Functionalization of Pyridines at Remote Synthetic Landscapes *via* Undirected Metalation and Capture

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ABSTRACT

The undirected functionalization of pyridines at positions remote to the N-atom remains an outstanding problem in organic synthesis. The inherent challenges associated with overriding the strong directing influence of the embedded N-atom within pyridine was overcome through the use of *n*-butylsodium which provided us an avenue to generate 4-sodiopyridine over traditionally observed 2-metalated products when organolithium bases are utilized. The freshly generated 4-sodiopyrdine was found to undergo transition metal free alkylation reactions directly with a variety of primary organic halides bearing diverse functional groups. In addition, after transmetalation to zinc chloride a simple and efficient Negishi cross-coupling protocol was formulated for a variety of aromatic and heteroaromatic halides. The robustness of this protocol was demonstrated through the late-stage installation of 4-pyridyl fragments into a variety of complex active pharmaceutical ingredients including loratadine and prochlorperazine. This protocol not only unlocks a new avenue to prepare 4-subsituted pyridines but highlights the preparative advantages and differences of organosodium bases over their lithium counterparts.

1.0 Introduction

Pyridine is one of the most extensively incorporated heteroaromatic subunits found in small molecule pharmaceuticals.[1] For instance, lifesaving pyridine containing therapeutics such as cerivastatin (cholesterol lowering agent) and isoniazid (antibiotic) have played essential roles in combating heart disease and infections which are currently leading causes of death (Fig. 1a). Classical medicinal chemistry structure-activity relationship studies have shown that the substitution pattern of the pyridine substructure within the active pharmaceutical ingredient greatly impacts their potency.[2-3] For example, the medicinal properties of isoniazid (antibiotic),[4] abiraterone (prostate cancer),[5] and disopyramide (antiarrhythmic)[6] were all found to have optimal activity when the pyridine subunit was functionalized at different positions (Fig. 1a). Therefore, it is imperative that highly general and selective syntheses of substituted pyridines are available for a range of biologically active molecules.

Regarding the direct C−H functionalization of pyridine, many methods have been developed to access the C2 position due to the intrinsic directing effects from the embedded N-atom.[7-14] Remote functionalization, on the other hand represents a more challenging topic because the strong influence of the N-atom is difficult to override (Fig. 1b).[15] Since the C3 position is the relatively electron-rich site, C3 functionalization can occur through electrophilic aromatic substitution reactions for certain substrate scopes,[7] or through alternative reaction pathways using catalysts with tailored tether lengths[16-17] or dearomatized intermediates.[18-21] As the C2 and C4 positions are both electrophilic, the modification of a C2-selective method is usually the starting point for C4 functionalization protocols. Although early discoveries generally suffer from poor C2/C4 selectivity, with adequately installed blocking groups, several C4-selective methods have been developed. Electron-rich reagents such as Ni^0 catalysts,[22] alkene-derived nucleophiles,[23-24] electron-rich radicals[25] and other soft nucleophiles[26-28] have been shown to be effective coupling partners for C4 functionalization (Fig. 1b). Unfortunately, selective C4 functionalization is generally dependent on directing and or blocking groups. This and other challenges still exist for developing C4 selective functionalization methods, especially for the alternative polar construction using pyridine-derived nucleophiles and carbon-based electrophiles.

Ironically, the most acidic C–H bond in pyridine, located at the C4 position,[29,30] is the most difficult position to selectively deprotonate because the Lewis basic N-atom directs bases to the C2 position.[31-34] Moreover, current methods to access pyridine-derived C4-carbanions *via* lithium-halogen exchange with halopyridines are impractical and challenging due to the highly unstable nature of the substrate towards dimerization.[35] Building on our program in designing new avenues to deprotonate and functionalize heterocycles at remote locations, we undertook this synthetic challenge of developing a C4 selective synthesis of pyridines. We show below a new scheme utilizing *n*-BuNa which avoids interactions with the embedded N-atom and allows access to 4-sodiopyridine (Fig. 1c). Upon surveying an array of parameters, we determined that the sodiated pyridine intermediate could undergo direct and transition metal-free alkylation reactions with primary alkyl halides incorporating a variety of functional groups as well as Negishi cross-couplings with various aromatic and heteroaromatic halides. The robustness of this deprotonation capture protocol was shown through our ability to directly install 4-substituted pyridines at late-stages into several pharmaceuticals including loratadine (antihistamine) and prochlorperazine (antipsychotic).

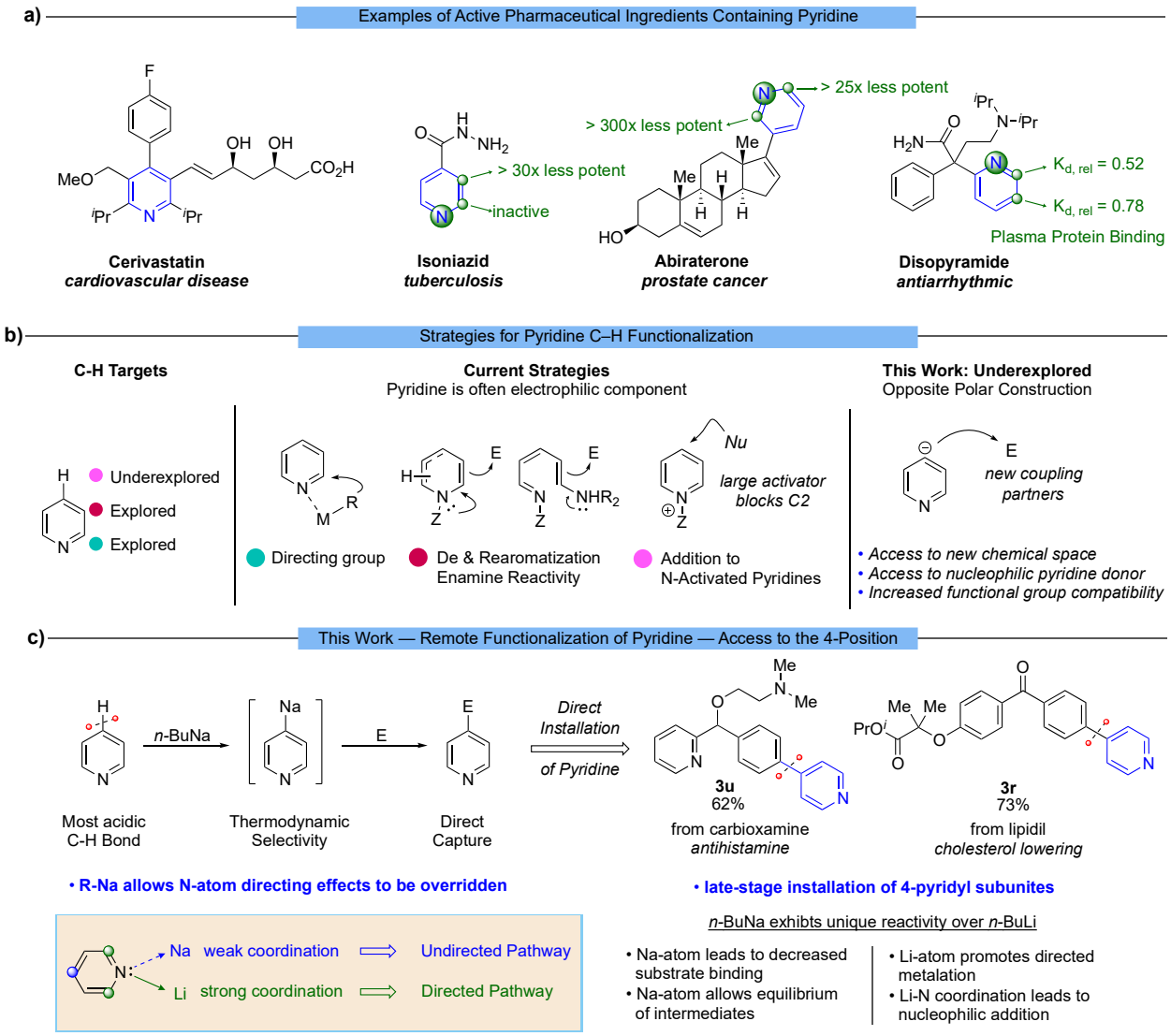


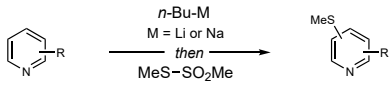
Fig. 1. Functionalization of pyridine. a. Examples of active pharmaceutical ingredients containing pyridine subunits and structure-activity relationship studies. **b.** Current strategies for pyridine C−H functionalization. **c.** This work: remote functionalization of pyridine through an undirected deprotonation capture approach.

2.0 Background

Organosodium chemistry has long been an overlooked field since the discovery of organolithium reagents in 1917.[36-39] As the strong Lewis acidity of the lithium cation makes directed *ortho*-metalation (DOM) a highly developed strategy for organolithium reagents, it hinders their effectiveness to select remote positions in heterocycles. Recently, there has been a resurgence of interest in organosodium chemistry, however most work has focused on developing analogous reactions that utilize organolithium reagents with the overall objective of replacing the lithium cation by its more earth abundant sodium counterpart.[40-43] Therefore, the potential for

organosodium reagents to unlock new and complementary reactivity patterns to organolithiums remains underexplored.[44,45] Given the stronger basicity and weaker coordination effects of organosodium reagents compared to organolithiums, combined with our knowledge that the C4−H bond in pyridines are often known to be the most acidic inspired us to explore strategies for undirected C4−H activation pathways with pyridines.

Initially, several substituted pyridines were subjected to strongly basic conditions followed by trapping with *S*-methyl methanethiosulfonate ($MeS\text{-}SO_2Me$)[46,47] such that both reactivity and selectivity could be compared between *n*-BuLi and *n*-BuNa (Table 1). For entries 1-4 we observed that *n*-BuNa resulted in a distribution of deprotonation and capture products in moderate yields that roughly parallels to the relative acidity of the substrates C−H bonds[29] whereas *n*-BuLi resulted in undesired side addition products. Of note, 2,6-di-*tert*-butylpyridine **1e** could not be metalated and captured when *n*-BuLi was employed; however, it was selectively functionalized at the 4-position with *n*-BuNa in satisfactory yields (65%). In addition, the pyridine substrates bearing either pyridine **1f**, methoxy **1g**, or fluorine **1h** substituents at the 2-position resulted in highly selective 3-subsititued pyridines in higher yields with *n*-BuNa (18-72%) over *n*-BuLi (0-28%). These preliminary results represent a general and practical way to access carbanions within heterocycles at locations that are typically not accessible with organolithium reagents which makes a notable advance in both our fundamental knowledge of strong base chemistry as well as synthetic methodology. In light of these results, our efforts became focused on the development of a general synthetic methodology to prepare 4-subsitiuted pyridines directly due to their biologically relevance and current lack of methods to access them.



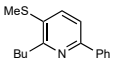
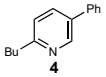
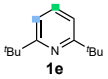
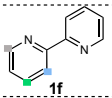
Entry	Substrate	Base	Deprotonation Selectivity A	B	C	(% Yield)	Other Observed Products (% Yield)
1	 1a	*n*-BuLi	0	0	0	(0)	 2 (30)
		n-BuNa	3.5	1.0	0	(59)	(0)
2	 1b	*n*-BuLi	0	0	0	(0)	 3 (13)
		n-BuNa	3.6	1.5	1.0	(61)	(0)
3	 1c	*n*-BuLi	0	0	0	0	 4 (10)
		n-BuNa	1.0	0	0	(16)[b]	(5)
4	 1d	*n*-BuLi	–	0	0	0	 5 (47)
		n-BuNa	–	0	1.0	(56)[c]	(0)
5	 1e	*n*-BuLi	0	0	–	(0)	–
		n-BuNa	1.0	0	–	(65)	
6	 1f	*n*-BuLi	0	0	0	(0)	–[b]
		n-BuNa	0	1.0	0	(18)	
7	 1g	*n*-BuLi	0	1.0	0	(9)	–
		n-BuNa	0	1.0	0	(52)	
8	 1h	*n*-BuLi	0	1.0	0	(28)[d]	–
		n-BuNa	0	1.0	0	(72)	

Table 1. Comparison of reactivities towards substituted pyridines between *n*-BuNa and *n*-BuLi. Reactions were carried out on 0.1 mmol scale (*n*-BuNa or *n*-BuNa) at −78 °C. Yields were determined by ^{1}H NMR spectroscopy with added 1,2,4,5-tetramethylbenzene as the internal standard. [a] Reaction performed in THF-d_8 and worked up without the use of reduced pressure. [b] Multiple dimerization and addition products were observed. [c] 4,4'-Diphenyl-3,3'-bipyridine (13%) was observed. [d] Unidentified dearomatization products were observed.

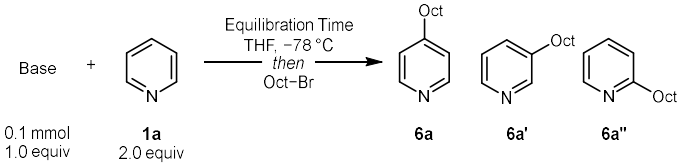
3. Result and Discussion

When devising our synthetic strategy pyridine (**1a**) was selected as the heteroaromatic component along with *n*-octyl bromide as the electrophile. A variety of bases known to be active toward the deprotonation of aromatic compounds were screened (Table 2). Both lithium and sodium amide bases were found to be insufficient in basicity to deprotonate pyridine (entries 1-3). Of note, commercially available organolithiums such as *n*-BuLi and *t*-BuLi were found to form unwanted side products such as nucleophilic addition products (entry 4-5).[48] Following our previously developed conditions to generate separated ion pairs (*t*-Bu^- // L_4Li^+) using hexamethylphosphormide (HMPA) and *t*-BuLi[49] resulted in no desired product (entry 6). Lochmann-Schlosser super bases generated from the addition of either potassium or sodium *tert*-

butoxide resulted in the observation of a thermodynamic product distribution favoring the C4 derived anion,[50] where the sodium analog gave lower yields (entry 7-9). Since it is suggested that the synergistic effect of Lochmann-Schlosser superbases comes from the *in situ* formation of the heavier organometallic species (strong Li−O affinity),[51] led us to prepare and isolate alkylsodium bases,[52] with the anticipation that the absence of the lithium cation would enhance the basicity as well as promote the subsequent trapping of the electrophile. In entry 10, *n*-BuNa in THF gave primarily the desired product **6a**, and the product ratio showed good correspondence with the prediction from theoretical pK_a difference of 0.7 (C4-H vs C3-H),[29] suggesting a thermodynamic equilibrium between pyridine anions. Notably, the combination of *n*-BuNa and *t*-BuOLi gave similar results as *n*-BuLi / *t*-BuONa mixtures, possibly due to the same intermediate being formed (entry 9 and 11).

After the determination of the adequate base, we then examined reaction conditions to favor the thermodynamic distribution. It was found that the reaction time of 2 h resulted in the optimal yield of the desired product **6a**. Longer reaction times showed no significant improvement of product ratio and led to the erosion of yield (entry 12-18). Additives were also tested in the attempt to shift the equilibrium position. Sodium-coordinating ligands such as tetramethylethylenediamine (TMEDA), pentamethyldiethylenetriamine (PMDTA) and hexamethylphosphoramide (HMPA) did not further shift the equilibrium position (entry 19-21).[53] Lewis acids such as $AlMe_3$ were found to give 4-nucleophilic addition products and provided no desired product **6a** (entry 22).

Table 2. Screening of reaction conditions.



Entry	Base[b]	Yield (%)[a] (6a/6a'/6a'')
1	LDA	0/0/0
2	NaTMP	0/0/0
3	NaDA	0/0/0
4	*n*-BuLi	0/0/0
5	*t*-BuLi	0/0/0
6	*t*-BuLi + 6 HMPA[e]	0/0/0
7	*n*-BuLi + *t*-BuOK[f]	43/11/1
8	*t*-BuLi + *t*-BuOK[f]	40/12/3
9	*n*-BuLi + *t*-BuONa[f]	13/6/3
10	***n*-BuNa[g]**	**67/15/0**
11	*n*-BuNa + *t*-BuOLi[f]	12/4/0
	n-BuNa: Equilibrium Time[c]	
12	1.0 min	41/30/7
13	5.0 min	49/31/2
14	10 min	51/28/0
15	30 min	55/29/1
16	60 min	58/24/0
17	**120 min[g]**	**67/15/0**
18	180 min	60/12/0
	n-BuNa: Additives[d]	
19	TMEDA (2.0 equiv)[h]	43/11/0
20	PMDETA (2.0 equiv)[h]	45/11/0
21	HMPA (2.0 equiv)[h]	44/11/0
22	$AlMe_3$ (1.0 equiv)[i]	0/0/0

[a]Yield determined by GC-FID relative to a 1,2,4,5-tetramethylbenzene internal standard. [b]Base (1.0 equiv) was dissolved in THF at –78 °C and added with pyridine (2.0 equiv), the reaction was stirred for 2 h before adding Oct–Br (1.1 equiv). [c]*n*-BuNa (1.0 equiv) was dissolved in THF at –78 °C and added with pyridine (2.0 equiv), the reaction was stirred for the specified time before adding Oct–Br (1.1 equiv). [d]*n*-BuNa (1.0 equiv) was dissolved in THF at –78 °C and added with pyridine (2.0 equiv) and the specified additive, the reaction was stirred for 2 h before adding Oct–Br (1.1 equiv). [e]6.0 equiv relative to organometallic base. [f]1.0 equiv relative to organometallic base. [g]Average of 3 runs. [h]Added after pyridine. [i]Premixed with pyridine. Please refer to Supporting Information for the complete condition screening table.

With the optimized reaction conditions in hand, we first investigated the substrate scope with respect to the primary alkyl halide coupling partner (Fig 2.). Importantly, as shown below the desired 4-substituted pyridine products could be easily separated and isolated from their C3-isomer *via* flash column chromatography. We found that a variety of substrates such as primary alkyl chlorides (**6b**), *tert*-butyldimethylsilyl ethers (**6c**), and acetals (**6d**) were well tolerated and provided their desired coupling products in good yields. Next, we evaluated Lewis acid sensitive functional groups such as epoxide (**6e**) which was also successful under the reaction conditions. Alkyl bromides tethered to various arenes were also found to undergo the direct alkylation reactions, showcasing the potential of this method to efficiently link pyridines into various structures (**6f** − **6h**). Notably, **6g** and **6h** which both contain relatively acidic functional groups (benzylic C−H and furan C5−H) provided good yields of their desired products. In addition, both terminal (**6i**) and internal (**6j**) derived olefins were successfully connected to pyridine in similar yields.

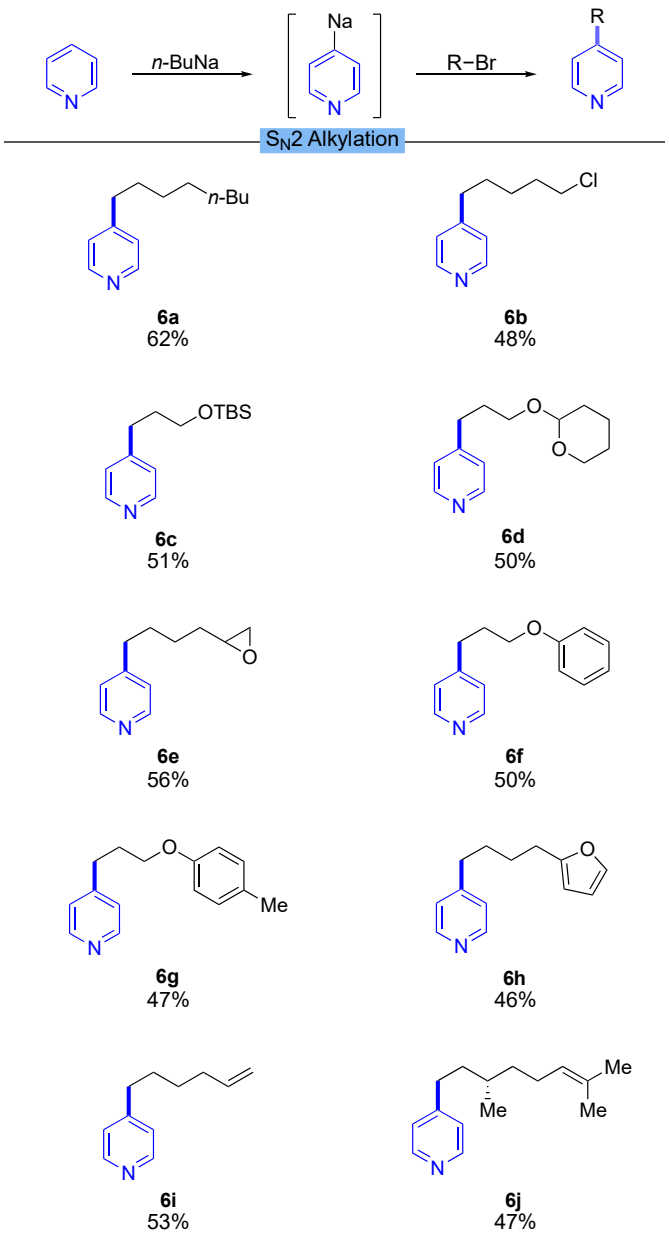


Fig. 2. **Substrate scope of direct alkylation reactions (SN2) with 4-sodiopyridine and primary alkyl bromides.** Standard reaction conditions were carried out on 0.5 mmol scale (*n*-BuNa) at −78 °C.

A particularly useful application of our ability to create carbanions at unique locations within pyridine would be to develop a Negishi cross-coupling protocol (Fig. 3). Organozinc reagents are ideal substrates for cross-coupling reactions because they typically do not require harsh reaction conditions and often exhibit immense functional group compatibilities.[54,55] Although 4-pyridiyl zinc chlorides are known they are typically challenging to access and often require the use of flow devices to overcome deleterious dimerization and side reactions.[56,57] Therefore, the next phase of our investigations focused on developing a single pot Negishi cross-coupling protocol. After capturing the 4-sodiopyridine with $ZnCl_2$ and a quick screen of the reaction conditions, a broad

range of aryl halides were successfully cross coupled with pyridine and isolated. Simple benzene derivatives such as 4-bromobiphenyl (**7a**), chlorobenzene (**7b**), 2-bromo and 2-chlorotoluene (**7c**), and even sterically demanding 2,4,6-trimethylbromobenzene (**7d**) underwent the reaction smoothly to give excellent yields. Benzene derivatives bearing electron-withdrawing groups (**7e**, **7f**) and electron-donating groups (**7g**-**7i**) were found to give the desired products in moderate to great yields. Selective cross-coupling of 1-chloro-4-iodobenzene at the carbon-iodine bond (**7j**) was also successful. Other substitution patterns on benzene were also found to be compatible with the reaction conditions, including nitro (**7k**), alkyne (**7m**), and cyano (**7l**) functional groups. Additionally, a range of aromatic systems can also be cross-coupled such as pyrene (**7n**), benzoxazole (**7o**), pyrazole (**7p**), thiophene (**7q**) giving the corresponding products in good yields.

To further establish the utility of our methodology, we applied it to the late-stage derivation of various pharmaceuticals. Lipidil (cholesterol lowering agent), Claritin (antihistamine), Compazine (antipsychotic), and Carbinoxamine (antihistamine) were functionalized with a 4-pyridyl fragment in good yields (**7r**-**7u**). These results show that the reaction provides a rapid and useful way to introduce a pyridine subunit into complex scaffolds at late-stages, which is essential for the construction and modification of pharmaceuticals.

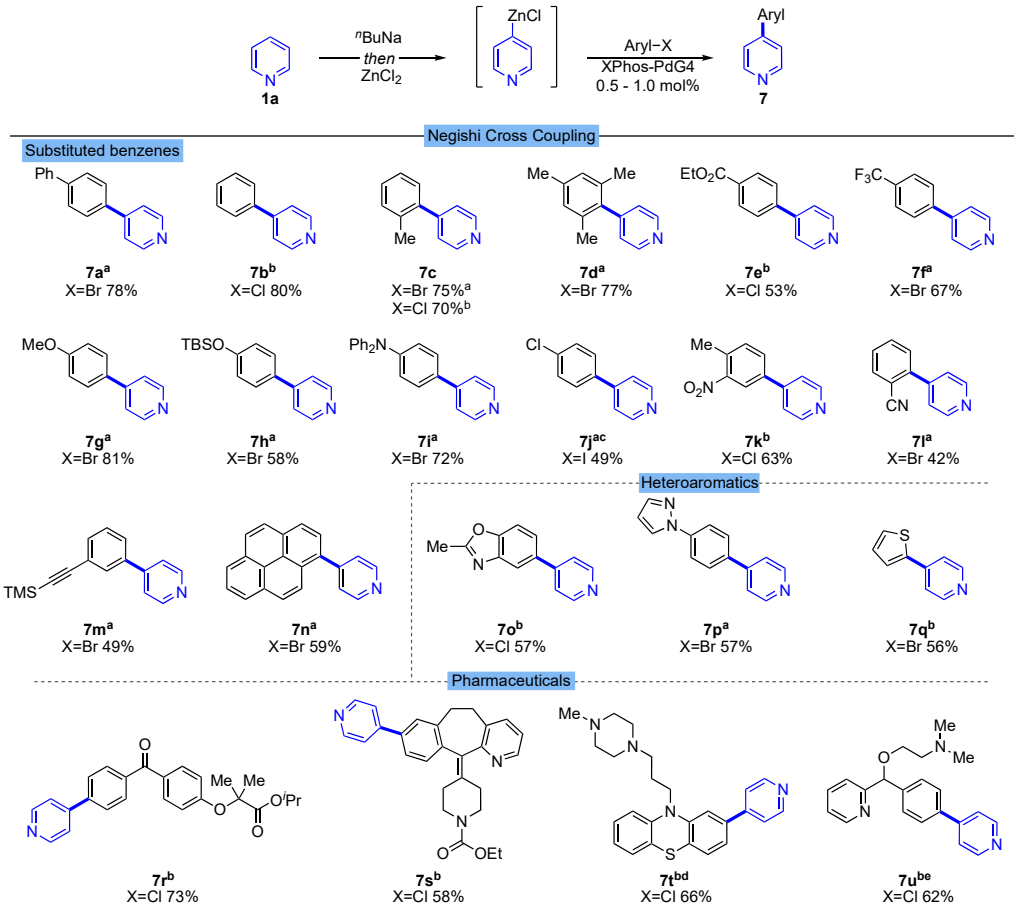


Fig. 3. **Substrate scope of palladium-catalyzed Negishi cross coupling reactions.** Standard reaction conditions were carried out on 0.5 mmol scale (Aryl-halide) at 80 °C employing (a) 0.5 mol% [Pd] or (b) 1.0 mol% [Pd]. [c]The reaction was conducted at 60 °C. [d] The product was isolated with its 3-pyridyl constitutional isomer.

4. Conclusion

In conclusion, we have developed the first preparation of 4-subsituted pyridines using the most simplifying C−H activation logic – a deprotonation-capture approach. The key to the success of this method was the use of *n*-BuNa which provided us an avenue to override the directing effects of the N-atom within pyridine and allow for the generation of 4-sodiopyridine. The 4-sodiopyridine was then shown to undergo a variety of carbon-carbon bond forming reactions such as alkylations and Negishi cross-couplings. Our methodology displayed a broad substrate scope, showed excellent functional group compatibility, and could be used to derivatize active pharmaceutical ingredients at late-stages. With this advancement, we envision that more devoted interest will be directed towards the investigation of the unique reactivity patterns of organosodium bases with heterocyclic scaffolds in the pursuit to extend the current synthetic landscape into new fronts.

5. Methods

General Procedure A for Direct Alkylation Reactions

In a glovebox, *n*-BuNa (40.0 mg, 0.50 mmol, 1.0 equiv) was weighed into a 25-mL round-bottom flask. The flask was removed from the glovebox and submerged into a dry ice-acetone bath (−78 °C) followed by the slow addition of THF (4.0 mL). A solution of pyridine in THF (1.0 M, 1.0 mL, 2.0 equiv) was added to the reaction flask dropwise to form a light-yellow solution, and the reaction was stirred for 2 h while maintaining the external bath at −78 °C. After 2 h, a THF solution of the desired alkyl bromide (1.0 M, 0.55 mL, 1.1 equiv) was added at −78 °C and stirred for 10 min. The flask was then removed from the bath and stirred at room temperature for an additional 1 h. The reaction was quenched with methanol (0.25 mL, 12.4 equiv), and the volatiles were removed *in vacuo*. The residue was washed with Et_2O (3 × 2 mL), filtered over a pad of celite and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel to afford the desired product.

General Procedure B for Palladium-Catalyzed Negishi Cross Coupling

In a glovebox, *n*-BuNa (80.0 mg, 1.0 mmol, 2.0 equiv) was weighed into a 25-mL Schlenk flask. The flask was removed from the glovebox and submerged into a dry ice-acetone bath (−78 °C) followed by the slow addition of THF (8.0 mL). A solution of pyridine in THF (1.0 M, 2.0 mL, 2.0 equiv) was added to the reaction flask dropwise to form a light-yellow solution, and the reaction was stirred for 2 h while maintaining the external bath at −78 °C. After 2 h, $ZnCl_2$ [1.0 M] (163.6 mg, 1.2 mmol, 2.4 equiv, 2.4 mL THF) was added to the reaction mixture at −78 °C and stirred for an additional 10 min. The vessel was transferred to a 0 °C ice-water bath and stirred for 5 min, to ensure the formation of the organozinc reagent. The desired aryl halide (0.5 mmol, 1.0 equiv) and XPhos-PdG4 (2.2 mg, 0.5 mol% or 1.1 mg, 1.0 mol%) was dissolved in 2 mL THF and stirred in a dram vial at room temperature under an argon atmosphere for 30 min. The mixture was added to the organozinc reagent at 0 °C and stirred at room temperature for 10 min, then heated to reflux in

a preheated oil bath (80 °C). The reaction was monitored until the aryl halide was consumed *via* GC-MS. The reaction mixture was quenched with water (1.0 mL) and extracted with 1.0 M NaOH solution (50 mL) and ethyl acetate (3 × 30 mL). The organic layers are combined and dried over sodium sulfate, filtered and the filtrate was concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel to afford the desired product.

Acknowledgements

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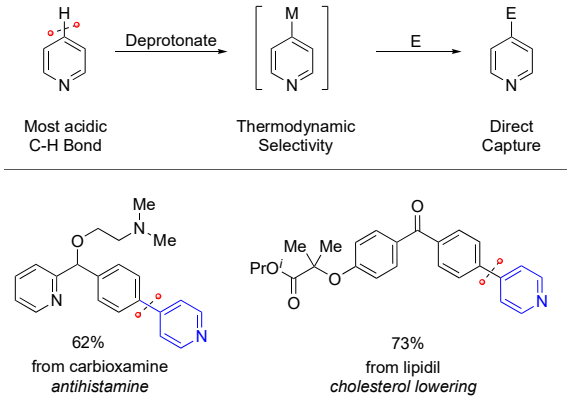

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