INTRODUCTION

Hydroxymethylated arene is attractive owing to its wide existence in bioactive natural products, pharmaceuticals, fragrances, and polymers.\(^1\) Moreover, they are vital synthetic intermediates in organic chemistry. Traditionally, there are two methods for the preparation of hydroxymethylated arenes. One is the direct reduction of aldehydes, carboxylic acids or esters. Another method is the addition of highly reactive organometallic reagents to formaldehyde.\(^2\) However, this approach requires prefunctionalization of substrates and the manipulation of air- and moisture-sensitive reagents, thus inevitably producing stoichiometric unwanted salt wastes.

Transition-metal-catalyzed C−H functionalization has emerged as a powerful strategy to access functionalized arenes. Recently, Rh(III)- or Mn(I)-catalyzed aryl C−H addition to aldehydes were developed to access desired alcohols (Scheme 1a and 1b).\(^3\) Despite a major breakthrough, however, these methods are largely limited to aryl or alkyl aldehydes and no hydroxymethylated arenes could be accessible. Until very recently, Ding and our group reported a Ru(II)-catalyzed addition of aryl C−H bonds to challenging formaldehyde by using pyridine, pyrimidine, oxazole, pyrazole, acylamido, or...
ketoxime as the directing groups, thus affording an efficient protocol to access hydroxymethylarenes (Scheme 1c). 4

![Scheme 1](image)

Scheme 1. Transition-metal-catalyzed addition of C(sp²)-H bonds to aldehydes

The azaindole ring system, particularly the 7-azaindole, is one of the most valuable heterocyclic moieties due to its ubiquity in numerous biologically active natural products, 5 two market drugs, 6 a variety of bioactive compounds, 7 luminescent molecules 8 and ligands. 9 Despite the unique structure of 7-azaindoles, however, only limited methods have been developed for functionalization of 7-azaindoles, 10 and studies on direct C–H functionalization by utilizing 7-azaindole as the directing group is still rare. 11 In this context, with our continuing interest in the sustainable organic synthesis, 12 we herein reported the Ru(II)-catalyzed regioselective C-H hydroxymethylation of N-aryl-7-azaindoles with paraformaldehyde through using 7-azaindole as the directing group (Scheme 1d).

RESULTS AND DISCUSSION

Our initial experiments were performed with N-phenyl-7-azaindole (1a) and paraformaldehyde (2a) in the presence of [RhCp*Cl₂]₂ (5 mol%) and AgSbF₆ (20 mol%) in DCE (1 mL) at 60 °C for 32 hours (Table 1, entry 1). Unfortunately, no desired product (3a) was observed. Subsequently, other catalytic systems were tested (entries 2-5) and we were pleased to find that the desired addition product (3a) was obtained in 42% yield when using [Ru(p-cymene)Cl₂]₂ as the catalyst (entry 5). Next, various additives were screened (entries 6-10) and the combination of AgSbF₆ and NaH₂PO₄ was found to be more effective (entry 10), providing the desired product 3a in 56% yield, also with a formate ester 3aa as a byproduct in 20% yield. A screening of the solvents proved DCE to be the optimal choice (entries 10-14). Finally, a one-pot procedure was developed to provide 3a in 83% yield through a subsequent one-pot treatment of the
resulting products in MeOH and K$_2$CO$_3$ at 60 °C (entry 15). The role of K$_2$CO$_3$ was to convert the 3aa into 3a. Other silver salts such as AgBF$_4$ and AgPF$_6$, were also tested, resulting in decreased yields (entries 16 and 17).

Table 1. Optimization of reaction conditions$^a$

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>additive</th>
<th>solvent</th>
<th>yield 3a (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[RhCp*Cl$_2$]$_2$</td>
<td>AgSbF$_6$</td>
<td>DCE</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>[IrCp*Cl$_2$]$_2$</td>
<td>AgSbF$_6$</td>
<td>DCE</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Cp*Co(CO)$_2$I$_2$</td>
<td>AgSbF$_6$</td>
<td>DCE</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Cp*Rh(MeCN)$_3$(SbF$_6$)$_2$</td>
<td>-</td>
<td>DCE</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>[Ru(p-cymene)Cl$_2$]$_2$</td>
<td>AgSbF$_6$</td>
<td>DCE</td>
<td>42</td>
</tr>
<tr>
<td>6</td>
<td>[Ru(p-cymene)Cl$_2$]$_2$</td>
<td>Cu(OTf)$_2$</td>
<td>DCE</td>
<td>&lt; 5</td>
</tr>
<tr>
<td>7</td>
<td>[Ru(p-cymene)Cl$_2$]$_2$</td>
<td>Zn(OTf)$_2$</td>
<td>DCE</td>
<td>35</td>
</tr>
<tr>
<td>8</td>
<td>[Ru(p-cymene)Cl$_2$]$_2$</td>
<td>AgOTf</td>
<td>DCE</td>
<td>31</td>
</tr>
<tr>
<td>9</td>
<td>[Ru(p-cymene)Cl$_2$]$_2$</td>
<td>AgSbF$_6$/PivOH</td>
<td>DCE</td>
<td>24</td>
</tr>
<tr>
<td>10</td>
<td>[Ru(p-cymene)Cl$_2$]$_2$</td>
<td>AgSbF$_6$/NaH$_2$PO$_4$</td>
<td>DCE</td>
<td>56</td>
</tr>
<tr>
<td>11</td>
<td>[Ru(p-cymene)Cl$_2$]$_2$</td>
<td>AgSbF$_6$/NaH$_2$PO$_4$</td>
<td>THF</td>
<td>5</td>
</tr>
<tr>
<td>12</td>
<td>[Ru(p-cymene)Cl$_2$]$_2$</td>
<td>AgSbF$_6$/NaH$_2$PO$_4$</td>
<td>DMF</td>
<td>0</td>
</tr>
<tr>
<td>13</td>
<td>[Ru(p-cymene)Cl$_2$]$_2$</td>
<td>AgSbF$_6$/NaH$_2$PO$_4$</td>
<td>1,4-dioxane</td>
<td>16</td>
</tr>
<tr>
<td>14</td>
<td>[Ru(p-cymene)Cl$_2$]$_2$</td>
<td>AgSbF$_6$/NaH$_2$PO$_4$</td>
<td>toluene</td>
<td>10</td>
</tr>
<tr>
<td>15$^c$</td>
<td>[Ru(p-cymene)Cl$_2$]$_2$</td>
<td>AgSbF$_6$/NaH$_2$PO$_4$</td>
<td>DCE</td>
<td>83</td>
</tr>
<tr>
<td>16$^c$</td>
<td>[Ru(p-cymene)Cl$_2$]$_2$</td>
<td>AgBF$_4$/NaH$_2$PO$_4$</td>
<td>DCE</td>
<td>52</td>
</tr>
<tr>
<td>17$^a$</td>
<td>[Ru(p-cymene)Cl$_2$]$_2$</td>
<td>AgPF$_6$/NaH$_2$PO$_4$</td>
<td>DCE</td>
<td>68</td>
</tr>
</tbody>
</table>

$^a$Conditions: 1a (0.1 mmol), 2a (0.3 mmol), catalysts (5 mol%), and additive (20 mol%) in the solvent (1 mL) at 60 °C for 32 h in a sealed tube. $^b$Isolated yield. $^c$1a (0.1 mmol), 2a (0.3 mmol), [Ru(p-cymene)Cl$_2$]$_2$ (5 mol%), silver salts (20 mol%) and NaH$_2$PO$_4$ (20 mol%) in the DCE (1 mL) at 60 °C for 32 h in a sealed tube. Then MeOH and K$_2$CO$_3$ (1 equiv) was added and the mixture was stirred at 60 °C for 2 h.

With the establishment of the optimal reaction conditions, the scope of substrates was next investigated (Scheme 2). The C-H hydroxymethylation proceeded efficiently over a broad range of substrates irrespective of their electronic nature. A variety of substrates containing electronic-donating group (3b, 3d and 3h) and electron-withdrawing group (3c, 3e-g) at the meta- (3h), or para- (3b-g) position of the phenyl ring were proved to be productive substrates for this coupling reaction, affording the corresponding products in moderate to good yields. Synthetically important functional groups, such as
halogen (3e-f, 3i, 3k and 3n), methoxy (3d and 3m), ester (3c), and ketone groups (3g and 3j) were well tolerated, enabling further functionalization. Moreover, for substrate bearing meta-Me group (3h), the C-H hydroxymethylation exhibited excellent regioselectivity in favor of the sterically more accessible C-H bond. Several aryl and aliphatic aldehydes were also examined by using the current catalytic system. No any desired product was observed when utilizing benzaldehyde (3o) and propionaldehyde (3p). To our delight, ethyl glyoxalate delivered the desired product 3q in 68% yield.

Scheme 2. Substrate Scope. Reactions were carried out by treating 1 (0.1 mmol), 2a (0.3 mmol), [Ru(p-cymene)Cl]2 (5 mol%), AgSbF6 (20 mol%) and NaH2PO4 (20 mol%) in the DCE (1 mL) at 60 °C for 32 h in a sealed tube. Then MeOH and K2CO3 (1 equiv) was added and the mixture was stirred at 60 °C for 2 h.
To highlight the synthetic utility of this direct C-H hydroxymethylation reaction developed herein, treatment of 3a with DMP in DCM at room temperature for 4 hours afforded the aldehyde 4a (Scheme 3). In addition, treatment of 3a with DMP in DCM and H2O at room temperature overnight, followed by treatment with MeOH and H2SO4, delivered the corresponding ester 4b in one-pot fashion.

Scheme 3. Synthetic application of 3a

A series of preliminary experiments were performed to probe the mechanism. First, treatment of 1a with [Ru(p-cymene)Cl2]2, AgSbF6 and NaH2PO4 in DCM/D2O (10:1) in the absence or presence of paraformaldehyde led to a deuterium incorporation (eq 1 and 2), indicating the cleavage of the ortho C-H bond was reversible. Furthermore, the competitive reaction by using equimolar amount of 1b, 1e and 2a under the standard conditions was also carried out, providing 3b and 3e in a 3.7:1 ratio, suggesting that the electron-rich substrate was kinetically favored (eq 3). This result could be attributed to an electrophilic C-H ruthenation.

In accordance with the above observations, we proposed a possible mechanism (Scheme 4). First, the cationic Ru(II) species facilitated a reversible cycloruthenation of 1a to form a six-membered complex A with the release of one equivalent of proton (H+). A nucleophilic addition to formaldehyde occurs to form the eight-membered Ru-O species B that is subsequently protonated to deliver the desired product 3a and regenerate the cationic ruthenium species.
CONCLUSION

In conclusion, we have developed an efficient Ru(II)-catalyzed C-H hydroxymethylation of 7-azaindoles under mild reaction condition. The reaction is compatible with air, shows high functional group tolerance and regioselectivity, and is an environmentally benign method without any undesired byproduct.

EXPERIMENTAL

General. Mass spectra and high-resolution mass spectra were measured on a Finnigan MAT-95 mass spectrometer. $^1$H and $^{13}$C NMR spectra were determined on Bruker AM-300, Bruker AM-400, Bruker AM-500 instruments using tetramethylsilane as internal reference. Data are presented as follows: chemical shift, multiplicity (s = singlet, br s = broad singlet, d = doublet, br d = broad doublet, t = triplet, m = multiplet), $J$ = coupling constant in hertz (Hz). Silica gel 60H (200 – 300 mesh) manufactured by Qingdao Haiyang Chemical Group Co. (China) was used for general chromatography.

Materials. All reagents were purchased from commercial sources and used without further purification, unless otherwise indicated. The paraformaldehyde (96% purity, powder) was purchased from Energy Chemical. The substrate $N$-aryl-7-azaindoles 1 were prepared according the references.$^{11a,15}$

General Synthetic Procedure for synthesizing compounds 3. A mixture of 1 (0.1 mmol), 2a (0.3 mmol), [RuCl$_2$(p-cymene)]$_2$ (5 mol%), AgSbF$_6$ (20 mol%), and NaH$_2$PO$_4$ (20 mol%) was dissolved in DCE (1 mL) in sealed tube and the mixture was stirred at 60 °C for 32 h. Then MeOH (1 mL) and K$_2$CO$_3$
(1 equiv) were added and the mixture was continued to stir at 60 °C for 2 h. Then the solvent was evaporated to give the residue which was purified by silica gel chromatography to give compound 3.

(2-(1H-Pyrrolo[2,3-b]pyridin-1-yl)phenyl)methanol (3a). Yield: 83%, 1H NMR (400 MHz, CDCl3) δ 8.25 (dd, J = 4.8, 1.5 Hz, 1H), 8.03 (dd, J = 7.9, 1.6 Hz, 1H), 7.70 (dd, J = 7.4, 1.8 Hz, 1H), 7.49 (td, J = 7.4, 1.5 Hz, 1H), 7.44 (td, J = 7.6, 1.8 Hz, 1H), 7.36 (d, J = 3.6 Hz, 1H), 7.22 (dd, J = 7.6, 1.4 Hz, 1H), 7.16 (dd, J = 7.8, 4.8 Hz, 1H), 6.68 (d, J = 3.6 Hz, 1H), 4.39 (s, 2H); 13C NMR (125 MHz, CDCl3) δ 148.8, 143.5, 138.4, 136.8, 132.0, 130.4, 130.3, 129.4, 129.1, 128.1, 121.7, 117.1, 102.2, 61.7; HRMS (ESI) Calcd for C14H13N2O [M+H]+ 225.1022, found 225.1022.

(2-(1H-Pyrrolo[2,3-b]pyridin-1-yl)benzyl formate (3aa). Yield: 20%, 1H NMR (400 MHz, CDCl3) δ 8.32 (dd, J = 4.7, 1.4 Hz, 1H), 8.00 (dd, J = 7.8, 1.5 Hz, 1H), 7.98 (s, 1H), 7.65 – 7.61 (m, 1H), 7.53 – 7.48 (m, 2H), 7.42 – 7.37 (m, 1H), 7.35 (d, J = 3.6 Hz, 1H), 7.14 (dd, J = 7.8, 4.7 Hz, 1H), 6.66 (d, J = 3.6 Hz, 1H), 5.05 (s, 2H).

(5-Methyl-2-(1H-pyrrolo[2,3-b]pyridin-1-yl)phenyl)methanol (3b). Yield: 66%, 1H NMR (400 MHz, CDCl3) δ 8.24 (d, J = 4.7 Hz, 1H), 8.02 (d, J = 7.8 Hz, 1H), 7.50 (s, 1H), 7.33 (d, J = 3.5 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 7.15 (dd, J = 7.8, 4.8 Hz, 1H), 7.10 (d, J = 8.0 Hz, 1H), 6.66 (d, J = 3.5 Hz, 1H), 5.23 (s, 1H), 4.34 (s, 2H), 2.45 (s, 3H). 13C NMR (125 MHz, CDCl3) δ 148.3, 143.0, 138.6, 137.5, 133.7, 132.0, 130.0, 129.7, 129.6, 127.4, 121.1, 116.5, 101.5, 61.2, 20.9; HRMS (ESI) Calcd for C15H15N2O3 [M+H]+ 239.1179, found 239.1181.

Methyl 3-(hydroxymethyl)-4-(1H-pyrrolo[2,3-b]pyridin-1-yl)benzoate (3c). Yield 74%, 1H NMR (400 MHz, CDCl3) δ 8.38 (d, J = 1.7 Hz, 1H), 8.25 (d, J = 4.7 Hz, 1H), 8.09 (dd, J = 8.2, 2.0 Hz, 1H), 8.03 (d, J = 7.9 Hz, 1H), 7.36 (d, J = 3.6 Hz, 1H), 7.29 (d, J = 8.2 Hz, 1H), 7.18 (dd, J = 7.8, 4.8 Hz, 1H), 6.71 (d, J = 3.6 Hz, 1H), 5.35 (t, J = 5.9 Hz, 1H), 4.44 (d, J = 4.9 Hz, 2H), 3.96 (s, 3H). 13C NMR (126 MHz, CDCl3) δ 166.6, 148.5, 143.6, 140.6, 138.4, 133.5, 133.5, 130.5, 130.4, 128.0, 121.8, 117.5, 103.1, 61.4, 52.7; HRMS (ESI) Calcd for C16H15N2O3 [M+H]+ 283.1077, found 283.1082.

(5-Methoxy-2-(1H-pyrrolo[2,3-b]pyridin-1-yl)phenyl)methanol (3d). Yield 45%, 1H NMR (400 MHz, CDCl3) δ 8.25 (d, J = 4.5 Hz, 1H), 8.02 (d, J = 7.8 Hz, 1H), 7.31 (d, J = 3.5 Hz, 1H), 7.20 (d, J = 2.9 Hz, 1H), δ 7.16 – 7.14 (m, 1H), 7.13 (s, 1H), 6.96 (dd, J = 8.7, 2.9 Hz, 1H), 6.65 (d, J = 3.6 Hz, 1H), 5.10 (s, 1H), 4.33 (s, 2H), 3.89 (s, 3H). 13C NMR (125 MHz, CDCl3) δ 160.0, 148.5, 143.6, 140.6, 138.4, 133.5, 133.5, 130.5, 130.4, 128.0, 121.8, 117.5, 103.1, 61.4, 52.7; HRMS (ESI) Calcd for C15H15N2O2 [M+H]+ 255.1128, found 255.1135.

(5-Fluoro-2-(1H-pyrrolo[2,3-b]pyridin-1-yl)phenyl)methanol (3e). Yield 61%, 1H NMR (400 MHz, CDCl3) δ 8.25 (d, J = 4.7 Hz, 1H), 8.03 (d, J = 7.8 Hz, 1H), 7.40 (dd, J = 8.9, 2.9 Hz, 1H), 7.30 (d, J = 3.6 Hz, 1H), 7.19 (td, J = 8.7, 4.0 Hz, 1H), 7.16 (d, J = 13.6 Hz, 1H), 7.12 (td, J = 8.5, 2.9 Hz, 1H), 6.68 (d, J = 3.6 Hz, 1H), 5.01 (s, 1H), 4.34 (s, 2H); 13C NMR (125 MHz, CDCl3) δ 163.4, 161.4, 148.5, 143.4,
140.6 (J = 7.5 Hz), 132.4, 130.1 (J = 14.5 Hz), 129.5 (J = 8.6 Hz), 121.3, 117.8 (J = 22.2 Hz), 117.0, 116.0 (J = 22.6 Hz), 102.1, 61.2; HRMS (ESI) Calcd for C_{14}H_{12}FN_{2}O [M+H]^+ 243.0928, found 243.0927.

(5-Bromo-2-(1H-pyrrolo[2,3-b]pyridin-1-yl)phenyl)methanol (3f). Yield 37%, \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.25 (d, J = 4.8 Hz, 1H), 8.03 (d, J = 7.9 Hz, 1H), 7.84 (d, J = 2.3 Hz, 1H), 7.55 (dd, J = 8.4, 2.2 Hz, 1H), 7.31 (d, J = 3.6 Hz, 1H), 7.17 (dd, J = 7.9, 4.8 Hz, 1H), 7.09 (d, J = 8.3 Hz, 1H), 6.69 (d, J = 3.5 Hz, 1H), 5.15 (s, 1H), 4.35 (s, 2H); \(^1^3\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 148.1, 143.2, 139.9, 135.3, 134.3, 131.9, 129.9, 129.5, 129.1, 122.2, 121.2, 116.9, 102.2, 60.8; HRMS (ESI) Calcd for C_{14}H_{12}BrN_{2}O [M+H]^+ 303.0128, found 303.0128.

1-(3-(Hydroxymethyl)-4-(1H-pyrrolo[2,3-b]pyridin-1-yl)phenyl)ethan-1-one (3g). Yield 62%, \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.28 (s, 1H), 8.26 (d, J = 4.8 Hz, 1H), \(\delta\) 8.06 – 8.00 (m, 2H), 7.37 (d, J = 3.6 Hz, 1H), 7.32 (d, J = 8.2 Hz, 1H), 7.19 (dd, J = 7.9, 4.8 Hz, 1H), 6.72 (d, J = 3.6 Hz, 1H), 5.39 (s, 1H), 4.47 (s, 2H), 2.67 (s, 3H); \(^1^3\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 197.5, 148.5, 143.6, 140.7, 138.4, 137.2, 132.5, 130.5, 129.9, 128.9, 128.2, 121.8, 117.5, 103.2, 61.5, 27.1; HRMS (ESI) Calcd for C_{16}H_{18}N_{2}O [M+H]^+ 267.1128, found 267.1132.

(4-Methyl-2-(1H-pyrrolo[2,3-b]pyridin-1-yl)phenyl)methanol (3h). Yield 64%, \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.24 (dd, J = 4.8, 1.1 Hz, 1H), 8.02 (dd, J = 7.8, 1.2 Hz, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.35 (d, J = 3.5 Hz, 1H), 7.29 (d, J = 7.7 Hz, 1H), 7.15 (dd, J = 7.8, 4.8 Hz, 1H), 7.03 (s, 1H), 6.67 (d, J = 3.6 Hz, 1H), 5.19 (s, 1H), 4.34 (s, 2H), 2.39 (s, 3H); \(^1^3\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 148.3, 143.0, 139.0, 136.2, 135.0, 131.4, 129.9, 129.7, 129.4, 128.1, 121.1, 116.6, 101.6, 61.0, 20.8; HRMS (ESI) Calcd for C_{15}H_{15}N_{2}O [M+H]^+ 239.1182, found 239.1179.

(2-(3-Iodo-1H-pyrrolo[2,3-b]pyridin-1-yl)phenyl)methanol (3i). Yield 49%, \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.28 (dd, J = 4.8, 3.0 Hz, 1H), 7.86 (dd, J = 7.9, 1.6 Hz, 1H), 7.70 (dd, J = 7.5, 1.7 Hz, 1H), 7.51 (td, J = 7.5, 1.4 Hz, 1H), 7.48 (s, 1H), 7.45 (td, J = 7.6, 1.7 Hz, 1H), 7.26 (dd, J = 4.7, 3.0 Hz, 1H), 7.23 (dd, J = 7.6, 1.1 Hz, 1H), 4.38 (s, 2H); \(^1^3\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 148.2, 144.5, 138.0, 135.7, 134.0, 131.8, 130.6, 129.3, 127.8, 123.9, 117.8, 61.4; HRMS (ESI) Calcd for C_{14}H_{12}I_{2}N_{2}O [M+H]^+ 350.9989, found 350.9984.

1-(1-(2-(Hydroxymethyl)phenyl)-1H-pyrrolo[2,3-b]pyridin-3-yl)ethan-1-one (3j). Yield 72%, \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.77 (d, J = 7.9 Hz, 1H), 8.33 (d, J = 4.7 Hz, 1H), 7.99 (s, 1H), 7.72 (d, J = 7.5 Hz, 1H), 7.56 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 7.6 Hz, 1H), 7.33 (dd, J = 7.9, 4.8 Hz, 1H), 7.29 (d, J = 7.7 Hz, 1H), 4.51 (t, J = 6.5 Hz, 1H), 4.37 (d, J = 6.1 Hz, 2H), 2.58 (s, 3H); \(^1^3\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 193.4, 149.2, 145.2, 138.4, 136.2, 135.6, 132.5, 132.0, 130.1, 129.6, 128.0, 119.7, 119.3, 117.4, 61.5, 27.6; HRMS (ESI) Calcd for C_{12}H_{13}N_{2}O [M+H]^+ 267.1128, found 267.1130.

(2-(4-Chloro-1H-pyrrolo[2,3-b]pyridin-1-yl)phenyl)methanol (3k). Yield 64%, \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.15 (dd, J = 5.2, 1.0 Hz, 1H), 7.70 (d, J = 7.9 Hz, 1H), 7.51 (t, J = 7.5 Hz, 1H), 7.45 (t, J = 7.5 Hz, 1H), 7.30 (d, J = 7.5 Hz, 1H), 7.28 (t, J = 7.5 Hz, 1H), 4.35 (s, 2H); \(^1^3\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 148.3, 143.0, 139.0, 136.2, 135.0, 131.8, 130.6, 129.3, 127.8, 123.9, 117.8, 61.4; HRMS (ESI) Calcd for C_{14}H_{12}ClN_{2}O [M+H]^+ 267.1128, found 267.1130.
Hz, 1H), 7.39 (d, J = 3.6 Hz, 1H), 7.23 (d, J = 7.8 Hz, 1H), 7.19 (d, J = 5.2 Hz, 1H), 6.79 (d, J = 3.6 Hz, 1H), 4.72 (s, 1H), 4.37 (s, 2H); 13C NMR (125 MHz, CDCl3) δ 149.0, 143.7, 138.0, 137.2, 136.1, 131.6, 130.6, 129.2, 127.8, 120.7, 117.1, 115.4, 100.5, 61.3; HRMS (ESI) Calcd for C14H12ClN2O [M+H]+ 259.0633, found 259.0640.

(2-(4-Cyclopropyl-1H-pyrrolo[2,3-b]pyridin-1-yl)phenyl)methanol (3l). Yield 74%, 1H NMR (400 MHz, CDCl3) δ 8.10 (d, J = 5.2 Hz, 1H), 7.68 (dd, J = 7.4, 1.7 Hz, 1H), δ 7.50 – 7.41 (m, 1H), 7.21 (dd, J = 3.6 Hz, 1H), 6.81 (d, J = 3.6 Hz, 1H), 6.65 (d, J = 5.2 Hz, 1H), 4.38 (s, 2H), 2.34 – 2.26 (m, 1H), 1.24 – 1.17 (m, 2H), 1.05 – 1.00 (m, 2H); 13C NMR (125 MHz, CDCl3) δ 148.4, 148.2, 143.7, 138.3, 137.0, 132.0, 129.4, 129.4, 129.0, 128.0, 121.2, 115.7, 111.5, 100.6, 61.6, 13.3, 10.2; HRMS (ESI) Calcd for C17H17N2O [M+H]+ 265.1335, found 265.1341.

(2-(4-Methoxy-1H-pyrrolo[2,3-b]pyridin-1-yl)phenyl)methanol (3m). Yield 68%, 1H NMR (400 MHz, CDCl3) δ 8.14 (d, J = 5.6 Hz, 1H), 7.68 (d, J = 7.2 Hz, 1H), δ 7.49 – 7.39 (m, 1H), 7.26 – 7.18 (m, 2H), 6.75 (d, J = 3.5 Hz, 1H), 6.61 (d, J = 5.6 Hz, 2H), 4.37 (s, 2H), 4.04 (s, 3H); 13C NMR (125 MHz, CDCl3) δ 160.6, 150.2, 145.4, 138.1, 136.7, 136.3, 132.2, 131.8, 128.8, 111.4, 99.3, 98.9, 61.4, 55.7; HRMS (ESI) Calcd for C15H15N2O2 [M+H]+ 255.1128, found 255.1122.

(2-(5-Bromo-1H-pyrrolo[2,3-b]pyridin-1-yl)phenyl)methanol (3n). Yield 56%, 1H NMR (400 MHz, CDCl3) δ 8.28 (d, J = 1.9 Hz, 1H), 8.14 (d, J = 1.9 Hz, 1H), 7.69 (d, J = 7.5 Hz, 1H), 7.50 (t, J = 7.5 Hz, 1H), 7.45 (t, J = 7.5 Hz, 1H), 7.37 (d, J = 3.6 Hz, 1H), 7.22 (d, J = 7.7 Hz, 1H), 6.63 (d, J = 3.5 Hz, 1H), 4.36 (s, 2H); 13C NMR (125 MHz, CDCl3) δ 147.1, 144.2, 138.3, 136.3, 132.2, 131.8, 131.8, 129.4, 128.0, 123.1, 112.9, 101.7, 61.6; HRMS (ESI) Calcd for C14H12BrN2O [M+H]+ 303.0128, found 303.0132.

Ethyl 2-(2-(1H-pyrrolo[2,3-b]pyridin-1-yl)phenyl)-2-hydroxyacetate (3q). Yield 68%. 1H NMR (500 MHz, CDCl3) δ 8.26 (d, J = 3.6 Hz, 1H), 8.00 (dd, J = 7.8, 1.4 Hz, 1H), 7.64 – 7.59 (m, 1H), 7.51 – 7.44 (m, 2H), 7.38 (s, 1H), 7.28 – 7.23 (m, 1H), 7.14 (dd, J = 7.8, 4.8 Hz, 1H), 6.67 (d, J = 3.5 Hz, 1H), 5.12 (s, 1H), 4.25 – 3.62 (m, 2H), 1.32 – 0.74 (m, 3H); 13C NMR (125 MHz, CDCl3) δ 172.1, 148.7, 143.3, 136.9, 136.4, 130.3, 129.9, 129.8, 129.1, 128.6, 121.2, 116.9, 102.1, 61.6, 14.0. HRMS (ESI) Calcd for C17H16N2O3 [M+H]+ 297.1234, found 297.1232.

Synthesis of Compound 4. (a) To a solution of 3a (1 mmol, 1 equiv) in DCM (2 mL) was added DMP (1 mmol, 1 equiv). The mixture was stirred at room temperature for 4 h. NaHCO3 aqueous solution was added and extracted with DCM. The organic layer was dried over anhydrous Na2SO4 and was concentrated to get the residue which was purified by silica gel chromatography to give 4a (68% yield). 1H NMR (400 MHz, CDCl3) δ 9.71 (s, 1H), 8.32 (s, 1H), 8.13 (dd, J = 7.8, 1.3 Hz, 1H), 8.02 (d, J = 7.8 Hz, 1H), 7.75 (td, J = 7.8, 1.5 Hz, 1H), 7.56 (t, J = 7.6 Hz, 1H), 7.52 – 7.43 (m, 2H), 7.22 – 7.12 (m, 1H), 6.73 (d, J = 3.6 Hz, 1H); 13C NMR (125 MHz, CDCl3) δ 189.4, 149.0, 144.3, 140.1, 134.8, 131.7, 129.6,
129.3, 128.8, 128.2, 127.7, 120.9, 117.4, 102.8. HRMS (ESI) Calcd for C₁₄H₁₁N₂O [M+H]+ 223.0866, found 223.0864.

(b) To a solution of 3a (1 mmol, 1 equiv) in DCM (2 mL) were added DMP (2 mmol) and H₂O (0.05 equiv). The mixture was stirred at room temperature overnight. And then MeOH (5 mL) and H₂SO₄ (0.1 equiv) were added and the mixture was refluxed overnight. After that, aq. NaHCO₃ was added and then extracted with EtOAc. The combined organic phase was washed with water, brine, dried over Na₂SO₄, and concentrated to get the residue which was purified by silica gel chromatograph to give 4b in 84\% yield. \(^\text{1H NMR (400 MHz, CDCl}_3\)) δ 8.28 (dd, J = 4.7, 1.5 Hz, 1H), 8.03 (dd, J = 7.7, 1.5 Hz, 1H), 7.97 (dd, J = 7.8, 1.5 Hz, 1H), 7.67 (td, J = 7.7, 1.6 Hz, 1H), 7.53 – 7.47 (m, 2H), 7.37 (d, J = 3.6 Hz, 1H), 7.10 (dd, J = 7.8, 4.7 Hz, 1H), 6.65 (d, J = 3.6 Hz, 1H), 3.46 (s, 3H). \(^\text{13C NMR (125 MHz, CDCl}_3\)) δ 166.8, 148.3, 143.5, 137.4, 132.9, 131.3, 129.2, 128.9, 128.8, 128.2, 127.7, 121.0, 116.6, 101.5, 52.2. HRMS (ESI) Calcd for C₁₅H₁₃N₂O₂ [M+H]+ 253.0972, found 253.0969.

ACKNOWLEDGEMENTS
This work is financially supported by National Natural Science Foundation of China (No. 21702218, 91753207), the National major science and technology project "major new drug creation" (Number: 2018ZX09711002-006-001, 2018ZX09711002-007), Youth Innovation Promotion Association (2017333), and Shanghai Rising-Star Program (Grant No. 17QA1405000).

REFERENCES


