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One pot synthesis of naphtho[1',2':4,5]imidazo[1,2-*a*]pyridin-5-yl(aryl)methanones *via* a sequential Sonogashira coupling/alkyne-carbonyl metathesis

Mirza Feroz Baig,[a,b] Siddiq Pasha Shaik,[a,b] Namballa Hari Krishna,[a,c] Neeraj Kumar Chouhan,[a,c] Abdullah Alarifi,[d] and Ahmed Kamal*[a,c,d]

Abstract:
An efficient one-pot route for the construction of naphtho[1',2':4,5]imidazo[1,2-*a*]pyridin-5-yl(aryl)methanones and 5-phenylnaphtho[1',2':4,5]imidazo[1,2-*a*]pyridines via a sequential Sonogashira coupling followed by TFA promoted alkyne-carbonyl metathesis (ACM) has been developed. 2-(2-bromophenyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde underwent preferentially ACM pathway with phenyl acetylenes. While intramolecular hydroarylation was the common pathway in the absence of carbonyl moiety at C-3 position under similar conditions. This protocol is compatible towards a wide variety of functional groups and delivered corresponding naphtho[1',2':4,5]imidazo[1,2-*a*]pyridines in good to excellent yields.

Introduction

Fused nitrogen heterocycles constitute an important class of polycyclic heterocycles which are ubiquitous structural skeletons in numerous natural products with interesting biological properties and pharmacologically active compounds. Among them, Imidazo[1,2-*a*]pyridines, particularly their fused variants are predominantly attractive because of their intriguing structural features, extensive applications in material science[1-3] and far-reaching pharmaceutical applications,[4,5] where they exhibit a plenty of biological activities such as antifungal **A**,[6] anticancer **B**,[7] and antimalarial **C**[8] (Figure 1), anticonvulsant, antiviral, antimicrobial, anti-inflammatory, and antibacterial. Despite their biological properties, not many synthetic approaches have reported in the literature[9]. Considering the importance of these fused heterocyclic motifs and limited synthetic approaches, development of efficient methodologies for the synthesis of these fused heterocycles is highly desirable. On the other hand, one pot domino reactions have emerged as powerful tools for the construction of fused heterocycles from relatively simple building blocks through atom and step economic transformations by forming multiple bonds in single operation, which enable the generation of huge libraries of scaffolds for high-throughput screening which is a key requisite for drug discovery process. Alkyne-carbonyl metathesis (ACM)[10-14] represents a valuable tool for the synthesis of substituted *α*, *β*-unsaturated carbonyl compounds via a [2+2] cycloaddition and cycloreversion process between C−O double bond and C−C triple bond in atom economical manner which is a viable alternative for the traditional aldol and Wittig reactions for the construction of C-C double bonds.[15]

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Particularly, intramolecular ACM version is attractive as it generates a variety of complex carbonyl and heterocycles from simple starting materials. Generally, these reactions are catalyzesd by Lewis acids, strong Brønsted acids or transition-metal catalysts.[16]

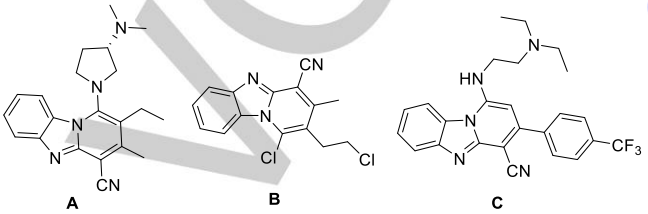
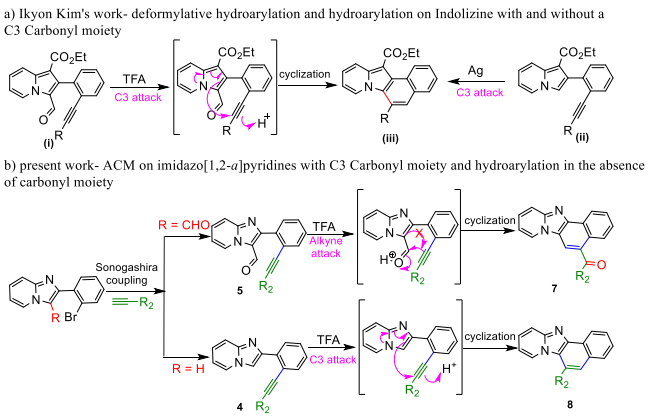


Figure1. Medicinally interesting imidazo[1,2-*a*] pyridine benzimidazole-fused heterocycles.

As part of our research interest in developing one pot operations for the synthesis of bio-active scaffolds,[17] we wish to synthesise naphtho[1',2':4,5]imidazo[1,2-*a*]pyridines with distinctive substitutions by employing intramolecular ACM on imidazo[1,2-*a*]pyridine substituted with formyl and alkyne functionalities at appropriate position, which was generated in-situ from imidazo[1,2-*a*]pyridine bearing formyl and bromo group through Sonogashira cross-coupling in one pot operation. While our studies are under way, Kim and co-workers reported a TFA promoted deformylative intramolecular hydroarylation on formyl and alkyne substituted indolizines as shown in Scheme 1 along with traces of intramolecular ACM product.[18]Interestingly, during our study, we were pleased to observe that intramolecular ACM was the major pathway resulting in generation of only naphtho[1',2':4,5]imidazo[1,2-*a*]pyridine (5) with an acyl substituent at the C5 position exclusively, these interesting results prompted us to scrutinize the method in detail, and the findings are presented here.

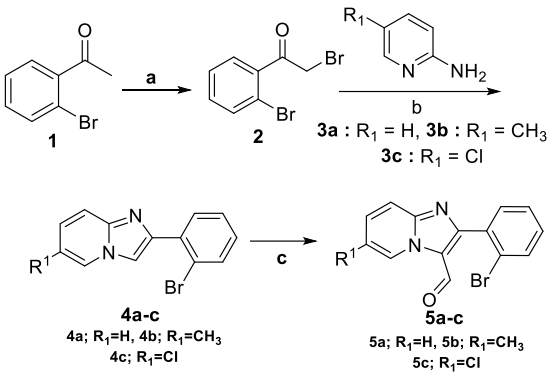
Scheme1. TFA promoted reactions of indolizines and imidazo[1,2-*a*]pyridines with and without C3 formyl group.



Results and Discussion

Our study commenced with the preparation of required starting materials for which relatively a straightforward synthetic approach was followed. Initially pyridin-2-amines are condensed with 2-bromo-1-(2-bromophenyl)ethanone (2), which were obtained from the corresponding 1-(2-bromophenyl)ethanone (1) to produce 2-(2-bromophenyl)imidazo[1,2-*a*]pyridine (4) under refluxing condition in presence of base. Compound 4 was subsequently subjected to Vilsmeier-Haack formylation to generate the required 2-(2-bromophenyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde (5) in good yields.

Scheme 2. Synthesis of 2-(2-bromophenyl)imidazo [1,2-a]pyridine-3-carbaldehyde 5a-c

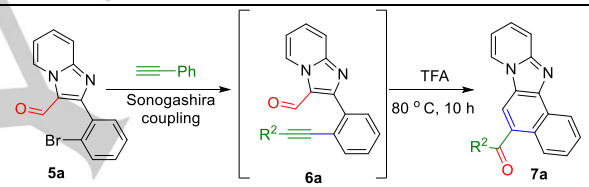


Reagents and conditions: (a) NBS, *p*-TSA, CH_3CN, 80 °C, 8 h, 85%; (b) EtOH, reflux, 8 h, 85-94%; and (c) $POCl_3$, DMF, $CHCl_3$, 0 °C to rt, 10 h, 80-89%.

After having the required starting materials in hand, the optimal conditions for one-pot Sonogashira cross-coupling/ACM operation were explored *via* a sequential exposure to Sonogashira conditions by changing the Pd catalyst as well as base followed by different acidic conditions and the results are summarized in Table 1. When 2-(2-bromophenyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde (**5**) was treated with phenyl acetylene in presence of $Pd(PPh_3)_4$ followed by different Lewis acids such as $In(OTf)_3$,$Bi(OTf)_3$ no required product was observed even in trace amounts. Usage of $Yb(OTf)_3$ resulted in formation of 1-(naphtho[1',2':4,5]imidazo[1,2-*a*]pyridin-5-yl)ethanone (**7**) in 14% yield (table 1, entry 3) and the structure was unambiguously confirmed by its spectroscopic data. It was found that increasing the temperature to refluxing conditions led to improvement in the yield (table 1, entry 4). Comparably better yields were obtained when the reaction was carried out in presence of TFA, and the yields were increased with increasing the temperature to 80 °C (table 1, entries 5 & 6). Switching the palladium source from $Pd(PPh_3)_4$ to $Pd(PPh_3)_2Cl_2$ has significantly improved the yield of the product, however in none of the conditions intramolecular hydroarylation product was observed. Moreover, decrease in the yield was observed with more polar solvent like DMF.

With the optimized conditions established, the generality and scope of this protocol was explored. As depicted in schemes 3 & 4, the reaction demonstrated wide substrate scope with respect to the aromatic terminal alkyne as well as imidazo[1,2-*a*]pyridine moiety. Electron rich (e.g., 3-OMe, 4-OMe) as well as electron-neutral (e.g., 3-Me, 4-Me, 4-Et, 2,4,5-Tri-Me) substituents on the aromatic alkyne increased the rate of reaction and provided the corresponding products (**7b, 7c, 7d, 7h, 7i** & **7l** as shown in Scheme 3, **7n**, **7o**, **7p**, **7q**, **7s**, **7t**, **7u**, **7v**, & **7w** as shown in Scheme 4) in excellent yield. However, aromatic alkynes bearing the inductively electron withdrawing (e.g., 4-F & 2, 4-Di-F) and electron deficient (4-formyl) substituents are relatively less reactive and comparably lesser yields of the products were observed (**7e** & **7f**, Scheme 3), which clearly demonstrates the influence of electronic nature on the rate and efficiency of the reaction. Furthermore, 2-ethynyl-6-methoxynaphthalene also reacted smoothly with various imidazo[1,2-*a*]pyridines to afford the expected products (**7l**: 83%, **7z:** 68%, & **7aa:** 74%) in good yield. In addition, heteroaryl alkyne such as thienyl acetylene was also well compatible with the optimized conditions and gave the corresponding product in 78% yield. Even aliphatic acetylene such as 3-ethynylcyclohex-1-ene also furnished the corresponding product however the yield is comparably less than the aromatic acetylenes. Subsequently, the substrate scope of this reaction was extended to imidazo[1,2-*a*]pyridine moiety, it is noteworthy to observed that the electron density on the imidazo[1,2-*a*]pyridine is not affect the efficiency of this reaction (Scheme 4).

Table 1. Optimization of reaction conditions for one-pot synthesis of 7a[a]

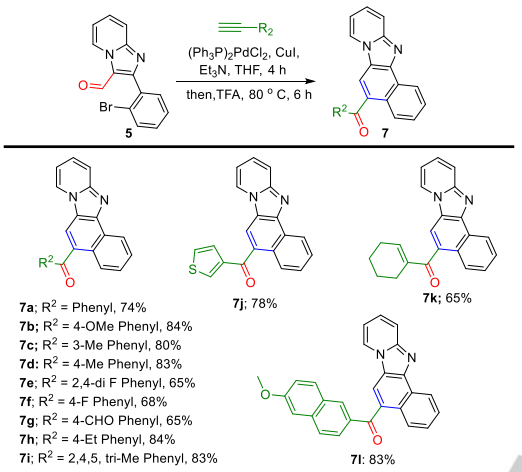


Enty	Catalyst (5 mol %)	Base/ Solvet	Acid	Temp(°C) /Time(h)	7a(%)[b]
1	$Pd(PPh_3)_4$	DIPA/ THF	$In(OTf)_3$ (5 mol %)	rt/16	nr
2	$Pd(PPh_3)_4$	Et_3N/ THF	$Bi(OTf)_3$ (5 mol %)	rt/16	nr
3	$Pd(PPh_3)_4$	Et_3N/ THF	$Yb(OTf)_3$ (5 mol %)	rt/16	14
4	$Pd(PPh_3)_4$	Et_3N/ THF	$Yb(OTf)_3$ (5 mol %)	80/10	27
5	$Pd(PPh_3)_4$	Et_3N/ THF	TFA	rt/12	35
6	$Pd(PPh_3)_4$	Et_3N/ THF	TFA	80/12	43
7	$Pd(PPh_3)_2Cl_2$	Et_3N/ THF	TFA	rt/16	52
8	**$Pd(PPh_3)_2Cl_2$**	**Et_3N/ THF**	**TFA**	**80/10**	**84**
9	$Pd(PPh_3)_2Cl_2$	DIPA/ THF	TFA	80/12	57
10	$Pd(PPh_3)_2Cl_2$	Et_3N/ DMF	TFA	90/12	35
11	$PdCl_2$	Et_3N/ THF	TFA	80/16	41

[a]The reactions were run with **5a** (0.16 mmol), alkynes (1.2 equiv), pd catalyst (5 mol %), CuI (5 mol %) and base (3 equiv) in solvent (4 mL) at 80 °C, after 4 h acid (0.5 mL) was added and heated for 6 more hours. [b]Isolated yield (%).

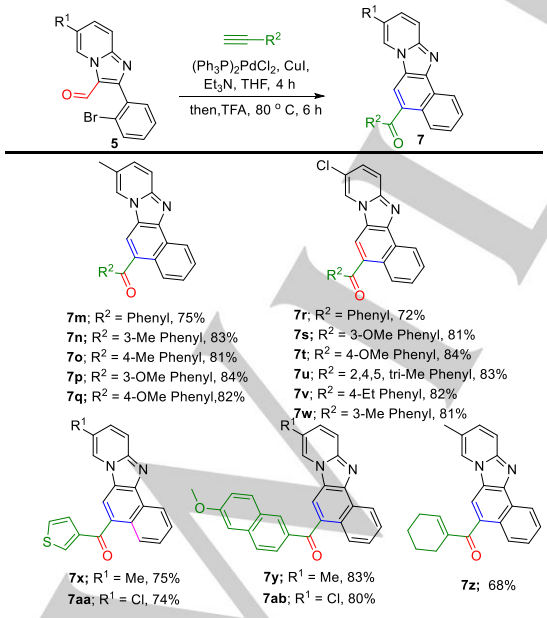
In light of these encouraging results, we expected that 2-(2-bromophenyl)imidazo[1,2-*a*]pyridine without formyl group could undergo intramolecular hydroarylation, thus cyclization of 2-(2-bromophenyl)imidazo[1,2-*a*]pyridine with 4-methoxy phenyl acetylene under the conditions mentioned above resulted in hydroarylated product i.e., naphtho[1',2':4,5]imidazo[1,2-*a*]pyridine with an aryl substituent at C6 position. This is similar to Kim's intramolecular hydroarylated product on indolizine with carboxylate and alkyne group (Scheme 5). Then to elaborate the substrate scope; a variety of alkyne partners were treated with 2-(2-bromophenyl)imidazo[1,2-*a*]pyridine which delivered the corresponding C6 arylated naphtho[1',2':4,5]imidazo[1,2-*a*]pyridines (**8a**, **8b** & **8c**) in good yields.

Scheme 3. Substrate Scope of phenyl acetylenesa,b



[a]The reactions were run with: 5 (0.16 mmol), alkynes (1.2 equiv), $(Ph_3P)_2PdCl_2$ (5 mol %), CuI (5 mol %) and Et_3N (3 equiv) in THF (4 mL) at 80 °C, after 4 h TFA (0.5 mL) was added and heated for 6 more hours. [b]Isolated yield (%).

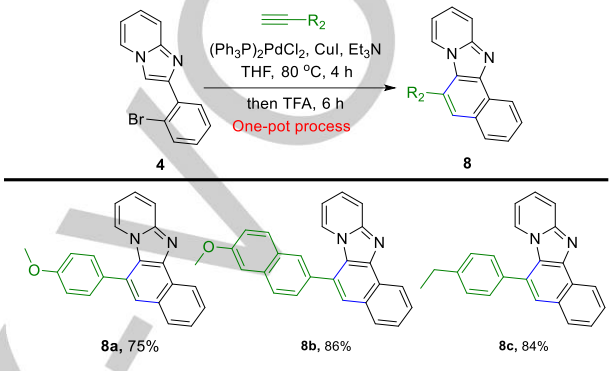
Scheme 4. Substrate Scope of imidazo[1,2-*a*]pyridines[a,b]



[a]The reactions were run with: 5 (0.16 mmol), alkynes (1.2 equiv), $(Ph_3P)_2PdCl_2$ (5 mol %), CuI (5 mol %) and Et_3N (3 equiv) in THF (4 mL) at 80 °C, after 4 h TFA (0.5 mL) was added and heated for 6 more hours. [b]Isolated yield (%).

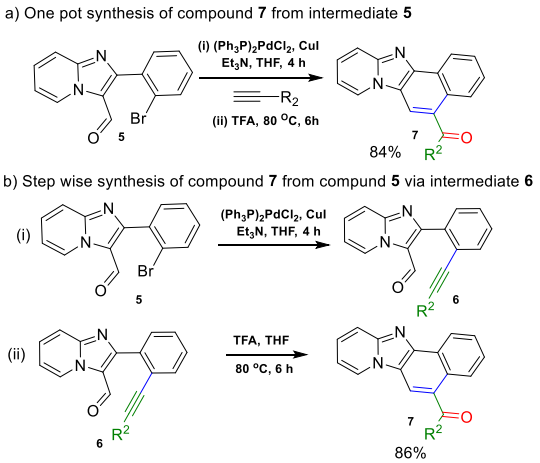
Finally to know whether the differential reactivity is due to substrate structure (indolizine and imidazopyridine) or due to the reaction conditions (two steps and one-pot), few controlled experiments were conducted. Accordingly a reaction was performed by isolating the product obtained after Sonogashira coupling i.e with compound **8** (equation ii, Scheme 6), which resulted in ACM product in 86% yields. This concludes that the differential reactivity is not due to the reactions conditions but due to the difference in substrate i.e imidazo [1,2-*a*]pyridine (Scheme 6).

Scheme 5. Synthesis of 8 from 4[a,b]



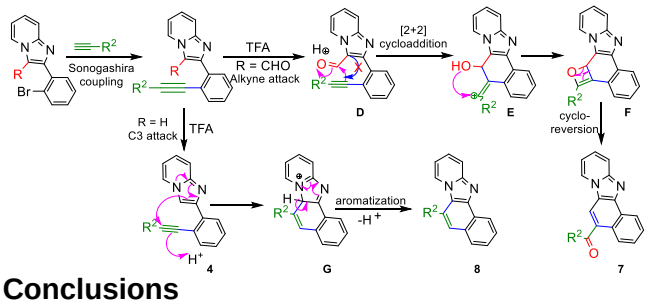
On bases of the related reports and based on our observations, the reasons behind the differential reactivity of indolizines and imidazo[1,2-*a*]pyridine moieties both bearing formyl and alkyne groups under similar catalysis could be explained by their electronic nature. It is seemed that the deformylative intramolecular hydroarylation on indolizines is due to the fact that the C3 site in indolizine is too electron rich to attack the neighbouring alkyne moiety that ultimately forms an indolizinium salt which after by subsequent extrusion of formyl group retains aromaticity. In contrast, the C3-site of imidazo[1,2-*a*]pyridine is not sufficiently nucleophilic to attack the alkyne moiety, which might be due to the presence of electronegative nitrogen atom at the C2-position in imidazo[1,2-*a*]pyridine (scheme 5). Instead, it is assumed that intramolecular [2+2] cycloaddition pathway is enabled resulting in oxetene (**F**) *via* a vinylic cation intermediate with hydroxyl group (**E**) due to attack of alkyne onto more

Scheme 6. Control Experiments



nucleophilic, protonated carbonyl carbon before C3-site attacks onto the alkyne group. This after subsequent cycloreversion delivers the desired product (**7**). However, in the absence of formyl group i.e. with 2-(2-bromophenyl)imidazo[1,2-*a*]pyridine (**4**) intramolecular hydroarylation is the predominant pathway, resulting in generation of C-6 aryl substituted naphtho[1',2':4,5]imidazo[1,2-*a*]pyridine **(8)**.

Scheme 7. Proposed Mechanism for formation of 6 and 7



Conclusions

In summary, an efficient one-pot method for the synthesis of naphtho[1',2':4,5]imidazo[1,2-*a*]pyridin-5-yl(aryl)methanones *via a* sequential Sonogashira coupling followed by TFA promoted alkyne-carbonyl metathesis was achieved. Noteworthy is the imidazo[1,2-*a*]pyridines propensity to deliver alkyne-carbonyl metathesis (ACM) product in contrast to the indolizines which induce hydroarylation under the similar conditions. Additionally, facile formation of C-6 aryl substituted naphtho[1',2':4,5]imidazo[1,2-*a*]pyridines from imidazo[1,2-*a*]pyridine without a formyl group at the C3 position *via* hydroarylation under the similar conditions was achieved. Further decoration of this skeleton by varying the substitution pattern and biological evaluation of the synthesized compounds are underway.

Experimental Section

General: Starting materials, reagents, and solvents were purchased as reagent grade and used without further purification. ^{1}H and 13C NMR spectra were recorded on a 300, 400 and 500 MHz spectrometer at 25 °C. Chemical shifts values are given in ppm and calibrated relative to the residual signal of the TMS solvent. The peak patterns are defined as follows: s, singlet; d, doublet; t, triplet; q, quartet; qui, quintet; m, multiplet; dd, doublet of doublets, and td, triplet of doublets. The coupling constants J, are reported in Hertz (Hz). Column chromatography was performed over silica gel (60− 120 mesh or 100−200 mesh) using a mixture of n-hexane and ethyl acetate (EtOAc) as the eluent. TLC plates (Silica gel GF254) were visualized by exposure to ultraviolet light. High resolution mass spectrometry (HRMS) was obtained on a QTOF micro spectrometer. Melting points were determined with a melting point apparatus without corrections. Organic solutions were concentrated by rotary evaporation below 45 °C in vacuum.

Synthetic Procedures:

2-(2-Bromophenyl)imidazo[1,2-*a*]pyridine (4a): A mixture of 2-bromo-2'-bromoacetophenone (3 g, 10.81 mmol) and 2-aminopyridine (10.81 mmol) in ethanol (30mL) was heated at 70 ºC for 8 h. After completion of reaction (monitored by TLC), the mixture was cooled and solvent was evaporated under reduced pressure. To this mixture, aqueous solution of $NaHCO_3$ was added to quench the reaction, and then extracted with ethyl acetate and dried over anhydrous Na_2SO_4. The crude compound was purified using silica gel (60-120 mesh) column chromatography to give **4a** as a Brown solid, 2.64 g, 91%; R_f = 0.3 (20% ethyl acetate in hexanes). Melting point: 131–132 ºC.1H NMR (500 MHz, $CDCl_3$) δ 8.28 (s, 1H), 8.17 – 8.14 (m, 1H), 8.14 – 8.12 (m, 1H), 7.67 (dd, J = 8.0, 1.2 Hz, 1H), 7.63 (d, J = 9.1 Hz, 1H), 7.43 – 7.39 (m, 1H), 7.17 (td, J = 7.6, 1.5 Hz, 2H), 6.78 (td, J = 6.7, 1.0 Hz, 1H).13C NMR (100 MHz, CDCl3) δ 144.5, 143.2, 134.4, 133.7, 131.7, 128.9, 127.6, 125.8, 124.8, 121.5, 117.6, 112.5, 112.1.HRMS (ESI)calcd for $C_{13}H_9BrN_2$ $[M+H]^+$273.00080, found 273.00219.

2-(2-Bromophenyl)-6-methylimidazo[1,2-*a*]pyridine (4b): Yellow solid, 2.74 g, 88%. R_f = 0.4 (20% ethyl acetate in hexanes).Melting point: 145–147 ºC; 1H NMR (400 MHz, $CDCl_3$) δ 8.20 (s, 1H), 8.13 (dd, J = 7.8, 1.7 Hz, 1H), 7.94 (s, 1H), 7.66 (dd, J = 8.0, 1.2 Hz, 1H), 7.55 (d, J = 9.2 Hz, 1H), 7.40 (tt, J = 5.5, 2.7 Hz, 1H), 7.20 – 7.13 (m, 1H), 7.04 (dd, J = 9.2, 1.6 Hz, 1H), 2.33 (s, 3H). ^{13}C NMR (100 MHz, CDCl3) δ 143.6, 142.8, 134.5, 133.7, 131.6, 128.8, 128.2, 127.6, 123.4, 122.2, 121.5, 116.9, 111.8, 18.2; HRMS (ESI) calcd for $C_{14}H_{12}BrN_2$ $[M]^+$ 287.01822, found 287.01784.

2-(2-Bromophenyl)-6-chloroimidazo[1,2-*a*]pyridine (4c): Brown solid, 2.7 g, 81%. R_f = 0.3 (25% ethyl acetate in hexanes).Melting point: 135–137 ºC ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 22.1 Hz, 1H), 7.99 (d, *J* = 6.8 Hz, 1H), 7.56 (t, *J* = 8.1 Hz, 1H), 7.52 – 7.44 (m, 1H), 7.35 – 7.26 (m, 1H), 7.19 (ddd, *J* = 23.0, 13.5, 6.4 Hz, 1H), 7.12 – 7.01 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 134.9, 133.8, 131.7, 129.8, 129.3, 127.7, 126.4, 123.6, 117.9, 112.3. HRMS (ESI) calcd for C13H8BrClN2 $[M+H]^+$306.96412, found 306.96322.

2-(2-Bromophenyl)imidazo[1,2-*a*]pyridine-3-carbaldehyde (5a): To a stirred solution of 4a(2 g, 6.7 mmol) in DMF (2 mL) at 0 °C was drop wise added $POCl_3$ (2.5 mL, 16.1 mmol) in $CHCl_3$ (18 mL). After being stirred at rt for 12 h, the reaction mixture was quenched with iced water and neutralized with aq. 2N NaOH solution at 0 °C. The solid was filtered and dried to furnish 5a as a pale brown solid, 1.8 g, 84%. R_f= 0.6 (20% ethyl acetate in hexanes). Melting point: 139.3–140.0 °C. 1H NMR (400 MHz, $CDCl_3$) δ 9.76 (s, 1H), 9.60 (dt, J = 6.8, 1.1 Hz, 1H), 7.84 (dt, J = 9.0, 1.0 Hz, 1H), 7.74 (dd, J = 8.0, 1.1 Hz, 1H), 7.63 – 7.59 (m, 1H), 7.59 – 7.55 (m, 1H), 7.49 – 7.43 (m, 1H), 7.37 (qd, J = 3.9, 2.0 Hz, 1H), 7.18 (td, J = 6.9, 1.2 Hz, 1H); 13C NMR (125 MHz, CDCl3) δ 179.4, 156.9, 147.6, 133.4, 133.4, 132.5, 131, 130.3, 128.6, 127.4, 123.4, 121.1, 117.7, 115.6 HRMS (ESI) calcd for $C_{14}H_9BrN_2O$ $[M]^+$ 300.99754, found 300.99710.

2-(2-Bromophenyl)-6-methylimidazo[1,2-*a*]pyridine-3-carbaldehyde (5b): Brown solid, 1.9 g, 89%; R_f = 0.7 (20% ethyl acetate in hexanes). Melting point: 141–142 °C.^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (s, 1H), 9.42 (s, 1H), 7.78 – 7.69 (m, 2H), 7.60 – 7.53 (m, 1H), 7.47 – 7.42 (m, 2H), 7.36 (td, J = 7.9, 1.4 Hz, 1H), 2.46 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.2, 156.8, 146.5, 133.6, 133.3, 133.1, 132.5, 130.9, 127.4, 126.6, 125.9, 123.4, 120.9, 116.9, 18.4.HRMS(ESI)calcd for $C_{15}H_{11}BrN_2O$ $[M+1]^+$ 315.01332, found 315.01275.

2-(2-Bromophenyl)-6-chloroimidazo[1,2-a]pyridine-3-carbaldehyde (5c) Yellow solid, 1.8 g, 85%. R_f = 0.4 (20% ethyl acetate in hexanes).Melting point: 148–149 ºC^{1}H NMR (500 MHz, $CDCl_3$) δ 9.78 – 9.64 (m, 1H), 8.43 (d, *J* = 26.3 Hz, 1H), 8.27 – 8.13 (m, 1H), 7.81 – 7.71 (m, 1H), 7.60 – 7.51 (m, 2H), 7.49 – 7.43 (m, 1H), 7.38 (td, *J* = 7.8, 1.8 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.5, 159.1, 156.9, 146.6, 145.8, 138.2, 133.4, 133.1, 132.4, 131.4, 127.5, 123.9, 121.2, 117.9; HRMS (ESI) calcd for $C_{14}H_8BrClN_2O$ $[M+H]^+$ 334.95884, found 334.95813.

Naphtho[1',2':4,5]imidazo[1,2-*a*]pyridin-5-yl(phenyl)methanone (7a): To a flask charged with 5a (80 mg, 0.26 mmol), $(Ph_3P)_2PdCl_2$ (9.3 mg, 0.05 equiv), CuI (2.5 mg, 0.05 equiv) and ethynylbenzene (27 mg, 1.5 equiv) in THF (4 mL) was added Et_3N (0.11 mL, 3.0 equiv) at rt. It was then after stirred at 80 °C for 2 h. Next, TFA (0.5 mL) was added and the resulting solution stirred at 80 ºC for 6 h. After concentration of the reactionmixture, purification by column chromatography on silica gel to give 7a as a pale yellow solid, 63 mg, 74%; R_f = 0.4 (30% ethyl acetate in

hexanes).Melting point: 204–205.0 °C^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (d, J = 8.1 Hz, 1H), 8.49 (d, J = 6.5 Hz, 1H), 8.33 (d, J = 8.5 Hz, 1H), 8.12 (s, 1H), 7.91 (d, J = 7.5 Hz, 3H), 7.74 (t, J = 7.4 Hz, 1H), 7.62 (q, J = 6.7 Hz, 2H), 7.50 (q, J = 7.8 Hz, 3H), 6.98 (t, J = 6.5 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.7, 148.8, 144.1, 143.3, 139.30, 136.4, 130.82, 130.7, 130.1, 129.3, 127.1, 127, 126.9, 124.8, 123.3, 122.8, 119, 114.1, 113.3, 111.9, 29.7; HRMS (ESI) calcd for $C_{22}H_{14}ON_2$ $[M+H]^+$ 323.11728, found 323.11789.

(4-Methoxyphenyl)(naphtho[1',2':4,5]imidazo[1,2-*a*]pyridin-5-yl)methanone (7b): Yellow solid, 78.5 mg, 84%; R_f = 0.5 (30% ethyl acetate in hexanes).Melting point: 197–198 °C.^{1}H NMR (300 MHz, $CDCl_3$) δ 8.93 (d, J = 8.1 Hz, 1H), 8.52 (d, J = 6.6 Hz, 1H), 8.21 (d, J = 8.4 Hz, 1H), 8.11 (s, 1H), 7.90 (d, J = 8.6 Hz, 2H), 7.74 (t, J = 7.2 Hz, 1H), 7.61 (d, J = 7.6 Hz, 1H), 7.57 – 7.48 (m, 2H), 7.01 (t, J = 5.9 Hz, 1H), 6.96 (d, J = 8.6 Hz, 2H), 3.90 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 196.3, 163.8, 148.6, 142.9, 132.8, 131.6, 131.3, 130, 128.8, 127, 126.9, 124.8, 123.3, 122.8, 118.2, 113.8, 112.6, 112, 55.6. HRMS (ESI)calcd for $C_{23}H_{16}O_2N_2$ $[M+H]^+$353.12831, found 353.12845.

Naphtho[1',2':4,5]imidazo[1,2-*a*]pyridin-5-yl(m-tolyl)methanone (7c): Yellow solid, 71 mg, 80%; R_f = 0.4 (30% ethyl acetate in hexanes).Melting point: 169–171 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.93 (d, J = 8.1 Hz, 1H), 8.50 (d, J = 6.7 Hz, 1H), 8.31 (d, J = 8.4 Hz, 1H), 8.11 (s, 1H), 7.94 (d, J = 9.1 Hz, 1H), 7.75 (t, J = 7.2 Hz, 2H), 7.67 – 7.59 (m, 2H), 7.55 – 7.51 (m, 1H), 7.44 (d, J = 7.5 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 7.01 (t, J = 6.7 Hz, 1H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 180,156.4, 147.8, 137.9, 134.4, 133.1, 132.1, 130.9, 129.9, 129.4, 128.6, 128.2, 123.6, 122.5, 121.1, 117.6, 115.34, 9.16, 87.9, 21.2.HRMS (ESI) calcd for $C_{23}H_{16}ON_2$ $[M+H]^+$337.13150, found 337.13354.

Naphtho[1',2':4,5]imidazo[1,2-*a*]pyridin-5-yl(*p*-tolyl)methanone (7d): Brown solid, 74 mg, 83%; R_f = 0.4 (30% ethyl acetate in hexanes). Melting point:198–199 °C.^{1}H NMR (500 MHz, $CDCl_3$) δ 8.93 (d, J = 8.1 Hz, 1H), 8.50 (d, J = 6.8 Hz, 1H), 8.28 (d, J = 8.4 Hz, 1H), 8.12 (s, 1H), 7.92 (d, J = 9.2 Hz, 1H), 7.81 (d, J = 8.0 Hz, 2H), 7.74 (t, J = 7.5 Hz, 1H), 7.60 (t, J = 7.4 Hz, 1H), 7.52 (t, 1H), 7.28 (d, J = 7.9 Hz, 2H), 7.00 (t, J = 6.7 Hz, 1H), 2.46 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.7, 148.8, 144.1, 143.3, 139.30, 136.4, 130.82, 130.7, 130.1, 129.3, 127.1, 127, 126.9, 124.8, 123.3, 122.8, 119, 114.1, 113.3, 111.9, 29.7.HRMS (ESI)calcd for $C_{23}H_{16}ON_2$ $[M+H]^+$337.13324, found 337.13354.

(2,4-Difluorophenyl)(naphtho[1',2':4,5]imidazo[1,2-*a*]pyridin-5-yl)methanone (7e): Yellow solid, 62.2 mg, 65%; R_f = 0.3 (30% ethyl acetate in hexanes).Melting point: 175–176 °C.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (d, J = 7.8 Hz, 1H), 8.66 (d, J = 8.3 Hz, 1H), 8.50 (d, J = 6.3 Hz, 1H), 8.16 (s, 1H), 7.92 (d, J = 9.0 Hz, 1H), 7.78 (dd, J = 15.1, 7.6 Hz, 2H), 7.73 – 7 .66 (m, 1H), 7.59 – 7.51 (m, 1H), 7.04 (dd, J = 11.8, 6.5 Hz, 2H), 6.91 (t, J = 8.6 Hz, 1H).^{13}C NMR (100 MHz, $CDCl_3$) δ 192.5, 162.63 (d, J = 248.856 Hz), 162.71 (d, J = 248.856) 149.3, 144.4 (d, J = 20.89 Hz), 114.3 (d, J = 19.98 Hz), 129.7, 129.5, 129.3, 127.7, 127.3, 126.9, 126.5, 124.9, 123.5, 122.7, 118.2, 115.3, 112.3, 105.3, 105., 104.8. HRMS (ESI) calcd for $C_{22}H_{12}ON_2F_2$ $[M+H]^+$ 359.09883, found 359.09905.

(**4-Fluorophenyl)(naphtho[1',2':4,5]imidazo[1,2-*a*]pyridin-5-yl)methanone (7f):** Yellow solid, 61.5 mg, 68%; R_f = 0.4 (30% ethyl acetate in hexanes).Melting point: 194–195 °C.^{1}H NMR (300 MHz, $CDCl_3$+DMSO) δ 8.93 (s, 1H), 8.61 (d, J = 6.3 Hz, 1H), 8.22 (d, J = 8.3 Hz, 1H), 8.15 (s, 1H), 8.09 (d, J = 9.4 Hz, 1H), 7.97 – 7.88 (m, 2H), 7.78 (s, 1H), 7.63 (t, J = 7.7 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 7.14 – 7.09 (m, 2H).^{13}C NMR (75 MHz, CDCl3+DMSO) δ 200, 172.2, 165.1 (d, J = 254.7 Hz) 139.7, 138.1, 137.9, 136.7, 135.6, 134.8, 132.5 (d, J = 9.4 Hz) 132.3, 131.5, 126.8 (d, J = 7.2 Hz) 121, 120.8, 120.5, 119.3, 118.6.HRMS (ESI)calcd for $C_{22}H_{13}ON_2F$ $[M+H]^+$ 341.10840, found 341.10847.

4-(Naphtho[1',2':4,5]imidazo[1,2-*a*]pyridine-5-carbonyl)benzaldehyde (7g): Yellow solid, 60.3 mg, 65%; R_f = 0.5 (30% ethyl acetate in hexanes).Melting point: 212–213 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (s, 1H), 9.67 (d, J = 6.8 Hz, 1H), 7.86 (d, J = 8.9 Hz, 2H), 7.80 – 7.76 (m, 3H), 7.74 (d, J = 2.0 Hz, 1H), 7.63 – 7.59 (m, 1H), 7.55 (ddd, J = 7.7, 5.5, 1.7 Hz, 2H), 7.45 (d, J = 8.3 Hz, 2H), 7.18 (td, J = 6.9, 1.1 Hz, 1H).^{13}C NMR (100 MHz, CDCl3) δ 191.4, 179.9, 156.1, 147.8, 135.6, 134.5, 133.3, 132, 131.1, 130.2, 129.6, 129.5, 129.4, 129, 128.6, 122.7, 121, 117.6, 115.6, 92.2, 91.9. HRMS(ESI)calcd for $C_{23}H_{14}O_2N_2$ $[M+H]^+$351.11169, found 351.11280.

(4-Ethylphenyl)(naphtho[1',2':4,5]imidazo[1,2-*a*]pyridin-5 yl)methanone (7h): Green solid, 79 mg, 84%; R_f = 0.4 (30% ethyl acetate in hexanes).Melting point:191–192 °C. $_1$H NMR (400 MHz, $CDCl_3$) δ 8.92 (d, J = 8.1 Hz, 1H), 8.48 (d, J = 6.6 Hz, 1H), 8.29 (d, J = 8.4 Hz, 1H), 8.10 (s, 1H), 7.89 (d, J = 9.1 Hz, 1H), 7.84 (d, J = 8.1 Hz, 2H), 7.73 (t, J = 7.5 Hz, 1H), 7.60 (t, J = 7.6 Hz, 1H), 7.54 – 7.44 (m, 1H), 7.30 (d, J = 8.0 Hz, 2H), 6.97 (t, J = 6.7 Hz, 1H), 2.75 (q, J = 7.6 Hz, 2H), 1.29 (t, J = 7.6 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.2, 150.2, 148.7, 143.2, 136.6, 130.8, 130.1, 128.9, 128.1, 127, 126, 126.9, 124.8, 123.3, 122.7, 118.1, 113.3, 111.9, 29.1, 15.2.HRMS (ESI)calcd for $C_{24}H_{19}ON_2$ $[M+H]^+$351.14895, found 351.14919.

Naphtho[1',2':4,5]imidazo[1,2-*a*]pyridin-5-yl(2,4,5-trimethylphenyl)methanone (7i): Yellow solid, 80.6 mg, 83%; Rf = 0.3 (20% ethyl acetate in hexanes).Melting point: 208–209 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.93 (d, J = 7.5 Hz, 1H), 8.69 (d, J = 8.4 Hz, 1H), 8.48 (d, J = 6.8 Hz, 1H), 8.08 (s, 1H), 7.91 (d, J = 9.2 Hz, 1H), 7.80 – 7.72 (m, 1H), 7.71 – 7.64 (m, 1H), 7.52 (ddd, J = 9.0, 6.8, 1.1 Hz, 1H), 7.21 (s, 1H) 7.12 (s, 1H), 6.98 (dd, J = 9.7, 3.8 Hz, 1H), 2.42 (s, 3H), 2.32 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.5, 149.1, 143.8, 140.3, 137.6, 135.9, 133.7, 132.9, 131.8, 131.3, 130.1, 129.1, 127.5, 127.1, 127 125, 123.3, 122.8, 118.1, 115.3, 112, 20.2, 19.81, 19.2.HRMS (ESI)calcd for $C_{25}H_{20}ON_2$ $[M+H]^+$365.16502, found 365.16484.

Naphtho[1',2':4,5]imidazo[1,2-*a*]pyridin-5-yl(thiophen-3-yl)methanone (7j):Brown solid, 68 mg, 78%. R_f = 0.4 (30% ethyl acetate in hexanes).Melting point:210–211 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (d, J = 8.0 Hz, 1H), 8.52 (d, J = 5.6 Hz, 1H), 8.37 (d, J = 8.4 Hz, 1H), 8.21 (s, 1H), 7.90 (d, J = 10.5 Hz, 2H), 7.74 (t, J = 7.3 Hz, 1H), 7.68 (d, J = 4.1 Hz, 1H), 7.63 (t, J = 7.5 Hz, 1H), 7.50 (d, J = 6.7 Hz, 1H), 7.44 – 7.39 (m, 1H), 7.00 (s, 1H). ^{13}C NMR (75 MHz, $CDCl_3$+DMSO) δ 195.3, 153.6, 148.1, 147.7, 140.3, 135.6, 134.3, 134.3, 133.1, 131.7, 131.3, 130.9, 127.9, 127.6, 122.3, 118.9, 116.9.HRMS (ESI)calcd for $C_{20}H_{12}ON_2S$ $[M+H]^+$329.07402, found 329.07431.

Cyclohex-1-en-1-yl(naphtho[1',2':4,5]imidazo[1,2-a]pyridin-5-yl)methanone (7k): Pale yellow solid, 57 mg, 65%.R_f = 0.5 (30% ethyl acetate in hexanes).Melting point: 181–183 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (d, J = 7.8 Hz, 1H), 8.55 (d, J = 6.5 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.74 – 7.68 (m, 1H), 7.68 – 7.58 (m, 2H), 7.49 (dd, J = 16.5, 7.7 Hz, 2H), 7.01 (t, J = 6.7 Hz, 1H), 6.63 (s, 1H), 2.59 (s, 2H), 2.20 (s, 2H), 1.84 – 1.77 (m, 2H), 1.74 – 1.66 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.1, 146.9, 141.1, 132.1, 130.1, 129.1, 128.6, 127.2, 126.9, 126.6, 124.7, 123.4, 122.6, 117.8, 117.5, 112.2, 111, 26.4, 23.6, 22.1, 21.7.HRMS (ESI)calcd for $C_{22}H_{18}ON_2$ $[M+H]^+$327.14831, found 327.14919.

(6-Methoxynaphthalen-2-yl)(naphtho[1',2':4,5]imidazo[1,2-*a*]pyridin-5-yl)methanone (7l): Brown solid, 88.8 mg, 83%. R_f = 0.3 (20% ethyl acetate in hexanes). Melting point: 222–223 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (d, J = 8.1 Hz, 1H), 8.48 (d, J = 6.7 Hz, 1H), 8.30 (d, J = 8.4 Hz, 1H), 8.23 (s, 1H), 8.17 (s, 1H), 8.06 (d, J = 8.5 Hz, 1H), 7.92 (d, J = 9.2 Hz, 1H), 7.83 (d, J = 8.6 Hz, 1H), 7.73 (dd, J = 16.0, 8.2 Hz, 2H), 7.59 (t, J = 7.4 Hz, 1H), 7.54 – 7.47 (m, 1H), 7.19 (s, 1H), 7.19 – 7.14 (m, 1H), 6.97 (t, J = 6.6 Hz, 1H), 3.96 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$+DMSO) δ 201.9, 164.7, 153.5, 1532, 147.8, 142.1, 138.9, 137.3, 136, 135.4, 134.8, 133.9, 132.4, 132, 131.6, 131, 130.2, 128, 127.7, 124.5, 122.6, 118.5, 116.8, 110.6, 60.2.HRMS (ESI)calcd for $C_{27}H_{19}O_2N_2$ $[M+H]^+$403.14284, found 403.14410.

(9-Methylnaphtho[1',2':4,5]imidazo[1,2-*a*]pyridin-5-yl)(phenyl)methanone (7m): Yellow solid, 63.7 mg, 75%. R_f = 0.4 (20% ethyl acetate in hexanes).Melting point: 218–219 °C.^{1}H NMR (500 MHz, $CDCl_3$) δ 8.92 – 8.88 (m, 1H), 8.35 (d, *J* = 8.5 Hz, 1H), 8.26 (s, 1H), 8.09 (s, 1H), 7.91 (dd, *J* = 8.2, 1.2 Hz, 2H), 7.81 (d, *J* = 9.3 Hz, 1H), 7.76 – 7.71 (m, 1H), 7.66 – 7.59 (m, 2H), 7.50 (dd, *J* = 10.8, 4.8 Hz, 2H), 7.37 (dd, *J* = 9.3, 1.5 Hz, 1H), 2.42 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 197.5, 148, 143.4, 139.2, 133, 132.3, 130.5, 130, 129.9, 128.5, 127, 126.9, 126.9, 123.3, 122.5, 122.4, 121.9, 117.4, 114.1, 18.3.HRMS (ESI)calcd for $C_{23}H_{16}ON_2$[M+H]$^+$ 337.13340, found 337.13354.

(9-Methylnaphtho[1',2':4,5]imidazo[1,2-*a*]pyridin-5-yl)(m-tolyl)methanone (7n): Brown solid, 73.5 mg, 83%. R_f = 0.4 (20% ethyl acetate in hexanes).Melting point: 174–176 °C.^{1}H NMR (400 MHz, CDCl3) δ 8.93 (d, J = 7.8 Hz, 1H), 8.32 (d, J = 9.4 Hz, 2H), 8.08 (s, 1H), 7.89 (d, J = 9.2 Hz, 1H), 7.74 (d, J = 8.4 Hz, 1H), 7.63 (dd, J = 18.4, 7.7 Hz, 2H), 7.45 (d, J = 7.7 Hz, 2H), 7.38 (dd, J = 15.8, 8.1 Hz, 2H), 2.45 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.6, 147.2, 139.1, 138.5, 134, 132.9, 132.2, 132.1, 132.1, 130.9, 130.8, 130.1, 128.6, 128.5, 128.4, 127.9, 127.3, 127.2, 126.8, 126.3, 123.5, 122.5, 122.3, 117, 113.5, 21.4, 18.3. HRMS(ESI)calcd for $C_{24}H_{18}ON_2$ [M+H]$^+$ 351.14809, found 351.14919.

(9-Methylnaphtho[1',2':4,5]imidazo[1,2-*a*]pyridin-5-yl)(p-tolyl)methanone (7o): Yellow solid, 70 mg, 81%. R_f = 0.4 (20% ethyl acetate in hexanes).Melting point: 231–232 °C.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (d, J = 8.0 Hz, 1H), 8.30 (d, J = 8.4 Hz, 1H), 8.24 (s, 1H), 8.06 (s, 1H), 7.80 (t, J = 8.6 Hz, 3H), 7.72 (t, J = 7.4 Hz, 1H), 7.59 (t, J = 7.5 Hz, 1H), 7.34 (d, J = 9.2 Hz, 1H), 7.28 (d, J = 7.9 Hz, 2H), 2.46 (s, 3H), 2.40 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 197.2, 147.9, 143.9, 143.2, 136.5, 132.1, 130.7, 130.3, 130, 129.2, 126.9, 126.8, 123.2, 122.5, 122.4, 121.8, 117.3, 113.6, 21.8, 18.2. HRMS (ESI)calcd for $C_{24}H_{19}ON_2$ [M+H]$^+$ 351.14884, found 351.14919.

(3-Methoxyphenyl)(9-methylnaphtho[1',2':4,5]imidazo[1,2-*a*]pyridin-5-yl)methanone (7p): Pale yellow solid, 71.5 mg, 84%. R_f = 0.3 (30% ethyl acetate in hexanes).Melting point: 161–163 °C.^{1}H NMR (500 MHz, $CDCl_3$) δ 8.89 (d, J = 8.1 Hz, 1H), 8.35 (d, J = 8.5 Hz, 1H), 8.26 (s, 1H), 8.09 (s, 1H), 7.85 (d, J = 9.2 Hz, 1H), 7.73 (t, J = 7.5 Hz, 1H), 7.64 – 7.59 (m, 1H), 7.52 (d, J = 1.4 Hz, 1H), 7.41 – 7.34 (m, 3H), 7.18 (ddd, J = 7.6, 2.5, 1.6 Hz, 1H), 3.86 (s, 3H), 2.42 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 197.2, 174.2, 159.8, 147.9, 143.1, 140.6, 132.4, 130, 129.9, 129.4, 127, 126.9, 126.8, 126.8, 123.5, 123.3, 122.4, 122, 119.6, 117, 114.4, 114.1, 55.6, 18.2.HRMS (ESI)calcd for $C_{24}H_{18}O_2N_2$ [M+H]$^+$367.14214, found 367.14410.

(4-Methoxyphenyl)(9-methylnaphtho[1',2':4,5]imidazo[1,2-*a*]pyridin-5-yl)methanone (7q): Brown solid, 69.8 mg, 82%. R_f = 0.4 (30% ethyl acetate in hexanes).Melting point: 219–220 °C.^{1}H NMR (500 MHz, $CDCl_3$) δ 8.90 (d, J = 8.1 Hz, 1H), 8.28 (s, 1H), 8.23 (d, J = 8.4 Hz, 1H), 8.07 (s, 1H), 7.90 (d, J = 8.8 Hz, 2H), 7.82 (d, J = 8.7 Hz, 1H), 7.72 (t, J = 7.5 Hz, 1H), 7.58 (t, J = 7.6 Hz, 1H), 7.37 (d, J = 9.1 Hz, 1H), 6.96 (d, J = 8.8 Hz, 2H), 3.90 (s, 3H), 2.43 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 196.3, 163.7, 147.7, 142.9, 132.9, 132.1, 131.7, 130.8, 130.7, 129.9, 126.9, 126.9, 126.7, 123.2, 122.6, 122.4, 121.8, 117.4, 113.8, 112.9, 55.6, 18.3.HRMS (ESI) calcd for $C_{24}H_{18}O_2N_2$ [M+H]$^+$367.14214, found 367.14410.

(9-Chloronaphtho[1',2':4,5]imidazo[1,2-a]pyridin-5 yl)(Phenyl)methanone (7r): Green solid, 61 mg, 72%; R_f = 0.4 (30% ethyl acetate in hexanes).Melting point: 156–157 °C.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (s, 1H), 8.31 (d, J = 8.2 Hz, 1H), 8.06 (s, 1H), 7.91 (d, J = 7.4 Hz, 3H), 7.77 (s, 1H), 7.64 (d, J = 5.2 Hz, 2H), 7.55 – 7.46 (m, 3H), 5.30 (s, 1H).^{13}C NMR (125 MHz, $CDCl_3$) δ 197.3, 146.9, 143.8, 138.8, 133.3, 131.3, 130.5, 130.1, 128.6, 127.4, 127.4, 127, 126.9, 123.3, 122.8, 122.6, 120.1, 118.6, 113.3.HRMS (ESI)calcd for $C_{22}H_{13}ON_2Cl$ [M+H]$^+$ 357.07864, found 357.07892.

(9-Chloronaphtho[1',2':4,5]imidazo[1,2-*a*]pyridin-5-yl)(3-methoxyphenyl)methanone (7s): Yellow solid, 74.3 mg, 81%; R_f = 0.4 (20% ethyl acetate in hexanes). Melting point: 188–191 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.87 (d, J = 8.2 Hz, 1H), 8.53 – 8.50 (m, 1H), 8.31 (d, J = 8.4 Hz, 1H), 8.05 (s, 1H), 7.84 (dd, J = 9.6, 0.7 Hz, 1H), 7.77 – 7.72 (m, 1H), 7.63 (ddd, J = 8.4, 7.0, 1.3 Hz, 1H), 7.52 (d, J = 1.8 Hz, 1H), 7.46 (dd, J = 9.6, 2.0 Hz, 1H), 7.39 – 7.36 (m, 2H), 7.21 – 7.17 (m, 1H), 3.87 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.1, 159.9, 146.9, 144.3, 143.6, 140.2, 138.6, 131.3, 130.2, 130.1, 129.5, 127.4, 127.4, 126.9, 123.5, 123.3, 122.8, 122.6, 120.2, 119.8, 118.5, 114.3, 113.3, 55.6.HRMS(ESI)calcd for $C_{23}H_{15}ClN_2O_2$ [M+H]$^+$ 387.08908, found 387.08948.

9-Chloronaphtho[1',2':4,5]imidazo[1,2-a]pyridin-5-yl)(4-methoxyphenyl)methanone (7t): Yellow solid, 77.5 mg, 84%; R_f = 0.4 (20% ethyl acetate in hexanes).Melting point: 196–198 °C.^{1}H NMR (500 MHz, $CDCl_3$) δ 8.88 (d, J = 8.1 Hz, 1H), 8.52 (s, 1H), 8.20 (d, J = 8.4 Hz, 1H), 8.01 (d, J = 10.1 Hz, 1H), 7.91 – 7.88 (m, 2H), 7.85 (d, J = 9.6 Hz, 1H), 7.74 (t, J = 7.4 Hz, 1H), 7.62 – 7.58 (m, 1H), 7.45 (dd, J = 9.6, 1.7 Hz, 1H), 6.98 – 6.94 (m, 2H), 3.90 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.1, 163.9, 146.7, 145.8, 143.2, 137.9, 132.9, 132.1, 131.4, 130, 129.9 127.3, 127.1, 126.9, 123.3, 122.7, 120, 118.5, 113.9, 112.2, 55.6.HRMS (ESI) calcd for $C_{23}H_{15}O_2N_2Cl$ [M+H]$^+$387.08915, found 387.08948.

(9-Chloronaphtho[1',2':4,5]imidazo[1,2-*a*]pyridin-5-yl)(3,4,5-trimethylphenyl)methanone (7u): Pale yellow solid, 78.7 mg, 83%; R_f = 0.3 (30% ethyl acetate in hexanes). Melting point: 185–188 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (d, J = 8.2 1H), 8.65 (d, J = 8.4 Hz, 1H), 8.49 (d, J = 1.2 Hz, 1H), 8.00 (s, 1H), 7.85 (d, J = 9.7 Hz, 1H), 7.80 – 7.74 (m, 1H), 7.69 (ddd, J = 8.4, 7.0, 1.4 Hz, 1H), 7.46 (dd, J = 9.6, 2.0 Hz, 1H), 7.20 (s, 1H), 7.13 (s, 1H), 2.43 (s, 3H), 2.33 (s, 3H), 2.18 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 199.3, 147.1, 144, 140.6, 137.2, 136.1 133.7, 132.9, 132.4, 131.9, 130.2, 130.1, 127.7, 127.4, 127.1, 126.9, 123.3, 122.9, 122.7, 120.1, 118.5, 114.7, 20.3, 19.8, 19.2. HRMS(ESI)calcd for $C_{25}H_{19}ON_2Cl$ [M+H]$^+$ 399.12596, found 399.12587.

(9-Chloronaphtho[1',2':4,5]imidazo[1,2-*a*]pyridin-5-yl)(4-ethylphenyl)methanone (7v): Green solid, 74.8 mg, 82%R_f= 0.4 (30% ethyl acetate in hexanes). Melting point: 236.1–237.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.87 (dd, J = 8.2, 0.7 Hz, 1H), 8.51 (dd, J = 1.9, 0.8 Hz, 1H), 8.28 (d, J = 8.4 Hz, 1H), 8.03 (s, 1H), 7.86 – 7.82 (m, 3H), 7.77 – 7.71 (m, 1H), 7.62 (ddd, J = 8.4, 7.0, 1.4 Hz, 1H), 7.47 – 7.43 (m, 1H), 7.32 (d, J = 8.3 Hz, 2H), 2.76 (q, J = 7.6 Hz, 2H), 1.33 – 1.28 (m, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 197, 150.4, 146.7, 143.4, 136.4, 131.6, 130.8, 130, 128.1, 127.3, 127.2, 126.9, 123.2, 122.8, 122.7, 120, 118.5, 112.9, 29.1, 15.2.HRMS(ESI) calcd for $C_{24}H_{17}ClN_2O$ [M+H]$^+$ 385.11149, found 385.11022.

(9-Chloronaphtho[1',2':4,5]imidazo[1,2-*a*]pyridin-5-yl)(m-tolyl)methanone (7w): Yellow solid, 71.5 mg, 81%. R_f = 0.4 (30% ethyl acetate in hexanes).Melting point: 186–188 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.87 (d, J = 8.0 Hz, 1H), 8.51 (s, 1H), 8.30 (d, J = 8.4 Hz, 1H), 8.03 (s, 1H), 7.84 (d, J = 9.6 Hz, 1H), 7.75 (t, J = 7.2 Hz, 2H), 7.63 (dd, J = 11.7, 7.3 Hz, 2H), 7.46 (d, J = 7.7 Hz, 2H), 7.37 (t, J = 7.5 Hz, 1H), 2.42 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.6, 146.8, 143.6, 138.9, 138.5, 134.1, 131.5, 130.8, 130.1, 128.4, 127.9, 127.4, 127.3, 126.9, 123.3, 122.8, 122.6, 120.1, 118.5, 113.2, 21.4.HRMS(ESI) calcd for $C_{23}H_{15}ClN_2O$ [M+H]$^+$ 371.09549, found 371.09457.

(9-Methylnaphtho[1',2':4,5]imidazo[1,2-a]pyridin-5-yl)(thiophen-3-yl)methanone (7x): Brown solid, 65 mg, 75%; R_f = 0.4 (30% ethyl acetate in hexanes).Melting point: 240–241 °C.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.88 (d, J = 7.7 Hz, 1H), 8.38 (d, J = 8.4 Hz, 1H), 8.28 (s, 1H), 8.18 (s, 1H), 7.93 (dd, J = 2.9, 1.2 Hz, 1H), 7.83 (d, J = 9.3 Hz, 1H), 7.76 – 7.71 (m, 1H), 7.69 (dd, J = 5.1, 1.2 Hz, 1H), 7.62 (ddd, J = 8.4, 7.0, 1.3 Hz, 1H), 7.42 (dd, J = 5.1, 2.9 Hz, 1H), 7.36 (dd, J = 9.3, 1.6 Hz, 1H), 2.43 (S, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ 190.7, 147.7, 143.6, 134.9, 132.5, 130.9, 129.6, 128.6, 127.2, 127, 126.7, 126.5, 123.3, 122.4, 122.1,

117.3, 113.2, 18.3.HRMS (ESI) calcd for $C_{21}H_{14}ON_2S$ $[M+H]^+$343.08815, found 343.08996.

(6-Methoxynaphthalen-2-yl)(9-methylnaphtho[1',2':4,5]imidazo[1,2-a]pyridin-5-yl)methanone (7y): Yellow solid, 87.2 mg, 83%; R_f = 0.3 (30% ethyl acetate in hexanes).Melting point: 213–214 °C.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.91 (d, J = 8.1 Hz, 1H), 8.32 (d, J = 8.4 Hz, 1H), 8.22 (d, J = 9.1 Hz, 2H), 8.11 (s, 1H), 8.06 (d, J = 8.5 Hz, 1H), 7.84 – 7.78 (m, 2H), 7.75 – 7.69 (m, 2H), 7.60 – 7.54 (m, 1H), 7.32 (d, J = 9.1 Hz, 1H), 7.20 – 7.13 (m, 2H), 3.94 (s, 3H), 2.36 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 197.2, 179.3, 160, 146.9, 137.5, 134.2, 133, 132.7, 131.3, 130.9, 130.2, 127.7, 127.4, 127.3, 126.9, 126.4, 126.2, 123.6, 122.6, 119.8, 116.9, 113.2, 105.9, 55.5, 18.3. HRMS(ESI) calcd for $C_{28}H_{20}O_2N_2$ $[M+H]^+$ 417.15853, found 417.15975.

Cyclohex-1-en-1-yl(9-methylnaphtho[1',2':4,5]imidazo[1,2-*a*]pyridin-5-yl)methanone (7z): Brown solid, 58.8 mg, 68%; R_f = 0.5 (20% ethyl acetate in hexanes).Melting point: 163–165 °C.^{1}H NMR (500 MHz, $CDCl_3$) δ 8.78 (d, J = 8.0 Hz, 1H), 8.23 (s, 1H), 8.01 (d, J = 8.3 Hz, 1H), 7.85 (s, 1H), 7.74 (d, J = 9.1 Hz, 1H), 7.62 (d, J = 7.1 Hz, 1H), 7.52 (t, J = 7.5 Hz, 1H), 7.34 (d, J = 9.0 Hz, 1H), 6.55 (s, 1H), 2.52 (s, 2H), 2.36 (s, 3H), 2.14 (s, 2H), 1.76 – 1.71 (m, 2H), 1.66 – 1.60 (m, 2H).^{13}C NMR (100 MHz, $CDCl_3$) δ 199.1, 146.9, 146.7, 141.4, 141.1, 132.2, 132.1, 132, 131.8, 129.9, 128.6, 128.5, 127, 126.7, 126.6, 126.5, 123.3, 122.4, 122.3, 122, 117.1, 111.2, 29.7, 26.4, 23.6, 22.1, 21.7, 18.3.HRMS (ESI) calcd for $C_{23}H_{20}ON_2$ $[M+H]^+$341.16370, found 341.16484.

(9-Chloronaphtho[1',2':4,5]imidazo[1,2-*a*]pyridin-5-yl)(thiophen-3-yl)methanone (7aa): Green solid, 64 mg, 74%; R_f = 0.3 (30% ethyl acetate in hexanes). Melting point: 172–174 °C. ^{1}H NMR (300 MHz, $CDCl_3$+DMSO) δ 13.76 (s, 1H), 13.52 (d, J = 8.1 Hz, 1H), 13.18 (s, 1H), 13.03 (d, J = 8.4 Hz, 1H), 12.68 (d, J = 1.8 Hz, 1H), 12.52 (d, J = 9.7 Hz, 1H), 12.41 (dd, J = 16.0, 6.2 Hz, 2H), 12.33 (d, J = 7.2 Hz, 1H), 12.23 – 12.16 (m, 2H).^{13}C NMR (75 MHz, DMSO) δ 189.9, 146.5, 142.6, 137.1, 130.3, 129.1, 127.9, 127.7, 127, 126.3, 125.5, 123, 122.8, 117.9, 115.3.HRMS(ESI)calcd for $C_{20}H_{11}ClN_2OS[M+H]^+$ 363.03493, found 363.03534.

(9-Chloronaphtho[1',2':4,5]imidazo[1,2-*a*]pyridin-5-yl)(6-methoxynaphthalen-2-yl)methanone (7ab): Brown solid, 77.5 mg, 80%; R_f = 0.3 (30% ethyl acetate in hexanes).Melting point: 141–143 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.92 (d, J = 8.3 Hz, 1H), 8.51 (s, 1H), 8.30 (d, J = 8.2 Hz, 1H), 8.23 (s, 1H), 8.10 – 8.05 (m, 1H), 7.85 (t, J = 8.6 Hz, 2H), 7.75 (dd, J = 19.7, 8.1 Hz, 2H), 7.67 – 7.57 (m, 1H), 7.46 (d, J = 9.7 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.24 – 7.15 (m, 2H), 3.96 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 197.1, 160.1, 146.6, 143.1, 142.9, 137.5, 134, 132.7, 132.2, 131.3, 130.2, 127.7, 127.5, 127.4, 127.3, 127, 126.9, 126.3, 123.4, 122.8, 120.3, 119.9, 118.4, 112.7, 105.9, 55.5; HRMS (ESI) calcd for $C_{27}H_{17}ClN_2O_2$ $[M+H]^+$ 437.10387, found 437.10513.

6-(4-Methoxyphenyl)naphtho[1',2':4,5]imidazo[1,2-*a*]pyridine (8a): To a flask charged with 4a (100 mg, 0.37 mmol), $(Ph_3P)_2PdCl_2$ (12.8 mg, 0.05 equiv), CuI (3.4 mg, 0.05 equiv) and 1-ethynyl-4-methoxybenzene (72.5 mg, 1.5 equiv) in THF (4 mL) was added Et_3N (0.05 mL, 3.0 equiv) at rt. It was then stirred at 80 °C for 2 h. Next, TFA (0.5 mL) was added and 1-ethynyl-3-methylbenzene the resulting solution stirred at 80 oC for 6 h. After concentration of the reactionmixture, purification by column chromatography on silica gel to give 8a as agreen solid, 71.5 mg, 75%. R_f = 0.4 (40% ethyl acetate in hexanes).Melting point: 171–173 °C. ^{1}HNMR (400 MHz, $CDCl_3$) δ 8.88 (d, J = 8.1 Hz, 1H), 7.96 (dd, J = 11.0, 7.6 Hz, 2H), 7.87 (d, J = 9.2 Hz, 1H), 7.70 (dd, J = 11.1, 4.0 Hz, 1H), 7.66 – 7.58 (m, 1H), 7.54 (s, 1H), 7.49 (d, J = 8.6 Hz, 2H), 7.40 – 7.32 (m, 1H), 7.11 (d, J = 8.6 Hz, 2H), 6.64 (t, J = 6.4 Hz, 1H), 3.95 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 131.6, 130.6, 128.1, 127.6, 126.7, 126.4, 123.9, 123.1, 117.8, 114.3, 110.9, 55.5; HRMS (ESI) calcd for $C_{22}H_{16}N_2O$ $[M+H]^+$ 325.13392, found 325.1335.

6-(6-methoxynaphthalen-2-yl)naphtho[1',2':4,5]imidazo[1,2-*a*]pyridine (8b): Brown solid, 95 mg, 86%; R_f = 0.3 (40% ethyl acetate in hexanes).Melting point: 179–181 °C.^{1}H NMR (500 MHz, $CDCl_3$) δ 8.91 (d, J = 8.1 Hz, 1H), 8.00 (d, J = 4.7 Hz, 2H), 7.92 (dd, J = 13.6, 7.7 Hz, 2H), 7.85 (dd, J = 16.9, 8.9 Hz, 2H), 7.72 (t, J = 7.5 Hz, 1H), 7.66 – 7.60 (m, 3H), 7.33 (dd, J = 8.4, 7.4 Hz, 1H), 7.27 (d, J = 10.4 Hz, 2H), 6.54 (t, J = 6.8 Hz, 1H), 4.00 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ 158.4, 147.9, 141.8, 134.2, 133.4, 131.6, 129.7, 128.9, 128.2, 128.1, 127.8, 127.4, 126.7, 126.4, 126.1, 124, 123.1, 122.6, 119.8, 117.9, 110.7, 105.9, 55.5.HRMS(ESI) calcd for $C_{26}H_{18}N_2O$ $[M+H]^+$ 375.14755, found 375.14919.

6-(4-Ethylphenyl)naphtho[1',2':4,5]imidazo[1,2-*a*]pyridine (8c): Yellow solid, 79 mg, 84%; R_f = 0.4 (40% ethyl acetate in hexanes). Melting point: 187–189 °C.^{1}H NMR (400 MHz, $CDCl_3$) δ 8.89 (d, J = 8.1 Hz, 1H), 8.27 (s, 1H), 8.17 – 8.12 (m, 2H), 7.66 (dd, J = 8.6, 6.0 Hz, 3H), 7.56 (s, 1H), 7.40 (d, J = 7.8 Hz, 2H), 7.18 (tdd, J = 7.6, 4.9, 2.5 Hz, 2H), 6.80 (t, J = 6.7 Hz, 1H), 2.82 (q, J = 7.6 Hz, 2H), 1.37 (t, J = 7.6 Hz, 3H).^{13}C NMR (125 MHz, $CDCl_3$) δ 144.4, 142.9, 134.2, 133.7, 131.7, 129.3, 129.1, 128.4, 128.2, 127.6, 126.5, 125.8, 125.2, 121.6, 117.5, 112.7, 112.1, 28.7, 15.6.HRMS(ESI)calcd for $C_{23}H_{18}N_2$ $[M+H]^+$ 323.15486, found 323.15428.

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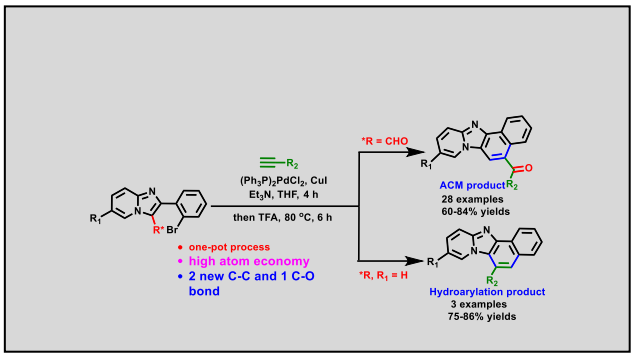
Graphical abstract:



2-(2-Bromophenyl)imidazo[1,2-*a*]pyridine with and without a C-3 aldehyde was studied for alkyne-carbonyl metathesis (ACM) vs hydroarylation. 2-(2-bromophenyl)imidazo[1,2-*a*]pyridine with a C-3 aldehyde underwent preferentially ACM pathway with phenyl acetylenes. While intramolecular hydroarylation was the common pathway in the absence of carbonyl moiety at C-3 position.

Mirza Feroz Baig,[a,b] Siddiq Pasha Shaik,[a,b] Namballa Hari Krishna,[a,c] Neeraj Kumar Chouhan,[a,c] Abdullah Alarifi,[d] and Ahmed Kamal[a,c,d]

One pot synthesis of naphtho[1',2':4,5]imidazo[1,2-a]pyridin-5-yl(aryl)methanone via a sequential Sonogashira coupling/alkyne-carbonyl metathesis