

# Palladium-Catalyzed Sonogashira Coupling Reaction of 2-Amino-3-Bromopyridines with Terminal Alkynes

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## Abstract

Palladium-catalyzed the Sonogashira coupling reaction of 3-halogen-2-aminopyridines **1** with terminal alkynes **2** afforded the corresponding 21 target products **3a-3u** in the presence of palladium catalyst. The structure of target products **3a-3u** was confirmed and characterized by <sup>1</sup>H NMR, <sup>13</sup>C NMR, and HRMS. The influences of different kinds of catalyst loading, bases, substrates and temperature were also investigated. Under the optimized conditions, including 2.5 mol% Pd (CF<sub>3</sub>COO)<sub>2</sub>, 5 mol% PPh<sub>3</sub> and 5 mol% CuI as additive, 1 mL Et<sub>3</sub>N, substrate **1** with terminal alkynes **2** for the cross-coupling reactions at 100°C for 3 h in DMF afforded the corresponding products of 2-amino-3-alkynylpyridines **3** in moderate to excellent yields (72% - 96%). The present methodology has provided an effective synthetic method including operational convenience, high efficiency and wide-application.

## Keywords

Palladium Catalyst, 2-Amino-3-Bromopyridines, Terminal Alkynes, Sonogashira Coupling Reaction

## 1. Introduction

Sonogashira reaction is the sp-sp<sup>2</sup> carbon cross-coupling reaction of terminal alkynes with aryl halides or alkenyl halide. This reaction is one of the most effective methods to form new carbon-carbon bonds [1]-[9]. As early as 1975, Heck [10], Cassar [11] and Sonogashira [12] independently discovered this reaction. After nearly 40 years, it has gradually known by people and become an important name reaction. At present, the Sonogashira reaction has been widely used in the synthesis of substituted alkynes and conjugated alkynes [13] [14] [15] [16]. It

also plays a key role in the synthesis of many natural products [17], pesticides, pharmaceuticals [18] [19] and new materials and nano-molecular devices [20] [21] [22] [23]. Since the discovery of the Sonogashira reactions [24]-[29], the most widely used catalysts have been Pd-type compounds. A lot of cross-coupling reactions catalyzed by Pd/Cu co-catalyst are the cross-coupling reactions of terminal alkyne with halogenated benzene, while the reactions of terminal alkynes with halogenated hydrocarbons containing hetero atoms are relatively few investigated. Nitrogen-containing heterocyclic compounds, the substrates of the Sonogashira cross-coupling reactions, of which pyridine and its derivatives are important raw materials in the preparation of pharmaceuticals, pesticides, dyes, surfactants, rubber chemicals, feed additives, food additives, adhesives and composite materials [30]. It also can be used for the preparation of high value-added fine chemicals. The products of 2-amino-3-alkynyl pyridine and its derivatives are important raw materials to synthesize indole and quinoline heterocyclic compounds. The indole containing nitrogen can be thought of as bioisosteres of indole, and indole plays a huge role in the process of life because many medicines contain indole. Azaindole molecules such as 7-azaindole, an important type of compounds, are widely used in the pharmaceuticals, pesticides, chemicals and food sectors [31] [32]. 7-Azaindole also plays an important role in materials science as metal ligands [33]. Therefore, 2-amino-3-alkynyl pyridine and its derivatives, prepared by cross-coupling reaction have a certain scientific significance and potential application values. One-pot reaction of 2-amino-3-bromopyridine reacts with terminal alkynes to synthesize a series of 2-amino-3-alkynyl pyridine and its derivatives in the presence of palladium catalyst. The few palladium catalytic loading, mild reaction conditions, wide raw material sources and 2-amino-3-bromopyridine and its derivatives with many functional groups make the Sonogashira coupling reaction to successfully explore the optimum reaction conditions, and expand the scope of the substrate **1**. The Sonogashira coupling reaction makes it possible to synthesize, further transform and apply to heterocyclic compounds.

## 2. Experimental

### 2.1. General Procedure

Under the protection of the nitrogen atmosphere, added Pd (CF<sub>3</sub>COO)<sub>2</sub> (4.2 mg, 2.5 mol%), PPh<sub>3</sub> (6.6 mg, 5.0 mol%), CuI (4.8 mg, 5.0 mol%) to 10 mL round-bottomed flask, then added 2.0 mL DMF solvent and stirred 30 min. Then added 2-amino-3-bromo-pyridine **1** (0.5 mmol) with terminal alkynes **2** (0.6 mmol), in the 100 °C heating circumstance 3 h, TLC monitor reaction process. After the reaction, took the reaction mixture into the saturated sodium chloride aqueous solution (10 mL), extracted with ethyl acetate (10 mL × 3) and collected organic phase, dry with anhydrous magnesium sulfate, filter, vacuum concentrate, wash away residue with petroleum ether and ethyl ester, and the residue is purified by column chromatography to afford the corresponding product **3**.

## 2.2. Spectra Data

**3-Phenylethynyl-2-aminopyridine (3a)** [29]. Prepared according to general procedure. A white solid (95.1 mg, 98% yield). m.p. 88°C - 89°C.  $R_f = 0.40$  on silica gel (ethyl acetate/petroleum ether 1:5, v/v).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.04 (dt,  $J = 10.7, 5.3$  Hz, 1H), 7.60 (dt,  $J = 13.9, 7.0$  Hz, 1H), 7.56 - 7.49 (m, 2H), 7.39 - 7.33 (m, 3H), 6.65 (dd,  $J = 7.5, 5.0$  Hz, 1H), 5.13 (s, 2H).  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  158.8, 147.9, 134.0, 131.5, 128.5, 128.5, 122.7, 113.5, 103.2, 95.5, 84.4. MS (EI) m/z:  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{13}\text{H}_{11}\text{N}_2$ , 195.08; found, 195.15.

**3-(4-Methylphenylethynyl)-2-aminopyridine (3b)**. Prepared according to general procedure. A light yellow solid (97.8 mg, 94% yield). m.p. 94°C - 89°C.  $R_f = 0.40$  on silica gel (ethyl acetate/petroleum ether 1:5, v/v).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.03 (dd,  $J = 5.0, 1.7$  Hz, 1H), 7.58 (dd,  $J = 7.5, 1.8$  Hz, 1H), 7.41 (d,  $J = 8.1$  Hz, 2H), 7.17 (d,  $J = 7.9$  Hz, 2H), 6.64 (dd,  $J = 7.5, 5.0$  Hz, 1H), 5.09 (s, 2H), 2.37 (s, 3H).  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  158.8, 147.8, 139.9, 138.9, 131.4, 129.3, 119.6, 113.6, 103.4, 95.7, 83.8, 21.5. HRMS (APCI-ion trap) m/z:  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{14}\text{H}_{13}\text{N}_2$ , 209.1000; found, 209.1001.

**3-(4-Propylphenylethynyl)-2-aminopyridine (3c)**. Prepared according to general procedure. A yellow solid (198.6 mg, 92% yield). m.p. 92°C - 93°C.  $R_f = 0.40$  on silica gel (ethyl acetate/petroleum ether 1:5, v/v).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.05 - 8.00 (m, 1H), 7.58 (dd,  $J = 7.5, 1.8$  Hz, 1H), 7.42 (t,  $J = 8.2$  Hz, 2H), 7.16 (d,  $J = 8.1$  Hz, 2H), 6.62 (dd,  $J = 7.5, 5.0$  Hz, 1H), 5.18 (s, 2H), 2.61 - 2.58 (m, 2H), 1.64 (dd,  $J = 15.0, 7.5$  Hz, 2H), 0.94 (t,  $J = 7.3$  Hz, 3H).  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  158.9, 147.8, 143.7, 139.9, 131.4, 128.7, 119.9, 113.5, 103.4, 95.7, 83.8, 38.0, 24.3, 13.8. HRMS (APCI-ion trap) m/z:  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{16}\text{H}_{17}\text{N}_2$ , 237.1313; found, 237.1314.

**3-Biphenylethynyl-2-aminopyridine (3d)**. Prepared according to general procedure. Tan oil (129.4 mg, 96% yield).  $R_f = 0.42$  on silica gel (ethyl acetate/petroleum ether 1:5, v/v).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.05 (dd,  $J = 5.0, 1.7$  Hz, 1H), 7.63 - 7.59 (m, 7H), 7.46 (dd,  $J = 10.5, 4.8$  Hz, 2H), 7.37 (t,  $J = 7.4$  Hz, 1H), 6.67 (dd,  $J = 7.5, 5.0$  Hz, 1H), 5.08 (s, 2H).  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  158.8, 148.0, 141.4, 140.2, 140.0, 131.9, 128.9, 127.8, 127.1, 127.1, 121.6, 113.7, 103.2, 95.4, 85.1. HRMS (APCI-ion trap) m/z:  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{19}\text{H}_{15}\text{N}_2$ , 271.1157; found, 271.1158.

**3-Cyclopropylethynyl-2-aminopyridine (3e)**. Prepared according to general procedure. Yellow oil (70.4 mg, 88% yield).  $R_f = 0.35$  on silica gel (ethyl acetate/petroleum ether 1:5, v/v).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.99 - 7.91 (m, 1H), 7.45 (dd,  $J = 7.5, 1.8$  Hz, 1H), 6.57 (dd,  $J = 7.5, 5.1$  Hz, 1H), 4.99 (s, 2H), 1.49 (tt,  $J = 8.3, 5.0$  Hz, 1H), 0.93 - 0.88 (m, 2H), 0.81 (dt,  $J = 7.2, 4.3$  Hz, 2H).  $^{13}\text{C NMR}$  (125 MHz,  $\text{CDCl}_3$ )  $\delta$  158.9, 146.7, 139.6, 113.1, 103.7, 99.6, 70.6, 8.6. HRMS (APCI-ion trap) m/z:  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{10}\text{H}_{11}\text{N}_2$ , 159.0844; found, 159.0845.

**3-Decynyl-2-aminopyridine (3f)**. Prepared according to general procedure. Yellow oil (103.5 mg, 90% yield).  $R_f = 0.45$  on silica gel (ethyl acetate/petroleum ether 1:5, v/v).  $^1\text{H NMR}$  (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.89 (dd,  $J = 5.0, 1.7$  Hz, 1H), 7.38 (dd,  $J = 7.5, 1.8$  Hz, 1H), 6.49 (dd,  $J = 7.5, 5.0$  Hz, 1H), 5.07 - 4.95 (m, 2H), 2.37

(t,  $J = 7.1$  Hz, 2H), 1.57 - 1.51 (m, 2H), 1.27 - 1.17 (m, 10H), 0.80 (d,  $J = 7.0$  Hz, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  159.0, 147.0, 139.7, 113.3, 104.1, 96.9, 75.8, 31.8, 29.2, 29.1, 28.9, 28.8, 22.7, 19.6, 14.1. HRMS (APCI-ion trap)  $m/z$ :  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{15}\text{H}_{23}\text{N}_2$ , 231.1783; found, 231.1785.

**5-Methyl-3-phenylethynyl-2-aminopyridine (3g)**. Prepared according to general procedure. A light yellow solid (96.7 mg, 93% yield). m.p.  $85^\circ\text{C} - 86^\circ\text{C}$ .  $R_f = 0.40$  on silica gel (ethyl acetate/petroleum ether 1:5, v/v).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.80 (d,  $J = 1.6$  Hz, 1H), 7.43 (dt,  $J = 9.2, 2.9$  Hz, 2H), 7.36 (dd,  $J = 9.9, 1.9$  Hz, 1H), 7.30 - 7.26 (m, 3H), 4.82 (d,  $J = 42.9$  Hz, 2H), 2.12 (s, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  156.9, 147.9, 140.6, 131.5, 128.5, 128.5, 122.8, 122.6, 102.9, 95.3, 84.6, 17.3. MS (EI)  $m/z$ :  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{14}\text{H}_{13}\text{N}_2$ , 209.10; found, 209.23.

**5-Methyl-3-(4-methylphenylethynyl)-2-aminopyridine (3h)**. Prepared according to general procedure. A light yellow solid (123.5 mg, 87% yield). m.p.  $90^\circ\text{C} - 91^\circ\text{C}$ .  $R_f = 0.35$  on silica gel (ethyl acetate/petroleum ether 1:5, v/v).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.86 (d,  $J = 1.7$  Hz, 1H), 7.43 (d,  $J = 2.0$  Hz, 1H), 7.40 (d,  $J = 8.1$  Hz, 2H), 7.16 (d,  $J = 7.9$  Hz, 2H), 4.92 (s, 2H), 2.37 (s, 3H), 2.18 (s, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  156.9, 147.7, 140.5, 138.8, 131.4, 129.2, 122.5, 119.7, 103.1, 95.5, 84.0, 21.5, 17.3. HRMS (APCI-ion trap)  $m/z$ :  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{15}\text{H}_{15}\text{N}_2$ , 223.1157; found, 223.1158.

**5-Methyl-3-(4-methoxyphenylethynyl)-2-aminopyridine (3i)**. Prepared according to general procedure. Tan oil (105.9 mg, 89% yield).  $R_f = 0.36$  on silica gel (ethyl acetate/petroleum ether 1:5, v/v).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.85 (d,  $J = 1.6$  Hz, 1H), 7.43 (ddd,  $J = 11.0, 6.4, 2.3$  Hz, 3H), 6.87 (t,  $J = 5.7$  Hz, 2H), 5.01 (s, 2H), 3.81 (s, 3H), 2.17 (s, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  159.9, 156.99, 147.5, 140.4, 133.0, 122.4, 114.9, 114.1, 103.3, 95.3, 83.3, 55.3, 17.3. MS (EI)  $m/z$ :  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{15}\text{H}_{15}\text{N}_2\text{O}$ , 239.11; found, 239.18.

**5-Methyl-3-(4-propylphenylethynyl)-2-aminopyridine (3j)**. Prepared according to general procedure. A yellow solid (110.9 mg, 89% yield). m.p.  $88^\circ\text{C} - 89^\circ\text{C}$ .  $R_f = 0.40$  on silica gel (ethyl acetate/petroleum ether 1:5, v/v).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.79 (d,  $J = 1.6$  Hz, 1H), 7.35 (dd,  $J = 8.1, 1.7$  Hz, 3H), 7.09 (d,  $J = 8.2$  Hz, 2H), 4.85 (s, 2H), 2.54 - 2.50 (m, 2H), 2.11 (s, 3H), 1.57 (dd,  $J = 15.0, 7.5$  Hz, 2H), 0.87 (t,  $J = 7.3$  Hz, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  156.9, 147.7, 143.6, 140.5, 131.4, 128.6, 122.5, 120.0, 103.1, 95.5, 84.0, 38.0, 24.3, 17.3, 13.8. HRMS (APCI-ion trap)  $m/z$ :  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{17}\text{H}_{19}\text{N}_2$ , 251.1470; found, 251.1471.

**5-Methyl-3-biphenyl ethynyl-2-aminopyridine (3k)**. Prepared according to general procedure. Tan oil (123.4 mg, 90% yield).  $R_f = 0.41$  on silica gel (ethyl acetate/petroleum ether 1:5, v/v).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.89 (d,  $J = 1.3$  Hz, 1H), 7.63 - 7.58 (m, 6H), 7.46 (dd,  $J = 9.5, 5.3$  Hz, 3H), 7.26 (s, 1H), 4.95 (s, 2H), 2.21 (s, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  156, 147.9, 141.4, 140.7, 140.2, 131.9, 128.9, 127.8, 127.1, 127.1, 122.6, 121.7, 95.3, 85.3, 17.3. HRMS (APCI-ion trap)  $m/z$ :  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{20}\text{H}_{17}\text{N}_2$ , 285.1313; found, 285.1314.

**4-Methyl-3-( $\alpha$ -thienylethynyl)-2-aminopyridine (3l)**. Prepared according to general procedure. Yellow oil (95.2 mg, 89% yield).  $R_f = 0.40$  on silica gel (ethyl

acetate/petroleum ether 1:5, v/v).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.96 (t,  $J$  = 6.0 Hz, 1H), 7.47 - 7.42 (m, 2H), 6.91 - 6.86 (m, 2H), 5.14 (s, 2H), 3.83 (s, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  160.2, 157.1, 145.9, 138.8, 133.1, 120.1, 114.2, 104.8, 96.6, 82.0, 55.4. HRMS (APCI-ion trap)  $m/z$ :  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{12}\text{H}_{11}\text{N}_2\text{S}$ , 215.0565; found, 215.0566.

**5-Methyl-3-cyclopropylethynyl-2-aminopyridine (3m)**. Prepared according to general procedure. Yellow oil (76.5 mg, 89% yield).  $R_f$  = 0.40 on silica gel (ethyl acetate/petroleum ether 1:5, v/v).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.79 (d,  $J$  = 1.5 Hz, 1H), 7.29 (d,  $J$  = 2.0 Hz, 1H), 4.80 (s, 2H), 2.14 (s, 3H), 1.48 (tt,  $J$  = 8.3, 5.0 Hz, 1H), 0.90 (dt,  $J$  = 8.1, 3.1 Hz, 2H), 0.80 (dt,  $J$  = 7.2, 4.3 Hz, 2H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  157.2, 146.8, 140.6, 122.4, 103.7, 99.7, 71.0, 17.2, 8.9. HRMS (APCI-ion trap)  $m/z$ :  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{11}\text{H}_{13}\text{N}_2$ , 173.1000; found, 173.1002.

**5-Methyl-3-decynyl-2-aminopyridine (3n)**. Prepared according to general procedure. Yellow oil (102.5 mg, 84% yield).  $R_f$  = 0.35 on silica gel (ethyl acetate/petroleum ether 1:5, v/v).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.80 (d,  $J$  = 1.6 Hz, 1H), 7.31 (d,  $J$  = 2.1 Hz, 1H), 4.81 (s, 2H), 2.44 (t,  $J$  = 7.1 Hz, 2H), 2.15 (s, 3H), 1.37 - 1.21 (m, 12H), 0.89 (t,  $J$  = 6.7 Hz, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  157.1, 146.8, 146.8, 140.5, 122.4, 96.7, 75.9, 31.8, 29.3, 29.1, 28.9, 28.8, 22.7, 19.6, 17.2, 14.1. HRMS (APCI-ion trap)  $m/z$ :  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{16}\text{H}_{25}\text{N}_2$ , 245.1939; found, 245.1940.

**3-Phenylethynyl-2-amino-5-chloropyridine (3o)**. Prepared according to general procedure. A white solid (101.4 mg, 89% yield). m.p. 84°C - 85°C.  $R_f$  = 0.40 on silica gel (ethyl acetate/petroleum ether 1:5, v/v).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.98 (d,  $J$  = 2.5 Hz, 1H), 7.56 (d,  $J$  = 2.5 Hz, 1H), 7.52 - 7.49 (m, 2H), 7.37 (dt,  $J$  = 4.5, 2.3 Hz, 3H), 5.18 (s, 2H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  157.2, 146.4, 139.1, 131.6, 129.0, 128.6, 122.2, 120.1, 104.3, 96.5, 83.2. HRMS (APCI-ion trap)  $m/z$ :  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{13}\text{H}_{10}\text{ClN}_2$ , 229.0454; found, 229.0455.

**3-(4-Propylphenylethynyl)-2-amino-5-chloropyridine (3p)**. Prepared according to general procedure. A Yellow solid (110.9 mg, 85% yield). m.p. 83°C - 84°C.  $R_f$  = 0.40 on silica gel (ethyl acetate/petroleum ether 1:5, v/v).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.97 (d,  $J$  = 1.9 Hz, 1H), 7.58 - 7.54 (m, 1H), 7.42 (d,  $J$  = 8.2 Hz, 2H), 7.18 (d,  $J$  = 8.2 Hz, 2H), 5.11 (s, 2H), 2.62 - 2.59 (m, 2H), 1.64 (t,  $J$  = 6.0 Hz, 2H), 0.96 - 0.93 (m, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  157.1, 146.1, 144.1, 138.9, 131.6, 131.6, 128.9, 128.6, 128.4, 119.3, 96.8, 82.6, 38.0, 24.3, 13.8. HRMS (APCI-ion trap)  $m/z$ :  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{16}\text{H}_{16}\text{ClN}_2$ , 271.0924; found, 271.0925.

**3-Decynyl-2-amino-5-chloropyridine (3q)**. Prepared according to general procedure. Colorless oil (118.8 mg, 90% yield).  $R_f$  = 0.45 on silica gel (ethyl acetate/petroleum ether 1:5, v/v).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.91 (d,  $J$  = 2.4 Hz, 1H), 7.43 (d,  $J$  = 2.5 Hz, 1H), 5.13 (s, 2H), 2.44 (t,  $J$  = 7.1 Hz, 2H), 1.43 (dd,  $J$  = 10.1, 4.7 Hz, 2H), 1.35 - 1.24 (m, 10H), 0.89 (t,  $J$  = 7.0 Hz, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  157.5, 145.3, 138.9, 119.8, 105.3, 98.2, 74.9, 31.8, 29.3, 29.1, 28.9, 28.6, 22.7, 19.6, 14.1. HRMS (APCI-ion trap)  $m/z$ :  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{15}\text{H}_{22}\text{ClN}_2$ , 265.1393; found, 265.1395.

**4-Methyl-3-( $\alpha$ -thienylethynyl)-2-amino-5-bromopyridine (3r)**. Prepared ac-

ording to general procedure. Colorless oil (113.8 mg, 78% yield).  $R_f = 0.40$  on silica gel (ethyl acetate/petroleum ether 1:5, v/v).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.88 (d,  $J = 1.7$  Hz, 1H), 7.43 (t,  $J = 4.6$  Hz, 1H), 7.33 - 7.29 (m, 1H), 7.28 - 7.26 (m, 1H), 4.96 (d,  $J = 42.1$  Hz, 2H), 2.19 (s, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  156.8, 148.2, 140.6, 132.1, 127.7, 127.2, 122.8, 122.6, 102.5, 88.3, 88.3, 17.3. HRMS (APCI-ion trap)  $m/z$ :  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{12}\text{H}_{10}\text{BrN}_2\text{S}$ , 292.9670; found, 292.9671.

**4-Methyl-3-cyclopropylethynyl-2-amino-5-bromopyridine (3s)**. Prepared according to general procedure. Light brown oil (90.3 mg, 72% yield).  $R_f = 0.43$  on silica gel (ethyl acetate/petroleum ether 1:5, v/v).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  7.73 (dd,  $J = 12.0, 1.7$  Hz, 1H), 4.75 (d,  $J = 42.5$  Hz, 2H), 2.06 (s, 3H), 1.41 (tt,  $J = 8.3, 5.0$  Hz, 1H), 0.87 - 0.77 (m, 2H), 0.70 (ddt,  $J = 12.4, 6.3, 4.0$  Hz, 2H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ )  $\delta$  157.0, 146.5, 140.3, 122.0, 103.3, 99.3, 70.7, 16.9, 8.6. MS (EI)  $m/z$ :  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{11}\text{H}_{12}\text{BrN}_2$ , 251.0106; found, 251.0107.

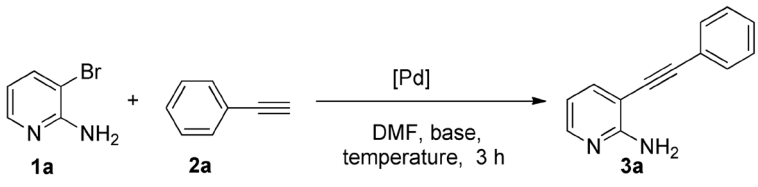
**5-Trifluoromethyl-3-phenylethynyl-2-aminopyridine (3t)**. Prepared according to general procedure. A light yellow solid (119.2 mg, 91% yield). m.p.  $79^\circ\text{C}$  -  $79^\circ\text{C}$ .  $R_f = 0.40$  on silica gel (ethyl acetate/petroleum ether 1:5, v/v).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.27 (s, 1H), 7.80 (d,  $J = 2.0$  Hz, 1H), 7.53 (dd,  $J = 6.5, 3.1$  Hz, 2H), 7.42 - 7.34 (m, 3H), 5.66 (s, 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  160.5, 145.3, 145.3, 136.9, 136.9, 131.6, 129.2, 128.6, 122.0, 102.9, 96.6, 82.9. MS (EI)  $m/z$ :  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{14}\text{H}_9\text{F}_3\text{N}_2$ , 263.07; found, 263.08.

**5-Carboxy-3-phenylethynyl-2-aminopyridine (3u)**. Prepared according to general procedure. Tan oil (107.1 mg, 90% yield).  $R_f = 0.40$  on silica gel (ethyl acetate/petroleum ether 1:5, v/v).  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ )  $\delta$  8.07 (d,  $J = 2.3$  Hz, 1H), 7.69 (d,  $J = 2.3$  Hz, 1H), 7.51 (dd,  $J = 6.6, 3.0$  Hz, 2H), 7.37 (dd,  $J = 5.0, 1.7$  Hz, 3H), 5.17 (s, 2H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ )  $\delta$  157.4, 148.5, 141.6, 131.5, 131.5, 129.0, 128.6, 122.2, 107.1, 104.9, 96.6, 83.1. HRMS (APCI-ion trap)  $m/z$ :  $[\text{M} + \text{H}]^+$  calcd for  $\text{C}_{14}\text{H}_9\text{F}_3\text{N}_2$ , 239.0742; found, 239.0741.

### 3. Results and Discussion

To get the best reaction conditions, we chose the cross-coupling of 2-amino-3-bromopyridine (0.5 mmol) (**1a**) with phenylacetylene (0.6 mmol) (**2a**) as the model reaction. We optimized the reaction conditions by using different bases and solvents, as well as changing the reaction temperature. The results are summarized in **Table 1**. First, we used Pd complexes combined with  $\text{Pd}(\text{OAc})_2$  (2.5 mol%) and  $\text{PPh}_3$  (5 mol%) as catalysts, CuI as a co-catalyst,  $\text{Et}_3\text{N}$  as base, dimethyl formamide (DMF) as a solvent for 3 h under  $100^\circ\text{C}$ , the product **3a** was obtained in the yield of 79% (**Table 1**, entry 1). Then, we began to optimize the Pd-type catalysts, such as  $\text{Pd}(\text{OAc})_2/\text{PPh}_3$ ,  $\text{PdCl}_2(\text{PPh}_3)_2/\text{PPh}_3$ , and  $\text{Pd}(\text{CF}_3\text{COO})_2/\text{PPh}_3$ . When chose  $\text{Pd}(\text{CF}_3\text{COO})_2/\text{PPh}_3$  as a catalyst, afforded the corresponding product **3a** in the yield of 96% (**Table 1**, entries 1 - 3). The amount loading of catalyst is also optimized. We chose  $\text{Pd}(\text{CF}_3\text{COO})_2/\text{PPh}_3$  as the catalyst, we found that the yield increased with the increase the amount of catalyst loading. When the amount of catalyst loading increased from 0.25 mol% to 0.50 mol%,



**Table 1.** Optimization of reaction conditions<sup>a</sup>.


Entry	Catalyst	Solvent	Base	Temp. (°C)	Yield <sup>b</sup> (%)
1	Pd(OAc) <sub>2</sub> (2.5 mol%) PPh <sub>3</sub> (5 mol%)/CuI (5 mol%)	DMF	Et <sub>3</sub> N (1.0 mL)	100	79
2	PdCl <sub>2</sub> (PPh <sub>3</sub> ) <sub>2</sub> (2.5 mol%)/CuI (5 mol%)	DMF	Et <sub>3</sub> N (1.0 mL)	100	56
3	Pd(CF <sub>3</sub> COO) <sub>2</sub> (2.5 mol%)/PPh <sub>3</sub> (5 mol%)/CuI (5 mol%)	DMF	Et <sub>3</sub> N (1.0 mL)	100	96
4	Pd(CF <sub>3</sub> COO) <sub>2</sub> (1.0 mol%) PPh <sub>3</sub> (2 mol%)/CuI (2 mol%)	DMF	Et <sub>3</sub> N (1.0 mL)	100	61
5	Pd(CF <sub>3</sub> COO) <sub>2</sub> (5 mol%) PPh <sub>3</sub> (10 mol%)/CuI (5 mol%)	DMF	Et <sub>3</sub> N (1.0 mL)	100	95
6	Pd(CF <sub>3</sub> COO) <sub>2</sub> (2.5 mol%) PPh <sub>3</sub> (5 mol%)	DMF	Et <sub>3</sub> N (1.0 mL)	100	66
7	Pd(CF <sub>3</sub> COO) <sub>2</sub> (2.5 mol%) PPh <sub>3</sub> (5 mol%)/CuI (2.5 mol%)	DMF	Et <sub>3</sub> N (1.0 mL)	100	78
8	Pd(CF <sub>3</sub> COO) <sub>2</sub> (2.5 mol%) PPh <sub>3</sub> (5 mol%)/CuI (7 mol%)	DMF	Et <sub>3</sub> N (1.0 mL)	100	97
9	Pd(CF <sub>3</sub> COO) <sub>2</sub> (2.5 mol%)/CuI (5 mol%)	DMF	Et <sub>3</sub> N (1.0 mL)	100	trace
10	PPh <sub>3</sub> (5 mol%)/CuI (5 mol%)	DMF	Et <sub>3</sub> N (1.0 mL)	100	-
11	Pd(CF <sub>3</sub> COO) <sub>2</sub> (2.5 mol%)/PPh <sub>3</sub> (5 mol%)/CuI (5 mol%)	DMSO	Et <sub>3</sub> N (1.0 mL)	100	91
12	Pd(CF <sub>3</sub> COO) <sub>2</sub> (2.5 mol%)/PPh <sub>3</sub> (5 mol%)/CuI (5 mol%)	THF	Et <sub>3</sub> N (1.0 mL)	100	-
13	Pd(CF <sub>3</sub> COO) <sub>2</sub> (2.5 mol%)/PPh <sub>3</sub> (5 mol%)/CuI (5 mol%)	DMF	-	100	trace
14	Pd(CF <sub>3</sub> COO) <sub>2</sub> (2.5 mol%) PPh <sub>3</sub> (5 mol%)/CuI (5 mol%)	DMF	K <sub>2</sub> CO <sub>3</sub> (1.2 equiv.)	100	86
15	Pd(CF <sub>3</sub> COO) <sub>2</sub> (2.5 mol%) PPh <sub>3</sub> (5 mol%)/CuI (5 mol%)	DMF	NaOAc (1.2 equiv.)	100	83
16	Pd(CF <sub>3</sub> COO) <sub>2</sub> (2.5 mol%) PPh <sub>3</sub> (5 mol%)/CuI (5 mol%)	DMF	Et <sub>3</sub> N (1.0 mL)	80	90
17	Pd(CF <sub>3</sub> COO) <sub>2</sub> (2.5 mol%) PPh <sub>3</sub> (5 mol%)/CuI (5 mol%)	DMF	Et <sub>3</sub> N (1.0 mL)	25	-
18	Pd(CF <sub>3</sub> COO) <sub>2</sub> (2.5 mol%) PPh <sub>3</sub> (5 mol%)/CuI (5 mol%)	DMF	Et <sub>3</sub> N (1.0 mL)	130	90
19 <sup>c</sup>	Pd(CF <sub>3</sub> COO) <sub>2</sub> (2.5 mol%) PPh <sub>3</sub> (5 mol%)/CuI (5 mol%)	DMF	Et <sub>3</sub> N (1.0 mL)	100	85

<sup>a</sup>Reaction conditions: Pd Catalyst, CuI and PPh<sub>3</sub> in DMF (2 mL) were stirred for 30 min under N<sub>2</sub> atm. Then, **1a** (0.5 mmol) with **2a** (1.2 equiv.) were added, and the reaction mixture was stirred for 3 h. <sup>b</sup>Isolated yields after column chromatography. <sup>c</sup>Without N<sub>2</sub> protection.

the yield was not changed. If we kept the same amount of palladium catalyst, changed the loading amount of the cuprous iodide, reaction yield has big changes. Without the cuprous iodide as additive, the yield is 66% (Table 1, entry 6); Continue to optimize the cuprous salt, we found that with the increment loading amount of cuprous iodide, the yield was increased, while it increased to 7 mol%, the yield was increased to be 97% (Table 1, entries 7 - 8). If no palladium only cuprous iodide as additive in the reaction, the reaction cannot occur (Table 1, entry 9). If only have Pd(CF<sub>3</sub>COO)<sub>2</sub> without triphenylphosphine, only a small amount of product **3a** by TLC testing (Table 1, entry 10). Next, the solvent was optimized, the reaction cannot be carried out in tetrahydrofuran (THF). It has a high yield when we chose *N,N*-dimethyl formamide (DMF) or dimethyl sulfoxide (DMSO) as solvents, while has a higher yield to use DMF as a solvent (Table 1, entries 3, 11 - 12). We found that the bases was also affected the cross-coupling reaction. It only produced trace amounts of products without base (Table 1, entry 13); Therefore, we added potassium carbonate or sodium acetate as the bases for the cross-coupling reaction (Table 1, entries 14 - 15). Temperature also influences the Sonogashira coupling reactions. At ambient temperature conditions, coupling reactions cannot occur, as temperatures rise, the yields have greatly improved; but when the temperature continues to rise, there is a slight fall in yield (Table 1, entries 16 - 18). It may be due to rising temperatures make alkynes couple itself, producing by-products. So the best coupling reaction temperature is 100°C. In the absence of nitrogen atmosphere protection, the yield is 85%, which indicates that the reaction can also occur in the air (Table 1, entry 19). Therefore, the optimal reaction conditions are 2.5 mol% Pd(CF<sub>3</sub>COO)<sub>2</sub> as catalyst, 5 mol% PPh<sub>3</sub> as ligand, 5 mol% CuI as additive, 1 mL Et<sub>3</sub>N as base, DMF as solvent, reaction time 3 h, and temperature 100°C for the Sonogashira cross-coupling reaction.

After the optimal reaction conditions, we began to expand the different substrates **1**, these substrates react with all kinds of terminal alkynes **2** afforded the corresponding products **3** in good yields (up to 96%) in Table 2.

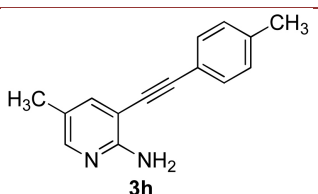
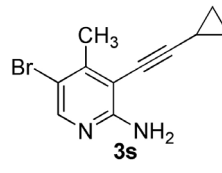
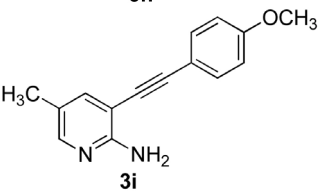
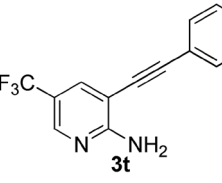
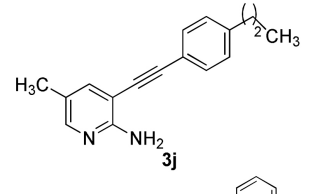
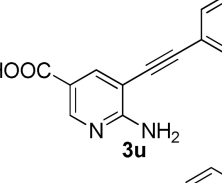
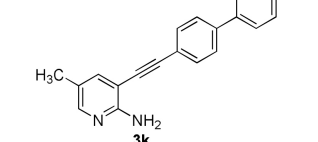
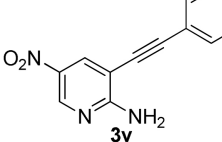
First of all, we took 2-amino-3-bromopyridine **1a** as the substrate and found that when it reacts with various aryl acetylene compounds, the yields are more than 90% (Table 2, entries 1 - 4); When 2-amino-3-bromopyridine **1a** reacts with cyclopropyl acetylene, the yield is 88% (Entry 5); When 1-decyne reacts with 2-amino-3-bromopyridine **1a**, the yield of which is slightly lower, just 85% (Table 2, entry 6). When we took pyridine ring with electronic pushing substituents 2-amino-3-bromo-5-methyl pyridine **1b** as a substrate, **1b** reacted with various terminal alkynes **2**, the yields are up to 93% (Table 2, entries 7 - 14). When we took pyridine ring with electronic withdrawing substituents **1c**, **1e**, and **1f** as substrates, no matter react with terminal aryl acetylene, or with the terminal alkyl acetylene, the yields are up to 91% (Table 2, entries 15 - 17 and 21 - 22); But with 2,5-dibromo-4-methyl-pyridin-3-yl amine **1d** as a substrate, the yield of the product decreased (Table 2, entries 18 - 19); And with 2-bromo-5-nitro-pyridin-3-yl amine **1g** as a substrate, the coupling reaction is not



**Table 2.** Coupling scope of palladium-catalyzed 2-amino-3-bromopyridines with various terminal alkynes<sup>a</sup>.

Entry	Compd. 3	Yield <sup>b</sup> (%)	Entry	Compd. 3	Yield <sup>b</sup> (%)
<p style="text-align: center;"> </p> <p style="text-align: center;"> <b>1</b> + <b>2</b> <math>\xrightarrow[\text{Et}_3\text{N, DMF, 100 }^\circ\text{C, 3 h}]{\text{Pd}(\text{CF}_3\text{COO})_2 \text{ (2.5 mol\%)}, \text{PPh}_3 \text{ (5 mol\%)}, \text{Cul (5 mol\%)}}</math> <b>3a ~ 3v</b> </p> <p style="text-align: center;"> <b>1a:</b> R<sup>1</sup> = H, R<sup>2</sup> = H  <b>1b:</b> R<sup>1</sup> = CH<sub>3</sub>, R<sup>2</sup> = H  <b>1c:</b> R<sup>1</sup> = Cl, R<sup>2</sup> = H  <b>1d:</b> R<sup>1</sup> = Br, R<sup>2</sup> = CH<sub>3</sub>  <b>1e:</b> R<sup>1</sup> = CF<sub>3</sub>, R<sup>2</sup> = H  <b>1f:</b> R<sup>1</sup> = COOH, R<sup>2</sup> = H  <b>1g:</b> R<sup>1</sup> = NO<sub>2</sub>, R<sup>2</sup> = H         </p>					
1		96	12		89
2		94	13		89
3		92	14		84
4		96	15		88
5		88	16		85
6		85	17		80
7		93	18		78

## Continued

8		87	19		72
9		89	20		91
10		89	21		90
11		90	22		-

<sup>a</sup>Reaction conditions: Pd(CF<sub>3</sub>COO)<sub>2</sub> (2.5 mol%), PPh<sub>3</sub> (5 mol%) and CuI (5 mol%) in DMF (2 mL) was stirred for 30 min under N<sub>2</sub> atm. Then, **1** (0.5 mmol) with **2** (1.2 equiv) were added, and the reaction mixture was stirred at 100 °C for 3 h. <sup>b</sup>Isolated yields after column chromatography.

able to occur (Table 2, entry 22).

#### 4. Conclusion

In summary, we have developed a simple and efficient method for preparing functionalized the 2-amino-3-ynylpyridine and its derivatives **3** via 2-amino-3-bromopyridines **1** with a series of terminal alkynes **2** catalyzed by palladium catalyst. A wide range of terminal alkynes were suitable to give the corresponding 2-amino-3-ynylpyridine and its derivative products **3** with high yields. On the other hand, the 2-amino-3-ynylpyridines **3** are the essential raw materials for the synthesis of the heterocycle compounds, such as azaindole, pyridines and quinolines. Further development of coupling reactions is underway in our laboratories and will be reported in due course.

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#### Competing Interests

Authors have declared that no competing interests exist.

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