Green Chemistry Approach to the Synthesis of 2-Amino-4-aryl-6-ferrocenyl-pyridine Derivatives by a One-pot Reaction in Aqueous Medium

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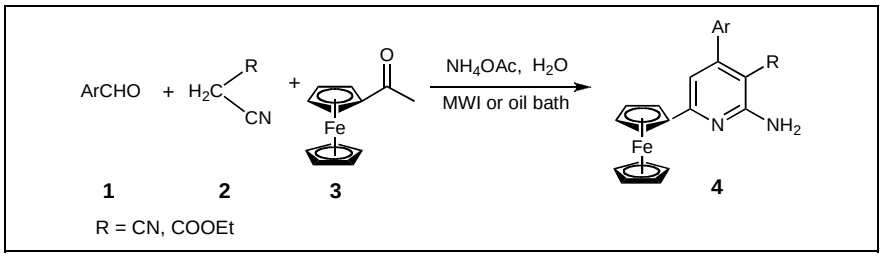

A clean and facile green chemistry method for the synthesis of a series of 2-amino-4-aryl-6-ferrocenylpyridine derivatives was afforded. The products were synthesized *via* the one-pot reaction of aromatic aldehyde, malononitrile or ethyl cyanoacetate, acetylferrocene and ammonium acetate in aqueous medium under microwave irradiation and conventional heating conditions without catalyst. This method had several advantages such as higher yield, lower cost, reduced environmental impact, and convenient procedure.

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INTRODUCTION

Metallocenes are known to exhibit a wide range of biological activities [1]. Among them, ferrocene has attracted special attention since it is neutral, chemically stable, non-toxic and able to cross cell membranes [2]. In fact, it is now well established that the incorporation of ferrocene units in organic molecules introduces significant and new properties in these materials [3]. Recently, ferrocenyl derivatives were reported to display antimalarial [4], antitumor [5], and DNA cleaving [6] activities. For these reasons, the synthesis of new compounds containing ferrocenyl is strongly desired.

Various methods to prepare ferrocene-containing compounds have been reported [7]. Analysis of these literatures reveals that the published approaches involve multi-step procedure, long reaction time, low yield and use of organic solvents. For the stringent and growing environmental regulations, organic chemists are requested to develop environmentally benign synthetic methodologies. One of the most promising approaches is to perform organic reactions in aqueous medium, including using microwave irradiation and conventional heating techniques.

In the most recent decades, the use of aqueous medium for organic reaction [8] is under extensive investigation for synthesis and also to exploit hydrophobic effect [9]. Water has high dielectric constant with a permanent dipole moment, which allows the coupling between the oscillating electric field and the molecular tumbling to occur with high efficient heating. Hence, at elevated temperature it acts as a pseudo-organic solvent and in its use, isolation of products is also facilitated due to decreased solubility of organic material upon post reaction cooling [10]. On the other hand, organic reactions in water without using harmful organic solvents are also one of the current focuses today especially in the environmentally conscious society, because water is abundant, nontoxic and environment-friendly when compared with organic solvents used accordingly [11].

Many important types of organic compounds have been synthesized in aqueous medium, such as triazine [10], acridine [11], quinoline [11,12], pyridine [13], indole [14], pyrazine [15], furan [16] and pyrimidine [17]. However, to the best of our knowledge, the organic synthesis of ferrocene-containing type heterocyclic compounds in aqueous medium has seldom been reported.

Herein, we developed a green multicomponent reaction consisting of an aromatic aldehyde **1**, an acetylferrocenyl **2**, a malononitrile or ethyl cyanoacetate **3** and ammonium acetate in aqueous medium under microwave irradiation or conventional heating to afford the target products 2-amino-4-aryl-6-ferrocenyl-3-subtituted pyridine derivatives **4** in excellent yields (Scheme 1). The procedure was simple and easy to operate.

Scheme 1

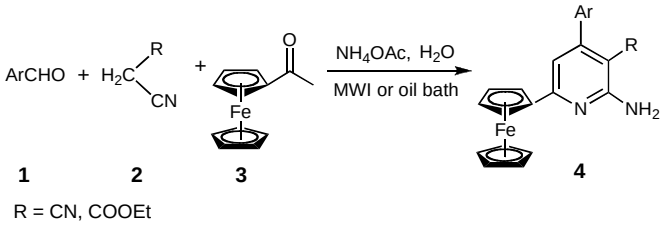


Table 1

Reaction Conditions Optimization of Synthesis of **4a**

Entry	Temp (°C)	Volume of water (mL)	Power (W)	Microwave irradiation		Conventional heating	
				Time (min)	Yield (%)	Time (min)	Yield (%)
1	70	2.0	300	18	61	360	54
2	80	2.0	300	16	67	330	61
3	90	2.0	300	14	72	280	65
4	100	2.0	300	10	75	240	70
5	110	2.0	300	8	88	210	82
6	120	2.0	300	6	94	180	84
7	130	2.0	300	6	93	180	83
8	140	2.0	300	6	92	180	83
9	120	1.0	300	6	82	180	76
10	120	1.5	300	6	89	180	83
11	120	2.0	300	6	94	180	84
12	120	2.5	300	6	91	180	82
13	120	3.0	300	6	85	180	80
14	120	2.0	100	6	85	—	—
15	120	2.0	150	6	94	—	—
16	120	2.0	200	6	95	—	—
17	120	2.0	250	6	94	—	—
18	120	2.0	300	6	94	—	—

Table 2

Physical and Analytical Data of Compounds **4**

Entry	Compound	Ar	R	Mp (℃)	Microwave irradiation		Conventional heating	
					Time (min)	Yield (%)	Time (min)	Yield (%)
1	**4a**	4-ClC_6H_4	CN	275-277	6	95	180	84
2	**4b**	4-BrC_6H_4	CN	>300	7	94	200	82
3	**4c**	2-ClC_6H_4	CN	218-219	8	90	240	78
4	**4d**	4-FC_6H_4	CN	236-238	6	91	180	79
5	**4e**	2,4-$Cl_2C_6H_3$	CN	246-247	6	94	180	82
6	**4f**	3,4-$Cl_2C_6H_3$	CN	213-215	7	95	200	84
7	**4g**	4-$NO_2C_6H_4$	CN	>300	6	89	190	77
8	**4h**	4-OH-3-$NO_2C_6H_3$	CN	208-210	5	88	160	75
9	**4i**	4-$CH_3OC_6H_4$	CN	249-250	8	89	260	77
10	**4j**	4-ClC_6H_4	COOEt	191-192	6	92	240	82
11	**4k**	4-FC_6H_4	COOEt	175-177	5	91	190	79
12	**4l**	4-BrC_6H_4	COOEt	185-187	5	88	180	76
13	**4m**	3, 4,5-$(CH_3O)_3C_6H_2$	COOEt	189-190	8	90	260	79
14	**4n**	4-$CH_3OC_6H_4$	COOEt	165-167	7	94	240	81
15	**4o**	2,4-$Cl_2C_6H_3$	COOEt	195-197	6	95	200	82
16	**4p**	3,4-$Cl_2C_6H_3$	COOEt	204-205	7	95	240	82
17	**4q**	4-$NO_2C_6H_4$	COOEt	277-279	6	89	200	75
18	**4r**	3, 4-$(CH_3O)_2C_6H_3$	COOEt	167-169	8	90	260	77
19	**4s**	4-$CH_3C_6H_4$	COOEt	163-165	7	91	220	78

RESULTS AND DISCUSSION

To optimize the reaction conditions, the effects of different reaction temperature, volume of water and microwave irradiation power were investigated in the synthesis of 2-amino-6-ferrocenyl-4-(4-chlorophenyl)-pyridine-3-carbonitriles **4a**. To optimize the reaction temperature, the reaction of 4-chlorobenzaldehyde **1a** (1 mmol), malononitrile (1 mmol) **2**, acetylferrocenyl **3** (1 mmol) in the presence of ammonium acetate (2 mmol) was carried out using water as solvent at temperatures ranging from 70 to 140 °C in increments of 10 °C each time. The results (entries 1-8 of Table 1) showed that the yield of product **4a** was improved and the reaction time was shortened as the temperature was increased from 70 °C to 120 °C. The yield levelled off when the temperature was further increased to 130 and 140 °C. Therefore, 120 °C was chosen for all further reactions. Furthermore, the water volume was found to be important as well. The same reaction was tested in different volumes of water at 120 °C under microwave irradiation conditions and conventional heating (entries 9-13 of Table 1). When 2.0

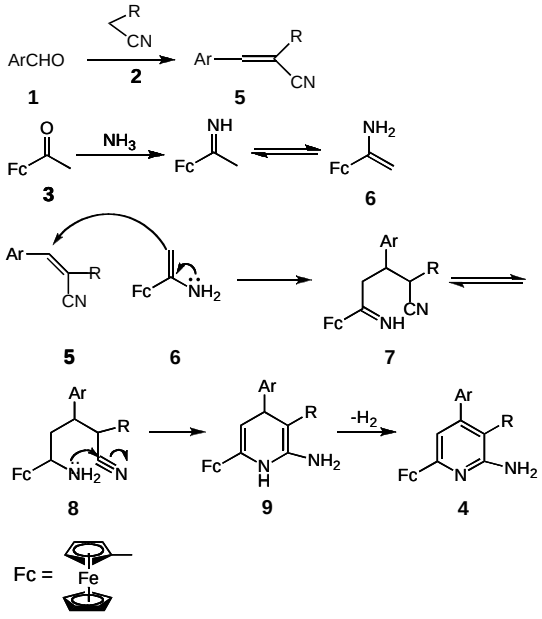
mL of water was used as solvent, the yield was the highest. In addition, the power of MWI was optimized by carrying out the same reaction at 100, 150, 200, 250 and 300 W respectively at 120 °C. The results were summarized in Table 1 (entries 14-18). It was showed that MWI at 200 W gave the highest yield.

Under these optimized reaction conditions, we synthesized a series of products 2-amino-4-aryl-6-ferrocenyl-3-subtituted pyridine derivatives **4** (entries 1-19 of Table 2). This reaction in aqueous medium can be performed efficiently under not only microwave irradiation but also conventional heating conditions.

The scope of the reaction regarding the aldehydes was examined and found that the substituted groups of aromatic aldehydes, such as electron-withdrawing groups and electron-donating groups, can tolerate the reaction conditions with excellent yields. When the heterocyclic aldehydes (such as thiophene-2-carbaldehyde and indole-3-carbaldehyde) and aliphatic aldehydes (such as pentanal and butyraldehyde) were employed instead of aromatic aldehydes under the identical reaction conditions, unfortunately, the anticipated result was not attained.

Although the detailed mechanism of the above reaction remains to be fully clarified, the formation of 2-amino-4-aryl-6-ferrocenyl-3-subtituted pyridine derivatives could be explained by a possible reaction sequence presented in Scheme 2. Compound **4** may be formed *via* sequential condensation, addition, cyclization and elimination. The condensation between aldehyde **1** and malononitrile or ethyl cyanoacetate **2** gave intermediate **5**, the condensation of acetylferrocene **3** with amine from ammonium acetate afforded 1-ferrocenylethenamine **6**. The addition between **5** and **6** furnished **7**, which upon isomerization, intermolecular cyclization gave rise to **9**, which is followed by loss of molecular hydrogen to furnish product **4**. This type of hydrogen loss is well precedented [18] (Scheme 2).

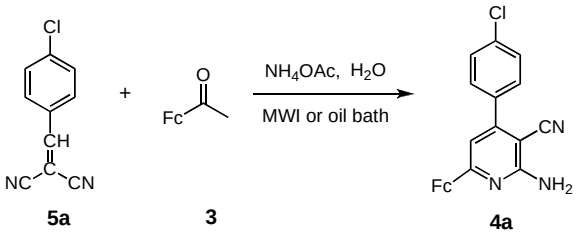
Scheme 2



To test the mechanism described above, the reaction of intermediate product **5a** [19] and acetylferrocene **3** was carried out in water under identical condition. The target compound **4a** was obtained with yield similar to the one-pot reaction. The result supported the proposed mechanism (Scheme 3).

All the products were characterized by IR, ^{1}H NMR spectra and elemental analyses. Furthermore, the structures of **4b**, **4e** and **4o** were established by X-ray crystallographic analyses (Figure 1-3, respectively) [20].

Scheme 3



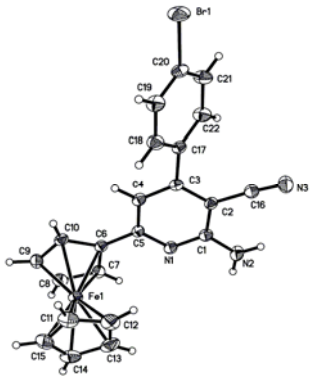


Figure 1. ORTEP diagram of **4b**.

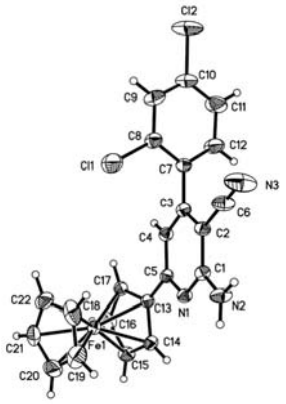


Figure 2. ORTEP diagram of **4e.**

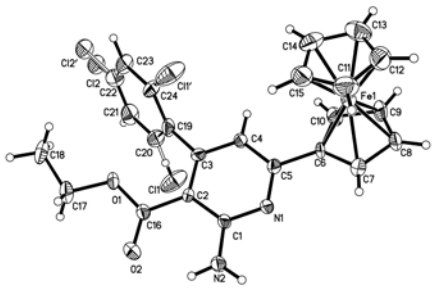


Figure 3. ORTEP diagram of **4o**.

In summary, we have developed a green chemistry method for the synthesis of ferrocene-containing compounds. It can availably expand the scope of class of important organic synthesis in aqueous medium. This method avoided using organic solvents and had the main advantages of convenient procedure and environmental friendliness.

EXPERIMENTAL

All reactions were performed in a monomodal Emrys™ Creator from Personal Chemistry, Uppsala, Sweden. Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a FT-IR-tensor 27 spectrometer. ^{1}H NMR spectra were measured on a DPX 400 MHz spectrometer using TMS as an internal standard and DMSO-d_6 as solvent. Elemental analysis was determined by using a Perkin-Elmer 240c elemental analysis instrument.

General procedure for 2-amino-4-aryl-6-ferrocenyl-3-subtituted pyridine derivatives (4). All microwave-assisted reactions were performed in a monomodal Emrys™ Creator from Personal Chemistry, Uppsala, Sweden. Typically, in a 10 mL Emrys™ reaction vial, aromatic aldehyde (1 mmol), acetylferrocenyl (1 mmol), malononitrile (1 mmol) or ethyl cyanoacetate and ammonium acetate (2 mmol) and water (2 mL) were mixed and then capped. The mixture were irradiated by microwave at 200 W and 120 °C or heated in an oil bath at 120 °C for a given time. The automatic mode stirring helped the mixing and uniform heating of the reactants. Upon completion, monitored by TLC, the reaction mixture was cooled to room temperature and washed with 2 mL ether, filtered to give the crude products, which were further purified by recrystallization from 95% EtOH. The reaction time and the yields are listed in Table 2.

2-Amino-6-ferrocenyl-4-(4-chlorophenyl)pyridine-3-carbonitrile (4a). This compound was obtained according to above general procedure; ir (potassium bromide): 3457, 3354, 3211, 2210, 1619, 1563, 1493, 1381, 1261, 1104, 1089, 832 cm^{-1}; ^{1}H nmr: δ 7.68 (d, 2H, ArH, J = 8.4 Hz), 7.64 (d, 2H, ArH, J = 8.4 Hz), 6.95 (s, 1H, ArH), 6.85 (s, 2H, NH_2), 5.04 (s, 2H, ferrocenyl), 4.50 (s, 2H, ferrocenyl), 4.10 (s, 5H, ferrocenyl). *Anal.* Calcd. for $C_{22}H_{16}ClFeN_3$: C, 63.87; H, 3.90; N, 10.16. Found: C, 63.77; H, 3.99; N, 10.21.

2-Amino-6-ferrocenyl-4-(4-bromophenyl)pyridine-3-carbonitrile (4b). ir (potassium bromide): 3457, 3354, 3211, 2211, 1619, 1572, 1491, 1261, 1103, 1010, 829 cm^{-1}; ^{1}H nmr: δ 7.77 (d, 2H, ArH, J = 8.4 Hz), 7.60 (d, 2H, ArH, J = 8.0 Hz), 6.94 (s, 1H, ArH), 6.83 (s, 2H, NH_2), 5.04 (s, 2H, ferrocenyl), 4.50 (s, 2H, ferrocenyl), 4.10 (s, 5H, ferrocenyl). *Anal.* Calcd. for $C_{22}H_{16}BrFeN_3$: C, 57.68; H, 3.52; N, 9.17. Found: C, 57.81; H, 3.34; N, 9.23.

2-Amino-6-ferrocenyl-4-(2-chlorophenyl)pyridine-3-carbonitrile (4c). ir (potassium bromide): 3456, 3339, 3215, 2220, 1624, 1570, 1479, 1353, 1256, 1103, 1026, 834 cm^{-1}; ^{1}H nmr: δ 7.66 (d, 1H, ArH, J = 8.4 Hz), 7.54-7.50 (m, 3H, ArH), 6.88 (s, 1H, ArH), 6.85 (s, 2H, NH_2), 5.03 (s, 2H, ferrocenyl), 4.49 (s, 2H, ferrocenyl), 4.09 (s, 5H, ferrocenyl). *Anal.* Calcd. for $C_{22}H_{16}ClFeN_3$: C, 63.87; H, 3.90; N, 10.16. Found: C, 63.99; H, 3.85; N, 10.26.

2-Amino-6-ferrocenyl-4-(4-fluorophenyl)pyridine-3-carbonitrile (4d). ir (potassium bromide): 3461, 3351, 3211, 2213, 1620, 1588, 1510, 1379, 1244, 1130, 1024, 998, 829 cm^{-1}; ^{1}H nmr: δ 7.71 (dd, 2H, ArH, J_1 = 8.8 Hz, J_2 = 5.2 Hz), 7.41 (t, 2H, ArH, J = 8.8 Hz), 6.95 (s, 1H, ArH), 6.82 (s, 2H, NH_2), 5.04 (s, 2H, ferrocenyl), 4.50 (s, 2H, ferrocenyl), 4.10 (s, 5H, ferrocenyl). *Anal.* Calcd. for $C_{22}H_{16}FFeN_3$: C, 66.52; H, 4.06; N, 10.58. Found: C, 66.41; H, 4.15; N, 10.43.

2-Amino-6-ferrocenyl-4-(2,4-dichlorophenyl)pyridine-3-carbonitrile (4e). ir (potassium bromide): 3449, 3337, 3213, 2217, 1623, 1592, 1479, 1263, 1104, 1025, 822 cm^{-1}; ^{1}H nmr: δ 7.86 (s, 1H, ArH), 7.63-7.54 (m, 2H, ArH), 6.88 (s, 1H, ArH), 6.85 (s, 2H, NH_2), 5.02 (s, 2H, ferrocenyl), 4.50 (s, 2H, ferrocenyl), 4.09 (s, 5H, ferrocenyl). *Anal.* Calcd. for $C_{22}H_{15}Cl_2FeN_3$: C, 58.96; H, 3.37; N, 9.38. Found: C, 58.83; H, 3.52; N, 9.21.

2-Amino-6-ferrocenyl-4-(3,4-dichlorophenyl)pyridine-3-carbonitrile (4f). ir (potassium bromide): 3455, 3347, 3210, 2213, 1619, 1568, 1476, 1381, 1242, 1134, 1000, 829 cm^{-1}; ^{1}H nmr: δ 7.93 (s, 1H, ArH), 7.65 (d, 1H, ArH, J = 8.0 Hz), 7.54 (d, 1H, ArH, J = 8.0 Hz), 6.99 (s, 1H, ArH), 6.88 (s, 2H, NH_2), 5.06 (s, 2H, ferrocenyl), 4.51 (s, 2H, ferrocenyl), 4.10 (s, 5H, ferrocenyl). *Anal.* Calcd. for $C_{22}H_{15}Cl_2FeN_3$: C, 58.96; H, 3.37; N, 9.38. Found: C, 58.86; H, 3.49; N, 9.25.

2-Amino-6-ferrocenyl-4-(4-nitrophenyl)pyridine-3-carbonitrile (4g). ir (potassium bromide): 3455, 3344, 3213, 2214, 1621, 1570, 1518, 1495, 1349, 1263, 1105, 1001, 828 cm^{-1}; ^{1}H nmr: δ 8.40 (d, 2H, ArH, J = 8.8 Hz), 7.93 (d, 2H, ArH, J = 8.8 Hz), 7.01 (s, 1H, ArH), 6.95 (s, 2H, NH_2), 5.06 (s, 2H, ferrocenyl), 4.52 (s, 2H, ferrocenyl), 4.11 (s, 5H, ferrocenyl). *Anal.* Calcd. for $C_{22}H_{16}FeN_4O_2$: C, 62.29; H, 3.80; N, 13.21. Found: C, 62.35; H, 3.65; N, 13.16.

2-Amino-6-ferrocenyl-4-(4-hydroxy-3-nitrophenyl)pyridine-3-carbonitrile (4h). ir (potassium bromide): 3463, 3356, 3210, 2203, 1619, 1570, 1440, 1248, 1038, 812 cm^{-1}; ^{1}H nmr: δ 11.59 (s, 1H, OH), 7.23 (s, 1H, ArH), 7.17 (d, 1H, ArH, J = 8.0 Hz), 7.10 (d, 1H, ArH, J = 8.0 Hz), 6.92 (s, 1H, ArH), 6.72 (s, 2H, NH_2), 5.04 (s, 2H, ferrocenyl), 4.50 (s, 2H, ferrocenyl), 4.01 (s, 5H, ferrocenyl). *Anal.* Calcd. for $C_{22}H_{16}FeN_4O_3$: C, 60.02; H, 3.66; N, 12.73. Found: C, 60.17; H, 3.54; N, 12.62.

2-Amino-6-ferrocenyl-4-(4-methoxyphenyl)pyridine-3-carbonitrile (4i). ir (potassium bromide): 3453, 3353, 3209, 2207, 1617, 1514, 1436, 1243, 1177, 1028, 829 cm^{-1}; ^{1}H nmr: δ 7.62 (d, 2H, ArH, J = 8.4 Hz), 7.12 (d, 2H, ArH, J = 8.4 Hz), 6.93 (s, 1H, ArH), 6.70 (s, 2H, NH_2), 5.04 (s, 2H, ferrocenyl), 4.50 (s, 2H, ferrocenyl), 4.10 (s, 5H, ferrocenyl), 3.86 (s, 3H, OCH_3). *Anal.* Calcd. for $C_{23}H_{19}FeN_3O$: C, 67.50; H, 4.68; N, 10.27. Found: C, 67.67; H, 4.53; N, 10.18.

Ethyl 2-amino-6-ferrocenyl-4-(4-chlorophenyl)pyridine-3-carboxylate (4j). ir (potassium bromide): 3416, 3304, 3267, 1681, 1573, 1491, 1286, 1263, 1103, 1011, 828 cm^{-1}; ^1H nmr: δ 7.51 (d, 2H, ArH, J = 8.4 Hz), 7.34 (d, 2H, ArH, J = 8.4 Hz), 6.76 (s, 1H, ArH), 6.69 (s, 2H, NH_2), 4.99 (s, 2H, ferrocenyl), 4.46 (s, 2H, ferrocenyl), 4.08 (s, 5H, ferrocenyl), 3.91 (q, 2H, CH_2, J = 6.8 Hz), 0.77 (t, 3H, CH_3, J = 6.8 Hz). *Anal.* Calcd. for $C_{24}H_{21}ClFeN_2O_2$: C, 62.56; H, 4.59; N, 6.08. Found: C, 62.70; H, 4.47; N, 6.19.

Ethyl 2-amino-6-ferrocenyl-4-(4-fluorophenyl)pyridine-3-carboxylate (4k). ir (potassium bromide): 3411, 3305, 3265, 1676, 1573, 1508, 1289, 1105, 826 cm^{-1}; ^1H nmr: δ 7.36 (t, 2H, ArH, J = 8.8 Hz), 7.28 (t, 2H, ArH, J = 8.8 Hz), 6.77 (s, 1H, ArH), 6.67 (s, 2H, NH_2), 5.00 (s, 2H, ferrocenyl), 4.45 (s, 2H, ferrocenyl), 4.08 (s, 5H, ferrocenyl), 3.90 (q, 2H, CH_2, J = 6.8 Hz), 0.76 (t, 3H, CH_3, J = 6.8 Hz). *Anal.* Calcd. for $C_{24}H_{21}FFeN_2O_2$: C, 64.88; H, 4.76; N, 6.31. Found: C, 64.76; H, 4.92; N, 6.23.

Ethyl 2-amino-6-ferrocenyl-4-(4-bromophenyl)pyridine-3-carboxylate (4l). ir (potassium bromide): 3418, 3303, 3267, 1682, 1572, 1488, 1264, 1104, 1009, 826 cm^{-1}; ^1H nmr: δ 7.64 (d, 2H, ArH, J = 8.4 Hz), 7.28 (d, 2H, ArH, J = 8.4 Hz), 6.76 (s, 1H, ArH), 6.72 (s, 2H, NH_2), 5.00 (s, 2H, ferrocenyl), 4.46 (s, 2H, ferrocenyl), 4.08 (s, 5H, ferrocenyl), 3.90 (q, 2H, CH_2, J = 6.8 Hz), 0.76 (t, 3H, CH_3, J = 7.2 Hz). *Anal.* Calcd. for $C_{24}H_{21}BrFeN_2O_2$: C, 57.06; H, 4.19; N, 5.55. Found: C, 57.21; H, 4.26; N, 5.70.

Ethyl 2-amino-6-ferrocenyl-4-(3,4,5-trimethoxyphenyl) pyridine-3-carboxylate (4m). ir (potassium bromide): 3443, 3301, 3284, 1691, 1621, 1574, 1505, 1387, 1273, 1238, 1130, 1002, 826 cm^{-1}; ^1H nmr: δ 6.84 (s, 1H, ArH), 6.59 (s, 2H, ArH), 6.54 (s, 2H, NH_2), 5.01 (s, 2H, ferrocenyl), 4.45 (s, 2H, ferrocenyl), 4.09 (s, 5H, ferrocenyl), 3.94 (q, 2H, CH_2, J = 7.2 Hz), 3.81 (s, 6H, $2OCH_3$), 3.70 (s, 3H, OCH_3), 0.81 (t, 3H, CH_3, J = 7.2 Hz). *Anal.* Calcd. for $C_{27}H_{28}FeN_2O_5$: C, 62.80; H, 5.47; N, 5.43. Found: C, 62.91; H, 5.32; N, 5.34.

Ethyl 2-amino-6-ferrocenyl-4-(4-methoxyphenyl)pyridine-3-carboxylate (4n). ir (potassium bromide): 3418, 3301, 3266, 1672 1509, 1463, 1367, 1286, 1143, 1029, 809 cm^{-1}; ^1H nmr: δ 7.26 (d, 2H, ArH, J = 8.0 Hz), 7.01 (d, 2H, ArH, J = 8.0 Hz), 6.77 (s, 1H, ArH), 6.49 (s, 2H, NH_2), 4.98 (s, 2H, ferrocenyl), 4.44 (s, 2H, ferrocenyl), 4.07 (s, 5H, ferrocenyl), 3.92 (q, 2H, CH_2, J = 6.8 Hz), 3.80 (s, 3H, OCH_3), 0.80 (t, 3H, CH_3, J = 7.2 Hz). *Anal.* Calcd. for $C_{25}H_{24}FeN_2O_3$: C, 65.80; H, 5.30; N, 6.14. Found: C, 65.69; H, 5.41; N, 6.09.

Ethyl 2-amino-6-ferrocenyl-4-(2,4-dichlorophenyl) pyridine-3-carboxylate (4o). ir (potassium bromide): 3421, 3303, 3266, 1682, 1589, 1476, 1287, 1265, 1103, 822 cm^{-1}; ^1H nmr: δ 7.71 (d, 1H, ArH, J = 1.6 Hz), 7.51 (dd, 1H, ArH, J_1 = 8.0 Hz, J_2 = 1.6 Hz), 7.36 (d, 1H, ArH, J = 8.8 Hz), 7.11 (s, 2H, NH_2), 6.67 (s, 1H, ArH), 5.00 (s, 2H, ferrocenyl), 4.47 (s, 2H, ferrocenyl), 4.08 (s, 5H, ferrocenyl), 3.88 (q, 2H, CH_2, J = 6.8 Hz), 0.73 (t, 3H, CH_3, J = 6.8 Hz). *Anal.* Calcd. for $C_{24}H_{20}Cl_2FeN_2O_2$: C, 58.21; H, 4.07; N, 5.66. Found: C, 58.13; H, 4.16; N, 5.78.

Ethyl 2-amino-6-ferrocenyl-4-(3,4-dichlorophenyl) pyridine-3-carboxylate (4p). ir (potassium bromide): 3418, 3301, 3264, 1674, 1613, 1571, 1475, 1289, 1251, 1106, 826 cm^{-1}; ^1H nmr: δ 7.70 (d, 1H, ArH, J = 8.8 Hz), 7.61 (d, 1H, ArH, J = 1.6 Hz), 7.31 (dd, 1H, ArH, J_1 = 8.0 Hz, J_2 = 1.6 Hz), 6.83 (s, 2H, NH_2), 6.78 (s, 1H, ArH), 5.01 (s, 2H, ferrocenyl), 4.47 (s, 2H, ferrocenyl), 4.09 (s, 5H, ferrocenyl), 3.93 (q, 2H, CH_2, J = 6.8 Hz), 0.79 (t, 3H, CH_3, J = 7.2 Hz). *Anal.* Calcd. for $C_{24}H_{20}Cl_2FeN_2O_2$: C, 58.21; H, 4.07; N, 5.66. Found: C, 58.29; H, 4.01; N, 5.74.

Ethyl 2-amino-6-ferrocenyl-4-(4-nitrophenyl)pyridine-3-carboxylate (4q). ir (potassium bromide): 3415, 3298, 3267, 1677, 1567, 1413, 1345, 1287, 1142, 1104, 1003, 845 cm^{-1}; ^1H nmr: δ 8.30 (d, 2H, ArH, J = 8.8 Hz), 7.61 (d, 2H, ArH, J = 8.4 Hz), 6.91 (s, 2H, NH_2), 6.78 (s, 1H, ArH), 5.01 (s, 2H, ferrocenyl), 4.48 (s, 2H, ferrocenyl), 4.10 (s, 5H, ferrocenyl), 3.89 (q, 2H, CH_2, J = 7.2 Hz), 0.71 (t, 3H, CH_3, J = 7.2 Hz). *Anal.* Calcd. for $C_{24}H_{21}FeN_3O_4$: C, 61.16; H, 4.49; N, 8.92. Found: C, 61.25; H, 4.34; N, 8.79.

Ethyl 2-amino-6-ferrocenyl-4-(3,4-dimethoxyphenyl) pyridine-3-carboxylate (4r). ir (potassium bromide): 3429, 3305, 3278, 1689, 1617, 1572, 1514, 1254, 1137, 804 cm^{-1}; ^1H nmr: δ 7.03 (d, 1H, ArH, J = 8.8 Hz), 6.87 (dd, 2H, ArH, J_1 = 8.0 Hz, J_2 = 2.4 Hz), 6.81 (s, 1H, ArH), 6.48 (s, 2H, NH_2), 4.99 (s, 2H, ferrocenyl), 4.44 (s, 2H, ferrocenyl), 4.08 (s, 5H, ferrocenyl), 3.94 (q, 2H, CH_2, J = 6.8 Hz), 3.80 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 0.82 (t, 3H, CH_3, J = 7.2 Hz). *Anal.* Calcd. for $C_{26}H_{26}FeN_2O_4$: C, 64.21; H, 5.39; N, 5.76. Found: C, 64.11; H, 5.47; N, 5.69.

Ethyl 2-amino-6-ferrocenyl-4-p-tolylpyridine-3-carboxylate (4s). ir (potassium bromide): 3496, 3372, 3319, 1681, 1572, 1510, 1494, 1382, 1280, 1104, 1001, 806 cm^{-1}; ^1H nmr: δ 7.26 (d, 2H, ArH, J = 7.6 Hz), 7.21 (d, 2H, ArH, J = 7.6 Hz), 6.76 (s, 1H, ArH), 6.53 (s, 2H, NH_2), 4.98 (s, 2H, ferrocenyl), 4.44 (s, 2H, ferrocenyl), 4.08 (s, 5H, ferrocenyl), 3.90 (q, 2H, CH_2, J = 6.8 Hz), 2.37 (s, 3H, CH_3), 0.82 (t, 3H, CH_3, J = 7.2 Hz). *Anal.* Calcd. for $C_{25}H_{24}FeN_2O_2$: C, 68.19; H, 5.49; N, 6.36. Found: C, 68.23; H, 5.37; N, 6.15.

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[20] The single-crystal growth was carried out in ethanol at room temperature. X-ray crystallographic analysis was performed with a Siemens SMART CCD and a Siemens P4 diffractometer. Crystal data for **4b**: $C_{22}H_{16}BrFeN_3$, red, crystal dimension 0.16 mm x 0.11 mm x 0.07 mm, monoclinic, space group $P2_1/n$, a = 12.250 (2), b = 7.4511 (12), c = 20.698 (3) Å, $\alpha = \gamma = 90.00$ °, β = 97.729 (3) °, V = 1872.2 (5) Å^3, M_r = 458.14, Z = 4, D_c = 1.625 g/cm^3, γ = 0.71073 Å, μ (Mo$K\alpha$) = 2.951 mm^{-1}, F (000) = 920, S = 1.016, R_1 = 0.0381 and wR_2 = 0.0841. Crystal data for **4e**: $C_{22}H_{15}Cl_2FeN_3$, red, crystal dimension 0.40 mm x 0.27 mm x 0.15 mm, monoclinic, space group $P2_1/n$, a = 12.108 (5), b = 7.661 (3), c = 21.566 (8) Å, $\alpha = \gamma = 90.00$ °, β = 96.853 (5) °, V = 1986.2 (13) Å^3, M_r = 448.12, Z = 4, D_c = 1.499 g/cm^3, γ = 0.71073 Å, μ (Mo$K\alpha$) = 1.041 mm^{-1}, F (000) = 912, S = 1.030, R_1 = 0.0467 and wR_2 = 0.0968. Crystal data for **4o**: $C_{24}H_{20}Cl_2FeN_2O_2$, red, crystal dimension 0.33 mm x 0.09 mm x 0.07 mm, monoclinic, space group $P2_1/n$, a = 7.490 (3), b = 11.363 (3), c = 25.769 (3) Å, $\alpha = \gamma = 90.00$ °, β = 94.021 (2)°, V = 2187.7 (11) Å^3, M_r = 495.17, Z = 4, D_c = 1.503 g/cm^3, γ = 0.71073 Å, μ (Mo$K\alpha$) = 0.958 mm^{-1}, F (000) = 1016, S = 1.095, R_1 = 0.0797 and wR_2 = 0.1616.