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Decarboxylative Cyclization of Amino Acids towards the Regioselective Synthesis of 2,4-Diarylpyridines *via* Relay Fe(III)/In(III)-Catalysis

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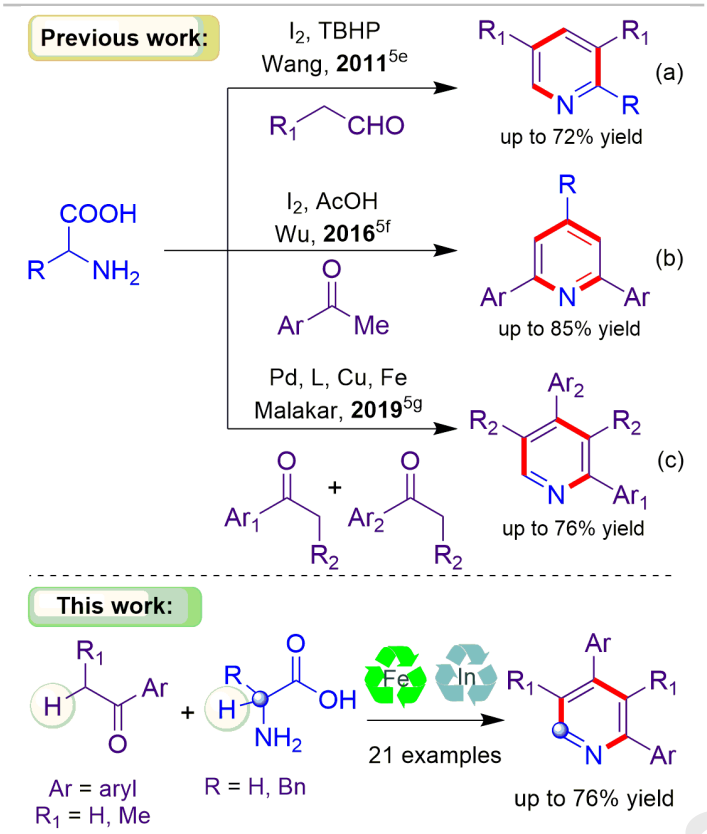
ABSTRACT

A competent relay Fe(III)-/In(III)-catalyzed decarboxylative cyclization of amino acids has been devised towards the exclusive preparation of 2,4-diarylpyridines. The efficacy of the developed conditions drives the reaction towards selective formation of 2,4-diarylpyridines over other pyridine derivatives. The described protocol showed good functional group tolerance with moderate to good yields of products.

Introduction

The metal-catalyzed strategies towards the synthesis of privileged *N*-heterocycles have been the ever charming topic of interest for the synthetic chemists.[1] In the process of preparing these *N*-heterocycles, chemists have come across all possible metal-catalysts using wide range of starting materials. The metal catalysts such as Pd, Cu, Rh and Co have more contributions towards the synthesis of these scaffolds.[2] Few of the d-block metals are not much explored when compare to the above mentioned metals. In this regard, the Fe-catalyzed reactions have gained considerable attention in the past decade.[3] The catalytic pathways possessed by Fe-catalysts are still points of investigations.[3c,e, 4] In a similar manner, the use of amino acids as C-N source is still rarely explored and only few reports are available towards the synthesis of *N*-heterocycles.[5] The combination of these two rarely explored fields towards preparation of novel *N*-heterocycles such as pyridines may attract the attention of synthetic organic chemists. Pyridine scaffolds are well-known for their medicinal and pharmacological activities such as antituberculosis, antihypertensive and antitumor.[6] In addition, pyridines have also found their role as ligands and catalysts in the field of synthetic organic chemistry.[7] Owing to their diverse range of applications in different research fields, chemists have formulated broad spectrum of methodologies for their efficient synthesis. The pyridine scaffolds were obtained by utilizing old traditional protocols[8] as well as metal[9] and metal-free approaches.[10] These *N*-heterocyclic moieties were accessed by employing wide range of C and N sources such as carbonyl compounds,[5e-g, 9h,k-q, 10a, c-f] DMSO,[9m] DMF,[9j-k] oximes[9e,i-j,q, 10e, g] and ammonium salts.[9k,m,p] There are only few handful reports available for the synthesis of pyridines, where amino acids are utilized as C-N source (Scheme 1).[5e-g]



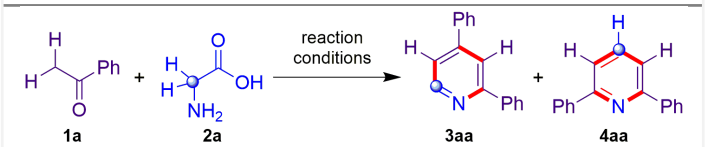
Scheme 1. Approaches towards the synthesis of pyridines using amino acids as C-N source.

Wang and co-workers coined an iodine-catalyzed protocol towards the synthesis of 2,3,5-trisubstituted pyridines (Scheme 1a).[5e] In 2016, Wu and co-workers reported I_2-catalyzed strategy for accessing 2,4,6-trisubstituted pyridines (Scheme 1b).[5f] Recently, our research group was successful in deriving symmetrical and unsymmetrical 2,4-diarylpyridines along with 2,6-diarylpyridines as minor products under Pd-catalyzed reaction conditions (Scheme 1c).[5g] The previously reported methods have proven their utility for the synthesis of symmetrical and unsymmetrical pyridines in moderate to excellent yields. The previous reports on using amino acids as C-N source have also suffered from drawbacks such as usage of strong acid, stoichiometric oxidants and ligands along with the formation of minor products. However, usage of amino acids as C-N source to obtain pyridines is still seldom-explored. Also, the concept of relay catalysis or dual metal catalysis plays an important role in synthesizing valuable *N*-heterocycles.[11] In this perspective, here we have described an efficient method for the synthesis of 2,4-diarylpyridines by adopting aryl ketones and amino acids under Fe(III)-/In(III)-catalyzed reaction conditions.

Having previously worked on identical scaffolds,[5g] we were determined to eliminate the formation of minor products and maximize the formation of 2,4-diarylpyridines. To establish an efficient protocol towards the exclusive synthesis of 2,4-diarylpyridines, we started our experimental studies by taking acetophenone (**1a**) and glycine (**2a**) as model substrates. To begin with, the reactions of acetophenone (**1a**) and glycine (**2a**) were carried out with 50 mol% $NaNO_3$ in DMSO at 120 °C for 24 h. The reaction conditions were found to be inefficient in obtaining either of 2,4-diphenylpyridine (**3aa**) or 2,6-diphenylpyridine (**4aa**) (Table 1, Entry 1). Next, the reactions of **1a** and **2a** were carried out with 10 mol% $Fe(NO_3)_3{\cdot}9H_2O$ in DMSO at 120 °C for 24 h. To our surprise, the reaction conditions gave 2,6-diphenylpyridine (**4aa**) as major product in 68% and 2,4-diphenylpyridine (**3aa**) as minor product in negligible amount (Entry 2). The yield of 2,4-diphenylpyridine (**3aa**) was drastically increased when the reactions of **1a** and **2a** were carried out with 50 mol% $Fe(NO_3)_3{\cdot}9H_2O$ in DMSO at 120 °C for 24 h. The reaction conditions were able to produce 2,4-diphenylpyridine (**3aa**) in 45% yield and 2,6-diphenylpyridine (**4aa**) in 32% yield (Entry 3). Replacing the Fe-catalysts with 50 mol% $Ce(NH_4)_2(NO_3)_6$, the corresponding 2,4-diphenylpyridine (**3aa**) and 2,6-diphenylpyridine (**4aa**) were obtained in 30% and 45% respectively (Entry 4). Similar results were obtained when the reactions of **1a** and **2a** were carried out with 1.0 equiv. of $Fe(NO_3)_3{\cdot}9H_2O$ or $Fe(OAc)_2$ or $FeBr_2$ (Entries 5-7). The product formation was not observed when the reactions of **1a** and **2a** were carried out using 1.0 equiv. of $Cu(NO_3)_3{\cdot}3H_2O$ (Entry 8). The increment in the amount of $Ce(NH_4)_2(NO_3)_6$ does not lead to drastic increase in formation of 2,4-diphenylpyridine (**3aa**) (Entry 9). On taking account of these unsatisfactory results, we inspired to screen the reaction conditions under the influence of an additive. To fulfill this purpose, we have examined the reactions of acetophenone (**1a**) and glycine (**2a**) with 50 mol% $Fe(NO_3)_3{\cdot}9H_2O$ in DMSO at 120 °C for 24 h under the influence of 50 mol% of AgOAc or NaOAc or $Sc(OTf)_3$ or $In(OTf)_3$

(Entries 10-13). Gratifyingly, the reaction conditions delivered **3aa** in higher yield than **4aa**. In particular, under the influence of additives $Sc(OTf)_3$ or $In(OTf)_3$ yields of 2,4-diphenylpyridine (**3aa**) were elevated (Entries 12-13). The exclusive formation of **3aa** (76%) was observed when the reactions of **1a** and **2a** were carried out with 50 mol% $Fe(NO_3)_3{\cdot}9H_2O$ and 50 mol% $In(OTf)_3$ in DMSO at 120 °C for 24 h (Entry 13). Next, we carried out the reactions of **1a** and **2a** using various amounts of $Fe(NO_3)_3{\cdot}9H_2O$ and $In(OTf)_3$; however, none of these conditions were efficient towards the improvement of the yield of 2,4-diphenylpyridine (**3aa**) (Entries 14-16). Next, we have investigated different solvents like DMF, DMA, toluene and dioxane to describe the solvent effect on reaction parameters (Entries 17-20). It was found that reasonable yield was obtained when the reactions were carried out with DMF (Entry 17) and negligible yields were obtained with other solvents (Entries 18-20).

Table 1. Screening of reaction conditions for the synthesis of 2,4-diphenylpyridine (**3aa**).[a]



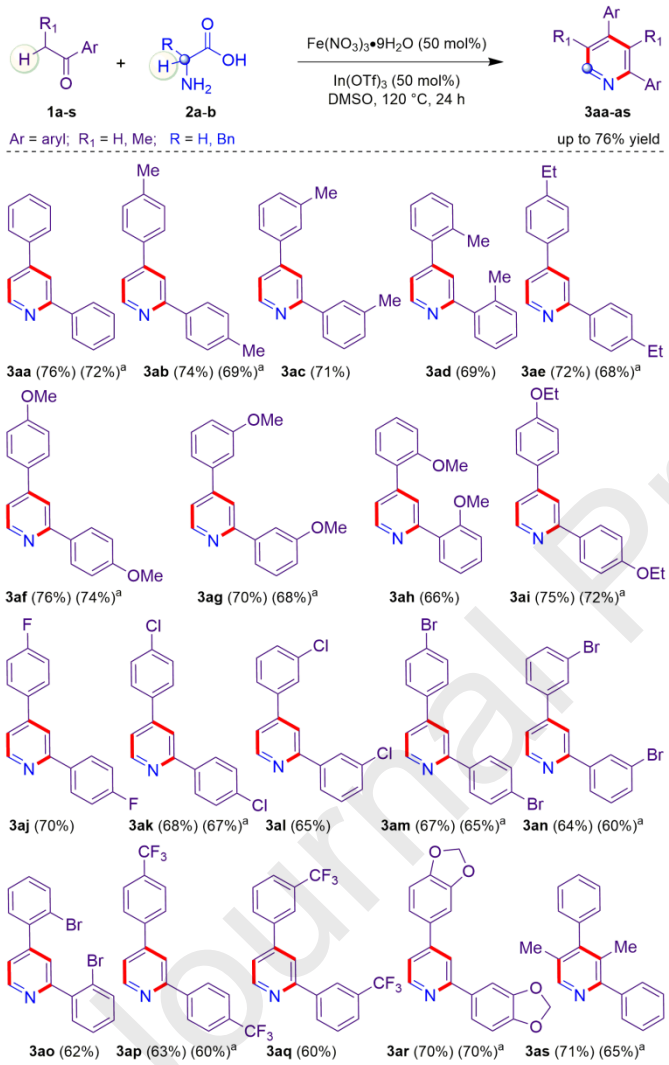
1a **2a** **3aa** **4aa**

Entry	Reaction Conditions (Equiv.)	% Yield 3aa[b]	% Yield 4aa[b]
1	$NaNO_3$ (0.5)	0[c]	0[c]
2	$Fe(NO_3)_3{\cdot}9H_2O$ (0.1)	5	68
3	$Fe(NO_3)_3{\cdot}9H_2O$ (0.5)	45	32
4	$Ce(NH_4)_2(NO_3)_6$ (0.5)	30	45
5	$Fe(NO_3)_3{\cdot}9H_2O$ (1.0)	42	34
6	$Fe(OAc)_2$ (1.0)	39	25
7	$FeBr_2$ (1.0)	21	44
8	$Cu(NO_3)_6{\cdot}3H_2O$ (1.0)	0[c]	0[c]
9	$Ce(NH_4)_2(NO_3)_6$ (1.0)	48	31
10	$Fe(NO_3)_3{\cdot}9H_2O$ (0.5)/AgOAc (0.5)	21	46
11	$Fe(NO_3)_3{\cdot}9H_2O$ (0.5)/NaOAc (0.5)	35	32
12	$Fe(NO_3)_3{\cdot}9H_2O$ (0.5)/$Sc(OTf)_3$ (0.5)	58	11
13	**$Fe(NO_3)_3{\cdot}9H_2O$ (0.5)/$In(OTf)_3$ (0.5)**	**76**	**0**
14	$Fe(NO_3)_3{\cdot}9H_2O$ (0.5)/$In(OTf)_3$ (0.3)	64	9
15	$Fe(NO_3)_3{\cdot}9H_2O$ (0.5)/$In(OTf)_3$ (0.7)	76	0
16	$Fe(NO_3)_3{\cdot}9H_2O$ (0.3)/$In(OTf)_3$ (0.5)	61	6
17[d]	$Fe(NO_3)_3{\cdot}9H_2O$ (0.5)/$In(OTf)_3$ (0.5)	67	0
18[e]	$Fe(NO_3)_3{\cdot}9H_2O$ (0.5)/$In(OTf)_3$ (0.5)	<10	<10
19[f]	$Fe(NO_3)_3{\cdot}9H_2O$ (0.5)/$In(OTf)_3$ (0.5)	0[c]	0[c]
20[g]	$Fe(NO_3)_3{\cdot}9H_2O$ (0.5)/$In(OTf)_3$ (0.5)	0[c]	0[c]
21[h]	$Fe(NO_3)_3{\cdot}9H_2O$ (0.5)/$In(OTf)_3$ (0.5)	49	0
22[i]	$Fe(NO_3)_3{\cdot}9H_2O$ (0.5)/$In(OTf)_3$ (0.5)	63	0
23[j]	$Fe(NO_3)_3{\cdot}9H_2O$ (0.5)/$In(OTf)_3$ (0.5)	71	0

[a] All reactions were performed using 1.0 mmol **1a**, 2.0 mmol **2a** and DMSO (1 mL). [b] Isolated yields. [c] Starting materials were recovered. [d] Reaction was

carried out with 1 mL DMF. [e] Reaction was carried out with 1 mL DMA. [f] Reaction was carried out with 1 mL Toluene. [g] Reaction was carried out with 1 mL Dioxane. [h] Reaction was carried out at 100 °C. [i] Reaction was carried out till 18 h. [j] Reaction was carried out till 30 h.

Finally, to study the influences of temperature and reaction time on product formation, we carried out the reactions of **1a** and **2a** under different temperature and reaction time (Entries 21-23). These reaction conditions have led to unsatisfactory results which encouraged us to consider Entry 13 as our standard reaction condition. After performing an extensive screening of reaction conditions for the synthesis of 2,4-diphenylpyridine (**3aa**), the maximum yield of **3aa** was observed, when the reaction between acetophenone (**1a**) and glycine (**2a**) was carried in presence of 50 mol% $Fe(NO_3)_3{\cdot}9H_2O$, 50 mol% $In(OTf)_3$ in DMSO at 120 °C for 24 h (Table 1, Entry 13).



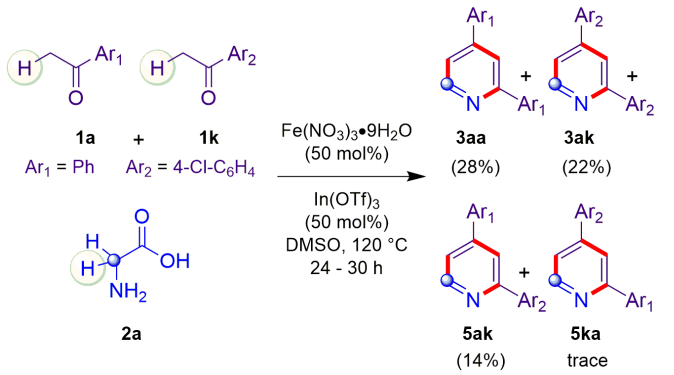
Scheme 2. Synthesis of 2,4-diarylpyridines **3** using amino acids as C-N source.[12]

[a] Reaction yields of 2,4-diarylpyridines **3** using phenylalanine **2b** as C-N source.

After having the best optimized reaction conditions for the synthesis of 2,4-diarylpyridines **3**, we carried out the reactions of a wide range of aryl ketones **1a-s** and amino acids **1a-b** under the standard reaction conditions (Scheme 2). The reactions of aryl ketones **1b-i** bearing electron rich functional groups such as methyl, ethyl, methoxy and ethoxy were tolerated under the developed conditions to deliver the 2,4-diarylpyridines **3ab-ai** in 66-76% yields. Similarly, electron withdrawing functional groups such as fluoro, chloro, bromo and trifluoromethyl on aryl ketone were also well tolerated to give 2,4-diarylpyridines **3aj-aq** in 60-70% yields. Next, the reactivity of 3,4-methylenedioxyacetophenone **1r** and propiophenone **1s** were examined. Both the substrates gave 2,4-diarylpyridines **3ar-as** in 65-75% yields under the

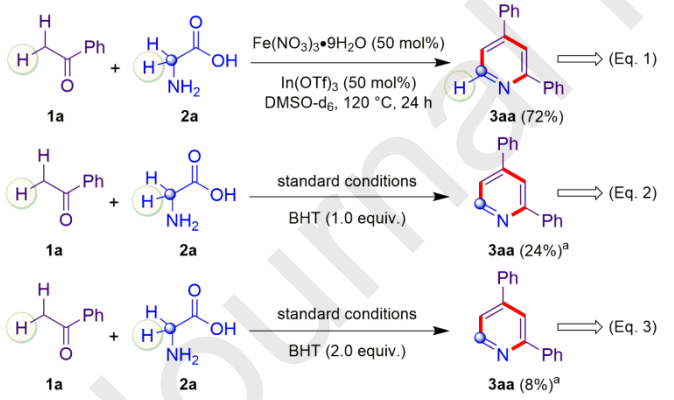
developed reaction conditions. It is evident that the reactions of amino acids glycine (**2a**) and phenylalanine (**2b**) under the standard reaction conditions gave similar yields.

Furthermore, the obtained results enforced us to extend scope of the reaction towards the synthesis of unsymmetrical 2,4-diarylpyridines. In this process, we have carried out the reactions of aryl ketones **1a**, **1k** and glycine (**2a**) under the standard reaction conditions (Scheme 3). To our disappointment, the reaction conditions resulted in higher portions of symmetrical 2,4-diarylpyridines **3aa**, **3ak** and unsymmetrical 2,4-diarylpyridine **5ak** in 14% yield. The other unsymmetrical 2,4-diarylpyridine **5ka** was observed in trace amounts. It was evident from the obtained results that, the present reaction conditions were not efficient enough to deliver unsymmetrical 2,4-diarylpyridines over symmetrical 2,4-diarylpyridines.



Scheme 3. Synthesis of symmetrical 2,4-diarylpyridines **3** and unsymmetrical 2,4-diarylpyridines **5**.

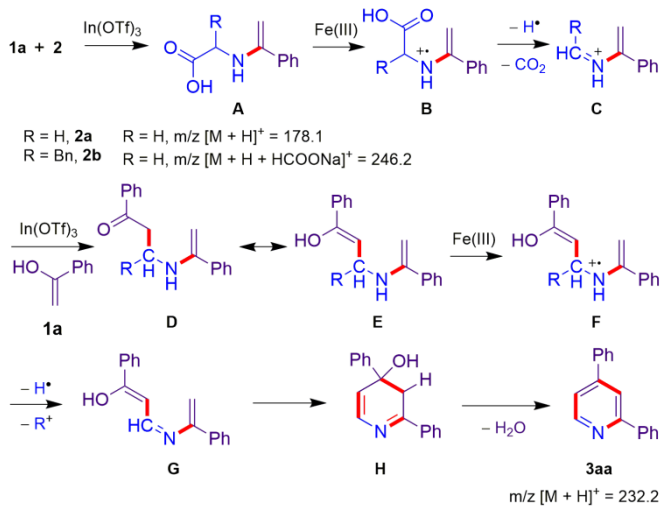
Next, we focused on gaining insight into the reaction mechanism of this chemical transformation towards the formation of 2,4-diarylpyridines. In doing this, we have carried out several control experiments to know the reaction pathway (Scheme 4). It was previously reported that, DMSO can act as C1 source for the synthesis of pyridine moieties.[9m] To clarify this doubt, we carried out the reaction of acetophenone (**1a**) and glycine (**2a**) with 50 mol% $Fe(NO_3)_3 \cdot 9H_2O$, 50 mol% $In(OTf)_3$ in DMSO-d_6 at 120 °C for 24 h.



Scheme 4. Control experiments to establish plausible reaction mechanism.
[a] Complex reaction mixture.

From the obtained results, it was evident that there was no incorporation of deuterium at C-6 position of pyridine (Scheme 4, Eq. 1). Hence, the probability of DMSO acting as C1 source was ruled out. Furthermore, the reactions of **1a** and **2a** were carried out under standard reaction conditions with added radical scavengers (Scheme 4, Eq. 2 and 3). The reaction conditions gave 24% of 2,4-diphenylpyridine (**3aa**) under the influence of 1.0 equiv. of BHT (Butylated hydroxytoluene) (Scheme 4, Eq. 2). The reaction yield of 2,4-diphenylpyridine (**3aa**) was further suppressed on using 2.0 equiv. of BHT (Scheme 4, Eq. 3), which assures the radical pathway of this chemical transformation. In both of the above mentioned experiments performed using different radical scavengers, the reaction conditions delivered inseperable complex mixture of products, due to which the attempt towards isolation of radiclal trapped product was unsuccessful. (Scheme 4, Eq. 2 and 3). Next, to better understand the reaction mechanism, we have carried out the reaction between acetophenone (**1a**) ($[M]^+$ = 120.1) and glycine (**2a**) under standard reaction conditions. The course of the reaction was inspected and evaluated by liquid chromatography-mass spectrometry (LC-MS) after an interval of 6 h, 12 h and 18 h. The mass-

spectroscopic data was able to identify the formation of possible intermediate **A** ([M + H]$^+$ = 178.1, ([M + H + HCOONa]$^+$ = 246.2) through which the desired product 2,4-diphenylpyridine (**3aa**) ([M + H]$^+$ = 232.2) was obtained (details of mass spectra are given in Figure 1, SI).



Scheme 5. Plausible reaction mechanism for the formation of 2,4-dipheylpyridine (**3aa**).

With this minimum information on intermediate formation, we proposed a plausible reaction mechanism on the basis of experimental and literature evidences.[13] According to the proposed reaction mechanism, intermediate **A** is formed by the condensation of **1a** and **2a** in presence of In(OTf)$_3$, which is followed by Fe(III)-catalyzed decarboxylation *via* single electron transfer (SET) phenomenon to deliver imine intermediate **C**. Further, the addition of a second molecule of acetophenone (**1a**) in to the intermediate **C** leading to the formation of intermediate **D**. The tautomeric form of intermediate **D** undergoes single electron transfer reaction followed by proton and hydrogen radical elimination to acquire intermediate **G**. In case of phenylalanine (**2b**) as substrate, the debenzylation and hydrogen radical elimination takes place to leave behind the intermediate **G**. The electrocyclic cyclization of intermediate **G** results in dihydropyridine intermediate **H**, which on dehydration give the desired 2,4-diphenylpyridine (**3aa**). Details for the formation of 2,6-diphenylpyridine (**4aa**) is provided in SI (See SI, Scheme 1).

To summarize, we have demonstrated an efficient relay Fe(III)-/In(III)-catalyzed reaction protocol for accessing 2,4-diarylpyridines from aryl ketones and amino acids as C-N source. The catalytic cycle was benefited by the addition of Lewis-acid to produce 2,4-diarylpyridines exclusively over the formation of 2,6-diarylpyridines. The developed reaction conditions revealed good functional group tolerance towards the formation of 2,4-diarylpyridines in moderate to good yields.

Acknowledgments

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Supplementary Material

A detailed supporting information is available which includes the purity and source of the reagents, additional optimization table, copies of LC-MS for investigation of the reaction mechanism, explanation for the formation of 2,6-diarylpyridine, experimental procedures, ^{1}H NMR and ^{13}C NMR of the final products. Supplementary material for this article can be found in online version, at doi……..

Experimental Section

General Method: All starting materials 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 performed in a 10 mL reaction vial with magnetic stirring. 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. Melting points were determined in open capillary tubes on EZ-Melt automated melting point apparatus and are uncorrected. All the compounds were fully characterized by ^{1}H and ^{13}C NMR and further confirmed by EI-HRMS analysis. All HRMS are recoreded in EI-QTOF method and LC-MS are recorded in APCI method in acetonitrile solvent. ^{1}H (^{13}C) NMR spectra were recorded at 400 (100) MHz on a Brucker spectrometer using $CDCl_3$ as a solvent. The ^{1}H 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 Pyridines 3aa-as, 5ak, 5ka using Aryl Ketones 1a-s and Amino Acids 2a-b: A 10 mL reaction vial was charged with a mixture of aryl ketones **1a-s** (1.0 mmol), amino acids **2a-b** (2.0 mmol), $Fe(NO_3)_3{\cdot}9H_2O$ (0.5 mmol, 202 mg), $In(OTf)_3$ (0.5 mmol, 281 mg), DMSO (1 mL). The reaction vial was then heated at 120 °C for 24 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 layers were washed with brine (3 × 10 mL) and dried over anhydrous Na_2SO_4. The solvent were removed under reduced pressure and the crude products were purified by column chromatography using silica gel (100-200 mesh) with hexane/EtOAc (9:1) as the eluent to obtain the desired products **3aa-as**, **5ak**, **5ka** in high yields.

2,4-Diphenylpyridine (3aa)[5g] (Scheme 2): **Yellow solid**, R_f = 0.50 (SiO_2, Hexane/EtOAc = 9:1); **m.p** = 59-60 °C (Lit[5g] 58-59 °C); **^{1}H NMR** (400 MHz, $CDCl_3$): δ = 8.75 (d, ^{3}J = 6.1 Hz, 1H; 6-H), 8.06 (d, ^{3}J = 8.0 Hz, 2H; 8-H), 7.94 (s, 1H; 3-H), 7.70 (d, ^{3}J = 7.6 Hz, 2H; 12-H), 7.54-7.44 (m, 7H; 5-H, 9-H, 10-H, 13-H and 14-H) ppm; **^{13}C NMR** (100 MHz, $CDCl_3$) δ = 158.24 (C-2), 150.2 (C-6), 149.4 (C-4), 139.64 (C-7), 138.68 (C-11), 129.24 (C-13), 129.15 (C-10), 128.88 (C-9 and C-14), 127.7 (C-8), 127.17 (C-12), 120.37 (C-5), 118.89 (C-3) ppm; **HRMS (EI-QTOF,** $[M + H]^+$): calculated for $C_{17}H_{14}N$: 232.1125; found: 232.1121.

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12. The yields of the reactions were observed in the range of 60-76%. The formation of any byproducts were not identified during these reactions. The probable reason for the moderate yields of the desired products may be associated to the decomposition of starting materials or reaction intermediates under the standard reaction conditions. When the reaction was carried out using 10 mmol of **1a** and 20 mmol of **2a**, the corresponding product **3aa** was isolated in 69% yield.
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Graphical Abstract

Decarboxylative Cyclization of Amino Acids towards the Regioselective Synthesis of 2,4-Diarylpyridines *via* Relay Fe(III)/In(III)-Catalysis

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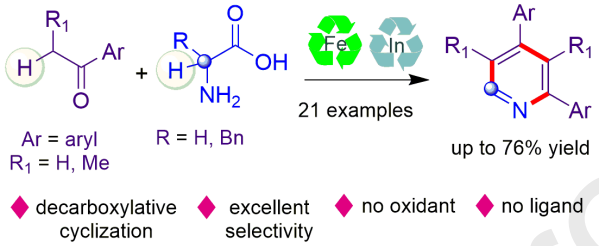

♦ decarboxylative cyclization ♦ excellent selectivity ♦ no oxidant ♦ no ligand

Decarboxylative Cyclization of Amino Acids towards the Regioselective Synthesis of 2,4-Diarylpyridines *via* Relay Fe(III)/In(III)-Catalysis

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- Relay Iron(III)/Indium(III)-catalyzed decarboxylative cyclization of amino acids.
- Regioselective synthesis of 2,4-diarylpyridines.
- Amino acids as C-N source.
- Single electron transfer (SET) phenomenon.
- Broad substrate scope with high yields of the products.

Decarboxylative Cyclization of Amino Acids towards the Regioselective Synthesis of 2,4-Diarylpyridines *via* Relay Fe(III)/In(III)-Catalysis

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Authors have NO conflict of interest to declare on the above cited manuscript.