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# Synthesis of aminopyridines from 2-fluoropyridine and lithium amides

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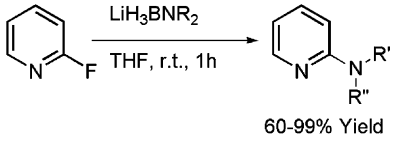
**Abstract**—Lithium amides promote the amination of 2-fluoropyridine under mild reaction conditions, providing 2-aminopyridines in good yields and purity. Treatment of 2-fluoropyridine with 1 equiv of lithium amide at room temperature affords complete conversion after 2 h. To our knowledge, this is the first study of lithium amide-promoted amination of fluoropyridines that are not further activated by electron-withdrawing groups.

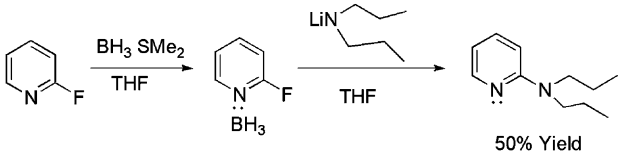

Aminopyridines have been shown to be biologically active molecules. There are several aminopyridine-based pharmaceuticals, which are used to treat a range of disorders.[1] Additionally, because of their chelating abilities, aminopyridines are commonly used as ligands in inorganic and organometallic chemistry.[2] If substituted with optically active groups, they could potentially serve as chiral auxiliaries or chiral ligands in asymmetric reactions. For these reasons, aminopyridines are valuable synthetic targets. The methods, which currently exist for the synthesis of aminopyridines from halopyridines include nucleophilic aromatic substitution reactions ($S_NAr$) with free amines under high pressure[3] and/or high temperature.[4] Several years ago, Buchwald and others have demonstrated transition metal-catalyzed cross-coupling of bromo and chloropyridines with amines as an efficient route to aminopyridines.[5] Recently, we have disclosed a method of converting 2-fluoropyridines to aminopyridines with lithium aminoborohydrides (LAB) (Scheme 1).[6] This method is also applicable to 2-chloro and 2-bromopyridines.




**Scheme 1.** Reaction of 2-Fluoropyridine with LAB.

Our investigations regarding a possible mechanism for the reaction of 2-fluoropyridine with LAB reagent led us to hypothesize that the pyridine could be activated by coordination to boron during the reaction. To check this hypothesis, we treated 2-fluoropyridine with $BH_3{\cdot}SMe_2$ to form a 2-fluoropyridine-borane complex. We then reacted the complex with lithium dipropylamide (formed from dipropylamine and *n*-BuLi) at 0 °C (Scheme 2). Interestingly, 2-dipropylaminopyridine was isolated from this reaction in 50% yield.

This result intrigued us since it is known that sterically hindered lithium amides such as LDA, do not promote amination of 2-halopyridines. Rather, these reactions result in *ortho*-lithiation.[7] To test the generality of this




**Scheme 2.** Reaction of 2-fluoropyridine with BMS and lithium dipropylamide.

*Keywords*: Aminopyridines; 2-Fluoropyridine; Lithium amides.
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reaction, we reacted three other lithium amides with the 2-fluoropyridine-borane complex. These results are summarized in Table 1.

In order to determine the importance of pre-activating 2-fluoropyridine with $BH_3$, we also performed the reaction in the absence of BMS. When 2-fluoropyridine was reacted with lithium pyrrolidide, we were pleasantly surprised to find that 2-pyrrolidinopyridine was obtained in 80% yield. Although we found no prior examples of simple lithium amides promoting nucleophilic substitution reactions of 2-fluoropyridine, it was recently reported that 2- and 4-cyanopyridines can be aminated with lithium amides in the presence of CsF.[8]

To determine the scope of this amination method, a series of primary and secondary lithium amides were reacted with 2-fluoropyridine to generate the corresponding aminopyridines (Table 2).[9] It is important to note that this methodology is complementary to the reaction of 2-fluoropyridine with LAB reagents. We found that monoalkylaminopyridines can be synthesized from primary lithium amides (Table 2, entries 5, 8 and 9), whereas these products were difficult to obtain using primary amine-derived LAB reagents.

By using enantiomerically pure lithium amides in this reaction, the synthesis of chiral aminopyridines has been achieved. When optically pure limonene-derived amino

**Table 1.** Aminopyridines obtained from the reaction of 2-fluoropyridine–borane complex and lithium amide

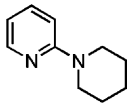
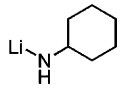
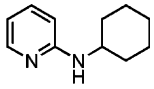
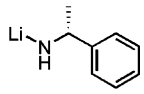
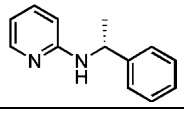
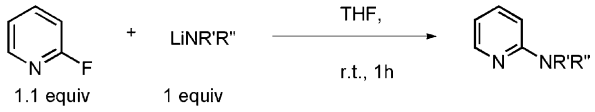
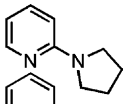
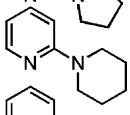
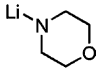
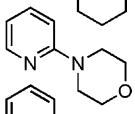
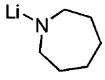
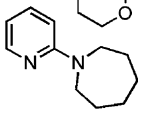
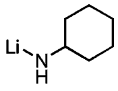
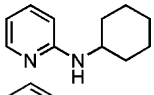
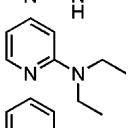
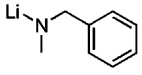
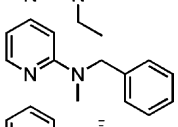
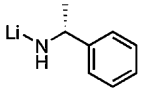
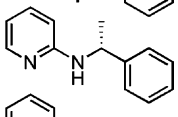
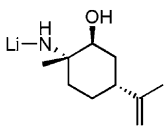
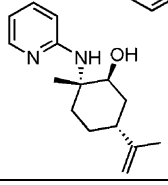
| Entry | Amide | Product | Yield (%) |
|---|---|---|---|
| 1 |  |  | 62 |
| 2 |  |  | 34 |
| 3 |  |  | 35 |

**Table 2.** Reactions of 2-fluoropyridine with various lithium amides




| Entry | Amide | Product | Yield (%)[a] |
|---|---|---|---|
| 1 |  |  | 80 |
| 2 |  |  | 82 |
| 3 |  |  | 85 |
| 4 |  |  | 83 |
| 5 |  |  | 40 |
| 6 |  |  | 64 |
| 7 |  |  | 82 |
| 8 |  |  | 64 |
| 9 |  |  | 10[b] |

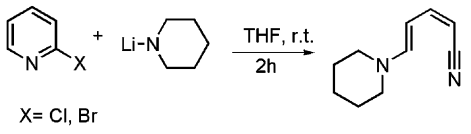
[a] Isolated yields.
[b] 2 equiv of *n*-BuLi was used, the product was purified by flush column chromatography (15% EtOAc/Hex).

alcohol ((1*S*,2*S*,5*R*)-2-amino-2-methyl-5-(prop-1-en-2-yl)cyclohexanol) was treated with *n*-BuLi (2 equiv) and reacted with 2-fluoropyridine, the aminopyridine product was isolated in low yield after column chromatography (Table 2, entry 9). This low yield is most likely due to steric hindrance from the methyl group. Conversely, when nonsterically demanding (*R*)-(+)-α-methylbenzylamine (Table 2, entry 8) was used in the same manner, the chiral aminopyridine product was obtained in 60% yield.

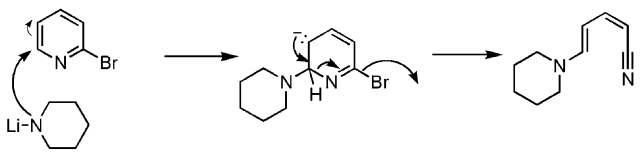
To determine the scope of this methodology, we attempted to extend the reaction to other halopyridines. Interestingly, when we reacted 2-chloro and 2-bromopyridine with lithium amides we observed opening of the pyridine ring (Scheme 3).

A literature search revealed that a similar type of pyridine ring opening reaction has been observed during the reaction of trialkylboranes with 2-bromo-6-lithiopyridine, as well as during irradiation of pyridine N-oxide in the presence of secondary amines.[10] A proposed explanation for our result is described mechanistically in Scheme 4.

The reaction of lithium amides with 2-fluoropyridine is an efficient route to 2-aminopyridines. It is possible however, to obtain 2-aminopyridines from the reaction of free amines with 2-fluoropyridine if the amine is exceptionally nucleophilic, or if the pyridine ring is further activated by electron-withdrawing substituents.[11] It has been reported that azetidine, a highly nucleophilic amine, reacts with 2-fluoropyridine at room temperature to give the corresponding aminopyridine in 50% yield.[12] Similarly, we found that by treating 2-fluoropyridine with pyrrolidine at room temperature, the aminopyridine product is obtained in 60% yield. Less nucleophilic amines do not react with 2-fluoropyridine even after extended reflux (Table 3, entry). We observed that very activated pyridines, such as 2-fluoro-4-trifluoromethylpyridine, react with free amines to generate aminopyridines. Using this substrate, even less nucleophilic free amines can be used to synthesize aminopyridines.[13] Table 3 summarizes the results obtained from reactions involving free amines and 2-fluoropyridines.

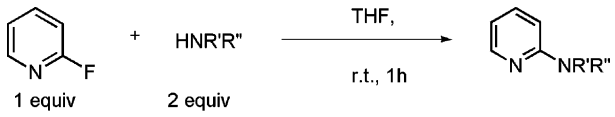


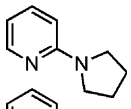
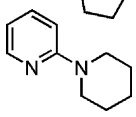
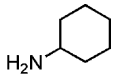
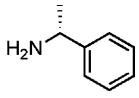
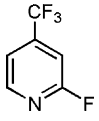
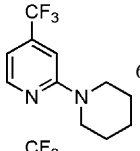
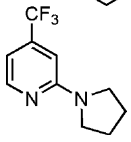

**Scheme 3.** Reaction of lithium amides with 2-bromo and 2-chloropyridines.




**Scheme 4.** Mechanistic explanation of opening of pyridine ring.

**Table 3.** Reactions of 2-fluoropyridine with free amines




| Entry | Fluoropyridine | Amine | Product | Yield (%)[a] |
|---|---|---|---|---|
| 1 |  |  |  | 60[b] 12[c] |
| 2 | |  |  | 15[b] |
| 3 | |  | — | NR[b,c] |
| 4 | |  | — | NR[b,c] |
| 5 |  |  |  | 62 |
| 6 | |  |  | 86 |

[a] Isolated yields.
[b] The reaction was run neat.

In conclusion, we have described mild and convenient method for the synthesis of 2-aminopyridines from 2-fluoropyridine and various lithium amides. Both primary and secondary lithium amides have been shown to be effective in these simple amination reactions. Using this method, we have successfully synthesized enantiomerically pure aminopyridines, which can serve as potential ligands in asymmetric reactions.

## Acknowledgements

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.06.132.

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Brunnemann, J.; Bunten, S. C. *Am. J. Ther.* **2002**, *9*, 29; (e) Cacchi, S.; Carangio, A.; Fabrizi, G.; Moro, L.; Pace, M. *Synlett* **1997**, 1400.
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9. Preparation of lithium piperidine is representative. To a cooled solution (0 °C) of piperidine (0.41 mL, 5 mmol) in anhydrous THF (4 mL) was added *n*-BuLi (2.5 M, in hexanes, 2 mL, 5 mmol) dropwise via syringe. After stirring at room temperature for 15 min, the resulting lithium amide was then added dropwise to the solution of 2-fluoropyridine (0.48 mL, 5.5 mmol, 1.1 equiv) in anhydrous THF (3 mL) at 0 °C. Reaction completion was followed by TLC. After quenching with $H_2O$ (5 mL), the product was extracted with 1:1 THF/ether (4×20 mL). The organics were dried ($MgSO_4$) and evaporated in vacuo to yield 2-piperdinopyridine as an orange oil (0.67 g, 82%).
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13. Amino-3-trifluoropyridines were also synthesized from 2-chloro-3-trifluoropyridine under drastic reaction conditions. Dunn, A. D. *J. Fluorine Chem.* **1999**, *93*, 153.