Abstract

WAGNER, FLORENCE FÉVRIER. Synthesis of Nicotine Derivatives from Natural Nicotine, Total Synthesis of (S)-Brevicolline, and Advances towards the Synthesis of Dihydrolycolucine. (Under the direction of Dr. Daniel Lee Comins.)

Nicotine and its derivatives are currently being synthesized and tested to explore their pharmaceutical capabilities in the treatment of Alzheimer’s disease, Parkinson’s disease, and other central nervous system disorders. One area of research the Comins group has been undertaking is the development of methodologies for the synthesis of nicotine derivatives from natural nicotine. Herein, regioselective substitutions of the pyridine ring of (S)-nicotine will be described. Efforts are underway to expand the scope of these methods and to apply them to the preparation of potential pharmaceuticals, insecticides, synthetic intermediates, and novel ligands for catalytic asymmetric synthesis. Nicotine was used as a building block for the syntheses of SIB-1508Y, a potential anti-Parkinson’s drug, which was successfully synthesized enantiomerically pure in only five steps. (S)-Brevicolline, a natural product of the β-carboline family was synthesized from nicotine in only six steps. Our goal is to transform inexpensive, commercially available (S)-nicotine from an underutilized natural product to a useful member of the chiral pool.

Our group previously reported the intramolecular Diels-Alder reaction of 1-acyl-2-alkenyl-1,2-dihydropyridines. A derivative of a dihydropyridine Diels-Alder product could be ring-opened via a Retro-Mannich reaction to give a cis-decahydroquinoline derivative. The potential of this methodology for the synthesis of dihydrolycolucine, natural product from the Lycopodium family, prompted us to carry the model studies described in Chapter IV.
SYNTHESIS OF NICOTINE DERIVATIVES FROM NATURAL NICOTINE,
TOTAL SYNTHESIS OF (S)-BREVICOLLINE,
AND ADVANCES TOWARDS THE SYNTHESIS OF DIHYDROLYCOLUCINE

by

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A dissertation submitted to the Graduate Faculty of
North Carolina State University
In partial fulfillement of the
Requirements for the Degree of
Doctor of Philosophy

CHEMISTRY

Raleigh, North Carolina, USA
August 2006

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Dedication

This manuscript is dedicated to my husband Ryan R. Wagner and to my parents, Jocelyne and Jacques Février, for their continuing love and support. You are part of everything I am and all that I have accomplished. I hope you will always know how grateful I am and how much I love you.

Cette thèse est dédiée à mon époux, Ryan R. Wagner, ainsi qu’à mes parents, Jocelyne et Jacques Février en remerciement de leur éternel amour et de leur infatigable soutien. Vous faites part de qui je suis aujourd’hui et de ce que j’ai accompli. J’espère que vous n’oublierez jamais à quel point je vous en suis reconnaissante et à quel point je vous aime.
Biography

The author, Florence Février Wagner, was born to Jacques and Jocelyne Février in Argenteuil, France on January 16, 1980. After graduating from Lycée Jean Monnet in Franconville (France), Florence prepared for the competitive examination regulating entry into School of Science and Technology at Janson de Sailly in Paris (France). Following the examination, she joined the Department of Chemistry and Process Engineering of CPE Lyon, France (Lyon School of Chemistry and Electronics). Between her junior and senior year at CPE Lyon, Florence traveled overseas and joined Scynexis, Inc (Durham, NC) as an intern in organic chemistry. She stayed in North Carolina and returned to school to earn her Ph.D. She began on her dissertation under the supervision of Dr Daniel Lee Comins at North Carolina State University, Raleigh, NC, while completing the requirement to earn her Bachelor and Master of Science in Chemistry from CPE Lyon in 2002. In 2003, Florence received the Burroughs-Wellcome Fellowship, research fellowship for a second year graduate student. In 2004, she received the Eli Lilly Fellowship, research fellowship for third year graduate student. In 2006, she was awarded the Percy Lavon Julian Award for excellence in teaching. Florence graduated from North Carolina State University in 2006. She is currently working at Metastatix in Tucker, GA.
Acknowledgments

I would like to express my gratitude to my advisor Dr. Daniel L. Comins, for his guidance and support. Thank you for giving me the opportunity to work in your lab and conduct exciting research projects. I would also like to thank the members of my committee, Dr. T. Brent Gunnoe, Dr. Jonathan S. Lindsey, Dr. Christian C. Melander, Dr. Suzanne Purrington and Dr. Coby Schal for their review of my work. I would like to extend my appreciation to the faculty and staff of the Department of Chemistry at North Carolina State University for the educational opportunity. I would like to acknowledge the Glaxo-Wellcome Fellowship for financial support throughout my second year and the Eli Lilly Fellowship for financial support throughout my third year. Finally I would like to thank PLU for helping me travel to conferences to present my research.

My deepest gratitude goes to the members of the Comins group, Dr. Anne-Cecile Hiebel, Dr. Lucas R. Marks, Dr. W. Steven McCall, Dr. Emilie D. Smith, Dr. Damian W. Young, Ibrahim Bori, Brandon M. Cash, Jason M. Dinsmore, Pauline W. Ondachi, Sonja M. Siefert and James Sahn for their support, encouragement and friendship, and to the wonderful Debbie Sloan, my “Chemistry Mom” for her patience, kindness. We had good laughs!

Finally, above all I would like to thank my husband, Ryan R. Wagner, for his continuing love and support through hard times. I would like to thank my parents, Jocelyne and Jean, and Jacques and Marie, as well as my best friend Ambre back home. You always supported my choices, you were always there for me, despite the distance between us, and I love you.
My new family here also helped me. Thank you Deb and Rob, Bob, Tina, Corinne and Jarod for your kindness and generosity, and for making me feel so welcome in your homes.
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<td>Å</td>
<td>Angstrom</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
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<tr>
<td>AD</td>
<td>Alzheimer’s Disease</td>
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<tr>
<td>[α]D</td>
<td>specific rotation</td>
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<td>AIBN</td>
<td>2,2’-azobisisobutyronitrile</td>
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<td>aq</td>
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<tr>
<td>Bn</td>
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<tr>
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<td>bp</td>
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<tr>
<td>br</td>
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<tr>
<td>brine</td>
<td>saturated solution of sodium chloride</td>
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<tr>
<td>Bu</td>
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<td>°C</td>
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<td>CIPE</td>
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<tr>
<td>CNS</td>
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<td>d</td>
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<td>de</td>
<td>diastereomeric excess</td>
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<td>4-(N,N-dimethylamino)pyridine</td>
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<tr>
<td>HRMS</td>
<td>high resolution mass spectrometry</td>
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<td>hertz</td>
</tr>
<tr>
<td>i-Pr</td>
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</tr>
<tr>
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</tr>
<tr>
<td>LDA</td>
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</tr>
<tr>
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<td>neurotransmitter</td>
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<tr>
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CHAPTER I:

INTRODUCTION OF NICOTINE CHEMISTRY
I. 1. Discovery, effects and mode of action

(S)-Nicotine (1) is present together with a number of minor alkaloids in tobacco and a wide variety of other plants. Dried leaves of the tobacco plants *Nicotiana rustica* and *N. tabacum* contain as much as 2-8% of (S)-nicotine. Interest in the actions of nicotine has remained high over the past century, primarily because of the widespread exposure of people to nicotine through recreational use of tobacco products. First isolated in 1828, the correct structure of nicotine was not proposed until 1883 by Pinner. Pictet and Rotschy are accredited with first synthesizing the alkaloid in 1904. In fresh *Nicotiana tabacum*, the alkaloid mixture typically consists of 93% (S)-nicotine (1), 3.9% (S)-anatabine (2), 2.4% (S)-nornicotine (3), and 0.5% (S)-anabasine (4) (Figure 1).

![Figure 1. Alkaloid mixture in fresh Nicotiana tabacum.](image)

A large scale application of nicotine was its use as an insecticide, as approximately 2,800 tons of (S)-nicotine were used as a crop protectant per year. Aqueous solutions of nicotine sulfate are still used throughout the world as insecticides. More recently, nicotine has attracted much attention because of its important pharmacological effects on central nervous system (CNS) diseases. In particular, (S)-nicotine may have beneficial effects in the
treatment of Parkinson’s disease (PD), Alzheimer’s disease (AD) and Tourette’s syndrome. An estimated 4.5 million Americans have AD. The number of Americans with AD has more than doubled since 1980 and still continues to grow. By 2050, the number of individuals with AD could range from 11.3 million to 16 million. PD affects over 1 million people in the US alone. One person in 200 will get PD during their lifetime, this risk increases with age since 1 in every 100 persons over 60 years of age has Parkinson's. Both neurodegenerative disorders have emerged as a major public health concern as a consequence of the post World War II baby boom and the changes in the global population age profile.

The neurotransmitter (NT) most consistently implicated in such neurodegenerative disorders is acetylcholine (ACh). Acetylcholine (5) was the first NT to be discovered and isolated. Furthermore, it is the NT at all first synapses outside the CNS. Alterations in the activity of acetylcholine-gated ion channels have been implicated in a number of CNS disorders. More than 25 years ago, a 50% reduction was noted in the level of choline acetyltransferase, the enzyme responsible for ACh synthesis in the frontal cortex and hippocampus of AD patients. ACh acts on two distinct receptors: nicotinic receptors (nAChR), which mediate fast synaptic events, and muscarinic ones (mAChR) controlling much slower changes (Figure 2). Nicotinic acetylcholine receptors are a group of ion channel receptors that play an important role in many biological processes related to a number of nervous system disorders. Substantial reductions in nicotinic and muscarinic cholinergic receptors have been reported in the cortex and hippocampus of AD patients. Accordingly, cholinergic channel activators may be therapeutically useful in ameliorating the cognitive decline.
This activation could be performed on either post-synaptic or pre-synaptic nicotinic receptors. Activation of postsynaptic nicotinic receptors causes the rapid opening of Na$^+$ channels, membrane depolarization and contraction. Exogenously applied nicotinic agonists, which mimic the actions of ACh, have been shown to directly excite neurons. Numerous drugs bind to cholinergic receptors, but few of them enter the brain and those that do are not effective. More recently much interest has been directed towards pre-synaptic nicotinic receptors that have shown an enhancement in the release of a number of NTs, i.e. ACh (5), but also Dopamine (DA) (6), Noradrenaline (NA, adrenaline) (7), glutamate (8) and γ-Aminobutyric acid (GABA) (9) (Figure 3). ACh increases neuronal accessibility and responsiveness in Alzheimer’s disease through activation of both nicotinic and muscarinic receptors.
Nicotine is dibasic. The nitrogens located on the pyridine and pyrrolidine ring have pKa values of 3.04 and 7.84 respectively. At pH 7.4, nicotine exists in two forms: the monoprotonated form 10 and the neutral form 1 in a 2:1 ratio (Figure 4). The uncharged nicotine can penetrate the lipoprotein membrane. This feature explains why nicotine is absorbed through skin and several organs such as the liver, lungs and the brain. The ionized form 10 mimics acetylcholine (5) as the positively charged pyrrolidine nitrogen mimics the positively charged quaternary nitrogen in 5.

Many groups of compounds have been isolated from natural sources or synthesized as ligands for the nicotinic acetylcholine receptors, of which nicotine and its analogs represent an important class. However, nicotine is not suitable for therapeutical use due to its
undesirable side effects including the potential for abuse and actions on the cardiovascular and gastrointestinal systems. Side effects are the result of activation of both cholinergic and non-cholinergic pathways in the central and peripheral nervous systems. The selective modulation of neuronal receptor subtypes has considerable potential for the treatment of disease with minimal adverse side effects. As a consequence, much effort has been devoted to the synthesis of nicotine analogs to furnish a selective nAChR ligand for the development of neurodegenerative disorder drugs which possess the positive effect of nicotine without the compound’s harmful side effects. With a similar structure to nicotine, (R)-epibatidine (11) (Figure 5), isolated by Daly from the skin of an Ecuadorian frog, *Epipedobates tricolor*, in trace amounts (less than 1 mg from 750 frogs), is a powerful analgesic agent. It was found to be >200-500 times more potent than morphine in bioassays of analgesic-like effects in mice that acts via neuronal nAChR, but was too toxic for therapeutic use. Recent advances in the synthesis of analogs have led to the discovery of compounds such as ABT-418 (12) and SIB-1508Y (13) (Figure 5), which have improved pharmacotherapeutic properties over nicotine. ABT-418 (12) is in clinical trials for the treatment of AD; while SIB-1508Y (13) is still under investigation after clinical trials were stopped in Phase II.

![Chemical structures of compounds](image)

**FIGURE 5. Potential compounds for the treatment of CNS disorders.**

Due to the therapeutic potential of nicotine (1), synthetic and medicinal chemists have concentrated much effort on the design of efficient syntheses of 1 and its analogs. Herein, we wish to report chemical advances that have made nicotine a useful member of the chiral pool.19 Since the first synthesis by Pictet in 1904,5 a plethora of ingenious syntheses of nicotine have been undertaken. Most of the early literature on the synthesis of nicotine and its analogs involved a pyridine moiety used as starting material onto which the pyrrolidine ring was constructed.

I. 2. a. Syntheses of (±) nicotine via construction of the pyrrolidine ring

In 1969, Breuer and Melumad reported the formation of nicotine (1) in one step from cyclopropyl 3-pyridyl ketone (14),20 via the following sequence: formation of the ketimine, its rearrangement to pyrroline, and a reduction to pyrrolidine (Scheme 1).

Leete in 1971,21 then Rondahl in 197722 prepared racemic 5-halonicotines 19-21 according to Scheme 2. The methylated lactam 16 was condensed onto nicotine ester 15a-c. Hydrolysis and subsequent decarboxylation followed by ring closure led to intermediate 18.
that was reduced to halonicotines 19-21 using NaBH₄. The synthesis of 5-iodonicotine (23) was obtained in two steps from 5-bromonicotine (19) via its conversion to 5-aminonicotine (22) and substitution of the corresponding aziridinium salt with KI.

SCHEME 2. Synthesis of 5-halonicotines.

In 1972, Leete and coworkers reported a four-step synthesis of myosmine (28) and nornicotine (3).²³ Pyridine-3-aldehyde (24) reacted with morpholine and sodium cyanide in the presence of perchloric acid to afford \( \alpha \)-morpholino-\( \alpha \)-(3-pyridyl)acetonitrile (25) (Scheme 3). Its anion then attacked acrylonitrile to yield Michael addition product 26. Acid hydrolysis affords keto nitrile 27 which was subsequently reduced to myosmine (28), and eventually to nornicotine (3) if a longer reaction time was used. This procedure was used
again for the formation of 2- and 4-methylnicotine,\textsuperscript{24} 6-methoxynicotine\textsuperscript{25} and bridged nicotine derivatives.\textsuperscript{18}

\begin{center}
\begin{tikzpicture}
  \node (A) at (0,0) {\textbf{24}}; \node (B) at (2,0) {\textbf{25}}; \node (C) at (4,0) {\textbf{26}}; \node (D) at (0,-2) {\textbf{27}}; \node (E) at (2,-2) {\textbf{28}}; \node (F) at (4,-2) {\textbf{3}};
  \draw [->] (A) -- node {morpholine, NaCN, HClO$_4$} (B);
  \draw [->] (B) -- node {1) KOH, t-BuOH, 2) CH$_2$=CHCN} (C);
  \draw [->] (D) -- node {$\text{H}^+$, H$_2$O} (E);
  \draw [->] (E) -- node {Raney Ni, H$_2$} (F);
\end{tikzpicture}
\end{center}

\textbf{SCHEME 3.} Leete’s syntheses of myosmine (28) and nornicotine (3).

In 1983, Andrieux and coworkers synthesized (+)-(1) via a tertiary azide.\textsuperscript{26} The condensation of 3-pyridyllithium (29) on cyclobutanone (30) leads to alcohol 31 (Scheme 4). The alcohol is displaced using hydrazoic acid, the subsequent ring expansion afforded myosmine (28). Reduction of 28 with sodium cyanoborohydride or by catalytic hydrogenation with Pd/C led to (+) nornicotine (3) which is further methylated using Eschweiler-Clarke’s method\textsuperscript{27} to access (+) nicotine (1).
In 1985, Meyers and coworkers designed a synthesis of 1 using a formamidine as an α-amino carbanion precursor.\textsuperscript{28} In this study, formamidine 33 was treated with \textit{n}-BuLi followed by the addition of 1-iodo-3-chloropropane to afford compound 34 (Scheme 5). The reaction of 34 with hydrazine in an ethanol/acetic acid mixture yielded (±) nicotine (1) in 60% yield.

Hutchinson and coworkers condensed the anion of methoxime 35 with 36 to give 37 by a Michael addition (Scheme 6).\textsuperscript{29} Reduction of 37 to the primary amine and sulfoxide to the thioacetal was obtained by treatment with diborane. The hydrolysis of thioacetal 38 was
followed by intramolecular cyclization and reduction to give 39. Eschweiler-Clark reductive methylation completed the synthesis of nicotine (1).

![Chemical structure diagram]

**SCHEME 6. Synthesis of nicotine from methoxime 35.**

In 1996, Crooks and coworkers proposed a simple route to nornicotine (3).\textsuperscript{30} Imine 41 was prepared from 3-(aminomethyl)pyridine (40) and benzophenone (Scheme 7). Deprotonation of the Schiff’s base with LDA, followed by addition of methanesulfonic acid 3-ethoxy-propyl ester, provides α-alkylated imine 42. Hydrolysis and basification to form the pyrrolidine ring complete the synthesis of 3.
I. 2. b. Synthesis of nicotine (1) via construction of the pyridine ring

Chavdarian and coworkers reported in 1982 the first synthesis of optically active nicotine. This synthesis was unique since an optically active starting material was used as the pyrrolidine source onto which the pyridine ring was built (Scheme 8). The synthesis starts with L-proline, manipulation of the side-chain leads to the formation of 43. Treatment of 43 with thionyl chloride gave 44. The chlorine was then displaced with sodium cyanide to afford 45. Condensation of the lithium anion of 45 with 3-ethoxyacrolein led to 46 which underwent cyclization upon treatment with a mixture of HBr/HOAc to afford 2-bromonicotine (47). Removal of the halogen by hydrogenolysis completed the synthesis of nicotine (1), obtained in 24% ee.
SCHEME 8. First synthesis of optically active nicotine (1) by Chavdarian.

I. 2. c. Formation of nornicotine (3) and nicotine (1) and their derivatives with optical purity.

As studies on the affinity of nicotine and its derivatives for nAChRs progressed, it was generalized that the affinity of the \((S)\) enantiomer was 10-100 times higher than that of the \((R)\) enantiomer. \(^{32}\) Synthetic efforts were then aimed towards the enantioselective synthesis or the isolation of both enantiomers of nicotine and their derivatives.

I. 2. c. i. Optical purity induced by stereospecific reactions.

Crooks and coworkers followed up in 1999 with an asymmetric version for the synthesis of \((S)\)- and \((R)\)-nornicotine (3) with moderately high optical purity via alkylation of a chiral 2-hydroxy-3-pinanone ketimine template (Scheme 9). \(^{33}\)
SCHEME 9. Crooks’ enantioselective synthesis of nornicotine (3).

SCHEME 10. Loh’s synthesis of (S)-nornicotine (3) using 2,3,4,6-tetra-O-pivaloyl-β-D-galactosylamine as a chiral auxiliary.

In 1999, Loh and coworkers reported a four-step stereoselective synthesis of (S)-nornicotine (3). Hydroxyketone 54 was obtained by halogen-exchange of 3-bromopyridine (52) with n-BuLi followed by treatment with lactone 53 (Scheme 10). A Swern oxidation
gave aldehyde 55. The diastereoselective reductive aminocyclization with 2,3,4,6-tetra-O-pivaloyl-β-D-galactosylamine 56 afforded compound 57. The source of the chiral amine was then cleaved by acidic hydrolysis to complete the synthesis of (S)-nornicotine (3) with an optical purity greater than 98%.

I. 2. c. ii. Optical purity obtained by resolution of a racemic mixture.

In 1982, Jacob reported the preparation of 5-bromonornicotine (62) and its subsequent resolution to get both isomers in high enantiomeric purity (Scheme 11).35 The enolate of N-vinylpyrrolidinone (58) was condensed on ethyl 5-bromonicotinate (15a). The hydrolysis of the enamine, decarboxylation and cyclization affords 5-bromomyosmine (61). Reduction with NaBH₄ gave 5-bromonornicotine (62) which was converted to the a diastereomeric salt with enantiomerically pure organic acids. After several recrystallizations and conversion to the free base, each enantiomer of 62 was obtained with an optical purity superior to 95%.

Seeman and coworkers followed with the resolution of (±) nornicotine (3). The racemic mixture was reacted with optically pure (-)-menthyl chloroformate. The diastereomers were separated and the carbamate removed using an acid-catalysed procedure. Each enantiomer was obtained in purity greater than 99%.

For some purposes, a racemic mixture can be of use. Racemization of an optically pure sample may be desired. In 1996, Jacob reported the racemization of nornicotine (3) using a pyridoxal catalyst (Scheme 12).

![Scheme 12. Racemization of nornicotine (3) using a pyridoxal catalyst.](image)

In 1982, the groups of Bowman and Tsujino separately reported two convenient methods for the racemization of (S)-nicotine. Bowman treated (-)-(1) with NaH in p-xylene to give (±)-(1). Tsujino observed that (S)-nicotine (1) was completely racemized by refluxing with a catalytic amount of Me$_3$COK.


Nicotine and its analogs represent a synthetic challenge to the chemist. Few examples of the enantioselective synthesis of nicotine and substituted nicotine analogs have been
reported. The selective chemical functionalization of nicotine at the pyridine or the pyrrolidine ring is difficult to control.\textsuperscript{40} More specifically, formation or preservation of the chiral pyrrolidine moiety has stimulated a great deal of synthetic activity over the years. As previously stated, individual enantiomers were obtained by resolution via the crystallization of diasteromeric salts.\textsuperscript{41} In an attempt to avoid the use of a resolution to obtain enantiopure material, chemists have been investigating the reactivity and substitution of natural nicotine.

\textit{I. 2. d. i. Early work on the reactivity of nicotine (1).}

The reactivity of (\textit{S})-nicotine (1) towards bases was tested by Tschitschibabin and Kirssanov in 1924 (Scheme 13).\textsuperscript{42} The 6- and 2-aminonicotines (66 and 67, respectively) were prepared by treatment with sodium and potassium amide. Under these reaction conditions the chiral center was racemized.

\begin{center}
\textbf{SCHEME 13. Reactivity of natural nicotine with sodium amide.}
\end{center}

These aminonicotines 66 and 67 were subsequently converted to the chloronicotines 68 and 69 using HCl and to the hydroxynicotines 70 and 71 via a arenediazonium salt (Scheme 14). Two 6-halonicotines (-Br, -F) analogs were prepared in the same way by diazotization of 6-aminonicotine, followed by the treatment of the diazonium salt with Br₂ in 48% HBr/HOAc, or 48% HBF₄, respectively.²⁵,⁴³

In 1981, Seeman and co-workers studied the radical and organometallic⁴⁴ methylation of nicotine. The reaction of 1 with two equivalents of methyllithium in refluxing toluene afforded 72, 73 and 74 in 17%, <1% and 19% yields, respectively, with 32% of recovered nicotine (1) (Scheme 15). In 1983, they followed up with another report discussing possible pathways for the loss of optical purity during the reaction that could occur according to three different pathways (Scheme 16).⁴⁴ Seeman and coworkers showed that the starting material does not racemize under the reaction conditions (Scheme 16, a) as the recovered nicotine was nearly optically pure. The methylnicotine could also racemize, (Scheme 16, b) but the treatment of methylnicotine of high optical purity with methyllithium (or other alkyl- or aryl-lithiums) did not lead to racemization.⁴⁵ It is noteworthy that 1 is also optically stable toward
LDA. It was postulated that equilibrium might exist between intermediate 77 and ring-opened intermediate 78 leading to racemization (Scheme 16, c).

Scheme 15. Radical and organometallic methylation of nicotine.

Scheme 16. Proposed mechanisms for the loss of optical purity in the radical and organometallic methylation of nicotine (1).
SCHEME 17. Pyrrolidine ring-opening with chloroformates.

In 1999, Cosford and Bleicher demonstrated the pyrrolidine would ring-open with inversion of configuration upon reaction with chloroformates and subsequently reclose with net retention of configuration (Scheme 17). Nicotine’s two nitrogen atoms are nucleophilic and can compete for electrophiles. When treating nicotine with iodomethane, a 2.5:1 ratio of monoalkylated products 80 and 81 was observed (Scheme 18).

SCHEME 18. Reactivity of nicotine with iodomethane.

The examples above demonstrate that the selective chemical functionalization of the pyridine ring of nicotine is difficult to control. Asymmetric chemical preparations of synthetic nicotine derivatives using nicotine as a starting material are rare. In 1997, Roduit and coworkers optimized the biotransformation of (S)-nicotine (1) to (S)-6-hydroxynicotine (70) using Arthrobacter oxydans NRRL-B-3603 as a micro-organism (Scheme 19).
hydroxynicotine (70) was isolated in 51% yield and up to 30 g/L were produced. Starting from 70, they were then able to synthesize (S)-6-chloronicotine (68) and (S)-5,6-dichloronicotine (83) in good yield with total retention of the chiral center.

**SCHEME 19. Roduit’s semi-synthetic transformation of (S)-nicotine.**

The enantioselective formation of nicotine (1) and substituted nicotines were recently marked by three milestones: the enantioselective syntheses of the tobacco alkaloids reported by Lebreton and co-workers and later by Helmchen and co-workers, and the enantioselective formation of substituted nicotines directly from natural (S)-nicotine by Comins and coworkers. These recent advances in nicotine chemistry are reported below.

*I. 2. d. ii. Enantioselective synthesis of tobacco alkaloids by Lebreton*

In 2000, Lebreton and coworkers described a short synthesis of (R)-nicotine (Scheme 20).50,51 Allylation of aldehyde 24 with B-allyldiisopinocamphenolborane afforded
homoallylic alcohol 84 in excellent optical purity. Chiral azide 85 was obtained from alcohol 84 without racemization. The pyrrolidine was constructed using an intramolecular hydroboration-cycloaddition of chiral azido-olefin 85 to yield (R)-nornicotine (3) that was methylated via the formation and reduction of its N-ethylcarbamate. (R)-Nicotine (1) was obtained in optical purity greater than 92% and in 15% overall yield.

SCHEME 20. Short synthesis of (R)-nicotine by Lebreton.

I. 2. d. iii. Enantioselective synthesis of (+)- and (-)-nicotine by Helmchen et al.

In 2005, Helmchen and coworkers reported the synthesis of nicotine (1) with ee greater than 99% via an asymmetric Ir-catalysed allylic amination followed by a ring closing metathesis (Scheme 21).
SCHEME 21. Enantioselective synthesis of (+)- and (-)-nicotine by Helmchen et al.

I. 2. d. iv. Comins’ C-4 regioselective substitution of the pyridine ring of nicotine

In 2005, our group discovered that the attack of dialkyl cuprates on the N-pivaloylpyridinium salt of nicotine (90) led to the exclusive formation of N-pivaloyl-1,4-dihydronicotines 91a-e and g as single diastereomers (Scheme 22). Subsequent rearomatization of dihydropyridines 91a-h with elemental sulfur yielded 4-substituted nicotines 92a-h without loss of optical purity.
SCHEME 22. Synthesis of C-4 substituted nicotine derivatives via an N-acylpyridinium salt of (S)-nicotine.
I. 2. d. iv. Comins’ reductive disilylation of nicotine

The reductive disilylation of nicotine afforded 1,4-bis(trimethylsilyl)-1,4-dihydronicotine \(93\) in 95 % yield after high vacuum distillation (Scheme 23).\(^5^5\),\(^5^6\) Several reactions of \(93\) were investigated and the results are summarized in Scheme 24. Detailed work aimed at proving the optical purity of the synthesized molecules will be reported in Chapter II, Section II.1.

SCHEME 23. Reductive disilylation of (S)-nicotine (1).
I. 3. Synthesis of SIB-1508Y

(S)-(−)-5-Ethynyl-3-(1-methyl-2-pyrrolidinyl)pyridine maleate (SIB-1508Y, 13), also known as Altinicline, was discovered and developed at SIBIA Neurosciences Inc. SIB-1508Y possesses the nicotine core structure that is substituted at the C-5 position with an acetylene group. This fairly simple compound is an agonist of human neuronal nAChRs. Functional assay studies led to the preclinical development of 13 for the treatment of Parkinson’s disease (PD); although, clinical trials in PD patients were stopped in Phase II in 1999. SIB-1508Y, however, is still the subject of ongoing research and its reported syntheses represent inventive and classical ways to construct or substitute the nicotine ring system.

I. 3. a. First synthesis of SIB-1508Y (13)

The first synthesis of SIB-1508Y (13) was reported by Cosford and coworkers in 1996. Ethyl 5-bromonicotinate (15a) was treated with the enolate of 1-vinylpyrrolidinone (58) to form 59 (Scheme 25). The subsequent hydrolysis of the enamine and decarboxylation allowed the ring closure of the intermediate to afford imine 61. Compound 61 was then reduced with NaBH₄ in the presence of CBz-D-proline, and the pyrrolidine nitrogen was methylated to give enantiomerically enriched 5-bromonicotine (62) (30 % ee) in good yield. Two consecutive recrystallizations of 62 as the diastereomeric dibenzoyl-L-tartrate salt furnished 62 in >99 % ee. The palladium-catalyzed Sonogashira cross-coupling reaction of 62 with 2-methyl-3-butyne-2-ol provided protected ethyne 101 in 92% yield. Finally, base-
catalyzed deprotection\textsuperscript{59} of the acetylene afforded 13. Soon after, Cosford described a method for the racemization of enantiomerically enriched (\textit{R})-62 to produce a mixture suitable for use in their classical resolution procedure.\textsuperscript{60} This route left room for improvement since the enantiomerically pure material was obtained after several costly fractional crystallizations.

\textbf{SCHEME 25. Cosford’s 1996 synthesis of SIB-1508Y.}
I. 3. b. First enantioselective synthesis of SIB-1508Y

In 2001, Lebreton and coworkers offered an intelligent enantioselective construction of the pyrrolidine ring of 5-bromonicotine (62) (Scheme 26). 61 5-Bromonicotinic acid (102) was converted to the corresponding aldehyde. 62 Allylation of 103 with allyl bromide in the presence of zinc gave racemic allyl alcohol 104 which was subsequently oxidized under the Dess-Martin oxidation conditions to 105. 63 The enantiomerically pure alcohol 104 was obtained using diisopinocamphenylchloroborane as the reducing agent. 64 Nucleophilic displacement of the corresponding mesyl alcohol by azide anion occurred with complete inversion of configuration. An intramolecular hydroboration-cycloaddition tandem reaction 65 of azido olefin 108 completed the formation of 62 in a 94% ee. SIB-1508Y (13) was synthesized in ten steps with an overall 18% yield and constituted the first enantioselective synthesis of the nAChR agonist.
I. 3. c. Synthesis of SIB-1508Y from natural nicotine

Finally, in 2006, our group reported a novel approach for the synthesis of SIB-1508Y (13) using (S)-nicotine (1) as an inexpensive starting material (Scheme 27).66 These methods
avoid the use of fractional crystallization of a diastereomeric salt, as the chiral integrity of the pyrrolidine ring is conserved throughout the synthesis. Treatment of (S)-nicotine (1) with lithium powder and chlorotrimethylsilane afforded 1,4-bis(trimethylsilyl)-1,4-dihydronicotine (93) in high-yield.\textsuperscript{55,56} Acylation of 93 with methyl carbonate in the presence of TBAF (10\%) gave the 1-acyl-1,4-dihydronicotine 95 (98\% ee). Formylation\textsuperscript{67} of 95 under Vilsmeier-Haack conditions afforded the desired C-5 aldehyde 109. The N-carbomethoxy group was removed under mild conditions (TEA, MeOH, rt, 1 d) to provide, after rearomatization using elemental sulfur in refluxing toluene, 5-formylnicotine (111). The synthesis was completed by using Seyferth-Gilbert homologation\textsuperscript{68} to convert 111 to 13. SIB-1508Y (13) was synthesized in six steps with an overall 20\% yield and constituted the first enantioselective synthesis of 13 directly from natural nicotine.

\textbf{SCHEME 27.} Comins’ first synthesis of SIB-1508Y (13) from natural nicotine (1).
In the same vein, we decided to investigate other methods for the regioselective substitution of the pyridine ring of natural nicotine. Herein, regioselective substitutions of the pyridine ring by directed lithiation of (S)-nicotine will be described. Efforts are underway to expand the scope of these methods and to apply them to the preparation of potential pharmaceuticals, insecticides, synthetic intermediates and novel ligands for catalytic asymmetric synthesis. Nicotine was used as an interesting building block for the synthesis of SIB-1508Y (Chapter III.1.), synthesized enantiomerically pure in only five steps, and for the synthesis of (S)-brevicolline (Chapter III.2.), a natural product of the β-carboline family synthesized in only six steps. Our goal is to transform inexpensive, commercially available (S)-nicotine from an underutilized natural product to a useful member of the chiral pool.
CHAPTER II: 

SYNTHESIS OF NICOTINE DERIVATIVES FROM 
NATURAL NICOTINE

In 1970, Sulzbach reported the reductive disilylation of pyridine with alkali metals and trimethylsilyl chloride.\textsuperscript{69} 1,4-Bis(trimethylsilyl)-1,4-dihydropyridine was isolated in 34 % yield and was found to be extremely air sensitive; oxidation occurred on exposure to air to give 4-(trimethylsilyl)pyridine. In 1984, Tsuge\textsuperscript{70} reinvestigated this reaction and found that the reaction of 1,4-dihydropyridine with aldehydes and ketones in the presence of a catalytic amount of tetrabutylammonium fluoride (TBAF) affords a variety of 3-alkylpyridines.

The reductive disilylation of nicotine afforded 1,4-bis(trimethylsilyl)-1,4-dihydronicotine (93) in 95 % after high vacuum distillation. Compound 93 oxidized readily in contact with air to give 4-(trimethylsilyl)nicotine (94a) (Scheme 28). Similarly, compound 94b is easily accessible from nicotine (1) via reductive disilylation of nicotine using allyl(dimethyl)silyl
chloride. Several reactions of 93 were investigated and the results are summarized in Scheme 29.

SCHEME 29. Reactivity of 1,4-bis(trimethylsilyl)-1,4-dihydronicotine (93).
To be of interest, these methods must afford nicotine derivatives with no significant racemization. To calculate the enantiomeric excess at the outcome of these reactions, some characteristic nicotine derivatives were resynthesized as a racemic mixtures. It is noteworthy to mention that the enantiopure products could not be racemized by the method reported by Bowman and coworkers in 1982.\textsuperscript{38} Racemic nicotine, however, could be obtained by refluxing ($S$)-nicotine with NaH in xylenes for 15 h (Scheme 30).

\begin{center}
\includegraphics[width=0.8\textwidth]{scheme30.png}
\end{center}

**SCHEME 30.** Racemization of ($S$)-nicotine.

\begin{center}
\includegraphics[width=0.8\textwidth]{scheme31.png}
\end{center}

**SCHEME 31.** Desilylation of 94a and 94b using TBAF and HPLC results.
The enantiopurity of 94a was obtained by HPLC and optical rotation. Compound 94 was desilylated using TBAF in THF (Scheme 31), and the sample obtained was analysed by HPLC against a sample of racemic nicotine. Compound 94a was obtained in 73% ee. The analogous reaction using allylchlorodimethylsilane afforded 4-(allyldimethylsilyl)nicotine (94b) in 86% ee by HPLC. This partial racemization is presumably due to free radical intermediates generated during the air oxidation step. To prove that no significant racemization occurs on formation of dihydronicotine 93, characteristic samples were resynthesized racemically and enatiomerically. The reaction of 93 with methylcarbonate in the presence of a catalytic amount of TBAF led to the formation of 1,4-dihydronicotine 95 in 91% yield and 98% ee (Scheme 29). The reaction of 93 with benzaldehyde in the presence of TBAF gave 56% yield of 5-benzylnicotine (98a) with a 98% ee. In conclusion, a variety of nicotine analogs can be synthesized from dihydronicotine 93 in an enantioselective manner.
II. 2. Regioselective C-2 and C-6 Substitution of (S)-Nicotine and Nicotine Derivatives

II. 2. a. Regioselective C-6 Substitution of (S)-Nicotine and Nicotine Derivatives

Lithiation of aromatic and heteroaromatic compounds has been widely used to introduce various functional groups. This reaction is a very attractive functionalization method as electrophilic substitutions are often difficult to achieve on \( \pi \)-deficient heterocycles. In order to investigate regioselectivity in the deprotonative metallation of nicotine, several metallating agents were screened. The choice of base was found to play a crucial role in accessing the desired lithiopyridine intermediates.

SCHEME 32. Fort’s unimetal complexation of 2-chloropyridine (112), and its complexation of (S)-nicotine (1).
Recent efforts toward functionalization of pyridines have focused on the development of directed ortho-metallation methods (DoM effect).\textsuperscript{75} The mechanism of this selective reaction was generally assumed to proceed via the well-known complex-induced proximity effect (CIPE) between the ortho-directing group and the lithiating agent promoting introduction of lithium at the ortho position. In 2000, Fort and co-workers reported a new base composed of \( n \text{-BuLi} \) and \( \text{Me}_2\text{N(CH}_2\text{)}_2\text{OLi} \).\textsuperscript{76} This unimetal complex called \( n \text{-BuLi}-\text{LiDMAE} \) induced a regioselective lithiation of pyridine derivatives even when an ortho-directing group, such as a chlorine, was present on the heterocyclic ring (Scheme 32). This selectivity strongly contrasted results observed with the well-known lithium diisopropylamide (LDA) and alkyllithium bases, which abstracted exclusively the hydrogen at C-3 in agreement with the DoM effect. The complete inhibition of the DoM effect of the C-2 chlorine of 112 with \( n \text{-BuLi}-\text{LiDMAE} \) was explained by the formation of aggregates between \( n \text{-BuLi}-\text{LiDMAE} \) and the substrate via lithium complexation by the pyridine nitrogen atom. The metallation had to be performed in apolar, non-coordinating solvents such as hexane. Aggregates were assumed first to deliver \( n \text{-BuLi} \) near the C-6 proton of 6-chloropyridine (112), and second to ensure stabilization of the formed C-6 lithiated intermediate.
The reaction of nicotine with $n$-BuLi-LiDMAE resulted in the selective deprotonation at the C-6 position of the pyridine ring (Scheme 32). The lack of lithiation at the C-2 position of the pyridine is probably due to steric hindrance resulting from the pyrrolidine ring at C-3. Initially, subsequent reaction with hexachloroethane afforded (S)-6-chloronicotine (68) was obtained in only 39% yield (Table 1). It is noteworthy to emphasize that this substitution of (S)-nicotine happens without racemization. The main side-reaction was the substitution by a butyl group onto the pyridine ring at the C-6 position. Interested by the potential synthetic utility of compound 68, solvent systems, number of equivalents of base and temperature were varied. The reaction’s outcome was found to be highly sensitive to solvents. When THF was used as a cosolvent (needed to dissolve the electrophile) (entry 2), classical nucleophilic aromatic substitution by $n$-BuLi at C-6 to give 6-$n$-butynicotine (114) was observed due to aggregate disruption. Toluene (entry 5), a less polar solvent, did not disrupt the aggregate thus providing a better cosolvent for this reaction. A lower temperature during the deprotonation (entries 3 and 5) limited the addition of the butyllithium to the pyridine ring.

### TABLE 1. Formation of (S)-6-chloronicotine (68).

<table>
<thead>
<tr>
<th>entry</th>
<th>$n$-BuLi (equiv)</th>
<th>T (°C)</th>
<th>solvent system</th>
<th>68, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.0</td>
<td>0</td>
<td>hexanes</td>
<td>39 - 60</td>
</tr>
<tr>
<td>2</td>
<td>6.0</td>
<td>0</td>
<td>hexanes/THF</td>
<td>36</td>
</tr>
<tr>
<td>3</td>
<td>6.0</td>
<td>-20</td>
<td>hexanes</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>5.4</td>
<td>0</td>
<td>hexanes</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>5.4</td>
<td>-20</td>
<td>hexanes/toluene</td>
<td>87</td>
</tr>
</tbody>
</table>

*R*Eactions were run on a 1.0 mmol scale.
affording higher yields of 6-chloronicotine (68). The synthesis of 68 was successfully performed on a large scale (20 mmol) in excellent yield.

Next, the reaction of the lithiated intermediate with various representative electrophiles was examined (Table 2). The addition of electrophiles to the heteroaryllithium was very exothermic, which facilitated the formation of the undesired regioisomer 116. The low yields of bromination and iodination (entries 2, 3, and 5) were due to decomposition of the starting material or butyl addition. The use of C₂Br₂Cl₄ (entry 4) afforded (S)-6-bromonicotine (115b) in good yield. Among other examples, (S)-6-(dimethylphenylsilyl)nicotine (115d) and (S)-6-(tributylstannyl)nicotine (115f) (entries 6 and 8) were obtained in high yield since these groups cannot be displaced by n-BuLi to form byproduct 114. The chlorination of substituted analogues was performed as well and afforded the C-6 regioisomer preferably (entries 10-12).
TABLE 2. Versatility of the lithiation of nicotine and nicotine derivatives with \( n\)-BuLi-LiDMAE.

![Diagram showing the reaction of nicotine with \( n\)-BuLi and LiDMAE](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>nicotine, R</th>
<th>electrophile</th>
<th>115, %</th>
<th>116, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ( ^b )</td>
<td>1, H</td>
<td>( \text{C}_2\text{Cl}_6 )</td>
<td>115a, 87</td>
<td>116a, 4</td>
</tr>
<tr>
<td>2</td>
<td>1, H</td>
<td>NBS</td>
<td>115b, 27</td>
<td>( ^c )</td>
</tr>
<tr>
<td>3</td>
<td>1, H</td>
<td>( \text{Br}_2 )</td>
<td>115b, 6</td>
<td>( ^c )</td>
</tr>
<tr>
<td>4 ( ^b )</td>
<td>1, H</td>
<td>( \text{C}_2\text{Br}_2\text{Cl}_4 )</td>
<td>115b, 67</td>
<td>116b, 21</td>
</tr>
<tr>
<td>5 ( ^b )</td>
<td>1, H</td>
<td>( \text{I}_2 )</td>
<td>115c, 55</td>
<td>116c, 4</td>
</tr>
<tr>
<td>6</td>
<td>1, H</td>
<td>( \text{PhSi}(\text{Me})_2\text{Cl} )</td>
<td>115d, 92</td>
<td>( ^c )</td>
</tr>
<tr>
<td>7</td>
<td>1, H</td>
<td>( \text{MeSSMe} )</td>
<td>115e, 70</td>
<td>116e, 6</td>
</tr>
<tr>
<td>8</td>
<td>1, H</td>
<td>( \text{ClSnBu}_3 )</td>
<td>115f, 55</td>
<td>( ^c )</td>
</tr>
<tr>
<td>9 ( ^b )</td>
<td>1, H</td>
<td>ethyl formate</td>
<td>115g, 26</td>
<td>( ^c )</td>
</tr>
<tr>
<td>10</td>
<td>94a, SiMe( _3 )</td>
<td>( \text{C}_2\text{Cl}_6 )</td>
<td>115h, 53</td>
<td>( ^c )</td>
</tr>
<tr>
<td>11</td>
<td>94b, Si(allyl)Me( _2 )</td>
<td>( \text{C}_2\text{Cl}_6 )</td>
<td>115i, 56</td>
<td>( ^c )</td>
</tr>
<tr>
<td>12</td>
<td>94c, SiMe( _2\text{Ph} )</td>
<td>( \text{C}_2\text{Cl}_6 )</td>
<td>115j, 43</td>
<td>( ^c )</td>
</tr>
</tbody>
</table>

\( ^a \) Reactions were run on a 1.0-2.0 mmol scale. \( ^b \) Spectral data matched the literature\(^{77,78} \). \( ^c \) Not observed.

**II. 2. b. Regioselective C-2 Substitution of (S)-Nicotine and Nicotine Derivatives\(^{72,73} \)**

Due to the bulky pyrrolidine ring at the C-3 position, functionalization of the C-2 position of the pyridine ring of nicotine appeared to be the most challenging via lithiation. The selectivity of various bases was investigated. In 1999, Kondo and coworkers reported the chemoselective formation of arylzincates using lithium \( \text{di-tert-butyldimethylpiperidinoo} \) zincate (TMP-Zincate) prepared from the addition of \( \text{di-tert-butyldimethylpiperidinoo} \) zincate.
to a solution of lithium tetramethylpiperidide (LiTMP).\textsuperscript{79} Most interestingly, $\alpha$-metallation of $\pi$-deficient aza-aromatics proceeded smoothly at room temperature to give the corresponding heteroarylzincates, which then reacted with various electrophiles. The $\alpha$-metallation of pyridine followed by treatment with I$_2$ gave 2-iodopyridine in 76\% yield. Based on this precedent, the $\alpha$-metallation of nicotine (1) using TMP-zincate was attempted (Table 3). When 1.0 equivalent of TMP-zincate was used as the base followed by addition of iodine, (S)-2-iodonicotine (116c) was obtained in only 19\% yield, and (S)-4-iodonicotine (117) was formed in 24\% yield. In all attempts, the reaction never went to completion and starting material was recovered.

**TABLE 3. Regioselectivity in the reaction of nicotine with TMP-Zincate.**

![Reaction Scheme]

<table>
<thead>
<tr>
<th>entry$^a$</th>
<th>TMP-Zincate (equiv)</th>
<th>116c, %</th>
<th>117, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0</td>
<td>19</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>2.0</td>
<td>7</td>
<td>20</td>
</tr>
</tbody>
</table>

$^a$ Reactions were run on a 1.0-2.0 mmol scale.
TABLE 4. Electrophile-dependent regioselectivity in the reaction of nicotine with LiTMP.

![Chemical Structure]

<table>
<thead>
<tr>
<th>entry</th>
<th>LiTMP (equiv)</th>
<th>electrophile</th>
<th>115, %</th>
<th>116, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.5</td>
<td>TMSCl</td>
<td>115k, 6</td>
<td>116k, 38</td>
</tr>
<tr>
<td>2</td>
<td>2.0</td>
<td>TMSCl</td>
<td>115k, 12</td>
<td>116k, 41</td>
</tr>
<tr>
<td>3</td>
<td>3.0</td>
<td>TMSCl</td>
<td>115k, 24</td>
<td>116k, 64</td>
</tr>
<tr>
<td>4</td>
<td>3.0</td>
<td>Cy3SnCl</td>
<td>-b</td>
<td>116l, 94</td>
</tr>
<tr>
<td>5</td>
<td>3.0</td>
<td>N-Methyl-N-pyridin-2-yl-benzamide</td>
<td>decomposition</td>
<td>-</td>
</tr>
</tbody>
</table>

*a Reactions were run on a 1.0-2.0 mmol scale. b Not observed.

FIGURE 6. Possible complexation of LiTMP favoring the deprotonation at the C-2 position of the pyridine ring of nicotine.

Reactivity of LiTMP with nicotine (1) was then investigated (Table 4). When nicotine was added to a solution containing both the base and chlorotrimethylsilane (TMSCl), the C-2 substituted nicotine 116k was obtained as the major product in 64% yield and C-6 substituted
115k in 24% yield (Table 4, entry 3). To rationalize these results, it is proposed that LiTMP coordinates at the pyrrolidine nitrogen in the transition state (Figure 6). The C-2 position of the pyridine ring is selectively deprotonated versus the C-6 position. Once the TMS group is attached, the coordination of another LiTMP to the pyridine nitrogen seems to be unlikely because of a steric effect. This may explain why a disubstituted nicotine was not obtained. Variation of the number of equivalents of base showed that the best yield of 116k was achieved using 3.0 equivalents of LiTMP (Table 4, entry 3). Given this interesting regioselectivity, other electrophiles were tested. N-Methyl-N-pyridin-2-yl-benzamide, which would have allowed access to a phenyl ketone, was not stable in the presence of LiTMP, and starting material was recovered (entry 5). However, the installment of a versatile tin functionality was achieved with the synthesis of compound 116l in an excellent yield of 94% (entry 4). The synthetic utility of 116l and related compounds was investigated and will be reported in section II. 4. b.
II. 3. Regioselective substitution at the C-5, C-4 and C-2 positions of the pyridine ring of (S)-6-chloronicotine (68)\textsuperscript{81,82}

Uses of nicotine derivatives as potential drugs is a valuable subject of studies for chemists. In 1998, Wang and coworkers demonstrated that the order of receptor affinity was dependent of the ring position of an additional methyl group. The order is 6-methyl > 2’-methyl > 5-methyl > 2-methyl > 4-methyl.\textsuperscript{83} With an easy access to C-6 substituted nicotine in one step, the next challenge was to investigate the formation of C-5 substituted nicotines \textbf{118} from 6-chloronicotine (68).

The deprotonation of the C-5 position, using the well described ortho-directing effect of the chlorine, was first attempted. Surprisingly, the lithiation of 6-chloronicotine (68) could not be obtained using various number of equivalents of LDA. Treatment of 68 with 1.1 equivalent of the stronger base, LiTMP, in THF at -78 °C, followed by addition of the appropriate electrophile afforded substitution of the C-5 position of the pyridine ring in good yield (Table 5). The facile reaction allowed the introduction of numerous functional groups at the C-5 position. The addition of iodomethane (entry 8), however, repeatedly afforded a complex mixture of 6-chloro-5-methyl- and 6-chloro-5-ethyl-nicotine that could not be separated by chromatography. The boronic ester \textbf{118i} was apparently formed as observed by TLC, but decomposed very rapidly during workup and purification (entry 9).
TABLE 5. Substitution of the C-5 position of the pyridine ring of (S)-6-chloronicotine (68) by lithiation using LiTMP.

![Chemical Structure](image)

1) 1.1 equiv LiTMP, THF, -78 °C, 1 h
2) 1.2 equiv of E⁺, -78 °C, 1 h

<table>
<thead>
<tr>
<th>entry</th>
<th>electrophile, E⁺</th>
<th>118, E</th>
<th>yieldb, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I₂</td>
<td>118a, I</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>C₂Cl₆</td>
<td>118b, Cl</td>
<td>87d</td>
</tr>
<tr>
<td>3</td>
<td>C₂Br₂Cl₄</td>
<td>118c, Br</td>
<td>37</td>
</tr>
<tr>
<td>4</td>
<td>ClSiPhMe₂</td>
<td>118d, SiPhMe₂</td>
<td>45</td>
</tr>
<tr>
<td>5</td>
<td>MeSSMe</td>
<td>118e, SMe</td>
<td>63</td>
</tr>
<tr>
<td>6</td>
<td>ClSnBu₃</td>
<td>118f, SnBu₃</td>
<td>66</td>
</tr>
<tr>
<td>7</td>
<td>ethyl formate</td>
<td>118g, CHO</td>
<td>58</td>
</tr>
<tr>
<td>8</td>
<td>MeI</td>
<td>118h, Me</td>
<td>-c</td>
</tr>
<tr>
<td>9</td>
<td>pinB</td>
<td>118i, pinB</td>
<td>-c</td>
</tr>
</tbody>
</table>

a Reactions were run on a 0.25-3.0 mmol scale. b Isolated yield after radial PLC. c Reaction resulted in an inseparable mixture of 118h and (S)-6-chloro-5-ethylnicotine. d 118b was dehalogenated to afford nicotine using 10 % Pd/C, H₂ in MeOH in > 99% ee. e Product formed but was not stable to purification.

Next, 6-chloro-4-iodonicotine (119a) was thought to be easily accessible through an iodine dance reaction on 6-chloro-5-iodonicotine (118a). However, multiple attempts using LDA or LiTMP in various amounts led to desired product formation in only very low yield, whereas diiododated 121 and C-2 iodonated 120a were observed (Table 6). More interestingly, treatment of 6-chloronicotine (68) with 3.0 equivalents of LiTMP followed by the addition of only 1.0 equivalent of iodine resulted in the near quantitative formation of 119a (Table 7). An attempt to use another electrophile, C₂Br₂Cl₄, under the same conditions failed and afforded (S)-5-bromo-6-chloronicotine (118c) and (S)-2,5-dibromo-6-chloronicotine.
TABLE 6. Attempts to form (S)-6-chloro-4-iodonicotine (119a) via an iodine dance reaction on (S)-6-chloro-5-iodonicotine (118a).

![Chemical Structures]

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>product</th>
<th>ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0 equiv LDA, THF, -78 °C, 2 h</td>
<td>121</td>
<td>-b,c</td>
</tr>
<tr>
<td>2</td>
<td>1.0 equiv LDA, THF, -78 °C, 30 min</td>
<td>118a:119a</td>
<td>2:1</td>
</tr>
<tr>
<td>3</td>
<td>2.0 equiv LDA, THF, -78 °C, 2 h</td>
<td>118a:119a:121</td>
<td>2:1:1</td>
</tr>
<tr>
<td>4</td>
<td>1.2 equiv LiTMP, THF, -78 °C, 1 h</td>
<td>118a:120a:121</td>
<td>1:2:2</td>
</tr>
</tbody>
</table>

a Reactions were run on a 0.1-0.5 mmol scale. b 52% isolated yield after radial PLC. c Traces of 119a. d Ratio determined by 1H NMR.

TABLE 7. Attempts at an iodine dance reaction from (S)-6-chloronicotine (68).

![Chemical Structures]

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>product</th>
<th>ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.0 equiv LiTMP, THF, -78 °C, 1 h</td>
<td>121:120a</td>
<td>1:2</td>
</tr>
<tr>
<td></td>
<td>1.0 equiv of I2, -78 °C, 1 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3.0 equiv LiTMP, THF, -78 °C, 1 h</td>
<td>120a:119a, 121</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td></td>
<td>1.0 equiv of I2, -78 °C, 1 h</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a Reactions were run on a 0.1-0.5 mmol scale. b 95 % isolated yield of 120a after radial PLC. c Crude product contained traces of 119a and 121. d Ratio determined by 1H NMR.

The proposed halogen dance mechanism for the formation of 120a is depicted in Scheme 33. The first lithiation occurring at C-5 gives pyridyllithium I which on addition of iodine affords 118a. A second equivalent of LiTMP deprotonates the C-2 position of 118a. This intermediate (II) might be stabilized by complexation to the pyrrolidine nitrogen. The C-2
lithiated intermediate II reacts with another molecule of 118a by abstracting the iodine at C-5 to form the diiodide 121 and the C-5 lithiated 6-chloronicotine intermediate I. Intermediate I then attacks 121 and affords C-5 lithiated 2-iodo-6-chloronicotine intermediate III, and 118a which reenters the reaction cycle. Quenching with a saturated aqueous solution of sodium bicarbonate provides compound 120a in very good yield. To provide evidence for this mechanism, 6-chloro-5-iodonicotine (118a) was added to a mixture of 1.0 equivalent of 2,2,6,6-tetramethylpiperidine with 2.0 equivalents of LiTMP at -78 °C for 1 h. After workup, 6-chloro-2-iodonicotine (120a) was the major product observed by crude 1H NMR (purity > 95 %).
Although other C-2 substituted 6-chloronicotines can likely be prepared from 120a using lithium-halogen exchange or cross-coupling reactions, a direct route from 68 was developed. Treatment of 6-chloronicotine (68) with $n$-BuLi-LiDMAE, the base complex reported by Fort and coworkers,\textsuperscript{76} in toluene at -78 °C, followed by addition of the electrophile afforded the
desired products in good yields (Table 8). It is noteworthy to add that the same reaction in hexanes did not lead to product formation, and starting material was recovered. The use of the more polar solvent, toluene, is believed to disrupt the aggregate and allow deprotonation at C-2.

**TABLE 8. Substitution of the C-2 position of the pyridine ring of (S)-6-chloronicotine (68) using \( n \)-BuLi-LiDMAE.**

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry(^a)</th>
<th>electrophile, E(^+)</th>
<th>120, E</th>
<th>yield(^b), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>C(_2)Cl(_6)</td>
<td>120b, Cl</td>
<td>72(^c)</td>
</tr>
<tr>
<td>2</td>
<td>MeSSMe</td>
<td>120c, SMe</td>
<td>53</td>
</tr>
<tr>
<td>3</td>
<td>ClSnBu(_3)</td>
<td>120d, SnBu(_3)</td>
<td>42</td>
</tr>
<tr>
<td>4</td>
<td>ethyl formate</td>
<td>120e, CHO</td>
<td>57</td>
</tr>
</tbody>
</table>

\(^a\) Reactions were run on a 1.0 mmol scale.\(^b\) Isolated yield after radial PLC.\(^c\) 120b was dehalogenated to afford nicotine using 10 % Pd/C, H\(_2\), NaOH in MeOH in > 99 % ee.
TABLE 9. Regioselective substitution at the C-4 position of the pyridine ring of (S)-6-chloronicotine (68).

![Chemical Reaction Diagram]

<table>
<thead>
<tr>
<th>entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>electrophile, E&lt;sup&gt;+&lt;/sup&gt;</th>
<th>119, E</th>
<th>yield&lt;sup&gt;b&lt;/sup&gt;, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I&lt;sub&gt;2&lt;/sub&gt;</td>
<td>119a, I</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>D&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>119b, D</td>
<td>79</td>
</tr>
<tr>
<td>3</td>
<td>C&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;6&lt;/sub&gt;</td>
<td>119c, Cl</td>
<td>63&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>C&lt;sub&gt;2&lt;/sub&gt;Br&lt;sub&gt;2&lt;/sub&gt;Cl&lt;sub&gt;4&lt;/sub&gt;</td>
<td>119d, Br</td>
<td>27</td>
</tr>
<tr>
<td>5</td>
<td>ethyl formate</td>
<td>119e, CHO</td>
<td>62</td>
</tr>
<tr>
<td>6</td>
<td>ClSnBu&lt;sub&gt;3&lt;/sub&gt;</td>
<td>119f, SnBu&lt;sub&gt;3&lt;/sub&gt;</td>
<td>51</td>
</tr>
<tr>
<td>7</td>
<td>MeSSMe</td>
<td>119g, SMe</td>
<td>34</td>
</tr>
<tr>
<td>8</td>
<td>PhCHO</td>
<td>119h-i, CH(OH)Ph</td>
<td>65&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reactions were run on a 0.5-3.0 mmol scale. <sup>b</sup> Isolated yield after radial PLC. <sup>c</sup> 119c was dehalogenated to afford nicotine using 10% Pd/C, H<sub>2</sub>, NaOH in MeOH in > 99% ee. <sup>d</sup> 1:1 ratio of diastereomers.

The formation of 4-substituted 6-chloronicotines 119a-i was achieved by simple treatment of 6-chloronicotine (68) with 1.1 equivalents of n-BuLi at -78 °C (Table 9). In particular, 6-chloro-4-iodonicotine (119a) was synthesized in 80% yield (entry 1).

Finally, there was an interest to develop a methodology for the synthesis of C-4 substituted 5-chloronicotines. (S)-5,6-Dichloronicotine (118b) was treated with zinc powder in hot acetic acid to afford (S)-5-chloronicotine (122a) in 45% yield with only 3% of the over-reduced product, nicotine (1) (Table 10, entry 1). Switching the solvent to a 1.0 M solution of HCl in acetic acid improved the yield of the desired product to 65%, while reducing the reaction time to 2 h (entry 2). The same reaction was carried out on (S)-4,6-dichloronicotine (119c), but led to exclusive formation of (S)-6-chloronicotine (68) and (S)-
4-chloronicotine was not observed. Reduction of (S)-5-bromo-6-chloronicotine (119c) under the same reaction conditions was not regioselective and afforded a 2:1 ratio of 68:122b (entries 3-4).

**TABLE 10. Regioselective dehalogenation.**

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>product</th>
<th>ratio$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>118b, 4.0 equiv Zn, AcOH, 70 °C, 8 h</td>
<td>122a : 1</td>
<td>15:1 (45% : 3%)$^b$</td>
</tr>
<tr>
<td>2</td>
<td>118b, 4.0 equiv Zn in 1.0 M HCl in AcOH, 60 °C, 2 h</td>
<td>122a : 1</td>
<td>13: 3(65% : 12%)$^b$</td>
</tr>
<tr>
<td>3</td>
<td>118c, 4.0 equiv Zn, in 1.0 M HCl in AcOH, 60 °C, 2 h</td>
<td>68:122b</td>
<td>2 :1</td>
</tr>
<tr>
<td>4</td>
<td>118c, 4.0 equiv Zn, AcOH, rt, 10 h</td>
<td>68:122b</td>
<td>1 :1</td>
</tr>
</tbody>
</table>

$^a$ Reactions were run on a 1.0 mmol scale. $^b$ Isolated yield after radial PLC. $^c$ Ratio determined by $^1$H NMR.
TABLE 11. Regioselective substitution at the C-4 position of the pyridine ring of (S)-5-chloronicotine (122a).

![Chemical structure of 122a and 123a-g]

<table>
<thead>
<tr>
<th>entry</th>
<th>electrophile, E⁺</th>
<th>123, E</th>
<th>yield⁺, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>D₂O</td>
<td>123a, D</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>I₂</td>
<td>123b, I</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>MeSSMe</td>
<td>123c, SMe</td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td>ethyl formate</td>
<td>123d, CHO</td>
<td>55</td>
</tr>
<tr>
<td>5</td>
<td>ClSnBu₃</td>
<td>123e, SnBu₃</td>
<td>58</td>
</tr>
<tr>
<td>6</td>
<td>ClSiMe₂Ph</td>
<td>123f, SiMe₂Ph</td>
<td>39</td>
</tr>
<tr>
<td>7</td>
<td>TMSCl</td>
<td>123g, TMS</td>
<td>56</td>
</tr>
</tbody>
</table>

a Reactions were run on a 0.1-0.5 mmol scale. b Isolated yield after radial PLC.

(S)-5-Chloronicotine (122a) was treated with 1.1 equivalent of n-BuLi in THF at -78 °C to effect a DoM reaction at C-4. Upon addition of electrophiles, C-4 substituted 5-chloronicotine derivatives 123a-g were obtained in moderate to good yield (Table 11).

In conclusion, a variety of novel C-2, C-4 and C-5 substituted 6-chloronicotines have been synthesized from (S)-6-chloronicotine (68) in moderate to high yield. The new methodologies described herein provide opportunities for exploring new routes to a variety of interesting and potentially useful compounds based on nicotine. Ongoing studies in our laboratories are directed toward the formation of derivatives and using those compounds as intermediates for cross-coupling reactions. Preliminary results will be reported in the following section.
II. 4. Cross-coupling reactions of nicotine derivatives and application to the synthesis of catalysts for the asymmetric addition of diethylzinc to aldehydes.

II. 4. a. Asymmetric dialkylzinc addition to carbonyl compounds

In the early years of organic chemistry, chemists became aware of the importance of chirality in nature. Producing mainly or exclusively one enantiomer was highlighted by the discovery of different biological activities of enantiomers. The development of asymmetric synthesis gave the opportunity to elaborate methods, reagents and reactions in order to prepare enantiomerically pure compounds. For example, the asymmetric organozinc additions to aldehydes allows the synthesis of chiral alcohols ubiquitous in the structures of natural products and drug compounds. Research on asymmetric organozinc additions to carbonyl compounds has became of wide interest since 1984, when Oguni and Omi reported on the reaction of diethylzinc with benzaldehyde in the presence of a catalytic amount of (S)-leucinol 124 (Figure 7). However, the enantioselectivity obtained was moderate with a 49% ee.85,86

\[
\begin{align*}
\text{(S)-leucinol, 124} & \\
\text{[(-)-DAIB], 125}
\end{align*}
\]

FIGURE 7. Catalysts for the asymmetric organozinc addition to carbonyl compounds.
In 1986, Noyori and co-workers reported the first highly enantioselective ligand for the dialkylzinc addition to carbonyl compounds using (-)-3-exo-dimethylaminoisoborneol [(-)-DAIB], \textbf{125}.\textsuperscript{87} It belongs to the amino alcohol class of ligands, which constitutes an important family of the chiral ligands for asymmetric synthesis. Scheme 34 shows the mechanism for the reaction catalyzed by \textbf{125} proposed by Noyori and coworkers in 1989.

**SCHEME 34. Proposed mechanism for the catalytic dimethylzinc addition to benzaldehyde.**

In the first step, the ligand reacts with the dialkylzinc to generate the zinc complex \textbf{126}. A second equivalent of dialkylzinc is needed to generate the zinc-based chiral Lewis acid complex \textbf{127}. Coordination of benzaldehyde converts the linear structure of the dialkylzinc
into an approximate tetrahedral structure depicted in 128. This reduces the bond order of the Zn-C bond and increases the nucleophilicity of the zinc alkyl groups (activation role). The chiral complex coordinates to the si face of the benzaldehyde, and the alkyl migrates to dissociate (S)-(1-phenyl)ethoxy-ZnMe from the chiral complex 130. An aqueous workup gives the desired alcohol.

II. 4. b. Nicotine based catalysts

There has been ongoing interest in the Comins group in developing chiral ligands based on nicotine. To this end, the synthesis of [3-(1-methylpyrrolidin-2-yl)-pyridin-2-yl]-phenylmethanol 131 (Figure 8) as a chiral catalyst for the addition of an alkyl group to carbonyl functionality was envisioned.

![Figure 8. Nicotine based amino alcohol.](image)

The target compound could be readily prepared using the key intermediate 2-iodonicotine (116c) which could be converted to the lithiated nicotine at the C-2 position of the pyridine ring by a lithium halogen exchange. The anion then would attack benzaldehyde to afford both diastereoisomers. Unfortunately, compound 116c could not be obtained in good enough yield using only a directed-lithiation reaction: TMP-zincate was only partially selective for
lithiation at C-6 over C-2, LiTMP afforded a selective lithiation at the C-2 position but the electrophile used must be unreactive to the metellation base.

The versatility of stannyl compound 116l was therefore studied. The cleavage of the carbon-tin bond could afford compound 116c via a tin-halogen exchange. However, in all attempts, this reaction gave very low yield (Table 12).

**TABLE 12. Tin-halogen exchange reaction on compound 116l.**

<table>
<thead>
<tr>
<th>entry</th>
<th>E⁺</th>
<th>E</th>
<th>yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>I₂</td>
<td>I</td>
<td>21</td>
</tr>
<tr>
<td>2</td>
<td>NBS</td>
<td>Br</td>
<td>decomposition</td>
</tr>
</tbody>
</table>

Our attention then turned to palladium chemistry. The number of applications of palladium chemistry to the synthesis of heterocycles has grown exponentially. The Stille reaction is the palladium-catalyzed cross-coupling between an organostannane and an organic electrophile, usually halides or triflates, to form a new C-C single bond. It is regarded as the most versatile method in Pd-catalyzed cross-coupling reactions with organometallic reagents for two reasons. First, the organostannanes are readily prepared, purified and stored. The groups that can be transferred from tin include alkyl, alkenyl, aryl, and alkynyl. Second, the Stille conditions are effective on a wide array of functional groups, including alcohols, halides, amines, the nitro group, aldehydes, ketones or esters, on either the organic or the
organometallic substrate. In contrast to the Suzuki, Kumada and Heck reactions that are under basic conditions, the Stille reactions can be run under neutral conditions. The pitfall of the Stille reaction is the toxicity of the stannanes, making it unsuitable for large scale synthesis. Usually, only one organic group from the tin is transferred as triorganotin halides are quite unreactive under these conditions. Among organotins, the order of reactivity follows the sequence alkynyl > vinyl > aryl > heteroalkyl > alkyl, which explains why organotributyltins or organotrimethyltins are good substrates in this reaction, the more reactive group being transferred first. Unfortunately, we have yet to synthesize nicotine bearing a trimethyl- or tributyl-tin group at C-2.

The Stille reaction on compound 116l was therefore attempted (Table 13). The statement that ‘the choice of catalyst can provide headaches’ was topical and can be extended to the choice of the co-catalyst(s) and solvent. The use of toluene proved to be efficient in this case. Solubility issues were encountered for the organotin substrate when 1,4-dioxane was used (entry 8). The use of nucleophiles to increase the reactivity of organotin species, via hypercoordinate intermediates, is a well established strategy.\(^88\) The addition of cesium carbonate to the reaction afforded a 53% yield of compound 116m.
TABLE 13. Optimization of the Stille reaction involving compound 116l.

<table>
<thead>
<tr>
<th>entry</th>
<th>Pd catalyst</th>
<th>% catalyst</th>
<th>solvent</th>
<th>yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(PPh₃)₄</td>
<td>0.5</td>
<td>chloroform, reflux, 48 h</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>Pd(PPh₃)₂(OAc)₂</td>
<td>0.5</td>
<td>chloroform, reflux, 48 h</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Pd(PhCH₂)(PPh₃)₂Cl</td>
<td>0.5</td>
<td>toluene, reflux, 48 h</td>
<td>16</td>
</tr>
<tr>
<td>4</td>
<td>Pd(PhCH₂)(PPh₃)₂Cl</td>
<td>0.5</td>
<td>THF, 48 h</td>
<td>16</td>
</tr>
<tr>
<td>5</td>
<td>Pd(PhCH₂)(PPh₃)₂Cl</td>
<td>10% Pd cat</td>
<td>toluene, reflux, 48 h</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.2 equiv CsF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Pd(PhCH₂)(PPh₃)₂Cl</td>
<td>10% Pd(cat)</td>
<td>toluene, reflux, 48 h</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10% CuCl₂</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10% LiCl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Pd(PhCH₂)(PPh₃)₂Cl</td>
<td>10% Pd(cat)</td>
<td>toluene, reflux, 48 h</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>c = 0.1 M</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Pd(PhCH₂)(PPh₃)₂Cl</td>
<td>10% Pd(cat)</td>
<td>dioxane, reflux, 48 h</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.2 equiv Cs₂CO₃</td>
<td>c = 0.1 M</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Pd(PPh₃)₂(Cl)₂</td>
<td>10% Pd cat</td>
<td>toluene, reflux, 48 h</td>
<td>40</td>
</tr>
<tr>
<td></td>
<td></td>
<td>10% KF.2H₂O</td>
<td>c = 0.1 M</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Pd(PhCH₂)(PPh₃)₂Cl</td>
<td>10% Pd(cat)</td>
<td>toluene, reflux, 48 h</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.2 eq Cs₂CO₃</td>
<td>c = 0.1 M</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10% Pd(cat)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Pd(PhCH₂)(PPh₃)₂Cl</td>
<td>2.2 equiv Cs₂CO₃</td>
<td>toluene, reflux, 48 h</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.2 equiv CuI</td>
<td>c = 0.1 M</td>
<td></td>
</tr>
</tbody>
</table>
TABLE 14. Reduction of 116m to 131.


<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NaBH₄, MeOH, 0°C to rt</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>L-Selectride, THF, 0 °C to rt</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>10% Pd/C, MeOH, H₂, balloon pressure or 42 psi</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>5% Pt/C, EtOH, H₂, balloon pressure</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>BH₃.THF, THF, 0 °C to r.t.</td>
<td>-</td>
</tr>
</tbody>
</table>

*no reaction

Finally, the reduction of compound 116m was then attempted. It was thought that the ortho pyrrolidine ring at C-3 could direct the reduction of 116m on one face of the ketone stereoselectively as opposed to the other. Unfortunately, no diastereoselectivity was observed using the conditions reported in Table 14. The reduction of 116m with sodium borohydride in methanol (entry 1) afforded a mixture of diastereomers in 89% yield. The two diasteromers could not be separated, and therefore, could not be tested as ligands for the asymmetric addition of diethylzinc to benzaldehyde.

FIGURE 9. Amino alcohols 119h and 119i.
Both diastereomeric amino alcohols 119h-i (Figure 9), whose syntheses were described previously (Section II.3. Table 9), were tested for the asymmetric addition of diethylzinc to benzaldehyde. Addition occurred in less than an hour, proving that those nicotinic ligands catalyzed the addition; however, determination of the enantiomeric excess using the chiral HPLC resulted in poor ee % of 6 and 12%, respectively (Table 15). Efforts are underway to synthesize other novel nicotinic ligands for catalytic asymmetric synthesis.
CHAPTER III:

EXPEDIENT FIVE-STEP SYNTHESIS OF
(S)-5-ETHENYL-3-(1-METHYL-2-
PYRROLIDINYL)PYRIDINE (SIB-1508Y) FROM
NATURAL NICOTINE

AND

A SIX-STEP SYNTHESIS OF (S)-BREVICOLLINE
FROM (S)-NICOTINE
III. 1. Expedient five-step synthesis of SIB-1508Y.

In order to utilize the methodologies described in Chapter II, the synthesis of (S)-(S)-5-ethynyl-3-(1-methyl-2-pyrrolidinyl)pyridine maleate (SIB-1508Y, 13) was investigated. After the report of our first synthesis of 13 in six steps from natural nicotine, we immediately followed with a second generation five-step synthesis of the nAChR agonist.

Two routes were investigated based on our recently developed regioselective C-5 halogenation of 6-chloronicotine (68) as shown in Scheme 35. It was envisioned that the chlorine at C-6 of 118a could be reduced first (route 1). The resulting C-5 halogenated nicotine 122 would then be submitted to a Sonogashira cross-coupling, previously reported in the literature. Otherwise, the cross-coupling reaction could be carried out first (route 2), followed by dehalogenation and deprotection of the acetylene group at C-5.

SCHEME 35. Retrosynthetic plan for the synthesis of SIB 1508Y (13).

In 1958 and 1959, Horner, Schläfer and Kammerer reported the reductive removal of aromatic halogen compounds with hydrogen, Raney nickel and alkali. Chlorinated
pyridines are reductively dehalogenated in good yield (75-85%) at room temperature with Raney nickel in the presence of hydrogen and 1 equivalent of potassium hydroxide. Dehalogenation of 2-chloropyridine is reported to take place in only 2 h, while dehalogenation of 3-chloropyridine took 16 h.

\[
\begin{align*}
\begin{array}{c}
\text{Cl} \quad \text{N} \\
\text{Cl} \quad \text{N}
\end{array}
\quad \xrightarrow{\text{Raney Ni, KOH}}
\quad \begin{array}{c}
\text{Cl} \quad \text{N} \\
\text{N}
\end{array}
\quad \xrightarrow{\text{MeOH, H}_2 \text{ (ballon pressure)}}
\quad \text{rt, 2 h}
\end{align*}
\]

\[
\begin{align*}
\begin{array}{c}
\text{Cl} \quad \text{N} \\
\text{Cl} \quad \text{N}
\end{array}
\quad \xrightarrow{\text{RedAl}}
\quad \begin{array}{c}
\text{I} \quad \text{N} \\
\text{Cl} \quad \text{N}
\end{array}
\quad \xrightarrow{\text{toluene, THF}}
\quad \text{rt, 2 h}
\end{align*}
\]

**SCHEME 36. Attempts to dehalogenate dihalogenated nicotine derivatives.**

Dichloronicotine 118b was submitted to these reaction conditions but after only two hours resulted in didehalogenation giving back nicotine (1) (Scheme 36). A regioselective reduction via the hydride source RedAl was also attempted on (S)-6-chloro-5-iodonicotine (118a) but afforded 6-chloronicotine (68) as the sole product.

Finally, the selective C-6 dehalogenation of (S)-5,6-dichloronicotine (118b), described in section II.3., was optimized. (S)-5-Chloronicotine (122a) is not, however, the best intermediate for a cross-coupling reaction. Chlorines are less prone to oxidative addition than bromines or iodines. Additionally, the C-5 position of the pyridine ring is not activated towards oxidative addition due to the polarization of the aromatic ring. Attempts to reduce
the C-6 chlorine of (S)-5-bromo-6-chloronicotine (118c) using the same conditions failed as an inseparable mixture of (S)-5-bromonicotine (122b) and (S)-6-chloronicotine (68) was isolated (Table 16).

**TABLE 16. Dechlorination of (S)-5-bromo-6-chloronicotine (117c).**

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.0 equiv Zn, 1.0 M HCl in AcOH, 60 °C, 2 h</td>
<td>2 :1 ratio of 122b:68</td>
</tr>
<tr>
<td>2</td>
<td>4.0 equiv, Zn, AcOH, room temperature, 10 h</td>
<td>1 :1 ratio of 122b:68</td>
</tr>
</tbody>
</table>

The second route was then investigated (Scheme 37), starting with a Sonogashira cross-coupling reaction on 6-chloro-5-iodonicotine (118a) with trimethylsilylacetylene using Pd(PPh₃)₂Cl₂ as a catalyst, copper iodide as a co-catalyst, and triethylamine as the solvent (72% yield). Submission of 132 to a Zn/AcOH mixture at 75 °C afforded deprotected 133 in a 1:1 ratio with starting material 132. Resubmission of 133 to a mixture and Zn/AcOH at 70 °C afforded vinlynicotine derivative 134 in 50% yield.
SCHEME 37. Attempts at C-2 dechlorination.

Table 17 presents attempts at C-6 dechlorination of compound 132. The Raney nickel reductive conditions described before led to decomposition of the starting material (entry 1). Ammonium formate catalytic hydrogen transfer reduction\(^91\) resulted in no reaction at room temperature or reflux (entry 2). Palladium-mediated hydrogenation in the presence of sodium acetate reduced the protected acetylene triple bond to the ethylsilane 136 (isolated in 11% yield). Longer reaction time cleaved the C-6 chloride to afford 137 in 41% isolated yield (entry 3). Attempts at a catalytic dechlorination of aromatic chlorides using Grignard reagents in the presence of \((\text{C}_5\text{H}_5)_2\text{TiCl}_2\) reported by Hara\(^92\) lead to recovery of starting materials (entry 4). Reductive dehalogenation of 132 with sodium borohydride in methanol led to deprotected acetylene compound 133 at room temperature and reduction of both the acetylene and the chlorine occurred at higher temperature to give 137 (entries 5 and 6).
TABLE 17. Attempts to C-6 dechlorination.

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Raney Ni, KOH, MeOH, H(_2) (balloon pressure)</td>
<td>decomposition</td>
</tr>
<tr>
<td>2</td>
<td>ammonium formate, Pd/C, MeOH, rt or reflux</td>
<td>NR</td>
</tr>
<tr>
<td>3</td>
<td>5% Pd/C, NaO(_2)CCH(_3), EtOH, H(_2) (balloon pressure)</td>
<td>136, 11%</td>
</tr>
<tr>
<td>4</td>
<td>n-PrMgBr or n-BuMgCl, 10% Cp(_2)TiCl(_2), -78 °C to 60 °C, 48 h</td>
<td>137, 41%</td>
</tr>
<tr>
<td>5</td>
<td>NaBH(_4), DMSO, rt</td>
<td>NR</td>
</tr>
<tr>
<td>6</td>
<td>NaBH(_4), MeOH, 0 °C to rt</td>
<td>133, 51%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>138 + 5% Pd/C, NaO₂CCH₃, EtOH, H₂ balloon pressure</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>138 + 5% Pd/C, NaOH, EtOH, H₂ balloon pressure</td>
<td>NR</td>
</tr>
<tr>
<td>3</td>
<td>138 + Pd(OH)₂, NaOH, MeOH, H₂ balloon pressure</td>
<td>140, 22%</td>
</tr>
<tr>
<td>4</td>
<td>138 + Pd(OH)₂, NaO₂CCH₃, MeOH or EtOAc, H₂ balloon pressure</td>
<td>NR</td>
</tr>
<tr>
<td>5</td>
<td>138 + Zn, AcOH, 60 °C to 75 °C overnight</td>
<td>139, 52%</td>
</tr>
</tbody>
</table>

The need for a more resistant protecting group for the acetylene moiety turned our attention to the bulkier triisopropylsilyl group (TIPS). The same Sonogashira cross-coupling conditions were used and afforded compound 138 quantitatively (Table 18). The palladium mediated dehalogenation using Pd/C was not induced by adding either sodium acetate or stronger sodium hydroxide (entries 1 and 2). Pearlman’s catalyst, Pd(OH)₂, in the presence of sodium hydroxide, led to reduction of the acetylene triple bond and dechlorination (entry 3). Finally, the reaction of 138 with a hot mixture of Zn/AcOH afforded desired dehalogenated product 139 in 52% yield (entry 5). The desilylation of the acetylene moiety using
tetrabutylammonium fluoride (TBAF) (99%) achieved the synthesis of SIB 1508Y (13) (Scheme 38). The spectral properties and optical rotation of our (-)-13 are in agreement with reported data ([α]30D -162 (c 0.77, EtOH); lit.61 [α],D -164 (c 5, EtOH)). The same methodology was applied to compound 141, obtained in 66% from 117a. Dehalogenation was achieved under the same conditions in 45% yield to afford nicotine derivative 142 (Scheme 39).

As a conclusion, enantiopure SIB-1508Y was prepared via a five-step sequence from (S)-nicotine in 32% overall yield. This strategy is amenable to the synthesis of various nicotine analogs of potential pharmaceutical value that are currently being tested.
III. 2. Six-Step Synthesis of (S)-Brevicolline from (S)-Nicotine

In the pursuit of our goal to transform commercially available (S)-nicotine from an underutilized natural product to a useful member of the chiral pool, we set out to use the methodologies described above towards the synthesis of a natural product. The β-carboline alkaloids (S)-brevicolline (143) and brevicarine (144) were the major alkaloids isolated in the late 60’s from the plant Carex brevicollis D.C. (Cyperacee) native to the southwestern part of the former U.S.S.R. (Figure 10).

![Figure 10. β-Carboline alkaloids (S)-brevicolline (143) and brevicarine (144).](image)

The structure and absolute configuration of 143 was determined by Lazarevski and Bláha, respectively. The β-carbolines are a group of pharmacologically interesting and biologically active compounds, which reported effects include antineoplastic (tubuline binding), anticonvulsive, hypnotic and anxiolytic (benzodiazepine receptor inhibitoric), antiviral, antimicrobial, topoisomerase II inhibition, and inhibition of cGMP-dependent processes. (S)-Brevicolline’s biological activities range from phototoxic effect on bacteria and fungi, to oxytocic effect, used against uterine internia of pregnant women. Several racemic syntheses of 143 have been reported, but the only enantioselective
synthesis\textsuperscript{104} was published by Mahboobi and coworkers in 1999 (Scheme 40). Their route utilizes an enantiomerically pure Michael-acceptor intermediate 146\textsuperscript{105} to prepare 2-indoly-1-nitroalkane 147a which is then reduced to the amine 147b. A subsequent Pictet-Spengler reaction afforded the tertahydro-β-carboline skeleton 149, which was transformed to 143 by catalytic dehydrogenation followed by reduction of the Boc protecting group.

\begin{center}
\includegraphics[width=0.9\textwidth]{scheme40.png}
\end{center}

\textbf{SCHEME 40. Mahboobi’s synthesis of (S)-brevicolline.}

(S)-Brevicolline possesses the core (S)-nicotine (1) structure. Since we have been investigating the synthesis of enantiopure nicotine derivatives using natural (S)-nicotine itself as an inexpensive starting material,\textsuperscript{73,82} we envisioned that 143 could be obtained through a
short synthesis starting from (S)-nicotine (1). It was anticipated that 143 could arise from a trisubstituted nicotine derivative such as 150 (Scheme 41). Following this plan, methylation of 150 via substitution at C-6 followed by a Buchwald catalytic amination at C-5, creating the carboline ring, would achieve the synthesis. Compound 150 could be derived from dichloronicotine 118b in a step involving a cross-coupling reaction. Finally, 118b is easily accessible in two steps from 1.

Our initial approach was to use a Suzuki cross-coupling reaction between (S)-5,6-dichloro-4-iodonicotine (151) and an amino boronate ester to afford compound 150, which, in turn, would be suitable for an intramolecular Buchwald amination. The synthesis of 151 was achieved in three steps and good yield from (S)-nicotine (1) (Scheme 42). We previously reported the formation of (S)-6-chloronicotine (68) from natural nicotine via an ortho-directed lithiation process.82 (S)-5,6-Dichloronicotine (118b) resulted from a regioselective lithiation-chlorination sequence on 68, using LiTMP as the base and hexachloroethane as the electrophile. Finally 151 was obtained from 118b via a third regioselective lithiation-

SCHEME 41. Retrosynthetic analysis of (S)-brevicolline.

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SCHEME 41. Retrosynthetic analysis of (S)-brevicolline.
substitution process, using $n$-BuLi as the base and iodine as the electrophile. To determine the regioselectivity of this reaction, the $^{13}\text{C} - ^1\text{H}$ coupling constant was analyzed. The $^{13}\text{C}$ satellite can indicate which regioisomer was obtained. Each organic compound contains 1.1% of the stable isotope $^{13}\text{C}$ in natural abundance. Since $^{13}\text{C}$ has a nuclear spin of $I = \frac{1}{2}$, these molecules show a spin-spin interaction between $^{13}\text{C}$ and the proton. That lead to the doublet splitting in the $^1\text{H}$ NMR called $^{13}\text{C}$ satellites. For the pyridine system, the changes of $^{13}\text{C}, ^1\text{H}$ spin-spin coupling constants (in Hz) have been recognized to be the most sensitive indicators for the detection of protonation sites.\textsuperscript{107} For an $\alpha$-proton the $^{13}\text{C}, ^1\text{H}$ coupling constant would be around 190 Hz, while for a $\gamma$-proton, the coupling constant would be around 170 Hz. The observed coupling constant was 196 Hz, indicating that the deprotonation took place at C-4. To confirm these observation, a Suzuki coupling with simple phenylboronic acid followed by reductive removal of both chlorines using Raney nickel afforded known (S)-4-phenylnicotine (153), the structure of which could be unequivocally assigned by NMR spectroscopy.\textsuperscript{53}
SCHEME 42. Synthesis of (S)-5,6-dichloro-4-iodonicotine (151) and formation of (S)-4-phenylnicotine (153) to unequivocally prove the regioselectivity in the iodination step.

With 4-iodonicotine 151 in hand, multiple conditions reported in the literature for the Suzuki coupling of amino boronic ester 154 with aryl iodides\textsuperscript{108} were tested without success (Table 19). The recovery of deiodonated compound 118b (entries 4, 6, 7 and 9) showed that the oxidative addition step was occurring rapidly (less than 2 h by TLC). The use of Pd(OAc)\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2} as a catalyst in dimethylacetamide gave, in a very low yield, undesired compound 156 where the Suzuki coupling occurs with the activated chlorine at C-6 after rapid reduction of the iodine at C-4.
**TABLE 19. Attempts at Suzuki couplings on halonicotine 151.**

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>results</th>
</tr>
</thead>
</table>
| 1     | one pot reaction \((a+b)\)
4 equiv Et3N, 5% Pd(OAc)₂
20% PCy₂(o-biph), 3.0 equiv pinBH
then, H₂O, 1.0 equiv 154,
Ba(OH)₂.8H₂O, 100 °C, 1h | decomposition |
| 2     | \(a\): 4 equiv Et₃N, 5% Pd(OAc)₂
20% PCy₂(o-biph), 3.0 equiv pinBH, 80 °C
then workup (NH₄Cl, ether) | 70-98% of 155 |
| 3     | \(b\): 5% Pd(PPh₃)₄, H₂O, Ba(OH)₂.8H₂O,
dioxane, 80 °C | decomposition |
| 4     | \(b\): 5% Pd(PPh₃)₄, H₂O, K₂CO₃,
DME, 80 °C | SM 151,
deiiodinated compound 118b |
| 5     | \(b\): 5% Pd(OAc)₂(PPh₃)₂, 2.0M Na₂CO₃
DMA, 100 °C | decomposition |
| 6     | \(b\): 5% Pd(OAc)₂(PPh₃)₂, 2.0M Na₂CO₃
DMA/EtOH (5/1), 100 °C | 118b recovered |
| 7     | \(b\): 5% Pd(OAc)₂(PPh₃)₂, 2.0M Na₂CO₃
DMA/EtOH (5/1), 100 °C | 118b recovered |
| 8     | \(b\): 5% Pd₂(dba)₃, 2.0M Na₂CO₃
DMA, 100 °C | decomposition |
| 9     | \(b\): 5% Pd(OAc)₂(PPh₃)₂, 2.0M Na₂CO₃
20% 2-(dicyclohexylphosphino)biphenyl,
DMA or DME, 100 °C or 80 °C | decomposition with DMA 118b with DME |
| 10    | \(b\): 5% Pd(OAc)₂(PPh₃)₂, 2.0M Na₂CO₃
DMA, 100 °C | low yield of 156\(^a\) |

\(^a\) Assignment made by \(^1\)H NMR.

The primary amine was thought to play a negative role on the coupling reaction, therefore the amine was masked as a nitro group. Coupling using 2-nitrobenzylboronic ester 157 was
therefore investigated. Submission of 157 and 151 to the Suzuki coupling conditions (Scheme 43) led to deiodinated 118b.

SCHEME 43. Attempt at Suzuki coupling with nitrobenzene boronic ester 157 as the nucleophile.

The need for a more nucleophilic coupling partner for 151 in the cross-coupling reaction pushed us to investigate the synthesis of 2-nitro-1-(tributylstannyl)benzene (159). The reported synthesis of 159 is slow, low yielding and uses extremely toxic ditin reagents. In 2002, Knochel and coworkers reported the synthesis of 2-substituted nitrobenzene from 2-iodonitrobenzene (160) but tributyltin chloride was never used as the electrophile. This reaction was carried out to afford 57% of the desired tin cross-coupling partner 159 (Scheme 44). Unfortunately, once again, attempts at the cross-coupling reaction at C-4 using 159 and 151 led to either decomposition or deiodination of 151 (Table 20).

SCHEME 44. Synthesis of 2-nitro(tributylstannyl)benzene 159.
TABLE 20. Attempts at cross-coupling reaction at C-4

![Chemical structure diagram]

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10 % Pd(OAc)$_2$(PPh$_3$)$_2$, DMA, 100 °C</td>
<td>decomposition of 151</td>
</tr>
<tr>
<td>2</td>
<td>10 % Pd(PPh$_3$)$_4$, DMF, 100 °C</td>
<td>decomposition</td>
</tr>
<tr>
<td>3</td>
<td>10 % Pd(PPh$_3$)$_4$, 8.0 equiv. CsF, DMF, 100 °C</td>
<td>deiodination to 118b</td>
</tr>
</tbody>
</table>

At this point we decided to reverse the nucleophile and the electrophile in the cross-coupling reaction. Our attention turned toward the introduction of the stannyl functionality at the C-4 position of nicotine. Stannylnicotine 161 was obtained in 62% yield from 118b using the ortho-directed lithiation previously developed (Table 21). The following cross-coupling reaction with 2-nitroiodobenzene (160) gave a disappointing 26 % yield of the desired product 158, while the aniline derivatives were inert to the conditions.

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>161 + 160 + 10% Pd(OAc)$_2$(PPh$_3$)$_2$, DMA, 100 °C</td>
<td>26% of 158</td>
</tr>
<tr>
<td>2</td>
<td>161 + 160 + 10% Pd(OAc)$_2$(PPh$_3$)$_2$, DMA, 100 °C</td>
<td>18% of 158</td>
</tr>
<tr>
<td></td>
<td>10% CuI</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>161 + 160 + 10% Pd(OAc)$_2$(PPh$_3$)$_2$, DMA, 100 °C</td>
<td>no product</td>
</tr>
<tr>
<td></td>
<td>10% LiCl</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>161 + 154 + 10% Pd(OAc)$_2$(PPh$_3$)$_2$, DMA, 80 °C</td>
<td>decomposition</td>
</tr>
</tbody>
</table>

The next step was to synthesize and investigate the reactivity of a boronate or a borane derivative. Any attempts to form a boronate on the pyridine of nicotine have been unsuccessful so far, the products form but are highly sensitive to any purification and could not be isolated. However, borane 162 was synthesized and isolated as white crystals in 57 % yield from 118b via the ortho-directed lithiation-substitution process (Table 22). Interestingly, that H2’ is shifted downfield in the $^1$H NMR (see appendix), indicating that the pyrrolidine nitrogen is coordinating to the boron at C-4. All attempts at a Suzuki cross
coupling reaction with 162 failed. It is thought that the B-N coordination shuts down the reactivity of borane 162 and no further investigation was undertaken.

**TABLE 22. Formation and reactivity of borane nicotine 162.**

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(PPh₃)₄, nPr₄N⁺Br⁻, KOH aq THF, reflux, 16h</td>
<td>decomposition</td>
</tr>
<tr>
<td>2</td>
<td>Pd(PPh₃)₄, nBu₄N⁺Br⁻, KOH powder THF, reflux, 16h</td>
<td>both SM recovered</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)₂(PPh₃)₂, KOH powder THF, reflux, 22 h</td>
<td>both SM recovered</td>
</tr>
<tr>
<td>4</td>
<td>Pd(OAc)₂(PPh₃)₂, KOH powder toluene, reflux, 22 h</td>
<td>both SM recovered</td>
</tr>
</tbody>
</table>
The last series of reactions that were attempted from a substituted 5,6-dichloronicotine used an organometallic at C-4 (Table 23). Both the cross-coupling reactions using organomanganese 163 (entries 1-3) or organozinc 164 (entry 4) failed as well. As a result of the low reactivity of the 4-substituted 5,6-dichloronicotines intermediates, our attention turned to the use of another route to brevicolline.
SCHEME 45. Second retrosynthetic route.

SCHEME 46. Synthesis of trihalo precursors 118a and 167b-c.

Another route to brevicolline where a Buchwald amination would be carried out first and followed by a ring closure at C-4 was investigated (Scheme 45). The amination at C-5 went smoothly for a number of different halogenated nicotine derivatives (118a and 167b-c) (Scheme 46) using 5% Pd$_2$dba$_3$, 1.5 eq Cs$_2$CO$_3$, 2-bromoaniline and Xantphos as a ligand in 1,4-dioxane (Table 24). When the reaction was stirred overnight at 110 °C (entry 2), disubstitution occurred at the activated C-5 and C-6 positions of 167b to form compound 168.
With the secondary amines (166a-c) in hand, several attempts to close the ring at C-4 using different types of cross-coupling reactions (Ullman, Suzuki, or Stille) or radical-mediated cyclization failed as decomposition occurred or starting material was recovered. However, to our surprise, under standard Buchwald amination conditions, the amino boronate ester 155 and 166c did not afford the desired boronate product. Instead, a Suzuki cross-coupling reaction took place and amino compound 169 was formed in 38 % yield (entry 5).
TABLE 24. Amination at C-5 of 118a and 167b-c.

<table>
<thead>
<tr>
<th>entry&lt;sup&gt;a&lt;/sup&gt;</th>
<th>conditions</th>
<th>results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>118a + 1.2 equiv 154 + 5% Pd&lt;sub&gt;2&lt;/sub&gt;dba&lt;sub&gt;3&lt;/sub&gt;, 1.5 equiv Cs&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;, 10 % Xantphos, dioxane, 110 °C</td>
<td>48% of 166c</td>
</tr>
<tr>
<td>2</td>
<td>167b + 1.2 equiv 154 + 5% Pd&lt;sub&gt;2&lt;/sub&gt;dba&lt;sub&gt;3&lt;/sub&gt;, 1.5 equiv Cs&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;, 10 % Xantphos, 1,4-dioxane, 110 °C, 18 h</td>
<td>inseparable mixture of 166a and 168</td>
</tr>
<tr>
<td>3</td>
<td>167b + 1.2 equiv 154 + 5% Pd&lt;sub&gt;2&lt;/sub&gt;dba&lt;sub&gt;3&lt;/sub&gt;, 1.5 equiv Cs&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;, 10 % Xantphos, 1,4-dioxane, 110 °C, 3 h</td>
<td>53% of 166a</td>
</tr>
<tr>
<td>4</td>
<td>167c + 1.2 equiv 154 + 5% Pd&lt;sub&gt;2&lt;/sub&gt;dba&lt;sub&gt;3&lt;/sub&gt;, 1.5 equiv Cs&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;, 10 % Xantphos, 1,4-dioxane, 110 °C, 3 h</td>
<td>68% of 166b</td>
</tr>
<tr>
<td>5</td>
<td>167c + 1.0 equiv 155 + 5% Pd&lt;sub&gt;2&lt;/sub&gt;dba&lt;sub&gt;3&lt;/sub&gt;, 1.5 equiv Cs&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;, 10 % Xantphos, 1,4-dioxane, 110 °C, 3 h</td>
<td>38% of 169 instead of 166d</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reactions were run on 0.3 to 0.8 mmol scale.

Because of this result, we decided to investigate additional cross-coupling reactions at C-4 of derivatives 170a-b (Scheme 47). Unfortunately, compounds 171a and b were formed in
low yield (20 % and 24 %, respectively). It was thought that once formed, compound 171b might ring close at C-5 under the same reaction conditions, but the desired product was not observed. The low yield in the Buchwald amination step was attributed to the activated C-6 chlorine that could participate in a subsequent cross-coupling reaction decreasing the yield of the desired product. We therefore decided to install the C-6 methyl of (S)-brevicolline (143) before attempting the Suzuki cross-coupling reaction at C-4.

\[
\text{SCHEME 47. Attempted Suzuki reaction at C-4.}
\]

One of the salient features of a heterocycle such as nicotine is the marked activation at position \( \alpha \) and \( \gamma \) to the pyridine nitrogen. The polarization of the aromatic ring activates it at the \( \alpha \) and \( \gamma \) positions toward nucleophilic attack. The order of reactivity between S\( _{\text{NAr}} \) displacement reactions and oxidative additions in palladium chemistry are similar. While chlorobenzene requires sterically hindered, electron-rich phosphine ligands, \( \alpha \) and \( \gamma \) chloropyridines are sufficiently activated for palladium-catalyzed reactions. Stille and
Kumada couplings with tetramethylditin and methyl Grignard, respectively, were carried out, but afforded no or low yields of (S)-5-chloro-6-methylnicotine (172) (Table 25, entries 1-5). After extensive optimization, compound 172 was formed in good yield from (S)-5,6-dichloronicotine (118b) via a Suzuki cross-coupling reaction using trimethylboroxine (173) (entry 6).\footnote{112}

**TABLE 25. Methylation at C-6.**

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me₄Sn, Pd(OAc)₂(PPh₃)₂, DMA, 70 °C, on</td>
<td>15%</td>
</tr>
<tr>
<td>2</td>
<td>Me₄Sn, Pd(OAc)₂(PPh₃)₂, DMA, reflux, on</td>
<td>27%</td>
</tr>
<tr>
<td>3</td>
<td>Me₄Sn, Pd₂(dba)₃, Ag₂O, NMP, 80 °C, 12 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>4</td>
<td>Me₄Sn, Pd(OAc)₂(PPh₃)₂, Ag₂O, DMA, 120 °C, 26 h</td>
<td>no reaction</td>
</tr>
<tr>
<td>5</td>
<td>(PPh₃)₂NiCl₂, CH₃MgBr, ether, rt, on</td>
<td>no reaction</td>
</tr>
<tr>
<td>6</td>
<td>1.0 equiv trimethylboroxine (173), 10 % Pd(PPh₃)₄, K₂CO₃, 1,4-dioxane, 110 °C, 2-3 d</td>
<td>70%</td>
</tr>
</tbody>
</table>
The iodination at C-4 of 172 constituted a tricky step due to the competitive deprotonation of the pseudo benzylic position at C-6. While addition of 172 to $n$-BuLi (inverse addition) afforded inconsistent results, addition of $n$-BuLi to 172 (normal addition) gave a 53% yield of the desired 4-iodo derivative 174b with 12% of the dinicotine adduct 176 (Scheme 48). The cross-coupling reaction between 174b and amino boronate ester 155 went smoothly to give 177 (Scheme 49). It is noteworthy to point out that the use of a sealed-tube in this reaction slightly increased the yield, but more importantly gave a cleaner product.

**Scheme 48. Iodination at C-4.**
Finally, an intramolecular Buchwald amination was chosen to close the indole ring to form 143. Standard Buchwald amination conditions on 177 did not affect the desired transformation. However, the use of Pd$_2$dba$_3$, Cs$_2$CO$_3$ and PCy$_2$(o-biph) as the ligand in 1,4-dioxane yielded (+)-brevicolline (143) in 80% isolated yield. The spectral properties of our (+)-143 are in agreement with the reported data. Since the ring-closure conditions only differ from the usual Buchwald amination conditions by the ligand, we thought that a one-pot, two-step process from 174b could be used; however, in all attempts only 177 was formed, and brevicolline was not observed.
SCHEME 50. Six-step total synthesis of (S)-brevicolline (143).

In conclusion, after extensive investigation and optimization, (S)-brevicolline (143) was synthesized in six steps from (S)-nicotine in a 17% overall yield (Scheme 50). This practical synthesis was carried out with retention of configuration on the pyrrolidine ring, and constitutes the shortest synthesis of this natural product to date.
CHAPTER IV:

ADVANCES TOWARDS THE TOTAL SYNTHESIS
OF DIHYDROLYCOLUCINE
IV. 1. Introduction

For the past 15 years, the Comins group has been developing methodology for the synthesis of members of the *Lycopodium* alkaloid family. These alkaloids have been studied since the early 1960’s and to date over 200 members have been isolated.\(^{113}\) One of the more complicated members of this alkaloid family is dihydrolycolucine (178) isolated in 1979 by Ayer and coworkers.\(^{114}\) Dihydrolycolucine (178) possesses a core tetracyclic structure, the synthesis of which is attempted and described herein. Our strategy for the synthesis of 178 is depicted in Scheme 51.

![Scheme 51: Retrosynthetic scheme for the synthesis of dihydrolycolucine (178).](image)

**SCHEME 51. Retrosynthetic scheme for the synthesis of dihydrolycolucine (178).**

Dihydrolycolucine (178) could come from the addition of the southern part 179 to the pyridine moiety of the northern part 180 of 178. While the synthesis of 179 has been achieved in 15 steps from 4-methoxy-3-TIPS-pyridine (188) in our lab, the synthesis of the northern portion of 180 remains a challenging target. Our synthetic plan is depicted in Scheme 52. Intermediate 181 can be obtained using a known ten-step procedure developed in our group years ago.\(^{115}\) An iodine could be introduced at the vinylic position as a latent cross-
coupling partner. A pyridine moiety such as compound 183 could be used as the nucleophilic partner to give 184. Subsequent hydrogenolysis, followed by the formation of the C-2 triflate would set the stage for an enolate cross-coupling reaction on 185 to close the seven-membered ring of the tetracyclic structure to get compound 186.

SCHEME 52. Synthetic plan to tetracyclic structure 186.
IV. 2. Advances toward the synthesis of the northern part of dihydrolcolicine.

IV. 2. a. Synthesis of key intermediate 181.

The synthesis starts with 4-methoxy-3-TIPS-pyridine (188) (Scheme 53). Formation of the chiral N-acylpyridinium salt followed by the addition of Grignard reagent 189 and workup gave dihydropyridone 190. Removal of the (+)-TCC carbamate with NaOMe and cleavage of the TIPS group at C-3 under acidic conditions yielded 191 which was subsequently reprotected as the benzyl carbamate to afford 192.

\[
\begin{align*}
\text{TIPS} & \quad \text{OMe} \\
\text{N} & \quad \text{ClCO}_2\text{R}^* \\
\text{R}^* & = (+)\text{-TCC} \\
1) & \quad \text{NaOMe, MeOH} \\
2) & \quad \text{THF, 10% HCl} \\
\text{N} & \quad \text{OMe} \\
\text{O} & \quad \text{H} \\
\text{N} & \quad \text{H} \\
1) & \quad n\text{-BuLi, THF, -78 °C} \\
2) & \quad \text{BnOCOCl} \\
\text{CO}_2\text{Bn} \\
\text{N} & \quad \text{H} \\
\end{align*}
\]


\(\alpha,\beta\)-Unsaturated ester 194 was previously formed via a two-step sequence where the terminal double bond of 192 was oxidatively cleaved using OsO\(_4\) and NaIO\(_4\) to afford
aldehyde 193 (Scheme 54). Aldehyde 193 was then reacted under Hörner-Wadsworth-Emmons reaction conditions to yield 194 in, at best, 73% overall yield. It was envisioned that 194 could be directly accessed from 192 via a cross-metathesis reaction using methyl acrylate (195) and the second generation Grubbs catalyst. After optimization (Table 26), compound 194 was obtained in near quantitative yield when a mixture of 5.0 equivalents of methyl acrylate (195) and 192 were warmed to 40 °C for 12 h.

SCHEME 54. Two-step process for the synthesis of dihydropyridone 194.

TABLE 26. Formation of 194 via cross-metathesis from 192.

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.0 equiv of 195, rt for 24 h</td>
<td>77% as a mixture of E and Z isomers (1.7:1 ratio)</td>
</tr>
<tr>
<td>2</td>
<td>3.0 equiv of 195, 40 °C, 24 h</td>
<td>34% of the E isomer, 45% of starting material</td>
</tr>
<tr>
<td>3</td>
<td>5.0 equiv of 195, 40 °C, 24 h</td>
<td>98% of the E isomer</td>
</tr>
</tbody>
</table>

* 5% mol Grubbs II catalyst
With compound 194 in hand, the vinylogous amide was reduced to the alcohol that was subsequently dehydrated using Furukawa’s reagent\textsuperscript{117,118} to afford triene 196 (Scheme 55). Triene 196 was then heated in xylenes at 145 °C for 65 h to yield Diels-Alder adduct 197. Compound 197 was hydrogenated over Pd/C in EtOAc to give free amine 198. Amine 198 is set up for a retro-Mannich reaction that would yield compound 181.

![Scheme 55. Formation of key intermediate 181.](image)

**IV. 2. b. Synthesis of the pyridine moiety.**

![Scheme 56. Retrosynthetic scheme for trisubstituted pyridine 199 or 200.](image)
The synthesis of the pyridine moiety such as compound 199 or 200 was investigated. Trisubstituted pyridines 199 or 200 could come from trihalopyridine 201 (Scheme 56). Compound 201 was synthesized directly from 2,6-difluoropyridine (202) by ortho-directed lithiation using LDA followed by the addition of I\(_2\) as the electrophile. Unfortunately, the displacement of one of the fluorines was not regioselective (Table 27) and this route was abandoned.

**TABLE 27. Formation of trihalopyridine 201 and displacement of a fluorine.**

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>products</th>
<th>ratio(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0 equiv NaOMe, MeOH, reflux, 20 h</td>
<td>203, 204, 205</td>
<td>1:2:2</td>
</tr>
<tr>
<td>2</td>
<td>1.0 equiv KOr-Bu, THF, room temp., 12 h</td>
<td>203, 204</td>
<td>2:1</td>
</tr>
</tbody>
</table>

\(^a\) Ratio were determined by \(^1\)H NMR

**SCHEME 57. Retrosynthetic scheme for trisubstituted pyridine 206 or 207.**
Instead, it was envisioned that a trisubstituted pyridine such as 206 or 207 could come from the regioslective deprotonation of 2-methoxy-6-methoxymethoxy-pyridine (208) where the two oxygens on the MOM group could chelate better to a lithiated base compared to only one oxygen on the methoxy group (Scheme 57). The synthesis of 2-methoxy-6-methoxymethoxy-pyridine (208) starts from the O-alkylation of 6-chloropyridin-2-ol (209) (Table 28).

**TABLE 28. O-Alkylation of 6-chloropyridin-2-ol (209).**

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>products</th>
<th>ratio&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
</table>
| 1     | 1) 1.1 equiv NaH, DMF, 2 h  
2) 2.2 equiv MOMCl, 0 °C to rt, 2 h | 210, 211 | 5:2  
(56% : 22% resp.) |
| 2     | 1) 1.2 equiv Cs₂CO₃, rt, 3 h  
2) 2.2 equiv MOMCl, ε KI, -20 °C to rt, 12 h | 209 | NR |
| 3     | 1) 1.1 equiv KOr-Bu, CH₂Cl₂, 0 °C to rt, 2 h  
2) 1.2 equiv MOMCl, 0 °C to rt, 12 h | 210, 211 | 5:95 |
| 4     | 1) 1.1 equiv KOr-Bu, THF, 0 °C to rt, 2 h  
2) 1.2 equiv MOMCl, 0 °C to rt, 12 h | 210, 211 | 3:10 |
| 5     | 1) 1.1 equiv KOr-Bu, DMF, 0 °C to rt, 2 h  
2) 1.2 equiv MOMCl, 0 °C to rt, 12 h | 210, 211 | 7:3  
(65-80% of 210) |

<sup>a</sup> Ratio were determined by 'H NMR

When 6-chloropyridin-2-ol (209) was treated with NaH in DMF followed by the addition of MOMCl, a 5:2 ratio of 210:211 was observed and only 56% of the desired O-alkylated product was isolated (entry 1). A larger counterion for the base, cesium, was used but only...
starting material was recovered (entry 2). Finally, when 209 was treated with K-OtBu in DMF, followed by the addition of MOMCl, the desired O-alkylated product was isolated in good yield (65 to 80% yield), while the formation of the N-alkylated product was minimized (entries 3-5). The C-2 chlorine of compound 210 was then displaced by methoxide under classical conditions (Table 29). Surprisingly, when 210 was treated with sodium methoxide, only starting material was recovered (entry 1). However, when the potassium salt was used the reaction went smoothly to afford a 64% isolated yield of 2-methoxy-6-methoxymethoxy-pyridine (208). Unfortunately, the subsequent ortho-directed lithiation\textsuperscript{119} of 208 did not present any regioslectivity (Scheme 58).

**TABLE 29. Formation of 2-methoxy-6-methoxymethoxy-pyridine (208).**

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>product</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.1 equiv of NaOMe, MeOH reflux, 18 h</td>
<td>210</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>1.2 equiv MeOH, KOt-Bu, THF, reflux, 12 h</td>
<td>208</td>
<td>40</td>
</tr>
<tr>
<td>3\textsuperscript{a}</td>
<td>1.2 equiv MeOH, KOt-Bu, THF, reflux, 12 h</td>
<td>208</td>
<td>64</td>
</tr>
</tbody>
</table>

\textsuperscript{a} reaction run on a larger scale.

**SCHEME 58.** No regioselectivity observed in the ortho-directed lithiation of 208.
The installment of an isopropoxide, instead of a methoxide, at the C-2 position was thought to provide enough steric hindrance to selectively direct the deprotonation ortho to the MOM group. Displacement of the C-2 chlorine with potassium isopropoxide, using the reaction conditions above, afforded a complex mixture of pyridines 208, 214 and 215 (Table 30).

**TABLE 30. Displacement of the C-2 chlorine with isopropoxide anion.**

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>product</th>
<th>ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0 equiv of NaOi-Pr, i-PrOH, reflux, 18 h</td>
<td>210, 214</td>
<td>9:1</td>
</tr>
<tr>
<td>2</td>
<td>1.2 equiv i-PrOH, 1.2 equiv KOr-Bu, DME, reflux, 3 h</td>
<td>decomposition</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>1.2 equiv KOr-Bu, i-PrOH i-PrOH, rt, 12 h</td>
<td>210</td>
<td>NR</td>
</tr>
<tr>
<td>4</td>
<td>1.2 equiv KOr-Bu, i-PrOH i-PrOH, reflux, 12 h</td>
<td>214, 208, 215</td>
<td>4:1:1</td>
</tr>
<tr>
<td>5</td>
<td>1.2 equiv i-PrOH, 1.2 equiv KOr-Bu, THF, 50 °C, 12 h</td>
<td>214, 208, 215</td>
<td>2.5:1:1</td>
</tr>
<tr>
<td>6</td>
<td>2.0 equiv i-PrOH, 1.0 equiv KOr-Bu, THF, 70 °C, 12 h</td>
<td>214, 208, 215</td>
<td>1:1:1</td>
</tr>
<tr>
<td>7</td>
<td>3.0 equiv i-PrOH, 1.1 equiv KOr-Bu, DMSO, 70 °C, 2 h</td>
<td>214, 208, 215</td>
<td>1.5:1:1</td>
</tr>
<tr>
<td>8</td>
<td>3.0 equiv i-PrOH, 1.1 equiv KOr-Bu, DMF, rt</td>
<td>210</td>
<td>NR</td>
</tr>
</tbody>
</table>

An alternate route to pyridine 214 is described in Scheme 59. 2,6-Dichloropyridine (216) was treated with potassium isopropoxide to yield chloropyridine 215. Displacement of the chloride with the potassium anion of benzyl alcohol gave compound 217 in 61% yield.
Removal of the benzyl group by hydrogenolysis gave pyridine 218, which was subsequently converted to 214 using MOMCl.

![Chemical structures](image)

**SCHEME 59. Alternate route to 214.**

**TABLE 31. Regioselective substitution of 214.**

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>product ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.1 equiv n-BuLi, -40 °C to rt, 1.2 equiv D$_2$O</td>
<td>219a, 220a 100:0</td>
</tr>
<tr>
<td>2</td>
<td>1.1 equiv n-BuLi, -40 °C to rt, 1.2 equiv ClSnBu$_3$</td>
<td>219b, 220b 100:0 (56 % yield)</td>
</tr>
</tbody>
</table>

The ortho-directed lithiation of 214 took place regioselectively using n-BuLi at -40 °C to room temperature (Table 31). The desired trisubstituted pyridine 219b was isolated in 56 % yield.

*Iv. 2. c. Model study towards the installment of an vinlylic halogen.*
Our attention then turned to the synthesis of a model for the installment of a vinylic halogen. In the real piece, an iodine must be installed at the vinylic position of the tetrahydropyridine ring of 181 as a latent cross-coupling partner (Scheme 60). Compound 224a was devised as the model piece. The synthesis of 224a\(^{120}\) starts from \(\delta\)-valerolactam (221) which was protected as the methyl carbamate to give 222a (Scheme 61). The enolate of 222a was trapped with diphenyl chlorophosphate then reduced to the tetrahyropyridine 224a. Unfortunately, the last step was low yielding. Consequently, the same route was used to form tetrahydropyridine 224b, where a phenyl carbamate was used instead of a methyl carbamate. Upon treatment with sodium methoxide in methanol, 224b was converted to the methyl carbamate 224a in 86% yield.

SCHEME 60. Installment of a vinylic halogen.

An alternative route to 224a was discovered by Sonesson and co-workers in 1995 (Scheme 62). Tetrahydropyridine 225 was protected as the methyl carbamate 226, and the double bond was then isomerized using 10% Pd/C in THF:TEA to afford 224a in quantitative yield.

SCHEME 62. Alternative route to 224a.
TABLE 32. Key-step: installment of a vinylic halogen.

224a, R = Me
224b, R = Ph

227a, R = Ph, E = I
227b, R = Ph, E = Br
228a, R = Me, E = I
228b, R = Me, E = Br

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>E</th>
<th>product</th>
<th>% yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.2 equiv ICl, 1.3 equiv PMP, 0 °C to rt, 12 h</td>
<td>I</td>
<td>SM 224b</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>2.0 equiv ICl, 2.2 equiv PMP, rt, 12 h</td>
<td>I</td>
<td>SM 224b</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>2.0 equiv Br2, 2.2 equiv PMP, rt, 1 h</td>
<td>Br</td>
<td>227b</td>
<td>24</td>
</tr>
<tr>
<td>4</td>
<td>1.0 equiv Br2, 1.1 equiv PMP, rt, 1 h</td>
<td>Br</td>
<td>227b</td>
<td>37</td>
</tr>
</tbody>
</table>

PMP = 1,2,2’,6,6’-pentamethyipuridine

SCHEME 63. First attempt at the key cross-coupling reaction.

Finally, attempts to install an iodine at the vinylic position using ICl (entries 1-2) in the presence of 1,2,2’,6,6’-pentamethyipuridine (PMP) as a strong base failed (Table 32). However, when Br2 was used as the electrophile (entries 3-4), the reaction went smoothly as starting material disappeared rapidly by TLC. Compound 227b was isolated by chromatography in 37% when only 1.0 equivalent of bromine was used. An initial attempt at the key cross-coupling reaction of vinyl bromide 228b to stannylpyridine 219b did not lead to the desired product. More experiments need to be attempted.
Conclusion

In conclusion, a variety of novel nicotine derivatives have been synthesized in moderate to high yield in a regioselective manner. The new methodologies described provide opportunities for exploring new routes to a variety of interesting and potentially useful compounds based on nicotine. Ongoing studies in our laboratories are directed toward the formation of derivatives using those compounds as intermediates for cross-coupling reactions.

The methodologies developed were applied towards an expedient synthesis of potential anti-Parkinson’s drug, SIB-1508Y, achieved in five steps. This represents the shortest synthesis of this synthetic compound. The biologically active natural product, (S)-brevicolline was synthesized as well in only six steps.

Finally, model studies directed at the synthesis of the tertracyclic ring system of dihydrolycolucine were conducted. The route to key-intermediate 182 was improved using a cross-metathesis reaction. The installment of a vinylic bromide on a model piece was described. The corresponding pyridine cross-coupling partner was synthesized in good yield. The key cross-coupling reaction and the intramolecular seven-membered ring closure need to be examined.
Experimental Section

All reactions were performed in oven or flame-dried glassware under a argon atmosphere and stirred magnetically. THF, Et₂O and toluene were distilled from sodium/benzophenone ketyl prior to use. Triethylamine, diisopropylamine and methylene chloride were distilled from calcium hydride and stored under argon over 4Å molecular sieves. n-Butyllithium was titrated against diphenylacetic acid according to the procedure of Kofron and Baclawski. Other reagents and solvents from commercial sources were stored under argon and used directly. Melting points were measured on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Radial preparative layer chromatography (radial PLC) was performed on a Chromatotron (Harrison Associates, Palo Alto, CA) using glass plates coated with 1, 2 or 4 mm layers of Kieselgel 60 PF254 containing gypsum. High-resolution mass spectral analysis (HRMS) was performed at North Carolina State University. NMR spectra were obtained using a Varian Gemini GN-300 (300 MHz), Varian Mercury 300 (300 MHz), G.E. GN-300 (300 MHz), or Varian Mercury 400 (400 MHz) spectrometer. Chemical shifts are in ppm units with TMS (0.0 ppm) used as the internal standard for ¹H NMR spectra and the CDCl₃ absorption of 77.23 ppm for ¹³C NMR. IR spectra were recorded on a Perkin-Elmer 1430, MIDAC M2000, or JASCO FT/IR-410 spectrometer. Optical rotations were determined with an autopol II automatic polarimeter (Rudolph Research, Flanders, NJ). HPLC was performed using Waters and Associates (Milifrod, MA) 600 E multi solvent delivery system with a 486 λ tunable detector equipped with a Chiracel OJ or OD column. X-ray analyses were done at North Carolina State University.
Preparation of (S)-2-chloro-5-(1-methyl-pyrrolidin-2-yl)pyridine (68) on large scale.

A solution of 2-(dimethylamino)ethanol (6.0 mL, 60.0 mmol, 3.0 equiv) in hexane (25 mL) was cooled to 0 °C and treated dropwise with n-butyllithium (108.0 mmol, 5.4 equiv) under an argon atmosphere. After 30 min at 0 °C, the mixture was cooled to -20 °C and (S)-nicotine (3.2 mL, 20.0 mmol, 1.0 equiv) was added dropwise. After 1 h at -20 °C, a brown-green solution was observed. The mixture was cooled to -78 °C and solid hexachloroethane (19.0 g, 80.0 mmol, 4.0 equiv) was added very slowly by removing the septum while flushing with argon. After 1 h at -78 °C, the mixture was quenched at -78 °C with a saturated solution of sodium bicarbonate (10 mL). The aqueous layer was immediately extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over potassium carbonate. After evaporation of solvents, the crude product was purified by column chromatography (1% Et3N/20% EtOAc/hexanes) and then distilled under pressure to give 3.5 g (87%) of pure product as a colorless oil. \[\alpha\]^28_D - 90 (c 0.4, CH₂Cl₂); IR (neat) 2969, 2943, 2809, 2779, 1584, 1573, 1567, 1454, 1104 cm⁻¹. \(^1\)H NMR (400 MHz, CDCl₃) δ 8.29 (d, \(J = 2.4\) Hz, 1H), 7.67 (dd, \(J = 2.4, 8.4\) Hz, 1H), 7.28 (d, \(J = 8.4\) Hz, 1H), 3.23 (dt, \(J = 2.4, 8.8\) Hz, 1H), 3.08 (t, \(J = 8.4\) Hz, 1H), 2.30 (q, \(J = 8.8\) Hz, 1H), 2.24-2.15 (m, 1H), 2.15 (s, 3H), 2.00-1.90 (m, 1H), 1.88-1.76 (m, 1H), 1.72-1.62 (m, 1H); \(^1^3\)C NMR (100 MHz, CDCl₃) δ 150.2,
149.4, 138.3, 138.1, 124.5, 57.2, 40.6, 35.5, 22.8; HRMS calcd for C_{10}H_{13}ClN_{2} ([M]^{+}) 196.0767, found 196.0754.

**General procedure for the preparation of (S)-6-substituted nicotines 115.**

A solution of 2-(dimethylamino)ethanol (300 µL, 3.0 mmol, 3.0 equiv) in dry hexanes (2 mL) was cooled to 0 °C, and treated dropwise with n-butyllithium (5.4 mmol, 5.4 equiv) under an argon atmosphere. After 30 min at 0 °C, the mixture was cooled to – 20 °C and (S)-nicotine (160 µL, 1.0 mmol, 1.0 equiv.) was added dropwise. After 1 h of stirring, a green-brown solution was observed. The mixture was cooled to – 78 °C and treated dropwise with the electrophile (4.0 mmol, 4.0 equiv.). After 1 h at -78 °C, the cold mixture was quenched with a saturated solution of sodium bicarbonate (1 mL) and immediately extracted with dichloromethane (10 mL). The combined organic layers were dried over potassium carbonate. After evaporation of solvents, the crude product was purified by radial PLC (silica gel, 1% Et₃N/EtOAc/hexanes) to give the product 115. Yields are reported in Table 2, p.42.

![Chemical Structure](image-url)

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![Chemical Structure](image-url)
(m, 1H), 1.92-1.79 (m, 1H), 1.79-1.64 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 150.0, 140.8, 138.7, 137.9, 128.3, 68.3, 57.2, 40.6, 35.5, 22.9; HRMS calcd for C$_{10}$H$_{13}$BrN$_2$ ([M+H]$^+$) 241.0340, found 241.0349. (S)-2-Bromonicotine (116b): [$\alpha$]$^2$$^0$D - 161 (c 2.7, CH$_2$Cl$_2$); IR (neat): 2966, 2941, 2841, 2779, 1573, 1555, 1449, 1400, 1347, 1332, 1042, 804, 742 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.20 (dd, $J = 2.0, 4.8$ Hz, 1H), 7.87 (dd, $J = 2.0, 7.6$ Hz, 1H), 7.24 (dd, $J = 7.6, 4.8$ Hz, 1H), 3.50 (t, $J = 8.4$ Hz, 1H), 3.22 (m, 1H), 2.50-2.30 (m, 2H), 2.19 (s, 3H), 1.90-1.70 (m, 2H), 1.50-1.40 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 148.3, 143.9, 140.8, 137.0, 123.5, 68.5, 57.1, 10.8, 33.7, 23.1; HRMS calcd for C$_{10}$H$_{13}$BrN$_2$ ([M+H]$^+$) 241.0340, found 241.0345.

(S)-6-Iodonicotine (115c): [$\alpha$]$^2$$^0$D - 137 (c 0.9, CH$_2$Cl$_2$); IR (neat): 2966, 2943, 2778, 1573, 1555, 1447, 1325, 1070 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.28 (d, $J = 2.8$ Hz, 1H), 7.67 (d, $J = 8.4$ Hz, 1H), 7.35 (dd, $J = 2.8, 2.8$ Hz, 1H), 3.22 (dt, $J = 2.0, 8.6$ Hz, 1H), 3.03 (t, $J = 8.4$ Hz, 1H), 2.29 (q, $J = 9.2$ Hz, 1H), 2.23-2.19 (m, 1H), 2.15 (s, 3H), 2.00-1.88 (m, 1H), 1.86-1.76 (m, 1H), 1.70-1.60 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 150.7, 139.1, 137.1, 135.1, 116.4, 68.4, 57.2, 40.6, 35.6, 22.9; HRMS calcd for C$_{10}$H$_{13}$IN$_2$ ([M+H]$^+$) 289.0202, found 289.0221. (S)-2- Iodonicotine (116c): [$\alpha$]$^{25}$D –126 (c 4.5, CH$_2$Cl$_2$); IR (neat) 2965, 2940, 2778, 1568, 1550, 1446, 1395, 1330, 1034, 805 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 8.22 (dd, 1H, $J = 4.6, 2.0$ Hz), 7.74 (dd, 1H, $J = 7.6, 2.0$ Hz), 7.24 (dd, 1H, $J = 7.6, 4.6$ Hz),
3.35 (t, 1H, $J = 8.4$ Hz), 3.25 (t, 1H, $J = 8.4$ Hz), 2.50-2.36 (m, 2H), 2.21 (s, 3H), 1.84-1.80 (m, 3H), 1.52-1.42 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 149.4, 143.1, 137.1, 135.9, 123.7, 72.4, 57.1, 40.7, 33.9, 23.0; HRMS calcd for C$_{10}$H$_{13}$IN$_2$ ([M+H]$^+$) 289.0202, found 289.0203.

(S)-6-[(Dimethylphenyl)silyl]nicotine (115d):

\[ \alpha^2_{24.5} \text{D} - 109 \ (c \ 1.95, \ CH_2Cl_2) \]; IR (neat) 2719, 2562, 1443, 1418, 1265, 1151, 915, 901 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.71 (s, 1H), 7.62-7.56 (m, 3H), 7.41 (d, 1H, $J = 7.6$ Hz), 7.37-7.35 (m, 3H), 3.23 (dt, 1H, $J = 8.2, 2.0$ Hz), 3.06 (t, 1H, $J = 8.4$ Hz), 2.29 (q, 1H, $J = 9.2$ Hz), 2.21-2.16 (m, 1H), 2.16 (s, 3H), 2.0-1.9 (m, 1H), 1.85-1.75 (m, 1H), 1.75-1.65 (m, 1H), 0.62 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 165.2, 150.6, 138.1, 137.7, 134.5, 133.0, 130.0, 129.5, 128.1, 69.2, 57.3, 40.7, 35.4, 22.9, -2.8; HRMS calcd for C$_{18}$H$_{24}$N$_2$Si ([M+H]$^+$) 297.1787, found 297.1788.

(S)-6-(Methylsulfamyl)nicotine (115e):

\[ \alpha^3_{31} \text{D} - 181 \ (c \ 1.5, \ CH_2Cl_2) \ ]; IR (neat) 2960, 2775, 1587, 1552, 1458, 1388, 1322, 1203, 1133, 1109, 1042, 899, 825 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.28 (d, $J = 2.0$ Hz, 1H), 7.47 (dd, $J = 2.0, 8.0$ Hz, 1H), 7.09 (d, $J = 8.0$ Hz, 1H),
3.19-3.13 (m, 1H), 2.95 (t, $J = 8.8$ Hz, 1H), 2.50 (s, 3H), 2.25-2.18 (m, 1H), 2.15-2.04 (m, 1H), 2.09 (s, 3H), 1.94-1.82 (m, 1H), 1.80-1.69 (m, 1H), 1.69-1.58 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 158.7, 149.3, 135.2, 134.4, 121.6, 68.6, 57.1, 40.5, 35.2, 22.7, 13.5; HRMS calcd for C$_{11}$H$_{16}$N$_2$S ([M+H$^+$]) 209.1112, found 209.1108.  

(S)-2-(Methylsulfamyl)nicotine (116e): $[\alpha]^{31}_D$ - 191 (c 0.85, CH$_2$Cl$_2$); IR (neat) 3044, 2968, 2940, 2842, 2779, 1575, 1560, 1404, 1349, 1187, 1043, 796, 752 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.33 (dd, $J = 2.0$, 5.2 Hz, 1H), 7.34 (dd, $J = 1.6$, 7.6 Hz, 1H), 7.01 (dd, $J = 5.2$, 7.6 Hz, 1H), 3.40 (t, $J = 8.4$ Hz, 1H), 3.26-3.20 (m, 1H), 2.57 (s, 3H), 2.44-2.30 (m, 2H), 2.20 (s, 3H), 1.96-1.78 (m, 2H), 1.58-1.46 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 157.9, 147.5, 137.0, 133.4, 119.7, 66.1, 57.1, 10.8, 33.2, 23.0, 13.3; HRMS calcd for C$_{11}$H$_{16}$N$_2$S ([M+H$^+$]) 209.1112, found 201.1111.

![Chemical structure](image)

(S)-6-(Tributylstannyl)nicotine (115f): $[\alpha]^{31}_D$ - 75 (c 1.25, CH$_2$Cl$_2$); IR (neat) 2957, 2928, 2872, 2852, 2779, 1462, 1199, 1047, 1024 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.63 (d, $J = 1.2$ Hz, 1H), 7.51 (dd, $J = 2.4$, 7.6 Hz, 1H), 7.36 (d, $J = 7.6$ Hz, 1H), 3.25-3.19 (m, 1H), 3.00 (t, $J = 8.4$ Hz, 1H), 2.28 (q, $J = 8.4$ Hz, 1H), 2.22-2.14 (m, 1H), 2.15 (s, 3H), 2.01-1.88 (m, 1H), 1.86-1.68 (m, 2H), 1.60-1.50 (m, 6H), 1.36-1.26 (m, 6H), 1.14-1.06 (m, 6H), 0.90-0.82 (m, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 172.5, 150.8, 136.9, 132.5, 132.3, 69.2, 57.3, 40.7,
35.2, 29.3, 27.6, 22.9, 13.9, 9.9; HRMS calcd for C\textsubscript{22}H\textsubscript{40}N\textsubscript{2}Sn ([M+H]\textsuperscript{+}) 453.2292, found 453.2296.

(S)-6-(Formyl)nicotine (115g): [\alpha]\textsuperscript{28}\textsubscript{D} - 137 \text{ (c 0.65, CH\textsubscript{2}Cl\textsubscript{2})} ; Spectral data matches those described in the literature\textsuperscript{25} 1H NMR (400 MHz, CDCl\textsubscript{3}) \delta 10.07 (s, 1H), 8.71 (d, J = 2.0 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.87 (dd, J = 2.0, 8.0 Hz, 1H), 3.30-3.18 (m, 2H), 2.35 (q, J = 8.4 Hz, 1H), 2.32-2.20 (m, 1H), 2.18 (s, 3H), 2.04-1.90 (m, 1H), 1.90-1.80 (m, 1H), 1.80-1.64 (m, 1H); 13C NMR (100 MHz, CDCl\textsubscript{3}) \delta 193.5, 152.3, 150.1, 144.7, 136.1, 122.0, 68.9, 57.3, 40.7, 35.7, 23.1.

2-Iodonicotine (116c) and 4-Iodonicotine (117).

Under an atmosphere of argon, 2,2,6,6-tetramethylpiperidine (370 \textmu L, 2.2 mmol, 1.1 equiv) in dry THF (5 mL) was cooled to – 78 °C and treated with n-butyllithium (2.0 mmol, 1.0 equiv). The solution was stirred at 0 °C for 30 min, then the mixture was cooled to – 78 °C and treated with di-t-butylzinc (2.4 mmol, 1.2 equiv), prepared from zinc chloride (4.8 mL, 0.5 M in THF, 2.4 mmol) and t-butyllithium (4.8 mmol, 2.4 equiv). The mixture was then
stirred at room temperature for 1 h. (S)-Nicotine (320 µL, 2.0 mmol, 1.0 equiv) was added dropwise at room temperature, and the mixture was stirred overnight. Iodine (2.03 g, 8.0 mmol, 4.0 equiv) was added to the reaction mixture. The flask was wrapped by aluminum foil to protect the reaction from light. The reaction was quenched with 1.0 mL of a saturated aqueous solution of sodium bicarbonate. The cold aqueous layer was extracted with methylene chloride, and the combined organic layers were dried over magnesium sulfate. The solvent was removed by evaporation to afford a yellow oil. The product was purified by radial PLC (silica gel, 1% TEA/hexanes). (S)-2-Iodonicotine was obtained in a 19 % yield (107 mg) as a light yellow oil, and (S)-4-Iodonicotine was obtained in a 24 % yield (139 mg) as a white solid. (S)-4-Iodonicotine (116): mp 97-98 °C; IR (thin film) 2966, 2937, 2830, 2779, 1559, 1537, 1453, 1394, 1453, 1394, 1354, 1218, 1057, 850 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.60 (s, 1H), 8.04 (d, 1H, J = 5.2 Hz), 7.70 (d, 1H, J = 5.2 Hz), 3.38 (t, 1H, J = 8.4 Hz), 3.27 (dt, 1H, J = 2.0 Hz, J = 8.2 Hz), 2.46-2.32 (m, 2H), 2.24 (s, 3H), 1.98-1.78 (m, 2H), 1.58-1.46 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 149.8, 148.4, 141.9, 134.3, 111.4, 72.5, 57.1, 40.8, 33.9, 22.9; HRMS calcd for C₁₀H₁₃IN₂ ([M+H]⁺) 289.0202, found 289.0200; [α]²⁵_D - 120 (c 4.2, CH₂Cl₂).

**General procedure for the preparation of (S)-2-substituted nicotines 116.**

(S)-Nicotine (160 µL, 1.0 mmol, 1.0 equiv) was added dropwise at - 78 °C to a solution containing lithium tetramethylpiperidide (3.0 mmol, 3.0 equiv) and the electrophile (2.0 mmol, 2.0 equiv). After 1 h at - 78 °C, the solution was stored at - 25 °C in a freezer overnight. The hydrolysis was performed at - 25 °C with 1.0 mL of saturated aqueous solution of sodium bicarbonate. The cold aqueous layer was extracted with methylene
chloride (2 × 10 mL). The combined organic layers were dried over magnesium sulfate. The solvent was removed by evaporation under reduced pressure to afford a light yellow oil. The product was purified by radial PLC (silica gel, 1% TEA/ EtOAc/hexanes) to afford the product 116. Yields are reported in Table 4, p.44.

![Diagram](image)

(S)-6-(Trimethylsilyl)nicotine (115k): \([\alpha]_{D}^{28.5} -113 (c 1.85, \text{CH}_2\text{Cl}_2)\); IR (neat) 2957, 2778, 1455, 1248, 1046, 840, 738 cm\(^{-1}\); \(^1\)H NMR (300 Hz, CDCl\(_3\)) \(\delta 8.66 (d, J = 1.2 \text{ Hz}, 1\text{H}), 7.60 (dd, J = 2.4, 8.0 \text{ Hz}, 1\text{H}), 7.48-7.48 (m, 1\text{H}), 3.23 (m, 1\text{H}), 3.05 (t, J = 8.0 \text{ Hz}, 1\text{H}), 2.28 (q, J = 8.8 \text{ Hz}, 1\text{H}), 2.20-2.12 (m, 1\text{H}), 2.15 (s, 3\text{H}), 2.00-1.90 (m, 1\text{H}), 2.85-1.65 (m, 2\text{H}), 0.32-0.29 (m, 9\text{H}); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 150.4, 149.7, 137.9, 132.9, 129.0, 69.2, 57.3, 40.7, 35.4, 22.8, -1.5; \)HRMS calcd for C\(_{10}\)H\(_{13}\)IN\(_2\) ([M+H]\(^+\)) 235.1631, found 235.1626. (S)-2-(Trimethylsilyl)nicotine (116k): \([\alpha]_{D}^{29} -185 (c 0.75, \text{CH}_2\text{Cl}_2)\); IR (neat) 3048, 3033, 2961, 2903, 2832, 2777, 1555, 1456, 1415, 1334, 1249, 1043, 846 cm\(^{-1}\); \(^1\)H NMR (300 Hz, CDCl\(_3\)) \(\delta 8.61 (dd, J = 2.0, 4.8 \text{ Hz}, 1\text{H}), 7.84 (dd, J = 2.0, 8.0 \text{ Hz}, 7.20 (dd, J = 4.8, 8.4 \text{ Hz}, 1\text{H}), 3.39 (t, J = 8.0 \text{ Hz}, 1\text{H}), 3.24 (m, 1\text{H}), 2.31 (q, J = 9.2 \text{ Hz}, 1\text{H}), 2.21-2.15 (m, 1\text{H}), 2.15 (s, 3\text{H}), 2.00-1.88 (m, 1\text{H}), 1.85-1.74 (m, 1\text{H}), 1.64-1.54 (m, 1\text{H}), 0.38 (s, 9\text{H}); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta 165.8, 148.6, 146.1, 133.4, 123.6, 68.0, 57.2, 40.5, 36.4, 23.0, 0.8; \)HRMS calcd for C\(_{10}\)H\(_{13}\)IN\(_2\) ([M+H]\(^+\)) 235.1631, found 235.1624.
(S)-3-(1-Methylpyrrolidin-2-yl)-2-tricyclohexylstannyl)pyridine (116l): mp: 122-123 °C; \([\alpha]^{25}_D\) - 74 (c 2.8, CH2Cl2); IR (thin film) 2916, 2845, 2776, 1445, 1169, 1049, 991 \text{cm}^{-1}; 

\begin{align*}
\text{\textsuperscript{1}H NMR} (300 MHz, CDCl_3) & \delta 8.60 (dd, 1H, J = 4.4, 2.0 Hz), 7.69 (dd, 1H, J = 8.0, 2.0 Hz), \\
& 7.10 (dd, 1H, J = 8.0, 4.4 Hz), 3.26 (t, 1H), 3.04 (t, 1H), 2.34 (q, 1H), 2.29-2.16 (m, 1H), \\
& 2.16 (t, 3H), 1.92-1.60 (m, 21H), 1.35-1.20 (m, 12H); \text{\textsuperscript{13}C NMR} (100 MHz, CDCl_3) & \delta 174.2, \\
& 149.3, 146.8, 132.2, 122.2, 70.8, 57.1, 40.4, 36.8, 32.7, 29.7, 27.5, 22.8 ; \text{HRMS} \text{calcd} \\
& \text{for C}_{28}\text{H}_{46}\text{N}_{2}\text{Sn} ([M+H]^+) 531.2761, \text{found} 531.2780.
\end{align*}

General procedure for the preparation of C-5 Substituted (S)-6-chloronicotines (118a-g).

A solution of 2,2,6,6-tetramethylpiperidine (370 \mu L, 2.2 mmol, 1.1 equiv) in dry THF (2.0 mL) was treated with \(n\)-butyllithium (1.1 equiv) at -78 °C. After 1 h at -78 °C, neat 6-chloronicotine (400 mg, 2.0 mmol, 1.0 equiv) was added dropwise at -78 °C. After 1 h at -78 °C, the electrophile (1.2 equiv) was added neat or as a solution in dry THF. After 1 h at -78 °C, the reaction was quenched with a saturated aqueous solution of sodium bicarbonate (1 mL). The aqueous layer was immediately extracted with methylene chloride (2 \times 10 mL). The combined organic layers were dried over potassium carbonate and filtered through Celite. The solvent was removed by evaporation under reduced pressure, and the crude product was purified by radial PLC (silica gel, 1% TEA/5-20% EtOAc/hexanes). Yields are reported in Table 5, p.47.
(S)-6-Chloro-5-iodonicotine (118a): $[\alpha]^2_{D} = -111$ (c 1.25, CH$_2$Cl$_2$); IR (neat) 2968, 2781, 1535, 1458, 1408, 1328, 1220, 1137, 1032, 906, 728 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.25 (d, 1H, $J = 2.4$ Hz), 8.16 (d, 1H, $J = 2.4$ Hz), 3.21 (dt, 1H, $J = 9.6$, 2.4 Hz), 3.05 (t, 1H, $J = 9.6$ Hz), 2.30 (q, 1H, $J = 8.4$ Hz), 2.24-2.17 (m, 1H), 2.17 (s, 3H), 2.00-1.85 (m, 1H), 1.85-1.75 (m, 1H), 1.70-1.60 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 149.1, 148.5, 147.9, 140.0, 95.2, 67.5, 57.1, 40.7, 35.7, 22.9; HRMS calcd for C$_{10}$H$_{12}$ClIN$_2$ ([M+H]$^{+}$) 322.9812, found 322.9820.

(5)-5,6-Chloronicotine (118b): $[\alpha]^{24}_{D} = -134$ (c 0.8, CH$_2$Cl$_2$); IR (neat) 2968, 2781, 1547, 1420, 1392, 1329, 1149, 1042 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.20 (d, 1H, $J = 2.4$ Hz), 7.81 (d, 1H, $J = 2.4$ Hz), 3.23 (dt, 1H, $J = 2.1$, 8.4 Hz), 3.11 (t, 1H, $J = 8.4$ Hz), 2.32 (q, 1H, $J = 8.4$ Hz), 2.25-2.19 (m, 1H), 2.17 (s, 3H), 2.00-1.60 (m, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 147.8, 146.9, 140.4, 137.9, 130.8, 67.6, 57.1, 40.6, 35.7, 22.9; HRMS calcd for C$_{10}$H$_{12}$Cl$_2$N$_2$ ([M+H]$^{+}$) 231.0456, found 231.0457.
(S)-5-Bromo-6-chloronicotine (118c): $[\alpha]_{D}^{28} -134$ (c 1.85, CH$_2$Cl$_2$); IR (neat) 2969, 2840, 2770, 1456, 1418, 1390, 1329, 1224, 1144, 1035, 905 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) 8.23 (d, $J = 2.1$ Hz, 1H), 7.97 (d, $J = 2.1$ Hz, 1H), 3.22 (t, $J = 8.0$ Hz, 1H), 3.09 (t, $J = 8.0$ Hz, 1H), 2.32 (q, $J = 9.2$ Hz, 1H), 2.21-2.19 (m, 1H), 2.17 (s, 3H), 2.0-1.9 (m, 1H), 1.9-1.76 (m, 1H), 0.67 (s, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 149.9, 147.5, 141.3, 140.4, 120.6, 67.6, 57.1, 40.6, 35.7, 22.9; HRMS calcd for C$_{10}$H$_{12}$BrClN$_2$ ([M+H]$^+$) 274.9951, found 274.9933.

(S)-6-Chloro-5-[(dimethylphenyl)silyl]nicotine (118d): $[\alpha]_{D}^{24.5}$ -95 (c 0.75, CH$_2$Cl$_2$); IR (neat) 2963, 2777, 1550, 1378, 1252, 1124, 1052 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.30 (d, $J = 2.4$ Hz, 1H), 8.62 (d, $J = 2.4$ Hz, 1H), 7.53-7.51 (m, 2H), 7.39-7.36 (m, 3H), 3.20 (dt, $J = 8.4$, 2.4 Hz, 1H), 3.01 (t, $J = 8.1$ Hz, 1H), 2.27 (q, $J = 9.0$ Hz, 1H), 2.19-2.16 (m, 1H), 2.14 (s, 3H), 1.95-1.60 (m, 3H), 0.67 (s, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 156.0, 150.2, 145.5, 137.3, 136.6, 134.4, 133.2, 129.7, 128.1, 68.5, 57.2, 40.6, 35.4, 22.8, -2.2; HRMS calcd for C$_{18}$H$_{23}$ClN$_2$Si ([M+H]$^+$) 331.1397, found 331.1408.
(S)-6-Chloro-5-(methylsulfamyl)nicotine (118e): $[\alpha]^{22}_D -102$ (c 0.55, CH$_2$Cl$_2$); IR (thin film) 2967, 2779, 1387, 1332, 1137, 1047 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.03 (d, 1H, $J$ = 2.1 Hz), 7.47 (d, 1H, $J$ = 2.1 Hz), 3.23 (dt, 1H, $J$ = 8.7 Hz, $J$ = 2.4 Hz), 3.08 (t, 1H, $J$ = 8.1 Hz), 2.49 (s, 3H), 2.32-2.25 (m, 1H), 2.25-2.18 (m, 1H), 2.16 (s, 3H), 2.00-1.60 (m, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 144.4, 140.9, 138.9, 136.0, 132.3, 68.4, 57.2, 40.7, 35.7, 22.8, 15.1; HRMS calcd for C$_{11}$H$_{15}$ClN$_2$S ([M+H]$^+$) 243.073, found 243.0728.

(S)-6-Chloro-5-(tributylstannyl)nicotine (118f): $[\alpha]^{24}_D - 73$ (c 2.6, CH$_2$Cl$_2$); IR (neat) 2955, 2894, 1542, 1462, 1377, 1113, 1039 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.20 (d, $J$ = 2.7 Hz, 1H), 8.65 (d, $J$ = 2.7 Hz, 1H), 3.22 (t, $J$ = 7.5 Hz, 1H), 3.01 (t, $J$ = 7.8 Hz, 1H), 2.30-2.14 (m, 2H), 2.14 (s, 3H), 2.00-1.60 (m, 3H), 1.52 (q, $J$ = 7.2 Hz, 6H), 1.32 (q, $J$ = 7.2 Hz, 6H), 1.16 (t, $J$ = 7.2 Hz, 6H), 0.88 (t, $J$ = 7.2 Hz, 9H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 157.9, 149.3, 146.5, 139.0, 137.3, 68.6, 57.2, 40.6, 35.4, 29.2, 27.5, 22.8, 13.9, 10.6; HRMS calcd for C$_{22}$H$_{39}$ClN$_2$Sn ([M+H]$^+$) 487.1902, found 487.1902.
(S)-6-Chloro-5-formylnicotine (118g): \([\alpha]_D^{26} -120\ (c\ 0.95,\ CH_2Cl_2)\); IR (neat) 2954, 2780, 1696, 1588, 1560, 1430, 1378, 1071 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\ 10.44\) (s, 1H), 8.55 (d, 1H, \(J = 2.4\) Hz), 8.20 (d, 1H, \(J = 2.4\) Hz), 3.28-3.16 (m, 2H), 2.33 (q, 1H, \(J = 8.4\) Hz), 2.30-2.20 (m, 1H), 2.17 (s, 3H), 2.02-1.62 (m, 3H); \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\ 189.7, 153.9, 152.2, 140.1, 137.4, 128.8, 67.9, 57.1, 40.6, 35.7, 23.0\); HRMS calcd for C\(_{11}\)H\(_{13}\)N\(_2\)O ([M+H]\(^+\)) 225.0795, found 225.0794.

(S)-6-Chloro-2-iodonicotine (120a):

A solution of 2,2,6,6-tetramethylpiperidine (0.76 mmol, 129 µL, 3.0 equiv) in dry THF (1.0 mL) was treated with \(n\)-butyllithium (3.0 equiv) at –78 °C. After 1 h at –78 °C, a solution of (S)-6-chloronicotine (50 mg, 0.25 mmol, 1.0 equiv) in dry THF (0.5 ml) was added dropwise at –78 °C. After 1 h at –78 °C, a solution of iodine (70 mg, 0.275 mmol, 1.1 equiv) in dry THF (1.0 mL) was added at –78 °C. The resulting mixture was stirred at –78 °C for 1 h before being quenched with a saturated aqueous solution of sodium bicarbonate (1 mL) and a saturated aqueous solution of sodium thiosulfate (1 mL). The aqueous layer was extracted with methylene chloride (2 × 5 mL). The combined organic layers were dried over potassium
carbonate and filtered through Celite. The solvent was removed by evaporation under reduced pressure to afford a yellow oil. The crude product was purified by radial PLC (silica gel, 1% TEA/hexanes as eluent) to afford 78 mg (97% yield) of **120a** as a colorless oil with traces amount of (S)-6-chloro-2,5-diiodonicotine (**121**). *(S)-6-Chloro-2-iodonicotine (120a):*

$[\alpha]^{28.5}_D$ - 147 (c 1.5, CH$_2$Cl$_2$); IR (neat) 2967, 2942, 2787, 1563, 1539, 1412, 1310 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.70 (d, $J$ = 8.4 Hz, 1H), 7.27 (d, $J$ = 8.4 Hz, 1H), 3.33 (t, $J$ = 8.0 Hz, 1H), 3.24 (dt, $J$ = 2.4, 8.0 Hz, 1H), 2.46-2.36 (m, 2H), 2.19 (s, 3H), 1.90-1.82 (m, 2H), 1.50-1.38 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 148.8, 143.4, 138.1, 134.5, 124.2, 71.8, 57.0, 40.6, 33.9, 23.1; HRMS calcd for C$_{10}$H$_{12}$IN$_2$Cl ([M+H]$^+$) 322.9812, found 322.9808.

*(S)-6-Chloro-2,5-diiodonicotine (121):* mp 156-157 °C. $[\alpha]^{26}_D$ -105 (c 0.35, CH$_2$Cl$_2$); IR (thin film) 2946, 2921, 2847, 2780, 1503, 1450, 1376, 1327, 1316, 1057, 1047, 912 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.12 (s, 1H), 3.30-3.20 (m, 2H), 2.46-2.36 (m, 2H), 2.21 (s, 3H), 1.92-1.80 (m, 2H), 1.48-1.38 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 150.3, 147.7, 144.9, 120.0, 95.2, 71.2, 57.0, 40.7, 33.9, 23.1; HRMS calcd for C$_{10}$H$_{11}$Cl$_2$N$_2$ ([M+H]$^+$) 448.8700, found 448.8774.

**General procedure for the preparation of C-2 Substituted (S)-6-chloronicotines (120b-e):**

A solution of (S)-6-chloronicotine (1.0 equiv) in freshly distilled toluene (1 mL) was added to a solution of $n$-BuLi-LiDMAE (3.0 equiv) in toluene (3.0 mL) at -78 °C. After 1 h at -78 °C, the electrophile (3.1 equiv) was added neat or as a solution in toluene. After 20 min at -78 °C, the reaction was quenched with 3.0 mL of a saturated aqueous solution of sodium
bicarbonate. The aqueous layer was extracted cold with methylene chloride (2 × 15 mL). The combined organic layers were dried over potassium carbonate and filtered through Celite. The solvent was removed by evaporation under reduced pressure. The crude product was purified by radial PLC (1% TEA/5-20% EtOAc/ hexanes). Yields are reported in Table 8, p.51.

(S)-2,6-Dichloronicotine (120b): [α]26D -191 (c 2.45, CH2Cl2) ; IR (neat) 2968, 2942, 2787, 1574, 1546, 1420, 1322, 1137, 1043 cm⁻¹; 1H NMR (400 MHz, CDCl3) 7.92 (d, 1H, J = 8.0 Hz), 7.27 (d, 1H, J = 8.0 Hz), 3.52 (t, 1H, J = 8.4 Hz), 3.25-3.19 (m, 1H), 2.46-2.32 (m, 2H), 2.20 (s, 3H), 1.92-1.78 (m, 2H), 1.54-1.42 (m, 1H) ; 13C NMR (100 MHz, CDCl3) δ 149.6, 148.2, 139.6, 137.6, 123.7, 66.1, 57.0, 40.8, 33.6, 23.1; HRMS calcd for C10H12Cl2N2 ([M+H]+) 231.0456, found 231.0448.

(S)-6-Chloro-2-(methylsulfanyl)nicotine (120c): [α]28D -163 (c 4, CH2Cl2) ; IR (neat) 2968, 2941, 2778, 1568, 1547, 1412, 1329, 1309, 1204, 1136, 822 cm⁻¹; 1H NMR (400 MHz, CDCl3) 7.67 (d, J = 8.0 Hz, 1H), 6.99 (d, J = 8.0 Hz, 1H), 3.34 (t, J = 8.4 Hz, 1H), 3.23-3.17 (m, 1H), 2.54 (s, 3H), 2.40-2.28 (m, 2H), 2.17 (s, 3H), 1.92-1.75 (m, 2H), 1.52-1.40 (m, 1H) ;
\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 158.65, 148.85, 136.19, 135.82, 119.52, 65.50, 57.02, 40.71, 33.11, 23.05, 13.60; HRMS calcd for C\(_{11}\)H\(_{15}\)ClN\(_2\)S ([M+H]\(^+\)) 243.0723, found 243.0717.

\((S)-6\)-Chloro-2-(tributylstannyl)nicotine (120d): \([\alpha]\)\(^{31}\)\(_D\) -94 (c 4.5, CH\(_2\)Cl\(_2\)) ; IR (neat) 2955, 2919, 2846, 2786, 1551, 1458, 1405, 1099 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.64 (d, \(J = 8.4\) Hz, 1H), 7.12 (d, \(J = 8.4\) Hz, 1H), 3.26-3.18 (m, 1H), 3.04-2.96 (m, 1H), 2.34-2.24 (m, 1H), 2.12 (s, 3H), 2.18-2.04 (m, 1H), 2.00-1.86 (m, 1H), 1.86-1.74 (m, 1H), 1.64-1.46 (m, 6H), 1.38-1.26 (m, 6H), 1.16-1.06 (m, 6H), 0.92-0.82 (m, 9H) ; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 174.78, 150.57, 145.70, 135.42, 123.12, 70.41, 57.08, 40.49, 36.54, 29.29, 27.52, 22.82, 13.91, 11.52; HRMS calcd for C\(_{22}\)H\(_{39}\)ClN\(_2\)Sn ([M+H]\(^+\)) 487.1902, found 487.1881.

\((S)-6\)-Chloro-2-formynicotine (120e): \([\alpha]\)\(^{32}\)\(_D\) -159 (c 1.45, CH\(_2\)Cl\(_2\)) ; IR (neat) 2958, 2782, 1714, 1439, 1165 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) 10.07 (s, 1H), 8.26 (d, \(J = 8.4\) Hz, 1H), 7.49 (d, \(J = 8.4\) Hz, 1H), 4.13 (t, \(J = 8.0\) Hz, 1H), 3.22-3.19 (m, 1H), 2.55-2.35 (m, 2H), 2.16 (s, 3H), 1.88-1.80 (m, 2H), 1.49-1.35 (m, 1H) ; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 196.6, 149.7,
149.6, 142.0, 139.7, 128.7, 64.0, 57.0, 40.8, 34.6, 23.3; HRMS calcd for C_{11}H_{13}ClN_{2}O ([M+H]^+) 225.0795, found 225.0787.

**General procedure for the preparation of C-4 Substituted (S)-6-chloronicotines (119a-h):**

A solution of n-butyllithium (1.1 equiv) was added to (S)-6-chloronicotine (1.0 equiv) in THF at -78 °C. After one hour, the electrophile was added neat or as a solution in THF. The reaction was quenched after 1 h with a saturated aqueous solution of sodium bicarbonate. The mixture was immediately extracted with methylene chloride (2 × 10 mL). The combined organic extracts were dried over potassium carbonate and filtered. The solvents were removed by evaporation, and the crude product was purified by radial PLC (1% TEA/ 5-20% EtOAc/ hexanes). Yields are reported in Table 9, p.52.

![reaction diagram]

(S)-6-Chloro-4-iodonicotine (119a): mp 100-101 °C. [α]_{D}^{27} = -141 (c 3.45, CH_{2}Cl_{2}); IR (thin film) 2961, 2936, 2804, 1553, 1531, 1438, 1361, 1111, 827 cm^{-1}; ^1H NMR (400 MHz, CDCl_{3}) δ 8.37 (s, 1H), 7.74 (s, 1H), 3.34 (t, J = 8.4 Hz, 1H), 3.24 (dt, J = 8.2, 2.0 Hz, 1H), 2.44-2.30 (m, 2H), 2.20 (s, 3H), 1.92-1.76(m, 2H), 1.50-1.40 (m, 1H); ^13C NMR (100 MHz, CDCl_{3}) δ 149.7, 149.1, 141.0, 112.5, 71.7, 57.0, 40.7, 33.9, 22.9; HRMS calcd for C_{10}H_{12}IN_{2}Cl ([M+H]^+) 322.9812, found 322.9804.
(S)-4,6-Dichloronicotine (119c): $[\alpha]^{27}_{D} - 182 \ (c \ 0.55, \text{CH}_2\text{Cl}_2)$; IR (neat) 2955, 2778, 1556, 1450, 1357, 1215, 1108, 876 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.55 (s, 1H), 7.30 (s, 1H), 3.54 (t, $J = 7.6 \text{ Hz, 1H}$), 3.23 (dt, $J = 1.6, 8.4 \text{ Hz, 1H}$), 2.42-2.30 (m, 2H), 2.22 (s, 3H), 1.94-1.76 (m, 2H), 1.58-1.47 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 150.0, 149.9, 145.3, 136.5, 124.2, 65.1, 57.0, 40.9, 33.7, 23.0; HRMS calcd for C$_{12}$H$_{12}$Cl$_2$N$_2$ ([M$^+$]) 230.0378, found 230.0363.

(5)-4-Bromo-6-chloronicotine (119c): $[\alpha]^{25}_{D} - 118 \ (c \ 0.95, \text{CH}_2\text{Cl}_2)$; IR (neat) 2969, 2842, 2786, 1562, 1537, 1440, 1360, 1310, 1223, 1115, 1049 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.53 (s, 1H), 7.50 (s, 1H), 3.53 (t, $J = 8.4 \text{ Hz, 1H}$), 3.25 (dt, $J = 2.0, 8.6 \text{ Hz, 1H}$), 2.46-2.33 (m, 2H), 2.24 (s, 3H), 1.96-1.78 (m, 2H), 1.58-1.48 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 150.0, 149.9, 138.0, 135.9, 127.4, 67.4, 57.0, 40.8, 33.7, 23.0; HRMS calcd for C$_{10}$H$_{12}$BrClN$_2$ ([M+H$^+$]) 273.9872, found 273.9852.
(S)-6-Chloro-4-formylnicotine (119e): $[\alpha]^D_{25} = 209$ (c 1.45, CH$_2$Cl$_2$); IR (neat) 2943, 2784, 1694, 1580, 1549, 1456, 1371, 1321, 1200, 1159, 1079, 1044 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 10.38 (s, 1H), 8.52 (s, 1H), 7.51 (s, 1H), 3.62 (t, $J = 8.4$ Hz, 1H), 3.23 (t, $J = 8.4$ Hz, $J = 2.4$ Hz, 1H), 2.44-2.34 (m, 2H), 2.18 (s, 3H), 2.20-1.86 (m, 2H), 1.86-1.74 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 187.2, 151.5, 150.6, 144.7, 138.0, 122.7, 66.5, 56.7, 40.4, 35.6, 23.4; HRMS calcd for C$_{11}$H$_{13}$ClN$_2$O ([M+H]$^+$) 225.0795, found 225.0796.

(5)-6-Chloro-4-(tributylstannyl)nicotine (119f): $[\alpha]^D_{27} = 81$ (c 3.9, CH$_2$Cl$_2$); IR (neat) 2955, 2922, 2871, 2851, 2778, 1556, 1450, 1357, 1108, 1055 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.42 (s, 1H), 7.29 (s, 1H), 3.24 (dt, $J = 2.4$, 9.2 Hz, 1H), 2.97 (t, $J = 8.4$ Hz, 1H), 2.28 (q, $J = 9.2$ Hz, 1H), 2.15-2.06 (m, 1H), 2.13 (s, 1H), 1.98-1.90 (m, 1H), 1.82-1.76 (m, 1H), 1.64-1.56 (m, 1H), 1.51-1.46 (m, 6H), 1.33 (q, $J = 7.2$ Hz, 6H), 1.11-1.07 (m, 6H), 0.89 (t, $J = 7.2$ Hz, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 157.0, 149.6, 148.5, 144.2, 131.3, 72.0, 57.0, 41.0, 36.8, 29.2, 27.6, 22.6, 13.9, 11.2; HRMS calcd for C$_{22}$H$_{39}$ClN$_2$Sn ([M+H]$^+$) 487.1902, found 487.1881.
(S)-6-Chloro-4-(methylsulfamyl)nicotine (119f): mp: 72 °C; [α]^{27}_D - 159 (c 1, CH₂Cl₂); IR (thin film) 2968, 2942, 2784, 1567, 1530, 1445, 1433, 1367, 1123 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.34 (s, 1H), 6.99 (s, 1H), 3.35 (t, J = 8.4 Hz, 1H), 3.23 (dt, J = 2, 8.4 Hz, 1H), 2.46 (s, 3H), 2.36-2.26 (m, 2H), 2.21 (s, 3H), 1.96-1.86 (m, 1H), 1.86-1.76 (m, 1H), 1.62-1.54 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 152.3, 250.2, 147.3, 134.5, 117.4, 65.6, 57.0, 40.7, 32.9, 23.1, 14.5; HRMS calcd for C₁₁H₁₅ClN₂S ([M+H]^+) 243.0723, found 243.0723.

(S)-(6-Chloronicotin-4-yl)phenyl-methanol (118h): mp 115-116 °C; [α]^{23}_D - 56 (c 1.85, CH₂Cl₂); IR (thin film) 3500-3200, 2968, 2944, 2843, 2790, 1584, 1455, 1374, 1149, 1090, 1041, 896, 699 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.23 (s, 1H), 8.03 (bs, 1H), 7.44-7.35 (m, 5H), 6.68 (s, 1H), 6.09 (s, 1H), 3.38 (t, J = 9.0 Hz, 1H), 3.32 (t, J = 7.6 Hz, 1H), 2.44-2.34 (m, 2H), 2.26-2.16 (m, 2H), 2.21 (s, 3H), 2.25-1.96 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 156.0, 152.1, 151.1, 140.2, 134.3, 128.8, 128.2, 127.3, 124.1, 71.2, 69.6, 57.3, 40.6, 32.6, 24.3; HRMS calcd for C₁₇H₁₉ClN₂O ([M+H]^+) 303.1264, found 303.1250. (S)-(6-Chloronicotin-4-yl)phenyl-methanol (118i): mp 124 °C; [α]^{23}_D - 34 (c 0.6, CH₂Cl₂); IR (thin film) 3450-3200, 2967, 2842, 2787, 1585, 1455, 1372, 1090, 1041, 911, 699 cm⁻¹; ¹H
NMR (400 MHz, CDCl₃) δ 8.36 (s, 1H), 7.42 (s, 1H), 7.34-7.29 (m, 5H), 7.22-7.10 (bs, 1H), 5.88 (s, 1H), 3.26-3.18 (m, 2H), 2.25-2.19 (m, 1H), 2.18 (s, 3H), 1.75-1.58 (m, 3H), 1.25-1.07 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 154.3, 151.6, 151.2, 143.4, 134.4, 128.8, 128.0, 126.6, 124.4, 75.1, 68.7, 56.6, 40.8, 32.6, 22.5; HRMS calcd for C₁₇H₁₉ClN₂O ([M+H]+) 303.1264, found 303.1248.

(S)-5-Chloronicotine (122):

To a solution of (S)-5,6-dichloronicotine (200 mg, 0.865 mmol, 1.0 equiv) in a 1.0 M solution of hydrochloric acid in acetic acid (2 mL) was added zinc powder (230 mg, 3.461 mmol, 4.0 equiv). The suspension was stirred at 60 °C until disappearance of starting material (~2 h, monitored by TLC, co-spot with a solution of 10 % ammonium hydroxide in water and dry). The reaction was then cooled to room temperature. The acetic acid was removed by reduced pressure. The residue was redissolved in deionized water and methylene chloride and solid sodium carbonate was added until pH = 10. The product was extracted with methylene chloride. The combined organic layers were dried over potassium carbonate, filtered through Celite, and the solvent was removed under reduced pressure. The product was purified by radial PLC (1% TEA/ 50% EtOAc/ hexanes) to afford 146 mg (86% yield) of a light yellow oil. [α]³¹_D -148 (c 0.9, CH₂Cl₂); IR (neat) 2968, 2944, 2780, 1581, 1563, 1453, 1418, 1354, 1292, 1214, 1100, 1044, 1022, 882, 709 cm⁻¹; ¹H NMR (400 Hz, CDCl₃) δ 8.44 (d, J = 2.4 Hz, 1H), 8.40 (d, J = 1.6 Hz, 1H), 7.71 (dd, J = 2.4, 1.6 Hz, 1H), 3.23 (dt, J = 2.4,
8.4 Hz, 1H), 3.11 (t, J = 8.0 Hz, 1H), 2.32 (q, J = 8.4 Hz, 1H), 2.26-2.18 (m, 1H), 2.18 (s, 3H), 2.01-1.8 (m, 1H), 1.88-1.76 (m, 1H), 1.7-1.64 (m, 1H); \(^{13}\text{C}\) NMR (100 MHz, CDCl\(_3\)) \(\delta\) 147.7, 147.5, 141.0, 134.7, 132.5, 68.3, 57.1, 40.6, 35.6, 22.9; HRMS calcd for C\(_{10}\)H\(_{13}\)ClN\(_2\) ([M+H]\(^+\)) 197.0846, found 197.0853.

**General procedure for the preparation of C-4 substituted (S)-5-chloronicotines (123a-g):** A solution of (S)-5-chloronicotine (50 mg, 0.251 mmol, 1.0 equiv) in THF (1.0 mL) was added to a solution of \(n\)-BuLi (0.276 mmol, 1.1 equiv) in THF (1.0 mL) at -78 °C. After 1 h at -78 °C, the electrophile (1.2 equiv) was added neat or as a solution in dry THF (1 mL) at -78 °C. The reaction was quenched after 5 min at -78 °C with a saturated aqueous solution of sodium bicarbonate (1 mL). The cold mixture was immediately extracted with methylene chloride (3 \(\times\) 2 mL). The combined organic layers were dried over potassium carbonate, filtered through Celite and silica gel, and concentrated under reduced pressure. The crude product was purified by radial PLC (1 % TEA/20 % EtOAc/hexanes). Yields are reported in Table 11, p.54.

![Chemical structure](image)

**(S)-5-Chloro-4-iodonicotine (123b):** mp 136-137 °C; \([\alpha]^{30}_D\) - 150 (c 1.5, CH\(_2\)Cl\(_2\)); IR (thin film) 2972, 2941, 2832, 2807, 1392, 1219, 1149, 1051 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.44 (s, 1H), 8.41 (s, 1H), 3.48 (t, J = 8.4 Hz, 1H), 3.28 (m, 1H), 2.51-2.34 (m, 2H), 2.25 (s.
3H), 1.98-1.78 (m, 2H), 1.54-1.42 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 146.9, 146.8, 144.8, 137.3, 115.5, 73.5, 57.1, 40.8, 33.8, 23.0; HRMS calcd for C$_{10}$H$_{12}$ClIN$_2$ ([M+H]$^+$) 322.9812, found 322.9801.

(S)-5-Chloro-4-methylsulfamylnicotine (123c): $[\alpha]_{D}^{31}$ -170 (c 2.2, CH$_2$Cl$_2$); IR (neat) 2966, 2944, 2778, 1556, 1455, 1397, 1209, 1147, 1045, 893, 739 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.68 (s, 1H), 8.48 (s, 1H), 3.88 (t, $J$ = 8.4 Hz, 1H), 3.26-3.21 (m, 1H), 2.41 (s, 3H), 2.40-2.30 (m, 2H), 2.21 (s, 3H), 2.00-1.76 (m, 2H), 1.60-1.46 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 147.8, 147.8, 147.5, 144.0, 136.7, 67.1, 57.2, 41.0, 35.0, 23.1, 18.6; HRMS calcd for C$_{11}$H$_{15}$ClN$_2$S ([M+H]$^+$) 243.0723, found 243.0712.

(S)-5-Chloro-4-(formyl)nicotine (123d): $[\alpha]_{D}^{31}$ -74 (c 1.25, CH$_2$Cl$_2$); IR (CH$_2$Cl$_2$) 3060, 3005, 1725, 1431, 1367, 1275, 1223, 1090, 902 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.57 (s, 1H), 8.49 (s, 1H), 8.46 (s, 1H), 3.88-3.80 (m, 1H), 3.14-3.06 (m, 1H), 2.56-2.48 (m, 1H), 2.38-2.30 (m, 1H), 2.33 (s, 3H), 1.86-1.70 (m, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 178.6,
149.0, 146.9, 143.1, 141.1, 129.4, 66.4, 55.2, 40.9, 35.5, 24.4; LRMS calcd for C_{11}H_{13}ClN_{2}O ([M+H]^+) 225.1, found 225.2.

(S)-5-Chloro-4-(tributylstannyl)nicotine (123e): [\alpha]^3_{D} -101 (c 1.55, CH_{2}Cl_{2}) ; IR (neat) 2956, 2920, 2871, 2776, 1457, 1387, 1165, 1137, 1050 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.64 (s, 1H), 8.34 (s, 1H), 3.28-3.20 (m, 1H), 3.08-3.02 (m, 1H), 2.27 (q, \(J = 8.8\) Hz, 1H), 2.17 (s, 3H), 2.17-2.08 (m, 1H), 2.04-1.90 (m, 1H), 1.86-1.74 (m, 1H), 1.70-1.60 (m, 1H), 1.60-1.46 (m, 6H), 1.36-1.26 (m, 6H), 1.24-1.96 (m, 6H), 0.87 (t, \(J = 7.2\) Hz, 9H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 152.9, 147.9, 146.4, 146.2, 140.3, 71.4, 57.0, 40.6, 36.7, 29.2, 27.5, 22.8, 13.9, 13.8; HRMS calcd for C\(_{22}\)H\(_{39}\)ClN\(_{2}\)Sn ([M+H]^+) 487.1842, found 487.1895.

(S)-5-Chloro-4-(dimethylphenylsilyl)nicotine (123f): [\alpha]^3_{D} -87 (c 1.5, CH\(_2\)Cl\(_2\)) ; IR (neat) 3069, 2966, 2941, 2779, 1429, 1394, 1253, 1112, 1073, 822, 781, 733, 704 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.75 (s, 1H), 8.39 (s, 1H), 7.48 (dd, \(J = 1.6, 7.6\) Hz, 2H), 7.40-7.30 (m, 3H), 3.24 (t, \(J = 8.0\) Hz, 1H), 3.07 (t, \(J = 7.6\) Hz, 1H), 2.06-1.96 (m, 1H), 1.90 (s, 3H), 1.88-1.74 (m, 1H), 1.66-1.38 (m, 3H), 0.76 (s, 3H), 0.75 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\)
147.9, 147.8, 147.4, 144.2, 139.5, 138.1, 133.8, 129.6, 128.3, 67.4, 56.7, 40.2, 36.1, 23.0, 2.6, 2.2; HRMS calcd for C18H23ClN2Si ([M+H]+) 331.1397, found 331.1383.

(S)-5-Chloro-4-(trimethylsilyl)nicotine (123g): [α]_D^{30} -158 (c 1.6, CH₂Cl₂); IR (neat) 2966, 2945, 2776, 1454, 1393, 1253, 1135, 1074, 849 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.78 (s, 1H), 8.35 (s, 1H), 3.50-3.45 (m, 1H), 3.25-3.18 (m, 1H), 2.64-2.45 (m, 1H), 2.45-2.16 (m, 1H), 2.17 (s, 3H), 2.02-1.85 (m, 1H), 1.85-1.70 (m, 1H), 1.70-1.58 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 147.7, 147.6, 146.7, 145.7, 137.9, 67.6, 57.0, 40.6, 36.7, 22.9, 3.4; HRMS calcd for C₁₃H₂₁ClN₂Si ([M+H]+) 269.1241, found 269.1222.

(S)-3-(1-Methylpyrrolidin-2-yl)-pyridin-2-yl)phenylmethanone (116m):
A solution of trans-benzyl(chloro)bis(triphenylphosphine)palladium(II) (23 mg, 0.03 mmol, 0.02 equiv) and cesium carbonate (1.09 mg, 3.34 mmol, 2.2 equiv) in 1.0 mL of toluene were degassed for 15 min under argon. Benzoyl chloride (215 µL, 1.82 mmol, 1.2 equiv) was added neat at room temperature. To the mixture was then added a degassed solution of (S)-3-(1-methylpyrrolidin-2-yl)-2-(tricyclohexylstannanyl)pyridine (805 mg, 1.52 mmol, 1.0 equiv)
in 2.5 mL of toluene. The mixture was stirred and heated to 110 °C for 36 h. The reaction was then cooled to room temperature and poured into a 1:1 mixture of methylene chloride and deionized water. The aqueous layer was extracted with methylene chloride (2 × 15 mL) and the combined organic layers were dried over magnesium sulfate, filtered and concentrated. The crude product was purified by radial PLC (silica gel, 1%TEA/MeOH) to afford 215 mg (53%) of a light yellow oil. \([\alpha]_{25}^{D} - 60 \) (c 1.55, CH₂Cl₂); IR (neat) 3059, 2966, 2941, 2840, 2782, 1673, 1449, 1288, 942 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.52 (dd, 1H, \(J = 4.5, 1.5 \) Hz), 8.02 (dd, 1H, \(J = 8.1, 1.8 \) Hz), 7.78 (dd, 2H, \(J = 6.9, 1.5 \) Hz), 7.54 (m, 1H), 7.44-7.36 (m, 3H), 3.32 (t, 1H, \(J = 7 \) Hz), 3.04 (t, 1H, \(J = 7 \) Hz), 2.30-2.15 (m, 2H), 2.03 (s, 3H), 1.90-1.50 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 194.7, 155.9, 147.3, 139.5, 137.0, 136.2, 133.4, 130.2, 128.6, 125.0, 66.7, 56.7, 40.9, 35.9, 23.3; HRMS calcd for C₁₇H₁₈N₂O ([M+H]⁺) 267.1497, found 267.1482.

\[
\begin{align*}
\text{(S)}-6\text{-Chloro-5-(trimethylsilyl)ethynynicotine (132):} \\
\text{A solution of 6-chloro-5-iodonicotine (188 mg, 0.58 mmol, 1.0 equiv), bis(triphenylphosphine)palladium(II) chloride (42 mg, 0.06 mmol, 0.1 equiv) and copper iodide (15 mg, 0.06 mmol, 0.1 equiv) in triethylamine (5 mL) was degassed for 20 min then treated dropwise with (trimethylsilyl)acetylene (95 µL, 0.64 mmol, 1.1 equiv). The mixture was stirred at room temperature for 18 h. The mixture was then diluted in ethyl ether and filtered through a pad of Celite. The filtrate was washed with a 10% solution of ammonium}
\end{align*}
\]
hydroxide until the persistent blue color disappeared. The organic layer was washed once with deionized water, dried over magnesium sulfate, filtered and concentrated. The crude product was purified using radial PLC (silica gel, 1% TEA/hexanes) to afford 122 mg (72 %) of a yellow oil. \([\alpha]^{22}_D -142 (c 0.8, \text{CH}_2\text{Cl}_2); \text{IR (neat)} 2964, 2780, 1396, 1354, 1249, 1077, 844 \text{ cm}^{-1}; \text{H NMR (400 MHz, CDCl}_3) \delta 8.21 (d, J = 2.8 \text{ Hz}, 1\text{H}), 7.82 (d, J = 2.8 \text{ Hz}, 1\text{H}), 3.21 (dt, J = 7.6, 2.4 \text{ Hz}, 1\text{H}), 3.06 (t, J = 8.4 \text{ Hz}, 1\text{H}), 2.31 (q, J = 8.4 \text{ Hz}, 1\text{H}), 2.22-2.16 (m, 1\text{H}), 2.15 (s, 3\text{H}), 2.00-1.87 (m, 1\text{H}), 1.85-1.75 (m, 1\text{H}), 1.70-1.60 (m, 1\text{H}), 0.26 (s, 9\text{H}); \text{C NMR (100 MHz, CDCl}_3) \delta 150.4, 148.1, 141.0, 138.1, 120.3, 103.0, 99.7, 67.9, 57.2, 40.6, 35.5, 22.9, -0.08; \text{HRMS calcd for C}_{15}\text{H}_{21}\text{ClN}_2\text{Si ([M+H] }^+) 293.1241, \text{found 293.1255.}

\[\text{(S)-6-chloro-5-ethynlnicotine (133):}\]

\text{Experimental #1:} A solution of (S)-6-chloro-5-[(trimethylsilyl)acetylene]nicotine (16 mg, 0.05 mmol) in methanol (1.0 mL) was treated dropwise with a 1\text{N} solution of sodium hydroxide (1.0 mL). The mixture was stirred at room temperature for 5 h. Acetic acid was added dropwise. The mixture was poured into a saturated aqueous solution of sodium bicarbonate, and treated with solid sodium carbonate until the pH was basic. The aqueous layer was extracted with ethyl ether. The organic layers were combined, dried over magnesium sulfate, filtered and concentrated. The crude product was purified by radial PLC (silica gel, 1%TEA/hexanes) to afford 10 mg (91 %) of pure a yellow oil.
Experimental #2: Zinc powder was added to a solution of (S)-6-chloro-5-[(trimethylsilyl)acetylene]nicotine (16 mg, 0.05 mmol) in acetic acid. After stirring at 70 °C for hours, the mixture was poured onto a saturated solution of sodium bicarbonate. Solid sodium carbonate was added to the mixture until basic pH was reached. The mixture was then extracted with ethyl ether. The combined organic layers were dried over sodium sulfate, filtered, and the solvents removed by evaporation to afford 6 mg of the product as a yellow oil (50% yield). \([\alpha]^{22}\)D -158 (c 1.75, CH₂Cl₂); IR (neat): 3294, 2968, 2780, 1397, 1351, 1164, 1072, 1043, 909 cm⁻¹ ; 

\[^1\text{H} NMR\) (300 MHz, CDCl₃) δ 8.26 (d, \(J = 2.4\) Hz, 1H), 7.85 (d, \(J = 2.4\) Hz, 1H), 3.45 (s, 1H), 3.22 (dt, \(J = 2.8, 8.5\) Hz, 1H), 3.08 (t, \(J = 8.4\) Hz, 1H), 2.30 (q, \(J = 9.0\) Hz, 1H), 2.20 (m, 1H), 2.15 (s, 3H), 2.00-1.88 (m, 1H), 1.86-1.76 (m, 1H), 1.70-1.60 (m, 1H); 

\[^13\text{C} NMR\) (100 MHz, CDCl₃) δ 151.2, 148.6, 141.4, 138.3, 119.3, 84.7, 78.8, 67.8, 57.1, 40.6, 35.5, 22.9; HRMS calcd for C₁₂H₁₃ClN₂ ([M+H]+) 221.0846, found 221.0838.

\[\text{132} \rightarrow \text{135} + \text{137}\]

(S)-6-Chloro-5-[2-(trimethylsilanyl)ethyl]nicotine (136) and (S)-5-[2-(trimethylsilanyl)ethyl]nicotine (137):

A solution of (S)-6-chloro-5-[(trimethylsilyl)acetylene]nicotine (110 mg, 0.375 mmol, 1.0 equiv) containing sodium acetate (155 mg, 1.878 mmol, 5.0 equiv) in ethanol (3 mL) was hydrogenated over 5% Pd/C at balloon pressure for 18 h. The reaction was filtered through a pad of Celite. The solvent was removed by evaporation. The crude product was purified by radial PLC (silica gel, 1%TEA/ 50% EtOAc/hexanes then 5% MeOH/ CH₂Cl₂) to afford 12
mg (11%) of (S)-6-chloro-5-[2-(trimethylsilanyl)ethyl]nicotine as a colorless oil and 40 mg (41%) of (S)-5-[2-(trimethylsilanyl)ethyl]nicotine as a yellow oil. (S)-6-chloro-5-[2-(trimethylsilanyl)ethyl]nicotine (136): $[\alpha]_{D}^{28} = -117 (c 0.6, \text{CH}_2\text{Cl}_2)$; IR (neat) 2951, 2777, 1560, 1450, 1429, 1404, 1248, 1114, 1066, 861, 835 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.11 (d, $J = 2.4$ Hz, 1H), 7.58 (d, $J = 2.4$ Hz, 1H), 3.24 (m, 1H), 3.05 (m, 1H), 2.71-2.66 (m, 2H), 2.30 (d, $J = 9.2$ Hz, 1H), 2.22-2.16 (m, 1H), 2.16 (s, 3H), 2.02-1.90 (m, 1H), 1.88-1.75 (m, 1H), 1.75-1.60 (m, 1H), 0.88-0.84 (m, 2H), 0.05 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 146.5, 146.5, 139.2, 138.2, 136.9, 68.4, 57.2, 40.6, 35.5, 27.8, 22.8, 16.8, -1.6; HRMS calcd for C$_{15}$H$_{25}$ClN$_2$Si ([M+H]$^+$) 297.1154, found 297.1153. (S)-5-[2-(trimethylsilanyl)ethyl]nicotine (137): $[\alpha]_{D}^{25} = -104 (c 2, \text{CH}_2\text{Cl}_2)$; IR (neat) 2950, 2777, 1456, 1430, 1247, 861, 836 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.33 (d, $J = 2.4$ Hz, 1H), 8.31 (d, $J = 2.4$ Hz, 1H), 7.52 (t, $J = 2.4$ Hz, 1H), 3.24 (m, 1H), 3.04 (m, 1H), 2.63-2.58 (m, 2H), 2.35-2.25 (m, 1H), 2.22-2.14 (m, 1H), 2.15 (s, 3H), 2.02-1.90 (m, 1H), 1.88-1.75 (m, 1H), 1.75-1.65 (m, 1H), 0.89-0.84 (m, 2H), 0.00 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 148.8, 147.2, 140.5, 138.3, 134.0, 69.1, 57.3, 40.7, 35.4, 27.5, 22.8, 18.7, -1.5; HRMS calcd for C$_{15}$H$_{26}$N$_2$Si ([M+H]$^+$) 263.1944, found 263.1934.
(S)-6-Chloro-5-[(triisopropylsilyl)acetylene]nicotine (138):

A solution of 6-chloro-5-iodonicotine (47.5 mg, 0.15 mmol, 1.0 equiv), bis(triphenylphosphine)palladium(II) chloride (11 mg, 0.015 mmol, 0.1 equiv) and copper iodide (3 mg, 0.015 mmol, 0.1 equiv) in freshly distilled triethylamine (3 mL) was degassed with argon for 20 min then treated dropwise with (triisopropylsilyl)acetylene (37 µL, 0.165 mmol, 1.1 equiv). The mixture was stirred at room temperature for 15 h. The mixture was diluted with ethyl ether and filtered through a pad of Celite. The filtrate was washed with a 10% solution of ammonium hydroxide until the persistent blue color disappeared. The organic layer was washed once with deionized water, dried over sodium sulfate, filtered and concentrated. The crude product was purified using radial PLC (silica gel, 1% TEA/20% EtOAc/hexanes) to afford 135 mg (99%) of a yellow oil. $[\alpha]_{D}^{31} -109$ (c 0.35, CH$_2$Cl$_2$); IR (neat) 2944, 2866, 2781, 1462, 1397, 1077, 882 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 8.22 (d, $J = 2.4$ Hz, 1H), 7.80 (d, $J = 2.4$ Hz, 1H), 3.24 (dt, $J = 2.4$, 8.4 Hz, 1H), 3.08 (t, $J = 8.1$ Hz, 1H), 2.32 (q, $J = 9.0$ Hz, 1H), 2.25 (m, 1H), 2.18 (s, 3H), 2.02-1.90 (m, 1H), 1.90-1.76 (m, 1H), 1.76-1.62 (m, 1H), 1.15-1.13 (m, 21H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 151.6, 148.0, 140.7, 137.9, 120.6, 101.4, 99.9, 68.1, 57.2, 40.7, 35.5, 22.9, 18.9, 11.5; HRMS calcd for C$_{21}$H$_{33}$Cl$_2$N$_2$Si ([M+H]$^+$) 377.2180, found 377.2202.

(5)-5-[(Triisopropylsilyl)acetylene]nicotine (139):

135
Zinc powder (100 mg) was added to a solution of (S)-6-chloro-5-[(triisopropylsilyl)acetylene]nicotine (40 mg, 0.10 mmol) in acetic acid (3 mL). The mixture was stirred at 75 °C for 16 h. Since starting material was present by TLC, an extra 140 mg of zinc powder was added to the reaction mixture. The starting material spot was gone after 5 h of additional stirring at 75 °C. The mixture was poured into a saturated aqueous solution of sodium bicarbonate and treated with solid sodium carbonate until a basic pH was reached. The aqueous layer was extracted with methylene chloride. The organic layers were combined, dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified by radial PLC (silica gel, 1%TEA/ 20% EtOAc/hexanes) to afford 19 mg (52 %) of the product as a yellow oil. [α]$^2$D -130 (c 0.5, CH$_2$Cl$_2$); IR (neat) 2944, 2865, 1780, 2158, 1500, 1414, 1153, 996, 883 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 8.57 (d, $J$ = 1.8 Hz, 1H), 7.44 (d, $J$ = 1.8 Hz, 1H), 7.75 (t, $J$ = 1.8 Hz), 3.25 (dt, $J$ = 1.5, 8.7 Hz, 1H), 3.07 (t, $J$ = 8.1 Hz, 1H), 2.31 (q, $J$ = 8.1 Hz, 1H), 2.24-2.14 (m, 1H), 2.17 (s, 3H), 2.04-1.68 (m, 3H), 1.15-1.11 (m, 21H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 151.9, 148.7, 138.5, 137.8, 120.7, 103.8, 94.6, 68.8, 57.3, 40.7, 35.4, 22.9, 18.9, 11.5; HRMS calcd for C$_{21}$H$_{34}$N$_2$Si ([M+H]$^+$) 343.2570, found 343.2560.
(S)-5-[2-triisopropylsilanyl]-ethyl]nicotine (140):

To a solution of (S)-6-chloro-5-[2-triisopropylsilanyl]acetylene]nicotine (20 mg, 0.053 mmol, 1.0 equiv) in 3.0 mL of methanol was treated with 3.0 mL of a 1 N solution of sodium hydroxide. Pearlman’s catalyst (palladium hydroxide) was added to the mixture which was degassed and back-filled with hydrogen three times. The reaction was stirred under hydrogen at balloon pressure for 2 hours at room temperature. The mixture was filtered through Celite and silica gel, and the filtrate was extracted with methylene chloride to afford the product as a colorless oil in 22 % yield (4 mg). $[\alpha]^{29}_D$ - 108 (c 0.2, CH$_2$Cl$_2$); IR (neat) 2942, 2866, 2778, 1461, 883, 694 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.34 (d, $J$ = 2.8 Hz, 1H), 8.33 (d, $J$ = 2.8 Hz, 1H), 7.51 (t, $J$ = 2.8 Hz, 1H), 3.25 (m, 1H), 3.05 (t, $J$ = 12.0 Hz, 1H), 2.69-2.63 (m, 2H), 2.30 (q, $J$ = 11.2 Hz, 1H), 2.24-1.98 (m, 1H), 2.17 (s, 3H), 2.04-1.68 (m, 3H), 1.10-1.04 (m, 21H), 0.96-0.90 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 148.6, 147.3, 133.9, 69.2, 57.3, 40.7, 35.3, 28.1, 22.7, 19.1, 12.0, 11.1; HRMS calcd for C$_{21}$H$_{38}$N$_2$Si ([M+H]$^+$) 347.2883, found 347.2878.
(S)- SIB-1508Y (13):

A solution of (S)-5-[(triisopropylsilyl)actelyene]nicotine (32 mg, 0.093 mmol, 1.0 equiv) in THF (2 mL) was treated at room temperature with a 1.0M solution of TBAF (112 μL, 0.112 mmol, 1.2 equiv). The mixture was stirred at room temperature for 20 min. The solvent was then removed under reduced pressure, and the crude product was purified by radial PLC (silica gel, 1%TEA/ 50% EtOAc/hexanes) to afford 17 mg (98%) of SIB-1508Y as a brown oil. [α]$_{30}^{D}$ -162 (c 0.77 , EtOH); $^1$H NMR (400 MHz, CDCl$_3$) δ 8.60 (d, $J$ = 2.4 Hz, 1H), 8.49 (d, $J$ = 2.4 Hz, 1H), 7.80 (t, $J$ = 2.4 Hz, 1H), 3.25 (t, $J$ = 8.4 Hz, 1H), 3.20 (s, 1H), 3.09 (t, $J$ = 8.4 Hz, 1H), 2.36-2.26 (m, 1H), 2.26-2.15 (m, 1H), 2.17 (s, 3H), 2.02-1.90 (m, 1H), 1.88-1.76 (m, 1H), 1.75-1.64 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 151.7, 149.2, 138.9, 138.2, 119.3, 80.8, 80.5, 68.6, 57.2, 40.6, 35.5, 22.9.

(S)-6-Chloro-5-(1-decyne)nicotine (141):

A solution of 6-chloro-5-iodonicotine (72 mg, 0.22 mmol, 1.0 equiv), bis(triphenylphosphine)palladium(II) chloride (15 mg, 0.022 mmol, 0.1 equiv) and copper iodide (4 mg, 0.022 mmol, 0.1 equiv) in freshly distilled triethylamine (3 mL) was degassed
with argon for 20 min then treated dropwise with 1-decyne (45 µL, 0.24 mmol, 1.1 equiv) for 42 h. One mL of a saturated aqueous solution of sodium bicarbonate was added. The mixture was extracted with methylene chloride (2 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. The crude product was purified using radial PLC (silica gel, 1% TEA/20% ethyl acetate/hexanes) to afford 48 mg (66%) of a colorless oil. [α]$_{30}^{D}$ -108 (c 1.4, CH$_2$Cl$_2$); IR (neat) 2927, 2855, 2783, 1399, 1095 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.17 (d, $J = 1.8$ Hz, 1H), 7.74 (d, $J = 1.8$ Hz, 1H), 3.21 (dt, $J = 1.8$, 8.4 Hz, 1H), 3.05 (t, $J = 8.4$ Hz, 1H), 2.46 (t, $J = 6.9$ Hz, 2H), 2.29 (q, $J = 8.4$ Hz, 1H), 2.22-2.18 (m, 2H), 2.15 (s, 3H), 2.10-1.88 (m, 1H), 1.88-1.78 (m, 1H), 1.70-1.60 (m, 2H), 1.52-1.42 (m, 2H), 1.36-1.24 (m, 8H), 0.90-0.85 (m, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 151.0, 147.3, 140.6, 138.0, 98.7, 94.5, 76.2, 68.0, 57.2, 40.6, 35.5, 32.1, 29.4, 29.3, 29.1, 28.6, 22.90, 22.88, 19.9, 14.4; HRMS calcd for C$_{20}$H$_{29}$ClN$_2$ ([M+H]$^+$) 333.2098, found 333.2108.

(S)-5-(1-Decyne)nicotine (142):
Zinc powder (120 mg) was added to a solution of (S)-6-chloro-5-(1-decyne)nicotine (28 mg, 0.075 mmol) in acetic acid (3 mL). The mixture was stirred at 70 °C for 10 h. The solvent was removed by evaporation, the residue was dissolved in methylene chloride and filtered through a pad of Celite. The crude product was purified by radial PLC (silica gel, 1% TEA/
20% EtOAc/hexanes) to afford 10 mg (46%) of the product as a colorless oil. \([\alpha]^{29}_D - 83\) (c 0.5, CH2Cl2); IR (neat) 2928, 2856, 2780, 1454 cm\(^{-1}\); \(^1\)H NMR (300 MHz, CDCl3) \(\delta\) 8.49 (d, \(J = 1.8\) Hz, 1H), 8.39 (d, \(J = 1.8\) Hz, 1H), 7.70 (t, \(J = 1.8\) Hz, 1H), 3.23 (dt, \(J = 1.8, 8.7\) Hz, 1H), 3.05 (t, \(J = 8.1\) Hz, 1H), 2.40 (t, \(J = 7.2\) Hz, 2H), 2.28 (q, \(J = 9.6\) Hz, 1H), 2.22-2.17 (m, 1H), 2.16 (s, 3H), 2.00-1.90 (m, 1H), 1.88-1.78 (m, 1H), 1.78-1.64 (m, 1H), 1.64-1.54 (m, 2H), 1.48-1.36 (m, 2H), 1.36-1.20 (m, 8H), 0.90-0.86 (m, 3H); \(^{13}\)C NMR (75 MHz, CDCl3) \(\delta\) 151.3, 148.0, 138.5, 137.6, 121.2, 100.1, 94.1, 77.5, 68.8, 57.2, 40.7, 35.4, 32.1, 29.4, 29.3, 29.2, 28.8, 22.9, 19.7, 14.4; HRMS calcd for C\(_{20}\)H\(_{30}\)N\(_2\) ([M+H]+) 299.2487, found 299.2487.

\(\text{(S)-5,6-Dichloro-4-iodonicotine (151):}\)

A solution of \(n\)-BuLi (0.71 mmol, 1.1 equiv) in hexanes was added to a solution of \(\text{(S)-5,6-dichloronicotine (150 mg, 0.65 mmol, 1.0 equiv) in THF (2 mL) at - 78 °C. After 1 h at -78 °C, a solution of iodine (200 mg, 0.78 mmol, 1.2 equiv) was added to the mixture at - 78 °C. After 5 min at - 78 °C, the reaction was quenched with a saturated solution of sodium bicarbonate (1 mL) and a saturated solution of sodium thiosulfate (1 mL). The mixture was immediately extracted with methylene chloride (2 \(\times\) 10 mL). The combined organic layers were dried over potassium carbonate and filtered. The solvents were removed by evaporation, and the crude product was purified by radial PLC (silica gel, 1% TEA/ 10% EtOAc/ hexanes) to afford 185 mg (80%) of a white solid, mp 107-108 °C. \([\alpha]^{27}_D - 158\) (c
1.6, CH₂Cl₂) ; IR (thin film) 2969, 2944, 2844, 2786, 1539, 1512, 1456, 1397, 1357, 1341, 1183, 1155 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.28 (s, 1H), 3.43 (t, J = 8.4 Hz, 1H), 3.27 (dt, J = 2.0, 8.2 Hz, 1H), 2.52-2.35 (m, 2H), 2.24 (s, 3H), 1.94-1.76 (m, 2H), 1.50-1.40 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 146.8, 146.5, 144.3, 135.2, 117.5, 73.5, 57.0, 40.8, 33.8, 23.0; HRMS calcd for C₁₀H₁₁Cl₂IN₂ ([M+H]⁺) 356.9422, found 356.9420.

N
N
Cl
Cl
Cl
Cl
SnBu₃
118b 161

(S)-5,6-Dichloro-4-(tributyl)stannynicotine (161):

(S)-5,6-Dichloronicotine (190 mg, 0.82 mmol, 1.0 equiv) was added to a solution of lithium diisopropylamine (0.90 mmol, 1.1 equiv) in THF (2 mL) at -78 °C. After 1 h at -78 °C, tributyltin chloride (270 mg, 0.99 mmol, 1.2 equiv) was added to the mixture at -78 °C. After 5 min at -78 °C, the reaction was quenched with a saturated solution of sodium bicarbonate (1 mL), and the mixture was warmed to room temperature. The mixture was extracted using methylene chloride (2 × 10 mL). The combined organic layers were dried over potassium carbonate and filtered. The solvents were removed by evaporation and the crude product was purified by radial PLC (1% TEA/20% EtOAc/hexanes) to afford 264 mg (62 %) of a clear oil. [α]²³D -196 (c 4, CH₂Cl₂) ; IR (neat) 2972, 2856, 2783, 1540, 1524, 1459, 1403, 1352, 1339, 1170, 1066, 1046, 875 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.46 (s, 1H), 3.22 (t, J = 8 Hz, 1H), 3.07 (m, 1H), 2.40-2.20 (m, 2H), 2.15 (s, 3H), 2.14-2.06 (m, 1H), 2.00-1.86 (m, 1H), 1.84-1.74 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 157.6, 149.6, 147.1,
146.0, 137.0, 70.6, 56.9, 40.5, 36.8, 29.1, 27.5, 22.8, 14.3, 13.8; HRMS calcd for C_{22}H_{38}Cl_{2}N_{2}Sn ([M+H]^+) 521.1512, found 521.1529.

(S)-5,6-Dichloro-4-[(diethyl)borane]nicotine (162):

(S)-5,6-Dichloronicotine (140 mg, 0.606 mmol, 1.0 equiv) was added to a solution of lithium diisopropylamine (0.666 mmol, 1.1 equiv) in THF (4 mL) at -78 °C. After 2 h at -78 °C, a 0.1 M solution of triethylborane in THF (1.33 mL, 1.33 mmol, 2.2 equiv) was added dropwise. The reaction was slowly warmed to -23 °C for 10 h. The mixture was then cooled to -78 °C and a solution of iodine (340 mg, 1.33 mmol, 2.2 equiv) was added. The reaction was quickly quenched with a saturated solution of sodium bicarbonate (1 mL) and a saturated solution of sodium thiosulfate (1 mL). The mixture was quickly extracted using methylene chloride (2 × 10 mL). The combined organic layers were dried over potassium carbonate and filtered. The solvents were removed by evaporation and the crude product was purified by radial PLC (silica gel, 1% TEA/ 20% EtOAc/ hexanes) to afford 104 mg (57 %) of a white solid, mp 129 °C. [α]_{D}^{28} + 8 (c 0.55, CH_{2}Cl_{2}); IR (thin film) 2949, 2907, 2871, 1572, 1461, 1421, 1311, 1163, 1125, 872, 729 cm⁻¹; ^{1}H NMR (400 MHz, CDCl_{3}) δ 7.84 (s, 1H), 4.50 (d, J = 8.0 Hz, 1H), 3.04 (m, 1H), 2.94 (m, 1H), 2.63 (s, 3H), 2.54-2.44 (m, 1H), 2.34-2.26 (m, 1H), 2.19-2.06 (m, 1H), 1.60 (d, J = 4.0 Hz, 1H), 1.15-1.10 (m, 1H), 0.97 (m, 3H), 0.75-
0.60 (m, 6H), 0.44-0.36 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 148.6, 140.1, 139.9, 132.6, 73.4, 56.5, 42.1, 27.5, 21.8, 10.9, 10.7; HRMS calcd for C$_{14}$H$_{21}$BCl$_2$N$_2$ ([M+H]$^+$) 299.1253, found 299.1249.

![Chemical Structure](image)

(S)-4,6-Dichloro-5-iodonicotine (167b):

A solution of (S)-4,6-dichloronicotine (115 mg, 0.497 mmol, 1.0 equiv) was added to a solution of lithium diisopropylamine (77 $\mu$L, 0.547 mmol, 1.1 equiv) in THF (3 mL) at –78 °C. After one hour at –78 °C, a solution of iodine (152 mg, 0.597 mmol, 1.2 equiv) in THF (1 mL) was added to the mixture at –78 °C. After an hour at –78 °C, the reaction was quenched with a saturated solution of sodium bicarbonate (1 mL) and a saturated solution of sodium thiosulfate (1 mL). The mixture was warmed to room temperature and the product was extracted with methylene chloride (3 × 5 mL). The combined organic layers were dried over potassium carbonate, filtered, and the solvents were removed under reduced pressure. The crude product was purified by radial PLC (silica gel, 1% TEA/ 20% EtOAc/ hexanes) to afford 134.1 mg (76% yield) of a white solid, mp: 74 °C. $[\alpha]_{D}^{23}$ -149 (c 3.85, CH$_2$Cl$_2$) ; IR (thin film) 2953, 2916, 2872, 2841, 2812, 2776, 1548, 1515, 1445, 1392, 1354, 1207, 1151, 1076, 1044, 838, 737 cm$^{-1}$; $^1$H NMR (400 Hz, CDCl$_3$) $\delta$ 8.50 (s, 1H), 3.57 (t, $J$ = 8.4 Hz, 1H), 3.24 (dt, $J$ = 2.0, 8.2 Hz, 1H), 2.45-2.25 (m, 2H), 2.24 (s, 3H), 1.95-1.70 (m, 2H), 1.60-1.40
\( ^{13}\text{C} \) NMR (100 MHz, CDCl\(_3\)) \( \delta \) 154.5, 150.0, 148.7, 137.7, 101.3, 66.9, 57.0, 40.9, 33.6, 23.1; HRMS calcd for \( \text{C}_{10}\text{H}_{11}\text{Cl}_{2}\text{I}_{2}([\text{M+H}]^+) \) 356.9422, found 356.9391.

\( \text{(S)-4-Bromo-6-chloro-5-iodonicotine (167c):} \)

A solution of (S)-4-bromo-6-chloronicotine (300 mg, 1.088 mmol, 1.0 equiv) in THF (2 mL) was added to a solution of lithium diisopropylamine (152 \( \mu \)L, 1.088 mmol, 1.0 equiv) in THF (3 mL) at \(-78^\circ\text{C}\). After one hour at \(-78^\circ\text{C}\), a solution of iodine (305 mg, 1.197 mmol, 1.1 equiv) was added to the reaction. After 5 min at \(-78^\circ\text{C}\), the reaction was quenched with a saturated solution of sodium bicarbonate (1 mL) and a saturated solution of sodium thiosulfate (1 mL). The product was extracted with methylene chloride (2 \( \times \) 2 mL). The combined organic layers were dried over potassium carbonate, filtered and concentrated. The crude product was purified by radial PLC (silica gel, 1% TEA/20% EtOAc/hexanes) to afford 379.6 mg (87%) of a white solid, mp: 82-83 \(^\circ\text{C}\). [\( \alpha \)]\text{D}\(^{29}\) -147 (c 2.25, CH\(_2\)Cl\(_2\)); IR (thin film) 2948, 2840, 2779, 1540, 1512, 1448, 1390, 1353, 1335, 1311, 1209, 1156 cm\(^{-1}\); \(^1\text{H} \) NMR (400 Hz, CDCl\(_3\)) \( \delta \) 8.49 (s, 1H), 3.57 (t, \( J = 8.0 \) Hz, 1H), 3.26 (t, \( J = 8.8 \) Hz, 1H), 2.48-2.32 (m, 2H), 2.25 (s, 3H), 1.94-1.78 (m, 2H), 1.56-1.44 (m, 1H); \(^{13}\text{C} \) NMR (100 MHz, CDCl\(_3\)) \( \delta \) 154.3, 148.6, 143.8, 140.1, 104.9, 69.8, 57.0, 40.9, 33.6, 23.1; HRMS calcd for \( \text{C}_{10}\text{H}_{11}\text{BrClI}_{2}([\text{M+H}]^+) \) 400.8917, found 400.8887.
(S)-Bromophenyl(2,4-dichloronicotin-5-yl)amine (166a):

A solution of (S)-4,6-dichloro-5-iodonicotine (110 mg, 0.308 mmol, 1.0 equiv), Pd$_2$(dba)$_3$ (14 mg, 0.015 mmol, 5 %), cesium carbonate (150 mg, 0.462 mmol, 1.5 equiv) and Xantphos (18 mg, 0.031 mmol, 10 %) in 3 mL of 1,4-dioxane was degassed for 15 minutes with argon. 2-Bromoaniline (5.8 mg, 0.339 mmol, 1.1 equiv) was then added to the mixture that was degassed for an additional 5 minutes. The mixture was then warmed to 110 °C and stirred for 3 h (disappearance of starting material by TLC). The reaction was then cooled to room temperature and poured into deionized water. The product was extracted with methylene chloride (3 × 5 mL). The combined organic layers were dried over potassium carbonate, filtered, and the solvents were removed under reduced pressure. The crude product was purified by radial PLC (silica gel, 1% TEA/ 50% EtOAc/hexanes) to afford 66 mg (53 % yield) of a yellow oil. [$\alpha$]$^\text{27}_D$ -110 (c 3.15, CH$_2$Cl$_2$) ; IR (neat) 3371, 2967, 2942, 2781, 1593, 1501, 1495, 1425, 1404, 1300, 1024, 744 cm$^{-1}$; $^1$H NMR (400 Hz, CDCl$_3$) $\delta$ 8.49 (s, 1H), 7.55 (dd, $J$ = 1.2, 8.0 Hz, 1H), 7.13 (dt, $J$ = 1.6, 8.4 Hz, 1H), 6.79 (dt, $J$ = 1.6, 7.8 Hz, 1H), 6.35 (dd, $J$ = 1.2, 8.0 Hz, 1H), 6.08 (bs, 1H), 3.59 (t, $J$ = 8.0 Hz, 1H), 3.26 (dt, $J$ = 1.6 Hz, $J$ = 8.4 Hz, 1H), 2.48-2.34 (m, 2H), 2.29 (s, 3H), 2.00-1.80 (m, 2H), 1.64-1.54 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 147.3, 145.5, 141.7, 140.4, 138.2, 133.0, 132.4, 128.1, 121.8, 115.2, 111.9, 65.8, 57.1, 41.0, 33.7, 23.1; HRMS calcd for C$_{16}$H$_{16}$BrCl$_2$N$_3$ ([M+H]$^+$) 399.9983, found 399.9966.
(S)-(2-Bromophenyl)[4-bromo-6-chloronicotin-3-yl]amine (166b):

To a solution of (S)-4-bromo-6-chloro-5-iodonicotine (300 mg, 0.747 mmol, 1.0 equiv), Pd$_2$dba$_3$ (34 mg, 0.037 mmol, 5 %), cesium carbonate (365 mg, 1.121 mmol, 1.5 equiv), and Xantphos (45 mg, 0.075 mmol, 10 %) in 3 mL of 1,4-dioxane was added 2-bromoaniline (101 µL, 0.897 mmol, 1.2 equiv). The mixture was degassed with argon for 15 min, then warmed to 110 °C and stirred for 20 h. The reaction was cooled to room temperature and poured into deionized water (5 mL). The product was extracted with methylene chloride (3 × 3mL). The combined organic layers were dried over potassium carbonate, filtered and concentrated. The crude product was purified by radial PLC (silica gel, 1% TEA / 18% EtOAc / 20% CH$_2$Cl$_2$/ hexanes) to afford 228 mg (68%) of a light-yellow foamy oil. [α]$^2$D - 106 (c 2.4, CH$_2$Cl$_2$); IR (neat) 3368, 3063, 2966, 2941, 2780, 1593, 1538, 1505, 1399, 1202, 1045, 1024, 907, 743 cm$^{-1}$; $^1$H NMR (400 Hz, CDCl$_3$) $\delta$ 8.44 (s, 1H), 7.56 (dt,$J$ = 1.6, 7.6 Hz, 1H), 7.13 (t,$J$ = 7.6 Hz, 1H), 6.79 (dt,$J$ = 7.6, 1.6 Hz, 1H), 6.34 (d,$J$ = 8.0 Hz, 1H), 6.11 (s, 1H), 3.57 (t,$J$ = 8.0 Hz, 1H), 3.28 (t,$J$ = 8.0 Hz, 1H), 2.50-2.35 (m, 2H), 2.29 (s, 3H), 2.00-1.80 (m, 1H), 1.62-1.50 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 147.5, 145.9, 140.5, 140.1, 135.3, 133.8, 133.0, 128.2, 121.7, 115.1, 111.7, 68.2, 57.1, 41.0, 33.8, 23.1, 23.0; HRMS calcd for C$_{16}$H$_{16}$Br$_2$ClN$_3$ ([M+H]$^+$) 443.9478, found 443.9434.
(S)-2-(Bromophenyl)[6-chloronicotin-3-yl]amine (166c):

A solution of (S)-6-chloro-5-iodonicotine (100 mg, 0.310 mmol, 1.0 equiv), Pd$_2$(dba)$_3$ (14 mg, 0.016 mmol, 5%), cesium carbonate (152 mg, 0.465 mmol, 1.5 equiv) and Xantphos (18 mg, 0.031 mmol, 10 %) in 3 mL of 1,4-dioxane was degassed for 15 minutes with argon. 2- Bromoaniline (80 mg, 0.465 mmol, 1.5 equiv) was then added to the mixture which was degassed for an additional 5 minutes. The mixture was warmed to 110 °C and stirred for 18 h. The reaction was cooled to room temperature and poured into deionized water. The product was extracted with methylene chloride (3 × 5 mL). The combined organic layers were dried over potassium carbonate, filtered, and the solvents were removed under reduced pressure. The crude product was purified by radial PLC (silica gel, 1% TEA/ 50% EtOAc/ hexanes) to afford 55 mg (48% yield) of a yellow oil. $[\alpha]_{D}^{30} -92$ (c 2.35, CH$_2$Cl$_2$); IR (neat) 3384, 2940, 2910, 2778, 1582, 1510, 1460, 1432, 1382, 1364, 1176, 1066, 1045, 1025, 992, 747 cm$^{-1}$; $^1$H NMR (400 Hz, CDCl$_3$) δ 7.89 (d, $J$ = 2.4 Hz, 1H), 7.60 (d, $J$ = 8.8 Hz, 1H), 7.58 (d, $J$ = 2.4 Hz, 1H), 7.27 (m, 2H), 6.91 (m, 1H), 6.45 (bs, 1H), 3.18 (dt, $J$ = 2.0, 8.6 Hz, 1H), 3.04 (t, $J$ = 2.4 Hz, 1H), 2.27 (q, $J$ = 8.8 Hz, 1H), 2.22-2.14 (m, 1H), 2.17 (s, 3H), 1.96-1.84 (m, 1H), 1.84-1.72 (m, 1H), 1.70-1.60 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 140.5, 139.5, 139.2, 139.0, 136.1, 133.7, 128.6, 123.8, 122.3, 118.8, 115.4, 68.3, 57.1, 40.6, 35.6, 22.8; HRMS calcd for C$_{16}$H$_{17}$BrClN$_3$ ([M+H]$^+$) 366.0373, found 366.0370.
(S)-6-Chloro-4-bromo-5-[(2-amino)phenyl]nicotine (169):

A solution of (S)-4-bromo-6-chloro-5-iodonicotine (90.0 mg, 0.213 mmol, 1.0 equiv), 2-aminophenylpinacolboronate (70.0 mg, 0.319 mmol, 1.5 equiv), Pd$_2$dba$_3$ (10.0 mg, 0.011 mmol, 0.05 equiv.), cesium carbonate (105.0 mg, 0.319 mmol, 1.5 equiv) and Xantphos (12.0 mg, 0.021 mmol, 0.1 equiv) in 1,4-dioxane (4.0 mL) was degassed with argon for 15 min and then warmed to 110 °C for 3 d. The reaction was cooled to room temperature and poured into deionized water (3 mL). The products were extracted with methylene chloride (3 × 3 mL). The combined organic layers were dried over potassium carbonate, filtered through Celite and concentrated. The crude product was purified by radial PLC (silica gel, 1% Et$_3$N/50% EtOAc/hexanes) to afford 30.0 mg (39% yield) of a yellow oil. [α]$^{32}_D$ -120 (c 0.3, CH$_2$Cl$_2$); IR (neat) 3471, 3364, 2971, 2946, 2784, 1620, 1539, 1457, 1370, 732 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.58 (s, 1H), 7.32-7.25 (m, 1H), 6.98-6.82 (m, 3H), 3.63-3.56 (m, 1H), 3.47 (brs, 1H), 3.31-3.24 (m, 1H), 2.55-2.32 (m, 2H), 2.29 (s, 3H), 1.96-1.80 (m, 2H), 1.64-1.50 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 149.1, 149.0, 143.5, 139.4, 134.6, 130.2, 130.1, 123.9, 119.0, 119.0, 116.2, 68.2, 57.0, 41.0, 33.7, 23.1; HRMS calcd for C$_{16}$H$_{17}$BrClN$_3$ ([M+H]$^+$) 366.0373, found 366.0345.
(S)-5-Bromo-6-chloro-4-iodonicotine (170b):

A solution of (S)-5-bromo-6-chloronicotine (320 mg, 1.161 mmol, 1.0 equiv) in THF (3 mL) was added to a solution of LDA (1.277 mmol, 1.1 equiv) in THF (3 mL) at -78 °C. After one hour, a solution of iodine (355 mg, 1.393 mmol, 1.2 equiv) in THF (2 mL) was added to the mixture. After 5 min at -78 °C, the reaction was quenched with a saturated solution of sodium bicarbonate, and the mixture was warmed to room temperature. The mixture was extracted using methylene chloride (2 × 5 mL). The combined organic extracts were dried over potassium carbonate and filtered. The solvents were removed by evaporation and the crude product was purified by radial PLC (silica gel, 1% TEA/10% EtOAc/hexanes) to afford 260 mg (56%) of a white solid, mp 120-122 °C. \([\alpha]_{D}^{30} -114 (c\, 1.4, \text{CH}_2\text{Cl}_2)\); IR (thin film) 2971, 2945, 2840, 2789, 1539, 1389, 1355, 1160, 1043, 709 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\) ) \(\delta\) 8.33 (s, 1H), 3.44 (t, \(J = 8.0\) Hz, 1H), 3.29-3.23 (m, 1H), 2.50-2.32 (m, 2H), 2.23 (s, 3H), 1.94-1.76 (m, 2H), 1.50-1.38 (m, 1H); \(^13\)C NMR (100 MHz, CDCl\(_3\) ) \(\delta\) 148.8, 147.1, 144.6, 128.8, 121.0, 74.1, 57.0, 40.9, 33.8, 23.1; HRMS calcd for C\(_{10}\)H\(_{11}\)BrClIN\(_2\) ([M+H])\(^+\) 400.8917, found 400.8915.
(S)-5,6-Dichloro-4-[(2-amino)phenyl]nicotine (171a):

A solution of (S)-5,6-dichloro-4-iodonicotine (185 mg, 0.518 mmol, 1.0 equiv), 2-aminophenylpinacolboronate (113 mg, 0.518 mmol, 1.0 equiv), Pd$_2$dba$_3$ (24 mg, 0.026 mmol, 0.05 equiv), cesium carbonate (253 mg, 0.777 mmol, 1.5 equiv) and Xantphos (30 mg, 0.052 mmol, 0.10 equiv) in 1,4-dioxane (4.0 mL) was degassed with argon for 15 min and then warmed to 110 °C for 15 h. The reaction was cooled to room temperature and poured into deionized water (3 mL). The products were extracted with methylene chloride (3 × 3 mL). The combined organic layers were dried over potassium carbonate, filtered through Celite and concentrated. The crude product was purified by radial PLC (silica gel, 1% Et$_3$N/50% EtOAc/hexanes) to afford 35 mg (21% yield) of a yellow oil. [α]$^\text{D}$ - 102 (c 0.25, CH$_2$Cl$_2$); IR (neat) 3467, 3358, 3225, 2970, 2943, 2783, 1620, 1505, 1456, 1355, 750 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 8.63 (s, 1H), 7.28-7.22 (m, 1H), 6.88-6.76 (m, 3H), 3.38 (br s, 2H), 3.18-3.10 (m, 1H), 3.02-2.96 (m, 1H), 2.18-2.08 (m, 1H), 2.14 (s, 3H), 2.08-1.96 (m, 1H), 1.96-1.78 (m, 2H), 1.70-1.50 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 149.0, 148.2, 147.7, 147.2, 143.8, 140.0, 130.2, 129.7, 128.9, 118.9, 116.1, 65.8, 56.9, 40.6, 35.1, 22.9; HRMS calcd for C$_{16}$H$_{17}$Cl$_2$N$_3$ ([M+H]$^+$) 322.0878, found 322.0875.
(S)-6-Chloro-5-bromo-4-(2-phenylamino)nicotine (171b):

A solution of (S)-5-bromo-6-chloro-4-iodonicotine (130 mg, 0.324 mmol, 1.0 equiv), Pd$_2$dba$_3$ (30 mg, 0.032 mmol, 10 %), cesium carbonate (160 mg, 0.486 mmol, 1.5 equiv), 2-(pinacolborane)aniline (70 mg, 0.324 mmol, 1.0 equiv) and Xantphos (37 mg, 0.065 mmol, 20 %) in 1,4-dioxane (4.0 mL) was degassed with argon for 15 min. The mixture was warmed to 110 °C and stirred for 20 h. The reaction was cooled to room temperature and poured into deionized water (5 mL). The product was extracted with methylene chloride (3 × 3 mL). The combined organic layers were dried over potassium carbonate, filtered and concentrated. The crude product was purified by radial PLC (silica gel, 20% MeOH/CH$_2$Cl$_2$) to afford 29 mg (24%) of a light-yellow oil. [α]$^0_{D} -114$ (c 1.45, CH$_2$Cl$_2$) ; IR (neat) 3470, 3358, 3225, 2970, 2942, 2786, 1618, 1456, 1356, 1155 cm$^{-1}$; $^1$H NMR (400 Hz, CDCl$_3$) δ 8.66 (s, 1H), 7.28-7.24 (m, 1H), 6.88-6.78 (m, 3H), 3.58 (bs, 2H), 3.16 (t, $J$ = 8.0 Hz, 1H), 2.99 (t, $J$ = 8.8 Hz, 1H), 2.20-2.0 (m, 2H), 2.14 (s, 3H), 1.90-1.80 (m, 1H), 1.70-1.54 (m, 2H), $^{13}$C NMR (100 MHz, CDCl$_3$) δ 150.8, 148.5, 147.9, 147.7, 143.5, 139.8, 130.2, 128.7, 123.5, 118.9, 116.1, 66.1, 56.9, 40.6, 35.1, 22.9; HRMS calcd for C$_{16}$H$_{17}$BrClN$_3$ ([M+H]$^+$) 366.0373, found 366.0363.
(S)-5-Chloro-6-methylnicotine (172):

A solution of (S)-5,6-dichloronicotine (800 mg, 3.461 mmol, 1.0 equiv), potassium carbonate (718 mg, 5.192 mmol, 1.5 equiv), Pd(PPh₃)₄ (400 mg, 0.346 mmol, 0.1 equiv) and trimethylboroxine (480 µL, 3.461 mmol, 1.0 equiv) in 1,4-dioxane (5 mL) was degassed with argon for 15 min, then stirred at 110 °C for 3 d. The mixture was cooled to room temperature, poured into deionized water (4 mL) and extracted with CH₂Cl₂ (3 × 3 mL). The combined organic layers were dried over K₂CO₃, filtered through a pad of Celite and silica, and concentrated. The crude product was purified by radial PLC (silica gel, 1% TEA/ 50% EtOAc/ hexanes) to afford 512 mg of a light-yellow oil (70% yield). [α]²⁹_D -155 (c 0.75, CH₂Cl₂ ); IR (neat): 2969, 2946, 2840, 2779, 1594, 1460, 1396, 1335, 1216, 1056, 902, 722 cm⁻¹ ; ¹H NMR (300 MHz, CDCl₃) δ 8.28 (d, J = 2.1 Hz, 1H), 7.66 (d, J = 2.1 Hz, 1H), 3.23 (t, J = 8.25 Hz, 1H), 3.06 (t, J = 8.1 Hz, 1H), 2.60 (s, 3H), 2.30 (q, J = 8.4 Hz, 1H), 2.21-2.17 (m, 1H), 2.17 (s, 3H), 2.00-1.90 (m, 1H), 1.90-1.80 (m, 1H), 1.80-1.65 (m,1H); ¹³C NMR (100 MHz, CDCl₃) δ 155.0, 146.8, 138.5, 135.5, 131.8, 68.2, 57.2, 40.6, 35.5, 22.8, 22.6 ; HRMS calcd for C₁₁H₁₅ClN₂ ([M+H]^⁺) 211.1002, found 211.1004.
(S)-5-chloro-4-iodo-6-methylnicotine (174b):

To a solution of (S)-5-chloro-6-methylnicotine (80 mg, 0.379 mmol, 1.0 equiv) in THF (2 mL) at –78 °C was added n-BuLi (0.759 mmol, 2.0 equiv.). After 1 h at –78 °C, a solution of iodine (96 mg, 0.379 mmol, 1.0 equiv) was added to the reaction. After 5 min at –78 °C, the reaction was quenched with a saturated solution of sodium bicarbonate (1 mL) and a saturated solution of sodium thiosulfate (1 mL). The product was extracted with methylene chloride (2 x 2 mL). The combined organic layers were dried over potassium carbonate, filtered and concentrated. The crude product was purified by radial PLC (silica gel, 1% TEA/20% EtOAc/ hexanes) to afford 72 mg (53%) of (S)-5-chloro-4-iodo-6-methylnicotine (174b) as a white solid and 11 mg (12%) of compound 176.

(S)-5-chloro-4-iodo-6-methylnicotine (174b): mp: 155-156 °C; [α]^{29}_D -154 (c 2.4, CH₂Cl₂); IR (CH₂Cl₂) 3055, 3004, 2987, 1422, 1364, 1264, 1222 cm⁻¹. ¹H NMR (400 Hz, CDCl₃) δ 8.32 (s, 1H), 3.41 (t, J = 8.4 Hz, 1H), 3.29-3.24 (m, 1H), 2.70 (s, 3H), 2.48-2.32 (m, 2H), 2.23 (s, 3H), 1.96-1.76 (m, 2H), 1.52-1.40 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 154.9, 146.4, 142.5, 136.0, 116.8, 73.8, 57.0, 40.8, 33.8, 24.9, 22.9; HRMS calcd for C₁₁H₁₄ClIN₂ ([M+H]^+) 336.9969, found 336.9944.

176: [α]^{31}_D - 144 (c 0.25, CH₂Cl₂); IR (neat) 2968, 2942, 2777, 1457, 1332, 1054, 903 cm⁻¹. ¹H NMR (400 Hz, CDCl₃) δ 8.33 (d, J = 2.0 Hz, 1H), 7.66 (d, J = 2.0 Hz, 1H), 3.37 (s, 2H), 3.26-3.18 (m, 1H), 3.07 (t, J = 8.4 Hz, 1H), 2.30 (q, J = 8.8 Hz, 1H), 2.26-2.16 (m, 1H), 2.18 (s, 3H), 2.04-1.90 (m, 1H), 1.88-1.76 (m, 1H), 1.76-1.64 (m, 1H); ¹³C NMR (100 MHz,
CDCl$_3$) $\delta$ 157.1, 147.0, 146.7, 135.6, 131.7, 68.2, 57.1, 40.5, 35.3, 33.5, 22.8; HRMS calcd for C$_{22}$H$_{28}$Cl$_2$N$_4$ ([M]$^+$) 419.1769, found 419.1759.

(S)-5-Chloro-6-methyl-4-(2-phenylamino)nicotine (177)

A solution of (S)-5-chloro-6-methyl-4-iodonicotine (100 mg, 0.297 mmol, 1.0 equiv), Pd$_2$dba$_3$ (14 mg, 0.015 mmol, 5 %), cesium carbonate (145 mg, 0.445 mmol, 1.5 equiv), 2-(pinacolborane)aniline (65 mg, 0.297 mmol, 1.0 equiv) and Xantphos (18 mg, 0.030 mmol, 10 %) in 1,4-dioxane (4.0 mL) was placed in a sealed tube and degassed with argon for 15 min. The mixture was then warmed to 110 $^\circ$C and stirred for 14 h. The reaction was cooled to room temperature and poured into deionized water (5 mL). The product was extracted with methylene chloride (3 $\times$ 3 mL). The combined organic layers were dried over potassium carbonate, filtered and concentrated. The crude product was purified by radial PLC (silica gel, 1% TEA/75% EtOAc/hexanes) to afford 69 mg (77%) of an off-white foam. [$\alpha$]$^\text{20}_D$ -117 ($c$ 1.9, CH$_2$Cl$_2$) ; IR (neat) 3464, 3338, 3218, 2971, 2944, 2844, 2784, 1652, 1632, 1615, 1582, 1506, 1498, 1452, 1382, 1305, 1182, 1082, 908, 748, 735 cm$^{-1}$; $^1$H NMR (400 Hz, CDCl$_3$) $\delta$ 8.72 and 8.69 (rotomers, s, 1H), 7.26-7.21 (m, 1H), 6.86-6.82 (m, 2H), 6.78 (dd, $J$ = 1.2, 8.4 Hz, 1H), 3.39 (bs, 2H), 3.13 (t, $J$ = 7.6 Hz, 1H), 2.96 (t, $J$ = 8.0 Hz, 1H), 2.68 (s, 3H), 2.16-2.06 (m, 1H), 2.13 (s, 3H), 2.06-1.96 (m, 1H), 1.90-1.76 (m, 1H), 1.68-1.54 (m,
$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 154.9, 147.2, 146.7 (due to rotomers), 145.4, 144.0, 142.7, 138.2 (due to rotomers), 137.9, 131.1, 129.9 (due to rotomers), 129.8 (due to rotomers), 129.7, 129.2, 121.8, 121.8 (due to rotomers), 118.7, 118.5 (due to rotomers), 115.8, 115.6 (due to rotomers), 66.6 (due to rotomers), 66.0, 57.0, 56.8 (due to rotomers), 40.8, 40.6, 35.4 (due to rotomers), 35.1, 23.5, 22.8, 22.7 (due to rotomers); HRMS calcd for C$_{17}$H$_{20}$ClN$_3$ ([M+H]$^+$) 302.1424, found 302.1429.

(S)-Brevicolline (143):

A solution of (S)-5-chloro-6-methyl-4[(2-amino)phenyl]nicotine (25 mg, 0.082 mmol, 1.0 equiv), Pd$_2$dba$_3$ (8 mg, 0.008 mmol, 0.1 equiv), (2-biphenyl)dicyclohexylphosphine (6 mg, 0.016 mmol, 0.2 equiv) and cesium carbonate (40 mg, 0.124 mmol, 1.5 equiv) in dioxane (2 mL) was degassed with argon for 15 min and then warmed to 100 °C for 23 h. The reaction was cooled to room temperature and poured into a saturated solution of sodium bicarbonate. The product was extracted with methylene chloride (3 × 3 mL). The combined organic layers were dried over potassium carbonate, filtered through Celite and concentrated. The crude product was purified by radial PLC (silica gel, 10% MeOH/CH$_2$Cl$_2$) to afford 18 mg (80%) of pure product, mp 228-229 °C. $[\alpha]^{31}_{D}$ - 165 (c 0.63, EtOH); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.04 (bs, 1H), 8.49 (s, 1H), 8.45 (d, $J$ = 8.0 Hz, 1H), 7.56-7.48 (m 1H), 7.53 (s, 1H), 7.31-
7.25 (m, 1H), 3.91 (t, J = 8.0 Hz, 1H), 3.39 (t, J = 8.0 Hz, 1H), 2.83 (s, 3H), 2.50-2.40 (m, 2H), 2.30 (s, 3H), 2.14-2.02 (m, 1H), 2.00-2.15 (m, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 140.5, 137.2, 134.8, 131.4, 127.8, 126.7, 125.8, 122.2, 120.2, 111.7, 104.3, 68.0, 57.4, 41.1, 33.3, 22.9, 20.3.

2-Chloro-6-methoxymethoxy-pyridine (210) and 6-Chloro-1-methoxymethyl-1H-pyridin-2-one (211):

2-Chloropyridinol (1.0 g, 7.771 mmol, 1.0 equiv) was added to a solution of NaH (200 mg, 8.490 mmol, 1.1 equiv) in DMF (5 mL). The mixture was stirred at room temperature for 2 h. The mixture was then cooled to 0 °C and MOMCl (1.3 mL, 16.980 mmol, 2.2 equiv) was added dropwise. The mixture was then warmed to room temperature and stirred for 2 h. The reaction was quenched with a saturated aqueous solution of sodium bicarbonate. The product was extracted with methylene chloride, the combined organic layers were dried over potassium carbonate, filtered through Celite and concentrated. The crude product was purified by radial PLC (silica gel, 1% TEA/10% EtOAc/hexanes) to afford 751 mg (56% yield) of 2-chloro-6-methoxymethoxy-pyridine and 292 mg (22% yield) of 6-chloro-1-methoxymethyl-1H-pyridin-2-one as clear oils. 2-Chloro-6-methoxymethoxy-pyridine (210): IR (neat) 2953, 2832, 1590, 1446, 1399, 1280, 1152, 1090, 962 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.54 (t, J = 7.8 Hz, 1H), 6.92 (dd, J = 7.8, 0.6 Hz, 1H), 6.69 (dd, J = 7.8, 0.6 Hz, 1H), 3.91 (t, J = 8.0 Hz, 1H), 3.39 (t, J = 8.0 Hz, 1H), 2.83 (s, 3H), 2.50-2.40 (m, 2H), 2.30 (s, 3H), 2.14-2.02 (m, 1H), 2.00-2.15 (m, 2H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 140.5, 137.2, 134.8, 131.4, 127.8, 126.7, 125.8, 122.2, 120.2, 111.7, 104.3, 68.0, 57.4, 41.1, 33.3, 22.9, 20.3.
6-Chloro-1-methoxymethyl-1H-pyridin-2-one (211): IR (neat) 3099, 2943, 2829, 1676, 1593, 1519, 1457, 1092, 795 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$) δ 7.15 (dd, $J$ = 9.3, 7.5 Hz, 1H), 6.40 (dd, $J$ = 9.3, 0.9 Hz, 1H), 6.19 (dd, $J$ = 7.5 Hz, 0.9 Hz, 1H), 5.53 (s, 2H), 3.36 (s, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 163.6, 139.8, 137.7, 119.3, 107.3, 75.6, 57.6; HRMS calcd for C$_7$H$_8$ClNO$_2$ ([M+H]$^+$) 174.0323, found 174.0322.

2-Methoxy-6-methoxymethoxy-pyridine (208):

Freshly distilled methanol (280 µL, 6.913 mmol, 1.3 equiv) was added to a solution of KO$_t$-Bu (775 mg, 6.913 mmol, 1.2 equiv) in THF at room temperature. After 30 min, a solution of 2-chloro-6-(methoxymethoxy)-pyridine (1.0 g, 5.761 mmol, 1.0 equiv) in THF (3 mL) was added dropwise to the milky solution. The mixture was warmed to 70 °C and stirred for 12 h. The solvent was removed by evaporation, deionized water was added, and the mixture was extracted with methylene chloride. The combined organic layers were dried over potassium carbonate, filtered and concentrated. The crude product was purified by radial PLC (silica gel, 10% EtOAc/hexanes) to afford 625 mg (64% yield) of a clear oil. IR (neat) 2953, 2828, 1604, 1584, 1468, 1451, 1316, 1239, 1156, 983 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.50 (t, $J$ = 7.6 Hz, 1H), 6.38-6.34 (m, 2H), 5.47 (s, 2H), 3.88 (s, 3H), 3.51 (s, 3H); $^{13}$C NMR (100
MHz, CDCl₃) δ 163.2, 161.6, 102.9, 101.7, 92.1, 57.1, 53.6; HRMS calcd for C₈H₁₁NO₃ ([M+H]+) 170.0817, found 170.0812.

2-Isopropoxy-6-(methoxymethoxy)pyridine (214): Freshly distilled isopropanol (1.2 mL, 15.623 mmol, 1.2 equiv) was added to a solution of KOr-Bu (1.75 g, 15.623 mmol, 1.2 equiv) in THF (15 mL) at room temperature. After 5 min, 2-chloro-6-(methoxymethoxy)-pyridine (2.26 g, 13.019 mmol, 1.0 equiv) was added dropwise to the milky solution. The mixture was warmed to 60 °C and stirred for 12 h. The solvent was removed by evaporation, deionized water was added, and the product was extracted with methylene chloride. The combined organic layers were dried over potassium carbonate, filtered and concentrated. The crude product was purified by radial PLC (silica gel, 2% EtOAc/hexanes) to afford 1,176 mg (48% yield) of 2-isopropoxy-6-methoxymethoxy-pyridine (214) as a clear oil, 511 mg (23% yield) of 2-chloro-6-isopropoxypyridine (215) and 262 mg (12% yield) of 2-methoxy-6-methoxymethoxy-pyridine (208) as a clear oil.

2-isopropoxy-6-methoxymethoxy-pyridine (214): IR (neat) 2978, 2936, 1600, 1580, 1447, 1312, 1236, 1158, 1141, 1114, 1009, 970 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.47 (t, J = 7.9 Hz, 1H), 6.34-6.27 (m, 2H), 5.45 (s, 2H), 5.19 (septet, J = 6.0 Hz, 1H), 3.50 (s, 3H), 1.32 (d, J = 6.0 Hz, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 162.4, 161.4,
141.4, 103.7, 101.4, 68.3, 57.0, 22.2; HRMS calcd for C_{10}H_{15}NO_{3} ([M+H]^+) 198.1130, found 198.1127; 2-chloro-6-isopropoxypyridine (215): IR (neat) 2980, 2936, 1592, 1559, 1441, 1302, 1159, 1109, 963, 788 cm^{-1}; ^1H NMR (400 MHz, CDCl₃) δ 7.46 (dd, J = 6.8 Hz, J = 8.0 Hz, 1H), 6.82 (d, J = 6.8 Hz, 1H), 6.56 (d, J = 8.0 Hz, 1H), 5.32-5.20 (m, 1H), 1.32 (d, J = 10.4 Hz, 6H); ^13C NMR (100 MHz, CDCl₃) δ 163.3, 148.4, 140.6, 115.9, 109.8, 69.1, 22.0; 2-methoxy-6-methoxymethoxy-pyridine (208): IR (neat) 2953, 2828, 1604, 1584, 1468, 1451, 1316, 1239, 1156, 983 cm^{-1}; ^1H NMR (400 MHz, CDCl₃) δ 7.50 (t, J = 7.6 Hz, 1H), 6.38-6.34 (m, 2H), 5.47 (s, 2H), 3.88 (s, 3H), 3.51 (s, 3H); ^13C NMR (100 MHz, CDCl₃) δ 163.2, 161.6, 102.9, 101.7, 92.1, 57.1, 53.6; HRMS calcd for C₆H₁₁NO₃ ([M+H]^+) 170.0817, found 170.0812.

2-Benzyloxy-6-isopropoxypyridine (217):

Benzyl alcohol (110 µL, 1.048 mmol, 1.2 equiv) was added to a solution of KOt-Bu (118 mg, 1.048 mmol, 1.2 equiv) in THF (5 mL) at room temperature. After 30 min, 2-chloro-6-isopropoxypyridine (150 mg, 0.874 mmol, 1.0 equiv) was added and the mixture was stirred at 60 ºC for 12 h. The reaction was allowed to cool to room temperature. The solvents were removed by evaporation and the product was extracted with methylene chloride (3 × 2 mL). The combined organic layers were dried over K₂CO₃, filtered and concentrated. The crude product was purified by radial PLC (silica gel, 2% EtOAc/hexanes) to afford 129 mg (61% yield) of a clear oil. IR (neat) 3088, 1064, 3033, 2977, 2936, 2876, 1596, 1579, 1444, 1371,
1312, 1237, 1140, 1041, 989, 788 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.50-7.25 (m, 5H), 6.35 (d, \(J = 7.6\) Hz, 1H), 6.27 (d, \(J = 7.6\) Hz, 1H), 5.36 (s, 2H), 5.28-5.18 (m, 1H), 1.34 (d, \(J = 6.4\) Hz, 1H); \(^1\)\(^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 162.5, 162.4, 141.2, 137.9, 128.6, 127.9, 102.4, 101.5, 68.3, 67.6, 22.3; HRMS calcd for C\(_{15}\)H\(_{17}\)NO\(_2\) ([M\(^+\)]\(^\dagger\)) 243.1259, found 243.1269.

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\end{array}
\quad \text{218}
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**6-Isopropoxy-1H-pyridin-2-one (218):**

A solution of 2-benzyloxy-6-isopropoxypyridine (188 mg, 0.772 mmol) in MeOH (5 mL) was hydrogenated over 5\% Pd/C at room temperature for 6 h. The mixture was filtered through Celite and the solids rinsed with methylene chloride. The crude product was purified by radial PLC (silica gel, 50\% EtOAc/hexanes) to afford 82 mg (69\% yield) of a white solid. mp: 107 °C; IR (neat) 3500-2500, 1648, 1599, 1453, 1372, 1273, 1109 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.35 (dd, \(J = 8.8, 7.6\) Hz, 1H), 6.15 (d, \(J = 8.8\) Hz, 1H), 5.62 (d, \(J = 7.6\) Hz, 1H), 4.66-4.60 (m, 1H), 1.31 (d, \(J = 6.4\) Hz, 6H); \(^1\)\(^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 165.2, 157.7, 142.9, 108.6, 89.4, 71.8, 21.8; HRMS calcd for C\(_8\)H\(_{11}\)NO\(_2\) ([M+H\(^+\)]\(^\dagger\)) 154.0868, found 154.0869.
6-Isopropoxy-2-(methoxymethoxy)-pyridine (214):

A solution of 6-isopropoxy-1H-pyridin-2-one (75 mg, 0.489 mmol, 1.0 equiv) in DMF (1 mL) was added to a solution of KOt-Bu (60 mg, 0.538 mmol, 1.1 equiv) in DMF (2 mL) at 0 °C. After 20 min at 0 °C, the mixture was warmed to room temperature and stirred for 2 h. The mixture was then cooled back down to 0 °C and MOMCl was added dropwise. After 5 min at 0 °C, the mixture was warmed to room temperature and stirred overnight (15 h). The reaction was quenched with deionized water and the mixture extracted with methylene chloride (2 × 3 mL). The combined organic layers were dried over K₂CO₃, filtered and concentrated. The crude product was purified by radial PLC (silica gel, 5% EtOAc/hexanes) to afford 79 mg (80% yield) of 2-isopropoxy-6-(methoxymethoxy)pyridine as a clear oil. Spectra data on page 158.

6-Isopropoxy-2-methoxymethoxy-3-tributylstannanyl-pyridine (219b):

A solution of n-BuLi (0.139 mmol, 1.1 equiv) in hexanes was added dropwise to a solution of 6-isopropoxy-2-methoxymethoxypyridine (25 mg, 0.126 mmol, 1.0 equiv) in THF (2 mL) at -40 °C. The mixture was stirred at -40 °C for 30 min then at room temperature for 30 min. Chlorotributyltin (55 μL, 0.190 mmol, 1.5 equiv) was added at room temperature and the
mixture was stirred for an additional 20 min before being quenched with a saturated aqueous solution of sodium bicarbonate (1 mL). The product was extracted with methylene chloride (2 × 2 mL). The combined organic layers were dried over K₂CO₃, filtered and concentrated. The crude product was purified by radial PLC (silica, 5% EtOAc/hexanes) to afford 34 mg (56% yield) of the desired product as a clear oil. IR (neat) 2956, 2925, 1573, 1449, 1351, 1299, 1157, 1114, 1042, 969 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.53 (d, J = 5.7 Hz, 1H), 6.30 (d, J = 5.7 Hz, 1H), 5.46 (s, 2H), 5.24-5.14 (m, 1H), 3.49 (s, 3H), 1.60-1.40 (m, 6H), 1.40-1.20 (m, 6H), 1.33 (d, J = 4.8 Hz, 6H), 1.10-0.95 (m, 6H), 0.90-0.80 (m, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 165.4, 163.2, 149.1, 110.6, 103.8, 91.7, 68.1, 57.3, 29.3, 27.5, 22.3, 13.9, 9.8; HRMS calcd for C₂₂H₄₁NO₃Sn ([M+H]⁺) 488.2187, found 488.2198.

5-Bromo-3,4-dihydro-2H-pyridine-1-carboxylic acid phenyl ester (226b):

A solution of bromine (13 µL, 0.246 mmol, 1.0 equiv) in CH₂Cl₂ (0.25 mL) was added to a solution of 3,4-dihydro-2H-pyridine-1-carboxylic acid phenyl ester (50 mg, 0.246 mmol, 1.0 equiv) and 1,2,2’,6,6’-pentamethylpiperidine (49 µL, 0.270 mmol, 1.1 equiv) in CH₂Cl₂ (2 mL) at room temperature. After one hour, the solvent was removed by evaporation and the crude product was purified by radial PLC (silica gel, 10% EtOAc/hexanes) to afford 26 mg (37%) of a clear oil. IR (neat) 3103, 2958, 2934, 2880, 2847, 1722, 1654, 1493, 1387, 1346, 1299, 1255, 1190, 1090 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.40-7.10 (m, 6H), 3.84-3.64
(m, 2H), 2.56-2.46 (m, 2H), 2.08-1.96 (m, 2H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 151.0, 129.6, 125.9, 125.8, 121.7, 103.7, 41.4, 31.5, 22.9; HRMS calcd for C$_{12}$H$_{12}$BrNO$_2$ ([M+H]$^+$) 281.0051, found 281.0043.
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APPENDICES
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115b
116k
118a
118g
118g
119e
119f
119g
119h

1st diastereomer
$^{2}\text{nd}\ diastereomer$
119i

2nd diastereomer
123b
133
167b
167c
169
171a
228b