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Cobalt-Catalyzed Regioselective Ortho C(sp^2)-H Bond Nitration of Aromatics through Proton-Coupled Electron Transfer Assistance

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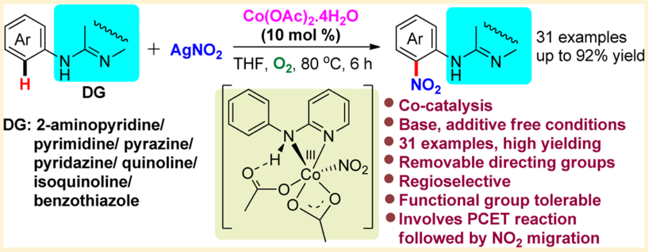
Supporting Information

ABSTRACT: A cobalt-catalyzed proton-coupled electron transfer (PCET) mediated regioselective *ortho*-specific nitration of aromatic C(sp^2)-H bonds using chelation-assisted removable vicinal diamine directing groups was developed. The reaction proceeded under mild conditions in the presence of $Co(OAc)_2{\cdot}4H_2O$ as the catalyst with $AgNO_2$ utilized as the nitro source as well as terminal oxidant in the presence of O_2 as an external oxidant. No external base or additives were required for this process. Controlled experiments and mechanistic investigations with DFT calculations revealed that the reaction proceeds through a PCET promoted nitro functional group transfer pathway. Moreover, the produced compounds are valuable and pharmaceutically quite relevant.



INTRODUCTION

Cobalt-catalyzed cross-coupling reactions received significant attention in the past few decades from the synthetic community as a way to construct carbon−carbon or carbon−heteroatom bonds because cobalt catalysts are less expensive, environmentally benign, and possess unique reactivity.[1] Thus, the use of a cobalt catalyst in C−C bond-forming reactions has attracted significant attention, mostly leading to alkylations, alkenylations, and arylations. In recent days, the research groups of Daugulis,[2] Yoshikai,[3] Nakamura,[4] Kanai,[5] Ackermann,[6] Glorius,[7] Song,[8] Chang,[9] and others[10] devised cobalt-catalyzed methods for chelation-assisted C−C/C−X bond formation by using different directing groups (DGs) via C−H bond activation. In comparison with the well-established chelation-assisted cobalt-catalyzed C−C bond formation via direct functionalization of C−H bonds, there are limited examples for direct C−N bond formation. In this context, direct amination/amidation of C−H bonds catalyzed by Co(II)/Co(III) systems were studied.[11] However, to the best of our knowledge, a cobalt-catalyzed direct *ortho*-specific C−H nitration of arenes is unprecedented.

Nitroarenes are important building blocks in organic synthesis and very often are essential constituents of therapeutic and pharmaceutically relevant molecules as well as being important in the chemical industry.[12] Numerous useful methods for their preparation have been developed, but regioselective nitration still remains a challenge.[13] Recently, transition-metal-catalyzed chelation-assisted *ortho*-nitrations of aromatic C−H bonds were accomplished.[14] Despite these advances, C−H nitrations are mostly dominated by expensive second-row transition-metal catalysts such as Pd, Rh, and Ru. In particular, two different groups recently established palladium catalyzed *ortho*-nitrations using $AgNO_2$ as the nitro source and $K_2S_2O_8$ as the external oxidant.[14f,g] In these reactions, as anticipated, Pd catalyst requires additives, which is not synthetically efficient or advantageous from an ecological point of view, and no regioselectivity was observed in case of *meta*-substituted substrates. Therefore, an economic, efficient, and environmentally benign regioselective *ortho*-specific nitration method is highly desirable. As a part of our continuing interest[15] in the development of C−H activation/functionalization, we became interested in the cobalt-catalyzed regioselective *ortho*-specific nitration of arenes. Herein, we describe the development of a novel cobalt-catalyzed *ortho*-specific C−H nitration of synthetically useful aromatic derivatives. Notable features of our general strategy include (a) use of 2-aminopyridine as an unusual ligand with the design based on a vicinal diamine dicoordinate removable directing group and (b) a proton-coupled electron transfer (PCET) reaction followed by an AcOH-AcO ion exchange and nitro functional group transfer. An added advantage of our strategy is predictable regiocontrol; challenging C−H/C−N functionalizations with unactivated arenes are reactions that are normally very difficult to achieve via traditional approaches (Scheme 1).

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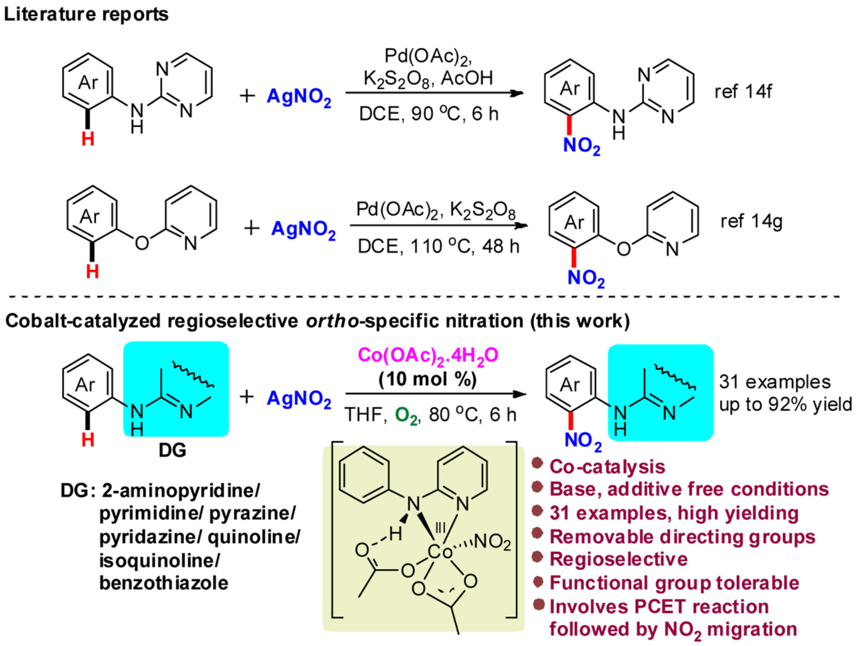
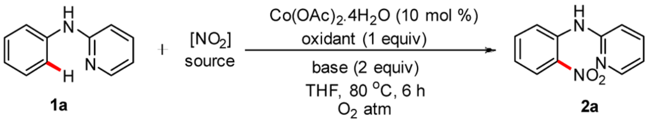
Scheme 1. Summary of This Work



RESULTS AND DISCUSSION

To probe the feasibility of this approach, a study was initiated with the reaction between $NaNO_2$ (1.1 equiv) and N-phenylpyridin-2-amine (**1a**) using $Co(OAc)_2{\cdot}4H_2O$ (10 mol %) in the presence of AgOAc (1 equiv) as oxidant, NaOAc (2 equiv) as base, and THF as solvent in O_2 atm at 80 °C for 6 h. Under these conditions, **2a** was isolated in 5% yield (Table 1, entry 1). When $AgNO_2$ was used as the nitro source, the desired product (**2a**) was obtained in 63% yield (Table 1, entries 2−3). When different external oxidants were used, no improvement of the isolated yield was observed (Table 1, entries 4−8). Interestingly, in the absence of NaOAc as the base, the product yield increased to 85% (Table 1, entry 9). When the reaction was performed without adding any external oxidant, the desired product was isolated in 70% yield (Table 1, entry 10). This indicates that $AgNO_2$ was acting as the nitro source as well as an oxidant. When the $AgNO_2$ concentration is increased to 1.5 equiv, the *ortho*-nitration product was obtained in 92% yield (Table 1, entry 11). When the reaction temperature was decreased, a reduction in the yield was observed (Table 1, entries 12 and 13), indicating that 80 °C is an optimal temperature for this transformation. Under open-air conditions, the yield dropped to 60%, and incomplete conversion was observed. A poor yield (30%) was observed under N_2 atm (Table 1, entries 14 and 15), suggesting that O_2 atm is necessary for this reaction. There is no reaction in the absence of $Co(OAc)_2{\cdot}4H_2O$ (Table 1, entry 16). Use of different solvents (DMF/toluene) instead of THF did not improve the yield (Table 1, entries 17 and 18). The C−H nitration of arenes using different directing groups (Figures 1A−M) was inefficient under the same optimized reaction conditions. However, reactions with substrates having a vicinal diamine system (**3a**−**g**) were found compatible to reaction conditions. This establishes the unique property of vicinal diamines as removable directing groups for the selective *ortho*-nitration of aromatics with interesting biological properties[16] under described reaction conditions.

Table 1. Optimization of Co-Catalyzed Aromatic C(sp^2)-H Nitration Reaction of Substrate 1a[a]



entry	[NO_2] source	oxidant	base	yield[b] **2a** (%)
1	$NaNO_2$	AgOAc	NaOAc	5
2	$AgNO_3$	AgOAc	NaOAc	40
3	$AgNO_2$	AgOAc	NaOAc	63
4	$AgNO_2$	Ag_2O	NaOAc	61
5	$AgNO_2$	Ag_2CO_3	NaOAc	50
6	$AgNO_2$	BQ	NaOAc	40
7	$AgNO_2$	AgOTf	NaOAc	60
8	$AgNO_2$	$K_2S_2O_8$	NaOAc	30
9	$AgNO_2$	AgOAc		85
10	$AgNO_2$			70
11[c]	**$AgNO_2$**			**92**
12[d]	$AgNO_2$			75
13[e]	$AgNO_2$			20
14[f]	$AgNO_2$			60
15[g]	$AgNO_2$			30
16[h]	$AgNO_2$			n.r.
17[i]	$AgNO_2$			30
18[j]	$AgNO_2$			15

[a] Reaction conditions: **1a** (0.29 mmol), [NO_2] source (1.1 equiv), $Co(OAc)_2{\cdot}4H_2O$ (10 mol %), oxidant (1 equiv), base (2.0 equiv), solvent (1.5 mL), 80 °C, in O_2 atm, 6 h. [b] Isolated yield. [c] $AgNO_2$ (1.5 equiv). [d] $AgNO_2$ (1.5 equiv), reaction at 60 °C. [e] $AgNO_2$ (1.5 equiv), reaction at rt. [f] $AgNO_2$ (1.5 equiv), reaction in air. [g] $AgNO_2$ (1.5 equiv), reaction in N_2 atm. [h] Without cobalt catalyst. [i] DMF was used as solvent. [j] Toluene was used as solvent.

With these optimized reaction conditions in hand, we probed the substrate scope for the nitration of N-phenylpyridin-2-amines (**1a**−**x**). As shown in Scheme 2, a wide variety of functionalized aromatic amines bearing both electron-rich (**2b**−**2d**) and electron-deficient (**2e**−**2i**) functional groups in the

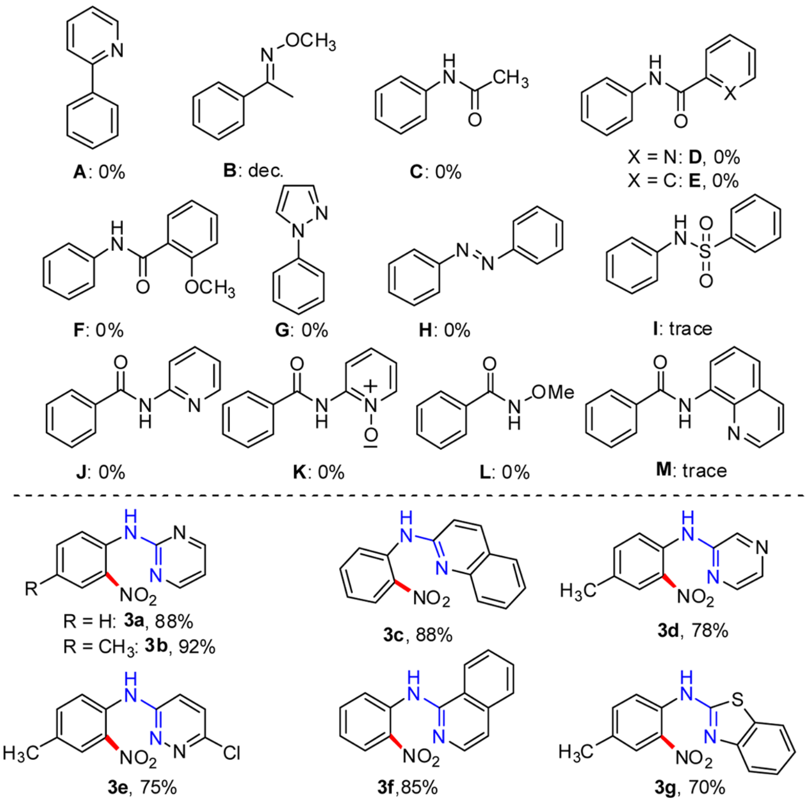
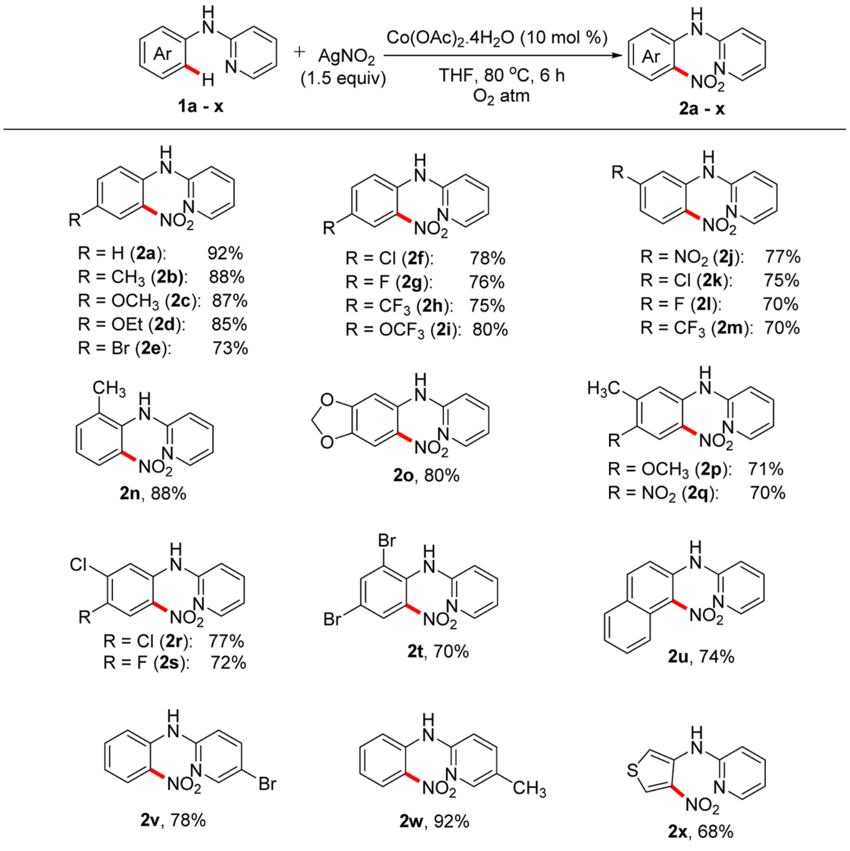


Figure 1. Screening of different directing groups for the aromatic C(sp^2)-H nitration reaction (dec. = decomposed).

Scheme 2. Cobalt-Catalyzed Aromatic C(sp^2)-H Bond Nitration of 1a–x with 2-Amino Pyridine as the Directing Group[a]

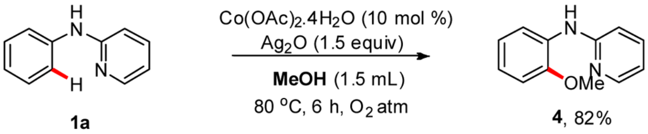


[a] Reaction conditions: **1a–x** (0.2 mmol), $AgNO_2$ (1.5 equiv), $Co(OAc)_2{\cdot}4H_2O$ (10 mol %), THF (1.5 mL), 80 °C, in O_2 atm. Six hours.

para-position afforded coupling products in good yields (73–90%), indicating that the electronic nature of the aromatics has no influence on the reaction. For *meta*-substituted substrates, the reactions proceeded with complete selectivity for the less-hindered *ortho*-position with good yields (**2j–m**; 70–77%). Notably, the fluoro, chloro, and bromo functional groups are well-tolerated under these reaction conditions. The functional group at the *ortho*-position did not inhibit the transformation, as the desired nitro product was obtained in good yield (**2n**, 88%). A similar *ortho*-product was obtained for the methylenedioxy compound (**2o**, 80%). Disubstituted substrates bearing methyl, methoxy, and nitro groups at the 3- and 4-positions provided the *ortho*-products (**2p** and **2q**) in good yields (70–72%). Similarly, disubstituted substrates bearing fluoro, chloro, and bromo groups at different positions provided the *ortho*-nitrated products in good yields (**2r–t**; 70–78%). In the case of the naphthyl group, the *mono*-nitration product (**2u**) was obtained in 74% yield. In this context, substituted pyridines were also tested. In the case of methyl substitution, the yield was 92% (**2w**), while the bromo derivative gave the *ortho*-product (**2v**) with decreased yield (78%). The heterocyclic substrate also underwent smooth nitration and afforded the product (**2x**) in 68% yield.

In continuation of nitration, we tried to extend the concept for C–H methoxylation of aromatics. For this reason, we tested the reaction of **1a** with $Co(OAc)_2{\cdot}4H_2O$ (10 mol %) and Ag_2O (1.5 equiv) in MeOH (1.5 mL) in O_2 atm for 6 h, and the *ortho*-methoxylated product **4** was isolated in 82% yield (Scheme 3).

Scheme 3. *ortho*-Methoxylation of Aromatic C–H Bond



Next, we applied our transformations in the rapid synthesis of biologically active compounds (Scheme 4). Selective reduction of **2a** and **3a**, carried out by the treatment with Zn dust/NH_4Cl in MeOH at 80 °C for 4 h, gave reduced compounds **5** and **6** in 75 and 70% yields, respectively. Using 10% Pd/C at 1 atm of H_2 in MeOH for 2 h at room temperature gave a 95% yield. These reduced amines (**5** or **6**) could be used for the rapid synthesis of biologically active compounds COX–II inhibitors[17] and monoamine reuptake inhibitors.[18]

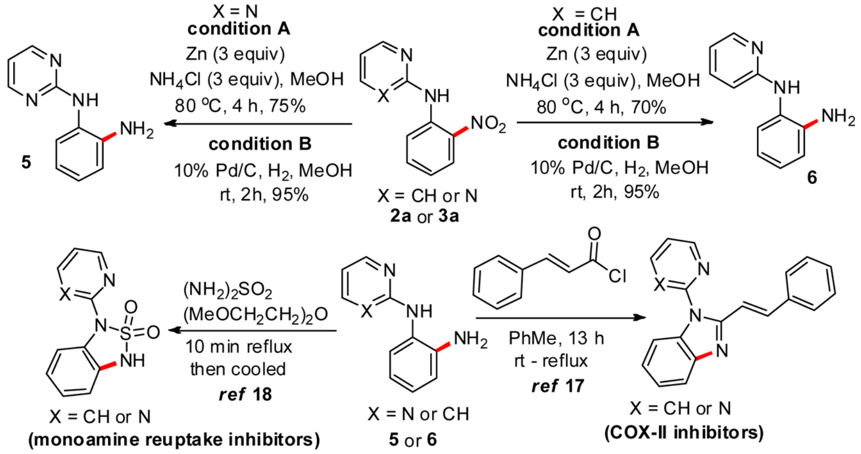
Removal of the directing groups was necessary to emphasize the efficiency of the method. The cleavage of pyrimidine and pyridine rings was performed in two steps: first, reduction by triethylsilane in TFA at 50 °C for 4 h, and then treatment with N_2H_4/AcOH in MeOH at rt for 15 h, which produced *o*-nitro aniline **7** in 72% yield. In another study, the reductive cleavage of pyrimidine and pyridine rings produced benzene-1,2-diamine **8** in 75% yield, reduced by Pd/C, H_2 1 atm, and HCl in isopropanol at rt for 16 h, followed by treatment with N_2H_4/AcOH in EtOH at 120 °C for 30 min (Scheme 5).

To gain insight into the mechanism of the C–H nitration reactions, a series of control experiments was conducted (Scheme 6). In experiment (eq 1), the addition of TEMPO (2 equiv) as a radical quencher completely inhibited the reaction. This indicates the reaction may involve a radical process.[19] To explore further the electronic effect on the rate of the reaction, we performed intermolecular competition experiments between **1b** and **1h** under the optimized conditions, which somewhat favors the electron-rich arene in a 1.1:1 ratio of **2b** and **2h** (eq 2). This suggested that direct cobaltation of arene C–H bonds is not happening. In another set of reactions with different substrates **9**, **10**, **11**, and **12** under standard conditions, no product formation was observed (eqs 3–6), which confirmed that a free NH group is essential. The kinetic isotope effect was also determined. A 1:1 mixture of [D_3]-**1a** and **1a** was treated with $AgNO_2$. No kinetic isotope effect (KIE; $K_H/K_D = 1$) was obtained (eq 7), indicating that C-H bond cleavage of the arenes is not the rate limiting step.

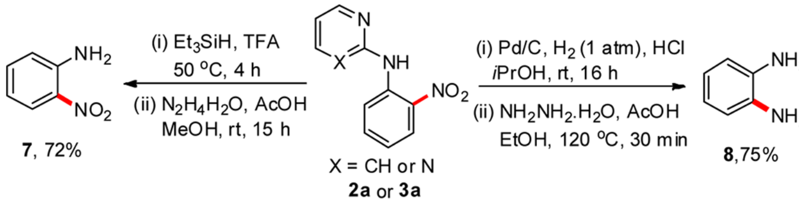
Through consideration of all of these observations and to elucidate the mechanism of the reaction outlined below, quantum chemical (density functional theory, DFT) calculations were employed (Scheme 7). The entire reaction mechanism study was performed using a model compound *N*-phenyl-2-aminopyridine (NPA). The entire reaction is classified into four steps: (i) an initial PCET reaction, (ii) AcOH-AcO ion exchange, (iii) nitro functional group transfer, and (iv) final H-abstraction to form a nitro product.[1,20–22]

Initially, precatalyst Co(II)$(OAc)_2$ is converted to the Co(III)$(OAc)_2(NO_2)$ in the presence of $AgNO_2$. The catalyst Co(III)$(OAc)_2(NO_2)$ forms an initial reactant complex (**RC**) by the coordination with *N*-aryl-2-aminopyridine, which is

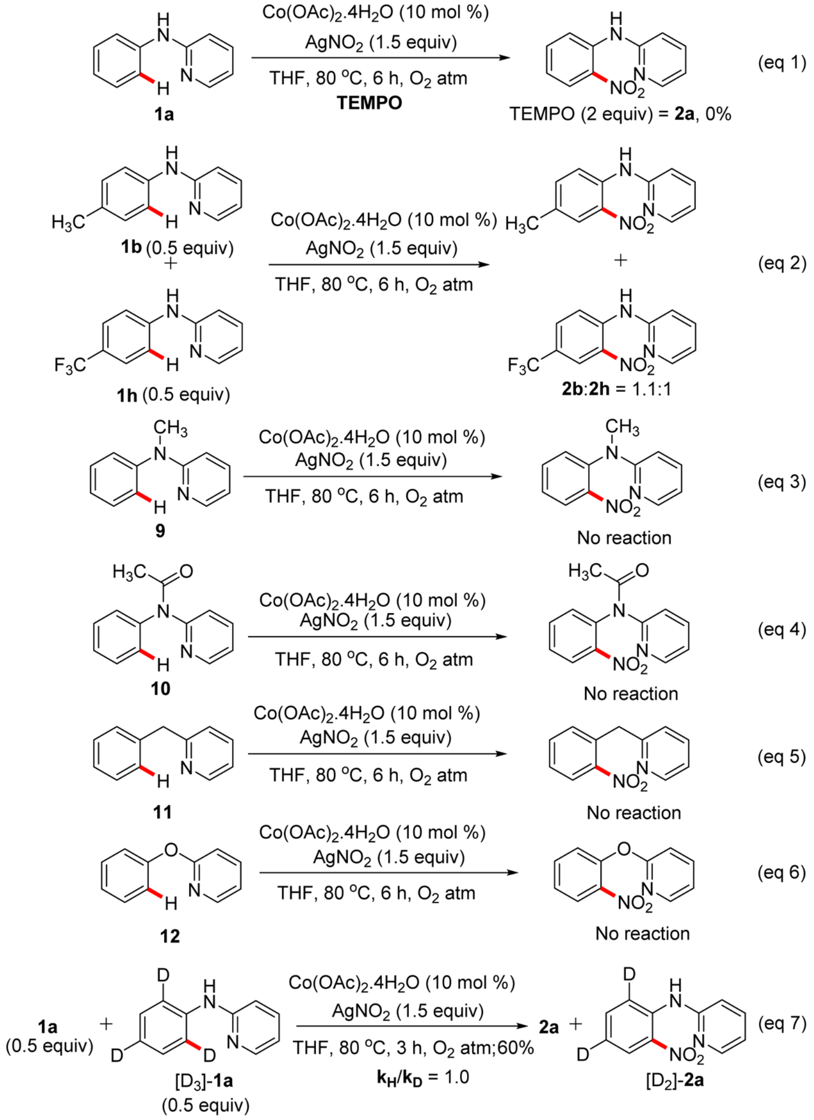
Scheme 4. Synthesis of Bioactive Compounds



Scheme 5. Removal of the Pyridine and Pyrimidine Directing Groups

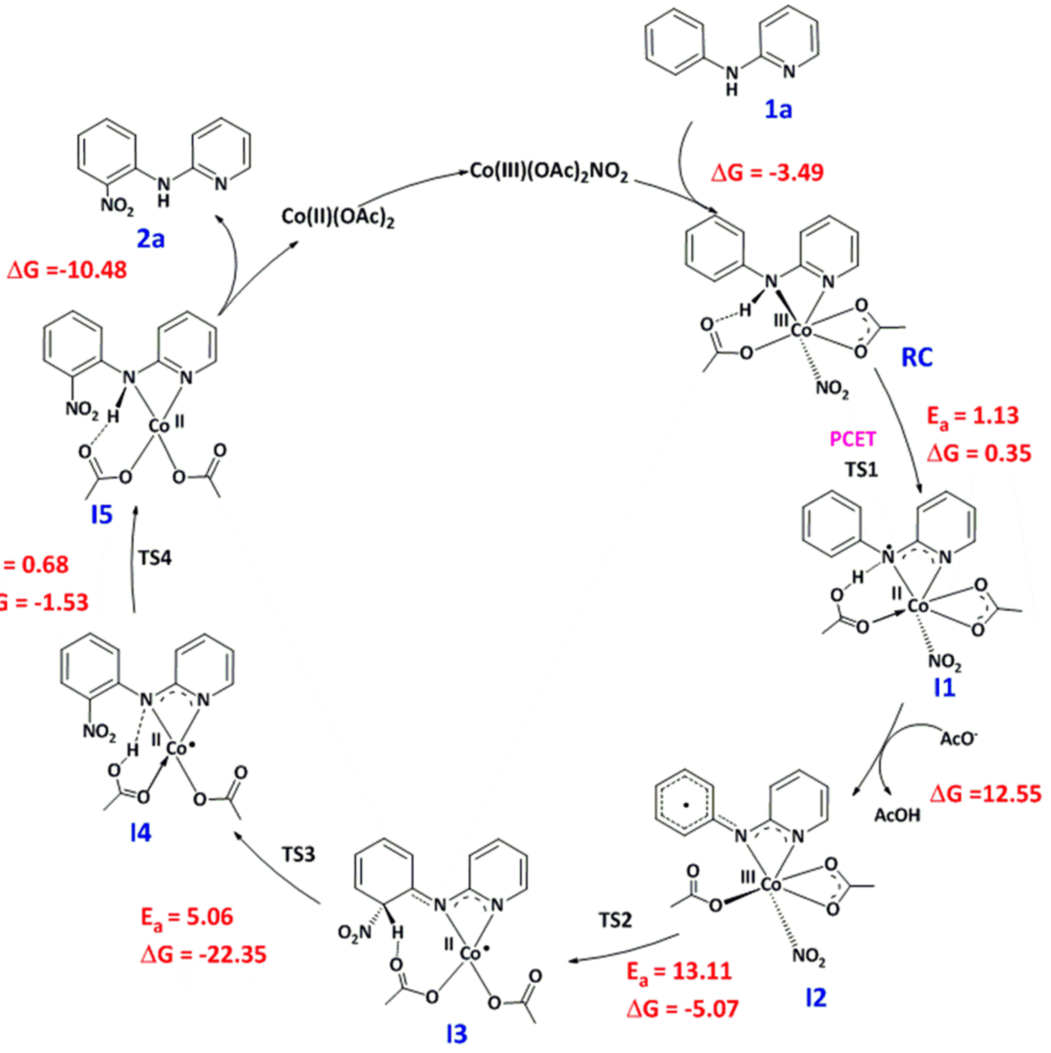


Scheme 6. Control and Kinetic Experiments



more stable by ~3.49 kcal/mol. The **RC** is characterized by a Co(III) center in an octahedral arrangement (one bidentate acetate, one monodentate acetate, nitro, and reactant **A** (bidentate)); it is also characterized by an AcO−H−N hydrogen bond which facilitates the hydrogen radical abstraction process (see Supporting Information for the 3D structures). The energy barrier for the hydrogen radical abstraction reaction is 1.13 kcal/mol via **TS1**, the resultant complex (**I1**) is marginally endergonic (0.35 kcal/mol). The molecular orbital analysis of the transition state showed that the abstraction of hydrogen follows a PCET mechanism. This is evident from the fact that the molecular orbitals are localized on the lone pair of nitrogen rather than the breaking N−H bond; such mechanism was reported for H-abstraction reaction from N−H bond.[1] In the PCET reaction, the proton transferred to acetate, and the electron delocalized to the cobalt metal (Co(III) reduced to Co(II)). To verify whether a SET (single electron transfer) process is involved, TD-DFT (B3LYP) calculations were performed; such mechanism has been reported in cobalt catalysis.[1] The energy barrier required for the transfer of an electron is ~35 kcal/mol; this value is much larger than the energy barrier for the hydrogen transfer process by a PCET (1.13 kcal/mol) reaction. Thus, the molecular orbital analysis as well as the energy profile of the reaction, confirmed that the H-abstraction reaction follows a PCET process rather than a SET mechanism. The energy

Scheme 7. Plausible Reaction Mechanism with DFT Calculations (Energy Values Are in kcal/mol)



barrier for the transfer of the nitro group from the cobalt center (Co(II)) to phenyl group is found to be very high (~45 kcal/mol) from **I1**; thus, it is worthy to consider the Co(III) center. Hence, the possibility of acetic acid group exchange with an acetate ion (forms a complex **I2**, a Co(III) species with the octahedral arrangement) is considered, and this is an endergonic process by ~12.55 kcal/mol. **I2** is characterized by an Ar−H···OAc interaction, and the 3D arrangement of atoms is suitable for NO_2 group transfer. The radical is delocalized on the aniline ring, which was confirmed by spin density calculations (the total spin density at the aniline ring is 1.2, which indicates that the aniline ring is adapting radical character). The transfer of nitro functional group from **I2** is only about 13.11 kcal/mol via **TS2** (which is much less than that from **I1**) and leads to the generation of an intermediate complex **I3**, giving a square planar arrangement at the Co(II) center. This is an exergonic process by ~5.07 kcal/mol. This is a rate limiting step for the nitration reaction. In **I3**, the reactive ortho carbon (of aryl group) adopts sp^3 hybridization (tetrahedral carbon), and the outgoing hydrogen atom is oriented toward an acetate ligand, which facilitates the H-transfer process. This H-transfer reaction leads to the formation nitro intermediate **I4** (which is an exergonic process by 22.35 kcal/mol); the energy barrier required for the H-transfer is 5.06 kcal/mol. In the **I3** → **I4** reaction, no change in the radical character at the metal center is observed (the spin density at Co center is 1 in both the intermediates **I3** and **I4**). Further, the proton transfers (via a PCET process) to the imino-functional group from AcOH (requires a small barrier of 0.68 kcal/mol via **TS4**) leads to the formation of **I5**; this is a slightly exergonic process (−1.53 kcal/mol). Intermediate **I5** does not carry any radical (during PCET process, the proton moves to nitrogen atom and the electron moves to the Co center, so the radical becomes neutralized). Finally, the complex **I5** dissociated to nitro product and $Co(OAc)_2$, which is an exergonic process (10.48 kcal/mol). Overall, this cobalt cycle is an exergonic process at ~30.02 kcal/mol, and all of the intermediate steps can be explained in terms of least motion pathways, supporting the proposed mechanism. 3D structures of intermediate complexes are provided in Supporting Information.

■ CONCLUSIONS

In conclusion, we developed the first cobalt-catalyzed *ortho*-specific nitration of aromatic C(sp^2)-H bonds using 2-aminopyridine as the vicinal diamine, a removable directing group. In this process, $AgNO_2$ acts as a nitro source as well as an oxidant. This rare Co-catalyzed protocol showed broad substrate scope, excellent functional group tolerance, and high regioselectivity, thus providing an appealing approach to the synthesis of *ortho*-nitro derivatives with challenging substitution patterns. The detailed studies on controlled experiments and mechanistic investigations with DFT calculations revealed that the reaction proceeds through a PCET promoted nitro functional group transfer pathway. Finally, we believe this finding will contribute to the expansion of the repertoire of cobalt catalysis.

■ EXPERIMENTAL SECTION

General Information. All purchased chemicals were used without further purification. All the starting substrates were prepared according to literature reported methods. Microwave reactions were carried out under a CEM discover monomode microwave synthesizer (the method of monitoring the reaction mixture temperature was an external surface sensor). All reactions were performed under an oxygen balloon atmosphere. THF was distilled with sodium metal. Analytical thin layer chromatography was performed using TLC precoated silica gel 60 F254 MERCK (20 × 20 cm). TLC plates were visualized by exposing UV light or by iodine vapors. Organic solutions were concentrated by rotatory evaporation on BUCHI-Switzerland; R-120 rotatory evaporator and vacuum pump V-710. Flash column chromatography was performed on Merck flash silica gel 100−200 mesh size. Melting points of solid compounds were determined on BUCHI-B-545-Switzerland melting point apparatus. ^{1}H and ^{13}C NMR spectra were recorded with BRUKER 500 and 400 MHz NMR instruments. Proton and carbon magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded using tetramethylsilane (TMS) in the solvent of $CDCl_3$ as the internal standard (^{1}H NMR: TMS at 0.00 ppm, $CHCl_3$ at 7.24 ppm; ^{13}C NMR: $CDCl_3$ at 77.0 ppm), using TMS in the solvent of DMSO-d_6 as the internal standard (^{1}H NMR: TMS at 0.00 ppm, DMSO at 2.50 ppm; ^{13}C NMR: DMSO at 40.0 ppm), or were recorded using TMS in the solvent of acetone-d_6 as the internal standard (^{1}H NMR: TMS at 0.00 ppm, acetone at 2.09 ppm;^{13}C NMR: acetone at 29.9 ppm, 206.7 ppm). All NMR spectra were processed in MestReNova. HRMS spectra were recorded with LCMS-QTOF Module no. G6540 A (UHD) instrument.

General Procedure for the Co-Catalyzed C(sp^2)-H Bond Nitration of Aromatics. An oven-dried 25 mL two-necked round bottomed flask with refluxing condenser was connected to an oxygen balloon. To this flask a solution of *N*-aryl-2-aminoheterocycles (1.0 equiv) in THF (1.5 mL) was added, and $Co(OAc)_2{\cdot}4H_2O$ (0.1 equiv) and $AgNO_2$ (1.5 equiv) were also added sequentially at room temperature with stirring. The flask was evacuated with an oxygen balloon after it was closed with septa, and the reaction mixture was stirred at 80 °C under an oxygen balloon atmosphere for 6 h. The progress of the reaction was monitored by TLC and, after completion of the reaction, THF was evaporated in vacuo, and then 10 mL of water was added to the reaction mixture at room temperature. The mixture was extracted with EtOAc (10 mL), further extracted two times with EtOAc (2 × 10 mL), and the combined organic phase was washed with sat. aq $NaHCO_3$ dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography to give pure *ortho*-specific nitrated *N*-aryl-2-amino heterocycles (**2a**−**x** and **3a**−**g**).

*N-(2-Nitrophenyl)pyridin-2-amine (**2a**).*[23] Eluent: petroleum ether:ethyl acetate (7:3). Yield: 58 mg (92%). Yellow solid, mp 157−159 °C; ^{1}H NMR (400 MHz, acetone-d$_6$) δ 9.04 (s, 1H), 8.18 (d, J = 4.2, 1H), 8.02 (d, J = 7.1, 2H), 7.88 (d, J = 9.1, 2H), 7.55 (t, J = 7.3, 1H), 6.86 (d, J = 8.3, 1H), 6.84−6.78 (m, 1H); ^{13}C NMR (125 MHz, acetone-d$_6$) δ 166.1, 155.7, 149.2, 148.3, 141.1, 138.6, 130.3, 125.8, 117.5, 117.4, 113.1; HRMS (ESI): calcd for $C_{11}H_{10}N_3O_2$ [M + H]$^+$, 216.0768; found: 216.0770.

*N-(4-Methyl-2-nitrophenyl)pyridin-2-amine (**2b**).* Eluent: petroleum ether:ethyl acetate (7:3). Yield: 55 mg (88%). Yellow solid, mp 88−90 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 3.9, 1H), 7.51−7.42 (m, 1H), 7.31 (S, 1H), 7.23 (d, J = 1.7, 1H), 7.20 (d, J = 8.4, 1H), 7.14 (d, J = 8.3, 1H), 6.82 (d, J = 8.5, 1H), 6.70 (t, J = 6.4, 1H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.4, 148.0, 146.8, 137.9, 133.3, 130.2, 129.9, 123.2, 121.3, 114.5, 107.8, 20.8; HRMS (ESI): calcd for $C_{12}H_{12}N_3O_2$ [M + H]$^+$, 230.0924; found: 230.0925.

*N-(4-Methoxy-2-nitrophenyl)pyridin-2-amine (**2c**).* Eluent: petroleum ether:ethyl acetate (7:3). Yield: 52 mg (87%). Yellow solid, mp 74−76 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.91 (s, 1H), 8.69 (d, J = 9.4 Hz, 1H), 8.36−8.21 (m, 1H), 7.67 (d, J = 3.1 Hz, 1H), 7.60 (td, J = 8.2, 1.9 Hz, 1H), 7.22 (dd, J = 9.4, 3.1 Hz, 1H), 6.90 (t, J = 7.0 Hz, 2H), 3.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1, 156.4, 147.6, 138.0, 132.9, 128.03, 124.3, 114.9, 114.6, 114.1, 107.3, 55.5; HRMS (ESI): calcd for $C_{12}H_{12}N_3O_3$ [M + H]$^+$, 246.0873; found: 246.0870.

*N-(4-Ethoxy-2-nitrophenyl)pyridin-2-amine (**2d**).* Eluent: petroleum ether:ethyl acetate (7:3). Yield: 52 mg (85%). Yellow solid, mp 112−114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.76 (s, 1H), 8.58 (dd, J = 8.3, 1.8, 1H), 8.47 (dd, J = 4.5, 1.8, 1H), 8.37 (d, J = 9.3, 1H), 7.66 (d, J = 3.0, 1H), 7.25−7.19 (m, 1H), 7.01−6.81 (m, 2H), 4.11 (q, J = 7.0, 2H), 1.46 (t, J = 7.0, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.6, 147.9, 145.9, 137.6, 127.9, 122.9, 121.7, 117.6, 114.8, 111.3, 110.3, 55.6, 22.5; HRMS (ESI): calcd for $C_{13}H_{14}N_3O_3$ [M + H]$^+$, 260.1030; found: 260.1035.

*N-(4-Bromo-2-nitrophenyl)pyridin-2-amine (**2e**).* Eluent: petroleum ether:ethyl acetate (7:3). Yield: 42 mg (73%). Yellow solid, mp 168−170 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 3.7, 1H), 8.13 (d, J = 8.7, 2H), 7.52 (d, J = 8.4, 2H), 7.27 (d, J = 7.8, 1H), 6.88 (d, J = 7.6, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.6, 147.6, 141.3, 138.5, 133.3, 132.6, 125.6, 123.6, 117.2, 117.0, 111.3; HRMS (ESI): calcd for $C_{11}H_9BrN_3O_2$ [M + H]$^+$, 293.9873; found: 293.9875.

*N-(4-Chloro-2-nitrophenyl)pyridin-2-amine (**2f**).* Eluent: petroleum ether:ethyl acetate (7:3). Yield: 48 mg (78%). Yellow solid, mp 150−152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.02 (s, 1H), 8.20 (d, J = 9.3, 1H), 7.43 (s, 1H), 7.31 (br, 4H), 6.69 (d, J = 9.2, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 158.0, 145.3, 137.3, 136.3, 135.6, 132.4, 129.5, 128.6, 122.4, 106.0; HRMS (ESI): calcd for $C_{11}H_9ClN_3O_2$ [M + H]$^+$, 250.0378; found: 250.0376.

*N-(4-Fluoro-2-nitrophenyl)pyridin-2-amine (**2g**).* Eluent: petroleum ether:ethyl acetate (7:3). Yield: 45 mg (76%). Yellow solid, mp 182−184 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.03 (s, 1H), 8.90 (dd, J = 9.6, 5.1 Hz, 1H), 8.32 (dd, J = 5.0, 1.2 Hz, 1H), 7.92 (dd, J = 8.9, 3.1 Hz, 1H), 7.63 (ddd, J = 8.2, 7.4, 1.9 Hz, 1H), 7.34 (ddd, J = 9.8, 7.1, 3.1 Hz, 1H), 6.95 (ddd, J = 7.3, 5.0, 0.8 Hz, 1H), 6.90 (d, J = 8.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.4, 159.6, 159.5 (d, J = 12.9), 151.9, 146.2, 144.4, 137.0, 133.6, 125.1 (d, J = 8.3), 116.6 (d, J = 22.8), 106.4; HRMS (ESI): calcd for $C_{11}H_9FN_3O_2$ [M + H]$^+$, 234.0674; found: 234.0675.

*N-(2-Nitro-4-(trifluoromethyl)phenyl)pyridin-2-amine (**2h**).* Eluent: petroleum ether:ethyl acetate (7:3). Yield: 45 mg (75%). Yellow solid, mp 130−132 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (d, J = 2.5, 1H), 8.32 (dd, J = 9.2, 2.6, 1H), 7.67−7.60 (m, 4H), 7.43 (s, 1H), 6.85 (d, J = 9.2, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.8, 145.9, 142.6, 137.1(d, J = 2.5), 132.4, 127.4 (q, J = 5.6), 126.1 (d, J = 3.2), 125.3, 123.1, 119.7, 117.0, 110.0 (d, J = 1.7); HRMS (ESI): calcd for $C_{12}H_9F_3N_3O_2$ [M + H]$^+$, 284.0643; found: 284.0648.

*N-(2-Nitro-4-(trifluoromethoxy)phenyl)pyridin-2-amine (**2i**).* Eluent: petroleum ether:ethyl acetate (7:3). Yield: 47 mg (80%). Yellow solid, mp 110−112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.18 (s, 1H), 8.97 (d, J = 9.5 Hz, 1H), 8.34 (dd, J = 4.9, 1.2 Hz, 1H), 8.11 (d, J = 2.6 Hz, 1H), 7.67 (ddd, J = 9.2, 8.3, 4.1 Hz, 1H), 7.44 (dd, J = 9.5, 2.7 Hz, 1H), 6.99 (ddd, J = 7.2, 5.0, 0.7 Hz, 1H), 6.94 (d, J = 8.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 146.4, 146.0, 137.3, 136.7, 133.5, 128.8 (q, J = 7.5), 123.3, 122.3, 121.5, 119.4, 107.2; ^{19}F NMR (376 MHz, $CDCl_3$) δ −58.51; HRMS (ESI): calcd for $C_{12}H_9F_3N_3O_3$ [M + H]$^+$, 300.0590; found: 300.0611.

*N-(2,5-Dinitrophenyl)pyridin-2-amine (**2j**).* Eluent: petroleum ether:ethyl acetate (7:3). Yield: 47 mg (77%). Yellow solid, mp 216−218 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 9.63 (s, 1H), 9.02 (s, 1H), 8.75 (s, 1H), 8.25 (dd, J = 9.2, 2.1, 1H), 8.02 (d, J = 8.1, 1H), 7.80 (d, J = 8.1, 1H), 7.52 (d, J = 8.1, 1H), 6.95 (d, J = 9.2, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 159.6, 149.6, 146.2, 142.0, 138.6, 133.6, 130.8, 126.2, 118.0, 114.7, 111.8; HRMS (ESI): calcd for $C_{11}H_9N_4O_4$ [M + H]$^+$, 261.0619; found: 261.0620.

N-(5-Chloro-2-nitrophenyl)pyridin-2-amine (***2k***). Eluent: petroleum ether:ethyl acetate (7:3). Yield: 46 mg (75%). Yellow solid, mp 146−148 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.48 (s, 1H), 8.21 (d, J = 3.9, 1H), 8.09 (d, J = 2.0, 1H), 7.92 (d, J = 9.2, 1H), 7.70−7.62 (m, 1H), 7.58−7.51 (m, 1H), 6.87 (d, J = 8.3, 1H), 6.85−6.79 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 153.9, 146.7, 146.7, 137.8, 137.2, 128.5, 127.2, 118.4, 116.2, 114.9, 112.1; HRMS (ESI): calcd for $C_{11}H_9ClN_3O_2$ [M + H]$^+$, 250.0378; found: 250.0372.

N-(5-Fluoro-2-nitrophenyl)pyridin-2-amine (***2l***). Eluent: petroleum ether:ethyl acetate (7:3). Yield: 42 mg (70%). Yellow solid, mp 178−180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 (d, J = 4.3, 1H), 8.08 (t, J = 8.8, 1H), 7.80 (dd, J = 14.1, 2.3, 1H), 7.69−7.63 (m, 1H), 7.26 (s, 1H), 7.12 (dd, J = 9.3, 1.9, 1H), 6.97 (dd, J = 7.0, 5.1, 1H), 6.90 (d, J = 8.3, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.5, 156.4, 154.2, 149.3, 147.5, 137.6, 128.0, 127.2 (d, J = 1.0), 117.0, 112.6 (d, J = 3.8), 104.8 (d, J = 26.8); HRMS (ESI): calcd for $C_{11}H_9FN_3O_2$ [M + H]$^+$, 234.0673; found: 234.0670.

N-(2-Nitro-5-(trifluoromethyl)phenyl)pyridin-2-amine (***2m***). Eluent: petroleum ether:ethyl acetate (7:3). Yield: 42 mg (70%). Yellow solid, mp 144−146 °C; ^{1}H NMR (400 MHz, MeOD) δ 8.99 (d, J = 2.5, 1H), 8.21 (dd, J = 9.3, 2.7, 1H), 8.08 (s, 1H), 7.81 (d, J = 7.8, 1H), 7.41 (t, J = 8.0, 1H), 7.23 (d, J = 7.7, 1H), 6.78 (d, J = 9.3, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.0, 149.5, 140.8 (d, J = 2.5), 138.3, 132.4, 130.9, 128.7, 127.4 (dd, J = 6.7, 1.8), 123.1, 117.0, 114.6 (d, J = 5.6), 111.1 (d, J = 2.8); HRMS (ESI): calcd for $C_{12}H_9F_3N_3O_2$ [M + H]$^+$, 284.0641; found: 284.0645.

N-(2-Methyl-6-nitrophenyl)pyridin-2-amine (***2n***). Eluent: petroleum ether:ethyl acetate (7:3). Yield: 55 mg (88%). Yellow solid, mp 126−128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41−8.28 (m, 1H), 8.10 (s, 1H), 8.08 (d, J = 2.6, 1H), 8.03−7.96 (m, 1H), 7.64 (ddd, J = 8.3, 7.3, 1.9, 1H), 6.99 (d, J = 8.3, 1H), 6.94 (ddd, J = 7.3, 5.0, 0.8, 1H), 6.66 (s, 1H), 2.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.8, 148.5, 145.3, 138.2, 126.3, 125.9, 123.4, 117.4, 116.0, 115.1, 111.3, 17.9; HRMS (ESI): calcd for $C_{12}H_{12}N_3O_2$ [M + H] $^+$, 230.0924; found: 230.0920.

N-(6-Nitrobenzo[d][1,3]dioxol-5-yl)pyridin-2-amine (***2o***). Eluent: petroleum ether:ethyl acetate (7:3). Yield: 49 mg (80%). Yellow solid, mp 142−144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (dd, J = 5.0, 1.2, 1H), 7.45−7.38 (m, 1H), 6.75 (s, 1H), 6.72 (d, J = 2.1, 1H), 6.67 (d, J = 2.1, 1H), 6.65 (d, J = 2.2, 1H), 6.63 (s, 1H), 5.96 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.3, 148.0, 145.0, 140.0, 137.3, 120.1, 115.1, 112.1, 108.7, 108.3, 101.4, 79.3; HRMS (ESI): calcd for $C_{12}H_{10}N_3O_4$ [M + H]$^+$, 260.0666; found: 260.0660.

N-(4-Methoxy-5-methyl-2-nitrophenyl)pyridin-2-amine (***2p***). Eluent: petroleum ether:ethyl acetate (7:3). Yield: 42 mg (71%). Yellow solid, mp 160−162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (s, 1H), 8.59 (d, J = 9.5 Hz, 1H), 8.12 (d, J = 1.7 Hz, 1H), 7.64 (d, J = 3.1 Hz, 1H), 7.42 (dd, J = 8.3, 2.3 Hz, 1H), 7.19 (dd, J = 9.5, 3.1 Hz, 1H), 6.82 (d, J = 8.3 Hz, 1H), 3.82 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.4, 148.1, 138.2, 132.6, 129.9, 125.2, 121.8, 117.8, 113.1, 110.6, 108.0, 56.3, 17.3; HRMS (ESI): calcd for $C_{13}H_{14}N_3O_3$ [M + H] $^+$, 260.1030; found: 260.1035.

N-(5-Methyl-2,4-dinitrophenyl)pyridin-2-amine (***2q***). Eluent: petroleum ether:ethyl acetate (7:3). Yield: 42 mg (70%). Yellow solid, mp 132−134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.14 (d, J = 2.4, 1H), 8.32 (d, J = 6.5, 1H), 8.21 (s, 1H), 7.66 (d, J = 8.2, 1H), 7.37 (d, J = 8.2, 1H), 7.31 (s, 1H), 6.78 (d, J = 9.2, 1H), 2.05 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.8, 151.0, 146.0, 144.0, 136.1, 133.0, 132.3, 124.6, 122.5, 121.7, 115.8, 17.0; HRMS (ESI): calcd for $C_{12}H_{11}N_4O_4$ [M + H]$^+$, 275.0774; found: 275.0772.

N-(4,5-Dichloro-2-nitrophenyl)pyridin-2-amine (***2r***). Eluent: petroleum ether:ethyl acetate (7:3). Yield: 45 mg (77%). Yellow solid, mp 196−198 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.22 (s, 1H), 9.29 (s, 1H), 8.39 (dd, J = 5.0, 1.3 Hz, 1H), 8.35 (s, 1H), 7.73−7.56 (m, 1H), 7.01 (ddd, J = 7.3, 5.0, 0.7 Hz, 1H), 6.93 (d, J = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ 159.5, 146.2, 140.7, 133.4, 132.7, 131.3, 125.8, 121.8, 120.4, 118.1, 111.6; HRMS (ESI): calcd for $C_{11}H_8Cl_2N_3O_2$ [M + H]$^+$, 283.9988; found: 283.9985.

N-(5-Chloro-4-fluoro-2-nitrophenyl)pyridin-2-amine (***2s***). Eluent: petroleum ether:ethyl acetate (7:3). Yield: 43 mg (72%). Yellow solid, mp 186−188 °C; ^{1}H NMR (400 MHz, MeOD) δ 8.96 (d, J = 2.5, 1H), 8.19 (dd, J = 9.3, 2.8, 1H), 7.92 (dd, J = 6.7, 2.7, 1H), 7.48−7.38 (m, 1H), 7.11 (t, J = 9.0, 1H), 6.75−6.67 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.3, 154.3, 151.9, 148.6 (d, J = 28.2), 144.4, 138.8, 137.0, 135.1, 128.4 (d, J = 7.2), 120.1 (d, J = 20.5), 106.4; HRMS (ESI): calcd for $C_{11}H_8ClFN_3O_2$ [M + H]$^+$, 268.0284; found: 268.0285.

N-(2,4-Dibromo-6-nitrophenyl)pyridin-2-amine (***2t***). Eluent: petroleum ether:ethyl acetate (7:3). Yield: 39 mg (70%). Yellow solid, mp 150−152 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (s, 1H), 8.26 (d, J = 7.0, 1H), 7.58 (s, 1H), 7.40 (d, J = 7.4, 1H), 7.25 (s, 1H), 7.03 (s, 1H), 6.74 (d, J = 9.3, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.3, 147.2, 144.8, 143.5, 137.4, 120.0, 119.9, 119.4, 116.4, 113.6, 112.1; HRMS (ESI): calcd for $C_{11}H_8Br_2N_3O_2$ [M + H]$^+$, 371.8977; found: 371.8974.

N-(1-Nitronaphthalen-2-yl)pyridin-2-amine (***2u***). Eluent: petroleum ether:ethyl acetate (7:3). Yield: 43 mg (74%). Yellow solid, mp 122−124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (dd, J = 20.6, 9.4, 2H), 7.93 (d, J = 9.0, 1H), 7.74 (d, J = 8.2, 1H), 7.60 (d, J = 8.5, 1H), 7.58−7.52 (m, 1H), 7.34 (d, J = 4.2, 1H), 7.12 (dd, J = 8.6, 2.3, 1H), 6.92 (d, J = 9.0, 1H), 6.80 (d, J = 9.1, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 156.5, 147.1, 145.1, 131.8, 129.6, 122.7, 122.5, 121.5, 121.4, 121.2, 120.1, 115.9, 111.2, 109.7, 109.0; HRMS (ESI): calcd for $C_{15}H_{12}N_3O_2$ [M + H]$^+$, 266.0924; found: 266.0920.

5-Bromo-N-(2-nitrophenyl)pyridin-2-amine (***2v***). Eluent: petroleum ether:ethyl acetate (7:3). Yield: 46 mg (78%). Yellow solid, mp 170−172 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (d, J = 2.2, 1H), 8.24−8.18 (m, 2H), 7.71 (dd, J = 8.7, 2.5, 1H), 7.61−7.55 (m, 2H), 6.92 (s, 1H), 6.82 (d, J = 8.7, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 152.3, 148.9, 146.3, 140.5, 126.2, 125.6, 117.0, 115.6, 112.5, 112.0; HRMS (ESI): calcd for $C_{11}H_9BrN_3O_2$ [M + H]$^+$, 293.9872; found: 293.9880.

5-Methyl-N-(2-nitrophenyl)pyridin-2-amine (***2w***). Eluent: petroleum ether:ethyl acetate (7:3). Yield: 57 mg (92%). Yellow solid, mp 158−160 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (dt, J = 5.0, 3.1, 3H), 7.52−7.47 (m, 2H), 7.45 (dd, J = 8.4, 1.9, 1H), 7.23 (s, 1H), 6.87 (d, J = 8.4, 1H), 2.29 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.5, 147.9, 147.4, 140.7, 138.9, 126.8, 125.7, 116.1, 111.3, 17.7; HRMS (ESI): calcd for $C_{12}H_{12}N_3O_2$ [M + H]$^+$, 230.0923; found: 230.0920.

N-(4-Nitrothiophen-3-yl)pyridin-2-amine (***2x***). Eluent: petroleum ether:ethyl acetate (7:3). Yield: 43 mg (68%). Yellow solid, mp 160−162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (s, 1H), 9.09 (d, J = 6.9, 1H), 7.96−7.90 (m, 1H), 7.78 (d, J = 8.8, 1H), 7.34 (d, J = 6.8, 1H), 7.20−7.07 (m, 1H), 6.80 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.7, 143.6, 133.6, 122.7, 122.1, 115.9, 112.7, 111.2, 104.1; HRMS (ESI): calcd for $C_9H_8N_3O_2S$ [M + H]$^+$, 222.0332; found: 222.0335.

N-(2-Nitrophenyl)pyrimidin-2-amine (***3a***).[14f] Eluent: petroleum ether:ethyl acetate (7:3). Yield: 56 mg (88%). Yellow solid, mp 134−136 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.49 (s, 1H), 8.98 (d, J = 8.7, 1H), 8.54 (d, J = 4.8, 2H), 8.24 (dd, J = 8.5, 1.5, 1H), 7.69−7.60 (m, 1H), 7.05 (ddd, J = 8.4, 7.2, 1.3, 1H), 6.91 (t, J = 4.8, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 158.0, 136.9, 135.7, 135.5, 126.1, 120.9, 120.8, 114.6; HRMS (ESI): calcd for $C_{10}H_9N_4O_2$ [M + H]$^+$, 217.0720; found: 217.0718.

N-(4-Methyl-2-nitrophenyl)pyrimidin-2-amine (***3b***).[14f] Eluent: petroleum ether:ethyl acetate (7:3). Yield: 57 mg (92%). Yellow solid, mp 142−144 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.26 (s, 1H), 8.75 (d, J = 8.7, 1H), 8.45 (d, J = 4.8, 2H), 7.97 (s, 1H), 7.38 (dd, J = 8.7, 1.6, 1H), 6.80 (t, J = 4.8, 1H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.4, 158.0, 136.5, 135.7, 134.5, 131.1, 125.7, 121.0, 114.4, 20.4; HRMS (ESI): calcd for $C_{11}H_{11}N_4O_2$ [M + H]$^+$, 231.0877; found: 231.0880.

N-(2-Nitrophenyl)quinolin-2-amine (***3c***). Eluent: petroleum ether:ethyl acetate (7:3). Yield: 53 mg (88%). Yellow solid, mp 220−222 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.45 (s, 1H), 9.43 (d, J = 8.2 Hz, 1H), 8.26 (dd, J = 8.5, 1.4 Hz, 1H), 8.04 (d, J = 8.8 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.67 (ddd, J = 8.7, 4.9, 1.7 Hz, 2H), 7.41 (t, J = 7.5 Hz, 1H), 7.08−6.90 (m, 2H); ^{13}C NMR (125

MHz, $CDCl_3$) δ 151.8, 150.71, 144.5, 141.7, 133.5, 132.8, 131.2, 130.7, 129.8, 128.9, 128.5, 127.8, 121.1, 119.2, 117.8; HRMS (ESI): calcd for $C_{15}H_{12}N_3O_2$ $[M + H]^+$, 266.0923; found: 266.0931.

N-(4-Methyl-2-nitrophenyl)pyrazin-2-amine ***(3d)***. Eluent: petroleum ether:ethyl acetate (7:3). Yield: 49 mg (78%). Yellow solid, mp 116−118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.18 (s, 1H), 8.67 (d, *J* = 8.7, 1H), 8.34 (d, *J* = 1.2, 1H), 8.23 (dd, *J* = 2.5, 1.4, 1H), 8.15 (d, *J* = 2.7, 1H), 8.07 (d, *J* = 1.0, 1H), 7.44 (dd, *J* = 8.7, 2.0, 1H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.6, 141.3, 136.9, 136.9, 136.5, 135.4, 135.2, 131.1, 125.9, 120.0, 20.4; HRMS (ESI): calcd for $C_{11}H_{11}N_4O_2$ $[M + H]^+$, 231.0876; found: 231.0879.

6-Chloro-N-(4-methyl-2-nitrophenyl)pyridazin-3-amine ***(3e)***. Eluent: petroleum ether:ethyl acetate (7:3). Yield: 45 mg (75%). Yellow solid, mp 196−198 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.19 (s, 1H), 8.83 (d, *J* = 8.7, 1H), 8.07 (s, 1H), 7.48 (d, *J* = 8.4, 1H), 7.41 (d, *J* = 9.2, 1H), 7.10 (d, *J* = 9.2, 1H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.3, 150.4, 137.3, 135.5, 134.6, 131.8, 130.3, 129.8, 125.9, 121.0, 20.5; HRMS (ESI): calcd for $C_{11}H_{10}ClN_4O_2$ $[M + H]^+$, 265.0487; found: 265.0489.

N-(2-Nitrophenyl)isoquinolin-1-amine ***(3f)***. Eluent: petroleum ether:ethyl acetate (7:3). Yield: 51 mg (85%). Yellow solid, mp 128−130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.13 (s, 1H), 8.93 (d, *J* = 8.6, 1H), 8.25 (d, *J* = 9.1, 1H), 8.14 (d, *J* = 9.0, 1H), 8.03 (d, *J* = 8.3, 1H), 7.89 (dd, *J* = 18.3, 8.6, 1H), 7.72 (d, *J* = 7.7, 2H), 7.45 (t, *J* = 7.8, 2H), 6.87 (d, *J* = 9.0, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.0, 144.7, 140.3, 132.8, 130.0, 128.8, 127.3, 126.0, 125.0, 123.6, 123.4, 123.1, 118.1, 117.5, 115.6; HRMS (ESI): calcd for $C_{15}H_{12}N_3O_2$ $[M + H]^+$, 266.0923; found: 266.0920.

N-(4-Methyl-2-nitrophenyl)benzo[d]thiazol-2-amine ***(3g)***. Eluent: petroleum ether:ethyl acetate (7:3). Yield: 42 mg (70%). Yellow solid, mp 198−200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 7.4, 1H), 8.12 (s, 1H), 7.47 (d, *J* = 7.7, 1H), 7.33 (dd, *J* = 16.3, 8.0, 1H), 7.00 (m, 2H), 6.94 (m, 2H), 2.23 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.0, 145.1, 143.6, 133.6, 133.5, 122.7, 122.1, 121.5, 121.2, 113.6, 111.2, 109.0, 104.1, 19.7; HRMS (ESI): calcd for $C_{14}H_{12}N_3O_2S$ $[M + H]^+$, 286.0645; found: 286.0640.

General Procedure for the Cobalt Catalyzed C(sp^2-H) Methoxylation of Aromatics. An oven-dried 25 mL two-necked round bottomed flask with a refluxing condenser was connected to an oxygen balloon. To this flask, a stirred solution of *N*-phenylpyridin-2-amine (0.294 mmol, 1.0 equiv) in MeOH (1.5 mL) was added. $Co(OAc)_2·4H_2O$ (0.0294 mmol, 0.1 equiv) and Ag_2O (0.44 mmol, 1.5 equiv) were also added sequentially at room temperature with stirring. The flask was evacuated with an oxygen balloon after it was closed with septa, and the reaction mixture was stirred at 80 °C under an oxygen balloon atmosphere for 6 h. The progress of the reaction was monitored by TLC and, after completion of the reaction, MeOH was evaporated in vacuo, and then 10 mL of water was added to the reaction mixture at room temperature. The mixture was extracted with EtOAc (10 mL), further extracted two times with EtOAc (2 × 10 mL), and the combined organic phase was washed with sat. aq $NaHCO_3$ dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (hexanes:EtOAc, 7:3) to give pure *ortho*-specific methoxylated *N*-(2-methoxyphenyl)pyridin-2-amine[24] (**4**) as a brown thick liquid (48 mg, 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.99 (s, 1H), 7.50 (s, 1H), 7.14 (s, 1H), 6.97 (s, 2H), 6.91 (s, 1H), 6.86 (d, *J* = 7.5, 1H), 6.73 (s, 1H), 3.89 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.6, 148.9, 147.7, 137.6, 130.0, 121.8, 120.8, 118.5, 114.8, 110.4, 109.5, 55.6; LC-MS (ESI) *m*/*z*: 201.10 [M + H].

General Procedures for the Selective Reduction of Nitro Groups. *Zn/NH_4Cl Mediated Synthesis of N-1-(Pyrimidin-2-yl)-benzene-1,2-diamine* ***(5)***. To a stirred solution of *N*-(2-nitrophenyl) pyrimidin-2-amine (0.231 mmol, 1.0 equiv) in MeOH (2 mL) were added Zn dust (1.388 mmol, 3 equiv) and NH_4Cl (1.388 mmol, 3 equiv) at room temperature. The reaction mixture was stirred at 80 °C for 4 h. The progress of the reaction was monitored by TLC and, after completion of the reaction, MeOH was evaporated in vacuo, and then 10 mL of water was added to the reaction mixture at room temperature. The mixture was extracted with EtOAc (20 mL), further extracted two times with EtOAc (2 × 20 mL), and the combined organic phase was washed with sat. aq $NaHCO_3$ dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (hexanes:EtOAc, 2:3) to give pure *N*-1-(pyrimidin-2-yl)benzene-1,2-diamine[23] (**5**) (33 mg, 75%) as light brown solid, mp 176−178 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 4.8, 2H), 7.40−7.33 (m, 1H), 7.08 (td, *J* = 7.8, 1.4, 1H), 7.00 (s, 1H), 6.84 (d, *J* = 7.6, 2H), 6.67 (t, *J* = 4.8, 1H), 3.98 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.4, 158.4, 141.7, 126.8, 126.1, 125.3, 119.2, 117.0, 111.9; HRMS (ESI): calcd For $C_{10}H_{11}N_4$ $[M + H]^+$, 187.0978; found:187.0980.

Pd/C Mediated Synthesis of N-1-(Pyrimidin-2-yl)benzene-1,2-diamine ***(5)***. To a stirred solution of *N*-(2-nitrophenyl) pyrimidin-2-amine (0.231 mmol, 1.0 equiv) in MeOH (2 mL) was added 10% Pd/C (0.0231 mmol, 0.1 equiv) at room temperature. The reaction mixture was stirred at room temperature under H_2 balloon atmosphere pressure for 2 h. The progress of the reaction was monitored by TLC and, after completion of the reaction, the solution was filtered through a Celite pad, and then MeOH was evaporated in vacuo. The crude product was purified by column chromatography (hexanes:EtOAc, 2:3) to give pure *N*-1-(pyrimidin-2-yl)benzene-1,2-diamine (**5**) (40 mg, 95%) as light brown solid.

Zn/NH_4Cl Mediated Synthesis of N-1-(Pyridin-2-yl)benzene-1,2-diamine ***(6)***. To a stirred solution of *N*-(2-nitrophenyl)pyridin-2-amine (0.231 mmol, 1.0 equiv) in MeOH (2 mL) were added Zn dust (1.388 mmol, 3 equiv) and NH_4Cl (1.388 mmol, 3 equiv) at room temperature. The reaction mixture was stirred at 80 °C for 4 h. The progress of the reaction was monitored by TLC and, after completion of the reaction, MeOH was evaporated in vacuo, and then 10 mL of water was added to the reaction mixture at room temperature. The mixture was extracted with EtOAc (20 mL), further extracted two times with EtOAc (2 × 20 mL), and the combined organic phase was washed with sat. aq $NaHCO_3$ dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (hexanes:EtOAc, 2:3) to give pure *N*-1-(pyridin-2-yl)benzene-1,2-diamine[23](**6**) (30 mg, 70%) as brown solid, mp 120−122 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14−8.10 (m, 1H), 7.41 (ddd, *J* = 9.1, 7.5, 1.9, 1H), 7.11−7.07 (m, 2H), 6.71−6.67 (m, 2H), 6.65−6.60 (m, 2H), 6.48 (s, 1H), 3.50 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.8, 148.1, 143.3, 137.7, 131.2, 125.0, 115.9, 113.8, 106.8; HRMS (ESI): calcd For $C_{11}H_{12}N_3$ $[M + H]^+$, 186.1026; found: 186.1029.

Pd/C Mediated Synthesis of N-1-(Pyridin-2-yl)benzene-1,2-diamine ***(6)***. To a stirred solution of *N*-(2-nitrophenyl)pyridin-2-amine (0.231 mmol, 1.0 equiv) in MeOH (2 mL) was added 10% Pd/C (0.0231 mmol, 0.1 equiv) at room temperature. The reaction mixture was stirred at room temperature under H_2 balloon atmosphere pressure for 2 h. The progress of the reaction was monitored by TLC and, after completion of the reaction, the solution was filtered through Celite pad, and then MeOH was evaporated in vacuo. The crude product was purified by column chromatography (hexanes:EtOAc, 2:3) to give pure *N*-1-(pyridin-2-yl)benzene-1,2-diamine (**6**) (40 mg, 95%) as a brown solid.

General Procedures for the Deprotection of Directing Groups. *Deprotection of Pyridine or Pyrimidine Rings for the Synthesis of Ortho-Nitro Anilines.* *N*-(2-nitrophenyl)pyridine-2-amine or *N*-(2-nitrophenyl)pyrimidine-2-amine (0.231 mmol, 1 equiv) was dissolved in TFA (1 mL) in a round bottomed flask. Et_3SiH (0.693 mmol, 3 equiv) was added, and the mixture was stirred at 50 °C under argon for 4 h. On completion of the reaction, the solvent was removed under reduced pressure; $N_2H_4·H_2O$ (1 mL), acetic acid (0.5 mL), and methanol (1 mL) were added, and the mixture was stirred under argon at room temperature for 15 h. On completion of the reaction, the solvents were removed under reduced pressure. After addition of 1 N NaOH solution (2 mL), the mixture was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated in vacuo. The product was purified by silica gel column chromatography (hexanes:EtOAc, 7:3) to give the pure 2-nitro aniline **7** as a yellow solid (23 mg, 72%), mp 72−74 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.6, 1H), 7.42−7.32 (m, 1H), 6.81 (d, *J* = 8.4, 1H), 6.75−

6.68 (m, 1H), 6.08 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.6, 135.7, 126.2, 118.7, 116.9; HRMS (ESI): calcd for $C_6H_7N_2O_2$ [M + H] $^+$, 139.0502; found: 139.0510.

Deprotection of Pyridine or Pyrimidine Rings for the Synthesis of ortho-Diamino Benzene. A round bottomed flask was charged with Pd/C (10% Pd-basis) and *i*PrOH (1 mL), and the mixture was stirred for 5 min under N_2 atmosphere. Afterward, **2a** or **3a** (0.231 mmol, 1 equiv), which was dissolved in *i*PrOH (1 mL) and 2 N HCl (300 μL, 1.386 mmol, 6 equiv) was added to the solution. The resulting mixture was flushed with H_2 three times and then stirred under H_2 (1 atm) at 50 °C for 16 h. Then, the solids were removed by filtration through Celite, and the solution was evaporated to dryness. Afterward, 1 N NaOH solution (1 mL) was added, and the reaction mixture was extracted with DCM (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated to dryness. The crude product was dissolved in 1 mL of $NH_2NH_2{\cdot}H_2O$, 0.5 mL of AcOH, and 1 mL EtOH in a microwave vial and flushed with argon. The vial was heated to 120 °C for 30 min in a microwave. The reaction mixture was allowed to cool to ambient temperature, and the volatiles were removed under reduced pressure. After addition of 1 N NaOH solution (1 mL), the mixture was extracted with Et_2O (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, filtered, and evaporated to dryness. The product was dried under high vacuum to give the pure *o*-phenylenediamine **8** as an off-white solid (19 mg, 75%), mp 102−104 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.76 (d, J = 7.4, 1H), 6.67 (s, 2H), 6.56 (s, 1H), 3.82 (s, 2H), 3.00 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 121.3, 119.7, 116.8, 116.3; HRMS (ESI): calcd For $C_6H_9N_2$[M + H]$^+$, 109.0760; found:109.0765.

Controlled Experiments. Reaction in the Presence of Radical Quencher TEMPO (eq 1). To a stirred solution of *N*-phenylpyridin-2-amine (0.294 mmol, 1 equiv) in THF (1.5 mL) was added $Co(OAc)_2{\cdot}4H_2O$ (0.0294 mmol, 0.1 equiv), $AgNO_2$ (0.441 mmol, 1.5 equiv), and TEMPO (0.588 mmol, 2 equiv) at room temperature. The reaction mixture was stirred at 80 °C under an oxygen atmosphere for 6 h and cooled to room temperature. The reaction mixture was diluted with 10 mL of CH_2Cl_2, filtered through a Celite pad, and then detected by TLC. The result showed that **2a** was not obtained.

Intermolecular Competition Reaction between ***1b*** *and* ***1h*** *(eq 2).* To a stirred solution of *N*-(*p*-tolyl)pyridin-2-amine (**1b**) (0.5 equiv) and *N*-(4-(trifluoromethyl)phenyl)pyridin-2-amine (**1h**) (0.5 equiv) (0.120 mmol, 1 equiv) in THF (1.5 mL) was added $Co(OAc)_2{\cdot}4H_2O$ (0.012 mmol, 0.1 equiv) and $AgNO_2$ (0.18 mmol, 1.5 equiv), at room temperature. The reaction mixture was stirred at 80 °C under an oxygen atmosphere for 6 h. The progress of the reaction was monitored by TLC and, after completion of the reaction, THF was evaporated in vacuo, and then 10 mL of water was added to the reaction mixture at room temperature. The mixture was extracted with EtOAc (10 mL) and further extracted two times with EtOAc (2 × 10 mL), and the combined organic phase was washed with sat. aq $NaHCO_3$ dried over Na_2SO_4 and concentrated in vacuo. The crude products were purified by column chromatography on silica gel. *N*-(4-methyl-2-nitrophenyl)pyridin-2-amine (**2b**, 40%) and *N*-(2-nitro-4-(trifluoromethyl)phenyl)pyridin-2-amine (**2h**, 35%) were isolated in 1.1:1 ratio.

Reaction with N-Methyl-N-phenylpyridin-2-amine (eq 3). To a stirred solution of *N*-methyl-*N*-phenylpyridin-2-amine (0.271 mmol, 1 equiv) in THF (1.5 mL) were added $Co(OAc)_2{\cdot}4H_2O$ (0.0271 mmol, 0.1 equiv) and $AgNO_2$ (0.406 mmol, 1.5 equiv) at room temperature. The reaction mixture was stirred at 80 °C under an oxygen atmosphere for 6 h and cooled to room temperature. The reaction mixture was diluted with 10 mL of CH_2Cl_2, filtered through a Celite pad, and then detected by TLC. The result showed that the corresponding ortho nitrated product was not formed.

Reaction with N-Phenyl-N-(pyridin-2-yl)acetamide (eq 4). To a stirred solution of *N*-phenyl- *N*-(pyridin-2-yl)acetamide (0.235 mmol, 1 equiv) in THF (1.5 mL) were added $Co(OAc)_2{\cdot}4H_2O$ (0.0235 mmol, 0.1 equiv) and $AgNO_2$ (0.353 mmol, 1.5 equiv) at room temperature. The reaction mixture was stirred at 80 °C under an oxygen atmosphere for 6 h and cooled to room temperature. The reaction mixture was diluted with 10 mL of CH_2Cl_2, filtered through a Celite pad, and then detected by TLC. The result revealed that the corresponding ortho nitrated product was not formed.

Reaction with 2-Benzylpyridine (eq 5). To a stirred solution of 2-benzylpyridine (0.295 mmol, 1 equiv) in THF (1.5 mL) were added $Co(OAc)_2{\cdot}4H_2O$ (0.0295 mmol, 0.1 equiv) and $AgNO_2$ (0.442 mmol, 1.5 equiv) at room temperature. The reaction mixture was stirred at 80 °C under an oxygen atmosphere for 6 h, and cooled to room temperature. The reaction mixture was diluted with 10 mL of CH_2Cl_2, filtered through a Celite pad, and then detected by TLC. The result revealed that the corresponding ortho nitrated product was not formed.

Reaction with 2-Phenoxy Pyridine (eq 6). To a stirred solution of 2-phenoxy pyridine (0.294 mmol, 1 equiv) in THF (1.5 mL) were added $Co(OAc)_2{\cdot}4H_2O$ (0.0294 mmol, 0.1 equiv) and $AgNO_2$ (0.442 mmol, 1.5 equiv) at room temperature. The reaction mixture was stirred at 80 °C under an oxygen atmosphere for 6 h and cooled to room temperature. The reaction mixture was diluted with 10 mL of CH_2Cl_2, filtered through a Celite pad, and then detected by TLC. The result revealed that the corresponding ortho nitrated product was not formed.

Kinetic Experiments. Synthesis of Benzen-2,4,6-d_3-amine. In a microwave reaction vial with a magnetic stir bar, aniline (2.15 mmol, 1 equiv) was added, followed by conc HCl (260 μL, 1 equiv) in 5 mL of D_2O. The vial was capped, sealed, and heated in the microwave synthesis apparatus for 30 min at a temperature of 180 °C. The reaction mixture can be directly concentrated to afford the DCl salt of the aniline. Alternatively, basic aqueous workup (via addition of 10 mL 3 M NaOH, 6 mL of brine, and 20 mL of Et_2O, separation of phases, and washing the organic phase with brine) can be used to afford the benzene-2,4,6-d_3-aniline as light brown liquid (186 mg, 90%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.13 (s, 1H), 3.57 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.5, 128.2, 128.1; LC-MS (ESI) m/z: 97.10 [M + H].

Synthesis of N-(Phenyl-2,4,6-d_3)pyridin-2-amine. To an oven-dried round-bottomed flask were added palladium diacetate (0.0318 mmol, 5 mol %), (±)-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl [(±)-BINAP] (0.0318 mmol, 5 mol %) and toluene (anhydrous, 5 mL), and the resulting mixture was then stirred under a stream of argon for 10 min. After this time, 2-bromo pyridine (0.636 mmol, 1 equiv) and 2,4,6-deuterated aniline (0.763 mmol, 1.2 equiv) were added with cesium carbonate (1.908 mmol, 3 equiv), and the reaction was fitted with a condenser and heated to reflux with vigorous stirring under argon for 14 h. After this time, the solids were removed by filtration through Celite; the pad was washed with DCM (2 × 20 mL), and the volatiles were removed under reduced pressure. The resulting residue was purified by columnar chromatography on silica gel to give pure *N*-(phenyl-2,4,6-d_3)pyridin-2-amine as a white solid (77 mg, 70%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24−8.19 (m, 1H), 7.54−7.46 (m, 1H), 7.34 (s, 2H), 6.88 (d, J = 8.4, 1H), 6.77−6.71 (m, 1H), 6.61 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.1, 147.3, 139.3, 136.6, 128.1, 128.0, 113.93, 107.1; LC-MS (ESI) m/z: 174.10 [M + H].

Determination of Kinetic Isotopic Effect. To a stirred solution of *N*-phenylpyridin-2-amine (0.5 equiv) and *N*-(phenyl-2,4,6-d_3)-pyridin-2-amine (0.5 equiv) in THF (1.5 mL) were added $Co(OAc)_2{\cdot}4H_2O$ (0.1 equiv) and $AgNO_2$ (1.5 equiv) at room temperature. The reaction mixture was stirred at 80 °C under an oxygen atmosphere for 3 h. THF was evaporated in vacuo, and then 10 mL of water was added to the reaction mixture at room temperature. The mixture was extracted with EtOAc (10 mL), further extracted two times with EtOAc (2 × 10 mL), and the combined organic phase was washed with sat. aq $NaHCO_3$, dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by column chromatography, and the KIE value was calculated as k_H/k_D = 1.0. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28−8.22 (m, 2H), 8.17−8.08 (m, 4H), 7.56 (td, J = 8.0, 1.9, 2H), 7.53−7.48 (m, 2H), 7.04 (s, 2H), 6.89−6.83 (m, 4H).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00808.

Copies of ^{1}H and ^{13}C NMR spectra and mechanistic studies (PDF)

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Notes

The authors declare no competing financial interest.

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