

HETEROCYCLES, Vol. 100, No. 6, 2020, pp. 934 - 945. © 2020 The Japan Institute of Heterocyclic Chemistry
Received, 5th April, 2020, Accepted, 7th May, 2020, Published online, 13th May, 2020
DOI: 10.3987/COM-20-14258

RUTHENIUM(II)-CATALYZED REGIOSELECTIVE C-H HYDROXYMETHYLATION OF N-ARYL-AZAINDOLES WITH PARAFORMALDEHYDE

Siqi Li,^{†,‡} Yang Yu,^{†,*} Yaxi Yang,^{‡,§} and Bing Zhou^{‡,§*}

[†]Department of Chemistry, College of Sciences, Shanghai University, 99 Shangda Road, Shanghai 200444, PR China. *Email: yangyu2017@shu.edu.cn [‡]State Key Laboratory of Drug Research, Department of Medicinal Chemistry, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, 555 Zu Chong Zhi Road, Shanghai 201203, PR China. *Email: zhoubing@simm.ac.cn [§]University of Chinese Academy of Sciences, Beijing 100049, PR China.

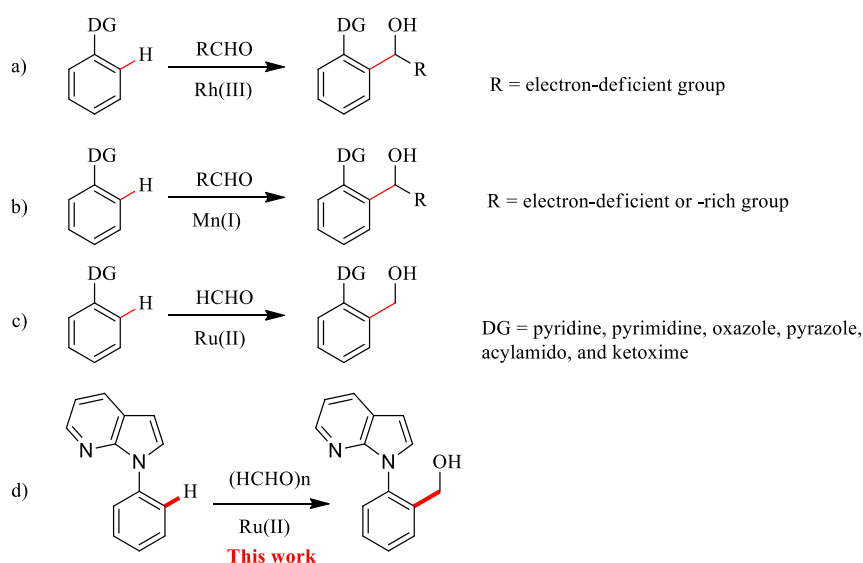
Abstract – A facile synthesis of hydroxymethylated *N*-aryl-azaindoles was developed via a Ru(II)-catalyzed regioselective C-H addition to paraformaldehyde. The reaction is compatible with air, shows high functional group tolerance and regioselectivity, and is an environmentally benign method without any undesired byproduct.

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

ketoimine as the directing groups, thus affording an efficient protocol to access hydroxymethylarenes (Scheme 1c).⁴



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

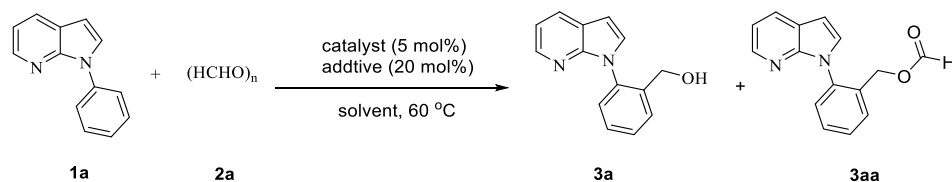
The azaindole ring system, particularly the 7-azaindole, is one of the most valuable heterocyclic moieties due to its ubiquity in numerous biologically active natural products,⁵ two market drugs,⁶ a variety of bioactive compounds,⁷ luminescent molecules⁸ and ligands.⁹ Despite the unique structure of 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 K₂CO₃ at 60 °C (entry 15). The role of K₂CO₃ was to convert the **3aa** into **3a**. Other silver salts such as AgBF₄ and AgPF₆, were also tested, resulting in decreased yields (entries 16 and 17).

Table 1. Optimization of reaction conditions^a

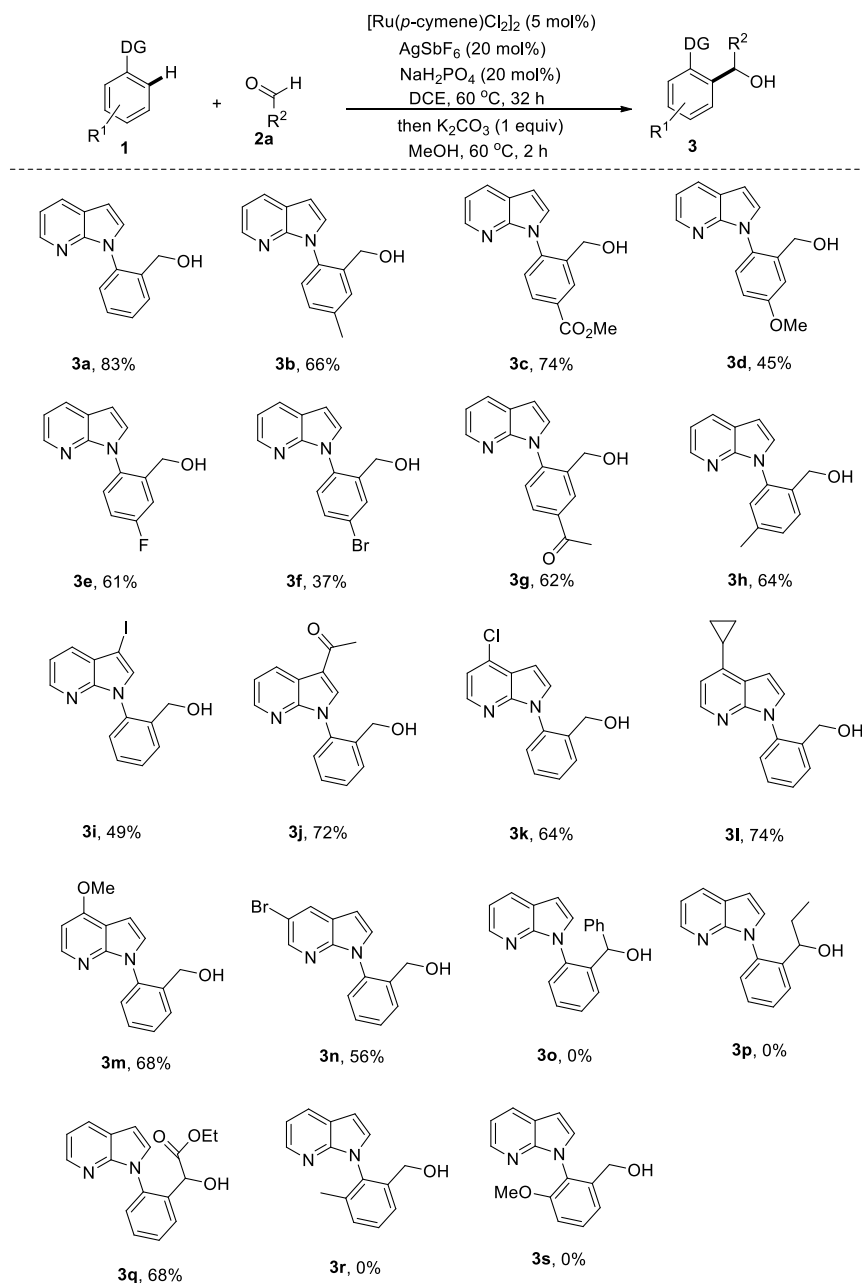


entry	catalyst	additive	solvent	yield 3a (%) ^b
1	[RhCp*Cl ₂] ₂	AgSbF ₆	DCE	0
2	[IrCp*Cl ₂] ₂	AgSbF ₆	DCE	0
3	Cp*Co(CO)I ₂	AgSbF ₆	DCE	0
4	Cp*Rh(MeCN) ₃ (SbF ₆) ₂	-	DCE	0
5	[Ru(<i>p</i> -cymene)Cl ₂] ₂	AgSbF ₆	DCE	42
6	[Ru(<i>p</i> -cymene)Cl ₂] ₂	Cu(OTf) ₂	DCE	< 5
7	[Ru(<i>p</i> -cymene)Cl ₂] ₂	Zn(OTf)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

^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)Cl₂]₂ (5 mol%), silver salts (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.

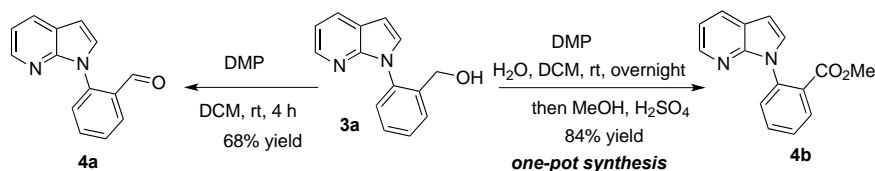
With the establishment of the optimal reaction conditions, the scope of substrates was next investigated (Scheme 2). The C-H hydroxymethylation proceeded efficiently over a broad range of substrates irrespective of their electronic nature. A variety of substrates containing electronic-donating group (**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.



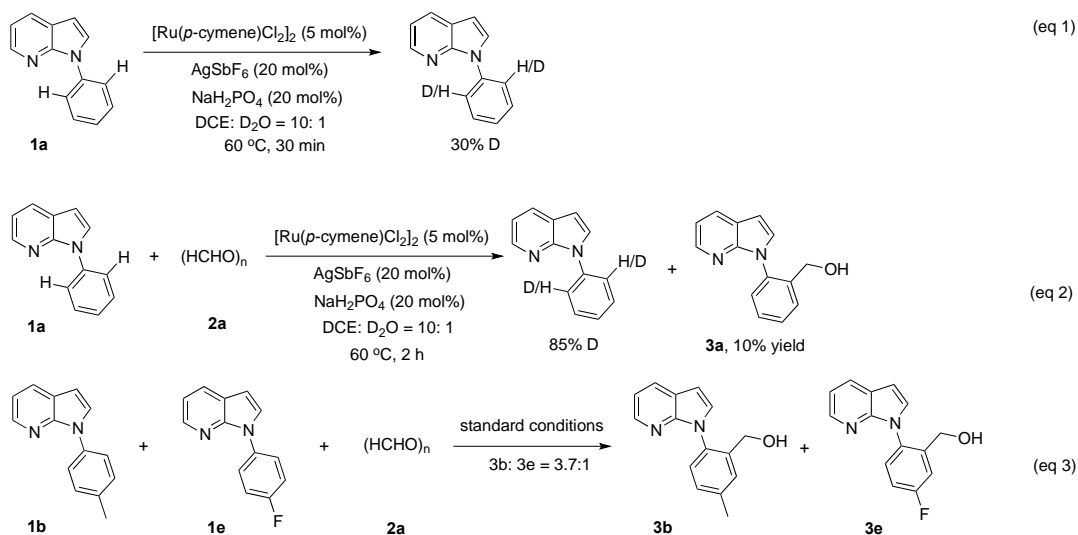
Scheme 2. Substrate Scope. Reactions were carried out by treating **1** (0.1 mmol), **2a** (0.3 mmol), $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$ (5 mol%), AgSbF_6 (20 mol%) and NaH_2PO_4 (20 mol%) in the DCE (1 mL) at 60 °C for 32 h in a sealed tube. Then MeOH and K_2CO_3 (1 equiv) was added and the 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 aldehyde¹³ **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 ester¹³ **4b** in one-pot fashion.

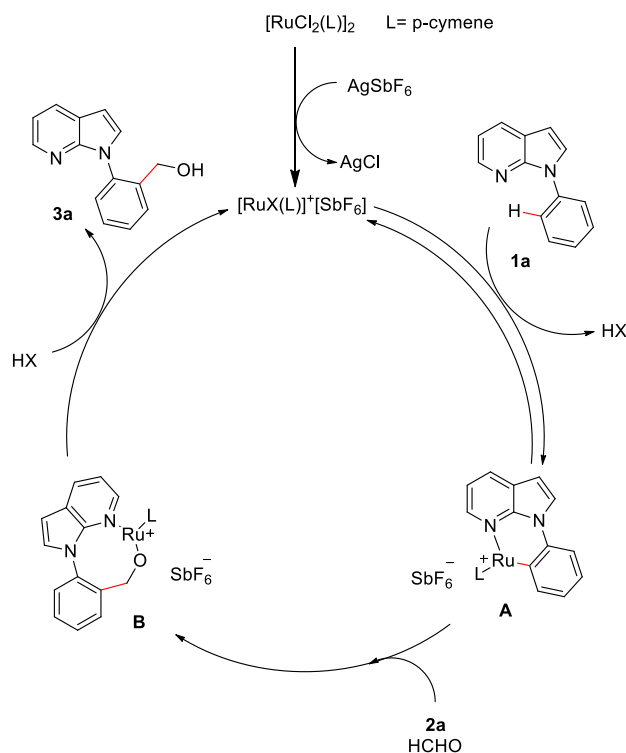


Scheme 3. Synthetic application of **3a**

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.¹⁴



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.



Scheme 4. Plausible mechanism

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. ¹H and ¹³C 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), [RuCl₂(*p*-cymene)]₂ (5 mol%), AgSbF₆ (20 mol%), and NaH₂PO₄ (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 K₂CO₃

(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-(1*H*-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-(1*H*-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-(1*H*-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 C₁₅H₁₅N₂O [M+H]⁺ 239.1179, found 239.1181.

Methyl 3-(hydroxymethyl)-4-(1*H*-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, 130.0, 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-(1*H*-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, 148.9, 143.5, 139.7, 130.5, 130.2, 129.6, 129.2, 121.5, 117.0, 115.9, 115.4, 101.8, 61.9, 56.0; HRMS (ESI) Calcd for C₁₅H₁₅N₂O₂ [M+H]⁺ 255.1128, found 255.1135.

(5-Fluoro-2-(1*H*-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 $C_{14}H_{12}FN_2O$ $[M+H]^+$ 243.0928, found 243.0927.

(5-Bromo-2-(1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)phenyl)methanol (3f). Yield 37%, 1H NMR (400 MHz, $CDCl_3$) δ 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 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 $C_{14}H_{12}BrN_2O$ $[M+H]^+$ 303.0128, found 303.0128.

1-(3-(Hydroxymethyl)-4-(1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)phenyl)ethan-1-one (3g). Yield 62%, 1H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.26 (d, $J = 4.8$ Hz, 1H), δ 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); ^{13}C NMR (126 MHz, $CDCl_3$) δ 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 $C_{16}H_{15}N_2O_2$ $[M+H]^+$ 267.1128, found 267.1132.

(4-Methyl-2-(1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)phenyl)methanol (3h). Yield 64%, 1H NMR (400 MHz, $CDCl_3$) δ 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 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 $C_{15}H_{15}N_2O$ $[M+H]^+$ 239.1182, found 239.1179.

(2-(3-Iodo-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)phenyl)methanol (3i). Yield 49%, 1H NMR (400 MHz, $CDCl_3$) δ 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 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 $C_{14}H_{12}IN_2O$ $[M+H]^+$ 350.9989, found 350.9984.

1-(1-(2-(Hydroxymethyl)phenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)ethan-1-one (3j). Yield 72%, 1H NMR (400 MHz, $CDCl_3$) δ 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); ^{13}C NMR (125 MHz, $CDCl_3$) δ 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 $C_{16}H_{15}N_2O_2$ $[M+H]^+$ 267.1128, found 267.1130.

(2-(4-Chloro-1*H*-pyrrolo[2,3-*b*]pyridin-1-yl)phenyl)methanol (3k). Yield 64%, 1H NMR (400 MHz, $CDCl_3$) δ 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), 7.39 (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); ^{13}C NMR (125 MHz, CDCl_3) 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 $\text{C}_{14}\text{H}_{12}\text{ClN}_2\text{O}$ $[\text{M}+\text{H}]^+$ 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, CDCl_3) 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, 2H), 7.32 (d, $J = 3.6$ Hz, 1H), 7.21 (dd, $J = 7.6, 1.3$ Hz, 2H), 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); ^{13}C NMR (125 MHz, CDCl_3) 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 $\text{C}_{17}\text{H}_{17}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$ 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, CDCl_3) 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); ^{13}C NMR (125 MHz, CDCl_3) δ 160.6, 150.2, 145.4, 138.1, 136.7, 131.8, 129.1, 128.8, 127.8, 111.4, 99.3, 98.9, 61.4, 55.7; HRMS (ESI) Calcd for $\text{C}_{15}\text{H}_{15}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ 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, CDCl_3) 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); ^{13}C NMR (125 MHz, CDCl_3) 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 $\text{C}_{14}\text{H}_{12}\text{BrN}_2\text{O}$ $[\text{M}+\text{H}]^+$ 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, CDCl_3) 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); ^{13}C NMR (125 MHz, CDCl_3) 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 $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$ 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. NaHCO_3 aqueous solution was added and extracted with DCM. The organic layer was dried over anhydrous Na_2SO_4 and was concentrated to get the residue which was purified by silica gel chromatography to give **4a** (68% yield). ^1H NMR (400 MHz, CDCl_3) 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). ^{13}C NMR (125 MHz, CDCl_3) 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. ¹H NMR (400 MHz, CDCl₃) 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). ¹³C NMR (125 MHz, CDCl₃) 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

- (a) R. J. Billedeau, R. K. Kondru, F. J. Lopez-Tapia, Y. Lou, T. D. Owens, Y. Qian, S. So, K. C. Thakkar, and J. Wanner, WO/2012/156334; (b) D. Bonafoux, H. M. Davis, K. E. Frank, M. M. Friedman, J. M. Herold, M. Z. Hoemann, R. Huntley, A. Osuma, G. Sheppard, and G. K. Somal, WO/2014/210255; (c) P. W. Glunz, D. F. Sitkoff, M. S. Bodas, N. D. Yadav, S. Patil, P. S. M. Rao, K. Thiyagarajan, and T. K. Maishal, WO/2016/144936; (d) K. Jones, M. D. Cheeseman, S. Linardopoulos, A. Faisal, O. R. Barbeau, and A. Kalusa, US/2015/0232462; (e) M. D. Cheeseman, A. Faisal, S. Rayter, O. R. Barbau, A. Kalusa, M. Westlake, R. Burke, M. Swan, R. van Montfort, S. Linardopoulos, and K. Jones, *Bioorg. Med. Chem. Lett.*, 2014, **24**, 3469; (f) K. Jones, M. D. Cheeseman, S. Linardopoulos, A. Faisal, O. R. Barbeau, and A. Kalusa, *PCT Int. Appl.*, WO/2014/030001; (g) R. Anand, J. M. Apgar, T. Biftu, P. Chen, L. Chu, V. J. Colandrea, G. Dong, J. F. Dropinski, D. Feng, J. D. Hicks, J. Jiang, A. J. Kim, K. J. Leavitt, B. Li, X. Qian, L. Sebhat, L. Wei, R. R. Wilkening, R. Robert, and Z. Wu, WO/2012/116145; (h) L. J. Gazzard, E. Hanan, S. Kintz, J. P. Lyssikatos, and H. E. Purkey, *PCT Int. Appl.*, WO/2012/080284.
- S. Kobayashi and H. Ishitani, *Chem. Rev.*, 1999, **99**, 1069.

3. (a) Y. Fukumoto, K. Sawada, M. Hagihara, N. Chatani, and S. Murai, [Angew. Chem. Int. Ed., 2002, 41, 2779](#); (b) Y. Kuninobu, Y. Nishina, T. Takeuchi, and K. Takai, [Angew. Chem. Int. Ed., 2007, 46, 6518](#); (c) Y. Kuninobu, Y. Fujii, T. Matsuki, Y. Nishina, and K. Takai, [Org. Lett., 2009, 11, 2711](#); (d) B.-J. Li and Z.-J. Shi, *Chem. Sci.*, 2011, **2**, 488; (e) L. Yang, C. A. Correia, and C.-J. Li, [Adv. Synth. Catal., 2011, 353, 1269](#); (f) Y. Li, X.-S. Zhang, Q.-L. Zhu, and Z.-J. Shi, [Org. Lett., 2012, 14, 4498](#); (g) Y. Li, X.-S. Zhang, K. Chen, K.-H. He, F. Pan, B.-J. Li, and Z.-J. Shi, [Org. Lett., 2012, 14, 636](#); (h) B. Zhou, Y. Hu, and C. Wang, [Angew. Chem. Int. Ed., 2015, 54, 13659](#); (i) H. Jo, J. Park, M. Choi, S. Sharma, M. Jeon, N. K. Mishra, T. Jeong, S. Han, and I. S. Kim, [Adv. Synth. Catal., 2016, 358, 2714](#).
4. (a) Y. X. Wu and B. Zhou, [ACS Catal., 2017, 7, 2213](#); (b) G.-F. Zhang, Y. Li, X.-Q. Xie, and C.-R. Ding, [Org. Lett., 2017, 19, 1216](#).
5. (a) J.-Y. Mérour and B. Joseph, [Curr. Org. Chem., 2001, 5, 471](#); (b) F. Popowycz, S. Routier, B. Joseph, and J.-Y. Mérour, [Tetrahedron, 2007, 63, 1031](#); (c) J. J. Song, J. T. Reeves, F. Gallou, Z. Tan, N. K. Yee, and C. H. Senanayake, [Chem. Soc. Rev., 2007, 36, 1120](#).
6. (a) A. Mullard, [Nat. Rev. Drug Discov., 2012, 11, 91](#); (b) A. J. Souers, J. D. Levenson, E. R. Boghaert, S. L. Ackler, N. D. Catron, J. Chen, B. D. Dayton, H. Ding, S. H. Enschede, W. J. Fairbrother, D. C. S. Huang, S. G. Hymowitz, S. Jin, S. L. Khaw, P. J. Kovar, L. T. Lam, J. Lee, H. L. Maecker, K. C. Marsh, K. D. Mason, M. J. Mitten, P. M. Nimmer, A. Oleksijew, C. H. Park, C.-M. Park, D. C. Phillips, A. W. Roberts, D. Sampath, J. F. Seymour, M. L. Smith, S. G. M. Sullivan, S. K. Tahir, C. Tse, M. D. Wendt, Y. Xiao, J. C. Xue, H. Zhang, R. A. Humerickhouse, S. H. Rosenberg, and S. W. Elmore, [Nat. Med., 2013, 19, 202](#).
7. Selected examples: (a) C. Marminon, A. Pierré, B. Pfeiffer, V. Pérez, S. Léonce, A. Joubert, C. Bailly, P. Renard, J. Hickman, and M. Prudhomme, [J. Med. Chem., 2003, 46, 609](#); (b) S. Hong, J. Kim, J. H. Seo, K. H. Jung, S.-S. Hong, and S. Hong, [J. Med. Chem., 2012, 55, 5337](#).
8. (a) Q. Wu, M. Estaghamatian, N.-X. Hu, Z. Popovic, G. Enright, S. R. Breeze, and S. Wang, [Angew. Chem. Int. Ed., 1999, 38, 985](#); (b) Q. Wu, A. Hook, and S. Wang, *Angew. Chem. Int. Ed.*, 2000, **39**, 3933
9. C. Waloch, J. Wieland, M. Keller, and B. Breit, [Angew. Chem. Int. Ed., 2007, 46, 3037](#).
10. (a) Y. Chen, S. Guo, K. Li, J. Qu, H. Yuan, Q. Hua, and B. Chen, [Adv. Synth. Catal., 2013, 355, 711](#); (b) P. Kannaboina, K. Anilkumar, S. Aravinda, R. Vishwakarma, and P.A. Das, [Org. Lett., 2013, 15, 5718](#); (c) M. P. Huestis and K. Fagnou, [Org. Lett., 2009, 11, 1357](#); (d) N. M. Barl, E. Sansiaume-Dagousset, K. Karaghiosoff, and P. Knochel, [Angew. Chem. Int. Ed., 2013, 52, 10093](#).
11. (a) G. Qian, X. Hong, B. Liu, H. Mao, and B. Xu, [Org. Lett., 2014, 16, 5294](#); (b) S.-S. Li, C.-Q. Wang, H. Lin, X.-M. Zhang, and L. Dong, [Org. Lett., 2015, 17, 3018](#); (c) S. S. Li, C.-Q. Wang, H.

- Lin, X.-M. Zhang, and L. Dong, [Org. Biomol. Chem.](#), 2016, **14**, 229; (d) B. Liu, X. Wang, Z. Ge, and R. Li, [Org. Biomol. Chem.](#), 2016, **14**, 2944; (e) A. Mishra, T. K. Vats, and I. Deb, [J. Org. Chem.](#), 2016, **81**, 6525; (f) W.-H. Li, L. Wu, S.-S. Li, C.-F. Liu, G.-T. Zhang, and L. Dong, [Chem. Eur. J.](#), 2016, **22**, 17926; (g) A. Mishra, T. K. Vats, M. P. Nair, A. Das, and I. Deb, [J. Org. Chem.](#), 2017, **82**, 12406.
12. Selected examples: (a) B. Zhou, Z. Chen, Y. Yang, W. Ai, H. Tang, Y. Wu, W. Zhu, and Y. Li, [Angew. Chem. Int. Ed.](#), 2015, **54**, 12121; (b) Y. Yang, X. Wang, Y. Li, and B. Zhou, [Angew. Chem. Int. Ed.](#), 2015, **54**, 15400; (c) Y. Wu, Z. Chen, Y. Yang, W. Zhu, and B. Zhou, *J. Am. Chem. Soc.*, 2018, **140**, 42; (d) Y. Wang, Y. Chen, Y. Yang, and B. Zhou, [Org. Chem. Front.](#), 2018, **5**, 1844; (e) M. Gao, Y. Yang, H. Chen, and B. Zhou, [Adv. Synth. Catal.](#), 2018, **360**, 100; (f) Y. Chen, S. Wan, Y. Wu, Y. Yang, and B. Zhou, [Tetrahedron Lett.](#), 2019, **60**, 1481.
13. S. D. Meyer and S. L. Schreiber, *J. Org. Chem.*, 1994, **59**, 7549.
14. For selected reviews on ruthenium(II)-catalyzed C–H functionalizations, see: (a) L. Ackermann, [Org. Process Res. Dev.](#), 2015, **19**, 260; (b) C. Bruneau, [Top. Organomet. Chem.](#), 2014, **48**, 195; (c) S. De Sarkar, W. Liu, S. I. Kozhushkov, and L. Ackermann, [Adv. Synth. Catal.](#), 2014, **356**, 1461; (d) B. Li and P. H. Dixneuf, [Chem. Soc. Rev.](#), 2013, **42**, 5744.
15. J. Z. Jiang, J. R. Koehl, S. Mehdi, N. D. Moorcroft, K. Y. Musick, P. M. Weintraub, and P. R. Eastwood, US/2005/0054631 A1.