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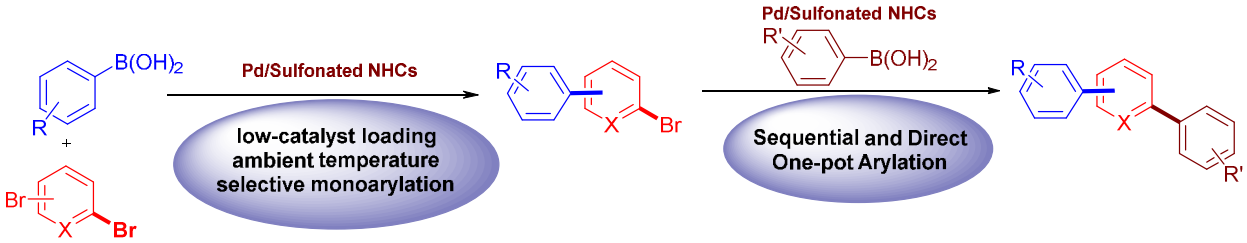

A selective palladium-catalysed arylation of dihalopyridines as well as dihaloarenes has been developed by employing N-heterocyclic carbene ligands. Selective mono-arylation was performed in water/acetonitrile solvent system at ambient temperature with catalyst loading of 0.1 mol%. This reaction was also found to proceed smoothly in water although at a slightly elevated temperature of 80 ^{o}C. Disubstituted and diversely substituted pyridines were also obtained in high yields which will be of importance to organic and medicinal chemists.

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Journal Name

ARTICLE

Selective Palladium-Catalysed Arylation of 2,6-Dibromopyridine Using N-Heterocyclic Carbene Ligands

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A selective palladium-catalysed arylation of 2,6-dibromopyridine has been developed by employing N-heterocyclic carbene ligands. Selective mono-arylation was performed in water/acetonitrile solvent system at ambient temperature with catalyst loading of 0.1 mol%. This reaction was also found to proceed smoothly in water although at a slightly elevated temperature of 80 °C. 2,6-Disubstituted and diversely substituted 2,6-pyridines were also obtained in high yields which will be of importance to organic and medicinal chemists.

1. Introduction

Palladium-mediated C-C bond forming technologies are among the most applied processes in academia and industries.[1] From the synthesis of simple biaryls to complex synthetic targets this methodology has been employed successfully.[2] This success can be attributed mainly to the rapid development of new ligand systems which in combination with different palladium precursors have resulted in a drastic improvement in reactivity.[3] N-Heterocyclic carbenes (NHCs)[4] comprise one such class of highly electron-rich, activating ligand systems that have found applications as ligands in metal-mediated processes[5] as well as organocatalytic carbene catalysis[6] in recent years. Consequently, this field has emerged as a highly useful area for organic synthesis.

Since the early independent reports of their isolation by Arduengo[7,8], N-heterocyclic carbenes have been used in a variety of synthetic transformations, while recently their Pd-complexes have also exhibited promising anticancer[9] properties. Their use in palladium-catalysed cross-coupling reactions has also seen rapid growth and has been employed extensively towards addressing a variety of synthetic problems with valuable contributions from the groups of Nolan and Organ.[10] Site selectivity in cross-coupling reactions is one such challenge, which has attracted a lot of attention due to its large synthetic applicability related to the selective activation of C-X bonds in polyhalogenated heteroaryls.[11] The development of efficient synthetic processes to tackle such a problem would be immensely beneficial towards their application for natural product synthesis.[12]

Pyridine as a structural motif has found wide applications in a variety of natural products as well as pharmaceutical intermediates; it has also proved to be one of the most useful building blocks.[13] Polyhalogenated pyridines and their application in synthetic chemistry has been immense and in the last few years the selective functionalisation of such structural motifs has been carried out extensively via palladium-catalysed cross-coupling reactions.[14] In that respect the type of ligands employed have also been shown to play an important role in deciding the outcome of such processes.[15] N-Heterocyclic carbenes to that matter have seldom been used for selective palladium-catalysed cross-coupling of polyhalogenated pyridines as is evident from the number of reports that have emerged in the last few years.[16]

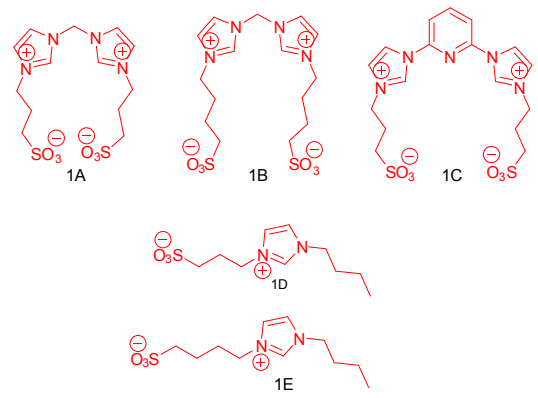

Figure 1: N-Heterocyclic Carbene ligands **1A-E** employed for selective Suzuki-Miyaura cross-coupling of dihalopyridines.

To address this issue for assessing the utility of N-heterocyclic carbenes for selective coupling of 2,6-dibromo(hetero)arenes, in this study we have employed some of the previously developed NHC ligands[17-20] (see Figure 1) for the development of efficient and selective arylation (monoarylation) procedures of 2,6-dibromopyridine[21]. The purpose for selecting 2,6-

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† Footnotes relating to the title and/or authors should appear here. Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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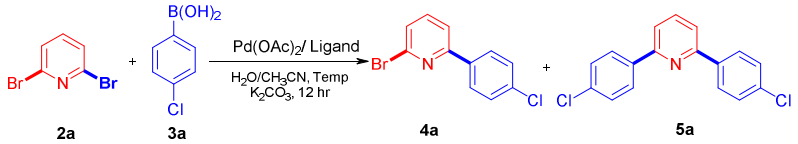
dibromopyridine especially as the substrate of choice is with respect to its occurrence in a variety of natural products such as Combretastatins A-4 analogues.[21h,22] Previous reports on the selective arylation of 2,6-dibromopyridines[21] have highlighted the importance of such a methodology. However, a closer look at these reports reveal several drawbacks such as high Pd content, lower selectivity towards mono-arylated product and higher temperature ranges.

With this in mind we report herein the mono-arylation of 2,6-dibromopyridine under relatively mild conditions at 0.1 mol% catalyst loading in H_2O/CH_3CN system at room temperature. Complete diarylation was also found to take place at higher temperature. Sequential one-pot and direct one-pot arylation protocols have also been developed and applied towards the synthesis of diversely substituted 2,6-diarylpyridines. Mechanistic studies have also been performed to get an insight into the possible coordination mode of the metal to the NHC ligands by comparison against ligand-less system. Presence of a homotopic catalyst has been proposed by subjecting the catalytic reactions to mercury-drop test and CS_2 addition tests giving preliminary support for such a proposal.

Table 1: Screening studies.[a]



2a 3a 4a 5a

No.	Ligand	Temp (°C)	Catalyst (mol%)	% Yield[b]		
				2a	4a	5a
1.	-	r.t.	5.0	55	35	10
2.	1A	r.t.	5.0	21	76	<2
3.	1B	r.t.	5.0	18	78	<2
4.	1C	r.t.	5.0	17	81 (80)[c]	<2
5.	1D	r.t.	5.0	57	40	<2
6.	1E	r.t.	5.0	21	75	<2
7.	IMes.HCl	r.t.	5.0	19	51	29
8.	IPr.HCl	r.t.	5.0	16	57	26
9.	$Pd(PPh_3)_4$	r.t.	5.0	26	49	23
10.	PEPPSI™-IPr	r.t.	5.0	12	63	24
11.	SPhos-Pd G2	r.t.	5.0	9	67	22
12.	1C	100	5.0	52	45	<2
13.	1C	80	5.0	45	51	<2
14.	1C	60	5.0	43	50	<5
15.	1C	r.t.	5.0	17	81	<2
16.	1C	r.t.	5.0	17	81 (16)[d]	<2
17.	1C	r.t.	1.0	16	81 (81)[d]	<2
18.	1C	r.t.	0.1	16	80 (800)[d]	<2
19.	-	r.t.	0.1	29	37	30
20.	-	r.t.	0.01	39	28	26
21.	1C	r.t.	0.01	28	69 (6900)[d]	<2
22.	1C	r.t.	0.001	87	10	<2

[a]1.0 mmol 2,6-dibromopyridine, 1.2 mmol arylboronic acid, K_2CO_3 (2.0 mmol) in H_2O/CH_3CN 1:1 (3.0 mL) at 30 °C. [b]Unless otherwise stated are isolated yields after column chromatography and characterized by LCMS and ^1H NMR. [c]Instead of H_2O/CH_3CN, neat water was used as solvent. [d]Values in bracket are TON (mol product/ mol catalyst) sec^{-1} (r.t. is 30 °C)

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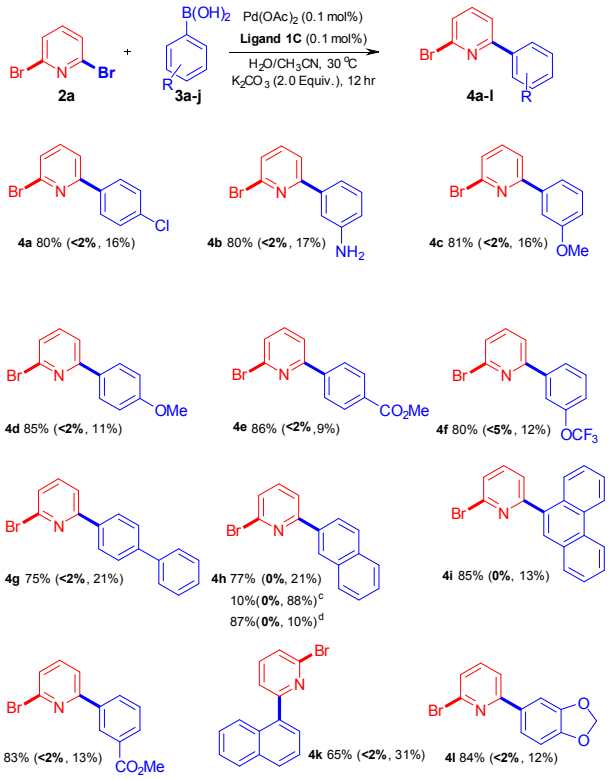
2. Palladium-catalysed selective mono-arylation of 2,6-dibromopyridine

At the outset of our studies we performed screening of all synthesised NHC ligands for the selective mono-arylation of 2,6-dibromopyridine with 4-chlorophenylboronic acid in H_2O/CH_3CN solvent system. $Pd(OAc)_2$ on its own without the presence of the ligand led to poor yield of both mono as well as diarylated products, possibly due to the formation of palladium-black at higher concentrations of palladium (entry 1, Table 1). Initial screening of different ligands revealed that ligand **1C** (entry 4, Table 1) possessing the pyridine backbone coupled with butane sultone gave relatively better yield of the selective mono-arylated product compared to other ligands, however given the close reactivity pattern it should be noted that other ligands too could perform at the same rate as **1C**.The catalytic system was also tested against some of the commercially available NHC ligands as well as complexes such as IMes.HCl, IPr.HCl, $Pd(PPh_3)_4$, PEPPSI™-IPr and SPhos-Pd G2 catalysts (entries 7-11, Table 1). Although, good conversion was observed in the case of PEPPSI™-IPr and SPhos-Pd G2, selectivity for mono-arylated product was found to be poor as compared to the **1C** with larger quantity of diarylated product also obtained (entry 10 and 11, Table 1).

The reaction proceeded smoothly at ambient temperature while increase in temperature led to loss in reactivity (entries 12-15, Table 1). We next turned our attention to catalyst loading experiments to check the possibility of reducing the catalyst concentration in order to make the protocol synthetically attractive. Lowering the catalyst concentration did not affect the catalytic activity and it was possible to reduce the loading to 0.1 mol% (entry 13, Table 1). The possibility of whether $Pd(OAc)_2$ could catalyse the reaction at lower concentrations through nanoparticular pathway[23] without the ligand was not found to be acting in such catalytic reaction as the reactivity and selectivity suffered drastically compared to the one with ligand (entry 14 & 15, Table 1). The reaction also proceeded smoothly at 0.01 mol%, however a slight reduction in the monoarylated product was observed (entry 16, Table 1).

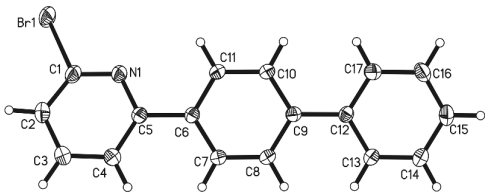
With a highly active catalytic system in hand we then explored its scope in the selective mono-arylation of 2,6-dibromopyridine with different aryl boronic acids at 0.1 mol% catalyst loading at ambient temperature in CH_3CN/H_2O solvent system (Scheme 1). In most cases very good yields of the mono-arylated product was obtained with no particular electronic influence (effect of substituents on the arylboronic acid) on the reactivity was observed. The coupling could also be performed in water however at higher temperature (80 °C) as poor yields were obtained at room temperature.

Scheme 1: Selective mono-arylation protocol.[a,b]



[a]1.0 mmol 2,6-dibromopyridine, 1.2 mmol arylboronic acid, $Pd(OAc)_2$ (0.1 mol%), Ligand **1C** (0.1 mol%), K_2CO_3 (2.0 mmol) in H_2O/CH_3CN 1:1 (3 mL) at 30 °C. for 12 h. [b]Isolated yields (Values in bracket: bold numbers signify the amount of diarylated product isolated, while the other part corresponds to the value related to the amount of starting 2,6-dibromopyridine isolated)-characterised by LCMS and ^{1}H NMR [c]Instead of H_2O/CH_3CN, neat H_2O was used (3 mL) at 30 °C. [d]Instead of H_2O/CH_3CN, H_2O was used (3 mL) at 80 °C.

The X-ray analysis of one of the mono-arylated product that crystallised in $CDCl_3$ (NMR tube) to give single crystals suitable for X-ray characterisation revealed interesting details regarding the positioning of different groups on the pyridine ring.



Single crystal X-ray for 4g

Figure 2 ORTEP representation of compounds **4g** with atomic labelling. Thermal ellipsoids are drawn at 50% probability. Selected bond lengths (Å) for compound **4g**: C(5)-C(6) 1.482 (3), C(5)-N(1) 1.344 (3), C(9)-C(12) 1.483 (3), C(1)-Br(1) 1.906 (2). Selected bond angles for compound **4g**: N(1)-C(5)-C(4) 121.7 (2), N(1)-C(5)-C(6) 116.79 (2), C(4)-C(5)-C(6) 121.5 (2), C(10)-C(9)-C(8) 116.4 (2).

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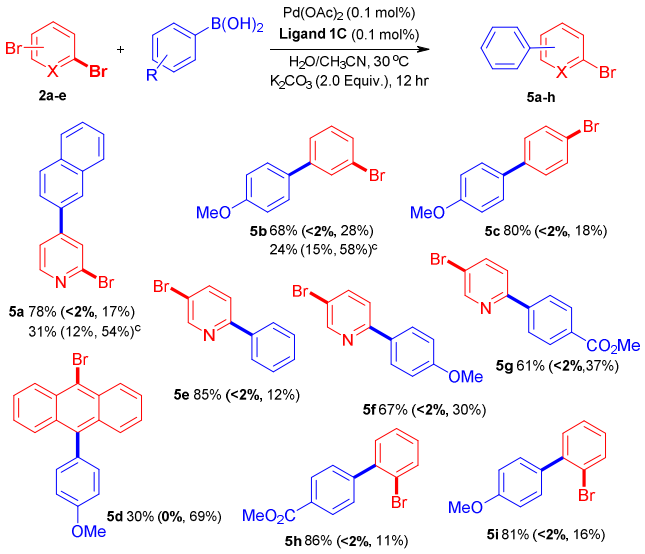
Mono-arylated product **4g** obtained from the coupling of 2,6-dibromopyridine **2a** and 4-biphenyl boronic acid **3g** (Scheme 1) crystallised to provide its X-ray crystal structure (Figure 2).[24] The torsion angle between the plane C6 to -C17 and the plane N1-C1 to-C5 was found to be 18.2° indicating that the aromaticity between the biaryl part and the pyridine part is not perfectly in resonance, while the two planes itself are almost entirely flat.

In order to demonstrate the generality of the catalytic system, other dibromoheteroarenes (although this is not the were also subjected to the mono-arylation conditions using 0.1 mol% catalyst loading in H_2O/CH_3CN as solvent at ambient temperature. 2,4-Dibromopyridine in comparison to its 2,6-dihalogenated analogue gave slightly lower yield of the mono-arylated product (70%). The catalytic system was found to be quite selective towards arylation at the 4-position of the pyridine ring (Scheme 2). Other unactivated substrates such as 1,3-dibromobenzene and 1,4-dibromobenzene when subjected to monoarylation conditions also furnished the desired product in good yields.

Scheme 2: Selective monoarylation of dibromo(hetero)arene.[a,b,c]



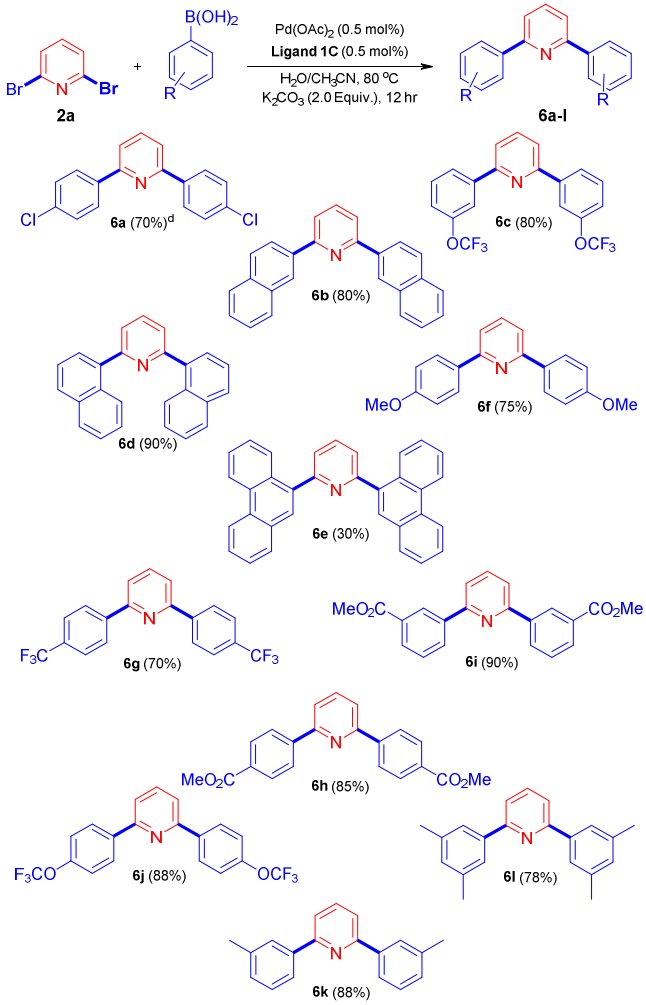
[a]1.0 mmol 2,6-dibromopyridine, 1.2 mmol arylboronic acid, $Pd(OAc)_2$ (0.1 mol%), Ligand **1C** (0.1 mol%), K_2CO_3 (2.0 mmol) in H_2O/CH_3CN 1:1 (3 mL) at 30 °C for 12 hr. [b]Isolated yields (Values in bracket: **bold** numbers signify the amount of diraylated product isolated, while the other part corresponds to the value related to the amount of starting dibromo(hetero)arene isolated)-characterised by LCMS and ^{1}H NMR. [c] Control experiment with $Pd(OAc)_2$ used on its own.

This was also found to be the case with 2,5-dibromopyridine and 9,10-dibromoanthracene giving the monoarylated product in good yield and slightly lower yields respectively, although with good selectivity in both the cases. These results point towards the general nature of the developed protocol which is independent of the type of substrate employed.

3. Palladium-catalysed diarylation of 2,6-dibromopyridine:

Given the unique reactivity of the catalytic system we became interested in exploring it further towards the diarylation of 2,6-dibromopyridine in H_2O/CH_3CN. In comparison to the mono-arylation of 2,6-dibromopyridine, the diarylation reaction when carried out at room temperature gave a mixture of mono-arylated and diarylated products (Scheme 3). For improving the selectivity towards achieving complete diarylation the reaction was performed at higher temperature (80 °C) in H_2O/CH_3CN with a catalyst loading of 0.5 mol%. As expected the increase of the reaction temperature resulted in complete diarylation of 2,6-dibromopyridine with no mono-arylation observed. Good to excellent yields of diarylated product was obtained regardless of the type of substituent on the arylboronic acid.

Scheme 3: Diarylation of 2,6-dibromopyridine.[a,b,c]



[a]1.0 mmol 2,6-dibromopyridine, 2.0 mmol arylboronic acid, $Pd(OAc)_2$ (0.1 mol%), Ligand **1C** (0.1 mol%), K_2CO_3 (4.0 mmol) in H_2O/CH_3CN 1:1 (3 mL) at 80 °C for 12 hr. [b]Isolated yields. [c]No monoarylated product was observed and remaining was starting material. [d] Reaction carried out only with $Pd(OAc)_2$ to give 37% of diarylated product

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In the case of diarylated product **6d** which was obtained by the reaction of 2,6-dibromopyridine **2a** and 1-naphthyl boronic acid (2.0 equiv.), the x-ray structure[25] (Figure 3) revealed that the two naphthalene rings are in an almost right angle to each other (89.8°). Naphthalene C1 to-C10 has an angle of 51.1° to the central pyridine ring and the other naphthalene is at 112.2°. There appears to be no π-π stacking interactions in the crystal lattice, which is unusual given the molecule's highly aromatic character.

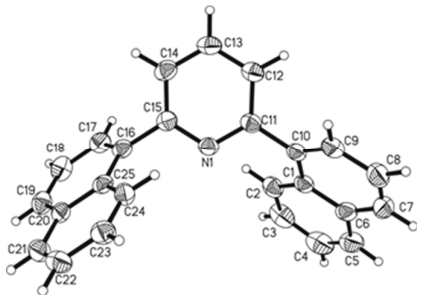


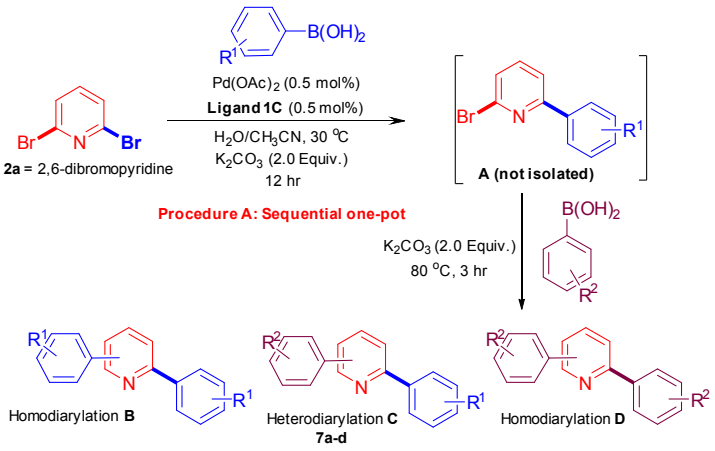
Figure 3 ORTEP representation of compound **6d** with atomic labelling. Thermal ellipsoids are drawn at 50% probability. Selected bond lengths (Å) for compound **6d**: C(1)-C(10) 1.433 (3), C(15)-C(16) 1.494 (3), C(15)-N(1) 1.348 (3), C(11)-N(1) 1.348 (3). Selected bond angles for compound **6d**: N(1)-C(11)-C(10) 116.97 (19), N(1)-C(15)-C(16) 115.6 (2), C(12)-C(11)-C(10) 121.0 (3), C(14)-C(15)-C(16) 121.8 (3).

4. Synthesis of diversely 2,6-disubstituted pyridines: Sequential and direct one-pot synthesis

The above results demonstrate the powerful nature of the catalytic system which could be further employed towards obtaining diversely 2,6-disubstituted pyridines in a sequential one-pot manner without the isolation of the mono-arylated intermediate. Sequential one-pot transformations[26] have in recent years gained a lot of interest and have emerged as a new and powerful technology in synthesis. One of the major advantages of such methodology is the reduction of waste leading to better reaction conditions.

Initially, for achieving mono-arylation 2,6-dibrompyridine was reacted with 4-methoxyphenylboronic acid at room temperature in H_2O/CH_3CN and the reaction mixture was stirred for 12 hrs after which the other arylboronic acid was added and the reaction continued at 80 °C for 3 more hours (Scheme 4). At the end of the reaction a differently substituted pyridine was isolated in good yield. The methodology was demonstrated to provide the 2,6-disubstituted pyridines (possible pyridine-based Combretastatin analogues[21h,22]) using 3 different arylboronic acids with the best results obtained for the combination of two electron-donating substituents on the aryl boronic acids (4-MeO and 3-MeO).

Scheme 4: Sequential one-pot arylation of 2,6-dibromopyridine with different boronic acids.[a]



No.	(hetero)arene	R^1	R^2	%Yield[b]				
				(hetero)arene	A	B	C	D
1.	2a	4-MeO	1-Naphthyl	<2% (2a)	7 (4d)	10 (6f)	79 (7a)	-
2.	2a	4-MeO	2-Naphthyl	<2% (2a)	6 (4d)	11 (6f)	81 (7b)	-
3.	2a	4-MeO	3-MeO	<2% (2a)	10 (4d)	13 (6f)	74 (7c)	-
4.	2a	4-MeO	3,4-$(MeO)_2$	<2% (2a)	16 (4d)	11 (6f)	70 (7d)	-

[a]1.0 mmol 2,6-dibromopyridine, 1.2 mmol R^1-$ArB(OH)_2$, $Pd(OAc)_2$ (0.5 mol%), Ligand **1C** (0.5 mol%), K_2CO_3 (2.0 mmol) in H_2O/CH_3CN 1:1 (3 mL) at 30 °C for 12 hr and then added K_2CO_3 (2.0 mmol), 1.2 mmol R^2-$ArB(OH)_2$ at 80 °C for 3 hr. [b]Isolated yields

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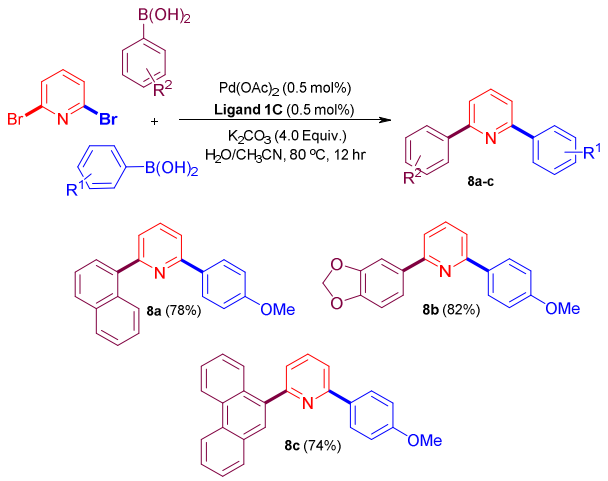
In literature such a system has not been employed for the substrates represented in this above scheme and gives the synthetic organic chemists and medicinal chemists a very good handle for obtaining diversely substituted pyridines and arenes. We next turned our attention to direct one-pot procedure for obtaining the diversely substituted 2,6-dibromopyridine by the addition of both the arylboronic acids at the same time. Direct one-pot synthetic procedures which involve a series of reactions in an uninterrupted sequence[27] has played a key role in redefining synthetic organic chemistry through better waste management and making the process energy intensive given the lesser number of steps required to obtain the desired product. One of the major applications of direct one-pot reactions is the possibility to perform multicomponent processes[28] in a more selective manner to provide the product containing all the components. To test our catalytic system for providing the heterodiarylated product we subjected 2,6-dibromopyridine to the direct one-pot procedure involving the addition of all the substrates at the same time in H_2O/CH_3CN solvent system at 80 ^oC for 12 hr (Scheme 5).

To our pleasant surprise the protocol furnished selectively the desired heterodiarylated product in good yield with the remaining amount being that of starting material and small amount of homodiarylated product was observed.

Scheme 5: Direct one-pot arylation of 2,6-dibromopyridine with different boronic acids.[a]



[a]1.0 mmol 2,6-dibromopyridine, 1.2 mmol R^1-$ArB(OH)_2$, 1.2 mmol R^1-$ArB(OH)_2$, $Pd(OAc)_2$ (0.5 mol%), Ligand **1C** (0.5 mol%), K_2CO_3 (4.0 mmol) in H_2O/CH_3CN 1:2 (3 mL) at 80 ^oC for 12 hr. [b]Isolated yields (remaining mass balance is starting material along with small amount of homodiarylated products, monoarylated products were not observed).

No monoarylation products were obtained, confirming the selective nature of the direct one-pot method leading to the minimisation of side products. These results also demonstrate the powerful nature of the catalytic system in hand.

5. Mechanistic studies

Given the reactivity of the catalytic system it was also important to verify the possibility of a nanoparticular pathway followed by the added Pd and whether the NHC ligands are acting as coordinating ligand[29]. To assess the nature of Pd species that could be forming under the conditions a simple but reliable Mercury-drop[30] test method was employed. Catalytic reactions with and without ligand were performed, excess of mercury was added at the initial stages.

Presence of a nanoparticular pathway was evident for the reaction performed without the addition of the ligand as complete retardation of the catalytic reaction was observed. The reaction failed to furnish any kind of product at the end of 12 hrs. However, to our surprise the addition of the mercury-drop failed to have any kind of effect on the catalytic activity of the reaction involving the added ligand **1C** furnishing the desired monoarylated product in good yield. Similar observations were made in the case of other catalyst poisons[31] such as triphenylphosphine (PPh_3) and carbon disulfide (CS_2) where no appreciable reduction in the yield of the cross-coupled product was observed. The employment of a nanoparticle stabilizer tetra-n-butylammonium bromide also failed to show any rate enhancement suggesting the lesser possibility for the involvement of a nanoparticular pathway and provide preliminarily support for the presence of a homotopic catalyst (active molecular catalyst).

Scheme 6: Homogeneity test for monoarylation of 2,6-dibromopyridine.

Conditions	Additive	%Yield
A = Without Ligand	Mercury drop test	0
B = With added ligand **1C**		74
B = With added ligand **1C**	Triphenylphosphine	67
B = With added ligand **1C**	Carbon disulphide	62
B = With added ligand **1C**	Tetra-n-butylammonium bromide	79

These results were also supported by the fact that the reaction solutions of these two catalytic systems showed a striking contrast to each other. As depicted in Figure 4 the catalytic solution containing $Pd(OAc)_2$ and ligand **1C** shows the possible presence of homogeneous Pd species in the aqueous phase while that of $Pd(OAc)_2$ on its own (without added ligand **1C**) showed colloidal Pd species in the organic phase.

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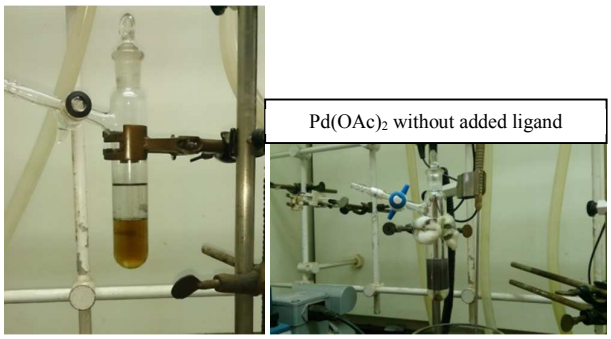
Figure 4: Pictorial representation of catalytic solutions (upper layer CH_3CN and lower H_2O).

$Pd(OAc)_2$ with added ligand **1C**.



Another important evidence for the presence of an active molecular catalyst ($Pd(OAc)_2$ with added ligand **1C**) was the observation of a linear reaction profile obtained on the injection of aliquots of the reaction at regular intervals into Gas Chromatograph-Mass Spectrometer (GCMS) (Figure 5). The reaction was found to proceed smoothly towards the predominant formation of the mono-arylated product after 12 hrs, although a slight induction period could be observed. In comparison the catalytic reaction performed without the added ligand **1C** (only $Pd(OAc)_2$ as catalyst) showed an initial induction period extending upto 2 hrs after which the reaction started to convert rapidly. However, the competing diarylation process brings about the reduction in the overall yield of the desired mono-arylated product.

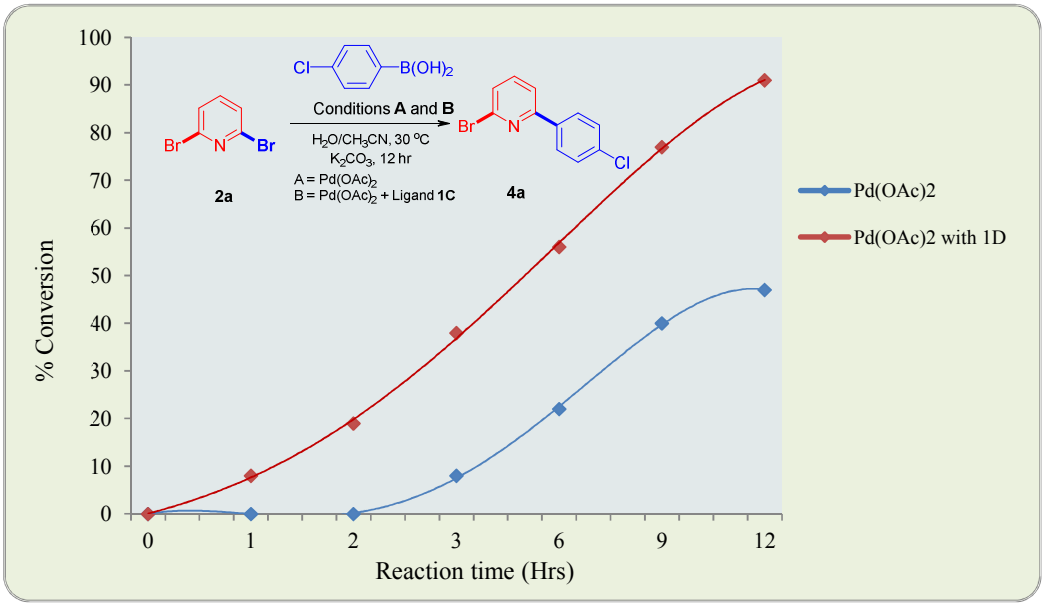


Figure 5: GC reaction profile for catalytic reactions (Hexadecane added as internal standard).

All the above results point towards the involvement of molecular Pd-catalyst[32] in the Suzuki-Miyaura selective coupling of 2,6-dibromopyridine with arylboronic acids. At this moment the possibility of mono-Pd-NHC coordinated species in solution compared to the doubly coordinated Pd species (known to be formed at higher temperatures)[19,33] is more probable. Such a monomeric species has already been shown to form under relatively mild conditions (similar to the one we have developed for the monoarylation reaction) for ruthenium and osmium.[17c] Although, to verify such an assumption further studies are required to be undertaken which are underway in our group for getting an insight into the possible coordination mode of the ligand to the Pd-centre and will be reported in due course.

6. Conclusion

A selective palladium-catalysed arylation of 2,6-dibromopyridine has been developed by employing N-heterocyclic carbene ligands. Selective mono-arylation was performed in water/acetonitrile solvent system at ambient temperature with catalyst loading of 0.1 mol%. This reaction was also found to proceed smoothly in water although at a slightly elevated temperature of 80 °C. Sequential and direct one-pot synthetic procedure was also shown to furnish the differently substituted 2,6-diarylpyridine in good yields. These molecules are of importance to organic as well as medicinal chemists and the protocol could provide an easy access to such molecules of synthetic relevance. The presence of a possible active molecular catalyst was found to be existent in the catalytic system and was confirmed by the catalyst poison experiments (mercury-drop test, CS_2 addition test) as well as on

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the basis of a non-sigmoidal reaction profile for the monoarylation reactions.

7. Experimental Section

7.1 General Remarks

All catalytic reactions were conducted under an inert atmosphere of N_2 on a Schlenk line. TLC analysis was performed on Merck 5554 aluminium backed silica gel plates and compounds visualized by ultraviolet light (254 nm), phosphomolybdic acid solution (5% in EtOH), or 1% ninhydrin in EtOH. Aryl boronic acids and other chemicals were obtained from commercial sources, and were used without further purification. PEPPSI™-IPr, SPhos-Pd G2, IMes.HCl, IPr.HCl and $Pd(PPh_3)_4$ were obtained from Sigma Aldrich. Yields refer to isolated compounds, estimated to be >95 % pure as determined by ^{1}H-NMR. NMR data (^{1}H, ^{13}C) were recorded on Bruker 500 MHz spectrometer. Chemical shifts are reported in parts per million downfield from an internal tetramethylsilane reference. Coupling constants (J values) are reported in hertz (Hz). LC-MS analyses were performed on an Agilent VL mass-spectrometer. Elemental analysis was performed using a Thermo-Fischer Scientific.

GC Parameters. GC analysis for the kinetic profile was done on a Shimadzu GC-MS Parvum 2 equipped with an autosampler. Separation was achieved using a Zebron ZB-1 capillary column, (I.d. 0.25 mm, length 30 m) with a temperature ramp from 50 to 250 ^{o}C at 10 ^{o}C min^{-1}. The injection volume was 1µl with a split ratio of 50.

X-ray structural analysis[45-36]*:* Diffraction data were collected at low temperature (-103.0 °C) using a STOE-IPDS 2T diffractometer with graphite-monochromated molybdenum K_α radiation, λ = 0.71073 Å. The structures were solved by direct methods (SHELXS-97) and refined by full-matrix least-squares techniques (SHELXL-97). All non-hydrogen-atoms were refined with anisotropic displacement parameters. The hydrogen atoms were refined isotropically on calculated positions using a riding model with their U_{iso} values constrained to 1.5 U_{eq} of their pivot atoms for terminal sp^3 carbon atoms and 1.2 times for all other carbon atoms. Copies of the data can be obtained free of charge by contacting the CCDC via e-mail: deposit@ccdc.cam.ac.uk.

Synthesis of Ligands 1A and 1B:

The preparation of compound **1A** and **1B** was carried out by reaction of bis(imidazolyl)methane and 1,3-propane sultone or 1,4-butane sultone, under different reaction conditions than those reported in the literature.

Ligand 1A[18]

A suspension of bis(imidazolyl)methane (1.0 g, 6.74 mmol) and 1,3-propane sultone (4.12 g, 33.8 mmol) in CH_3CN (25 mL) was heated at 100 ^{o}C during 12 h in a Pyrex tube. The generated solid was collected by filtration and washed with CH_2Cl_2 and MeOH. Compound **1A** was isolated as a white, air- and moisture-stable solid in 75% yield.

^{1}H NMR (500 MHz, D_2O): 9.31 (s, 2H), 7.81-7.79 (m, 2H), 7.70-7.68 (m, 2H), 6.68 (s, 2H), 4.43-4.41 (m, 4H), 2.93-2.91 (m, 4H), 2.33-2.31 (m, 4H); ^{13}C NMR (125 MHz, D_2O): 123.7, 122.1, 58.9, 48.4, 47.1, 24.7; ESI-MS (m/z): 415 ($M^+ + Na^+$); Anal.Calcd (%) for $C_{13}H_{20}N_4S_2O_6$: C, 39.79; H, 5.14; N, 14.28. Found: C, 39.69; H, 5.09; N, 14.21.

Ligand 1B

A suspension of bis(imidazolyl)methane (1.0 g, 6.74 mmol) and 1,4-butane sultone (33.8 mmol) in CH_3CN (25 mL) was heated at 100 ^{o}C during 12 h in a Pyrex tube. The so-generated solid was collected by filtration and washed with CH_2Cl_2 and MeOH. Compound **1B** was isolated as a white, air- and moisture-stable solid in 81% yield.

^{1}H NMR (500 MHz, D_2O): 7.79-7.77 (m, 2H), 7.68-7.66 (m, 2H), 6.69 (s, 2H), 4.34-4.31 (m, 4H), 2.96-2.92 (m, 4H), 2.07-2.02 (m, 4H), 1.78-1.72 (m, 4H); ^{13}C NMR (125 MHz, D_2O): , 123.8, 122.2, 58.9, 49.8, 49.6, 27.6, 20.8; ESI-MS (m/z): 443 ($M^+ + Na^+$); Anal.Calcd (%) for $C_{15}H_{24}N_4S_2O_6$: C, 42.85; H, 5.75; N, 13.32. Found: C, 42.77; H, 5.69; N, 13.27.

Synthesis of Ligands 1C and 1D:

Ligand 1C[19]

A suspension of 2,6-bis(imidazol-1-yl)pyridine (1.06 g, 5.02 mmol) and 1,3-propane sultone (3.06 g, 25.2 mmol) in CH_3CN (20 mL) was heated at 100 ^{o}C during 12 h in a Pyrex tube. The solid was collected by filtration and washed subsequently with CH_2Cl_2 and MeOH. Compound **1C** was isolated as a white, air- and moisture-stable solid in 72% yield.

^{1}H NMR (500 MHz, D_2O): 9.74 (s, 2H), 8.28-8.26 (m, 1H), 8.24-8.21 (m, 2H), 7.88-7.85 (m, 2H), 7.69 (s, 2H), 4.42-4.40 (m, 4H), 2.85-2.83 (m, 4H), 2.33-2.31 (m, 4H); ^{13}C NMR (125 MHz, DMSO-d_6): 147.2, 146.4, 136.7, 125.2, 121.4, 116.4, 50.3, 48.8, 26.5; ESI-MS (m/z): 478 ($M^+ + Na^+$); Anal.Calcd (%) for $C_{17}H_{21}N_5S_2O_6$: C, 44.83; H, 4.65; N, 15.37. Found: C, 44.75; H, 4.61; N, 15.29.

Synthesis of Ligands 1D and 1E:

Ligand 1D[20]

3-(1-Butyl-3-imidazolio)propanesulfonate **1D** was obtained by refluxing 1-butylimidazole (5 mmol) with 1,3-propanesultone (25 mmol) in acetone (25 mL) under dry nitrogen at room temperature for 24 h. The insoluble precipitate was separated by filtration. The product was washed with acetone several times. The resultant product was obtained as a white powder in 82% yield.

^{1}H NMR (500 MHz, DMSO-d_6): 9.20 (s, 1H), 7.81-7.79 (m, 2H), 4.31-4.28 (m, 2H), 4.17-4.14 (m, 2H), 2.41-2.39 (m, 2H), 2.12-2.06 (m, 2H), 1.82-1.74 (m, 2H), 1.30-1.25 (m, 2H), 0.92 (t, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): 136.4, 122.6, 48.5, 47.8, 47.6, 31.3, 26.3, 18.7, 13.2; ESI-MS (m/z): 269 ($M^+ + Na^+$); Anal.Calcd (%) for $C_{10}H_{18}N_2SO_3$: C, 48.76; H, 7.37; N, 11.37. Found: C, 48.69; H, 7.31; N, 11.32.

Ligand 1E

3-(1-Butyl-3-imidazolio)butaneulfonate **1E** was obtained by refluxing 1-butylimidazole (5 mmol) with 1,3-butanesultone (25 mmol) in acetone (25 mL) under dry nitrogen at room

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temperature for 24 h. The insoluble precipitate was separated by filtration. The product was washed with acetone several times. The resultant product was obtained as a white powder in 61% yield.
^{1}H NMR (500 MHz, DMSO-d_6): 9.26 (s, 1H), 7.82 (s, 2H), 4.21-4.15 (m, 4H), 2.47-2.43 (m, 2H), 1.89-1.87 (m, 2H), 1.79-1.76 (m, 2H), 1.55-1.52 (m, 2H), 1..27-1.25 (m, 2H), 0.90 (t, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): 136.3, 122.5, 50.5, 48.5, 31.3, 28.6, 21.7, 18.7, 13.2; ESI-MS (m/z): 283 ($M^+ + Na^+$); Anal.Calcd (%) for $C_{11}H_{20}N_2SO_3$: C, 50.75; H, 7.74; N, 10.76. Found: C, 50.70; H, 7.69; N, 10.69.

Representative procedure for palladium-catalysed selective mono-arylation of 2,6-dibromopyridine:
In a dry Schlenk tube, $Pd(OAc)_2$/ligand **1C** (0.1 mol% in 3 mL 1:1 H_2O:CH_3CN) solution was stirred under N_2 atmosphere. To this was added 2,6-dibromopyridine **2a** (0.5 mmol, 0.118 g), K_2CO_3 (1.0 mmol, 0.138 g) and the resultant solution was stirred at room temperature for 10 mins. To this was added 4-chlorophenyl boronic acid **3a** (0.6 mmol, 0.093 g) and the resultant solution was stirred at 30 ^{o}C for 12 hr. At the end of the reaction, solvent was removed under vacuo and the resultant crude product was purified using column chromatography (95:5 Hexane:EtOAc) to give the product **4a** in 80% yield.

2-Bromo-6-(4-chlorophenyl)pyridine (4a):[37a] ^{1}H NMR (500 MHz, $CDCl_3$): 8.08-8.05 (m, 1H), 7.94 (d, *J* = 7.8 Hz, 2H), 7.64-7.59 (m, 2H), 7.44 (d, *J* = 7.7 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): 157.2, 142.2, 139.0, 135.8, 128.9, 128.8, 128.2, 126.6, 118.7; MS (EI, m/z): 268 (100).
2-Bromo-6-(3-aminophenyl)pyridine (4b): ^{1}H NMR (500 MHz, DMSO-d_6): 7.70-7.68 (m, 1H), 7.82-7.79 (m, 1H), 7.57-7.55 (m, 1H), 7.29 (s, 1H), 7.17-7.14 (m, 2H), 6.68-6.65 (m, 1H), 5.29 (s, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): 158.6, 149.6, 141.5, 140.7, 137.8, 129.7, 126.6, 119.6, 115.8, 114.5, 112.2; MS (EI, m/z): 249 (100). Anal.Calcd (%) for $C_{11}H_9N_2Br$: C, 53.04; H, 3.64; N, 11.25. Found: C, 52.91; H, 3.60; N, 11.20.
2-Bromo-6-(3-methoxyphenyl)pyridine (4c): ^{1}H NMR (500 MHz, DMSO-d_6): 7.87-7.85 (m, 1H), 7.60-7.52 (m, 3H), 7.42-7.37 (m, 1H), 7.00-6.95 (m, 1H), 3.89 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): 160.0, 158.3, 142.0, 138.9, 127.9, 126.4, 119.3, 115.5, 112.2, 55.4; MS (EI, m/z): 264 (100). Anal.Calcd (%) for $C_{12}H_{10}NBrO$: C, 54.57; H, 3.82; N, 5.30. Found: C, 54.51; H, 3.79; N, 5.26.
2-Bromo-6-(4-methoxyphenyl)pyridine (4d):[37b] ^{1}H NMR (500 MHz, $CDCl_3$): 7.96 (d, *J* = 7.6 Hz, 2H), 7.59-7.54 (m, 2H), 7.32-7.29 (m, 1H), 6.99 (d, *J* = 7.7 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 160.9, 158.2, 142.0, 138.8, 130.2, 128.3, 125.4, 118.0, 114.1, 110.9, 55.3; MS (EI, m/z): 264 (100).
Methyl 4-(6-bromopyridin-2-yl)benzoate (4e):[37c] ^{1}H NMR (500 MHz, $CDCl_3$): 8.11-8.05 (m, 4H), 7.72-7.70 (m, 1H), 7.63-7.61 (m, 1H), 7.45-7.43 (m, 1H), 3.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 166.7, 157.2, 142.3, 141.5, 139.1, 130.8, 130.0, 127.1, 126.8, 119.5, 52.2; MS (EI, m/z): 292 (100).
2-Bromo-6-(3-trifluoromethoxyphenyl)pyridine (4f): ^{1}H NMR (500 MHz, DMSO-d_6): 7.93-7.86 (m, 2H), 7.68-7.62 (m, 2H), 7.52-7.45 (m, 2H), 7.34-7.26 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): 156.8, 142.3, 139.7, 139.1, 130.1, 127.1, 125.2, 121.8, 119.6, 119.1; MS (EI, m/z): 318 (100). Anal.Calcd (%) for $C_{12}H_7NOF_3Br$: C, 45.31; H, 2.22; N, 4.40. Found: C, 45.22; H, 2.19; N, 4.36.
2-Bromo-6-(4-biphenyl)pyridine (4g): ^{1}H NMR (500 MHz, $CDCl_3$): 8.09-8.06 (m, 2H), 7.73-7.57 (m, 6H), 7.49-7.38 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): 158.1, 142.3, 142.2, 140.3, 138.9, 136.4, 128.8, 127.6, 127.4, 127.3, 127.0, 126.3, 118.8; MS (EI, m/z): 310 (100). Anal.Calcd (%) for $C_{17}H_{12}NBr$: C, 65.83; H, 3.90; N, 4.52. Found: C, 65.72; H, 3.86; N, 4.54.
2-Bromo-6-(2-naphthyl)pyridine (4h): ^{1}H NMR (500 MHz, $CDCl_3$): 8.50 (s, 1H), 8.13-8.10 (m, 1H), 7.95-7.81 (m, 4H), 7.65-7.63 (m, 1H), 7.54-7.50 (m, 2H), 7.45-7.42 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 158.5, 142.2, 139.0, 134.9, 133.9, 133.3, 128.8, 128.5, 127.6, 126.8, 126.7, 126.4, 126.3, 124.2, 119.2; MS (EI, m/z): 284 (100). Anal.Calcd (%) for $C_{15}H_{10}NBr$: C, 63.40; H, 3.55; N, 4.93. Found: C, 63.31; H, 3.54; N, 4.89.
2-Bromo-6-(9-phenanthrenyl)pyridine (4i): ^{1}H NMR (500 MHz, $CDCl_3$): 8.81-8.79 (m, 1H), 8.75-8.73 (m, 1H), 8.10-8.07 (m, 1H), 7.97-7.95 (m, 1H), 7.90 (s, 1H), 7.75-7.70 (m, 3H), 7.67-7.59 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): 160.2, 141.7, 138.6, 135.4, 131.0, 130.7, 130.5, 129.8, 129.1, 128.9, 127.3, 126.8, 126.7, 126.5, 126.0, 123.9, 122.9, 122.5; MS (EI, m/z): 334 (100). Anal.Calcd (%) for $C_{19}H_{12}NBr$: C, 68.28; H, 3.62; N, 4.19. Found: C, 68.22; H, 3.59; N, 4.15.
Methyl 3-(6-bromopyridin-2-yl)benzoate (4j): ^{1}H NMR (500 MHz, $CDCl_3$): 8.56 (s, 1H), 8.21-8.19 (m, 1H), 8.08-8.06 (m, 1H), 7.71 (d, *J* = 7.8 Hz, 1H), 7.59 (t, *J* = 7.6 Hz, 1H), 7.52 (t, J = 7.6 Hz, 1H), 7.41 (d, *J* = 7.8 Hz, 1H), 3.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 166.7, 157.3, 142.2, 139.1, 137.9, 131.4, 130.7, 130.5, 128.9, 127.8, 126.8, 119.1, 52.2; MS (EI, m/z): 292 (100). Anal.Calcd (%) for $C_{13}H_{10}NO_2Br$: C, 53.45; H, 3.45; N, 4.79. Found: C, 53.41; H, 3.43; N, 4.77.
2-Bromo-6-(1-naphthyl)pyridine (4k):[37d] ^{1}H NMR (500 MHz, $CDCl_3$): 8.16-8.14 (m, 1H), 7.99-7.96 (m, 2H), 7.73-7.70 (m, 2H), 7.62-7.57 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): 160.1, 141.7, 138.6, 136.7, 133.8, 130.8, 129.4, 128.4, 127.7, 126.7, 126.3, 126.0, 125.2, 125.1, 123.8; MS (EI, m/z): 284 (100).
2-Bromo-6-(5-methylenedioxyphenyl)pyridine (4l): ^{1}H NMR (500 MHz, $CDCl_3$): 7.60-7.56 (m, 2H), 7.54-7.52 (m, 2H), 7.39-7.37 (m, 1H), 6.92-6.89 (m, 1H), 6.05 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): 157.9, 148.9, 148.2, 141.8, 138.8, 131.9, 125.6, 121.1, 118.2, 108.4, 107.2, 101.4; MS (EI, m/z): 278 (100). Anal.Calcd (%) for $C_{12}H_8NO_2Br$: C, 51.83; H, 2.90; N, 5.04. Found: C, 51.79; H, 2.87; N, 5.00.

Representative procedure for palladium-catalysed selective mono-arylation of dibromo(hetero)arenes:
In a dry Schlenk tube, $Pd(OAc)_2$/ligand **1C** (0.1 mol% in 3 mL 1:1 H_2O:CH_3CN) solution was stirred under N_2 atmosphere. To this was added dibromo(hetero)arene **2b-e** (0.5 mmol), K_2CO_3 (1.0 mmol, 0.138 g) and the resultant solution was stirred at 30 ^{o}C for 10 mins. To this was added 4-chlorophenyl boronic acid

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3d (0.6 mmol, 0.093 g) and the resultant solution was stirred at room temperature for 12 hr. At the end of the reaction, solvent was removed under vacuo and the resultant crude product was purified using column chromatography (95:5 Hexane:EtOAc) to give the products **5a-d**.

2-Bromo-4-(2-naphthyl)pyridine (**5a**): ^{1}H NMR (500 MHz, $CDCl_3$): 8.48-8.467 (m, 1H), 8.13 (s, 1H), 8.00-7.91 (m, 4H), 7.87 (s, 1H), 7.74-7.72 (m, 1H), 7.63-7.58 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): 151.2, 150.5, 142.9, 133.8, 133.6, 133.2, 129.1, 128.4, 127.7, 127.1, 126.8, 126.7, 126.0, 124.2, 121.0; MS (EI, m/z): 331 (100). Anal.Calcd (%) for $C_{15}H_{10}NBr$: C, 63.40; H, 3.55; N, 4.93. Found: C, 63.36; H, 3.54; N, 4.91.

3-Bromo-4'-methoxy-1,1'-biphenyl (**5b**):[37e] ^{1}H NMR (500 MHz, $CDCl_3$): 7.69 (s, 1H), 7.49 (d, J = 7.8 Hz, 2H), 7.45-7.41 (m, 2H), 7.28-7.26 (m, 1H), 6.96 (d, J = 7.8 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 159.5, 142.9, 132.1, 130.2, 129.7, 129.5, 128.1, 125.2, 122.8, 114.3, 55.3; MS (EI, m/z): 263 (100).

4-Bromo-4'-methoxy-1,1'-biphenyl (**5c**):[37f] ^{1}H NMR (500 MHz, $CDCl_3$): 7.51-7.47 (m, 4H), 7.40 (d, J = 7.6 Hz, 2H), 6.96 (d, J = 7.6 Hz, 2H), 3.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 159.3, 139.6, 132.4, 131.7, 128.2 127.9, 120.7, 114.2, 55.3; MS (EI, m/z): 263 (100).

9-Bromo-10-(4-methoxyphenyl)anthracene (**5d**):[37g] ^{1}H NMR (500 MHz, $CDCl_3$): 8.60 (d, J = 7.6 Hz, 2H), 7.70 (d, J = 8.9 Hz, 2H), 7.59-7.56 (m, 2H), 7.38-7.34 (m, 2H), 7.30 (d, J = 7.6 Hz, 2H), 7.11 (d, J = 8.6 Hz, 2H), 3.94 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 159.1, 137.6, 132.1, 131.3, 130.3, 130.2, 127.7, 127.4, 126.8, 125.4, 122.5, 113.8, 55.3; MS (EI, m/z): 363 (100).

5-Bromo-2-phenylpyridine (**5e**)[37h]: ^{1}H NMR (500 MHz, $CDCl_3$): 8.78-8.74 (m, 1H), 8.01-7.97 (m, 2H), 7.90-7.87 (m, 1H), 7.67-7.64 (m, 1H), 7.51-7.42 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): 155.4, 150.3, 138.9, 137.7, 129.1, 126.4, 121.4, 119.4; MS (EI, m/z): 234 (100).

5-Bromo-2-(4-methoxyphenyl)pyridine (**5f**): ^{1}H NMR (500 MHz, $CDCl_3$): 8.87 (s, 1H), 7.91-7.88 (m, 2H), 7.81-7.78 (m, 1H), 7.55-7.53 (m, 1H), 6.98-6.95 (m, 2H), 3.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 160.9, 155.5, 150.5, 139.1, 130.8, 128.0, 120.8, 118.3, 114.2, 55.3; MS (EI, m/z): 263 (100).

Methyl 4-(5-bromopyridin-2-yl)benzoate (**5g**): ^{1}H NMR (500 MHz, $CDCl_3$): 8.73 (s, 1H), 8.11-8.09 (m, 2H), 8.02-7.99 (m, 2H), 7.88-7.85 (m, 1H), 7.65-7.63 (m, 1H), 3.92 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 166.7, 154.5, 150.9, 142.2, 139.4, 130.6, 130.1, 126.6, 121.9, 120.2, 52.2; MS (EI, m/z): 291 (100).

Methyl 2'-bromo-[1,1'-biphenyl]-4-carboxylate (**5h**): ^{1}H NMR (500 MHz, $CDCl_3$): 8.09-8.07 (m, 2H), 7.67-7.65 (m, 1H), 7.48-7.45 (m, 2H), 7.38-7.34 (m, 1H), 7.31-7.28 (m, 1H), 7.25-7.22 (m, 1H), 3.93 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 166.8, 145.5, 141.5, 133.2, 131.0, 129.4, 129.2, 127.4, 122.2, 52.1; MS (EI, m/z): 290 (100).

2-Bromo-4'-methoxy-1,1'-biphenyl (**5i**): ^{1}H NMR (500 MHz, $CDCl_3$): 7.67-7.65 (m, 1H), 7.38-7.33 (m, 4H), 7.19-7.15 (m, 1H), 6.99-6.96 (m, 2H), 3.86 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 159.0, 142.2, 133.5, 133.1, 131.3, 130.5, 128.4, 127.4, 122.9, 113.3, 55.2; MS (EI, m/z): 262 (100).

Representative procedure for palladium-catalysed diarylation of 2,6-dibromopyridine:

In a dry Schlenk tube, $Pd(OAc)_2$/ligand **1C** (0.5 mol% in 3 mL 1:1 H_2O:CH_3CN) solution was stirred under N_2 atmosphere. To this was added 2,6-dibromopyridine **2a** (0.5 mmol, 0.118 g), K_2CO_3 (2.0 mmol, 0.138 g) and the resultant solution was stirred at room temperature for 10 mins. To this was added 4-chlorophenyl boronic acid (1.0 mmol, 0.155 g) and the resultant solution was stirred at 80 ^{o}C for 12 hr. At the end of the reaction, solvent was removed under vacuo and the resultant crude product was purified using column chromatography (90:10 Hexane:EtOAc) to give the product **6a** in 70% yield.

2,6-Di-(4-chlorophenyl)pyridine (**6a**): ^{1}H NMR (500 MHz, $CDCl_3$): 8.01 (d, J = 7.8 Hz, 4H), 7.72-7.69 (m, 1H), 7.60-7.57 (m, 2H), 7.43 (d, J = 7.7 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): 155.7, 137.7, 137.6, 135.2, 128.9, 128.2, 118.6; MS (EI, m/z): 300 (100). Anal.Calcd (%) for $C_{17}H_{11}NCl_2$: C, 68.02; H, 3.69; N, 4.67. Found: C, 67.95; H, 3.66; N, 4.63.

2,6-Di-(2-naphthyl)pyridine (**6b**): ^{1}H NMR (500 MHz, $CDCl_3$): 8.59 (s, 2H), 8.29-8.25 (m, 2H), 7.98-7.92 (m, 4H), 7.88-7.80 (m, 5H), 7.52-7.45 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): 156.6, 138.3, 135.6, 133.8, 133.4, 128.8, 128.4, 127.6, 127.0, 126.7, 126.3, 124.8, 119.6, 110.8; MS (EI, m/z): 331 (100). Anal.Calcd (%) for $C_{25}H_{17}N$: C, 90.60; H, 5.17; N, 4.23. Found: C, 90.53; H, 5.14; N, 4.20.

2,6-Di-(3-trifluoromethoxyphenyl)pyridine (**6c**): ^{1}H NMR (500 MHz, $CDCl_3$): 8.08-8.01 (m, 4H), 7.90-7.84 (m, 1H), 7.73-7.70 (m, 2H), 7.55-7.50 (m, 2H), 7.32-7.28 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): 155.3, 149.8, 141.2, 137.9, 130.0, 125.1, 121.3, 119.5, 119.3; MS (EI, m/z): 399 (100). Anal.Calcd (%) for $C_{19}H_{11}NO_2F_6$: C, 57.15; H, 2.78; N, 3.51. Found: C, 57.12; H, 2.75; N, 3.48.

2,6-Di-(1-naphthyl)pyridine (**6d**): ^{1}H NMR (500 MHz, $CDCl_3$): 8.25-8.20 (m, 2H), 7.97-7.87 (m, 5H), 7.73-7.70 (m, 2H), 7.65-7.55 (m, 4H), 7.52-7.46 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): 159.0, 138.6, 136.5, 133.9, 131.2, 128.8, 128.3, 127.6, 126.3, 125.8, 125.7, 125.3, 123.4; MS (EI, m/z): 331 (100). Anal.Calcd (%) for $C_{25}H_{17}N$: C, 90.60; H, 5.17; N, 4.23. Found: C, 90.54; H, 5.15; N, 4.21.

2,6-Di-(9-phenanthrenyl)pyridine (**6e**): ^{1}H NMR (500 MHz, $CDCl_3$): 8.82-8.75 (m, 4H), 8.30-8.27 (m, 2H), 8.07-8.04 (m, 1H), 8.03-7.97 (m, 5H), 7.76-7.64 (m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$): 159.1, 137.2, 136.7, 131.3, 130.8, 130.4, 129.0, 128.6, 126.9, 126.7, 126.6, 126.5, 123.6, 122.9, 122.5; MS (EI, m/z): 431 (100). Anal.Calcd (%) for $C_{33}H_{21}N$: C, 91.85; H, 4.91; N, 3.25. Found: C, 91.76; H, 4.87; N, 3.23.

2,6-Di-(4-methoxyphenyl)pyridine (**6f**):[37i] ^{1}H NMR (500 MHz, $CDCl_3$): 8.13 (d, J = 8.8 Hz, 4H), 7.77-7.65 (m, 1H), 7.61-7.59 (m, 2H), 7.05 (d, J = 8.7 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): 160.3, 156.2, 137.2, 132.1, 128.1, 117.1 113.9, 55.28; MS (EI, m/z): 292 (100).

2,6-Di-(4-trifluoromethylphenyl)pyridine (**6g**):[37j] ^{1}H NMR (500 MHz, $CDCl_3$): 8.24-8.22 (m, 4H), 7.91-7.87 (m, 1H), 7.78-7.74 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): 155.5, 142.3, 137.9, 130.7, 127.2, 125.6, 120.7, 119.7; MS (EI, m/z): 367 (100).

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Dimethyl 4,4'-(pyridine-2,6-diyl)dibenzoate (6h):[37k] ^{1}H NMR (500 MHz, $CDCl_3$): 8.21-8.19 (m, 4H), 8.16-8.14 (m, 4H), 7.87-7.83 (m, 1H), 7.77-7.75 (m, 2H), 3.94 (s, 6H).; ^{13}C NMR (125 MHz, $CDCl_3$): 166.8, 155.7, 143.2, 137.8, 130.4, 130.0, 126.8, 119.8, 52.2; MS (EI, m/z): 347 (100).

Dimethyl 3,3'-(pyridine-2,6-diyl)dibenzoate (6i):[37l] ^{1}H NMR (500 MHz, $CDCl_3$): 8.73-8.71 (m, 2H), 8.43-8.41 (m, 2H), 8.11-8.09 (m, 2H), 7.86-7.84 (m, 1H), 7.78-7.75 (m, 2H),7.60-7.56 (m, 2H), 3.96 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): 167.0, 155.8, 139.5, 137.8, 131.5, 130.5, 130.0, 128.9, 127.9, 119.2, 52.2; MS (EI, m/z): 347 (100).

2,6-Di-(4-trifluoromethoxyphenyl)pyridine (6j): ^{1}H NMR (500 MHz, $CDCl_3$): 8.16-8.14 (m, 4H), 7.84-7.80 (m, 1H), 7.67 (d, J = 7.9 Hz, 2H), 7.34-7.32 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): 155.5, 149.9, 137.8, 128.3, 121.7, 121.0, 119.1, 118.8; MS (EI, m/z): 399 (100). Anal.Calcd (%) for $C_{19}H_{11}NO_2F_6$: C, 57.15; H, 2.78; N, 3.51. Found: C, 57.09; H, 2.75; N, 3.49.

2,6-Di-(3-methylphenyl)pyridine (6k): ^{1}H NMR (500 MHz, DMSO-d_6): 8.03-7.99 (m, 4H), 7.95-7.85 (m, 3H), 7.45-7.39 (m, 2H), 7.30-7.24 (m, 2H), 2.43 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6): 155.9, 138.8, 138.2, 137.9, 129.8, 128.7, 127.2, 123.9, 118.8, 21.1; MS (EI, m/z): 259 (100). Anal.Calcd (%) for $C_{19}H_{17}N$: C, 87.99; H, 6.61; N, 5.40. Found: C, 87.94; H, 6.57; N, 5.37.

2,6-Bis-(3,5-dimethylphenyl)pyridine (6l): ^{1}H NMR (500 MHz, DMSO-d_6): 7.94-7.91 (m, 1H), 7.86-7.84 (m, 2H), 7.78 (s, 4H), 7.10 (s, 2H), 2.39 (s, 12H); ^{13}C NMR (125 MHz, DMSO-d_6): 156.1, 138.9, 138.1, 137.8, 130.6, 124.5, 118.9, 21.0; MS (EI, m/z): 287 (100). Anal.Calcd (%) for $C_{21}H_{21}N$: C, 87.76; H, 7.37; N, 4.87. Found: C, 87.71; H, 7.33; N, 4.86.

Representative procedure for palladium-catalysed synthesis of diversely substituted pyridines from 2,6-dibromopyridine by sequential one-pot method:

In a dry Schlenk tube, $Pd(OAc)_2$/ligand **1C** (0.5 mol% in 3 mL 1:1 H_2O:CH_3CN) solution was stirred under N_2 atmosphere. To this was added 2,6-dibromopyridine **2a** (0.5 mmol), K_2CO_3 (1.0 mmol) and the resultant solution was stirred at room temperature for 10 mins. To this was added 4-methoxyphenyl boronic acid **3d** (0.6 mmol) and the resultant solution was stirred at 30 ^{o}C for 12 hrs. After this the reaction mixture was cooled and to this was added K_2CO_3 (1.0 mmol) and aryl boronic acid (0.6 mmol) and the solution was stirred for further 3 hrs at 80 ^{o}C. On completion of the reaction, the resultant mixture was evaporated under vacuo and the crude product was purified using column chromatography (Hexane:EtOAc 90:10).

2-(4-Methoxyphenyl)-6-(1-naphthyl)pyridine (7a):[37m] ^{1}H NMR (500 MHz, DMSO-d_6): 8.31-8.28 (m, 1H), 8.12-8.10 (m, 2H), 7.96-7.95 (m, 2H), 7.90-7.87 (m, 1H), 7.78-7.75 (m, 1H), 7.73-7.71 (m, 1H), 7.62-7.59 (m, 1H), 7.56-7.49 (m, 3H), 7.04-7.02 (m, 2H), 3.89 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): 160.4, 158.6, 156.4, 138.8, 137.0, 133.9, 131.9, 131.2, 128.7, 128.3, 127.5, 126.2, 125.9, 125.7, 125.2, 122.6, 117.7, 114.0, 55.2; MS (EI, m/z): 311 (100).

2-(4-Methoxyphenyl)-6-(2-naphthyl)pyridine (7b): ^{1}H NMR (500 MHz, DMSO-d_6): 8.63 (s, 1H), 8.35-8.33 (m, 1H), 8.20-8.17 (m, 2H), 8.02-7.98 (m, 2H), 7.92-7.81 (m, 3H), 7.70-7.68 (m, 1H), 7.55-7.52 (m, 2H), 7.10-7.07 (m, 2H), 3.92 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): 160.4, 156.4, 137.4, 136.8, 133.6, 133.4, 132.1, 128.6, 128.2, 127.6, 126.3, 126.2, 126.1, 124.7, 118.2, 117.9, 114.0, 55.3; MS (EI, m/z): 311 (100). Anal.Calcd (%) for $C_{22}H_{17}NO$: C, 84.86; H, 5.50; N, 4.50. Found: C, 84.80; H, 5.45; N, 4.47.

2-(3-Methoxyphenyl)-6-(4-methoxyphenyl)pyridine (7c): ^{1}H NMR (500 MHz, DMSO-d_6): 8.16-8.14 (m, 2H), 7.81-7.78 (m, 2H), 7.72-7.70 (m, 1H), 7.67-7.64 (m, 2H), 7.45-7.42 (m, 1H), 7.06-7.04 (m, 2H), 7.02-7.00 (m, 1H), 3.95 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): 160.4, 159.9, 156.3, 141.0, 137.3, 131.9, 129.5, 128.2, 119.3, 118.0, 114.4, 114.0, 112.5, 55.3; MS (EI, m/z): 291 (100). Anal.Calcd (%) for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.25; H, 5.84; N, 4.79.

2-(3,4-Dimethoxyphenyl)-6-(4-methoxyphenyl)pyridine (7d):[37n] ^{1}H NMR (500 MHz, DMSO-d_6): 8.09 (d, J = 8.6 Hz, 2H), 7.80 (s, 1H), 7.75-7.71 (m, 1H), 7.64-7.62 (m, 1H), 7.57 (d, J = 7.8 Hz, 2H), 7.01 (d, J = 8.6 Hz, 2H), 6.96 (d, J = 8.2 Hz, 1H), 4.01 (s, 3H), 3.93 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): 160.4, 156.2, 149.8, 149.1, 137.2, 132.5, 132.1, 128.1, 119.4, 117.3, 114.0, 110.9, 110.0, 55.9, 55.3; MS (EI, m/z): 321 (100).

Representative procedure for palladium-catalysed synthesis of diversely substituted pyridines from 2,6-dibromopyridine by direct one-pot method:

In a dry Schlenk tube, $Pd(OAc)_2$/ligand **1C** (0.5 mol% in 3 mL 1:1 H_2O:CH_3CN) solution was stirred under N_2 atmosphere. To this was added 2,6-dibromopyridine **2a** (0.5 mmol), K_2CO_3 (2.0 mmol) and the resultant mixture was stirred at room temperature for 10 minutes after which 4-methoxyphenyl boronic acid **3d** (0.6 mmol) and 1-naphthyl boronic acid (0.6 mmol) **3i** were subsequently added and the solution was stirred at 30 ^{o}C for 12 hrs. On completion of the reaction, the resultant mixture was evaporated under vacuo and the crude product was purified using column chromatography (Hexane:EtOAc 90:10) to furnish the diversely arylated pyridine **6d** as a colourless solid in 45% yield.

2-(4-Methoxyphenyl)-6-(1-naphthyl)pyridine 8a:[37o] ^{1}H NMR (500 MHz, DMSO-d_6): 8.31-8.28 (m, 1H), 8.12-8.10 (m, 2H), 7.96-7.95 (m, 2H), 7.90-7.87 (m, 1H), 7.78-7.75 (m, 1H), 7.73-7.71 (m, 1H), 7.62-7.59 (m, 1H), 7.56-7.49 (m, 3H), 7.04-7.02 (m, 2H), 3.89 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): 160.4, 158.6, 156.4, 138.8, 137.0, 133.9, 131.9, 131.2, 128.7, 128.3, 127.5, 126.2, 125.9, 125.7, 125.2, 122.6, 117.7, 114.0, 55.2; MS (EI, m/z): 311 (100).

2-(5-Methylenedioxyphenyl)-6-(4-methoxyphenyl)pyridine 8b: ^{1}H NMR (500 MHz, DMSO-d_6): 8.13-8.11 (m, 2H), 7.78-7.74 (m, 2H), 7.67-7.65 (m, 1H), 7.62-7.60 (m, 1H), 7.57-7.55 (m, 1H), 7.05-7.02 (m, 2H), 6.95-6.93 (m, 1H), 6.06 (s, 2H), 3.91 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): 160.4, 156.1, 155.9, 148.1, 137.3, 134.0, 132.0, 128.1, 120.8, 117.3, 113.9, 108.2, 107.4, 101.1, 55.2; MS (EI, m/z): 305 (100). Anal.Calcd (%) for $C_{19}H_{15}NO_3$: C, 74.74; H, 4.95; N, 4.59. Found: C, 74.72; H, 4.91; N, 4.55.

2-(4-Methoxyphenyl)-6-(9-phenanthrenyl)pyridine 8c: ^{1}H NMR (500 MHz, DMSO-d_6): 8.83-8.80 (m, 1H), 8.78-8.75 (m,

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1H), 8.27-8.24 (m, 1H), 8.13-8.10 (m, 2H), 7.98-7.96 (m 2H), 7.93-7.90 (m, 1H), 7.80-7.77 (m, 1H), 7.73-7.70 (m 1H), 7.67-7.59 (m, 2H), 7.56-7.53 (m 1H), 7.04-7.02 (m, 2H), 3.89 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): 160.4, 158.9, 156.5, 137.5, 137.1, 131.9, 131.4, 130.8, 130.4, 128.9, 128.4, 128.3, 126.9, 126.8, 126.7, 126.6, 126.4, 122.8, 122.7, 122.5, 117.9, 114.0, 55.3; MS (EI, m/z): 361 (100). Anal.Calcd (%) for $C_{26}H_{19}NO$: C, 86.40; H, 5.30; N, 3.88. Found: C, 86.35; H, 5.28; N, 3.85.

Catalyst Poisoning Experiments:

a) **Hg drop experiments**:

To a 3.0 ml (0.1 mol%) of catalyst stock solution, 0.235 g (1.0 mmol) of 2,6-dibromopyridine and 0.152 g (1.0 mmol) of 4-methoxy phenylborornic acid and potassium carbonate (2.0 mmol, 0.276 g) were added at 30 ^{o}C followed by a drop of Mercury (300 Equiv.).

b) **CS_2 poisoning test**:

To a 3.0 ml (0.1 mol%) of catalyst stock solution, 0.235 g (1.0 mmol,1.0 equiv.) of 2,6-dibromopyridine and 0.152 g (1.0 mmol, 1.0 equiv.) of 4-methoxy phenylborornic acid and potassium carbonate (2.0 mmol, 0.276 g) were added and then 0.1 mol% (1 ml from stock solution) of carbon disulfide (CS_2) was added.

[stock solution: 0.0076g(0.006ml) of CS_2 in 100 ml of MeCN]

To a 3.0 ml (0.1 mol%) of catalyst stock solution, 0.235 g (1.0 mmol, 1.0 equiv.) of 2,6-dibromopyridine and 0.152 g (1.0 mmol 1.0 equiv.) of 4-methoxy phenylborornic acid and potassium carbonate (2.0 mmol, 0.276 g) were added and then 1.0 mmol (0.076 g, 1.0 equiv.) of carbon disulfide (CS_2) was added at 30 ^{o}C.

c) **Triphenylphosphine**:

To a 3.0 ml (0.1 mol %) of catalyst stock solution, 0.235 g (1.0 mmol) of 2,6-dibromopyridine and 0.152 g (1.0 mmol) of 4-methoxy phenylborornic acid and potassium carbonate (2.0 mmol, 0.276 g) were added at room Temperature followed by 0.262 g (1mmol, 1.0 equiv.) of triphenyl phoshphine.

d) **TBAB**:

To a 3.0 ml (0.1 mol%) of catalyst stock solution, 0.235 g (1.0 mmol) of 2,6-dibromopyridine and 0.152 g (1.0 mmol) of 4-methoxy phenylborornic acid and potassium carbonate (2.0 mmol, 0.276 g) were added followed by 0.322 g (1.0 mmol, 1.0 equiv.) of tetrabutyl ammonium bromide.

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