Suzuki–Miyaura Cross-Coupling of 2-Pyridyl Trimethylammonium Salts by N–C Activation Catalyzed by Air- and Moisture-Stable Pd–NHC Precatalysts: Application to the Discovery of Agrochemicals

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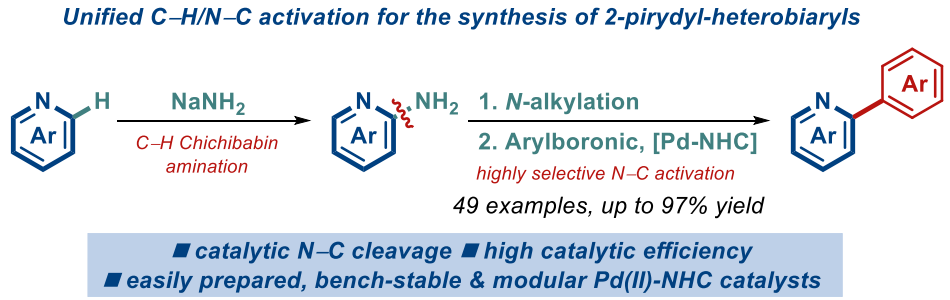
Supporting Information



ABSTRACT: We report the first Suzuki–Miyaura cross-coupling of 2-pyridyl ammonium salts by highly selective N–C activation catalyzed by air- and moisture-stable Pd(II)–NHC (NHC = N-heterocyclic carbene) precatalysts. The use of well-defined and highly reactive [Pd(IPr)(3-CF_3-An)Cl_2] (An = aniline) or [Pd(IPr)(cin)Cl] (cin = cinnamyl) Pd(II)–NHC catalysts permits for exceptionally broad scope of the cross-coupling to furnish valuable biaryl and heterobiaryl pyridines that are ubiquitous in medicinal chemistry and agrochemistry research. The overall process leverages the Chichibabin C–H amination of pyridines with N–C activation to enable an attractive strategy to the 2-pyridyl problem. The utility of the method to the discovery of potent agrochemicals is presented. Considering the importance of 2-pyridines and the versatility of N–C activation methods, we envision that this new C–H/N–C activation strategy will find broad application.

2-Aryl and 2-heteroarylpyridines are among the most important motifs in medicinal chemistry and agrochemistry research.[1] Recent applications in the discovery of small molecule therapeutics that hinge upon 2-arylpyridies include a potent kinase inhibitor, Vactosertib, antimalarial, Enpiroline, neurotoxic agent, Nemertelline, herbicide Halauxifen and many other bioactive compounds (Figure 1A).[2] Furthermore, 2-aryl pyridines are a ubiquitous motif in functional materials, dyes, photovoltaics and ligands, where the properties of the pyridine core are modulated by the aryl or heteroaryl substituent at the 2-position.[3]

The current shortcomings in the development of synthetic approaches to 2-arylpyridines have led to defining the "2-pyridyl problem" in the cross-coupling of pyridyl derivatives as nucleophilic coupling partners (Figure 1B).[4] Although organometallic reagents at the 2-position of the pyridine ring are easily available, the 2-pyridyl-metal bond is prone to protodemetallation, rendering this pathway extremely challenging.[5] Although this challenge can be circumvented by a polarity reversal in the cross-coupling using halopyridines, these substrates are less attractive in medicinal chemistry and agrochemistry research because this approach relies on the availability of prefunctionalized and highly reactive substrates.[4,6]

In this context, we became interested to leverage the well-known C–H Chichibabin amination of pyridines with selective N–C bond activation of 2-pyridyl ammonium salts (Figure 1C).[7,8] We recognized that the recent progress in N–C bond activation may allow for unconventional bond disconnection of 2-aminopyridines,[9a,10] while providing an attractive orthogonal strategy to the 2-pyridyl problem. Herein, we report the development of the first Suzuki–Miyaura cross-coupling of 2-pyridyl ammonium salts by highly selective N–C activation. Studies by MacMillan and Reeves on Ni-catalyzed Suzuki[9b] and Pd-catalyzed Kumada cross-coupling[14] as well as by

Uchiyama on less common organoaluminum reagents[9c] provided support for the hypothesis that the selective oxidative addition could be feasible using well-defined and highly selective Pd(II)–NHCs in combination with common boronic acids. We identified two well-defined, air- and moisture-stable Pd(II)–NHC precatalysts, [Pd(IPr)(3-CF_3-An)Cl_2][10f,11] and [Pd(IPr)(cin)Cl],[12] that permit for exceptionally broad scope of the cross-coupling to furnish valuable biaryl and heterobiaryl pyridines. Furthermore, the utility of the method to the discovery of potent agrochemicals is presented. In light of the broad application of 2-arylpyridines,[1-3] the commercial availability of Pd(II)–NHC precatalysts,[11,12] operational simplicity of the process and the versatility of N–C activation methods,[8-10] we anticipate that this C–H/N–C bond activation strategy will find wide application in organic synthesis.

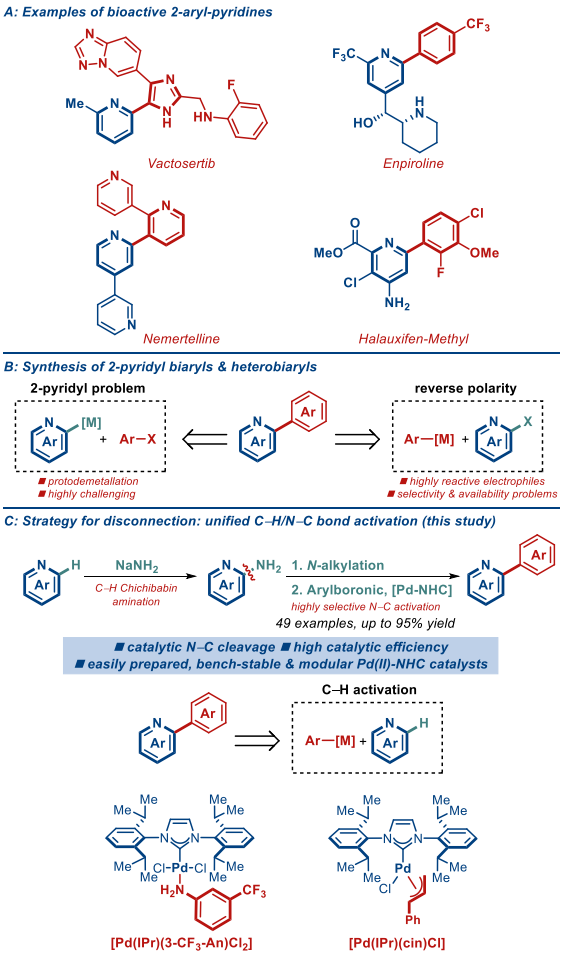
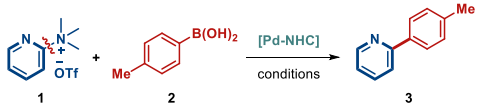


Figure 1. (a) Examples of bioactive 2-arylpyridines (common names given as available). (b) Synthesis of 2-pyridyl biaryls. (c) 2-Pyridyl ammonium salts as an attractive C–H/N–C activation strategy to the 2-pyridyl problem (this study).

The proposed strategy was first evaluated using trimethylammonium 2-pyridine triflate (**1**), the reagent available in bulk via Chichibabin 2-amination and *N*-alkylation,[13,14] and 4-tolylboronic acid (**2**) using [Pd(IPr)(3-CF_3-An)Cl_2] precatalyst bearing 3-CF_3-aniline as an ancillary ligand (Table 1). This catalyst was selected for the initial screen due to the high reactivity of this catalyst in recent N–C bond activation methods developed by our group[10f,11] and facile activation to monoligated Pd(0) compared with other Pd(II)–NHC precatalysts.[15,16] After extensive optimization, we identified conditions using CsF as a base and THF as a solvent at 80 °C that furnished the desired cross-coupling product in 42% yield (entry 1). Evaluation of different bases identified Cs_2CO_3 as the preferred base for this process (entries 2-7). Furthermore, solvent screen found dioxane to be the most suitable (entries 8-9). We determined that the reaction temperature had a significant impact on the yield with optimal temperature of 60 °C under these conditions (entries 10-14). Optimization of the reaction time (entries 15-16) and reagent stoichiometry (entries 17-18) showed that the reaction is highly efficient after shorter reaction time (entry 15) and using stoichiometric amount of base (entry 18), consistent with fast activation of Pd(II)–NHC to Pd(0) and facile oxidative addition of the N–C bond.[17] Next, we determined that the addition of water further improves the yield with 5 equiv of water proving to be optimal (entries 19-22). Finally, we were interested to examine the effect of ammonium salt stoichiometry and found that the reaction is effective at different stoichiometries of boronic acid and trimethylammonium salt (entries 23-25), which is important for selecting valuable substrates in discovery programs.

Table 1. Optimization of the Reaction Conditions[a,b]



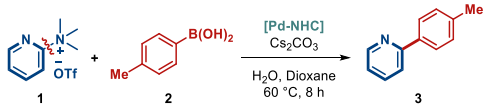
entry	base	solvent	H_2O (equiv)	*T* (°C)	time (h)	yield (%)
1	CsF	THF	0	80	8	42
2	KF	THF	0	80	8	4
3	Cs_2CO_3	THF	0	80	8	58
4	K_3PO_4	THF	0	80	8	16
5	$K_3PO_4 \cdot 3H_2O$	THF	0	80	8	35
6	*t*-BuOK	THF	0	80	8	6
7	K_2CO_3	THF	0	80	8	23
8	Cs_2CO_3	Toluene	0	80	8	36
9	Cs_2CO_3	Dioxane	0	80	8	74
10	Cs_2CO_3	Dioxane	0	40	8	<2
11	Cs_2CO_3	Dioxane	0	60	8	82
12	Cs_2CO_3	Dioxane	0	70	8	72
13	Cs_2CO_3	Dioxane	0	90	8	66
14	Cs_2CO_3	Dioxane	0	100	8	26
15	Cs_2CO_3	Dioxane	0	80	4	72
16	Cs_2CO_3	Dioxane	0	80	12	77
17[c]	Cs_2CO_3	Dioxane	0	80	8	74
18[d]	Cs_2CO_3	Dioxane	0	80	8	70
19	Cs_2CO_3	Dioxane	3	60	8	79
20	Cs_2CO_3	Dioxane	3	80	8	78
21	Cs_2CO_3	Dioxane	5	60	8	93
22	Cs_2CO_3	Dioxane	5	80	8	90
23[e]	Cs_2CO_3	Dioxane	5	60	8	55
24[f]	Cs_2CO_3	Dioxane	5	80	8	85
25[g]	Cs_2CO_3	Dioxane	5	60	8	86

[a]Conditions: **1** (2.0 equiv), **2** (1.0 equiv), [Pd(IPr)(3-CF_3-An)Cl_2] (10 mol%), base (2.0 equiv), solvent (0.20 M), *T*, 8 h. [b]GC/^{1}H NMR yields. [c][Pd-NHC] (3 mol%). [d]base (1.0 equiv). [e]**1**:**2** = 1:1. [f]**1**:**2** = 1:2. [g]**1**:**2** = 1:3.

Next, we evaluated different Pd(II)–NHC precatalysts bearing various ancillary ligands (Table 2, see SI, Chart 1 for structures of catalysts).[10,18] The catalyst selection was guided by the availability of the catalysts and their potential to undergo facile activation to monoligated Pd(0)–NHC complex. We focused on catalyst variations bearing both different NHC ligands and different ancillary throw-away ligands. In particular, we found that the allyl-based catalyst, [Pd(IPr)(cin)Cl], developed by Nolan and co-workers,[12] shows comparable efficiency to [Pd(IPr)(3-CF_3-An)Cl_2] (entries 1-2). Interestingly,

catalysts bearing other ancillary ligands, such as PEPPSI-based [Pd(IPr)(3-Cl-Py)Cl_2] and indenyl-based [Pd(IPr)(*t*-Bu-ind)Cl] were less effective (entries 3-4). Furthermore, examination of the catalysts in the saturated imidazolin-2-ylidene series showed that SIPr ligand is less effective (entries 5-7). Moreover, an IMes-based catalyst was detrimental (entry 8), highlighting that IPr is the privileged ligand for N–C coupling. Further, it should be noted that the SingaCycle A3 catalyst bearing amide palladacycle as an ancillary ligand showed high activity (entry 9), while the chloro-dimer complex, [Pd(IPr)(μ-Cl)Cl]$_2$, was less effective under these conditions despite its well-known fast dissociation to the monomer (entry 10).[18b] A representative Pd–PR_3 complex, [Pd(PPh_3)$_2$$Cl_2$],[19] was unreactive under the reaction conditions (entry 11), showing the expected superior performance of NHC ligands on this coupling.

Table 2. Screening of Pd–NHC Precatalysts[a,b]



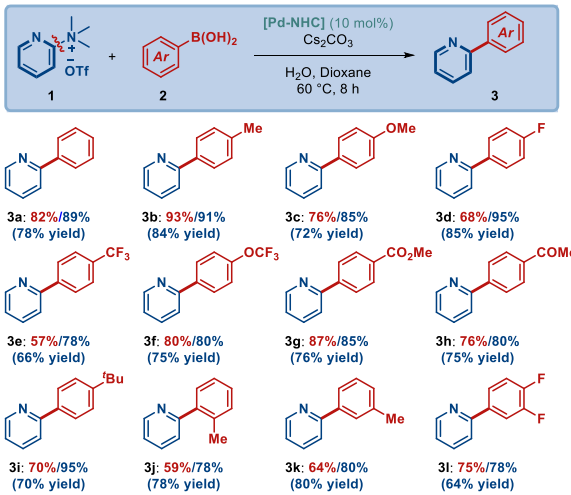
entry	catalyst	yield (%)
1	[Pd(IPr)(3-CF_3-An)Cl_2]	93
2	[Pd(IPr)(cin)Cl]	91
3	[Pd(IPr)(3-Cl-Py)Cl_2]	78
4	[Pd(IPr)(*t*-Bu-ind)Cl]	71
5	[Pd(SIPr)(An)Cl_2]	68
6	[Pd(SIPr)(cin)Cl]	64
7	[Pd(SIPr)(3-Cl-Py)Cl_2]	35
8	[Pd(IMes)(allyl)Cl]	36
9	SingaCycle A3	84
10	[Pd(IPr)(μ-Cl)Cl]$_2$	68
11	[Pd(PPh_3)$_2$$Cl_2$]	<10

[a]Conditions: **1** (2.0 equiv), **2** (1.0 equiv), [Pd] (10 mol%), Cs_2CO_3 (2.0 equiv), dioxane (0.20 M), H_2O (5.0 equiv), 60 °C, 8 h. [b]GC/^{1}H NMR yields.

With the optimized conditions in hand, the scope of this cross-coupling was examined (Scheme 1). We first focused on the scope of boronic acids. The reactions were performed using the two most reactive catalysts identified in the optimization studies, namely [Pd(IPr)(3-CF_3-An)Cl_2] and [Pd(IPr)(cin)Cl]. We found that the scope of boronic acids is very broad and encompasses various electron-neutral (**3a**), electron-rich (**3b–3c**) and electron-deficient boronic acids (**3d–3h**). Importantly, fluorinated motifs that are privileged in medicinal chemistry and agrochemistry[20] can be readily installed using this method (**3d–3f**). Furthermore, the method is well-compatible with sensitive electrophiles that would be problematic using hard organometallics (**3g–3h**). Furthermore, steric-hindrance (**3j**) and meta-substitution (**3k–3l**) are well-tolerated. Interestingly, we found that for some substrates [Pd(IPr)(3-CF_3-An)Cl_2] is the preferred catalyst, while in other examples [Pd(IPr)(cin)Cl] gave higher yields. We performed kinetic studies to gain insight into the rate of catalyst activation (see SI) and found that [Pd(IPr)(3-CF_3-An)Cl_2] is a faster activating catalyst, while [Pd(IPr)(cin)Cl] is slightly preferred for the reversed stoichiometry of the boronic acid. These results highlight the importance of testing various Pd(II)–NHC precatalysts with different classes of ancillary ligands, where the overall reaction outcome depends on catalyst activation, stability and cross-coupling efficiency. The effect of [Pd(IPr)(3-CF_3-An)Cl_2] and [Pd(IPr)(cin)Cl] is intriguing since these catalysts are established to operate through the same monoligated Pd(0)–NHC.[15,17] We hypothesize that the different rate of catalyst activation and stabilization by re-coordination contributes to the difference in reactivity.

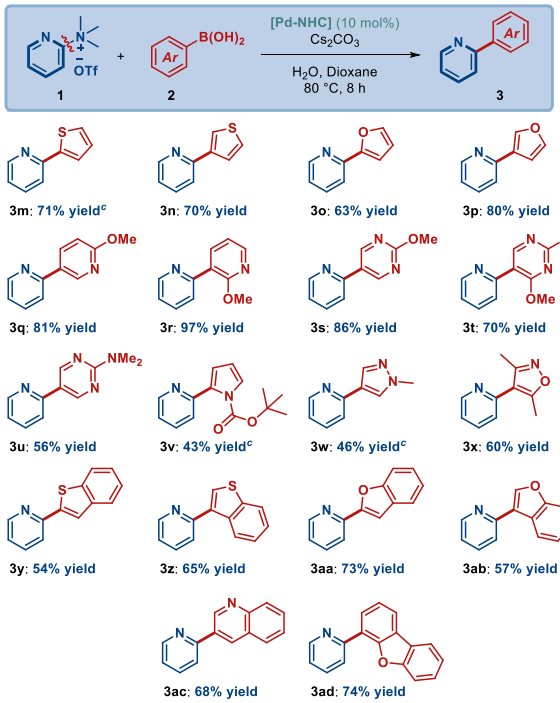
Next, we evaluated the scope of heteroaryl boronic acids to furnish pyridine heterobiaryls (Scheme 2). Notably, we found that this reaction is compatible with a broad range of heterocycles, including differently substituted thiophenes (**3m–3n**), furans (**3o–3p**), pyridines (**3q–3r**), pyrimidines (**3s–3u**), pyrroles (**3v**), pyrazoles (**3w**), isoxazoles (**3x**), benzothiophenes (**3y–3z**), benzofurans (**3aa–3ab**), quinolines (**3ac**) and dibenzofurans (**3ad**). It is particularly noteworthy that this method

Scheme 1. Pd–NHC Catalyzed Suzuki Cross-Coupling of 2-Pyridyl Ammonium Salts: Scope of Boronic Acids[a,b]



[a]Conditions: **1** (2.0 equiv), **2** (1.0 equiv), [Pd-NHC] (10 mol%), Cs_2CO_3 (2.0 equiv), H_2O (5.0 equiv), dioxane (0.20 M), 60 °C, 8 h. [b] ^{1}H NMR yields with [Pd(IPr)(3-CF_3-An)Cl_2]/[Pd(IPr)(cin)Cl]. Isolated yield is shown in brackets.

Scheme 2. Pd–NHC Catalyzed Suzuki Cross-Coupling of 2-Pyridyl Ammonium Salts: Scope of Heterobiaryls[a,b]

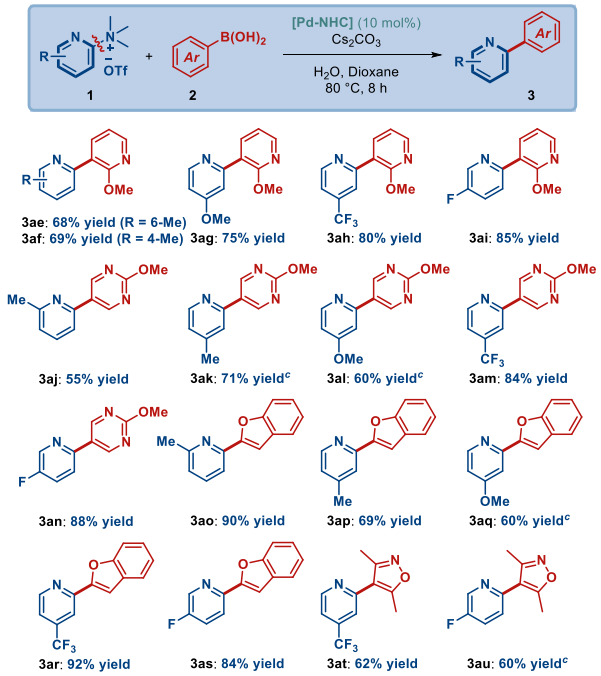


[a]Conditions: **1** (1.0 equiv), **2** (2.0 equiv), [Pd(IPr)(cin)Cl] (10 mol%), Cs_2CO_3 (2.0 equiv), H_2O (5.0 equiv), dioxane (0.20 M), 80 °C, 8 h. [b]Isolated yields. [c]**2** (3.0 equiv).

allows for the synthesis of valuable heterobiaryls that are ubiquitous in medicinal chemistry and agrochemistry research. We found that [Pd(IPr)(cin)Cl] is preferred for substrate scope in this case using reverse stoichiometry of boronic acids.

Finally, we also evaluated the scope of 2-pyridyl ammonium salts (Scheme 3). These substrates are readily available by Chichibabin 2-amination and *N*-alkylation, enabling for a combined C–H/N–C bond activation. This new process is well-compatible with various electron-rich (**3ae–3ag**, **3aj–3al**, **3ao–3aq**) and electron-deficient (**3ah–3ai**, **3am–3an**, **3ar–3au**) substituents on the pyridine ring to furnish valuable pyridine heterobiaryls that serve as prominent motifs in drug discovery and agrochemistry research. The functional group tolerance including esters, ketones, carbamates, amines as well as a range of various electron-rich and electron-deficient five- and six-membered heterocycles should be noted. As expected, the method is no compatible with aryl chlorides and bromides.[12] We anticipate that even higher levels of reaction selectivity will be possible through NHC ligand tuning.[15,16] Interestingly, 3-amino-pyridyl ammonium salts are not compatible, as expected from electronic-delocalization.[4,7] Studies to expand the scope by facilitating oxidative addition of unconjugated substrates are currently underway.

Scheme 3. Pd–NHC Catalyzed Suzuki Cross-Coupling of 2-Pyridyl Ammonium Salts: Scope of 2-Pyridines[a,b]

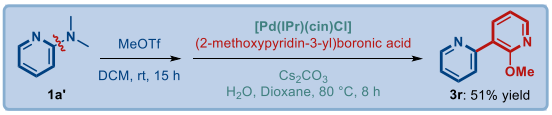


[a]Conditions: **1** (1.0 equiv), **2** (2.0 equiv), [Pd(IPr)(cin)Cl] (10 mol%), Cs_2CO_3 (2.0 equiv), H_2O (5.0 equiv), dioxane (0.20 M), 80 °C, 8 h. [b]Isolated yields. [c]**2** (3.0 equiv), Cs_2CO_3 (3.0 equiv).

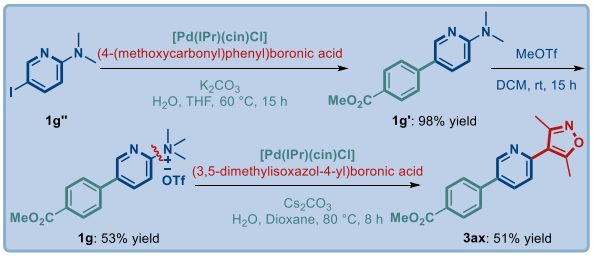
We conducted preliminary studies to gain insight into the reaction mechanism (see SI). An intriguing feature is that one-pot, telescoped N–C activation of the Chichibabin amination products by in situ quaternization is feasible, showcasing compatibility with well-defined Pd(II)–NHC precatalysts (Scheme 4). Furthermore, the orthogonal nature of the N–C activation is highlighted in the sequential cross-coupling using the same Pd(II)–NHC precatalyst (Scheme 5). This process by C–X cross-coupling/*N*-alkylation/N–C activation allows for the synthesis of 2-pyridyl heteroterphenyls, which have found wide application in organic synthesis.

One of the most important applications of 2-aryl pyridine motifs is in the synthesis of novel agrochemicals. We showcased the utility of this process in the design of a new family of potent antifungal agents by "scaffold hopping" of inverse 2-pyridyl-indoles (Scheme 6).[21] The antifungal activity was assessed against 5 species of pathogenic fungi (Table 3). **3ay** showed excellent activity against all tested fungi, superseding those of antifungal agent **5u**[2c] and commercial fungicide Boscalid. Thus, this C–H/N–C activation is an attractive method for the discovery of new pesticides with potent efficacy.

Scheme 4. One-Pot Alkylation/N–C Cross-Coupling



Scheme 5. Sequential C–X/N–C Cross-Coupling



Scheme 6. Synthesis of Agrochemical Derivatives

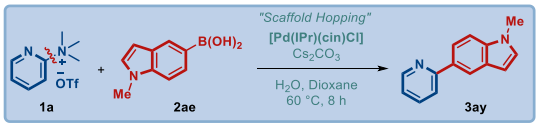
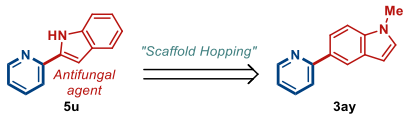


Table 3. Antifungal Activity vs. Pathogenic Fungi[a,b]



compd	*R. s*		*B. c*		*F. g*		*V. m*		*A. s*	
	100	50	100	50	100	50	100	50	100	50
3ay	93	92	98	96	99	78	99	80	97	81
5u	86	66	51	39	60	49	67	43	57	30
Boscalid	82	80	95	92	53	47	73	65	91	80

[a]Inhibition rates (%) at 100 and 50 μg/mL. [b]*R. s: Rhizoctonia solani, B. c: Botrytis cinerea, F. g: Fusarium graminearum, V. m: Valsa mali, A.s: Alternaria solani*.

In summary, we have reported the first Suzuki–Miyaura cross-coupling of 2-pyridyl ammonium salts catalyzed by air- and moisture-stable Pd(II)–NHC precatalysts. The reaction shows broad compatibility with various functional groups and heterocycles, allowing for a rapid access to valuable biaryl and heterobiaryl pyridines that are among the most common motifs in organic synthesis. Considering the predominance of the 2-aryl pyridine core in organic synthesis, we expect that this activation strategy will find broad application.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

Experimental details, characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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