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Synthesis of 3-Iminoindol-2-amines and Cyclic Enaminones via Palladium-Catalyzed Isocyanide Insertion-Cyclization

Yuan-Yuan Pan,[†] Ya-Nan Wu,[†] Zhen-Zhen Chen,[†] Wen-Juan Hao,*[,†] Guigen Li,[‡,§] Shu-Jiang Tu,*[,†] and Bo Jiang*[,†]

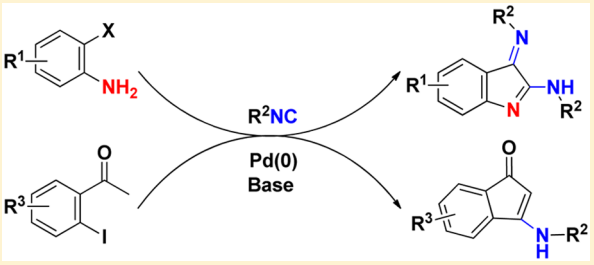
[†]School of Chemistry and Chemical Engineering, Jiangsu Key Laboratory of Green Synthetic Chemistry for Functional Materials, Jiangsu Normal University, Xuzhou 221116, P. R. China

[‡]Institute of Chemistry & Biomedical Sciences, Nanjing University, Nanjing 210093, P. R. China

[§]Department of Chemistry and Biochemistry, Texas Tech University, Lubbock, Texas 79409-1061, United States

Supporting Information

ABSTRACT: A palladium-catalyzed isocyanide insertion-cyclization using low-cost and readily accessible 2-haloanilines, 2-iodophenylethanones, and isocyanides for efficient synthesis of 3-iminoindol-2-amine and cyclic enaminone derivatives has been developed. The method features low-cost and readily accessible starting materials, reliable scalability, and bond-forming efficiency as well as simple one-pot operation, which makes this strategy highly attractive. A reasonable mechanism for forming 3-iminoindol-2-amine involved double isocyanide insertion/cyclization process is proposed.



INTRODUCTION

Indole nucleus is a key structural component in a myriad of non-naturally and naturally occurring products,[1] which has served as "privileged structures" in a large family of medicinally relevant compounds due to its high receptor binding affinity.[2] As a result, a vast number of various methodologies for the construction and functionalization of indoles have been developed with ever-expanding use of intermolecular and intramolecular methods.[3] Still, versatile and efficient methods for the regioselective synthesis of functional indoles from simple and readily available starting materials are highly valuable, especially for their direct amination.

Over the past decades, Larock's indole synthesis has become one of the most powerful synthetic strategies to indole derivatives through palladium-catalyzed cyclization of 2-haloanilines with alkynes (Scheme 1, eq 1).[4] Whitby and co-workers developed a palladium-catalyzed double insertion of isonitriles into aryl bromides with trapping by sodium alkoxides for the formation of α-iminoimidates (Scheme 1, eq 2).[5] Recently, Ji and co-workers reported an iodine-mediated oxidation of indoles with anilines to the *N*-aryl-3-aryliminoindol-2-amines, but this protocol has some clear limitations including the narrow substrate scopes (only an aromatic amine is suitable) and excess oxidants such as peroxides.[6] However, in sharp contrast, a palladium-enabled process initiated by the electrophilicity of isocyanides and involving double isocyanide insertion[5,7] toward indole skeleton is virtually unexplored. Enlightened by palladium-catalyzed isocyanide insertion reactions[8] and our recent findings on domino reactions,[9−11] we assume that an efficient and general palladium-catalyzed domino cyclization of 2-haloanilines with isocyanides to synthesize 3-iminoindol-2-amine derivatives would be more reliable since isocyanides bears inherently both electrophilic and nucleophilic character.[8] Herein, we present a palladium-

Scheme 1. Methods of Synthesis of Indoles, α-Iminoimidates, and Cyclic Enaminones

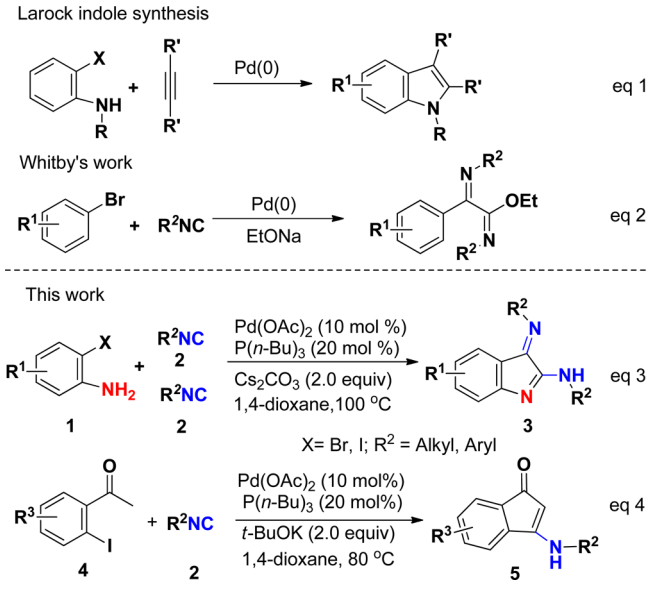


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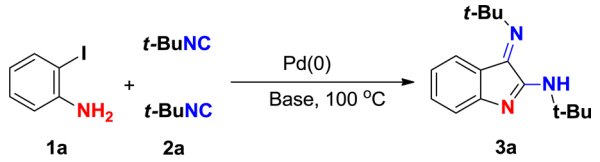
Table 1. Optimization Conditions for Synthesis of 3a[a]



entry	Pd source (mol %)	ligand (mol %)	base (equiv)	solvent	yield (%)[b]
1	$Pd(OAc)_2$ (5)	PPh_3(10)	Cs_2CO_3 (2.0)	1,4-dioxane	64
2	$Pd_2(dba)_3$ (5)	PPh_3(10)	Cs_2CO_3(2.0)	1,4-dioxane	58
3	$Pd(acac)_2$ (5)	PPh_3(20)	Cs_2CO_3 (2.0)	1,4-dioxane	60
4	$PdCl_2(PPh_3)_2$(5)	–	Cs_2CO_3 (2.0)	1,4-dioxane	51
5	$PdCl_2$ (5)	PPh_3(20)	Cs_2CO_3 (2.0)	1,4-dioxane	57
6	$Pd(OAc)_2$ (10)	PPh_3(20)	Cs_2CO_3 (2.0)	1,4-dioxane	79
7	$Pd(OAc)_2$ (15)	PPh_3(30)	Cs_2CO_3 (2.0)	1,4-dioxane	77
8	$Pd(OAc)_2$ (10)	PPh_3(20)	K_2CO_3 (2.0)	1,4-dioxane	73
9	$Pd(OAc)_2$ (10)	PPh_3(20)	Et_3N (2.0)	1,4-dioxane	30
10	$Pd(OAc)_2$ (10)	PPh_3(20)	*t*-BuOK (2.0)	1,4-dioxane	74
11	$Pd(OAc)_2$ (10)	PPh_3(20)	Cs_2CO_3 (2.0)	DMF	76
12	$Pd(OAc)_2$ (10)	PPh_3(20)	Cs_2CO_3 (2.0)	DMSO	74
13	$Pd(OAc)_2$ (10)	PPh_3(20)	Cs_2CO_3 (2.0)	CH_3CN	61[c]
14	$Pd(OAc)_2$ (10)	–	Cs_2CO_3 (2.0)	1,4-dioxane	32
15	$Pd(OAc)_2$ (10)	P(*n*-Bu)$_3$(20)	Cs_2CO_3 (2.0)	1,4-dioxane	83
16	$Pd(OAc)_2$ (10)	X-Phos (20)	Cs_2CO_3 (2.0)	1,4-dioxane	63
17	$Pd(OAc)_2$ (10)	P(*n*-Bu)$_3$(20)	Cs_2CO_3 (2.0)	1,4-dioxane	68[d]

[a]Reactions conditions. All reactions were performed with **1a** (1.0 mmol), **2a** (2.2 mmol), base (2.0 equiv), and solvent (5 mL) at 100 °C under N_2 conditions. [b]Isolated yields are based on **1a**. [c]The reaction in refluxing conditions. [d]The reaction was carried out under air conditions

catalyzed double isocyanide insertion-cyclization between 2-haloanilines and isocyanides to form 3-iminoindol-2-amines through three consecutive in situ steps—the insertion of isocyanides into aryl halides, followed second isocyanide insertion, and subsequent reductive elimination (Scheme 1, eq 3). This fascinating strategy features indole annulation and its C2 amination and C3 imidization, which has not been reported by a Pd-catalyzed system to date. Using 2-iodophenylethanones **4** as replacement for 2-haloanilines **1**, this isocyanide insertion-cyclization reaction gave cyclic enaminones (Scheme 1, eq 4).

RESULTS AND DISCUSSION

Our initial efforts were focused on the investigations with the reaction of 2-iodoaniline (**1a**) with *t*-butyl isonitrile (**2a**) to search for the optimal reaction conditions. The results of these studies are listed in Table 1. We were pleased to find that, in the presence of $Pd(OAc)_2$ (5 mol %) with PPh_3 (10 mol %) in 1,4-dioxane at 100 °C for 10 min, the treatment of **1a** with **2a** in 1:2.2 mol ratio underwent a formal [3 + 1 + 1] cycloaddition to give the desired 3-iminoindol-2-amines **3a** in 64% yield (entry 1). Use of different Pd sources, such as $Pd_2(dba)_3$, $Pd(acac)_2$, and $PdCl_2$, all gave a relatively inferior result (Table 1, entries 2−5). Then we investigated the dosage of $Pd(OAc)_2$ catalyst. When the amount of $Pd(OAc)_2$ was increased to 10 mol % from 5 mol %, the corresponding yield increased from 64% to 79%. While the loading of $Pd(OAc)_2$ was continuously increased to 15 mol %, the reaction resulted in slightly lower yield of **3a** (77%) (entry 7). Next, different bases were investigated (entries 8−10). The use of K_2CO_3 or *t*-BuOK gave the product with a slightly lower yield. An extremely lower yield was isolated when the reaction was conducted by the use of Et_3N as a base promoter (entry 9). Subsequently, different solvents such as *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), and CH_3CN were evaluated in these identical reactions. All these solvents led to slightly lower yields of the desired product **3a** (entries 11−13). Without PPh_3, the reaction catalyzed by 10 mol % of $Pd(OAc)_2$ gave a poor yield of **3a** (32%). Next, the ligand was screened, including P(*n*-Bu)$_3$ and 2-(dicyclohexylphosphino)-2′,4′,6′-tri-isopropyl-1,1′-biphenyl (X-Phos). Use of P(*n*-Bu)$_3$ as a ligand delivered a higher yield (83%) while X-Phos decreased the catalytic activity (63%). Alternatively, the combination of $Pd(OAc)_2$ and P(*n*-Bu)$_3$ ligand under an air condition gave 68% yield of indoles **3a**, which indicated that that oxygen is adverse to this transformation (entry 17).

With the optimal conditions to access functional 3-iminoindol-2-amines in hand, we then turned to evaluating the scope of the palladium-catalyzed formal [3 + 1 + 1] cycloaddition reaction for different substituted 2-iodoanilines and isocyanides (Scheme 2). Upon repeating the reaction with *t*-butyl isocyanide **2a**, we are pleased to find that a variety of functional groups of substituted 2-iodoanilines including both electron-withdrawing and -donating groups were well tolerated under the above conditions to give corresponding 3-iminoindol-2-amine products (**3b**−**3g**) in good to excellent yields of 71−92%. Generally, except for 4-fluoro-2-iodoaniline **1e**, other 2-iodoanilines with electron-poor groups (**1d**−**1g**) afforded higher yields of the desired indoles than that of electron-rich groups (**1b**, **1c**), and the latter demanded more reaction time. Notably, the reaction of heterocyclic 4-iodopyridin-3-amine (**1h**) worked very well to furnish the corresponding 5-azaindoles (pyrrolo[3,2-*c*]pyridines) **3h** in 85% yield. Various alkyl-, cycloalkyl-, and aryl-substituted isocyanides (**2b**−**2i**) were also utilized to investigate the scope of the reaction substrates. As expected, all the isocyanides were efficiently converted into the corresponding indole derivatives in good yields. Even if sterically bulky 1,1,3,3-tetramethylbutyl

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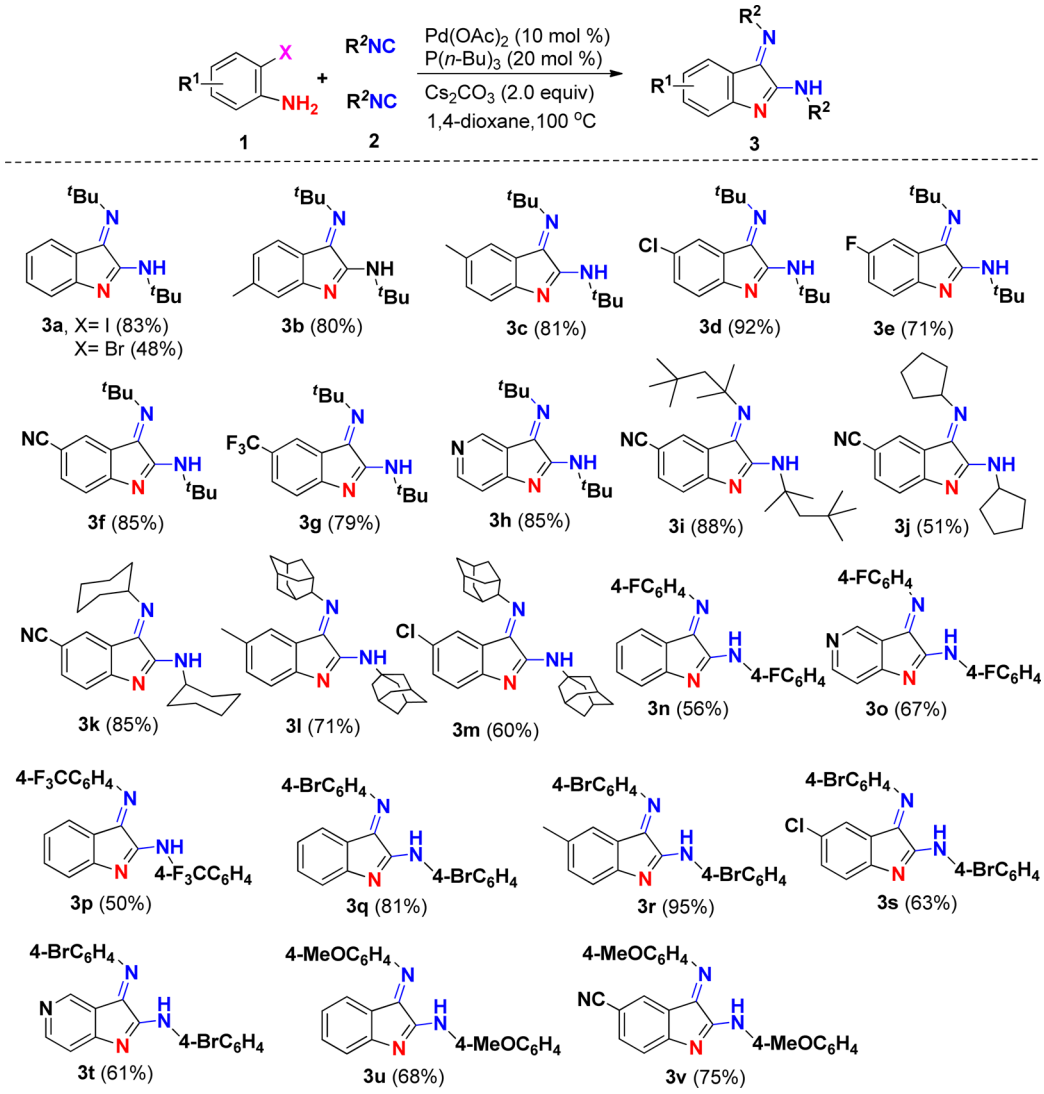
Scheme 2. Scope of Palladium-Catalyzed Domino Reactions[a,b]

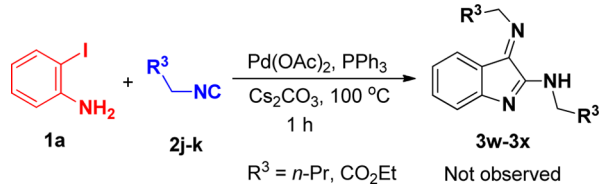


[a]Reaction conditions: **1** (1.0 mmol), **2** (2.2 mmol), 1,4-dioxane (5.0 mL), 100 °C, N_2. [b]Isolated yield are based on **1**

(**2b**) and 1-adamantyl (**2e**) isocyanides were found to have no influence on the course of the reaction, with 3-iminoindol-2-amines **3i**, **3l**, and **3m** afforded in 60−88% yields. Similarly, replacing the alkyl and cycloalkyl isocyanides with their aryl counterpart bearing an electron-withdrawing (**2f**, **2g**, and **2h**) or electron-donating (**2i**) group at the para position of the aromatic ring formed the corresponding *N*-arylamino indole derivatives **3n**−**3v** in 50−95% yields. Likewise, 5-azaindoles **3o** and **3t** with direct C2 amination and C3 imidization were obtained in 63% and 61% yields, respectively, from the corresponding reactions of starting isocyanides **2f**−**2h** with **1h**. Obviously, this domino cycloaddition can tolerate structurally diverse substrates with steric bulk and a different electronic nature. Most functionalities of synthetic indole products offer a flexible access to their further structural modifications. Compared with previous reports,[4,5] the present work represents a special example for the formation of richly decorated *N*-alkyl substituted indol-2-amines, which are normally difficult to prepare through other methods.

Additionally, the reaction can also be conducted with 2-bromoaniline and afforded very lower yield (48%) of the indole products, due to its less reactivity. Unfortunately, the reaction failed to provide indoles **3w**−**x** when isocyanides with methylene group at α-position such as *n*-butyl isocyanide and ethyl 2-isocyanoacetate were employed in this reaction system (Scheme 3). Although 3-iminoindol-2-amines **3** were fully

Scheme 3. Scope of Palladium-Catalyzed Isocyanide Insertion Reactions



characterized by their NMR spectroscopy and HRMS, their structures were determined by X-ray diffraction of compound **3a** (see the Supporting Information).

Cyclic enaminones endowed with an HN−C═C moiety are privileged building blocks in organic, medicinal, and materials chemistry,[12] and methods for their direct cyclization have become one of the most intriguing issues in the synthetic

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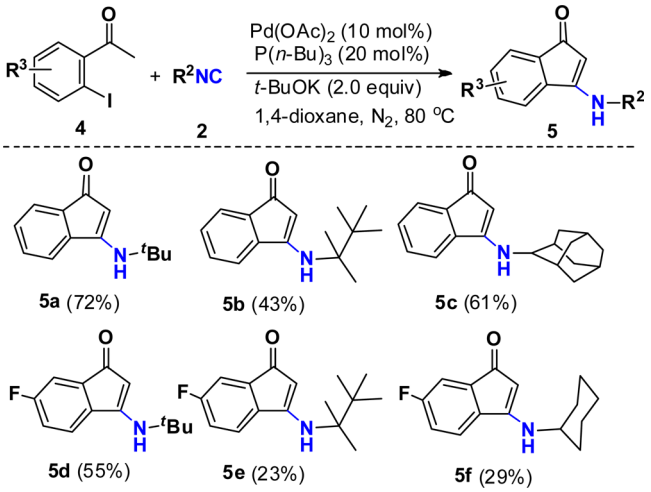
community, as their C,N-nucleophilic sites simultaneously participate in the assembly of elaborate compounds in a highly efficient fashion. Considering the significance of cyclic enaminones, we attempted to evaluate the feasibility of their synthesis through a insertion-cyclization strategy. Delightedly, the insertion-cyclization between 2-iodophenylethanone (**4a**) and *t*-butyl isonitrile (**2a**) was conducted in 1,4-dioxane at 80 °C using 10 mol % of $Pd(OAc)_2$ and 20 mol % of $P(n\text{-}Bu)_3$ ligand, generating the expected 3-*t*-butylamino inden-1-one (**5a**) in 20% yield together with lots of unreacted starting material. This reason may be attributed to the soft basicity in reaction system, which is unfavorable to form carbanion for further cyclization. Next, we considered adjusting the stronger bases like trimethylamine (Et_3N), diisopropylamine ($(i\text{-}Pr)_2NH$), potassium *tert*-butoxide (*t*-BuOK), and sodium *tert*-butoxide (*t*-BuONa) to improve the yield of product **5**. The use of 2.0 equiv of Et_3N (10%) and $(i\text{-}Pr)_2NH$ (12%) was met with little success. *t*-BuONa and *t*-BuOK were then attempted, and 2.0 equiv of *t*-BuONa gave the enaminone product **5a** in 49% yield. Exchanging *t*-BuOK for *t*-BuONa delivered a higher 72% yield through an isocyanide insertion/cyclization sequence.

With the established acceptable conditions, we set out to explore the substrate scope of isocyanides **2**. As depicted in Scheme 4, this protocol tolerates the sterically bulky 1,1,3,3-

Scheme 4. Palladium-Catalyzed Synthesis of Cyclic Enaminones 5[a,b]

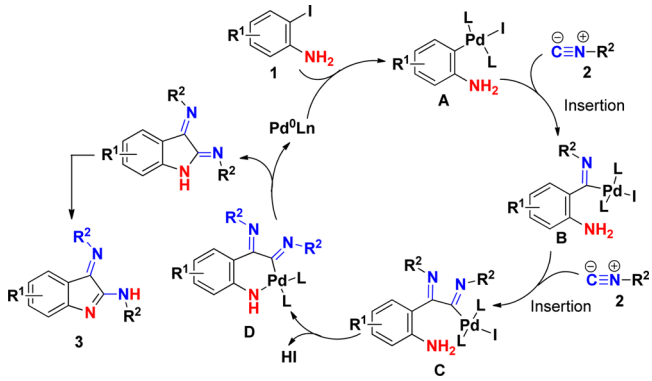


[a]Reaction conditions **2** (1.5 mmol), **4** (1.0 mmol), 1,4-dioxane (5.0 mL), 80 °C, N_2; [b]Isolated yield based on substrate **4**.

tetramethylbutyl (**2b**) and 1-adamantyl (**2e**) isocyanides, leading to the aminated 1-indanone in 43% and 61% yields, respectively. Despite its poor reactive behavior, 5-fluoro-2-iodophenylethanone was also a suitable substrate for this transformation, giving products **5e**–**5f** in a lower yields. In general, this insertion-cyclization gives a new example for the formation of aminated 1-indanones, which are ubiquitous structural units in a substantial number of bioactive compounds.

On the basis of literature reports[13−15] and our experiments, a plausible mechanism for the formation of 3-iminoindol-2-amines **3** is shown in Scheme 5. First, oxidative addition of **1** to the Pd(0) catalyst results in the palladium complex **A**, followed by isocyanide insertion[8] to yield palladium complex **B**. Then, the second isocyanide insertion occurs to afford intermediate

Scheme 5. Proposed Mechanism for Forming Products 3



C.[7] With the assistance of Cs_2CO_3, intermediate **C** removes HI to form the intermediate **D**, which undergoes reductive elimination, and the following tautomerization affords final 3-iminoindol-2-amines **3**. Similar to the former, the latter undergoes isocyanide insertion and cycloisomerization to convert into the aminated 1-indanones.

In conclusion, reliable palladium-catalyzed isocyanide insertions/cyclization cascades have been developed using low-cost and readily accessible 2-iodoanilines, 2-iodophenylethanones, and isocyanides, by which a wide set of aminated indoles and 1-indanones with a wide diversity in substituents are rapidly synthesized in a convergent fashion. Two straightforward and operationally simple methods allow to simultaneously install indole and 1-indanone skeleton and their direct amination. The mild reaction conditions, reliable scalability, and broad substrate scopes as well as flexibility of structural modification make this strategy highly viable for future applications.

EXPERIMENTAL SECTION

General Procedure for the Synthesis of 3. *Example for the Synthesis of* ***3a****.* 2-Iodoaniline (**1a**, 1 mmol, 220.3 mg), *tert*-butyl isocyanide (**2a**, 2.2 mmol, 183.4 mg), Cs_2CO_3 (2.0 mmol, 652.1 mg), $Pd(OAc)_2$ (10 mol %, 22.4 mg)/ $P(n\text{-}Bu)_3$ (20 mol %, 40.4 mg), and 1.4-dioxane (5.0 mL) were added into a 25 mL Schlenk tube under N_2 conditions. The mixture was stirred at 100 °C as monitored by TLC. After the completion of the reaction, the solution was poured into 50 mL of water. The mixture was then extracted with ethyl acetate. The combined organic layers were dried over magnesium sulfate anhydrous, filtered, and evaporated under vacuum. The flash column chromatography on silica gel was first eluted with petroleum ether/triethylamine (10:1 v/v). Next, the residue was purified by above column chromatography (eluents, petroleum ether/ethyl acetate 45:1 v/v) to afford the pure product **3a**.

*(E)-N-(tert-Butyl)-3-(tert-butylimino)-3H-indol-2-amine (**3a**).* Red solid, 216 mg, yield 83%; mp 109−110 °C; ^1H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.53 (d, J = 7.2 Hz, 1H), 7.24−7.20 (m, 1H), 7.09 (d, J = 7.6 Hz, 1H), 6.83−6.79 (m, 1H), 6.07 (s, 1H), 1.50 (s, 9H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 160.6, 157.0, 133.2, 128.2, 122.6, 120.8, 119.2, 118.2, 55.9, 51.4, 29.1, 28.8; IR (KBr, ν, cm^{-1}) 3361, 3065, 2968, 2933, 1579, 1459, 1443, 1218, 1194, 759; HRMS (APCI-TOF) m/z calcd for $C_{16}H_{24}N_3$, 258.1970 $[M + H]^+$; found 258.1969.

*(E)-N-(tert-Butyl)-3-(tert-butylimino)-6-methyl-3H-indol-2-amine (**3b**).* Red solid, 217 mg, yield 80%; mp 101−103 °C; ^1H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.41 (d, J = 7.6 Hz, 1H), 6.93 (s, 1H), 6.63 (d, J = 7.6 Hz, 0H), 6.08 (s, 0H), 2.30 (s, 3H), 1.49 (s, 9H), 1.47 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.6, 161.2, 156.9, 144.0, 128.0, 121.4, 119.1, 116.7, 55.6, 51.3, 29.1, 28.8, 21.8; IR (KBr, ν, cm^{-1})

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3368, 3081, 2963, 2922, 1587, 1420, 1221, 803, 775; HRMS (APCI-TOF) m/z calcd for $C_{17}H_{26}N_3$, 272.2127 $[M + H]^+$; found 272.2123.

(E)-N-(tert-Butyl)-3-(tert-butylimino)-5-methyl-3H-indol-2-amine ***(3c)***. Red solid, 219 mg, yield 81%; mp 86−87 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.33 (s, 1H), 7.05−7.00 (m, 2H), 6.01 (s, 1H), 2.28 (s, 3H), 1.49 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 171.2, 162.8, 157.1, 133.5, 130.0, 129.0, 119.2, 117.7, 55.8, 51.3, 29.1, 28.8, 21.1; IR (KBr, ν, cm^{-1}) 3355, 3026, 2971,2926, 1596, 1460,1232, 825; HRMS (APCI-TOF) m/z calcd for $C_{17}H_{26}N_3$, 272.2127 $[M + H]^+$; found 272.2126.

(E)-N-(tert-Butyl)-3-(tert-butylimino)-5-chloro-3H-indol-2-amine ***(3d)***. Red solid, 270 mg, yield 92%; mp 171−174 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.46 (d, J = 2.0 Hz, 1H), 7.19 (d, J = 8.4 Hz, 1H), 7.01 (d, J = 8.0 Hz, 1H), 6.06 (s, 1H), 1.49 (s, 9H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 163.9, 160.8, 156.2, 132.5, 128.0, 125.6, 120.4, 118.9, 56.2, 51.5, 29.3, 28.7; IR (KBr, ν, cm^{-1}) 3341, 2965, 2927, 1632, 1577, 1438, 1262, 833; HRMS (APCI-TOF) m/z calcd for $C_{16}H_{23}ClN_3$, 292.1581 $[M + H]^+$; found 292.1578.

(E)-N-(tert-Butyl)-3-(tert-butylimino)-5-fluoro-3H-indol-2-amine ***(3e)***. Red solid, 195 mg, yield 71%; mp 143−144 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.26−7.23 (m, 1H), 7.00 (s, 1H), 6.96−6.91 (m, 1H, Ar−H), 6.00 (s, 1H), 1.49 (s, 9H), 1.48 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 160.7, 157.7 (J_{CF} = 236.1 Hz), 157.6 (J_{CF} = 2.1 Hz), 156.5, 119.5 (J_{CF} = 7.8 Hz), 118.8 (J_{CF} = 22.7 Hz), 118.2 (J_{CF} = 7.5 Hz), 115.5 (J_{CF} = 26 Hz), 56.1, 51.4, 29.21, 28.7; IR (KBr, ν, cm^{-1}) 3065, 2964, 2927, 1738, 1584, 1458, 1261, 1099, 780; HRMS (APCI-TOF) m/z calcd for $C_{16}H_{23}FN_3$, 276.1876 $[M + H]^+$; found 276.1870.

(E)-2-(tert-Butylamino)-3-(tert-butylimino)-3H-indole-5-carbonitrile ***(3f)***. Red solid, 240 mg, yield 85%; mp 132−133 °C; ^{1}H NMR (400 MHz, DMSO-d_6; δ, ppm) 7.84 (d, J = 1.2 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.08 (d, J = 8.0 Hz, 1H), 6.50 (s, 1H), 1.45 (s, 9H), 1.44 (s, 9H); ^{13}C NMR (100 MHz, DMSO-d_6; δ, ppm) 169.3, 162.3, 154.7, 138.6, 131.6, 119.9, 119.4, 118.9, 102.9, 56.8, 52.4, 29.4, 28.5; IR (KBr, ν, cm^{-1}) 3316, 2974, 2931, 2223, 1587, 1556, 1451, 1319, 1217; HRMS (APCI-TOF) m/z calcd for $C_{17}H_{23}N_4$, 283.1923 $[M + H]^+$; found 283.1922.

(E)-N-(tert-Butyl)-3-(tert-butylimino)-5-(trifluoromethyl)-3H-indol-2-amine ***(3g)***. Red solid, 257 mg, yield 79%; mp 86−87 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.64 (s, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.13 (d, J = 8.4 Hz, 1H), 6.20 (s, 1H), 1.51 (s, 9H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 168.6, 161.8, 155.8, 130.4 (J_{CF} = 3.7 Hz), 124.6 (J_{CF} = 269.6 Hz), 124.7 (J_{CF} = 3.8 Hz), 122.6 (J_{CF} = 32.0 Hz), 119.2, 118.0, 56.2, 51.8, 29.2, 28.7; IR (KBr, ν, cm^{-1}) 3340, 2970, 2932, 1598, 1571, 1459, 1321, 1268, 835; HRMS (APCI-TOF) m/z calcd for $C_{17}H_{23}F_3N_3$, 326.1844 $[M + H]^+$; found 326.1840.

(E)-N-(tert-Butyl)-3-(tert-butylimino)-3H-pyrrolo[3,2-c]pyridin-2-amine ***(3h)***. Red solid, 220 mg, yield 85%; mp 149−151 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.64 (s, 1H), 8.30 (d, J = 5.6 Hz, 1H), 7.03 (d, J = 5.6 Hz, 1H), 6.36 (s, 1H), 1.51 (s, 9H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 172.1, 162.2, 155.1, 153.7, 147.3, 116.2, 113.9, 56.5, 52.1, 29.0, 28.6; IR (KBr, ν, cm^{-1}) 3309, 2872, 2929, 1634, 1573, 1439, 1327, 1222, 859; HRMS (APCI-TOF) m/z calcd for $C_{15}H_{23}N_4$, 259.1923 $[M + H]^+$; found 259.1922.

(E)-2-((2,4,4-trimethylpentan-2-yl)amino)-3-((2,4,4-trimethylpentan-2-yl)imino)-3H-indole-5-carbonitrile ***(3i)***. Red solid, 347 mg, yield 88%; mp 66−68 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.77 (d, J = 1.2 Hz, 1H), 7.51 (d, J = 8.4 Hz, 1H), 7.11−7.06 (m, 1H, Ar−H), 6.46 (s, 1H), 1.85 (d, J = 11.2 Hz, 4H), 1.57−1.49 (m, 12H), 1.02−0.98 (m, 18H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 170.2, 161.9, 154.0, 137.4, 131.1, 120.0, 119.9, 118.8, 102.8, 60.6, 55.9, 55.5, 52.1, 32.00, 31.7, 31.5, 29.0, 28.9; IR (KBr, ν, cm^{-1}) 2965, 2901, 2866, 2217, 1585, 1557, 1447, 1311, 1218, 1121, 835; HRMS (APCI-TOF) m/z calcd for $C_{25}H_{39}N_4$, 395.3175 $[M + H]^+$; found 395.3175.

(E)-2-(Cyclopentylamino)-3-(cyclopentylimino)-3H-indole-5-carbonitrile ***(3j)***. Red solid, 156 mg, yield 51%; mp 167−168 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.75 (d, J = 1.6 Hz, 1H), 7.54 (d, J = 8.0 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 6.14 (s, 1H), 4.63−4.57 (m, 1H), 4.37−4.32 (m, 1H), 2.14−2.04 (m, 4H), 1.88 (s, 2H), 1.76−1.61 (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 166.6, 163.6, 155.8, 137.7, 129.0, 121.5, 119.7, 118.3, 103.8, 63.1, 53.8, 34.6, 33.2, 24.8, 23.8; IR (KBr, ν, cm^{-1}) 3419, 2950, 2862, 2217, 1633, 1591, 1455, 1303, 1227, 1116, 830, 537; HRMS (APCI-TOF) m/z calcd for $C_{19}H_{23}N_4$, 307.1923 $[M + H]^+$; found 307.1928.

(E)-2-(Cyclohexylamino)-3-(cyclohexylimino)-3H-indole-5-carbonitrile ***(3k)***. Red solid, 284 mg, yield 85%; mp 120−121 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.64 (d, J = 1.2 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 6.14 (d, J = 7.2 Hz, 1H), 4.11−4.04 (m, 1H), 3.94−3.87 (m, 1H), 2.11−2.07 (m, 2H), 1.91−1.83 (m, 4H), 1.80−1.75 (m, 3H), 1.68−1.63 (m, 2H), 1.60−1.54 (m, 2H), 1.50−1.40 (m, 4H), 1.37−1.28 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 167.0, 163.1, 155.5, 137.8, 129.0, 121.3, 119.7, 118.3, 103.7, 61.0, 51.0, 33.24, 32.9, 25.5, 25.4, 24.7, 24.4; IR (KBr, ν, cm^{-1}) 2929, 2854, 2217, 1637, 1591, 1454, 1303, 1223, 1114, 832, 539; HRMS (APCI-TOF) m/z calcd for $C_{21}H_{27}N_4$, 335.2236 $[M + H]^+$; found 335.2234.

(E)-N-(Adamantan-1-yl)-3-(adamantan-2-ylimino)-5-methyl-3H-indol-2-amine ***(3l)***. Red solid, 303 mg, yield 71%; mp 193−195 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.45 (s, 1H), 7.02 (d, J = 8.0 Hz, 1H), 6.96 (d, J = 7.6 Hz, 1H), 6.02 (s, 1H), 2.28 (s, 3H), 2.13 (s, 9H), 2.09 (d, J = 2.0 Hz, 5H), 1.77 (s, 6H), 1.73 (s, 3H), 1.70 (s, 3H), 1.67 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 160.2, 156.8, 138.9, 133.3, 129.6, 125.8, 119.8, 117.8, 56.5, 51.7, 41.6, 40.90, 36.4, 36.4, 29.6, 29.5, 21.3; IR (KBr, ν, cm^{-1}) 2904, 2850, 2657, 1631, 1577, 1519, 1455, 1318, 1289, 1097, 827; HRMS (APCI-TOF) m/z calcd for $C_{29}H_{38}N_3$, 428.3066 $[M + H]^+$; found 428.3065.

(E)-N-(Adamantan-1-yl)-3-(adamantan-2-ylimino)-5-chloro-3H-indol-2-amine ***(3m)***. Red solid, 268 mg, yield 60%; mp 133−135 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.58 (s, 1H), 7.17 (d, J = 8.0 Hz, 1H), 6.97 (s, 1H), 6.04 (s, 1H), 2.21 (s, 3H), 2.13 (s, 9H), 2.06 (d, J = 2.4 Hz, 5H), 1.78 (s, 6H), 1.73 (s, 3H), 1.71 (s, 3H), 1.68 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) δ 160.5, 155.5, 137.6, 132.3, 128.6, 125.4, 120.9, 118.9, 57.0, 52.0, 41.5, 41.0, 36.3, 36.3, 29.6, 29.5; IR (KBr, ν, cm^{-1}) 2905, 2850, 1628, 1568, 1435, 1307, 1261, 1099, 824,753; HRMS (APCI-TOF) m/z calcd for $C_{28}H_{35}ClN_3$, 448.2520 $[M + H]^+$; found 448.2519.

(E)-N-(4-Fluorophenyl)-3-((4-fluorophenyl)imino)-3H-indol-2-amine ***(3n)***. Red solid, 187 mg, yield 56%; mp 230−231 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.82 (s, 3H), 7.29 (d, J = 7.6 Hz, 1H), 7.20−7.04 (m, 7H), 6.76 (d, J = 7.2 Hz, 1H), 6.72−6.68 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 162.1, 162.0, 159.6, 159.0 (J_{CF} = 249.0 Hz), 158.9 (J_{CF} = 256.0 Hz), 144.7 (J_{CF} = 2.4 Hz), 144.6 (J_{CF} = 2.5 Hz), 134.8, 125.7, 125.5, 122.8, 120.8 (J_{CF} = 8.2 Hz), 120.7 (J_{CF} = 8.1 Hz), 119.3, 116.3 (J_{CF} = 22.5 Hz), 116.0 (J_{CF} = 22.6 Hz); IR (KBr, ν, cm^{-1}) 3054, 1629, 1571, 1499, 1445, 1200, 838, 826; HRMS (APCI-TOF) m/z calcd for $C_{20}H_{14}F_2N_3$, 334.1156 $[M + H]^+$; found 334.1158.

(E)-N-(4-Fluorophenyl)-3-((4-fluorophenyl)imino)-3H-pyrrolo[3,2-c]pyridin-2-amine ***(3o)***. Red solid, 324 mg, yield 97%; mp 234−235 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.41 (d, J = 4.4 Hz, 1H), 8.14 (s, 1H), 8.02 (s, 1H), 7.89−7.86 (m, 2H), 7.21−7.09 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 169.6, 161.6 (J_{CF} = 245.7 Hz), 159.5 (J_{CF} = 243.4 Hz) 159.5, 158.7, 155.4, 144.9, 144.4 (J_{CF} = 1.1 Hz), 133.7 (J_{CF} = 4.1 Hz), 121.5 (J_{CF} = 8.0 Hz), 121.2 (J_{CF} = 8.3 Hz), 116.6 (J_{CF} = 22.7 Hz), 116.4, 116.2 (J_{CF} = 22.7 Hz), 114.80; IR (KBr, ν, cm^{-1}) 3100, 3011, 1605, 1553, 1446, 1268, 1232, 1159, 921, 840, 742; HRMS (APCI-TOF) m/z calcd for $C_{19}H_{13}F_2N_4$, 335.1108 $[M + H]^+$; found 335.1110.

(E)-N-(4-(Trifluoromethyl)phenyl)-3-((4-(trifluoromethyl)phenyl)-imino)-3H-indol-2-amine ***(3p)***. Red solid, 217 mg, yield 50%; mp 232−234 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.97 (s, 2H), 7.75−7.68 (m, 4H), 7.32−7.17(m, 5H), 6.74 (s, 1H), 6.61 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) δ 160.3, 151.6, 138.5, 135.3, 127.9 (J_{CF} = 32.8 Hz), 126.8 (J_{CF} = 3.7 Hz), 126.7 (J_{CF} = 3.9 Hz), 126.6 (J_{CF} = 3.8 Hz), 125.9, 125.7 (J_{CF} = 1.4 Hz), 124.2 (J_{CF} = 269.8 Hz), 124.1 (J_{CF} = 270.2 Hz), 125.3 (J_{CF} = 2.1 Hz), 125.0 (J_{CF} = 5.5 Hz), 123.6, 119.2, 119.0, 114.2; IR (KBr, ν, cm^{-1}) 1671, 1599, 1572, 1546, 1448, 1326, 1112, 1068, 852, 831, 763; HRMS (APCI-TOF) m/z calcd for $C_{22}H_{14}F_6N_3$, 434.1092 $[M + H]^+$; found 434.1092.

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*(E)-N-(4-Bromophenyl)-3-((4-bromophenyl)imino)-3H-indol-2-amine (**3q**).* Red solid, 368 mg, yield 81%; mp 219−220 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.74 (s, 3H), 7.58 (d, J = 8.4 Hz, 2H), 7.51 (d, J = 8.4 Hz, 2H), 7.31−7.27 (m, 1H), 7.20 (d, J = 6.0 Hz, 1H), 6.96 (d, J = 8.4 Hz, 2H), 6.75−6.70 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 160.3, 147.6, 135.0, 132.6, 132.4, 132.2, 132.0, 125.8, 125.7, 123.1, 120.9, 120.8, 119.2, 119.0, 116.7, 116.2; IR (KBr, ν, cm^{-1}) 1623, 1592, 1562, 1445, 1298, 1202, 1070, 1009, 834, 812, 761; HRMS (APCI-TOF) m/z caled for $C_{20}H_{14}Br_2N_3$, 455.9534 $[M + H]^+$; found 455.9523.

*(E)-N-(4-Bromophenyl)-3-((4-bromophenyl)imino)-5-methyl-3H-indol-2-amine (**3r**).* Red solid, 445 mg, yield 95%; mp 225−226 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.73 (s, 3H), 7.59 (s, 1H), 7.57 (s, 1H), 7.51 (s, 1H), 7.48 (s, 1H), 7.09 (s, 2H), 6.97 (s, 1H), 6.95 (s, 1H), 6.57 (s, 1H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 160.3, 160.2, 157.4, 157.3, 147.5, 135.4, 132.7, 132.5, 132.2, 132.0, 126.3, 120.9, 120.7, 118.9, 116.7, 116.0, 21.0; IR (KBr, ν, cm^{-1}) 1586, 1465, 1299, 1200, 1069, 1007, 840, 814, 796; HRMS (APCI-TOF) m/z calcd for $C_{21}H_{16}Br_2N_3$, 469.9691 $[M + H]^+$; found 469.9698.

*(E)-N-(4-Bromophenyl)-3-((4-bromophenyl)imino)-5-chloro-3H-indol-2-amine (**3s**).* Red solid, 308 mg, yield 63%; mp 253−254 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.75 (d, J = 7.2 Hz, 3H), 7.61 (d, J = 8.0 Hz, 2H), 7.51 (d, J = 8.8 Hz, 2H), 7.25 (d, J = 4.4 Hz, 2H), 7.13 (d, J = 8.0 Hz, 1H), 6.96 (d, J = 8.0 Hz, 2H), 6.76 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 159.0, 146.7, 137.7, 134.4, 132.7, 132.5, 132.3, 132.0, 128.1, 125.5, 120.9, 120.8, 120.3, 119.7, 116.7, 116.5; IR (KBr, ν, cm^{-1}) 3042, 1655, 1623, 1560, 1443, 1297, 1206, 1072, 1010, 840, 829; HRMS (APCI-TOF) m/z calcd for $C_{20}H_{13}Br_2ClN_3$, 489.9145 $[M + H]^+$; found 489.9143.

*(E)-N-(4-Bromophenyl)-3-((4-bromophenyl)imino)-3H-pyrrolo-[3,2-c]pyridin-2-amine (**3t**).* Red solid, 278 mg, yield 61%; mp 203−204 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 8.42 (d, J = 5.2 Hz, 1H), 8.13 (s, 1H), 7.97 (s, 1H), 7.79 (d, J = 8.0 Hz, 2H), 7.62−7.61 (m, 1H), 7.60−7.59 (m, 1H), 7.53 (d, J = 8.8 Hz, 2H), 7.16 (d, J = 4.8 Hz, 1H), 7.00−6.99 (m, 1H), 6.98−6.97 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 169.5, 159.4, 158.7, 155.5, 147.3, 145.0, 136.6, 132.9, 132.4, 121.5, 121.0, 117.5, 116.7, 116.2, 114.9; IR (KBr, ν, cm^{-1}) 3038, 1591, 1556, 1448, 1331, 1267, 1233, 1164, 1072, 1009, 914, 835, 813; HRMS (APCI-TOF) m/z calcd for $C_{19}H_{13}Br_2N_4$, 456.9487 $[M + H]^+$; found 456.9463.

*(E)-N-(4-Methoxyphenyl)-3-((4-methoxyphenyl)imino)-3H-indol-2-amine (**3u**).* Red solid, 244 mg, yield 68%; mp 173−174 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.78 (d, J = 8.0 Hz, 3H), 7.24 (d, J = 7.2 Hz, 1H), 7.18 (d, J = 7.6 Hz, 1H), 7.10−7.07 (m, 2H), 7.00−6.99 (m, 1H), 6.98−6.93 (m, 4H), 3.88 (s, 3H), 3.82 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 159.3, 158.0, 155.9, 141.6, 134.3, 125.2, 122.3, 121.1, 120.7, 119.6, 118.9, 116.4, 114.8, 114.7, 114.6, 114.5, 55.5, 55.5; IR (KBr, ν, cm^{-1}) 1644, 1599, 1564, 1501, 1441, 1294, 1238, 1202, 1025, 837,757; HRMS (APCI-TOF) m/z calcd for $C_{22}H_{20}N_3O_2$, 358.1556 $[M + H]^+$; found 358.1557.

*(E)-2-((4-Methoxyphenyl)amino)-3-((4-methoxyphenyl)imino)-3H-indole-5-carbonitrile (**3v**).* Red solid, 287 mg, yield 75%; mp 241−243 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.80 (d, J = 8.4 Hz, 3H), 7.55 (d, J = 7.2 Hz, 1H), 7.34 (s, 1H), 7.29 (s, 1H), 7.11 (d, J = 8.4 Hz, 2H), 7.02 (d, J = 8.4 Hz, 4H), 6.97 (d, J = 8.0 Hz, 1H), 3.91 (s, 3H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 159.5, 158.9, 156.6, 156.5, 140.5, 140.5, 138.4, 128.3, 121.4, 5121.2, 120.2, 119.4, 119.4, 119.2, 114.9, 114.6, 104.8, 55.6, 55.6; IR (KBr, ν, cm^{-1}) 2964, 2218, 1601, 1562, 1504, 1455, 1262, 1191, 1095, 1025, 823, 800; HRMS (APCI-TOF) m/z calcd for $C_{23}H_{19}N_4O_2$, 383.1503 $[M + H]^+$; found 383.1486.

*Example for the Synthesis of **7a**.* 2-Acetylphenyl iodide (**4a**, 1.0 mmol, 264.2 mg), $Pd(OAc)_2$ (10 mol %, 22.8 mg), P(n-Bu)$_3$ (20 mol %, 40.5 mg), and t-BuOK (2.0 equiv, 224.8 mg) were added into a 25 mL Schlenk tube under N_2 conditions. *tert*-Butyl isocyanide (**2a**, 1.5 mmol, 124.5 mg) and 1.4-dioxane (5 mL) were then successively added. Subsequently, the reaction vial was stirred at 80 °C until complete consumption of starting material as monitored by TLC. After the reaction finished, the reaction mixture was extracted with ethyl acetate and water. The combined organic extracts were dried over magnesium sulfate anhydrous and concentrated in vacuum. The resulting residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate) to afford the desired product **5a**.

*3-(tert-Butylamino)-1H-inden-1-one (**5a**).* Yellow solid, 145 mg, yield 72%; mp 140−142 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.48−7.46 (m, 1H), 7.38−7.32 (m, 2H), 7.14 (d, J = 6.0 Hz, 1H), 5.44 (s, 1H), 5.07 (s, 1H), 1.49 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 193.9, 161.5, 139.4, 134.9, 130.3, 130.2, 120.4, 115.8, 94.01, 53.1, 28.9; IR (KBr, ν, cm^{-1}) 3732, 3416, 3274, 2977, 1653, 1551, 1472, 1372, 1209, 119, 1097, 763; HRMS (APCI-TOF) m/z calcd for $C_{13}H_{16}NO$, 202.1232 $[M + H]^+$; found 202.1248.

*3-((2,4,4-Trimethylpentan-2-yl)amino)-1H-inden-1-one (**5b**).* Yellow solid, 111 mg, yield 43%; mp 160−162 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.48−7.46 (m, 1H), 7.38−7.32 (m, 2H), 7.11−7.09 (m, 1H), 5.44 (s, 1H), 5.08 (s, 1H), 1.80 (s, 2H), 1.53 (s, 6H), 1.05 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 193.8, 161.1, 139.5, 134.9, 130.3, 130.2, 120.4, 115.5, 94.1, 57.12, 51.9, 31.8, 31.4, 29.3; IR (KBr, ν, cm^{-1}): 3552, 3414, 2944, 1638, 1616, 1552, 1097, 626; HRMS (APCI-TOF) m/z calcd for $C_{17}H_{24}NO$, 258.1858 $[M + H]^+$; found 258.1879.

*3-(Adamantan-1-ylamino)-1H-inden-1-one (**5c**).* Yellow solid, 170 mg, yield 61%; mp 243−244 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.47−7.45 (m, 1H), 7.37−7.33 (m, 2H), 7.15−7.13 (m, 1H), 5.37 (s, 1H), 5.13 (s, 1H), 2.20 (s, 3H), 2.06−2.08 (m, 5H), 1.78−1.69 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 193.8, 160.9, 139.5, 134.9, 130.3, 130.2, 120.3, 115.8, 94.4, 53.7, 41.7, 36.1, 29.4; IR (KBr, ν, cm^{-1}) 3552, 3414, 3043, 2912, 1650, 1613, 1565, 1082, 745; HRMS (APCI-TOF) m/z calcd for $C_{19}H_{22}NO$, 280.1701 $[M + H]^+$; found 280.1707.

*3-(tert-Butylamino)-6-fluoro-1H-inden-1-one (**5d**).* Yellow solid, 120 mg, yield 55%; mp 240−241 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.29−7.17 (m, 1H), 7.08−7.05 (m, 1H), 7.01−6.96 (m, 1H), 5.37 (s, 1H), 5.11 (s, 1H), 1.50 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 191.5, 164.8 (J_{CF} = 249.3 Hz), 161.2, 138.1 (J_{CF} = 7.4 Hz), 134.5 (J_{CF} = 3.0 Hz), 116.9 (J_{CF} = 8.5 Hz), 115.6 (J_{CF} = 23.5 Hz), 109.3 (J_{CF} = 2.8 Hz), 94.6, 53.34, 28.9; IR (KBr, ν, cm^{-1}) 3269, 3060, 2979, 1665, 1619, 1474, 1216, 1112, 821, 731, 629; HRMS (APCI-TOF) m/z calcd for $C_{13}H_{15}FNO$, 220.1138 $[M + H]^+$; found 220.1138.

*6-Fluoro-3-((2,4,4-trimethylpentan-2-yl)amino)-1H-inden-1-one (**5e**).* Yellow solid, 63 mg, yield 23%; mp 173−174 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.18−7.14 (m, 2H), 6.98−6.94 (m, 1H), 5.78 (s, H), 5.09 (s, 1H), 1.79 (s, 2H), 1.52 (s, 6H), 1.03 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 191.5, 166.0, 162.3 (J_{CF} = 237.1 Hz), 138.2 (J_{CF} = 7.5 Hz), 134.6 (J_{CF} = 3.0 Hz), 117.0 (J_{CF} = 8.0 HZ), 115.6 (J_{CF} = 23.4 Hz), 109.2 (J_{CF} = 24.4 Hz), 94.5, 57.4, 51.8, 31.8, 31.4, 29.3; IR (KBr, ν, cm^{-1}): 3414, 3274, 3062, 1947, 1654, 1617, 1555, 1477, 1180, 875, 830, 734, 662; HRMS (APCI-TOF) m/z calcd for $C_{17}H_{23}FNO$, 276.1764 $[M + H]^+$; found 276.1804.

*3-(Cyclohexylamino)-6-fluoro-1H-inden-1-one (**5f**).* Yellow solid, 71 mg, yield 29%; mp 191−194 °C; ^{1}H NMR (400 MHz, $CDCl_3$; δ, ppm) 7.28−7.24 (m, 1H), 7.16−7.13 (m, 1H), 6.98−6.93 (m, 1H), 6.20 (d, J = 7.1 Hz, 1H), 4.95 (s, 1H), 3.41−3.39 (m, 1H), 2.11 (s, 2H), 1.84−1.82 (m, 2H), 1.44−1.37 (m, 4H), 1.27 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$; δ, ppm) 191.06, 164.9 (J_{CF} =230.0 Hz), 163.57, 139.5 (J_{CF} = 7.4 Hz), 133.5(J_{CF} = 3.0 Hz), 117.8(J_{CF} = 8.5 Hz), 115.6 (J_{CF} = 23.4 Hz), 109. (J_{CF} = 24.4 Hz), 92.2, 54.3, 32.6, 25.3, 24.7; IR (KBr, ν, cm^{-1}):3552, 3480, 3413, 3236, 2931, 1637, 1617, 1567, 1261, 907, 619; HRMS (APCI-TOF) m/z calcd for $C_{15}H_{17}FNO$, 246.1294 $[M + H]^+$; found 246.1286.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for all pure products; X-ray crystal data (CIF) for **3a**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00727.

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AUTHOR INFORMATION

Corresponding Authors

*Fax 86-516-83500065. E-mail wjhao@jsnu.edu.cn.
*Fax 86-516-83500065. E-mail laotu@jsnu.edu.cn.
*Fax 86-516-83500065. E-mail jiangchem@jsnu.edu.cn.

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For selected recent reviews on indole-containing natural products, see: (a) Ishikura, M.; Abe, T.; Choshi, T.; Hibino, S. *Nat. Prod. Rep.* **2013**, *30*, 694. (b) Huguchi, K.; Kawasaki, T. *Nat. Prod. Rep.* **2007**, *24*, 843. (c) O'Connor, S. E.; Maresh, J. *Nat. Prod. Rep.* **2006**, *23*, 532. (d) Kawasaki, T.; Huguchi, K. *Nat. Prod. Rep.* **2005**, *22*, 761. (e) Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2004**, *21*, 278. (f) Lounasmaa, M.; Tolvanen, N. *Nat. Prod. Rep.* **2000**, *17*, 175.

(2) For some selected recent examples of biological activities of indoles, see: (a) Sundberg, R. J. *Indoles*; Academic Press: London, 1996. (b) Petit, S.; Duroc, Y.; Larue, V.; Giglione, C.; Leon, C.; Soulama, C.; Denis, A.; Dardel, F.; Meinnel, T.; Artaud, I. *ChemMedChem.* **2009**, *4*, 26. (c) Sharma, V.; Kumar, P.; Pathak, D. *J. Heterocycl. Chem.* **2010**, *47*, 491. (d) Kochanowska-Karamyan, A. J.; Hamann, M. T. *Chem. Rev.* **2010**, *110*, 4489. (e) Patil, S. A.; Patil, R.; Miller, D. D. *Curr. Med. Chem.* **2011**, *18*, 615. (f) Biswal, S.; Sethy, S.; Kumar, H. K. S.; Banerjee, M. *Asian J. Pharm. Clin. Res.* **2012**, *5*, 1. (g) Ali, N. A.; Dar, B. A.; Pradhan, V.; Farooqui, M. *Mini Rev. Med. Chem.* **2012**, *12*, 1.

(3) For some recent reviews on the construction of the indole skeleton, see: (a) Inman, M.; Moody, C. J. *Chem. Sci.* **2013**, *4*, 29. (b) Shi, Z.; Glorius, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 9220. (c) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2011**, *111*, PR215. (d) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875. (e) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (f) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (g) Platon, M.; Amardeil, R.; Djakovitchb, L.; Hierso, J.-C. *Chem. Soc. Rev.* **2012**, *41*, 3929. (h) Shiri, M. *Chem. Rev.* **2012**, *112*, 3508.

(4) (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689. (b) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652. (c) Kurti, L.; Czako, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier, Inc.: New York, 2005; pp 260. (d) Leogane, O.; Lebel, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 350. (e) Liang, J.; Hu, W.; Tao, P.; Jia, Y. *J. Org. Chem.* **2013**, *78*, 5810. (f) Shan, D.; Gao, Y.; Jia, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 4902. (g) Batail, N.; Bendjeriou, A.; Lomberget, T.; Barret, R.; Dufaud, V.; Djakovitch, L. *Adv. Synth. Catal.* **2009**, *351*, 2055. (h) Shan, D.; Gao, Y.; Jia, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 4902.

(5) Whitby, R. J.; Saluste, C. G.; Furber, M. *Org. Biomol. Chem.* **2004**, *2*, 1974.

(6) Cai, Z.-J.; Wang, S.-Y.; Ji, S.-J. *Org. Lett.* **2013**, *15*, 5226.

(7) (a) Vlaar, T.; Cioc, R. C.; Mampuys, P.; Maes, B. U. W.; Orru, R. V. A.; Ruijter, E. *Angew. Chem., Int. Ed.* **2012**, *51*, 13058. (b) Odabachian, Y.; Tong, S.; Wang, Q.; Wang, M.-X.; Zhu, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 10878. (c) Liu, B.; Yin, M.; Gao, H.; Wu, W.; Jiang, H. *J. Org. Chem.* **2013**, *78*, 3009. (d) Qiu, G.; Ding, Q.; Wu, J. *Chem. Soc. Rev.* **2013**, *42*, 5257.

(8) (a) Liu, B.; Gao, H.; Yu, Y.; Wu, W.; Jiang, H. *J. Org. Chem.* **2013**, *78*, 10319. (b) Boissarie, P. J.; Hamilton, Z.; Lang, E. S.; Murphy, J. A.; Suckling, C. J. *Org. Lett.* **2011**, *13*, 6256. (c) Vlaar, T.; Ruijter, E.; Znabet, A.; Janssen, E.; de Kanter, F. J. J.; Maes, B. U. W.; Orru, R. V. A. *Org. Lett.* **2011**, *13*, 6496. (d) Baelen, G. V.; Kuijer, S.; Rycek, L.; Sergeyev, S.; Janssen, E.; de Kanter, F. J. J.; Maes, B. U. W.; Ruijter, E.; Orru, R. V. A. *Chem.—Eur. J.* **2011**, *17*, 15039. (e) Miura, T.; Nishida, Y.; Morimoto, M.; Yamauchi, M.; Murakami, M. *Org. Lett.* **2011**, *13*, 1429. (f) Liu, G.; Liu, H.; Qiu, G.; Pu, S.; Wu, J. *Chem. Commun.* **2012**, *48*, 7049.

(9) (a) Jiang, B.; Ye, Q.; Fan, W.; Wang, S.-L.; Tu, S.-J.; Li, G. *Chem. Commun.* **2014**, *50*, 6108. (b) Jiang, B.; Fan, W.; Sun, M.-Y.; Ye, Q.; Wang, S.-L.; Tu, S.-J.; Li, G. *J. Org. Chem.* **2014**, *79*, 5258. (c) Fan, W.; Ye, Q.; Xu, H.-W.; Jiang, B.; Wang, S.-L.; Tu, S.-J. *Org. Lett.* **2013**, *15*, 2258. (d) Jiang, B.; Wang, X.; Xu, H.-W.; Tu, M.-S.; Tu, S.-J.; Li, G. *Org. Lett.* **2013**, *15*, 1540.

(10) For some recent reviews on domino reactions, see: (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Jiang, B.; Rajale, T.; Wever, W.; Tu, S.-J.; Li, G. *Chem.-Asian J.* **2010**, *5*, 2318. (c) Jiang, B.; Tu, S.-J. *Chimia* **2011**, *65*, 925. (d) Tan, C. K.; Yeung, Y.-Y. *Chem. Commun.* **2013**, *49*, 7985. (e) Guo, X.; Hu, W. *Acc. Chem. Res.* **2013**, *46*, 2427. (f) Pellissier, H. *Chem. Rev.* **2013**, *113*, 442. (g) Zhang, D.-H.; Tang, X.-Y.; Shi, M. *Acc. Chem. Res.* **2014**, *47*, 913.

(11) For some recent reviews on isocyanide-based domino reactions, see: (a) Chakrabarty, S.; Choudhary, S.; Doshi, A.; Liu, F.-Q.; Mohan, R.; Ravindra, M. P.; Shah, D.; Yang, X.; Fleming, F. F. *Adv. Synth. Catal.* **2014**, *356*, 2135. (b) Koopmanschap, G.; Ruijter, E.; Orru, R. V. A. *Beilstein J. Org. Chem.* **2014**, *10*, 544. (c) Cioc, R. C.; Ruijter, E.; Orru, R. V. A. *Green Chem.* **2014**, *16*, 2958. (d) *Isocyanide Chemistry*; Nenajdenko, V. G., Ed.; Wiley-VCH: Weinheim, Germany, 2012. (e) van Berkel, S. S.; Boegels, B. G. M.; Wijdeven, M. A.; Westermann, B.; Rutjes, F. P. J. T. *Eur. J. Org. Chem.* **2012**, 3543.

(12) (a) Yang, Z.; Hao, W.-J.; Xu, H.-W.; Wang, S.-L.; Jiang, B.; Li, G.; Tu, S.-J. *J. Org. Chem.* **2015**, *80*, 2781. (b) Campos, P. J.; Arranz, J.; Rodriguez, M. A. *Tetrahedron Lett.* **1997**, *38*, 8397. (c) Zhao, F.-J.; Sun, M.-Y.; Dang, Y.-J.; Meng, X.-Y.; Jiang, B.; Hao, W.-J.; Tu, S.-J. *Tetrahedron* **2014**, *70*, 9628. (d) Jiang, B.; Liang, Y.-B.; Kong, L.-F.; Tu, X.-J.; Hao, W.-J.; Ye, Q.; Tu, S.-J. *RSC Adv.* **2014**, *4*, 54480. (e) Shi, Q.-Q.; Fu, L.-P.; Shi, Y.; Ding, H.-Q.; Luo, J.-H.; Jiang, B.; Tu, S.-J. *Tetrahedron Lett.* **2013**, *54*, 3176. (f) Naeimi, H.; Rashid, Z.; Zarnanib, A. H.; Ghahremanzadeh, R. *New J. Chem.* **2014**, *38*, 348.

(13) (a) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534. (b) Lang, S. *Chem. Soc. Rev.* **2013**, *42*, 4867.

(14) (a) Thirupathi, N.; Hari Babu, M.; Dwivedi, V.; Kant, R.; Sridhar Reddy, M. *Org. Lett.* **2014**, *16*, 2908. (b) Tang, T.; Fei, X.-D.; Ge, Z.-Y.; Chen, Z.; Zhu, Y.-M.; Ji, S.-J. *J. Org. Chem.* **2013**, *78*, 3170. (c) Vlaar, T.; Mampuys, P.; Helliwell, M.; Maes, B. U. W.; Orru, R. V. A.; Ruijter, E. *J. Org. Chem.* **2013**, *78*, 6735. (d) Vlaar, T.; Maes, B. U. W.; Ruijter, E.; Orru, R. V. A. *Angew. Chem., Int. Ed.* **2013**, *52*, 7084. (e) Vlaar, T.; Ruijter, E.; Znabet, A.; Janssen, E.; de Kanter, F. J. J.; Maes, B. U. W.; Orru, R. V. A. *Org. Lett.* **2011**, *13*, 6496.

(15) (a) Hu, Z.; Liang, D.; Zhao, J.; Huang, J.; Zhu, Q. *Chem. Commun.* **2012**, *48*, 7371. (b) Tyagi, V.; Khan, S.; Giri, A.; Gauniyal, H. M.; Sridhar, B.; Chauhan, P. M. S. *Org. Lett.* **2012**, *14*, 3126. (c) Qiu, G.; Liu, G.; Pu, S.; Wu, J. *Chem. Commun.* **2012**, *48*, 2903.

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