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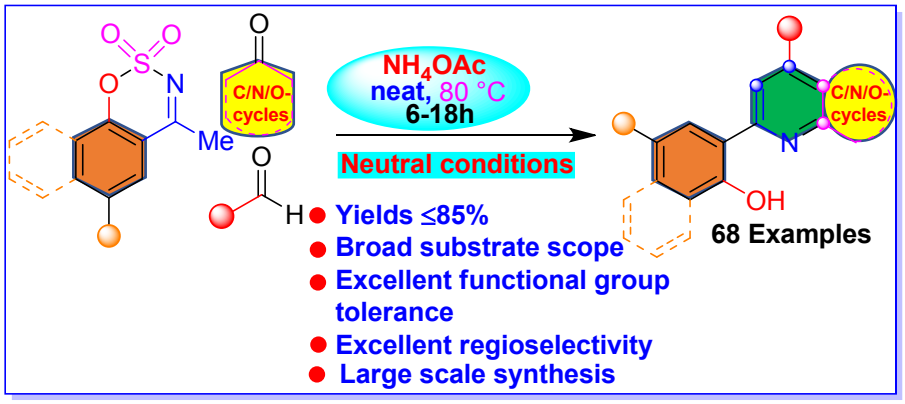
*Meher Prakash, Santosh K. Gudimella, Rajni Lodhi, Soumitra Guin and Sampak Samanta**

Discipline of Chemistry, Indian Institute of Technology Indore, Simrol, Indore-453552, Madhya Pradesh, India.

*Corresponding author. Tel +91-731-2438753

Email: sampaks@iiti.ac.in



ABSTRACT: A new metal-oxidant-and solvent-free based eco-friendly domino method for the modular synthesis of a diverse range of medicinally promising hydroxyarylated unsymmetrical pyridines in good to high chemical yields with an excellent regioselectivity has been established. This domino process involves a range of N-sulfonyl ketimines as C,N-binucleophiles, enolizable ketones and aromatic/heteroaromatic aldehydes using ammonium acetate as an ideal promoter under neat conditions which creates new two C-C and one C-N bonds. Notably, the neutral reaction conditions are mild enough to tolerate a range of functionalities and cover a variety of substrates, thus bestowing a powerful avenue to access tri-and tetra-substituted pyridines including carbo-and heterocyclic-fused ones. Interestingly, a practical, scalable and high yielding synthesis of pyridylphenol derivative was successfully accomplished by our unique method.

KEYWORDS: N-Sulfonyl ketimines, ammonium acetate, hydroxyarylated pyridines, neat conditions, green method.

INTRODUCTION:

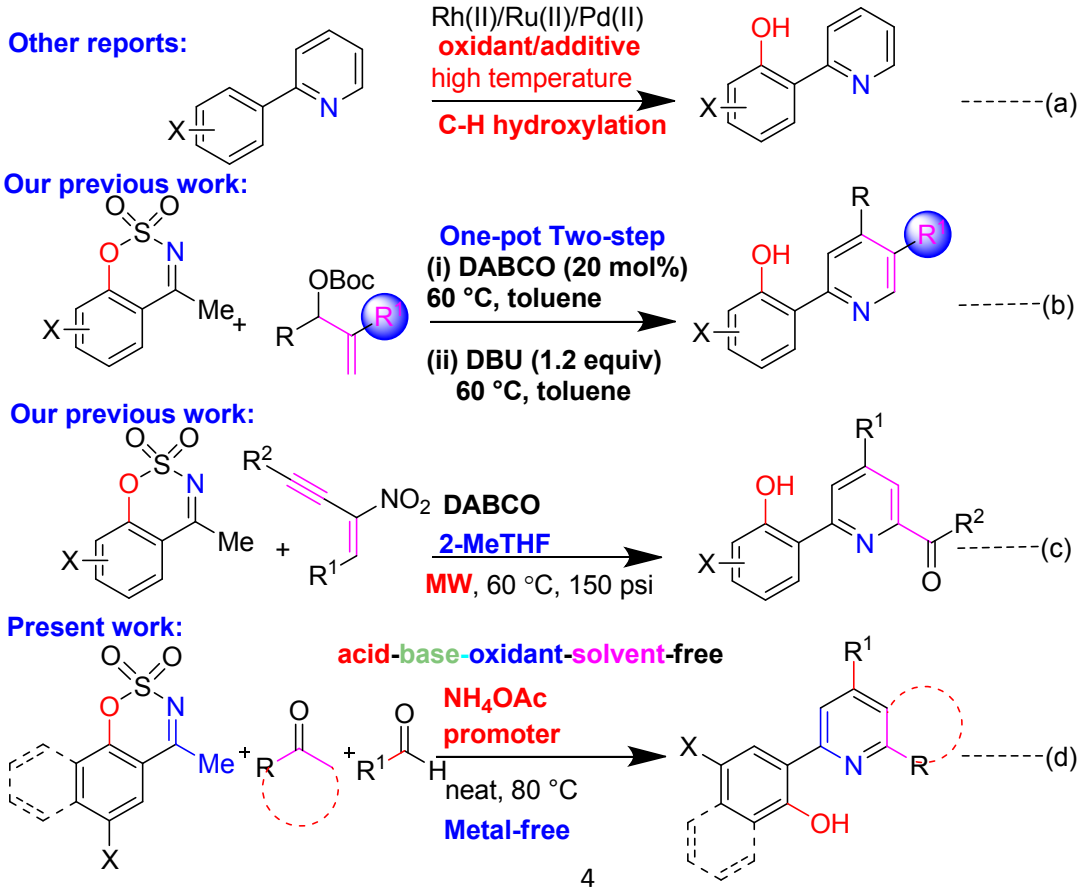
Pyridine ring systems are certainly one of the most explored heterocyclic molecules which are profoundly present in a plethora of natural alkaloids including an essential subunit of vitamins (B6 and B3) and enzymes that regulate many therapeutic actions in our metabolic systems. [1-2] Besides, the substituted pyridines have impressive applications in a variety of research fields such as drug discovery program,[3] pharmaceutical chemistry,[4] agrochemicals,[5] functional materials,[6] coordination chemistry,[7] supramolecular chemistry,[8] catalysis[9] etc. Consequently, efficient synthesis of pyridine skeletons with biologically prevalent functionalities is a lucrative target for chemists.[10] In this context, massive efforts have been paid by chemists since 19th century to establish many concise synthetic routes for the facile access to a diverse set of functionalized pyridine frameworks with unprecedentedly high molecular complexity.[1-10] Traditionally, several hallmark methods to prepare substituted pyridines via a condensation-cyclization reaction employing amines (or ammonia) and active carbonyl compounds/alkyl aldehydes were effectively established by Hantzsch, Chichibabin and other groups independently.[11-12] Similarly, Bohlmann-Rahtz,[13] Bagely[14] and Tsuda[15] groups also synthesized functionalized pyridines from isolated or in situ produced enamines and enones/ynones in AcOH medium. During past decades, many elegant and powerful approaches have been also discovered for the predominant synthesis of pyridine building blocks which comprise [4+2][16]/[2+2+2][17] cycloaddition reactions of α,β-unsaturated oximes/enamides/nitriles with alkynes catalyzed by different kinds of transition metal-salts, 6π-electrocyclization,[18] C-H functionalization on the pyridine rings[19] etc. Most importantly, the multicomponent reaction (MCR) has been greatly exercised as one of the most atom-and step-

economical routes to functionalized pyridines.[20-23] For example, Kröhnke et al.[21] designed a three-component reaction of N-phenacylpyridinium salts, α,β-unsaturated ketones with NH_4OAc in AcOH medium at 100-140°C to produce 2,4,6-trisubstituted pyridines. However, both the non-commercial starting materials must be prepared before executing the reaction. So, this approach is usually considered to be a relatively expensive, less atom-economical and with harsher conditions. Alternatively, an improved solvent-free method was nicely developed via a domino MCR of arylaldehydes, acetophenones and large excess amounts of ammonium acetate as a N-sourcing agent using several acid-catalysts/heterogeneous LPSF-nanocatalyst under heating conditions, establishing a general access to tri-arylsubstituted symmetrical pyridines only.[22] Furthermore, Cui, Jiang and Yoshikai groups have documented novel Cu(I)-and base-catalyzed domino reaction between oxime esters, aldehydes and active methylene compounds under heating conditions to serve unsymmetrical pyridine frameworks.[23] Even though these are magnificent advancements, the one-pot synthesis of hydroxyarylated unsymmetrical pyridines (especially fused ones) [24,25] has not been studied in a systematic manner despite their potential applications in bioactive substances[26] and light-emitting materials.[27] The common synthetic approach to pyridylphenol derivatives is based on the direct C-H hydroxylation at specific site (i.e. C2-position) of the phenyl ring of 2-arylpyridines in the presence of a variety of oxidants such as TBHP, H_2O_2, $K_2S_2O_8$, oxone, PIDA and NHPI catalyzed by precious transition-metal-salts (e.g. Pd(II),[24a-d] Rh(III)[24e-f] and Ru(II)[24g]) at heating conditions (Scheme 1a).[24] However, the above C-H functionalization technique has several serious weaknesses such as necessity of a large excess amount of powerful oxidants or additives, high temperature, longer reaction time, poor functional group tolerance, use of costly metal-salts, unsatisfactory yields, the use of hazardous and volatile organic solvents, the need for tedious extraction procedures to eliminate the toxic metals from the reaction mixtures

etc. In addition to the above complications, the described technique in general does not tolerate substitution on the pyridine ring, leading to the less practical utility of the method. Towards our efforts, we also recently documented organobase-promoted a number of promising domino techniques to build functionalized pyridines including 2-pyridylphenol derivatives from cyclic sulfamidate imines as C-nucleophiles and different kinds of 1,3-bielectrophiles including α-arylacetylenyl-β-aryl-nitroolefins,[28a] MBH adducts[28b] and β,γ-unsaturated α-keto carbonyls[28c] (Scheme 1b-c).[28] However, they always need high loading of base and prefunctionalization of both the starting materials which interferes with the further growth of synthetic process.

Therefore, we are highly focused on the development a new, eco-friendly, convenient, acid-base-oxidant-solvent-and metal-free based reliable one-pot synthetic strategy for preparing unsymmetrical substituted pyridines and fused ones with one or more hydroxyaryl moieties from

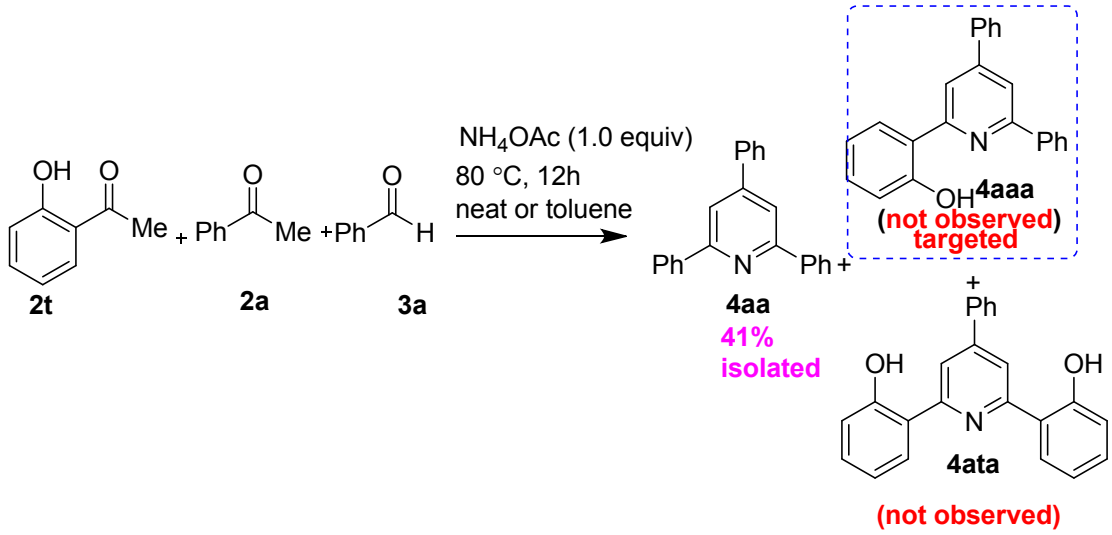
Scheme 1. One-Pot Approach to the Synthesis of Hydroxylated Arylpyridine Frameworks



easily accessible starting substances under neutral conditions, which is still a thought-provoking exercise for organic chemists. Enthused by these precedents as well as a part of our research program related to the development of new synthetic routes for the synthesis of unsymmetrical substituted pyridines,[29] herein, we further demonstrate a solvent-free three-component chemical transformation that delivers different kinds of pyridyl-substituted phenols by taking N-sulfonyl ketimines, enolizable ketones and aldehydes promoted by ammonium acetate under neutral conditions (Scheme 1d).

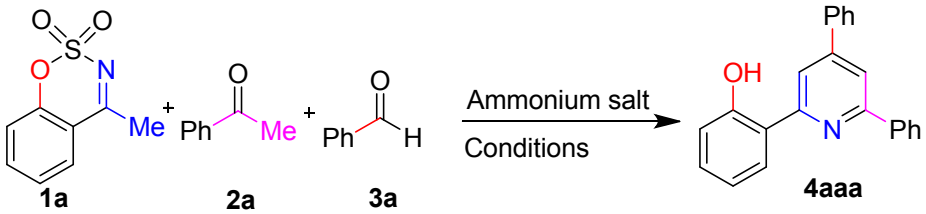
RESULTS AND DISCUSSION: Our initial attempt was to synthesize 2-(4,6-diphenylpyrdin-2-yl)phenol (**4aaa**) by taking an equimolecular mixture of 2-hydroxyacetophenone (**2t**), acetophenone (**2a**) and benzaldehyde (**3a**) with ammonium acetate at 80 °C in toluene or a neat condition for 12h as shown in Scheme 2. Surprisingly, instead of targeted pyridine **4aaa,** a trisubstituted symmetrical pyridine (**4aa**) was isolated in 41% yield. The above result clearly showed that a less nucleophilic 2-hydroxyacetophenone (**2t**) did not participate in this [2+2+1+1]

Scheme 2. Multicomponent Reaction for the Construction of Substituted Pyridines



cyclization process at all and recovered it fully. Therefore, we envisaged that a more reactive N-sulfonyl ketimine **1a** as a powerful C/N-binucleophile in the place of its unmasked form **(2t,** less reactive**)** may react with aldehyde **3a** faster than acetophenone in the presence of ammonium acetate which inhibits the formation of unwanted **4aa.** To verify our proposed idea, we performed this reaction by employing the suitable reactants N-sulfonyl ketimine **1a, 2a** and **3a** using ammonium acetate in toluene at 80 °C. To our delight, after 12h, the cyclization reaction gave an astonishing result that provided good yield (71%) of expected phenolic-substituted pyridine **4aaa** (entry 1, Table 1). This interesting outcome inspired us to examine this three-component reaction in detail. In this connection, other organic solvents like 2-MeTHF, EtOH, PEG-400 and DMF were screened and led to the desired pyridine **4aaa** in mediocre to good yields (41-73%, entries 2-5). Pleasantly, when the reaction was carried out in a neat condition, a high yield (81%) of **4aaa** was observed after 10h. However, marginally dropped yields were observed when the reaction was conducted either at lower (70 °C) or higher temperature (90 °C, slight decomposition of **1a**) than 80 °C. In order to find out the best promoter for this transformation, a range of commercially accessible ammonium salts [NH_4CO_2H, NH_4HCO_3, $(NH_4)_2CO_3$, NH_4Cl and $(NH_4)_2SO_4$] and amino-acids (glycine and L-proline) were tested under solvent-free conditions at 80 °C. Results indicated that ammonium format was found to be an equipotent with ammonium acetate, giving a comparable yield 79% (entry 10). However, other ammonium salts including amino-acids were not capable of promoting this reaction effectively, providing inferior yields (5-36%, entries 11-16). It should be noted that 2.0 equiv of ammonium acetate provided 82% yield of **4aaa** (entry 9). Furthermore, under microwave heating at 80 ˚C, the reaction furnished a mediocre yield (57%) of **4aaa** along with undesired pyridine derivative **4aa** in 15% yield (entry 18).

Table 1. Optimization of Reaction Conditions[a,b]



Entry	Solvent	salt	Temp (°C)	Time (h)	Yield (%)[b]
1[d]	toluene	NH_4OAc	80	12	71
2[d]	2-MeTHF	NH_4OAc	80	12	68
3[d]	EtOH	NH_4OAc	80	12	51
4[d]	PEG-400	NH_4OAc	80	12	41
5[d]	DMF	NH_4OAc	80	12	73
6	neat	NH_4OAc	80	10	81
7	neat	NH_4OAc	90	10	75
8	neat	NH_4OAc	70	10	70
9[e]	neat	NH_4OAc	80	10	82
10	neat	HCO_2NH_4	80	12	79
11	neat	NH_4HCO_3	80	12	36
12	neat	$(NH_4)_2CO_3$	80	12	35
13	neat	NH_4Cl	80	12	<5
14	neat	$(NH_4)_2SO_4$	80	12	<5
15	neat	$NH_2CH_2CO_2H$	80	12	31
16	neat	L-Proline	80	12	<5
17[c]	neat	NH_4OAc	80	12	48

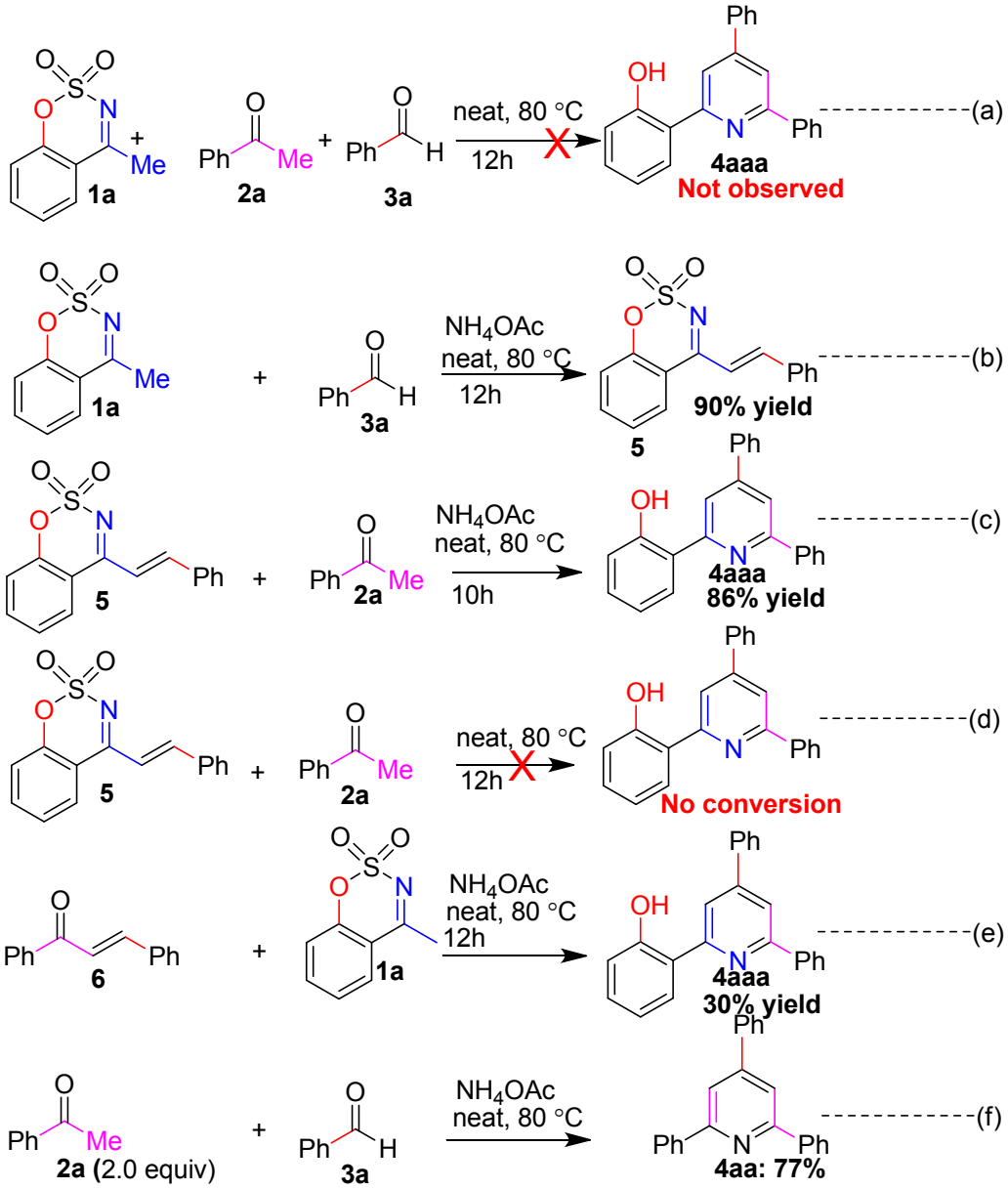
18[f,g]	neat	NH_4OAc	MW	1h	57

[a]Reaction conditions: **1a** (0.15 mmol), **2a** (0.18 mmol), benzaldehyde **3a** (0.18 mmol) and ammonium salt (0.15 mmol) in a neat condition at 90 °C. [b]Isolated yield. [c]50 mol% NH4OAc was used. [d]1.0 mL dry solvent was used. [e]2.0 equivalent of NH_4OAc was used.[f] Microwave (MW) heating at 80 °C. [g]15% yield of compound **4aa** was isolated.

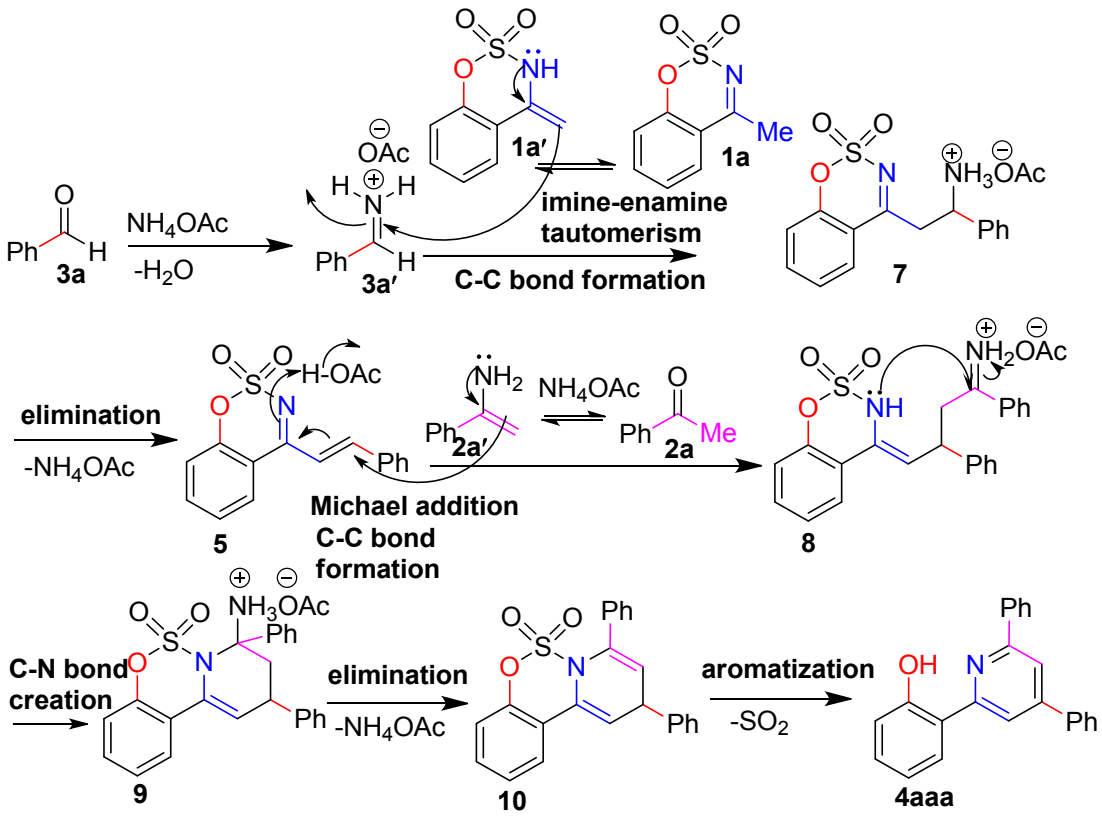
To gain deeper insight of the mechanism, several control experiments were conducted as shown in Scheme 3. First, a mixture of compound **1a, 2a** and **3a** was heated at 80 °C for 12h without using ammonium acetate. Reaction did not occur which suggested that ammonium acetate was inevitable for this conversion (Scheme 3a). Next, N-sulfonyl ketimine **1a** has been shown as a potential C-nucleophile in the condensation reaction with a benzaldehyde (**3a**) promoted by ammonium acetate to form condensation product **5** in 90% yield (Scheme 3b). Furthermore, acetophenone (**2a**) efficiently reacted with ketimine **5** under standard conditions, leading to the desired pyridine **4aaa** in 86% yield (Scheme 3c). However, in the absence of ammonium acetate, pyridine **4aaa** was not observed (Scheme 3d). These results indicated that ammonium acetate may involve in the condensation reaction with acetophenone (**2a**) to form a more nucleophilic species enamine (increasing HOMO energy) which facilitates the cyclization process. Alternatively, the chalcone (**6**) could react with **1a** in the established conditions, capable of forming **4aaa** in 30% yield only. Therefore, the originating of **4aaa** from the combination of chalcone (**6**) and **1a** is very unlikely. Furthermore, under present conditions, the condensation of benzaldehyde (**3a**) with acetophenone (**2a**, 2.0 equiv) provided only 2,4,6-triphenylpyridine (**4aa)** in 77% yield in Scheme

3f. Thus, the conjugate addition of **2a** to unsaturated imine **5** is a preferential route for making product **4aaa** in Scheme 3c.

Scheme 3. Control Experiments



Scheme 4. Plausible Mechanism

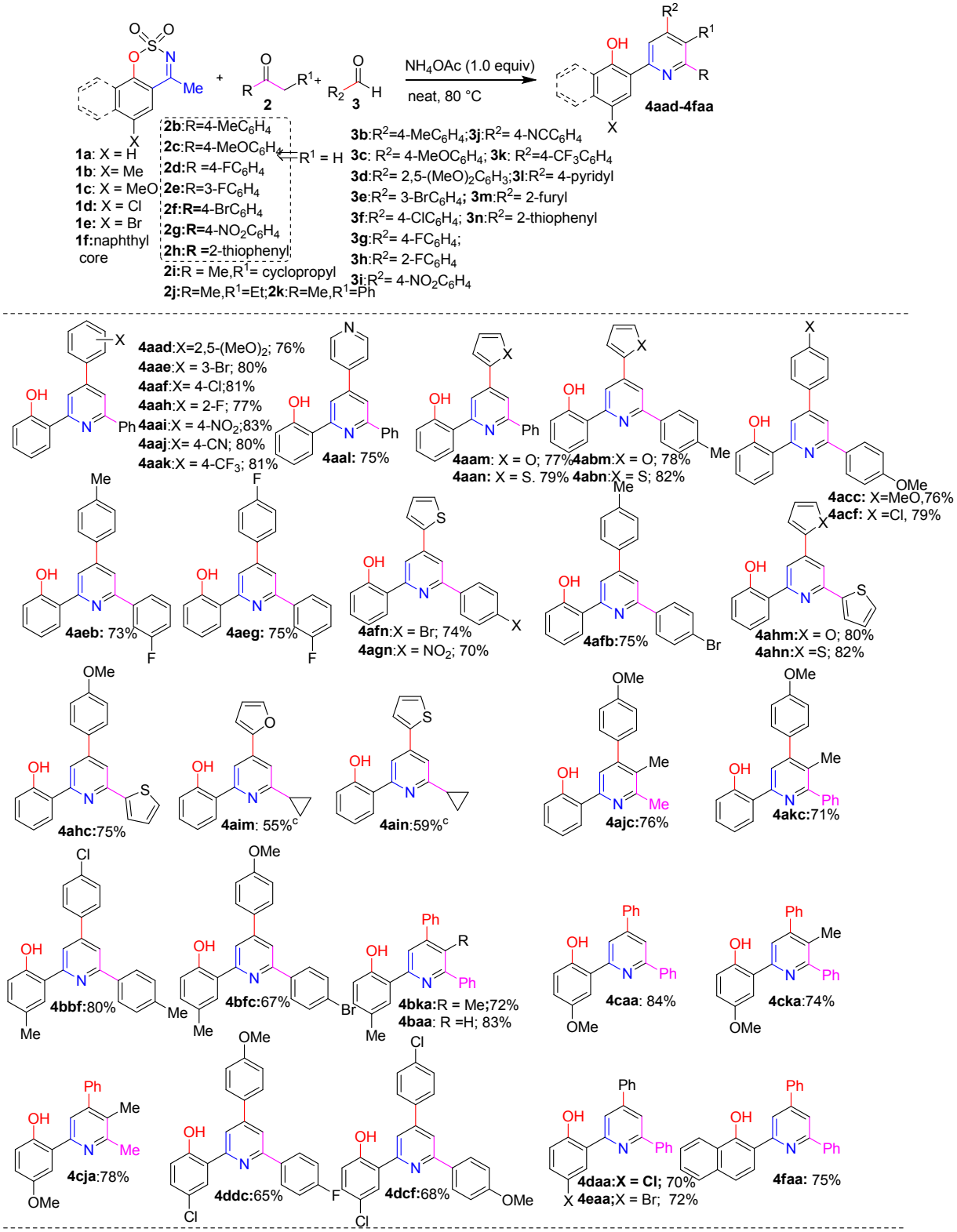


Based on the above experimental results, we proposed a plausible reaction mechanism as depicted in Scheme 4. At the beginning, ammonium acetate may react with a benzaldehyde to form a very reactive iminium ion **3a′** (lowering LUMO activation energy). The latter involves in C-C bond formation reaction with enamine intermediate **1a′** to generate an adduct **7** which is subsequently liberated ammonium acetate, resulting in unsaturated imine **5.** Afterwards, the conjugate addition of enamine **2a′** [in situ generated from the combination of **2a** and ammonium salt] to aza-diene **5** leads to the intermediate **8** which in turn converts into cyclic intermediate **9** via an intramolecular C-N bond making process. Finally, it eliminates ammonium acetate to form sulfamate-fused-dihydropyridine **10** which undergoes aromatization by releasing SO_2 in the present conditions that

would eventually lead to the **4aaa.** However, the detailed mechanism for the conversion from **10** to **4aaa** is not clear to us.

With the established reaction conditions in hand, we examined the generality and scope of this three-component reaction by altering a group of 4-methyl N-sulfonyl ketimines as 2C1N (two carbon one nitrogen source) units for pyridine synthesis, C-H activated acyclic ketones (2C synthons) and aromatic/heteroaromatic aldehydes (1C sources) using ammonium acetate as a promoter under solvent-free conditions. The obtained results are summarized in Table 2. It was found that not only a benzaldehyde but also a wide range of aromatic aldehydes bearing electron donating (MeO) and electron withdrawing (F, Cl, Br, CN, NO_2 and CF_3) functionalities underwent C-C and C-N bonds forming reaction with N-sulfonyl ketimine **1a** and **2a** to produce uniformly good to high yields (76-83%) of the corresponding trisubstituted unsymmetrical pyridines (**4aad-4aak**). Next we turned our attention to apply aldehydes bearing a heteroaryl moiety such as pyridine, furan or thiophene in this cyclization process. All the heterocycles easily coupled with **1a** and **2a** by this method**,** leading to the 4-heteroaryl-substituted pyridine scaffolds **4aak**, **4aam** and **4aan** in 75%, 77% and 79% yields respectively. Moreover, incorporation of electron poor substituents such as F, Br, and NO_2 on the aryl rings of acetophenones afforded relatively lesser yields of the products (**4aeb-4afb**; 70-75%) as compared to electron donating ones (**4abm-4acf**; 76-82%). Furthermore, heteroaryl methyl ketone (**2h**) also afforded desired pyridine derivative (**4ahm-4ahc**) in 75-82% yields; Interestingly, by using an unsymmetrical ketone (ethyl methyl

Table 2. MCR Approach to Hydroxylarylated Tri-and Tetra-Substituted Pyridines (4aad-4faa)[a,b,c]

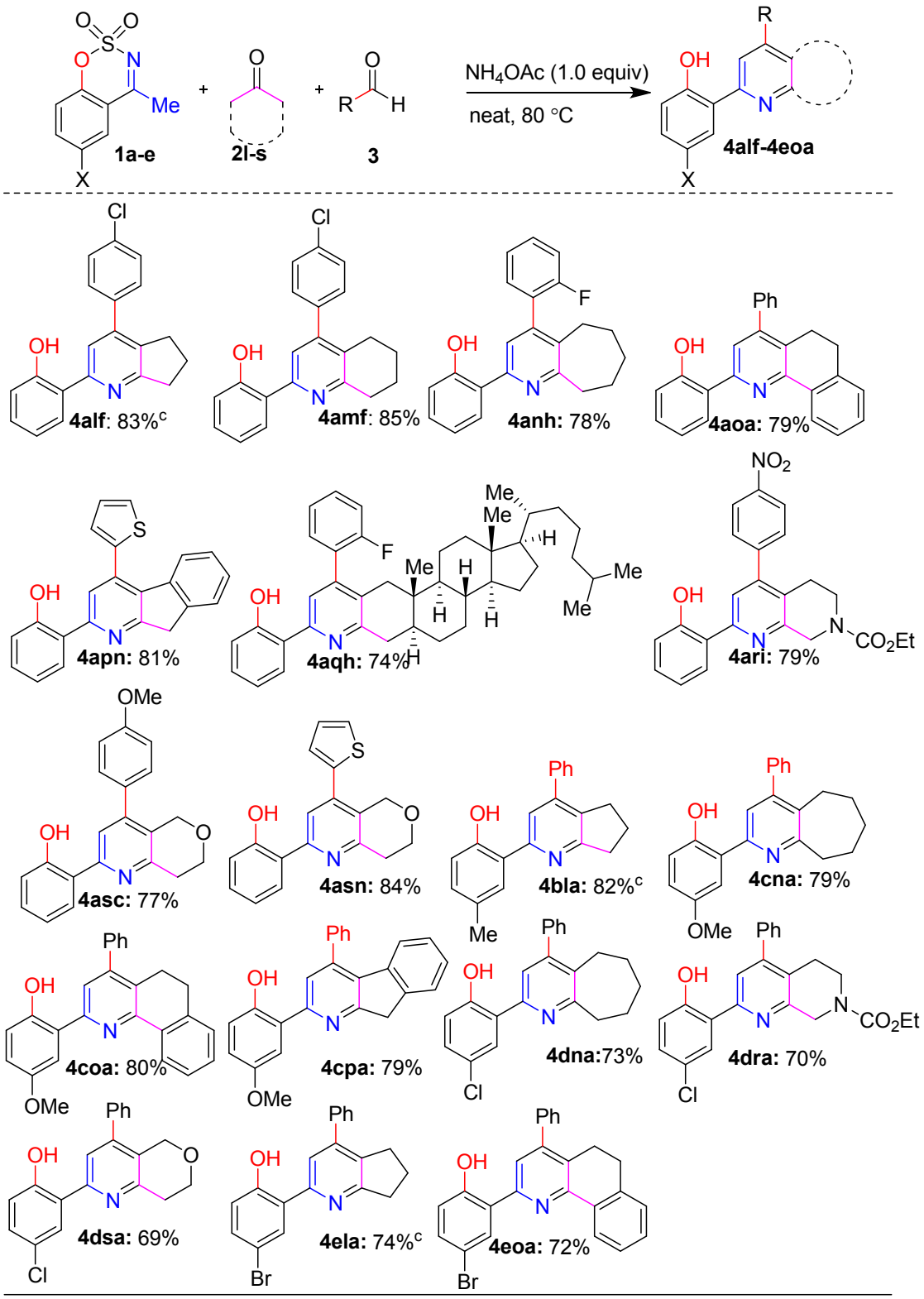


[a]Reaction conditions: **1a-f** (0.15 mmol), ketone (**2a-k**, 0.18 mmol), aldehyde (**3a-n**, 0.18 mmol) and NH_4OAc (0.15 mmol) at 80 °C in a neat condition for 10-18h. [b]Isolated yield. [c]ketones **2i** and **2j** were used 0.3 mmol (2.0 equiv.).

ketone, **2j**), a regioselective C-C bond formation occurred quantitively at the CH_2 position to produce only one regioisomer **4ajc** in 76% yield. Pleasantly, propiophenone (**2k**) also actively participated in this cyclization process, leading to the tetrasubstituted pyridine **4akc** in a satisfactory chemical yield (71%). It should be mentioned that using cyclopropyl methyl ketone (**2i**) as a 2C reaction partner, C-C bond formation was happened at the methyl site to afford the corresponding **4aim** and **4ain** in moderate yields (55-59%). Expectedly, the presence of halide atoms (Cl, Br) at the aryl-rings of N-sulfonyl ketimines (**1d** and **1e**) diminished their nucleophilicities which resulted in 5-10% lower yields as compared to donating ones (65-75% vs 67-84%). Moreover, they needed additional times (14-16h) to complete the cyclization process. Gratifyingly, N-sulfonyl ketimine **1f** with a naphthyl group was witnessed to be an appropriate nucleophile for this cyclization reaction to afford 75% yield of **4faa** with an interesting class of α-naphthol moiety. Importantly, the neutral reaction conditions are mild in nature which protect successfully several chemically sensitive functionalities including Me, MeO, Br, Cl, F, NO_2, CN, CF_3, OH, furan, thiophene, phenol and cyclopropane ring.

Next, the application of our designed protocol was further expanded towards the construction of an important class of carbo-and heterocyclic fused pyridine building blocks involving different kinds of cyclic C-H activated carbonyls as donors (Table 3). For instance, when 5-, 6-and 7-membered alicyclic ketones (**2l, 2m** and **2n**) were employed as 2C units for pyridine access, all the annulation reactions proceeded efficiently with **1a** and 1C sources such as **3f** and **3h** in a

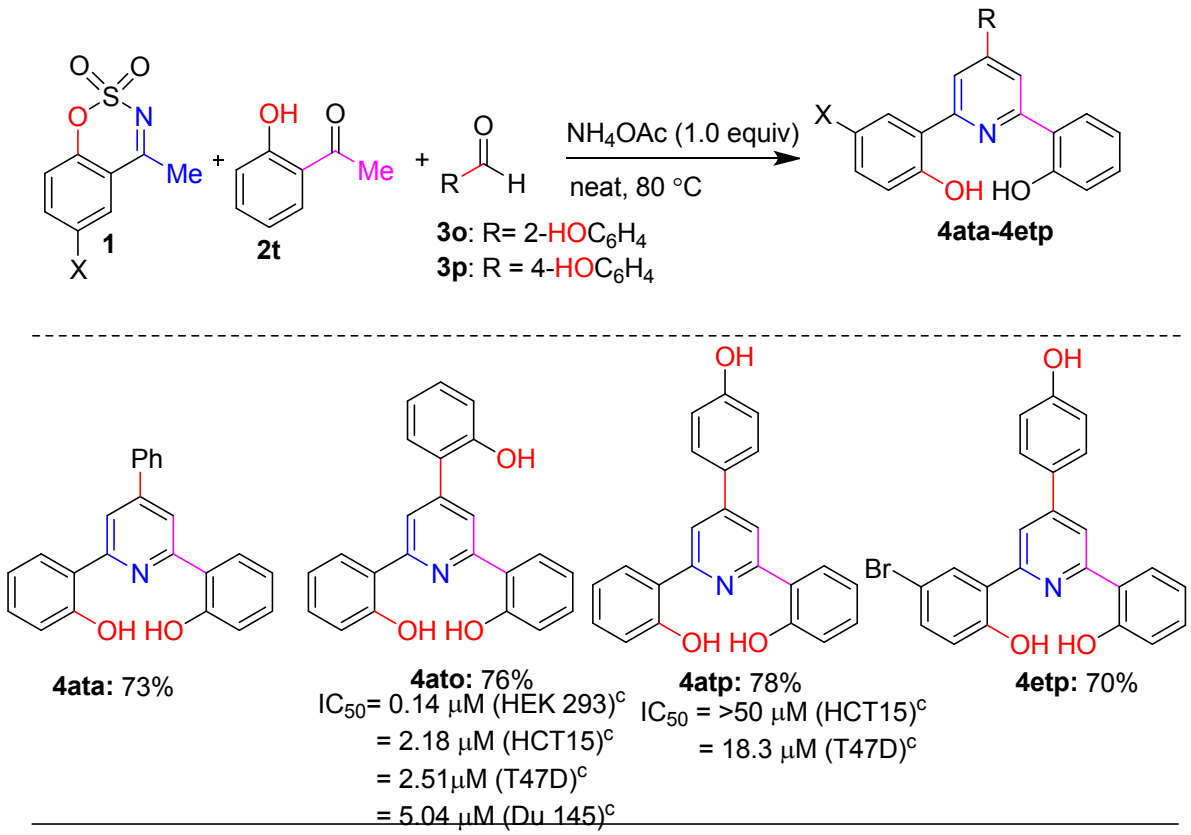
Table 3: Pot-Economy Approach to Carbo-and Heterocyclic Fused Pyridine Scaffolds (4alf-4eoa)[a, b,c]



[a]Reaction conditions: **1a-e** (0.15 mmol), **2l-s** (0.18 mmol), aldehyde **3**(0.18 mmol) and NH_4OAc (0.15 mmol) at 80 °C in a solvent-free condition for 8-12h. [b]Isolated yield. [c]1.5 equiv. of **2l** was used.

spotless manner. Consequently, they delivered the corresponding 5-, 6-and 7-membered carbocyclic rings-fused-pyridine frameworks **4alf, 4amf** and **4anh** in 83%, 85% and 78% yields respectively. Furthermore, by taking α-tetralone (**2o**) and 1-indanone (**2p**) as reactants, the targeted tricyclic-fused-pyridines **4aoa** and **4apn** were successfully isolated in 79% and 81% yields respectively, while reacting with **1a** and aldehydes **(3a** and **3n)**. In order to synthesize a pharmacologically as well as synthetically interesting pyridine fused steroid scaffold, a steroidal ketone **2q** derived from a cholesterol has been used in the domino reaction with **1a** and 2-fluorobenzaldehyde (**3h**). We were pleased to find that the above combination gave steroidal-A-ring fused pyridine (**4aqh,** enantiomerically pure pyridine) as a single regio-and stereoisomer in 74% yield after 12h. Notably, we did not detect other possible regioisomeric product. Furthermore, six-membered heterocyclic ketones namely N-protected piperidin-4-one (**2r**) and tetrahydro-4*H*-pyran-4-one (**2s**) were subjected to cyclize with a number of aldehydes and ketimine **1a** to give 77-84% yields of 6-membered heterocyclic fused pyridines (**4ari-4asn**) which are usually difficult to synthesize by reported methods. Moreover, this modular approach was not limited only for N-sulfonyl imine **1a** as a 2C1N unit**,** but it could also be tolerant to several aryl-substituted N-sulfonyl ketimines (**1b-1e**) with Me, MeO, Cl or Br substituents on the aryl rings and delivered a wide array of carbo-and heterocyclic fused pyridines **(4bla-4eoa)** in 69-82% yields.

Scheme 5. Synthesis of Di-and Tri-hydroxyarylated Pyridines (4ata-4etp)[a,b,c]

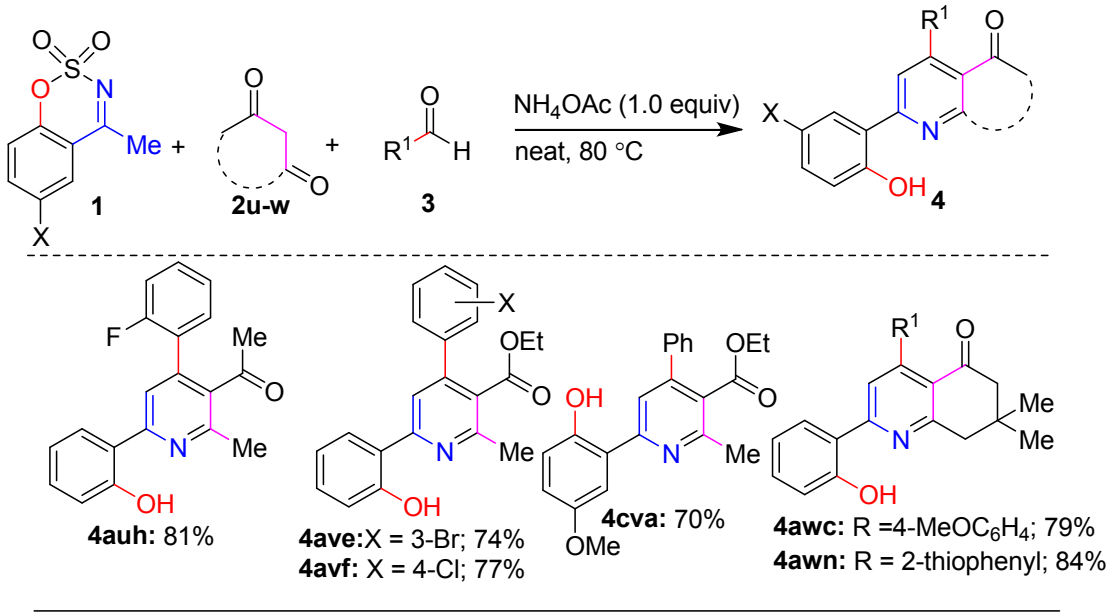


[a]Reaction conditions: **1a** (0.15 mmol), **2t** (0.18 mmol), aldehyde **3**(0.18 mmol) and NH_4OAc (0.15 mmol) at 80 °C in neat conditions for 9-12h. [b]Isolated yield. [c]Reported data, see reference[30a].

After efficiently synthesizing pyridine scaffolds bearing a one phenolic moiety, we are now greatly interested to construct two or more hydroxylated 2,4,6-triarylpyridine derivatives. Because these novel building blocks displayed highly potent selective topoisomerase II inhibitors and cytotoxicity against human cancer cell lines (HEK 293, HCT15, T47D and DU 145).[30] However, the reported chemical method has a number of shortcoming such as the use of strong base, acidic solvent, excess amounts of N-sourcing agent, two step methods, lower yields, less atom-

economical, higher temperature etc which obstacle the efficacy of the method. Therefore, an alternative one-pot metal-and oxidant-solvent-free based benign method is demanded for their efficient access. Towards this aim, a chemically challenging 2-hydroxyacetophenone (**2t)** has been selected as 2C unit for pyridine synthesis. Surprisingly, it nicely made C-C and C-N bonds with N-sulfonyl ketimines **1a-1e** and several aldehydes (**3a, 3o** and **3p**) in neutral reaction conditions, affording the corresponding biologically active di or trihydoxylated-2,4,6-pyridines **(4ata-4etp**) in good 70-78% yields (Scheme 5).

Scheme 6: Synthesis of 6-Hydroxyayl-2,3,4-Trisubstituted Pyridines from 1,3-Dicarbonyls **a,b**



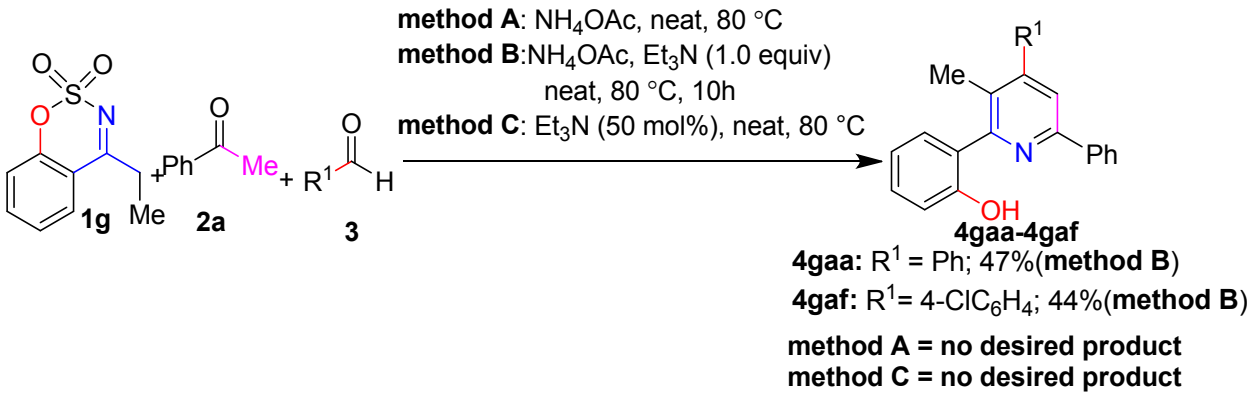
[a]Reaction conditions: **1a-c** (0.15 mmol), **2u-w** (0.18 mmol), aldehyde **3**(0.18 mmol) and NH_4OAc (0.15 mmol) at 80 °C in neat conditions for 12h. [b]Isolated yield.

Furthermore, switching mono ketones by more reactive diketone compounds such as acetyl acetone (**2u**), ethyl acetoacetate (**2v**) and dimedone (**2w**), the domino reaction took place exclusively at the C-3 position of 1,3-dicarbonyls due to the presence of an activated methylene

group. Consequently, the corresponding tetra-substituted pyridines (**4auh-4awn,** nicotinic acid derivatives) possessing a special class of carbonyl group at C-3 position were obtained in 70-84% yields with great regioselectivities (Scheme 6).

Next, we deliberated to employ 4-ethyl N-sulfonyl ketimine as a poor enamine donor in this aza-cyclization reaction with acetophenone (**2a**) and benzaldehyde (**3a**) under standard conditions (method A, Scheme 7). Surprisingly, the substrate **1g** could not participate in the cyclization process due to its poor nucleophilicity in neutral conditions. Therefore, we contemplated that base may necessitate for abstracting a proton from **1g** which triggers the condensation reaction with aldehyde that may produce desired scaffold. To our delight, by using method B, a moderate yield (47%) of **4gaa** was isolated. However, without NH_4OAc, only triethyl amine did not afford the desired product (method C). Similarly, the desired product **4gaf** was obtained in 44% yield while using aldehyde **3f** and ketone **2a**.

Scheme 7. MCR Approach to Tetra-Substituted Pyridine Scaffolds



CONCLUSIONS

In the current manuscript, we have established a unique modular synthetic strategy for the de novo synthesis of a diverse set of a biologically relevant tri-and tetra-substituted unsymmetrical pyridines including ring annulated building blocks bearing an interesting class of phenol, α-naphthol, acetyl and ester moieties at the C-6 and C-3 positions. Notably, many of our synthesized pyridines (especially fused ones) are otherwise tedious to prepare or not capable of being prepared by traditional techniques. This eco-friendly technique is simple that proceeds under acid-base-solvent-and metal-free conditions via a condensation-addition-cyclization-aromatization (two C-C and one C-N bonds) sequence reaction between a group of N-sulfonyl ketimines, a wide range of acyclic and cyclic ketones/1,3-dicarbonyls and aromatic/heteroaromatic aldehydes using ammonium acetate as a cheap, non-toxic and biodegradable promoter. In addition, our logical design method has significant merits such as good to high yields, a broad substrate scope, excellent functional group tolerance, great regioselectivity, neutral reaction conditions, operational simplicity, no need for organic solvents as well as toxic transition metal-salts, no stochiometric oxidants etc. Thus, we believe that this modular approach will find potential applications in heterocyclic chemistry, medicinal chemistry and material sciences. Moreover, additional works towards the biological study of prepared scaffolds are in progress. The fruitful results will be documented in due course of time.

EXPERIMENTAL SECTION

General Information: All the N-sulfonyl ketimines **(1a-1g),**[31] ketones **(2a-2w)** and aldehydes **(3a-3n)** were synthesized by literature known procedures or purchased from commercial sources.

All the reactions were carried out either under inert atmosphere or air and monitored by TLC using Merck 60 F_{254} pre coated silica gel plates and the products were visualized by UV detection. Flash chromatography was carried out using silica gel (200-300 mesh). ^{1}H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer. Data for ^{1}H NMR are reported as a chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant *J* (Hz), integration, and assignment, data for ^{13}C are reported as a chemical shift. High resolutions mass spectral analyses (HRMS) were carried out using ESI-TOF-MS. Melting points were recorded on an Electro thermal melting points apparatus and are uncorrected.

General Procedure for the Synthesis of Pyridines: A mixture of N-sulfonyl ketimine **1** (0.15 mmol), ketone **2** (0.18 mmol), aldehyde **3** (0.18 mmol) and ammonium acetate (0.15 mmol) was heated in oil bath at 80 °C. The progress of the reaction was judged by TLC. After completion of the reaction, the crude product was directly purified by silica-gel column chromatography using ethyl acetate/hexane as eluent to yield the corresponding substituted pyridine derivative in a pure form. All the obtained products in Tables 2-3 and Schemes 4-7 were characterized by ^{1}H NMR, ^{13}C NMR and HRMS data.

2-(4,6-Diphenylpyridin-2-yl)phenol (4aaa):[25a] Following the general procedure, the reaction of N-sulfonyl ketimine **1a** (29.6 mg, 0.15 mmol), acetophenone (**2a**; 21.6 mg, 0.18 mmol), benzaldehyde (**3a**; 18.9 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave **4aaa** as a pale yellow solid; yield 81% (39.3 mg); mp 156 - 158 °C; R_f = 0.8 (ethyl acetate/hexane = 1:20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.82 (s, 1H), 8.06 (s, 1H), 8.01 (d, *J* = 7.2 Hz, 2H), 7.95 (d, *J* = 7.4 Hz, 1H), 7.85 (s, 1H), 7.75 (d, *J* = 7.0 Hz, 2H), 7.61-7.46 (m, 6H), 7.39-7.31 (m, 1H), 7.08 (d, *J* = 8.1 Hz, 1H), 6.96 (t, *J* = 7.5 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.1, 158.1, 155.2, 151.2, 138.5, 138.3, 131.6, 129.6, 129.4, 129.2, 129.1, 127.6, 127.4, 127.1, 126.4,

118.9, 118.6, 117.2, 115.8 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{23}H_{18}NO$ 324.1383, found 324.1411.

Large Scale Preparation of Compound 4aaa: Following the procedure, the reaction of N-sulfonyl ketimine **1a** (1.97 g, 10 mmol), acetophenone (**2a**; 1.44 g, 12 mmol), benzaldehyde (**3a**; 1.272 g, 12 mmol) and ammonium acetate (0.77 gm,10.0 mmol) at 80 °C for 12h afforded **4aaa**; After usual work-up and purification, the product yielded in 78% (2.52 g).

2-(4-(2,5-Dimethoxyphenyl)-6-phenyl)pyridin-2-yl)phenol (4aad): Following the general procedure, the reaction of N-sulfonyl ketimine **1a** (29.6 mg, 0.15 mmol), acetophenone (**2a**; 21.6 mg, 0.18 mmol), aldehyde **3d** (29.9 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave **4aad** as a pale yellow solid; yield 76% (43.7 mg); mp 164 - 167 ^oC; R_f= 0.60 (ethyl acetate/hexane = 1:15); ^1H NMR (400 MHz, $CDCl_3$) δ 14.87 (s, 1H), 8.04 (s, 1H), 7.99 (d, *J* = 7.3 Hz, 2H), 7.89 (d, *J* = 7.6 Hz, 1H), 7.82 (s, 1H), 7.54-7.45 (m, 3H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.07 (d, *J* = 8.1 Hz, 1H), 7.01-6.98 (m, 3H), 6.95-6.91 (m, 1H), 3.85 (s, 3H), 3.82 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.1, 157.4, 154.5, 153.9, 150.8, 148.9, 138.3, 131.4, 129.4, 129.0, 128.8, 127.0, 126.4, 119.8, 119.2, 118.5, 118.4, 118.3, 116.3, 114.9, 112.9, 56.4, 55.9 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{25}H_{22}NO_3$ 384.1594, found 384.1598.

2-(4-(3-Bromophenyl)-6-phenyl)pyridin-2-yl)phenol (4aae): Following the general procedure, the reaction of N-sulfonyl ketimine **1a** (29.6 mg, 0.15 mmol), acetophenone (**2a**; 21.6 mg, 0.18 mmol), aldehyde **3e** (33.3 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave **4aae** as a pale yellow solid; yield 80% (48.2 mg); mp 136 - 138 ^oC; R_f= 0.82 (ethyl acetate/hexane = 1:20); ^1H NMR (400 MHz, $CDCl_3$) δ 14.68 (s, 1H), 7.99 (d, *J* = 6.0 Hz, 3H), 7.93 (d, *J* = 7.8 Hz, 1H), 7.87 (s, 1H), 7.77 (s, 1H), 7.64 (t, *J* = 8.1 Hz, 2H), 7.59-7.46 (m, 3H), 7.41 (t, *J* = 7.8 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.07 (d, *J* = 8.1 Hz, 1H), 6.96 (t, *J* = 7.4 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR

(100 MHz, $CDCl_3$) δ 160.1, 158.3, 155.6, 149.7, 140.6, 137.9, 132.3, 131.8, 130.7, 130.3, 129.8, 129.1, 127.0, 126.4, 125.9, 123.4, 118.9, 118.9, 118.6, 117.0, 115.6 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{23}H_{17}NO^{79}Br$ 402.0488, found 402.0486; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{23}H_{17}NO^{81}Br$ 404.0469, found 404.0460.

2-(4-(4-Chlorophenyl)-6-phenyl)pyridin-2-yl)phenol (4aaf): Following the general procedure, the reaction of N-sulfonyl ketimine **1a** (29.6 mg, 0.15 mmol), acetophenone (**2a**; 21.6 mg, 0.18 mmol), aldehyde **3f** (25.3 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave **4aaf** as a pale yellow solid; yield 81% (43.4 mg); mp 152 - 155 °C; R_f = 0.82 (ethyl acetate/hexane = 1:20); ^1H NMR (400 MHz, $CDCl_3$) δ 14.70 (s, 1H), 7.99 (d, *J* = 8.1 Hz, 3H), 7.93 (d, *J* = 7.8 Hz, 1H), 7.79 (s, 1H), 7.68 (d, *J* = 8.3 Hz, 2H), 7.60-7.46 (m, 5H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.07 (d, *J* = 8.2 Hz, 1H), 6.96 (t, *J* = 7.4 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.1, 158.3, 155.5(2C), 150.0, 137.9, 136.9, 135.7, 131.8, 129.8, 129.5, 129.1, 128.5, 127.0, 126.4, 118.9, 118.6, 116.9, 115.5 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{23}H_{17}NOCl$ 358.0993, found 358.0989.

2-(4-(2-Fluorophenyl)-6-phenyl)pyridin-2-yl)phenol (4aah): Following the general procedure, the reaction of N-sulfonyl ketimine **1a** (29.6 mg, 0.15 mmol), acetophenone (**2a**; 21.6 mg, 0.18 mmol), aldehyde **3h** (22.34 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave **4aah** as a pale yellow solid; yield 77% (39.4 mg); mp 100 - 102 °C; R_f = 0.81 (ethyl acetate/hexane = 1:20); ^1H NMR (400 MHz, $CDCl_3$) δ 14.64 (s, 1H), 7.97 (s, 1H), 7.92 (d, *J* = 7.4 Hz, 2H), 7.84 (d, *J* = 7.9 Hz, 1H), 7.76 (s, 1H), 7.55-7.39 (m, 4H), 7.29-7.23 (m, 2H), 7.22-7.16 (m, 2H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.88 (t, *J* = 7.5 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.1, 159.6 (d, $J_{C\text{-}F}$ = 248.6 Hz), 157.9, 155.0, 146.2, 138.0, 131.7, 131.1 (d, *J* = 8.4 Hz), 130.4 (d, *J* = 2.8 Hz), 129.7, 129.1, 127.0, 126.5, 124.9 (d, *J* = 3.7 Hz), 119.1, 118.8, 118.6,

117.6, 116.7, 116.5**;** HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{23}H_{17}NOF$ 342.1289, found 342.1284.

2-(4-(4-Nitrophenyl)-6-phenylpyridin-2-yl)phenol (4aai): Following the general procedure, the reaction of N-sulfonyl ketimine **1a** (29.6 mg, 0.15 mmol), acetophenone (**2a**; 21.6 mg, 0.18 mmol), aldehyde **3i** (27.2 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave **4aai** as a pale yellow solid; yield 83% (45.8 mg); mp 210-212 ^oC; R_f= 0.65 (ethyl acetate/hexane = 1:15); ^1H NMR (400 MHz, $CDCl_3$) δ 14.51 (s, 1H), 8.41 (d, *J* = 8.6 Hz, 2H), 8.04 (s, 1H), 8.00 (d, *J* = 6.9 Hz, 2H), 7.97.89 (m, 3H), 7.83 (s, 1H), 7.65-7.47 (m, 3H), 7.38 (t, *J* = 7.3 Hz, 1H), 7.09 (d, *J* = 8.1 Hz, 1H), 6.98 (t, *J* = 7.5 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.1, 158.6, 155.9, 148.9, 148.4, 144.8, 137.6, 132.1, 130.0, 129.2, 128.3, 127.0, 126.4, 124.4, 119.0, 118.7, 118.6, 117.1, 115.8 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{23}H_{17}N_2O_3$ 369.1234, found 369.1230.

2-(4-(4-Cyanophenyl)-6-phenylpyridin-2-yl)phenol (4aaj): Following the general procedure, the reaction of N-sulfonyl ketimine **1a** (29.6 mg, 0.15 mmol), acetophenone (**2a**; 21.6 mg, 0.18 mmol), aldehyde **3j** (23.6 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave **4aaj** as a pale yellow solid; yield 80% (41.7 mg); mp 185-187 ^oC; R_f= 0.7 (ethyl acetate/hexane = 1:15); ^1H NMR (400 MHz, DMSO-d_6) δ 14.20 (s, 1H), 8.52 (s, 1H), 8.32-8.29 (m, 4H), 8.15 (d, *J* = 7.2 Hz, 2H), 8.08 (d, *J* = 8.3 Hz, 2H), 7.60-7.55 (m, 3H), 7.38 (t, *J* = 7.2 Hz, 1H), 7.00-6.98 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d_6) δ 164.3, 162.9, 160.1, 154.0, 146.9 142.7, 138.2, 137.0, 135.2, 134.5, 133.9, 133.2, 132.1, 124.4, 124.3, 123.9, 123.1, 122.5, 122.0, 117.4 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{24}H_{17}N_2O$ 349.1335, found 349.1337.

2-(4-(4-Trifluoromethylphenyl)-6-phenylpyridin-2-yl)phenol (4aak): Following the general procedure, the reaction of N-sulfonyl ketimine **1a** (29.6 mg, 0.15 mmol), acetophenone (**2a**; 21.6

mg, 0.18 mmol), aldehyde **3k** (31.3 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave **4aak** as a pale yellow solid; yield 81% (47.5 mg); mp 162 - 164 ^{o}C; R_f= 0.77 (ethyl acetate/hexane = 1:20);^{1}H NMR (400 MHz, $CDCl_3$) δ 14.63 (s, 1H), 8.04 (s, 1H), 8.00 (d, *J* = 7.0 Hz, 2H), 7.94 (d, *J* = 7.3 Hz, 1H), 7.84-7.80 (m, 5H), 7.53-7.48 (m, 3H), 7.37-7.35 (m, 1H), 7.08 (d, *J* = 7.9 Hz, 1H), 6.97 (t, *J* = 7.5 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.1, 158.4, 155.7, 149.8, 142.1, 137.8, 131.9, 131.6, 131.2, 129.9, 129.2, 127.7, 127.0, 126.4, 126.3, 126.2, 126.2, 126.1, 118.9, 118.8, 118.7, 117.2, 115.8 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{24}H_{17}F_3NO$ 392.1257, found 392.1283.

2-(6-Phenyl-[4,4'-bipyridin]-2-yl)phenol (4aal): Following the general procedure, the reaction of N-sulfonyl ketimine **1a** (29.6 mg, 0.15 mmol), acetophenone (**2a**; 21.6 mg, 0.18 mmol), aldehyde **3l** (19.3 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave **4aal** as a pale yellow solid; yield 75% (36.5 mg); mp 165 - 167 ^{o}C; R_f= 0.5 (ethyl acetate/hexane = 1:15);^{1}H NMR (400 MHz, $CDCl_3$) δ 14.62 (s, 1H), 9.02 (s, 1H), 8.76 (d, *J* = 4.0 Hz, 1H), 8.09-8.03 (m, 2H), 8.01 (d, *J* = 7.0 Hz, 2H), 7.94 (d, *J* = 7.1 Hz, 1H), 7.83 (d, *J* = 0.8 Hz, 1H), 7.60-7.47 (m, 4H), 7.41-7.33 (m, 1H), 7.08 (d, *J* = 7.9 Hz, 1H), 6.98 (t, *J* = 7.6 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.1, 158.5, 155.8, 150.5, 148.2, 148.1, 137.8, 134.6, 131.9, 129.9, 129.2, 127.0, 126.4, 123.9, 119.0, 118.7, 117.0, 115.6 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{22}H_{17}N_2O$ 325.1335, found 325.1345.

2-(4-(Furan-2-yl)-6-phenyl)pyridin-2-yl)phenol (4aam): Following the general procedure, the reaction of N-sulfonyl ketimine **1a** (29.6 mg, 0.15 mmol), acetophenone (**2a**; 21.6 mg, 0.18 mmol), aldehyde **3m** (17.3 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave **4aam** as a pale yellow solid; yield 77% (36.1 mg); mp 157 - 159 ^{o}C; R_f= 0.8 (ethyl acetate/hexane = 1:20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.79 (s, 1H), 8.11 (s, 1H), 8.02-7.92 (m, 3H), 7.88 (d, *J*

= 0.9 Hz, 1H), 7.63 (d, *J* = 1.2 Hz, 1H), 7.55-7.46 (m, 3H), 7.40-7.31 (m, 1H), 7.06-7.06 (m, 2H), 7.00 – 6.93 (m, 1H), 6.61-6.60 (m, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.1, 158.2, 155.3, 151.3, 144.2, 139.8, 138.0, 131.6, 129.7, 129.1, 126.9, 126.4, 118.9, 118.8, 118.5, 113.0, 112.3, 111.5, 109.5 ppm; HRMS (ESI-TOF): *m/z* $[M + Na]^+$ calcd for $C_{21}H_{15}NO_2Na$ 336.0995, found 336.0982.

2-(4-(Thiophen-2-yl)-6-phenyl)pyridin-2-yl)phenol (4aan): Following the general procedure, the reaction of N-sulfonyl ketimine **1a** (29.6 mg, 0.15 mmol), acetophenone (**2a**; 21.6 mg, 0.18 mmol), aldehyde **3n** (20.17 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave **4aan** as a pale yellow solid; yield 79% (39.0 mg); mp 175 - 178 °C; R_f = 0.8 (ethyl acetate/hexane = 1:20); ^1H NMR (400 MHz, $CDCl_3$) δ 14.72 (s, 1H), 8.02 (s, 1H), 7.98 (d, *J* = 7.1 Hz, 2H), 7.91 (d, *J* = 7.5 Hz, 1H), 7.81 (s, 1H), 7.64 (d, *J* = 3.2 Hz, 1H), 7.59-7.45 (m, 4H), 7.37-7.33 (m, 1H), 7.23-7.16 (m, 1H), 7.07 (d, *J* = 8.1 Hz, 1H), 6.97 (t, *J* = 7.5 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.1, 158.3, 155.5(2C), 144.0, 141.2, 137.9, 131.7, 129.7, 129.1, 128.6, 127.7, 126.9, 126.3, 125.9, 118.8, 118.6, 115.4, 113.8 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{21}H_{16}NSO$ 330.0947, found 330.0949.

2-(6-(4-Methylphenyl)-4-(furan-2-yl)pyridin-2-yl)phenol (4abm): Following the general procedure, the reaction of N-sulfonyl ketimine **1a** (29.6 mg, 0.15 mmol), ketone **2b**(24.14 mg, 0.18 mmol), aldehyde **3m** (17.3 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave **4abm** as a pale yellow solid; yield 78% (38.3 mg); mp 157 - 159 °C; R_f = 0.8 (ethyl acetate/hexane = 1:20);^1H NMR (400 MHz, $CDCl_3$) δ 14.87 (s, 1H), 8.08 (s, 1H), 7.94 (d, *J* = 7.9 Hz, 1H), 7.89 (d, *J* = 7.8 Hz, 2H), 7.85 (s, 1H), 7.62 (s, 1H), 7.36-7.32 (m, 3H), 7.11-7.01 (m, 2H), 6.96 (t, *J* = 7.5 Hz, 1H), 6.60 (s, 1H), 2.44 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.2, 158.1, 155.3, 151.4, 144.1, 139.8, 135.2, 131.6, 129.8, 126.8, 126.4, 119.0, 118.7, 118.5, 112.7,

112.7, 112.3, 111.2, 109.4, 21.3 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{22}H_{18}NO_2$ 328.1332, found 328.1339.

2-(6-(4-Methylphenyl)-4-(thiophen-2-yl)pyridin-2-yl)phenol (4abn): Following the general procedure, the reaction of N-sulfonyl ketimine **1a** (29.6 mg, 0.15 mmol), ketone **2b** (24.14 mg, 0.18 mmol), aldehyde **3n** (20.17 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave **4abn** as a pale yellow solid; yield 82% (42.2 mg); mp 145-147 ^oC; R_f = 0.8 (ethyl acetate/hexane = 1:20); ^1H NMR (400 MHz, $CDCl_3$) δ 14.79 (s, 1H), 8.01 (s, 1H), 7.92-7.87 (m, 3H), 7.80 (s, 1H), 7.65 (d, *J* = 2.8 Hz, 1H), 7.49 (d, *J* = 4.8 Hz, 1H), 7.36-7.33 (m, 3H), 7.21-7.91 (m, 1H), 7.06 (d, *J* = 8.2 Hz, 1H), 6.97 (t, *J* = 7.5 Hz, 1H), 2.44 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.2, 158.2, 155.5, 143.9, 141.4, 139.9, 135.1, 131.6, 129.8, 128.5, 127.6, 126.8, 126.3, 125.9, 118.9, 118.8, 118.6, 115.1, 113.5, 21.3 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{22}H_{18}NOS$ 344.1104, found 344.1118.

2-(4,6-Di(4-methoxyphenyl)pyridin-2-yl)phenol (4acc):[25a] Following the general procedure, the reaction of N-sulfonyl ketimine **1a** (29.6 mg, 0.15 mmol), ketone **2c** (27.01 mg, 0.18 mmol), aldehyde **3c** (24.5 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave **4acc** as a pale yellow solid; yield 76% (43.6 mg); mp 128 - 130 ^oC; R_f = 0.6 (ethyl acetate/hexane = 1:20); ^1H NMR (400 MHz, $CDCl_3$) δ 15.03 (s, 1H), 7.92-7.90 (m, 4H), 7.74-7.64 (m, 3H), 7.33 (t, *J* = 7.2 Hz, 1H), 7.10-7.00 (m, 5H), 6.94 (t, *J* = 7.4 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.9, 160.8, 160.2, 157.8(2C), 154.8, 150.6, 131.4, 130.8, 130.7, 128.4, 128.3, 126.3, 119.2, 118.7, 118.5, 115.9, 114.6, 114.4, 55.4 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{25}H_{22}NO_3$ 384.1594, found 384.1606.

2-(4-(4-Chlorophenyl)-6-(4-methoxyphenyl)pyridin-2-yl)phenol (4acf): Following the general procedure, the reaction of N-sulfonyl ketimine **1a** (29.6 mg, 0.15 mmol), ketone **2c** (27.01 mg,

0.18 mmol), aldehyde **3f** (25.3 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave **4acf** as a pale yellow solid; yield 79% (40.6 mg); mp 135 - 137 ^{o}C; R_f = 0.7 (ethyl acetate/hexane = 1:20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.82 (s, 1H), 7.94-7.90 (m, 4H), 7.73 (s, 1H), 7.67 (d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 8.3 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.06-7.04 (m, 3H), 6.95 (t, *J* = 7.5 Hz, 1H), 3.89 (s, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 161.0, 160.1, 158.0, 155.0, 149.8, 137.0, 135.6, 131.6, 130.3, 129.4, 128.4, 128.2, 126.3, 118.9, 118.8, 118.5, 116.0, 114.7, 114.5, 55.4 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{24}H_{19}ClNO_2$ 388.1099, found 388.1118.

2-(6-(3-Fluorphenyl)-4-(4-methylphenyl)pyridin-2-yl)phenol (4aeb): Following the general procedure, the reaction of N-sulfonyl ketimine **1a** (29.6 mg, 0.15 mmol), ketone **2e** (22.33 mg, 0.18 mmol), aldehyde **3b** (21.62 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave **4aeb** as a pale yellow solid; yield 73% (38.9 mg); mp 129 - 131 ^{o}C; R_f = 0.8 (ethyl acetate/hexane = 1:20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.55 (s, 1H), 8.07 (s, 1H), 7.94 (d, *J* = 7.9 Hz, 1H), 7.79 (d, *J* = 7.9 Hz, 2H), 7.67-7.64 (m, 3H), 7.53-7.47 (m, 1H), 7.36 (t, *J* = 7.0 Hz, 3H), 7.18 (t, *J* = 8.1 Hz, 1H), 7.07 (d, *J* = 8.2 Hz, 1H), 6.96 (t, *J* = 7.5 Hz, 1H), 2.46 (s, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.3 (d, J_{C-F} = 245.1 Hz), 160.0, 158.2, 154.0, 153.9, 151.3, 140.6, 140.5, 139.8, 135.2, 131.7, 130.7 (d, J_{C-F} = 8.2 Hz), 130.0, 127.0, 126.4, 122.7 , 118.9 (d, J_{C-F} = 2.9 Hz), 118.5, 117.1, 116.4 (d, J_{C-F} = 21.1 Hz), 116.0, 114.0, 113.8, 21.3 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{24}H_{19}FNO$ 356.1445, found 356.1448.

2-(6-(3-Fluorphenyl)-4-(4-fluorophenyl)pyridin-2-yl)phenol (4aeg): Following the general procedure, the reaction of N-sulfonyl ketimine **1a** (29.6 mg, 0.15 mmol), ketone **2e** (22.33 mg, 0.18 mmol), aldehyde **3g** (22.33 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave **4aeg** as a pale yellow solid; yield 75% (40.4 mg); mp 176 - 178 ^{o}C; R_f = 0.76 (ethyl

acetate/hexane = 1:20);^{1}H NMR (400 MHz, $CDCl_3$) δ 14.44 (s, 1H), 8.03 (s, 1H), 7.93 (d, *J* = 7.8 Hz, 1H), 7.79-7.71 (m, 4H), 7.67 (d, *J* = 9.8 Hz, 1H), 7.53-7.48 (m, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.27-7.16 (m, 3H), 7.08 (d, *J* = 8.2 Hz, 1H), 6.97 (t, *J* = 7.5 Hz, 1H) ppm; $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 163.7 (d, J_{C-F} = 248.6 Hz), 163.3 (d, J_{C-F} = 245.3 Hz), 160.0, 158.3, 154.2, 154.1, 150.3, 140.3, 140.2, 134.4, 134.3, 131.8, 130.7 (d, J_{C-F} = 8.2 Hz), 129.1 (d, J_{C-F} = 8.3 Hz), 126.4, 122.6 (d, J_{C-F} = 2.9 Hz), 119.1, 118.6, 118.5, 117.1, 116.6 (d, J_{C-F} = 21.1 Hz), 116.5 (d, J_{C-F} = 3.2 Hz), 116.3 (d, J_{C-F} = 21.6 Hz) 114.0, 113.8 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{23}H_{16}F_2NO$ 360.1194, found 360.1185.

2-(6-(4-Bromophenyl)-4-(thiophenyl-2-yl)pyridin-2-yl)phenol (4afn): Following the general procedure, the reaction of N-sulfonyl ketimine **1a** (29.6 mg, 0.15 mmol), ketone **2f** (35.83 mg, 0.18 mmol), aldehyde **3n** (20.17 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave **4afn** as a pale yellow solid; yield 74% (45.3 mg); mp 160 - 163 ^{o}C; R_f = 0.75 (ethyl acetate/hexane = 1:20);[1] ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.45 (s, 1H), 8.04 (s, 1H), 7.91 (d, *J* = 7.9 Hz, 1H), 7.84 (d, *J* = 8.3 Hz, 2H), 7.77 (s, 1H), 7.66 (d, *J* = 8.0 Hz, 3H), 7.51 (d, *J* = 5.0 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.21 (t, *J* = 4.2 Hz, 1H), 7.06 (d, *J* = 8.2 Hz, 1H), 6.98 (t, *J* = 7.6 Hz, 1H) ppm; $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 160.0, 158.5, 154.5, 144.2, 141.0, 136.9, 132.3, 131.9, 128.6, 128.4, 127.9, 126.4, 126.1, 124.2, 119.1, 118.8, 118.6, 115.2, 114.2 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{21}H_{15}{}^{79}BrNOS$ 408.0052, found 408.0029; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{21}H_{15}{}^{81}BrNOS$ 410.0032, found 410.0011.

2-(6-(4-Nitrophenyl)-4-(thiophenyl-2-yl)pyridin-2-yl)phenol (4ago): Following the general procedure, the reaction of N-sulfonyl ketimine **1a** (29.6 mg, 0.15 mmol), ketone **2g** (29.72 mg, 0.18 mmol), aldehyde **3o** (20.18 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave **4ago** as a pale yellow solid;yield 70% (39.3 mg); mp 210 - 213 ^{o}C; R_f = 0.65 (ethyl

acetate/hexane = 1:15);^{1}H NMR (400 MHz, $CDCl_3$) δ 14.10 (s, 1H), 8.40 (d, *J* = 8.5 Hz, 2H), 8.19-8.09 (m, 3H), 7.93 (d, *J* = 7.9 Hz, 1H), 7.86 (s, 1H), 7.69 (d, *J* = 3.0 Hz, 1H), 7.54 (d, *J* = 4.8 Hz, 1H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.26-7.18 (m, 1H), 7.08 (d, *J* = 8.2 Hz, 1H), 7.00 (t, *J* = 7.5 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.8, 158.9, 153.2, 148.5, 144.4, 143.9, 140.5, 132.2, 128.8, 128.3, 127.8, 126.5, 126.4, 124.3, 119.2, 118.7, 118.6, 116.1, 115.2 ppm; HRMS (ESI-TOF): *m/z* [M + H]$^{+}$ calcd for $C_{21}H_{15}N_2O_3S$ 375.0798, found 375.0806.

2-(4-(4-Methylphenyl)-6-(4-bromophenyl)pyridin-2-yl)phenol (4afb): Following the general procedure, the reaction of **1a** (29.6 mg, 0.15 mmol), ketone **2f** (35.83 mg, 0.18 mmol), aldehyde **3b** (21.62 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave **4afb** as a pale yellow solid; yield 75% (46.8 mg); mp 180 - 185 ^{o}C; R_f = 0.75 (ethyl acetate/hexane = 1:20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.59 (s, 1H), 8.06 (s, 1H), 7.94 (d, *J* = 7.9 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 2H), 7.79 (s, 1H), 7.71-7.61 (m, 4H), 7.35-7.33 (m, 3H), 7.07 (d, *J* = 8.2 Hz, 1H), 6.96 (t, *J* = 7.5 Hz, 1H), 2.46 (s, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.0, 158.2, 154.1, 151.3, 139.8, 137.1, 135.3, 132.2, 131.7, 130.0, 128.5, 127.0, 126.4, 124.1, 119.0, 118.9, 118.5, 116.8, 115.9, 21.3 ppm; HRMS (ESI-TOF): *m/z* [M + H]$^{+}$ calcd for $C_{24}H_{19}{}^{79}BrNO$ 416.0645, found 416.0656; HRMS (ESI-TOF): *m/z* [M + H]$^{+}$ calcd for $C_{24}H_{19}{}^{81}BrNO$ 418.0625, found 418.0641.

2-(4-(Furan-2-yl)-6-(thiophen-2-yl)pyridin-2-yl)phenol (4ahm): Following the general procedure, the reaction of **1a** (29.6 mg, 0.15 mmol), ketone **2h** (22.7 mg, 0.18 mmol), aldehyde **3m** (17.3 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave **4ahm** as a pale yellow solid; yield 80% (38.3 mg); mp 158 - 160 ^{o}C; R_f = 0.75 (ethyl acetate/hexane = 1:20);^{1}H NMR (400 MHz, $CDCl_3$) δ 14.05 (s, 1H), 7.97 (s, 1H), 7.88 (d, *J* = 7.9 Hz, 1H), 7.77 (s, 1H), 7.68 (d, *J* = 2.0 Hz, 1H), 7.60 (s, 1H), 7.45 (d, *J* = 4.7 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.15 (s, 1H), 7.06 (d, *J* = 8.2 Hz, 1H), 7.01 (s, 1H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.58 (s, 1H) ppm; ^{13}C{^{1}H} NMR

(100 MHz, $CDCl_3$) δ 159.8, 158.0, 151.0, 149.9, 144.2, 142.8, 139.7, 131.7, 128.3, 127.8, 126.5, 125.6, 118.9, 118.8, 118.6, 112.3, 111.4, 111.1, 109.6 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{19}H_{14}NO_2S$ 320.0740, found 320.0728.

2-(4,6-Di(thiophen-2-yl)pyridin-2-yl)phenol (4ahn):[25a] Following the general procedure, the reaction of **1a** (29.6 mg, 0.15 mmol), ketone **2h** (22.7 mg, 0.18 mmol), aldehyde **3n** (20.17 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave **4ahn** as a pale yellow solid; yield 82% (41.2 mg); mp 154 - 158 °C; R_f = 0.75 (ethyl acetate/hexane = 1:20);^{1}H NMR (400 MHz, $CDCl_3$) δ 14.00 (s, 1H), 7.93 (s, 1H), 7.88 (d, *J* = 7.9 Hz, 1H), 7.75 (s, 1H), 7.71 (d, *J* = 2.2 Hz, 1H), 7.64 (d, *J* = 2.2 Hz, 1H), 7.48 (dd, *J* = 10.6, 4.8 Hz, 2H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.24-7.13 (m, 2H), 7.08 (d, *J* = 8.2 Hz, 1H), 6.96 (t, *J* = 7.4 Hz, 1H) ppm ; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.8, 158.0, 150.0, 143.8, 142.6, 140.9, 131.7, 128.5, 128.3, 127.9, 127.7, 126.4, 126.0, 125.6, 118.9, 118.7, 118.6, 113.7, 113.3 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{19}H_{14}NOS_2$ 356.0511, found 356.0534.

2-(4-(4-Methoxyphenyl)-6-(thiophen-2-yl)pyridin-2-yl)phenol (4ahc): Following the general procedure, the reaction of **1a** (29.6 mg, 0.15 mmol), ketone **2h** (22.7 mg, 0.18 mmol), aldehyde **3c** (24.5 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave **4ahc** as a pale yellow solid; yield 75% (40.4 mg) ;mp 130 - 133 °C; R_f = 0.6 (ethyl acetate/hexane = 1:20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.16 (s, 1H), 7.88 (d, *J* = 6.2 Hz, 2H), 7.67-7.64 (m, 4H), 7.44 (d, *J* = 4.9 Hz, 1H), 7.37-7.30 (m, 1H), 7.18-7.13 (m, 1H), 7.06-7.03 (m, 3H), 6.94 (t, *J* = 7.5 Hz, 1H), 3.88 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.8, 159.8, 157.7, 150.5, 149.7, 143.0, 131.5, 130.4, 128.4, 128.3, 127.7, 126.4, 125.4, 119.0, 118.9, 118.6, 115.0, 114.7, 114.7, 55.4 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{22}H_{18}NO_2S$ 360.1053, found 360.1063.

2-(6-Cyclopropyl-4-(furan-2-yl)pyridin-2-yl)phenol (4aim): Following the general procedure, the reaction of **1a** (29.6 mg, 0.15 mmol), ketone **2i** (29.49 mg, 0.3 mmol), aldehyde **3m** (17.3 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave **4aim** as a pale yellow solid; yield 56% (23.3 mg); mp 82 - 84 ^{o}C; R_f = 0.8 (ethyl acetate/hexane = 1:20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.51 (s, 1H), 7.90 (s, 1H), 7.86 (d, *J* = 7.8 Hz, 1H), 7.58 (s, 1H), 7.36-7.25 (m, 2H), 7.00 (d, *J* = 8.1 Hz, 1H), 6.94-6.89 (m, 2H), 6.56 (d, *J* = 1.0 Hz, 1H), 2.20-2.04 (m, 1H), 1.18-1.03 (m, 4H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.7, 160.0, 157.8, 151.4, 144.0, 138.9, 131.4, 126.3, 119.0, 118.7, 118.4, 113.8, 112.2, 110.0, 109.2, 16.9, 9.9 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{18}H_{16}NO_2$ 278.1176, found 278.1199.

2-(6-Cyclopropyl-4-(thiophen-2-yl)pyridin-2-yl)phenol (4ain): Following the general procedure, the reaction of **1a** (29.6 mg, 0.15 mmol), ketone **2i** (29.49 mg, 0.3 mmol), aldehyde **3n** (20.17 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave **4ain** as a pale yellow solid; yield 59% (25.9 mg); mp 84 - 85 ^{o}C; R_f = 0.8 (ethyl acetate/hexane = 1:20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.45 (s, 1H), 7.88-7.80 (m, 2H), 7.56 (d, *J* = 2.0 Hz, 1H), 7.45 (d, *J* = 4.9 Hz, 1H), 7.37-7.27 (m, 2H), 7.17-1.16 (m, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.92 (t, *J* = 7.6 Hz, 1H), 2.18-2.06 (m, 1H), 1.14-1.10 (m, 4H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.9, 160.1, 157.9, 143.0, 141.3, 131.4, 128.5, 127.4, 126.2, 125.7, 118.9, 118.7, 118.4, 116.2, 112.3, 16.8, 10.0 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{18}H_{16}NOS$ 294.0947, found 294.0969.

2-(4-(4-Methoxyphenyl)-5,6-dimethylpyridin-2-yl)phenol (4ajc): Following the general procedure, the reaction of **1a** (29.6 mg, 0.15 mmol), ketone **2j** (21.6 mg, 0.3 mmol), aldehyde **3c** (24.5 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave **4ajc** as a pale yellow solid; yield 76% (34.8 mg); mp 165 - 168 ^{o}C; R_f = 0.6 (ethyl acetate/hexane = 1:20); ^{1}H NMR

(400 MHz, $CDCl_3$) δ 14.90 (s, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.59 (s, 1H), 7.27-7.23 (m, 3H), 7.00 (d, *J* = 8.4 Hz, 3H), 6.84 (t, *J* = 7.5 Hz, 1H), 3.87 (s, 3H), 2.60 (s, 3H), 2.21 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.0, 159.5, 154.1, 153.8, 151.2, 132.0, 130.8, 129.9, 127.4, 125.8, 119.0, 118.5, 118.4, 117.8, 113.9, 55.4, 22.9, 16.0 ppm; HRMS (ESI-TOF): m/z $[M + H]^+$ calcd for $C_{20}H_{20}NO_2$ 306.1489, found 306.1493.

2-(4-(4-Methoxyphenyl)-5-methyl-6-phenylpyridin-2-yl)phenol (4akc): Following the general procedure, the reaction of **1a** (29.6 mg, 0.15 mmol), ketone **2k** (24.14 mg, 0.18 mmol), aldehyde **3c** (24.5 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave **4akc** as a pale yellow solid; yield 71% (37.8 mg); mp 107 - 109 °C; R_f = 0.6 (ethyl acetate/hexane = 1:20); ^1H NMR (400 MHz, $CDCl_3$) δ 14.66 (s, 1H), 7.83 (d, *J* = 7.7 Hz, 1H), 7.75 (s, 1H), 7.62 (d, *J* = 7.2 Hz, 2H), 7.50 - 7.41 (m, 3H), 7.36 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 7.5 Hz, 1H), 7.04 – 6.97 (m, 3H), 6.88 (t, *J* = 7.3 Hz, 1H), 3.89 (s, 3H), 2.27 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.0, 159.6, 156.0, 154.4, 152.7, 139.8, 132.0, 131.1, 130.0, 129.0, 128.5, 128.4, 127.0, 126.0, 118.8, 118.6, 118.5, 118.4, 114.0, 55.4, 17.9 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{23}H_{18}NO_3$ 356.1281, found 356.1307.

2-(4-(4-Chlorophenyl)-6-(4-methylphenyl)pyridin-2-yl)-4-methylphenol (4bbf): Following the general procedure, the reaction of **1b** (31.69 mg, 0.15 mmol), ketone **2b** (24.14 mg, 0.18 mmol), aldehyde **3f** (25.3 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave **4bbf** as a pale yellow solid; yield 80% (46.2 mg); mp 165 – 167 °C; R_f = 0.75 (ethyl acetate/hexane = 1:20); ^1H NMR (400 MHz, $CDCl_3$) δ 14.53 (s, 1H), 7.95 (s, 1H), 7.88 (d, *J* = 8.1 Hz, 2H), 7.74 (d, *J* = 0.8 Hz, 1H), 7.68 (d, *J* = 8.5 Hz, 3H), 7.52 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 7.18 -7.15 (m, 1H), 6.97 (d, *J* = 8.3 Hz, 1H), 2.44 (s, 3H), 2.37 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 158.2, 157.8, 155.4, 149.8, 139.9, 137.1, 135.6, 135.1, 132.5, 129.8, 129.4, 128.5,

127.7, 126.8, 126.5, 118.5, 118.3, 116.4, 115.1, 21.3, 20.7 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{25}H_{21}ClNO$ 386.1306, found 386.1310.

2-(6-(4-Bromophenyl)-4-(4-methoxyphenyl)pyridin-2-yl)-4-methylphenol (4bfc): Following the general procedure, the reaction of **1b** (31.69 mg, 0.15 mmol), ketone **2f** (35.83 mg, 0.18 mmol), aldehyde **3c** (24.5 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave **4bfc** as a pale yellow solid; yield 67% (44.8 mg): mp 158-159 ^oC; R_f = 0.6 (ethyl acetate/hexane = 1:20); ^1H NMR (400 MHz, $CDCl_3$) δ 14.36 (s, 1H), 8.01 (s, 1H), 7.85 (d, *J* = 8.5 Hz, 2H), 7.75 (d, *J* = 0.9 Hz, 1H), 7.74-7.68 (m, 3H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.16 (dd, J_1 = 8.3 Hz, J_2 = 1.4 Hz, 1H), 7.07 (d, *J* = 8.7 Hz, 2H), 6.96 (d, *J* = 8.3 Hz, 1H), 3.90 (s, 3H), 2.38 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.9, 158.2, 157.7, 154.0, 150.8, 137.2(2C), 132.5, 132.2, 130.5, 128.4, 127.8, 126.5, 124.0, 118.6, 118.3, 116.3, 115.4, 114.7, 55.4, 20.8 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{25}H_{21}{}^{79}BrNO_2$ 446.0750, found 446.0757 ; HRMS (ESI-TOF): m/z [M + H]+ calcd for $C_{25}H_{21}{}^{81}BrNO_2$ 448.0731, found 448.0737.

4-Methyl-2-(5-methyl-4,6-diphenylpyridin-2-yl)phenol (4bka): Following the general procedure, the reaction of **1b** (31.69 mg, 0.15 mmol), ketone **2k** (24.14 mg, 0.18 mmol), aldehyde **3a** (18.9 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave **4bka** as a pale yellow solid; yield 72% (37.9 mg); mp 122 - 125 ^oC; R_f = 0.7 (ethyl acetate/hexane = 1:20); ^1H NMR (400 MHz, $CDCl_3$) δ 14.36 (s, 1H), 7.75 (s, 1H), 7.62 (d, *J* = 6.9 Hz, 3H), 7.54-7.39 (m, 8H), 7.14-7.04 (m, 1H), 6.89 (d, *J* = 8.3 Hz, 1H), 2.31 (s, 3H), 2.25 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 157.7, 156.0, 154.5, 152.9, 139.8, 139.7, 131.9, 129.0, 128.6, 128.5, 128.4, 128.4, 128.2, 127.5, 126.7, 126.2, 118.4, 118.3, 118.2, 20.7, 17.7 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{25}H_{22}NO$ 352.1696, found 352.1690.

2-(4,6-Diphenylpyridin-2-yl)-4-methylphenol (4baa): Following the general procedure, the reaction of **1b** (31.69 mg, 0.15 mmol), ketone **2a** (21.6 mg, 0.18 mmol), aldehyde **3a** (18.9 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave **4baa** as a pale yellow solid; yield 83%; mp 132 - 134 ^{o}C; R_f = 0.7 (ethyl acetate/hexane = 1:20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.57 (s, 1H), 8.11-7.97 (m, 3H), 7.83 (s, 1H), 7.81-7.71 (m, 3H), 7.57-7.48 (m, 6H), 7.17 (d, *J* = 8.1 Hz, 1H), 6.98 (d, *J* = 8.2 Hz, 1H), 2.38 (s, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.1, 157.9, 155.2, 151.1, 138.6, 138.1, 132.5, 129.6, 129.4, 129.2, 129.1, 127.7, 127.2, 126.9, 126.5, 118.6, 118.3, 117.0, 115.7, 20.8 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{24}H_{20}NO$ 338.1539, found 338.1549.

2-(4,6-Diphenylpyridin-2-yl)-4-methoxyphenol (4caa): Following the general procedure, the reaction of **1c** (34.1 mg, 0.15 mmol), ketone **2a** (21.6 mg, 0.18 mmol), aldehyde **3a** (18.9 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave **4caa** as a pale yellow solid; yield 84% (44.5 mg); mp 146 - 148 ^{o}C; R_f = 0.5 (ethyl acetate/hexane = 1:20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.26 (s, 1H), 8.00 (d, *J* = 7.1 Hz, 3H), 7.84 (d, *J* = 0.7 Hz, 1H), 7.74 (d, *J* = 6.9 Hz, 2H), 7.52-7.48 (m, 6H), 7.45 (d, *J* = 2.6 Hz, 1H), 7.02 (d, *J* = 8.9 Hz, 1H), 6.97 (dd, J_1 = 8.9 Hz, J_2 = 2.7 Hz, 1H), 3.86 (s, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 157.8, 155.4, 154.2, 152.2, 151.2, 139.3, 138.7, 138.3, 129.6, 129.6, 128.9, 127.9, 127.6, 127.1, 119.0, 117.9, 117.6, 115.8, 111.4, 56.1 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{24}H_{20}NO_2$ 354.1489, found 354.1488.

4-Methoxy-2-(5-methyl-4,6-diphenylpyridin-2-yl)phenol (4cka): Following the general procedure, the reaction of **1c** (34.1 mg, 0.15 mmol), ketone **2k** (24.14 mg, 0.18 mmol), aldehyde **3a** (18.9 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave **4cka** as a pale yellow solid; yield 74% (40.7 mg); mp 105 - 107 ^{o}C; R_f = 0.5 (ethyl acetate/hexane = 1:20); ^{1}H

NMR (400 MHz, $CDCl_3$) δ 14.42 (s, 1H), 8.18-7.52 (m, 12H), 7.26 (s, 2H), 4.14 (s, 3H), 2.59 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 156.2, 154.2, 154.1, 153.0, 152.1, 139.8, 139.7, 129.0, 128.7, 128.6, 128.5, 128.4, 128.2, 127.0, 119.0, 118.7, 118.5, 117.7, 110.7, 56.0, 17.8 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{25}H_{22}NO_2$ 368.1645, found 368.1648.

2-(4-phenyl-5,6-dimethylpyridin-2-yl)-4-methoxyphenol (4cja): Following the general procedure, the reaction of **1c** (34.1 mg, 0.15 mmol), ketone **2j** (21.6 mg, 0.3 mmol), aldehyde **3a** (18.9 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave **4cja** as a pale yellow solid; yield 78% (35.7 mg); mp 85-87 °C; R_f = 0.5 (ethyl acetate/hexane = 1:20); ^1H NMR (400 MHz, $CDCl_3$) δ 14.27 (s, 1H), 7.56 (s, 1H), 7.52-7.42 (m, 3H), 7.37-7.30 (m, 2H), 6.95 (d, J = 8.9 Hz, 1H), 6.89 (dd, J_1= 8.9, J_2=2.8 Hz, 1H), 3.79 (s, 3H), 2.62 (s, 3H), 2.22 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 154.4, 154.0, 153.6, 152.0, 151.5, 139.7, 128.6, 128.5, 128.0, 127.4, 118.9, 117.7, 117.4, 113.5, 110.6, 56.0, 22.9, 15.9 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{20}H_{20}NO_2$ 306.1489, found 306.1473.

4-Chloro-2-(6-(4-fluorophenyl)-4-(4-methoxyphenyl)pyridin-2-yl)phenol (4ddc): Following the general procedure, the reaction of **1d** (34.75 mg, 0.15 mmol), ketone **2d** (22.33 mg, 0.18 mmol), aldehyde **3c** (24.5 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave **4ddc** as a pale yellow solid; yield 65% (39.5 mg)**;** mp 164 – 167 °C; R_f = 0.5 (ethyl acetate/hexane = 1:20); ^1H NMR (400 MHz, $CDCl_3$) δ 14.76 (s, 1H), 7.95 (dd, J_1 = 8.8 Hz, J_2 = 5.1 Hz, 3H), 7.88 (d, J = 2.3 Hz, 1H), 7.78 (s, 1H), 7.71 (d, J = 8.7 Hz, 2H), 7.31-7.25 (m, 2H), 7.21 (d, J = 8.6 Hz, 1H), 7.08 (d, J = 8.7 Hz, 2H), 7.00 (d, J = 8.8 Hz, 1H), 3.91 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 163.8 (d, J_{C-F} = 248.0 Hz), 161.0, 158.6, 156.7, 154.41, 151.1, 134.2 (d, J_{C-F} = 3.2 Hz), 131.3, 130.2, 129.3 (d, J_{C-F} = 8.4 Hz), 128.4, 125.9, 123.5, 120.0, 119.9, 116.9, 116.1 (d, J_{C-}

$_F$ = 21.6 Hz), 115.1, 114.7, 55.5 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{24}H_{18}ClFNO_2$ 406.1005, found 406.1025.

4-Chloro-2-(4-(4-chlorophenyl)-6-(4-methoxyphenyl)pyridin-2-yl)phenol (4dcf): Following the general procedure, the reaction of **1d** (34.75 mg, 0.15 mmol), ketone **2c**; (27.01 mg, 0.18 mmol), aldehyde **3f** (25.3 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave **4dcf** as a pale yellow solid 68% yield; mp 181 – 182 ^oC; R_f = 0.5 (ethyl acetate/hexane = 1:20); ^1H NMR (400 MHz, $CDCl_3$) δ 14.85 (s, 1H), 7.93-7.85 (m, 4H), 7.76 (d, *J* = 0.6 Hz, 1H), 7.68 (d, *J* = 8.5 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 7.34-7.22 (m, 1H), 7.06-6.99 (m, 3H), 3.89 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 161.1, 158.7, 156.7, 155.2, 150.1, 136.7, 135.8, 131.3, 130.1, 129.5, 128.5, 128.3, 125.8, 123.5, 119.9, 119.9, 116.7, 114.8, 114.5, 55.4 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{24}H_{18}Cl_2NO_2$ 422.0709, found 422.0703.

4-**Chloromo-2-(4,6-diphenylpyridin-2-yl)phenol (4daa):** Following the general procedure, the reaction of **1d** (34.75 mg, 0.15 mmol), ketone **2a** (21.6 mg, 0.18 mmol), aldehyde **3a** (18.9 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave **4daa** as a pale yellow solid; yield 70% (37.5 mg); mp 135 - 138 ^oC; R_f = 0.7 (ethyl acetate/hexane = 1:20); ^1H NMR (400 MHz, $CDCl_3$) δ 14.84 (s, 1H), 7.97 (d, *J* = 5.9 Hz, 3H), 7.91-7.83 (m, 2H), 7.74 (d, *J* = 7.0 Hz, 2H), 7.61-7.46 (m, 6H), 7.31-7.24 (m, 1H), 7.00 (d, *J* = 8.8 Hz, 1H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 158.8, 156.8, 155.5, 151.6, 138.2, 137.9, 131.3, 129.8, 129.6, 129.3, 129.2, 127.3, 127.0, 125.9, 123.5, 120.0, 120.0 117.8, 115.8 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{23}H_{17}ClNO$ 358.0993, found 358.0997.

4-**Bromo-2-(4,6-diphenylpyridin-2-yl)phenol (4eaa):** Following the general procedure, the reaction of **1e** (41.4 mg, 0.15 mmol), ketone **2a** (21.6 mg, 0.18 mmol), aldehyde **3a** (18.9 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave **4eaa** as a pale yellow solid; yield

72% (43.5 mg); mp 135 - 138 °C; R_f = 0.7 (ethyl acetate/hexane = 1:20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.88 (s, 1H), 8.02 (d, *J* = 2.2, Hz, 1H), 7.97 (d, *J* = 6.48 Hz, 3H) 7.87 (s, 1H), 7.75 (d, *J* = 6.9 Hz, 2H), 7.64-7.45 (m, 6H), 7.41 (dd, J_1 = 8.7 Hz, J_2 = 2.3 Hz, 1H), 6.96 (d, *J* = 8.7 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.2, 156.6, 155.4, 151.5, 138.1, 137.8, 134.1, 129.8, 129.6, 129.3, 129.1, 128.8, 127.2, 126.9, 120.6, 120.4, 117.8, 115.7, 110.6 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{23}H_{17}{}^{79}BrNO$ 402.0488, found 402.0489; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{23}H_{17}{}^{81}BrNO$ 404.0469, found 404.0476.

2-(4,6-diphenylpyridin-2-yl)naphthalen-1-ol (4faa) : Following the general procedure, the reaction of **1f** (37.1 mg, 0.15 mmol), ketone **2a** (21.6 mg, 0.18 mmol), aldehyde **3a** (18.9 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave 4**faa** as a pale yellow solid; 75% (41.8 mg); mp 192 - 195 °C; R_f = 0.6 (ethyl acetate/hexane = 1:20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.02 (s, 1H), 8.56-8.50 (m, 1H), 8.12 (s, 1H), 8.07 (d, *J* = 7.3 Hz, 2H), 7.99 (d, *J* = 8.9 Hz, 1H), 7.83 (d, *J* = 0.8 Hz, 1H), 7.79-7.77 (m, 3H), 7.62-7.48 (m, 8H), 7.40 (d, *J* = 8.8 Hz, 1H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.4, 157.9, 155.1, 151.3, 138.7, 138.1, 135.3, 129.6, 129.4, 129.2, 129.1, 127.7, 127.3, 127.2, 127.0, 126.4, 125.3, 123.6, 122.9, 118.1, 116.8, 115.7, 111.5 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{27}H_{20}NO$ 374.1539, found 374.1520.

2-(4-(4-Chlorophenyl)-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)phenol (4alf): Following the general procedure, the reaction of **1a** (29.6 mg, 0.15 mmol), ketone **2l** (18.9 mg, 0.225 mmol), aldehyde **3f** (25.3 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave 4**alf** as a pale yellow solid; yield 83% (40.0 mg); mp 105 - 107 °C; R_f = 0.7 (ethyl acetate/hexane = 1:20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.35 (s, 1H), 7.79 (d, *J* = 7.9 Hz, 1H), 7.64 (s, 1H), 7.50 – 7.40 (m, 4H), 7.27 (t, *J* = 7.8 Hz, 1H), 7.02 (d, *J* = 8.2 Hz, 1H), 6.88 (t, *J* = 7.5 Hz, 1H), 3.11 (t, *J* = 7.6

Hz, 2H), 3.01 (t, *J* = 7.2 Hz, 2H), 2.17 (p, *J* = 7.4 Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 163.2, 159.8, 156.4, 146.0, 137.0, 134.8, 133.0, 130.9, 129.5, 129.0, 126.1, 119.2, 118.7, 118.5, 115.9, 34.1, 30.6, 23.3 ppm. HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{20}H_{17}NOCl$ 322.0993, found 322.0990.

2-(4-(4-Chlorophenyl)-5,6,7,8-tetrahydroquinolin-2-yl)phenol (4amf): Following the general procedure, the reaction of **1a** (29.6 mg, 0.15 mmol), ketone **2m** (17.6 mg, 0.18 mmol), aldehyde **3f** (25.3 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave 4**amf** as a pale yellow solid; 85% (42.75 mg); mp 138 - 140 °C; R_f = 0.7 (ethyl acetate/hexane = 1:20); ^1H NMR (400 MHz, $CDCl_3$) δ 14.78 (s, 2H), 7.75 (d, *J* = 7.7 Hz, 1H), 7.54 (s, 1H), 7.45 (d, *J* = 8.3 Hz, 2H), 7.33-7.20 (m, 3H), 7.01 (d, *J* = 8.1 Hz, 1H), 6.86 (t, *J* = 7.5 Hz, 1H), 3.03 (t, *J* = 6.4 Hz, 2H), 2.61 (t, *J* = 6.1 Hz, 2H), 2.01-1.87 (m, 2H), 1.84-1.70 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.1, 154.5, 154.4, 150.3, 137.5, 134.3, 131.0, 129.8, 128.7, 128.2, 125.9, 118.7, 118.6, 118.4, 117.1, 32.3, 27.1, 22.8, 22.6 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{21}H_{19}NOCl$ 336.1150, found 336.1144.

2-(4-(2-Fluorophenyl)-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-2-yl)phenol (4anh): Following the general procedure, the reaction of **1a** (29.6 mg, 0.15 mmol), ketone **2n** (20.18 mg, 0.18 mmol), aldehyde **3h** (22.34 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave 4**anh** as a yellow solid; yield 78% (38.9 mg) ; mp 140 - 142 °C; R_f = 0.7 (ethyl acetate/hexane = 1:20); ^1H NMR (400 MHz, $CDCl_3$) δ 14.80 (s, 1H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.58 (s, 1H), 7.48-7.38 (m, 1H), 7.27-7.24 (m, 3H), 7.18 (t, *J* = 9.0 Hz, 1H), 7.00 (d, *J* = 8.2 Hz, 1H), 6.84 (t, *J* = 7.5 Hz, 1H), 3.15-3.14 (m, 2H), 2.66-2.65 (m, 2H), 1.96-1.84 (m, 2H), 1.83-1.74 (m, 2H), 1.71-1.53 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.5, 160.0, 159.2 (d, J_{C-F} = 245.5 Hz), 153.6, 144.9, 134.9, 130.9, 130.9, 130.2 (d, J_{C-F} = 7.9 Hz), 127.3, 127.1, 125.9, 124.4 (d, J_{C-F} = 3.6

Hz), 118.9, 118.6, 118.4, 118.1, 115.8 (d, J_{C-F} = 21.7 Hz), 39.2, 32.2, 30.1, 27.2, 26.2 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{22}H_{21}FNO$ 334.1602, found 334.1602.

2-(4-Phenyl-5,6-dihydrobenzo[*h*]quinolin-2-yl)phenol (4aoa): Following the general procedure, the reaction of **1a** (29.6 mg, 0.15 mmol), ketone **2o** (26.31 mg, 0.18 mmol), aldehyde **3a** (18.9 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave 4**aoa** as a pale yellow solid; yield 79% (41.3 mg); mp 141 - 143 °C; R_f = 0.65 (ethyl acetate/hexane = 1:20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.93 (s, 1H), 8.19 (d, *J* = 7.5 Hz, 1H), 7.83 (d, *J* = 7.3 Hz, 1H), 7.75 (s, 1H), 7.53-7.46 (m, 3H), 7.44-7.27 (m, 6H), 7.07 (d, *J* = 8.0 Hz, 1H), 6.90 (t, *J* = 7.5 Hz, 1H), 2.94-2.91 (m, 2H), 2.87-2.84 (m, 2H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.9, 155.1, 150.6, 150.0, 138.7, 138.4, 133.4, 131.2, 129.7, 128.7, 128.6, 128.4, 128.0 127.9, 127.5, 126.1, 124.9, 119.0, 118.8, 118.8, 118.4, 28.0, 25.2 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{25}H_{20}NO$ 350.1539, found 350.1537.

2-(4-(Thiophen-2-yl)-9*H*-indeno[2,1-*b*]pyridin-2-yl)phenol (4apn):[30d] Following the general procedure, the reaction of **1a** (29.6 mg, 0.15 mmol), ketone **2p** (23.78 mg, 0.18 mmol), aldehyde **3n** (20.17 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave 4**apn** as a yellow solid; yield 81% (41.4 mg); mp 205 - 207 °C; R_f = 0.7 (ethyl acetate/hexane = 1:20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.11 (s, 1H), 7.84 (d, *J* = 6.1 Hz, 2H), 7.57-7.54 (m, 2H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.37–7.27 (m, 3H), 7.23-7.18 (m, 2H), 7.05 (d, *J* = 8.2 Hz, 1H), 6.91 (t, *J* = 7.6 Hz, 1H), 4.09 (s, 2H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.2, 159.7, 155.0, 141.3, 138.9, 138.8, 138.6, 131.7, 131.3, 127.8, 127.7, 127.6, 127.1, 126.9, 126.4, 125.1, 122.9, 119.8, 119.1, 119.0, 118.6, 38.4 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{22}H_{16}NOS$ 342.0947, found 342.0941.

2-((1*R*,3a*S*,3b*R*,5a*S*,11a*S*,11b*S*,13a*R*)-7-(2-fluorophenyl)-11a,13a-dimethyl-1-((*R*)-6-methylheptan-2-yl)-2,3,3a,3b,4,5,5a,6,11,11a,11b,12,13,13a-tetradecahydro-1*H*-cyclopenta[5,6]naphtho[2,1-*g*]quinolin-9-yl)phenol (4aqh); Following the general procedure, the reaction of **1a** (29.6 mg, 0.15 mmol), ketone **2q** (69.6 mg, 0.18 mmol), aldehyde **3h** (22.34 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave 4**aqh** as a yellow solid; yield 74% (67.4 mg); mp 190 - 195 °C; R_f = 0.7 (ethyl acetate/hexane = 1:15); ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.74 (s, 1H), 7.74 (d, *J* = 7.8 Hz, 1H), 7.58 (s, 1H), 7.43-7.40 (m, 1H), 7.31-7.14 (m, 4H), 7.01 (d, *J* = 8.1 Hz, 1H), 6.85 (t, *J* = 7.4 Hz, 1H), 2.98-2.92 (m, 1H), 2.82-2.63 (m, 1H), 2.51 (d, *J* = 16.2 Hz, 1H), 2.24 (s, 1H), 2.10-1.55 (m, 6H), 1.49-1.47 (m, 1H), 1.31-1.00 (m, 8H), 1.20-0.90 (m, 8H), 0.86 (d, *J* = 5.3 Hz, 8), 0.74 (s, 3H), 0.64 (s, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) **δ** 160.0, 154.3, 153.3, 146.4, 130.9, 130.5 (d, J_{C-F} = 3.2 Hz), 130.3 (d, J_{C-F} = 7.6 Hz), 128.6, 126.8, 126.6, 125.9, 124.5, 124.4, 118.8, 118.5, 118.4, 117.9, 115.8 (d, J_{C-F} = 21.6 Hz), 56.4, 56.3, 53.5, 42.4, 41.5, 39.8, 39.5, 36.3, 36.1, 35.7, 35.5, 35.0, 31.5, 28.4, 28.2, 28.0, 24.2, 23.8, 22.8, 22.5, 21.1, 18.6, 11.9, 11.81 ppm; HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{42}H_{55}FNO$ 608.4262, found 608.4263.

Ethyl 2-(2-hydroxyphenyl)-4-(4-nitrophenyl)-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate (4ari): Following the general procedure, the reaction of **1a** (29.6 mg, 0.15 mmol), ketone **2r** (30.81 mg, 0.18 mmol), aldehyde **3i** (27.20 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave 4**ari** as a pale yellow solid; yield 79% (49.7 mg); mp 148 - 150 °C; R_f = 0.6 (ethyl acetate/hexane = 1:15); ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.07 (s, 1H), 8.38 (d, *J* = 8.4 Hz, 2H), 7.76 (d, *J* =7.5 Hz, 1H), 7.63 (s, 1H), 7.55 (d, *J* = 8.6 Hz, 2H), 7.32 (dd, *J* = 11.3, 4.1 Hz, 1H), 7.04 (d, *J* = 8.1 Hz, 1H), 6.90 (t, *J* = 7.4 Hz, 1H), 4.48 (s, 2H), 4.23-4.06 (m, 2H), 3.86 (t, *J* = 6.0 Hz, 2H), 3.15 (t, *J* = 5.9 Hz, 2H), 1.26-1.24 (m, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz,

$CDCl_3$) δ 155.2, 151.2, 150.6, 147.6, 143.3, 142.9, 139.3, 127.0, 124.6, 121.4, 119.4(2C), 114.2, 113.9, 113.4, 112.7, 57.1, 38.8, 36.1, 27.0, 9.9 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{23}H_{22}N_3O_5$ 420.1554, found 420.1571.

2-(4-(4-Methoxyphenyl)-7,8-dihydro-5*H*-pyrano[4,3-*b*]pyridin-2-yl)phenol (4asc); Following the general procedure, the reaction of **1a** (29.6 mg, 0.15 mmol), ketone **2s** (18.02 mg, 0.18 mmol), aldehyde **3c** (24.50 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave 4**asc** as a pale yellow solid; yield 77% (38.5 mg); mp 149 - 150 °C; R_f= 0.6 (ethyl acetate/hexane = 1:20); ^1H NMR (400 MHz, $CDCl_3$) δ 14.47 (s, 1H), 7.78 (dd, J_1= 7.9 Hz, J_2= 0.96 Hz, 1H), 7.62 (s, 1H), 7.33-7.22 (m, 3H), 6.99-7.01 (m, 3H), 6.91-6.84 (m, 1H), 4.69 (s, 2H), 4.11 (t, *J* = 5.9 Hz, 2H), 3.87 (s, 3H), 3.11 (t, *J* = 5.8 Hz, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.0(2C), 155.7, 150.6, 148.6, 131.2, 129.6, 129.4, 126.4, 126.0, 118.8, 118.7, 118.5, 117.7, 114.2, 66.4, 65.3, 55.4, 31.3 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{21}H_{20}NO_3$ 334.1438, found 334.1437.

2-(4-(Thiophen-2-yl)-7,8-dihydro-5*H*-pyrano[4,3-*b*]pyridin-2-yl)phenol (4asn); Following the general procedure, the reaction of **1a** (29.6 mg, 0.15 mmol), ketone **2s** (18.02 mg, 0.18 mmol), aldehyde **3n** (20.18, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave 4**asn** as a pale yellow solid; yield 84% (38.9 mg); mp 162 - 164 °C; R_f= 0.7 (ethyl acetate/hexane = 1:20); ^1H NMR (400 MHz, $CDCl_3$) δ 14.29 (s, 1H), 7.85-7.78 (m, 2H), 7.53-7.47 (m, 1H), 7.34-7.27 (m, 1H), 7.18-7.16 (m, 2H), 7.06-6.99 (m, 1H), 6.95-6.88 (m, 1H), 4.90 (s, 2H), 4.13 (t, *J* = 5.9 Hz, 2H), 3.12 (t, *J* = 5.8 Hz, 2H)ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 159.9, 155.8, 151.2, 141.1, 138.2, 131.4, 128.0, 127.9, 127.6, 126.1, 126.0, 118.8, 118.6, 118.5, 117.5, 66.6, 65.1, 31.4 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{18}H_{16}NO_2S$ 310.0896, found 310.0901.

4-Methyl-2-(4-phenyl-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)phenol (4bla): Following the general procedure, the reaction of **1b** (31.69 mg, 0.15 mmol), ketone **2l** (18.9 mg, 0.225 mmol),

aldehyde **3a** (18.9 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave 4**bla** as a pale yellow solid; yield 82% (37.0 mg); mp 138 - 140 ^{o}C; R_f = 0.7 (ethyl acetate/hexane = 1:20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.21 (s, 1H), 7.70 (s, 1H), 7.61 (s, 1H), 7.56-7.42 (m, 5H), 7.09 (dd, J_1 = 8.3 Hz, J_2 = 1.4 Hz, 1H), 6.93 (d, J = 8.3 Hz, 1H), 3.12 (t, J = 7.7 Hz, 2H), 3.06 (t, J = 7.3 Hz, 2H), 2.33 (s, 3H), 2.13-2-21 (m, 2H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.0, 157.5, 156.3, 147.2, 138.7, 133.0, 131.6, 128.7, 128.5, 128.1, 127.5, 126.3, 118.9, 118.2, 116.2, 34.1, 30.6, 23.4, 20.7 ppm; HRMS (ESI-TOF): *m/z* [M + H]$^{+}$ calcd for $C_{21}H_{20}NO$ 302.1539, found 302.1544.

4-Methoxy-2-(4-phenyl-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-2-yl)phenol (4cna): Following the general procedure, the reaction of **1c** (34.1 mg, 0.15 mmol), ketone **2n** (20.18 mg, 0.18 mmol), aldehyde **3a** (18.9 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave 4**cna** as a pale yellow solid; yield 79% (40.9 mg); mp 105-107 ^{o}C; R_f = 0.7 (ethyl acetate/hexane = 1:20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.35 (s, 1H), 7.53 (s, 1H), 7.47-7.43 (m, 3H), 7.34-7.29 (m, 2H), 7.26 (d, J = 2.2 Hz, 1H), 6.95 (d, J = 8.9 Hz, 1H), 6.88 (dd, J_1 = 8.9 Hz, J_2 = 2.8 Hz, 1H), 3.78 (s, 3H), 3.23-3.07 (m, 2H), 2.80-2.68 (m, 2H), 1.94-1.86 (m, 2H), 1.83-1.75 (m, 2H), 1.64-1.60 (m, 2H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 160.8, 154.1, 153.1, 152.0, 150.8, 139.8, 134.1, 128.7, 128.4, 127.9, 118.9, 118.9, 117.8, 117.4, 110.6, 56.0, 39.1, 32.2, 29.5, 27.7, 26.3 ppm; HRMS (ESI-TOF): *m/z* [M + H]$^{+}$ calcd for $C_{23}H_{24}NO_2$ 346.1802, found 346.1808.

4-Methoxy-2-(4-phenyl-5,6-dihydrobenzo[*h*]quinolin-2-yl)phenol (4coa); Following the general procedure, the reaction of **1c** (34.1 mg, 0.15 mmol), ketone **2o** (26.31 mg, 0.18 mmol), aldehyde **3a** (18.9 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave 4**coa** as a pale yellow solid; yield 80% (45.5 mg); mp 140-142 ^{o}C; R_f = 0.5 (ethyl acetate/hexane = 1:20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.38 (s, 1H), 8.19 (d, J = 7.6 Hz, 1H), 7.70 (s, 1H), 7.51-7.48 (m,

3H), 7.39-7.33 (m, 5H), 7.28 (s, 1H), 7.01 (d, J = 8.9 Hz, 1H), 6.94 (dd, J_1 = 8.9 Hz, J_2 = 2.8 Hz, 1H), 3.82 (s, 3H), 2.96-2.91 (m, 2H), 2.87-2.84 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$) δ 154.8, 154.0, 152.2, 150.6, 150.1, 138.7, 138.4, 133.4, 129.7, 128.7, 128.6, 128.4, 128.1, 127.9, 127.5, 125.0, 119.20, 118.9, 118.8, 117.7, 110.9, 56.1, 28.0, 25.2 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{26}H_{22}NO_2$ 380.1645, found 380.1657.

4-Methoxy-2-(4-phenyl-9*H*-indeno[2,1-*b*]pyridin-2-yl)phenol (4cpa): Following the general procedure, the reaction of **1c** (34.1 mg, 0.15 mmol), ketone **2p** (23.78 mg, 0.18 mmol), aldehyde **3a** (18.9 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave 4**cpa** as a yellow solid; yield 79% (43.2 mg); mp 206 - 208 °C; R_f = 0.5 (ethyl acetate/hexane = 1:20); ^1H NMR (400 MHz, $CDCl_3$) δ 13.77 (s, 1H), 7.70 (s, 1H), 7.58-7.56 (m, 6H), 7.36-7.27 (m, 2H), 7.17-7.06 (m, 2H), 7.00 (d, J = 8.9 Hz, 1H), 6.93 (dd, J_1 = 8.9 Hz, J_2 = 2.7 Hz, 1H), 4.10 (s, 2H), 3.81 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 162.1, 154.9, 153.9, 152.3, 146.2, 141.4, 138.8, 138.4, 131.1, 128.9, 128.8, 128.3, 127.6, 126.8, 125.1, 123.0, 119.1, 119.2, 118.9, 117.8, 111.0, 56.0, 38.4 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{25}H_{20}NO_2$ 366.1489, found 366.1487.

4-Chloro-2-(4-phenyl-6,7,8,9-tetrahydro-5*H*-cyclohepta[*b*]pyridin-2-yl)phenol (4dna): Following the general procedure, the reaction of **1d** (34.75 mg, 0.15 mmol), ketone **2n** (20.18 mg, 0.18 mmol), aldehyde **3a** (18.9 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave 4**dna** as a pale yellow solid; yield 73% (38.2 mg); mp 160 - 162 °C; R_f = 0.7 (ethyl acetate/hexane = 1:20); ^1H NMR (400 MHz, $CDCl_3$) δ 14.94 (s, 1H), 7.70 (d, J = 2.4 Hz, 1H), 7.53 (s, 1H), 7.52-7.41 (m, 3H), 7.30 (d, J = 6.6 Hz, 2H), 7.20 (dd, J_1 = 8.8, J_2 = 2.4 Hz, 1H), 6.94 (d, J = 8.8 Hz, 1H), 3.20-3.10 (m, 2H), 2.82-2.71 (m, 2H), 1.97-1.85 (m, 2H), 1.85-1.74 (m, 2H), 1.70-1.60 (m, 2H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 160.8, 158.6, 152.1, 151.1,

139.5, 134.7, 130.5, 128.6, 128.5, 128.0, 125.4, 123.2, 120.0, 119.7, 117.9, 39.0, 32.1, 29.5, 27.6, 26.2 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{22}H_{21}ClNO$ 350.1306, found 350.1312.

Ethyl 2-(5-chloro-2-hydroxyphenyl)-4-phenyl-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate (4dra): Following the general procedure, the reaction of **1d** (34.75 mg, 0.15 mmol), ketone **2r** (20.18 mg, 0.18 mmol), aldehyde **3a** (18.9 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave 4**dra** as a pale yellow solid; yield 70% (42.9 mg); mp 145 - 147 °C; R_f = 0.6 (ethyl acetate/hexane = 1:15); ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.26 (s, 1H), 7.73 (d, *J* = 2.4 Hz, 1H), 7.59 (s, 1H), 7.51-7.41 (m, 2H), 7.37-7.32 (m, 2H), 7.24-7.21 (m, 1H), 6.96 (d, *J* = 8.8 Hz, 1H), 4.54 (s, 2H), 4.15 (dd, J_1 = 13.8 Hz, J_2 = 6.8 Hz, 2H), 3.85 (t, *J* = 6.0 Hz, 2H), 3.12 (t, *J* = 5.8 Hz, 2H), 1.66-1.47 (m, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.5, 155.4, 154.3, 152.0, 150.3, 137.3, 131.1, 128.9(2C), 128.8, 128.0, 125.7, 123.5, 119.9, 119.5, 118.1, 61.7, 43.8, 40.9, 31.8, 14.6 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{23}H_{22}ClN_2O_3$ 409.1313, found 409.1306.

4-Chloro-2-(4-phenyl-7,8-dihydro-5*H*-pyrano[4,3-*b*]pyridin-2-yl)phenol (4dsa): Following the general procedure, the reaction of **1d** (34.75 mg, 0.15 mmol), ketone **2s** (18.02 mg, 0.18 mmol), aldehyde **3a** (18.9 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave 4**dsa** as a yellow solid 69% (34.9 mg); mp 185 - 190 °C; R_f = 0.7 (ethyl acetate/hexane = 1:20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.44 (s, 1H), 7.74 (d, *J* = 2.3 Hz, 1H), 7.58 (s, 1H), 7.51-7.46 (m, 3H), 7.34 -7.28 (m, 2H), 7.23 (dd, J_1 = 8.8 Hz, J_2 = 2.4 Hz, 1H), 6.96 (d, *J* = 8.8 Hz, 1H), 4.69 (s, 2H), 4.12 (t, *J* = 5.9 Hz, 2H), 3.13 (t, *J* = 5.8 Hz, 2H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 158.5, 154.4, 150.9, 149.2, 137.1, 131.0, 128.9, 128.8, 128.0, 127.1, 125.6, 123.5, 119.9, 119.7, 117.7, 66.3, 65.2, 31.3 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{20}H_{17}ClNO_2$ 338.0942, found 338.0947.

4-Bromo-2-(4-phenyl-6,7-dihydro-5*H*-cyclopenta[*b*]pyridin-2-yl)phenol (4ela): Following the general procedure, the reaction of **1e** (41.4 mg, 0.15 mmol), ketone **2l** (18.9 mg, 0.225 mmol), aldehyde **3a** (18.9 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave 4**ela** as a pale yellow solid; yield 74% (40.6 mg); mp 155–158 ^{o}C; R_f = 0.7 (ethyl acetate/hexane = 1:20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.53 (s, 1H), 7.91 (d, J = 2.2 Hz, 1H), 7.64 (s, 1H), 7.56-7.42 (m, 5H), 7.34 (dd, J_1 = 8.7 Hz, J_2 = 2.3 Hz, 1H), 6.91 (d, J = 8.7 Hz, 1H), 3.13 (t, J = 7.7 Hz, 2H), 3.07 (t, J = 7.3 Hz, 2H), 2.22-2.14 (m, 2H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 163.2, 158.8, 154.8, 147.5, 138.3, 134.0, 133.3, 128.8, 128.6, 128.1, 121.0, 120.3, 116.3, 110.4, 34.1, 30.6, 23.4 ppm; HRMS (ESI-TOF): *m/z* [M + H]$^{+}$ calcd for $C_{20}H_{17}{}^{79}BrNO$ 366.0488, found 366.0479; HRMS (ESI-TOF): *m/z* [M + H]$^{+}$ calcd for $C_{20}H_{17}{}^{81}BrNO$ 368.0468, found 368.0497.

4-Bromo-2-(4-phenyl-5,6-dihydrobenzo[*h*]quinolin-2-yl)phenol (4eoa): Following the general procedure, the reaction of **1e** (41.4 mg, 0.15 mmol), ketone **2o** (26.31 mg, 0.18 mmol), aldehyde **3a** (18.9 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave 4**eoa** as a pale yellow solid; yield 72% (46.2 mg); mp 184-186 ^{o}C; R_f = 0.7 (ethyl acetate/hexane = 1:20); ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.99 (s, 1H), 8.15 (d, J = 7.1 Hz, 1H), 7.92 (d, J = 2.2 Hz, 1H), 7.69 (s, 1H), 7.57-7.46 (m, 3H), 7.40-7.36 (m, 5H), 7.27 (d, J = 10.1 Hz, 1H), 6.96 (d, J = 8.7 Hz, 1H), 2.94-2.92 (m, 2H), 2.87-2.85 (m, 2H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 159.0, 153.6, 150.9, 150.1, 138.4, 138.4, 133.7, 133.1, 129.9, 128.7, 128.6, 128.6, 128.6, 128.5, 127.9, 127.5, 124.9, 120.7, 120.2, 118.8, 110.5, 27.9, 25.2 ppm; HRMS (ESI-TOF): *m/z* [M + H]$^{+}$ calcd for $C_{25}H_{19}{}^{79}BrNO$ 428.0645, found 428.0675;HRMS (ESI-TOF): *m/z* [M + H]$^{+}$ calcd for $C_{25}H_{18}{}^{81}BrNO$ 430.0643, found 430.0660.

1-(4-(2-Fluorophenyl)-6-(2-hydroxyphenyl)-2-methylpyridin-3-yl)ethenone (4auh): Following the general procedure, the reaction of **1a** (29.6 mg, 0.15 mmol), ketone **2u** (18.02 mg,

0.18 mmol), aldehyde **3h** (22.34 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave 4**auh** as a pale yellow solid; yield 81% (39.0 mg); mp 134-137 ^{o}C; R_f = 0.6 (ethyl acetate/hexane = 1:15);^{1}H NMR (400 MHz, $CDCl_3$) δ 14.21 (s, 1H), 7.79 (d, *J* = 7.3 Hz, 1H), 7.75 (s, 1H), 7.51-7.42 (m, 1H), 7.36-7.26 (m, 3H), 7.25-7.19 (m, 1H), 7.04 (d, *J* = 8.1 Hz, 1H), 6.90 (t, *J* = 7.5 Hz, 1H), 2.64 (s, 3H), 2.12 (s, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 203.6, 160.3, 158.9 (d, J_{C-F} = 246.9 Hz), 157.3, 151.7, 142.6, 134.4, 132.0, 131.3 (d, J_{C-F} = 8.0 Hz), 131.1, 131.0, 126.5, 125.5, 125.4, 124.8 (d, J_{C-F} = 3.7 Hz), 118.9, 118.7, 118.3, 118.2, 118.2, 116.3 (d, J_{C-F} = 21.5 Hz), 31.4, 22.6 ppm; HRMS (ESI-TOF): *m/z* [M + H]$^{+}$ calcd for $C_{20}H_{17}FNO_2$ 322.1238, found 322.1239.

Ethyl 4-(4-chlorophenyl)-6-(2-hydroxyphenyl)-2-methylnicotinate (4avf): Following the general procedure, the reaction of **1a** (29.6 mg, 0.15 mmol), ketone **2v** (23.42 mg, 0.18 mmol), aldehyde **3f** (25.3 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave 4**avf** as a pale yellow solid; 77% (42.4 mg) yield; mp 145-147 ^{o}C; R_f = 0.6 (ethyl acetate/hexane = 1:15) ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.23 (s, 1H), 7.79 (d, *J* = 7.92 Hz, 1H), 7.69 (s, 1H), 7.43 (d, *J* = 92 Hz, 2H), 7.36-7.31 (m, 3H), 7.03 (d, *J* = 8.2 Hz, 1H), 6.90 (t, *J* = 7.3 Hz, 1H), 4.17-4.12 (m, 2H), 2.69 (s, 3H), 1.06 (t, *J* = 6.96 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.8, 160.3, 157.8, 153.4, 148.8, 137.0, 135.1, 132.1, 129.2, 128.9, 126.5, 126.0, 118.9, 118.8, 118.1, 116.9, 61.7, 22.5, 13.7 ppm; HRMS (ESI-TOF): *m/z* [M + H]$^{+}$ calcd for $C_{21}H_{19}ClNO_3$ 368.1048, found 368.1057.

Ethyl 4-(3-bromophenyl)-6-(2-hydroxyphenyl)-2-methylnicotinate (4ave): Following the general procedure, the reaction of **1a** (29.6 mg, 0.15 mmol), ketone **2v** (23.42 mg, 0.18 mmol), aldehyde **3e** (33.3 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave 4**ave** as a

pale yellow solid; yield 74% (45.7 mg); mp 108 - 110 °C; R_f = 0.6 (ethyl acetate/hexane = 1:15); ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.19 (s, 1H), 7.80 (d, *J* = 7.2 Hz, 1H), 7.70 (s, 1H), 7.59-7.57 (m, 2H), 7.37-7.28 (m, 3H), 7.03 (d, *J* = 7.9 Hz, 1H), 6.91 (dd, *J* = 11.2, 3.9 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 2.70 (s, 3H), 1.07 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 167.6, 160.3, 157.9, 153.5, 148.4, 140.5, 132.2, 131.8, 130.8, 130.2, 126.6, 126.5 126.0, 122.7, 119.0, 118.7, 118.1, 116.9, 61.7, 22.6, 13.7 ppm; HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{21}H_{19}{}^{79}BrNO_3$ 412.0543, found 412.0569; HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{21}H_{19}{}^{81}BrNO_3$ 414.0542, found 414.0551.

Ethyl 6-(2-hydroxy-5-methoxyphenyl)-2-methyl-4-phenylnicotinate (4cva); Following the general procedure, the reaction of **1c** (34.1 mg, 0.15 mmol), ketone **2v** (23.42 mg, 0.18 mmol), aldehyde **3a** (18.9 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave 4 **cva** as a pale yellow solid; 70% (40.4 mg); mp 84 - 86 °C; R_f = 0.6 (ethyl acetate/hexane = 1:15); ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.81 (s, 1H), 7.68 (s, 1H), 7.49-7.44 (m, 3H), 7.41-7.40 (m, 2H), 7.30 (d, *J* = 2.1 Hz, 1H), 7.02-6.92 (m, 2H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.81 (s, 3H), 2.70 (s, 3H), 0.99 (t, *J* = 7.1 Hz, 3H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 168.0, 157.4, 154.4, 153.3, 152.2, 150.1, 138.6, 128.7, 127.8, 126.3, 119.3, 118.7, 118.2, 117.2, 111.0, 61.5, 56.0, 22.5, 13.6 ppm; HRMS (ESI-TOF): *m/z* [M + Na]$^+$ calcd for $C_{22}H_{21}NO_4Na$ 386.1363, found 386.1361

2-(2-Hydroxyphenyl)-4-(4-methoxyphenyl)-7,7-dimethyl-7,8-dihydroquinolin-5(6*H*)-one (4awc): Following the general procedure, the reaction of **1a** (29.6 mg, 0.15 mmol), ketone **2w** (25.23 mg, 0.18 mmol), aldehyde **3c** (24.5 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave 4**awc** as a pale yellow solid; yield 79% (39.2 mg); mp 170 - 175 °C; R_f = 0.6 (ethyl acetate/hexane = 1:15); ^{1}H NMR (400 MHz, $CDCl_3$) δ 14.37 (s, 1H), 7.82 (d, *J* = 7.3 Hz, 1H), 7.65 (s, 1H), 7.39-7.33 (m, 1H), 7.24-7.22 (m, 2H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 8.6

Hz, 2H), 6.90 (t, *J* = 7.5 Hz, 1H), 3.87 (s, 3H), 3.14 (s, 2H), 2.56 (s, 2H), 1.17 (s, 6H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 196.7, 161.0 160.8, 159.7, 159.6, 152.6, 132.8, 131.9, 129.3, 126.8, 123.4, 120.4, 119.0, 118.9, 118.0, 113.6, 55.3, 53.7, 47.0, 32.7, 28.2 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{24}H_{24}NO_3$ 374.1751, found 374.1737.

2-(2-Hydroxyphenyl)-4-(thiophen-2-yl)-7,7-dimethyl-7,8-dihydroquinolin-5(6*H*)-one (4awn): Following the general procedure, the reaction of **1a** (29.6 mg, 0.15 mmol), ketone **2w** (25.23 mg, 0.18 mmol), aldehyde (**3n**; 20.17 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave 4**awn** as a pale yellow solid; 84% (44.0 mg); mp 145 - 147 °C; R_f = 0.7 (ethyl acetate/hexane = 1:15); ^1H NMR (400 MHz, $CDCl_3$) δ 14.20 (s, 1H), 7.85-7.76 (m, 2H), 7.47 (d, *J* = 4.8 Hz, 1H), 7.37 (t, *J* = 7.2 Hz, 1H), 7.20 (d, *J* = 2.9 Hz, 1H), 7.15-7.09 (m, 1H), 7.04 (d, *J* = 8.2 Hz, 1H), 6.92 (t, *J* = 7.5 Hz, 1H), 3.14 (s, 2H), 2.59 (s, 2H), 1.17 (s, 6H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 196.4, 160.9, 160.9, 159.7, 145.2, 140.0, 133.0, 128.0, 127.3, 127.1, 126.9, 123.6, 121.0, 119.1, 118.9, 117.8, 53.7, 47.0, 32.7, 28.2 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{21}H_{20}NO_2S$ 350.1209, found 350.1191.

2,2'-(4-phenylpyridine-2,6-diyl)diphenol (4ata):[30c] Following the general procedure, the reaction of **1a** (29.6 mg, 0.15 mmol), ketone **2t** (24.5 mg, 0.18 mmol), aldehyde **3a** (18.9 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave 4**ata** as a yellow solid; 73% (41.5 mg); mp 175 - 177 °C; ^1H NMR (400 MHz, DMSO) δ 12.30 (s, 2H), 8.32 (s, 1H), 8.23 (s, 2H), 7.99 (d, *J* = 7.5 Hz, 3H), 7.63-7.52 (m, 3H), 7.34 (t, *J* = 7.1 Hz, 2H), 6.99-6.97 (m, 4H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, DMSO-d6) δ 157.7, 155.8, 150.1, 138.0, 131.4, 130.0, 129.6, 129.1, 127.8, 122.5, 119.6, 118.1, 117.7 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{23}H_{18}NO_2$ 340.1332, found 340.1339.

2,2',2''-(Pyridine-2,4,6-triyl)triphenol (4ato):[30a] Following the general procedure, the reaction of **1a** (29.6 mg, 0.15 mmol), ketone **2t** (24.5 mg, 0.18 mmol), aldehyde **3o** (21.98 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave 4**ato** as a yellow solid; yield 76% (40.5 mg); mp 255 - 260 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.33 (s, 2H), 9.99 (s, 1H), 8.15 (s, 2H), 7.89 (d, *J* = 7.6 Hz, 2H), 7.57 (d, *J* = 7.3 Hz, 1H), 7.34 (t, *J* = 7.2 Hz, 3H), 7.12–6.93 (m, 6H) ppm; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 162.6, 160.2, 159.8, 153.9, 136.2, 135.8, 135.7, 133.8, 130.4, 127.6, 125.6, 125.1, 124.6, 122.7, 121.8 ppm. HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{23}H_{18}NO_3$ 356.1281, found 356.1307.

2,2'-(4-(4-Hydroxyphenyl)pyridine-2,6-diyl)diphenol (4atp):[30a] Following the general procedure, the reaction of **1a** (29.6 mg, 0.15 mmol), ketone **2t** (24.5 mg, 0.18 mmol), aldehyde **3p** (21.98 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave 4**atp** as a yellow solid; 78% (41.5 mg) yield; mp 155 - 160 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.34 (s, 2H), 9.91 (s, 1H), 8.14 (s, 2H), 7.95 (d, *J* = 7.6 Hz, 2H), 7.85 (d, *J* = 8.5 Hz, 2H), 7.32 (t, *J* = 7.5 Hz, 2H), 7.04-6.86 (m, 6H) ppm; ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 159.6, 157.9, 155.8, 150.1, 131.5, 129.3, 129.2, 128.5, 122.8, 119.7, 117.9, 117.3, 116.6 ppm; HRMS (ESI-TOF): *m/z* [M + H]$^+$ calcd for $C_{23}H_{18}NO_3$ 356.1281, found 356.1309.

2-(6-(2-hydroxyphenyl)-4-(4-hydroxyphenyl)pyridin-2-yl)-4-bromophenol(4etp): Following the general procedure, the reaction of **1e** (41.4 mg, 0.15 mmol), ketone **2t** (24.5 mg, 0.18 mmol), aldehyde **3p** (21.98 mg, 0.18 mmol) and ammonium acetate (11.55 mg, 0.15 mmol) gave **4etp** as a yellow solid; mp 210 - 212 °C; yield 70% (45.6 mg); ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.11 (br s, 2H), 9.66 (s, 1H), 8.17–8.11 (m, 2H), 7.94 – 7.90 (m, 1H), 7.87 – 7.81 (m, 2H), 7.46 (d, *J* = 7.7 Hz, 1H), 7.32 (d, *J* = 6.8 Hz, 1H), 7.03 – 6.93 (m, 6H) ppm; ^{13}C{^{1}H} NMR (100 MHz, DMSO-d_6) δ 159.5 (159.6), 157.7 (157.6), 157.4 (157.5), 157.3 (157.0), 155.5 (155.6), 154.3 (154.4),

149.9 (150.1), 133.7 (133.8), 131.3 (131.4), 129.4 (129.5), 129.2 (129.3), 129.0 (129.1), 128.3 (128.4), 128.1 (128.2), 124.4 (124.6), 122.6 (122.8), 119.6 (119.7), 117.7 (117.9), 117.1 (117.6), 116.4 (116.5), 110.7 (110.8)* ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{23}H_{17}{}^{79}BrNO_3$ 434.0386, found 434.0412; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{23}H_{17}{}^{81}BrNO_3$ 436.0385, found 436.0409. * In parentheses, the peaks of rotamer.

2,4,6-Triphenylpyridine (4aa): Yield 41%; ^1H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 7.4 Hz, 4H), 7.91 (s, 2H), 7.77 (d, *J* = 7.4 Hz, 2H), 7.55-7.44 (m, 9H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 157.5, 150.2, 139.6, 139.1, 129.2, 129.1, 129.0, 128.7, 127.3, 127.2, 117.1 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{23}H_{18}N$ 308.1434, found 308.1405.

2-(3-Methyl-4,6-diphenylpyridin-2-yl)phenol (4gaa): A mixture of compound **1g** (42.24 mg, 0.2 mmol), **2a** (28.8 mg, 0.24 mmol), **3a** (25.44, 0.24 mmol) and distilled triethylamine (10.1 mg, 14.0 µL, 0.1 mmol) was added ammonium acetate (18.5 mg, 0.2 mmol) for 10h at 80 °C. After purification, a pure **4gaa** was isolated in 47% (31.7 mg) yield; mp 131 - 133 °C; R_f = 0.70 (ethyl acetate/hexane = 1:20); ^1H NMR (400 MHz, $CDCl_3$) δ 12.09 (s, 1H), 8.01 (d, *J* = 7.5 Hz, 2H), 7.61 (s, 2H), 7.55 –7.40 (m, 8H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.13 (d, *J* = 8.1 Hz, 1H), 6.96 (t, *J* = 7.5 Hz, 1H), 2.42 (s, 3H) ppm; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 157.4, 157.0, 154.4, 152.4, 140.0, 137.8, 130.5, 130.4, 129.3, 128.9, 128.7, 128.6, 128.2, 128.0, 126.6, 122.3, 119.8, 118.4, 117.9, 19.5 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{24}H_{20}NO$ 338.1539, found 338.1568.

2-(3-Methyl-4-Chlorophenyl-6-phenylpyridin-2-yl)phenol (4gaf): Following the above procedure, the reaction of compound **1g** (42.24 mg, 0.2 mmol), **2a** (28.8 mg, 0.24 mmol), **3a** (25.44, 0.24 mmol) and distilled triethylamine (10.1 mg, 14.0 µL, 0.1 mmol) was added ammonium acetate (18.5 mg, 0.2 mmol) gave **4gaf**: yield 44% (32.6 mg); mp 81 - 83 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 11.96 (s, 1H), 7.99 (d, *J* = 7.4 Hz, 2H), 7.58 (d, *J* = 10.5 Hz, 2H), 7.50-7.42

(m, 5H), 7.40-7.29 (m, 3H), 7.12 (d, J = 8.1 Hz, 1H), 6.96 (t, J = 7.5 Hz, 1H), 2.40 (s, 3H) ppm; $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 157.4, 157.2, 153.1, 152.6, 138.4, 137.7, 134.5, 130.6, 130.4, 130.1, 129.4, 129.0, 128.9, 127.8, 126.6, 122.2, 119.6, 118.5, 117.9, 19.4 ppm; HRMS (ESI-TOF): *m/z* $[M + H]^+$ calcd for $C_{24}H_{19}ClNO$ 372.1150, found 372.1179.

ASSOCIATED CONTENT

Supporting Information

"This material is available free of charge via the Internet at http://pubs.acs.org." copies of ^{1}H and ^{13} NMR spectra for the products are available in ESI.

ORCID[id]

Sampak Samanta**:** 0000-0002-9659-8216

NOTES

The authors declare no competing financial interest.

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REFERENCES:

(1) (a) Henry, G. D. *De novo* synthesis of substituted pyridines. *Tetrahedron* **2004**, *60***,** 6043-6061.

(b) Heller, B.; Hapke, M. The fascinating construction of pyridine ring systems by transition metal-catalysed [2 + 2 + 2] cycloaddition reactions. *Chem. Soc. Rev.* **2007**, *36*, 1085-1094. (c)

Hill, M. D. Recent Strategies for the Synthesis of Pyridine Derivatives. *Chem. Eur. J*. **2010**, *16***,** 12052-12062.

(2) Michael, J. P. Quinoline, quinazoline and acridone alkaloids. *Nat. Prod. Rep*. **2005**, *22*, 627-646.

(3) (a) Baumann M.; Baxendale, I. R. An overview of the synthetic routes to the best -selling drugs containing 6-membered heterocycles. *Beilstein J. Org. Chem*. **2013**, *9***,** 2265-2319. (b) Longstreet, A. R.; Opalka, S. M.; Campbell, B. S.; Gupton; B. F.; McQuade, D. T. Investigating the continuous synthesis of a nicotinonitrile precursor to nevirapine. *Beilstein J. Org. Chem*. **2013,** *9,* 2570-2578.

(4) (a) Sinthupoom, N.; Prachayasittikul, V.; Prachayasittikul, S.; Ruchirawat, S.; Prachayasittikul, V. Nicotinic acid and derivatives as multifunctional pharmacophores for medical applications. *Eur. Food Res. Technol.* **2015**, *240,* 1-17. (b) Trist, I. M. L.; Nannetti, G.; Tintori, C.; Fallacara, A. L.; Deodato, D.; Mercorelli, B.; Palu, G.; Wijtmans, M. l.; Gospodova, T.; Edink, E.; de Esch, M.; Verheij, I.; Viteva, L.; Loregian, A.; Botta, M. 4,6-Diphenylpyridines as Promising Novel Anti-Influenza Agents Targeting the PA–PB1 Protein–Protein Interaction: Structure–Activity Relationships Exploration with the Aid of Molecular Modeling. *J. Med. Chem.* **2016,** *59***,** 2688-2703.

(5) Guan, A.-Y.; Liu, C.-L.; Sun, X.-F.; Xie, Y.; Wang, M.-A. Discovery of pyridine-based agrochemicals by using Intermediate Derivatization Methods. *Bioorg. Med. Chem*. **2016**, *24***,** 342-353.

(6) (a) *Functional Organic Materials*, ed. T. J. J. Müller and U. H. F. Bunz, Wiley-VCH, Weinheim, **2007**. (b*)* Sasabe, H.; Kido, J. Multifunctional Materials in High-Performance OLEDs: Challenges for Solid-State Lighting. *Chem. Mater*. **2011**, *23***,** 621-630.

(7) (a) Tomasik, P.; Ratajewicz, Z.; Newkome, G. R.; Strekowski, L. σ-Pyridine Coordination Compounds with Transition Metals, in Chemistry of Heterocyclic Compounds: Pyridine Metal Complexes; John Wiley & Sons, Inc., **1985**; Part 6, Vol. 14, pp 186. (b) Sumby, C. J. Bridging ligands comprising two or more di-2-pyridylmethyl or amine arms: Alternatives to 2,2′-bipyridyl-containing bridging ligands. *Coord. Chem. Rev.* **2011**, *255,* 1937-1967.

(8) Mishra, A.; Gupta, R. Supramolecular architectures with pyridine-amide based ligands: discrete molecular assemblies and their applications. *Dalton Trans*. **2014**, *43*, 7668-7682.

(9) (a) Tseberlidis, G.; Intrieri, D.; Caselli, A. Catalytic Applications of Pyridine-Containing Macrocyclic Complexes. *Eur. J. Inorg. Chem*. **2017**, 3589-3603. (b) Yazıcıoğlu, E. Y.; Tanyeli, C. A method for the synthesis of pyridine-based C2-symmetrical chiral nucleophilic organocatalysts via Pd-catalyzed coupling. *Tetrahedron: Asymmetry* **2012**, *23*, 1694-1699.

(10) (a) Allais, C.; Grassot, J. M.; Rodriguez, J.; Constantieux, T. Metal-Free Multicomponent Syntheses of Pyridines. *Chem. Rev*. **2014**, *114*, 10829-10868. (b) Uredi, D.; Motati, D. R.; Watkins, E. B. A simple, tandem approach to the construction of pyridine derivatives under metal-free conditions: a one-step synthesis of the monoterpene natural product, (−)-actinidine. *Chem. Commun.* **2019**, *55,* 3270-3273. (c) Hirai, S.; Horikawa, Y.; Asahara, H.; Nishiwaki, N. Tailor-made synthesis of fully alkylated/arylated nicotinates by $FeCl_3$-mediated condensation of enamino esters with enones. *Chem. Commun*. **2017**,*53*, 2390-2393.

(11) Hantzsch, A. Condensationprodukte aus Aldehydammoniak und Ketonartigen Verbindungen. *Ber. Dtsch. Chem. Ges*. **1881**, *14***,** 1637-1638.

(12) (a) Chichibabin, A. E. Über Kondensation der Aldehyde mit Ammoniak zu Pyridinebasen. *J. Prakt. Chem*. **1924**, *107*, 122-128. (b) Li, Z.; Huang, X.; Chen, F.; Zhang,

C.; Wang, X.; Jiao, N. Cu-Catalyzed Concise Synthesis of Pyridines and 2‑(1*H*)‑Pyridonesfrom Acetaldehydes and Simple Nitrogen Donors. *Org. Lett.* **2015**, *17***,** 584-587.

(13) Bohlmann, F.; Rahtz, D. Über eine neue pyridinsynthese. *Chem. Ber*. **1957**, *90***,** 2265-2272.

(14) Bagley, M. C.; Glover, C.; Merritt, E. A. The Bohlmann-Rahtz Pyridine Synthesis: From Discovery to Applications. *Synlett* **2007**, *16*, 2459-2482.

(15) Tsuda, K.; Satch, Y.; Ikekawa, N.; Mishima, H. Reaction Between Acrolein and Ethyl β-Aminocrotonate. *J. Org. Chem*. **1956**, *21*, 800-801.

(16) Selected examples of transition metal-catalyzed [4 +2] cycloaddition to form pyridines: (a) Zhang, Q.-R.; Huang, J.-R.; Zhang, W.; Dong, L. Highly Functionalized Pyridines Synthesis from N-Sulfonyl Ketimines and Alkynes Using the N–S Bond as an Internal Oxidant. *Org. Lett.* **2014**, *16*, 1684-1687. (b) Martin, R. M.; Bergman, R. G.; Ellman, J. A. Synthesis of Pyridines from Ketoximes and Terminal Alkynes via C–H Bond Functionalization. *J. Org. Chem.* **2012**, *77*, 2501-2507. (c) Neely, J. M.; Rovis, T. Rh(III)-Catalyzed Decarboxylative Coupling of Acrylic Acids with Unsaturated Oxime Esters: Carboxylic Acids Serve as Traceless Activators. *J. Am. Chem. Soc*. **2014,** *136,* 2735-2738. (d) Parthasarathy, K.; Jeganmohan, M.; Cheng, C.-H. Rhodium-Catalyzed One-Pot Synthesis of Substituted Pyridine Derivatives from α,β-Unsaturated Ketoximes and Alkynes. *Org. Lett*. **2008**, *10*, 325-328. (e) Wu, J.; Xu, W.; Yu, Z.-X.; Wang, J. Ruthenium-Catalyzed Formal Dehydrative [4 + 2] Cycloaddition of Enamides and Alkynes for the Synthesis of Highly Substituted Pyridines: Reaction Development and Mechanistic Study. *J. Am. Chem. Soc.* **2015**, *137*, 9489-9496.

(17) Selected examples for transition-metal-catalyzed [2 + 2 + 2] cycloaddition to form pyridines: (a) Goswami, A.; Ohtaki, K.; Kase, K.; Ito, T.; Okamoto, S. Synthesis of Substituted 2,2′-Bipyridines and 2,2′:6′,2″-Terpyridines by Cobalt-Catalyzed Cycloaddition Reactions of

Nitriles and α,ω-Diynes with Exclusive Regioselectivity. *Adv. Synth. Catal.* **2008**, *350*, 143-152. (b) Komine, Y.; Tanaka, K. Rhodium-Catalyzed Complete Regioselective Intermolecular Cross-Cyclotrimerization of Aryl Ethynyl Ethers and Nitriles or Isocyanates at Room Temperature. *Org. Lett*. **2010**, *12***,** 1312-1315. (c) Onodera, G.; Shimizu, Y.; Kimura, J.; Kobayashi, J.; Ebihara, Y.; Kondo, K.; Sakata, K.; Takeuchi, R. Iridium-Catalyzed [2 + 2 + 2] Cycloaddition of α,ω-Diynes with Nitriles. *J. Am. Chem. Soc*. **2012,** *134***,** 10515-10531. (d) Kumar, P.; Prescher, S.; Louie, J. A Serendipitous Discovery: Nickel Catalyst for the Cycloaddition of Diynes with Unactivated Nitriles. *Angew. Chem. Int. Ed*. **2011**, *50***,** 10694-10698. Metal-free conditions, see: (e) Xie, L.-G.; Shaaban, S.; Chen, X.; Maulide, N. Metal-Free Synthesis of Highly Substituted Pyridines by Formal [2+2+2] Cycloaddition under Mild Conditions. *Angew. Chem. Int. Ed*. **2016**, *128*, 13056-13059.

(18) Pyridines synthesis via 6-π-electrocyclization : (a) Nakamura, I.; Oyama, Y.; Zhang, D.; Terada, M. Efficient synthesis of multisubstituted 2-alkenylpyridines via 2,3-rearrangement of O-homoallenylic oximes. *Org. Chem. Front*. **2017**, *4,* 1034-1036**.** (b) Wei, H.; Li, Y.; Xiao, K.; Cheng, B.; Wang, H.; Hu, L.; Zhai, H. Synthesis of Polysubstituted Pyridines via a One-Pot Metal-Free Strategy. *Org. Lett.* **2015**, *17,* 5974-5977. (c) Jiang, Y.; Park, C.-M.; Loh, T.-P. Transition-Metal-Free Synthesis of Substituted Pyridines via Ring Expansion of 2-Allyl-2*H*-azirines. *Org. Lett.* **2014**, *16***,** 3432-3435. (d) Jiang, Y.; Park, C.-M. A catalyst-controlled selective synthesis of pyridines and pyrroles. *Chem. Sci.* **2014**, *5*, 2347-2351. (e) Liu, S.; Liebeskind, L. S. A Simple, Modular Synthesis of Substituted Pyridines. *J. Am. Chem. Soc*. **2008**, *130*, 6918-6919.

(19) Direct C-H functionalization on the pyridines: (a) Mai, D. N.; Baxter, R.D. Unprotected Amino Acids as Stable Radical Precursors for Heterocycle C–H Functionalization. *Org. Lett*.

2016, *18,* 3738-3741. (b) Berman, A. M.; Lewis, J. C.; Bergman, R. G.; Ellman, J. A. Rh(I)-Catalyzed Direct Arylation of Pyridines and Quinolines. *J. Am. Chem. Soc*. **2008**, *130*, 14926-14927.

(20) (a) Sasada, T.; Sakai, N.; Konakahara, T. Me_3SiCl-Promoted Three-Component Coupling Reaction of a Functionalized Enamine, an Acetal, and an Alkyne: An Unprecedented Approach to the Synthesis of Tetrasubstituted Pyridines via a [3 + 2 + 1] Intermolecular Cyclization. *J. Org. Chem.* **2008**, *73*, 6905-6908. (b) He, Z.; Dobrovolsky, D.; Trinchera,P.; Yudin, A. K. Synthesis of Multisubstituted Pyridines. *Org. Lett.* **2013**, *15,* 334-337. (c) Song, Z.; Huang, X.; Yi, W.; Zhang, W. One-Pot Reactions for Modular Synthesis of Polysubstituted and Fused Pyridines. *Org. Lett*. **2016**, *18*, 5640-5643. (d) Allais, C.; Constantieux, T.; Rodriguez, J. Use of β,γ-Unsaturated α-Ketocarbonyls for a Totally Regioselective Oxidative Multicomponent Synthesis of Polyfunctionalized Pyridines. *Chem. Eur. J.* **2009**, *15*, 12945-12948. (e) Ranu, B.C.; Jana. R.; Sowmiah, S. An Improved Procedure for the Three-Component Synthesis of Highly Substituted Pyridines Using Ionic Liquid. *J. Org. Chem*. **2007**, *72,* 3152-3154.

(21) (a) Kröhnke, F.; Zecher, W. Syntheses Using the Michael Adddition of Phridinium Salts. *Angew. Chem., Int. Ed. Engl*. **1962**, *1*, 811. (b) Kröhnke, F. The Specific Synthesis of Pyridines and Oligopyridines. *Synthesis* **1976**, 1-24.

(22) (a) Yin, G.; Liu, Q.; Ma, J.; She, N. Solvent-and catalyst-free synthesis of new hydroxylated trisubstituted pyridines under microwave irradiation. *Green Chem.* **2012**, *14*, 1796-1798. (b) Heravi, M. M.; Bakhtiari, K. H.; Daroogheha, Z.; Bamoharram, F. F. An efficient synthesis of 2,4,6-triarylpyridines catalyzed by heteropolyacid under solvent-free conditions. *Catal. Commun*. **2007**,*8*, 1991-1994. (c) Tu, S.; Jia, R.; Jiang, B.; Zhang, J.; Zhang, Y.; Yao, C.; Ji, S. Kröhnke reaction in aqueous media: one-pot clean synthesis of 4-aryl-

2,2′:6′,2″-terpyridines. *Tetrahedron* **2007**, *63*, 381-388. (d) Maleki, A.; Firouzi-Haji, R. L-Proline functionalized magnetic nanoparticles: A novel magnetically reusable nanocatalyst for one-pot synthesis of 2,4,6-triarylpyridines. *Scientific Rep.* **2018***, 8*, 17303.

(23) (a) Wu, Q.; Zhang, Y.; Cui, S. Divergent Syntheses of 2-Aminonicotinonitriles and Pyrazolines by Copper-Catalyzed Cyclization of Oxime Ester. *Org. Lett.* **2014,** *16*, 1350-1353. (b) Tan, W. W.; Ong, Y. J.; Yoshikai, N. Synthesis of Highly Substituted Pyridines through Copper-Catalyzed Condensation of Oximes and α,β-Unsaturated Imines. *Angew. Chem. Int. Ed*. **2017**, *56*, 8240-8244. (c) Jiang, H.; Yang, J.; Tang, X.; Li, J. Wu, W. Cu-Catalyzed Three-Component Cascade Annulation Reaction: An Entry to Functionalized Pyridines. *J. Org. Chem.* **2015**, *80*, 8763-8771.

(24) C-H Hydroxylation of 2-arylpyridines, see: (a) Das, P.; Saha, D.; Guin, J. Aerobic Direct C(sp^2)-H Hydroxylation of 2-Arylpyridines by Palladium Catalysis Induced with Aldehyde Auto-Oxidation. *ACS Catal.* **2016**, *6*, 6050-6054. (b) Dong, J.; Liu, P.; Sun, P. Palladium-Catalyzed Aryl C(sp^2)–H Bond Hydroxylation of 2-Arylpyridine Using TBHP as Oxidant. *J. Org. Chem*. **2015**, *80*, 2925-2929. (c) Yan, Y.; Feng, P.; Zheng, Q.-Z.; Liang, Y.-F.; Lu, J.-F.; Cui, Y.; Jiao, N. $PdCl_2$ and N-hydroxyphthalimide co-catalyzed C(sp^2)-H hydroxylation by dioxygen activation. *Angew. Chem. Int. Ed.* **2013**, *52*, 5827-5831. (d) Yamaguchi, T.; Yamaguchi, E.; Tada, N.; Itoh, A. Direct ortho-Hydroxylation of 2-Phenylpyridines using Palladium(II) Chloride and Hydrogen Peroxide. *Adv. Synth. Catal*. **2015**, *357*, 2017-2021. (e) Wu, Y.; Zhou, B. Rhodium(III)-Catalyzed Selective C–H Acetoxylation and Hydroxylation Reactions. *Org. Lett*. **2017**, *19*, 3532-3535. (f) Kim, K.; Hyun, J.; Kim, J.; Kim, H. Water as a Hydroxy Source in a Rh^{III}-Catalyzed Directed C−H Hydroxylation of 2-Arylpyridines. *Asian J. Org. Chem*. **2017**, *6,* 907-912. (g) Shome, S.; Singh, S. P. Design and synthesis of ruthenium

bipyridine catalyst: An approach towards low-cost hydroxylation of arenes and heteroarenes. *Tetrahedron Lett*. **2017**, *58,* 3743-3746.

(25) (a) Qing, X.; Wang, T.; Zhang, F.; Wang, C. One-pot synthesis of 2,4,6-triarylpyridines from β-nitrostyrenes, substituted salicylic aldehydes and ammonium acetate. *RSC Adv*. **2016**, *6*, 95957-95964. (b) Shaibu, B. S.; Kawade, R. K.; Liu, R.-S. Regioselective synthesis of 2-(2-hydroxyaryl)pyridines from the reactions of benzynes with pyridine N-oxides. *Org. Biomol. Chem*. **2012**, *10,* 6834-6839. (c) Qi, X.; Xiang, H.; He, Q.; Yang, C. Synthesis of Multisubstituted 2-Aminopyrroles/pyridines via Chemoselective Michael Addition/Intramolecular Cyclization Reaction. *Org. Lett*. **2014**, *16,* 4186-4189.

(26) (a) Kim, H.; Eum, S. J.; Cho, Y. J.; Kwon, H. J.; Kim, B. O.; Kim, S. M.; Yoon, S. S. *European Patent Application* EP 2080 795A1, **2009**. (b) Zhang, Z.; Bi, H.; Zhang, Y.; Yao, D.; Gao, H.; Fan, Y.; Zhang, H.; Wang, Y.; Wang, Y.; Chen, Z.; Ma, D. Luminescent Boron-Contained Ladder-Type π-Conjugated Compounds. *Inorg. Chem*. **2009**, *48,* 7230-7236. (c) Kim, N. G.; Shin, C. H.; Lee, M. H.; Do, Y. Four-coordinate boron compounds derived from 2-(2-pyridyl)phenol ligand as novel hole-blocking materials for phosphorescent OLEDs. *J. Organomet. Chem.* **2009**, *694***,** 1922-1928.

(27) Zhu, W.; Chen, H.; Wang, Y.; Wang, J.; Peng, X.; Chen, X.; Gao, Y.; Li, C.; He, Y.; Ai, J.; Geng, M.; Zheng, M.; Liu, H. Design, Synthesis, and Pharmacological Evaluation of Novel Multisubstituted Pyridin-3-amine Derivatives as Multitargeted Protein Kinase Inhibitors for the Treatment of Non-Small Cell Lung Cancer. *J. Med. Chem*. **2017**, *60*, 6018-6035.

(28) (a) Guin, S.; Majee, D.; Biswas, S.; Samanta, S. Microwave-Assisted and Base-Promoted Domino Reaction of Cyclic N-Sulfonyl Ketimines with α,β-Disubstituted Nitroalkenes: A Green Access to 2-Hydroxyarylpyridines. *Asian J. Org. Chem.* **2018**, *7*, 1810-1814. (b) Guin,

S.; Gupta, R.; Majee, D.; Samanta, S. DABCO-and DBU-promoted one-pot reaction of N-sulfonyl ketimines with Morita–Baylis–Hillman carbonates: a sequential approach to (2-hydroxyaryl) nicotinate derivatives. *Beilstein J. Org. Chem.* **2018**, *14,* 2771-2778. (c) Biswas, S.; Majee, D.; Guin, S.; Samanta, S. Metal-and Solvent-Free Approach to Diversely Substituted Picolinates via Domino Reaction of Cyclic Sulfamidate Imines with β,γ-Unsaturated α-Ketocarbonyls. *J. Org. Chem.* **2017**, *82,* 10928-10938.

(29) (a) Majee, D.; Biswas, S.; Mobin, S. M.; Samanta, S. Access to 4,6-Diarylpicolinates via a Domino Reaction of Cyclic Sulfamidate Imines with Morita–Baylis–Hillman Acetates of Nitroolefins/Nitrodienes. *J. Org. Chem.* **2016,** *81*, 4378-4385. (b) Majee, D.; Biswas, S.; Mobin, S. M.; Samanta, S. Domino reaction of cyclic sulfamidate imines with Morita–Baylis–Hillman acetates promoted by DABCO: a metal-free approach to functionalized nicotinic acid derivatives. *Org. Biomol. Chem*. **2017**, *15,* 3286-3297. (c) Majee, D.; Guin, S.; Biswas, S.; Samanta, S. A Metal-Free Based New Approach to 2,4-Disubstituted Pyridines via One-Pot Sequential Reaction of Cyclic Sulfamidate Imines with β-Substituted Acroleins. *ChemistrySelect* **2017**, *2*, 3423-3427.

(30) (a) Karki, R.; Park, C.; Jun, K.-Y.; Jee, J.-G.; Lee, J.-H.; Thapa, P.; Kadayat, T. M.; Kwon, Y.; Lee, E.-S. Synthesis, antitumor activity, and structure-activity relationship study of trihydroxylated 2,4,6-triphenyl pyridines as potent and selective topoisomerase II inhibitors. *Eur. J. Med. Chem*. **2014**, *84*, 555-565. (b) Bist, G.; Park, S.; Song, C.; Magar, T. B. T.; Shrestha, A.; Kwon, Y.; Lee, E.-S. Dihydroxylated 2,6-diphenyl-4-chlorophenylpyridines: Topoisomerase I and IIα dual inhibitors with DNA non-intercalative catalytic activity. *Eur. J. Med. Chem.* **2017**, *133*, 69-84. (c) Karki, R.; Thapa, P.; Kang, M. J.; Jeong, T.C.; Nam, J. M.; kim, H.-L.; Na, Y.; Cho, W.-J.; Kwon, Y.; Lee, E.-S. Synthesis, topoisomerase I and II

inhibitory activity, cytotoxicity, and structure–activity relationship study of hydroxylated 2,4-diphenyl-6-arylpyridines. *Bioorg. Med. Chem.* **2010,** *18*, 3066-3077. (d) Kadayat, T. M.; Song, C.; Kwon, Y.; Lee, E.-S. Modified 2,4-diaryl-5*H*-indeno[1,2-*b*]pyridines with hydroxyl and chlorine moiety: Synthesis, anticancer activity, and structure-activity relationship study. *Bioorg. Chem.* **2015***, 62,* 30-40.

(31) Osborne, C. A.; Endean, T. B. D.; Jarvo, E. R. Silver-Catalyzed Enantioselective Propargylation Reactions of N-Sulfonylketimines. *Org. Lett*. **2015,** *17*, 5340-5343.