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Nucleophilic amination of methoxypyridines by a sodium hydride-iodide composite

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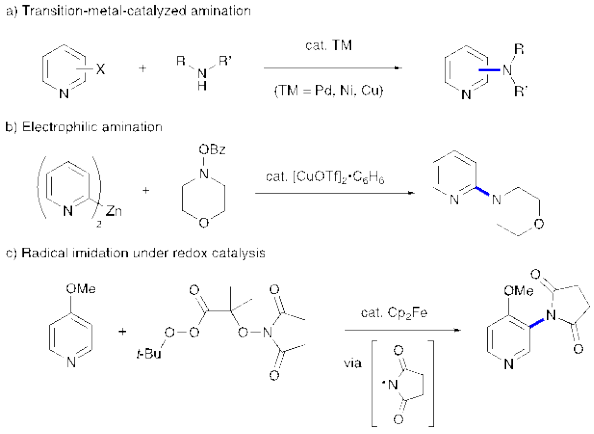
Jia Hao Pang,[a] Atsushi Kaga,[a] and Shunsuke Chiba*[a]

A new protocol for nucleophilic amination of methoxypyridines and their derivatives was developed using sodium hydride (NaH) in the presence of lithium iodide (LiI). The method offers a concise access to various aminopyridines which are potentially of medicinal interest.

The pyridine ring is one of the most essential aromatic heterocycles found in small molecule pharmaceuticals and agrochemicals.[1] Therefore, it is highly important to exploit new methods to construct substituted pyridines and to install functionality of interest onto the pyridine ring, while inherent electron-deficient and basic nature of pyridines often hampers development of versatile reaction tools to construct and functionalize them. Especially, installation of amine functionality (i.e. amination of pyridines) offers a direct access to aminopyridines, which are utilized as an important core of various pharmaceutical drugs.[2] At present, the state-of-the-art approach for synthesis of aminopyridines involves transition-metal-catalyzed amination of halopyridines (Scheme 1a).[3,4] Electrophilic amination of pyridyl metal nucleophiles with N-electrophiles such as hydroxylamine derivatives (typically under Cu catalysis)[5] and radical imidation/amination of pyridines under redox catalysis have proven promising as an alternative method (Scheme 1b and c).[6] On the other hand, the recent rigid guideline to the level of residual transition-metal contamination in the pharmaceutical ingredients attracts attention to the needs for transition-metal-free processes. In this context, nucleophilic aromatic substitution of (pseudo)halopyridines with amine nucleophiles, that proceed via the S_NAr mechanism or via the corresponding pyridyne intermediates, is one of the reliable way to install amine functionality onto the pyridine rings.[7-9] However, these methods have thus far been proven successful only for the C2- and C4-amination in terms of the regioselectivity due to the inherent reactivity of the pyridines or pyridyne intermediates.[10,11]



Scheme 1. Amination of pyridines.

We recently disclosed that unprecedented use of sodium hydride (NaH) by its solvothermal treatment with sodium iodide (NaI) or lithium iodide (LiI). The resulting NaH-iodide composites could show hydride-donor reactivity, enabling hydrodecyanation, reduction of amides into aldehydes, and hydrodehalogenation of bromo- and iodoarenes as well as dearylation of arylphosphine oxides.[12] During these studies, we observed that the pyridine rings, which are often susceptible to the common hydride reagents,[13] are tolerated in the reductive transformations in the presence of the NaH-iodide composite (Scheme 2a and 2b). We also found that nucleophilic amination of methoxyarenes was enabled by the NaH-iodide composite (Scheme 2c).[14,15] Stimulated by these discoveries, we wondered if the NaH-iodide composite is capable of functionalizing methoxypyridines through nucleophilic amination without undesired collapse of the pyridine ring. Optimization of the reaction conditions, scope and limitation, and synthetic application of the nucleophilic

[a] *Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637371, Singapore.*

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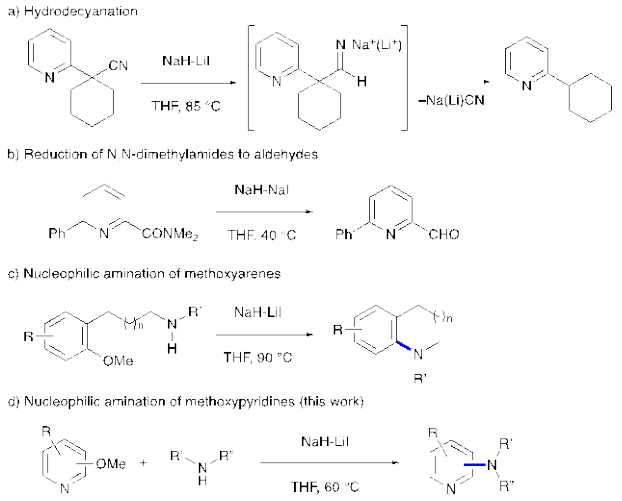
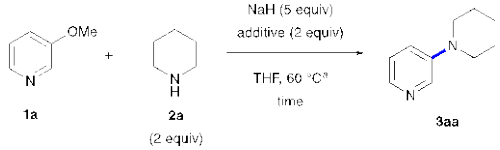
amination of methoxypyridines by the NaH-LiI system are described herein (Scheme 2D).



Scheme 2. Molecular Transformations by NaH-iodide composite

We commenced our studies with the reactions of 3-methoxypyridine (**1a**) and piperidine (**2a**) (Table 1). The reaction of **1a** with 2 equiv of **2a** in the presence of NaH (5 equiv) and NaI (2 equiv) in THF at 60 °C gave 3-(piperidin-1-yl)pyridine (**3aa**) in 7% yield with incomplete conversion (37%) even after stirring for 24 h (Entry 1). We found that use of LiI (2 equiv) in place of NaI dramatically enhanced the reaction efficiency, resulting in full conversion within 8 h to provide **3aa** in 88% yield (Entry 2). This protocol could be performed efficiently in a large (50 mmol) scale. It should be noted that the reaction was not mediated only with NaH (Entry 3).

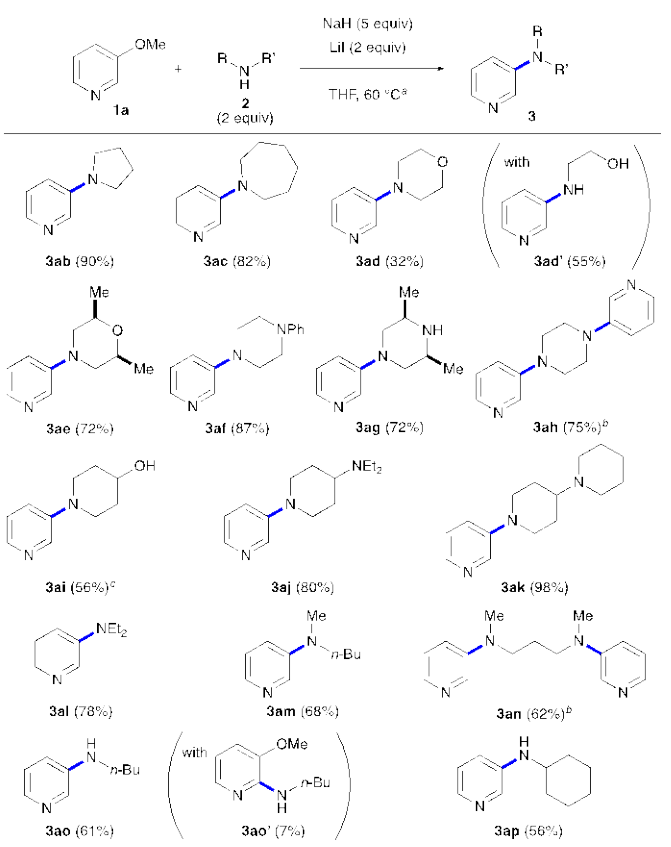
Table 1 Optimization of the reaction conditions



Entry	Additive	Time [h]	Yield [%]	Conversion [%][c]
1	NaI	24	7	37
2	LiI	8	88 (92)[b]	>99
3	–	24	0	23

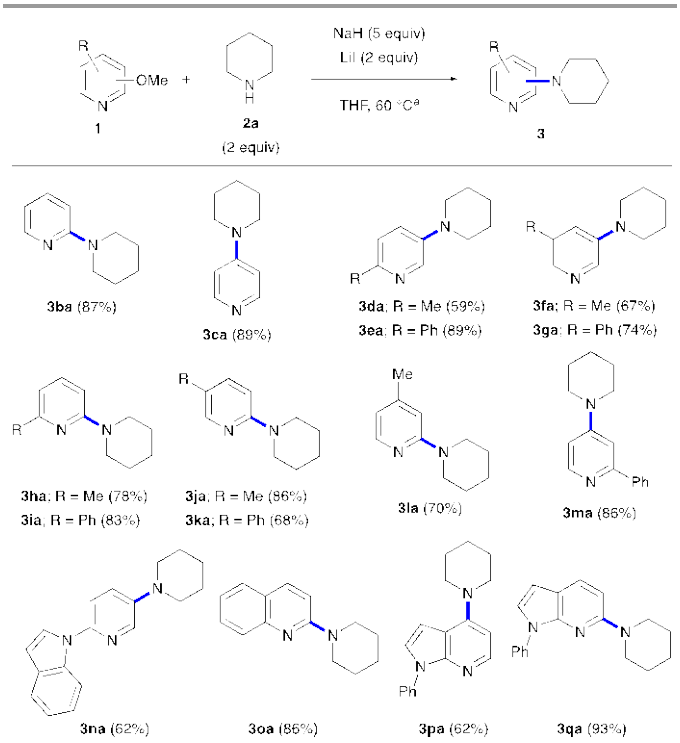
[a] The reactions were conducted using 0.5 mmol of 3-methoxypyridine (**1a**) and 1 mmol of piperidine (**2a**) in THF (0.5 mL: 1 M) and isolated yield of **3aa** were noted above. [b] Isolated yield in 50 mmol scale. [c] ^{1}H NMR yields based on an internal standard.

Having optimized the reaction conditions with the NaH-LiI system, we investigated C3-amination of 3-methoxypyridine (**1a**) using various amines **2** (Scheme 3). Installation of aliphatic nitrogen-heterocycles such as pyrrolidine (for **3ab**) and azepane (for **3ac**) worked smoothly. The reactions of morpholine (**2d**) afforded not only morpholine adduct **3ad** but also ethanolamine adduct **3ad'** in 32% and 55% yields, respectively. Formation of **3ad'** occurred presumably via deprotonation at the α-oxy position and subsequent ring-opening of the morpholine adduct **3ad** followed by hydrolysis of the resulting enol intermediate (see ESI for more details). This ring-fragmentation of the morpholine moiety was prevented using *cis*-2,6-dimethylmorpholine (**2e**), affording **3ae** as a sole product. Amination with piperazines took place efficiently (for **3af**-**3ah**). It is of worthy to note that the reaction with *cis*-2,6-dimethylpiperazine (**2g**) proceeded selectively at the less hindered site, while double amination took place with none-substituted piperazine (**2h**). Unique chemoselectivity was observed in the reaction with 4-hydroxypiperidine (**2i**), that affords amination product **3ai** keeping a free hydroxyl group intact. Use of 4-aminopiperidines **2j** and **2k** gave the corresponding amination products **3aj** and **3ak**, respectively, in good yields. Acyclic secondary amines **2l** and **2m** also worked smoothly. The reaction of 1,3-propanediamine **1n** with 2.1 equiv of **1a** afforded bis-pyridyl adduct **3an** in 61% yield. We found that the reaction of n-butylamine (**2o**) provides 3-aminated pyridine **3ao** in 61% yield through nucleophilic substitution of the 3-methoxy group along with formation of Chichibabin amination product, 2-aminopyridine **3ao'** in 7% yield,[16] whereas that of bulkier cyclohexylamine (**2p**) gave nucleophilic amination product **3ap** in 56% yield as a sole product.



Scheme 3. Screening of amines **2**. [a] The reactions were conducted using 0.5 mmol of 3-methoxypyridine (**1a**) and 1 mmol of amines **2** in THF (0.5 mL: 1 M) and isolated yields of 3-aminopyridines **3** were noted above. [b] The reaction was conducted using 1 mmol of **1a** and 0.5 mmol of amine **2** and isolated yield of **3** was calculated based on amine **2**. [c] The reaction was conducted using 7 equiv of NaH and 2 equiv of LiI at 90 °C in sealed tube.

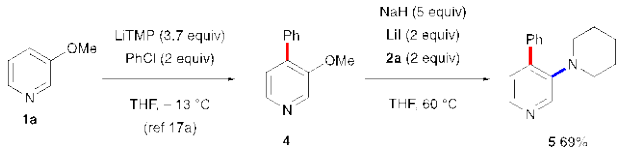
We next searched a scope and limitation of pyridine derivatives **1** using piperidine **2a** as a nucleophile (Scheme 4). Amination of even 2/4-alkoxypyridines commonly requires assist of an electron-withdrawing group (EWG) such as a nitro group on the pyridine ring.[17] On the other hand, our protocol with the NaH-LiI system enabled amination at either C2- or C4-position smoothly without the assist of EWG (for **3ba** and **3ca**). We also confirmed that NaH alone does not mediate the C2/4 amination. We found that the methyl and phenyl substituents in various positions do not affect the efficiency of the present amination (for **3da**-**3ma**). This protocol was found applicable to the amination of 1-(5-methoxypyridin-2-yl)-1*H*-indole (**1n**) and 2-methoxyquinoline (**1o**) as well as 4- and 6-methoxy-1-phenyl-1*H*-pyrrolo[2,3-*b*]pyridines (**1p** and **1q**).



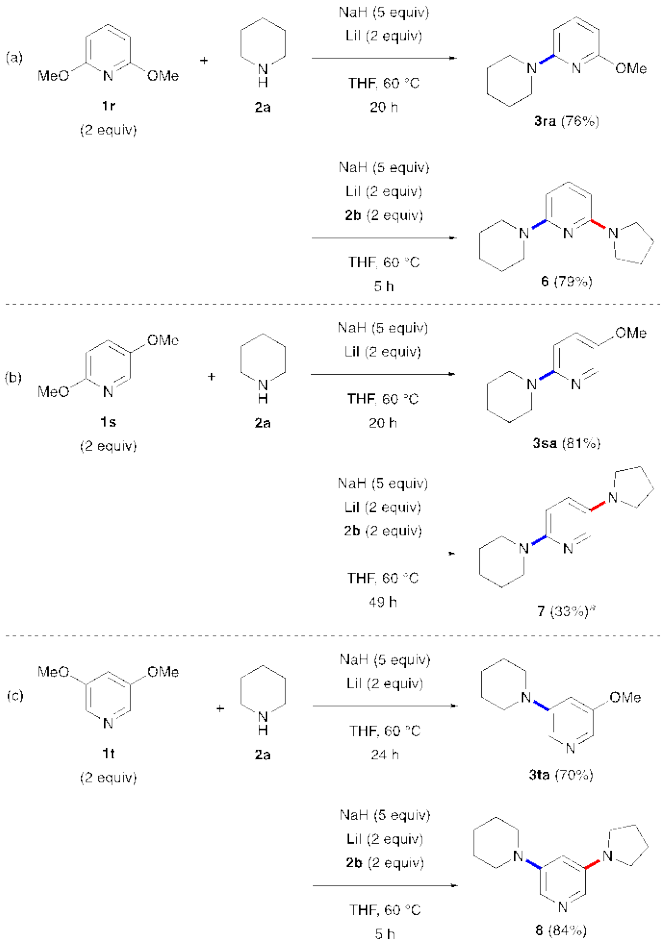
Scheme 4. Screening of methoxypyridines **1**. [a] All the reactions were conducted using 0.5 mmol of methoxypyridines **1** and 2 equiv of piperidine (**2a**) with NaH (5 equiv) and LiI (2 equiv) in THF (0.5 mL: 1 M) at 60 °C. Isolated yields of the products were noted above.

The methoxy group on the pyridine ring can be used as a directing group for deprotonative ortho-metallation, thus capable of further installation of functionality through the reactions of the resulting pyridyl metal species with various electrophiles.[18] For example, it was recently reported by Daugulis that the methoxy group on **1a** can be used for the directed lithiation followed by arylation at the C4 position to afford **4** (Scheme 5).[17a] We took advantage of this method together with our current amination protocol for synthesis of 4-phenyl-3-(piperidin-1-yl)pyridine (**5**).

We found that the present procedure is amenable to sequential double amination of dimethoxypyridines (Scheme 6). For example, mono-amination of 2,6-dimethoxypyridine (**1r**) with piperidine (**2a**) was attained to give **3ra** in 76% yield (Scheme 6a), that can be followed by second-amination with pyrrolidine (**2b**) to afford **6** in 79% yield. The first amination of 2,5-dimethoxypyridine (**1s**) took place exclusively at C2 to afford **3sa** in 81% yield, while moderate efficiency was observed in the second C5-amination of **3sa** to **7** (Scheme 6b). Sequential diamination could be conducted on 3,5-dimethoxypyridine (**1t**) in good yields (Scheme 6c).



Scheme 5 Sequence of directed C-H phenylation and nucleophilic amination of 3-methoxypyridine (**1a**).



Scheme 6 Sequential amination of dimethoxypyridines **1r**, **1s** and **1t**. [a] 76% yield based on the recovery of **3sa**.

This work demonstrates new use of the NaH-iodide composite for unprecedented nucleophilic amination of methoxypyridines to prepare aminopyridine derivatives in a concise fashion. Further investigation on use of the NaH-iodide composite to explore other types of molecular transformations is ongoing in our laboratory.

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