Preparation of Nitrogen-containing Heterocycles via Cyclization of Pyridine-tethered Organolithiums

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Preparation of Nitrogen-containing Heterocycles via Cyclization of Pyridine-tethered Organolithiums

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B.A., Connecticut College, 2010

A Thesis
Submitted in Partial Fulfillment of the Requirements for the Degree of Master of Science
at the University of Connecticut
2012
Master of Science Thesis

Preparation of Nitrogen-containing Heterocycles via Cyclization of Pyridine-tethered Organolithiums

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University of Connecticut
2012
Acknowledgements

To everyone who has helped me to achieve so much I extend a heartfelt thank you—I would not be here today without your help:

- My advisor Dr. William Bailey, whose guidance and enthusiasm have prepared me to take on life after graduate school. Although you are convinced otherwise, you have been nothing but a pleasure to work for.

- Dr. James Bobbitt, your love of chemistry and everything in life has been an inspiration to me.

- Amy Howell, if you had not reached out to me when I first applied I would certainly not be here today completing this program.

- My Bailey group members Johanna Bakonyi, Ashley Bartelson, and Nyle Blanck I couldn’t have asked for better people to work with every day.

- My professors Dr. Michael Smith, Dr. Christian Brückner, Dr. Mark Peczuh, and Dr. Dennis Wright for advancing my knowledge of chemistry.

- The Chemistry department staff, especially Dan Daleb, Martha Morton, Emilie Hogrebe, Brian Cardinal, and Charlene Fuller, who kept everything running smoothly during my time here.

- My BI mentors Dr. Keith Fandrick and Dr. Daniel Marshall who have taught me an incredible amount of chemistry during such a short time and have been an absolute pleasure to work with.

- Madre, Papala, Nonny, and Abuela, you have made everything in life possible, including this degree.
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Part I: Introduction

Organolithium Chemistry

The preparation of organolithium compounds has been widely used in organic synthesis in order to achieve a multitude of transformations. There are several, well-documented routes to organolithium compounds, one of the most popular being the lithium-halogen exchange, thus named because the reaction involves exchange of a halide and an organolithium to form a new organolithium and halide.

Discovered separately by Wittig\(^1\) and Gilman\(^2\) in 1938, the mechanism for the exchange is presumed to proceed through an intermediate “ate” complex (Scheme 1).\(^3\) This mechanism supports the observation that the exchange proceeds most rapidly with polarizable iodide, occurs readily with bromide, but very rarely occurs with chloride.\(^4,5\)

\[
\begin{align*}
R{-}\text{Li} + R'{-}X & \leftrightarrow [R{-}\tilde{X}R' \text{ Li}^+] \leftrightarrow R'{-}\text{Li} + R{-}X \\
& \quad \text{“ate complex”}
\end{align*}
\]

Scheme 1

The exchange is an equilibrium that favors the more stable organolithium.\(^6\) Thus, exchange occurs most readily to form aryl and vinylolithiums, which are more stable than the alkylolithiums from which they are formed.\(^7\)

The lithium-halogen exchange is most readily performed using commercially prepared solutions of \(t\)-butyllithium. While the exchange proceeds with other organolithiums, side reactions are more common, and the reaction with \(t\)-butyllithium can be rendered irreversible by the use of two equivalents of organolithium (Scheme 2). The first equivalent performs the lithium-halogen exchange and produces \(t\)-butyl halide,
which is subsequently consumed by a second equivalent of $t$-butyllithium to irreversibly form isobutane, isobutene, and lithium halide.$^{8,9}$

Scheme 2

The reactivity of $t$-butyllithium has also been well-studied and it is understood that it can exist in several different aggregation states depending on the solvent (Figure 1).$^{10}$ In general, the higher the aggregation state, the lower the reactivity; thus, while organolithium reactions can be performed in hydrocarbon solvent, where $t$-butyllithium is a tetramer, a mixture of solvents is often employed, or an additive such as TMEDA is included, in order to place the organolithium in a more reactive dimeric of monomeric aggregation state.
Although solvents such as diethyl ether or THF are necessary to promote reactivity, they are also consumed by t-butyllithium quite rapidly at warmer temperatures (Table 1).\textsuperscript{11} This is another reason for using a mixture of hydrocarbon and ethereal solvents and for running the reaction at very low temperatures. For example, a robust system for the lithium-halogen exchange is 9:1 pentane/diethyl ether at \(-78\, ^\circ\text{C}\).

Table 1. Half-Life of t-Butyllithium in Ethereal Solvents\textsuperscript{11}

<table>
<thead>
<tr>
<th>solvent</th>
<th>T, °C</th>
<th>approx. $t_{\frac{1}{2}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Et$_2$O</td>
<td>-20</td>
<td>8 h</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>1 h</td>
</tr>
<tr>
<td></td>
<td>20</td>
<td>10 min</td>
</tr>
<tr>
<td>THF</td>
<td>-40</td>
<td>5 h</td>
</tr>
<tr>
<td></td>
<td>-20</td>
<td>40 min</td>
</tr>
</tbody>
</table>

**Organolithiums and Pyridine**

Nitrogen containing-heterocycles represent an indispensable moiety in organic chemistry. In 2010, of the top twenty small molecule drugs, eighteen contained at least one nitrogen-containing heterocycle.\textsuperscript{12} One of the most important nitrogen heterocycles is pyridine. Pyridine systems can be found in many biologically active molecules such as pharmaceuticals, herbicides, fungicides, and insecticides (Figure 2). Their ubiquitous appearance makes the novel synthesis of pyridine-derived systems a valuable target.
One of the ways to functionalize a pyridine ring is to take advantage of the inherent electrophilicity at the 2, 4, and 6-positions (Scheme 3). Such a reaction was first reported by Chichibabin in 1914, producing 2-aminopyridine through the nucleophilic addition of amide anion into the azomethine linkage.\textsuperscript{13}

It was subsequently discovered that organolithiums are also capable of nucleophilic addition into the pyridine ring, as reported by Ziegler in 1930.\textsuperscript{14,15} Similar to the Chichibabin reaction, addition occurs into the azomethine linkage; rearomatization of the pyridine can then be obtained by losing lithium hydride through heating or by low-temperature quenching of the reaction mixture to produce a dihydro intermediate followed by oxidation (Scheme 4).
Addition into unsubstituted pyridine occurs almost exclusively at the 2-position, possibly due to coordination of the lithium and nitrogen atoms, with the regioselectivity thus resulting from proximity of the coordinated organolithium to this position. This trend is still observed in the case of many 3-substituted pyridines. For example, 3-methyl and 3-ethyl pyridine are actually activated to organolithium attack at the 2-position, while 3-isopropyl and 3-cyclohexyl, while also resulting in some of the 3,6-isomer, still yield the 2,3-substituted isomer as the major product.

Although t-butyllithium is the organolithium of choice for performing the lithium-halogen exchange, it adds to the pyridine ring, even at temperatures as low as –70 °C (Scheme 5). Addition of one equivalent of t-butyllithium predictably leads to substitution at the 2-position while addition of two equivalents leads to the 2,6-disubstituted product.

While intermolecular addition of organolithiums to pyridine has been recognized for decades, intramolecular addition has gone largely unstudied. Harrowven attempted an intramolecular addition during the total synthesis of toddaquinoline (Scheme 6), but
his conditions led predominantly to an undesired product that was likely the result of the rearrangement of the organolithium following lithium-halogen exchange. The desired product was formed in only 11% yield.

\[
\begin{align*}
\text{O} & \quad \text{N} & \quad \text{Br} & \quad \text{O} & \quad \text{N} & \quad \text{OMe} \\
\text{1. } n\text{-BuLi, THF, } & \text{, } -78 \degree \text{C} & \quad \text{1. } n\text{-BuLi, THF, } & \text{, } -78 \degree \text{C} & \quad \text{1. } n\text{-BuLi, THF, } & \text{, } -78 \degree \text{C} \\
\text{2. } & \text{, } 0 \degree \text{C} & \quad \text{2. } & \text{, } 0 \degree \text{C} & \quad \text{2. } & \text{, } 0 \degree \text{C} \\
& \quad \text{32\%} & \quad \text{OMe} & \quad \text{OMe} & \quad \text{11\%} & \quad \text{OMe} & \quad \text{OMe}
\end{align*}
\]

**Scheme 6**

Recently, the Bailey group has successfully performed the intramolecular cyclization of pyridine-tethered aryllithiums in order to synthesize benzoquinolines (Scheme 7). The first reaction sequence utilized 3-(2'-bromophenethyl)pyridine; low temperature lithium-halogen exchange followed by warming to room temperature led to a mixture of the quenched product, 3-phenethylpyridine, and two cyclized products, 5,6-dihydrobenzo[h]quinoline and 5,6-dihydrobenzo[f]quinoline (Scheme 7). The formation of 5,6-dihydrobenzo[f]quinolone was suprising since addition to the 4-position of pyridine is generally not seen in 3-substituted pyridines. The ratio of products was heavily dependent on the reaction temperature, solvent system, and whether or not an additive was included. Depending on the conditions chosen, 5,6-dihydrobenzo[f]quinoline could be prepared in up to 77% yield and 5,6-dihydrobenzo[f]quinoline was generated in up to 59% yield.
This methodology could also be applied to the formation of benzo[h]quinoline and benzo[f]quinolone (Scheme 8). Again, the results were heavily dependent on reaction conditions, and remaining starting material and undesired byproducts were much more prevalent. In this case, benzo[h]quinoline could be produced in up to 72% yield and benzo[f]quinolone in up to 39% yield.

Formation of an indenopyridine derivative was not as successful and quenching of the organolithium led to the major product (Scheme 9). Although the lithium-halogen exchange proceeded efficiently, it was likely that subsequent metalation of the benzylic position resulted in an organolithium unable to cyclize, leading to formation of the
quenched product. This route could likely be improved upon by creating a quaternary system at the benzylic position, preventing metalation from occurring at this position.

### Scheme 9

**Synthesis of Monoazabiphenylenes**

The monoazabiphenylene ring system is an uncommon pyridine-containing heterocycle. The 1- and 2- isomers were first synthesized in 1975 by Barton and Walker via photocyclisation of 3-phenylazopyridine followed by vacuum thermolysis to give 1- and 2-azabiphenylene (Scheme 10).\(^{21}\) The reaction conditions employed were quite harsh: irradiation of 3-phenylazopyridine in concentrated H\(_2\)SO\(_4\) for 72 h followed by vacuum thermolysis at 800 °C.

### Scheme 10

Azabiphenylene analogues were subsequently synthesized by Leonard\(^{22}\) and Vollhardt\(^{23}\) using methodology developed by Vollhardt in 1982\(^{24}\) toward the synthesis of
biphenylene. The methodology employs the cocyclization of ethynylpyridines and bis(trimethylsilyl)acetylene in the presence of the cobalt catalyst, CpCo(CO)₂, and light.

Leonard used this protocol to synthesize methoxy derivatives of the azabiphenylenes in order to study the rearrangements they undergo. The four-step process (Scheme 11) gave 4-methoxy-1-azabiphenylene in 13% overall yield and 1-methoxy-2-azabiphenylene in only 6% overall yield.²²

Scheme 11

Vollhardt later used this methodology toward the synthesis heteophenylenes.²³ Preliminary experiments showed that the cobalt-catalyed photoreaction could lead to 6,7-bis(trimethylsilyl)-2-azabiphenylene as well as the parent 2-azabiphenylene through desilylation (Scheme 12, sequence 1). The reaction sequence was also applied toward the synthesis of 1-azabiphenylene (Scheme 12, sequence 2).

Scheme 12
As noted above the only known methods to synthesize the azabiphenylene ring system and both involve photochemistry. A novel route to the azabiphenylenes could be approached using organolithium chemistry. One could envision attack of a tethered phenyl-lithium, generated by a lithium-halogen exchange, into the pyridine ring. Subsequent rearomatization of the dihydro intermediate would then lead to the desired ring system (Scheme 13). This would provide an alternative route that does not involve photochemistry to access a ring system which to this point has not been well-studied.

Scheme 13

Synthesis of 2,3-Cycloalkenopyridines

The 2,3-cycloalkenopyridine series is another pyridine series whose importance had been recognized for decades. Their reactivity has been extensively studied, particularly at the methylene position attached to the 2-position of the pyridine ring (Scheme 14). For example, conversion to the N-oxide allows this position to be functionalized with a halogen or hydroxyl, which in turn can be further functionalized. This position can also be metalated with Grignard reagents or organolithiums, allowing access to carboxylic acids, esters, amides, thioamides, and nitriles. In addition, the methylene position is reactive toward aldehydic carbonyls such as formaldehyde and benzaldehyde.
There are many routes available to access 2,3-cycloalkenopyridines. The earliest synthesis to form a series of ring sizes was developed by Prelog and Szpilfogel in 1945 utilizing a cyclic amino ester (Scheme 15). Cyclization with a di-ester forms the pyridine ring and subsequent steps remove the superfluous functional groups via hydrolysis, chlorination, and reduction in order to elucidate the cycloalkenopyridine series with ring sizes five through seven and fifteen.

\[ \text{Scheme 14} \]

\[ \text{Scheme 15} \]
In 1958, another synthesis was devised by Ishiguro et al. that proceeded via a catalytic vapor phase reaction of ammonia, allyl alcohol, and cycloalkanones of ring sizes five through seven (Scheme 16).\textsuperscript{27} The catalyst was any of a variety of transition-metal complexes and the yield ranged from 18 to 38%.

![](image1)

**Scheme 16**

The German company, Degussa, expanded and improved upon this methodology accessing a variety of 2,3-cycloalkenopyridines via the reaction of a cycloalkanone, acrolein, and ammonia at high temperature, utilizing a catalyst derived from aluminum oxide, magnesium nitrate, and titanium tetrafluoride (Scheme 17).\textsuperscript{28} Substituted cycloalkanones and alkenones can be utilized in order to achieve substituted 2,3-cycloalkenopyridines. The Degussa methodology afforded 2,3-cycloalkenones in 37 to 89% yield, with an average yield of 59%, and employed readily available starting materials, making the synthesis of this compound series more accessible.

![](image2)

**Scheme 17**

In 1970, Breitmaier and Bayer also utilized cycloalkanones and successfully prepared a series of 2,3-cycloalkenopyridines by cyclizing the ketones with 3-aminoacroleins at 120 °C in the presence of triethylamine and piperidine acetate as catalyst (Scheme 18).\textsuperscript{29}
It was soon discovered that 2,3-cycloalkenopyridines could also be accessed through the rearrangement of an oxime O-allyl ether, prepared from the appropriately-sized cyclic ketone and O-allylhydroxylamine hydrochloride (Scheme 19). The reaction is thought to proceed via a [2,3]-sigmatropic rearrangement.\(^\text{30}\)

While many reactions are available to access 2,3-cycloalkenopyridines, all of the known methodologies involve high temperature conditions and some use harsh reagents as well. Additionally, all of the reported procedures begin with the cycloalkyl ring intact and subsequently form the pyridine ring; there are no reported methodologies for forming a 2,3-cycloalkenopyridine series with the pyridine ring already intact.

Organolithium chemistry offers an avenue by which to form a 2,3-cycloalkenopyridine by addition into the pyridine ring. A 3-alkyl-substituted pyridine containing a primary halogen could undergo lithium-halogen exchange, forming a primary organolithium, which, upon addition into the azomethine linkage and rearomatization would produce the desired series (Scheme 20).
Organolithium chemistry provides a potential alternate route for the synthesis of pyridine-containing heterocycles. It has already been shown that organolithium chemistry is useful for the synthesis of 5,6-dihydrobenzo[h]quinoline and 5,6-dihydrobenzo[f]quinoline and could potentially be used for the synthesis of certain indenopyridine derivatives. Therefore, it is likely that organolithium chemistry could allow access to azabiphenylene systems; work toward this synthesis is outlined below. The methodology will then be expanded outward from pyridine-tethered aryllithiums to pyridine-tethered alkylolithiums toward the synthesis of 2,3-cycloalkenopyridines.

**Scheme 20**

**Summary**

Organolithium chemistry provides a potential alternate route for the synthesis of pyridine-containing heterocycles. It has already been shown that organolithium chemistry is useful for the synthesis of 5,6-dihydrobenzo[h]quinoline and 5,6-dihydrobenzo[f]quinoline and could potentially be used for the synthesis of certain indenopyridine derivatives. Therefore, it is likely that organolithium chemistry could allow access to azabiphenylene systems; work toward this synthesis is outlined below. The methodology will then be expanded outward from pyridine-tethered aryllithiums to pyridine-tethered alkylolithiums toward the synthesis of 2,3-cycloalkenopyridines.


Part II: Results and Discussion

Synthesis of Monoazabiphenylenes

The substrate 3-(2-bromophenyl)pyridine (3), was synthesized according to Scheme 1. It was envisioned that 3 could be made by a Suzuki coupling reaction of the two aryl halves of the molecule. Suzuki coupling reactions had already been achieved using tris(3-pyridyl)boroxin (1),¹ which may be readily synthesized on a large scale² from commercially available 3-bromopyridine. The coupling partner, 1-bromo-2-iodobenzene (2), was prepared via a Sandmeyer reaction from commercially available o-bromoaniline.³
The Suzuki reaction conditions were chosen based upon previous work utilizing 1 as a coupling partner. Thus, Pd(PPh)$_2$Cl$_2$ was chosen as the catalyst. It is important to note that the stoichiometry of this particular Suzuki reaction is important, because even though coupling to an iodide is much faster than coupling to a bromide, coupling can and does occur at both positions when the ratio of starting materials is close or favors tris(3-pyridyl)boroxin (Scheme 2). This problem can easily be overcome by using an excess of 2, ensuring that only the more reactive iodide is given the chance to react.
With the desired compound in hand, the next step was to perform the lithium-halogen exchange. Initially, a modification of a typical procedure was used, in which 3-(2-bromophenyl)pyridine 3 was dissolved in Et₂O, cooled to −78 °C, and 2.0 eq t-butyllithium in heptane added dropwise. After stirring for 30 min at −78 °C, the reaction was quenched with MeOH. This gave the desired lithium-halogen exchange product 4 as well as a t-butyl addition product (5) in the ratio 68:32, respectively.

The byproduct was isolated and identified as 2-tert-butyl-5-phenylpyridine (5) on the basis of ¹H NMR. It is known that t-butyllithium can add to the pyridine ring, with the potential for addition at the 2, 4, or 6 positions. The byproduct contained one resonance at δ 8.81, indicating only one proton was adjacent to the nitrogen of the pyridine ring; this fact excludes the 4 isomer from consideration. This resonance was a doublet with a J of
2.1 Hz, which is consistent with long range coupling that would be observed between the protons at the 2 and 4 positions, indicating the 6 isomer as the correct identification.

The large amount of byproduct observed in the initial reaction was not acceptable, so conditions were altered in order to optimize the lithium-halogen exchange (Table 1). It is known that decreasing the amount of ether can decrease the addition reaction, so the solvent system was changed to pentane/Et₂O (3:2 by vol), which was the lowest amount of Et₂O in which the starting compound was soluble at −78 °C. This solvent system gave 29% of the addition product (entry 2). It is also known that decreasing the temperature can make the lithium-halogen exchange more competitive with the addition, so the temperature was dropped to −98 °C (entry 3). This did not offer a great improvement; 23% addition was still seen, and 10% of the starting material remained, presumably due to a lack of solubility at such a low temperature. Since it was not feasible to decrease the amount of Et₂O further due to limited solubility, a reverse addition was attempted; thus, the starting material was dissolved in 5 mL of pentane and Et₂O (4:1 by vol) and added dropwise to a solution of t-butyllithium in 10 mL pentane/Et₂O (4:1 by vol) at −78 °C (entry 4). This still offered no improvement, so the starting material was dissolved in 1 mL Et₂O and added dropwise to a solution of t-butyllithium in 10 mL pentane at −78 °C (entry 5). This gave only 12% of the addition product. When the temperature was decreased to −98 °C (entry 6), only 1% addition product was formed.
Table 1: Optimization of Lithium-Halogen Exchange of 3-(2-Bromophenyl)pyridine

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>pentane/Et₂O</th>
<th>temp</th>
<th>inverse addition?(^a)</th>
<th>products, % by GC(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et₂O</td>
<td>−78°C</td>
<td>No</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>32</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>3:2</td>
<td>−78°C</td>
<td>No</td>
<td>71</td>
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<td>29</td>
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<td>10:1</td>
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<td>99</td>
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<tr>
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<td></td>
<td></td>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\) A solution of 3 was added to a solution of t-butyllithium in the appropriate solvent system

\(^b\) Yields were determined by GC analysis of reaction mixtures.
With the optimized conditions for the lithium-halogen exchange established, the cyclization was attempted as illustrated in Scheme 4. Following the lithium-halogen exchange, the reaction mixture was removed from the cold bath and stirred for 85 min. Disappointingly, there was no evidence for the formation of new products by GC. It is known that the inclusion of certain Lewis bases to the reaction mixture may deaggregate lithium species and encourage a sluggish reaction to proceed. Thus, 1 mL of THF was added to the reaction mixture while it stirred at room temperature. Again, no new products were seen by GC. TMEDA was then used as an additive and the reaction stirred 60 minutes; when no new products were observed, the same conditions were used but the reaction allowed to stir for 180 min, but still no new products formed.

Scheme 4

The possibility that the organolithium was undergoing an intermolecular metalation reaction, placing the lithium at an alternate position of the molecule, was considered. Although these isomers would appear identical by GC, if the organolithiums were quenched with D₂O, multiple peaks would be observed by deuterium NMR. However, this experiment revealed only one deuterium resonance, indicating unwanted metalations were not occurring.

Curiously, it was noted that following quenching of the reaction mixture, a solid would precipitate that was not soluble in common organic solvents or water. If the
cyclization was not proceeding, the reactive aryllithium could instead react in an intermolecular fashion, adding into the pyridine ring of another molecule, forming unwanted polymeric byproducts. If the unknown solid was the result of polymerization, at the conclusion of the reaction, there would be an observable decrease in the amount of 3-phenylpyridine in the reaction mixture by GC.

Thus, a series of reactions were performed, summarized in Table 2, in which an internal hydrocarbon standard was added so that % yield by GC of 3-phenylpyridine and 3-phenyl-6-tert-butylpyridine could be determined. For ease, the lithium-halogen exchange was run at −78 °C with an excess of t-butyllithium to ensure completion of the exchange. As a basis for comparison, one reaction was quenched at −78 °C; three subsequent reactions were then allowed to stir at room temperature for 1, 3, and 6 hours. As seen in Table 2, it is clear that the percent yield of both 3-phenylpyridine and 3-phenyl-6-tert-butylpyridine decreased dramatically the longer the reaction was left to stir at room temperature. Since no new products could be observed by GC, it was evident that intermolecular polymerization must be the cause for the unaccounted products and insoluble solid.
Table 2: Rate of Disappearance of Pyridine Products derived from the Organolithium of 3-(2-Bromophenyl)pyridine

<table>
<thead>
<tr>
<th>entry</th>
<th>time (h)</th>
<th>% yield 4&lt;sup&gt;a&lt;/sup&gt;</th>
<th>% yield 5&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>74.8</td>
<td>11.1</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>64.9</td>
<td>14.0</td>
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<tr>
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<td>3</td>
<td>59.1</td>
<td>9.4</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>30.6</td>
<td>7.5</td>
</tr>
</tbody>
</table>

<sup>a</sup>Yields were determined by GC analysis of reaction mixtures.

Although the failed cyclization was disheartening, a new synthesis was devised in order to include fluorine at the 2-position of the pyridine ring. It was reasoned that a 2-fluoropyridine would be more prone to attack by the tethered organolithium. Inclusion of fluorine was readily accomplished according to Scheme 5.
It was again envisioned that a Suzuki reaction could be used to piece together the two aryl halves of the molecule. Thus, the known pinacol boronic ester \( \text{6} \) was prepared from previously-synthesized 1-bromo-2-iodobenzene (2) via lithiation at the iodide and nucleophilic attack on triisopropylborate. Hydrolysis of the resulting isopropyl ester and condensation with pinacol gave 6 in good yield. Because 6 contains a bromine that needed to be retained following the Suzuki reaction, it was key that the coupling partner contain a more reactive iodide. This led to the selection of 2-fluoro-3-iodopyridine (7) as the coupling partner.\(^8\) Molecules 6 and 7 were then coupled using the previously established Suzuki reaction conditions to give 8 as the major product.

With molecule 8 in hand, the lithium-halogen exchange was attempted by treating 8 with 2.2 equivalents \( t \)-butyllithium at \(-78 \, ^\circ \text{C} \) (Scheme 6). After 30 min, the reaction was quenched with methanol, giving the desired lithium-halogen exchange
product 9 as the major product. No further efforts were made to optimize the conditions for the exchange, since the greater point of interest was whether or not the cyclization would occur.

Scheme 6

Indeed, initial attempts at cyclization did not appear promising. When a solution of the organolithium derived from 8 following lithium-halogen exchange was warmed to room temperature, no new products were seen by GC; addition of TMEDA led to no improvement. It was quickly concluded that the reaction was likely proceeding by the same intermolecular pathway seen during the attempted cyclization of 3.

In order to test if this was indeed the case, the reaction was monitored by GC using an internal standard (Table 3). Not only did the amount of 9 decrease over time, as had been seen in the case of 4, but the intermolecular reaction was occurring at a much more rapid pace. While there was still 3% of the lithium-halogen exchange product of 3 remaining after 6 h (Table 2, entry 4), the lithium-halogen exchange product of 8 is nearly gone after only 30 min (Table 3, entry 2) and completely absent after 3 h (Table 3, entry 4). Clearly, the fluorine did enhance the reaction, but instead of encouraging the intramolecular addition as hoped, it had caused the undesired intermolecular addition to proceed much more rapidly.
Table 3: Rate of Disappearance of Pyridine Products Derived from the Organolithium of 3-(2-Bromophenyl)-2-fluoropyridine

<table>
<thead>
<tr>
<th>entry</th>
<th>time (h)</th>
<th>% yield 9(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.0</td>
<td>62.3</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td>7.4</td>
</tr>
<tr>
<td>3</td>
<td>1.0</td>
<td>6.0</td>
</tr>
<tr>
<td>4</td>
<td>3.0</td>
<td>--</td>
</tr>
</tbody>
</table>

\(^a\) Yields were determined by GC analysis of reaction mixtures.

Although this methodology would have been an interesting route to the azabiphenylenes, lithium-halogen exchange initiated cyclization is clearly not a viable methodology for its synthesis.

**Synthesis of 2,3-Cyclopentenopyridines**

To this point, pyridine cyclizations had only been attempted using aryllithium derivatives. Could the same methodology be applied to the synthesis of alkyllithiums?
Saturated nitrogen-containing heterocycles could be derived from the cyclization of a primary organolithium (Scheme 7), which could in turn be accessed via a primary iodide. A primary bromide would not be a viable alternative since the exchange is slow enough that t-butyllithium can competitively act as a base and cause elimination. The primary iodide was envisioned as being derived from a primary alcohol.

**Scheme 7**

While 3-pyridinepropanol is a commercially available starting material, alcohols of other chain lengths were synthesized according to the known methodology outlined in Scheme 8. Thus, 3-bromopropanol and 3-bromobutanol were combined with TBDMSCI to yield the protected alcohols 10 and 11. These were then coupled to the anion of 3-picoline to deliver the protected pyridine alcohols 12 and 13. Deprotection with TBAF gave the desired pyridine alcohols 14 and 15 with chain lengths 4 and 5, respectively.

**Scheme 8**
Subsequent conversion of the primary alcohols to iodides proved to be a difficult task due to the inherent instability of a pyridine derivative tethered to a primary iodide. The nitrogen of the pyridine can easily displace the primary iodide, giving a pyridinium salt (Scheme 9). Because the salt still contains a primary iodide, the salt can then react intramolecularly, producing a dimer, or can continue to react in an intermolecular fashion, producing a variety of polymeric compounds. The dimerization can be used advantageously, such as in the synthesis of cyclostellattamines A-F by Wanner and Koomen,\textsuperscript{10} but for the purpose of this work, the formation of dimeric and polymeric compounds needed to be minimized.

\begin{center}
\textbf{Scheme 9}
\end{center}

Unfortunately, it quickly became apparent that this was easier said than done because the pure iodide product could not be isolated due to rapid polymerization. There are many different ways to convert a primary alcohol to an iodide, but the ideal method in the present case would have to satisfy several requirements:

i. be compatible with a basic nitrogen;

ii. give a good yield of product;
iii. not require column purification since it was found that 17 did not readily survive chromatographic separation;

iv. not result in byproducts which could potentially be incompatible with organolithiums. Additionally, an accurate means of determining reaction yield would be to concentrate an aliquot of the iodide product, then extrapolate the mass of product in the entire solution. The presence of byproducts would make this calculation erroneous.

In order to find the optimal method of conversion, commercially available 3-pyridine propanol, 16, was chosen as a model compound. The first pathway tried was the traditional conversion using triphenylphosphine, imidazole, and iodine (Scheme 10). While the conversion did take place, the product was partitioning into both the aqueous and organic phases at the conclusion of the reaction. This led to a loss of yield or necessitated a lengthy workup to try and recover both portions of product. Additionally, the triphenylphosphine oxide coproduct could not be easily removed from the reaction mixture.

![Scheme 10](image)

Thus, the triphenylphosphine, imidazole route was not a viable option, since without a practical means of removing the byproducts, an accurate measure of yield could not be determined.
The next attempts at preparation of 17 involved slight variation utilizing chlorodiphenylphosphine, imidazole, and iodine (Scheme 11). This set of conditions promised a much cleaner reaction since the byproduct, diphenylphosphonic acid, may be extracted into aqueous base. Additionally, the use of base at the conclusion of the reaction would ensure that no pyridinium salts would be lost to the aqueous wash as had occurred with the previous conditions.

![Scheme 11](image)

Initial results seemed discouraging: following the literature conditions resulted in a tarry mixture and no starting material or product at the conclusion of the reaction. It was observed that nearing the end of the iodine addition, the color of the reaction mixture rapidly changed from yellow to dark brown. Halting the reaction at this time point, rather than stirring for an additional 10 min, yielded an identifiable peak for 17 by GC.

Since the conditions appeared to be incompatible with the basic nitrogen, it was thought that blocking the nitrogen would result in a more robust reaction. The simplest group with which to block the nitrogen would be a proton, since the basic aqueous workup would neutralize the salt and give free 17 at the end of the reaction.

Thus, a solution of 3-pyridinepropanol in DCM was protonated with anhydrous HCl in diethyl ether, prepared from equimolar amounts of methanol and acetyl chloride. The pyridinium salt was then subjected to the chlorodiphenylphosphine reaction conditions. No tarry residues were observed and the reaction appeared by GC to give a
greater amount of 17; unfortunately, although the reaction had a much-reduced quantity of phosphine byproducts, a small amount still remained, meaning there was still no accurate way to gage exactly how much 17 was present in the reaction product.

Scheme 12

In search of the perfect set of reaction conditions, a novel iodination reaction using a thioimminium salt was attempted. The literature procedure had been used on an amine, albeit a less basic aniline-type derivative. In addition, the byproducts, dimethylformamide and methanethiol should be sufficiently volatile that they would not complicate product isolation. However, the somewhat harsh reaction conditions, heating at 85 °C for 90 min, proved to be too much for the highly unstable 17, and only small amounts survived to be observed by GC.

Scheme 13

The isolation of 17 as a solid salt, rather than as a solution seemed an attractive option. For instance, 17 can be isolated as a solid HCl salt by precipitating it from ether using ethereal HCl. Unfortunately, upon neutralization, GC-MS shows evidence of chloride substitution for the iodide. However, it was reasoned, if 17 could be isolated as
the HI salt, competitive substitution would not be an issue. Anders had shown that 4-(hydroxymethyl)pyridinium iodide could be isolated by cooling a mixture of 4-(hydroxymethyl)pyridine and aqueous HI and filtering the resulting solid.\textsuperscript{14} The salt was then converted to the iodide using P\textsubscript{2}I\textsubscript{3}. When an analagous crystallization procedure was attempted using 16, no solid resulted.

The final iodination attempted was a mesylation/iodination sequence, which also had literature precedent for success on 3-pyridinepropanol.\textsuperscript{15} This approach proved to be the cleanest reaction sequence: there were no notable byproducts and the yield of 17 was 44% over the two-step sequence.

\begin{center}
\textbf{Scheme 14}
\end{center}

Since there appeared to be no perfect set of iodination conditions for the synthesis of 17, it was at this point of greater interest whether the methodology could be used to perform the cyclization. However, further hurdles remained. First, the rate of the lithium-iodine exchange is comparable to the rate of the reaction of t-butyllithium with water. This means that any moisture remaining in the reaction mixture would quench the organolithium product instead of merely consuming excess t-butyllithium. Normally, the substrate for lithium-halogen exchange is dissolved in dry solvent, but the inability to isolate 17 meant that a solution of 17 from the iodination reaction had to be thoroughly dried prior to use.
In addition, the solvents from the iodination reaction are incompatible with organolithiums. It is well known that addition reactions can occur at the electrophilic carbonyl carbon of acetone. Additionally, an interesting side reaction can occur in the presence of DCM. Following the lithium-halogen exchange, the newly-formed organolithium can deprotonate a molecule of DCM, which can then lose LiCl to give a carbene. Addition of another molecule of organolithium into the carbene, followed again by loss of LiCl, gives a new carbene, which then undergoes a hydride shift to produce a terminal alkene. Evidence for this mechanism is given by the presence of a molecule corresponding to the mass of alkene 18 when DCM is present during the lithium-halogen exchange.

\[
\begin{align*}
\text{Scheme 15}
\end{align*}
\]

In an attempt to prevent quenching of the organolithium and unnecessary side reactions, the following procedure was devised: following the iodination reaction, 17 was extracted with 10% aqueous HCl. The aqueous solution was placed under vacuum to remove most residual solvent, then washed with three portions of Et₂O to remove any remaining traces of acetone or CH₂Cl₂. The solution was overlaid with the solvent for the lithium-halogen exchange, then neutralized with solid NaOH. The aqueous phase was
discarded, and the organic phase was dried over MgSO₄, filtered, and further dried over NaH for one hour (it was found that even after stirring overnight, CaH₂ did not provide sufficient drying). The dried solution was then transferred via cannula through a plug of glass wool into a clean, flame-dried flask that had been purged with argon. The lithium-halogen exchange and cyclization could then be performed.

Thus, 16 was converted to 17 as illustrated in Scheme 16 and the product was dissolved in dry toluene. Since the yield of 17 was not known, two equivalents of t-butyllithium were added at −78 °C, followed by warming to room temperature for one hour and quenching of the reaction mixture with methanol. This method gave a 29% isolated yield of 19.

![Scheme 16](image)

Scheme 16

Alternatively, the cyclization was attempted using the mesylation/iodination protocol depicted in Scheme 17. Instead of toluene, 17 was isolated as a solution in pentane and 1 mL of dry Et₂O was added just prior to the lithium-halogen exchange. By this route, 19 was isolated in 14% yield based on the quantity of 16 used.
To see if the iodination/cyclization route could be applied to the formation of six- and seven-membered rings, 14 and 15 were subjected to the mesylation/iodination/cyclization protocol (Scheme 18). In the event, 20 was isolated in 46% yield, but following cyclization, 21 could only be isolated in 18% yield. While the iodination of 15 was successful, producing 22 in 37% yield, following cyclization 23 was seen as only a minor product by GC-MS and was not isolated; the major product was the quenched alkyl-pyridine.
Future Work

These experiments represent a good proof-of-concept that this route can be used for the cyclization of pyridine-tethered alkyllithiums. The greater issue lies with the preparation of the iodide substrate. The iodination could be improved by converting the pyridine to a pyridinium salt, some examples of which are shown in Figure 1. A pyridinium salt would be unable to polymerize, thus simplifying product isolation and improving yield.

Addition of organometallics such as Grignard, organozinc, organotin, and organocopper reagents to pyridinium salts have been extensively studied. However, addition of an organolithium into a pyridinium salt is not as well-documented. Clearly some salts would be incompatible with an organolithium; for example, addition of an organolithium could easily occur into the carbonyl of an acyl-pyridinium salt. It would be
necessary to find a salt that is compatible with organolithiums, or utilize a salt for the iodination reaction but free the salt before the lithium-halogen exchange step.

If an optimized sequence could be found, it would be of interest to explore the preparation of a substrate that would lead to a four-membered ring. The necessary alcohol starting material could be prepared as outlined in Scheme 19. Commercially available 3-pyridinecarboxaldehyde could be converted to the terminal alkene by a Wittig reaction and the terminal hydroxyl could then be installed via hydroboration-oxidation.

Scheme 19


Part III: Experimental

General Procedures

Gas-liquid chromatography (GC) was performed on a Hewlett-Packard 5890 gas chromatograph equipped with a flame-ionization detector and fitted with a 25-m x 0.20-mm x 0.33-μm DB-5 (5% diphenyl / 95% dimethylpolysiloxane) fused silica glass capillary column (J & W Scientific).

Gas-liquid chromatography-mass spectrometry (GC/MS) was performed on a Hewlett-Packard 5890 gas chromatograph fitted with a 25-m x 0.20-mm x 0.33-μm DB-5 (5% diphenyl / 95% dimethylpolysiloxane) fused silica glass capillary column (J & W Scientific) and interfaced with a Hewlett-Packard 5971 mass selective detector with electron impact ionization. Percent deuterium incorporation was determined by mass spectrometry using the method developed by Ashby.\(^1\)

\(^1\)H NMR, \(^2\)H NMR, and \(^13\)C NMR were obtained using a Bruker DRX-400 or DRX-300 spectrometer using CDCl\(_3\) as the solvent. Proton and carbon spectra were referenced at \(\delta = 7.26\) and \(\delta = 77.23\), respectively.

Flash chromatography was performed with 40-63 μm silica gel (Dynamic Adsorbents, Inc.) using glass columns packed with the slurry method. Thin layer chromatography was performed using Baker-flex (J.T. Baker) Silica Gel IB-F plates and visualized with UV.

Organolithiums were handled under an atmosphere of “ultra high purity” argon in flame dried glassware using standard syringe techniques.\(^2\) The concentrations of \(t-\)
butyllithium in heptane (FMC), \(n\)-butyllithium in hexanes (FMC) and \(n\)-butyllithium in cyclohexane (Aldrich) were determined by titration against a solution of known concentration of 2-butanol in xylenes with 1,10-phenanthroline in benzene as indicator, as developed by Watson and Eastham.\(^3\)

Anhydrous diethyl ether and tetrahydrofuran were prepared by distillation from a dark blue or purple solution of sodium and benzophenone. Pentane was purified by repetitive washings with concentrated sulfuric acid until the acid layer remained clear followed by successive washings with water, saturated sodium bicarbonate, and water. The pentane was then dried with magnesium sulfate and distilled from sodium, benzophenone, and tetraklyme. Toluene, TMEDA, triethylamine, and diisopropylamine were distilled from CaH\(_2\) prior to use.

**Detailed Procedures**

**Tris(3-pyridyl)boroxin**

\[
\text{Br} \quad \text{B(OPr-)}_3 \quad \begin{array}{c}
1. \text{BuLi} \\
2. \text{aq. HCl}
\end{array} \xrightarrow{\text{crystallization}} \quad \text{CH}_3\text{CN}
\]

The title compound was prepared according to the procedure by Li et al.\(^4\) A solution of 3.9 mL (40 mmol) of 3-bromopyridine and 11.1 mL (48 mmol) of triisopropyl borate in 64 mL of toluene and 16 mL of THF was cooled to \(-78^\circ\)C in a dry ice/acetone bath and 26.7 mL of 1.8 M \(n\)-butyllithium in hexane (48 mmol) was added dropwise via cannula.
The reaction mixture was stirred for 30 min at −78 °C, and then allowed to warm to approximately −20 °C, before addition of 40 mL of 2 N aq HCl. The reaction mixture was then allowed to warm to room temperature. The mixture was poured into a separatory funnel, the aqueous layer was collected, and 5 N aq NaOH was added until the pH was 7.6 to 7.7 according to pH paper. The aqueous solution was saturated with solid NaCl, transferred to a separatory funnel and extracted with three 50-mL portions of THF. The combined THF was concentrated by rotary evaporation to yield an off-white solid. The solid was stirred with 16 mL of acetonitrile for 30 min in a 70 °C oil bath. The mixture was then allowed to cool slowly to room temperature and then cooled further to 0 °C in an ice bath. After stirring for 30 min, the ice bath was removed and the mixture was filtered through a fritted funnel to yield a white solid that was washed with three 15-mL portions of cold acetonitrile and air-dried overnight to yield 3.94 g (94%) of the title compound, which was used without further purification.

3-Phenylpyridine

![Chemical structure of 3-Phenylpyridine](image)

The title compound was prepared using the Suzuki reaction conditions developed by Leadbeater and Marco.\(^5\) Thus, a suspension of 1.12 g (7.10 mmol) of bromobenzene, 0.55 g (1.7 mmol) of tris(3-pyridyl)boroxin, 0.50 g (4.7 mmol) of Na\(_2\)CO\(_3\), 0.011 g (0.05
mmol) of palladium (II) acetate, and 0.40 g (1.2 mmol) of tetra-n-butylammonium bromide in 6 mL of water was stirred in an oil bath at 110 °C for 14 h, and then an additional 5 h at room temperature, before being diluted with 40 mL water. The mixture was extracted with three 20-mL portions of Et₂O. The combined organic phases were dried (MgSO₄) and concentrated on a rotary evaporator to give a dark-orange oil which was purified by silica gel chromatography (9:1 hexane/EtOAc) to give 0.542 g (68%) of the title compound as a yellow oil: ¹H NMR (CDCl₃) δ 8.86 (d, J = 1.7 Hz, 1H), 8.60 (d, J = 4.7 Hz, 1H), 7.89 (d, J = 7.6 Hz, 1H), 7.60-7.57 (m, 2H), 7.51-7.46 (m, 2H), 7.42-7.25 (m, 2H); ¹³C (CDCl₃) δ 148.3, 148.2, 137.8, 136.9, 134.7, 129.2, 128.3, 127.3, 123.7.

1-Bromo-2-iodobenzene

The title compound was prepared according to the procedure by Heaney and Millar. To a stirred solution of 25 mL concentrated HCl and 9.17 g (53.3 mmol) o-bromoaniline was added 16.7 g of ice to give a deep purple solution. To this solution was added 16.7 mL of 2.85 M aq NaNO₂ (47.6 mmol) to give a brown solution that was stirred 15 min then poured through a plug of glass wool into 30.0 g (181 mmol) of KI dissolved in 100 mL of water. After standing overnight at room temperature, the mixture was poured into a separatory funnel, the aqueous layer was discarded, and the remaining oil was washed sequentially with two 10-mL portions of 10% aq NaOH, 10 mL of H₂O, 10 mL of 5% aq
NaHSO₃, and 10 mL of H₂O, and then dried (MgSO₄). The oil was distilled under vacuum to give 4.66 g (31%) of the title compound as a slightly pink oil: ^1^H NMR (CDCl₃) δ 7.86 (dd, J = 8.0 Hz, J = 1.5 Hz, 1H), 7.63 (dd, J = 8.0 Hz, J = 1.6 Hz, 1H), 7.21 (td, J = 7.7 Hz, J = 1.6 Hz, 1H), 6.99 (td, J = 7.6 Hz, J = 1.5 Hz, 1H); ^1^C (CDCl₃) δ 140.6, 133.0, 129.9, 129.6, 128.6, 101.4.

**Dichlorobis(triphenylphosphine)palladium(II)**

![Dichlorobis(triphenylphosphine)palladium(II)](image)

Triphenylphosphine was crushed in a mortar and pestle prior to use. To a solution of 1.27 g (30.0 mmol) of anhydrous lithium chloride and 2.66 g (15.0 mmol) of palladium (II) chloride in 23 mL of methanol was added 8.26 g (31.5 mmol) of powdered triphenylphosphine. The viscous mixture was stirred in a hot water bath for 1 h until a pale yellow precipitate formed. The solid was isolated by vacuum filtration and washed with 5 mL of methanol. The yellow solid was dried under nitrogen overnight to yield 10.3 g (98%) of the title compound, which was used without further purification.⁷
The title compound was prepared using the Suzuki reaction conditions developed by Cioffi et al. The 1,4-dioxane and Na₂CO₃ solution were sparged with nitrogen prior to use. To a stirred solution of 1.33 g (4.23 mmol) of tris(3-pyridyl)boroxin and 0.84 g (1.2 mmol) of Pd(PPh₃)₂Cl₂ in 60 mL of 1,4-dioxane was added 4.41 g (15.6 mmol) of 1-bromo-2-iodobenzene. The resulting solution was stirred 30 min, then 24 mL of 2 M aq Na₂CO₃ (48 mmol) was added and the solution was heated at reflux under nitrogen for 40 min to give a dark brown suspension containing a white solid. The suspension was filtered and concentrated under reduced pressure. The residue was taken up in EtOAc then extracted with two 5-mL portions of 10% aq HCl. The solution was made basic with NaOH pellets and the resulting oil was dissolved in Et₂O. The solution was washed with brine, dried (MgSO₄) and concentrated under reduced pressure to give an orange oil. The product was purified using silica gel chromatography (EtOAc) to yield 2.11 g (71%) of the title compound as a pale yellow oil: ¹H NMR (CDCl₃) δ 8.68 (s, 1H), 8.65 (d, J = 4.6 Hz, 1H), 7.78 (d, J = 7.8 Hz, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.43-7.25 (m, 4H); ¹³C (CDCl₃) δ 150.0, 148.8, 139.1, 137.1, 137.0, 133.5, 131.4, 129.8, 127.9, 123.0, 122.9; HRMS-ESI: [M + H]⁺ calc for C₁₁H₈BrN, 233.9918; Found, 233.9904.
The 1,4-dioxane and Na$_2$CO$_3$ solution were sparged with nitrogen prior to use. To a stirred solution of 0.780 g (2.48 mmol) of tris(3-pyridyl)boroxin and 0.211 g (0.300 mmol) of Pd(PPh$_3$)$_2$Cl$_2$ in 15 mL of dioxane was added 0.849 g (3.00 mmol) of 1-bromo-2-iodobenzene. The solution was stirred 30 min at room temperature, then 9.6 mL of 2 M aq Na$_2$CO$_3$ (19.2 mmol) was added and the solution was heated at reflux under nitrogen for 75 min to give a dark brown suspension containing a white solid. The suspension was filtered and concentrated under reduced pressure. The residue was taken up in EtOAc then extracted with two 5-mL portions of 10% aq HCl. The solution was made basic with NaOH pellets and the resulting oil was dissolved in Et$_2$O. The solution was washed with brine, dried (MgSO$_4$) and concentrated under reduced pressure to give 0.60 g (86%) of the product as an off-white solid, mp 96.4-97.3 °C: $^1$H NMR (CDCl$_3$) δ 8.46 (dd, $J = 4.8$ Hz, $J = 1.3$ Hz, 2H), 8.43 (d, $J = 2.0$ Hz, 2H), 7.52-7.49 (m, 2H), 7.47-7.44 (m, 2H), 7.39 (d, $J = 7.7$ Hz, 2H), 7.17-7.14 (m, 2H); $^{13}$C (CDCl$_3$) δ 150.3, 148.0, 137.4, 137.2, 136.6, 130.9, 128.8, 123.1; HRMS-ESI: [M + H]$^+$ calc for C$_{18}$H$_{13}$N$_2$, 233.1079; Found, 233.1068.
2-tert-Butyl-5-phenylpyridine

![Chemical structure diagram]

A solution of 0.234 g (1.00 mmol) of 3-(2-bromophenyl)pyridine in 10 mL of n-pentane/Et₂O (3:2 by vol) was cooled to –78 °C and 1.3 of mL of 1.9 M t-butyllithium in heptane (2.5 mmol) was added dropwise. The solution was stirred 30 min at –78 °C then quenched with 1 mL of methanol. The solution was washed with three 5-mL portions water, dried (MgSO₄), and concentrated under reduced pressure to give 0.159 g of an orange oil. Silica gel chromatography (20% EtOAc/hexane to 100% EtOAc) gave 0.097 g (46%) of the title compound as a pale yellow oil: ¹H NMR (CDCl₃) δ 8.81 (d, J = 2.1 Hz, 1H), 7.81 (dd, J = 8.3 Hz, J = 2.1 Hz, 1 H), 7.59-7.57 (m, 1H), 7.17-7.36 (m, 5H), 1.41 (s, 9H); ¹³C (CDCl₃) δ 168.3, 147.1, 138.1, 134.7, 133.6, 129.1, 127.8, 127.1, 119.1, 37.3, 30.3. HRMS-ESI: [M + H]⁺ calc for C₁₅H₁₈N, 212.1439; Found, 212.1416.

Optimization of Lithium Halogen Exchange of 3-(2-Bromophenyl)pyridine

![Chemical process diagram]
Table 1, entries 1-3: A flame-dried flask containing 10 mL of the appropriate solvent system was charged with 0.234 g (1.00 mmol) of 3-(2-bromophenyl)pyridine. The solution was cooled to the appropriate temperature and t-butyllithium in heptane (2.00 mmol) was added dropwise. The solution was stirred for 30 min at –78 ºC, quenched with 1 mL MeOH, then washed with three 5-mL portions water, dried (MgSO₄) and analyzed by GC on a 25-m x 0.20-mm x 0.33-μm DB-5 (5% diphenyl / 95% dimethylpolysiloxane) fused silica glass capillary column.

Table 1, entry 4: A mixture of 10 mL of n-pentane and Et₂O (4:1 by vol) was cooled to –78 ºC and t-butyllithium in heptane (2.00 mmol) was added. In a separate flask, 0.234 g (1.00 mmol) of 3-(2-bromophenyl)pyridine was dissolved in 5 mL of n-pentane/Et₂O (4:1 by vol) and added dropwise to the t-butyllithium solution. The resulting solution was stirred for 30 min at –78 ºC, quenched with 1 mL MeOH, then washed with water three 5-mL portions water, dried (MgSO₄) and analyzed by GC using the conditions noted above.

Table 1, entries 5-6: A 10 mL portion of pentane was cooled to the appropriate temperature and t-butyllithium in heptane (2.00 mmol) was added. In a separate flask, 0.234 g (1.00 mmol) of 3-(2-bromophenyl)pyridine was dissolved in 1 mL of Et₂O and added dropwise to the t-butyllithium solution. The resulting solution was stirred for 30 min at –78 ºC, quenched with 1 mL MeOH, then washed with three 5-mL portions water, dried (MgSO₄) and analyzed by GC using the conditions noted above.

Results are summarized in Table 1.
General Procedure for Attempted Cyclization of the Aryllithium Derived from 3-(2-Bromophenyl)pyridine

A 10 mL portion of n-pentane was cooled to –98 °C and t-butyllithium in heptane (2.00 mmol) was added. In a separate flask, 0.234 g (1.00 mmol) of 3-(2-bromophenyl)pyridine was dissolved in 1 mL of Et₂O and added dropwise to the t-butyllithium solution. The resulting solution was stirred for 30 min at –98 °C, then allowed to warm to –80 °C, at which point either 1 mL THF or 2 equiv TMEDA was added. The reaction was then allowed to warm to room temperature for a designated time, quenched with 1 mL MeOH, then washed with three 5-mL portions water, dried (MgSO₄) and analyzed by GC on a 25-m x 0.20-mm x 0.33-μm DB-5 (5% diphenyl / 95% dimethy polysiloxane) fused silica glass capillary column.

Analysis for Deuterium Scrambling during the Attempted Cyclization of 2-(3-Pyridyl)phenyllithium

pentane/Et₂O (3:2 by vol) 2.2 t-BuLi 2.2 t-BuLi 2.2 t-BuLi -78°C, 30 min rt 1 h D₂O
A solution of 0.234 g (1.00 mmol) of 3-(2-bromophenyl)pyridine in 10 mL of pentane/Et₂O (3:2 by vol) was cooled to –78 °C and t-butyllithium in heptane (2.5 mmol) was added dropwise. The resulting solution was stirred at –78 °C for 30 min, the cold bath was then removed, and the reaction was stirred for 1 h, quenched with 1 mL of D₂O, then washed with three 5-mL portions water, and dried (MgSO₄). The 3-phenylpyridine product was separated by silica gel chromatography (20% EtOAc/hexanes to 100% EtOAc) to give 130 mg of orange oil. Analysis by deuterium NMR showed only one singlet, indicating formation of only one product.

**Rate of Disappearance of Products derived from 2-(3-Pyridyl)phenyllithium**

![Reaction Scheme](image)

A standard solution containing known masses of n-tetradecane, 3-phenylpyridine, and 2-tert-butyl-5-phenylpyridine was prepared and the response ratios were calculated for n-tetradecane:3-phenylpyridine and n-tetradecane:2-tert-butyl-5-phenylpyridine. A known mass of 3-(2-bromophenyl)pyridine (1 mmol) and a known mass of n-tetradecane (~0.5 mmol) was dissolved in 10 mL of pentane/Et₂O (3:2 by vol). The solution was cooled to –78 °C and t-butyllithium in heptane (2.2 equ) was added dropwise. The solution was stirred at –78 °C for 30 min, then the cold bath was removed and the reaction was quenched with 1 mL MeOH after the appropriate length of time. The solution was washed with three 5-mL portions of water, dried (MgSO₄) and analyzed by GC. All
calculations were performed using the average of three GC runs on a 25-m x 0.20-mm x 0.33-μm DB-5 (5% diphenyl / 95% dimethyldiphenylsiloxane) fused silica glass capillary column. The results are summarized in Table 2.

2-(2-Bromophenyl)-4,4,5,5-tetramethyl[1,3,2]dioxaborolane

A stirred solution of 4.5 mL (35 mmol) of 1-bromo-2-iodobenzene and 9.7 mL (42 mmol) of triisopropyl borate in 54 mL of toluene and 14 mL of THF was cooled to –78 °C and 18.8 mL (39.0 mmol) of 2.07 M n-butyllithium in hexanes was added dropwise. The suspension was stirred for 5 min then the cooling bath was removed and the mixture was stirred for 1 h, at which point 60 mL of 2 M aq HCl was added and stirring was continued an additional 30 min. The mixture was combined with 100 mL of Et₂O and poured into a separatory funnel. The aqueous layer was discarded and the organic layer was washed with 50 mL of water then concentrated under reduced pressure. The residual solids were added to 80 mL benzene and 5.70 g (48.2 mmol) of pinacol and the solution was heated at reflux for 2 h using a Dean-Stark apparatus to remove water. The solution was then concentrated under reduced pressure and the residue was subjected to vacuum distillation (145-150 °C, 7 mm) to yield 7.35 g (74%) of the title compound as a pale-yellow oil: ¹H NMR (CDCl₃) δ 7.62-7.60 (m, 1 H), 7.55-7.52 (m, 1 H), 7.26 (m, 2
H), 1.38 (s, 12 H); $^{13}$C (CDCl$_3$) δ 136.5, 132.8, 132.0, 128.2, 126.4, 84.4, 24.9, C bound to B not observed.

2-Fluoro-3-iodopyridine

The title compound was prepared according to the procedure by Estel, et al.$^{10}$ Thus, a solution of 3.35 mL (23.9 mmol) of diisopropylamine in 43 mL of dry THF was cooled to 0 °C and 11.5 mL (23.8 mmol) of 2.07 M n-butyllithium in hexanes was added dropwise. The solution was stirred for 10 min at 0 °C, cooled to −78 °C, and 2.43 g (25.0 mmol) of 2-fluoropyridine was added dropwise. The resulting solution was stirred 4 h at −78 °C, before dropwise addition of 6.35 g (25.0 mmol) of iodine dissolved in 20 mL of dry THF. The resulting solution was stirred an additional 1 h at −78 °C, before addition of 1.0 mL of water. The solution was then poured into 50 mL of equal volumes of saturated aq NaHCO$_3$ and saturated aq Na$_2$S$_2$O$_3$, extracted with two 40-mL of portions Et$_2$O, washed with brine, dried (MgSO$_4$), and concentrated to give a dark residue which chromatographed on silica gel (9:1 hexane/EtOAc) to give 4.40 g (79%) of the title compound as an off-white solid: $^1$H NMR (CDCl$_3$) δ 8.19-8.15 (m, 2H), 6.98-6.94 (m, 1H); $^{13}$C (CDCl$_3$) δ 162.3 (d, $J = 236.7$ Hz), 150.3 (d, $J = 3.0$ Hz), 147.4 (d, $J = 13.4$ Hz), 122.9 (d, $J = 4.8$ Hz), 77.4 (one line of C-F doublet obscured by CDCl$_3$).
The 1,4-dioxane and Na$_2$CO$_3$ solution were sparged with nitrogen prior to use. A solution of 2.21 g (9.91 mmol) of 2-fluoro-3-iodopyridine, 2.55 g (9.01 mmol) of 2-(2-bromophenyl)-4,4,5,5-tetramethyl[1,3,2]dioxaborolane, and 0.632 g (0.90 mmol) of Pd(PPh$_3$)$_2$Cl$_2$ in 45 mL of 1,4-dioxane was stirred for 30 min, at which point 13.5 mL of 2 M aq Na$_2$CO$_3$ solution (27 mmol) was added and the mixture heated at reflux under nitrogen for 60 min to give a dark red suspension containing a white solid. The mixture was filtered, then concentrated under reduced pressure. The residue was taken up in Et$_2$O and washed with two 15-mL portions water, dried (MgSO$_4$), and concentrated under reduced pressure to give a brown oil, which was purified by silica gel chromatography (10% EtOAc/hexane) to give 1.41 g (62%) of the title compound as a yellow oil. $^1$H NMR (CDCl$_3$) δ 8.27 (d, J = 4.3 Hz, 1H), 7.72 (m, 2H), 7.38 (d, J = 7.6 Hz, 1H), 7.29 (m, 3H); $^{13}$C (CDCl$_3$) δ 160.4 (d, J = 239.6 Hz), 147.6 (d, J = 14.5 Hz), 142.2 (d, J = 4.1 Hz), 135.3 (d, J = 4.3 Hz), 133.3, 131.6, 130.3, 127.7, 123.8 (d, J = 14.2 Hz), 123.6 (d, J = 16.9 Hz), 121.4 (d, J = 4.4 Hz); HRMS-ESI: [M + H]$^+$ calc for C$_{11}$H$_8$BrFN, 251.9824; Found, 251.9844.
A solution of 0.252 g (1.00 mmol) of 3-(2-bromophenyl)-2-fluoropyridine in 10 mL of pentane/Et₂O (3:2 by vol) was cooled to –78 °C and 1.35 mL (2.2 mmol) 1.63 M of t-butyllithium in heptane was added dropwise. The solution was stirred 30 min at –78 °C and then quenched with 1 mL methanol, washed with three 5-mL portions of water dried (MgSO₄), and concentrated under reduced pressure to give an orange oil. The crude product was chromatographed on silica gel (10% EtOAc/hexane) to give 70.0 mg (40%) of the title compound as a yellow oil: \(^1\)H NMR (CDCl₃) \(\delta\) 8.20 (d, \(J = 4.7\) Hz, 1H), 7.88 (ddd, \(J = 9.7\) Hz, \(J = 7.6\) Hz, \(J = 2.0\) Hz, 1H), 7.59-7.56 (m, 2H), 7.50-7.46 (m, 2H), 7.44-7.42 (m, 1H), 7.30-7.27 (m, 1H); \(^{13}\)C (CDCl₃) \(\delta\) 160.6 (d, \(J = 240.2\) Hz), 146.5 (d, \(J = 14.7\) Hz), 140.8 (d, \(J = 4.5\) Hz), 134.0 (d, \(J = 5.0\) Hz), 128.94 (d, \(J = 2.9\) Hz), 128.85, 128.58, 124.1 (d, \(J = 28.2\) Hz), 121.9 (d, \(J = 4.5\) Hz); HRMS-ESI: [M + H]\(^+\) calc for C\(_{11}\)H\(_9\)FN, 174.0719; Found, 174.0694.
General Procedure for Attempted Cyclization of the Aryllithium Derived from 3-(2-Bromophenyl)-2-fluoropyridine

A solution of 0.252 g (1.00 mmol) of 3-(2-bromophenyl)-2-fluoropyridine in 10 mL of pentane:Et$_2$O (3:2 by vol) was cooled to −78 °C and t-butyllithium in heptane (2.2 mmol) was added dropwise. The solution was then stirred for 30 min at −78 °C, the cold bath was removed and, when appropriate, TMEDA was added. The reaction was then stirred for an appropriate length of time, quenched with 1 mL MeOH, washed with three 5-mL portions water, dried (MgSO$_4$), and analyzed by GC on a 25-m x 0.20-mm x 0.33-μm DB-5 (5% diphenyl / 95% dimethypolysiloxane) fused silica glass capillary column.

Rate of Disappearance of Pyridine Products Produced from the Aryllithium Derived from 3-(2-Bromophenyl)-2-fluoropyridine
A standard solution containing known masses of \( n \)-tetradecane and 2-fluoro-3-phenylpyridine was prepared and the response ratio was calculated for \( n \)-tetradecane:2-fluoro-3-phenylpyridine. A solution of 1 mmol of 3-(2-bromophenyl)-2-fluoropyridine and 0.5 mmol \( n \)-tetradecane in 10 mL of pentane/Et₂O (3:2 by vol) was cooled to –78 °C and \( t \)-butyllithium in heptane (2.2 equ) was added dropwise. The solution was stirred at –78 °C for 30 min, then the cold bath was removed and the reaction was quenched with 1 mL MeOH after the appropriate length of time, washed with three 5-mL portions water, dried (MgSO₄), and analyzed by GC. All calculations were performed using the average of three GC runs. The results are summarized in Table C.

3-(tert-Butyldimethylsiloxy)-1-bromopropane

A 3-necked flask, equipped with a mechanical stirrer, was charged with 35.8 g (258 mmol) of 3-bromopropanol, 46.0 g (305 mmol) of TBDMSCl, and 1.56 g (12.8 mmol) of 4-dimethylaminopyridine, 75 mL of of Et₂O and 2 g of activated 4 Å molecular sieves. The solution was cooled to 0 °C in an ice/salt bath and 42.3 mL (303 mmol) of triethylamine was added dropwise. The viscous mixture was stirred overnight and gradually warmed to room temperature. The mixture was then poured into a separatory funnel and washed with three 25-mL portions of 3% aqueous phosphoric acid, two 25-mL portions of water, brine, then dried (MgSO₄) and concentrated. The residue was washed through a short silica gel plug with hexanes to give 57.7 g (88%) of the title compound as a colorless oil: \(^1\)H NMR (CDCl₃) δ 3.72 (t, \( J = 5.7 \) Hz, 2H), 3.51 (t, \( J = 6.4 \))
Hz, 2H), 2.02 (pentet, J = 6.1 Hz, 2H), 0.87 (s, 9H), 0.06 (s, 6H); $^{13}$C (CDCl$_3$) δ 60.5, 35.7, 30.8, 26.0, 18.4, –5.2.$^{11}$

**4-(3-Pyridyl)butyl-tert-butyldimethylsilyl ether**

A solution of 5.50 mL (39.2 mmol) of diisopropylamine in 20 mL of THF at 0 °C was treated with 19.2 mL (38.0 mmol) of 2.0 M n-butyllithium in cyclohexane. After 20 min the solution was cooled to –78 °C and added dropwise to a solution of 4.35 g (46.7 mmol) of 3-picoline in 8 mL of THF at –78 °C. The resulting solution was stirred for 30 min, at which point 9.90 g (39.1 mmol) of 3-(tert-butyldimethylsiloxy)-1-bromopropane was added and the solution was stirred overnight, gradually warming to room temperature. The reaction was then quenched with 1 mL of methanol, washed with brine, dried (MgSO$_4$) and concentrated. The crude product was distilled under vacuum (143–145 °C, 7 mm) to give 5.73 g (57%) of the title compound as a colorless oil: $^1$H NMR (CDCl$_3$) δ 8.44-8.43 (m, 2H), 7.49 (d, J = 7.8 Hz, 1H), 7.20 (dd, J = 7.7 Hz, J = 4.8 Hz, 1H), 3.63 (t, J = 6.2 Hz, 2H), 2.63 (t, J = 7.6 Hz, 2H), 1.71-1.64 (m, 2H), 1.60-1.53 (m, 2H), 0.89 (s, 9H), 0.04 (s, 6H); $^{13}$C (CDCl$_3$) δ 150.2, 147.4, 137.9, 135.9, 123.6, 62.9, 32.9, 32.4, 27.5, 26.1, 18.5, –5.2.$^{11}$
4-(3-Pyridyl)-1-butanol

A solution of 5.74 g (21.6 mmol) of 4-(3-pyridyl)butyl-tert-butyldimethylsilyl ether in 10 mL of THF was treated at room temperature with 43.2 mL (43.2 mmol) of a 1.0 M solution of tetrabutylammonium fluoride in THF. The resulting solution was stirred 2 h, concentrated under reduced pressure, diluted with 25 mL of water, extracted with three 15-mL portions CH₂Cl₂, dried (MgSO₄), and concentrated. The crude product was purified by silica gel chromatography (EtOAc) to give 2.13 g (65%) of the title compound as a colorless oil: ¹H NMR (CDCl₃) δ 8.42 (m, 2H), 7.49 (d, J = 7.7 Hz, 1H), 7.20 (dd, J = 7.7 Hz, J = 4.9 Hz, 1H), 3.67 (m, 2H), 2.64 (t, J = 7.5 Hz, 2H), 1.75-1.67 (m, 2H), 1.64-1.57 (m, 2H); ¹³C (CDCl₃) δ 150.0, 147.4, 137.6, 136.0, 123.4, 62.6, 32.9, 32.3, 27.5.¹¹

4-Bromo-1-butanol

To 225 mL of THF (2.77 mol) heated at reflux was added 101 mL of 48% aqueous HBr (0.893 mol) slowly dropwise. The solution was heated at reflux for 1 h then cooled to room temperature. Excess HBr was neutralized with solid NaHCO₃ and 50 mL of water was then added. The mixture was transferred to a separatory funnel and the aqueous
layer was discarded. The organic layer was washed with brine, dried (MgSO₄) and concentrated under reduced pressure to give 38.3 g (28%) of the title compound as a clear oil: ¹H NMR (CDCl₃) δ 3.68 (t, J = 3.68, 2H), 3.44 (t, J = 6.8 Hz, 2H), 1.96 (p, J = 7.1 Hz, 2H), 1.74-1.68 (m, 2H).¹²

4-(tert-Butyldimethylsiloxy)-1-bromobutane

A 3-necked flask, equipped with a mechanical stirrer, was charged with 37.6 g (246 mmol) of 4-bromo-1-butanol, 44.4 g (295 mmol) of TBDMSI, 1.50 g (12.3 mmol) of 4-dimethylaminopyridine, and 70 mL of Et₂O. The solution was cooled to 0 °C in an ice/salt bath and 41.1 mL (295 mmol) of triethylamine was added dropwise. The viscous mixture was stirred overnight and gradually warmed to room temperature. The mixture was poured into a separatory funnel and washed with three 15-mL portions of 3% aqueous phosphoric acid, two 15-mL portions of water, brine, then dried (MgSO₄) and concentrated. The residue was washed through a short silica gel plug with hexanes to give 41.4 g (63%) of the title compound as a colorless oil: ¹H NMR (CDCl₃) δ 3.63 (t, J = 6.1 Hz, 2H), 3.44 (t, J = 6.8 Hz, 2H), 1.93 (p, J = 7.1 Hz, 2H), 1.68-1.62 (m, 2H), 0.88 (s, 9H), 0.04 (s, 6H); ¹³C (CDCl₃) δ 62.3, 34.1, 31.4, 29.6, 26.1, 18.5, −5.2.¹¹
5-(3-Pyridyl)pentyl-tert-butyldimethylsilyl ether

A solution of 10.6 mL (75.6 mmol) of diisopropylamine in 37 mL of THF at 0 °C was treated with 37.8 mL (75.6 mmol) of 2.0 M n-butyllithium in cyclohexane. After 20 min the solution was cooled to –78 °C and added dropwise to a solution of 8.35 g (89.7 mmol) of 3-picoline in 15 mL of THF at –78 °C. The resulting solution was stirred 30 min at –78 °C, at which point 20.0 g (74.8 mmol) of 4-(tert-butyldimethylsiloxy)-1-bromobutane was added and the solution was stirred overnight, gradually warming to room temperature. The reaction was then quenched with 1 mL methanol, washed with brine, dried (MgSO₄) and concentrated. The crude product was distilled under vacuum (150–158 °C, 7 mm) to give 13.4 g (64%) of the title compound as a colorless oil: ¹H NMR (CDCl₃) δ 8.44-8.42 (m, 2H), 7.48 (d, J = 7.8 Hz, 1H), 7.19 (dd, J = 7.7 Hz, J = 4.8 Hz, 1H), 3.60 (t, J = 6.5 Hz, 2H), 2.61 (t, J = 7.7 Hz, 2H), 1.64 (pentet, J = 7.7 Hz, 2H), 1.55 (pentet, J = 7.0 Hz, 2H), 1.42-1.34 (m, 2H), 0.88 (s, 9H), 0.04 (s, 6H); ¹³C (CDCl₃) δ 150.2, 147.4, 137.9, 135.9, 123.3, 63.2, 33.2, 32.7, 31.1, 26.1, 25.5, 18.5, –5.1.¹¹

5-(3-Pyridyl)-1-pentanol

1. OTBDMS
2. TBAF
A solution of 13.4 g (47.9 mmol) of 5-(3-pyridyl)pentyl-tert-butyldimethylsilyl ether in 20 mL of THF was treated at room temperature with 95.7 mL of (95.7 mmol) of a 1.0 M solution of tetrabutylammonium fluoride in THF. The solution was stirred 2 h, concentrated under reduced pressure, diluted with 50 mL water, extracted with three 30-mL portions of CH₂Cl₂, dried (MgSO₄), and concentrated. The crude product was purified by silica gel chromatography (EtOAc) to give 4.49 g (57%) of the title compound as a colorless oil: ¹H NMR (CDCl₃) δ 8.43-8.42 (m, 2H), 7.48 (d, J = 7.8 Hz, 1H), 7.20 (dd, J = 7.7 Hz, J = 4.8 Hz, 1H), 3.67-3.62 (m, 2H), 2.62 (t, J = 7.7 Hz, 2H), 1.70-1.57 (m, 4H), 1.45-1.38 (m, 2H); ¹³C (CDCl₃) δ 150.0, 147.3, 137.8, 136.0, 123.4, 62.8, 33.1, 32.6, 31.1, 25.5.¹¹

Synthesis of 3-(3-Iodopropyl)pyridine via Triphenylphosphine, Imidazole, and Iodine

A stirred solution of 1.57 g (6.00 mmol) of triphenylphosphine and 0.408 g (6.00 mmol) of imidazole in 13 mL of toluene and 8 mL of acetonitrile was treated with 1.52 g (6.00 mmol) of iodine. After stirring for 10 min, 0.548 g (4.00 mmol) of 3-pyridinepropanol dissolved in 3 mL toluene was added and stirred 1 h, at which point the mixture was poured into a separatory funnel containing 80 mL of petroleum ether, 60 mL of H₂O, and 30 mL of acetonitrile. The organic layer was discarded and the aqueous layer was washed with 40 mL of 1:1 toluene/petroleum ether. The aqueous phase was overlaid with 40 mL of diethyl ether and neutralized with solid Na₂CO₃. The aqueous layer was
discarded, and the organic layer was dried (MgSO₄) to give the title compound as a solution in diethyl ether. A small sample, isolated by concentration of the ethereal solution displayed the following spectroscopic properties: ¹H NMR (CDCl₃) δ 8.45 (m, 2H), 7.51 (d, J = 7.8 Hz, 1H), 7.21 (dd, J = 7.8 Hz, J = 4.8 Hz, 1H), 3.15 (t, J = 6.7, 2H), 2.73 (t, J = 7.4 Hz, 2H), 2.11 (pentet, J = 7.0 Hz, 2H); ¹³C (CDCl₃) δ 150.1, 147.9, 136.1, 135.8, 123.5, 34.5, 33.5, 5.6; HRMS-ESI: [M + H]^+ calc for C₈H₁₁IN, 247.9936; Found, 247.9917.

**Synthesis of 3-(3-Iodopropyl)pyridine via Chlorodiphenylphosphine, Imidazole, and Iodine**

![Synthesis Reaction Diagram]

To a solution of 0.45 g (6.6 mmol) of imidazole in 20 mL of toluene was added 0.45 g (3.3 mmol) of 3-pyridinepropanol followed by 0.59 mL (3.3 mmol) of chlorodiphenylphosphine. A saturated solution of iodine in toluene was added until the mixture became iodine-colored, at which point the mixture was poured into a separatory funnel containing 20 mL of saturated aqueous Na₂CO₃. The mixture was shaken vigorously until the color disappeared, the aqueous layer was discarded, and the organic layer was washed with one 15-mL portion of saturated aqueous Na₂CO₃, three 15-mL portions of water, then extracted with two 10-mL portions of 10% aqueous HCl. The aqueous phase was overlaid with 20 mL toluene, then neutralized with solid NaOH. The aqueous layer was discarded, and the organic layer was dried (MgSO₄), giving the product as a solution in toluene.
Synthesis of 3-(3-Iodopropyl)pyridine via HCl, Chlorodiphenylphosphine, Imidazole, and Iodine

To a solution of 0.41 g (3.0 mmol) of 3-pyridinepropanol in 30 mL CH₂Cl₂ was added 1.5 mL (3.0 mmol) of 2.0 M HCl in diethyl ether (prepared from acetyl chloride and methanol), followed by 0.45 g (6.6 mmol) of imidazole, 0.70 mL (3.9 mmol) of chlorodiphenylphosphine, and 1.20 g (4.7 mmol) of iodine in quick succession. After turning iodine-colored, the mixture was stirred 5 min then poured into a separatory funnel containing 30 mL of saturated aqueous Na₂CO₃. The mixture was shaken vigorously until the color disappeared, the aqueous layer was discarded, and the organic layer was washed with one 15-mL portion of saturated aqueous Na₂CO₃, two 15-mL portions of water, then extracted with two 10-mL portions of 10% aqueous HCl. The aqueous phase was overlaid with 20 mL toluene, then neutralized with solid NaOH. The aqueous layer was discarded, and the organic layer was dried (MgSO₄), giving the product as a solution in toluene.

*N,N-Dimethyl-N-(methylsulfanylmethylene)ammonium iodide*
A solution of 3.00 g (33.6 mmol) of \(N,N\)-dimethylthioformamide and 5.26 g (37.1 mmol) of iodomethane in 70 mL of diethyl ether was stirred overnight at ambient temperature. The resulting white precipitate was collected by filtration and dried under argon to give 4.27 g (55%) of the title compound as a white solid, which was used without further purification.\(^{15}\)

**Synthesis of 3-(3-Iodopropyl)pyridine via a Thioiminium Salt**

\[
\text{Pyridine} + \text{N,N-Dimethyl}-N-(methylsulfanylmethylene)ammonium iodide \rightarrow \text{3-(3-Iodopropyl)pyridine}
\]

A solution of 0.41 g (3.0 mmol) of 3-pyridinepropanol in 14 mL of toluene was heated to 86 °C in an oil bath, then 0.10 g (1.5 mmol) of imidazole and 1.04 g (4.5 mmol) of \(N,N\)-Dimethyl-\(N\)-(methylsulfanyl)methylene)ammonium iodide were added and the mixture was stirred at 86 °C for 2 h, at which point the mixture was cooled to room temperature, washed with one 5-mL portion of water, one 5-mL portion of brine, then extracted with 10 mL of 10% aqueous HCl. The aqueous phase was overlaid with 20 mL of diethyl ether, then neutralized with solid NaOH. The aqueous layer was discarded, and the organic layer was dried (\(\text{MgSO}_4\)), giving the title compound as a solution in diethyl ether.\(^{15}\)

**Synthesis of 3-(3-Iodopropyl)pyridine via Mesylation/Iodination**

\[
\text{Pyridine} + 1. \text{MsCl} + 2. \text{Nal} \rightarrow \text{3-(3-Iodopropyl)pyridine}
\]
The title compound was prepared according to the method of Clayden et al.\textsuperscript{16} A stirred solution of the 1.37 g (10.0 mmol) of 3-pyridinepropanol and 1.55 mL (11.1 mmol) of triethylamine in 50 mL of CH\textsubscript{2}Cl\textsubscript{2} was cooled to 0 °C and treated with 0.85 mL (11.0 mmol) of methanesulfonyl chloride. The solution was stirred 30 min, diluted with 50 mL CH\textsubscript{2}Cl\textsubscript{2}, washed with three 25-mL portions water, brine, dried (MgSO\textsubscript{4}) and concentrated so that some CH\textsubscript{2}Cl\textsubscript{2} remained. The residue was dissolved in 50 mL acetone, 1.65 g (11.0 mmol) of NaI was added, and the solution was heated at reflux for 2 h. The resulting mixture was filtered and concentrated so that some acetone remained. The residue was diluted with 60 mL of Et\textsubscript{2}O, washed with 15 mL of 10% aq Na\textsubscript{2}S\textsubscript{2}O\textsubscript{3}, three 15-mL portions of water, then extracted with two 20-mL portions of 10% aq HCl. The solution was placed on a rotary evaporator for 15 min to remove most of the residual CH\textsubscript{2}Cl\textsubscript{2} and acetone. The solution was then washed with four 10-mL portions of Et\textsubscript{2}O to remove final traces of solvent. The aqueous solution was overlaid with 40 mL of pentane, then made basic with solid NaOH. The aqueous layer was extracted with two 10-mL portions of pentane, then the combined organic layers were dried (MgSO\textsubscript{4}) and poured into a graduated cylinder. A 2.00-mL aliquot was removed and evaporated to dryness; the mass of the residue was used to extrapolate the mass of product in the entire solution (1.09 g; 44%).

3-Propylypyridine

\[
\begin{array}{c}
\text{Pyridine} \\
\text{I} \\
1. \text{t-BuLi, } -78 \degree C \\
2. \text{MeOH} \\
\text{Pyridine} \\
\end{array}
\]
A solution of 1.02 g (4.13 mmol) of 3-(3-iodopropyl)pyridine in pentane was dried (NaH) for 1 h, at which point it was transferred via cannula through a plug of glass wool into a flame-dried flask containing 1 mL of dry Et₂O. The solution was cooled to −78 °C and 5.62 mL (8.71 mmol) of 1.55 M t-butyllithium in heptane was added dropwise. The solution was stirred 2 min, then 1 mL of methanol was added. The mixture was poured into a separatory funnel and washed with three 5-mL portions of water. The solution was concentrated and the residue purified by silica gel chromatography (50% Et₂O/pentane) to give 0.217 g (18%) of the title compound as a yellow oil: ¹H NMR (CDCl₃) δ 8.43 (m, 2 H), 7.48 (d, J = 7.7 Hz, 1 H), 7.19 (dd, J = 7.6 Hz, J = 4.9 Hz, 1 H), 2.58 (t, J = 7.6 Hz, 2 H), 1.65 (sextet), J = 7.4 Hz, 2 H), 0.94 (t, J = 7.3 Hz, 3 H); ¹³C (CDCl₃) δ 150.2, 147.4, 137.8, 135.9, 123.3, 35.2, 24.4, 13.8; HRMS-ESI: [M + H]⁺ calc for C₇H₁₂N, 122.0970; Found, 122.0981.

2,3-Cyclopentenopyridine

A solution of 3-(3-iodopropyl)pyridine in pentane or toluene was dried (NaH) for 1 h, at which point it was transferred via cannula through a plug of glass wool into a flame-dried flask containing 1 mL dry Et₂O. The solution was cooled to −78 °C and 2 eq of t-BuLi in heptane (for the chlorodiphenylphosphine route, 2 eq based on 3-pyridinepropanol were used; for mesylation route, 2 eq based on 3-(3-iodopropyl)pyridine) was added dropwise. The solution was stirred 2 min, the cold bath was then removed and stirring was continued for 1 h at ambient temperature, at which point 1 mL of methanol was added.
The mixture was poured into a separatory funnel and washed with three 5-mL portions of water. The solution was concentrated and the residue purified by silica gel chromatography (9:1 hex/EtOAc) to give the title compound\(^{17}\) as a yellow oil (29% via the chlorodiphenylphosphine route, 14% via the mesylation route): \(^1\)H NMR (CDCl\(_3\)) \(\delta\) 8.33 (d, \(J = 4.7\) Hz, 1H), 7.48 (d, \(J = 7.6\) Hz, 1 H), 7.01 (m, 1H), 3.02 (t, \(J = 7.7\) Hz, 2H), 2.94 (t, \(J = 7.4\) Hz, 2H), 2.12 (pentet, \(J = 7.6\) Hz, 2H); \(^{13}\)C (CDCl\(_3\)) \(\delta\) 165.8, 147.6, 137.0, 132.1, 121.0, 34.4, 30.9, 23.2; HRMS-ESI: [M + H]\(^+\) calc for C\(_8\)H\(_9\)N, 120.0813; Found, 120.0837.

3-(4-Iodobutyl)pyridine

![Chemical Structure](image)

A stirred solution of the 1.21 g (8.00 mmol) of 4-(3-pyridyl)-1-butanol and 1.24 mL (8.80 mmol) of triethylamine in 40 mL of CH\(_2\)Cl\(_2\) was cooled to 0 °C and treated with 0.68 mL (8.80 mmol) of methanesulfonyl chloride. The solution was stirred 30 min, diluted with 40 mL CH\(_2\)Cl\(_2\), washed with three 20-mL portions water, brine, dried (MgSO\(_4\)) and concentrated so that some CH\(_2\)Cl\(_2\) remained. The residue was dissolved in 40 mL acetone, 1.32 g (8.80 mmol) of NaI was added, and the solution was heated at reflux for 2 h. The resulting mixture was filtered and concentrated so that some acetone remained. The residue was diluted with 50 mL of Et\(_2\)O, washed with 15 mL of 10% aq Na\(_2\)S\(_2\)O\(_3\), three 15-mL portions of water, then extracted with two 15-mL portions of 10% aq HCl. The solution was placed on a rotary evaporator for 15 min to remove most of the residual CH\(_2\)Cl\(_2\) and acetone. The solution was then washed with four 10-mL portions of
Et$_2$O to remove final traces of solvent. The aqueous solution was overlaid with 40 mL of pentane, then made basic with solid NaOH. The aqueous layer was extracted with two 10-mL portions of pentane, then the combined organic layers were dried (MgSO$_4$) and poured into a graduated cylinder. A 2.00-mL aliquot was removed and evaporated to dryness; the mass of the residue was used to extrapolate the mass of 3-(4-iodobutyl)pyridine in the entire solution (0.95 g, 45%); $^1$H NMR (CDCl$_3$) $\delta$ 8.45 (s, 2H), 7.50 (d, $J = 7.8$ Hz, 1H), 7.21 (dd, $J = 7.6$ Hz, $J = 4.9$ Hz, 1H), 3.20 (t, $J = 6.7$ Hz, 2H), 2.64 (t, $J = 7.5$ Hz, 2H), 1.86 (pentet, $J = 7.1$ Hz, 2H), 1.75 (pentet, $J = 7.4$ Hz, 2H); $^{13}$C (CDCl$_3$) $\delta$ 150.1, 147.7, 137.1, 135.9, 123.5, 32.8, 32.01, 31.97, 6.4; HRMS-ESI: [M + H]$^+$ calc for C$_9$H$_{13}$IN, 262.0093; Found, 262.0077.

3-Butylpyridine

A solution of 0.945 g (3.62 mmol) of 3-(4-iodobutyl)pyridine in pentane was dried (NaH) for 1 h, at which point it was transferred via cannula through a plug of glass wool into a flame-dried flask containing 1 mL dry Et$_2$O. The solution was cooled to $-78$ °C and 2 eq of t-BuLi in heptane was added dropwise. The solution was stirred 2 min, then 1 mL of methanol was added. The mixture was poured into a separatory funnel and washed with three 5-mL portions of water. The solution was concentrated and the residue purified by silica gel chromatography (20% Et$_2$O/pentane) to give 0.253 g (23% based on 4-(3-pyridyl)-1-butanol) of the title compound as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 8.43 (m, 2H), 7.48 (d, $J = 7.7$ Hz, 1 H), 7.19 (dd, $J = 7.6$, $J = 4.9$, 1H), 2.61 (t, $J = 7.7$ Hz, 2H), 1.60
(pentet, $J = 7.6$ Hz, 2H), 1.36 (sextet, $J = 7.4$ Hz, 2H), 0.93 (t, $J = 7.3$ Hz, 3H); $^{13}$C (CDCl$_3$) $\delta$ 150.1, 147.3, 138.0, 135.9, 123.3, 33.4, 32.8, 22.3, 14.0; HRMS-ESI: [M + H]$^+$ calc for C$_9$H$_{14}$N, 136.1126; Found, 136.1133.

5,6,7,8-Tetrahydroquinoline

A solution of 1.15 g (4.42 mmol) of 3-(4-iodobutyl)pyridine in pentane was dried (NaH) for 1 h, at which point it was transferred via cannula through a plug of glass wool into a flame-dried flask containing 1 mL dry Et$_2$O. The solution was cooled to $-78$ °C and 2 eq of t-BuLi in heptane was added dropwise. The solution was stirred 2 min, then the cold bath was removed and stirring was continued for 1 h at ambient temperature, at which point 1 mL of methanol was added. The mixture was poured into a separatory funnel and washed with three 5-mL portions of water. The organic phase was concentrated and the residue purified by silica gel chromatography (20% Et$_2$O/hex) to give 0.108 g (18% based on 4-(3-pyridyl)-1-butanol) of the title compound$^{18}$ as a yellow oil: $^1$H NMR (CDCl$_3$) $\delta$ 8.33 (d, $J = 4.5$, 1H), 7.34 (d, $J = 7.6$, 1H), 7.09 (dd, $J = 7.5$, $J = 4.9$, 1H), 2.92 (t, $J = 7.4$, 2H), 2.76 (t, $J = 6.2$, 2H), 1.89 (m, 2H), 1.81 (m, 2H); $^{13}$C (CDCl$_3$) $\delta$ 157.5, 146.9, 136.9, 132.4, 121.0, 32.6, 28.9, 23.2, 22.8; HRMS-ESI: [M + H]$^+$ calc for C$_9$H$_{12}$N, 134.0970; Found, 134.0991.
A stirred solution of the 1.16 g (7.00 mmol) of 5-(3-pyridyl)-1-pentanol and 1.08 mL (7.70 mmol) of triethylamine in 35 mL of DCM was cooled to 0 °C and treated with 0.60 mL (7.70 mmol) of methanesulfonyl chloride. The solution was stirred 30 min, diluted with 35 mL CH$_2$Cl$_2$, washed with three 15-mL portions water, brine, dried (MgSO$_4$) and concentrated so that some CH$_2$Cl$_2$ remained. The residue was dissolved in 35 mL acetone, 1.16 g (7.70 mmol) of NaI was added, and the solution was heated at reflux for 2 h. The resulting mixture was filtered and concentrated so that some acetone remained. The residue was diluted with 45 mL of Et$_2$O, washed with 10 mL of 10% aq Na$_2$S$_2$O$_3$, three 10-mL portions of water, then extracted with two 15-mL portions of 10% aq HCl. The solution was placed on a rotary evaporator for 15 min to remove most of the residual CH$_2$Cl$_2$ and acetone. The solution was then washed with four 10-mL portions of Et$_2$O to remove final traces of solvent. The aqueous solution was overlaid with 35 mL of pentane, then made basic with solid NaOH. The aqueous layer was extracted with two 10-mL portions of pentane, then the combined organic layers were dried (MgSO$_4$) and poured into a graduated cylinder. A 2.00-mL aliquot was removed and evaporated to dryness; the mass of the residue was used to extrapolate the mass of 3-(5-iodopentyl)pyridine in the entire solution (0.549 g, 29%); $^1$H NMR (CDCl$_3$) $\delta$ 8.43 (s, 2H), 7.47 (d, $J = 7.8$ Hz, 1H), 7.19 (dd, $J = 7.5$ Hz, $J = 5.1$ Hz, 1H), 3.16 (t, $J = 6.9$ Hz, 2H), 2.61 (t, $J = 7.6$ Hz, 2H), 1.84 (pentet, $J = 7.2$ Hz, 2H), 1.63 (pentet, $J = 7.7$ Hz, 2H), 1.43 (pentet, $J = 7.5$ Hz, 2H); $^{13}$C (CDCl$_3$) $\delta$ 150.0, 147.5, 137.5, 135.8, 123.4, 33.3, 32.9, 30.10, 30.06, 6.8; HRMS-ESI: [M + H]$^+$ calc for C$_{10}$H$_{15}$IN, 276.0249; Found, 276.0215.
3-\textit{n}-Pentylpyridine

A solution of 0.478 g (1.74 mmol) of 3-\((5\text{-iodopentyl})\)pyridine in pentane was dried (NaH) for 1 h, at which point it was transferred via cannula through a plug of glass wool into a flame-dried flask containing 1 mL dry Et\(_2\)O. The solution was cooled to \(-78 \, ^\circ\text{C}\) and 2.35 mL (3.65 mmol) of 1.55 M \textit{t}-butyllithium in heptane was added dropwise. The solution was stirred 2 min, then 1 mL of methanol was added. The mixture was poured into a separatory funnel and washed with three 5-mL portions of water. The solution was concentrated and the residue purified by silica gel chromatography (50% Et\(_2\)O/pentane) to give 0.082 g (8% based on 5-\((3\text{-pyridyl})\)-1-pentanol) of the title compound as a yellow oil: \(^1\text{H NMR (CDCl}_3\text{)} \delta 8.45 \text{ (m, 2H), 7.51 \text{ (d, J = 7.8, 1H)}, 7.22 \text{ (dd, J = 7.7 Hz, J = 4.8 Hz, 1H), 2.62 \text{ (t, J = 7.7 Hz, 2H), 1.64 \text{ (pentet, J = 7.4 Hz, 2H)}, 1.35 \text{ (m, 4H)}, 0.92 \text{ (t, J = 6.7 Hz, 3H)}; \text{^13C (CDCl}_3\text{)} \delta 150.1, 147.3, 138.1, 135.9, 123.3, 33.1, 31.4, 30.9, 22.6, 14.1; HRMS-ESI: [M + H]\(^+\) \text{calc for C}_{10}\text{H}_{16}\text{N, 150.1283; Found, 150.1297.}\)

2,3-\textit{Cycloheptenopyridine}

A solution of 1.12 g (4.06 mmol) of 3-\((5\text{-iodopentyl})\)pyridine in pentane was dried (NaH) for 1 h, at which point it was transferred via cannula through a plug of glass wool into a
flame-dried flask containing 1 mL dry Et₂O. The solution was cooled to –78 °C and 4.06 mL (8.53 mmol) of t-BuLi in heptane was added dropwise. The solution was stirred 2 min, then the cold bath was removed and stirring was continued for 1 h at ambient temperature, at which point 1 mL of methanol was added. The mixture was poured into a separatory funnel and washed with three 5-mL portions of water. The title compound was identified on the basis of mass spectrometry, but was a minor product and no isolated yield was obtained.


Current Data Parameters
NAME  2fluoroiodopyridine
EXPNO  1
PROCNO  1

F2 - Acquisition Parameters
Date  20120401
Time  13.22
INSTRUM  spect
PROBD  5 mm PABSO 80/80
FIELD  5930
TD  65536
SOLV  CDC13
NS  16
DS  2
SWH  8012.020 Hz
FIDRES  0.122826 Hz
AQ  4.0884966 sec
RG  181
DW  62.400 usec
DT  6.50 usec
TE  238.0 K
DI  1.00000000 sec
TD0  1

----------- CHANNEL f1 ---------
NUC1  1H
P1  15.00 usec
P1W1  12.00000000 W
SF01  400.144711 MHz

F2 - Processing parameters
SI  65536
SF  400.1440194 MHz
WDW  0
SSB  0 0.30 Hz
GB  0
PC  1.00