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One-Pot Protocol To Synthesize 2-Aminophenols from Anilines via Palladium-Catalyzed C−H Acetoxylation

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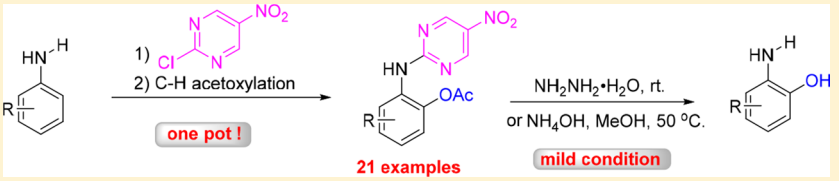
Supporting Information



ABSTRACT: This paper describes a facile one-pot protocol to synthesize 2-aminophenol derivatives via a palladium-catalyzed C−H acetoxylation strategy with 5-nitropyrimidine as a directing group (DG), which can be easily preinstalled and readily removed under mild condition after the coupling. In addition, the transformation is operationally simple, has high functional group tolerance, and is amenable to gram-scale. Moreover, several examples were shown that introduction/removal of 5-nitropyrimidine and the C−H oxylation sequence could be integrated in one pot.

INTRODUCTION

In recent years, with the rise of transition-metal-catalyzed C−H bond activation, directing group (DG) assisted Csp^2−H bond functionalization has attracted wide attention.[1−14] Various directing groups, such as amine,[15] imine,[16] oxime,[17] diazene,[18] amide,[19−24] carboxylic acid,[25] among others,[26−29] were exploited to achieve regioselective C−H functionalization. The pyrimidyl and pyridyl moieties, strongly coordinated DGs, which easily formed a thermodynamically stable five- or six-membered metallacycle with the transition metal for facilitating the C−H activation step, have been more actively studied.[30−37] The inevitable major problems associated with pyrimidyl/pyridyl-directed C−H functionalization are separate step to introduce them and harsh condition to remove them.[38−41] Notably, ortho-functionalization of 2-phenoxypridines and 2-phenoxypyrimidines have been extensively reported, while similar transformations were seldom able to apply to aniline derivatives because the free amino group could facilitate other side reactions.[42−51]

Pyrimidyl/pyridyl assisted ortho-oxylation phenols with an easily accessible palladium catalyst have been well established.[33,42,52−54] The developed catalytic system could be extended to various aniline derivatives after certain modification, such as protected phenylamide,[55−58] phenylnitrous amide,[59,60] and phenyldiazene[61,62] (Figure 1), while these reactions often suffer limited substrate group and difficult-to-remove directing group. Structurally versatile pyrimidyl/pyridyl anilines are not capable for these transformations thus far. We questioned whether it might be possible to expand application of palladium-catalyzed oxylation to anilines masked by functional pyrimidyl/pyridyl group, proving a short cut to aminophenols which are key structural motifs of numerous bioactive compounds used in crop protection and medicinal chemistry.[63−67] To provide more practicable C−H functionalization for sustainable synthesis, we present here a synthetically convenient Pd-catalyzed C−H acetoxylation reaction for aniline/phenol substrates with easy-to-handle directing groups (Figure 1). Our method enables the direct preparation of ortho-oxylation-free anilines. Notable features of our general strategy include (1) structurally diversified aniline derivatives can be successfully ortho-acetoxylated under one-pot reaction condition; (2) both the C−H functionalization and the mild directing group removal procedure have high function group tolerance; and (3) the transformation from aniline derivatives to 2-aminophenol derivatives is amenable to a gram-scale

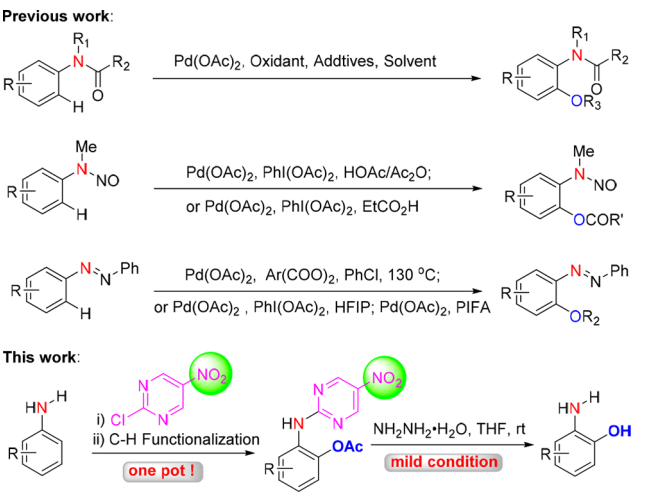


Figure 1. C(sp^2)−H functionalization of phenol and aniline derivatives with directing groups.

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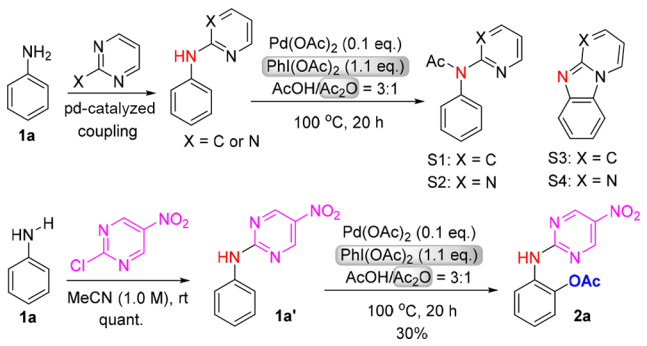
synthesis and the practical auxiliary, 5-nitropyrimidine, was successfully applied as a transient directing group during introduction of DG, C−H functionalization and removal of DG.

RESULTS AND DISCUSSION

There is much difference between DG-assisted functionalization of anilines and phenols, especially involving oxidant during the transformation. Preprotection of anilines is usually employed to avoid the nitrogen being oxidized or acting as a reactive site to participate further transformation.[59,68−71] In our initial study, the coupling reaction between different pyrimidyl/pyridyl- derivatives and aniline, along with further potential DG assisted ortho-acetoxylated were invested (Scheme 1). The results turned out to be that 5-nitropyrimidine, unlike pyridine and pyrimidine units, was the easiest to be introduced, which could avoid aniline derivatives to be further protected by Ac2O and oxidized by PhI(OAc)2.[68−70] Moreover, 5-nitropyrimidine could work as a DG to promote ortho-acetoxylation of aniline.

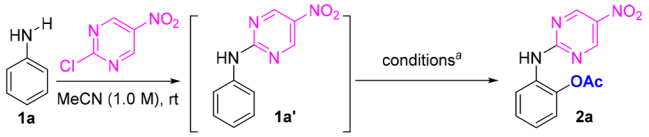
Scheme 1. Reactivity of Different DGs



The reaction optimization was outset by using aniline **1a** as model substrate which was mixed with 2-chloro-5-nitropyrimidine to give the intermediate compound **1a′** for the directly usage of next step. After the addition of HOAc (0.2 M **1a**), $Pd(OAc)_2$ (10 mol %), $PhI(OAc)_2$ (1.5 equiv), the reaction was stirred for 12 h.[72−75] Subsequent workup furnished the ortho-acetoxylation product **2a** in 35% yield (Table 1, entry 1). Encouraged by this, various solvents, oxidants, and metal catalysts were screened to get the optimal yield of the product **2a**. Among the solvents screened, a mixed solvent system ($HOAc/Ac_2O$ = 1:1) turned out to be the most effective choice to deliver product in 60% yield (Table 1, entries 2−6). The oxidant $PhI(OAc)_2$ was crucial for the acetoxylation. Its absence or the replacement with another oxidant, such as $K_2S_2O_8$, benzoxyl peroxide, H_2O_2, or O_2, would not result in any significant amount of product (Table 1, entries 7−11). The amount of $PhI(OAc)_2$ directly affected the efficiency of the reaction, and 1.1 equiv of $PhI(OAc)_2$ gave the best yield and only a monofunctionalization product was observed (Table 1, entries 12, 13). Gratifyingly, a better yield was obtained in a much shorter reaction time (Table 1, entries 14, 15). Palladium acetate was superior to other tested metal-catalysts, including $[RhCp^*Cl_2]_2$ and $RuCl_2$(p-cymene) (Table 1, entries 16−18) for this transformation.

With the optimized condition in hand, the versatility of C−H acetoxylation of aniline derivatives was carefully explored (Table 2). Electron-rich aniline derivatives with or without ortho- and meta-substituted groups did not show much difference and gave the desired products **2a**−**2d** in 63%−75%

Table 1. Optimization of the One-Pot Procedure



entry	catalyst[b]	oxidant	solvent	time (h)	yield[c]
1	$Pd(OAc)_2$	$PhI(OAc)_2$ (1.5 equiv)	HOAc	12	35%
2	$Pd(OAc)_2$	$PhI(OAc)_2$ (1.5 equiv)	Ac_2O	12	trace
3	$Pd(OAc)_2$	$PhI(OAc)_2$ (1.5 equiv)	HOAc:MeCN = 1.1	12	10%
4	$Pd(OAc)_2$	$PhI(OAc)_2$ (1.5 equiv)	$HOAc:Ac_2O$ = 3.1	12	39%
5	$Pd(OAc)_2$	$PhI(OAc)_2$ (1.5 equiv)	$HOAc:Ac_2O$ = 1.3	12	29%
6	$Pd(OAc)_2$	$PhI(OAc)_2$ (1.5 equiv)	$HOAc:Ac_2O$ = 1.1	12	58%[d]
7	$Pd(OAc)_2$	–	$HOAc:Ac_2O$ = 1.1	12	0
8	$Pd(OAc)_2$	$K_2S_2O_8$ (1.1 equiv)	$HOAc:Ac_2O$ = 1.1	12	trace
9	$Pd(OAc)_2$	benzoxyl peroxide	$HOAc:Ac_2O$ = 1.1	12	trace
10	$Pd(OAc)_2$	H_2O_2 (1.1 equiv)	$HOAc:Ac_2O$ = 1.1	12	trace
11	$Pd(OAc)_2$	O_2(buloom)	$HOAc:Ac_2O$ = 1.1	12	trace
12	$Pd(OAc)_2$	$PhI(OAc)_2$ (0.5 equiv)	$HOAc:Ac_2O$ = 1.1	12	35%
13	$Pd(OAc)_2$	$PhI(OAc)_2$ (1.1 equiv)	$HOAc:Ac_2O$ = 1.1	12	68%
14	$Pd(OAc)_2$	$PhI(OAc)_2$ (1.1 equiv)	$HOAc:Ac_2O$ = 1.1	6	75%
15	$Pd(OAc)_2$	$PhI(OAc)_2$ (1.1 equiv)	$HOAc:Ac_2O$ = 1.1	4	56%
16	–	$PhI(OAc)_2$ (1.1 equiv)	$HOAc:Ac_2O$ = 1.1	6	0
17	$[RhCp^*Cl_2]_2$	$Cu(OAc)_2$ (2.2 equiv)	$HOAc:Ac_2O$ = 1.1	6	trace
18	$RuCl_2$(p-cymene)	$PhI(OAc)_2$ (1.1 equiv)	$HOAc:Ac_2O$ = 1.1	6	trace

[a]All reactions were run on a 0.5 mmol scale of **1a** with its concentration of 0.2 M at 100 °C. [b]The loading of catalyst was tested, and the yield of product is similar when 5 mol % or 10 mol % of $Pd(OAc)_2$ was used. A lower yield was obtained when we only use 2 mol % of the catalyst. [c]Isolated yield. [d]bis-C-H acetoxylation product was detected by LC-MS.

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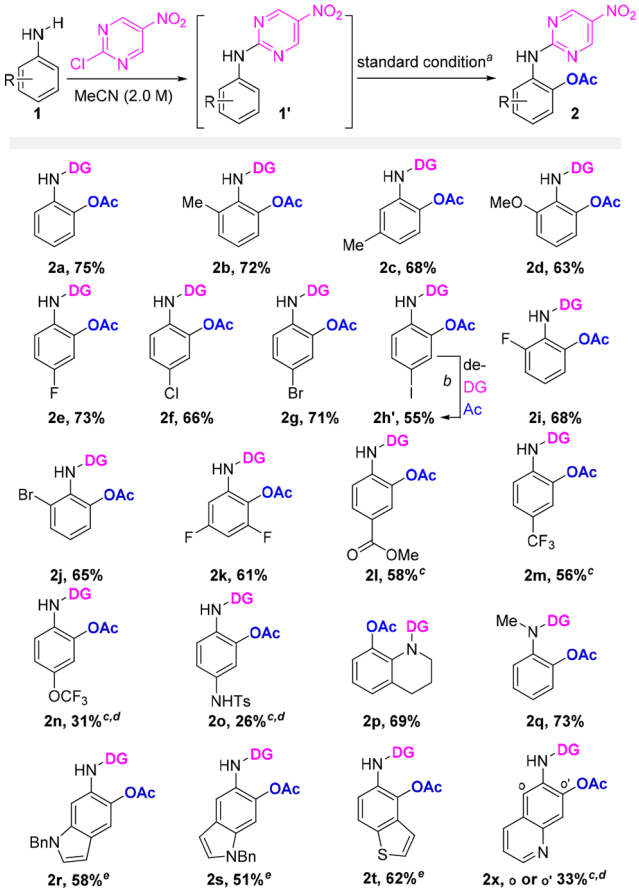
Table 2. Substrate Scope of Pd-Catalyzed C−H Acetoxylation of Aniline Derivatives

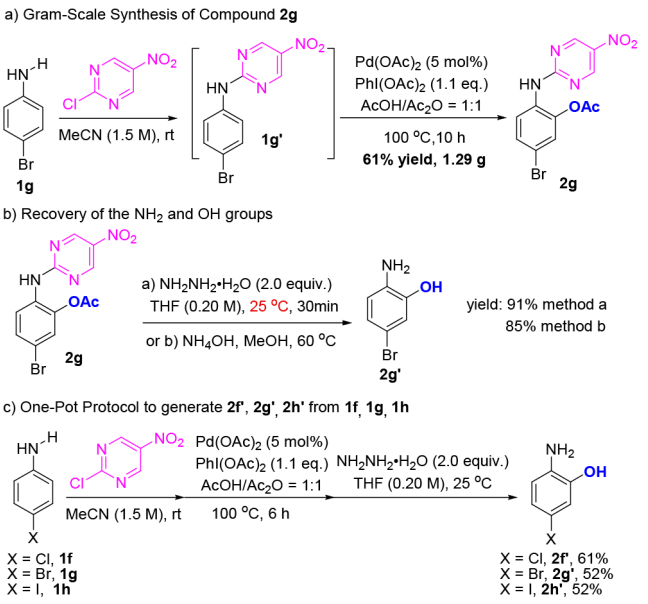


[a]The reactions were run on a 1.0 mmol scale of **1** with the concentration of 0.2 M ($HOAc/Ac_2O$ = 1:1), $Pd(OAc)_2$ (5 mol %), $PhI(OAc)_2$(1.1 equiv) at 100 °C for 6 h. [b]Hydrazine monohydrate, THF, 25 °C. [c]The reaction time is 4 h. [d]NMR yield. [e]0.12 mmol of **1** was used.

yields. The reaction exhibited very good regio-selectivity so that only less crowded product **2c** (68% yield) was furnished for *m*-toluidine. Various halogen substituted anilines also successfully delivered acceptable to good yield (**2e**−**2k**, 60%−73% yields). Because of the difficulty in separation, compound **2h** was directly mixed with hydrazine monohydrate to give **2h′** in a overall yield of 55%. Substrates with an electron-withdrawing group, such as MeCOO-, CF_3-, -OCF_3 groups, afforded the desired products (**2l**, 58%; **2m**, 56%, **2n** 31% yield) in low yield with than the tested amines with an electron-donating group or without substitutions. It is worthwhile to mention that extending the reaction time will lead to lower yields for electron deficient substrates, indicating thermal decomposition of the corresponding products under acidic condition at high temperature. Ts-protected amine group can be tolerated to give product **2o** in 26% NMR yield. Isolation of the product was met with limited success due to its high polarity and contamination with unknown byproducts. Compounds with protected secondary amines smoothly underwent Pd-catalyzed C−H acetoxylation, providing the desired product in good yields (**2p**, 69%; **2q**, 73% yield). It was encouraging to observe that the reaction was applicable to heterocyclic substrates as well. Indeed, the transformation was effective on indole, benzothiophene, and quinoline derivatives, which readily delivered the desired product with less steric hindrance in moderate yields (**2r**, 58%, **2s**, 51%, **2t**, 62%, **2x**, 33%).

To demonstrate both the practicality and effectiveness of our method, compound **2g** with a bromo group for further transformation was prepared on a gram scale under the standard condition in the slightly longer time (Scheme 2a).

Scheme 2. Further Investigation of This Transformation



Both the directing group (2-*N*- and -*O*- 5-nitropyrimidine) and the acyl group can be cleaved by hydrazine monohydrate in THF at room temperature or ammonium hydroxide in methanol at 50 or 60 °C if safer handling is required (Scheme 2b). Moreover, the two-step ortho-acetoxylation and removal of the directing group sequence in one pot was carried out to give compound **2f′**, **2g′**, **2h′** in 61%, 52%, 52% yield, respectively (Scheme 2c).

CONCLUSIONS

In summary, we have developed a convenient and efficient synthetic methodology for the synthesis of 2-amino phenol derivatives, which are key structural motifs of numerous bioactive compounds and blockbuster drugs. The nitro-pyrimidine directing group can be introduced and removed easily, facilitating a wide range of function group tolerance. Moreover, introduction/removal of the directing group and the C−H functionalization sequence can be integrated in one pot. More applications of the directing group for step-efficient synthesis of biologically interesting molecules are under way.

EXPERIMENTAL SECTION

Attempt To Use Pyridine Unit as a DG. Under N_2 atmosphere, an oven-dried 25 mL flask was charged with *N*-phenylpyridin-2-amine (0.170 g, 1.00 mmol, 1.00 equiv), AcOH (6.0 mL) and Ac_2O (2.0 mL), followed by the addition of $Pd(OAc)_2$ (5.60 mg, 0.05 mmol, 0.05 equiv) and $PhI(OAc)_2$ (0.365 g, 1.10 mmol, 1.10 equiv). After it was stirred for 20 h at 100 °C, the reaction mixture was concentrated under vacuo. The residue was purified by column chromatography on silica gel (PE/EtOAc = 5/1 to 2/1 as the eluent) to give compound **S1** (yellow solid, 0.08 3 g, 0.39 mmol, 39% yield) and **S3** (white solid, 0.050 g, 0.30 m10 mol, 30% yield). Compound **S1**, R_f = 0.25 (PE/EtOAc = 2/1(v/v)). NMR spectroscopy: ^1H NMR (300 MHz,

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$CDCl_3$, 25 °C, δ): 8.43 (dd, J = 3.0 Hz, J = 6.0 Hz, 1 H), 7.71 (t, J = 3.0 Hz, J = 6.0 Hz, 1 H), 7.46 (d, J = 8.7 Hz, 1 H), 7.41 (d, J = 8.7 Hz, 1 H), 7.36−7.28 (m, 3 H), 7.13 (dd, J = 3.0 Hz, J = 6.0 Hz, 1 H), 2.11 (s, 3 H). Compound **S3**, R_f = 0.15 (PE/EtOAc = 1/1(v/v)). NMR spectroscopy: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, δ): 8.46 (d, J = 6.0 Hz, 1 H), 7.93 (dd, J = 9.0 Hz, J = 12.0 Hz, 2 H), 7.71 (d, J = 8.7 Hz, 1 H), 7.54 (t, J = 6 Hz, J = 15 Hz, 1 H), 7.46−7.35 (m, 2 H), 6.86 (t, J = 6.0 Hz, J = 15.0 Hz, 1 H). Compounds **S1** and **S3** are known.[68]

Attempt To Use Pyrimidine Unit as a DG. Under N_2 atmosphere, an oven-dried 25 mL flask was charged with *N*-phenylpyrimidin-2-amine (0.136 g, 0.80 mmol, 0.80 equiv), AcOH (6.0 mL), and Ac_2O (2.0 mL), followed by addition of $Pd(OAc)_2$(4.48 mg, 0.04 mmol, 0.05 equiv) and $PhI(OAc)_2$(0.320 g, 0.88 mmol, 1.10 equiv). After it was stirred for 20 h at 100 °C, the reaction mixture was concentrated under vacuo. The residue was purified by column chromatography on silica gel (PE/EtOAc = 2/1 to PE/EtOAc = 1/1 as the eluent) to give the title compound **S2** (dark brown solid, 0.094 g, 55 mmol, 55% yield) and **S4** (dark brown solid, 0.062 g, 37 mmol, 37% yield). **S2**: R_f = 0.32 (PE/EtOAc = 2/1(v/v)). NMR spectroscopy: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, δ): 8.68 (dd, J = 3.0 Hz, J = 6.0 Hz, 1 H), 7.47−7.42 (m, 2 H), 7.37 (d, J = 6.0 Hz, 2 H), 7.30−7.26 (m, 2 H), 7.11 (t, J = 3.0 Hz, J = 9.0 Hz, 1 H), 2.32 (s, 3 H). **S4**: R_f= 0.12 (PE/EtOAc = 1/1(v/v)). NMR spectroscopy: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, δ): 9.53 (dd, J = 3.0 Hz, J = 6.0 Hz, 1 H), 8.84 (dd, J = 3.0 Hz, J = 6.0 Hz, 1 H), 8.42 (d, J = 8.7 Hz, 1 H), 7.87 (d, J = 8.7 Hz, 1 H), 7.57 (t, J = 6 Hz, J = 15 Hz, 1 H), 7.44 (t, J = 6.0 Hz, J = 15.0 Hz, 1 H), 7.16 (dd, J = 6.0 Hz, J = 9.0 Hz, 1 H). Compounds **S2** and **S4** are known.[69]

Representative Reaction Procedure (I): Synthesis of 2-((5-Nitropyrimidin-2-yl)amino) Phenylacetate (2a). Under N_2 atmosphere, an oven-dried 50 mL flask was charged with the aniline (0.0931 g, 1.00 mmol, 1.00 equiv) and 2-chloro-5-nitropyrimidine (0.1593 g, 1.00 mmol, 1.00 equiv) in CH_3CN (2.0 mL, 0.50 M). The reaction mixture was stirred for 4 h at rt, and the reaction was monitored via TLC until the disappearance of 2-chloro-5-nitropyrimidine (R_f = 0.79 (PE/EtOAc = 5/1 (v/v)). AcOH (4.0 mL) and Ac_2O (4.0 mL) (AcOH/Ac_2O = 1/1) were directly added to the reaction mixture, followed by $Pd(OAc)_2$ (11.2 mg, 0.05 mmol, 0.05 equiv) and $PhI(OAc)_2$ (0.3482 g, 0.21 mmol, 1.10 equiv). The reaction was cooled to rt after stirring at 100 °C for 6 h, which was concentrated by reduced pressure. The residue was purified by column chromatography (PE/EtOAc = 25/1 to 5/1(v/v)) to afford **2a** as a brown solid (0.204 g, 0.75 mmol, 75% yield). R_f = 0.54 (PE/EtOAc = 5/1). NMR spectroscopy: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C,δ): (ppm) 9.19 (s, 2 H), 8.19 (d, J = 7.7 Hz, 1 H), 7.71 (s, 1 H), 7.35−7.29 (m, 1 H), 7.25−7.21 (m, 2 H), 2.37 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C,δ): 168.8, 161.4, 155.1, 141.9, 136.1, 129.4, 126.6, 126.0, 123.5, 122.7, 21.2. Mass spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{12}H_{11}N_4O_4^+$ ([M + H] $^+$), 275.0775; found, 275.0771.

3-Methyl-2-((5-nitropyrimidin-2-yl)amino) Phenylacetate (2b). According to the representative reaction procedure (I): Light brown solid (0.207 g, 0.72 mmol, 72% yield); R_f = 0.52 (PE/EtOAc = 5/1(v/v)). NMR spectroscopy: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C,δ): 9.16 (s, 2 H), 7.76 (d, J = 8.7 Hz, 1 H), 7.41 (s, 1 H), 7.05−6.98 (m, 2 H), 2.32 (s, 3 H), 2.31 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C,δ): 169.8, 162.2, 155.4, 148.7, 135.9, 133.2, 132.9, 131.1, 125.4, 123.9, 120.0, 21.3, 18.3. Mass spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{13}H_{13}N_4O_4^+$ ([M + H] $^+$), 289.0931; found, 289.0930.

2-Methyl-6-((5-nitropyrimidin-2-yl)amino) Phenylacetate (2c). According to the representative reaction procedure (I): Light yellow solid (0.195 g, 0.68 mmol, 68% yield); R_f = 0.53 (PE/EtOAc = 5/1(v/v)). NMR spectroscopy: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C,δ): 9.19 (s, 1H), 7.95 (s, 1H), 7.63 (s, 1H), 7.11−7.04 (m, 2H), 2.40 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C,δ): 169.1, 161.5, 155.2, 140.0, 136.7, 136.1, 129.0, 126.8, 124.2, 122.3, 21.4, 21.1. Mass spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{13}H_{13}N_4O_4^+$ ([M + H] $^+$), 289.0931; found, 289.0927.

3-Methoxy-2-((5-nitropyrimidin-2-yl)amino) Phenylacetate (2d). According to the representative reaction procedure (I): Brown solid (0.191 g, 0.63 mmol, 63% yield); R_f = 0.47 (PE/EtOAc = 5/1(v/v)). NMR spectroscopy: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, δ): 9.20 (s, 2 H), 8.46 (d, J = 8.7 Hz, 1 H), 8.27 (s, 1 H), 6.77 (dd, J = 2.4 Hz, 8.7 Hz, 1 H), 6.73 (d, J = 2.4 Hz, 1 H), 3.92 (s, 3 H), 2.32 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C,δ): 169.7, 160.9, 155.0, 149.3, 133.3, 126.7, 124.8, 120.4, 113.6, 104.9, 56.2, 21.2. Mass spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{13}H_{13}N_4O_5^+$ ([M + H]$^+$), 305.0880; found, 305.0883.

5-Fluoro-2-((5-nitropyrimidin-2-yl)amino) Phenylacetate (2e). According to the representative reaction procedure (I): Light yellow solid (0.213 g, 0.73 mmol, 73% yield); R_f = 0.59 (PE/EtOAc = 5/1(v/v)). NMR spectroscopy: ^{1}H NMR (300 MHz, $CDCl_3$,25 °C, δ): 9.17 (s, 2 H), 8.11- 8.05 (m, 1 H), 7.54 (s, 1 H), 7.08−6.99 (m, 2 H), 2.35 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C,δ): 168.3, 161.6, 158.2, 155.2, 143.1 (t, J = 11.3 Hz), 136.3, 125.7 (t, J = 3.8 Hz), 125.2 (t, J = 9.0 Hz), 113.5 (t, J = 21.6 Hz), 110.7 (t, J = 25.5 Hz), 21.1. Mass spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{12}H_{10}FN_4O_4^+$ ([M + H]+), 293.0681; found, 293.0677. ^{19}F NMR (75 MHz, $CDCl_3$, 25 °C,δ): −114.1.

5-Chloro-2-((5-nitropyrimidin-2-yl)amino) Phenylacetate (2f). According to the representative reaction procedure (I): Light yellow solid (0.204 g, 0.66 mmol, 66% yield). R_f= 0.56 (PE/EtOAc = 5/1(v/v)). NMR spectroscopy: ^{1}H NMR (300 MHz, $CDCl_3$,25 °C, δ): 9.20 (s, 2 H), 8.21 (d, J = 8.7 Hz, 1 H), 7.64 (s, 1 H), 7.31−7.26 (m, 1 H), 2.38 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C,δ): 168.3, 161.2, 155.2, 141.9, 130.4, 128.2, 126.8, 123.9, 123.1, 21.1. Mass spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{12}H_{10}ClN_4O_4^+$ ([M + H]$^+$), 309.0385; found, 309.0385.

5-Bromo-2-((5-nitropyrimidin-2-yl)amino) Phenylacetate (2g). According to the representative reaction procedure (I): Light yellow solid (0.250 g, 0.71 mmol, 71% yield). R_f= 0.53 (PE/EtOAc = 5/1(v/v)). NMR spectroscopy: ^{1}H NMR (300 MHz, $CDCl_3$,25 °C, δ): 9.20 (s, 2 H), 8.18 (d, J = 8.7 Hz, 1 H), 7.64 (s, 1 H), 7.46−7.38 (m, 2 H), 2.38 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C,δ): 168.3, 161.1, 155.2, 141.9, 136.4, 129.7, 128.8, 125.9, 124.1, 117.6, 21.1. Mass spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{12}H_{10}BrN_4O_4^+$ ([M + H]$^+$), 352.9880; found, 352.9875.

2-Amino-5-iodophenol (2h′). According to the representative reaction procedure (I), crude compound **2h** was obtained as a brown solid (0.240 g) which was dissolved in THF (2.50 mL, 0.20 M). Hydrazine monohydrate (0.05 g, 1.0 mmol, 2.0 equiv) was added dropwise, and the reaction was stirred for 30 min at 25 °C. The reaction mixture was monitored via TLC until the disappearance of starting material (R_f = 0.55 (PE/EtOAc = 5/1 (v/v)). The reaction was quenched by water and extracted with ethyl acetate (10 mL δ 3). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE/EtOAc = 2:1 as an eluent) to give **2h′** as light yellow solid (0.129 g, 0.55 mmol, 55% yield); R_f = 0.25 (PE/EtOAc = 2/1(v/v)). NMR spectroscopy: ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C, δ): 9.40 (brs, 1 H), 6.89 (d, J = 1.7 Hz, 1H). 6.82 (dd, J = 8.1, 1.7 Hz, 1H), 6.40 (d, J = 8.1 Hz, 1H), 4.69 (brs, 2H). ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C, δ): 145.4, 136.9, 127.9, 122.1, 116.2, 75.8. Mass spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_6H_7INO^+$ ([M + H]$^+$), 235.9567; found, 235.9561.

3-Fluoro-2-((5-nitropyrimidin-2-yl)amino) Phenylacetate (2i). According to the representative reaction procedure (I): Brown solid (0.198 g, 0.68 mmol, 68% yield); R_f = 0.42 (PE/EtOAc = 3/1(v/v)). NMR spectroscopy: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, δ): 9.31 (s, 2 H), 7.48−7.39(m,1H), 7.32−7.26 (m, 1 H), 7.25−7.18 (m, 2 H), 2.63 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C,δ): 172.0, 162.7, 159.9, 156.5, 154.3, 138.3, 130.6 (t, J = 8.3 Hz), 130.3, 125.1 (t, J = 3.8 Hz), 116.9 (t, J = 19.5 Hz), 26.6. Mass spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{12}H_{10}FN_4O_4^+$([M + H] $^+$), 293.0681; found, 293.0680. ^{19}F NMR (75 MHz, $CDCl_3$, 25 °C,δ): −121.88.

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3-Bromo-2-((5-nitropyrimidin-2-yl)amino) Phenylacetate (2j). According to the representative reaction procedure (I): Light yellow solid (0.229 g, 0.65 mmol, 65% yield); R_f = 0.51, (PE/EtOAc = 5/1(v/v)). NMR spectroscopy: ^{1}H NMR (300 MHz, $CDCl_3$,25 °C, δ): 9.31 (s, 2 H), 7.73 (d, J = 7.8 Hz, 1 H), 7.46 (t, J = 7.5 Hz, 1 H), 7.38−7.26 (m, 2 H), 2.62 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, δ): 171.9, 162.3, 154.2, 139.5, 138.1, 133.8, 130.6, 130.3, 128.9, 123.7, 26.9. Mass spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{12}H_{10}BrN_4O_4^+$ ([M + H]$^+$), 352.9880; found, 352.9876.

2,4-difluoro-6-((5-nitropyrimidin-2-yl)amino) Phenylacetate (2k). According to the representative reaction procedure (I): Light yellow solid (0.189 g, 0.61 mmol, 61% yield); R_f = 0.54 (PE/EtOAc = 5/1(v/v)). NMR spectroscopy: ^{1}H NMR (300 MHz, $CDCl_3$,25 °C, δ): 9.25 (s, 2 H), 8.16 (dt, J = 2.4 Hz, 10.7 Hz, 1 H), 7.82 (s, 1 H), 6.77−6.69 (m, 1 H), 2.44 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, δ): 167.5, 160.7, 158.4 (t, J = 6.0 Hz), 156.0 (t, J = 15.0 Hz), 155.0, 136.8, 132.3 (tt, J = 4.5 Hz, 14.3 Hz), 125.1 (t, J = 21 Hz), 104.1 (tt, J = 3.8 Hz, 29.3 Hz), 100.3 (tt, J = 2.3 Hz, 27.8 Hz), 20.4. Mass spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{12}H_9F_2N_4O_4^+$ ([M + H]$^+$), 311.0586; found, 311.0574. ^{19}F NMR (75 MHz, $CDCl_3$, 25 °C,δ): −110.9, −122.8.

Methyl 3-acetoxy-4-((5-nitropyrimidin-2-yl)amino)-benzoate (2l). According to the representative reaction procedure (I): Light yellow solid (0.193 g, 0.58 mmol, 58% yield); R_f = 0.53 (PE/EtOAc = 2/1(v/v)). NMR spectroscopy: ^{1}H NMR (300 MHz, $CDCl_3$,25 °C, δ): 9.19 (s, 1H), 7.95 (s, 1H), 7.63 (s, 1H), 7.11−7.04 (m, 2H), 2.40 (s, 3H) 2.34 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, δ): 168.8, 165.2, 161.2, 155.1, 142.2, 136.1, 134.8, 126.6, 126.0, 124.4, 124.3, 52.3, 21.2. Mass spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{14}H_{13}N_4O_6^+$ ([M + H]$^+$), 333.0830; found, 333.0836.

2-((5-Nitropyrimidin-2-yl) amino)-5-(trifluoromethoxy) Phenylacetate (2m). According to the representative reaction procedure (I): Light yellow solid (0.191 g, 0.56 mmol, 56% yield); R_f = 0.35 (PE/EtOAc = 5/1(v/v)). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, δ): 9.25 (s, 2 H), 8.57 (d, J = 8.6 Hz, 1 H), 7.85 (s, 1 H), 7.56 (d, J = 8.7 Hz, 1 H), 7.52 (s, 1 H), 2.43 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C,δ): 168.3, 160.9, 155.1, 140.3, 136.7, 132.8, 127.0, 126.5, 123.6 (J = 15.1 Hz), 122.0, 120.0 (J = 15.6 Hz), 21.2. ^{19}F NMR (75 MHz, $CDCl_3$, 25 °C,δ): −62.2. HRMS (ESI-TOF) (m/z): calcd for $C_{13}H_{10}F_3N_4O_4^+$ ([M + H]$^+$), 343.0649, found, 343.0643.

1-(5-Nitropyrimidin-2-yl)-1, 2, 3, 4-tetrahydroquinolin-8-yl Acetate (2p). According to the representative reaction procedure (I): Reddish brown solid (0.216 g, 0.69 mmol, 69% yield); R_f = 0.52 (PE/EtOAc = 5/1(v/v)). ^{1}H NMR (300 MHz, $(CD_3)_2SO$, 25 °C, δ): 9.15 (s, 2 H), 7.29−7.23 (t, J = 15.4 Hz, 1 H), 7.17 (d, J = 6.0 Hz, 1H), 7.09 (dd, J = 1.4 Hz, J = 7.9 Hz, 1 H), 2.75 (s, 2 H), 1.99 (s, 2 H), 1.86 (s, 3 H), 1.24 (m, 2 H) ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, δ): 168.3, 161.3, 154.6, 144.8, 136.3, 135.2, 131.1, 126.9, 125.8, 121.0, 45.6, 26.3, 24.1, 21.1. HRMS (ESI-TOF) (m/z): calcd for $C_{15}H_{15}N_4O_4^+$ ([M + H]$^+$), 315.1088, found, 315.1080.

2-(Methyl (5-nitropyrimidin-2-yl)amino) Phenylacetate (2q). According to the representative reaction procedure (I): Yellow brown solid (0.210 g, 0.73 mmol, 73% yield); R_f = 0.47 (PE/EtOAc = 5/1(v/v)). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, δ): 9.19 (d, J = 3.1 Hz, 1 H), 9.00 (d, J = 3.18 Hz, 1 H), 7.45−7.34 (m, 3 H), 7.26−7.23 (m, 1 H), 3.53 (s, 3 H), 2.09 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C,δ): 168.7, 162.4, 154.9, 146.5, 136.0, 134.9, 129.2, 128.3, 127.3, 123.9, 39.0, 20.8. HRMS (ESI-TOF) (m/z): calcd for $C_{13}H_{13}N_4O_4^+$([M + H]$^+$), 289.0931, found, 289.0933

1-Benzyl-6-((5-nitropyrimidin-2-yl)amino)-1*H*-indol-5-yl Acetate (2r). According to the representative reaction procedure (I): Reddish brown solid (0.233 g, 0.58 mmol, 58% yield); R_f = 0.24 (PE/EtOAc = 2/1(v/v)). ^{1}H NMR (400 MHz, DMSO, 25 °C,δ): 10.84 (s, 1 H), 9.18 (s, 2 H), 8.01 (s, 1 H), 7.57 (s, 1 H), 7.41 (d, J = 8.5 Hz, 1 H), 7.35−7.31 (m, 3 H), 7.28−7.26 (m, 3 H), 5.34 (s, 2 H), 2.33 (s, 3 H). ^{13}C NMR (101 MHz, DMSO, 25 °C,δ): 168.5, 161.0, 155.1, 137.8, 134.7, 133.3, 132.9, 128.8, 128.6, 127.5, 120.3, 118.4, 117.5, 117.2, 114.5, 102.8, 49.2, 20.7. HRMS (ESI-TOF) (m/z): calcd for $C_{21}H_{18}N_5O_4^+$ ([M + H]$^+$), 404.1353, found, 404.1363.

1-Benzyl-5-((5-nitropyrimidin-2-yl)amino)-1*H*-indol-6-yl Acetate (2s). According to the representative reaction procedure (I): Reddish brown solid (0.205 g, 0.51 mmol, 51% yield); R_f = 0.24 (PE/EtOAc = 2/1(v/v)). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, δ): 9.15 (s, 2 H), 7.90 (s, 1H), 7.83 (s, 1 H), 7.55 (d, J = 8.4 Hz, 1H), 7.36 (s, 1 H), 7.32−7.30 (m, 3 H), 7.17 (d, J = 7.1 Hz, 1H), 7.12 (d, J = 8.6 Hz, 1 H), 5.28 (s, 2 H), 2.36 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, δ): 168.6, 161.3, 155.2, 137.0, 135.4, 133.4, 132.5, 130.0, 129.0, 128.0, 127.1, 118.5, 118.2, 114.6, 102.8, 50.5, 21.1. HRMS (ESI-TOF) (m/z): calcd for $C_{21}H_{18}N_5O_4^+$ ([M + H]$^+$), 404.1353, found, 404.1358.

5-((5-Nitropyrimidin-2-yl)amino) Benzo [*b*] thiophen-4-yl Acetate (2t). According to the representative reaction procedure (I): Light yellow solid (0.204 g, 0.62 mmol, 62% yield); R_f = 0.47 (PE/EtOAc = 2/1(v/v)). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C,δ): 9.18 (s, 2 H), 7.93 (d, J = 8.7 Hz, 1 H), 7.82 (d, J = 8.6 Hz, 1 H), 7.80 (s, 1 H), 7.52 (d, J = 5.5 Hz, 1 H), 7.23 (d, J = 5.5 Hz, 1 H), 2.45 (s, 3 H). ^{13}C NMR (101 MHz, $CDCl_3$, 25 °C,δ): 168.6, 162.0, 155.4, 139.1, 138.0, 133.8, 128.8, 125.6, 121.9, 120.8, 120.0, 21.0. HRMS (ESI-TOF) (m/z): calcd for $C_{14}H_{11}N_4O_4S^+$ ([M + H]$^+$), 331.0496, found, 331.0494.

Procedure for Synthesis of 2-Amino-5-chlorophenol (2f′). Under N_2 atmosphere, an oven-dried 25 mL flask was charged with the 5-chloro-2-((5-nitropyrimidin-2-yl)amino) phenylacetate (0.154 g, 0.5 mmol, 1.0 equiv) in THF (2.50 mL, 0.20 M). Hydrazine monohydrate (0.05 g, 1.0 mmol, 2.0 equiv) was added dropwise, and the reaction was stirred for 30 min at 25 °C. The reaction mixture was monitored via TLC until the disappearance of starting material (R_f = 0.20 (PE/EtOAc = 5/1 (v/v)). The reaction was quenched by water and extracted with ethyl acetate (10 mL ⊆ 3). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE/EtOAc = 5:1 to 2:1 as an eluent) to give **2f′** as dark brown solid (0.082 g, 0.44 mmol, 88% yield); R_f = 0.28 (PE/EtOAc = 5/1(v/v)). NMR spectroscopy: ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, δ): 6.78−6.72 (m, 2 H), 6.70−6.63 (m, 1 H). ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, δ): 145.3, 134.0, 122.1, 119.4, 115.7, 115.0. Compound **2f′** is known.[76]

2-Amino-5-bromophenol (2g′). The same procedure as obtaining **2f′**: Dark brown solid (0.0855 g, 0.45 mmol, 91% yield); R_f= 0.31 (PE/EtOAc = 5/1(v/v)). NMR spectroscopy: ^{1}H NMR (300 MHz, $(CD_3)_2SO$, 25 °C, δ): 9.49 (brs, 1H), 6.77 (d, J = 2.2 Hz, 1H), 6.68 (dd, J = 8.3, 2.2 Hz, 1H), 6.53 (d, J = 8.3 Hz, 1H), 4.7 (brs, 2H). ^{13}C NMR (75 MHz, $(CD_3)_2SO$, 25 °C,δ): 145.2, 136.4 121.9, 116.7, 115.4, 106.2. Compound **2g′** is known.[77]

Gram-Scale Synthesis of Compound 2g. Under N_2 atmosphere, an oven-dried 250 mL flask was charged with 4-bromoaniline (1.03 g, 6.0 mmol, 1.0 equiv) and 2-chloro-5-nitropyrimidine (0.96 g, 6.0 mmol, 1.0 equiv) in CH_3CN (9.0 mL, 1.50 M). The reaction mixture was stirred for 4 h at room temperature, which was monitored via TLC until the disappearance of 2-chloro-5-nitropyrimidine (R_f = 0.79, (PE/EtOAc = 5/1 (v/v)). AcOH (12.0 mL) and Ac_2O (12.0 mL) were directly added to the reaction mixture, followed by $Pd(OAc)_2$ (67.2 mg, 0.3 mmol, 0.05 equiv) and $PhI(OAc)_2$ (2.19 g, 6.6 mmol, 1.10 equiv). After stirring for 10 h at 100 °C, the reaction mixture was concentrated under vacuo, purified by column chromatography (eluent, PE/EtOAc = 25/1 to 5/1(v/v)) to give the desired product as light yellow solid (1.12 g, 3.66 mmol, 61% yield). R_f = 0.52 (PE/EtOAc = 5/1(v/v)).

One-Pot Procedure for Synthesis of Compound 2g′. Under N_2 atmosphere, an oven-dried 25 mL flask was charged with 4-bromoaniline (0.172 g, 1.00 mmol, 1.00 equiv) and 2-chloro-5-nitropyrimidine (0.159 g, 1.0 mmol, 1.00 equiv) in CH_3CN (1.50 mL, 1.50 M). The reaction mixture was stirred for 4 h at room temperature, which was monitored via TLC until the disappearance of 2-chloro-5-nitropyrimidine (R_f = 0.79, (PE/EtOAc = 5/1 (v/v)). AcOH (2.0 mL) and Ac_2O (2.0 mL) were directly added to the reaction mixture, followed by $Pd(OAc)_2$ (5.60 mg, 0.05 mmol, 0.05 equiv) and $PhI(OAc)_2$ (0.365 g, 1.10 mmol, 1.10 equiv). After it was stirred for 6 h at 100 °C, the reaction mixture was concentrated under vacuo, which was redissolved in THF (2.50 mL, 0.20 M). Hydrazine monohydrate (101 mg, 2 mmol) was added dropwise. After stirring at 25 °C for 30 min. The reaction was concentrated under vacuo, diluted with water (10 mL), extracted with ethyl acetate (10 mL ⊆ 3). The

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combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated. The residue was purified by column chromatography on silica gel (PE/EtOAc = 5/1 to 2/1 as an eluent) to give **2g′** as a dark brown solid (0.097 g, 52 mmol, 52% yield).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.9b00113.

NMR spectra and chemical structures of new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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