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Ligand-free Pd-catalysed decarboxylative arylation of Imidazo[1,2-*a*]pyridine-3-carboxylic acids with Aryl bromides†

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A facile ligand-free method for $Pd(OAc)_2$ catalysed decarboxylative arylation of imidazo[1,2-*a*]pyridine-3-carboxylic acids with hetero(aryl) bromides has been developed. This method is applicable to variety of (hetero)aryl bromides as coupling partner. Electron withdrawing and donating groups on imidazo[1,2-*a*]pyridine-3-carboxylic acids are well tolerated. It represent the first general protocol for ligand-free $Pd(OAc)_2$ catalysed decarboxylative arylation of imidazo[1,2-*a*]pyridine-3-carboxylic acids with (hetero)aryl halides. Few of the compounds synthesized using this protocol showed antibacterial activity against *Staphylococcus aureus*.

Introduction

The imidazopyridines have attracted much attention due to their unique biological properties in recent time.[1] Imidazo[1,2-*a*]pyridine, in particular, is an important scaffold and has shown various biological activities including antiviral, analgesic, anthelmintic, antifungal, antibacterial, antiprotozoal, anxiolytic etc.[2] A preclinical candidate Q203 has been developed for its antimycobacterial potential and has shown significant activity against the multidrug resistant strains of Mycobacterium tuberculosis.[3] The marketed drugs zolpidem, necopidem, olprinone, saripidem, alpidem contain imidazo[1,2-*a*]pyridine scaffold.[4] As a result modifications of imidazo[1,2-*a*]pyridine have been a focus of drug discovery research. Chemically diverse set of compounds can be obtained in one step within a reasonably short duration of time using palladium catalyzed cross-coupling reactions. The modification of imidazo[1,2-*a*]pyridines using Suzuki-type cross-coupling[5] and Stille cross-coupling[6] have been reported. However, these reactions showed limited substrate scope, and commercial availability of heteroaromatic boronic acids or stannanes limits its applicability. Further, the strategy for regioselective palladium-catalyzed arylation of imidazo[1,2-*a*]pyridine with aryl/heteroaryl bromide has been described and depends on triphenyl phosphine as ligand or $Pd(PPh_3)_4$.[2c, 7] Recently palladium catalyzed oxidative cross-coupling reaction to obtain 3-aryl imidazo[1,2-*a*]pyridine has been demonstrated albeit with generation of two regioisomers in few cases.[8] The direct arylation of imidazo[1,2-*a*]pyridines has also been reported.[9] These methods make use of aryl bromides or tosylate or mesylate. However, they have either limited substrate scope with respect to substituents on imidazo[1,2-*a*]pyridines core[9a, 9b, 9e] or limited to C-2 substituted[9c, 9d] imidazo[1,2-*a*]pyridines.

The decarboxylative arylation reaction makes use of carboxylic acids and aryl halides. In general, aromatic acids are stable solids, thereby easy to handle, making such strategy an important synthetic method.[10] Only two methods have been reported for the decarboxylative arylation of imidazo[1,2-*a*]pyridine-3-carboxylic acid till date. First method uses Pd(0)bis(carbene) complex, prepared from NHC ligand precursor and palladium precursor[11], and has limited substrate scope.[12] The second method uses aryl chloride with 5 mol% $Pd(OAc)_2$ and S-Phos as ligand in DMA/H_2O medium.[10] This method requires phosphine ligand and many a times it become difficult to separate such ligands from the product, jeopardizing its applicability. Hence, a ligand-free catalytic approach becomes the method of choice in such scenario. Ligandless catalytic process are the most economical and efficient ones and hence are widely used in industries.[13] Hence, there is a need for a ligandless facile synthesis of C-3 substituted imidazo[1,2-*a*]pyridines. Herein, we report a method for synthesis of C-3 aryl/heteroaryl imidazo[1,2-*a*]pyridines from aryl/heteroaryl bromides and imidazo[1,2-*a*]pyridine-3-carboxylic acids with palladium acetate in the absence of ligand. This facile protocol offers good tolerability towards various aryl/heteroaryl bromides and also applicable to various imidazo[1,2-*a*]pyridine-3-carboxylic acids. Till date there is no report on ligand-free palladium (II) catalyzed decarboxylative arylation of imidazo[1,2-*a*] pyridine-3-carboxylic acid with aryl halides.

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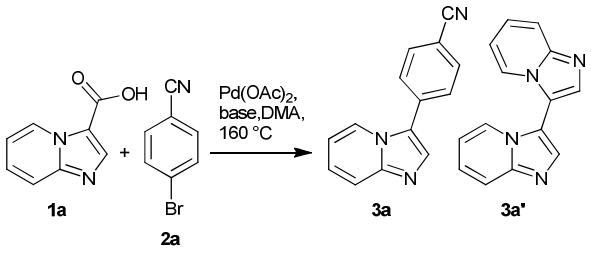
Results and Discussion

For initial optimization of reaction conditions, the decarboxylative arylation between imidazo[1,2-*a*]pyridine-3-carboxylic acid (**1a**) with 4-bromobenzonitrile (**2a**) in the presence of catalytic amount of $Pd(OAc)_2$ at 160 °C in DMA solvent was selected as a model reaction. The results are summarized in table 1.

Table 1. Optimization of $Pd(OAc)_2$ catalysed decarboxylative arylation[a,b]



1a 2a 3a 3a'

Entry	**1a**(equiv.)	Base (equiv.)	$Pd(OAc)_2$ (equiv.)	**3a**(%)[b]
1	1.2	Ag_2CO_3 (2)	0.10	42
2[c]	1.2	Ag_2CO_3 (1)	0.10	17
3	1.2	AgOAc (2)	0.10	50
4	1.2	KOAc (2)	0.10	62
5	1.2	$Cu(OAc)_2$ (2)	0.10	25
6	1.2	KOAc (2)	0.05	84
7	1.2	KOAc (2)	0.02	71
8[c]	1.2	KOAc (2)	0.01	67
9	1.2	KOAc (2)	0.02	71
10	1.3	KOAc (2)	0.02	80
11	1.4	KOAc (2)	0.02	85
12[d]	1.5	KOAc (2)	0.02	84
13[d]	1.6	KOAc (2)	0.02	83
14[e]	1.4	KOAc (2)	0.02	80
15[f]	1.4	KOAc (2)	0.02	75
16[g]	1.4	KOAc (2)	0.02	60
17[h]	1.4	KOAc (2)	0.02	77

[a]Reaction conditions: **1a**, **2a** (0.1g, 1 equivalent), base, $Pd(OAc)_2$ in 7 mL DMA at 160 °C for 24 hrs under N_2 atmosphere. [b]isolated yields. [c]starting material **1a** was present after 24 hrs of reaction time. [d]traces of decarboxylative homodimerization product **3a'** observed. [e]0.5 equivalent of TBAB was used. [f]0.5 equivalent of TBAI was used. [g]NMP was used as solvent. [h]DMF was used as solvent.

The screening of various bases with 10 mol% $Pd(OAc)_2$ resulted in low to moderate yield of **3a** (entry 1 to 5). Of note the use of Ag_2CO_3 as base resulted in byproducts formation along with **3a** whilst the use of AgOAc slightly suppressed the byproduct formation. Furthermore, use of KOAc (2 equivalent) produced **3a** in moderate yields with negligible amounts of byproducts. We were pleased to observe that the catalyst loading could be reduced to 5 to 2 mol% with high yields of **3a** along with complete suppression of byproducts (entry 6, 7). This is in agreement with the observation that the low catalytic loading reduces colloid formation of Pd(0) species and hence increases the efficiency of reaction as observed in Heck reaction involving ligand free $Pd(OAc)_2$ as catalyst and aryl bromide as coupling partner.[14] Further reduction in $Pd(OAc)_2$ (1 mol%) did not result in completion of the reaction in 24 hrs. Next, we turned our attention to the stoichiometry of reactants wherein **1a** (from 1.2 to 1.6 equivalent) was employed with **2a** (1 equivalent), $Pd(OAc)_2$ (2 mol%), KOAc (2 equivalents) in DMA (entry 9 to 13). The 1.4 equivalent of **1a** resulted in high yield, 85%, of **3a**. The use of 1.5 and 1.6 equivalent of **1a** furnished eventually similar yields of **3a** although with traces of decarboxylative homodimerization (**3a'**). Furthermore, neither additives such as TBAB and TBAI (entry 14 and 15) nor the use of NMP or DMF as solvents (entry 16 and 17) showed any improvement in the yield of **3a**. This led to the identification of optimized reaction condition as illustrated in table 1, entry 11.

The substrate scope and generality of decarboxylative arylation was investigated under optimized condition and results are summarized in table 2. The electron deficient aryl bromides reacted with **1a** to produce coupled products in moderate to good yield (**3i**-**3p**). High reactivity was observed for most of the electron deficient aryl bromides (**2i**-**2k**, **2n**-**2p** table 2, supporting information) with exception of 3-bromobenzaldehyde (**2m**) which took 24 hrs to complete the reaction. The ortho substituted aryl bromides furnished **3l** in 68% yield. The longer reaction time in this case may be attributed to the steric hindrance caused by ortho-substituent. The trisubstituted 2-bromo-4,6-dimethoxybenzaldehyde successfully furnished **3q** in modest yield. Furthermore, electron rich aryl bromides successfully furnished **3b-3h** in moderate to high yields. In general, the electron rich aryl bromides required longer reaction time compared to electron deficient aryl bromides. **2e** reacted sluggishly with **1a** (5 days reaction time) resulting in complex reaction mixture allowing to isolate **3e** in 20%. The reaction of bromo naphthalenes with **1a** produced **3g**, **3h** in high yield (91% and 95% respectively). The reaction tolerated variety of electron withdrawing and donating groups as shown in table 2.

The scope of the decarboxylative arylation was extended to aryl chlorides and is shown in table 2 (condition I). Compound **3a, 3j** and **3n** were obtained in 44%, 58% and 85% respectively. In this protocol when 4-chloroanisole, 2-chloronaphthalene, 1-chloronaphthalene, and 4-chlorobezotrifluoride were treated with **1a**, the decarboxylative arylated products **3d**, **3g**, **3h** and **3i** were obtained in lower yields along with the protodecarboxylation of **1a**. The protodecarboxylation was the only product isolated when **1a** was treated with chlorobenzene or 3-chlorobenzaldehyde or 4-chlorotoluene, indicating limitation for some of the aryl chlorides in this protocol.

Further, the scope of reaction was studied with respect to heteroaryl bromides (table 3). The decarboxylative arylation between **1a** with bromides of quinoline, isoquinoline, indole, furan, thiophene, quinoxaline, and pyridine successfully furnished diverse molecules (table 3, **3r**-**3y**). These hybrid-chemotypes are important as they contain various heterocycles which are known to be the privileged scaffolds in drug discovery.[15] The heteroatom in these privileged motifs often take part in various interactions with biological

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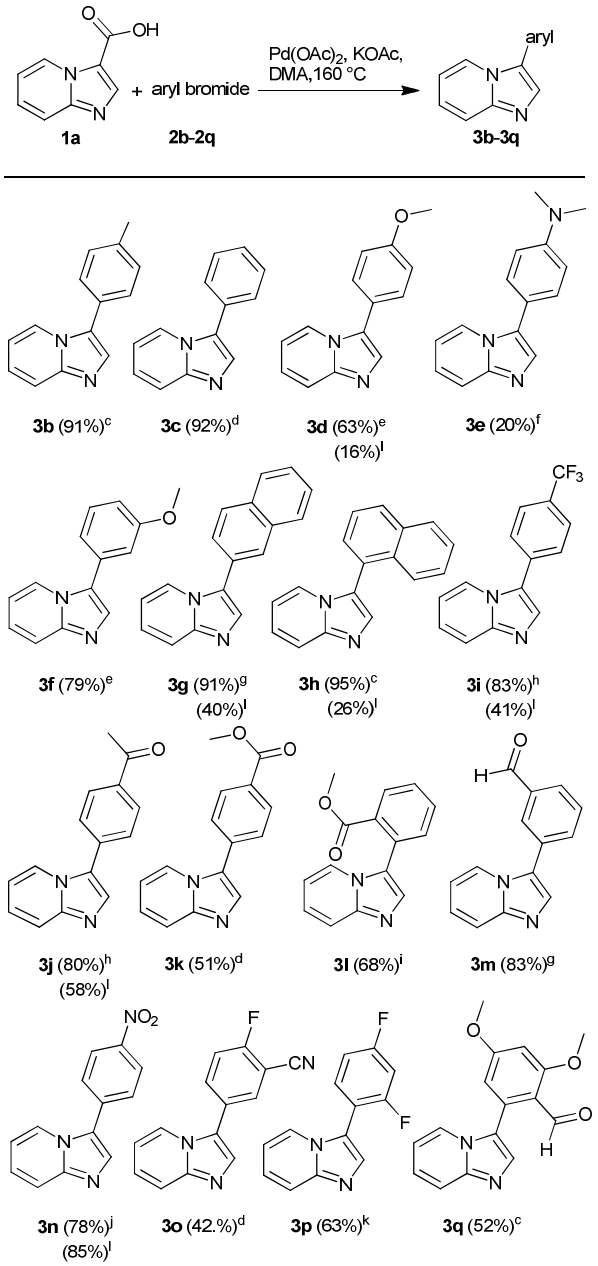
targets/proteins.[16] The coupling of 3-bromoquinoline, 5-bromoisoquinoline and 4-bromo indole with **1a** resulted **3r**, **3s** and **3t** in high yields whereas 5-bromo indole gave **3u** in 50% yield. Presence of electron withdrawing groups like ester on furan (**3v**) was tolerated. The 2-bromothiophene and 6-bromoquinoxaline could produce **3w**, **3x** respectively in moderate yield. The 3-bromopyridine successfully coupled with **1a** to produce **3y**. The protocol tolerated free NH group in indole substrate (**3t**, **3u**).

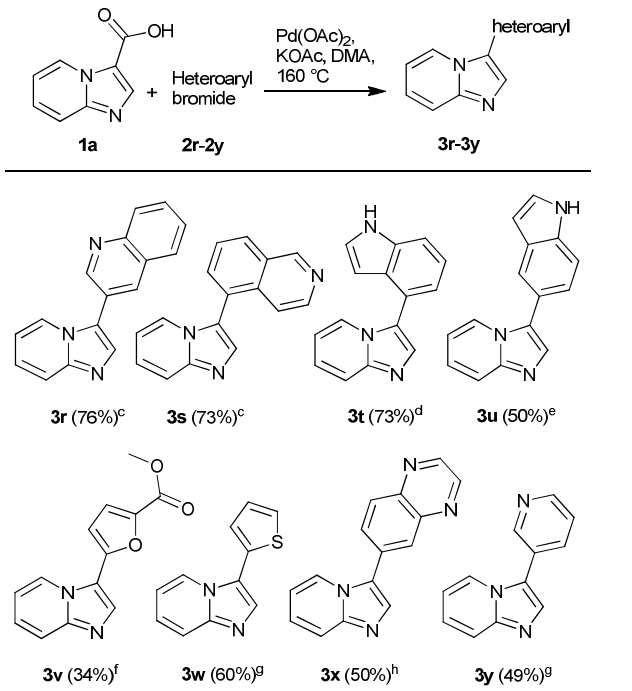
Table 2. Scope of aryl bromides[a,b]



[a]Reaction conditions: **1a** (1.4 equivalents), **2b**-**2q** (1 equivalent), KOAc (2 equivalents), 2 mol% $Pd(OAc)_2$ in DMA at 160 °C under N_2 atmosphere. Aryl bromide structures are shown in supplementary information. [b]isolated yield. [c]for 14 hrs. [d]for 5 hrs. [e]for 20 hrs. [f]for 5 days. [g]for 24 hrs. [h]for 3.5 hrs. [i]for18 hrs. [j]for 8 hrs. [k]for 12 hrs. [l]aryl chlorides (1 equivalent) were used instead of aryl bromides with **1a** (1.4 equivalents), KOAc (2 equivalents), 2 mol% $Pd(OAc)_2$ in DMA at 160 °C under N_2 atmosphere.

Upon having successfully studied scope of the method with respect to various aryl/heteroaryl bromides, we next turned our attention to study the scope of method with respect to various imidazo[1,2-*a*]pyridine-3-carboxylic acids. The results of this study is summarized in table 4. Various imidazo[1,2-*a*]pyridine-3-carboxylic acids **1b**-**1i** were synthesized according to the reported method or modifications therof.[17] Details of their synthesis has been described in the supporting information. Imidazo[1,2-*a*]pyridine-3-carboxylic acids with methyl substituent at various positions underwent decarboxylative arylation with good yields (**4a**, **4c**, **4f** and **4g**). In addition, electron withdrawing groups like chloro, trifluoromethyl on imidazo[1,2-*a*]pyridine-3-carboxylic acid were well tolerated in the reaction (**4h**, **4k** and **4l**). Furthermore, we were pleased to find that the reaction is applicable to substituted imidazo[1,2-*a*]pyridine-3-carboxylic acids with various heteroaryl bromides producing **4b**, **4d**, **4e**, **4i**, **4j** and **4m** in various yields.

Table 3. Scope of heteroaryl bromide[a,b]



[a]Reaction conditions: **1a** (1.4 equivalents), **2r**-**2y** (1 equivalent), KOAc (2 equivalents), 2 mol% $Pd(OAc)_2$ in DMA at 160 °C under N_2 atmosphere. Heteroaryl bromide structures are shown in supplementary information. [b]isolated yield. [c]for 3 hrs. [d]for 12 hrs. [e]for 5 hrs. [f]for 36 hrs. [g]for 13 hrs. [h]for 4 hrs.

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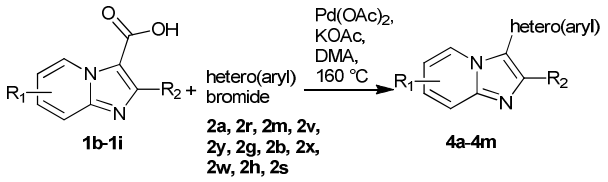
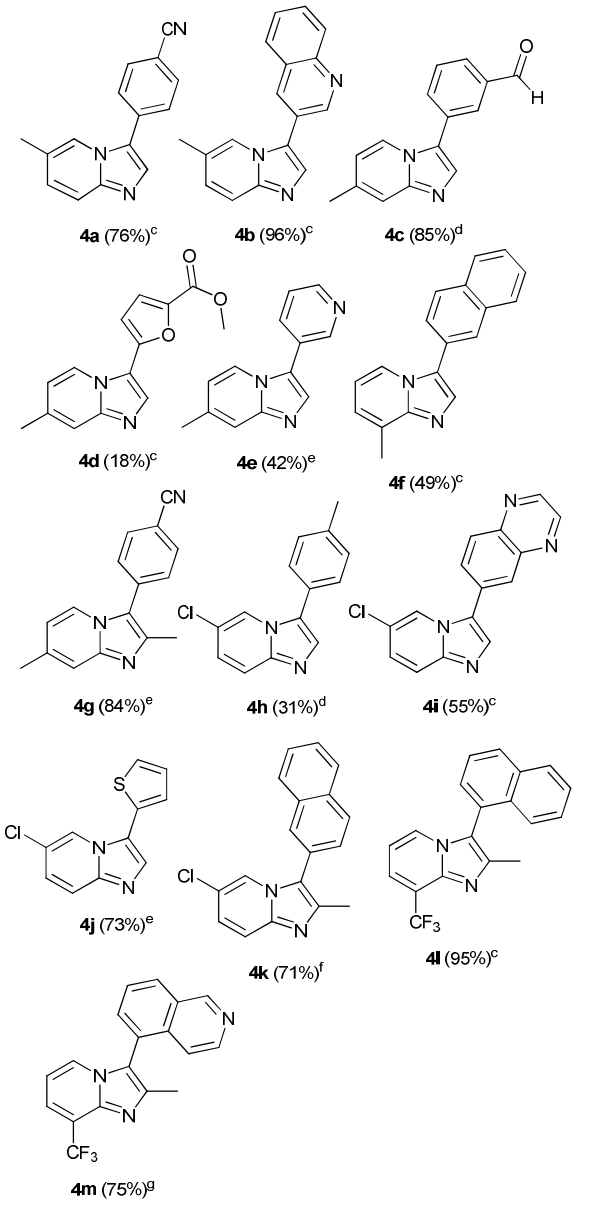
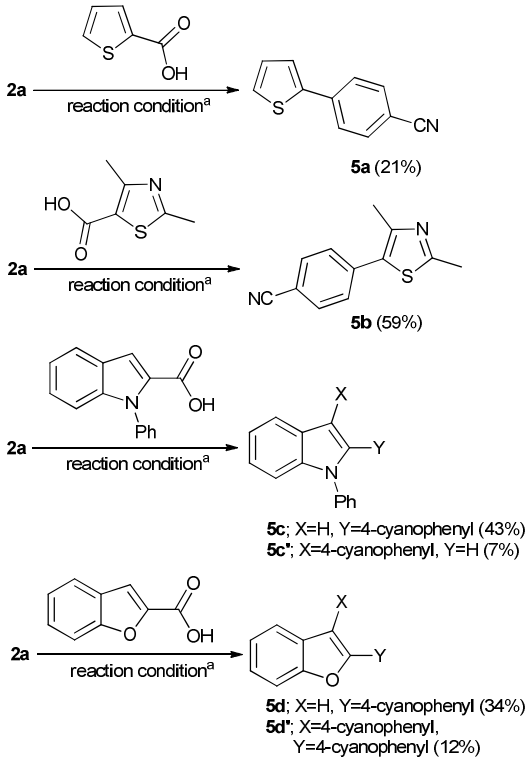
Table 4. Scope of substituted imidazo[1,2-*a*]pyridine-3-carboxylic acids with hetero(aryl) bromide[a,b]





[a]Reaction conditions: **1b**-**1i** (1.4 equivalents), aryl/heteroaryl bromide (1 equivalent), KOAc (2 equivalents), 2 mol % $Pd(OAc)_2$ in DMA at 160 °C under N_2 atmosphere. aryl and heteroaryl bromide structures are shown in supplementary information. [b]isolated yield. [c]for 12 hrs. [d]for 4 hrs. [e]for 18 hrs. [f]for 2 days. [g]for 6 hrs



Scheme 1. Scope of various heterocyclic acids with aryl bromides

The scope of the ligand-free Pd-catalysed decarboxylative arylation reaction was further extended to different heterocyclic acids as shown in scheme 1. The 2-thiophenecarboxylic acid, 2,4-disubstituted thiazole-5-carboxylic acid underwent decarboxylative arylation with **2a** and produced **5a** (21%) and **5b** (59%) respectively. Further, *N*-substituted indole 2-carboxylic acid produced 2-arylated *N*-substituted indole **5c** (43%) with minor amount of 3-arylated *N*-substituted indole **5c'** (7%). When benzofuran-2-carboxylic acid was used in the protocol, the expected 2-arylated benzofuran **5d** was obtained in 34% yield along with 12% 2,3-diarylated benzofuran **5d'**.

The previous study on decarboxylative arylation of **1a** with aryl chloride in the presence of palladium acetate, S-Phos are reported by Wu et al and proposed via Pd(0) species.[10] The generation of Pd(0) species was proposed through decarboxylative homocoupling of **1a**, although formation of homodimer **3a'** in the presence of aryl chloride was not observed. To understand the decarboxylative arylation process, we submitted **1a** under standard condition without aryl bromide and isolated 74% homodimer **3a'**, while in the absence of aryl chloride, Wu et al isolated homodimer **3a'** in 98%[10] yield. Additionally, we observed **3a'** only in the cases where excess (1.5 equivalent and more; entry 12 and 13 in table 1) of **1a** with **2a** (1 equivalent) was used indicating the formation of **3a'** may be a consequence of excess amount of **1a**. Based on these observations a plausible mechanism for decarboxylative arylation is proposed and is shown in scheme 2.

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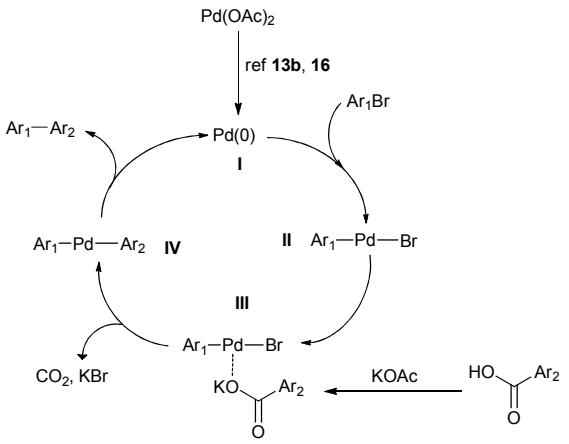

Scheme 2. Plausible mechanism of decarboxylative arylation

The catalytic cycle begins with formation of Pd(0) species **I** in the reaction. Formation of Pd(0) species from $Pd(OAc)_2$ catalysed Heck reaction in ligand-free condition at high temperature has been reported by de Vries et al.[13b, 14] The Pd(0) initially is in soluble palladium cluster form[13b] which further can form insoluble palladium black. Hence such ligandless systems work well with low catalyst loading so as to avoid the insoluble palladium black formation due to aggregation.[9b, 13b, 18] We observed that the yield of arylated product decreased in case of 10 mol% $Pd(OAc)_2$ as compared to 5 mol% $Pd(OAc)_2$ (entry 4 and 6, table 1) which probably is due to the formation of palladium black. The next step in plausible mechanism is the oxidative addition of aryl bromide to **I** resulting in intermediate **II**. This palladium (II) complex coordinates with carboxylate and forms intermediate **III** which upon decarboxylation collapses in intermediate **IV**. Finally, reductive elimination converts Pd(II) to Pd(0) with release of 3-aryl imidazo[1,2-*a*]pyridine.

Finally compounds were screened on bacteria panel consisting of *E. coli*, *S. aureus*, *P. aeruginosa*, *K. pneumoniae* and *A. baumannii*. The MIC of active compounds was determined and was defined as the lowest concentration of a compound that inhibited visible growth of bacteria after 24 hrs. Compound **3i**, **4l**, **4f** and **3h** showed MIC of 50, 50, 25 and 50 μM against *S. aureus* respectively. Modifications of **4f** are in progress to obtain more potent analogues and the results pertaining to this will be published in due course.

Conclusion

In summary, we have successfully developed a facile ligand-free palladium catalysed decarboxylative arylation reaction of imidazo[1,2-*a*]pyridine-3-carboxylic acids with various aryl and heteroaryl bromides. This method provides a broad substrate scope and excellent functional group tolerance. The protocol is applied to generate heteroaryl-hetero(aryl) motifs and few of these motifs showed antibacterial activity against *S. aureus*. The efforts are underway to modify these motifs to obtain more potent and drug like compounds. Further, generation of new heteroaryl-hetero(aryl) motif will find importance in drug discovery.

Experimental

In a typical procedure, the mixture of **2** (0.1g, 1 equivalent), **1** or **heterocyclic acids** [2-thiophenecarboxylic acid/2,4-disubstituted thiazole-5-carboxylic acid/*N*-substituted indole 2-carboxylic acid/ benzofuran-2-carboxylic acid] (1.4 equivalent), $Pd(OAc)_2$ (2 mol%), KOAc (2 equivalent) in 7 mL DMA were stirred at 160 °C. The progress of reaction was monitored through TLC. Upon completion of the reaction, the mixture was diluted with 200 mL of water and extracted with ethyl acetate (2x70 mL). The ethyl acetate layer was washed with water (200 mL), brine (100 mL) and dried with sodium sulfate. The organic solvent evaporated under vacuum and residue was purified by column chromatography to afford pure 3-aryl imidazo[1,2-*a*]pyridines **3** or 4.

4-(Imidazo[1,2-*a*]pyridin-3-yl)benzonitrile (3a).[12] Yellow solid. Yield: 102 mg (85%). mp= 177°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (dt, *J* = 7.0, 1.1 Hz, 1H), 7.82-7.78 (m, 3H), 7.74-7.68 (m, 3H), 7.31-7.25 (m, 1H), 6.91 (td, *J* = 6.9, 1.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.2, 134.3, 134.1, 133.2 (x2), 127.8 (x2), 125.4, 124.1, 123.3, 118.8, 118.6, 113.6, 111.4; HRMS (ESI-MS): Calc. for $C_{14}H_{10}N_3$ [$(M+H)^+$]: 220.0869, Found: 220.0891.

3-(*p*-Tolyl)imidazo[1,2-*a*]pyridine (3b).[12] Yellow solid. Yield: 110 mg (90%). mp= 78-80°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.31 (d, *J* = 7.0 Hz, 1H), 7.69-7.64 (m, 2H), 7.45 (d, *J* = 8.1 Hz, 2H), 7.33 (d, *J* = 8.1 Hz, 1H), 7.21-7.16 (m, 1H), 6.80 (td, *J* = 6.8, 1.1 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.0, 138.3, 132.4, 128.2, 126.4, 125.9, 124.2, 123.5, 118.4, 112.5, 21.5; HRMS (ESI-MS):Calc. for $C_{14}H_{13}N_2$ [$(M+H)^+$]: 209.1073, Found: 209.1062.

3-phenylimidazo[1,2-*a*]pyridine (3c).[12] Brown liquid. Yield: 115 mg (92%) ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (d, *J* = 7.0 Hz, 1H), 7.67 (s, 1H), 7.65 (d, *J* = 9.1 Hz, 1H), 7.57-7.45 (m, 4H), 7.38 (t, *J* = 7.5 Hz, 1H), 71.6 (t, *J* = 7.5 Hz, 1H), 6.77 (t, *J* = 6.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.0, 132.4, 129.2, 128.1, 127.9, 125.6, 124.2, 123.3, 118.1, 112.5; HRMS (ESI-MS): Calc. for $C_{13}H_{10}N_2Na$ [$(M+Na)^+$]: 217.0736, Found: 217.0729.

3-(4-Methoxyphenyl)imidazo[1,2-*a*]pyridine (3d).[9b] Brown solid. Yield: 75 mg (63%). mp= 116°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.25 (dt, *J* = 7.0, 1.1 Hz, 1H), 7.66 (d, *J* = 10.0 Hz, 1H), 7.63 (s, 1H), 7.50-7.45 (m, 2H), 7.20-7.15 (m, 1H), 7.08-7.03 (m, 2H), 6.78 (td, *J* = 6.8, 1.1 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.8, 145.9, 132.1, 129.8, 125.7, 124.1, 123.4, 121.7, 118.3, 114.8, 112.5, 55.6; HRMS (ESI-MS):Calc. for $C_{14}H_{13}N_2O$ [$(M+H)^+$]: 225.1022, Found: 225.1013.

4-(Imidazo[1,2-*a*]pyridin-3-yl)-*N*,*N*-dimethylaniline (3e).[9b] Yellow solid. Yield: 23 mg (20%). mp= 128°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.27 (dt, *J* = 7.0, 1.1 Hz, 1H), 7.64 (d, *J* = 10.0 Hz, 1H), 7.60 (s, 1H), 7.44-7.38 (m, 2H), 7.17-7.12 (m, 1H), 6.87-6.81 (m, 2H), 6.76 (td, *J* = 6.8, 1.1 Hz, 1H), 3.03 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.5, 145.6, 131.4, 129.4, 126.3, 123.8,

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123.6, 118.1, 116.7, 112.8, 112.3, 40.5; HRMS (ESI-MS):Calc. for $C_{15}H_{15}N_3Na$ [(M+Na)$^+$]: 260.1158, Found: 260.1171.

3-(3-Methoxyphenyl)imidazo[1,2-*a*]pyridine (3f).[9e] White solid. Yield: 95 mg (79%). mp= 110°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.37 (dt, *J* = 7.0, 1.1 Hz, 1H), 7.70 (s, 1H), 7.68 (dt, *J* = 9.1, 1.1 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.23-7.18 (m, 1H), 7.17-7.14 (m, 1H), 7.11-7.07 (m, 1H), 6.99-6.93 (m, 1H), 6.82 (td, *J* = 6.9, 1.1 Hz, 1H), 3.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.4, 146.3, 132.7, 130.7, 130.5, 125.8, 124.4, 123.7, 120.4, 118.4, 113.9, 113.7, 112.7, 55.5; HRMS (ESI-MS):Calc. for $C_{14}H_{13}N_2O$ [(M+H)$^+$]: 225.1022, Found: 225.1032.

3-(Naphthalen-2-yl)imidazo[1,2-a]pyridine (3g).[9e] Brown liquid. Yield: 108 mg (91%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.43 (d, *J* = 6.9 Hz, 1H), 8.01 (s, 1H), 8.97 (d, *J* = 8.4 Hz, 1H), 7.92-7.88 (m, 2H), 7.81 (s, 1H), 7.75 (d, *J* = 9.0 Hz, 1H), 7.64 (d, *J* = 9.0 Hz, 1H), 7.56-7.51 (m, 2H), 7.24 (t, *J* = 8.0 Hz, 1H), 6.85 (t, *J* = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.1, 133.7, 133.0, 132.5, 129.2, 128.1, 128.0, 126.9 (overlapped), 126.7, 126.6, 125.9, 125.8, 123.5, 118.3, 113.0; HRMS (ESI-MS):Calc. for $C_{17}H_{13}N_2$ [(M+H)$^+$]: 245.1073, Found: 245.1085.

3-(Naphthalen-1-yl)imidazo[1,2-*a*]pyridine (3h).[9e] Yellow semisolid. Yield: 100 mg (84%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.02-7.94 (m, 2H), 7.79 (s, 1H), 7.74 (d, *J* = 9.1 Hz, 1H), 7.70 (d, *J* = 6.9 Hz, 1H), 7.61-7.56 (m, 2H), 7.56-7.48 (m, 2H), 7.46-7.38 (m, 1H), 7.21 (t, *J* = 8.0 Hz, 1H), 6.68 (t, *J* = 6.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.9, 134.0, 133.8, 132.1, 129.7, 129.2, 128.8, 127.0, 126.4, 126.3, 125.7, 125.2, 124.4, 124.1, 123.7, 118.1, 112.3; HRMS (ESI-MS):Calc. for $C_{17}H_{12}N_2Na$ [(M+Na)$^+$]: 267.0893, Found: 267.0909.

3-(4-(Trifluoromethyl)phenyl)imidazo[1,2-*a*]pyridine (3i).[9b] Yellow solid. Yield: 100 mg (85%). mp= 152°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.36 (dt, *J* = 7.0, 1.1 Hz, 1H), 7.81-7.74 (m, 3H), 7.74- 7.67 (m, 3H), 7.29-7.21 (m, 1H), 6.88 (td, *J* = 7.0, 1.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.8, 133.7, 133.1, 130.2, 129.9, 128.0, 126.4, 124.5, 123.3, 118.7, 113.2; HRMS (ESI-MS):Calc. for $C_{14}H_{10}F_3N_2$ [(M+H)$^+$]: 263.0791, Found: 263.0821.

1-(4-(Imidazo[1,2-*a*]pyridin-3-yl)phenyl)ethanone (3j).[9b] Yellow solid. Yield: 95 mg (80%). mp= 164°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (d, *J* = 6.8 Hz, 1H), 8.10 (d, *J* = 8.2 Hz, 2H), 7.80 (s, 1H), 7.75-7.65 (m, 3H), 7.28-7.21 (m, 1H), 6.88 (t, *J* = 6.8 Hz, 1H), 2.66 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 197.1, 146.8, 136.1, 133.9, 133.7, 129.3, 127.2, 124.8, 124.7, 123.4, 118.4, 113.1, 26.6; HRMS (ESI-MS):Calc. for $C_{15}H_{13}N_2O$ [(M+H)$^+$]: 237.1022, Found: 237.1032.

Methyl 4-(imidazo[1,2-*a*]pyridin-3-yl)benzoate (3k).[9b] Yellow solid. Yield: 60 mg (51%); mp= 145°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (dt, *J* = 7.0, 1.1 Hz, 1H), 8.21-8.15 (m, 2H), 7.80 (s, 1H), 7.71 (dt, *J* = 9.1, 1.0 Hz, 1H), 7.68-7.64 (m, 2H), 7.29-7.22 (m, 1H), 6.88 (td, *J* = 7.0, 1.1 Hz, 1H), 3.97 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.7, 146.7, 133.9, 133.7, 130.7, 129.4, 127.4, 125.0, 123.5, 118.6, 113.2, 52.4; HRMS (ESI-MS):Calc. for $C_{15}H_{13}N_2O_2$ [(M+H)$^+$]: 253.0972, Found: 253.0985.

Methyl 2-(imidazo[1,2-*a*]pyridin-3-yl)benzoate (3l).[9b] Yellow semisolid. Yield: 80 mg (68%). 1H NMR (500 MHz, $CDCl_3$): δ 8.10 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.76-7.70 (m, 2H), 7.66 (td, *J* = 7.6, 1.4 Hz, 1H), 7.62 (s, 1H), 7.57 (td, *J* = 7.6, 1.4 Hz, 1H), 7.48 (dd, *J* = 7.6, 1.4 Hz, 1H), 7.24-7.20 (m, 1H), 6.77 (t, d, *J* = 6.8 Hz, 1H), 3.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 145.6, 133.0, 132.7, 132.2, 131.3, 131.2, 129.4, 129.1, 124.7, 124.1, 124.0, 117.9, 112.4, 52.4; HRMS (ESI-MS):Calc. for $C_{15}H_{13}N_2O_2$ [(M+H)$^+$]: 253.0972, Found: 253.0983.

3-(Imidazo[1,2-*a*]pyridin-3-yl)benzaldehyde (3m).[9b] Yellow solid. Yield: 100 mg (83%). mp= 76°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.11 (s, 1H), 8.35 (dt, *J* = 7.0, 1.1 Hz, 1H), 8.10 (t, *J* = 1.6 Hz, 1H), 7.93 (dt, *J* = 7.6, 1.4 Hz, 1H), 7.85 (dt, *J* = 7.6, 1.4 Hz, 1H), 7.79 (s, 1H), 7.75-7.69 (m, 2H), 7.30-7.22 (m, 1H), 6.88 (td, *J* = 7.0, 1.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.9, 146.6, 137.4, 133.8, 133.2, 130.6, 130.2, 129.7, 128.4, 125.0, 124.5, 123.2, 118.5, 113.3; HRMS (ESI-MS):Calc. for $C_{14}H_{11}N_2O$ [(M+H)$^+$]: 223.0866, Found: 223.0878.

3-(4-Nitrophenyl)imidazo[1,2-*a*]pyridine (3n).[9b] Yellow solid. Yield: 95 mg (80%). mp= 185°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.42 (d, *J* = 7.0 Hz, 1H), 8.40-8.36 (m, 2H), 7.86 (s, 1H), 7.78-7.75 (m, 2H),7.74 (d, *J* = 9.1 Hz, 1H), 7.34-7.27 (m, 1H), 6.94 (td, *J* = 7.0, 1.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.4, 147.0, 136.0, 134.7, 127.7, 125.6, 124.9, 123.8, 123.4, 118.9, 113.8; HRMS (ESI-MS):Calc. for $C_{13}H_{10}N_3O_2$ [(M+H)$^+$]: 240.0768, Found: 240.0776.

2-Fluoro-5-(imidazo[1,2-*a*]pyridin-3-yl)benzonitrile (3o).[19] Brown solid. Yield: 50 mg (42%). mp= 217-219°C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.61 (dt, *J* = 7.0, 1.1 Hz, 1H), 8.27 (dd, *J* = 6.1, 2.3 Hz, 1H), 8.11-8.06 (m, 1H), 7.86 (s, 1H), 7.73-7.65 (m, 2H), 7.38-7.33 (m, 1H), 7.00 (td, *J* = 7.0, 1.1 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 161.7 (d, *J* = 256.4 Hz), 145.9, 135.3 (d, *J* = 8.5 Hz), 133.6, 132.7, 126.7 (d, *J* = 3.2 Hz), 125.3, 124.4, 122.4, 120.5, 117.6 (d, *J* = 19.8 Hz), 117.5, 113.8, 113.2; HRMS (ESI-MS):Calc. for $C_{14}H_9FN_3$ [(M+H)$^+$]: 238.0775, Found: 238.0774.

3-(2,4-Difluorophenyl)imidazo[1,2-*a*]pyridine (3p). White solid. Yield: 75 mg (63%). mp= 95°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 (dt, *J* = 7.0, 1.1 Hz, 1H), 7.73-7.66 (m, 2H), 7.52-7.45 (m, 1H), 7.26-7.21 (m, 1H), 7.08-6.98 (m, 2H), 6.84 (td, *J* = 7.0, 1.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.4 (dd, *J* = 251.4, 11.7 Hz), 160.3 (dd, *J* = 251.5, 11.7 Hz), 146.5, 134.0, 132.4(AB q, *J* = 4.7 Hz), 124.7, 124.2 (d, *J* =3.7 Hz), 119.3, 118.3, 113.5 (dd, *J* =15.2, 3.3 Hz), 112.7, 112.4 (dd, *J* = 21.6, 3.4 Hz), 105.0 (t, *J* =25.6 Hz); HRMS (ESI-MS):Calc. for $C_{13}H_9F_2N_2$ [(M+H)$^+$]:231.0728, Found: 231.0734.

6-(Imidazo[1,2-*a*]pyridin-3-yl)-2,3dimethoxybenzaldehyde (3q). Yellow semisolid. Yield: 60 mg (52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 9.68 (s, 1H), 7.93 (dt, *J* = 6.8, 1.0 Hz, 1H), 7.72 (dt, *J* = 9.1, 1.0 Hz, 1H), 7.70 (s, 1H), 7.61 (s, 1H), 7.29-7.23 (m, 1H), 6.93 (s, 1H), 6.84 (dt, *J* = 6.8, 1.0 Hz, 1H), 4.02 (s, 3H), 3.96 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ: 189.9, 154.4, 150.2, 146.2, 134.9, 128.8, 126.7, 125.1, 123.3, 120.5, 118.3, 113.4, 113.1, 109.6, 56.6, 56.4; HRMS (ESI-MS):Calc. for $C_{16}H_{15}N_2O_3$ [(M+H)$^+$]: 283.1077, Found: 283.1095.

3-(Imidazo[1,2-*a*]pyridin-3-yl)quinoline (3r).[9b] Brown solid. Yield: 90 mg (76%). mp= 140°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.13 (d, *J* = 2.2 Hz, 1H), 8.39 (d, *J* = 6.9 Hz, 1H), 8.33 (d, *J* = 2.1 Hz, 1H), 8.17 (d, *J* = 8.5 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.87 (s, 1H), 7.78 (t, *J* = 8.1 Hz, 1H), 7.74 (d, *J* = 9.1 Hz, 1H), 7.64 (t, *J* = 7.2 Hz, 1H), 7.31-7.24 (m, 1H), 6.90 (t, *J* = 6.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.9, 147.5, 146.8, 133.9, 133.8, 130.1,

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129.5, 127.9 (x2), 127.6, 125.0, 123.1, 122.8, 122.6, 118.6, 113.2; HRMS (ESI-MS):Calc. for $C_{16}H_{11}N_3Na$ [(M+Na)$^+$]: 268.0845, Found: 268.0858.

5-(Imidazo[1,2-*a*]pyridin-3-yl)isoquinoline (3s). Brown solid. Yield: 85 mg (73%). mp= 133°C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.38 (d, *J* = 1.2 Hz, 1H), 8.51 (d, *J* = 6.0 Hz, 1H), 8.13 (d, *J* = 8.2 Hz, 1H), 7.86 (dd, *J* = 7.1, 1.2 Hz, 1H), 7.82 (s, 1H), 7.80-7.73 (m, 3H), 7.39 (d, *J* = 6.0 Hz, 1H), 7.30-7.25 (m, 1H), 6.78 (td, *J* = 6.8, 1.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.3, 146.2, 144.1, 134.8, 134.2, 133.0, 129.1, 127.3, 125.7, 124.9, 123.8, 122.1, 118.3, 118.0, 112.9; HRMS (ESI-MS):Calc. for $C_{16}H_{12}N_3$ [(M+H)$^+$]: 246.1026, Found: 246.1034.

3-(1*H*-Indol-4-yl)imidazo[1,2-*a*]pyridine (3t). Brown solid. Yield: 60 mg (50%). mp= 198-200°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.55 (bs, 1H), 8.22 (dt, *J* = 7.0, 1.1 Hz, 1H), 7.85 (s, 1H), 7.72 (dt, *J* = 9.1, 1.0 Hz, 1H), 7.50 (dt, *J* = 7.5, 1.0 Hz, 1H),7.36-7.30 (m, 2H), 7.29 (t, *J* = 2.8 Hz, 1H), 7.24-7.19 (m, 1H), 6.77 (td, *J* = 6.8, 1.1 Hz, 1H), 6.43-6.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.9, 136.4, 132.7, 126.8, 125.2, 124.8, 124.4, 122.3, 121.0, 120.6, 118.0, 112.2, 111.7, 102.2; HRMS (ESI-MS):Calc. for $C_{15}H_{11}N_3Na$ [(M+Na)$^+$]: 256.0845, Found: 256.0867.

3-(1*H*-Indol-5-yl)imidazo[1,2-*a*]pyridine (3u). Brown semisolid. Yield: 60 mg (50%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.27 (bs, 1H), 8.36 (d, *J* = 7.0, Hz, 1H), 7.83 (s, 1H), 7.71(s, 1H), 7.67 (d, *J* = 9.1 Hz, 1H), 7.54 (d, *J* = 8.3 Hz, 1H), 7.38-7.30 (m, 2H), 7.22-7.15 (m, 1H), 6.78 (td, *J* = 6.8, 0.9 Hz, 1H), 6.66-6.60 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.6, 135.9, 131.7, 128.6, 127.3, 125.7, 124.1, 123.7, 122.6, 120.9, 120.3, 117.9, 112.4, 112.1, 102.7; HRMS (ESI-MS):Calc. for $C_{15}H_{12}N_3$ [(M+H)$^+$]: 234.1026, Found: 234.1056.

Methyl 5-(imidazo[1,2-*a*]pyridin-3-yl)furan-2-carboxylate (3v).[20] Yellow solid. Yield: 34 mg (40%). mp= 133-135°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.85 (dt, *J* = 7.0, 1.1 Hz, 1H), 8.02 (s, 1H), 7.72 (dt, *J* = 9.1, 1.0 Hz, 1H), 7.35-7.19 (m, 2H), 7.00 (td, *J* = 6.9, 1.0 Hz, 1H), 6.72 (d, *J* = 3.6, 1.0 Hz, 1H), 3.94 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.1, 149.0, 146.9, 143.2, 134.5, 125.9, 125.8, 119.9, 118.3, 116.7, 114.0, 107.4, 52.1; HRMS (ESI-MS):Calc. for $C_{13}H_{10}N_2NaO_3$ [(M+Na)$^+$]: 265.0584, Found: 265.0607.

3-(Thiophen-2-yl)imidazo[1,2-*a*]pyridine (3w).[21] Yellow oil. Yield: 92 mg (75%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (d, *J* = 4.9, Hz, 1H), 7.77 (s, 1H); 7.68(d, *J* = 9.1 Hz, 1H), 7.44 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.29 (dd, *J* = 3.6, 1.1 Hz, 1H), 7.25-7.22 (m, 1H), 7.22-7.18 (m, 1H), 6.87 (t, *J* = 6.8, 1.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.2, 133.5, 129.9, 127.8, 125.9 (x2), 124.5, 123.8, 119.2, 118.0, 112.9; HRMS (ESI-MS):Calc. for $C_{11}H_9N_2S$ [(M+H)$^+$]: 201.0481, Found: 201.0476.

6-(Imidazo[1,2-*a*]pyridin-3-yl)quinoxaline (3x). Yellow solid. Yield: 62 mg (50%). mp= 143-145°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.91 (d, *J* = 1.8, Hz, 1H), 8.89 (d, *J* = 1.8 Hz, 1H), 8.58 (d, *J* = 7.0 Hz, 1H), 8.34 (d, *J* = 1.9 Hz, 1H), 8.26 (d, *J* = 8.7 Hz, 1H), 8.03 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.93 (s, 1H), 7.76 (d, *J* = 9.1 Hz, 1H), 7.33-7.27 (m, 1H), 6.93 (td, *J* = 6.8, 1.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.0, 145.9, 145.2, 143.5, 142.5, 134.2, 131.3, 130.8, 130.1, 126.5, 125.3, 124.5, 123.5, 118.6, 113.5; HRMS (ESI-MS):Calc. for $C_{15}H_{11}N_4$ [(M+H)$^+$]: 247.0978, Found: 247.0991.

3-(Pyridin-3-yl)imidazo[1,2-*a*]pyridine (3y).[9b] Brown semisolid. Yield: 60 mg (49%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.84 (d, *J* = 2.2 Hz, 1H), 8.65 (dd, *J* = 1.6, 1H), 8.28 (d, *J* = 6.0 Hz, 1H), 7.90-7.84 (m, 1H), 7.75 (s, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.45 (dd, *J* = 4.9, 3.0 Hz, 1H), 7.28-7.22 (m, 1H), 6.88 (td, *J* = 6.8, 1.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.3, 148.9, 146.7, 135.2, 133.4, 125.7, 125.0, 124.0, 123.0, 122.3, 118.5, 113.2; HRMS (ESI-MS):Calc. for $C_{12}H_9N_3Na$ [(M+Na)$^+$]: 218.0689, Found: 218.0684.

4-(6-methylimidazo[1,2-*a*]pyridin-3-yl)benzonitrile (4a). White solid. Yield: 100 mg (78%). mp= 152-154°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.13 (s, 1H), 7.82-7.76 (m, 2H), 7.73 (s, 1H), 7.71-7.65 (m, 2H), 7.60 (d, *J* = 15.8 Hz, 1H), 7.12 (dd, *J* = 9.2, 1.6 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.2, 134.3, 134.0, 133.1 (x2), 128.5, 127.7 (x2), 123.7, 123.3, 120.8, 118.7, 117.9, 111.7, 18.5; HRMS (ESI-MS):Calc. for $C_{15}H_{12}N_3$ [(M+H)$^+$]: 234.1026, Found: 234.1033.

3-(6-Methylimidazo[1,2-*a*]pyridin-3-yl)quinoline (4b). Brown solid. Yield: 120 mg (96%). mp= 138-140°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.12 (d, *J* = 2.2 Hz, 1H), 8.32 (d, *J* = 2.0 Hz, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 8.15(s, 1H), 7.91 (d, *J* = 7.9 Hz, 1H), 7.81 (s, 1H), 7.80-7.76 (m, 1H), 7.69-7.60 (m, 2H), 7.13 (dd, *J* = 9.2, 1.4 Hz, 1H), 2.34 (d, *J* = 0.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.0, 147.5, 145.9, 134.1, 133.6, 130.1, 129.6, 128.3, 128.0, 127.9, 127.6, 123.1, 123.0, 122.3, 120.7, 117.9, 18.5; HRMS (ESI-MS):Calc. for $C_{17}H_{14}N_3$ [(M+H)$^+$]: 260.1182, Found: 260.1194.

3-(7-Methylimidazo[1,2-*a*]pyridin-3-yl)benzaldehyde (4c). Yellow solid. Yield: 110 mgs (85%). mp= 80-82°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 10.10 (s, 1H), 8.23 (d, *J* = 7.0 Hz, 1H), 8.07 (s, 1H), 7.89 (dt, *J* = 7.6, 1.2 Hz, 1H), 7.82 (dt, *J* = 7.7, 1.9, 1.2 Hz, 1H), 7.70 (s, 1H), 7.69 (t, *J* = 7.6 Hz, 1H), 7.45 (s, 1H), 6.69 (dd, *J* = 7.0, 1.5 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 191.9, 147.2, 137.3, 135.9, 133.6, 133.2, 130.9, 130.2, 129.4, 128.2, 123.9, 122.5, 116.9, 115.8, 21.4; HRMS (ESI-MS):Calc. for $C_{15}H_{13}N_2O$ [(M+H)$^+$]: 237.1022, Found: 237.1033.

Methyl 5-(7-methylimidazo[1,2-*a*]pyridin-3-yl)furan-2-carboxylate (4d). Yellow solid. Yield: 23 mg (18%). mp= 124°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.69 (d, *J* = 7.1 Hz, 1H), 7.92 (s, 1H), 7.44 (s, 1H), 7.29 (d, *J* = 3.6 Hz, 1H), 6.80 (dd, *J* = 7.1, 1.6 Hz, 1H), 6.65 (d, *J* = 3.6, Hz, 1H), 3.93 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.1, 149.2, 147.3, 143.0, 137.1, 134.2, 125.1, 120.0, 116.6, 116.1, 106.9, 52.1, 21.4; HRMS (ESI-MS):Calc. for $C_{14}H_{13}N_2O_3$ [(M+H)$^+$]: 257.0921, Found: 257.0937.

7-Methyl-3-(pyridin-3-yl)imidazo[1,2-*a*]pyridine (4e). Yellow semisolid. Yield: 55 mg (42%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.81 (s, 1H), 8.61 (d, *J* = 4.8, 1.5 Hz, 1H), 8.15 (d, *J* = 7.0 Hz, 1H), 7.86-7.81 (m, 1H), 7.66 (s, 1H), 7.47-7.38 (m, 2H), 6.68 (d, *J* = 7.0 Hz, 1H), 2.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.1, 147.8, 146.2, 135.2, 134.1, 132.0, 124.9, 123.0, 121.3, 120.9, 115.8, 114.9, 20.4; HRMS (ESI-MS):Calc. for $C_{13}H_{11}N_3Na$ [(M+Na)$^+$]: 232.0845, Found: 232.0835.

8-Methyl-3-(naphthalen-2-yl)imidazo[1,2-*a*]pyridine (4f). Yellow solid. Yield: 61 mg (49%). mp= 106°C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31 (d, *J* = 6.9 Hz, 1H), 8.02 (s, 1H), 7.97 (d, *J* = 8.5 Hz, 1H), 7.92-7.85 (m, 2H), 7.80 (s, 1H), 7.66 (d, *J* = 8.5 Hz, 1H), 7.59-7.50 (m, 2H), 7.03 (d, *J* = 6.8 Hz, 1H), 6.76 (t, *J* = 6.8

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Hz, 1H), 2.68 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.7, 133.7, 132.9, 132.3, 129.1, 128.1, 127.9, 127.0, 126.8 (x2), 126.6, 126.3, 126.0, 123.4, 121.4, 112.9, 17.2; HRMS (ESI-MS):Calc. for $C_{18}H_{15}N_2$[(M+H)$^+$]: 259.123, Found: 259.1237

4-(2,7-Dimethylimidazo[1,2-*a*]pyridin-3-yl)benzonitrile (4g). White solid. Yield: 114 mg (84%). mp= 169-171°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.01 (d, *J* = 7.0 Hz, 1H), 7.83-7.78 (m, 2H), 7.60-7.55 (m, 2H), 7.35 (s, 1H), 6.63 (dd, *J* = 7.0, 1.6 Hz, 1H), 2.48 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.9, 142.4, 136.3, 135.6, 134.7, 133.0, 129.3, 122.1, 119.3, 118.8, 115.9, 115.3, 111.0, 21.4, 14.3; HRMS (ESI-MS):Calc. for $C_{16}H_{14}N_3$ [(M+H)$^+$]:248.1182, Found: 248.1209.

6-Chloro-3-(*p*-tolyl)imidazo[1,2-*a*]pyridine (4h). Brown semisolid. Yield: 45 mg (32%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.83 (dd, *J* = 1.9, 0.7 Hz, 1H), 7.67 (s, 1H), 7.62 (d, *J* = 9.2 Hz, 1H), 7.42 (d, *J* = 8.1 Hz, 2H), 7.35 (d, *J* = 7.9 Hz, 2H), 7.15 (dd, *J* = 9.5, 1.9 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 144.3, 138.9, 134.5, 133.0, 130.2, 128.2, 126.5, 126.1, 125.7, 121.4, 121.1, 118.6, 118.3, 21.5; HRMS (ESI-MS):Calc. for $C_{14}H_{12}ClN_2$ [(M+H)$^+$]: 243.0684, Found: 243.0704.

6-(6-Chloroimidazo[1,2-*a*]pyridin-3-yl)quinoxaline (4i). Yellow solid. Yield: 75 mg (55%). mp= 222°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.92 (d, *J* = 1.7 Hz, 1H), 8.90 (d, *J* = 1.8 Hz, 1H), 8.57 (d, *J* = 1.3 Hz, 1H), 8.32 (d, *J* = 1.8 Hz, 1H), 8.28 (d, *J* = 8.7 Hz, 1H), 7.99 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.93 (s, 1H), 7.70 (d, *J* = 9.5 Hz, 1H), 7.28-7.23 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.0, 145.5, 145.4, 143.5, 142.8, 135.0, 131.1, 130.7, 130.0, 127.0, 126.6, 125.1, 122.0, 121.4, 119.1; HRMS (ESI-MS):Calc. for C15H10ClN4 [(M+H)$^+$]: 281.0589, Found: 281.0603.

6-Chloro-3-(thiophen-2-yl)imidazo[1,2-*a*]pyridine (4j). Green semisolid. Yield: 88 mg (62%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.40 (dd, *J* = 2.0, 0.8 Hz, 1H), 7.77 (s, 1H), 7.63 (dd, *J* = 9.5, 0.8 Hz, 1H), 7.48 (dd, *J* = 5.2, 1.1 Hz, 1H), 7.30 (dd, *J* = 3.6, 1.1 Hz, 1H), 7.24-7.18 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.7, 134.6, 129.2, 128.1, 126.7, 126.6, 126.0, 121.8, 121.5, 119.8, 118.6; HRMS (ESI-MS):Calc. for $C_{11}H_7ClN_2NaS$ [(M+Na)$^+$]: 256.9911, Found: 256.9927.

6-Chloro-2-methyl-3-(naphthalen-2-yl)imidazo[1,2-*a*]pyridine (4k). Brown semisolid. Yield: 100 mg (70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.16 (d, *J* = 1.3 Hz, 1H), 8.03 (d, *J* = 8.5 Hz, 1H), 7.96-7.89 (m, 3H), 7.62-7.56 (m, 3H), 7.53 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.16 (dd, *J* = 9.5, 2.0 Hz, 1H); 2.53 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.8, 142.2, 133.7, 133.1, 129.3, 129.0, 128.2, 128.0, 127.0 (X2), 126.7, 126.1, 125.8, 122.3, 121.1, 120.7, 117.4, 14.0; HRMS (ESI-MS):Calc. for $C_{18}H_{14}ClN_2$ [(M+H)$^+$]: 293.084, Found: 293.0843.

2-Methyl-3-(naphthalen-1-yl)-8-(trifluoromethyl)imidazo[1,2-*a*]pyridine (4l). Yellow solid. Yield: 120 mg (95%). mp= 95-98°C. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03 (d, *J* = 8.2 Hz, 1H), 7.98 d, *J* = 8.2 Hz, 1H), 7.66 (d, *J* = 7.0 Hz, 1H), 7.63 (t, *J* = 7.2 Hz, 1H), 7.57-7.50 (m, 3H), 7.42 (t, *J* = 7.1 Hz, 1H), 7.31 (d, *J* = 8.4 Hz, 1H), 6.68 (t, *J* = 7.0 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.7, 140.2, 134.1, 132.2, 130.1, 129.9, 128.9, 127.2, 127.1, 126.6, 125.8, 125.7, 124.9, 123.2 (q, *J* = 272.1 Hz, CF3), 122.6, 122.5, 120.9, 110.1, 14.2; HRMS (ESI-MS):Calc. for $C_{19}H_{14}F_3N_2$ [(M+H)$^+$]: 327.1104, Found: 327.1139.

5-(2-Methyl-8-(trifluoromethyl)imidazo[1,2-*a*]pyridin-3-yl)isoquinoline (4m). Yellowish liquid. Yield: 118 mg (75%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.38 (s, 1H), 8.47 (d, *J* = 5.5 Hz, 1H), 8.15 (d, *J* = 8.0 Hz, 1H), 7.82-7.75 (m, 2H), 7.67 (d, *J* = 6.9 Hz, 1H), 7.54 (d, *J* = 7.0 Hz, 1H), 7.15 (d, *J* = 5.8 Hz, 1H), 6.75 (t, *J* = 7.0 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 153.4, 144.3, 144.2, 140.6, 134.9, 130.0, 129.6, 129.2, 127.4, 126.8, 125.1, 123.0, 123.1 (q, J = 272.1 Hz, CF3), 122.9, 119.4, 117.7, 110.6, 14.2; HRMS (ESI-MS):Calc. for $C_{18}H_{12}F_3N_3Na$ [(M+Na)$^+$]: 350.0876, Found: 350.0911.

4-(Thiophen-2-yl)benzonitrile (5a).[22] Yellow solid. Yield: 44 mg (21%). mp= 79-81°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71-7.68 (m, 2H), 7.67-7.64(m, 2H), 7.43-7.39 (m, 2H), 7.13 (dd, *J* = 5.1, 3.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 142.2, 138.8, 132.9 (x2), 128.7, 127.0, 126.2 (x2), 125.2, 119.0, 110.7; HRMS (ESI-MS):Calc. for $C_{11}H_7NNaS$ [(M+Na)$^+$]: 208.0191, Found: 208.0194.

4-(2,4-dimethylthiazol-5-yl)benzonitrile (5b).[23] Yellow solid. Yield: 70 mg (59%). mp= 69-70°C; ^{1}H NMR (400 MHz, $CDCl_3$): 7.69 (d, *J* = 8.5, Hz, 2H), 7.51 (d, *J* = 8.5 Hz, 2H), 2.71 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 165.0, 148.9, 137.3, 132.6 (x2), 129.6 (x2), 118.7, 111.1, 19.3, 16.5; HRMS (ESI-MS):Calc. for $C_{12}H_{11}N_2S$ [(M+H)$^+$]: 215.0637, Found: 215.0645.

4-(1-phenyl-1*H*-indol-2-yl)benzonitrile (5c).[24] Yellow solid. Yield: 70 mg (43%). mp= 184-186°C; ^{1}H NMR (400 MHz, $CDCl_3$): 7.76-7.72 (m, 1H), 7.57-7.53 (m, 2H), 7.50-7.47 (m, 2H), 7.43-7.46 (m, 1H), 7.37-7.40 (m, 2H), 7.31-7.34 (m, 1H), 7.27-7.30 (m, 2H), 7.27-7.26 (m, 1H), 7.21-7.25 (m, 1H), 6.95 (S, 1H); ^{13}C NMR (100 MHz, $CDCl_3$):139.8, 138.5, 138.1, 137.1, 132.1 (x2), 129.7 (x2), 129.0 (x2), 128.0 (x2), 127.9, 123.6, 121.3, 121.1, 118.9, 110.9, 110.6, 105.8; HRMS (ESI-MS):Calc. for $C_{21}H_{14}N_2Na$ [(M+Na)$^+$]: 317.1049, Found: 317.1059.

4-(1-phenyl-1*H*-indol-3-yl)benzonitrile (5c').[25] Yellow solid. Yield: 12 mg (7%). mp= 105-107°C; ^{1}H NMR (400 MHz, $CDCl_3$): 7.99-7.95 (m, 1H), 7.84-7.80 (m, 2H), 7.75-7.71 (m, 2H), 7.62-7.59 (m, 2H), 7.58-7.53 (m, 4H), 7.46-7.41 (m, 1H), 7.34-7.28 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): 140.3, 139.1, 137.1, 132.8 (x2), 130.0 (x2), 127.6 (x2), 127.4, 126.9, 126.5, 124.8 (x2), 123.5, 121.7, 119.9, 119.5, 117.4, 111.4, 109.3; HRMS (ESI-MS):Calc. for $C_{21}H_{14}N_2Na$ [(M+Na)$^+$]: 317.1049, Found: 317.1043.

4-(benzofuran-2-yl)benzonitrile (5d).[26] Yellow solid. Yield: 82 mg (34%). mp= 121-125°C; ^{1}H NMR (400 MHz, $CDCl_3$):7.97-7.93 (m, 2H), 7.74-7.71 (m, 2H), 7.65-7.61 (m, 1H), 7.56-7.53 (m, 1H), 7.38-7.33 (m, 1H), 7.30-7.25 (m, 1H), 7.18 (d, *J* = 0.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 155.4, 153.7, 134.6, 132.7 (x2), 128.8, 125.7, 125.2 (x2), 123.6, 121.6, 118.9, 111.6 (x2), 104.5; HRMS (ESI-MS):Calc. for $C_{15}H_9NNaO$ [(M+Na)$^+$]: 242.0576, Found: 242.0586.

4,4'-(benzofuran-2,3-diyl)dibenzonitrile (5d').[26] Yellow solid. Yield: 43 mg (12%). mp= 165-167°C; ^{1}H NMR (400 MHz, $CDCl_3$): 7.83-7.78 (m, 2H), 7.72-7.68 (m, 2H), 7.64-7.58 (m, 5H), 7.49-7.40 (m, 2H), 7.34-7.29 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): 154.5, 149.1, 137.4, 134.3, 133.2 (x2), 132.6 (x2), 130.5 (x2), 129.1, 127.4 (x2), 126.5, 124.0, 120.1, 118.7, 118. 6, 118.5, 112.3 (x2), 111.8; HRMS (ESI-MS):Calc. for $C_{22}H_{12}N_2NaO$ [(M+Na)$^+$]: 343.0842, Found: 343.0868.

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Notes and references

1. F. Couty and G. Evano, in *Comprehensive Heterocyclic Chemistry III*, eds. A. R. Katritzky, C. A. Ramsden, E. F. V. Scriven and R. J. K. Taylor, Elsevier, Oxford, 2008, vol. 11, pp. 409-499.
2. (a)C. Enguehard-Gueiffier and A. Gueiffier, *Mini-Rev Med Chem*, 2007, **7**, 888-899; (b)S. Feng, D. Hong, B. Wang, X. Zheng, K. Miao, L. Wang, H. Yun, L. Gao, S. Zhao and H. C. Shen, *ACS Med Chem Lett*, 2015, **6**, 359-362; (c)A. C. Humphries, E. Gancia, M. T. Gilligan, S. Goodacre, D. Hallett, K. J. Merchant and S. R. Thomas, *Bioorg Med Chem Lett*, 2006, **16**, 1518-1522; (d)S. Ulloora, R. Shabaraya, S. Aamir and A. V. Adhikari, *Bioorg Med Chem Lett*, 2013, **23**, 1502-1506; (e)C. Enguehard, J. L. Renou, H. Allouchi, J. M. Leger and A. Gueiffier, *Chem Pharm Bull (Tokyo)*, 2000, **48**, 935-940; (f)Z. A. Kaplancikli, G. Turan-Zitouni, A. Ozdemir and G. Revial, *J Enzym Inhib Med Ch*, 2008, **23**, 866-870; (g)M. H. Fisher and A. Lusi, *J Med Chem*, 1972, **15**, 982-985; (h)Y. Rival, G. Grassy, A. Taudou and R. Ecalle, *Eur J Med Chem*, 1991, **26**, 13-18; (i)C. Hamdouchi, J. de Blas, M. del Prado, J. Gruber, B. A. Heinz and L. Vance, *J Med Chem*, 1999, **42**, 50-59; (j)J. J. Kaminski and A. M. Doweyko, *J Med Chem*, 1997, **40**, 427-436; (k)M. Lhassani, O. Chavignon, J. M. Chezal, J. C. Teulade, J. P. Chapat, R. Snoeck, G. Andrei, J. Balzarini, E. De Clercq and A. Gueiffier, *Eur J Med Chem*, 1999, **34**, 271-274; (l)Y. Maruyama, K. Anami and Y. Katoh, *Arzneimittelforschung*, 1978, **28**, 2102-2107; (m)M. A. Ismail, R. K. Arafa, T. Wenzler, R. Brun, F. A. Tanious, W. D. Wilson and D. W. Boykin, *Bioorg Med Chem*, 2008, **16**, 683-691; (n)N. S. Rao, C. Kistareddy, B. Balaram and B. Ram, *Der Pharma Chemica*, 2012, **4**, 2408-2415.
3. K. Pethe, P. Bifani, J. C. Jang, S. Kang, S. Park, S. Ahn, J. Jiricek, J. Y. Jung, H. K. Jeon, J. Cechetto, T. Christophe, H. Lee, M. Kempf, M. Jackson, A. J. Lenaerts, H. Pham, V. Jones, M. J. Seo, Y. M. Kim, M. Seo, J. J. Seo, D. Park, Y. Ko, I. Choi, R. Kim, S. Y. Kim, S. Lim, S. A. Yim, J. Nam, H. Kang, H. Kwon, C. T. Oh, Y. Cho, Y. Jang, J. Kim, A. Chua, B. H. Tan, M. B. Nanjundappa, S. P. S. Rao, W. S. Barnes, R. Wintjens, J. R. Walker, S. Alonso, S. Lee, J. Kim, S. Oh, T. Oh, U. Nehrbass, S. J. Han, Z. No, J. Lee, P. Brodin, S. N. Cho, K. Nam and J. Kim, *Nat Med*, 2013, **19**, 1157-1160.
4. A. K. Bagdi, S. Santra, K. Monir and A. Hajra, *Chem Commun*, 2015, **51**, 1555-1575.
5. (a)C. Enguehard, J. L. Renou, V. Collot, M. Hervet, S. Rault and A. Gueiffier, *J Org Chem*, 2000, **65**, 6572-6575; (b)S. C. Goodacre, L. J. Street, D. J. Hallett, J. M. Crawforth, S. Kelly, A. P. Owens, W. P. Blackaby, R. T. Lewis, J. Stanley, A. J. Smith, P. Ferris, B. Sohal, S. M. Cook, A. Pike, N. Brown, K. A. Wafford, G. Marshall, J. L. Castro and J. R. Atack, *J Med Chem*, 2006, **49**, 35-38; (c)M. Crawforth, S. C. Goodacre, D. J. Hallet, T. Harrison, A. P. Owens, M. Rowley and M. R. Teall, *PCT Int Appl*, WO2001038326A2, 2001; (d)T. Bilodeau, M. E. Fraley and Z. Wu, *PCT Int Appl*, WO2003092595A2, 2003.
6. (a)A. M. Badger, P. E. Bender, K. M. Esser, D. E. Griswolds, H. Nabil, J. C. Lee, B. J. Votta and P. L. Simon, *PCT Int Appl*, WO 1991000092 A1, 1991; (b)Y. Kawai, S. Satoh, H. Yamasaki, N. Kayakiri, K. Yoshihara and T. Oku, *PCT Int Appl*, WO 1996034866 A1, 1996.
7. J. Koubachi, S. El Kazzouli, S. Berteina-Raboin, A. Mouaddib and G. Guillaumet, *Synlett*, 2006, 3237-3242.
8. S. H. Wang, W. J. Liu, J. H. Cen, J. Q. Liao, J. P. Huang and H. Y. Zhan, *Tetrahedron Lett*, 2014, **55**, 1589-1592.
9. (a)J. Lee, J. Chung, S. M. Byun, B. M. Kim and C. Lee, *Tetrahedron*, 2013, **69**, 5660-5664; (b)H. Y. Fu, L. Chen and H. Doucet, *J Org Chem*, 2012, **77**, 4473-4478; (c)H. Cao, H. Y. Zhan, Y. G. Lin, X. L. Lin, Z. D. Du and H. F. Jiang, *Org Lett*, 2012, **14**, 1688-1691; (d)S. Marhadour, M. A. Bazin and P. Marchand, *Tetrahedron Lett*, 2012, **53**, 297-300; (e)P. Y. Choy, K. C. Luk, Y. Wu, C. M. So, L. L. Wang and F. Y. Kwong, *J Org Chem*, 2015, **80**, 1457-1463.
10. B. Mu, Y. Wu, J. Li, D. Zou, J. Chang and Y. Wu, *Org Biomol Chem*, 2016, **14**, 246-250.
11. (a)J. Y. Lee, P. Y. Cheng, Y. H. Tsai, G. R. Lin, S. P. Liu, M. H. Sie and H. M. Lee, *Organometallics*, 2010, **29**, 3901-3911; (b)K. J. Cavell, D. J. Stufkens and K. Vrieze, *Inorganica Chimica Acta*, 1981, **47**, 67-76.
12. D. Nandi, Y. M. Jhou, J. Y. Lee, B. C. Kuo, C. Y. Liu, P. W. Huang and H. M. Lee, *J Org Chem*, 2012, **77**, 9384-9390.
13. (a)J. G. de Vries, *Can J Chem*, 2001, **79**, 1086-1092; (b)A. H. M. de Vries, J. M. C. A. Mulders, J. H. M. Mommers, H. J. W. Henderickx and J. G. de Vries, *Org Lett*, 2003, **5**, 3285-3288.
14. J. G. de Vries, *Dalton Trans*, 2006, 421-429.
15. (a)R. W. DeSimone, K. S. Currie, S. A. Mitchell, J. W. Darrow and D. A. Pippin, *Comb Chem High Throughput Screen*, 2004, **7**, 473-494; (b)N. S. Gray, L. Wodicka, A. M. Thunnissen, T. C. Norman, S. Kwon, F. H. Espinoza, D. O. Morgan, G. Barnes, S. LeClerc, L. Meijer, S. H. Kim, D. J. Lockhart and P. G. Schultz, *Science*, 1998, **281**, 533-538; (c)F. R. de Sa Alves, E. J. Barreiro and C. A. Fraga, *Mini Rev Med Chem*, 2009, **9**, 782-793; (d)M. E. Welsch, S. A. Snyder and B. R. Stockwell, *Curr Opin Chem Biol*, 2010, **14**, 347-361; (e)B. R. Stockwell, *Nature*, 2004, **432**, 846-854; (f)R. Breinbauer, I. R. Vetter and H. Waldmann, *Angew Chem Int Ed* 2002, **41**, 2879-2890; (g)H. B. Rode, M. L. Sos, C. Grutter, S. Heynck, J. R. Simard and D. Rauh, *Bioorg Med Chem*, 2011, **19**, 429-439; (h)S. J. Haggarty, *Curr Opin Chem Biol*, 2005, **9**, 296-303; (i)E. J. Barreiro, in *Privileged Scaffolds in Medicinal Chemistry : Design, Synthesis, Evaluation* ed. S. Bräse Royal Society of Chemistry 2015, pp. 1-11.
16. J. A. Blair, D. Rauh, C. Kung, C. H. Yun, Q. W. Fan, H. Rode, C. Zhang, M. J. Eck, W. A. Weiss and K. M. Shokat, *Nat Chem Biol*, 2007, **3**, 229-238.
17. (a)G. C. Moraski, L. D. Markley, P. A. Hipskind, H. Boshoff, S. Cho, S. G. Franzblau and M. J. Miller, *ACS Med Chem Lett*, 2011, **2**, 466-470; (b) F. Hongli, L. Xin, L. Xinsheng and C. Jintao, *PCT Chin Appl*, CN 103965190 A, 2014.
18. (a)J. Roger, F. Pozgan and H. Doucet, *Green Chem*, 2009, **11**, 425-432; (b)J. J. Dong, J. Roger, F. Pozgan and H. Doucet, *Green Chem*, 2009, **11**, 1832-1846; (c)J. Roger and H. Doucet, *Adv Synth Catal*, 2009, **351**, 1977-1990; (d)J. Roger and H. Doucet, *Tetrahedron*, 2009, **65**, 9772-9781.
19. B. Frett, N. McConnell, C. C. Smith, Y. Wang, N. P. Shah and H. Y. Li, *Eur J Med Chem*, 2015, **94**, 123-131.

View Article Online
DOI: 10.1039/C6RA12166G

20. H. Y. Fu, L. Q. Zhao, C. Bruneau and H. Doucet, *Synlett*, 2012, 2077-2082.
21. G. P. Liu, X. F. Cong, J. H. He, S. Z. Luo, D. Wu and J. B. Lan, *J Chem Res*, 2012, 687-690.
22. S. Shaaban, A. Jolit, D. Petkova and N. Maulide, *Chem Commun*, 2015, **51**, 13902-13905.
23. X. X. He, Y. F. Li, J. Huang, D. S. Shen and F. S. Liu, *J Organomet Chem*, 2016, **803**, 58-66.
24. U. Sharma, R. Kancherla, T. Naveen, S. Agasti and D. Maiti, *Angew Chem Int Ed Engl*, 2014, **53**, 11895-11899.
25. R. Kancherla, T. Naveen and D. Maiti, *Chem Eur J*, 2015, **21**, 8723-8726.
26. T. Dao-Huy, M. Haider, F. Glatz, M. Schnurch and M. D. Mihovilovic, *European J Org Chem*, 2014, **2014**, 8119-8125.

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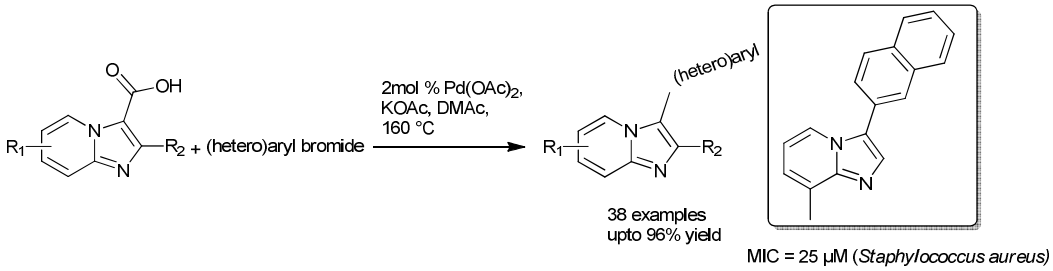

A facile ligand-free method for $Pd(OAc)_2$ catalysed decarboxylative arylation of imidazo[1,2-*a*]pyridine-3-carboxylic acids with hetero(aryl) bromides has been developed. This method is applicable to variety of (hetero)aryl bromides as coupling partner. Electron withdrawing and donating groups on imidazo[1,2-*a*]pyridine-3-carboxylic acids are well tolerated. It represent the first general protocol for ligand-free $Pd(OAc)_2$ catalysed decarboxylative arylation of imidazo[1,2-*a*]pyridine-3-carboxylic acids with (hetero)aryl bromides. Few of the compounds generated using this protocol showed antibacterial activity against *Staphylococcus aureus*.