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ARTICLE

Scope of regioselective Suzuki reactions in the synthesis of arylpyridines and benzylpyridines and subsequent intramolecular cyclizations to azafluorenes and azafluorenones

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The current investigation on regioselective Suzuki reactions of 2,3-dihalopyridines and 2-halo-3-halomethylpyridines yielded unexplored synthesis of arylpyridines and benzylpyridines bearing synthetic handles for further functionalizations. Indeed, the scope of intramolecular cyclizations of arylpyridines and benzylpyridines prepared in this study for the synthesis of azafluorenes and azafluorenones has been investigated.

Introduction

Among many other C-C bond formation at the frontier of organic chemistry, Suzuki reaction has become a fundamental tool for C-C bond forming reactions, largely practiced both in academia and industry.[1] Often, regioselective Suzuki reactions have been developed delivering biaryls that are otherwise difficult to obtain by direct arylation[2] or oxidative coupling.[3]

Arylpyridines and benzylpyridines represent important structural motifs ubiquitously found in natural products, fine chemicals, and functional materials.[4] In addition, they have been demonstrated as building blocks for the preparation various pyridine-fused heterocycles.[5] 2-Arylpyridines have been functionalized at the ortho-position of aryl ring wherein pyridine acts as the directing group.[6] Despite all these documented utilities, their synthesis endorses only a limited success. The palladium-catalyzed direct arylation[7] or arylation via oxidative coupling[8] of pyridines is a commonly recognized synthetic challenge. In addition, high Lewis basicity of the sp^2-nitrogen in pyridine often results in catalyst coordination and/or poisoning of the catalyst. In this regard, Suzuki reaction on pyridines has been demonstrated an alternative beneficial approach for the synthesis of arylpyridines and benzylpyridines.[9] However, regioselectivity could be an issue in Suzuki reactions of dihalopyridines.[10] An exploratory investigation on this issue appears to be a reasonable task for the synthetic chemists. Our previous contributions on understanding the reactivity of halopyridines[11] and subsequent development to the synthesis of pyridine-fused heterocycles fuelled to embark us on exploratory investigation on this issue. Herein, we describe our investigational findings on regioselective Suzuki reactions of pyridines that led to the unexplored synthesis of arylpyridines and benzylpyridines, which could be used as advanced intermediates in the synthesis of pyridine-fused heterocycles. Indeed, arylpyridines and benzylpyridines are demonstrated to undergo palladium-catalyzed intramolecular cyclization to the synthesis of azafluorenes and azafluorenones in the current study. The regioselective Suzuki reactions on pyridines and subsequent intramolecular cyclizations of the compounds described in this study may fall under preliminary investigation. Taken together, the current study should merit as further advancement on pyridine chemistry.

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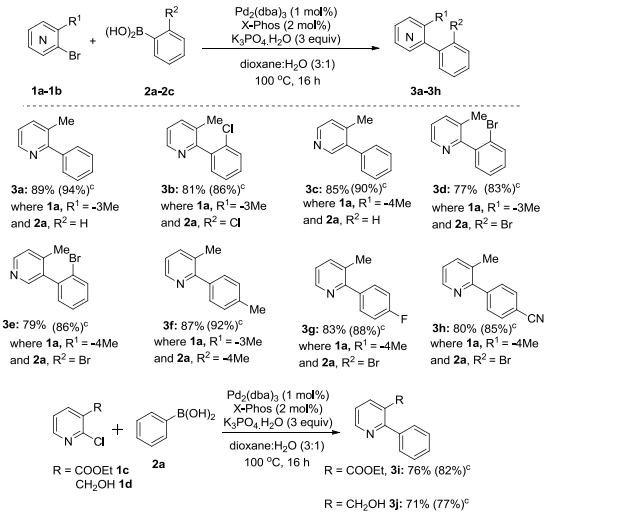
Result and discussion

Synthesis of Arylpyridines

Our initial investigation was largely focused on regioselective Suzuki reactions on 2,3-diahlopyridines and 2-halo-3-halomethylpyridines. Unlike Suzuki reactions of haloarenes with aryl boronic acids or boronates, halopyridines could feature distinct reactivity depending upon the position of the halogen on the pyridine ring. Suzuki reaction of substituted 2- or 3-bromopyridine and 2-substituted phenylboronic acids in the presence of $Pd_2(dba)_3$, X-Phos and $K_3PO_4.H_2O$ in 1,4 dioxane:H_2O (3:1) at 100 °C for 16 h gave the corresponding 2- and 3-arylpyridines **3a-3e** in 77-89% yields (Scheme 1). In addition, 4-substituted boronic acids also underwent Suzuki coupling with halopyridines to successfully form the corresponding products **3f-3h** in good yields. Apparently, 2-bromopyridine parallels the reactivity of 3-bromopyridine under this condition. Similarly, substituted 2-chloropyridines react with phenylboronic acid affording 2-arylpyridines **3i** and **3j** in 76% and

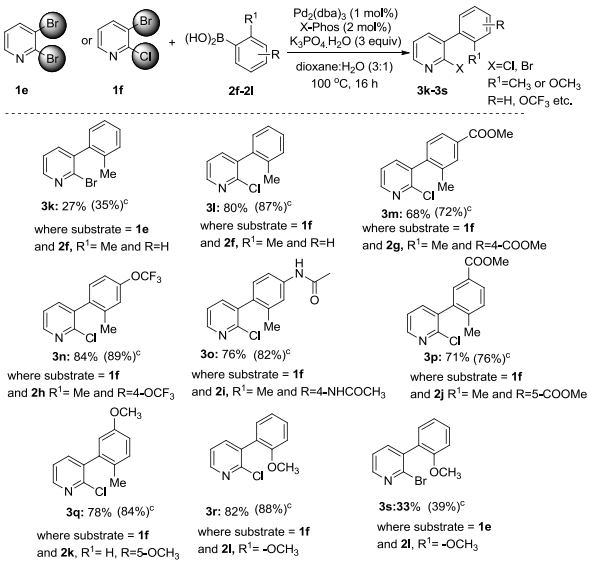
71% yields, respectively. While a direct comparison of the reactivity of 2-bromopyridine and 2-chloropyridine is difficult from these studies, both of them react under Suzuki condition to give the corresponding arylated products. The question remains whether both 2- and 3-halogen in 2,3-dihalopyridine would react similarly under Suzuki condition to yield a double arylated product, or a regioselective Suzuki reaction of 2,3-dihalopyridine would be possible to develop.



[a] Reaction conditions:**1a-1b** (0.25 mmol), **2a-2c** (0.27 mmol), Pd-catalyst (1 mol%), ligand (2 mol%), base (3.0 equiv), solvent (1 mL), 16 h. [b] Isolated yield, [c] yield in the parenthesis is conversion on the basis of HPLC.

Scheme 1 Suzuki reactions on 2- or 3-bromo/chloropyridines.

Indeed, reaction of 2,3-dibromopyridine and 2-methylphenylboronic acid in the presence of $Pd_2(dba)_3$, X-Phos and $K_3PO_4.H_2O$ in dioxane:H_2O (3:1) at 100 °C for 16 h gave only 3-arylpyridine **3k** in 27% yield (Scheme 2).



a Reaction conditions:**1e** or **1f** (0.25 mmol), **2f-2l** (0.27 mmol), Pd-catalyst (1mol%), ligand (2 mol%), base (3 equiv), solvent (1 mL), 16 h. [b] Isolated yield, [c] yield in parenthesis is the conversion on the basis of HPLC.

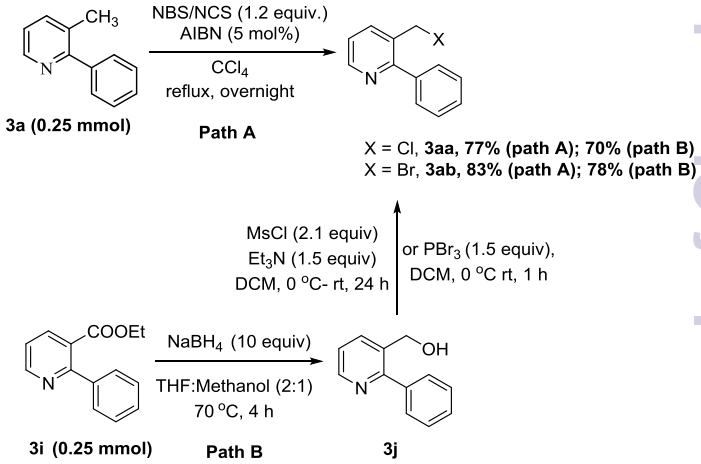
Scheme 2 Regioselective Suzuki reactions on 2,3-dihalopyridines.

Importantly, Suzuki reaction occurred selectively at the 3-position of 2,3-dibromopyridine affording 3-arylpyridine **3k**. It should be mentioned that the starting material remain unreacted in case of 2,3 dibromo pyridine with formation of one side (**3k**) and two side Suzuki product (**3k'**) (see S.I. for NMR) due to the equal reactivity of both bromo substituents on pyridine ring.

Moreover, another comparable study was performed wherein substituted boronic acid reacted with 2,3-dibromopyridine and 2-chloro-3-bromopyridine yielding the products **3r** and **3s** in 82% and 33% yields, respectively.

Similarly, reaction of 3-bromo-2-chloropyridine and 2-methylphenylboronic acid resulted in the formation of **3l** under the similar condition. Furthermore, investigation of the reactions of substituted 3-bromo-2-chloropyridine and 2-methylphenylboronic acid under the similar condition resulted in the preparation of substituted 3-arylpyridines containing the 2-chloro group. Perhaps most importantly, the current investigation unveiled that 2-halo and 3-halo present in 2,3-dihalopyridines could exhibit different reactivity profile towards arylboronic acid. It is important to note here that the arylpyridines bearing a halogen could potentially be used as building blocks for the preparation of pyridine fused heterocycles.

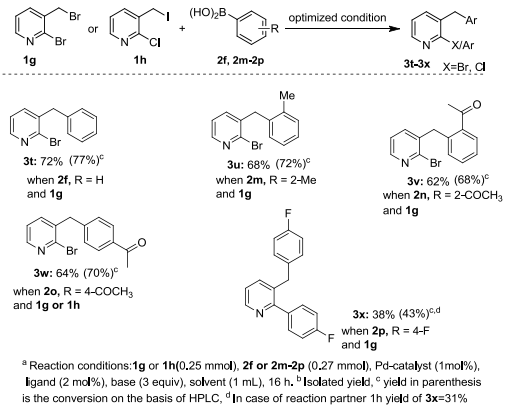
Further synthetic manipulations provided arylpyridines containing a halomethyl group poised for intramolecular cyclization (Scheme 3). Thus, halogenations of arylpyridine **3a** with NBS or NCS in the presence of a catalytic amount of AIBN produced arylpyridines **3aa-3ab** (Path A) containing a haolmethyl group. These arylpyridines **3aa-3ab** were also prepared from the arylpyridines containing an ester group via reduction followed by halogenations of the hydroxymethyl group (Path B).



Scheme 3 Synthetic manipulations on arylpyridines.

Synthesis of Benzylpyridines: While Suzuki reactions of halopyridines have been well investigated, reactions of halomethyl pyridines with arylboronic acids under Suzuki conditions remain underdeveloped, however in some cases with other heteroarenes are known.[12] Unlike oxidative addition of palladium (0) into the C-Br bond of pyridine, the oxidative addition of palladium (0) into the benzylic -CH_2-Br bond of pyridine would seem difficult to achieve.[13] More precisely, regioselectivity in Suzuki reactions of pyridines

containing both halogen and halomethyl group has been a rare investigation. Considering these cumulative limitations, exploration of regioselective Suzuki reactions on *2*-halo-3-halomethylpyridines, which could provide arylpyridines containing a halomethyl group, or benzylpyridines containing a halogen group was the focus of our subsequent investigation. Reaction of 2-bromo-3-bromomethylpyridine and arylboronic acid under Suzuki conditions gave the coupled product **3t** corresponding to the reaction at 3-bromomethyl site. The reaction demonstrated a reasonable substrate scope including use of 2-methyl, 2-acetyl, and 4-acetylphenyl boronic acids as the coupling partner. However, 4-fluorophenyl boronic acid gave a double Suzuki coupled product **3t** arising from reactions at both 2-bromo and 3-bromomethyl sites. In this case, attempted isolation of a regioselective Suzuki product was unsuccessful. The use of a seemingly different reaction partner, 2-chloro-3-iodomethylpyridine **1h** also gave **3x**. Further attempt was made involving the reaction between o-halo-o´-bromomethylpyridine and 4-cyano-phenylboronic acid. However, only a poor regioselectivity was observed. Attempted efforts to improve the regioselectivity by decreasing the amount or changing the base were unsuccessful. The current investigation disclosed that 2-halo and 3-halomethyl present in 2-halo-3-halomethylpyridines could exhibit different reactivity profile towards arylboronic acid. Notably, regioselective Suzuki reaction at the 2-position in 2-halo-3-halomethylpyridines could possess significant challenge and is the subject of further investigation.



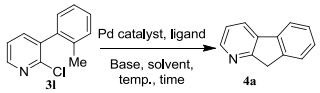
[a] Reaction conditions:**1g** or **1h**(0.25 mmol), **2f or 2m-2p** (0.27 mmol), Pd-catalyst (1mol%), ligand (2 mol%), base (3 equiv), solvent (1 mL), 16 h. [b] Isolated yield. [c] yield in parenthesis is the conversion on the basis of HPLC, [d] In case of reaction partner 1h yield of **3x**=31%

Scheme 4 Scope of selective Suzuki coupling on o-halo-o´-halomethylpyridine.

Intramolecular Cyclization of Arylpyridines and Benzylpyridines to the Synthesis of Azafluorenes: Among various heterocycles embedded with pyridine nucleus, azafluorenes and azafluorenones contribute a major part.[14] Many of them are effective physiologically active substances with sedative, neuroleptic, antihistamine, antibacterial, antioxidant, pesticide and adrenolytic activities.[15] Derivatives of azafluorene have been found to produce marked effects on the CNS disorders.[16] They also possess good emission and absorption properties, which make them useful in the preparation of dyes and light emitting materials.[17] However, a few literatures are available for the synthesis of azafluorenes.[18] Some reports have used prefunctionalized moieties for the synthesis of this privileged scaffold.[18f] Although fluorenes are structurally similar to azafluorenes, many synthetic approaches dealing with the synthesis of fluorenes have been found incompatible for azafluorene synthesis.[19] Moreover, arylpyridines or benzylpyridines have never been demonstrated to the synthesis of azafluorenes. Leveraging our previous experiences on the synthesis of pyridine fused heterocycles,[20] we decided to explore further the palladium-catalyzed intramolecular cyclizations of arylpyridines and benzylpyridines prepared in this study.

Intramolecular cyclization reactions of **3l** in the presence of a palladium-catalyst, ligand, base and solvent were examined (Table 1). Thus, heating **3l** in the presence of 10 mol% $Pd(OAc)_2$, BINAP, and Na_2CO_3 in DMA for 24 h resulted in the formation of **4a** in 34% yield (entry 1). Subsequent experimentations revealed that an alkyl phosphine has tremendous influence in the reaction affording **4a** in 87% yield (entries 2-5). The other bases had an adverse effect in the reaction (entries 6-8). Similarly, the other solvents exerted deleterious effect in the reaction (entries 9-11). A different palladium also did not prove effective (entries 12-13).

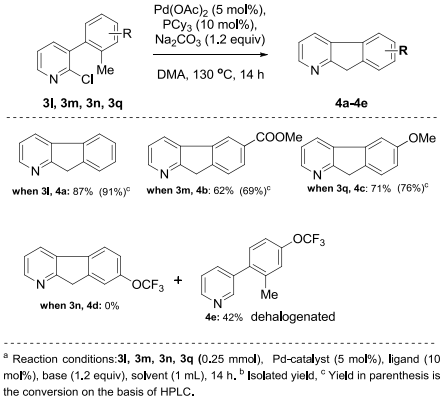
Table 1 Intramolecular cyclization of arylpyridines to azafluorenes[a]



Entry	Catalyst	Ligand	Base	Solvent	Temp(°C)	Yield[b] (%)
1	$Pd(OAc)_2$	BINAP	Na_2CO_3	DMA	130	34
2	$Pd(OAc)_2$	PPh_3	Na_2CO_3	DMA	130	0
3	$Pd(OAc)_2$	PCy_3	Na_2CO_3	DMA	130	87
4	$Pd(OAc)_2$	$P(o\text{-}tol)_3$	Na_2CO_3	DMA	130	0
5	$Pd(OAc)_2$	X-Phos	Na_2CO_3	DMA	130	25
6	$Pd(OAc)_2$	PCy_3	Cs_2CO_3	DMA	130	22
7	$Pd(OAc)_2$	PCy_3	K_2CO_3	DMA	130	06
8	$Pd(OAc)_2$	PCy_3	CsF	DMA	130	13
9	$Pd(OAc)_2$	PCy_3	K_2CO_3	DMF	130	0
10	$Pd(OAc)_2$	PCy_3	Na_2CO_3	1,4 Dioxane	110	08
11	$Pd(OAc)_2$	PCy_3	Na_2CO_3	Toluene	110	16
12	$PdCl_2$	PCy_3	Na_2CO_3	DMA	130	12
13	$Pd(PPh_3)_4$	PCy_3	Na_2CO_3	DMA	130	0

[a] Reaction conditions: 3l (0.25 mmol), Pd-catalyst (5 mol%), ligand (10 mol%), base (1.2 equiv), solvent (1 mL), 24 h. [b] Isolated yield.

Having optimized condition in hand, we further investigated intramolecular cyclization of various arylpyridines prepared in this study to the synthesis of azafluorene (Scheme 5).

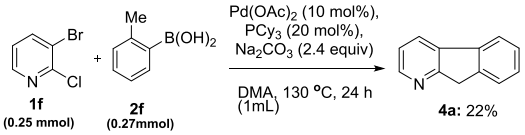


[a] Reaction conditions:**3l, 3m, 3n, 3q** (0.25 mmol), Pd-catalyst (5 mol%), ligand (10 mol%), base (1.2 equiv), solvent (1 mL), 14 h. [b] Isolated yield. [c] Yield in parenthesis is the conversion on the basis of HPLC.

Scheme 5 Substrate scope for azafluorene synthesis.

A small set of examples to the synthesis of azafluorenes have been prepared. However, azafluorene[4d] containing a -OCF_3 group was not obtained under the condition. Instead, a dehalogenated product 4e was obtained in this case.

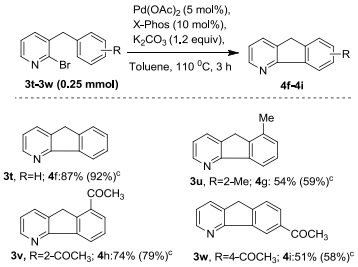
Having successfully prepared the azafluorenes in two steps, we further investigated the opportunity of integrating two steps into a one-pot strategy.



Scheme 6 One-pot synthesis of azafluorene.

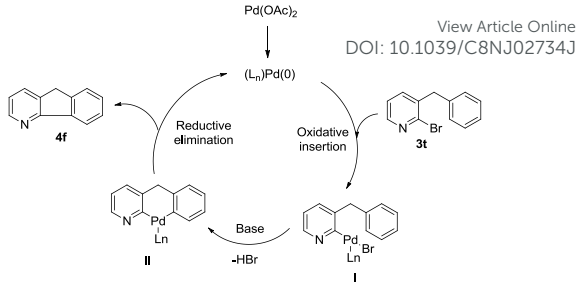
Thus, a regioselective Suzuki coupling of 2-chloro-3-bromopyridine and tolylboronate followed by intramolecular cyclization of the coupling product, generated in situ, yielded azafluorene **4a** albeit in low yield (Scheme 6).

Subsequent to the intramolecular cyclization of arylpyridines, we investigated the scope of intramolecular cyclization of benzylpyridines to the synthesis of azafluorenes (Scheme 7). Benzylpyridines have been utilized for various applications including in biological and material chemistry.[21] However, their intramolecular cyclizations to the synthesis of azafluorenes, to the best of our knowledge, remain unexplored. While the optimized reaction condition that was successful affecting the intramolecular cyclization of arylpyridines, further experimentation was required to showcase an intramolecular cyclization on benzylpyridines. Thus, heating a solution of benzylpyridines in the presence of palladium acetate (10 mol%), X-Phos (20 mol%) and K_2CO_3 in toluene at 110 °C for 3 h gave the cyclized products **4f-4i** in 51-87% yields. The current investigation pertaining to the intramolecular cyclization of benzylpyridines could complement the synthesis of azafluorenes available in literature.



Scheme 7 Substrate scope in the synthesis of azafluorene.

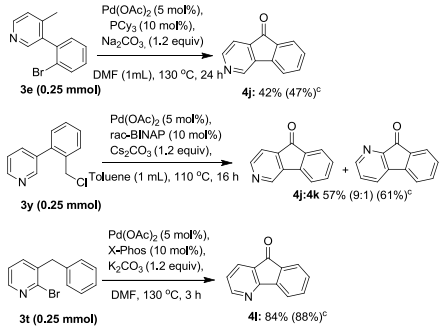
The mechanism for the synthesis of azafluorene is presented in scheme 8. Initially oxidative insertion of Pd^0 to aryl halide could give intermediate **I**. Further, nucleophilic displacement could give intermediate **II** and then reductive elimination could give azafluorenone formation.



Scheme 8 Mechanism involves in the synthesis of azafluorene.

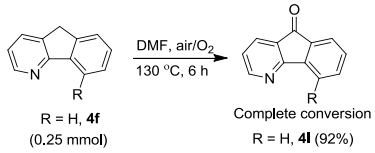
Intramolecular Cyclization of Arylpyridines to the Serendipitous Synthesis of Azafluorenones:

As described in the previous section, intramolecular sp^3 C-H arylation of 3-arylpyridines containing an ortho-methyl group on the phenyl ring gave 1-azafluorene. In contrast, reaction of 3-arylpyridines containing an ortho-methyl group on the pyridine ring yielded serendipitous formation of 3-azafluorenone **4j** in 42% yield under a slightly modified condition [$Pd(OAc)_2$ (10 mol%), PCy_3 (20 mol%), Na_2CO_3 (1.2 equiv), DMF (4 mL/mmol), 130°C, 24 h). It is noteworthy that sp^3 C-H functionalization of unactivated pyridine, considered to be a challenging task, has been achieved in this preliminary investigation. Subsequently, palladium-catalyzed intramolecular benzylation of 3-pyridylbenzyl chloride **3y** was investigated. After several experimentations, intramolecular cyclization of **3y** produced a mixture of 3-azafluorenone **4j** and 1-azafluorenone **4i** (Scheme 9) in a combined 57% yield with a high regioselectivity (9:1). The viability of a complementary approach was also investigated wherein alkyl halide group is present on the pyridine ring. Indeed, palladium-catalyzed intramolecular benzylation of (3-bromomethyl)-2-phenylpyridine also gave 4-azafluorenone **4k** in 84% yield.



Scheme 9 Serendipitous synthesis of azafluorenones.

A control experiment to understand the mechanism of the formation of azafluorenones indicated that azafluorene could undergo oxidation in the presence of air or oxygen. Thus, heating 4-azafluorenenes **4f** in DMF at 130 °C for 6 h led to the formation of their corresponding azafluorenones **4l**. Further experiments are required to confirm the formation of azafluorenones in these intramolecular cyclizations (Scheme 10).



Scheme 10 Understanding the mechanism for the synthesis of azafluorenones.

Conclusion

In conclusion, we have developed regioselective Suzuki reactions on pyridines that led to the unexplored synthesis of arylpyridines and benzylpyridines. The arylpyridines and benzylpyridines prepared in this study were subjected to the palladium-catalyzed intramolecular cyclizations affording novel syntheses of azafluorenes and azafluorenones. Although a preliminary investigation has been described herein, the current study could reflect further advancement on pyridine chemistry.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Scope of regioselective Suzuki reactions in the synthesis of arylpyridines and benzylpyridines and subsequent intramolecular cyclizations to azafluorenes and azafluorenones

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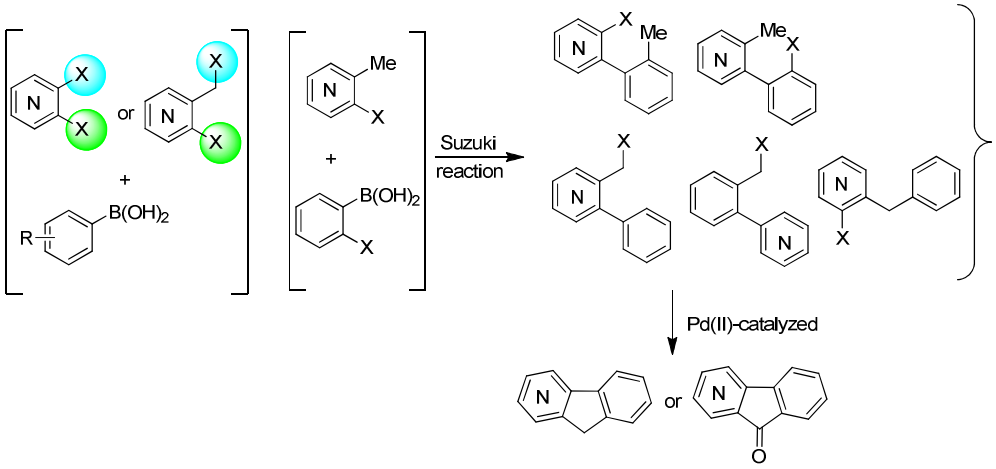

The current investigation on regioselective Suzuki reactions of *2*,3-dihalopyridines and *2*-halo-3-halomethylpyridines yielded unexplored synthesis of arylpyridines and benzylpyridines bearing synthetic handles for further functionalizations. Indeed, the scope of intramolecular cyclizations of arylpyridines and benzylpyridines prepared in this study in the synthesis of azafluorenes and azafluorenones has been investigated.