Biphenyl]-4-yl)-1,4-di-tert-butyl-1,4-dihydropyrrolo[3,2-b]indole (**5c**).* Eluent: petroleum ether/ethyl acetate 40/1; yield: 90% (38 mg) as a white solid; mp: 298−300 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92−7.86 (m, 1H), 7.77−7.72 (m, 1H), 7.66 (d, J = 7.4 Hz, 2H), 7.61 (d, J = 8.0 Hz, 2H), 7.50 (d, J = 8.0 Hz, 2H), 7.45 (t, J = 7.6 Hz, 2H), 7.34 (t, J = 7.3 Hz, 1H), 7.24 (s, 1H), 7.13 (d, J = 2.6 Hz, 1H), 6.87 (s, 1H), 1.80 (s, 9H), 1.61 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 141.0, 139.3, 138.7, 133.1, 130.9, 128.8, 127.1, 127.0, 126.6, 122.5, 121.6, 119.5, 118.5, 117. 8, 117.3, 114.9, 108.4, 57.3, 55.1, 31.5, 29.7 ppm; ν_{max}(KBr)/cm^{-1} 2917, 2855, 1667, 1597, 1455, 1385, 1204, 1107; HRMS-ESI (m/z): calcd for $C_{30}H_{33}N_2$, [M + H]$^+$: 421.2638, found 421.2623.

*1,4-Di-tert-butyl-3-(4-chlorophenyl)-1,4-dihydropyrrolo[3,2-b]-indole (**5d**).* Eluent: petroleum ether/ethyl acetate 40/1; yield: 87% (33 mg) as a yellow solid; mp: 218−220 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, J = 6.7, 2.4 Hz, 1H), 7.73 (dd, J = 7.1, 2.1 Hz, 1H), 7.36−7.33 (m, 2H), 7.33−7.29 (m, 2H), 7.16−7.09 (m, 2H), 6.79 (s, 1H), 1.77 (s, 9H), 1.57 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 138.8, 132.9, 131.9, 131.9, 128.0, 122.3, 121.6, 119.7, 118.6, 117.9, 117.2, 114.9, 107.5, 57.2, 55.1, 31.6, 29.6 ppm; ν_{max}(KBr)/cm^{-1} 2923, 2856, 1671, 1593, 1532, 1458, 1374, 1262, 1014; HRMS-ESI (m/z): calcd for $C_{24}H_{28}ClN_2$, [M + H]$^+$: 379.1936, found 379.1927.

*3-Phenyl-1,4-bis(2,4,4-trimethylpentan-2-yl)-1,4-dihydropyrrolo-[3,2-b]indole (**5e**).* Eluent: petroleum ether/ethyl acetate 50/1; yield: 82% (37 mg) as a brown solid; mp: 139−141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 7.4 Hz, 1H), 7.76 (d, J = 8.3 Hz, 1H), 7.41 (d, J = 6.8 Hz, 2H), 7.35−7.30 (m, 2H), 7.24 (s, 1H), 7.09 (dd, J = 13.4, 7.2 Hz, 2H), 6.81 (s, 1H), 2.22 (s, 2H), 2.07 (s, 2H), 1.81 (s, 6H), 1.60 (s, 6H), 0.72 (s, 9H), 0.68 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.8, 140.7, 133.4, 131.9, 127.5, 126.3, 123.8, 121.4, 119.2, 118.9, 117.2, 116.8, 114.7, 108.5, 61.0, 58.4, 51.9, 51.8, 33.1, 31.8, 31.6, 31.0, 30.7, 30.2 ppm; ν_{max}(KBr)/cm^{-1} 2952, 1684, 1601, 1545, 1471, 1394, 1217, 1061; HRMS-ESI (m/z): calcd for $C_{32}H_{45}N_2$, [M + H]$^+$: 457.3577, found 457.3581.

■ ASSOCIATED CONTENT

Supporting Information

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Copies of ^{1}H and ^{13}C NMR spectral data for all compounds (PDF)
Crystallographic information file for **4g** (CIF)

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Notes

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REFERENCES

(1) (a) Gulevich, A. V.; Dudnik, A. S.; Chernyak, N.; Gevorgyan, V. *Chem. Rev.* **2013**, *113*, 3084−3213. (b) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395−3442. (c) Estévez, V.; Villacampa, M.; Menéndez, J. C. *Chem. Soc. Rev.* **2010**, *39*, 4402−4421. (d) Estévez, V.; Villacampa, M.; Menéndez, J. C. *Chem. Soc. Rev.* **2014**, *43*, 4633−4657. (e) Balme, G. *Angew. Chem., Int. Ed.* **2004**, *43*, 6238−6241. (f) Liu, J.; Fang, Z.; Zhang, Q.; Liu, Q.; Bi, X. *Angew. Chem., Int. Ed.* **2013**, *52*, 6953−6957. (g) Barluenga, J.; Riesgo, L.; Vicente, R.; López, L. A.; Tomás, M. *J. Am. Chem. Soc.* **2008**, *130*, 13528−13529.

(2) (a) Li, J. J. *Heterocyclic Chemistry in Drug Discovery*; Wiley: New York, 2013. (b) Pavlovic, D.; Mutak, S.; Andreotti, D.; Biondi, S.; Cardullo, F.; Paio, A.; Piga, E.; Donati, D.; Lociuro, S. *ACS Med. Chem. Lett.* **2014**, *5*, 1133−1137. (c) Baraldi, P. G.; Preti, D.; Fruttarolo, F.; Tabrizi, M. A.; Romagnoli, R. *Bioorg. Med. Chem.* **2007**, *15*, 17−35. (d) Bando, T.; Sugiyama, H. *Acc. Chem. Res.* **2006**, *39*, 935−944. (e) Dose, C.; Farkas, M. E.; Chenoweth, D. M.; Dervan, P. B. *J. Am. Chem. Soc.* **2008**, *130*, 6859−6866.

(3) (a) Gholap, S. S. *Eur. J. Med. Chem.* **2016**, *110*, 13−31. (b) Domagala, A.; Jarosz, T.; Lapkowski, M. *Eur. J. Med. Chem.* **2015**, *100*, 176−187. (c) LoVerme, J.; Duranti, A.; Tontini, A.; Spadoni, G.; Mor, M.; Rivara, S.; Stella, N.; Xu, C.; Tarzia, G.; Piomelli, D. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 639−643. (d) Khajuria, R.; Dham, S.; Kapoor, K. K. *RSC Adv.* **2016**, *6*, 37039−37066.

(4) (a) Jung, E. K.; Leung, E.; Barker, D. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 3001−3005. (b) Takayama, T.; Umemiya, H.; Amada, H.; Yabuuchi, T.; Shiozawa, F.; Katakai, H.; Takaoka, A.; Yamaguchi, A.; Endo, M.; Sato, M. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 108−111. (c) Chenoweth, D. M.; Harki, D. A.; Dervan, P. B. *J. Am. Chem. Soc.* **2009**, *131*, 7175−7181. (d) Sasada, T.; Sawada, T.; Ikeda, R.; Sakai, N.; Konakahara, T. *Eur. J. Org. Chem.* **2010**, *22*, 4237−4244.

(5) Wang, Y.; Lei, X.; Tang, Y. *Chem. Commun.* **2015**, *51*, 4507−4510.

(6) Li, K.; You, J. *J. Org. Chem.* **2016**, *81*, 2327−2339.

(7) (a) Vlaar, T.; Ruijter, E.; Maes, B. U. W.; Orru, R. V. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 7084−7097. (b) Qiu, G.; Ding, Q.; Wu, J. *Chem. Soc. Rev.* **2013**, *42*, 5257−5269. (c) Boyarskiy, V. P.; Bokach, N. A.; Luzyanin, K. V.; Kukushkin, V. Y. *Chem. Rev.* **2015**, *115*, 2698−2779. (d) Jiang, H.; Gao, H.; Liu, B.; Wu, W. *RSC Adv.* **2014**, *4*, 17222−17225. (e) Liu, B.; Gao, H.; Yu, Y.; Wu, W.; Jiang, H. *J. Org. Chem.* **2013**, *78*, 10319−10328. (f) Liu, J.; Fang, Z.; Zhang, Q.; Liu, Q.; Bi, X. *Angew. Chem., Int. Ed.* **2013**, *52*, 6953−6957. (g) Wang, Y.; Kumar, R. K.; Bi, X. *Tetrahedron Lett.* **2016**, *57*, 5730−5741.

(8) (a) Dömling, A. *Chem. Rev.* **2006**, *106*, 17−89. (b) Gao, Q.; Zhou, P.; Liu, F.; Hao, W.; Yao, C.; Jiang, B.; Tu, S. *Chem. Commun.* **2015**, *51*, 9519−9522. (c) Tian, Y.; Tian, L.; He, X.; Li, C.; Jia, X.; Li, J. *Org. Lett.* **2015**, *17*, 4874−4877. (d) Qiu, G.; He, Y.; Wu, J. *Chem. Commun.* **2012**, *48*, 3836−3838.

(9) (a) Lang, S. *Chem. Soc. Rev.* **2013**, *42*, 4867−4880. (b) Pan, Y.; Wu, Y.; Chen, Z.; Hao, W.; Li, G.; Tu, S.; Jiang, B. *J. Org. Chem.* **2015**, *80*, 5764−5770. (c) Jiang, H.; Liu, B.; Li, Y.; Wang, A.; Huang, H. *Org. Lett.* **2011**, *13*, 1028−1031. (d) Liu, B.; Li, Y.; Jiang, H.; Yin, M.; Huang, H. *Adv. Synth. Catal.* **2012**, *354*, 2288−2300. (e) Liu, B.; Li, Y.; Yin, M.; Wu, W.; Jiang, H. *Chem. Commun.* **2012**, *48*, 11446−11448.

(10) (a) Xiao, Q.; Zhang, Y.; Wang, J. *Acc. Chem. Res.* **2013**, *46*, 236−247. (b) Huang, Y.; Li, X.; Yu, Y.; Zhu, C.; Wu, W.; Jiang, H. *J. Org. Chem.* **2016**, *81*, 5014−5020. (c) Gao, Y.; Xiong, W.; Chen, H.; Wu, W.; Peng, J.; Gao, Y.; Jiang, H. *J. Org. Chem.* **2015**, *80*, 7456−7467. (d) Barluenga, J.; Florentino, L.; Aznar, F.; Valdés, C. *Org. Lett.* **2011**, *13*, 510−513.

(11) (a) Barluenga, J.; Moriel, P.; Valdés, C.; Aznar, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 5587−5590. (b) Peng, C.; Cheng, J.; Wang, J. *J. Am. Chem. Soc.* **2007**, *129*, 8708−8709. (c) Chen, S.; Wang, J. *Chem. Commun.* **2008**, 4198−4200. (d) Chen, Z.; Duan, X.; Wu, L.; Ali, S.; Ji, K.; Zhou, P.; Liu, X.; Liang, Y. *Chem. - Eur. J.* **2011**, *17*, 6918−6921. (e) Zhou, L.; Ye, F.; Zhang, Y.; Wang, J. *Org. Lett.* **2012**, *14*, 922−955. (f) Zhang, Z.; Liu, Y.; Gong, M.; Zhao, X.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 1139−1142. (g) Dai, Q.; Jiang, Y.; Guo, S.; Yu, J.; Cheng, J. *Chem. Commun.* **2015**, *51*, 14781−14784.

(12) Zhou, F.; Ding, K.; Cai, Q. *Chem. - Eur. J.* **2011**, *17*, 12268−12271.

(13) (a) Krzeszewski, M.; Thorsted, B.; Brewer, J.; Gryko, D. T. *J. Org. Chem.* **2014**, *79*, 3119−3128. (b) Tasior, M.; Chotkowski, M.; Gryko, D. T. *Org. Lett.* **2015**, *17*, 6106−6109. (c) Qiu, L.; Yu, C.; Zhao, N.; Chen, W.; Guo, Y.; Wan, X.; Yang, R.; Liu, Y. *Chem. Commun.* **2012**, *48*, 12225−12227.

(14) Ho, H. E.; Oniwa, K.; Yamamoto, Y.; Jin, T. *Org. Lett.* **2016**, *18*, 2487−2490.

(15) Truong, M. A.; Nakano, K. *J. Org. Chem.* **2015**, *80*, 11566−11572.

(16) Fors, B. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **2010**, *132*, 15914−15917.

(17) (a) Li, Y.; Zhao, J.; Chen, H.; Liu, B.; Jiang, H. *Chem. Commun.* **2012**, *48*, 3545−3547. (b) Liu, B.; Yin, M.; Gao, H.; Wu, W.; Jiang, H. *J. Org. Chem.* **2013**, *78*, 3009−3020. (c) Jiang, H.; Gao, H.; Liu, B.; Wu, W. *Chem. Commun.* **2014**, *50*, 15348−15351. (d) Jiang, H.; Yin, M.; Li, Y.; Liu, B.; Zhao, J.; Wu, W. *Chem. Commun.* **2014**, *50*, 2037−2039.

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