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Mohamed Niyaz Vellala Syed Ali, Linhao Liu, Monika Ravi, Henri Doucet. Synthesis of Heteroarylated Pyridines via a Double C-H Bond Functionalization using Palladium-catalyzed 1,4-Migration Combined with Direct Arylation. *ChemCatChem*, 2023, *Chemcatchem*, 16 (3), pp.e202301226. 10.1002/cctc.202301226 . hal-04415205

HAL Id: hal-04415205

<https://hal.science/hal-04415205v1>

Submitted on 10 Oct 2024

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Synthesis of Heteroarylated Pyridines via a Double C–H Bond Functionalization using Palladium-catalyzed 1,4-Migration Combined with Direct Arylation

Mohamed Niyaz Vellala Syed Ali,^[a] Linhao Liu,^[a] Monika Ravi,^[a] and Henri Doucet*^[a]

The C–H bond functionalization of pyridyl C3-position of 4-arylpyridines using Pd 1,4-migration has been investigated. Under suitable reaction conditions, oxidative addition of 4-(2-bromoaryl)pyridines to palladium followed by a Pd 1,4-migration activates these pyridyl C3-positions. Next, the Pd-catalyzed coupling *via* C–H bond activation of the heteroarenes affords the C3-heteroarylated 4-arylpyridines. The new C–C bond created in this coupling reaction results from the functionaliza-

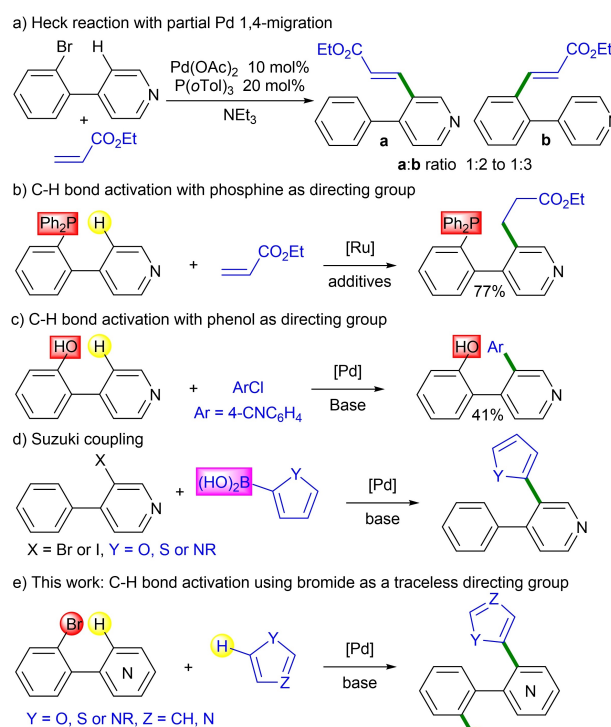
tion of two C–H bonds. For this coupling reaction, a bromo-substituent on the aryl unit of 4-arylpyridines was employed as a traceless directing group. This heteroarylation method tolerates a range of substituents on the benzene ring as well as several heteroarenes. Moreover, from 3-arylpyridines, C2- or C4-functionalization of the pyridine ring also proved possible. In addition, this procedure uses an air-stable catalyst and an inexpensive base.

Introduction

Pyridine derivatives are ubiquitous in pharmaceutical compounds and organic materials.^[1] Consequently, the discovery of new effective routes to these compounds, enabling the functionalization of specific positions, is a very important aspect of current research involving pyridine derivatives.^[2] Metal-catalyzed C–H bond activation/functionalization of (hetero)arenes currently represents one of the simplest method for the preparation of bi(hetero)aryls.^[3–8] However, to our knowledge, the synthesis of 4-aryl-3-heteroarylpyridines *via* activation of the C–H bond at the C3-position of pyridines has not been reported to date.

We recently reported that during the Pd-catalyzed direct heteroarylation of 2-(2-bromoaryl)thiophenes, partial Pd 1,4-migration^[9,10] occurred at the thienyl β -positions,^[11] leading to a mixture of 1,2-diheteroarylated benzenes and also to β -heteroarylated 2-arylthiophene derivatives such as 2'-aryl-2,3'-bithiophenes. This Pd 1,4-migration methodology is an appealing method for functionalizing C–H bonds in proximity to 2-bromoaryl units. We have therefore tried to extend this methodology to (2-haloaryl)pyridines. To date, little is known about Pd-catalyzed 1,4-migration of these substrates. Gallagher et al. reported that the Heck reaction of 4-(2-bromoaryl)pyridines with an acrylate gave a mixture of the classical Heck type product and also the Pd 1,4-migration

vinylation product in a ratio of 2:1 to 3:1 (Scheme 1, a).^[12] Activation of the C–H bond in the C3 position of the pyridyl ring of 4-arylpyridines using a phosphine or phenol as directing groups has also recently been described (Scheme 1, b and c).^[13] However, in general the current preparation of 4-aryl-3-heteroarylpyridine derivatives still requires a multi-step syn-



Scheme 1. Pd-catalyzed functionalization of the C3-position of the pyridyl unit of 4-arylpyridines.

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Supporting information for this article is available on the WWW under <https://doi.org/10.1002/cctc.202301226>

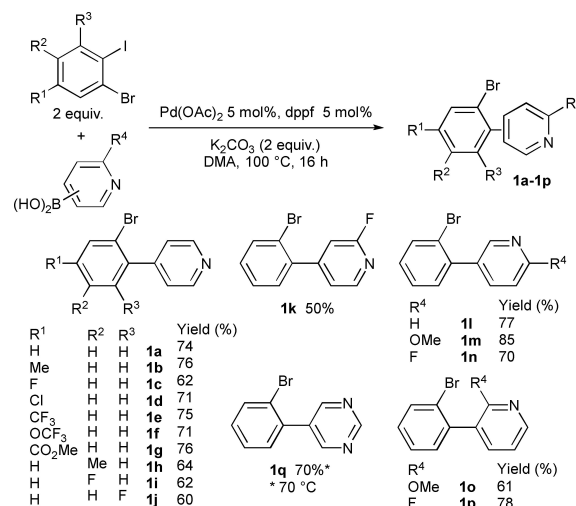
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thesis. In many cases, this involves the preparation of 4-halo-3-heteroarylpyridines, which is rather difficult, as the last step in their synthesis generally consists of Suzuki coupling between bromopyridines and heteroaryl boronic acids (Scheme 1, d).^[14] Consequently, the outcome of Pd-catalyzed direct arylation reaction of 4-(2-bromoaryl)pyridines needed to be explored. Our aim was to find conditions favoring Pd 1,4-migration associated with direct arylation for access to 4-aryl-3-heteroarylpyridines *via* a double C–H bond functionalization. Here, we report *i*) the conditions for Pd-catalyzed regioselective direct heteroarylations of the pyridyl unit of 4-(2-bromoaryl)pyridines using bromide substituent as a traceless directing group,^[15] *ii*) and on the scope the Pd 1,4-migration associated with direct arylation for the formation of 4-aryl-3-heteroarylpyridines *via* a double C–H bond functionalization, *iii*) on the reactivity of 3-(2-bromoaryl)pyridines (Scheme 1, e).

Results and Discussion

First, we prepared a set of 3- or 4-(2-bromoaryl)pyridines *via* Suzuki coupling of 3- and 4-pyridineboronic acids with 1-bromo-2-iodobenzenes (Scheme 2).^[13] The desired arylated pyridines **1a–1p** were obtained in good yields in all cases. 5-(2-Bromophenyl)pyrimidine **1q** was prepared from pyrimidin-5-ylboronic acid and 1-bromo-2-iodobenzene by the same method.

Next, the selectivity of the Pd-catalyzed reaction of 4-(2-bromophenyl)pyridine **1a** with 2-isopropyl-4-methylthiazole was investigated (Table 1). A high selectivity of 87% for the desired Pd-catalyzed 1,4-migration product **2a** was obtained using 2 mol% Pd(OAc)₂ catalyst combined with KOAc base in DMA at 150 °C; while the product **2b** resulting from the heteroarylation of the aryl unit was obtained with a selectivity of 13%. (Table 1, entry 1). However, with this phosphine-free



Scheme 2. Preparation of the (2-bromoaryl)pyridines **1a–1p** and 5-(2-bromophenyl)pyrimidine **1q**.

Table 1. Influence of the reaction conditions on the Pd-catalyzed coupling of 4-(2-bromophenyl)pyridine **1a** with 2-isopropyl-4-methylthiazole.^[a]

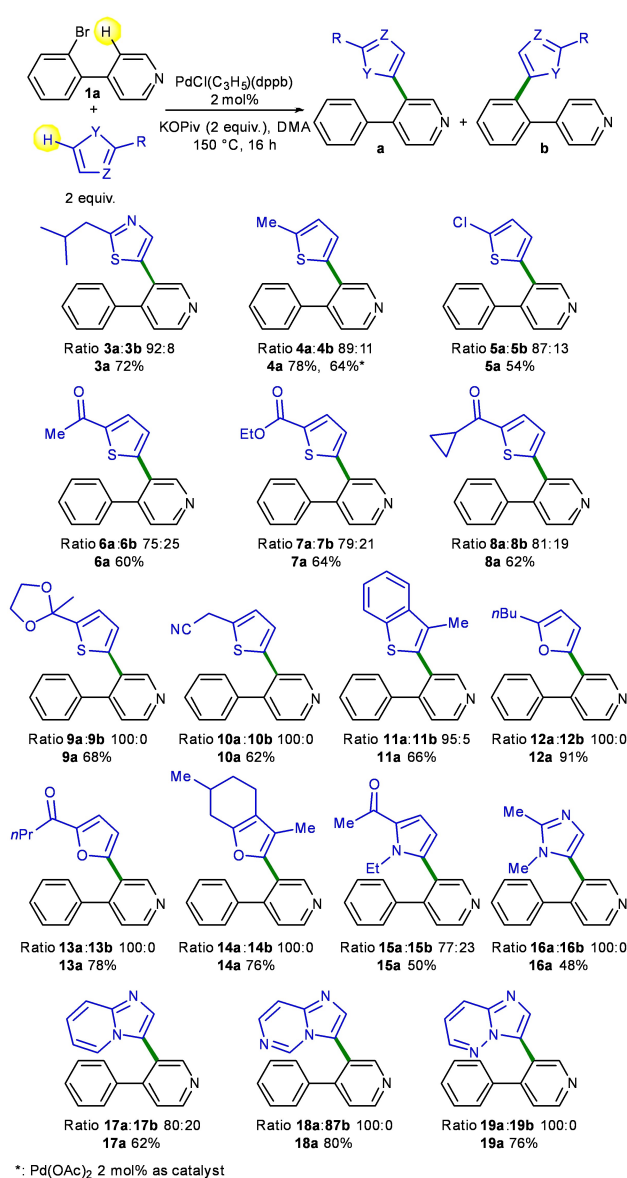
Entry	Catalyst	Solvent	Base	Conv. (%)	Ratio 2a : 2b	Yield in 2a (%)
1	Pd(OAc) ₂	DMA	KOAc	94	87:13	60
2	PdCl(C ₃ H ₅)(dppb)	DMA	KOAc	100	87:13	61
3	PdCl(C ₃ H ₅)(dppb)	DMA	Cs ₂ CO ₃	45	–	–
4	PdCl(C ₃ H ₅)(dppb)	DMA	K ₂ CO ₃	15	–	–
5	PdCl(C ₃ H ₅)(dppb)	DMA	NaOAc	100	88:12	58
6	PdCl(C ₃ H ₅)(dppb)	DMA	CsOAc	56	78:22	–
7	PdCl(C ₃ H ₅)(dppb)	DMA	KOPiv	100	89:11	63
8	PdCl(C ₃ H ₅)(dppb)	DMF	KOAc	100	89:11	60
9	PdCl(C ₃ H ₅)(dppb)	NMP	KOAc	100	85:15	57
10	PdCl(C ₃ H ₅)(dppb)	xylene	KOAc	0	–	–
11	PdCl(C ₃ H ₅)(dppb)	xylene	CsOAc	0	–	–
12	PdCl(C ₃ H ₅)(dppb)	xylene	KOPiv	0	–	–
13	PdCl(C ₃ H ₅)(dppb)	DEC	KOAc	0	–	–
14	PdCl(C ₃ H ₅)(dppb)	TBAA ^[b]	KOAc	100	88:12	61
15	PdCl(C ₃ H ₅)(dppb)	DMA	KOAc	33	91:9	– ^[c]

[a] [Pd] (0.02 equiv.), 4-(2-bromophenyl)pyridine **1a** (1 equiv.), 2-isopropyl-4-methylthiazole (2 equiv.), base (2 equiv.), 150 °C, 16 h, **2a**:**2b** ratios determined by ¹H NMR and GC/MS analysis of the crude mixtures, isolated yields. [b] TBAA: tetrabutylammonium acetate (2 mL). [c] 130 °C.

catalyst, conversion of **1a** was not complete, therefore we used PdCl(C₃H₅)(dppb)^[16] catalyst which gave a similar **2a**:**2b** selectivity of 87:13 and a **2a** yield of 61% with full conversion of **1a** (Table 1, entry 2). The use of carbonate bases Cs₂CO₃ and K₂CO₃ proved ineffective, and the formation of several unidentified products was observed (Table 1, entries 3 and 4). In contrast, NaOAc and CsOAc led to good selectivities in **2a** and KOiPr gave **2a** in 89% selectivity and 63% yield (Table 1, entries 5–7). We also determined the influence of solvent, but DMF and NMP led to slightly lower yields in **2a**; while xylene and DEC were ineffective (Table 1, entries 8–13).^[17] Using tetrabutylammonium acetate (TBAA) as solvent, **2a** was obtained with a good selectivity of 88% and a yield of 61% (Table 1, entry 14).^[18] This solvent could therefore replace DMA, which is undesirable from the point of view of sustainable chemistry. A lower reaction temperature of 130 °C instead of 150 °C provided **2a**:**2b** with similar selectivity (91:9) but low yield due to partial conversion of **1a** (Table 1, entry 15).

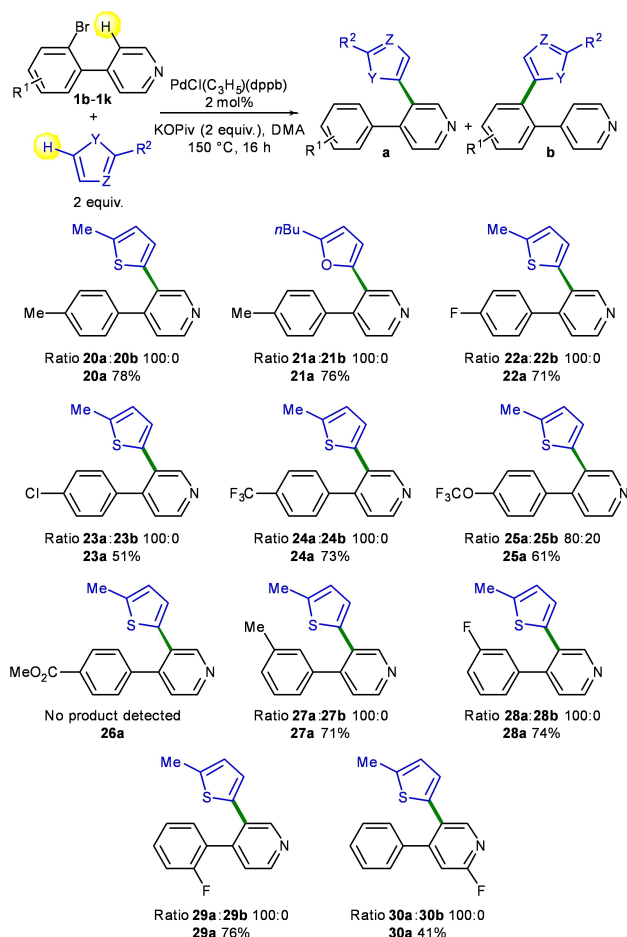
Then, the scope of the coupling reaction of 4-(2-bromophenyl)pyridine **1a** with a set of heteroarenes was studied (Scheme 3). From 2-isopropylthiazole and **1a**, we obtained an **a**:**b** ratio of 92:8 with the formation of the Pd 1,4-migration product **3a** in 72% yield. In the presence of 2-methylthiophene and 2-chlorothiophene, very high **a** isomers selectivities were also observed, and products **4a** and **5a** were isolated in 78% and 54% yield, respectively. No cleavage of the C–Cl bond of the thienyl ring was observed, allowing further transformations. Slightly lower **a** isomers selectivities were achieved using 2-acetylthiophene, ethyl thiophene-2-carboxylate and cyclopropyl-2-thienylketone affording products **6a**–**8a** in yields of 60–64%. In contrast, in the presence of 2-methyl-2-(thiophen-2-yl)-1,3-dioxolane and 2-(thiophen-2-yl)acetonitrile, only the **9a** and **10a** isomers were detected. 3-Methylbenzothiophene gave **11a** with 95% selectivity and 66% yield. Furan derivatives were also suitable substrates for this reaction. 2-Butylfuran and 1-furan-2-ylbutan-1-one afforded products **12a** and **13a** with 100% selectivity and in good yields. The natural product menthofuran was also used successfully, affording product **14a** with complete selectivity and 76% yield. Conversely, quite sluggish reactions were observed with a 2-acetylpyrrole and 1,2-dimethylimidazole, with the formation of **15a** and **16a** in only 50% and 48% yield, respectively due to the formation of some unidentified side-products. Imidazo[1,2-*a*]pyrazine, imidazo[1,2-*c*]pyrimidine and imidazo[1,2-*b*]pyridazine afforded products **17a**–**19a** in 62–80% yields.

We had previously observed that with 2-(2-bromoaryl)thiophenes, Pd 1,4-migration was favored by the presence of electron-donating substituents on their aryl moiety, whereas electron-withdrawing substituents led to mixtures of products due to partial Pd 1,4-migration.^[11] Therefore, the selectivity of the reaction using a set of 4-(2-bromophenyl)pyridine bearing a *para*-substituent on the aryl unit was investigated (Scheme 4). As expected, the presence of a methyl *para*-substituent (**1b**) using 2-methylthiophene and 2-butylfuran as reaction partners had practically no influence, affording the products **20a** and **21a** with 100% selectivity and 78% and 76% yield, respectively. The electron-deficient 4-



Scheme 3. C3-heteroarylations of the pyridyl ring of 4-(2-bromophenyl)pyridine **1a** via Pd 1,4-migration combined with direct arylation.

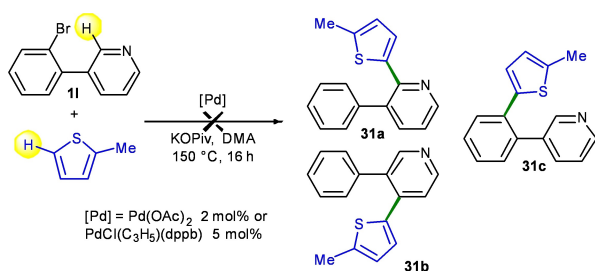
arylpyridines **1c** and **1e** substituted with 4-fluoro and 4-trifluoromethyl, were also well tolerated, with the selective formation of Pd 1,4-migration products **22a** and **24a** in similar yields. Conversely, a 4-trifluoromethoxy substituent (**1f**) gave a mixture of products **25a** and **25b** in 80:20 ratio, and an ester substituent (**1g**) gave no coupling products **26a** or **26b** but decomposition of 4-arylpyridine **1g** was observed. The low selectivity for product **25a** is possibly due to the coordination of the OCF₃ group to palladium. Methyl or fluoro substituents at *meta*-position of the 4-arylpyridine (**1h** and **1i**) gave products **27a** and **28a** with complete selectivity and yield of 71% and 74%, respectively. An *ortho*-fluoro substituent was also well tolerated and furnished product **29a** in similar yield. The selectivity of the reaction with a 4-(2-bromophenyl)pyridine bearing a 2-fluoro substituent on the pyridine ring **1k** was also



Scheme 4. C3-heteroarylations of the pyridyl ring of 4-(2-bromophenyl)pyridine derivatives **1b-1k** via Pd 1,4-migration combined with direct arylation.

studied. The heteroarylation was regioselective in favor of the C5-position of the pyridyl ring to give **30a**.

To determine the influence of the position of the nitrogen atom on the pyridine ring on the reactivity and selectivity of the Pd 1,4-migration/direct arylation reaction, the result of the reaction with 3-(2-bromophenyl)pyridine **1j** was examined (Scheme 5). Using 2-methylthiophene as the reaction partner, no formation of coupling products **31a-c** was detected by GC/MS analysis with $\text{Pd}(\text{OAc})_2$ (2 mol%) or $\text{PdCl}(\text{C}_3\text{H}_5)(\text{dppb})$

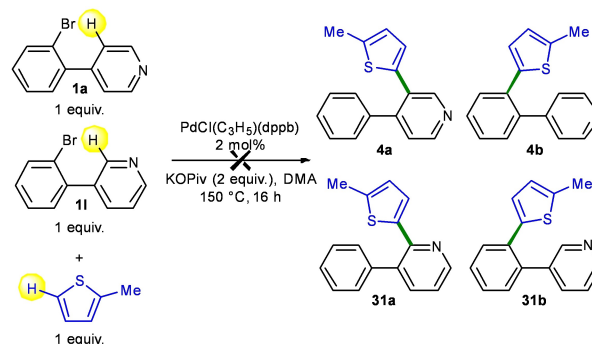


Scheme 5. Reactivity of 3-(2-bromophenyl)pyridine **1j** with 2-methylthiophene.

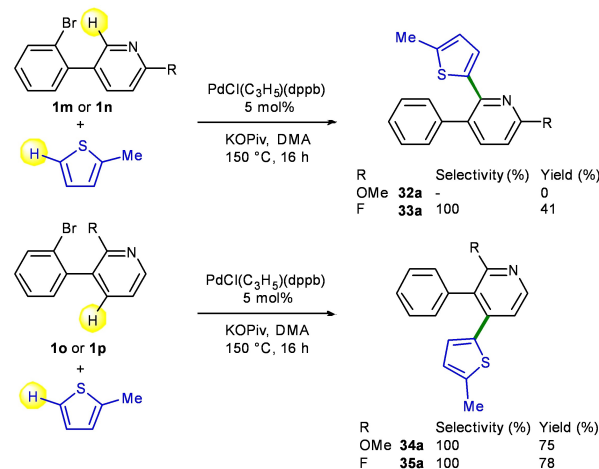
(5 mol%) catalysts, and 3-(2-bromophenyl)pyridine **1l** was recovered unreacted. A similar result was observed with 2-butylfuran as the heteroaryl source. This lack of reactivity could be explained by the formation of a stable Pd complex by reaction with 3-(2-bromophenyl)pyridine **1l** or **31a**, as 2-(thiophen-2-yl)pyridines can give stable palladacycles by C–H activation.^[19] With 5-(2-bromophenyl)pyrimidine **1q** in the presence of 2-methylthiophene, an identical result was observed. The starting material **1q** was recovered and no coupling product was detected, which is consistent with the formation of a stable palladacycle.

To confirm the poisoning of the Pd catalyst by 3-(2-bromophenyl)pyridine **1l**, we performed a reaction using an equimolar mixture of 3- and 4-(2-bromophenyl)pyridines **1a** and **1l** with 2-methylthiophene as the heteroaryl coupling partner (Scheme 6). No coupling product formation was detected and arylpyridines **1a** and **1l** were recovered.

The influence of substituents on the adjacent positions of the nitrogen atom of 3-(2-bromophenyl)pyridines was then examined, as their electronic or blocking properties may result in a different reactivity to 3-(2-bromophenyl)pyridine **1l** (Scheme 7). 5-(2-Bromophenyl)-2-methoxypyridine **1m** gave an inseparable mixture of products in very low yields, and a large amount of **1m** was recovered. Conversely, from 5-(2-bromo-



Scheme 6. Reactivity of an equimolar mixture of 3- and 4-(2-bromophenyl)pyridines **1a** and **1l** with 2-methylthiophene.

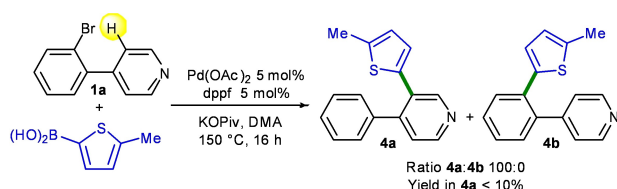


Scheme 7. Reactivity of substituted 3-(2-bromophenyl)pyridines **1m-1p**.

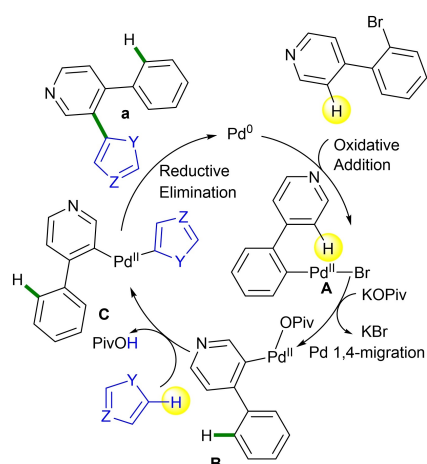
phenyl)-2-fluoropyridine **1n**, we were pleased to observe that regioselective arylation at the C6 position on the pyridine ring was observed to give product **33a** in 41% yield. Both 3-(2-bromophenyl)-2-methoxypyridine **1o** and 3-(2-bromophenyl)-2-fluoropyridine **1p** also reacted nicely to give C4-heteroarylated products **34a** and **35a** in good yields. With these two substrates, the presence of a substituent at the C2-position on the pyridine ring may prevent catalyst poisoning by the formation of palladacycles with 2-(thiophen-2-yl)pyridine derivatives.

The selectivity and yield of the reaction of **1a** with (5-methylthiophen-2-yl)boronic acid instead of 2-methylthiophene using the Pd(OAc)₂/dppf catalyst and KO^tPiv base were also determined (Scheme 8). Selective formation of the product **4a** from 1,4-migration reaction with Suzuki coupling^[20] was also observed, albeit in very low yield (<10%). Consequently, the use of the Pd 1,4-migration reaction in combination with direct arylation seems more attractive than Pd 1,4-migration reaction in combination with Suzuki type coupling for the preparation of such compounds.

A possible mechanism for access to 3-heteroarylated pyridines **a** is described in Scheme 9. The first step is the oxidative addition of aryl bromide to palladium to form intermediate **A**. Next, ligand exchange with KO^tPiv and Pd-1,4-migration provides intermediate **B**. After a concerted metalation deprotonation (CMD)^[21] of the 5-membered ring heteroarene coupling partner, intermediate **C** is produced. Finally, reductive elimination affords 4-aryl-3-heteroarylpyridines **a** with catalyst regeneration.



Scheme 8. Selectivity of the Suzuki coupling with 4-(2-bromophenyl)pyridine **1a** and a thiophen-2-ylboronic acid.



Scheme 9. Proposed catalytic cycle for the access to **a** products.

Conclusions

In summary, bromo-substituent as a traceless directing group was successfully employed to access heteroarylated pyridine derivatives. From both 3- and 4-(2-bromophenyl)pyridines, Pd 1,4-migration combined with direct arylation enabled the introduction of heteroarenes at positions 2, 3 or 4 on the pyridine rings. The new C–C bond created during this coupling reaction, results from the functionalization of two C–H bonds. The reaction proceeds nicely with a wide variety of heteroarenes and tolerates several substituents on the phenyl and pyridine rings of (2-bromophenyl)pyridines. In addition, this procedure employs an air stable palladium source combined with an inexpensive base and readily available 3- or 4-pyridineboronic acids and dihalobenzenes. Consequently, this methodology constitutes a powerful tool for the heteroarylation of pyridines and could certainly be applied to introduce other functional groups on C–H bonds of pyridines.

Experimental section

Procedure for the preparation of arylated arylpyridines 2a–35a: As a typical experiment, the reaction of the (2-bromoaryl)pyridine derivative **1a–1p** (1 mmol), heteroarene (2 mmol) and KO^tPiv (0.280 g, 2 mmol) at 150 °C during 16 h in DMA (4 mL) in the presence of PdCl(C₃H₃)(dppb) (12.2 mg, 0.02 mmol) under argon affords the coupling product after evaporation of the solvent and purification on silica gel using a CombiFlash NextGen 300 with Buchi FlashPure cartridges containing 40 μm irregular silica. The a:b ratios were determined by ¹H NMR and GC/MS analysis of the crude mixtures.

Supporting Information

The authors have cited additional references within the Supporting Information.^[22,23]

Acknowledgements

We are grateful to the CSC for a grant to L. L. We thank CNRS and “Rennes Metropole” for providing financial support.

Conflict of Interests

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: C–H bond activation • Heteroarylation • Homogeneous catalysis • Migration • Palladium • Pyridines

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Manuscript received: October 2, 2023

Revised manuscript received: November 16, 2023

Accepted manuscript online: November 20, 2023

Version of record online: December 20, 2023