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Formation of Methylene Linkage for *N*-Heterocycles: Sequential C–H and C–O Bond Functionalization of Methanol with Cosolvent Water

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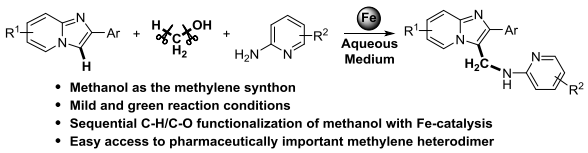
Supporting Information Placeholder

TOC:



ABSTRACT: An iron-catalyzed methylene forming strategy is disclosed through sequential C–H and C–O bond functionalization of methanol with cosolvent water. This protocol provides an easy and novel access to methylene tethered imidazo[1,2-*a*]pyridine and 2-aminopyridine analogues in a sustainable manner, and represents a complementary approach to traditional methylene forming strategies.

INTRODUCTION

Nitrogen-containing heterocycles are ubiquitous structural motifs of numerous natural products and pharmaceuticals,[1] thus their syntheses and late-stage functionalizations have become an important focus for organic and medicinal chemists.[2] Specifically, use of covalent linkage to tether stable and highly accessible *N*-heterocycles has substantially expanded access to diverse pharmaceutically valuable molecules.[3] For instance, some well-developed drugs such as *esomeprazole*,[4] *alosetron*,[5] *baquiloprim*,[6] and *motesanib*[7] were found in the series of methylene-tethered *N*-heterocycles (e.g., imidazole and 2-aminopyridine analogues) (Figure 1). Therefore, various methods have been developed to construct the methylene-linked *N*-heterocycles, one of which prepositiones methylene linker on either *N*-heterocycle, thus suffers from operational complexity, poor step- and atom-economy.[8] Another noteworthy strategy by using small molecules to serve as the methylene synthon has been actively pursued, which involves direct metalation of C–H bonds on either *N*-heterocycle. With this strategy, the commonly used solvent *N*,*N*-dimethylacetamide has been successfully explored to synthesize methylene bisimidazo[1,2-*a*]pyridines.[9] Furthermore, C_1-feedstocks such as formaldehyde (via nucleophilic addition and subsequent dehydration reaction)[10] or the toxic and explosive diazomethane (via transition metal such as Pd-catalyzed migratory insertion reaction[11]) are capable of installing the methylene linkage for limited *N*-heterocycles. However, as a simple and easily-handling C_1-precursor, methanol is not frequently used as the methylene source thus far.

Recently, as an emerging field in C–H functionalizations, cross-

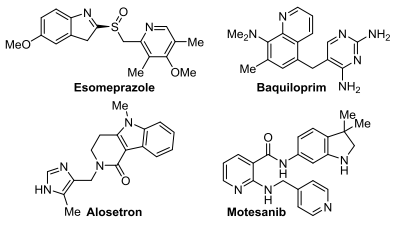
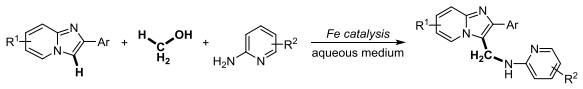


Figure 1. Some pharmaceuticals with methylene-tethered heterocyclic pairs.

dehydrogenative coupling (CDC) between C–H bonds (especially the intrinsically inert sp^3 C–H bond in small molecules) has become a highly attractive yet challenging C–C bond-forming strategy due to its step- and atom-economic features.[12] One typical example is the CDC reaction between methanol C–H and pyridyl C–H bond (also known as the Minisci reaction[13]), which has provided a useful means to forge C–C bonds. This protocol has captured considerable attentions from synthetic chemists, although more catalytic systems should be exploited to showcase its generality (e.g., CDC coupling of methanol C–H bond with electron-sufficient substrates) and practicality (e.g., CDC coupling of methanol C–H bond under milder reaction conditions, cheaper catalytic systems, greener reaction mediums).[14] Moreover, to expand the utilization of CDC reaction with methanol, various methods can be applied in late-stage functionalization of the resulting hydroxymethyl products (mainly involving transformations of the hydoxyl group). Apart from traditional functional group transformation strategies,[15] an appealing approach is the direct amination/amidation of hydroxyl group through a hydrogen-borrowing process[16] via Ir-,[17] Ru-,[18] or other transition-

metal-catalysis.[19] Given the state of art, we questioned that whether a general and sustainable protocol could be devised with methanol as the methylene synthon for selective linkage of *N*-heterocycles through a consequtive C–H and C–O bond functionalization of methanol. Herein, we present an iron-catalyzed methylene-forming strategy from methanol with cosolvent water, which can be applied to tether imidazo[1,2-*a*]pyridine and 2-aminopyridine via sequential C–C and C–N bond formation (Scheme 1).

Scheme 1. Iron-catalyzed methylene formation from methanol (this work)

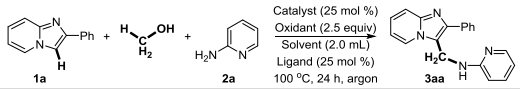


RESULTS AND DISCUSSION

Our efforts on developing this methylene-forming strategy from methanol began with the evaluation of the reaction with 2-phenylimidazo[1,2-*a*]pyridine (**1a**) and 2-aminopyridine (**2a**) (Table 1). We found that the treatment of **1a** and **2a** with catalyst $FeCp_2$ (25 mol %) and oxidant TBHP (70% aqueous solution, 2.5 equiv) in methanol at 100 °C under an argon atmosphere for 24 h gave the desired methylene-linked heterodimer **3aa** (confirmed by X-ray diffraction; please refer to pS1 in the Supporting Information) in 44% yield (Table 1, entry 1). Fortunately, a marked increase in efficiency was observed when the model reaction was performed in MeOH/H_2O (7:3 v/v ratio), affording **3aa** in 75% yield (entry 2). Seeking to improve on this result, $FeCp^*_2$, dppf, $FeCl_2$ and $FeCl_3$ were examined, among which $FeCp_2$ afforded **3aa** in the highest 72% yield (entries 2-6). Remarkably, it was found that oxidant significantly influenced the efficiency of the reaction: TBHP (5.5 M in decane) decreased the reaction efficiency slightly, while DTBP, CHP or DCP reduced the yield dramatically (entries 7-10); and surprisingly, $(BzO)_2$ or $BzOOBu^t$ completely inhibited the reaction (entries 11 and 12). Meanwhile, changing the volume ratio of MeOH to H_2O was found to be detrimental to this reaction (entries 13 and 14). Afterwards, a variety of *N,N*-, *P,P*- and *P,N*-bidentate ligands were tested (entries 15-22). Nevertheless, a further improvement was observed when using 2,2′-bipyridine ($\mathbf{L_1}$) as the ligand (entry 15, 80% yield). More endeavors to increase the reaction efficiency were also attempted. For instance, screening of reaction temperature and time achieved a superior result (85% yield) at 90 °C for 30 h (entries 23 and 24), while performing the reaction under an air atmosphere did not (entry 25). Notably, no or only 59% of **3aa** was produced when running the reaction in the absence of oxidant or catalyst (entries 26 and 27), thus demonstrating that the combination of catalyst $FeCp_2$ and oxidant TBHP is crucial for this transformation.

With the optimized reaction conditions in hand, we began an exploration of the scope of 2-aminopyridine component for this methylene-forming protocol. As shown in Scheme 2, electron-neutral and electron-rich 2-aminopyridines bearing alkyl and methoxyl functionality may be employed in good to excellent yields (**3aa-ae**, 62-82% yield; **CD_2-3aa**, 53% yield), while electron-deficient ones containing fluoro, chloro, bromo groups readily reacted with **1a** to afford the desired products in good yields (**3af-aj**, 53-70% yield). The tolerance of these functionalities with coupling capability potentially allows for late-stage functionalization of

Table 1. Screening of the reaction conditions[a]



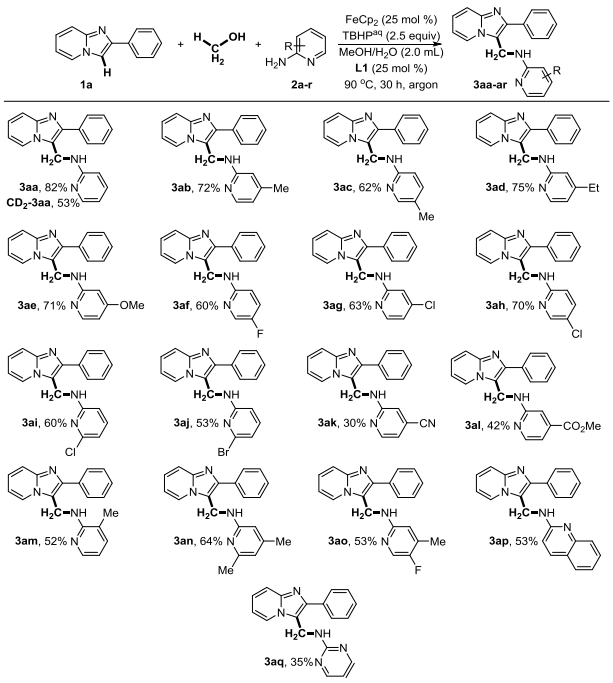
1a 2a 3aa

entry	Catalyst	Oxidant	Solvent	Ligand	yield (%)[b]
1	$FeCp_2$	$TBHP^{aq}$	MeOH	-	44
2	$FeCp_2$	$TBHP^{aq}$	MeOH/H_2O (7:3)	-	75
3	$FeCp^*_2$	$TBHP^{aq}$	MeOH/H_2O (7:3)	-	58
4	dppf	$TBHP^{aq}$	MeOH/H_2O (7:3)	-	48
5[c]	$FeCl_2$	$TBHP^{aq}$	MeOH/H_2O (7:3)	-	58
6	$FeCl_3$	$TBHP^{aq}$	MeOH/H_2O (7:3)	-	65
7	$FeCp_2$	$TBHP^{dec}$	MeOH/H_2O (7:3)	-	72
8	$FeCp_2$	DTBP	MeOH/H_2O (7:3)	-	24
9	$FeCp_2$	CHP	MeOH/H_2O (7:3)	-	47
10	$FeCp_2$	DCP	MeOH/H_2O (7:3)	-	31
11	$FeCp_2$	$(BzO)_2$	MeOH/H_2O (7:3)	-	-
12	$FeCp_2$	$BzOOBu^t$	MeOH/H_2O (7:3)	-	-
13	$FeCp_2$	$TBHP^{aq}$	MeOH/H_2O (8:2)	-	58
14	$FeCp_2$	$TBHP^{aq}$	MeOH/H_2O (6:4)	-	59
15	$FeCp_2$	$TBHP^{aq}$	MeOH/H_2O (7:3)	L_1	80
16	$FeCp_2$	$TBHP^{aq}$	MeOH/H_2O (7:3)	L_2	70
17	$FeCp_2$	$TBHP^{aq}$	MeOH/H_2O (7:3)	L_3	71
18	$FeCp_2$	$TBHP^{aq}$	MeOH/H_2O (7:3)	L_4	42
19	$FeCp_2$	$TBHP^{aq}$	MeOH/H_2O (7:3)	L_5	43
20	$FeCp_2$	$TBHP^{aq}$	MeOH/H_2O (7:3)	L_6	76
21	$FeCp_2$	$TBHP^{aq}$	MeOH/H_2O (7:3)	L_7	76
22	$FeCp_2$	$TBHP^{aq}$	MeOH/H_2O (7:3)	L_8	42
23[c]	$FeCp_2$	$TBHP^{aq}$	MeOH/H_2O (7:3)	L_1	80
24[d]	**$FeCp_2$**	**$TBHP^{aq}$**	**MeOH/H_2O (7:3)**	**L_1**	**85**
25[e]	$FeCp_2$	$TBHP^{aq}$	MeOH/H_2O (7:3)	L_1	72
26[f]	$FeCp_2$	-	MeOH/H_2O (7:3)	L_1	-
27	-	$TBHP^{aq}$	MeOH/H_2O (7:3)	L_1	59

[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), Catalyst (25 mol %), Oxidant (2.5 equiv), Solvent (2.0 mL), Ligand (25 mol %), 100 °C, 24 h, under argon. [b]Yields determined by ^{1}H NMR analysis of the crude reaction mixture using mesitylene as an internal standard. [c]Reaction was conducted at 90 °C. [d]Reaction was carried out for 30 h. [e]Reaction was conducted under air. Cp = cyclopentadienyl, Cp* = pentamethylcyclopentadienyl, $TBHP^{aq}$ = tert-butyl hydroperoxide (70% aqeous solution), $TBHP^{dec}$ = *tert*-butyl hydroperoxide (5.5 M in decane), DTBP = *tert*-butyl peroxide, CHP = cumene hydroperoxide (techanicial grade, 80%), DCP = dicumyl peroxide, L_1 = 2,2′-bipyridine, L_2 = 4,4′-dimethyl-2,2′-bipyridine, L_3 = 2,2′-biquinoline, L_4 = bathophenanthroline, L_5 = 1,10-phenanthroline, L_6 = DavePhos, L_7 = 1,4-bis(diphenylphosphino)-butane, L_8 = *N,N,N′,N′*-tetramethylethylenediamine.

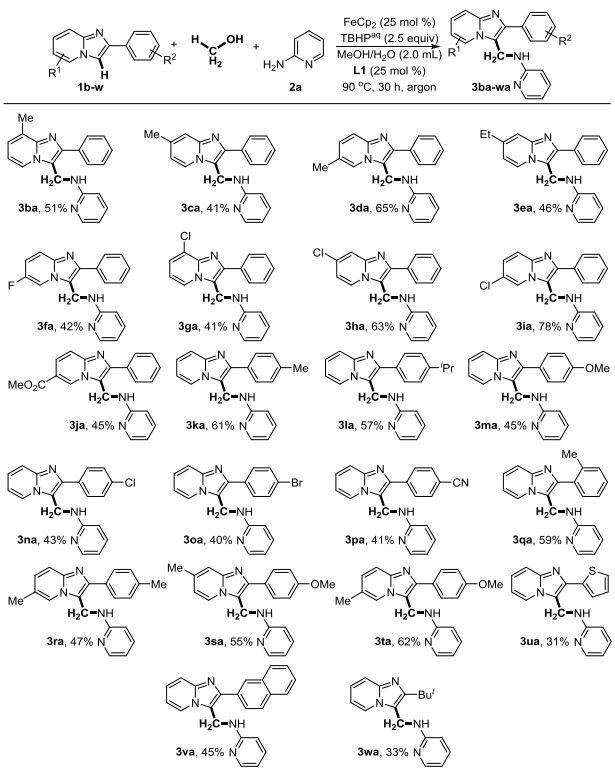
the products. Besides, cyano and ester groups were also tolerated to provide the desired products in useful yields (**3ak** and **3al**, 30 and 42% yield). Notably, the efficiency of the reaction was impeded by ortho substituent (to amino group on pyridyl unit) (cf. **3am** and **3ab**/**3ac**, 52% versus 72%/62% yield). And 2-aminopyridine with polysubstituents succeeded in generating the desired products in good yields (**3an** and **3ao**, 64 and 53% yield). Additionally, we were pleased to find that the extended aromatic system (e.g., 2-aminoquinoline) and pharmaceutically relevant heterocycles (e.g., pyrimidyl) were competent coupling partners to provide an encouraging quantity of the desired products (**3ap** and **3aq**, 35 and 35% yield).

Scheme 2. Scope for 2-aminopridine component[a]



[a]General reaction conditions: **1a** (0.2 mmol), **2a-r** (0.6 mmol), $FeCp_2$ (0.05 mmol, 25 mol %), $TBHP^{aq}$ (2.5 equiv), $MeOH/H_2O$ (2.0 mL, 7:3 v/v ratio), $\mathbf{L_1}$ (0.05 mmol, 25 mol %), 90 °C, 30 h, under argon atmosphere. Yields of isolated products are given.

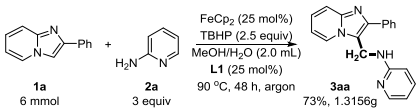
Scheme 3. Scope for 2-arylimidazo[1,2-*a*]pyridine component[a]



[a]General reaction conditions: **1b-w** (0.2 mmol), **2a** (0.6 mmol), $FeCp_2$ (0.05 mmol, 25 mol %), $TBHP^{aq}$ (2.5 equiv), $MeOH/H_2O$ (2.0 mL, 7:3 v/v ratio), $\mathbf{L_1}$ (0.05 mmol, 25 mol %), 90 °C, 30 h, under argon atmosphere. Yields of isolated products are given.

We next sought to explore the generality of this protocol with respect to 2-arylimidazo[1,2-*a*]pyridine component. As shown in Scheme 3, substrate containing either electron-donating (e.g., Me, Et; **3ba-ea**, 41-65% yield) or -withdrawing groups (e.g., F, Cl and CO_2Me; **3fa-ja**, 41-78% yield) on pyridyl unit readily underwent the titled reaction in moderate to good yields. Furthermore, electron-donating groups on phenyl unit (e.g., Me, ^{i}Pr and OMe; **3la-ma**, 45-61% yield) generally displayed higher efficiency than electron-withdrawing groups (e.g., Cl, Br and CN; **3na**-pa, 40-43% yield). The steric limit of substituent on phenyl unit was also investigated, but no detrimental effect on coupling efficiency was observed when 2´-methylated substrate **1q** was employed (cf. **3ka** and **3qa**). Moreover, reactants bearing both substituent on pyridyl and phenyl unit were smoothly converted to the desired products in moderate to good yields (**3ra-ta**, 47-62% yield). And substrates with oxidation-vulnerable aromatic rings (e.g., thienyl and naphthyl; **3ua** and **3va**, 31 and 45% yield) were examined to evaluate the power of this methylene-forming protocol, and fortunately they were tolerated in this transformation, albeit in diminished yields. Finally, 2-*tert*-butylimidazo[1,2-*a*]pyridine was also found to be suitable for this transformation (**3wa**, 33% yield).

Scheme 4. Gram-scale synthesis of product 3aa.



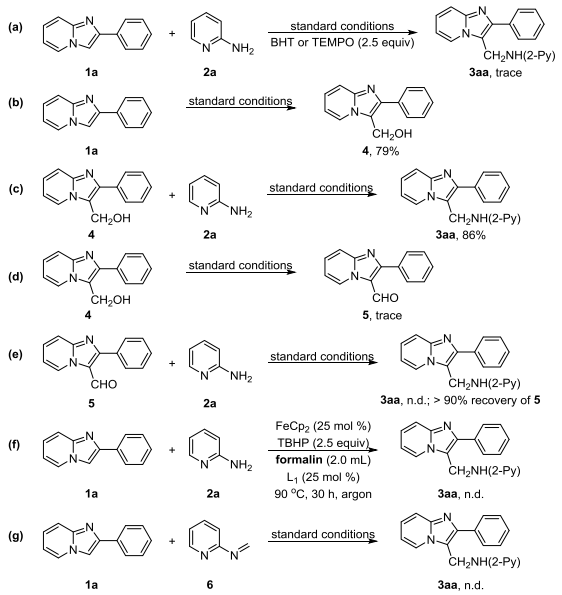
As far as we know, the coupling products may bind or interact with the modularory sites on a large number of different gamma-aminobutryric acid (GABA) receptor complexes, indicating that there are excellent prospects for developing more selective drugs for the treatment of central nervous system (CNS) disorders.[20,21] We thereby evaluated the scalability of this methylene-forming protocol by performing reaction on a 6 mmol scale. The reaction of 2-phenylimidazo[1,2-*a*]pyridine (**1a**) and 2-aminopyridine (**2a**) in methanol smoothly furnished product **3aa** in 73% yield without significant decrease in efficiency (versus 82% for the reaction on a 0.2 mmol scale for **3aa**) (Scheme 4), thus showing its great potential in practical synthesis.

Further investigations were performed to gain some insights into the reaction mechanism (Scheme 5). We first conducted experiments to explore the existence of the radical intermediates. When a radical scavenger, (2,2,6,6-tetramethyl-piperidin-1-yl)oxyl (TEMPO) or butylated hydroxytoluene (BHT) was added into the reaction of **1a** and **2a** under standard conditions, nearly no desired product **3aa** was observed (Scheme 5a), implying that radical intermediates are involved under this iron-catalysis. Additionally, in the absence of **2a**, **1a** under standard conditions could capture the radical intermediate to afford the hydroxymethylation product **4** in 79% yield, therefore suggesting the generation of a hydroxymethyl radical during the reaction (Scheme 5b).

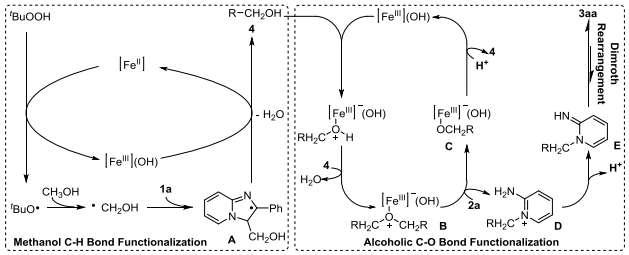
Subsequently, exposure **4** and **2a** to the standard conditions afforded **3aa** in 86% yield, indicating that product **4** is most probably involved in the reaction (Scheme 5c). On the other hand, as benzyl alcohol analogues are prone to be transformed into aldehyde through transition-metal involved dehydrogenation[22] or hydrogen-borrowing process,[16] product **4** was thereby subjected into the standard conditions; however, only trace amount of aldehyde **5** was

observed (Scheme 5d). Besides, the desired coupling reaction of **5** with **2a** did not occur either, with more than 90% recovery of the starting material **5** (Scheme 5e). These results demonstrate that there is little chance to form the C–N bond if dehydrogenation or hydrogen-borrowing process of **4** is involved in the titled reaction. Furthermore, another pathway to **3aa** involving the in-situ oxidation of methanol to formaldehyde and a subsequent Mannich-type reaction[21a,23] of either **1a**, **2a** and formaldehyde or **1a** and imine **6** (generated from condensation of formaldehyde and **2a**) may be excluded as well (Scheme 5f-g).

Scheme 5. Investigation into the reaction mechanism



Scheme 6. Plausible mechanism



Based on these experimental observations, a plausible mechanism for this reaction is proposed in Scheme 6. Initiation occurs by reducing TBHP with $FeCp_2$ to generate Fe^{III}(OH)-complex and the *tert*-butoxyl radical,[24] which then abstracts a hydrogen from methanol to putatively afford the hydroxymethyl radical. This ensuing radical could be well-suited to add to 2-phenylimidazo[1,2-*a*]pyridine **1a** to give radical **A**,[25] which is believed to undergo direct oxidation by Fe^{III}(OH)-complex and deprotonation to give product **4**. Afterwards, product **4** may be rapidly converted to dimeric ether by eliminating water with the assistance of Fe^{III}(OH)-complex.[26] Presumably, the polarization of ether with Fe^{III}(OH)-complex (by forming intermediate **B**) may generate an incipient allyl-type carbocation, which can result in a nucleophilic attack reaction in the presence of nucleophile **2a** to provide intermediates **C** and **D**.[12i,26e] Subsequently, deprotonation of **D** can generate intermediate **E**, followed by the Dimroth rearrangment to afford the final product **3aa**.[27] Meanwhile, upon reaction of proton, **C** can release **4** and Fe^{III}(OH)-complex to accomplish the catalytic cylcle of alcoholic C–O bond functionalization.

CONCLUSION

In summary, we have reported an iron-catalyzed sequentional C–H/C–O bond functionalization of methanol with cosolvent water, generating the methylene linker to bridge pharmaceutically important 2-arylimidazo[1,2-*a*]pyridine and 2-aminopyridine fragments through a consecutive C–C and C–N bond-forming process. The power of this protocol has been fully exemplified by the substantial structural diversity of the resulting pharmaceutically important methylene heterodimers, as well as by the green reaction medium, mild reaction conditions, operational simplicity, and the numerous opportunities for late-stage functionalization of the resulting methylene heterodimers. Perhaps most important, this strategy employs methanol as the methylene synthon, thus representing an uncommon utilization of "methanol chemistry". Further exploration on tethering other heterocycles is currently underway in our laboratory. We expect this protocol to be widely adopted by the synthetic and drug discovery community as a sustainable and complementary platform for the construction of methylene heterodimers.

EXPERIMENTAL SECTION

General Methods. All reactions were carried out under an argon atmosphere unless otherwise stated. All work-up and purification procedures were carried out with reagent-grade solvents. Flash column chromatography was performed on silica gel (300-400 mesh) with an appropriate solvent system (see details below). Melting point was recorded on SGW X-4B. ^{1}H and ^{13}C-NMR spectra were recorded on Varian 600 MHz and Bruker 400 MHz spectrometers in $CDCl_3$ or d_6-DMSO solutions and chemical shifts (δ, ppm) were determined with internal solvent signal as reference ($CDCl_3$: 7.26 for ^{1}H-NMR and 77.0 for ^{13}C-NMR; d_6-DMSO: 2.50 for ^{1}H -NMR and 39.5 for ^{13}C-NMR). NMR data are reported as following: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, td = doublet of triplets, q = quartet, m = multiplet, br = broad signal), coupling constant (Hz), and integration. High-resolution mass spectra were recorded on Thermo Scientific LTQ Orbitrap Discovery (Bremen, Germany) (mass analyzer type: linear ion trap). Materials were purchased from Alfa-Aesar, Acros, Aldrich, Aladdin, Energy-Chemical, Bide Pharmatech. Ltd., and Ouhe-Chemicals. Unless otherwise noted, commercial reagents were used without further purifications. All compounds and their ^{1}H and ^{13}C NMR spectra are provided in *Supporting Information*.

Preparation of imidazo[1,2-*a*]pyridine derivatives 1. Method A[28]: To an ethanol solution containing 2-bromoacetophenones (5.024 mmol, 1.0 equiv) and 2-aminopyridines (6.280 mmol, 1.25 equiv) was added $NaHCO_3$ (7.837 mmol, 1.56 equiv). After The reaction mixture was stirred at room temperature for 6 hours. After completion of the reaction, the resulting mixture was diluted with water (15 ml) and extract with ether (3 × 20 ml). The combined organic layer was washed with brine (25 ml), dried with anhydrous $MgSO_4$, concentrated under vacuum to give the crude product, which was purified by silica gel

column with petroleum ether/ethyl acetate as the eluent to give the analytical pure 2-arylimidazo[1,2-*a*]pyridine **1a-m** and **1p-s** in 45-90% yields. The ^{1}H and ^{13}C NMR data of **1a-m** and **1p-s** were in accordance with literature.[25]

Method B[29]: An clean oven-dried 10 mL round bottom vessel was charged with acetophenones (1.0 mmol), 2-amino pyridines (1.2 mmol), CuI (0.2 mmol) and 1,4-dioxane (3.0 mL). Then the vessel was sealed, placed into an oil bath and heated at 100 °C for 4 h. The resulting mixture was cooled to room temperature, filtered through a short silica gel pad and washed with ethyl acetate. The above solution was evaporated under vacuum, and the residue was purified by silica gel column with petroleum ether/ethyl acetate as the eluent to give the analytically pure product 2-phenylimidazo[1,2-*a*]pyridine **1n-o** and **1t-u** in 40-75% yield. The ^{1}H and ^{13}C NMR data of **1n-o** and **1t-u** were in accordance with literature.[25]

Methyl 2-phenylimidazo[1,2-a]pyridine-6-carboxylate ***(1j)***. Prepared with **Method A**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.89 (s, 1 H), 7.96 (d, *J* = 7.08 Hz, 2 H), 7.91 (s, 1 H), 7.72 (dd, *J* = 9.42, 1.74 Hz, 1 H), 7.62 (d, *J* = 9.48 Hz, 1 H), 7.45 (t, *J* = 7.59 Hz, 2 H), 7.36 (t, *J* = 7.35 Hz, 1 H), 3.95 (s, 3 H). ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 165.3, 147.6, 146.1, 133.0, 129.7, 128.8, 128.5, 126.2, 124.4, 116.7, 116.5, 108.9, 52.4.

Typical procedures for the synthesis of methylene-tethered 2-arylimidazo[1,2-*a*]pyridine and 2-aminopyridine. An oven-dried round bottom reaction vessel was charged with imidazo[1,2-*a*]pyridine **1** (0.2 mmol), 2-aminopyridine **2** (0.6 mmol), 2,2'-bpy (7.8 mg, 0.05 mmol, 25 mol %), and $FeCp_2$ (9.3 mg, 0. 05 mmol, 25.0 mol %). After the vessel was filled with argon, TBHP (70 wt. % in H_2O, 69.0 *u*L, 0.5 mmol), MeOH/H_2O (2.0 mL, 7:3 v/v ratio) was added by syringe under argon, and the reaction mixture was stirred at room temperature for 5 min. Then the vessel was sealed, placed into an oil bath and heated to 90 °C. After 30 h, the resulting mixture was cooled to room temperature, filtered through a short silica gel pad and washed with ethyl acetate. The above solution was concentraed under vacuum, and the residue was purified by silica gel column chromatography to give the analytically pure product.

N-((2-Phenylimidazo[1,2-a]pyridin-3-yl)methyl)pyridin-2-amine ***(3aa)***.[21b] White solid, m.p. 173.7-174.4 °C; Isolated yield 82% (49.3 mg). Eluent: petroleum ether/ethyl acetate/chloroform/methanol 10:5:2:2. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.16 (d, *J* = 6.12 Hz, 2 H), 7.77 (d, *J* = 6.60 Hz, 2 H), 7.62 (d, *J* = 9.00 Hz, 1 H), 7.42 (t, *J* = 7.65 Hz, 3 H), 7.35 (t, *J* = 7.41 Hz, 1 H), 7.20 (t, *J* = 7.89 Hz, 1 H), 6.78 (t, *J* = 6.81 Hz, 1 H), 6.65 (td, *J* = 6.15, 2.04 Hz, 1 H), 6.46 (d, *J* = 8.34 Hz, 1 H), 5.01 (d, *J* = 4.98 Hz, 2 H), 4.71 (s, 1 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.0, 147.8, 145.0, 144.5, 137.4, 133.9, 128.6, 128.4, 127.9, 124.8, 124.3, 117.4, 117.0, 113.5, 112.4, 108.4, 35.5. HR-ESI-MS $[M+H]^+$ calcd for $C_{19}H_{17}N_4$ 301.1448; found 301.1446.

N-((2-Phenylimidazo[1,2-a]pyridin-3-yl)methyl-d$_2$)pyridin-2-amine ***(CD$_2$-3aa)***. White solid, m.p. 170.3-171.4 °C. Eluent: petroleum ether/ethyl acetate/chloroform/methanol 10:5:2:2; Isolated yield 53% (32.1 mg) ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.18 (t, *J* = 6.66 Hz, 2 H), 7.78 (d, *J* = 7.56 Hz, 2 H), 7.64 (d, *J* = 9.00 Hz, 1 H), 7.45-7.41 (m, 3 H), 7.36 (t, *J* = 7.44 Hz, 1 H), 7.21 (td, *J* = 7.89, 1.26 Hz, 1 H), 6.80 (t, *J* = 6.75 Hz, 1 H), 6.66 (td, *J* = 6.15, 2.10 Hz, 1 H), 6.45 (d, *J* = 8.34 Hz, 1 H), 4.65 (s, 1 H). HR-ESI-MS $[M+H]^+$ calcd for $C_{19}H_{15}N_4D_2$ 303.1573; found 303.1569.

4-Methyl-N-((2-phenylimidazo[1,2-a]pyridin-3-yl)methyl)pyridin-2-amine ***(3ab)***.[21b] Light brown solid, m.p. 165.1-165.8 °C; Isolated yield 72% (45.3 mg). Eluent: petroleum ether/ethyl acetate/chloroform/methanol 10:5:2:2. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.20 (d, *J* = 6.84 Hz, 1 H), 8.01 (d, *J* = 5.28 Hz, 1 H), 7.79 (d, *J* = 6.66 Hz, 2 H), 7.65 (d, *J* = 9.06 Hz, 1 H), 7.46 (t, *J* = 7.65 Hz, 2 H), 7.38 (t, *J* = 7.41 Hz, 1 H), 7.22 (t, *J* = 7.89 Hz, 1 H), 6.81 (t, *J* = 6.60 Hz, 1 H), 6.50 (d, *J* = 3.90 Hz, 1 H), 6.24 (s, 1 H), 5.01 (d, *J* = 5.04 Hz, 2 H), 4.75 (br, s, 1 H), 2.20 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.6, 149.7, 145.8, 145.1, 144.5, 134.0, 128.7, 128.5, 128.0, 125.0, 124.4, 117.3, 116.7, 115.1, 112.5, 108.6, 35.5, 21.2. HR-ESI-MS $[M+H]^+$ calcd for $C_{20}H_{19}N_4$ 315.1604; found 315.1596.

5-Methyl-N-((2-phenylimidazo[1,2-a]pyridin-3-yl)methyl)pyridin-2-amine ***(3ac)***. White solid, m.p. 190.4-191.2 °C; Isolated yield 62% (38.9 mg). Eluent: petroleum ether/ethyl acetate/chloroform/methanol 10:5:2:2. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.18 (d, *J* = 6.90 Hz, 1 H), 7.97 (d, *J* = 1.38 Hz, 1 H), 7.77 (dd, *J* = 8.31, 1.50 Hz, 2 H), 7.63 (d, *J* = 9.06 Hz, 1 H), 7.43 (t, *J* = 7.68 Hz, 2 H), 7.35 (td, *J* = 7.41 Hz, 1 H), 7.26 (dd, *J* = 8.19, 2.40 Hz, 1 H), 7.21-7.19 (m, 1 H), 6.78 (t, *J* = 6.81, 1.20 Hz, 1 H), 6.39 (d, *J* = 8.40 Hz, 1 H), 4.98 (d, *J* = 5.22 Hz, 2 H), 4.65 (t, *J* = 5.25 Hz, 1 H), 2.21 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 156.2, 146.9, 145.1, 144.5, 138.9, 134.0, 128.7, 128.5, 128.0, 124.9, 124.5, 122.5, 117.4, 117.2, 112.5, 108.1, 35.8, 17.5. HR-ESI-MS $[M+H]^+$ calcd for $C_{20}H_{19}N_4$ 315.1604; found 315.1600.

4-Ethyl-N-((2-phenylimidazo[1,2-a]pyridin-3-yl)methyl)pyridin-2-amine ***(3ad)***. Brown solid, m.p. 156.9-157.8 °C; Isolated yield 75% (49.4 mg). Eluent: petroleum ether/ethyl acetate/chloroform/methanol 10:5:2:2. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.17 (d, *J* = 6.90 Hz, 1 H), 7.99 (d, *J* = 5.40 Hz, 1 H), 7.75 (d, *J* = 7.50 Hz, 2 H), 7.61 (d, *J* = 9.00 Hz, 1 H), 7.41 (t, *J* = 7.56 Hz, 2 H), 7.34 (t, *J* = 7.41 Hz, 1 H), 7.18 (t, *J* = 7.83 Hz, 1 H), 6.76 (t, *J* = 6.72 Hz, 1 H), 6.50 (d, *J* = 5.22 Hz, 1 H), 6.25 (s, 1 H),5.06 (br, s, 1 H), 4.97 (d, *J* = 4.68 Hz, 2 H), 2.47 (q, *J* = 7.64 Hz, 2 H), 1.15 (t, *J* = 7.62 Hz, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.1, 155.0, 145.95, 145.0, 144.4, 133.9, 128.6, 128.4, 127.9, 124.9, 124.4, 117.3, 116.9, 114.0, 112.4, 107.2, 35.6, 28.3, 14.1. HR-ESI-MS $[M+H]^+$ calcd for $C_{21}H_{21}N_4$ 329.1761; found 329.1760.

4-Methoxy-N-((2-phenylimidazo[1,2-a]pyridin-3-yl)methyl)pyridin-2-amine ***(3ae)***. White solid, m.p. 159.1-159.6 °C; Isolated yield 71% (46.9 mg). Eluent: petroleum ether/ethyl acetate/chloroform/methanol 10:5:2:2. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 (d, *J* = 6.84 Hz, 1 H), 7.95 (d, *J* = 6.06 Hz, 1 H), 7.79 (dd, *J* = 8.13, 1.50 Hz, 2 H), 7.64 (d, *J* = 9.00 Hz, 1 H), 7.45 (t, *J* = 7.68 Hz, 2 H), 7.37 (t, *J* = 7.41 Hz, 1 H), 7.23-7.20 (m, 1 H), 6.80 (td, *J* = 6.81, 1.26 Hz, 1 H), 6.27 (dd, *J* = 6.00, 2.22 Hz, 1 H), 5.88 (d, *J* = 2.16 Hz, 1 H), 5.00 (d, *J* = 4.92 Hz, 2 H), 4.87 (br, s, 1 H), 3.70 (s, 3 H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.3, 159.7, 148.4, 145.1, 144.5, 134.0, 128.7, 128.5, 128.0, 124.9, 124.4, 117.4, 116.8, 112.4, 102.7, 91.3, 54.9, 35.8. HR-ESI-MS $[M+H]^+$ calcd for $C_{20}H_{19}N_4O$ 331.1553; found 331.1552.

5-Fluoro-N-((2-phenylimidazo[1,2-a]pyridin-3-yl)methyl)pyridin-2-amine ***(3af)***. White solid, m.p. 163.2-163.9 °C; Isolated yield 60% (38.3 mg). Eluent: petroleum ether/ethyl acetate/chloroform/methanol 10:5:2:2. ^{1}H NMR (600 MHz,

$CDCl_3$) δ 8.16 (d, *J* = 6.90 Hz, 1 H), 8.04 (d, *J* = 3.00 Hz, 1 H), 7.75 (dd, *J* = 8.25, 1.50 Hz, 2 H), 7.64 (d, *J* = 9.00 Hz, 1 H), 7.42 (t, *J* = 7.65 Hz, 2 H), 7.35 (t, *J* = 7.35 Hz, 1 H), 7.24-7.20 (m, 2 H), 6.81 (td, *J* = 6.81, 1.14 Hz, 1 H), 6.46 (dd, *J* = 9.00, 3.48 Hz, 1 H), 4.98 (d, *J* = 5.10 Hz, 2 H), 4.67 (br, s, 1 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 154.8, 153.8 (d, J_{C-F} = 241.1 Hz), 144.8, 144.1, 134.3 (d, J_{C-F} = 24.4 Hz), 133.6, 128.6, 128.3, 125.4 (d, J_{C-F} = 20.6 Hz), 125.1, 124.3, 116.20, 117.2, 117.0, 112.5, 108.9 (d, J_{C-F} = 4.0 Hz), 35.9. HR-ESI-MS $[M+H]^+$ calcd for $C_{19}H_{16}N_4F$ 319.1354; found 319.1351.

4-Chloro-N-((2-phenylimidazo[1,2-a]pyridin-3-yl)methyl)pyridin-2-amine ***(3ag)***. White solid, m.p. 210.5-211.5 °C; Isolated yield 63% (42.3 mg). Eluent: petroleum ether/ethyl acetate/chloroform/methanol 10:5:2:2. ^1H NMR (600 MHz, $CDCl_3$) δ 8.17 (d, *J* = 6.84 Hz, 1 H), 8.03 (d, *J* = 5.64 Hz, 1 H), 7.74 (d, *J* = 7.56 Hz, 2 H), 7.63 (d, *J* = 9.00 Hz, 1 H), 7.40 (t, *J* = 7.56 Hz, 2 H), 7.33 (t, *J* = 7.47 Hz, 1 H), 7.23 (t, *J* = 8.04 Hz, 1 H), 6.83 (t, *J* = 6.78 Hz, 1 H), 6.65 (d, *J* = 5.52 Hz, 1 H), 6.56 (s, 1 H), 5.25 (br, s, 1 H), 4.99 (d, *J* = 4.80 Hz, 2 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 158.2, 149.7, 144.7, 143.9, 139.6, 133.3, 128.7, 128.3, 128.1, 125.4, 124.6, 117.0, 116.9, 112.8, 112.6, 106.5, 35.4. HR-ESI-MS $[M+H]^+$ calcd for $C_{19}H_{16}N_4Cl$ 335.1058; found 335.1054.

5-Chloro-N-((2-phenylimidazo[1,2-a]pyridin-3-yl)methyl)pyridin-2-amine ***(3ah)***.[21b] Light brown solid, m.p. 211.2-213.1 °C; Isolated yield 70% (46.7 mg). Eluent: petroleum ether/ethyl acetate/chloroform/methanol 10:5:2:2. ^1H NMR (600 MHz, $CDCl_3$) δ 8.17 (d, *J* = 6.90 Hz, 1 H), 8.13 (d, *J* = 2.52 Hz, 1 H), 7.75 (d, *J* = 6.90 Hz, 2 H), 7.64 (d, *J* = 9.00 Hz, 1 H), 7.42 (t, *J* = 7.71 Hz, 2 H), 7.39 (dd, *J* = 8.76, 2.58 Hz, 1 H), 7.34 (t, *J* = 7.38 Hz, 1 H), 7.23 (td, *J* = 7.91, 1.26 Hz, 1 H), 6.83 (td, *J* = 6.83, 1.14 Hz, 1 H), 6.48 (d, *J* = 8.76 Hz, 1 H), 5.00 (d, *J* = 4.86 Hz, 2 H), 4.88 (br, s, 1 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 156.5, 146.2, 144.5, 143.5, 137.3, 133.0, 128.7, 128.4, 128.2, 125.6, 124.6, 120.5, 117.2, 117.0, 113.0, 109.6, 35.4. HR-ESI-MS $[M+H]^+$ calcd for $C_{19}H_{16}N_4Cl$ 335.1058; found 335.1056.

6-Chloro-N-((2-phenylimidazo[1,2-a]pyridin-3-yl)methyl)pyridin-2-amine ***(3ai)***. White solid, m.p. 174.2-175.1 °C; Isolated yield 60% (40.0 mg). Eluent: petroleum ether/ethyl acetate/chloroform/methanol 10:5:2:2. ^1H NMR (600 MHz, $CDCl_3$) δ 8.17 (d, *J* = 6.78 Hz, 1 H), 7.70 (d, *J* = 7.26 Hz, 2 H), 7.58 (d, *J* = 9.06 Hz, 1 H), 7.39-7.31 (m, 4 H), 7.19 (t, *J* = 7.86 Hz, 1 H), 6.79 (t, *J* = 6.78 Hz, 1 H), 6.65 (d, *J* = 7.56 Hz, 1 H), 6.41 (d, *J* = 8.10 Hz, 1 H), 5.11 (s, 1 H), 4.96 (d, *J* = 4.98 Hz, 2 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 158.2, 149.6, 144.6, 143.9, 139.5, 133.2, 128.6, 128.3, 128.0, 125.4, 124.5, 117.0, 116.8, 112.7, 112.5, 106.4, 35.3. HR-ESI-MS $[M+H]^+$ calcd for $C_{19}H_{16}N_4Cl$ 335.1058; found 335.1050.

6-Bromo-N-((2-phenylimidazo[1,2-a]pyridin-3-yl)methyl)pyridin-2-amine ***(3aj)***. White solid, m.p. 203.3-204.1 °C; Isolated yield 53% (40.2 mg). Eluent: petroleum ether/ethyl acetate/chloroform/methanol 10:5:2:2. ^1H NMR (600 MHz, $CDCl_3$) δ 8.23 (d, *J* = 6.84 Hz, 1 H), 7.71 (dd, *J* = 8.28, 1.62 Hz, 2 H), 7.61 (d, *J* = 9.06 Hz, 1 H), 7.39 (t, *J* = 7.65 Hz, 2 H), 7.32 (t, *J* = 7.41 Hz, 1 H), 7.25 (t, *J* = 7.80 Hz, 1 H), 7.22-7.19 (m, 1 H), 6.83-6.80 (m, 2 H), 6.45 (d, *J* = 8.10 Hz, 1 H), 5.10 (br, s, 1 H), 4.97 (d, *J* = 5.04 Hz, 2 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 158.3, 145.0, 144.5, 140.3, 139.4, 133.8, 128.7, 128.2, 127.9, 125.0, 124.4, 117.2, 116.6, 116.4, 112.5, 106.7, 35.5. HR-ESI-MS $[M+H]^+$ calcd for $C_{19}H_{16}N_4Br$ 379.0553; found 379.0553.

2-((2-Phenylimidazo[1,2-a]pyridin-3-yl)methylamino) isonicotinonitrile ***(3ak)***. White solid, m.p. 184.4-185.4 °C; Isolated yield 30% (19.5 mg). Eluent: petroleum ether/ethyl acetate/chloroform/methanol 10:5:2:2. ^1H NMR (600 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 5.22, 0.78 Hz, 1 H), 8.07 (d, *J* = 6.84 Hz, 1 H), 7.66 (d, *J* = 6.84 Hz, 2 H), 7.58 (d, *J* = 9.00 Hz, 1 H), 7.36 (t, *J* = 7.44 Hz, 2 H), 7.31 (t, *J* = 7.35 Hz, 1 H), 7.21 (t, *J* = 7.32 Hz, 1 H), 6.82-6.77 (m, 3 H), 5.60 (br, s, 1 H), 4.98 (d, *J* = 4.80 Hz, 2 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 158.2, 1447, 143.9, 140.3, 139.4, 133.2, 128.7, 128.3, 128.1, 125.4, 124.6, 117.0, 116.8, 116.5, 112.8, 106.7, 35.4. HR-ESI-MS $[M+H]^+$ calcd for $C_{20}H_{16}N_5$ 326.1400; found 326.1397.

Methyl 2-((2-phenylimidazo[1,2-a]pyridin-3-yl)methylamino)isonicotinate ***(3al)***. Light yellow solid, m.p. 163.8-164.2 °C; Isolated yield 42% (30.2 mg). Eluent: petroleum ether/ethyl acetate/chloroform/methanol 10:5:2:2. ^1H NMR (600 MHz, $CDCl_3$) δ 8.24 (d, *J* = 5.22 Hz, 1 H), 8.11 (d, *J* = 6.90 Hz, 1 H), 7.75 (d, *J* = 7.56 Hz, 2 H), 7.59 (d, *J* = 9.06 Hz, 1 H), 7.40 (t, *J* = 7.59 Hz, 2 H), 7.33 (t, *J* = 7.41 Hz, 1 H), 7.18 (t, *J* = 7.92 Hz, 1 H), 7.14 (dd, *J* = 5.28, 1.32 Hz, 1 H), 7.04 (s, 1 H), 6.77 (t, *J* = 6.69 Hz, 1 H), 5.17 (br, s, 1 H), 5.02 (d, *J* = 4.86 Hz, 2 H), 3.87 (s, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 166.0, 158.6, 148.8, 145.0, 144.5, 138.7, 133.7, 128.6, 128.3, 128.0, 125.0, 124.2, 117.3, 116.7, 112.5, 112.2, 108.4, 52.5, 35.6 . HR-ESI-MS $[M+H]^+$ calcd for $C_{21}H_{19}N_4O_2$ 359.1503; found 359.1498.

3-Methyl-N-((2-phenylimidazo[1,2-a]pyridin-3-yl)methyl)pyridin-2-amine ***(3am)***. Brown solid, m.p. 150.2-152.1 °C; Isolated yield 52% (32.6 mg). Eluent: petroleum ether/ethyl acetate/chloroform/methanol 10:5:2:2. ^1H NMR (600 MHz, $CDCl_3$) δ 8.26 (d, *J* = 6.78 Hz, 1 H), 8.12 (dd, *J* = 5.13, 1.80 Hz, 1 H), 7.83 (d, *J* = 6.90 Hz, 2 H), 7.71 (d, *J* = 9.06 Hz, 1 H), 7.46 (t, *J* = 7.68 Hz ,2 H), 7.38 (t, *J* = 7.41 Hz, 1 H), 7.28-7.24 (m, 2 H), 6.84 (td, *J* = 6.81, 1.20 Hz, 1 H), 6.64 (dd, *J* = 6.15, 1.20 Hz, 1 H), 5.20 (d, *J* = 5.04 Hz, 2 H), 4.28 (s, 1 H), 2.03 (s, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 155.2, 144.1, 143.5, 142.4, 136.3, 132.2, 127.8, 127.5, 127.2, 124.6, 123.7, 116.7, 116.3, 116.0, 112.6, 111.9, 34.3, 16.0. HR-ESI-MS $[M+H]^+$ calcd for $C_{20}H_{19}N_4$ 315.1604; found 315.1596.

4,6-Dimethyl-N-((2-phenylimidazo[1,2-a]pyridin-3-yl)methyl)pyridin-2-amine ***(3an)***. White solid, m.p. 163.8-164.1 °C; Isolated yield 64% (42.1 mg). Eluent: petroleum ether/ethyl acetate/chloroform/methanol 10:5:2:2. ^1H NMR (600 MHz, $CDCl_3$) δ 8.25 (d, *J* = 6.90 Hz, 1 H), 7.79 (d, *J* = 7.08 Hz, 2 H), 7.64 (d, *J* = 9.00 Hz , 1 H), 7.46 (t, *J* = 7.59 Hz, 2 H), 7.38 (t, *J* = 7.44 Hz, 1 H), 7.22 (t, *J* = 7.89 Hz, 1 H), 6.81 (t, *J* = 6.78 Hz, 1 H), 6.37 (s, 1 H), 6.04 (s, 1 H), 4.97 (d, *J* = 4.86 Hz, 2 H), 4.92 (s, 1 H), 2.38 (s, 3 H), 2.15 (s, 3 H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 158.0, 156.6, 148.9, 145.1, 144.6, 134.2, 128.7, 128.5, 127.9, 124.7, 124.5, 117.4, 117.3, 114.5, 112.2, 104.8, 35.9, 24.2, 21.0. HR-ESI-MS $[M+H]^+$ calcd for $C_{21}H_{21}N_4$ 329.1761; found 329.1758.

5-Fluoro-4-methyl-N-((2-phenylimidazo[1,2-a]pyridin-3-yl)methyl)pyridin-2-amine ***(3ao)***. Light yellow solid, m.p. 210.6-211.5 °C; Isolated yield 53% (35.2 mg). Eluent: petroleum ether/ethyl acetate/chloroform/methanol 10:5:2:2. ^1H NMR (600 MHz, $CDCl_3$) δ 8.13 (d, *J* = 6.66 Hz, 1 H), 7.91 (d, *J* = 1.50 Hz, 1 H), 7.74 (d, *J* = 7.02 Hz, 2 H), 7.61 (d, *J* = 9.06 Hz, 1 H), 7.42 (t, *J*

= 7.62 Hz, 2 H), 7.35 (t, *J* = 7.41 Hz, 1 H), 7.19 (td, *J* = 7.88, 1.26 Hz, 1 H), 6.78 (td, *J* = 6.75, 1.20 Hz, 1 H), 6.26 (d, *J* = 5.04 Hz, 1 H), 4.93 (d, *J* = 5.04 Hz, 2 H), 4.57 (s, 1 H), 2.18 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 154.7, 153.5 (d, J_{C-F} = 239.0 Hz), 145.1, 144.5, 136.3 (d, J_{C-F} = 17.1 Hz), 134.0, 133.7 (d, J_{C-F} = 25.9 Hz), 128.7, 128.4, 128.0, 124.9, 124.4, 117.4, 117.1, 112.4, 109.7 (d, J_{C-F} = 1.7 Hz), 36.1, 14.6 (d, J_{C-F} = 3.2 Hz). HR-ESI-MS $[M+H]^+$ calcd for $C_{20}H_{18}N_4F$ 333.1510; found 333.1507.

N-((2-Phenylimidazo[1,2-a]pyridin-3-yl)methyl) quinolin-2-amine ***(3ap)***. White solid, m.p. 186.5-187.3 °C; Isolated yield 35% (24.5 mg). Eluent: petroleum ether/ethyl acetate/chloroform/methanol 10:5:2:2. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.29 (d, *J* = 6.84 Hz, 1 H), 7.82 (d, *J* = 8.82 Hz, 1 H), 7.78 (t, *J* = 8.76 Hz, 3 H), 7.63 (d, *J* = 7.92 Hz, 1 H), 7.60-7.57 (m, 2 H), 7.40 (t, *J* = 7.56 Hz, 2 H), 7.33 (t, *J* = 7.35 Hz, 1 H), 7.27 (t, *J* = 7.29 Hz, 1 H), 7.16 (t, *J* = 7.80 Hz, 1 H), 6.73 (t, *J* = 6.78 Hz, 1 H), 6.68 (d, *J* = 8.76 Hz, 1 H), 5.25 (d, *J* = 4.92 Hz, 2 H), 5.15 (s, 1 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 156.2, 147.5, 145.0, 144.4, 137.5, 133.9, 129.7, 128.6, 128.3, 127.9, 127.5, 126.2, 124.9, 124.7, 122.60, 122.5, 117.4, 117.2, 112.4, 112.3, 34.8. HR-ESI-MS $[M+H]^+$ calcd for $C_{23}H_{19}N_4$ 351.1604; found 351.1601.

N-((2-Phenylimidazo[1,2-a]pyridin-3-yl)methyl) pyrimidin-2-amine ***(3aq)***.[21b] Light yellow solid, m.p. 119.4-120.1 °C; Isolated yield 35% (21.1 mg). Eluent: petroleum ether/ethyl acetate/chloroform/methanol 10:5:2:2. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 (d, *J* = 6.90 Hz, 1 H), 8.15 (br, s, 1 H), 7.80 (d, *J* = 6.90 Hz, 2 H), 7.67 (d, *J* = 9.00 Hz, 1 H), 7.46 (t, *J* = 7.56 Hz, 2 H), 7.38 (t, *J* = 7.38 Hz, 1 H), 7.22 (td, *J* = 7.85, 1.26 Hz, 1 H), 6.80 (td, *J* = 6.83, 1.20 Hz, 1 H), 6.54 (t, *J* = 4.83 Hz, 1 H), 5.93 (s, 1 H), 5.08 (d, *J* = 5.10 Hz, 2 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 162.1, 158.1, 145.0, 144.5, 133.7, 128.8, 128.5, 128.2, 125.2, 124.4, 117.4, 116.9, 112.7, 111.4, 35.2. HR-ESI-MS $[M+H]^+$ calcd for $C_{18}H_{16}N_5$ 302.1400; found 302.1398.

N-((8-Methyl-2-phenylimidazo[1,2-a]pyridin-3-yl)methyl)pyridin-2-amine ***(3ba)***. Light brown solid, m.p. 159.1-159.8 °C; Isolated yield 51% (31.4 mg). Eluent: petroleum ether/ethyl acetate/chloroform/methanol 10:5:2:2. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15 (dd, *J* = 5.16, 1.74 Hz, 1 H), 8.03 (d, *J* = 6.78 Hz, 1 H), 7.76 (dd, *J* = 8.19, 1.50 Hz, 2 H), 7.44-7.40 (m, 3 H), 7.33 (t, *J* = 7.41 Hz, 1 H), 7.01 (d, *J* = 6.84 Hz, 1 H), 6.71 (t, *J* = 6.84 Hz, 1 H), 6.66-6.64 (m, 1 H), 6.47 (d, *J* = 8.34 Hz, 1 H), 4.97 (d, *J* = 4.92 Hz, 2 H), 4.84 (br, s, 1 H), 2.66 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 158.0, 147.6, 145.4, 143.9, 137.5, 134.0, 128.6, 128.5, 127.8, 127.3, 123.8, 122.1, 117.2, 113.4, 112.5, 108.4, 35.6, 17.1. HR-ESI-MS $[M+H]^+$ calcd for $C_{20}H_{19}N_4$ 315.1604; found 315.1601.

N-((7-Methyl-2-phenylimidazo[1,2-a]pyridin-3-yl)methyl)pyridin-2-amine ***(3ca)***. Light yellow solid, m.p. 167.6-168.7 °C; Isolated yield 41% (25.7 mg). Eluent: petroleum ether/ethyl acetate/chlorofomr/methanol 10:5:2:2. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.16 (d, *J* = 3.18 Hz, 1 H), 8.02 (d, *J* = 6.90 Hz, 1 H), 7.75 (d, *J* = 7.08 Hz, 2 H), 7.44-7.39 (m , 3 H), 7.37 (s, 1 H), 7.33 (t, *J* = 7.32 Hz, 1 H), 6.65 (td, *J* = 6.09, 2.04 Hz, 1 H), 6.60 (dd, *J* = 6.96, 1.68 Hz, 1 H), 6.48 (d, *J* = 8.28 Hz, 1 H), 4.97 (d, *J* = 4.92 Hz, 2 H), 4.76 (s, 1 H), 2.38 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 158.2, 147.9, 145.4, 144.0, 137.4, 135.9, 134.0, 128.6, 128.3 , 127.8, 123.5, 116.4, 115.7, 115.0, 113.5, 108.4, 35.5, 21.3. HR-ESI-MS $[M+H]^+$ calcd for $C_{20}H_{19}N_4$ 315.1604; found 315.1601.

N-((6-Methyl-2-phenylimidazo[1,2-a]pyridin-3-yl)methyl)pyridin-2-amine ***(3da)***.[21b] Yellow solid, m.p. 166.4-167.2 °C; Isolated yield 65% (40.9 mg). Eluent: petroleum ether/ethyl acetate/chloroform/methanol 10:5:2:2. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.17 (d, *J* = 3.24 Hz, 1 H), 7.95 (s, 1 H), 7.75 (d, *J* = 7.56 Hz, 2 H), 7.53 (d, *J* = 9.12 Hz, 1 H), 7.44 (td, *J* = 7.77, 1.92 Hz, 1 H), 7.41 (t, *J* = 7.59 Hz, 2 H), 7.33 (t, *J* = 7.44 Hz, 1 H), 7.05 (dd, *J* = 9.12, 1.68 Hz, 1 H), 6.66 (dd, *J* = 6.06, 2.10 Hz, 1 H), 6.51 (d, *J* = 8.34 Hz, 1 H), 4.95 (d, *J* = 4.74 Hz, 2 H), 4.86 (s, 1 H), 2.28 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 157.1, 146.5, 142.81, 142.78, 136.6, 132.6, 127.7, 127.4, 127.3, 126.9, 121.4, 121.1, 115.7, 115.4, 112.5, 107.5, 34.6, 17.3. HR-ESI-MS $[M+H]^+$ calcd for $C_{20}H_{19}N_4$ 315.1604; found 315.1595.

N-((7-Ethyl-2-phenylimidazo[1,2-a]pyridin-3-yl)methyl)pyridin-2-amine ***(3ea)***. Yellow solid, m.p. 166.7-167.6 °C; Isolated yield 46% (30.1 mg). Eluent: petroleum ether/ethyl acetate/chloroform/methanol 10:5:2:2. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.17 (d, *J* = 4.92, 1.86 Hz, 1 H), 8.06 (d, *J* = 7.02 Hz, 1 H),7.76 d, *J* = 7.08 Hz, 2 H), 7.44-7.40 (m, 4 H), 7.34 (t, *J* = 7.35 Hz, 1 H), 6.65 (td, *J* = 5.73, 2.40 Hz, 2 H), 6.45 (d, *J* = 8.28 Hz, 1 H), 4.98 (d, *J* = 4.98 Hz, 2 H), 4.67 (s, 1 H), 2.69 (q, *J* = 7.56 Hz, 2 H), 1.27 (t, *J* = 7.56 Hz, 3 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 158.3, 148.0, 145.6, 144.2, 142.0, 137.4, 134.2, 128.6, 128.3, 127.7, 123.7, 116.4, 114.3, 114.0, 113.5, 108.4, 35.6, 28.4, 14.4. HR-ESI-MS $[M+H]^+$ calcd for $C_{21}H_{21}N_4$ 329.1761; found 329.1758.

N-((6-Fluoro-2-phenylimidazo[1,2-a]pyridin-3-yl)methyl)pyridin-2-amine ***(3fa)***. Yellow solid, m.p. 169.5-170.4 °C; Isolated yield 42% (26.7 mg). Eluent: petroleum ether/ethyl acetate/chloroform/methanol 10:5:2:2. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.24 (dd, *J* = 4.38, 1.98 Hz, 1 H), 8.17 (dd, *J* = 5.46, 1.86 Hz, 1 H), 7.73 (dd, *J* = 8.31, 1.62 Hz, 2 H), 7.58 (dd, *J* = 9.78, 5.10 Hz, 1 H), 7.45-7.42 (m, 3 H), 7.36 (t, *J* = 7.38 Hz, 1 H), 7.13-7.10 (m, 1 H), 6.67 (td, *J* = 6.15, 1.20 Hz, 1 H), 6.48 (d, *J* = 8.28 Hz, 1 H), 5.00 (d, *J* = 5.16 Hz, 2 H), 4.81 (s, 1 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 157.8, 153.2 (d, J_{C-F} = 235.6 Hz), 147.3, 145.7 (d, J_{C-F} = 2.14 Hz), 142.6, 137.8, 133.6, 128.7, 128.3, 128.1, 118.7 (d, J_{C-F} = 2.16 Hz), 117.7 (d, J_{C-F} = 9.02 Hz), 116.9 (d, J_{C-F} = 25.46 Hz), 113.7, 111.5 (d, J_{C-F} = 41.0 Hz), 108.7, 35.4. HR-ESI-MS $[M+H]^+$ calcd for $C_{19}H_{16}N_4F$ 319.1354; found 319.1347.

N-((8-Chloro-2-phenylimidazo[1,2-a]pyridin-3-yl)methyl)pyridin-2-amine ***(3ga)***. White solid, m.p. 218.5-219.5 °C; Isolated yield 41% (27.3 mg). Eluent: petroleum ether/ethyl acetate/chloroform/methanol 10:5:2:2. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.14 (d, *J* = 6.84 Hz, 1 H), 8.12 (d, *J* = 4.26 Hz, 1 H), 7.72 (d, *J* = 7.08 Hz, 2 H),7.45 (td, *J* = 7.82, 1.92 Hz, 1 H), 7.38 (t, *J* = 7.44 Hz, 2 H), 7.33 (t, *J* = 7.29 Hz, 1 H), 7.25 (d, *J* = 7.80 Hz, 1 H), 6.70 (t, *J* = 7.08 Hz, 1 H), 6.66 (t, *J* = 6.12 Hz, 1 H), 6.54 (d, *J* = 8.40 Hz, 1 H), 5.37 (s, 1 H), 5.00 (d, *J* = 5.04 Hz, 2 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 157.8, 147.2, 145.4, 143.3, 137.9, 133.4, 128.8, 128.4, 128.3, 126.4, 122.7, 120.7, 117.9, 117.6, 113.8, 108.8, 35.5. HR-ESI-MS $[M+H]^+$ calcd for $C_{19}H_{16}N_4Cl$ 335.1058; found 335.1055.

N-((7-Chloro-2-phenylimidazo[1,2-a]pyridin-3-yl)methyl)pyridin-2-amine ***(3ha)***. Light yellow solid, m.p. 163.7-164.3 °C; Isolated yield 63% (42.0 mg). Eluent: petroleum ether/ethyl acetate/chloroform/methanol 10:5:2:2. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15 (d, *J* = 7.14 Hz, 2 H), 7.70 (d, *J* = 6.96 Hz, 2 H),7.56 (s, 1 H), 7.45-7.40 (m, 3 H), 7.35 (t, *J* = 7.41 Hz, 1 H), 6.76 (dd, *J*

= 7.29, 2.16 Hz, 1 H), 6.66 (td, *J* = 6.17, 0.84 Hz, 1 H), 6.49 (d, *J* = 8.34 Hz, 1 H), 5.04 (s, 1 H), 4.99 (d, *J* = 4.74 Hz, 2 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 157.7, 147.1, 145.1, 144.7, 137.9, 133.4, 131.6, 128.7, 128.3, 128.2, 125.0, 117.4, 116.1, 114.0, 113.6, 108.7, 35.2. HR-ESI-MS $[M+H]^+$ calcd for $C_{19}H_{16}N_4Cl$ 335.1058; found 335.1050.

N-((6-Chloro-2-phenylimidazo[1,2-a]pyridin-3-yl)methyl)pyridin-2-amine ***(3ia)***. Light yellow solid, m.p. 172.2-173.4 °C; Isolated yield 78% (52.3 mg). Eluent: petroleum ether/ethyl acetate/chloroform/methanol 10:5:2:2. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.37 (d, *J* = 1.98 Hz, 1 H), 8.16 (dd, *J* = 4.83, 2.04 Hz, 1 H), 7.73 (d, *J* = 7.02 Hz, 2 H), 7.55 (d, *J* = 9.42 Hz, 1 H), 7.46-7.42 (m, 3 H), 7.37 (t, *J* = 7.38 Hz, 1 H), 7.16 (dd, *J* = 9.54, 1.92 Hz, 1 H), 6.68 (td, *J* = 6.17, 1.07 Hz, 1 H), 6.49 (d, *J* = 8.34 Hz, 1 H), 5.02 (br, s, 1 H), 4.99 (d, *J* = 3.66 Hz, 2 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 157.7, 147.2, 145.3, 143.3, 137.9, 133.4, 128.7, 128.3, 128.2, 126.3, 122.7, 120.7, 117.8, 117.6, 113.7, 108.7, 35.4. HR-ESI-MS $[M+H]^+$ calcd for $C_{19}H_{16}N_4Cl$ 335.1058; found 335.1057.

Methyl 2-phenyl-3-((pyridin-2-ylamino)methyl)imidazo [1,2-a] pyridine-6-carboxylate ***(3ja)***. White solid, m.p. 153.6-154.7 °C; Isolated yield 45% (32.2 mg). Eluent: petroleum ether/ethyl acetate/chloroform/methanol 10:5:2:2. ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.16 (s, 1 H), 8.18 (d, *J* = 3.00 Hz, 1 H), 7.77 (d, *J* = 7.08 Hz, 2 H), 7.73 (dd, *J* = 9.48, 1.68 Hz, 1 H), 7.59 (d, *J* = 9.36 Hz, 1 H), 7.45-7.42 (m, 3 H), 7.37 (t, *J* = 7.29 Hz, 1 H), 6.66 (dd, *J* = 6.15, 2.04 Hz, 1 H), 6.47 (d, *J* = 8.28 Hz, 1 H), 5.06 (d, *J* = 5.16 Hz, 2 H), 4.90 (br, s, 1 H), 3.90 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 165.4, 157.8, 147.6, 146.1, 145.5, 137.7, 133.5, 129.2, 128.8, 128.5, 128.4, 124.6, 118.7, 116.6, 116.3, 113.7, 108.6, 52.4, 35.2. HR-ESI-MS $[M+H]^+$ calcd for $C_{21}H_{19}N_4O_2$ 359.1503; found 359.1497.

N-((2-p-Tolylimidazo[1,2-a]pyridin-3-yl)methyl)pyridin -2-amine ***(3ka)***.[21b] Light yellow solid, m.p. 169.1-169.7 °C; Isolated yield 61% (38.3 mg). Eluent: petroleum ether/ethyl acetate/chloroform/methanol 10:5:2:2. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 (d, *J* = 6.78 Hz, 1 H), 8.16 (d, *J* = 5.22, 1.80 Hz, 1 H), 7.66 (d, *J* = 7.74 Hz, 2 H), 7.64 (d, *J* = 9.30 Hz, 1 H), 7.43 (t, *J* = 8.73 Hz, 1 H), 7.23 (d, *J* = 8.10 Hz, 2 H), 7.20 (d, *J* = 8.28 Hz, 1 H), 6.79 (t, *J* = 6.78 Hz, 1 H), 6.66 (t, *J* = 6.12 Hz, 1 H), 6.49 (d, *J* = 8.34 Hz, 1 H), 5.01 (d, *J* = 4.80 Hz, 2 H), 4.90 (s, 1 H), 2.38 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 158.2, 148.0, 145.0, 144.6, 137.7, 137.4, 131.1, 129.4, 128.2, 124.7, 124.3, 117.3, 116.7, 113.5, 112.3, 108.4, 35.6, 21.3. HR-ESI-MS $[M+H]^+$ calcd for $C_{20}H_{19}N_4$ 315.1604; found 315.1601.

N-((2-(4-Isopropylphenyl)imidazo[1,2-a]pyridin-3-yl)methyl)pyridin-2-amine ***(3la)***. Light yellow solid, m.p. 148.9-149.5 °C; Isolated yield 57% (39.0 mg). Eluent: petroleum ether/ethyl acetate/chloroform/methanol 10:5:2:2. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.15 (d, *J* = 3.36 Hz, 1 H), 8.13 (d, *J* = 6.84 Hz, 1 H), 7.68 (d, *J* = 7.86 Hz, 2 H), 7.60 (d, *J* = 9.06 Hz, 1 H), 7.42 (td, *J* = 7.74, 1.92 Hz, 1 H), 7.27 (d, *J* = 7.86 Hz, 2 H), 7.17 (t, *J* = 7.89 Hz, 1 H), 6.74 (t, *J* = 6.72 Hz, 1 H), 6.64 (t, *J* = 6.09 Hz, 1 H), 6.47 (d, *J* = 8.22 Hz, 1 H), 4.99 (d, *J* = 4.98 Hz, 2 H), 4.76 (s, 1 H), 2.93 (heptet, *J* = 6.91 Hz, 1 H), 1.27 (d, *J* = 7.02 Hz, 6 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 158.1, 148.6, 147.9, 144.9, 144.5, 137.3, 131.3, 128.2, 126.7, 124.6, 124.3, 117.2, 116.7, 113.4, 112.2, 108.4, 35.5, 33.8, 23.9. HR-ESI-MS $[M+H]^+$ calcd for $C_{22}H_{23}N_4$ 343.1917; found 343.1914.

N-((2-(4-Methoxyphenyl)imidazo[1,2-a]pyridin-3-yl)methyl)pyridin-2-amine ***(3ma)***.[21b] Light yellow solid, m.p. 144.9-145.6 °C; Isolated yield 45% (29.7 mg). Eluent: petroleum ether/ethyl acetate/chloroform/methanol 10:5:2:2. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.17 (d, *J* = 3.24 Hz, 1 H), 8.14 (d, *J* = 6.84 Hz, 1 H), 7.70 (d, *J* = 8.70 Hz, 2 H),7.61 (d, *J* = 9.06 Hz, 1 H), 7.43 (td, *J* = 7.76, 1.86 Hz, 1 H), 7.20-7.17 (m, 1 H), 6.95 (d, *J* = 8.70 Hz, 2 H), 6.77 (td, *J* = 6.78, 1.14 Hz, 1 H), 6.65 (td, *J* = 6.17, 0.96 Hz, 1 H), 6.49 (d, *J* = 8.28 Hz, 1 H), 4.98 (d, *J* = 4.98 Hz, 2 H), 4.80 (s, 1 H), 3.83 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 159.5, 158.1, 147.8, 144.7, 144.0, 137.5, 129.5, 126.2, 124.9, 124.3, 117.0, 116.3, 114.1, 113.5, 112.4, 108.5, 55.2, 35.5. HR-ESI-MS $[M+H]^+$ calcd for $C_{20}H_{19}N_4O$ 331.1553; found 331.1551.

N-((2-(4-Chlorophenyl)imidazo[1,2-a]pyridin-3-yl)methyl)pyridin-2-amine ***(3na)***.[21b] White solid, m.p. 151.6-152.9 °C; Isolated yield 43% (28.7 mg). Eluent: petroleum ether/ethyl acetate/chloroform/methanol 10:5:2:2. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.17 (t, *J* = 2.70 Hz, 1 H), 8.14 (t, *J* = 6.81 Hz, 1 H), 7.68 (t, *J* = 7.14 Hz, 2 H), 7.60 (t, *J* = 7.56 Hz, 1 H), 7.45 (td, *J* = 7.71, 1.80 Hz, 1 H), 7.36 (t, *J* = 7.41 Hz, 2 H), 7.23-7.19 (m, 1 H), 6.81-6.77 (m, 1 H), 6.67 (t, *J* = 6.18 Hz, 1 H), 6.50 (dd, *J* = 8.37, 3.60 Hz, 1 H), 4.97 (d, *J* = 4.98 Hz, 2 H), 4.78 (s, 1 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 158.0, 147.9, 145.0, 143.2, 137.6, 133.9, 132.4, 129.5, 128.8, 125.2, 124.4, 117.3, 117.2, 113.7, 112.6, 108.5, 35.4. HR-ESI-MS $[M+H]^+$ calcd for $C_{19}H_{16}N_4Cl$ 335.1058; found 335.1057.

N-((2-(4-Bromophenyl)imidazo[1,2-a]pyridin-3-yl)methyl)pyridin-2-amine ***(3oa)***.[21b] White solid, m.p. 165.3-166.5 °C; Isolated yield 40% (30.2 mg). Eluent: petroleum ether/ethyl acetate/chloroform/methanol 10:5:2:2. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.12 (dd, *J* = 5.10, 1.80 Hz, 1 H), 8.11 (d, *J* = 6.90 Hz, 1 H), 7.59 (d, *J* = 8.22 Hz, 2 H), 7.57 (d, *J* = 9.12 Hz, 1 H), 7.48 (d, *J* = 8.52 Hz, 2 H), 7.44 (td, *J* = 7.71, 1.92 Hz, 1 H), 7.19 (td, *J* = 7.92, 1.26 Hz, 1 H), 6.77 (td, *J* = 6.80, 1.20 Hz, 1 H), 6.66 (td, *J* = 6.17, 0.90 Hz, 1 H), 6.52 (d, *J* = 8.28 Hz, 1 H), 4.95-4.94 (m, 3 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 157.9, 147.7, 144.9, 143.0, 137.6, 132.7, 131.7, 129.7, 125.2, 124.3, 122.2, 117.3, 117.2, 113.6, 112.6, 108.5, 35.4. HR-ESI-MS $[M+H]^+$ calcd for $C_{19}H_{16}N_4Br$ 379.0553; found 379.0548.

4-(3-((Pyridin-2-ylamino)methyl)imidazo[1,2-a]pyridin-2-yl)benzonitrile ***(3pa)***.[21b] Light yellow solid, m.p. 137.6-138.1 °C; Isolated yield 41% (26.7 mg). Eluent: petroleum ether/ethyl acetate/chloroform/methanol 10:5:2:2. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.17 (d, *J* = 5.16 Hz, 1 H), 8.14 (d, *J* = 6.66 Hz, 1 H), 7.84 (d, *J* = 7.68 Hz, 2 H), 7.61 (d, *J* = 7.98 Hz, 2 H), 7.58 (d, *J* = 9.06 Hz, 1 H), 7.45 (td, *J* = 7.73, 1.86 Hz, 1 H), 7.23 (t, *J* = 7.86 Hz, 1 H), 6.80 (t, *J* = 6.75 Hz, 1 H), 6.68 (t, *J* = 6.12 Hz, 1 H), 6.53 (d, *J* = 8.28 Hz, 1 H), 4.97 (d, *J* = 5.16 Hz, 2 H), 4.95 (s, br, 1 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 157.9, 148.0, 145.3, 142.2, 138.5, 137.6, 132.4, 128.5, 125.6, 124.5, 118.9, 118.4, 117.6, 113.9, 113.0, 111.2, 108.6, 35.4. HR-ESI-MS $[M+H]^+$ calcd for $C_{20}H_{16}N_5$ 326.1400; found 326.1394.

N-((2-o-Tolylimidazo[1,2-a]pyridin-3-yl)methyl)pyridin -2-amine ***(3qa)***. Light brown solid, m.p. 146.3-147.1 °C; Isolated yield 59% (37.0 mg). Eluent: petroleum ether/ethyl acetate/chloroform/methanol 10:5:2:2. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.23 (d, *J* = 6.78 Hz, 1 H), 8.06 (d, *J* = 5.40 Hz, 1 H),

7.60 (d, *J* = 8.88 Hz, 1 H), 7.35 (t, *J* = 7.80 Hz, 1 H), 7.31-7.26 (m, 3 H), 7.19 (t, *J* = 8.22 Hz, 2 H), 6.77 (t, *J* = 6.69 Hz, 1 H), 6.58 (t, *J* = 6.09 Hz, 1 H), 6.32 (d, *J* = 8.46 Hz, 1 H), 4.78 (d, *J* = 5.10 Hz, 2 H), 4.72 (s, 1 H), 2.32 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 158.1, 147.7, 145.0, 144.8, 137.62, 137.57, 133.3, 130.7, 130.4, 128.4, 125.5, 124.70, 124.66, 118.1, 117.4, 113.5, 112.3, 108.1, 35.3, 20.3. HR-ESI-MS $[M+H]^+$ calcd for $C_{20}H_{19}N_4$ 315.1604; found 315.1598.

N-((6-Methyl-2-p-tolylimidazo[1,2-a]pyridin-3-yl)methyl)pyridin-2-amine ***(3ra)***. White solid, m.p. 167.5-168.2 °C; Isolated yield 47% (30.8 mg). Eluent: petroleum ether/ethyl acetate/chloroform/methanol 10:5:2:2.^{1}H NMR (600 MHz, $CDCl_3$) δ 8.16 (d, *J* = 4.14 Hz, 1 H), 7.89 (s, 1 H), 7.62 (d, *J* = 7.74 Hz, 2 H), 7.50 (d, *J* = 9.12 Hz, 1 H), 7.43 (td, *J* = 7.77, 1.92 Hz, 1 H), 7.19 (d, *J* = 7.74 Hz, 2 H), 7.02 (dd, *J* = 9.06, 1.56 Hz, 1 H), 6.65 (td, *J* = 6.15, 2.04 Hz, 1 H), 6.52 (d, *J* = 8.34 Hz, 1 H), 4.91-4.88 (m, 3 H), 2.36 (s, 3 H), 2.26 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 158.0, 156.6, 148.9, 145.1, 144.6, 134.2, 128.7, 128.5, 127.9, 124.7, 124.5, 117.4, 117.3, 114.5, 112.2, 104.8, 35.9, 24.2, 21.0. HR-ESI-MS $[M+H]^+$ calcd for $C_{21}H_{21}N_4$ 329.1761; found 329.1757.

N-((2-(4-Methoxyphenyl)-7-methylimidazo[1,2-a]pyridin-3-yl)methyl)pyridin-2-amine ***(3sa)***. Light red solid, m.p. 146.9-147.6 °C; Isolated yield 55% (37.8 mg). Eluent: petroleum ether/ethyl acetate/chloroform/methanol 10:5:2:2. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.18 (d, *J* = 3.18 Hz, 1 H), 8.01 (d, *J* = 6.90 Hz, 1 H), 7.69 (d, *J* = 8.70 Hz, 2 H), 7.43 (td, *J* = 7.77, 1.92 Hz, 1 H), 7.36 (s, 1 H), 6.95 (d, *J* = 8.76 Hz, 2 H), 6.65 (td, *J* = 6.12, 2.10 Hz, 1 H), 6.60 (dd, *J* = 7.05, 1.68 Hz, 1 H), 6.48 (d, *J* = 8.34 Hz, 1 H), 4.94 (d, *J* = 4.86 Hz, 2 H), 4.71 (s, 1 H), 3.83 (s, 3 H), 2.38 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 159.4, 158.2, 147.9, 145.3, 143.9, 137.4, 135.8, 129.5, 126.6, 123.4, 115.7, 115.6, 114.9, 114.1, 113.5, 108.3, 55.3, 35.6, 21.3. HR-ESI-MS $[M+H]^+$ calcd for $C_{21}H_{21}N_4O$ 345.1710; found 345.1707.

N-((2-(4-Methoxyphenyl)-6-methylimidazo[1,2-a]pyridin-3-yl)methyl)pyridin-2-amine ***(3ta)***. Light yellow solid, m.p. 166.6-167.5 °C; Isolated yield 62% (42.6 mg). Eluent: petroleum ether/ethyl acetate/chloroform/methanol 10:5:2:2. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.16 (dd, *J* = 5.22, 1.02 Hz, 1 H), 7.84 (s, 1 H), 7.65 (d, *J* = 8.82 Hz, 2 H), 7.46 (d, *J* = 9.12 Hz, 1 H), 7.44 (td, *J* = 7.73, 1.98 Hz, 1 H), 7.00 (dd, *J* = 9.12, 1.68 Hz, 1 H), 6.90 (d, *J* = 8.76 Hz, 2 H), 6.65 (td, *J* = 6.11, 0.90 Hz, 1 H), 6.54 (d, *J* = 8.28 Hz, 1 H), 4.98 (br, s, 1 H), 4.88 (d, *J* = 4.68 Hz, 2 H), 3.81 (s, 3 H), 2.25 (s, 3 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 159.4, 158.2, 148.0, 145.4, 143.9, 137.4, 135.8, 129.5, 126.6, 123.5, 115.7, 115.6, 114.9, 114.1, 113.5, 108.4, 55.3, 35.7, 21.4. HR-ESI-MS $[M+H]^+$ calcd for $C_{21}H_{21}N_4O$ 345.1710; found 345.1706.

N-((2-(Thiophen-2-yl)imidazo[1,2-a]pyridin-3-yl)methyl)pyridin-2-amine ***(3ua)***.[21b] Light brown solid, m.p. 152.2-153.4 °C; Isolated yield 31% (18.9 mg). Eluent: petroleum ether/ethyl acetate/chloroform/methanol 10:5:2:2. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 (td, *J* = 5.04, 2.22 Hz, 2 H), 7.57 (d, *J* = 9.06 Hz, 1 H), 7.44-7.41 (m, 2 H), 7.33 (d, *J* = 4.98, 1.08 Hz, 1 H), 7.17 (t, *J* = 7.92 Hz, 1 H), 7.07 (t, *J* = 4.35 Hz, 1 H), 6.76 (t, *J* = 6.81 Hz, 1 H), 6.66 (td, *J* = 6.15, 1.98 Hz, 1 H), 6.51 (d, *J* = 8.28 Hz, 1 H), 5.09 (d, *J* = 5.04 Hz, 2 H), 4.85 (s, 1 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 157.7, 146.9, 145.0, 138.8, 138.0, 136.7, 127.8, 125.9, 125.25, 125.21, 124.4, 117.1, 116.4, 113.5, 112.6, 108.8, 35.2. HR-ESI-MS $[M+H]^+$ calcd for $C_{17}H_{15}N_4S$ 307.1012; found 307.1006.

N-((2-(Naphthalen-2-yl)imidazo[1,2-a]pyridin-3-yl)methyl)pyridin-2-amine ***(3va)***. Yellow solid, m.p. 182.6-183.7 °C; Isolated yield 45% (31.5 mg). Eluent: petroleum ether/ethyl acetate/chloroform/methanol 10:5:2:2. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.22 (s, 1 H), 8.17 (dd, *J* = 5.25, 2.46 Hz, 1 H), 8.15 (d, *J* = 6.84 Hz, 1 H), 7.90 (d, *J* = 8.52 Hz, 1 H), 7.85 (d, *J* = 8.58 Hz, 1 H), 7.81 (d, *J* = 5.82 Hz, 2 H), 7.63 (d, *J* = 9.00 Hz, 1 H), 7.46-7.45 (m, 2 H), 7.42 (t, *J* = 6.99 Hz, 1 H), 7.17 (t, *J* = 7.92 Hz, 1 H), 6.74 (t, *J* = 6.78 Hz, 1 H), 6.66 (t, *J* = 6.15 Hz, 1 H), 6.49 (d, *J* = 8.34 Hz, 1 H), 5.07 (d, *J* = 4.80 Hz, 2 H), 4.93 (s, 1 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 158.1, 147.9, 145.1, 144.3, 137.6, 133.5, 133.0, 131.3, 128.40, 128.36, 127.7, 127.5, 126.3, 126.2, 125.1, 124.4, 117.5, 117.4, 113.7, 112.6, 108.5, 35.6. HR-ESI-MS $[M+H]^+$ calcd for $C_{23}H_{19}N_4$ 351.1604; found 351.1601.

N-((2-(tert-Butyl)imidazo[1,2-a]pyridin-3-yl)methyl)pyridin-2-amine ***(3wa)***.[21b] White solid, m.p. 196.3-197.8 °C; Isolated yield 33% (18.6 mg). Eluent: petroleum ether/ethyl acetate/chloroform/methanol 10:5:2:2. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.18 (d, *J* = 5.22 Hz, 1 H), 8.03 (d, *J* = 6.78 Hz, 1 H), 7.60 (d, *J* = 9.00 Hz, 1 H), 7.43 (td, *J* = 7.77, 1.92 Hz, 1 H), 7.14 (t, *J* = 7.83 Hz, 1 H), 6.74 (t, *J* = 6.75 Hz, 1 H), 6.65 (t, *J* = 6.09 Hz, 1 H), 6.44 (d, *J* = 8.34 Hz, 1 H), 4.98 (d, *J* = 4.80 Hz, 2 H), 4.30 (s, 1 H), 1.50 (s, 9 H). $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 158.1, 153.7, 148.1, 143.6, 137.4, 124.0, 123.6, 117.2, 115.4, 113.5, 112.1, 108.3, 36.0, 33.4, 31.2. HR-ESI-MS $[M+H]^+$ calcd for $C_{17}H_{21}N_4$ 281.1761; found 281.1754.

Gram-scale synthesis of product 3aa. An oven-dried round bottom reaction vessel was charged with 2-phenylimidazo[1,2-*a*]pyridine **1a** (6 mmol), 2-aminopyridine **2a** (18 mmol), 2,2'-bpy (234.3 mg, 1.5 mmol, 25 mol %), and $FeCp_2$ (279.1 mg, 1.5 mmol, 25 mol %). After the vessel was filled with argon, TBHP (70 wt. % in H_2O, 2.07 mL, 15 mmol), MeOH/H_2O (60 mL, 7:3 v/v ratio) was added by syringe under argon, and the reaction mixture was stirred at room temperature for 5 min. Then the vessel was sealed, placed into an oil bath and heated to 90 °C. After 48 h, the resulting mixture was cooled to room temperature, filtered through a short silica gel pad and washed with ethyl acetate. The above solution was concentraed under vacuum, and the residue was purified by silica gel column chromatography to give the analytically pure product **3aa** (73%; 1.3156 g).

ASSOCIATED CONTENT

Supporting Information

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

X-ray crystallographic structure and data for **3aa** and Copies of ^{1}H and ^{13}C NMR spectra for the products (PDF)

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Notes

The authors declare no competing financial interest.

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