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Graphical Abstract

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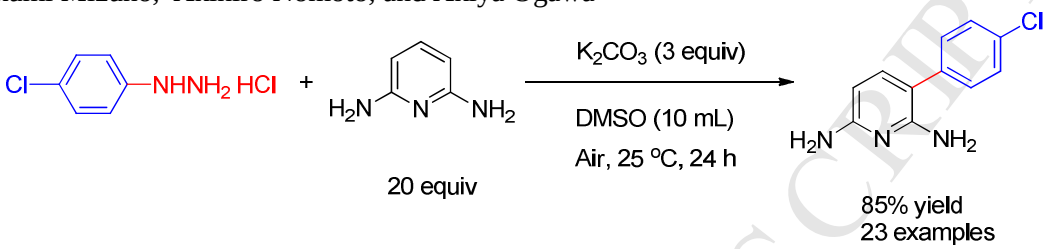

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Metal-free C–H arylation of aminoheterocycles with arylhydrazines

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ABSTRACT

A direct C–H arylation of aminoheterocycles with arylhydrazine hydrochlorides was developed. The reaction proceeds via a homolytic aromatic substitution mechanism involving aryl radicals as the intermediates. The new reaction takes place readily at room temperature in air and in the presence of an inexpensive base. Moreover, the reactivity of this radical arylation correlated with the HOMO energy of aminoheterocycles. This method provides not only a rapid access to diverse arylated heterocycles, but also an atom-efficient alternative to conventional transition-metal-catalyzed cross-coupling between halides and organometallics.

1. Introduction

The use of transition-metal catalysts helped to rapidly develop aromatic coupling reactions, which are very important in organic chemistry, e.g., Mizoroki–Heck reaction,[1] Suzuki–Miyaura coupling,[2] and Negishi coupling.[3] The great success of cross-coupling reactions using transition-metal catalysts led to the Nobel Prize in chemistry in 2010. To use these reactions in industrial scale, however, researchers in companies often face to the following problems: 1) Most of the transition-metal catalysts, e.g., Pd catalysts, are very expensive, and some of them are toxic. 2) The removal of transition metal residues from the target products is very costly. Therefore, the development of aromatic substitutions in the absence of transition-metal catalysts is strongly desired from practical perspective.

A conceptually different approach about aromatic substitution is the direct C–H radical arylation of arenes involving a homolytic aromatic substitution (HAS) mechanism.[4] A similar type of reaction was first reported by Gomberg and Bachmann in 1924.[5] Recently, much attention has been paid to the use of arylhydrazines as the radical sources in HAS mechanism.[6] New elegant arylations of anilines with arylhydrazines or aryldiazonium salts have been reported to be a valuable alternative to transition-metal-based arylations.[7] In the reported reaction systems, the free amino functionality of anilines led to high ortho regioselectivities, and 2-arylanilines have been synthesized in reasonable yields.

Substituted heterocycles are valuable building blocks in many fields such as medicinal chemistry and materials science. In particular, an important subgroup of substituted heterocycles is diaminoheterocycles. For example, lamotrigine was developed as an anticonvulsant for the treatment of bipolar depression.[8] Moreover, compounds **A** and **B** are selective $Na_v1.8$ modulators[9] (Figure 1).

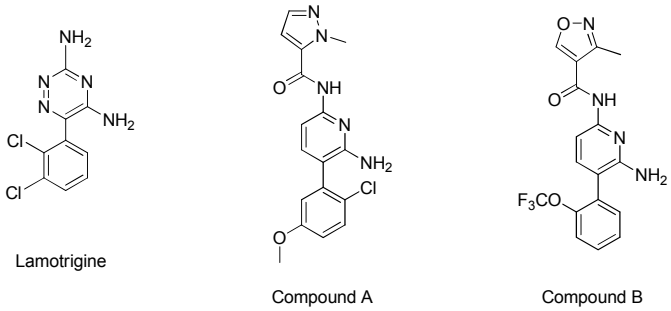


Figure 1. Lamotrigine and compounds **A** and **B**.

Our company manufactures aromatic diamines, which are not only useful as the raw materials of functional plastics, but also significant as the polymer intermediates for aerospace applications and information technology. Therefore, we studied the practical arylation of heterocyclic diamines without using transition-metal catalysts. Particularly, the challenge was to perform the radical arylation of aminoheterocycles with regioselectivity. Recently, the direct arylation of pyridines with

arylhydrazine hydrochlorides under mild conditions was reported, although the regioselectivity of this arylation reaction was not satisfactory.[6f]

2. Results and discussion

First, the arylation of 2,6-diaminopyridine **2a** (10 equiv) with *p*-chlorophenylhydrazine hydrochloride **1a** in the presence of potassium carbonate at 25 °C for 24 h in air was investigated. To our delight, a regioselective reaction occurred, affording 2,6-diamino-3-(4′-chlorophenyl)pyridine **3aa** in a high yield (78%, Table 1, entry 1). Herein, we report the arylation of aminoheterocycles with arylhydrazine hydrochlorides as the radical source in detail. To the best of our knowledge, this is the first example of the radical arylation of aminoheterocycles with arylhydrazines.

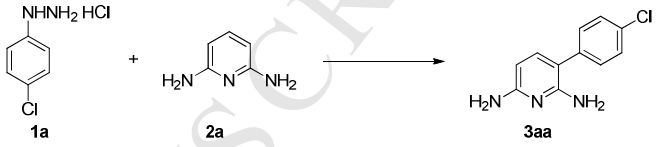
In the selection of solvents, a combination of DMSO and potassium carbonate[6c,6g] worked well the present radical arylation, producing **3aa** in a good yield (78%, entry 1). When DMF or DMA was used instead of DMSO, the yield of **3aa** decreased (entries 2 and 3). Acetonitrile provided **3aa** in a moderate yield[6b,6d,7f] (entry 4). Because **2a** is soluble in water, the use of water as a solvent was also investigated for the arylation. However, the arylation in water almost did not proceed (entry 5). The use of HFIP (1,1,1,3,3,3-hexafluoro-2-propanol), an effective radical stabilizer for the chelated radical–anion oxidative coupling of phenols in the presence of an iron catalyst,[10a] provided an inferior result. The product **3aa** was not obtained at all (entry 6).

Next, several bases were screened; **3aa** was obtained in moderate-to-good yields when lithium carbonate, sodium carbonate, or cesium carbonate was used (entries 7–9). The addition of an aqueous solution of KOH or NaOH was not effective for the formation of **3aa** (entries 10 and 11). Triethylamine furnished **3aa** in a moderate yield (entry 12). Surprisingly, in the absence of a base, the product **3aa** was obtained in a fair yield (55%, entry 13). Excess **2a** may have worked as a base as shown in the previous report.[6f] High reaction temperatures did not improve the yield of **3aa** (entries 14 and 15). The best yield (85%) of **3aa** was obtained when 20 equiv of **2a** was used (entry 16). Under a nitrogen atmosphere, a low yield of **3aa** was obtained (entry 17). When the amount of **2a** was reduced, the yield of **3aa** decreased (entries 18 and 19). Slow addition of **1a** was tried into the mixture of **2a** (1equiv) and K_2CO_3 for 4 h using syringe pump (entry 20). However, improvement of the yield was not observed. Different reaction times (48 h or 8 h) did not improve the yield of **3aa** (entries 21 and 22).

With the optimized conditions, the substrate scope and limitations of the arylation of aminoheterocycles **2a**–**2k** with various arylhydrazine hydrochlorides **1a–1i** were investigated (Table 2). The arylation of 2,6-diaminopyridine **2a** with arylhydrazine hydrochlorides **1a**–**1e** bearing electron-withdrawing groups such as Cl, F, Br, and CN smoothly afforded the corresponding target compounds **3aa**–**3ea** in good-to-excellent yields (entries 1–5). Moreover, phenylhydrazine hydrochloride and arylhydrazine hydrochlorides bearing electron-donating groups such as OMe and Me showed similar reactivities, producing **3fa**–**3ha** in good yields (entries 6–8). However, 4-nitrophenylhydrazine **1i** bearing a strong electron-withdrawing group provided a trace amount of **3ia** (entry 9). The results clearly indicate the high radical-scavenging ability of 2,6-diaminopyridine **2a** for phenyl radicals. The attack of phenyl radicals may be facilitated at the ortho and para positions of the amino group in **2a**.

Next, 2-aminopyridine **2b** underwent cross-coupling reaction at the 3-position preferentially, affording **3ab** and **3cb** in moderate yields (entries 10 and 11). Moreover, 5-substituted and 5,6-disubstituted 2-aminopyridines produced the corresponding products **3ac**, **3ad**, **3ae**, **3af**, and **3bf** in moderate yields (entries 12–16). Further, 3-aminopyridine **2g** underwent cross-coupling reaction at the 2-position preferentially, furnishing **3ag**–**3cg** in moderate-to-good yields (entries 17–19). A reported oxidative chlorination of **2g** with hydrochloric acid and hydrogen peroxide showed similar regioselectivity, resulting in the chlorination of **2g** at the 2-position.[11] As shown in entries 17–19, 4-isomers **3ag′**–**3cg′** and 6-isomers **3ag″**–**3cg″** were obtained as the minor products. Interestingly, 3-aminoquinoline **2h** afforded 4-substituted product **3ah** in a good yield (entry 20). The radical intermediate obtained by the reaction of **2h** might be resonance-stabilized, and 4-isomer **3ah** was obtained selectively. Moreover, 2-isomer **3ah′** was obtained as a minor product.

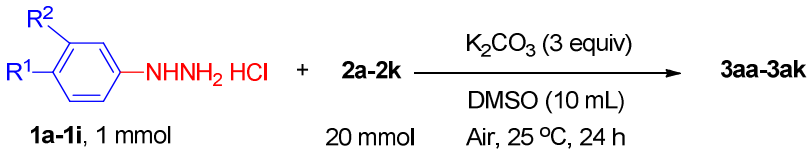
Table 1. Optimization of Synthesis of **3aa**

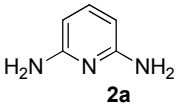
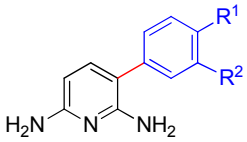
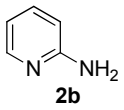
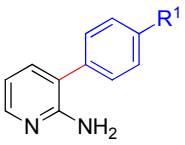
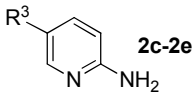
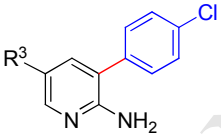
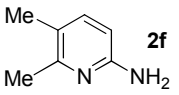
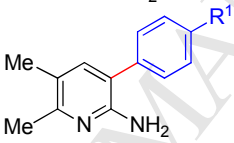
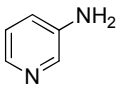
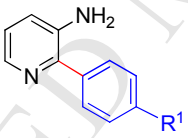
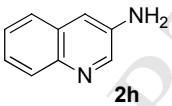
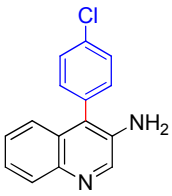
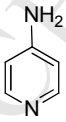
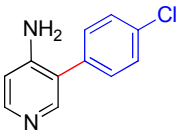
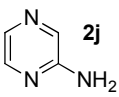
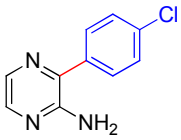
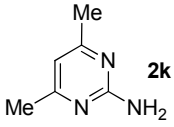
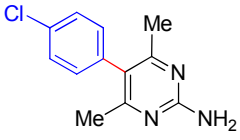


Entry	Solvent	Base	Temp (°C)	Equiv of **2a**	Time (h)	Yield (%)[a]
1	DMSO	K_2CO_3	25	10	24	78
2	DMF	K_2CO_3	25	10	24	44
3	DMA	K_2CO_3	25	10	24	61
4	MeCN	K_2CO_3	25	10	24	48
5	H_2O	K_2CO_3	25	10	24	trace
6	HFIP[b]	K_2CO_3	25	10	24	0
7	DMSO	Li_2CO_3	25	10	24	66
8	DMSO	Na_2CO_3	25	10	24	76
9	DMSO	Cs_2CO_3	25	10	24	43
10	DMSO	KOH	25	10	24	trace[c]
11	DMSO	NaOH	25	10	24	trace[c]
12	DMSO	Et_3N	25	10	24	49
13	DMSO	none	25	10	24	55
14	DMSO	K_2CO_3	50	10	24	66
15	DMSO	K_2CO_3	100	10	24	16
16	DMSO	K_2CO_3	25	20	24	85
17	DMSO	K_2CO_3	25	20	24	40[d]
18	DMSO	K_2CO_3	25	5	24	59
19	DMSO	K_2CO_3	25	2	24	40
20	DMSO	K_2CO_3	25	1	24	26[e]
21	DMSO	K_2CO_3	25	10	48	76
22	DMSO	K_2CO_3	25	10	8	74

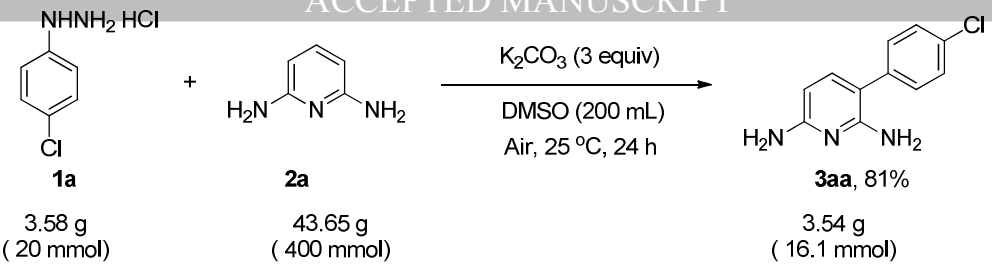
Reaction conditions: **1a** (1.0 mmol), base (3.0 mmol), and solvent (10 mL) in air. [a] Isolated yields based on **1a**. [b] 1,1,1,3,3,3-Hexafluoro-2-propanol. [c] An aqueous solution (1 N, 3.0 mL) of KOH or NaOH was used. [d] Under a nitrogen atmosphere. [e] DMSO (5 mL) solution of **1a** was slowly added into the mixture of **2a** (1equiv) and K_2CO_3 in DMSO (5 mL) for 4 h.

Table 2. The Reaction of Arylhydrazines with Aminoheterocycles



Entry	2a-2k	3aa-3ak		Yield (%)[a]
1			**3aa**; R^1 = Cl, R^2 = H	85
2			**3ba**; R^1 = F, R^2 = H	76
3			**3ca**; R^1 = Br, R^2 = H	74
4			**3da**; R^1 = CN R^2 = H	60
5			**3ea**; R^1 = Cl, R^2 = Cl	63
6	**2a**		**3fa**; R^1 = H, R^2 = H	59
7			**3ga**; R^1 = OMe, R^2 = H	58
8			**3ha**; R^1 = Me, R^2 = H	60
9			**3ia**; R^1 = NO_2, R^2 = H	trace
10			**3ab**; R^1 = Cl	36[b]
11	**2b**		**3cb**; R^1 = Br	37[b]
12			**3ac**; R^3= Me	37
13			**3ad**; R^3 = Cl	47
14	**2c-2e**		**3ae**; R^3 = Br	49
15			**3af**; R^1 = Cl	34
16	**2f**		**3bf**; R^1 = F	30
17			**3ag**; R^1 = Cl	75[c]
18			**3bg**; R^1 = F	55[d]
19	**2g**		**3cg;** R^1 = Br	63[e]
20	 **2h**		**3ah**	83[f]
21	 **2i**		**3ai**	trace
22	 **2j**		**3aj**	56
23	 **2k**		**3ak**	19

[a] Isolated yields after purification by column chromatography, based on arylhydrazines. [b] A small amount of isomer was also formed, but not isolated. [c] 2-Isomer (**3ag**, 52%), 4-isomer (**3ag′**, 15%) and 6-isomer (**3ag″**, 8%) were obtained. [d] 2-Isomer (**3bg**, 38%), 4-isomer (**3bg′**, 11%) and 6-isomer (**3bg″**, 6%) were formed. [e] 2-Isomer (**3cg**, 47%) , 4-isomer (**3cg′**, 11%) and 6-isomer (**3cg″**, 5%) were obtained. [f] 4-Isomer (**3ah**, 74%) and 2-Isomer (**3ah′**, 9%) were formed.



Scheme 1. Large-Scale Synthesis of **3aa**

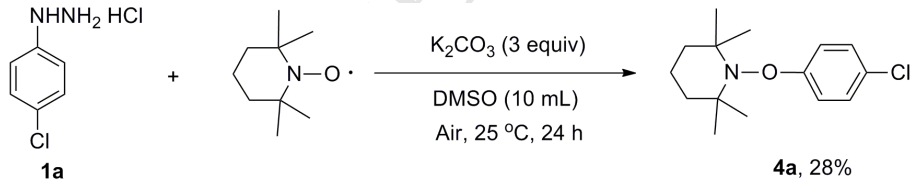
In contrast, 4-aminopyridine did not afford the corresponding product **3ai** (entry 21). These results clearly show the difference in the reactivities between 2,6-diaminopyridine **2a**, 2-aminopyridine **2b**, 3-aminopyridine **2g**, and 4-aminopyridine **2i**. Finally, the cross-coupling reactions with other aminoheterocycles **2j** and **2k** were carried out successfully (entries 22 and 23).

Next, the feasibility of a large-scale synthesis (20-fold) of **3aa** was investigated (Scheme 1). Starting from **1a** and **2a**, the desired 2,6-diamino-3-(4′-chlorophenyl)pyridine (**3aa**) was obtained in 81% yield and excess **2a** was recovered in almost 90% yield without the formation of any byproducts.

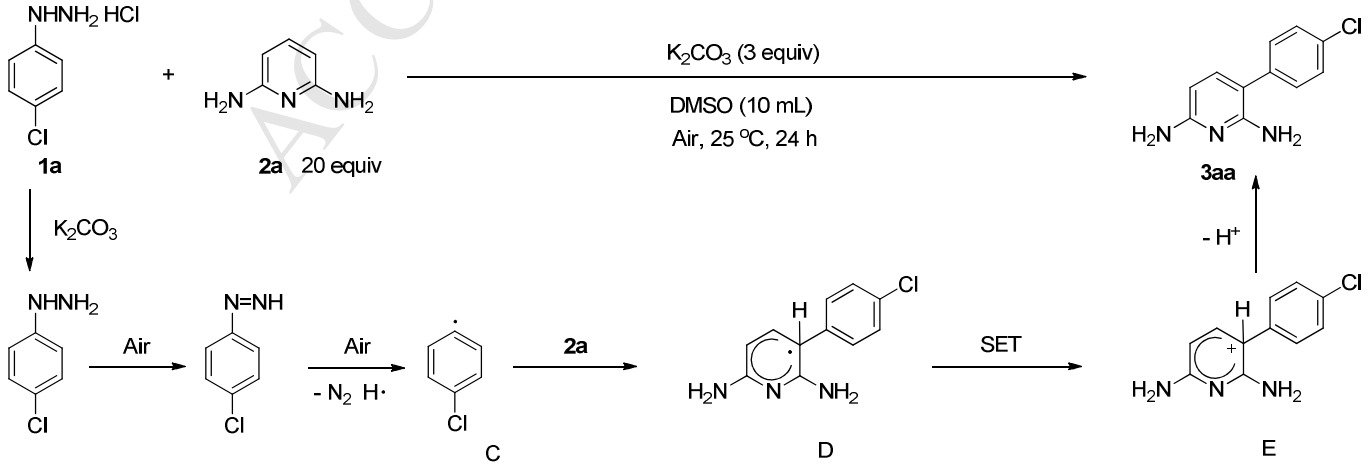
To better understand the arylation with **2**, DFT calculations at the B3LYP/6-31G(d,p) level were carried out. Recently, a correlation between the energy of the HOMO of a molecule and its relative nucleophilicity was shown in the radical–anion oxidative coupling of phenols, and a global scale of calculated nucleophilicity, N, was determined.[10] The HOMO energy levels of the aminoheterocycles in this arylation system correlated with their nucleophilicity. 2,6-Diaminopyridine (**2a**) with a high HOMO energy (–5.14 eV) had a high global nucleophilicity. In fact, **2a** showed a high reactivity with *p*-chlorophenyl radical, producing **3aa** in an excellent yield (Table 2, entry 1). 2-Aminopyridine (**2b**) and 3-aminopyridine (**2g**) had moderate HOMO energies, –5.74 eV and –5.77 eV, respectively, and reacted with aryl radicals to afford the corresponding products in moderate to good yields. Conversely, 4-aminopyridine (**2i**) with a very low HOMO energy (–6.10 eV) was expected to have a low global nucleophilicity. When **2i** was used, the corresponding product **3ai** was not obtained.

To support the radical mechanism, a radical-trapping experiment was carried out using TEMPO. The oxidation of **1a** with TEMPO (1.5 equiv) in air under the optimized conditions (Table 1, entry 16) afforded 4-chloro-1-(2,2,6,6-tetramethyl-piperidinyloxy)benzene **4a** in 28% yield (Scheme 2).

Based on the experimental results and previous studies on HAS reactions,[4,7] a plausible reaction mechanism for the arylation of **2a** with **1a** is proposed in Scheme 3. After the preparation of the free-base hydrazine from **1a** by treating with K_2CO_3, the free-base hydrazine is oxidized by air to form the corresponding diazene. Then, the diazene is converted into radical **C** by oxidation with air. The addition of radical **C** to **2a** provides the intermediate cyclohexadienyl radical **D**. The radical **D** converts into cation **E** via single electron transfer (SET). Finally, the elimination of a hydrogen cation from cation **E** affords **3aa**.



Scheme 2. Phenyl Radical-Trapping Experiment



Scheme 3. Plausible Reaction Mechanism for the Formation of **3aa**

3. Conclusion

In conclusion, a metal-free arylation of aminoheterocycles with arylhydrazine hydrochlorides was developed with air as the oxidant. In this reaction system, the HOMO energy levels of the aminoheterocycles correlated with their nucleophilicity. This direct C–H arylation reaction without transition-metal catalysts could be not only a useful and practical method but also an alternative for Pd-catalyzed cross-coupling reactions.

4. Experimental

4.1. General

All starting materials were purchased from commercial sources and used without further purification. IR spectra were reported in wave numbers (cm^{-1}). ^1H NMR spectra were recorded on 400 MHz spectrometers using $CDCl_3$ or DMSO-d_6 as solvent referenced to TMS (0 ppm) and $CHCl_3$ (7.26 ppm) or DMSO (2.50 ppm). ^{13}C NMR spectra were recorded at 100 MHz in $CDCl_3$ and DMSO-d_6 using $CDCl_3$ (77.0 ppm) and DMSO-d_6 (39.5 ppm) as standard. Chemical shifts are reported in parts per million (ppm). Coupling constants are reported in hertz (*J*, Hz). The following abbreviations are used for the description of signals: s (singlet), bs (broad singlet), d (doublet), dd (double doublet), t (triplet), q (quadruplet), m (multiplet). Mass spectra and exact mass spectra were recorded using electron impact (EI), electrospray ionization (ESI), and direct analysis in real time (DART). Analytical TLC was carried out on silica gel plates using short wave (254 nm) UV light. Silica gel (230−400 mesh) was used for column chromatography. DFT calculations were carried out at the B3LYP/6-31G(d,p) level using the Q-Chem 4.0.1 program package.[12] Optimized geometries of calculated compounds were confirmed by the absence of imaginary frequencies.

4.2. General procedure for the arylation of aminoheterocycles with arylhydrazine hydrochlorides

A mixture of the arylhydrazine hydrochlorides (1.0 mmol), aminopyridines (20.0 mmol), and potassium carbonate (415 mg, 3.0 mmol) in DMSO (10 mL) was stirred at 25 °C in air. The reactions were completed after 24 h, monitored by thin layer chromatography (TLC). Then, quenched by the addition of water, the reaction mixture was extracted with ethyl acetate. The organic layer was washed with water and brine solution and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give the crude products. Purified by column chromatography over silica gel (hexane/AcOEt), the pure products were afforded.

*4.2.1. 2,6-Diamino-3-(4´-chlorophenyl)pyridine (**3aa**).* Compound **3aa** was synthesized from 4-chlorophenylhydrazine hydrochloride **1a** (179 mg, 1.0 mmol) and 2,6-diaminopyridine **2a** (2.18 g, 20.0 mmol) according to the general procedure. The excess of **2a** was almost removed by extracted with water. By the purification with column chromatography (inner diameter: 2 cm and length: 30 cm), **3aa** (188 mg, 0.85 mmol, 85%) was obtained. Recrystallized from hexane/AcOEt=1:1, **3aa** was given as a pale brown crystal; R_f (hexane/AcOEt=1:3) 0.3; mp 116.5-117.5 °C (Lit.[13] 114-115 °C); ν_{max} (neat) 3469, 3427, 3303, 3103, 1591, 1467, 1421, 1082 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.26 (bs, 2H, N-H), 4.35 (bs, 2H, N-H), 5.98 (d, *J* 8.0 Hz, 1H, C-H), 7.16 (d, *J* 8.0 Hz, 1H, C-H), 7.34 (d, *J* 9.0 Hz, 2H, C-H), 7.38 (d, *J* 9.0 Hz, 2H, C-H); δ_C (100 MHz, $CDCl_3$) 98.5, 110.2, 129.0, 130.1, 132.5, 137.3, 140.0, 154.5, 157.1; *m/z* (EI) 219 (100, M^+), 183 (15), 140 (27), 92 (29), 43 (52%); HRMS (ESI): MH^+, found 220.0610. $C_{11}H_{11}ClN_3$ requires 220.0636.

*4.2.2. 2,6-Diamino-3-(4´-fluorophenyl)pyridine (**3ba**).* Compound **3ba** was synthesized from 4-fluorophenylhydrazine hydrochloride **1b** (163 mg, 1.0 mmol) and **2a** (2.18 g, 20.0 mmol) according to the general procedure. The excess of **2a** was almost removed by extracted with water. Purification with column chromatography (inner diameter: 2 cm and length: 30 cm) gave **3ba** (154 mg, 0.76 mmol, 76%). Recrystallized from hexane/AcOEt=3:7, **3ba** was given as a pale brown needle; R_f (AcOEt) 0.3; mp 124.0-125.0 °C; ν_{max} (neat) 3460, 3397, 3308, 3144, 1593, 1475, 1430, 1353, 1214 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.26 (bs, 2H, N-H), 4.35 (bs, 2H, N-H), 5.98 (d, *J* 7.7 Hz, 1H, C-H), 7.09 (dd, J_{HF} 9.0 Hz, *J* 9.0 Hz, 2H, C-H), 7.15 (d, *J* 7.7 Hz, 1H, C-H), 7.36 (dd, J_{HF} 5.5 Hz, *J* 9.0 Hz, 2H, C-H); δ_C (100 MHz, $CDCl_3$) 98.4, 110.5, 115.7 (d, J_{CF} 21.1 Hz), 130.4 (d, J_{CF} 8.6 Hz), 134.7, 140.1, 154.6, 157.1, 161.7 (d, J_{CF} 247.2 Hz); *m/z* (EI) 203 (100, M^+), 185 (13), 158 (18), 133 (17), 44 (54%); HRMS (ESI): MH^+, found 204.0922. $C_{11}H_{11}FN_3$ requires 204.0932.

*4.2.3. 2,6-Diamino-3-(4´-bromophenyl)pyridine (**3ca**).* Compound **3ca** was prepared from 4-bromophenylhydrazine hydrochloride **1c** (224 mg, 1.0 mmol) and **2a** (2.18 g, 20.0 mmol) according to the general procedure. The excess of **2a** was almost removed by extracted with water. By the purification with column chromatography (inner diameter: 2 cm and length: 30 cm), **3ca** (195 mg, 0.74 mmol, 74%) was obtained. Recrystallized from hexane/AcOEt=1:1, **3ca** was given as a cream color solid; R_f (hexane/AcOEt=2:13) 0.3; mp 129.0-130.0 °C; ν_{max} (neat) 3432, 3365, 3302, 3112, 1589, 1469, 1420, 1067 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.27 (bs, 2H, N-H), 4.36 (bs, 2H, N-H), 5.99 (d, *J* 8.2 Hz, 1H, C-H), 7.16 (d, *J* 8.2 Hz, 1H, C-H), 7.29 (d, *J* 8.5 Hz, 2H, C-H), 7.53 (d, *J* 8.5 Hz, 2H, C-H); δ_C (100 MHz, $CDCl_3$) 98.5, 110.2, 120.6, 130.4, 132.0, 137.8, 140.0, 154.5, 157.2; *m/z* (EI) 263 (100, M^+), 183 (39), 140 (45), 92 (62), 43 (68%); HRMS (ESI): MH^+, found 264.0110. $C_{11}H_{11}{}^{79}BrN_3$ requires 264.0131.

*4.2.4. 2,6-Diamino-3-(4´-cyanophenyl)pyridine (**3da**).* Compound **3da** was obtained from 4-cyanophenylhydrazine hydrochloride **1d** (170 mg, 1.0 mmol) and **2a** (2.18 g, 20.0 mmol) according to the general procedure. The excess of **2a** was almost removed by extracted with water. To the AcOEt solution including the product, hexane was added slowly. The generated precipitate was filtered with a funnel to give **3da** (26 mg, 0.60 mmol, 60%). Recrystallized from AcOEt, **3da** was given as a pale orange solid; R_f (hexane/AcOEt=1:3) 0.4; mp 221.5-222.5 °C; ν_{max} (neat) 3429, 3377, 3174, 2225, 1570, 1471, 1442 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 5.37 (bs, 2H, N-H), 5.76 (bs, 2H, N-H), 5.85 (d, *J* 8.0 Hz, 1H, C-H), 7.13 (d, *J* 8.0 Hz, 1H, C-H), 7.57 (d, *J* 8.5 Hz, 2H, C-H), 7.78 (d, *J* 8.5 Hz, 2H, C-H); δ_C (100 MHz, DMSO-d_6) 97.7, 106.0, 107.4, 119.3, 128.6, 132.5, 139.5, 144.8, 155.2, 158.9; *m/z* (EI) 210 (100, M^+), 192 (21), 155 (13), 139 (13), 44 (96%); HRMS (ESI): MH^+, found 211.0958. $C_{12}H_{11}N_4$ requires 211.0978.

*4.2.5. 2,6-Diamino-3-(3´,4´-dichlorophenyl)pyridine (**3ea**).* Compound **3ea** was prepared from 3,4-dichlorophenylhydrazine hydrochloride **1e** (213 mg, 1.0 mmol) and **2a** (2.18 g, 20.0 mmol) according to the general procedure. The excess of **2a** was almost removed by extracted with water. Purification with column chromatography (inner diameter: 2 cm and length: 30 cm) gave **3ea** (161 mg, 0.63 mmol, 63%). Recrystallized from hexane/AcOEt=1:3, **3ea** was given as a white solid; R_f (hexane/AcOEt=1:3) 0.3; mp 126.0-127.0 °C; ν_{max} (neat) 3417, 3338, 3132, 1574, 1460, 1435, 1022 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 5.32 (bs, 2H, N-H), 5.67 (bs, 2H, N-H), 5.82 (d, *J* 8.4 Hz, 1H, C-H), 7.08 (d, *J* 8.4 Hz, 1H, C-H), 7.34 (dd, *J* 2.2 Hz, *J* 8.5 Hz,

1H, C-H), 7.56 (d, *J* 2.2 Hz, 1H, C-H), 7.58 (d, *J* 8.5 Hz, 1H, C-H); δ_C (100 MHz, DMSO-d_6) 97.4, 105.4, 128.4, 129.8, 130.6, 131.1, 139.4, 140.4, 155.1, 158.7; *m/z* (EI) 253 (100, M^+), 217 (16), 174 (24), 109 (20), 91 (16), 43 (84%); HRMS (ESI): MH^+, found 254.0223. $C_{11}H_{10}Cl_2N_3$ requires 254.0246.

*4.2.6. 2,6-Diamino-3-phenylpyridine (**3fa**).* Compound **3fa** was given from phenylhydrazine hydrochloride **1f** (145 mg, 1.0 mmol) and **2a** (2.18 g, 20.0 mmol) according to the general procedure. The excess of **2a** was almost removed by extracted with water. Purification with column chromatography (inner diameter: 2 cm and length: 30 cm) gave **3fa** (109 mg, 0.59 mmol, 59%). Recrystallized from hexane/AcOEt=1:3, **3fa** was given as a white needle; R_f (hexane/AcOEt=1:3) 0.3; mp 113.5-114.5 °C (Lit.[13] 114-115 °C); ν_{max} (neat) 3429, 3379, 3309, 3130, 1593, 1469, 1408 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.25 (bs, 2H, N-H), 4.41 (bs, 2H, N-H), 5.99 (d, *J* 7.8 Hz, 1H, C-H), 7.20 (d, *J* 7.8 Hz, 1H, C-H), 7.28-7.31 (m, 1H, C-H), 7.40-7.42 (m, 4H, C-H); δ_C (100 MHz, $CDCl_3$) 98.4, 111.6, 126.7, 128.8, 128.9, 138.8, 140.1, 154.6, 157.0; *m/z* (EI) 185 (100, M^+), 140 (17), 92 (17), 43 (29%); HRMS (ESI): MH^+, found 186.1029. $C_{11}H_{12}N_3$ requires 186.1026.

*4.2.7. 2,6-Diamino-3-(4´-methoxyphenyl)pyridine (**3ga**).* Compound **3ga** was prepared from 4-methoxyphenylhydrazine hydrochloride **1g** (175 mg, 1.0 mmol) and **2a** (2.18 g, 20.0 mmol) according to the general procedure. The excess of **2a** was almost removed by extracted with water. Purification with column chromatography (inner diameter: 2 cm and length: 30 cm) gave **3ga** (125 mg, 0.58 mmol, 58%). Recrystallized from hexane/AcOEt=1:3, **3ga** was given as a pale yellow solid; R_f (hexane/AcOEt=1:3) 0.2; mp 129.5-130.5 °C; ν_{max} (neat) 3440, 3327, 3186, 1585, 1477, 1427, 1174 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.83 (s, 3H, O-CH_3), 4.21 (bs, 2H, N-H), 4.36 (bs, 2H, N-H), 5.98 (d, *J* 8.0 Hz, 1H, C-H), 6.95 (d, *J* 8.7 Hz, 2H, C-H), 7.16 (d, *J* 8.0 Hz, 1H, C-H), 7.32 (d, *J* 8.7 Hz, 2H); δ_C (100 MHz, $CDCl_3$) 55.3, 98.3, 111.3, 114.3, 129.9, 131.0, 140.0, 154.8, 156.7, 158.5; *m/z* (EI) 215 (100, M^+), 200 (69), 156 (12), 128 (13), 100 (13), 43 (25%); HRMS (ESI): MH^+, found 216.1109. $C_{12}H_{14}N_3O$ requires 216.1131.

*4.2.8. 2,6-Diamino-3-(4´-tolyl)pyridine (**3ha**).* Compound **3ha** was obtained from 4-methylphenylhydrazine hydrochloride **1h** (159 mg, 1.0 mmol) and **2a** (2.18 g, 20.0 mmol) according to the general procedure. The excess of **2a** was almost removed by extracted with water. Purification with column chromatography (inner diameter: 2 cm and length: 30 cm) gave **3ha** (119 mg, 0.60 mmol, 60%). Recrystallized from hexane/AcOEt=1:3, **3ha** was given as a cream color needle; R_f (hexane/AcOEt=1:3) 0.4; mp 119.5-120.3 °C; ν_{max} (neat) 3464, 3425, 3309, 3111, 1591, 1471, 1419 cm^{-1}. δ_H (400 MHz, $CDCl_3$) 2.38 (s, 3H, -CH_3), 4.21 (bs, 2H, N-H), 4.38 (bs, 2H, N-H), 5.98 (d, *J* 7.8 Hz, 1H, C-H), 7.18 (d, *J* 7.8 Hz, 1H, C-H), 7.22 (d, *J* 8.5 Hz, 2H, C-H), 7.30 (d, *J* 8.5 Hz, 2H, C-H); δ_C (100 MHz, $CDCl_3$) 21.1, 98.4, 111.6, 128.6, 129.6, 135.8, 136.4, 140.1, 154.7, 156.8; *m/z* (EI) 199 (100, M^+), 181 (17), 99 (21), 43 (25%); HRMS (ESI): MH^+, found 200.1155. $C_{12}H_{14}N_3$ requires 200.1182.

*4.2.9. 2-Amino-3-(4´-chlorophenyl)pyridine (**3ab**).* Compound **3ab** was prepared from **1a** (179 mg, 1.0 mmol) and 2-aminopyridine **2b** (1.88 g, 20.0 mmol) according to the general procedure. The excess of **2b** was almost removed by extracted with water. Purification with column chromatography (inner diameter: 2 cm and length: 30 cm) gave **3ab** (74 mg, 0.36 mmol, 36%. Recrystallized from hexane/AcOEt=7:3, **3ab** was given as a white solid; R_f (hexane/AcOEt=1:1) 0.3; mp 121.0-122.0 °C; ν_{max} (neat) 3437, 3286, 3134, 1631, 1577, 1446, 1090 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.54 (bs, 2H, N-H), 6.75 (dd, *J* 5.0 Hz, *J* 7.3 Hz, 1H, C-H), 7.33 (dd, *J* 2.0 Hz, *J* 7.3 Hz, 1H, C-H), 7.39 (d, *J* 8.8 Hz, 2H, C-H), 7.44 (d, *J* 8.8 Hz, 2H, C-H), 8.08 (dd, *J* 2.0 Hz, *J* 5.0 Hz, 1H, C-H); δ_C (100 MHz, $CDCl_3$) 114.6, 120.6, 129.3, 130.1, 133.8, 136.5, 137.8, 147.7, 155.7; *m/z* (EI) 204 (57, M^+), 203 (100), 168 (46), 115 (15), 84 (34%); HRMS (ESI): MH^+, found 205.0510. $C_{11}H_{10}ClN_2$ requires 205.0527.

*4.2.10. 2-Amino-3-(4´-bromophenyl)pyridine (**3cb**).* Compound **3cb** was prepared from **1c** (224 mg, 1.0 mmol) and **2b** (1.88 g, 20.0 mmol) according to the general procedure. The excess of **2b** was almost removed by extracted with water. Purification with column chromatography (inner diameter: 3 cm and length: 30 cm) gave **3cb** (92 mg, 0.37 mmol, 37%). Recrystallized from hexane/AcOEt=9:1, **3cb** was given as a white needle; R_f (hexane/AcOEt=1:2) 0.34; mp 126.0-127.0 °C; ν_{max} (neat) 3433, 3284, 3129, 1631, 1576, 1443, 1071 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.54 (bs, 2H, N-H), 6.75 (dd, *J* 5.0 Hz, *J* 8.0 Hz, 1H, C-H), 7.33 (d, *J* 8.0 Hz, 1H, C-H), 7.33 (d, *J* 8.0 Hz, 2H, C-H), 7.59 (d, *J* 8.0 Hz, 2H, C-H), 8.08 (dd, *J* 2.0 Hz, *J* 5.0 Hz, 1H, C-H); δ_C (100 MHz, $CDCl_3$) 114.6, 120.6, 121.9, 130.4, 132.3, 137.0, 137.7, 147.7, 155.6; HRMS (ESI): MH^+, found 248.9996. $C_{11}H_{10}{}^{79}BrN_2$ requires 249.0022.

*4.2.11. 2-Amino-3-(4´-chlorophenyl)-5-methylpyridine (**3ac**).* Compound **3ac** was prepared from **1a** (179 mg, 1.0 mmol) and 2-amino-5-methylpyridine **2c** (2.16 g, 20.0 mmol) according to the general procedure. Purification with column chromatography (inner diameter: 2 cm and length: 30 cm) gave **3ac** (80 mg, 0.37 mmol, 37%). Recrystallized from hexane/AcOEt=1:1, **3ac** was given as a pale orange solid; R_f (hexane/AcOEt=1:1) 0.44; mp 164.0-165.0 °C; ν_{max} (neat) 3448, 3278, 3130, 1628, 1468, 1089 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.23 (s, 3H, -CH_3), 4.37 (bs, 2H, N-H), 7.18 (d, *J* 2.0 Hz, 1H, C-H), 7.39 (d, *J* 8.7 Hz, 2H, C-H), 7.43 (d, *J* 8.7 Hz, 2H, C-H), 7.91 (d, *J* 2.0 Hz, 1H, C-H); δ_C (100 MHz, $CDCl_3$) 17.3, 120.3, 123.5, 129.2, 130.0, 133.6, 136.6, 138.8, 147.2, 153.6; *m/z* (EI) 218 (73, M^+), 217 (100), 182 (34), 91 (19), 44 (80%); HRMS (ESI): MH^+, found 219.0655. $C_{12}H_{12}ClN_2$ requires 219.0684.

*4.2.12. 2-Amino-5-chloro-3-(4´-chlorophenyl)pyridine (**3ad**).* Compound **3ad** was obtained from **1a** (179 mg, 1.0 mmol) and 2-amino-5-chloropyridine **2d** (2.57 g, 20.0 mmol) according to the general procedure. By the purification with column chromatography (inner diameter: 5 cm and length: 30 cm), **3ad** (112 mg, 0.47 mmol, 47%) was obtained. Recrystallized from hexane/AcOEt=1:1, **3ad** was given as a pale yellow needle; R_f (hexane/AcOEt=1:2) 0.76; mp 156.8-157.7 °C (Lit.[14] 140-141 °C); ν_{max} (neat) 3450, 3280, 3143, 1624, 1456, 1090, 1011 cm^{-1}. δ_H (400 MHz, $CDCl_3$); 4.54 (bs, 2H, N-H), 7.33 (d, *J* 2.6 Hz, 1H, C-H), 7.38 (d, *J* 8.6 Hz, 2H, C-H), 7.45 (d, *J* 8.6 Hz, 2H, C-H), 8.03 (d, *J* 2.6 Hz, 1H, C-H); δ_C (100 MHz, $CDCl_3$) 121.3, 121.6, 129.5, 129.9, 134.4, 135.2, 137.3, 145.8, 154.1; *m/z* (EI) 238 (68, M^+), 237(100), 202 (41), 168 (27), 140 (31%); HRMS (ESI): MH^+, found 239.0123. $C_{11}H_9Cl_2N_2$ requires 239.0137.

*4.2.13. 2-Amino-5-bromo-3-(4´-chlorophenyl)pyridine (**3ae**).* Compound **3ae** was prepared from **1a** (179 mg, 1.0 mmol) and 2-amino-5-bromopyridine **2e** (3.46 g, 20.0 mmol) according to the general procedure. Purification with column chromatography (inner diameter: 5 cm and length: 30 cm) gave **3ae** (140 mg, 0.49 mmol, 49%). Recrystallized from hexane/AcOEt=1:2, **3ae** was given as a pale orange needle; R_f (hexane/AcOEt=1:2) 0.79; mp 150.0-151.0 °C; ν_{max} (neat) 3454, 3284, 3151, 1620, 1454, 1088, 1011 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.59 (bs, 2H, N-H), 7.37 (d, *J* 8.8 Hz, 2H, C-H), 7.44 (d, *J* 2.4 Hz, 1H, C-H), 7.48 (d, *J* 8.8 Hz, 2H, C-H), 8.11 (d, *J* 2.4 Hz, 1H, C-H); δ_C (100 MHz, $CDCl_3$) 108.5, 122.2, 129.5, 129.9, 134.4, 135.1, 139.7, 148.0, 154.4; *m/z* (EI) 283 (100), 282 (59, M^+), 281(76), 202 (52), 168 (45), 140

(38), 84 (48%); HRMS (ESI): MH^+, found 282.9605. $C_{11}H_9{}^{79}BrClN_2$ requires 282.9632.

*4.2.14. 2-Amino-3-(4′-chlorophenyl)-5,6-dimethylpyridine (**3af**).* Compound **3af** was prepared from **1a** (179 mg, 1.0 mmol) and 2-amino-5,6-dimethylpyridine **2f** (2.44 g, 20.0 mmol) according to the general procedure. Purification with column chromatography (inner diameter: 2 cm and length: 30 cm) gave **3af** (78 mg, 0.34 mmol, 34%). Recrystallized from hexane/AcOEt=1:1, **3af** was given as a pale orange needle; R_f (hexane/AcOEt=1:1) 0.2; mp 109.5-110.5 °C; ν_{max} (neat) 3483, 3438, 3288, 3156, 1450, 1391, 1092 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.18 (s, 3H, $-CH_3$), 2.37 (s, 3H, $-CH_3$), 4.35 (bs, 2H, N-H), 7.09 (s, 1H, C-H), 7.37 (d, *J* 8.8 Hz, 2H, C-H), 7.40 (d, *J* 8.8 Hz, 2H, C-H); δ_C (100 MHz, $CDCl_3$) 17.9, 21.9, 117.9, 121.5, 129.1, 130.1, 133.3, 136.8, 139.5, 153.0, 154.6; HRMS (ESI): MH^+, found 233.0813. $C_{13}H_{14}ClN_2$ requires 233.0840.

*4.2.15. 2-Amino-3-(4′-fluorophenyl)-5,6-dimethylpyridine (**3bf**).* Compound **3bf** was prepared from **1b** (163 mg, 1.0 mmol) and **2f** (2.44 g, 20.0 mmol) according to the general procedure. Purification with column chromatography (inner diameter: 3 cm and length: 30 cm) gave **3bf** (64 mg, 0.30 mmol, 30%). Recrystallized from hexane/AcOEt=9:1, **3bf** was given as a pale orange plate crystal; R_f (hexane/AcOEt=1:2) 0.28; mp 109.0-110.0 °C; ν_{max} (neat) 3480, 3292, 3169, 1454, 1216 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.18 (s, 3H, $-CH_3$), 2.38 (s, 3H, $-CH_3$), 4.33 (bs, 2H, N-H), 7.09 (s, 1H, C-H), 7.12 (dd, J_{HF} 8.8 Hz, *J* 8.8 Hz, 2H, C-H), 7.40 (dd, J_{HF} 5.4 Hz, *J* 8.8 Hz, 2H, C-H); δ_C (100 MHz, $CDCl_3$) 17.9, 21.9, 115.9 (d, J_{CF} 21.0 Hz), 118.2, 121.4, 130.4 (d, J_{CF} 7.6 Hz), 134.3, 139.7, 153.1, 154.3, 162.1 (d, J_{CF} 245.1 Hz); HRMS (ESI): MH^+, found 217.1127. $C_{13}H_{14}FN_2$ requires 217.1136.

*4.2.16. 3-Amino-2-(4′-chlorophenyl)pyridine (**3ag**), 3-Amino-4-(4′-chlorophenyl)pyridine (**3ag′**), and 3-Amino-6-(4′-chlorophenyl)pyridine (**3ag″**).* Compounds **3ag**, **3ag′**, and **3ag″** were synthesized from **1a** (179 mg, 1.0 mmol) and 3-aminopyridine **2g** (1.88 g, 20.0 mmol) according to the general procedure. Purification with column chromatography (inner diameter: 2 cm and length: 30 cm) gave **3ag** (107 mg, 0.52 mmol, 52%), and **3ag′** (31 mg, 0.15 mmol, 15%), and **3ag″** (17 mg, 0.08 mmol, 8%). 3-Amino-2-(4′-chlorophenyl)pyridine (**3ag**): Recrystallized from hexane/AcOEt=1:1, **3ag** was given as a pale yellow needle; R_f (hexane/AcOEt=1:3) 0.64; mp 86.6-87.5 °C; ν_{max} (neat) 3458, 3309, 3184, 1631, 1579, 1444, 1088 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.80 (bs, 2H, N-H), 7.05 (dd, *J* 1.8 Hz, *J* 8.0 Hz, 1H, C-H), 7.08 (dd, *J* 4.8 Hz, *J* 8.0 Hz, 1H, C-H), 7.45 (d, *J* 8.8 Hz, 2H, C-H), 7.64 (d, *J* 8.8 Hz, 2H, C-H), 8.12 (dd, *J* 1.8 Hz, *J* 4.8 Hz, 1H, C-H); δ_C (100 MHz, $CDCl_3$) 122.9, 123.3, 129.0, 129.9, 134.1, 137.0, 139.9, 140.1, 143.7; *m/z* (EI) 203 (100, M^+), 168 (45), 84 (22), 41 (47%); HRMS (ESI): MH^+, found 205.0504. $C_{11}H_{10}ClN_2$ requires 205.0527. 3-Amino-4-(4′-chlorophenyl)-pyridine (**3ag′**): Recrystallized from hexane/AcOEt=9:1, **3ag′** was given as a brown needle; R_f (hexane/AcOEt=1:3) 0.16; mp 146.5-147.5 °C; δ_H (400 MHz, $CDCl_3$); 3.77 (bs, 2H, N-H), 7.00 (d, *J* 5.0 Hz, 1H, C-H), 7.41 (d, *J* 8.6 Hz, 2H, C-H), 7.46 (d, *J* 8.6 Hz, 2H, C-H), 8.07 (d, *J* 5.0 Hz, 1H, C-H), 8.16 (s,1H, C-H); δ_C (100 MHz, $CDCl_3$) 123.9, 129.3, 129.8, 132.3, 134.3, 135.3, 138.3, 139.6, 140.3; HRMS (ESI): MH^+, found 205.0509. $C_{11}H_{10}ClN_2$ requires 205.0527. 3-Amino-6-(4′-chlorophenyl)-pyridine (**3ag″**): Recrystallized from hexane/AcOEt=9:1, **3ag″** was given as a brown solid; mp 96.5-98.2 °C; δ_H (400 MHz, $CDCl_3$) 3.77 (bs, 2H, N-H), 7.05 (dd, *J* 3.1 Hz, *J* 8.3 Hz, 1H, C-H), 7.39 (d, *J* 8.6 Hz, 2H, C-H), 7.51 (d, *J* 8.3 Hz, 1H, C-H), 7.83 (d, *J* 8.6 Hz, 2H, C-H), 8.17 (d, *J* 3.1 Hz, 1H, C-H); δ_C (100 MHz, $CDCl_3$) 120.6, 122.2, 127.2, 128.7, 133.6, 137.2, 137.9, 141.5, 146.8; HRMS (ESI): MH^+, found 205.0501. $C_{11}H_{10}ClN_2$ requires 205.0527.

*4.2.17. 3-Amino-2-(4′-fluorophenyl)pyridine (**3bg**), 3-Amino-4-(4′-fluorophenyl)pyridine (**3bg′**), and 3-Amino-2-(4′-fluorophenyl)pyridine (**3bg″**).* Compounds **3bg**, **3bg′**, and **3bg″** were synthesized from **1b** (163 mg, 1.0 mmol) and **2g** (1.88 g, 20.0 mmol) according to the general procedure. Purification with column chromatography (inner diameter: 3 cm and length: 30 cm) gave **3bg** (71 mg, 0.38 mmol, 38%), and **3bg′** (21 mg, 0.11 mmol, 11%), and **3bg″** (12 mg, 0.06 mmol, 6%). 3-Amino-2-(4′-fluorophenyl)pyridine (**3bg**): Recrystallized from hexane/AcOEt=9:1, **3bg** was given as a pale yellow needle; R_f (hexane/AcOEt=1:3) 0.52; mp 74.4-75.4 °C; ν_{max} (neat) 3393, 3295, 3208, 3055, 1624, 1584, 1509, 1217 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 3.79 (bs, 2H, N-H), 7.05 (dd, *J* 1.8 Hz, *J* 7.8 Hz, 1H, C-H), 7.08 (dd, *J* 3.8 Hz, *J* 7.8 Hz, 1H, C-H), 7.16 (dd, J_{HF} 8.8 Hz, *J* 8.8 Hz, 2H, C-H), 7.67 (dd, J_{HF} 5.6 Hz, *J* 8.8 Hz, 2H, C-H), 8.12 (dd, *J* 1.8 Hz, *J* 3.8 Hz, 1H, C-H); δ_C (100 MHz, CDCl3) 115.7 (d, J_{CF} 21.0 Hz), 122.8, 123.1, 130.3 (d, J_{CF} 7.7 Hz), 134.7, 139.9, 140.1, 144.1, 162.9 (d, J_{CF} 246.0 Hz); HRMS (ESI): MH^+, found 189.0796. $C_{11}H_{10}FN_2$ requires 189.0823. 3-Amino-4-(4′-fluorophenyl)pyridine (**3bg′**): Recrystallized from hexane/AcOEt=9:1, **3bg′** was given as a pale yellow needle; R_f (hexane/AcOEt=1:3) 0.12; mp 108.5-109.5 °C; δ_H (400 MHz, $CDCl_3$) 3.81 (bs, 2H, N-H), 6.99 (d, *J* 5.2 Hz, 1H, C-H), 7.17 (dd, J_{HF} 8.8 Hz, *J* 8.8 Hz, 2H, C-H), 7.44 (dd, J_{HF} 5.2 Hz, *J* 8.8 Hz, 2H, C-H), 8.05 (d, *J* 5.2 Hz, 1H, C-H), 8.15 (s, 1H, C-H); δ_C (100 MHz, $CDCl_3$) 116.1 (d, J_{CF} 21.0 Hz), 124.1, 130.2 (d, J_{CF} 8.6 Hz), 132.6, 132.8, 138.2, 139.7, 140.2, 162.5 (d, J_{CF} 247.0 Hz); HRMS (ESI): MH^+, found 189.0808. $C_{11}H_{10}FN_2$ requires 189.0823. 3-Amino-6-(4′-fluorophenyl)pyridine (**3bg″**): Recrystallized from hexane/AcOEt=9:1, **3bg″** was given as a pale orange crystal; R_f (hexane/AcOEt=1:3) 0.40; mp 98.0-99.5 °C; δ_H (400 MHz, $CDCl_3$) 3.74 (bs, 2H, N-H), 7.04 (dd, *J* 2.8 Hz, *J* 8.4 Hz, 1H,C-H), 7.10 (dd, J_{HF} 8.8 Hz, *J* 8.8 Hz, 2H, C-H), 7.48 (d, *J* 8.4 Hz, 1H), 7.86 (dd, J_{HF} 5.6 Hz, *J* 8.8 Hz, 2H, C-H), 8.16 (d, *J* 2.8 Hz, 1H, C-H); δ_C (100 MHz, $CDCl_3$) 115.4 (d, J_{CF} 21.0 Hz), 120.4, 122.4, 127.6 (d, J_{CF} 7.7 Hz), 135.7, 137.1, 141.3, 147.2, 162.7 (d, J_{CF} 245.0 Hz); HRMS (ESI): MH^+, found 189.0801. $C_{11}H_{10}FN_2$ requires 189.0823.

*4.2.18. 3-Amino-2-(4′-bromophenyl)pyridine (**3cg**), 3-Amino-4-(4′-bromophenyl)pyridine (**3cg′**),and 3-Amino-6-(4′-bromophenyl)pyridine (**3cg″**).* Compounds **3cg**, **3cg′**, and **3cg″** were synthesized from **1c** (224 mg, 1.0 mmol) and **2g** (1.88 g, 20.0 mmol) according to the general procedure. Purification with column chromatography (inner diameter: 3 cm and length: 30 cm) gave **3cg** (117 mg, 0.47 mmol, 47%), and **3cg′** (27 mg, 0.11 mmol, 11%), and **3cg″** (13 mg, 0.05 mmol, 5%). 3-Amino-2-(4′-bromophenyl)pyridine (**3cg**): Recrystallized from hexane/AcOEt=9:1, **3cg** was given as a pale yellow solid; R_f (hexane/AcOEt=1:3) 0.60; mp 98.0-99.0 °C (Lit.[15] 99-101 °C); ν_{max} (neat) 3467, 3313, 3183, 1633, 1579, 1445, 1075 cm^{-1}. δ_H (400 MHz, $CDCl_3$); 3.80 (bs, 2H, N-H), 7.05 (dd, *J* 2.0 Hz, *J* 8.0 Hz, 1H, C-H), 7.08 (dd, *J* 4.0 Hz, *J* 8.0 Hz, 1H, C-H), 7.58 (d, *J* 8.8 Hz, 2H, C-H), 7.61 (d, *J* 8.8 Hz, 2H, C-H), 8.13 (dd, *J* 2.0 Hz, *J* 4.0 Hz, 1H, C-H); δ_C (100 MHz, CDCl3) 122.4, 122.9, 123.3, 130.2, 131.9, 137.5, 139.9, 140.2, 143.7; HRMS (ESI): MH^+, found 249.0016. $C_{11}H_{10}{}^{79}BrN_2$ requires 249.0022. 3-Amino-4-(4′-bromophenyl)pyridine (**3cg′**): Recrystallized from hexane/AcOEt=9:1, **3cg′** was given as a pale orange solid; R_f (hexane/AcOEt=1:3) 0.14; mp 159.0-160.5 °C; δ_H (400 MHz, $CDCl_3$); 3.80 (bs, 2H, N-H), 6.99 (d, *J* 4.8 Hz, 1H, C-H), 7.35 (d, *J* 8.6 Hz, 2H, C-H), 7.61 (d, *J* 8.6 Hz, 2H, C-H), 8.06 (d, *J* 4.8 Hz, 1H, C-H), 8.15 (s, 1H, C-H); δ_C (100 MHz, $CDCl_3$) 122.4, 123.8, 130.1, 132.3, 135.7, 138.3, 139.5, 140.2; HRMS (ESI): MH^+,

found 248.9995. $C_{11}H_{10}{}^{79}BrN_2$ requires 249.0022. 3-Amino-6-(4′-bromophenyl)pyridine (**3cg″**): Recrystallized from hexane/AcOEt=9:1, **3cg″** was given as a pale orange block crystal; R_f (hexane/AcOEt=1:3) 0.42; mp 133.0-134.0 °C; δ_H (400 MHz, $CDCl_3$) 3.78 (bs, 2H, N-H), 7.03 (dd, *J* 2.8 Hz, *J* 8.6 Hz, 1H, C-H), 7.50 (d, *J* 8.6 Hz, 1H, C-H), 7.53 (d, *J* 8.8 Hz, 2H, C-H), 7.77 (d, *J* 8.8 Hz, 2H, C-H), 8.15 (d, *J* 2.8 Hz, 1H, C-H); δ_C (100 MHz, $CDCl_3$) 120.5, 121.8, 122.2, 127.5, 131.7, 137.2, 138.4, 141.6, 146.7; HRMS (ESI): MH^+, found 249.0001. $C_{11}H_{10}{}^{79}BrN_2$ requires 249.0022.

*4.2.19. 3-Amino-4-(4′-chlorophenyl)quinoline (**3ah**) and 3-Amino-2-(4′-chlorophenyl)quinoline (**3ah′**).* Compounds **3ah** and **3ah′** were synthesized from **1a** (179 mg, 1.0 mmol) and 3-aminoquinoline **2h** (2.88 g, 20.0 mmol) according to the general procedure. Purification with column chromatography (inner diameter: 5 cm and length: 30 cm) gave **3ah** (189 mg, 0.74 mmol, 74%) and **3ah′** (22 mg, 0.09 mmol, 9%). 3-Amino-4-(4′-chlorophenyl)quinoline (**3ah**): Recrystallized from AcOEt, **3ah** was given as a pale yellow needle; R_f (hexane/AcOEt=1:1) 0.24; mp 217.5-218.5 °C; ν_{max} (neat) 3448, 3289, 3178, 1625, 1581, 1479, 1380, 1347, 1085 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 5.23 (bs, 2H, N-H), 7.15 (dd, *J* 1.6 Hz, *J* 7.6 Hz, 1H, C-H), 7.31-7.36 (m, 2H, C-H), 7.35 (d, *J* 8.2 Hz, 2H, C-H), 7.63 (d, *J* 8.2 Hz, 2H, C-H), 7.84 (dd, *J* 1.6 Hz, *J* 7.6 Hz, 1H, C-H), 8.59 (s, 1H, C-H); δ_C (100 MHz, DMSO-d_6) 120.9, 122.8, 123.9, 126.7, 127.8, 129.0, 129.3, 132.0, 132.6, 133.4, 138.8, 141.1, 143.7; HRMS (ESI): MH^+, found 255.0666. $C_{15}H_{12}ClN_2$ requires 255.0684. 3-Amino-2-(4′-chlorophenyl)quinoline (**3ah′**): Recrystallized from AcOEt, **3ah′** was given as a yellow solid; R_f (hexane/AcOEt=1:1) 0.74; δ_H (400 MHz, DMSO-d_6) 5.32 (bs, 2H, N-H), 7.34-7.42 (m, 2H, C-H), 7.41 (s, 1H, C-H), 7.57 (d, *J* 8.4 Hz, 2H, C-H), 7.65 (dd, *J* 1.6 Hz, *J* 7.6 Hz, 1H, C-H), 7.78 (d, *J* 8.4 Hz, 2H, C-H), 7.79-7.81 (m, 1H, C-H); δ_C (100 MHz, DMSO-d_6) 114.8, 124.7, 125.2, 126.6, 128.5, 128.6, 129.1, 130.5, 133.1, 137.5, 140.1, 141.3, 148.4; HRMS (ESI): MH^+, found 255.0655. $C_{15}H_{12}ClN_2$ requires 255.0684.

*4.2.20. 2-Amino-3-(4′-chlorophenyl)pyrazine (**3aj**).* Compound **3aj** was prepared from **1a** (179 mg, 1.0 mmol) and 2-aminopyrazine **2j** (1.90 g, 20.0 mmol) according to the general procedure. Purification with column chromatography (inner diameter: 2 cm and length: 30 cm) gave **3aj** (116 mg, 0.56 mmol, 56%). Recrystallized from hexane/AcOEt=9:1, **3aj** was given as a color less needle; R_f (hexane/AcOEt=1:2) 0.52; mp 125.5-126.5 °C; ν_{max} (neat) 3303, 3153, 1643, 1525, 1433, 1088 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 4.76 (bs, 2H, N-H), 7.48 (d, *J* 8.4 Hz, 2H, C-H), 7.68 (d, *J* 8.4 Hz, 2H, C-H), 7.99 (d, *J* 2.6 Hz, 1H, C-H), 8.03 (d, *J* 2.6 Hz, 1H, C-H); δ_C (100 MHz, $CDCl_3$) 129.3, 129.5, 134.7, 135.1, 135.6, 139.6, 141.3, 152.2 ; *m/z* (EI) 205 (97, M^+), 170 (38), 151 (23), 137 (30), 42 (100), 41 (97%); HRMS (ESI): MH^+, found 206.0455. $C_{10}H_9ClN_3$ requires 206.0480.

*4.2.21. 2-Amino-5-(4′-chlorophenyl)-4,6-dimethylpyrimidine (**3ak**).* Compound **3ak** was given from **1a** (179 mg, 1.0 mmol) and 2-amino-4,6-dimethylpyrimidine **2k** (2.46 g, 20.0 mmol) according to the general procedure. By the purification with column chromatography (inner diameter: 2 cm and length: 30 cm), **3ak** (45 mg, 0.19 mmol, 19%) was given. Recrystallized from hexane/AcOEt=1:1, **3ak** was given as a white solid; R_f (hexane/AcOEt=1:4) 0.30; mp 204.7-205.5 °C; ν_{max} (neat) 3307, 3186, 1626, 1545, 1466, 1090 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 2.09 (s, 6H, $-CH_3$), 4.99 (bs, 2H, N-H), 7.09 (d, *J* 8.6 Hz, 2H, C-H), 7.41 (d, *J* 8.6 Hz, 2H, C-H); δ_C (100 MHz, $CDCl_3$) 22.8, 123.4, 129.0, 131.1, 133.5, 136.0, 161.3, 165.5; *m/z* (EI) 233 (100, M^+), 197 (17), 115 (46), 42 (69%); HRMS (ESI): MH^+, found 234.0768. $C_{12}H_{13}ClN_3$ requires 234.0793.

4.3. A larger-scale synthesis of 3aa

Compound **3aa** was prepared from a mixture of 4-chlorophenylhydrazine hydrochloride **1a** (3.58 g, 20.0 mmol), 2,6-diaminopyridine **2a** (43.65 g, 400 mmol) and potassium carbonate (8.29 g, 60.0 mmol) in DMSO (200 mL), according to the general procedure. The reaction was completed after 24 h, monitored by thin layer chromatography (TLC). Then, quenched by the addition of water, the reaction mixture was extracted with ethyl acetate. The excess of **2a** was isolated in almost 90% yield by extracted with water. The organic layer was washed with water and brine solution, and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give a crude product. Purified by column chromatography (inner diameter: 5 cm and length: 30 cm) over silica gel (hexane/AcOEt=1:4), the pure product **3aa** (3.54g, 81%) was afforded.

4.4. Radical-trapping experiment with TEMPO (4a)

To a mixture of 4-chlorophenylhydrazine hydrochloride (**1a**, 895 mg, 5.0 mmol) and TEMPO (1.17 g, 7.5 mmol) in DMSO (50 mL), potassium carbonate (2.07 g, 15.0 mmol) was added. The solution was stirred at room temperature in air for 24 h. The resulting solution was quenched by the addition of water and extracted with ethyl acetate. The organic layer was washed with water and brine solution, and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure to give a crude product. Purification by column chromatography over silica gel using hexane, 4-chloro-1-(2,2,6,6-tetramethylpiperidinyloxy)-benzene (**4a**) (380 mg, 1.42 mmol, 28%) was afforded. Recrystallized from hexane, **4a** was given as a colorless plate crystal; R_f (hexane) 0.62; mp 89.5-90.5 °C; ν_{max} (neat) 2977, 2925, 1585, 1480, 827 cm^{-1}; δ_H (400 MHz, $CDCl_3$) 0.99 (s, 6H, $-CH_3$), 1.21 (s, 6H, $-CH_3$), 1.38-1.44 (m, 1H, CH_2), 1.53-1.68 (m, 5H, CH_2), 7.11 (d, *J* 9.4 Hz, 2H, C-H), 7.15 (d, *J* 9.4 Hz, 2H, C-H); δ_C (100 MHz, $CDCl_3$) 17.0, 20.4, 32.5, 39.7, 60.4, 115.2, 124.3, 128.5, 162.2; HRMS (DART): MH^+ found 268.1462. $C_{15}H_{23}ClNO$ requires 268.1463.

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Supplementary data

^{1}H-NMR, ^{13}C-NMR spectra, and details of density functional theory (DFT) calculations.

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