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The Pd-Catalyzed Decarboxylation and Dual C(sp^3)-H Functionalization Protocols for the Synthesis of 2,4-Diarylpyridines

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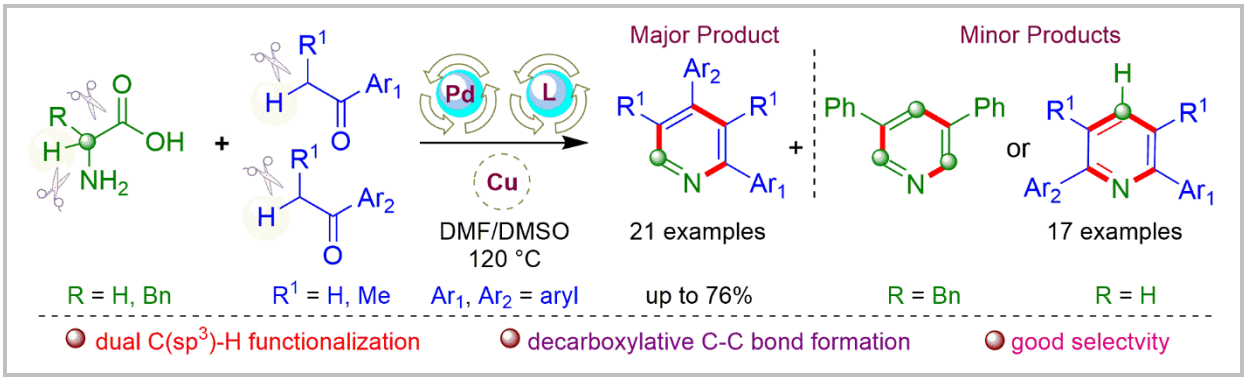
ABSTRACT: The Pd-catalyzed decarboxylation and dual C(sp^3)-H bond functionalization approaches have been described for the preparation of symmetrical and unsymmetrical 2,4-diarylpyridines. The developed transformations were realized using non-activated aromatic ketones and amino acids as C-N source. The efficacy of the catalyst and reagent combination drives the transformation towards the formation of desired products with high yields and selectivity. The described reaction conditions have seduced the self-reaction of phenylalanine *via* [2+2+2] cycloaddition and minimized the formation of 3,5-phenylpyridine as side product, whereas using glycine as C-N source the corresponding 2,6-diarylpyridines were formed as minor products.

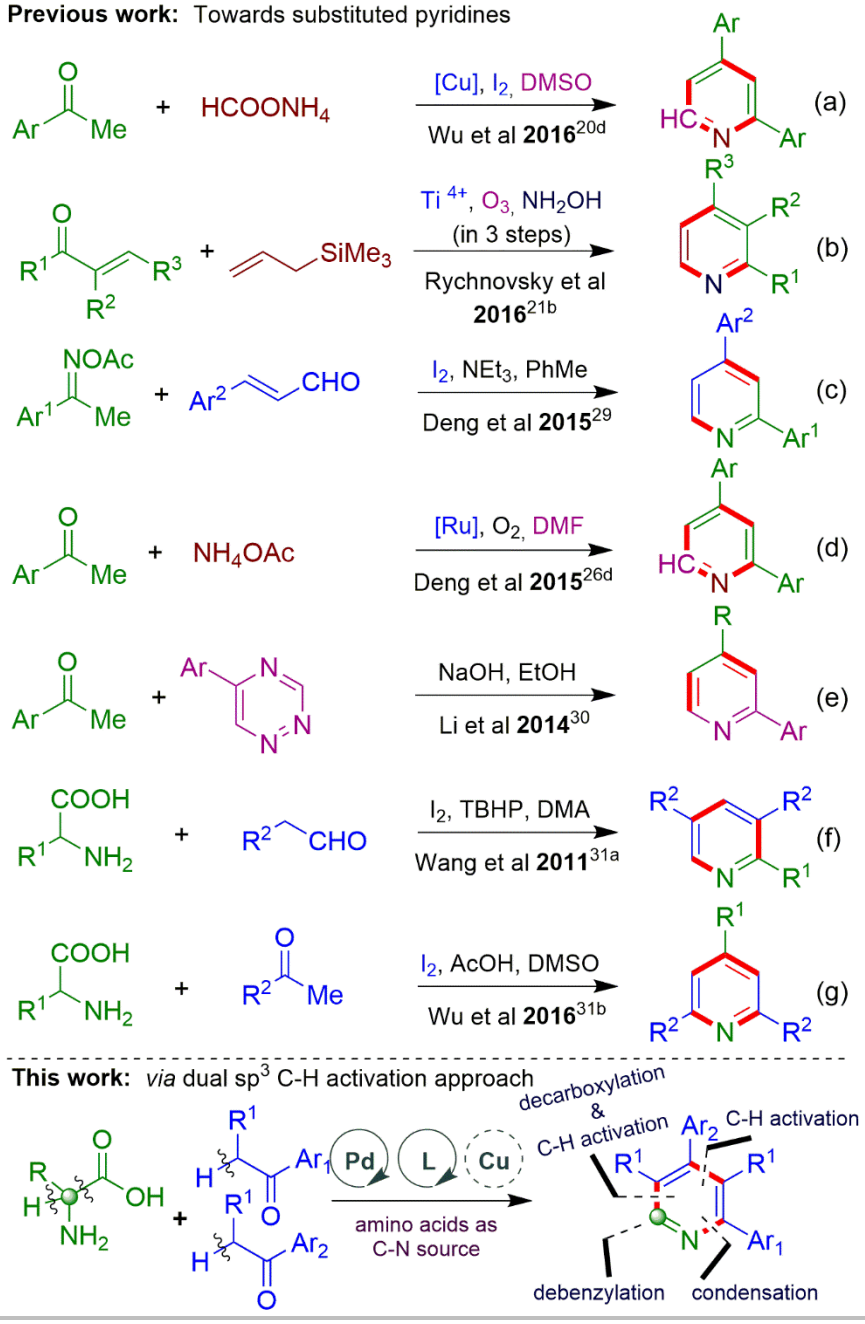


INTRODUCTION

Pyridines belong to the eminently crucial cast of biological important scaffolds among the heterocyclic framework.[1] Pyridine embedded molecules witnessed their occurrence in numerous natural products,[2] in the valued marketed drugs[3] as well as in clinically approved pharmaceuticals.[4] Medicinal impact of the pyridines aroused from their naturally occurring congeners including niacin (vitamins B_3), pyridoxine (vitamin B_6), nicotine and NADP.[5] This is due to their decisive positions in the pivotal biological mechanisms.[5] Pyridine containing pharmaceuticals like isoniazide (anti-tuberculosis drug),[6] amlodipine (anti-hypertensive drug),[7] loratadine (treating allergies)[8] and crizotinib[9] (treating lung cancer) are associated to the treatment for several life-threatening diseases and biological disorders.[10] In extension to their prominent pharmacological properties, a number of pyridine analogues have been recognized as agriculturally active agents.[11] In recent years, pyridine scaffolds have received ample attention in material science, especially towards the synthesis of functional materials.[12] Moreover, the pyridine derivatives could serve as unique ligands for the novel catalytic transformations;[13] for example the first-row transition-metals form distinct reactive complexes with pyridine derivatives and that drives to the selective chemical transformations.[14] Therefore, the renowned application of the pyridine scaffolds in diverse field of research appeals their "easy-to-operate", efficient and selective synthesis using simple substrates.

A broad spectrum of strategic methods have been described towards the synthesis of pyridine scaffolds using diversely functionalized precursors. In the recent years, the field has gained noticeable attention in the field of drug discovery research as well as in material chemistry. To serve this purpose, a number of classical approaches rely on condensation of amines with carbonyl compounds have been reported. These methods are well-recognized as Hantzsch pyridine synthesis,[15] Chichibabin reaction,[16] Vilsmeier-Haack reaction[17] and Bohlmann-Rahtz pyridine synthesis.[18] In consideration with the modern synthetic tools, an array of transition-metals such as Mn,[19] Cu,[20] Ti,[21] Zr,[22] Ni,[23] Pd,[24] Rh[25] and Ru[26] have been investigated in varieties of transformations for the synthesis of functionalized pyridines. Among these methods, the Ru-catalyzed cycloisomerization of 3-azadienynes,[26a] the Cu- or Pd-catalyzed reaction of oxime carboxylates,[20,24] Rh-catalyzed ring expansion,[25a] the metal catalyzed cycloaddition,[27] and C–H functionalization[28] have gained remarkable attention to achieve the construction of pyridine derivatives. In addition to the noticeable isolated yields associated to the previous reported protocols, some of the methods suffer from the limitations such as, use of complex precursors for which the required synthetic routes remains rather long with low isolated yields. In view of the structural diversification, investigation of the chemical transformations with high selectivity towards specific regio-isomer is always of significance especially in the method development. In this regards, a spectrum of synthetic strategies have been established for the preparation of symmetrical and unsymmetrical pyridines using simple substrates and various nitrogen source.[15-28] Wu and co-workers recently described a novel method by the reaction between carbonyl compounds and ammonium acetate using equivalent amounts of both $Cu(NO_3)_2.3H_2O$ and molecular iodine as reagents in which DMSO acts as both solvent and C1-source (Scheme 1a).[20d] Rychnovsky and co-workers reported a three steps method for the synthesis of functionalized pyridines using enones from which 1,5-dicarbonyls are obtained *via* two step Hosomi-Sakurai allylation/oxidative cleavage sequence. Finally, the cyclization reaction was carried out with hydroxylamine hydrochloride to afford corresponding pyridines (Scheme 1b).[21b] Deng et al has demonstrated the chemoselective synthesis of 2,4-disubstituted pyridines from the reaction between enones and oximes using I_2/NEt_3 as reagents combination (Scheme 1c).[29] The one-pot synthesis of 2,4-functionalized pyridines was demonstrated by Deng and co-workers. The reaction was carried out using acetophenones, ammonium acetate and DMF as substrates under the oxygen atmosphere (Scheme 1d).[26d] The 2,4-functionalized pyridines were also obtained *via* inverse electron demand Diels–Alder/retro-Diels-Alder reactions of ketones with 1,2,4-triazines using simple base as reagents (Scheme 1e).[30] The previous reported methods or their modified procedures are proved to be powerful and general for the synthesis of symmetrical and unsymmetrical pyridines. However, using amino acids as C-N source the synthesis of pyridines is still remains rarely explored.[31] For the first time, Wang and coworkers have explored the synthesis of 2,3,5-trisubstituted pyridines using amino acids as N-source by the reaction of amino acids with aryl/alkyl aldehydes in the presence of I_2/TBHP catalyzed reaction conditions (Scheme 1f).[31a] Recently, Chen et al has reported the molecular iodine mediated synthesis of 3,5-diarylpyridines and 2,6-diarylpyridines using amino acids as source of nitrogen (Scheme 1g).[31b] The present protocol represents the first Pd-catalyzed preparation of symmetrical and unsymmetrical 2,4-diarylpyridines using the combination of aromatic ketones and amino acids (Scheme 1).

Scheme 1. Related approaches for the synthesis of pyridines

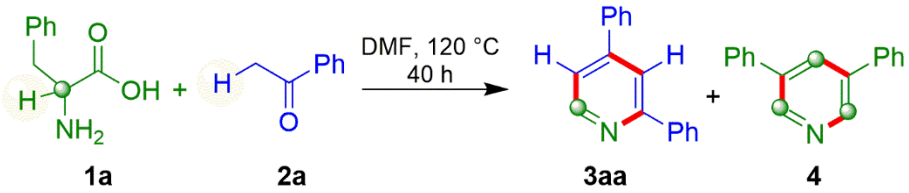


RESULTS AND DISCUSSION

Having the objective of developing efficient method for the preparation of a diverse range of substituted pyridines, we began with the screening experiments using phenylalanine (**1a**) as C-N source and acetophenone (**2a**) as starting material. To check the feasibility, initially a reaction has been attempted between phenylalanine (**1a**) and acetophenone (**2a**) using 10 mol% $Pd(OAc)_2$, 40 mol% $FeCl_3$ and 1.0

equiv. $Cu(OAc)_2·H_2O$. Interestingly, the reaction proceeded in DMF/DMSO (3:1) as solvent at 120 °C for 40 h leading to the formation of the products 2,4-diphenylpyridine (**3aa**) and 3,5-diphenylpyridine (**4**) in 58% and 26% yield respectively (Table 1, Entry 1). Next, the control experiments revealed that the combination of $Cu(OAc)_2·H_2O$ and $FeCl_3$ delivers higher yield of the major product **3aa** (Table 1, Entries 1-3). It was also investigated that the addition of DavePhos as ligand increases the efficacy of the reaction towards selective formation of the product **3aa**, when the reaction was performed using 10 mol% $Pd(OAc)_2$ as catalyst only in combination with $Cu(OAc)_2·H_2O$ as an oxidant and $FeCl_3$ as an additive (Table 1, Entries 4-7). Moreover, it should also be noted that the combination of catalyst, ligand, oxidant and additive remains crucial for the formation of **3aa** as major product (Table 1, Entries 8-12).

Table 1. Initial Optimization for the reaction between amino acid **1a** and ketone **2a**[a]



1a **2a** **3aa** **4**

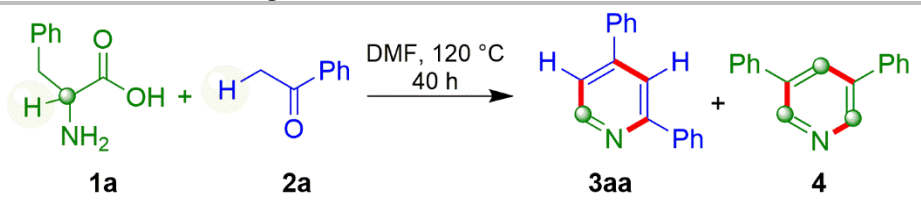
Entry	Catalyst	Ligand	Oxidant/Additive	3aa (% Yield)[b]	4 (% Yield)[b]
1	$Pd(OAc)_2$	-	$Cu(OAc)_2·H_2O/FeCl_3$	58	26
2	$Pd(OAc)_2$	-	$FeCl_3$	< 10	16
3	$Pd(OAc)_2$	-	$Cu(OAc)_2·H_2O$	33	29
4	$Pd(OAc)_2$	DavePhos	$Cu(OAc)_2·H_2O/FeCl_3$	76	16
5	$Pd(OAc)_2$	DavePhos	$Cu(OAc)_2·H_2O$	45	35
6	$Pd(OAc)_2$	DavePhos	$FeCl_3$	12	18
7	$Pd(OAc)_2$	DavePhos	-	< 10	12
8	-	DavePhos	$Cu(OAc)_2·H_2O/FeCl_3$	19	27
9	-	-	$Cu(OAc)_2·H_2O/FeCl_3$	15	22
10	-	-	$Cu(OAc)_2·H_2O$	< 10	17
11	-	-	$FeCl_3$	0	10
12	$Pd(OAc)_2$	-	-	0	0

[a]Unless otherwise indicated: All reactions were performed using 2 mmol of **1a**, 2.6 mmol of **2a**, 10 mol% $Pd(OAc)_2$, 10 mol% Davephos, 1 equiv. $Cu(OAc)_2·H_2O$ and 40 mol% $FeCl_3$ in 1.5 mL DMF/0.5 mL DMSO at 120 °C for 40 h. [b]Isolated yields.

After having an overview of the initial optimization, a wide range of additives (e.g. $In(OTf)_3$, $Sc(OTf)_3$), palladium catalysts (e.g. $Pd(TFA)_2$, $PdCl_2$, $Pd(dppf)Cl_2$, $Pd(PPh_3)_2Cl_2$, $Pd(PPh_3)_4$,) and phosphine ligands (e.g. PPh_3, $P(Cy)_3$, $P(p\text{-}CF_3\text{-}Ph)_3$, $P(2\text{-furyl})_3$, $P(o\text{-tolyl})_3$) were scrutinized carefully (Table 2, Entries 1-12). It is noteworthy that the presence of $In(OTf)_3$ and $Sc(OTf)_3$ as additives were inefficient than $FeCl_3$ for the formation of the desired major product **3aa** (Table 2, Entries 1-2). On the other hand, among the Pd-catalysts and ligands were tested, the combination of $Pd(OAc)_2$ and DavePhos has shown highest efficacy for the reaction between **1a** and **2a** (Table 2, Entries 3-12) to deliver the expected product **3aa**. Next, the scope of a wide range of oxidants has been investigated (Table 2, Entries 13-18). It was observed that among the tested oxidants, the best yield of the product **3aa** was obtained using $Cu(OAc)_2·H_2O$ (Table 1, Entry 4). Further, optimization studies revealed that decreasing the catalyst loading, reaction temperature and time leading to the unsatisfactory yields of 2,4-diphenylpyridine (**3aa**) (details of further optimization given in SI). Hence, from the screening of the reaction conditions, it was concluded that a combination of $Pd(OAc)_2$ (10 mol%) as catalyst, DavePhos (10 mol%) as ligand, $Cu(OAc)_2·H_2O$ (1 equiv.) as oxidant and $FeCl_3$ (40 mol%) as additive in DMF/DMSO (3:1) at 120 °C for 40 h has shown maximum efficiency for the formation of the desired 2,4-diphenylpyridine (**3aa**) in 76%

yield along with the formation of the side product 3,5-diphenylpyridine (**4**) in 16% yield (Table 1, Entry 4).

Table 2. Further screening of the reaction conditions between **1a** and **2a**[a]



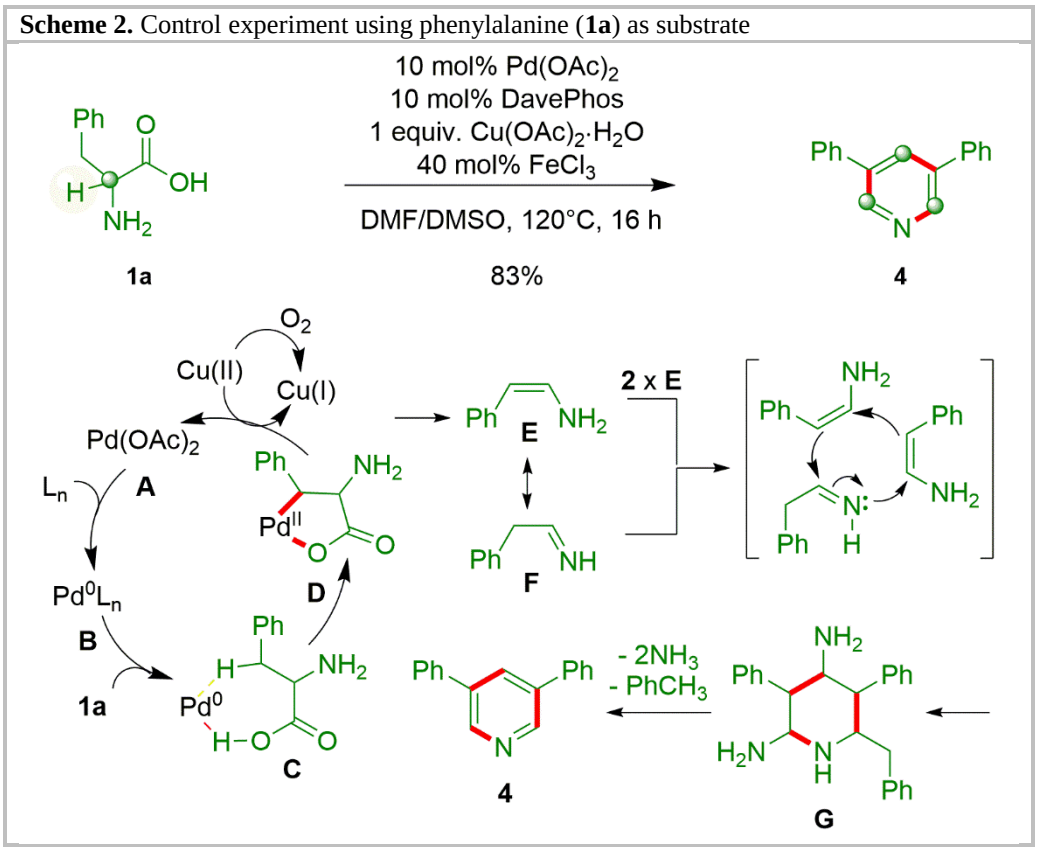
1a **2a** **3aa** **4**

Entry	Catalyst	Ligand	Oxidant/Additive	3aa (% Yield)[b]	4 (% Yield)[b]
1	$Pd(OAc)_2$	DavePhos	$Cu(OAc)_2{\cdot}H_2O/In(OTf)_3$	14	43
2	$Pd(OAc)_2$	DavePhos	$Cu(OAc)_2{\cdot}H_2O/Sc(OTf)_3$	35	27
3	$Pd(TFA)_2$	DavePhos	$Cu(OAc)_2{\cdot}H_2O/FeCl_3$	32	38
4	$PdCl_2$	DavePhos	$Cu(OAc)_2{\cdot}H_2O/FeCl_3$	44	27
5	$Pd(dppf)Cl_2$	DavePhos	$Cu(OAc)_2{\cdot}H_2O/FeCl_3$	29	31
6	$Pd(PPh_3)_2Cl_2$	DavePhos	$Cu(OAc)_2{\cdot}H_2O/FeCl_3$	21	35
7	$Pd(PPh_3)_4$	DavePhos	$Cu(OAc)_2{\cdot}H_2O/FeCl_3$	26	34
8	$Pd(OAc)_2$	PPh_3	$Cu(OAc)_2{\cdot}H_2O/FeCl_3$	53	31
9	$Pd(OAc)_2$	$P(Cy)_3$	$Cu(OAc)_2{\cdot}H_2O/FeCl_3$	49	30
10	$Pd(OAc)_2$	$P(p\text{-}CF_3\text{-}Ph)_3$	$Cu(OAc)_2{\cdot}H_2O/FeCl_3$	62	32
11	$Pd(OAc)_2$	$P(2\text{-furyl})_3$	$Cu(OAc)_2{\cdot}H_2O/FeCl_3$	57	29
12	$Pd(OAc)_2$	$P(o\text{-tolyl})_3$	$Cu(OAc)_2{\cdot}H_2O/FeCl_3$	46	21
13	$Pd(OAc)_2$	DavePhos	$AgSbF_6/FeCl_3$	41	30
14	$Pd(OAc)_2$	DavePhos	$Ag_2CO_3/FeCl_3$	53	19
15	$Pd(OAc)_2$	DavePhos	$AgOAc/FeCl_3$	49	15
16	$Pd(OAc)_2$	DavePhos	$K_2S_2O_8/FeCl_3$	17	43
17	$Pd(OAc)_2$	DavePhos	$MnO_2/FeCl_3$	25	39
18	$Pd(OAc)_2$	DavePhos	$KNO_3/FeCl_3$	9	48

[a]Unless otherwise indicated: All reactions were performed using 2 mmol of **1a**, 2.6 mmol of **2a**, 10 mol% catalyst, 10 mol% ligands, 1 equiv. oxidant and 40 mol% additive in 1.5 mL DMF/0.5 mL DMSO at 120 °C for 40 h. [b]Isolated yields.

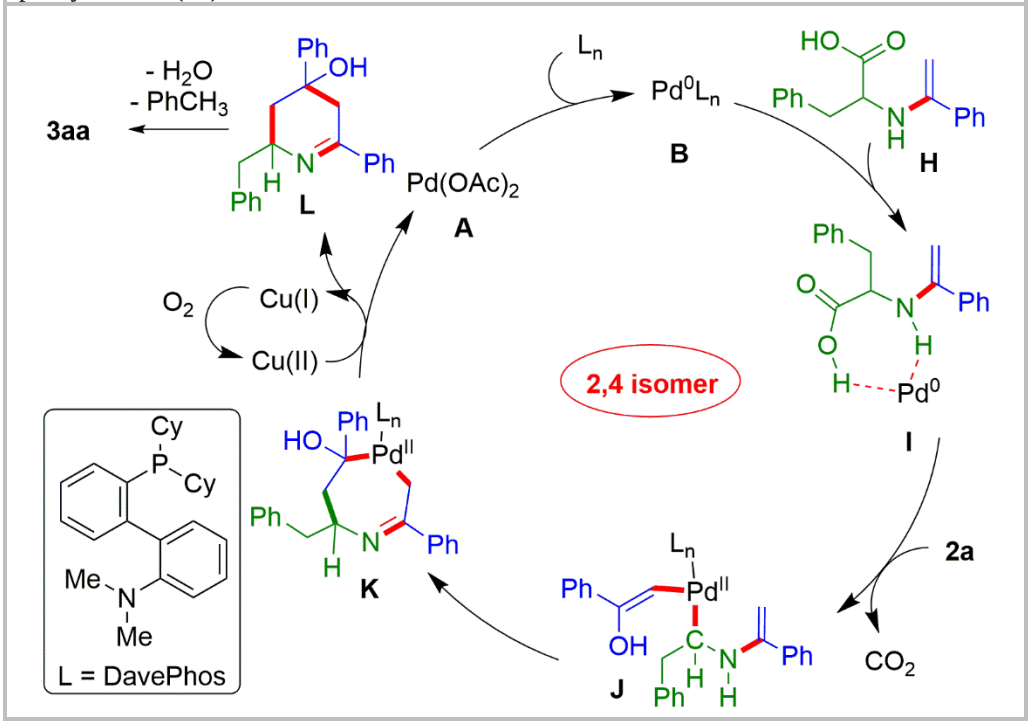
To have an overview for the reaction mechanism, a reaction has been conducted using only phenylalanine (**1a**) as starting material under the optimal conditions for 16 h (Scheme 2). It was observed that the reaction leading to the formation of exclusively 3,5-diphenylpyridine (**4**) as product. The formation of the product **4** can be realized by the self-cyclization of phenylalanine (**1a**).[31b] It is assumed that in the presence of Pd(II)-catalyst, the decarboxylation[32] of amino acid **1a** would result an imine intermediate **E**, which followed by tautomerization gives an enamine intermediate **F**. Further, the [2+2+2] cycloaddition[33] between two molecules of **E** and one molecule of **F** gives an unstable penta-substituted piperidine intermediate **G**, which followed by deamination, debenzylation and aromatization delivers the 3,5-diphenylpyridine (**4**).

Scheme 2. Control experiment using phenylalanine (**1a**) as substrate



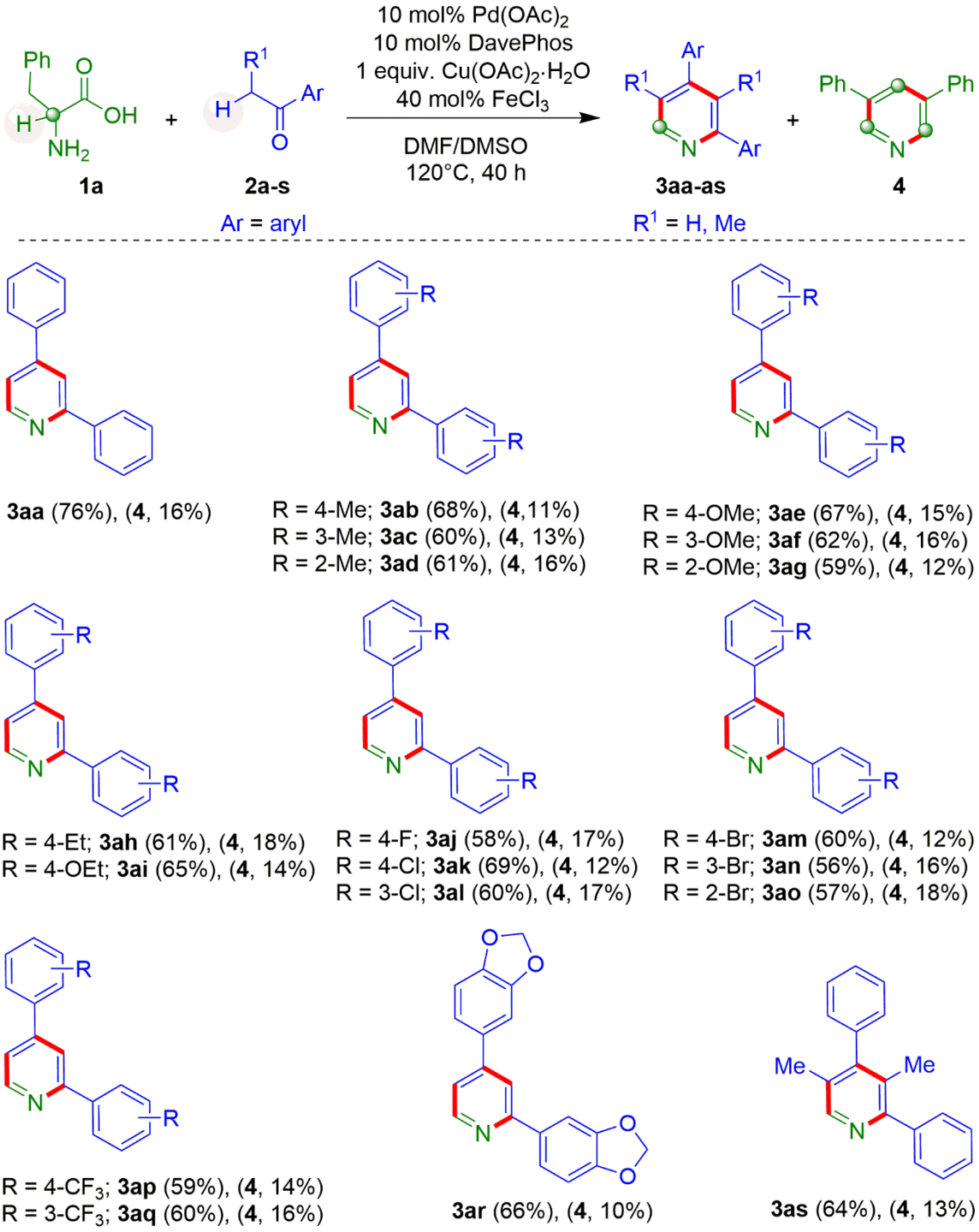
On the other hand, we looked into the plausible pathways for the formation of the major product 2,4-diphenylpyridine (**3aa**) (Scheme 3). It is assumed that the intermediate **H** could be formed by the condensation between **1a** and **2a**. Simultaneously, the $Pd(OAc)_2$ undergoes ligand exchange processes to give the Pd(0) species **B**. Then, consecutive Pd-catalyzed decarboxylation of the intermediate **H** and functionalization with substrate **2a** *via* sp^3 C-H activation leading to the formation of an intermediate **J**. The migratory insertion of palladium[34] followed by C-H functionalization of methylene group could result the intermediate **K**. The reductive elimination delivers the Pd(0) species along with the formation of cyclic intermediate **L**. The Pd(II) species is regenerated back to the catalytic cycle by Cu(II) in the presence of aerial oxygen. Finally, the aromatization followed by the debenzylation of intermediate **L** leading to the formation of the desired product **3aa**.

Scheme 3. Plausible mechanism for the formation of 2,4-diphenylpyridine (**3aa**) using phenylalanine (**1a**).



Having successfully realized the detailed optimization process and the plausible reaction mechanism, the scope of this transformation was explored using phenylalanine (**1a**) and a series of acetophenone derivatives **2** (Scheme 4). It was investigated that irrespective of the electronic nature of the substitution pattern on acetophenones **2**, all substrates were well tolerated under the standard conditions to deliver the corresponding 2,4-diarylpyridines **3ab-as** in yields ranging from 56 - 69%, along with the formation of side product 3,5-diphenylpyridine (**4**) in yields ranging from 10 - 18%. In all investigated examples the side product **4** was realized under the reaction conditions, which is due to the competitive self-cyclization of phenylalanine (**1a**) *via* [2+2+2] cycloaddition reaction.

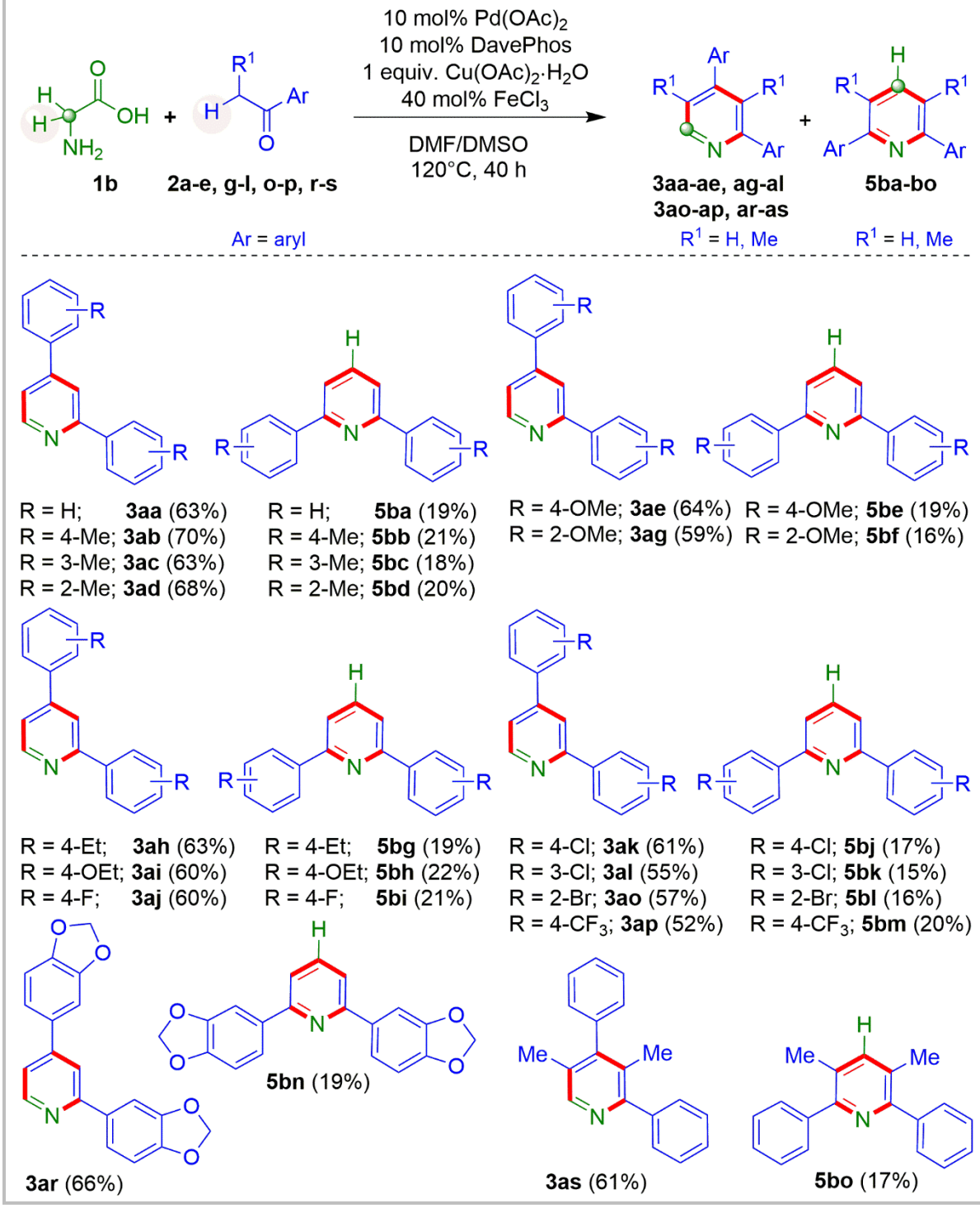
Scheme 4. Pd-Catalyzed synthesis of 2,4-diarylpyridines **3** using phenylalanine (**1a**) as C-N source.



After, the successful development of the first multicomponent process using phenylalanine (**1a**), the scope of this method was investigated using glycine (**1b**) as C-N source. A series of acetophenones **2** with both

electron-donating (Ar = 2-MeC_6H_4, 3-MeC_6H_4, 4-MeC_6H_4, 2-$MeOC_6H_4$, 4-$MeOC_6H_4$, 4-EtC_6H_4 and 4-$EtOC_6H_4$) and electron-withdrawing (4-FC_6H_4, 3-ClC_6H_4, 4-ClC_6H_4, 2-BrC_6H_4, 4-$CF_3C_6H_4$ and 3,4-$OCH_2OC_6H_4$) substituents were then subjected to the reaction with glycine (**1b**) under the developed conditions (Scheme 5). This investigation reveals that all substituents were efficient for the transformation, which delivered the desired products in good yields ranging from 52-70%. Notably, the electron-withdrawing groups present in aromatic ring have slight impact in the yield of final products. Additionally, the reactivity of the propiophenone (**2o**) with glycine (**1b**) has been verified, which delivers the corresponding tetra-substituted pyridine **3as** in 61% yield. It is also noteworthy that in all examples along with the major products **3aa-ae**, **ag-al**, **ao-ap**, **ar-as** a considerable amounts of 2,6-diarylpyridines **5ba-bo** have been observed as side products (Scheme 5), whereas in case of phenylalanine (**1a**) as substrate the 3,5-diphenylpyridine (**4**) was recognized as by-product (Scheme 4).[31b]

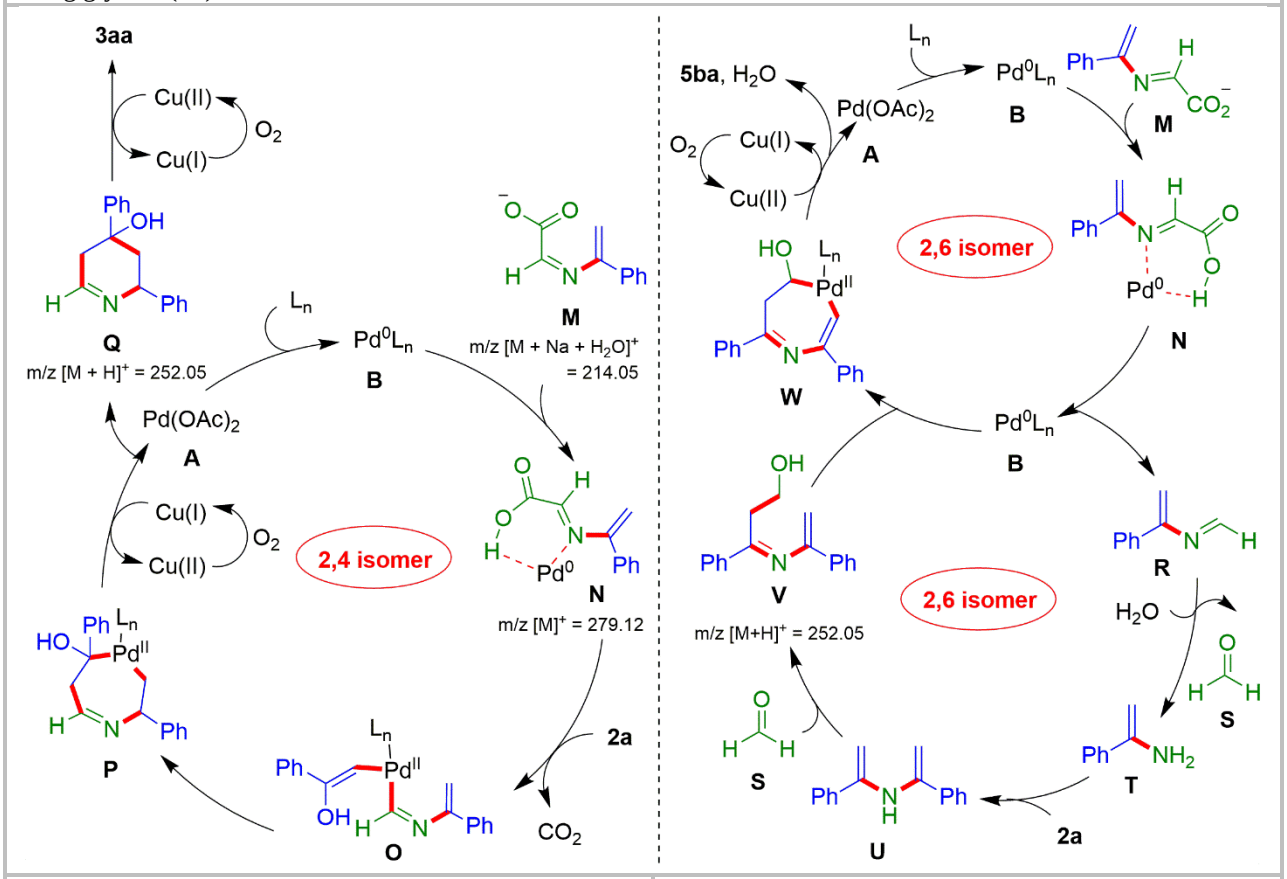
Scheme 5. Pd-Catalyzed Synthesis of 2,4-diarylpyridines **3**, 2,6-diarylpyridines **5** using glycine (**1b**) as N- and C1 source.



According to the proposed mechanism, it appears that the intermediate **M** could be formed by the condensation between **1b** and **2a**. The intermediate **M** then undergoes decarboxylation[32] through an intermediate **N**. The intermediate **N** undergo functionalization with one more molecule of **2a** *via* sp^3 C-H

functionalization leading to the formation of an intermediate **O**. This intermediate further undergoes migratory insertion of palladium[34] and subsequent sp^2 C-H functionalization of methylene group results in the formation of intermediate **P**. The palladacycle then undergoes reductive elimination leading to the formation of intermediate **Q** and leaving behind the Pd(0) species back to the catalytic cycle. Finally, intermediate **Q** undergoes dehydration followed by Cu(II)-mediated aerial oxidation to obtain the 2,4-diphenylpyridine (**3aa**) (Scheme 6a). On the other hand, the intermediate **N** undergoes decarboxylation[32] and resulting in intermediate **R**. The hydrolysis of intermediate **R** would deliver formaldehyde (**S**) and an enamine **T**, which after condensation with one more molecule of ketone **2a** produces an enamine **U**. Addition of formaldehyde (**S**) into enamine **U** gives an intermediate **V**. Next, the Pd-catalyzed intra-molecular cross-dehydrogenative-coupling (CDC)[35] of intermediate **V**, leading to the side product 2,6-diphenylpyridine (**5ba**) *via* the formation of palladacycle **W**. Finally, the Pd(II) species is regenerated back to catalytic cycle by Cu(II) in presence of aerial oxygen (Scheme 6b).

Scheme 6. Plausible mechanism for the formation of 2,4-diphenylpyridines (**3aa**) and 2,6-diphenylpyridines (**5ba**) using glycine (**1b**) as amino acid.



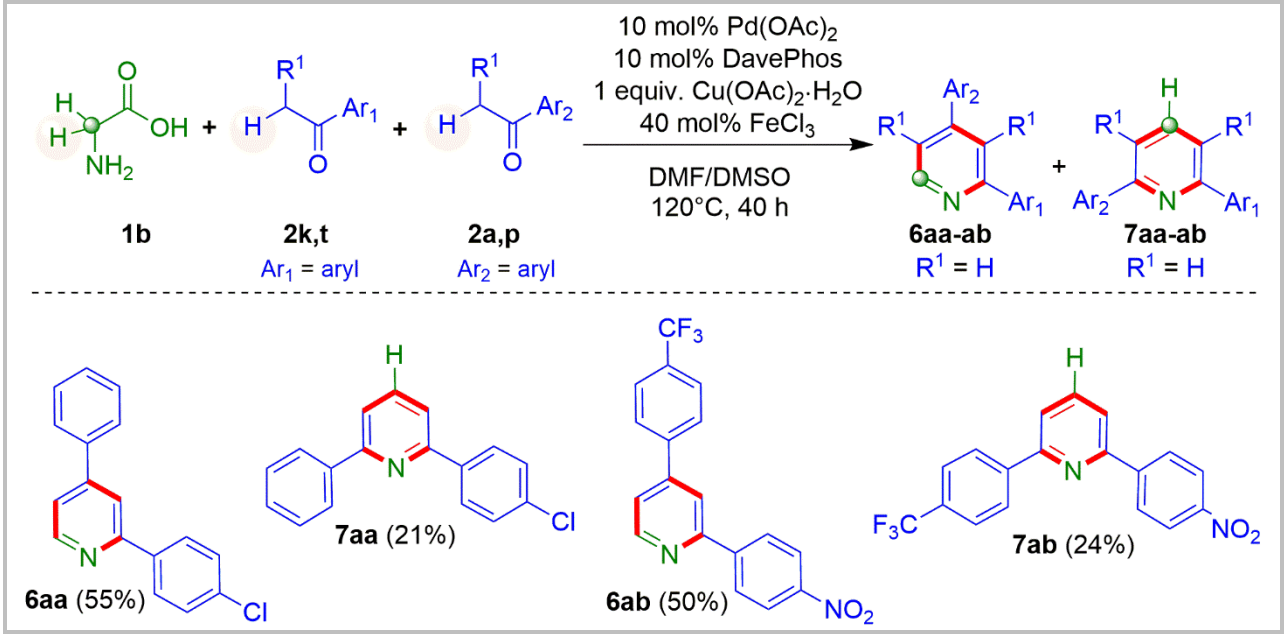
Scheme **6a** | Scheme **6b**

Finally, in order to confirm the proposed reaction mechanism, an experiment was performed using glycine (**1b**) and acetophenone (**2a**) under the standard conditions, for which the course of reaction was monitored and analyzed by LC-MS. The reaction mixture was analysed by using LC-MS after an interval of every 10 h. From mass spectroscopy data it was identified that the proposed mechanism (Scheme 6) has the involvement of intermediates **M**, **N**, **Q** and **V** (details of mass spectra is given in Figure 1, SI). It

was observed that the intermediate **M** ($[M+Na+H_2O]^+$ = 214.05), along with the formation of corresponding tetra-saturated pyridine intermediate ($[M+H]^+$ = 236.07) can be identified after 10 h of the reaction. When the reaction mixture was analysed after 20 h, the corresponding peaks of the products **3aa** and **5ba** ($[M+H]^+$ = 232.09) started appearing along with the intermediate **N** ($[M+H]^+$ = 279.12) and **M**. Interestingly, the scenario has been improved after 30 h as the product peak appears as major with decreasing amounts of intermediates **M**, **N**, **Q** and **V**. Moreover, after 40 h of the reaction the product **3aa** and **5ba** ($[M+H]^+$ = 232.1132) were found exclusively. Hence, having observed the experimental results, it was concluded that the reaction proceeds *via* the proposed mechanistic pathway. It was also assumed that the investigated selectivity towards formation of 2,4-diarylpyridines **3** over 2,6-diarylpyridines **5** or self-cyclized 3,5-diphenylpyridine (**4**) can be explained due to the electron-donating ability of DavePhos to the metal ion, which is facilitating the formation of products **3**. This electronic nature of the DavePhos could drive the tendency of metal ion to accommodate the second molecule of aryl ketone **2** to generate the intermediate **J** (Scheme 3) and intermediate **O** (Scheme 6a), rather than formation of a Pd(0) species **B** (Scheme 6).[36]

Moreover, to gain further insight into the potential of described method, it was extended towards installation of two different aryl moieties on the pyridine ring (Scheme 7). Hence, the glycine (**1b**) was subjected to a combination of two acetophenone derivatives **2** under the standard reaction conditions. It was investigated that the developed protocol is not only restricted to the synthesis of symmetrically functionalized 2,4-diarylpyridines **3**, rather it can be extended to the preparation of unsymmetrically functionalized 2,4-diarylpyridines **6** in moderate yields ranging from 50-55%, along with the formation of unsymmetrically functionalized 2,6-diarylpyridines **7** as side products in yields ranging from 21-24%. Additionally, it is noteworthy that the formation of the symmetrically functionalized 2,4-diarylpyridines remains unnoticeable during the reaction.

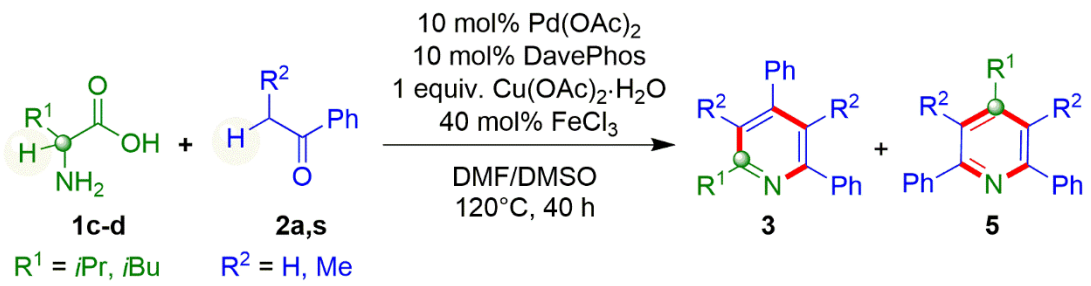
Scheme 7. Scope of unsymmetrically functionalized 2,4-diarylpyridines **6** and 2,6-diarylpyridines **7**.



To further explore the substrate scope the amino acids such as valine (**1c**) and leucine (**1d**) were investigated in this transformation (Table 3). It was found that the reactions with valine (**1c**) and leucine (**1d**) did not proceed in the similar way as phenylalanine (**1a**) and glycine (**1b**). When, valine (**1c**) or

leucine (**1d**) were reacted with acetophenone (**2a**) or propiophenone (**2s**) under the optimized conditions, the corresponding 2,6-diarylpyridines **5ba** or **5bo** were isolated in yields ranging from 33-45%. However, in these reactions the corresponding 2,4-diarylpyridines **3** were not observed.

Table 3. Pd-Catalyzed Synthesis of 2,6-diarylpyridines **5** using valine (**1c**) and leucine (**1d**) as nitrogen source.[a,b]



1c, R^1 = *i*Pr	**2a**, R^2 = H	**3ca** (0%)	R^1 = H, **5ba** (33%)[c]
1c, R^1 = *i*Pr	**2s**, R^2 = Me	**3cs** (0%)	R^1 = H, **5bo** (45%)[c]
1d, R^1 = *i*Bu	**2a**, R^2 = H	**3da** (0%)	R^1 = H, **5ba** (29%)[c]
1d, R^1 = *i*Bu	**2s**, R^2 = Me	**3ds** (0%)	R^1 = H, **5bo** (40%)[c]

[a]Unless otherwise indicated: All reactions were performed using 2 mmol of **1c-d**, 2.6 mmol of **2a,s**, 10 mol% catalyst, 10 mol% ligands, 1 equiv. oxidant and 40 mol% additive in 1.5 mL DMF/0.5 mL DMSO at 120 °C for 40 h. [b]Isolated yields. [c]Complex reaction mixture.

CONCLUSIONS

In summary, a rapid one-pot tandem process for the synthesis of di-substituted pyridines involving condensation, decarboxylation, dual C-H functionalization and debenzylation has been described. The transformation was realized using various amino acids as C-N source and aryl ketones as easy available and cheap substrates. Under the influence of Pd-catalysis, the potential of the developed one-pot multi-bond forming process delivered a diverse range of symmetrical and unsymmetrical 2,4-diarylpyridines in high yields with good selectivity. The proposed mechanistic pathway was verified by several control experiments and mass spectrometry. Further, the investigation on the applications of the described one-pot multistep process is currently on-going in our laboratory.

EXPERIMENTAL SECTION

General methods: All starting materials (including **1a-b**, **2a-t**) were purchased from commercial suppliers (Sigma-Aldrich, Alfa-Aesar, SD fine chemicals, Merck, HI Media) and were used without further purification unless otherwise indicated. All reactions were carried out under an argon atmosphere in oven-dried glassware with magnetic stirring. The reactions were performed in pressure tube purchased from Sigma-Aldrich glassware. Solvents used in extraction and purification were distilled prior to use. Thin-layer chromatography (TLC) was performed on TLC plates purchase from Merck. Compounds were visualized with UV light (λ = 254 nm) and/or by immersion in $KMnO_4$ staining solution followed by heating. Products were purified by column chromatography on silica gel, 100 - 200 mesh. ^1H (^{13}C) NMR spectra were recorded at 600 (150) MHz and 400 (100) MHz on a Brucker spectrometer using $CDCl_3$ as a solvent. The ^1H and ^{13}C chemical shifts were referenced to residual solvent signals at $\delta_{H/C}$ 7.26

/77.28 ($CDCl_3$) relative to TMS as internal standards. Coupling constants J [Hz] were directly taken from the spectra and are not averaged. Splitting patterns are designated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), overlapped and br (broad).

General experimental procedure for the synthesis of 2,4-diarylpyridines (3aa-as) and 3,5-diphenylpyridine (4) using phenylalanine (1a)

A 10 mL reaction vial was charged with phenylalanine **1a** (2.0 mmol), arylketones **2a-s** (2.6 mmol), $FeCl_3$ (0.4 mmol), $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol), DavePhos (0.2 mmol), $Pd(OAc)_2$ (0.2 mmol) and DMF:DMSO (3:1) (2 mL)**.** The reaction vial was then closed and heated at 120 °C for 40 h. After completion of the reaction (progress was monitored by TLC; SiO_2, Hexane/EtOAc = 9:1), the mixture was diluted with ethyl acetate (15 mL) and water (20 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine (3 × 10 mL) and dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the remaining residue was purified by column chromatography over silica gel using hexane / ethyl acetate = 9:1 as an eluent to obtain the desired 2,4-arylpyridines **3aa-as** and 3,5-diphenylpyridine **4** in high yields.

General experimental procedure for the synthesis of 2,4-diarylpyridines (3aa-ae, ag-al, ao-ap, ar-as) and 2,6-diarylpyridines (5ba-bo) using glycine (1b)

A 10 mL reaction vial was charged with glycine **1b** (2.0 mmol), arylketones **2a-e, g-l, o-p, r-s** (2.6 mmol), $FeCl_3$ (0.4 mmol), $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol), DavePhos (0.2 mmol), $Pd(OAc)_2$ (0.2 mmol) and DMF:DMSO (3:1) (2 mL)**.** The reaction vial was then closed and heated at 120 °C for 40 h. After completion of the reaction (progress was monitored by TLC; SiO_2, Hexane/EtOAc = 9:1), the mixture was diluted with ethyl acetate (15 mL) and water (20 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine (3 × 10 mL) and dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the remaining residue was purified by column chromatography over silica gel using hexane / ethyl acetate = 9:1 as an eluent to obtain the desired 2,4-arylpyridines **3aa-ae, ag-al, ao-ap, ar-as** and 2,6-diarylpyridines **5ba-bo** in high yields.

General experimental procedure for the synthesis of 2,4-diarylpyridines (6aa-ab) and 2,6-diarylpyridines (7aa-ab) using glycine (1b)

A 10 mL reaction vial was charged with glycine **1b** (2.0 mmol), arylketones **2k**,**t**, (1.3 mmol), arylketones **2a**,**p** (1.3 mmol), $FeCl_3$ (0.4 mmol), $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol), DavePhos (0.2 mmol), $Pd(OAc)_2$ (0.2 mmol) and DMF:DMSO (3:1) (2 mL)**.** The reaction vial was then closed and heated at 120 °C for 40 h. After completion of the reaction (progress was monitored by TLC; SiO_2, Hexane/EtOAc = 9:1), the mixture was diluted with ethyl acetate (15 mL) and water (20 mL) and extracted with ethyl acetate (3 × 10 mL). The combined organic layer was washed with brine (3 × 10 mL) and dried over anhydrous Na_2SO_4. Solvent was removed under reduced pressure and the remaining residue was purified by column chromatography over silica gel using hexane / ethyl acetate = 9:1 as an eluent to obtain the desired 2,4-arylpyridines **6aa-ab** and 2,6-diarylpyridines **7aa-ab** in high yields.

Experimental procedures and analytical data of synthesized 2,4-diarylpyridines (3aa-as), 3,5-diphenylpyridine (4) and 2,6-diarylpyridines (5ba-bo)

Preparation of 2,4-diphenylpyridine (3aa) and 3,5-diphenylpyridine (4)

According to the general procedure, reactions between phenylalanine **1a** (2.0 mmol, 330 mg) acetophenone **2a** (2.6 mmol, 312 mg) were performed using $FeCl_3$ (0.4 mmol, 64.8 mg), $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol, 398 mg), DavePhos (0.2 mmol, 78.6 mg), $Pd(OAc)_2$ (0.2 mmol, 44.8 mg) to obtain the desired 2,4-diphenylpyridine **3aa** in 76% (176 mg) and 3,5-diphenylpyridine **4** in 16% (37 mg) yield as yellow solid and black solid respectively (Scheme 4).

2,4-diphenylpyridine (**3aa**)[20d] (Table 1-2, Scheme 3, 4, 5): **Yellow solid**, $\mathbf{R_f}$ = 0.50 (SiO_2, Hexane/EtOAc = 9:1); **m.p** = 58 - 59 °C (Lit[20d] 57 - 61 °C); **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 8.75 (d, ^3J = 5.1 Hz, 1H; 6-H), 8.05 (d, ^3J = 7.8 Hz, 2H; 8-H), 7.94 (s, 1H; 3-H), 7.70 (d, ^3J = 7.6 Hz, 2H; 12-H), 7.53 – 7.44 (m, 7H; 5-H, 9-H, 10-H, 13-H and 14-H) ppm; **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ = 158.1 (C-2), 150.0 (C-6), 149.4 (C-4), 139.4 (C-7), 138.5 (C-11), 129.1 (C-13), 129.05 (C-10), 129.04 (C-14), 128.8 (C-9), 127.1 (C-8), 127.0 (C-12), 120.3 (C-5), 118.8 (C-3) ppm; **HRMS (EI-QTOF,** $[M + H]^+$): calculated for $C_{17}H_{14}N$: 232.1125; found: 232.1128.

3,5-diphenylpyridine (**4**)[31b] (Table 1-2, Scheme 2, 4): **Black solid**, $\mathbf{R_f}$ = 0.75 (SiO_2, Hexane/EtOAc = 9:1); **m.p** = 133 - 134 °C (Lit[31b] 132 - 135 °C); **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 8.83 (s, 2H; 2-H and 6-H), 8.06 (s, 1H; 4-H), 7.65 (dd, ^3J = 7.7 Hz, 4H; 8-H), 7.51 (td, ^3J = 8.0 Hz, 4H; 9-H), 7.44 (dt, ^3J = 8.6 Hz, 2H; 10-H) ppm; **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ = 146.9 (C-2 and C-6), 137.7 (C-7), 136.7 (C-3 and C-5), 132.9 (C-4), 129.1 (C-9), 128.2 (C-10), 127.2 (C-8) ppm; **HRMS (EI-QTOF,** $[M + H]^+$): calculated for $C_{17}H_{14}N$: 232.1125; found: 232.1121.

Preparation of 2,4-diphenylpyridine (3aa) and 2,6-diphenylpyridine (5ba)

According to the general procedure, reactions between glycine **1b** (2.0 mmol, 150 mg) acetophenone **2a** (2.6 mmol, 312 mg) were performed using $FeCl_3$ (0.4 mmol, 64.8 mg), $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol, 398 mg), DavePhos (0.2 mmol, 78.6 mg), $Pd(OAc)_2$ (0.2 mmol, 44.8 mg) to obtain the desired 2,4-diphenylpyridine **3aa** in 63% (146 mg) and 2,6-diphenylpyridine **5ba** in 19% (44 mg) yield as yellow solid and white solid respectively (Scheme 5).

2,6-diphenylpyridine (**5ba**)[31b] (Scheme 5): **White solid**, $\mathbf{R_f}$ = 0.45 (SiO_2, Hexane/EtOAc = 9:1); **m.p** = 76 - 77 °C (Lit[31b] 75 - 78 °C); **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 8.16 (dd, ^3J = 7.6 Hz, 4H; 8-H), 7.82 (t, ^3J = 7.8 Hz, 1H; 4-H), 7.70 (dd, ^3J = 7.8 Hz, 2H; 3-H and 5-H), 7.50 (t, ^3J = 7.6 Hz, 4H; 9-H), 7.43 (t, ^3J = 7.8 Hz, 2H; 10-H) ppm; **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ = 156.8 (C-2 and C-6), 139.5 (C-4), 137.4 (C-7), 128.9 (C-9), 128.6 (C-8), 127.0 (C-10), 118.6 (C-3 and C-5) ppm; **HRMS (EI-QTOF,** $[M + H]^+$): calculated for $C_{17}H_{14}N$: 232.1125; found: 232.1126.

Preparation of 2,4-di-*p*-tolylpyridine (3ab) and 2,6-di-*p*-tolylpyridine (5bb)

According to the general procedure, reactions between phenylalanine **1a** (2.0 mmol, 330 mg) 4′-methylacetophenone **2b** (2.6 mmol, 348.4 mg) were performed using $FeCl_3$ (0.4 mmol, 64.8 mg), $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol, 398 mg), DavePhos (0.2 mmol, 78.6 mg), $Pd(OAc)_2$ (0.2 mmol, 44.8 mg) to obtain the desired 2,4-di-*p*-tolylpyridine **3ab** in 68% (176 mg) and 3,5-diphenylpyridine **4** in 11% (28.5 mg) yield as white solid and black solid respectively (Scheme 4).

According to the general procedure, reactions between glycine **1b** (2.0 mmol, 150 mg) 4′-methylacetophenone **2b** (2.6 mmol, 348.4 mg) were performed using $FeCl_3$ (0.4 mmol, 64.8 mg), $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol, 398 mg), DavePhos (0.2 mmol, 78.6 mg), $Pd(OAc)_2$ (0.2 mmol, 44.8 mg) to obtain the desired 2,4-di-*p*-tolylpyridine **3ab** in 70% (181 mg) and 2,6-di-*p*-tolylpyridine **5bb** in 21% (54 mg) yield as white solid and pale white solid respectively (Scheme 5).

2,4-di-*p*-tolylpyridine (**3ab**)[20d] (Scheme 4, 5): **White solid**, $\mathbf{R_f}$ = 0.50 (SiO_2, Hexane/EtOAc = 9:1); **m.p** = 108 - 109 °C (Lit[20d] 107 - 110 °C); **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 8.69 (d, ^3J = 5.2 Hz, 1H; 6-H), 8.08 (d, ^3J = 7.8 Hz, 2H; 8-H), 7.89 (s, 1H; 3-H), 7.58 (d, ^3J = 7.6 Hz, 2H; 12-H), 7.42 (dd, ^3J = 7.8 Hz, 1H; 3-H), 7.31 – 7.29 (m, 4H; 9-H and 13-H), 2.42 (s, 3H; 15-H), 2.41 (s, 3H; 16-H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 158.1 (C-2), 150.0 (C-6), 149.2 (C-4), 139.2 (C-7), 139.1 (C-11), 136.8 (C-14), 135.7 (C-10), 129.9 (C-13), 129.6 (C-9), 129.5 (C-12), 127.0 (C-8), 119.9 (C-5), 118.4 (C-3), 21.4 (C-15), 21.3 (C-16) ppm; **HRMS (EI-QTOF,** $[M + H]^+$): calculated for $C_{19}H_{18}N$: 260.1434; found: 260.1431.

2,6-di-*p*-tolylpyridine (**5bb**)[37g] (Scheme 5): **Pale white solid**, $\mathbf{R_f}$ = 0.75 (SiO_2, Hexane/EtOAc = 9:1); **m.p** = 162 - 165 °C (Lit[37g] 163 - 165 °C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.05 (d, ^3J = 8.2 Hz, 4H; 8-H), 7.76 (t, ^3J = 7.8 Hz, 1H; 4-H), 7.63 (d, ^3J = 7.8 Hz, 2H; 3-H and 5-H), 7.30 (d, ^3J = 8.3 Hz, 4H; 9-H), 2.42 (s, 6H; 11-H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 156.8 (C-2 and C-6), 139.0 (C-4), 137.4 (C-7), 136.9 (C-10), 129.5 (C-9), 127.0 (C-8), 118.1 (C-3 and C-5), 21.4 (C-11) ppm; **HRMS (EI-QTOF,** $[M + H]^+$): calculated for $C_{19}H_{18}N$: 260.1434; found: 260.1429.

Preparation of 2,4-di-*m*-tolylpyridine (3ac) and 2,6-di-*m*-tolylpyridine (5bc)

According to the general procedure, reactions between phenylalanine **1a** (2.0 mmol, 330 mg) 3′-methylacetophenone **2c** (2.6 mmol, 348.4 mg) were performed using $FeCl_3$ (0.4 mmol, 64.8 mg), $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol, 398 mg), DavePhos (0.2 mmol, 78.6 mg), $Pd(OAc)_2$ (0.2 mmol, 44.8 mg) to obtain the desired 2,4-di-*m*-tolylpyridine **3ac** in 60% (155 mg) and 3,5-diphenylpyridine **4** in 13% (30 mg) yield as yellow oil and black solid respectively (Scheme 4).

According to the general procedure, reactions between glycine **1b** (2.0 mmol, 150 mg) 3′-methylacetophenone **2c** (2.6 mmol, 348.4 mg) were performed using $FeCl_3$ (0.4 mmol, 64.8 mg), $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol, 398 mg),

DavePhos (0.2 mmol, 78.6 mg), $Pd(OAc)_2$ (0.2 mmol, 44.8 mg) to obtain the desired 2,4-di-*m*-tolylpyridine **3ac** in 63% (163 mg) and 2,6-di-*m*-tolylpyridine **5bc** in 18% (47 mg) yield as yellow oil and white solid respectively (Scheme 5).

2,4-di-*m*-tolylpyridine (**3ac**)[37d] (Scheme 4, 5): **Orange yellow oil**, $\mathbf{R_f}$ = 0.40 (SiO_2, Hexane/EtOAc = 9:1); **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 8.72 (d, *J* = 5.1 Hz, 1H; 6-H), 7.90 (d, *J* = 6.4 Hz, 2H; 8-H and 12-H), 7.82 (d, *J* = 7.8 Hz, 1H; 5-H), 7.50 (d, *J* = 7.9 Hz, 2H; 3-H and 14-H), 7.44 - 7.37 (m, 3H; 11-H, 17-H and 18-H), 7.28 - 7.25 (m, 2H; 10-H and 16-H), 2.46 (s, 6H; 19-H and 20-H) ppm; **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ = 158.2 (C-2), 149.9 (C-6), 149.4 (C-4), 139.5 (C-13), 138.8 (C-9), 138.6 (C-15), 138.4 (C-7), 138.3 (C-8), 129.7 (C-16), 129.0 (C-11), 128.6 (C-17), 127.8 (C-14), 127.7 (C-10), 124.2 (C-12), 124.1 (C-18), 120.2 (C-5), 118.8 (C-3), 21.52 (C-19), 21.50 (C-20) ppm; **HRMS (EI-QTOF,** $[M + H]^+$): calculated for $C_{19}H_{18}N$: 260.1434; found: 260.1422.

2,6-di-*m*-tolylpyridine (**5bc**)[37c] (Scheme 5): **White solid**, $\mathbf{R_f}$ = 0.65 (SiO_2, Hexane/EtOAc = 9:1); **m.p** = 65 - 67 °C (Lit[37a] 64 - 65 °C); **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 7.96 (s, 2H; 4-H), 7.91 (d, *J* = 7.7 Hz, 2H; 12-H), 7.79 (t, *J* = 7.8 Hz, 1H; 3-H), 7.66 (d, *J* = 7.8 Hz, 2H; 12-H), 7.38 (t, *J* = 7.6 Hz, 2H; 12-H), 7.24 (d, *J* = 7.6 Hz, 2H; 12-H), 2.47 (s, 6H; 13-H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 156.8 (C-2), 139.51 (C-4), 139.44 (C-9), 139.39 (C-7), 129.3 (C-8), 128.6 (C-11), 126.9 (C-10), 123.4 (C-12), 118.7 (C-3 and C-5), 19.9 (C-13) ppm; **HRMS (EI-QTOF,** $[M + H]^+$): calculated for $C_{19}H_{18}N$: 260.1434; found: 260.1437.

Preparation of 2,4-di-*o*-tolylpyridine (3ad) and 2,6-di-*o*-tolylpyridine (5bd)

According to the general procedure, reactions between phenylalanine **1a** (2.0 mmol, 330 mg) 2′-methylacetophenone **2d** (2.6 mmol, 348.4 mg) were performed using $FeCl_3$ (0.4 mmol, 64.8 mg), $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol, 398 mg), DavePhos (0.2 mmol, 78.6 mg), $Pd(OAc)_2$ (0.2 mmol, 44.8 mg) to obtain the desired 2,4-di-*o*-tolylpyridine **3ad** in 61% (158 mg) and 3,5-diphenylpyridine **4** in 16% (37 mg) yield as yellow oil and black solid respectively (Scheme 4).

According to the general procedure, reactions between glycine **1b** (2.0 mmol, 150 mg) 2′-methylacetophenone **2d** (2.6 mmol, 348.4 mg) were performed using $FeCl_3$ (0.4 mmol, 64.8 mg), $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol, 398 mg), DavePhos (0.2 mmol, 78.6 mg), $Pd(OAc)_2$ (0.2 mmol, 44.8 mg) to obtain the desired 2,4-di-*o*-tolylpyridine **3ad** in 68% (176 mg) and 2,6-di-*o*-tolylpyridine **5bd** in 20% (52 mg) yield as yellow oil and white solid respectively (Scheme 5).

2,4-di-*o*-tolylpyridine (**3ad**)[20d] (Scheme 4, 5): **Yellow oil**, $\mathbf{R_f}$ = 0.35 (SiO_2, Hexane/EtOAc = 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.72 (d, *J* = 5.0 Hz, 1H; 6-H), 7.43 (d, *J* = 7.6 Hz, 1H; 5-H), 7.37 (s, 1H; 3-H), 7.31 - 7.26 (m, 7H; 9-H, 10-H, 12-H, 15-H, 16-H, 17-H and 18-H), 7.22 (t, *J* = 6.6 Hz, 1H; 11-H), 2.41 (s, 3H; 19-H), 2.33 (s, 3H; 20-H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 159.9 (C-2), 150.0 (C-6), 149.2 (C-4), 140.5 (C-7), 139.3 (C-13), 135.8 (C-8), 135.2 (C-14), 130.85 (C-9), 130.79 (C-15), 129.8 (C-16), 129.4 (C-10), 128.5 (C-11), 128.4 (C-17), 126.2 (C-18), 126.0 (C-12), 124.7 (C-3), 122.3 (C-5), 20.50 (C-19), 20.49 (C-20) ppm; **HRMS (EI-QTOF,** $[M + H]^+$): calculated for $C_{19}H_{18}N$: 260.1434; found: 260.1440.

2,6-di-*o*-tolylpyridine (**5bd**)[37g] (Scheme 5): **White solid**, $\mathbf{R_f}$ = 0.60 (SiO_2, Hexane/EtOAc = 9:1); **m.p** = 65 - 67 °C (Lit[37g] 66 - 68 °C); **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 7.81 (td, *J* = 7.7 Hz, 1H; 4-H), 7.45 (d, *J* = 6.2 Hz, 2H; 12-H), 7.36 (dd, *J* = 7.7 Hz, 2H; 3-H and 5-H), 7.29 - 7.26 (m, 6H; 9-H, 10-H, and 11-H), 2.43 (s, 6H; 13-H) ppm; **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ = 159.5 (C-2), 140.6 (C-4), 136.2 (C-8), 135.8 (C-7), 130.6(C-9), 129.8 (C-10), 128.1 (C-11), 125.8 (C-12), 121.9 (C-3 and C-5), 20.5 (C-13) ppm; **HRMS (EI-QTOF,** $[M + H]^+$): calculated for $C_{19}H_{18}N$: 260.1434; found: 260.1426.

Preparation of 2,4-bis(4-methoxyphenyl)pyridine (3ae) and 2,6-bis(4-methoxyphenyl)pyridine (5be)

According to the general procedure, reactions between phenylalanine **1a** (2.0 mmol, 330 mg) 4′-methoxyacetophenone **2e** (2.6 mmol, 390 mg) were performed using $FeCl_3$ (0.4 mmol, 64.8 mg), $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol, 398 mg), DavePhos (0.2 mmol, 78.6 mg), $Pd(OAc)_2$ (0.2 mmol, 44.8 mg) to obtain the desired 2,4-bis(4-methoxyphenyl)pyridine **3ae** in 67% (195 mg) and 3,5-diphenylpyridine **4** in 15% (35 mg) yield as light yellow solid and black solid respectively (Scheme 4).

According to the general procedure, reactions between glycine **1b** (2.0 mmol, 150 mg) 4′-methoxyacetophenone **2e** (2.6 mmol, 390 mg) were performed using $FeCl_3$ (0.4 mmol, 64.8 mg), $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol, 398 mg),

DavePhos (0.2 mmol, 78.6 mg), $Pd(OAc)_2$ (0.2 mmol, 44.8 mg) to obtain the desired 2,4-bis(4-methoxyphenyl)pyridine **3ae** in 64% (186 mg) and 2,6-bis(4-methoxyphenyl)pyridine **5be** in 19% (55 mg) yield as light yellow solid and white solid respectively (Scheme 5).

2,4-bis(4-methoxyphenyl)pyridine (**3ae**)[20d] (Scheme 4, 5): **Light yellow solid**, $\mathbf{R_f}$ = 0.40 (SiO_2, Hexane/EtOAc = 9:1); **m.p** = 152 - 154 °C (Lit[20d] 153 - 156 °C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.66 (d, ^3J = 5.5 Hz, 1H; 6-H), 7.99 (d, ^3J = 7.9 Hz, 2H; 8-H), 7.83 (s, 1H; 3-H), 7.65 (d, ^3J = 8.0 Hz, 2H; 12-H), 7.36 (d, ^3J = 7.8 Hz, 1H; 5-H), 7.04 - 7.01 (m, 4H; 9-H and 13-H), 3.88 (s, 6H; 15-H and 16-H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 160.5 (C-10), 157.7 (C-14), 150.0 (C-2), 148.7 (C-4 and C-6), 132.2 (C-7), 131.0 (C-11), 128.3 (C-12), 128.2 (C-8), 119.1 (C-5), 117.5 (C-3), 114.5 (C-9), 114.1 (C-13), 55.43 (C-15), 55.39 (C-16) ppm; **HRMS (EI-QTOF,** $[M + H]^+$): calculated for $C_{19}H_{18}NO_2$: 292.1332; found: 292.1312.

2,6-bis(4-methoxyphenyl)pyridine (**5be**)[37g] (Scheme 5): **Pale white solid**, $\mathbf{R_f}$ = 0.65 (SiO_2, Hexane/EtOAc = 9:1); **m.p** = 184 - 187 °C (Lit[37g] 185 - 188 °C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.09 (d, ^3J = 8.4 Hz, 4H; 8-H), 7.73 (t, ^3J = 7.8 Hz, 1H; 4-H), 7.56 (d, ^3J = 7.8 Hz, 2H; 3-H and 5-H), 7.01 (d, ^3J = 8.2 Hz, 4H; 9-H), 3.87 (s, 6H; 11-H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 160.4 (C-10), 156.3 (C-2 and C-6), 137.3 (C-4), 132.3 (C-7), 128.2 (C-8), 117.1 (C-3 and C-5), 114.0 (C-9), 55.3 (C-11) ppm; **HRMS (EI-QTOF,** $[M + H]^+$): calculated for $C_{19}H_{18}NO_2$: 292.1332; found: 292.1329.

Preparation of 2,4-bis(3-methoxyphenyl)pyridine (3af)

According to the general procedure, reactions between phenylalanine **1a** (2.0 mmol, 330 mg) 3′-methoxyacetophenone **2f** (2.6 mmol, 390 mg) were performed using $FeCl_3$ (0.4 mmol, 64.8 mg), $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol, 398 mg), DavePhos (0.2 mmol, 78.6 mg), $Pd(OAc)_2$ (0.2 mmol, 44.8 mg) to obtain the desired 2,4-bis(3-methoxyphenyl)pyridine **3af** in 62% (181 mg) and 3,5-diphenylpyridine **4** in 16% (37 mg) yield as yellow solid and black solid respectively (Scheme 4).

2,4-bis(3-methoxyphenyl)pyridine (**3af**) (Scheme 4): Y**ellow solid**, $\mathbf{R_f}$ = 0.35 (SiO_2, Hexane/EtOAc = 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.78 (d, ^3J = 5.8 Hz, 1H; 6-H), 7.93 (s, 1H; 3-H), 7.65 - 7.61 (m, 2H; 8-H and 12-H), 7.49 - 7.42 (m, 3H; 11-H, 17-H and 18-H), 7.30 (d, ^3J = 7.9 Hz, 1H; 5-H), 7.23 (s, 1H. 14-H), 7.04 - 7.02 (overlapped, 2H; 10-H and 16-H), 3.94 (s, 3H; 15-H), 3.93 (s, 3H; 16-H)ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 160.2 (C-9), 160.1 (C-15), 157.9 (C-2), 149.9 (C-4), 149.3 (C-6), 140.9 (C-13), 139.9 (C-7), 130.2 (C-11), 129.8 (C-17), 120.5 (C-5), 119.54 (C-12), 119.51 (C-18), 119.2 (C-3), 115.3 (C-16), 114.3 (C-8), 112.9 (C-14), 112.2 (C-10), 55.44 (C-19 and C-20) ppm; **HRMS (EI-QTOF,** $[M + H]^+$): calculated for $C_{19}H_{18}NO_2$: 292.1332; found: 292.1312.

Preparation of 2,4-bis(2-methoxyphenyl)pyridine (3ag) and 2,6-bis(2-methoxyphenyl)pyridine (5bf)

According to the general procedure, reactions between phenylalanine **1a** (2.0 mmol, 330 mg) 2′-methoxyacetophenone **2g** (2.6 mmol, 390 mg) were performed using $FeCl_3$ (0.4 mmol, 64.8 mg), $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol, 398 mg), DavePhos (0.2 mmol, 78.6 mg), $Pd(OAc)_2$ (0.2 mmol, 44.8 mg) to obtain the desired 2,4-bis(2-methoxyphenyl)pyridine **3ag** in 59% (172 mg) and 3,5-diphenylpyridine **4** in 12% (28 mg) yield as yellow oil and black solid respectively (Scheme 4).

According to the general procedure, reactions between glycine **1b** (2.0 mmol, 150 mg) 2′-methoxyacetophenone **2g** (2.6 mmol, 390 mg) were performed using $FeCl_3$ (0.4 mmol, 64.8 mg), $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol, 398 mg), DavePhos (0.2 mmol, 78.6 mg), $Pd(OAc)_2$ (0.2 mmol, 44.8 mg) to obtain the desired 2,4-bis(2-methoxyphenyl)pyridine **3ag** in 59% (172 mg) and 2,6-bis(2-methoxyphenyl)pyridine **5bf** in 16% (47 mg) yield as yellow oil and white solid respectively (Scheme 5).

2,4-bis(2-methoxyphenyl)pyridine (**3ag**)[20d] (Scheme 4, 5): **Yellow oil**, $\mathbf{R_f}$ = 0.30 (SiO_2, Hexane/EtOAc = 9:1); **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 8.71 (d, J = 5.1 Hz, 1H; 6-H), 7.95 (s, 1H; 3-H), 7.78 (dd, J = 7.6 Hz, 1H; 5-H), 7.42 - 7.36 (m, 4H; 10-H, 12-H, 16-H and 18-H), 7.10 - 7.06 (m, 2H; 9-H and 15-H), 7.01 (t, J = 7.7 Hz, 2H; 11-H and17-H), 3.86 (s, 3H; 19-H), 3.85 (s, 3H; 20-H) ppm; **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ = 157.0 (C-8), 156.6 (C-14), 156.0 (C-2), 148.94 (C-6), 148.93 (C-4), 145.9 (C-13), 131.3 (C-12), 130.6 (C-16), 129.8 (C-8), 129.7 (C-10), 129.6 (C-7), 128.3 (C-17), 125.6 (C-11), 122.5 (C-3), 121.0 (C-15), 120.98 (C-5), 111.4 (C-9), 55.7 (C-19), 55.6 (C-20) ppm; **HRMS (EI-QTOF,** $[M + H]^+$): calculated for $C_{19}H_{18}NO_2$: 292.1332; found: 292.1331

2,6-bis(2-methoxyphenyl)pyridine (**5bf**)[37g] (Scheme 5): **White solid**, $\mathbf{R_f}$ = 0.65 (SiO_2, Hexane/EtOAc = 9:1); **m.p** = 121 - 123 °C (Lit[37g] 122 - 124 °C); **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 7.94 (dd, *J* = 7.5 Hz, 2H; 12-H), 7.77 (d, *J* = 7.7 Hz, 2H; 3-H and 5-H), 7.72 (dd, *J* = 8.6 Hz, 1H; 4-H), 7.36 (td, *J* = 7.9 Hz, 2H; 10-H), 7.09 (t, *J* = 7.5 Hz, 2H; 11-H), 7.01 (dd, *J* = 8.3 Hz, 2H; 9-H), 3.88 (s, 6H; 13-H) ppm; **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ = 157.1 (C-8), 155.4 (C-2 and C-6), 135.1 (C-4), 131.5 (C-12), 129.62 (C-10), 129.58 (C-7), 123.0 (C-11), 121.0 (C-3 and C-5), 111.4 (C-9), 55.6 (C-13) ppm; **HRMS (EI-QTOF,** [M + H]$^+$): calculated for $C_{19}H_{18}NO_2$: 292.1332; found: 292.1316.

Preparation of 2,4-bis(4-ethylphenyl)pyridine (3ah) and 2,6-bis(4-ethylphenyl)pyridine (5bg)

According to the general procedure, reactions between phenylalanine **1a** (2.0 mmol, 330 mg) 4′-ethylacetophenone **2h** (2.6 mmol, 384.8 mg) were performed using $FeCl_3$ (0.4 mmol, 64.8 mg), $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol, 398 mg), DavePhos (0.2 mmol, 78.6 mg), $Pd(OAc)_2$ (0.2 mmol, 44.8 mg) to obtain the desired 2,4-bis(4-ethylphenyl)pyridine **3ah** in 61% (175 mg) and 3,5-diphenylpyridine **4** in 18% (42 mg) yield as yellow solid and black solid respectively (Scheme 4).

According to the general procedure, reactions between glycine **1b** (2.0 mmol, 150 mg) 4′-ethylacetophenone **2h** (2.6 mmol, 384.8 mg) were performed using $FeCl_3$ (0.4 mmol, 64.8 mg), $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol, 398 mg), DavePhos (0.2 mmol, 78.6 mg), $Pd(OAc)_2$ (0.2 mmol, 44.8 mg) to obtain the desired 2,4-bis(4-ethylphenyl)pyridine **3ah** in 63% (181 mg) and 2,6-bis(4-ethylphenyl)pyridine **5bg** in 19% (55 mg) yield as yellow solid and pale yellow solid respectively (Scheme 5).

2,4-bis(4-ethylphenyl)pyridine (**3ah**) (Scheme 4, 5): **Yellow solid**, $\mathbf{R_f}$ = 0.35 (SiO_2, Hexane/EtOAc = 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.71 (d, ^3J = 6.0 Hz, 1H; 6-H), 7.98 (d, ^3J = 7.6 Hz, 2H; 8-H), 7.91 (s, 1H; 3-H), 7.63 (d, ^3J = 8.2 Hz, 2H; 12-H), 7.42 (dd, ^3J = 5.2 Hz, 1H; 5-H), 7.36 - 7.33 (m, 4H; 9-H and 13-H), 2.73 (q, 4H; 15-H and 17-H), 1.30 (t, 6H; 16-H and 18-H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 158.1 (C-2), 150.0 (C-4), 149.1 (C-6), 145.4 (C-14), 145.3 (C-10), 137.0 (C-11), 135.9 (C-7), 128.7 (C-9), 128.3 (C-13), 127.3 (C-12), 127.0 (C-8), 119.8 (C-5), 118.3 (C-3), 28.71 (C-15), 28.66 (C-17), 15.58 (C-16 and C-18) ppm; **HRMS (EI-QTOF,** [M + H]$^+$): calculated for $C_{21}H_{22}N$: 288.1752; found: 288.1750.

2,6-bis(4-ethylphenyl)pyridine (**5bg**) (Scheme 5): **Pale yellow solid**, $\mathbf{R_f}$ = 0.60 (SiO_2, Hexane/EtOAc = 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.09 (d, ^3J = 8.0 Hz, 4H; 8-H), 7.78 (t, ^3J = 8.0 Hz, 1H; 4-H), 7.65 (d, ^3J = 8.0 Hz, 2H; 3-H and 5-H), 7.34 (d, ^3J = 8.0 Hz, 4H; 9-H), 2.74 (q, ^3J = 8.0 Hz, 4H; 11-H), 1.31 (t, ^3J = 7.0 Hz, 6H; 12-H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 158.6 (C-2 and C-6), 145.2 (C-10), 137.3 (C-4), 137.1 (C-7), 128.2 (C-9), 127.0 (C-8), 118.1 (C-3 and C-5), 28.7 (C-11), 15.7 (C-12) ppm; **HRMS (EI-QTOF,** [M + H]$^+$): calculated for $C_{21}H_{22}N$: 288.1752; found: 288.1750.

Preparation of 2,4-bis(4-ethoxyphenyl)pyridine (3ai) and 2,6-bis(4-ethoxyphenyl)pyridine (5bh)

According to the general procedure, reactions between phenylalanine **1a** (2.0 mmol, 330 mg) 4′-ethoxyacetophenone **2i** (2.6 mmol, 426.4 mg) were performed using $FeCl_3$ (0.4 mmol, 64.8 mg), $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol, 398 mg), DavePhos (0.2 mmol, 78.6 mg), $Pd(OAc)_2$ (0.2 mmol, 44.8 mg) to obtain the desired 2,4-bis(4-ethoxyphenyl)pyridine **3ai** in 65% (207 mg) and 3,5-diphenylpyridine **4** in 14% (32 mg) yield as white solid and black solid respectively (Scheme 4).

According to the general procedure, reactions between glycine **1b** (2.0 mmol, 150 mg) 4′-ethoxyacetophenone **2i** (2.6 mmol, 426.4 mg) were performed using $FeCl_3$ (0.4 mmol, 64.8 mg), $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol, 398 mg), DavePhos (0.2 mmol, 78.6 mg), $Pd(OAc)_2$ (0.2 mmol, 44.8 mg) to obtain the desired 2,4-bis(4-ethoxyphenyl)pyridine **3ai** in 60% (191 mg) and 2,6-bis(4-ethoxyphenyl)pyridine **5bh** in 22% (70 mg) yield as white solid and pale white solid respectively (Scheme 5).

2,4-bis(4-ethoxyphenyl)pyridine (**3ai**)[20d] (Scheme 4, 5): **White solid**, $\mathbf{R_f}$ = 0.35 (SiO_2, Hexane/EtOAc = 9:1); **m.p** = 156 - 157 °C (Lit[20d] 155 - 158 °C); **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 8.64 (d, ^3J = 5.1 Hz, 1H; 6-H), 7.98 (d, ^3J = 7.6 Hz, 2H; 8-H), 7.83 (s, 1H; 3-H), 7.63 (d, ^3J = 8.7 Hz, 2H; 12-H), 7.35 (dd, ^3J = 5.2 Hz, 1H; 5-H), 7.02 – 6.99 (m, 4H; 9-H and 13-H), 4.10 (q, 4H; 15-H and 17-H), 1.45 (t, 6H; 16-H and 18-H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 159.8 (C-10), 157.7 (C-14), 149.8 (C-2 and C-6), 148.7 (C-4), 132.0 (C-7), 130.7 (C-11), 128.3 (C-12), 128.2 (C-8), 119.0 (C-5), 117.4 (C-3), 115.0 (C-9), 114.6 (C-13), 63.63 (C-15), 63.54 (C-17), 14.86 (C-16), 14.83 (C-18) ppm; **HRMS (EI-QTOF,** [M + H]$^+$): calculated for $C_{21}H_{22}NO_2$: 320.1645; found: 320.1642.

2,6-bis(4-ethoxyphenyl)pyridine (**5bh**)[37f] (Scheme 5): **Pale white solid**, $\mathbf{R_f}$ = 0.55 (SiO_2, Hexane/EtOAc = 9:1); **m.p** = 85 - 88 °C (Lit[37f] 85 - 87 °C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.09 (d, ^3J = 8.0 Hz, 4H; 8-H), 7.73 (t, ^3J = 7.8 Hz, 1H; 4-H), 7.57 (d, ^3J = 8.0 Hz, 2H; 3-H and 5-H), 7.00 (d, ^3J = 8.0 Hz, 4H; 9-H), 4.11 (q, ^3J = 8.0 Hz, 4H; 11-H), 1.45 (t, ^3J = 7.0 Hz, 6H; 12-H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 159.8 (C-10), 156.3 (C-2 and C-6), 137.3 (C-4), 132.1 (C-7), 128.2 (C-8), 117.1 (C-3 and C-5), 114.5 (C-9), 63.5 (C-11), 14.9 (C-12) ppm; **HRMS (EI-QTOF,** $[M + H]^+$): calculated for $C_{21}H_{22}NO_2$: 320.1645; found: 320.1636.

Preparation of 2,4-Bis(4-fluorophenyl)pyridine (3aj) and 2,6-Bis(4-fluorophenyl)pyridine (5bi)

According to the general procedure, reactions between phenylalanine **1a** (2.0 mmol, 330 mg) 4′-fluoroacetophenone **2j** (2.6 mmol, 359 mg) were performed using $FeCl_3$ (0.4 mmol, 64.8 mg), $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol, 398 mg), DavePhos (0.2 mmol, 78.6 mg), $Pd(OAc)_2$ (0.2 mmol, 44.8 mg) to obtain the desired 2,4-bis(4-fluorophenyl)pyridine **3aj** in 58% (155 mg) and 3,5-diphenylpyridine **4** in 17% (40 mg) yield as yellow solid and black solid respectively (Scheme 4).

According to the general procedure, reactions between glycine **1b** (2.0 mmol, 150 mg) 4′-fluoroacetophenone **2j** (2.6 mmol, 359 mg) were performed using $FeCl_3$ (0.4 mmol, 64.8 mg), $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol, 398 mg), DavePhos (0.2 mmol, 78.6 mg), $Pd(OAc)_2$ (0.2 mmol, 44.8 mg) to obtain the desired 2,4-bis(4-fluorophenyl)pyridine **3aj** in 60% (160 mg) and 2,6-bis(4-fluorophenyl)pyridine **5bi** in 21% (56 mg) yield as yellow solid and pale yellow solid respectively (Scheme 5).

2,4-Bis(4-fluorophenyl)pyridine (**3aj**)[20d] (Scheme 4, 5): **Yellow solid**, $\mathbf{R_f}$ = 0.40 (SiO_2, Hexane/EtOAc = 9:1); **m.p** = 77 - 79 °C (Lit[20d] 78 - 81 °C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.71 (d, *J* = 4.7 Hz, 1H; 2-H), 8.03 (m, 2H; 8-H), 7.83 (s, 1H; 3-H), 7.66 (m, 2H; 12-H), 7.39 (d, *J* = 5.1 Hz, 1H; 5-H), 7.22 - 7.16 (m, 4H; 9-H and 13-H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 164.8 (d, *J* = 246.2 Hz, C-14), 162.3 (d, *J* = 247.9 Hz, C-10), 157.2 (C-2), 150.2 (C-4), 148.4 (C-6), 135.6 (d, *J* = 3.1 Hz, C-11), 134.6 (d, *J* = 3.4 Hz, C-7), 128.9 (d, *J* = 1.3 Hz, C-8), 128.8 (d, *J* = 1.3 Hz. C-12), 120.0 (C-5), 118.2 (C-3), 116.2 (d, *J* = 21.4 Hz, C-9), 115.7 (d, *J* = 21.5 Hz, C-13) ppm; **HRMS (EI-QTOF,** $[M + H]^+$): calculated for $C_{17}H_{12}F_2N$: 268.0937; found: 268.0940.

2,6-Bis(4-fluorophenyl)pyridine (**5bi**)[37g] (Scheme 5): **Pale yellow solid**, $\mathbf{R_f}$ = 0.60 (SiO_2, Hexane/EtOAc = 9:1); **m.p** = 92 - 94 °C (Lit[37g] 93 - 95 °C); **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 8.12 (m, 4H; 8-H), 7.81 (t, *J* = 7.8 Hz, 1H; 4-H), 7.64 (d, *J* = 7.7 Hz, 2H; 3-H and 5-H), 7.17 (m, 4H; 9-H) ppm; **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ = 163.1 (d, *J* =247.0 Hz, C-10), 155.8 (C-2 and C-6), 137.6 (C-4), 135.48 (d, *J* =3.0 Hz, C-7), 128.73 (d, *J* =8.3 Hz, C-8), 118.2 (C-5), 115.6 (d, *J* =21.7 Hz, C-9) ppm; **HRMS (EI-QTOF,** $[M + H]^+$): calculated for $C_{17}H_{12}F_2N$: 268.0937; found: 268.0940.

Preparation of 2,4-Bis(4-chlorophenyl)pyridine (3ak) and 2,6-Bis(4-chlorophenyl)pyridine (5bj)

According to the general procedure, reactions between phenylalanine **1a** (2.0 mmol, 330 mg) 4′-chloroacetophenone **2k** (2.6 mmol, 403 mg) were performed using $FeCl_3$ (0.4 mmol, 64.8 mg), $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol, 398 mg), DavePhos (0.2 mmol, 78.6 mg), $Pd(OAc)_2$ (0.2 mmol, 44.8 mg) to obtain the desired 2,4-bis(4-chlorophenyl)pyridine **3ak** in 69% (207 mg) and 3,5-diphenylpyridine **4** in 12% (28 mg) yield as yellow solid and black solid respectively (Scheme 4).

According to the general procedure, reactions between glycine **1b** (2.0 mmol, 150 mg) 4′-chloroacetophenone **2k** (2.6 mmol, 403 mg) were performed using $FeCl_3$ (0.4 mmol, 64.8 mg), $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol, 398 mg), DavePhos (0.2 mmol, 78.6 mg), $Pd(OAc)_2$ (0.2 mmol, 44.8 mg) to obtain the desired 2,4-bis(4-chlorophenyl)pyridine **3ak** in 61% (183 mg) and 2,6-bis(4-chlorophenyl)pyridine **5bj** in 17% (51 mg) yield as yellow solid and white solid respectively (Scheme 5).

2,4-Bis(4-chlorophenyl)pyridine (**3ak**)[20d] (Scheme 4, 5): **Yellow solid**, $\mathbf{R_f}$ = 0.50 (SiO_2, Hexane/EtOAc = 9:1); **m.p** = 98 - 100 °C (Lit[20d] 99 - 102 °C); **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 8.73 (d, *J* = 4.7 Hz, 1H; 2-H), 7.99 (dd, *J* = 8.6 Hz, 2H; 8-H), 7.85 (s, 1H; 3-H), 7.62 (dd, *J* = 8.5 Hz, 2H; 12-H), 7.50 - 7.41 (m, 4H; 9-H and 13-H), 7.42 (d, *J* = 5.1 Hz, 1H; 5-H) ppm; **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ = 157.0 (C-2), 150.3 (C-6), 148.2 (C-4), 137.7 (C-11), 136.8 (C-7), 135.4 (C-13), 135.3 (C-10), 129.4 (C-9), 129.0 (C-13), 128.33 (C-8), 128.27 (C-12), 120.2 (C-5), 118.2 (C-3) ppm; **HRMS (EI-QTOF,** $[M + H]^+$): calculated for $C_{17}H_{12}Cl_2N$: 300.0341; found: 300.0312.

2,6-Bis(4-chlorophenyl)pyridine (**5bj**)[31b] (Scheme 5): **White solid**, R_f = 0.60 (SiO_2, Hexane/EtOAc = 9:1); **m.p** = 158 - 161 °C (Lit[31b] 157 - 160 °C); **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 8.07 (d, *J* = 8.2 Hz, 4H; 8-H), 7.83 (t, *J* = 7.8 Hz, 1H; 4-H), 7.67 (d, *J* = 7.7 Hz, 2H; 3-H and 5-H), 7.46 (d, *J* = 8.2 Hz, 4H; 9-H) ppm; **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ = 155.7 (C-2 and C-6), 137.7 (C-4), 137.6 (C-7), 135.2 (C-10), 128.9 (C-8), 128.2 (C-9), 118.6 (C-3 and C-5) ppm; **HRMS (EI-QTOF,** $[M + H]^+$): calculated for $C_{17}H_{12}Cl_2N$: 300.0341; found: 300.0345.

Preparation of 2,4-Bis(3-chlorophenyl)pyridine (3al) and 2,6-Bis(3-chlorophenyl)pyridine (5bk)

According to the general procedure, reactions between phenylalanine **1a** (2.0 mmol, 330 mg) 3′-chloroacetophenone **2l** (2.6 mmol, 403 mg) were performed using $FeCl_3$ (0.4 mmol, 64.8 mg), $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol, 398 mg), DavePhos (0.2 mmol, 78.6 mg), $Pd(OAc)_2$ (0.2 mmol, 44.8 mg) to obtain the desired 2,4-bis(3-chlorophenyl)pyridine **3al** in 60% (180 mg) and 3,5-diphenylpyridine **4** in 17% (39 mg) yield as brown solid and black solid respectively (Scheme 4).

According to the general procedure, reactions between glycine **1b** (2.0 mmol, 150 mg) 3′-chloroacetophenone **2l** (2.6 mmol, 403 mg) were performed using $FeCl_3$ (0.4 mmol, 64.8 mg), $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol, 398 mg), DavePhos (0.2 mmol, 78.6 mg), $Pd(OAc)_2$ (0.2 mmol, 44.8 mg) to obtain the desired 2,4-bis(3-chlorophenyl)pyridine **3al** in 55% (165 mg) and 2,6-bis(3-chlorophenyl)pyridine **5bk** in 15% (45 mg) yield as brown solid and yellow oil respectively (Scheme 5).

2,4-Bis(3-chlorophenyl)pyridine (**3al**)[26d] (Scheme 4, 5): **Brown solid**, R_f = 0.60 (SiO_2, Hexane/EtOAc = 9:1); **m.p** = 95 - 96 °C (Lit[26d] 95 - 97 °C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.75 (d, *J* = 5.1 Hz, 1H; 6-H), 8.06 (s, 1H; 8-H), 7.95 (d, *J* = 7.6 Hz, 1H; 12-H), 7.82 (s, 1H; 3-H), 7.66 (s, 1H; 14-H), 7.51 (d, *J* = 2.6 Hz, 1H; 5-H), 7.45 - 7.41 (m, 5H; 10-H, 11-H, 16-H, 17-H and 18-H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 157.0 (C-2), 150.4 (C-6), 148.2 (C-4), 141.0 (C-13), 140.1 (C-7), 135.3 (C-9), 135.0 (C-15), 130.5 (C-8), 130.1 (C-11), 129.3 (C-16), 129.28 (C-17), 127.33 (C-10), 127.33 (C-14), 125.4 (C-12), 125.2 (C-18), 120.8 (C-5), 118.8 (C-3) ppm; **HRMS (EI-QTOF,** $[M + H]^+$): calculated for $C_{17}H_{12}Cl_2N$: 300.0341; found: 300.0340.

2,6-Bis(3-chlorophenyl)pyridine (**5bk**)[37g] (Scheme 5): **Yellow oil**, R_f = 0.70 (SiO_2, Hexane/EtOAc = 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.12 (s, 2H; 8-H), 7.98 (t, *J* = 7.5 Hz, 2H; 11-H), 7.81 (t, *J* = 8.0 Hz, 1H; 4-H), 7.66 (d, *J* = 7.6 Hz, 2H; 3-H and 5-H), 7.42 - 7.36 (m, 4H; 10-H and 12-H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 155.6 (C-2 and C-6), 141.0 (C-4), 137.9 (C-7), 134.9 (C-9), 130.0 (C-8), 129.2 (C-11), 127.2 (C-10), 125.1 (C-12), 119.3 (C-3 and C-5) ppm; **HRMS (EI-QTOF,** $[M + H]^+$): calculated for $C_{17}H_{12}Cl_2N$: 300.0341; found: 300.0331.

Preparation of 2,4-bis(4-bromophenyl)pyridine (3am)

According to the general procedure, reactions between phenylalanine **1a** (2.0 mmol, 330 mg) and 4′-bromoacetophenone **2m** (2.6 mmol, 517 mg) were performed using $FeCl_3$ (0.4 mmol, 64.8 mg), $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol, 398 mg), DavePhos (0.2 mmol, 78.6 mg), $Pd(OAc)_2$ (0.2 mmol, 44.8 mg) to obtain the desired 2,4-bis(4-bromophenyl)pyridine **3am** in 60% (233 mg) and 3,5-diphenylpyridine **4** in 12% (28 mg) yield as yellow solid and black solid respectively (Scheme 4).

2,4-bis(4-bromophenyl)pyridine (**3am**)[26d] (Scheme 4): **Yellow solid**, R_f = 0.45 (SiO_2, Hexane/EtOAc = 9:1); **m.p** = 137 - 139 °C (Lit[26d] 136 - 138 °C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.71 (d, *J* = 4.6 Hz, 1H; 6-H), 7.97 (d, *J* = 8.0 Hz, 2H; 8-H), 7.84 (s, 1H; 3-H), 7.61 (d, *J* = 7.6 Hz, 2H; 12-H), 7.47 (d, *J* = 8.2 Hz, 4H; 9-H and 13-H), 7.40 (d, *J* = 7.8 Hz, 1H, 5-H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 156.7 (C-2), 150.3 (C-6), 148.2 (C-4), 137.7 (C-11), 136.8 (C-7), 132.8, 132.0, 128.4, 128.3, 127.1, 124.9, 120.3 (C-5), 118.2 (C-3) ppm; **HRMS (EI-QTOF,** $[M + H]^+$): calculated for $C_{17}H_{12}Br_2N$: 387.9336; found: 387.9301.

Preparation of 2,4-bis(3-bromophenyl)pyridine (3an)

According to the general procedure, reactions between phenylalanine **1a** (2.0 mmol, 330 mg) and 3′-bromoacetophenone **2n** (2.6 mmol, 517 mg) were performed using $FeCl_3$ (0.4 mmol, 64.8 mg), $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol, 398 mg), DavePhos (0.2 mmol, 78.6 mg), $Pd(OAc)_2$ (0.2 mmol, 44.8 mg) to obtain the desired 2,4-bis(3-bromophenyl)pyridine **3an** in 56% (218 mg) and 3,5-diphenylpyridine **4** in 16% (37 mg) yield as reddish brown solid and black solid respectively (Scheme 4).

2,4-bis(3-bromophenyl)pyridine (**3an**)[26d] (Scheme 4): **Reddish brown solid**, $\mathbf{R_f}$ = 0.40 (SiO_2, Hexane/EtOAc = 9:1); **m.p** = 87 - 89 °C (Lit[26d] 89 - 91 °C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.74 (d, *J* = 4.7 Hz, 1H; 6-H), 8.05 (s, 1H; 8-H), 7.90 (d, *J* = 7.6 Hz, 1H; 12-H), 7.84 (s, 1H; 3-H), 7.65 (s, 1H; 14-H), 7.57 – 7.51 (m, 2H; 10-H and 16-H), 7.44 - 7.40 (m, 4H, 5-H, 11-H, 17-H and 18-H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 158.3 (C-2), 150.3 (C-6), 147.9 (C-4), 140.4 (C-7), 139.2 (C-13), 130.4 (C-14), 129.2 (C-17), 129.1 (C-11), 129.0 (C-8), 128.8 (C-16), 127.3 (C-10), 127.1 (C-12), 127.06 (C-18), 125.8 (C-9), 125.3 (C-15), 120.1 (C-5), 118.7 (C-3) ppm; **HRMS (EI-QTOF,** $[M + H]^+$): calculated for $C_{17}H_{12}Br_2N$: 387.9336; found: 387.9322.

Preparation of 2,4-bis(2-bromophenyl)pyridine (3ao) and 2,6-Bis(2-bromophenyl)pyridine (5bl)

According to the general procedure, reactions between phenylalanine **1a** (2.0 mmol, 330 mg) 2′-bromoacetophenone **2o** (2.6 mmol, 517 mg) were performed using $FeCl_3$ (0.4 mmol, 64.8 mg), $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol, 398 mg), DavePhos (0.2 mmol, 78.6 mg), $Pd(OAc)_2$ (0.2 mmol, 44.8 mg) to obtain the desired 2,4-bis(2-bromophenyl)pyridine **3ao** in 57% (222 mg) and 3,5-diphenylpyridine **4** in 18% (42 mg) yield as brown solid and black solid respectively (Scheme 4).

According to the general procedure, reactions between glycine **1b** (2.0 mmol, 150 mg) 2′-bromoacetophenone **2o** (2.6 mmol, 517 mg) were performed using $FeCl_3$ (0.4 mmol, 64.8 mg), $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol, 398 mg), DavePhos (0.2 mmol, 78.6 mg), $Pd(OAc)_2$ (0.2 mmol, 44.8 mg) to obtain the desired 2,4-bis(2-bromophenyl)pyridine **3ao** in 57% (222 mg) and 2,6-bis(2-bromophenyl)pyridine **5bl** in 16% (62 mg) yield as brown solid and yellow solid respectively (Scheme 5).

2,4-bis(2-bromophenyl)pyridine (**3ao**)[26e] (Scheme 4): **Brown solid**, $\mathbf{R_f}$ = 0.40 (SiO_2, Hexane/EtOAc = 9:1); **m.p** = 125 - 128 °C (Lit[26e] 124 - 126 °C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.77 (d, *J* = 4.7 Hz, 1H; 6-H), 8.08 (d, *J* = 7.6 Hz, 2H; 9-H and 15-H), 7.96 (s, 1H; 3-H), 7.74 – 7.72 (d, *J* = 8.0 Hz, 2H; 12-H and 18-H), 7.45 – 7.46 (m, 5H; 5-H, 10-H, 11-H, 16-H and 17-H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 158.1 (C-2), 150.1 (C-6), 149.3 (C-4), 139.5 (C-7), 138.6 (C-13), 130.9 (C-15), 130.3 (C-9), 130.0 (C-16), 129.7 (C-18), 129.15 (C-10), 129.1 (C-12), 129.07 (C-17), 128.8 (C-11), 127.1 (C-14), 127.0 (C-8), 120.3 (C-5), 118.8 (C-3) ppm; **HRMS (EI-QTOF,** $[M + H]^+$): calculated for $C_{17}H_{12}Br_2N$: 387.9336; found: 387.9326.

2,6-Bis(2-bromophenyl)pyridine (**5bl**) (Scheme 5): **Yellow solid**, $\mathbf{R_f}$ = 0.65 (SiO_2, Hexane/EtOAc = 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 7.8 Hz, 2H; 12-H), 7.82 (t, *J* = 7.5 Hz, 1H; 4-H), 7.62 (d, *J* = 7.2 Hz, 2H; 3-H and 5-H), 7.57 - 7.44 (m, 6H; 9-H, 10-H and 11-H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 156.8 (C-2 and C-6), 139.5 (C-13), 137.5 (C-4), 129.0 (C-9), 128.8 (C-12), 128.7 (C-10, 127.1 (C-11), 123.2 (C-8), 118.7 (C-3 and C-5) ppm; **HRMS (EI-QTOF,** $[M + H]^+$): calculated for $C_{17}H_{12}Br_2N$: 387.9336; found: 387.9337.

Preparation of 2,4-bis(4-(trifluoromethyl)phenyl)pyridine (3ap) and 2,6-bis(4-(trifluoromethyl)phenyl)pyridine (5bm)

According to the general procedure, reactions between phenylalanine **1a** (2.0 mmol, 330 mg) 4′-(trifluoromethyl)acetophenone **2p** (2.6 mmol, 489 mg) were performed using $FeCl_3$ (0.4 mmol, 64.8 mg), $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol, 398 mg), DavePhos (0.2 mmol, 78.6 mg), $Pd(OAc)_2$ (0.2 mmol, 44.8 mg) to obtain the desired 2,4-bis(4-(trifluoromethyl)phenyl)pyridine **3ap** in 59% (217 mg) and 3,5-diphenylpyridine **4** in 14% (32 mg) yield as yellow solid and black solid respectively (Scheme 4).

According to the general procedure, reactions between glycine **1b** (2.0 mmol, 150 mg) 4′-(trifluoromethyl)acetophenone **2p** (2.6 mmol, 489 mg) were performed using $FeCl_3$ (0.4 mmol, 64.8 mg), $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol, 398 mg), DavePhos (0.2 mmol, 78.6 mg), $Pd(OAc)_2$ (0.2 mmol, 44.8 mg) to obtain the desired 2,4-bis(4-(trifluoromethyl)phenyl)pyridine **3ap** in 52% (191 mg) and 2,6-bis(4-(trifluoromethyl)phenyl)pyridine **5bm** in 20% (73 mg) yield as yellow solid and pale yellow solid respectively (Scheme 5).

2,4-bis(4-(trifluoromethyl)phenyl)pyridine (**3ap**)[37i] (Scheme 4, 5): **Yellow solid**, $\mathbf{R_f}$ = 0.55 (SiO_2, Hexane/EtOAc = 9:1); **m.p** = 68 - 69 °C (Lit[37i] 69 - 70 °C); **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 8.81 (d, ^3J = 5.1 Hz, 1H; 6-H), 8.17 (d, ^3J = 8.0 Hz, 2H; 8-H), 7.95 (s, 1H; 3-H), 7.83 - 7.72 (m, 6H; 9-H, 13-H and 14-H), 7.51 (d, ^3J = 7.8 Hz, 1H; 5-H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 156.8 (C-2), 150.6 (C-6), 148.2 (C-4), 142.4 (C-12), 141.8 (C-7), 131.2

(q, *J* = 16.8 Hz, C-10 and C-15), 127.6 (C-13), 127.3 (C-8), 126.2 (q, *J* = 3.7 Hz, C-9), 125.8 (q, *J* = 3.7 Hz, C-14), 124.0 (q, *J* = 251.7 Hz, C-11 and C-16), 121.1 (C-5), 119.1 (C-3) ppm; **HRMS (EI-QTOF,** $[M + H]^+$): calculated for $C_{19}H_{12}F_6N$: 368.0873; found: 368.0861.

2,6-bis(4-(trifluoromethyl)phenyl)pyridine (**5bm**)[37g] (Scheme 5): **Pale yellow solid**, R_f = 0.65 (SiO_2, Hexane/EtOAc = 9:1); **m.p** = 144 - 146 °C (Lit[37g] 143 - 145 °C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.25 (d, ^3J = 8.0 Hz, 4H; 8-H), 7.91 (t, ^3J = 7.9 Hz, 1H; 4-H), 7.80 - 7.76 (m, 6H; 3-H, 5-H and 9-H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 155.65 (C-2 and C-6), 142.4 (C-4), 138.0 (C-7), 131.0 (q, *J* = 28.0 Hz, C-10), 127.3 (C-8), 125.7 (q, *J* = 240.6 Hz, C-11), 122.83 (C-9), 119.8 (C-3 and C-5) ppm; **HRMS (EI-QTOF,** $[M + H]^+$): calculated for $C_{19}H_{12}F_6N$: 368.0873; found: 368.0871.

Preparation of 2,4-bis(3-(trifluoromethyl)phenyl)pyridine (3aq)

According to the general procedure, reactions between phenylalanine **1a** (2.0 mmol, 330 mg) 3′-(trifluoromethyl)acetophenone **2q** (2.6 mmol, 489 mg) were performed using $FeCl_3$ (0.4 mmol, 64.8 mg), $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol, 398 mg), DavePhos (0.2 mmol, 78.6 mg), $Pd(OAc)_2$ (0.2 mmol, 44.8 mg) to obtain the desired 2,4-bis(3-(trifluoromethyl)phenyl)pyridine **3aq** in 60% (220 mg) and 3,5-diphenylpyridine **4** in 16% (37 mg) yield as yellow solid and black solid respectively (Scheme 4).

2,4-bis(3-(trifluoromethyl)phenyl)pyridine (**3aq**) (Scheme 4): **Yellow solid**, R_f = 0.40 (SiO_2, Hexane/EtOAc = 9:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.81 (d, ^3J = 5.1 Hz, 1H; 6-H), 8.33 (s, 1H, 8-H), 8.23 (d, ^3J = 8.0 Hz, 1H; 12-H), 7.94 (s, 2H; 3-H and 14-H), 7.87 (d, ^3J = 8.0 Hz, 1H; 10-H), 7.76 - 7.63 (m, 4H; 11-H, 16-H, 17-H and 18-H), 7.51 (d, ^3J = 7.8 Hz, 1H; 5-H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 156.8 (C-2), 150.5 (C-6), 148.3 (C-4), 139.8 (C-13), 141.8 (C-7), 131.5 (q, *J* = 16.8 Hz, C-10 and C-15), 130.5, 130.3, 130.05, 129.8, 129.4, 125.8 124.0 (q, *J* = 251.7 Hz, C-19, C-20), 120.0 (C-5), 118.9 (C-3) ppm; **HRMS (EI-QTOF,** $[M + H]^+$): calculated for $C_{19}H_{12}F_6N$: 368.0873; found: 368.0861.

Preparation of 2,4-bis(benzo[*d*][1,3]dioxol-5-yl)pyridine (3ar) and 2,6-bis(benzo[*d*][1,3]dioxol-5-yl)pyridine (5bn)

According to the general procedure, reactions between phenylalanine **1a** (2.0 mmol, 330 mg) 3,4-methylenedioxyacetophenone **2r** (2.6 mmol, 426 mg) were performed using $FeCl_3$ (0.4 mmol, 64.8 mg), $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol, 398 mg), DavePhos (0.2 mmol, 78.6 mg), $Pd(OAc)_2$ (0.2 mmol, 44.8 mg) to obtain the desired 2,4-bis(benzo[d][1,3]dioxol-5-yl)pyridine **3ar** in 66% (211 mg) and 3,5-diphenylpyridine **4** in 10% (23 mg) yield as yellow solid and black solid respectively (Scheme 4).

According to the general procedure, reactions between glycine **1b** (2.0 mmol, 150 mg) 3,4-methylenedioxyacetophenone **2r** (2.6 mmol, 426 mg) were performed using $FeCl_3$ (0.4 mmol, 64.8 mg), $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol, 398 mg), DavePhos (0.2 mmol, 78.6 mg), $Pd(OAc)_2$ (0.2 mmol, 44.8 mg) to obtain the desired 2,4-bis(benzo[d][1,3]dioxol-5-yl)pyridine **3ar** in 66% (211 mg) and 2,6-bis(benzo[d][1,3]dioxol-5-yl)pyridine **5bn** in 19% (61 mg) yield as yellow solid and pale yellow solid respectively (Scheme 5).

2,4-bis(benzo[*d*][1,3]dioxol-5-yl)pyridine (**3ar**)[20d] (Scheme 4, 5): **Yellow solid**, R_f = 0.45 (SiO_2, Hexane/EtOAc = 9:1); **m.p** = 116 - 118 °C (Lit[20d] 115 - 117 °C); **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 8.63 (d, ^3J = 5.1 Hz, 1H; 6-H), 7.75 (s, 1H; 8-H), 7.56 (s, 1H; 15-H), 7.54 (dd, ^3J = 8.8 Hz, 1H; 13-H), 7.32 (dd, ^3J = 5.2 Hz, 1H; 5-H), 7.18 (dd, ^3J = 8.2 Hz, 1H; 20-H), 7.15 (s, 1H; 3-H), 6.94 – 6.90 (m, 2H; 12-H and 19-H), 6.04 (s, 2H; 10-H), 6.03 (s, 2H; 17-H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 157.5 (C-2), 149.8 (C-4), 149.0 (C-6), 148.57 (C-9), 148.55 (C-16 and C-18), 148.3 (C-11), 133.8 (C-14), 132.6 (C-7), 121.1 (C-13), 121.05 (C-20), 119.5 (C-5), 117.9 (C-3), 108.9 (C-8), 108.5 (C-12), 107.5 (C-19), 107.3 (C-15), 101.5 (C-10), 101.4 (C-17) ppm; **HRMS (EI-QTOF,** $[M + H]^+$): calculated for $C_{19}H_{14}NO_4$: 320.0917; found: 320.0907.

2,6-bis(benzo[*d*][1,3]dioxol-5-yl)pyridine (**5bn**)[37h] (Scheme 5): **Pale yellow solid**, R_f = 0.60 (SiO_2, Hexane/EtOAc = 9:1); **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 7.72 (t, ^3J = 7.8 Hz, 1H; 8-H), 7.69 (s, 2H; 8-H), 7.61 (dd, ^3J = 8.1 Hz, 2H; 13-H), 7.54 (d, ^3J = 7.8 Hz, 2H; 3-H and 5-H), 6.91 (d, ^3J = 8.1 Hz, 2H; 12-H), 6.03 (s, 4H; 10-H) ppm; **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ = 156.0 (C-2 and C-6), 148.4 (C-9), 148.2 (C-11), 137.4 (C-4), 134.0 (C-7), 120.9 (C-13), 117.5 (C-3 and C-5), 108.3 (C-8), 107.4 (C-12), 101.2 (C-10) ppm; **HRMS (EI-QTOF,** $[M + H]^+$): calculated for $C_{19}H_{14}NO_4$: 320.0917; found: 320.0910.

Preparation of 3,5-dimethyl-2,4-diphenylpyridine (3as) and 3,5-dimethyl-2,6-diphenylpyridine (5bo)

According to the general procedure, reactions between phenylalanine **1a** (2.0 mmol, 330 mg) and propiophenone **2s** (2.6 mmol, 348.4 mg) were performed using $FeCl_3$ (0.4 mmol, 64.8 mg), $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol, 398 mg), DavePhos (0.2 mmol, 78.6 mg), $Pd(OAc)_2$ (0.2 mmol, 44.8 mg) to obtain the desired 3,5-dimethyl-2,4-diphenylpyridine **3as** in 64% (166 mg) and 3,5-diphenylpyridine **4** in 13% (30 mg) yield as white solid and black solid respectively (Scheme 4).

According to the general procedure, reactions between glycine **1b** (2.0 mmol, 150 mg) and propiophenone **2s** (2.6 mmol, 348.4 mg) were performed using $FeCl_3$ (0.4 mmol, 64.8 mg), $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol, 398 mg), DavePhos (0.2 mmol, 78.6 mg), $Pd(OAc)_2$ (0.2 mmol, 44.8 mg) to obtain the desired 3,5-dimethyl-2,4-diphenylpyridine **3as** in 61% (158 mg) and 3,5-dimethyl-2,6-diphenylpyridine **5bo** in 17% (44 mg) yield as white solid and pale yellow solid respectively (Scheme 5).

3,5-dimethyl-2,4-diphenylpyridine (**3as**)[37b] (Scheme 4, 5): **White solid**, $\mathbf{R_f}$ = 0.50 (SiO_2, Hexane/EtOAc = 9:1); **m.p** = 82 - 84 °C (Lit[37b] 84 - 85 °C); **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 8.52 (s, 1H; 6-H), 7.55 (d, ^3J = 7.9 Hz, 2H; 8-H), 7.51 – 7.46 (m, 4H), 7.42 (d, ^3J = 4.8 Hz, 2H; 13-H), 7.15 (d, ^3J = 4.8 Hz, 2H), 2.08 (s, 3H; 15-H), 2.03 (s, 3H; 16-H) ppm; **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ = 156.3 (C-2), 149.3 (C-4), 146.2 (C-6), 143.1 (C-11), 137.3 (C-7), 130.0, 129.7, 129.2, 129.01, 128.4, 128.3, 128.0, 127.6, 17.9 (C-15), 17.6 (C-16) ppm; **HRMS (EI-QTOF,** [M + H]$^+$): calculated for $C_{19}H_{18}N$: 260.1439; found: 260.1428.

3,5-dimethyl-2,6-diphenylpyridine (**5bo**)[20d] (Scheme 5): **Pale yellow solid**, $\mathbf{R_f}$ = 0.75 (SiO_2, Hexane/EtOAc = 9:1); **m.p** = 128 - 129 °C (Lit[20d] 127 - 130 °C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 7.60 (d, ^3J = 7.8 Hz, 4H; 8-H), 7.48 (s, 1H; 4-H), 7.44 (t, ^3J = 8.2 Hz, 4H; 9-H), 7.36 (t, ^3J = 8.4 Hz, 2H; 10-H), 2.39 (s, 6H; 11-H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 155.8 (C-2), 141.1 (C-4), 140.7 (C-7), 129.2 (C-9), 129.1 (C-3 and C-5), 128.0 (C-8), 127.7 (C-10), 19.6 (C-11) ppm; **HRMS (EI-QTOF,** [M + H]$^+$): calculated for $C_{19}H_{18}N$: 260.1439; found: 260.1431.

Experimental procedures and analytical data of synthesized 2,4-diarylpyridines (6aa-ab) and 2,6-diarylpyridines (7aa-ab)

Preparation of 2-(4-Chlorophenyl)-4-phenylpyridine (6aa) and 2-(4-Chlorophenyl)-6-phenylpyridine (7aa)

According to the general procedure, reactions between glycine **1b** (2.0 mmol, 150 mg), acetophenone **2a** (1.3 mmol, 312 mg) and 4′-chloroacetophenone **2k** (1.3 mmol, 403 mg) were performed using $FeCl_3$ (0.4 mmol, 64.8 mg), $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol, 398 mg), DavePhos (0.2 mmol, 78.6 mg), $Pd(OAc)_2$ (0.2 mmol, 44.8 mg) to obtain the desired 2-(4-Chlorophenyl)-4-phenylpyridine **6aa** in 55% (146 mg) and 2-(4-Chlorophenyl)-6-phenylpyridine **7aa** in 21% (56 mg) yield as off white solid and pale white solid respectively (Scheme 7).

2-(4-Chlorophenyl)-4-phenylpyridine (**6aa**)[30] (Scheme 7): **Off white solid**, $\mathbf{R_f}$ = 0.40 (SiO_2, Hexane/EtOAc = 9:1); **m.p** = 56 - 58 °C (Lit[30] 57 - 58 °C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.71 (d, ^3J = 4.8 Hz, 1H; 6-H), 7.98 (d, ^3J = 8.2 Hz, 2H; 8-H), 7.89 (s, 1H; 3-H), 7.68 (d, ^3J = 7.6 Hz, 2H; 12-H), 7.53 – 7.44 (m, 6H; 5-H, 9-H, 13-H and 14-H) ppm; **^{13}C{^{1}H} NMR** (100 MHz, $CDCl_3$) δ = 156.9 (C-2), 150.3 (C-6), 149.6 (C-4), 138.4 (C-11), 138.0 (C-7), 135.3 (C-10), 129.3 (C-9), 129.0 (C-13), 128.9 (C-14), 128.4 (C-8), 127.2 (C-12), 120.6 (C-5), 118.6 (C-3) ppm; **HRMS (EI-QTOF,** [M + H]$^+$): calculated for $C_{17}H_{13}ClN$: 266.0737; found: 266.0732.

2-(4-Chlorophenyl)-6-phenylpyridine (**7aa**)[37e] (Scheme 7): **Pale white solid**, $\mathbf{R_f}$ = 0.65 (SiO_2, Hexane/EtOAc = 9:1); **m.p** = 105 - 107 °C (Lit[37e] 104 - 105 °C); **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 8.16 (d, ^3J = 8.0 Hz, 2H; 8-H), 8.10 (d, ^3J = 7.6 Hz, 2H; 12-H), 7.82 (t, ^3J = 7.5 Hz, 1H; 4-H), 7.70 (d, ^3J = 7.8 Hz, 2H; 3-H and 5-H), 7.50 (t, ^3J = 8.2 Hz, 4H; 9-H and 13-H), 7.43 (t, ^3J = 7.9 Hz, 1H; 14-H) ppm; **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ = 156.8 (C-2), 155.6 (C-6), 139.5 (C-4), 137.6 (C-11), 137.4 (C-7), 135.0 (C-10), 129.1 (C-9), 128.8 (C-12), 128.6 (C-8), 128.2 (C-14), 127.0 (C-13), 118.9 (C-5), 118.6 (C-3) ppm; **HRMS (EI-QTOF,** [M + H]$^+$): calculated for $C_{17}H_{13}ClN$: 266.0737; found: 266.0715.

Preparation of 2-(4-nitrophenyl)-4-(4-(trifluoromethyl)phenyl)pyridine (6ab) and 2-(4-nitrophenyl)-6-(4-(trifluoromethyl)phenyl)pyridine (7ab)

According to the general procedure, reactions between glycine **1b** (2.0 mmol, 150 mg), 4′-(trifluoromethyl)acetophenone **2p** (1.3 mmol, 244 mg) and 4′-nitroacetophenone **2t** (1.3 mmol, 215 mg) were performed using $FeCl_3$ (0.4 mmol, 64.8 mg), $Cu(OAc)_2{\cdot}H_2O$ (2.0 mmol, 398 mg), DavePhos (0.2 mmol, 78.6 mg),

$Pd(OAc)_2$ (0.2 mmol, 44.8 mg) to obtain the desired 2-(4-nitrophenyl)-4-(4-(trifluoromethyl)phenyl)pyridine **6ab** in 50% (172 mg) and 2-(4-nitrophenyl)-6-(4-(trifluoromethyl)phenyl)pyridine **7ab** in 24% (83 mg) yield as orange solid and yellow solid respectively (Scheme 7).

2-(4-nitrophenyl)-4-(4-(trifluoromethyl)phenyl)pyridine (**6ab**) (Scheme 7): **Orange solid**, $\mathbf{R_f}$ = 0.40 (SiO_2, Hexane/EtOAc = 9:1); **m.p** = 55 - 58 °C; **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 8.82 (d, ^3J = 5.1 Hz, 1H; 6-H), 8.34 (dd, ^3J = 7.8 Hz, 2H; 8-H), 8.17 (d, ^3J = 8.1 Hz, 2H; 9-H), 7.95 (s, 1H; 3-H), 7.80 – 7.77 (m, 4H; 12-H and 13-H), 7.51 (dd, ^3J = 5.1 Hz, 1H; 5-H) ppm; **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ = 156.8 (C-2), 150.5 (C-6), 148.5 (C-4), 148.3 (C-10), 144.9 (C-11), 138.1 (C-7), 131.5 (q, J = 208.0 Hz, C-14), 127.5 (C-8), 127.3 (C-9), 126.2 (q, J = 28.0 Hz, C-13), 125.8 (q, J = 256.0 Hz, C-15), 124.0 (C-9), 120.1 (C-5), 119.1 (C-3) ppm; **HRMS (EI-QTOF,** $[M + H]^+$): calculated for $C_{18}H_{12}F_3N_2O_2$: 345.0851; found: 345.0841.

2-(4-nitrophenyl)-6-(4-(trifluoromethyl)phenyl)pyridine (**7ab**) (Scheme 7): **Yellow solid**, $\mathbf{R_f}$ = 0.55 (SiO_2, Hexane/EtOAc = 9:1); **^{1}H NMR** (600 MHz, $CDCl_3$): δ = 8.35 (dd, ^3J = 8.8 Hz, 4H; 8-H), 8.25 (dd, ^3J = 8.1 Hz, 2H; 8-H), 7.95 (t, ^3J = 7.9 Hz, 1H; 4-H), 7.84 (dd, ^3J = 7.8 Hz, 2H; 3-H and 5-H), 7.78 (d, ^3J = 8.2 Hz, 2H; 9-H) ppm; **^{13}C{^{1}H} NMR** (150 MHz, $CDCl_3$) δ = 155.9 (C-2), 154.6 (C-6), 144.9 (C-10), 142.1 (C-4), 138.1 (C-7 and C-11), 132.4 (q, J = 33.6 Hz, C-14), 127.7 (C-8), 127.6 (q, J = 15.73 Hz, C-13), 127.3 (C-12), 125.7 (q, J = 269.0 Hz, C-15), 124.0 (C-9), 120.3 (C-5), 120.1 (C-3) ppm; **HRMS (EI-QTOF,** $[M + H]^+$): calculated for $C_{18}H_{12}F_3N_2O_2$: 345.0851; found: 345.0846.

ASSOCIATED CONTENT

Additional optimization tables, copies of LC-MS for investigation of the reaction mechanism, copies of ^{1}H NMR and ^{13}C NMR spectra for all synthesized compounds are available free of charge *via* the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest

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