Pd–NHC (NHC = N-Heterocyclic Carbene)-Catalyzed B-Alkyl Suzuki Cross-Coupling of 2-Pyridyl Ammonium Salts by N–C Activation: Application to the Discovery of Agrochemical Molecular Hybrids

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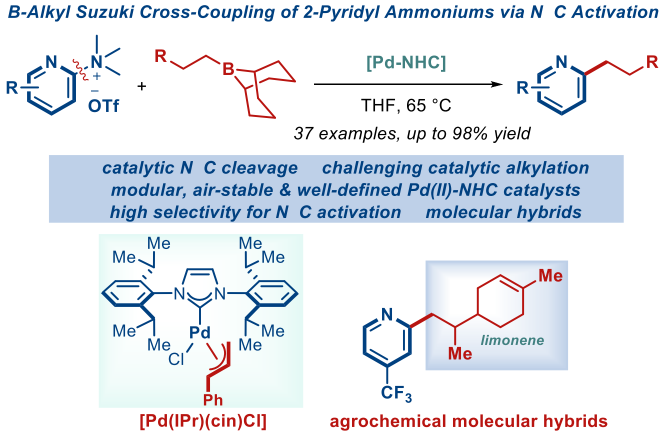
Supporting Information



ABSTRACT: 2-Alkylpyridines are a privileged scaffold throughout the realm of organic synthesis and play a key role in natural products, pharmaceuticals, and agrochemicals. Herein, we report the first B-alkyl Suzuki cross-coupling of 2-pyridyl ammonium salts to access functionalized 2-alkylpyridines. The use of well-defined, operationally-simple Pd–NHCs permits for exceptionally broad scope of the challenging B-alkyl C–N cross-coupling with organoboranes containing β-hydrogen, representing a novel method for the discovery of highly sought-after molecules for plant protection.

2-Alkypyridines represent a pivotal class of heterocycles within the realm of organic synthesis with applications ranging from natural products to the discovery of potent pharmaceuticals and novel agrochemicals (Figure 1A).[1,2] The privileged role of the 2-alkylpyridine scaffold stems from the crucial positioning of the C(sp^3)-hybridized center in the close vicinity to the pyridine nitrogen, which has found broad application in the design of bioactive small molecules as well as novel ligands and molecular motors.[3,4] For example, a recent study demonstrated strong analgesic activity of TRPV1 antagonists by introducing alkyl substituents at the C2 position of the pyridine ring.[4a] Further examples include the synthesis of interlocked catenanes and C2-alkyl-functionalized ligands for Pd(II)-catalysis.[5]

However, in contrast to the synthesis 2-arylpyridines, which are readily synthesized by the biaryl Suzuki cross-coupling of appropriate precursors,[6] the synthesis of 2-alkylpyridines remains a significant challenge due β-hydride elimination degrading the organometallic reagent and slower transmetallation step.[3c,7] Critically, the presence of the basic pyridine nitrogen often coordinates to the metal and slows down the already challenging alkylative catalytic cycle.[8] Further, the competing β-hydride elimination of alkyl organometallics leads to the formation of olefins, which undergo reinsertion, resulting in regioselectivity issues.[7a] Previously, we reported the biaryl Suzuki cross-coupling of 2-pyridinium ammonium salts.[6] This approach leverages the valuable C–H Chichibabin amination of pyridines to access 2-pyridinium ammonium electrophiles, which can be engaged in a generic C–N activation, thus obviating the need for prefunctionalized or highly reactive substrates (Figure 1B).[9-11] Considering the importance of 2-alkylpyridines and the urgent need to develop new methods for the synthesis of this privileged scaffold,[1-4] we questioned whether the significantly more challenging alkylative C–N Suzuki cross-coupling could be achieved by leveraging the versatile Pd(II)–NHC catalysts to overcome the difficulties poised by C–N oxidative addition and transmetallation with alkyl organoboranes.[12-14] Notably, we recognized that B-alkyl Suzuki cross-coupling with quaternary ammonium salts has not been previously reported in any fashion. We further recognized that if successful, such a process would represent a highly attractive method for medicinal chemistry and agrochemistry research owing to the availability of 2-aminopyridine precursors and the central importance of 2-alkylpyridine products.[1-4,15]

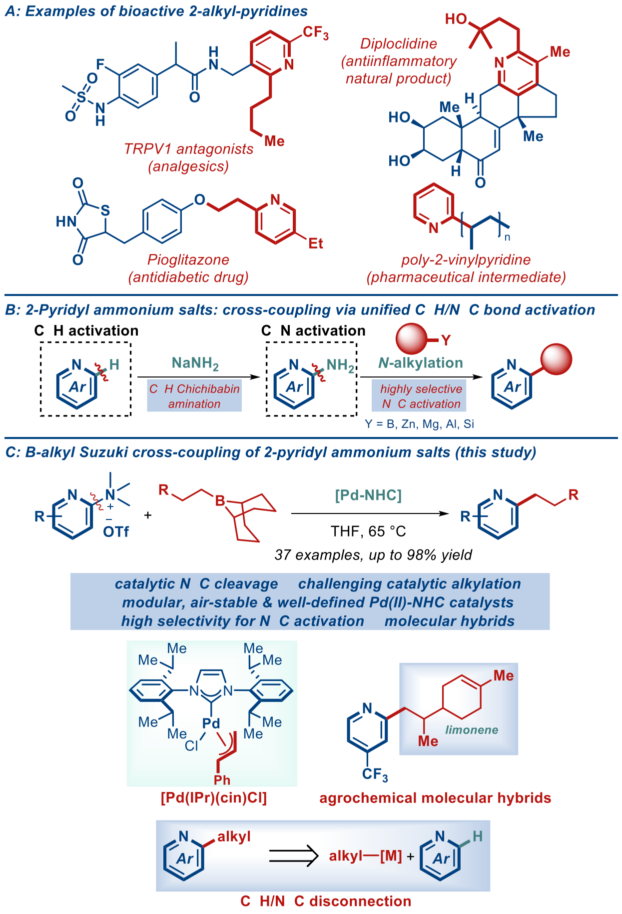
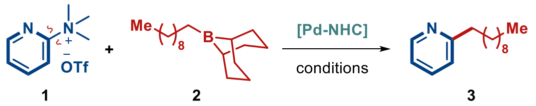


Figure 1. (A) Examples of bioactive 2-alkypyridines. (B) Synthesis of 2-alkypyridines via C-H/C-N bond activation. (C) B-alkyl Suzuki cross-coupling of 2-pyridyl ammonium salts (this study).

Herein, we report the first B-alkyl Suzuki cross-coupling of 2-pyridyl ammonium salts to access functionalized 2-alkylpyridines (Figure 1C). This reaction has been enabled by air-, moisture-stable, well-defined Pd(II)–NHC catalysts, which permits for exceptionally broad scope of the challenging B-alkyl C–N cross-coupling with organoboron nucleophiles containing β-hydrogen.[14] Crucially, the utility of the method in the synthesis of potent agrochemical molecular hybrids by exploiting natural product amalgamation into the pyridine scaffolds by the alkyl tether is demonstrated.[16] Considering the importance of 2-alkylpyridines in various facets of chemistry,[1-4] we anticipate that this C–N alkylation approach will find wide application.

Our proposed strategy was first evaluated in the cross-coupling of trimethylammonium 2-pyridine triflate (**1**) with n-$C_{10}H_{21}$-BBN (Table 1). The ammonium precursor is readily available in bulk via Chichibabin 2-amination and N-alkylation of pyridine.[6,9] The allyl-based Pd(II)–NHC catalyst, [Pd(IPr)(cin)Cl], was selected for the initial optimization because of the generally high reactivity of this catalyst in N–C bond activation reactions developed by us and facile activation to the active Pd(0)–NHC catalyst.[12c] After very extensive optimization, we were delighted to find that this catalyst promoted the desired coupling in 13% yield using K_2CO_3 as a base in THF at 65 °C (entry 1). The effect of the base was extensively evaluated (entries 2-10) and we identified t-BuONa as the most effective base (entry 8). Interestingly, several other bases, such as $K_3PO_4\cdot 3H_2O$ (entry 3), NaOH (entry 6) and t-BuOK (entry 7) also provided promising results, while KF (entry 4), KOH (entry 5), LiHMDS (entry 9) and KHMDS (entry 10) were less effective. We found that further improvement in the reaction efficiency could be realized by adjusting the reagent stoichiometry (entries 11-15) with t-BuONa (entry 12) providing the optimal results. Next, the effect of water was examined since this additive is often critical to enhance the transmetallation step using Pd(II)–NHCs.[6,11d] However, we found that in most cases examined, water had a negative impact on this reaction (entries 16-19). The effect of temperature was also investigated, demonstrating that the reaction can proceed even at temperatures as low as 40 °C (entries 20-21),

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



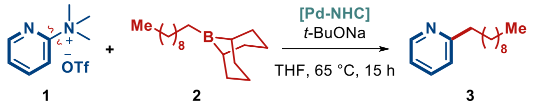
entry	x/y/z	base	H_2O (equiv)	T (°C)	yield (%)
1	1/2/2	K_2CO_3	0	65	13
2	1/2/2	K_3PO_4	0	65	16
3	1/2/2	$K_3PO_4\cdot 3H_2O$	0	65	35
4	1/2/2	KF	0	65	<5
5	1/2/2	KOH	0	65	24
6	1/2/2	NaOH	0	65	42
7	1/2/2	t-BuOK	0	65	35
8	1/2/2	t-BuONa	0	65	43
9	1/2/2	LiHMDS	0	65	<2
10	1/2/2	KHMDS	0	65	<2
11	1/2/3	NaOH	0	65	52
12	1/2/3	t-BuONa	0	65	64
13	1/2/4.5	t-BuONa	0	65	58
14	1/3/3	t-BuONa	0	65	61
15	1/3/4.5	t-BuONa	0	65	45
16	1/2/2	NaOH	5	65	32
17	1/2/2	t-BuONa	5	65	39
18	1/2/3	NaOH	5	65	50
19	1/2/3	t-BuONa	5	65	52
20	1/2/3	t-BuONa	0	40	56
21	1/2/3	t-BuONa	0	80	38
22[c]	1/2/3	t-BuONa	0	65	64
23	2/1/3	t-BuONa	0	65	99
24	2/1/3	t-BuONa	5	65	59
25[d]	2/1/3	t-BuONa	0	65	0

[a]Conditions: **1** (x equiv), **2** (y equiv), [Pd(IPr)(cin)Cl] (5 mol%), base (z equiv), THF (0.25 M), T, 15 h. [b]GC/^{1}H NMR yields. [c][Pd-NHC] (10 mol%). [d][Pd-NHC] (0 mol%).

consistent with the high activity of strongly σ-donating NHC ligands.[12] Finally, we established that the optimal conditions involved inverting the reagent stoichiometry (entries 22-24), resulting in a quantitative yield of the desired product. As expected, control reactions in the absence of Pd–NHC catalysts resulted in no conversion (entry 25), emphasizing the key role of the catalyst and excluding an S_NAr-type process.

Next, we were keen to evaluate different classes of Pd(II)–NHC catalysts in this novel alkylative Suzuki cross-coupling (Table 2, structures of catalysts are shown in Chart S1, SI). Interestingly, we found that although [Pd(IPr)(cin)Cl] was the best catalyst for this process (entry 1), several other Pd(II)–NHCs performed very well (entries 2-5), affording the coupling product in >95% yields under the optimized conditions. These catalysts included aniline-based [Pd(IPr)(3-CF_3-An)Cl_2] (AN = aniline) (entry 2), PEPPSI-based [Pd(IPr)(3-Cl-Py)Cl_2] (entry 3), indenyl-based [Pd(IPr)(*t*-Bu-ind)Cl] (entry 4) as well as allyl-based [Pd(IPr)(allyl)Cl] (entry 5). In contrast, imidazolin-2-ylidene-based catalysts were generally less effective, [Pd(SIPr)(cin)Cl] (entry 6), [Pd(SIPr)(3-Cl-Py)Cl_2] (entry 7). The higher reactivity of Pd-ligated imidazol-2-ylidenes appears to be a common reactivity trend in challenging N–C activations.[12a] Furthermore, the amide-based palladacycle SingaCycle A3 (entry 8) and the chloro-dimer complex [Pd(IPr)(μ-Cl)Cl]$_2$ (entry 9) were also less effective under these conditions. Finally, a representative Pd/phosphine complex, [Pd(PPh_3)$_2$$Cl_2$], was completely unreactive under the reaction conditions, highlighting the key role of strongly σ-donating NHC ligands to promote the challenging C–N oxidative addition.[12] The promising reactivity of various classes of Pd(II)–NHC catalysts is highly beneficial from the availability standpoint and will be useful in the development of future cross-coupling protocols of 2-pyridyl ammonium salts.

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



entry	catalyst	yield (%)
1	[Pd(IPr)(cin)Cl]	99
2	[Pd(IPr)(3-CF_3-An)Cl_2]	96
3	[Pd(IPr)(3-Cl-Py)Cl_2]	96
4	[Pd(IPr)(*t*-Bu-ind)Cl]	96
5	[Pd(IPr)(allyl)Cl]	98
6	[Pd(SIPr)(cin)Cl]	51
7	[Pd(SIPr)(3-Cl-Py)Cl_2]	41
8	SingaCycle A3	72
9	[Pd(IPr)(μ-Cl)Cl]$_2$	80
10	[Pd(PPh_3)$_2$$Cl_2$]	<5

[a]Conditions: **1** (2.0 equiv), **2** (1.0 equiv), [Pd] (5 mol%), *t*-BuONa (3.0 equiv), THF (0.25 M), 65 °C, 15 h. [b]GC/^{1}H NMR yields.

With the optimized conditions in hand, the scope of this novel alkylative Suzuki cross-coupling of 2-pyridyl ammonium salts was next investigated (Scheme 1). As shown, the reaction showed excellent functional group tolerance and compatibility with various organoboranes bearing simple alkyl (**3a**), substituted alkyl (**3b**), and aryl-substituted (**3c-3d**) alkyl–9-BBN reagents. It is important to point out that phenethyl reagents, such as **3c** and **3d**, are especially prone to β-hydride elimination.[14] Extending the alkyl chain (**3e-3f**) was well-tolerated. Moreover, the use of electronically-activated reagents, such as **3g**, that are prone to β-elimination/chain walking was also well-compatible with this process.[14] The functional group tolerance includes fused arenes (**3h**), benzyl ethers (**3i**), and acidic protons (**3j**). Furthermore, valuable functional handles can be readily introduced by the use of alkyl-TMS (**3k**) functional group, which was also readily tolerated under the developed reaction conditions.

Next, the scope with respect to 2-pyridyl ammonium salts was investigated (Scheme 2). As shown, this process is well-compatible with various combinations of substituted electron-rich (**3l-3m**, **3q-3r**, **3u-3v**, **3z-3aa**) and electron-deficient (**3n-3p**, **3s-3t**, **3w-3y**, **3ab-3ae**) pyridines with a range of alkyl-9-BBN reagents to afford valuable 2-alkylpyridines that are considered privileged motifs in medicinal chemistry and agrochemistry campaigns.

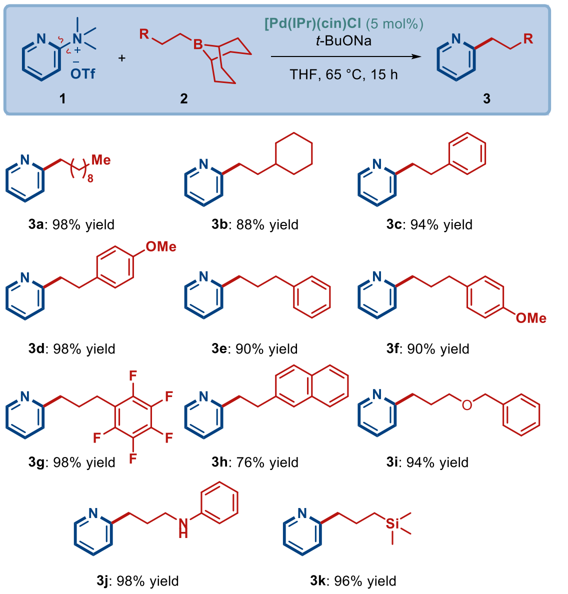
Importantly, this C–N B-alkyl cross-coupling can be implemented in a one-pot, telescoped in situ quaternization/C–N alkylation (Scheme 3), emphasizing the excellent compatibility of Pd(II)–NHCs with challenging reaction conditions. Furthermore, this method can be readily performed on a gram scale (88% yield), highlighting its scalability (see SI).

Preliminary selectivity studies to gain insight into the reaction mechanism were conducted (Scheme 4). (1) Intermolecular competition experiments using differently substituted organoboranes showed that electron-rich nucleophiles are more reactive (n-$C_{10}H_{21}$:n-$(CH_2)_3C_6F_5$ >95:5), which is consistent with faster transmetallation.[6,12c] (2) Interestingly, competition experiments using alkyl vs. Ar nucleophiles showed that alkyl organoboron reagents are more reactive under these conditions (n-$C_{10}H_{21}$:Ph = 64:36), which bodes well for the future development of Pd(II)–NHC-catalyzed alkylative Suzuki cross-couplings of unconventional electrophiles. Mechanistically, it should be noted that the pyridine nitrogen is likely involved in assisting oxidative addition. Our present efforts are focused on expanding the scope of substrates to other heterocycles and complementary substitution using Pd and Ni catalysis. Furthermore, it is important to point out that less sterically-hindered Pd-NHCs result in the formation of olefin by-products. Overall, these findings are consistent with a facile reductive elimination and rate-limiting transmetalation.

Most importantly, from the outset, we were interested to probe the utility of 2-alkylpyridines in the synthesis of novel agrochemical molecular hybrids (Scheme 5). This approach can enhance the activity of natural products in plant protection by binding them to heterocycles via a versatile alkyl handle. Thus, we showcased the utility of this process in the derivatization of active natural products, such as limonene (**3af-3ah**), carvone (**3ai**) and β-pinene (**3aj-3ak**)[17] by the alkylative C–N cross-coupling. We conducted bioactivity tests against four important plant pathogenic fungi (Table 3). After introducing 2-pyridine through this process, the antifungal activities of all target products have been significantly improved (**3af-3ah** > limonene, **3ai** > carvone, **3aj-3ak** > β-pinene).

Notably, all target products showed good fungistasis against *Rhizoctonia solani*, which causes rice sheath blight, one of the most significant diseases on the major crops worldwide.[18] Thus, this alkylative N–C activation is an effective method for structural derivatization of active natural products, as well as will represent an attractive method for the discovery of new agrochemicals with potent efficacy, enhancing its practical value in plant protection.

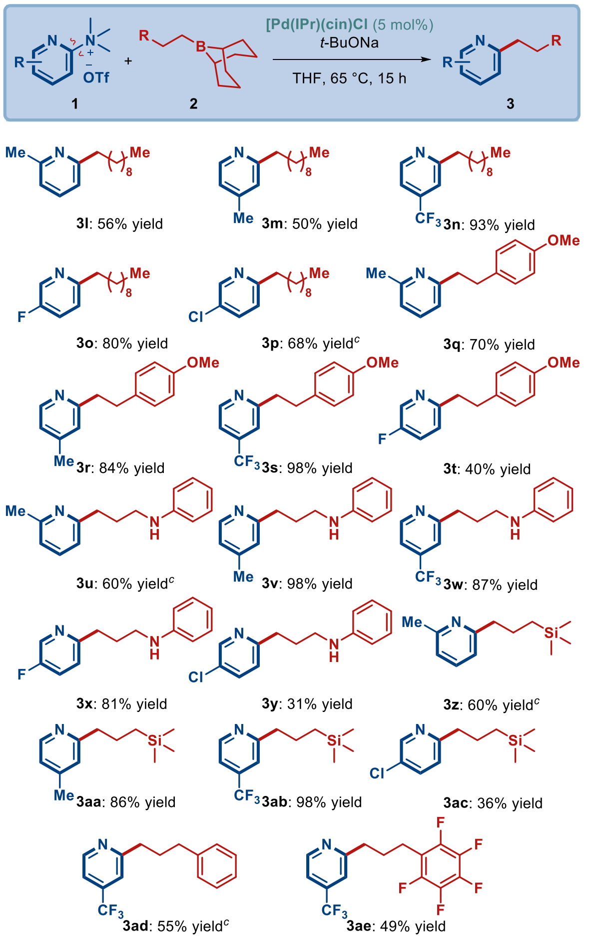
Scheme 1. Pd–NHC Catalyzed Alkylation of 2-Pyridyl Ammonium Salts: Scope of B-Alkyl Reagents[a,b]



3a: 98% yield
3b: 88% yield
3c: 94% yield
3d: 98% yield
3e: 90% yield
3f: 90% yield
3g: 98% yield
3h: 76% yield
3i: 94% yield
3j: 98% yield
3k: 96% yield

[a]Conditions: **1** (2.0 equiv), **2** (1.0 equiv), [Pd-NHC] (5 mol%), *t*-BuONa (3.0 equiv), THF (0.25 M), 65 °C, 15 h. [b]Isolated yields.

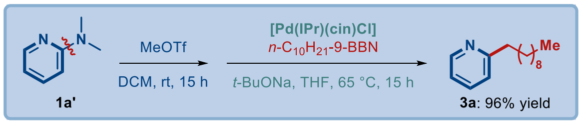
Scheme 2. Pd–NHC Catalyzed Alkylation of 2-Pyridyl Ammonium Salts: Scope of 2-Pyridines[a,b]



3l: 56% yield
3m: 50% yield
3n: 93% yield
3o: 80% yield
3p: 68% yield[c]
3q: 70% yield
3r: 84% yield
3s: 98% yield
3t: 40% yield
3u: 60% yield[c]
3v: 98% yield
3w: 87% yield
3x: 81% yield
3y: 31% yield
3z: 60% yield[c]
3aa: 86% yield
3ab: 98% yield
3ac: 36% yield
3ad: 55% yield[c]
3ae: 49% yield

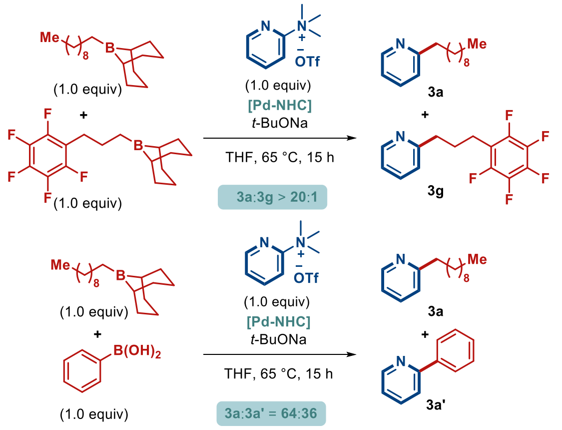
[a]Conditions: **1** (2.0 equiv), **2** (1.0 equiv), [Pd-NHC] (5 mol%), *t*-BuONa (3.0 equiv), THF (0.25 M), 65 °C, 15 h. [b]Isolated yields. [c][Pd-NHC] (10 mol%).

Scheme 3. One-Pot Alkylation/N–C Cross-Coupling



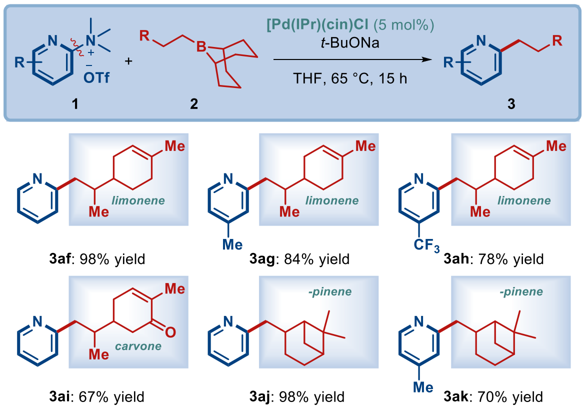
3a: 96% yield

Scheme 4. Mechanistic Studies



3a
3g
3a
3a'

Scheme 5. Synthesis of Molecular Agrochemical Hybrids



3af: 98% yield
3ag: 84% yield
3ah: 78% yield
3ai: 67% yield
3aj: 98% yield
3ak: 70% yield

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

compd	Inhibition Rates (%)/50 μg/mL			
	R. s	*B. c*	*S. s*	*V. m*
3af	74	37	40	70
3ag	73	52	19	61
3ah	52	29	14	72
3ai	72	36	52	71
3aj	67	40	20	55
3ak	71	52	30	20
Limonene[b]	33	5	18	19
Carvone[b]	48	8	39	19
β-Pinene[b]	32	4	15	14

[a]*R. s: Rhizoctonia solani, B. c: Botrytis cinerea, S. s: Sclerotinia sclerotiorum, V. m: Valsa mali.*[b]Inhibition rates (%) at 100 μg/mL.

In summary, we have reported the first B-alkyl Suzuki cross-coupling of 2-pyridyl ammonium salts. This reaction enables access to functionalized 2-alkylpyridines, which are privileged motifs in various facets of organic synthesis and play a key role in the discovery of new pharmaceuticals and agrochemicals. This method takes advantage of merging the Chichibabin C–H amination with N–C activation, which is not easily available from halopyridines, and represents an attractive avenue for applications in medicinal chemistry. Furthermore, we have presented the utility of the method to the synthesis of potent agrochemical molecular hybrids. In a broader sense, the merger of N–C activation with alkylative coupling of natural products delivers highly sought-after molecules for plant protection, and may find application in other areas of bioactive molecule generation.

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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REFERENCES

(1) (a) Li, J. F.; Pan, D.; Wang, H. R.; Zhang, T.; Li, Y.; Huang, G. P.; Ye, M. C. Enantioselective C2-H Alkylation of Pyridines with 1,3-Dienes via Ni-Al Bimetallic Catalysis. *J. Am. Chem. Soc.* **2022**, *144*, 18810-18816. (b) Gressies, S.; Süsse, L.; Casselman, T.; Stoltz, B. M. Tandem Dearomatization/Enantioselective Allylic Alkylation of Pyridines. *J. Am. Chem. Soc.* **2023**, *145*, 11907-11913.

(2) (a) Islam, M. B.; Islam, M. I.; Nath, N.; Emran, T. B.; Rahman, M. R.; Sharma, R.; Matin, M. M. Recent Advances in Pyridine Scaffold: Focus on Chemistry, Synthesis, and Antibacterial Activities. *Biomed Res. Int.* **2023**, *2023*, 9967591. (b) O'Hagan, D. Pyrrole, pyrrolidine, pyridine, piperidine and tropane alkaloids. *Nat. Prod. Rep.* **2000**, *17*, 435-446.

(3) (a) Gladfelder, J. J.; Ghosh, S.; Podunavac, M.; Cook, A. W.; Ma, Y.; Woltornist, R. A.; Keresztes, I.; Hayton, T. W.; Collum, D. B.; Zakarian, A. Enantioselective Alkylation of 2-Alkylpyridines Controlled by Organolithium Aggregation. *J. Am. Chem. Soc.* **2019**, *141*, 15024-15028. (b) Laulhé, S.; Blackburn, J. M.; Roizen, J. L. Selective and Serial Suzuki-Miyaura Reactions of Polychlorinated Aromatics with Alkyl Pinacol Boronic Esters. *Org. Lett.* **2016**, *18*, 4440-4443. (c) Hara, N.; Aso, K.; Li, Q. Z.; Sakaki, S.; Nakao, Y. C2-selective alkylation of pyridines by rhodium-aluminum complexes. *Tetrahedron* **2021**, *95*, 132339.

(4) (a) Ryu, H.; Seo, S.; Cho, S. H.; Kim, H. S.; Jung, A.; Kang, D. W.; Son, K.; Cui, M.; Hong, S. H.; Sharma, P. K.; Choi, S.; Blumberg, P. M. Frank-Foltyn, R.; Bahrenberg, G.; Stockhausen, H.; Schiene, K.; Christoph, T.; Frormann, S.; Lee, J. 2-Alkyl/alkenyl substituted pyridine C-region analogues of 2-(3-fluoro-4-methylsulfonylaminophenyl) propanamides as highly potent TRPV1 antagonists. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 4039-4043. (b) De, S.; Kumar, S. K. A.; Shah, S. K.; Kazi, S.; Sarkar, N.; Banerjee, S.; Dey, S. Pyridine: the scaffolds with significant clinical diversity. *RSC Adv.* **2022**, *12*, 15385-15406.

(5) (a) Zhang, Y. H.; Shi, B. F.; Yu, J. Q. Pd(II)-Catalyzed Olefination of Electron-Deficient Arenes Using 2,6-Dialkylpyridine Ligands. *J. Am. Chem. Soc.* **2009**, *131*, 5072-5074. (b) Goldup, S. M.; Leigh, D. A.; Lusby, P. J.; McBttrney, R. T.; Slawin, A. M. Z. Gold (I)-template catenane and rotaxane synthesis. *Angew. Chem., Int. Ed.* **2008**, *47*, 6999-7003.

(6) Hu, Y. G.; Gao, Y. Q.; Ye, J. H.; Ma, Z. Q.; Feng, J. T.; Liu, X. L.; Lei, P.; Szostak, M. 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. *Org. Lett.* **2023**, *25*, 2975-2980.

(7) (a) Blackburn, J. M.; Roizen, J. L. Catalytic Strategies to Convert 2-Halopyridines to 2-Alkylpyridines. *Asian J. Org. Chem.* **2019**, *8*, 920-930. (b) Cook, X. A. F.; de Gombert, A.; McKnight, J.; Pantaine, L. R. E.; Willis, M. C. The 2-Pyridyl Problem: Challenging Nucleophiles in Cross-Coupling Arylations. *Angew. Chem., Int. Ed.* **2021**, *60*, 11068-11091.

(8) Dick, G. R.; Woerly, E. M.; Burke, M. D. A General Solution for the 2-Pyridyl Problem. *Angew. Chem., Int. Ed.* **2012**, *51*, 2667-2672.

(9) Lewis, D. E. Aleksei Yevgen'evich Chichibabin: A Century of Pyridine Chemistry. *Angew. Chem., Int. Ed.* **2017**, *56*, 9660-9668.

(10) (a) Blakey, S. B.; MacMillan, D. W. C. The first Suzuki cross-couplings of aryltrimethylammonium salts. *J. Am. Chem. Soc.* **2003**, *125*, 6046-6047. (b) Ouyang, K. B.; Hao, W.; Zhang, W. X.; Xi, Z. F. Transition-Metal-Catalyzed Cleavage of C-N Single Bonds. *Chem. Rev.* **2015**, *115*, 12045-12090.

(11) (a) Ni, S.; Li, C. X.; Mao, Y.; Han, J.; Wang, Y.; Yang, H.; Pan, Y. Ni-catalyzed deaminative cross-electrophile coupling of Katritzky salts with halides via C–N bond activation. *Sci. Adv.* **2019**, *5*, 9516. (b) Ielo, L.; Touqeer, S.; Roller, A.; Langer, T.; Holzer, W.; Pace, V. Telescoped, Divergent, Chemoselective C1 and C1-C1 Homologation of Imine Surrogates: Access to Quaternary Chloro- and Halomethyl-Trifluoromethyl Aziridines. *Angew. Chem., Int. Ed.* **2019**, *58*, 2479-2484. (c) Tang, J.; Fan, F.; Cong, X.; Zhao, L.; Luo, M.; Zeng, X. Reductive Cross-Coupling between Unactivated C(aryl)–N and C(aryl)–O Bonds by Chromium Catalysis Using a Bipyridyl Ligand. *J. Am. Chem. Soc.* **2020**, *142*, 12834-12840. (d) Lei, P.; Mu, Y.; Wang, Y.; Wang, Y.; Ma, Z.; Feng, J.; Liu, X.; Szostak, M. Green Solvent Selection for Suzuki–Miyaura Coupling of Amides. *ACS Sustainable Chem. Eng.* **2021**, *9*, 552-559..

(12) (a) Shi, S. C.; Nolan, S. P.; Szostak, M. Well-Defined Palladium(II)-NHC Precatalysts for Cross-Coupling Reactions of Amides and Esters by Selective N-C/O-C Cleavage. *Accounts Chem. Res.* **2018**, *51*, 2589-2599. (b) Zhao, Q.; Meng, G.; Li, G.; Flach, C.; Mendelsohn, R.; Lalancette, R.; Szostak, R.; Szostak, M. IPr#–Highly Hindered, Broadly Applicable N-Heterocyclic Carbenes. *Chem. Sci.* **2021**, *12*, 10583-10589. (c) Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. Modified (NHC)Pd(allyl)Cl (NHC = N-heterocyclic carbene) complexes for room-temperature Suzuki-Miyaura and Buchwald-Hartwig reactions. *J. Am. Chem. Soc.* **2006**, *128*, 4101-4111.

(13) Voloshkin, V. A.; Tzouras, N. V.; Nolan, S. P. Recent advances in the synthesis and derivatization of N-heterocyclic carbene metal complexes. *Dalton Trans.* **2021**, *50*, 12058-12068.

(14) Meng, G. R.; Szostak, M. Palladium/NHC (NHC = N-Heterocyclic Carbene)-Catalyzed B-Alkyl Suzuki Cross-Coupling of Amides by Selective N-C Bond Cleavage. *Org. Lett.* **2018**, *20*, 6789-6793.

(15) Rao, R. N.; Chanda, K. 2-Aminopyridine - an unsung hero in drug discovery. *Chem. Commun.* **2022**, *58*, 343-382.

(16) Bérubé, G. An overview of molecular hybrids in drug discovery. *Expert. Opin. Drug Discov.* **2016**, *11*, 281-305.

(17) Silva, L. N.; Zimmer, K. R.; Macedo, A. J.; Trentin, D. S. Plant Natural Products Targeting Bacterial Virulence Factors. *Chem. Rev.* **2016**, *116*, 9162-9236.

(18) Li, D. Y.; Li, S.; Wei, S. H.; Sun, W. X. Strategies to Manage Rice Sheath Blight: Lessons from Interactions between Rice and *Rhizoctonia solani*. *Rice* **2021**, *14*, 21.