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Synthesis of 2-Aminopyridines via a Base-Promoted Cascade Reaction of *N*-Propargylic *β*-Enaminones with Formamides

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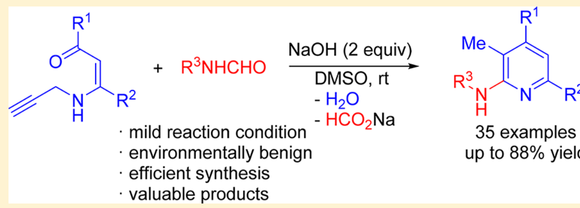
Supporting Information

ABSTRACT: *N*-Substituted formamides as nucleophiles react with in situ-generated 1,4-oxazepines from *N*-propargylic *β*-enaminones followed by spontaneous *N*-deformylation to deliver densely substituted 2-aminopyridines in good yields (31−88%). The formyl group is found to be a superior traceless activating group of free amines and would ultimately be removed in situ. This reaction proceeds smoothly at room temperature, in the presence of NaOH as sole additive, without protection from the atmosphere and generates H_2O and sodium formate as byproducts.



INTRODUCTION

The 2-aminopyridine moiety represents an important motif in pharmaceuticals and natural products (Figure 1)[1] as well as ligands in organic synthesis and functional materials.[2] Intense efforts have been devoted to developing various methods for the synthesis of 2-aminopyridines and their derivatives. Transition metal-catalyzed amination of aryl halides, typically including palladium-catalyzed Buchwald−Hartwig amination[3,4] and copper-catalyzed Ullmann-type amination,[5] provide powerful protocols to build such scores (Scheme 1, a). However, sophisticated ligands are always required, and aliphatic amines are not well tolerated in those amination reactions.[6] Ruthenium-[7] and copper-[8] catalyzed cyclization have also been developed for the divergent synthesis of 2-aminopyridines (Scheme 1, b). An important additional drawback of the these approaches has to do with the toxicity of transition metals in biological contexts, which seriously limit their applications in biological and medicinal research. Although the 2-aminopyridines could be synthesized by the traditional Chichibabin reaction from sodium amide and pyridines,[9] the nucleophilic addition,[10] and the 1,3-dipolar cycloaddition reaction of pyridine derivatives,[11] the functionalized pyridine cores as starting materials are always required. Consequently, developing efficient access to 2-aminopyridines from readily available materials under transition metal-free conditions is of great significance.

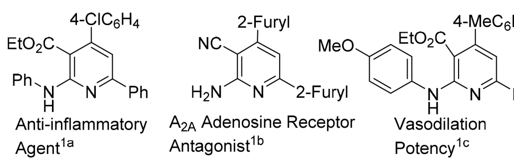
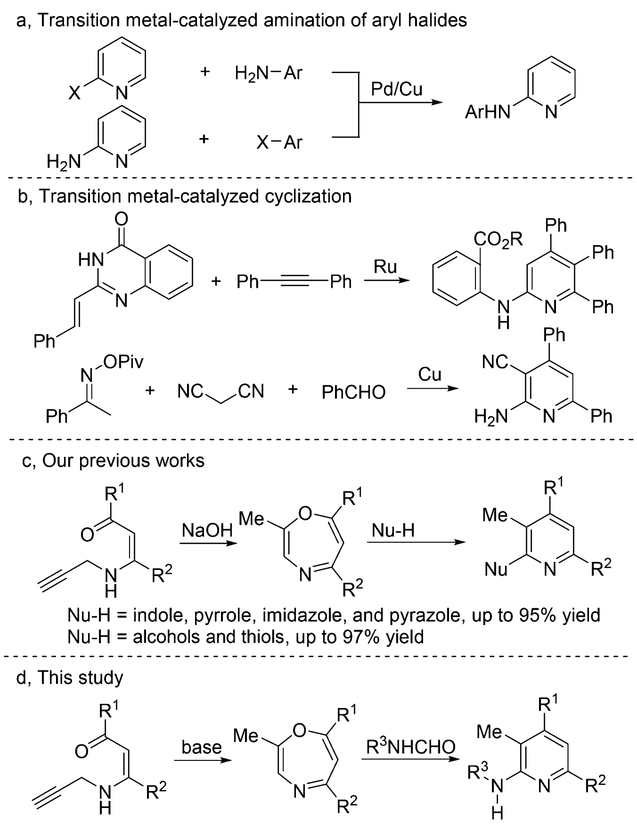


Figure 1. Selected biologically active compounds containing 2-aminopyridines.

Scheme 1. Reported and Present Synthetic Strategy for the Synthesis of 2-Aminopyridines



During our ongoing studies on the synthesis of heterocyclic compounds,[12] we have recently documented that a variety of

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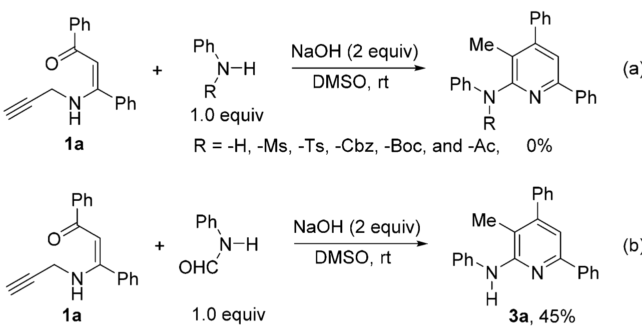
N-H heteroarenes, alcohols, and thiols could be used as nucleophiles for the capture of 1,4-oxazepine intermediates leading to *N*-substituted heteroarenes (Scheme 1, c)[12a−c] As research continues, we disclose herein a simple and highly efficient cascade approach to multisubstituted 2-aminopyridines from *N*-propargylic *β*-enaminones[13] and formamides (Scheme 1, d). In this scenario, the formyl group would function as a traceless activating group to facilitate nucleophilic addition of formamides to in situ-generated 1,4-oxazepines and would spontaneously be released to produce 2-aminopyridines. In contrast to previous work,[3−8] the advantages of our reported reaction includes (i) mild reaction conditions (room temperature and using NaOH as the only additive), (ii) environmentally friendly (transition metal-free with H_2O and sodium formate as the byproducts), and (iii) high efficiency (cascade reaction in one-pot mode).

At the outset of our studies, free alkyl/aryl amines were used to react with *N*-propargylic *β*-enaminone **1a**; however, no desired 2-aminopyridine products were observed, probably because of the considerably lower nucleophilicity of free amines. Considering that amides could be deprotonated under strongly basic conditions, their conjugate bases may serve as nucleophiles. Thus, a variety of activating groups, including -Ms, -Ts, -Cbz, -Boc, and -Ac, were screened, but still no desired products were formed (Scheme 2, a). Back and co-

Scheme 2. Screening Activating Groups of Aniline for the Synthesis of 2-(Phenylamino)pyridines

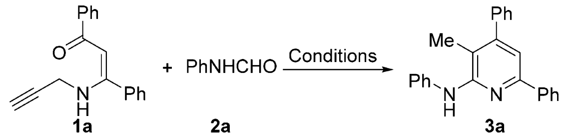


workers reported that *N*-formyl anilines were more nucleophilic analogues than anilines under basic conditions for the conjugate addition to acetylenic sulfones.[14] When *N*-formyl aniline was subjected to react with **1a**, it was to our delight that the unpredictable *N*-deformylation product **3a** was obtained in 45% isolated yield (Scheme 2, b).

■ RESULTS AND DISCUSSION

(*Z*)-1,3-Diphenyl-3-(prop-2-yn-1-ylamino)prop-2-en-1-one **1a** and formanilide **2a** were chosen as the model substrates for the optimization of the reaction conditions, and the results are summarized in Table 1. NaOH, KOH, and LiOH were found to be efficient bases for this cascade reaction, among which NaOH gave the best result (Table 1, entries 1−3). The lower yields were encountered for other stronger bases (entries 4−6). Subsequently, various solvents were investigated in the presence of 2 equiv of NaOH as the base (entries 7−9). No better result was obtained than that of DMSO, and 70% isolated yield was obtained when the loading of **2a** was decreased to 1.5 equiv (entry 10). Further raising the reaction temperature could improve the yields slightly (entry 13, 14). Therefore, the optimized reaction conditions were found to

Table 1. Screening of the Reaction Conditions[a]



entry	base	solvent[b]	temp (°C)	yield (%)[c]
1	NaOH	DMSO	rt	70
2	KOH	DMSO	rt	67
3	LiOH	DMSO	rt	69
4	KO*t*Bu	DMSO	rt	56
5	NaO*t*Bu	DMSO	rt	53
6	Cs_2CO_3	DMSO	rt	14
7	NaOH	DMF	rt	50
8	NaOH	NMP	rt	49
9	NaOH	CH_3CN	rt	0
10[d]	NaOH	DMSO	rt	75 (70)
11[e]	NaOH	DMSO	rt	48
12[f]	NaOH	DMSO	rt	68
13	NaOH	DMSO	50	76 (70)
14	NaOH	DMSO	80	79 (72)

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), base (0.4 mmol), and solvent (1 mL) at room temperature under air atmosphere. [b]DMSO = dimethyl sulfoxide, DMF = *N*,*N*-dimethylformamide, NMP = *N*-methyl-2-pyrrolidone. [c]Yields were determined by GC analysis with dodecane as internal standard; isolated yields in parentheses. [d]Using 1.5 equiv of **2a**. [e]Using 1.2 equiv of **2a**. [f]Using 1.5 equiv of NaOH.

entail the use of **1a** and **2a** in a molar ratio of 1:1.5 with NaOH (2 equiv) as the base at room temperature under air atmosphere (entry 10).

On the basis of the optimized conditions, the generality of this reaction was investigated. As shown in Scheme 3, a variety of substituted formanilides ran smoothly, affording the corresponding products in moderate to good yields (**3a**−**k**, yields 45−77%). The structure of **3a** was confirmed by single-crystal X-ray diffraction analysis. At first, formanilides with electron-donating groups (Me, OMe) were tested and smoothly converted to the desired products (**3b**−**e**). The *o*-methyl-substituted substrates (**3b**, **3d**) led to lower yields than *p*-methyl-substituted substrate (**3c**), implying that the steric hindrance of the amides had an obvious effect on the reaction. Formanilides bearing halogen groups (F, Cl, Br, I) at the meta or para position of the aryl ring afforded the desired products in moderate yields (**3f**−**k**, yields 45−72%); thus, the corresponding products are suitable for further functionalization. Remarkably, 1-naphthalenyl amides (**3l**) and heterocyclic aromatic amides (**3m**, **3n**) could be compatible with this procedure, providing the desired products in 51, 31, and 66% yields, respectively. In addition, various aliphatic formamides, including terminal alkene and alkyne, furnished the corresponding 2-aminopyridines in moderate yields (**3o**−**s**, yields 45−63%).

Furthermore, the scope of *N*-propargylic *β*-enaminones was also explored (Scheme 4). The steric hindrance of the *N*-propargylic *β*-enaminones also had an obvious effect on the reaction (**4a**, yield 56%). In general, enaminone components bearing electron-donating substituents (**4b**−**e** and **4o**, yields 42−73%) tended to give slightly lower yields than those bearing electron-withdrawing substituents (**4f**−**k**, **4n**, yields 72−88%). Remarkably, when R^1 was 2-thienyl and 2-furyl, the

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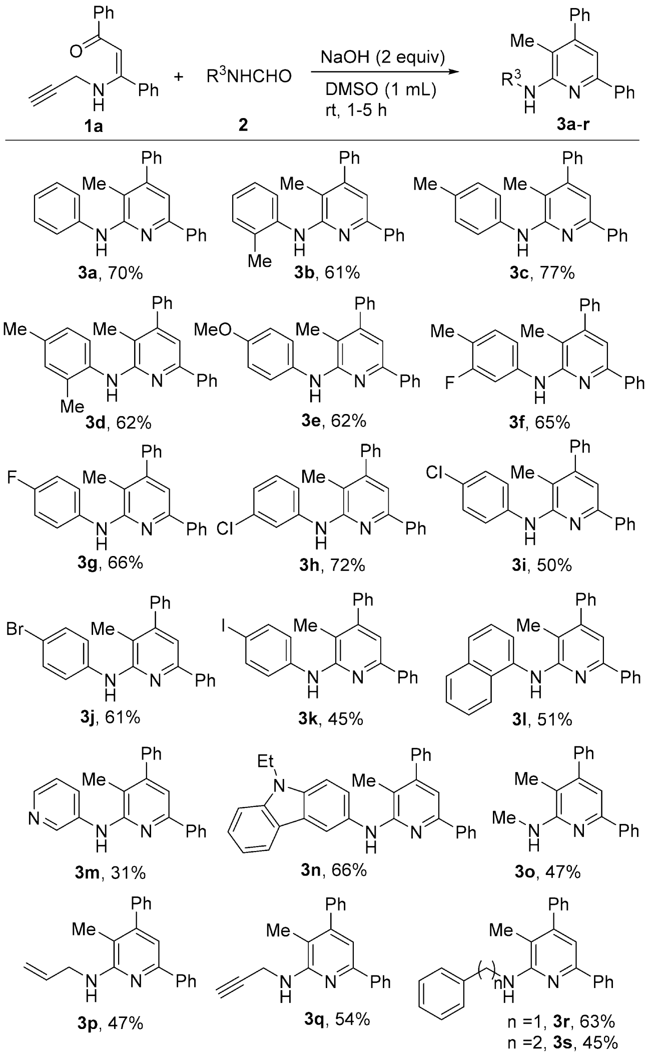
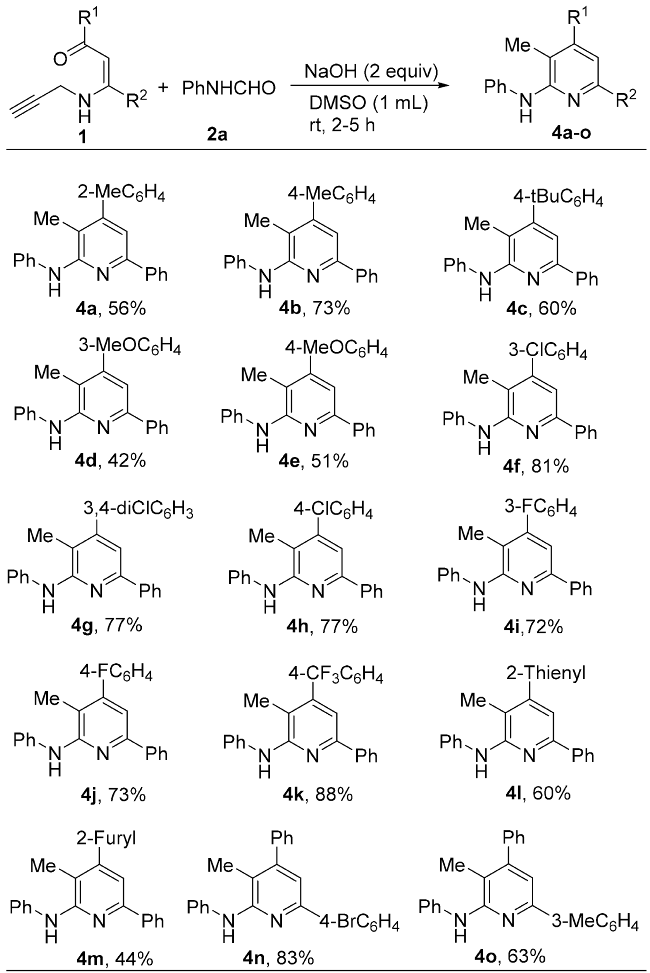
Scheme 3. Scope of Formamides[a]



[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.3 mmol), and NaOH (2 equiv) in DMSO (1 mL) at room temperature under air atmosphere. Yields based on **1a**.

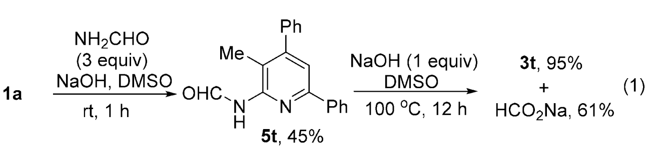
Scheme 4. Scope of *N*-Propargylic β-Enaminones[a]



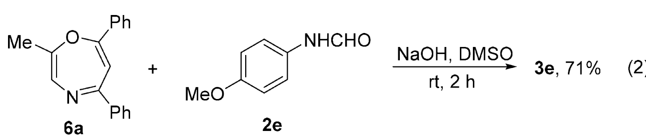
[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.3 mmol), and NaOH (2 equiv) in DMSO (1 mL) at room temperature under air atmosphere. Yields based on **1**.

desired products **4l** and **4m** were obtained in 60 and 44% yields, respectively.

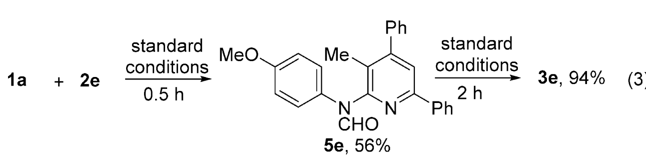
When **1a** was treated with methanamide under the standard reaction conditions, interestingly, *N*-(3-methyl-4,6-diphenylpyridin-2-yl) formamide **5t** was obtained instead of the decarboxylative product **3t**. Then, **5t** was treated with 1 equiv of NaOH at 100 °C for 12 h, and **3t** and sodium formate were obtained in 95 and 61% yields, respectively. Those results indicated that the intermediates **5** could proceed through a base-promoted decarbonylation to produce sodium formate (eq 1). Our previous work[12a−c] had indicated that the active



intermediate 1,4-oxazepines were generated from base-promoted 7-*exo-dig* cyclization of *N*-propargylic β-enaminones, which could be used as pyridylation reagents of various *N*-heteroarenes, alcohols, and thiols. Then, the intermediate 1,4-oxazepine **6a** was treated with formamide **2e** under the standard reaction, and **3e** was obtained in 71% yield (eq 2). For



the reaction mechanism to be clarified further, the reaction of **1a** with *N*-(4-methoxyphenyl) formamide **2e** was quenched with water after stirring at room temperature for 0.5 h, and the formamide intermediate **5e** was isolated in 56% yield, which could be further transformed to **3e** under standard conditions for 2 h (eq 3).



On the basis of the results presented above and our previous research,[12a] a possible mechanism is proposed (Scheme 5).

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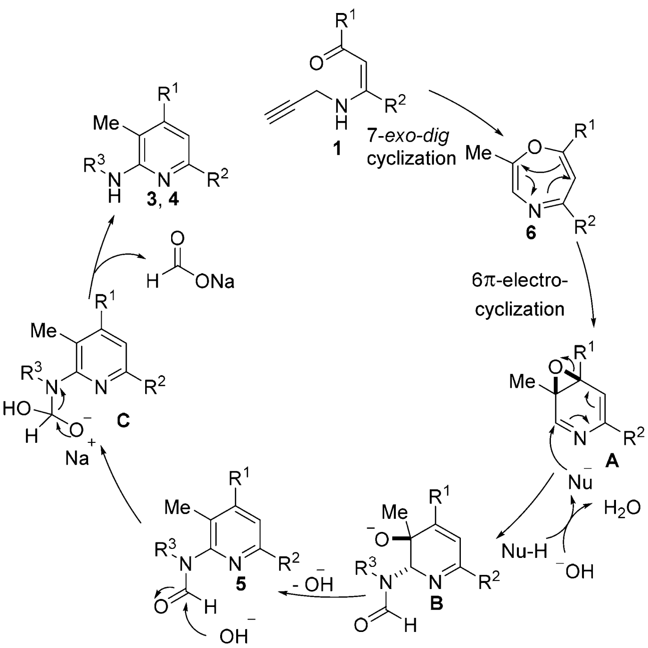
Scheme 5. Plausible Mechanism for the Synthesis of 2-Aminopyridines



Initially, the active intermediate 1,4-oxazepine **6** was formed by base-promoted cyclization from **1**. Subsequently, **6** was isomerized to provide epoxide intermediate **A** undergoing 6π-electrocyclization. Then, nucleophilic addition of formamide to epoxide **A** generated 2,3-dihydropyridine intermediates **B**, which subsequently aromatized to intermediate **5**. Finally, *N*-deformylation occurred, leading to the final 2-aminopyridine products **3** and **4**.

■ CONCLUSIONS

In summary, we have developed a concise and efficient protocol for the synthesis of a variety of 2-aminopyridine derivatives from *N*-propargylic β-enaminones at room temperature. In this reaction, the formyl group was used as a traceless activating group of amines, which would ultimately be released without any other process followed.

■ EXPERIMENTAL SECTION

General Information. All reagents were used directly without further purification. All melting points were determined on a Beijing Science Instrument Dianguang Instrument Factory XT4B melting point apparatus and were uncorrected. ^{1}H and ^{13}C NMR spectra were measured on a 400 MHz Bruker spectrometer (^{1}H 400 MHz, ^{13}C 100 MHz) using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as the internal standard at room temperature. HRMS-APCI spectra were obtained on an Agilent 6450 Q-TOF spectrometer. IR data were recorded on a Nicolet iS10 spectrometer. The products listed below were determined by ^{1}H and ^{13}C NMR. PE is petroleum ether (60−90 °C). 2-Methyl-5,7-diphenyl-1,4-oxazepine **6a** was prepared according to protocols in the literature.[12a,b]

Preparation of *N*-Propargylic β-Enaminones 1.[13c] A mixture of propargylamine (1.1 g, 20 mmol), propynones (20 mmol), and CH_3OH (50 mL) was stirred at room temperature under air overnight. After propynones were completely exhausted (as monitored by TLC), the solvent was evaporated, and the residue was purified by chromatography (silica gel, 5% EtOAc in PE) to give **1**.

Preparation of Formamides 2.[15] A mixture of amide or aniline (10 mmol), methanamide (10 mmol), and L-proline (115 mg, 1 mmol) was stirred in sealed tubes at the indicated temperature for the indicated reaction time (see ref 15). After being cooled to room temperature, 20 mL of water was added and extracted with DCM (20 mL × 3). After removal of the solvent, the crude reaction mixture was purified by recrystallization or chromatography.

Preparation of 3-Methyl-4,6-diphenylpyridin-2-amine 3t and Sodium Formate. A mixture of *N*-(3-methyl-4,6-diphenylpyridin-2-yl)formamide **5t** (144 mg, 0.5 mmol) and NaOH (20 mg, 0.5 mmol) in DMSO (1 mL) was stirred at 100 °C for 12 h. Then, DCM (10 mL) was poured into the reaction mixture, and the resulting solution was stirred for an additional 5 min. Subsequently, the mixture was allowed to cool to 0 °C overnight, and the resulting white solid was filtered off, washed with DCM, and dried in vacuo to give sodium formate (21 mg, 61%). The organic residue was concentrated and purified by chromatography (silica gel, 5% EtOAc in PE) to give **3t** (123 mg, 95%).

Sodium Formate. ^{1}H NMR (400 MHz, D_2O) δ 8.3 (s, 1H); ^{13}C NMR (100 MHz, D_2O) δ 171.1.

Preparation of *N*-(4-Methoxyphenyl)-3-methyl-4,6-diphenylpyridin-2-amine 3e. A mixture of 2-methyl-5,7-diphenyl-1,4-oxazepine **6a** (52 mg, 0.2 mmol), *N*-(4-methoxyphenyl)formamide **2e** (45 mg, 0.3 mmol), and NaOH (16 mg, 0.4 mmol) in DMSO (1 mL) was stirred at room temperature for 2 h. Then, the reaction was quenched with H_2O (4 mL) and extracted with EtOAc (5 mL × 3). The combined EtOAc extracts were dried over Na_2SO_4 and concentrated. Then, solvent was evaporated, and the residue was purified by chromatography (silica gel, 5% EtOAc in PE) to give **3e** (52 mg, 71%).

Preparation of Multisubstituted 2-Aminopyridines 3 and 4. A mixture of *N*-propargylic β-enaminones **1** (0.2 mmol), formamides **2** (0.3 mmol), and NaOH (16 mg, 0.4 mmol) in DMSO (1 mL) was stirred at room temperature. After *N*-propargylic β-enaminones **1** was exhausted completely (monitored by TLC), the reaction was quenched with H_2O (4 mL) and extracted with EtOAc (5 mL × 3). The combined EtOAc extracts were dried over Na_2SO_4 and concentrated. Then, the solvent was evaporated, and the residue was purified by chromatography (silica gel, 5% EtOAc in PE).

*3-Methyl-N,4,6-triphenylpyridin-2-amine (**3a**).* Reaction time: 1 h; 47 mg (70%); white solid; mp 151−154 °C; IR (KBr) ν 1603, 1529, 1492, 1368, 751, 689, 491 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.2 Hz, 2H), 7.73 (d, *J* = 7.7 Hz, 2H), 7.49−7.40 (m, 5H), 7.39−7.34 (m, 5H), 7.21 (s, 1H), 7.03 (t, *J* = 7.4 Hz, 1H), 6.39 (s, 1H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 152.1, 151.1, 141.2, 140.5, 139.5, 128.9, 128.8, 128.6, 128.4, 128.4, 127.7, 126.6, 121.7, 119.4, 114.0, 113.4, 13.9; HRMS *m/z* (APCI) calcd for $C_{24}H_{21}N_2$ (M + H)$^+$ 337.1699, found 337.1705.

*3-Methyl-4,6-diphenyl-N-(o-tolyl)pyridin-2-amine (**3b**).* Reaction time: 2 h; 43 mg (61%); pale green solid; mp 157−160 °C; IR (KBr) ν 1597, 1530, 1482, 1455, 1368, 759 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.1 Hz, 1H), 8.01 (d, *J* = 7.2 Hz, 2H), 7.50−7.25 (m, 9H), 7.24−7.21 (m, 2H), 7.00 (t, *J* = 7.4 Hz, 1H), 6.21 (s, 1H), 2.36 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 152.1, 151.1, 140.5, 139.5 (2C), 130.3, 128.9, 128.5, 128.4, 127.7, 127.2, 126.6, 122.1, 120.5, 114.4, 113.3, 18.2, 13.9; HRMS *m/z* (APCI) calcd for $C_{25}H_{23}N_2$ (M + H)$^+$ 351.1856, found 351.1866. (Note that three carbon peaks overlap with other peaks.)

*3-Methyl-4,6-diphenyl-N-(p-tolyl)pyridin-2-amine (**3c**).* Reaction time: 2 h; 54 mg (77%); white solid; mp 143−146 °C; IR (KBr) ν 1608, 1529, 1401, 1370, 772, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08−7.99 (m, 2H), 7.61 (d, *J* = 8.4 Hz, 2H), 7.47−7.30 (m, 8H), 7.20−7.13 (m, 3H), 6.29 (s, 1H), 2.34 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 152.0, 150.9, 140.6, 139.7, 138.6, 131.2, 129.4, 128.9, 128.6, 128.4, 127.7, 126.7, 119.8, 113.8, 113.1, 20.9, 13.9; HRMS *m/z* (APCI) calcd for $C_{25}H_{23}N_2$ (M + H)$^+$ 351.1856, found 351.1864. (Note that two carbon peaks overlap on each other.)

*N-(2,4-Dimethylphenyl)-3-methyl-4,6-diphenylpyridin-2-amine (**3d**).* Reaction time: 2 h; 45 mg (62%); white solid; mp 148−152 °C; IR (KBr) ν 1609, 1530, 1493, 1398, 1373, 772, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.1 Hz, 1H), 7.99 (d, *J* = 7.5 Hz, 2H), 7.49−7.29 (m, 8H), 7.18 (s, 1H), 7.08 (d, *J* = 8.3 Hz, 1H), 7.05 (s, 1H), 6.11 (s, 1H), 2.33 (s, 3H), 2.32 (s, 3H), 2.16 (s, 3H); ^{13}C

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NMR (100 MHz, $CDCl_3$) δ 154.4, 152.0, 150.9, 140.5, 139.5, 136.8, 131.7, 131.0, 128.8, 128.4, 128.3, 128.3, 127.7, 127.6, 126.9, 126.5, 121.2, 113.9, 112.9, 20.8, 18.1, 13.9; HRMS m/z (APCI) calcd for $C_{26}H_{25}N_2$ $(M + H)^+$ 365.2012, found 365.2019.

N-(4-Methoxyphenyl)-3-methyl-4,6-diphenylpyridin-2-amine (**3e**). Reaction time: 2 h; 38 mg (52%); white solid; mp 162−165 °C; IR (KBr) ν 1530, 1506, 1241, 1036, 824, 772, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07−7.96 (m, 2H), 7.66−7.58 (m, 2H), 7.50−7.25 (m, 8H), 7.16 (s, 1H), 6.99−6.84 (m, 2H), 6.23 (s, 1H), 3.82 (s, 3H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 154.2, 151.9, 150.8, 140.5, 139.6, 134.4, 128.8, 128.5, 128.3, 127.6, 126.5, 121.7, 114.0, 113.3, 112.8, 55.6, 13.8; HRMS m/z (APCI) calcd for $C_{25}H_{23}N_2O$ $(M + H)^+$ 367.1805, found 367.1811. (Note that two carbon peaks overlap on each other.)

N-(3-Fluoro-4-methylphenyl)-3-methyl-4,6-diphenylpyridin-2-amine (**3f**). Reaction time: 2 h; 48 mg (65%); yellow solid; mp 101−104 °C; IR (KBr) ν 1607, 1509, 1372, 1262, 1103, 1027, 803, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 7.5 Hz, 2H), 7.74 (dd, J = 12.4, 1.8 Hz, 1H), 7.49−7.31 (m, 8H), 7.17−7.22 (m, 2H), 7.10 (t, J = 8.4 Hz, 1H), 6.36 (s, 1H), 2.25 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.30 (d, J = 242.0 Hz), 153.5, 152.1, 151.1, 140.4, 140.3, 139.4, 131.0 (d, J = 6.7 Hz), 128.8, 128.6, 128.5, 128.4, 127.7, 126.6, 117.4 (d, J = 17.7 Hz), 114.5 (d, J = 2.7 Hz), 113.9, 113.5, 106.5 (d, J = 27.5 Hz), 14.0 (d, J = 2.8 Hz), 13.8; HRMS m/z (APCI) calcd for $C_{25}H_{22}FN_2$ $(M + H)^+$ 369.1762, found 369.1766.

N-(4-Fluorophenyl)-3-methyl-4,6-diphenylpyridin-2-amine (**3g**). Reaction time: 2 h; 47 mg (66%); white solid; mp 141−145 °C; IR (KBr) ν 1610, 1503, 1398, 1371, 1202, 771 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.04−7.97 (m, 2H), 7.69−7.63 (m, 2H), 7.50−7.33 (m, 8H), 7.20 (s, 1H), 7.11−7.01 (m, 2H), 6.30 (s, 1H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1 (d, J = 240.3 Hz), 153.9, 152.0, 151.1, 140.4, 139.5, 137.1 (d, J = 2.6 Hz), 128.8, 128.6, 128.5, 128.4, 127.8, 126.6, 121.4 (d, J = 7.6 Hz), 115.3 (d, J = 22.2 Hz), 113.6, 113.4, 13.8; HRMS m/z (APCI) calcd for $C_{24}H_{20}FN_2$ $(M + H)^+$ 355.1605, found 355.1612.

N-(3-Chlorophenyl)-3-methyl-4,6-diphenylpyridin-2-amine (**3h**). Reaction time: 2 h; 53 mg (72%); yellow solid; mp 100−105 °C; IR (KBr) ν 1601, 1532, 1480, 1396, 1371, 768, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 8.1 Hz, 2H), 7.99 (s, 1H), 7.52−7.32 (m, 9H), 7.27−7.21 (m, 2H), 6.98 (d, J = 7.9 Hz, 1H), 6.39 (s, 1H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 152.1, 151.3, 142.3, 140.2, 139.24, 134.4, 129.6, 128.8, 128.6, 128.6, 128.4, 127.8, 126.6, 121.4, 119.3, 117.1, 114.2, 113.9, 13.8; HRMS m/z (APCI) calcd for $C_{24}H_{20}ClN_2$ $(M + H)^+$ 371.1310, found 371.1301.

N-(4-Chlorophenyl)-3-methyl-4,6-diphenylpyridin-2-amine (**3i**). Reaction time: 2 h; 37 mg (50%); white solid; mp 153−156 °C; IR (KBr) ν 1605, 1527, 1489, 1397, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.06−7.97(m, 2H), 7.72−7.64 (m, 2H), 7.49−7.28 (m, 10H), 7.22 (s, 1H), 6.35 (s, 1H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 152.1, 151.2, 140.3, 139.8, 139.4, 128.8, 128.7, 128.6, 128.6, 128.4, 127.8, 126.6, 126.3, 120.7, 114.0, 113.7, 13.9; HRMS m/z (APCI) calcd for $C_{24}H_{20}ClN_2$ $(M + H)^+$ 371.1310, found 371.1278.

N-(4-Bromophenyl)-3-methyl-4,6-diphenylpyridin-2-amine (**3j**). Reaction time: 2 h; 51 mg (61%); white solid; mp 173−175 °C; IR (KBr) ν 1604, 1524, 1486, 1393, 1369, 1029, 799 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.1 Hz, 2H), 7.63 (d, J = 8.5 Hz, 2H), 7.52−7.29 (m, 10H), 7.22 (s, 1H), 6.35 (s, 1H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 152.0, 151.2, 140.2 (2C), 139.3, 131.6, 128.8, 128.6, 128.5, 128.4, 127.8, 126.5, 121.0, 114.0, 113.7, 113.7, 13.8; HRMS m/z (APCI) calcd for $C_{24}H_{20}BrN_2$ $(M + H)^+$ 415.0804, found 415.0784. (Note that two carbon peaks overlap on each other.)

N-(4-Iodophenyl)-3-methyl-4,6-diphenylpyridin-2-amine (**3k**). Reaction time: 5 h; 42 mg (45%); white solid; mp 194−196 °C; IR (KBr) ν 1603, 1520, 1484, 1392, 1369, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.06−7.96 (m, 2H), 7.68−7.60 (m, 2H), 7.54−7.52 (m, 2H), 7.49−7.33 (m, 8H), 7.23 (s, 1H), 6.36 (s, 1H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 152.1, 151.2, 140.9, 140.2, 139.3, 137.5, 128.8, 128.6, 128.5, 128.4, 127.8, 126.5, 121.3, 114.1, 113.8, 83.7, 13.8; HRMS m/z (APCI) calcd for $C_{24}H_{20}IN_2$ $(M + H)^+$ 463.0666, found 463.0667.

3-Methyl-N-(naphthalen-1-yl)-4,6-diphenylpyridin-2-amine (**3l**). Reaction time: 5 h; 39 mg (51%); pale purple solid; mp 177−180 °C; IR (KBr) ν 1599, 1537, 1498, 1414, 1372, 769, 701 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 7.5 Hz, 1H), 8.08−8.03 (m, 1H), 7.94 (d, J = 7.9 Hz, 2H), 7.91−7.86 (m, 1H), 7.61 (d, J = 8.1 Hz, 1H), 7.56−7.45 (m, 5H), 7.45−7.28 (m, 6H), 7.26 (s, 1H), 6.81 (s, 1H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 152.3, 151.4, 140.4, 139.4, 136.6, 134.4, 128.9, 128.7, 128.5, 128.4, 127.8, 127.2, 126.6, 125.9, 125.7, 125.6, 122.9, 121.2, 117.2, 115.0, 113.9, 14.3; HRMS m/z (APCI) calcd for $C_{28}H_{23}N_2$ $(M + H)^+$ 387.1856, found 387.1858. (Note that two carbon peaks overlap on each other.)

3-Methyl-4,6-diphenyl-N-(pyridin-3-yl)pyridin-2-amine (**3m**). Reaction time: 2 h; 21 mg (31%); brown solid; mp 161−165 °C; IR (KBr) ν 1601, 1525, 1484, 1372, 1261, 1094, 1025, 803, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.83 (d, J = 2.3 Hz, 1H), 8.42−8.32 (m, 1H), 8.27 (d, J = 3.8 Hz, 1H), 8.07−7.95 (m, 2H), 7.53−7.34 (m, 8H), 7.34−7.28 (m, 1H), 7.26 (s, 1H), 6.43 (s, 1H), 2.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 152.2, 151.4, 142.6, 141.2, 140.1, 139.2, 137.8, 128.8, 128.6, 128.6, 128.4, 127.9, 126.6, 126.3, 123.4, 114.2, 13.8; HRMS m/z (APCI) calcd for $C_{23}H_{20}N_3$ $(M + H)^+$ 338.1652, found 338.1657. (Note that two carbon peaks overlap on each other.)

9-Ethyl-N-(3-methyl-4,6-diphenylpyridin-2-yl)-9H-carbazol-3-amine (**3n**). Reaction time: 2 h; 60 mg (66%); brown solid; mp 68−72 °C; IR (KBr) ν 1596, 1528, 1489, 1370, 1090, 1025, 802, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.71 (s, 1H), 8.20−8.09 (m, 3H), 7.73−7.67 (m, 1H), 7.54−7.33 (m, 11H), 7.28−7.22 (m, 2H), 6.53 (s, 1H), 4.40 (q, J = 7.2 Hz, 2H), 2.25 (s, 3H), 1.48 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 151.8, 150.8, 140.7, 140.4, 139.6, 136.2, 133.2, 128.9, 128.5, 128.3, 127.6, 126.5, 125.5, 123.1, 123.1, 120.4, 120.1, 118.4, 113.3, 112.5, 112.5, 108.7, 108.3, 37.6, 13.9; HRMS m/z (APCI) calcd for $C_{32}H_{28}N_3$ $(M + H)^+$ 454.2278, found 454.2280. (Note that two carbon peaks overlap with other peaks.)

N,3-Dimethyl-4,6-diphenylpyridin-2-amine (**3o**). Reaction time: 2 h; 26 mg (47%); white solid; mp 101−105 °C; IR (KBr) ν 1590, 1557, 1509, 1365, 776, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.08 (d, J = 7.6 Hz, 2H), 7.47−7.30 (m, 8H), 7.02 (s, 1H), 4.35 (brs, 1H), 3.19 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 151.9, 149.6, 140.74, 140.0, 128.8, 128.4, 128.2, 128.1, 127.4, 126.5, 112.5, 110.8, 29.0, 13.3; HRMS m/z (APCI) calcd for $C_{19}H_{19}N_2$ $(M + H)^+$ 275.1543, found 275.1549.

N-Allyl-3-methyl-4,6-diphenylpyridin-2-amine (**3p**). Reaction time: 2 h; 28 mg (47%); colorless oil; IR (KBr) ν 1592, 1560, 1510, 1373, 773, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09−8.00 (m, 2H), 7.48−7.29 (m, 8H), 7.03 (s, 1H), 6.20−6.07 (m, 1H), 5.38−5.26 (m, 1H), 5.21−5.13 (m, 1H), 4.44−4.35 (m, 1H), 4.35−4.28 (m, 2H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 151.8, 149.9, 140.7, 139.9, 136.5, 128.8, 128.4, 128.2, 128.1, 127.44, 126.5, 115.6, 112.4, 111.1, 44.5, 13.3; HRMS m/z (APCI) calcd for $C_{21}H_{21}N_2$ $(M + H)^+$ 301.1699, found 301.1705.

3-Methyl-4,6-diphenyl-N-(prop-2-yn-1-yl)pyridin-2-amine (**3q**). Reaction time: 2 h; 32 mg (54%); brown solid; mp 88−91 °C; IR (KBr) ν 3281, 1594, 1560, 1506, 1070, 1027, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 7.4 Hz, 2H), 7.48−7.30 (m, 8H), 7.09 (s, 1H), 4.47 (brs, 3H), 2.25 (s, 1H), 2.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.6, 151.7, 150.2, 140.4, 139.6, 128.8, 128.4, 128.3, 127.5, 126.5, 112.9, 111.9, 82.2, 70.5, 31.7, 13.3; HRMS m/z (APCI) calcd for $C_{21}H_{19}N_2$ $(M + H)^+$ 299.1543, found 299.1537. (Note that two carbon peaks overlap on each other.)

N-Benzyl-3-methyl-4,6-diphenylpyridin-2-amine (**3r**). Reaction time: 1 h; 44 mg (63%); white solid; mp 79−81 °C; IR (KBr) ν 1592, 1559, 1511, 772, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.11−7.98 (m, 2H), 7.54−7.25 (m, 13H), 7.06 (s, 1H), 4.88 (d, J = 5.2 Hz, 2H), 4.63 (t, J = 4.7 Hz, 1H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5, 151.8, 149.9, 140.7, 140.6, 139.9, 128.8, 128.5, 128.4, 128.2, 128.1, 128.0, 127.5, 127.0, 126.5, 112.4, 111.2, 46.1, 13.4; HRMS m/z (APCI) calcd for $C_{25}H_{23}N_2$ $(M + H)^+$ 351.1856, found 351.1859.

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3-Methyl-N-phenethyl-4,6-diphenylpyridin-2-amine ***(3s)***. Reaction time: 2 h; 33 mg (45%); white solid; mp 93−97 °C; IR (KBr) ν 1593, 1511, 1028, 774, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12−8.06 (m, 2H), 7.47−7.24 (m, 13H), 7.04 (s, 1H), 4.40 (t, *J* = 5.3 Hz, 1H), 3.97−3.86 (m, 2H), 3.06 (t, *J* = 7.0 Hz, 2H), 1.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 151.8, 149.8, 140.7, 140.1, 140.0, 129.0, 128.8, 128.5, 128.4, 128.2, 128.1, 127.4, 126.5, 126.2, 112.5, 110.9, 43.3, 36.0, 13.2; HRMS *m/z* (APCI) calcd for $C_{26}H_{25}N_2$ (M + H)$^+$ 365.2012, found 365.2017.

3-Methyl-4,6-diphenylpyridin-2-amine ***(3t)***. This reaction was carried out in 0.5 mmol scale in the presence of 1 equiv of NaOH; reaction time: 12 h; white solid; 123 mg (95%); mp 107−109 °C; IR (KBr) ν 3296, 3174, 1627, 1591, 767, 702 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97−7.90 (m, 2H), 7.45−7.36 (m, 5H), 7.35−7.30 (m, 3H), 7.05 (s, 1H), 4.64 (s, 2H), 2.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.5, 152.8, 150.8, 140.2, 139.6, 128.7, 128.4, 128.2, 127.5, 126.6, 113.0, 112.5, 13.7; HRMS *m/z* (APCI) calcd for $C_{18}H_{17}N_2$ (M + H)$^+$ 261.1386, found 261.1389. (Note that two carbon peaks overlap on each other.)

3-Methyl-N,6-diphenyl-4-(o-tolyl)pyridin-2-amine ***(4a)***. Reaction time: 2 h; 39 mg (56%); colorless oil; IR (KBr) ν 1602, 1526, 1495, 1372, 752, 693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.6 Hz, 2H), 7.76 (d, *J* = 8.1 Hz, 2H), 7.46−7.24 (m, 8H), 7.17−7.11 (m, 2H), 7.03 (t, *J* = 7.4 Hz, 1H), 6.37 (s, 1H), 2.13 (s, 3H), 2.01 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 152.0, 150.8, 141.1, 140.0, 139.5, 135.4, 130.0, 128.8, 128.7, 128.5, 128.4, 127.8, 126.5, 125.8, 121.6, 119.3, 114.5, 113.1, 19.7, 13.4; HRMS *m/z* (APCI) calcd for $C_{25}H_{23}N_2$ (M + H)$^+$ 351.1856, found 351.1850.

3-Methyl-N,6-diphenyl-4-(p-tolyl)pyridin-2-amine ***(4b)***. Reaction time: 4 h; 51 mg (73%); white solid; mp 140−142 °C; IR (KBr) ν 1607, 1533, 1495, 1371, 751, 692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 7.4 Hz, 2H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.47−7.39 (m, 2H), 7.39−7.31 (m, 3H), 7.30−7.23 (m, 4H), 7.20 (s, 1H), 7.01 (t, *J* = 7.3 Hz, 1H), 6.37 (s, 1H), 2.42 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 152.0, 151.0, 141.2, 139.6, 137.5, 129.0, 128.8, 128.7, 128.5, 128.3, 126.6, 121.6, 119.3, 114.0, 113.5, 21.2, 13.9; HRMS *m/z* (APCI) calcd for $C_{25}H_{23}N_2$ (M + H)$^+$ 351.1856, found 351.1848. (Note that two carbon peaks overlap on each other.)

4-(4-(tert-Butyl)phenyl)-3-methyl-N,6-diphenylpyridin-2-amine ***(4c)***. Reaction time: 2 h; 47 mg (60%); white solid; mp 159−162 °C; IR (KBr) ν 1604, 1527, 1498, 1372, 747, 689 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, *J* = 8.1 Hz, 2H), 7.73 (d, *J* = 8.3 Hz, 2H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.39−7.28 (m, 5H), 7.23 (s, 1H), 7.02 (t, *J* = 7.3 Hz, 1H), 6.38 (s, 1H), 2.21 (s, 3H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 152.0, 151.0, 150.7, 141.2, 139.6, 137.4, 128.8, 128.6, 128.5, 128.3, 126.6, 125.2, 121.6, 119.4, 114.1, 113.6, 34.6, 31.4, 14.0; HRMS *m/z* (APCI) calcd for $C_{28}H_{29}N_2$ (M + H)$^+$ 393.2325, found 393.2330.

4-(3-Methoxyphenyl)-3-methyl-N,6-diphenylpyridin-2-amine ***(4d)***. Reaction time: 2 h; 31 mg (42%); yellow solid; mp 83−85 °C; IR (KBr) ν 1600, 1525, 1494, 1371, 752, 692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08−8.00 (m, 2H), 7.77−7.69 (m, 2H), 7.46−7.33 (m, 6H), 7.21 (s, 1H), 7.06−6.99 (m, 1H), 6.98−6.92 (m, 2H), 6.91−6.88 (m, 1H), 6.39 (s, 1H), 3.85 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.5, 153.8, 152.0, 150.9, 141.8, 141.1, 139.5, 129.4, 128.8, 128.5, 128.4, 126.6, 121.7, 121.2, 119.4, 114.5, 113.9, 113.2, 113.1, 55.3, 13.9; HRMS *m/z* (APCI) calcd for $C_{25}H_{23}N_2O$ (M + H)$^+$ 367.1805, found 367.1802.

4-(4-Methoxyphenyl)-3-methyl-N,6-diphenylpyridin-2-amine ***(4e)***. Reaction time: 5 h; 37 mg (51%); white solid; mp 207−209 °C; IR (KBr) ν 1602, 1519, 1369, 1238, 1026, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09−7.98 (m, 2H), 7.72 (d, *J* = 8.0 Hz, 2H), 7.47−7.39 (m, 2H), 7.39−7.33 (m, 3H), 7.30 (d, *J* = 8.6 Hz, 2H), 7.20 (s, 1H), 7.06−6.95 (m, 3H), 6.38 (s, 1H), 3.87 (s, 3H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 153.8, 152.0, 150.7, 141.2, 139.6, 132.7, 130.0, 128.8, 128.5, 128.3, 126.6, 121.6, 119.3, 114.1, 113.8, 113.6, 55.3, 13.9; HRMS *m/z* (APCI) calcd for $C_{25}H_{23}N_2O$ (M + H)$^+$ 367.1805, found 367.1812.

4-(3-Chlorophenyl)-3-methyl-N,6-diphenylpyridin-2-amine ***(4f)***. Reaction time: 2 h; 60 mg (81%); white solid; mp 125−128 °C; IR (KBr) ν 1602, 1524, 1496, 1371, 1015, 750, 690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.1 Hz, 2H), 7.72 (d, *J* = 8.2 Hz, 2H), 7.46−7.31 (m, 8H), 7.25−7.18 (m, 1H), 7.15 (s, 1H), 7.03 (t, *J* = 7.3 Hz, 1H), 6.37 (s, 1H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 152.2, 149.5, 142.2, 141.0, 139.3, 134.3, 129.6, 128.9, 128.8, 128.5, 127.8, 127.0, 126.6, 121.8, 119.5, 113.8, 113.0, 13.8; HRMS *m/z* (APCI) calcd for $C_{24}H_{20}ClN_2$ (M + H)$^+$ 371.1310, found 371.1299. (Note that two carbon peaks overlap on each other.)

4-(3,4-Dichlorophenyl)-3-methyl-N,6-diphenylpyridin-2-amine ***(4g)***. Reaction time: 2 h; 62 mg (77%); white solid; mp 166−170 °C; IR (KBr) ν 1605, 1531, 1495, 752, 692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.3 Hz, 2H), 7.71 (d, *J* = 8.0 Hz, 2H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.48−7.40 (m, 3H), 7.39−7.30 (m, 3H), 7.21−7.15 (m, 1H), 7.12 (s, 1H), 7.04 (t, *J* = 7.3 Hz, 1H), 6.37 (s, 1H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.9, 152.4, 148.5, 140.9, 140.3, 139.1, 132.6, 132.1, 130.7, 130.4, 128.8, 128.6, 128.6, 128.2, 126.6, 122.0, 119.6, 113.6, 112.7, 13.8; HRMS *m/z* (APCI) calcd for $C_{24}H_{19}Cl_2N_2$ (M + H)$^+$ 405.0920, found 405.0929.

4-(4-Chlorophenyl)-3-methyl-N,6-diphenylpyridin-2-amine ***(4h)***. Reaction time: 5 h; 57 mg (77%); white solid; mp 184−186 °C; IR (KBr) ν 1606, 1533, 1492, 1371, 751, 693 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.1 Hz, 2H), 7.72 (d, *J* = 8.3 Hz, 2H), 7.48−7.40 (m, 4H), 7.39−7.32 (m, 3H), 7.32−7.26 (m, 2H), 7.15 (s, 1H), 7.03 (t, *J* = 7.3 Hz, 1H), 6.37 (s, 1H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 152.2, 149.8, 141.0, 139.3, 138.8, 133.8, 130.2, 128.8, 128.6, 128.6, 128.5, 126.6, 121.8, 119.5, 113.8, 113.0, 13.8; HRMS *m/z* (APCI) calcd for $C_{24}H_{20}ClN_2$ (M + H)$^+$ 371.1310, found 371.1298.

4-(3-Fluorophenyl)-3-methyl-N,6-diphenylpyridin-2-amine ***(4i)***. Reaction time: 5 h; 51 mg (72%); white solid; mp 110−114 °C; IR (KBr) ν 1604, 1531, 1493, 1373 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.0 Hz, 2H), 7.72 (d, *J* = 8.2 Hz, 2H), 7.48−7.31(m, 6H), 7.17 (s, 1H), 7.15−6.98 (m, 4H), 6.38 (s, 1H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6 (d, *J* = 246.9 Hz), 153.8, 152.2, 149.7, 142.5 (d, *J* = 7.6 Hz), 141.0, 139.3, 130.0 (d, *J* = 8.3 Hz), 128.8, 128.6, 128.5, 126.6, 124.6 (d, *J* = 2.7 Hz), 121.8, 119.5, 115.9 (d, *J* = 21.7 Hz), 114.6 (d, *J* = 21.0 Hz), 113.8, 112.9, 13.8; HRMS *m/z* (APCI) calcd for $C_{24}H_{20}FN_2$ (M + H)$^+$ 355.1605, found 355.1601.

4-(4-Fluorophenyl)-3-methyl-N,6-diphenylpyridin-2-amine ***(4j)***. Reaction time: 5 h; 52 mg (73%); white solid; mp 150−154 °C; IR (KBr) ν 1607, 1533, 1494, 1216, 839, 753, 691 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.2 Hz, 2H), 7.72 (d, *J* = 8.2 Hz, 2H), 7.47−7.39 (m, 2H), 7.39−7.27 (m, 5H), 7.20−7.07 (m, 3H), 7.02 (t, *J* = 7.2 Hz, 1H), 6.37 (s, 1H), 2.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4 (d, *J* = 247.0 Hz), 153.8, 152.1, 150.0, 141.0, 139.4, 136.3 (d, *J* = 3.2 Hz), 130.5 (d, *J* = 8.0 Hz), 128.8, 128.5, 128.5, 126.6, 121.8, 119.4, 115.3 (d, *J* = 21.4 Hz), 113.9, 113.3, 13.8; HRMS *m/z* (APCI) calcd for $C_{24}H_{20}FN_2$ (M + H)$^+$ 355.1605, found 355.1600.

3-Methyl-N,6-diphenyl-4-(4-(trifluoromethyl)phenyl)pyridin-2-amine ***(4k)***. Reaction time: 2 h; 71 mg (88%); white solid; mp 168−170 °C; IR (KBr) ν 1606, 1533, 1496, 1321, 1172, 1126, 1067 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.4 Hz, 2H), 7.77−7.67 (m, 4H), 7.50−7.40 (m, 4H), 7.40−7.32 (m, 3H), 7.15 (s, 1H), 7.04 (t, *J* = 7.3 Hz, 1H), 6.38 (s, 1H), 2.14 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 152.3, 149.5, 144.0, 140.9, 139.2, 129.9 (d, *J* = 32.6 Hz), 129.2, 128.8, 128.6, 126.6, 125.4 (d, *J* = 3.6 Hz), 124.1 (d, *J* = 272.2 Hz), 121.9, 119.5, 113.7, 112.8, 13.8; HRMS *m/z* (APCI) calcd for $C_{25}H_{20}F_3N_2$ (M + H)$^+$ 405.1573, found 405.1577. (Note that two carbon peaks overlap on each other.)

3-Methyl-N,6-diphenyl-4-(thiophen-2-yl)pyridin-2-amine ***(4l)***. Reaction time: 2 h; 41 mg (60%); brown solid; mp 115−119 °C; IR (KBr) ν 1604, 1534, 1495, 1386, 743, 698 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.0 Hz, 2H), 7.69 (d, *J* = 8.2 Hz, 2H), 7.49−7.29 (m, 7H), 7.14 (d, *J* = 3.0 Hz, 2H), 7.03 (t, *J* = 7.3 Hz, 1H), 6.39 (s, 1H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.1, 152.3, 143.3, 141.3, 141.0, 139.3, 128.8, 128.5, 128.5, 127.5, 127.3, 126.6, 126.2, 121.8, 119.5, 114.5, 113.8, 14.1; HRMS *m/z* (APCI) calcd for $C_{22}H_{19}N_2S$ (M + H)$^+$ 343.1263, found 343.1262.

4-(Furan-2-yl)-3-methyl-N,6-diphenylpyridin-2-amine ***(4m)***. Reaction time: 2 h; 29 mg (44%); brown solid; mp 108−114 °C; IR (KBr) ν 1601, 1525, 1495, 1412, 747, 694 cm^{-1}; ^{1}H NMR (400 MHz,

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$CDCl_3$) δ 8.06 (d, J = 7.5 Hz, 2H), 7.64 (d, J = 8.0 Hz, 2H), 7.59 (s, 1H), 7.55 (s, 1H), 7.48−7.41 (m, 2H), 7.41−7.31 (m, 3H), 7.02 (t, J = 7.3 Hz, 1H), 6.70 (d, J = 3.3 Hz, 1H), 6.62−6.50 (m, 1H), 6.42 (s, 1H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.2, 152.5, 152.1, 142.9, 141.3, 139.4, 138.9, 128.8, 128.5, 128.5, 126.6, 121.7, 119.3, 113.2, 111.5, 111.0, 110.7, 14.3; HRMS m/z (APCI) calcd for $C_{22}H_{19}N_2O$ $(M + H)^+$ 327.1492, found 327.1490.

6-(4-Bromophenyl)-3-methyl-N,4-diphenylpyridin-2-amine (**4n**). Reaction time: 2 h; 69 mg (83%); white solid; mp 124−128 °C; IR (KBr) ν 1605, 1531, 1495, 1370 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 8.5 Hz, 2H), 7.69 (d, J = 7.9 Hz, 2H), 7.51−7.30 (m, 9H), 7.15 (s, 1H), 7.03 (t, J = 7.3 Hz, 1H), 6.37 (s, 1H), 2.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 151.1, 150.8, 141.0, 140.2, 138.0, 134.3, 128.8, 128.8, 128.7, 128.4, 127.8, 127.8, 121.9, 119.5, 114.3, 113.1, 13.8; HRMS m/z (APCI) calcd for $C_{24}H_{20}BrN_2$ $(M + H)^+$ 415.0804, found 415.0805.

3-Methyl-N,4-diphenyl-6-(m-tolyl)pyridin-2-amine (**4o**). Reaction time: 3 h; 44 mg (63%); white solid; mp 134−136 °C; IR (KBr) ν 1599, 1517, 1448, 1368, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89−7.82 (m, 2H), 7.73 (d, J = 8.2 Hz, 2H), 7.50−7.29 (m, 8H), 7.20 (s, 1H), 7.17 (d, J = 7.5 Hz, 1H), 7.02 (t, J = 7.2 Hz, 1H), 6.38 (s, 1H), 2.41 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.7, 152.2, 151.0, 141.2, 140.4, 139.4, 138.0, 129.2, 128.8, 128.7, 128.4, 128.3, 127.7, 127.3, 123.7, 121.6, 119.3, 113.9, 113.4, 21.6, 13.9; HRMS m/z (APCI) calcd for $C_{25}H_{23}N_2$ $(M + H)^+$ 351.1856, found 351.1858.

N-(4-Methoxyphenyl)-N-(3-methyl-4,6-diphenylpyridin-2-yl)-formamide (**5e**, *Rotameric Mixture, 54:46 Ratio of the Rotamers*). This reaction was carried out in 0.3 mmol scale; reaction time: 0.5 h; 66 mg (56%); white solid; mp 148−151 °C; IR (KBr) ν 1683, 1510, 1246, 1027 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98−8.63 (m, 1H), 8.07 (d, J = 6.9 Hz, 1H), 7.95 (d, J = 6.2 Hz, 1H), 7.72−7.61 (m, 1H), 7.51−7.26 (m, 10H), 6.92 (m, 2H), 3.80 (s, 3H), 2.26−1.92 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.8, 161.7, 158.4, 157.8, 154.6, 154.0, 153.9, 153.2, 153.0, 151.8, 139.1, 138.9, 138.3, 137.8, 133.3, 131.6, 129.2, 128.9, 128.7, 128.4, 128.3, 128.1, 127.2, 126.7, 126.3, 125.9, 125.3, 121.1, 120.5, 114.6, 114.2, 55.4, 15.6, 15.0; HRMS m/z (APCI) calcd for $C_{26}H_{23}N_2O_2$ $(M + H)^+$ 395.1754, found 395.1760.

N-(3-Methyl-4,6-diphenylpyridin-2-yl)formamide (**5t**). Reaction time: 2 h; 26 mg (45%); white solid; mp 208−212 °C; IR (KBr) ν 1696, 1374, 1262, 1101, 467 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.75 (d, J = 10.2 Hz, 1H), 8.45 (d, J = 9.8 Hz, 1H), 8.01 (d, J = 7.2 Hz, 2H), 7.52−7.37 (m, 7H), 7.37−7.31 (m, 2H), 2.20 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 152.7, 152.7, 149.4, 139.3, 138.2, 129.1, 128.7, 128.7, 128.5, 128.2, 126.6, 117.5, 115.3, 13.3; HRMS m/z (APCI) calcd for $C_{19}H_{17}N_2O$ $(M + H)^+$ 289.1335, found 289.1336.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b00128.

Copies of ^{1}H NMR and ^{13}C NMR for all synthesized compounds (PDF)

X-ray crystallographic data of **3a** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Girgis, A. S.; Tala, S. R.; Oliferenko, P. V.; Oliferenko, A. A.; Katritzky, A. R. *Eur. J. Med. Chem.* **2012**, *50*, 1. (b) Mantri, M.; de Graaf, O.; van Veldhoven, J.; Göblyös, A.; von Frijtag Drabbe Künzel, J. K.; Mulder-Krieger, T.; Link, R.; de Vries, H.; Beukers, M. W.; Brussee, J.; Ijzerman, A. P. *J. Med. Chem.* **2008**, *51*, 4449. (c) Girgis, A. S.; Mishriky, N.; Farag, A. M.; El-Eraky, W. I.; Farag, H. *Eur. J. Med. Chem.* **2008**, *43*, 1818.

(2) (a) Horie, H.; Koyama, I.; Kurahashi, T.; Matsubara, S. *Chem. Commun.* **2011**, *47*, 2658. (b) Kempe, R. *Eur. J. Inorg. Chem.* **2003**, *2003*, 791. (c) Fuhrmann, H.; Brenner, S.; Arndt, P.; Kempe, R. *Inorg. Chem.* **1996**, *35*, 6742.

(3) For selected reviews, see: (a) Torborg, C.; Beller, M. *Adv. Synth. Catal.* **2009**, *351*, 3027. (b) Hartwig, J. F. *Acc. Chem. Res.* **2008**, *41*, 1534. (c) Schlummer, B.; Scholz, U. *Adv. Synth. Catal.* **2004**, *346*, 1599. (d) Littke, A. F.; Fu, G. C. *Angew. Chem., Int. Ed.* **2002**, *41*, 4176.

(4) For recent selected examples, see: (a) Brusoe, A. T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2015**, *137*, 8460. (b) Park, N. H.; Vinogradova, E. V.; Surry, D. S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2015**, *54*, 8259. (c) Green, R. A.; Hartwig, J. F. *Org. Lett.* **2014**, *16*, 4388.

(5) (a) Wang, D.; Kuang, D.; Zhang, F.; Liu, Y.; Ning, S. *Tetrahedron Lett.* **2014**, *55*, 7121. (b) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954. (c) Liu, Y.; Bai, Y.; Zhang, J.; Li, Y.; Jiao, J.; Qi, X. *Eur. J. Org. Chem.* **2007**, *2007*, 6084.

(6) (a) Chartoire, A.; Frogneux, X.; Nolan, S. P. *Adv. Synth. Catal.* **2012**, *354*, 1897. (b) Maiti, D.; Fors, B. P.; Henderson, J. L.; Nakamura, Y.; Buchwald, S. L. *Chem. Sci.* **2011**, *2*, 57. (c) Grasa, G. A.; Viciu, M. S.; Huang, J.; Nolan, S. P. *J. Org. Chem.* **2001**, *66*, 7729.

(7) Kumar, D.; Vemula, S. R.; Cook, G. R. *ACS Catal.* **2016**, *6*, 3531.

(8) Wu, Q.; Zhang, Y.; Cui, S. *Org. Lett.* **2014**, *16*, 1350.

(9) (a) McGill, C. K.; Rappa, A. *Adv. Heterocycl. Chem.* **1988**, *44*, 1. (b) Leffler, M. T. *Org. React.* **1942**, *1*, 91. (c) Chichibabin, A. E.; Zeide, O. A. *J. Russ. Phys. Chem. Soc.* **1914**, *46*, 1216.

(10) Thomas, S.; Roberts, S.; Pasumansky, L.; Gamsey, S.; Singaram, B. *Org. Lett.* **2003**, *5*, 3867.

(11) Vamos, M.; Cosford, N. D. P. *J. Org. Chem.* **2014**, *79*, 2274.

(12) (a) Cheng, G.; Weng, Y.; Yang, X.; Cui, X. *Org. Lett.* **2015**, *17*, 3790. (b) Cheng, G.; Xue, L.; Weng, Y.; Cui, X. *J. Org. Chem.* **2017**, *82*, 9515. (c) Shen, J.; Yang, X.; Wang, F.; Wang, Y.; Cheng, G.; Cui, X. *RSC Adv.* **2016**, *6*, 48905. (d) Cheng, G.; Lv, W.; Kuai, C.; Wen, S.; Xiao, S. *Chem. Commun.* **2018**, *54*, 1726. (e) Yang, X.; Cheng, G.; Shen, J.; Kuai, C.; Cui, X. *Org. Chem. Front.* **2015**, *2*, 366. (f) Cheng, G.; Zeng, X.; Shen, J.; Wang, X.; Cui, X. *Angew. Chem., Int. Ed.* **2013**, *52*, 13265. (g) Cheng, G.; Cui, X. *Org. Lett.* **2013**, *15*, 1480.

(13) For recent studies on N-propargyl β-enaminones, see: (a) Arshadi, S.; Vessally, E.; Edjlali, L.; Ghorbani-Kalhor, E.; Hosseinzadeh-Khanmiri, R. *RSC Adv.* **2017**, *7*, 13198. (b) Yang, X.; Hu, F.; Wang, Y.; Yang, C.; Zou, X.; Liu, J.; Zhang, Q. *Chem. Commun.* **2017**, *53*, 7497. (c) Goutham, K.; Ashok Kumar, D.; Suresh, S.; Sridhar, B.; Narender, R.; Karunakar, G. V. *J. Org. Chem.* **2015**, *80*, 11162.

(14) (a) Zhu, Y.; Back, T. G. *J. Org. Chem.* **2014**, *79*, 11270. (b) Gao, D.; Parvez, M.; Back, T. G. *Chem. - Eur. J.* **2010**, *16*, 14281. (c) Gao, D.; Back, T. G. *Chem. - Eur. J.* **2012**, *18*, 14828.

(15) Rao, S. N.; Mohan, D. C.; Adimurthy, S. *Org. Lett.* **2013**, *15*, 1496.

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