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NEW SYNTHETIC METHODS

A. LITHIATION OF METHOXYPYRIDINES AND N-METHYLINDOLES DIRECTED BY α-AMINO ALKOXIDES

B. SYNTHETIC METHODS USING N-ACYLIMINIUM IONS AND 1-ACYLPYRIDINIUM SALTS

by

Michael O. Killpack

A dissertation submitted in partial fulfillment
of the requirements for the degree

DOCTOR OF PHILOSOPHY

in

Chemistry

Approved

Major Professor	Committee Member
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UTAH STATE UNIVERSITY
Logan, Utah

1990

DEDICATION

To my wife, Colleen, and my parents, Mars and Edith Killpack.

ACKNOWLEDGEMENTS

I would like to express appreciation to the United States Air Force and the United States Air Force Academy for affording me the opportunity to return to Utah State University under the Air Force Institute of Technology/ Civilian Institute Program. I am thankful to my research advisor, Dr. Daniel L. Comins. He has given constant encouragement and has been a vast source of knowledge, and more importantly, a friend. I would also like to thank my committee members, Dr. Joseph G. Morse, Dr Richard K. Olsen, Dr. Vernon Parker, and Dr. John Evans, for their time and help throughout the program here at USU.

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I would also like to thank my colleagues, Dr. Sean O'Connor, Michael Weglarz, Ali Dehghani, Donald LaMunyon, and Larry Morgan, for their friendship and discussion.

Michael O. Killpack

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LIST OF ABBREVIATIONS AND TERMS

Abbreviation or Term	Explanation
A	Amps
Å	Angstrom
Anal.	analysis
aq	aqueous
$BF_3 \cdot OEt_2$	boron trifluoride etherate
br	broad
brine	saturated aqueous sodium chloride
tert-BuOK	potassium *tert*-butoxide
°C	degree(s) Celsius
^{13}C NMR	carbon-13 nuclear magnetic resonance spectroscopy
calcd.	calculated
cm^{-1}	reciprocal centimeters
d	doublet
dd	doublet of doublet
dt	doublet of triplet
δ	parts per million chemical shift from tetramethylsilane
DIA	diisopropylamine

DMF	N,N-dimethylformamide
E	electrophile(s)
E+	electrophile(s)
eq	equivalent(s)
equiv	equivalent(s)
Et_2O	diethyl ether
EtOAc	ethyl acetate
ether	diethyl ether
g	gram(s)
GC	gas chromatography
H-	hydride
^1H NMR	proton nuclear magnetic resonance spectroscopy
h	hour
H+	proton or protic acid
Hz	hertz
IR	infrared spectroscopy
J	coupling constant
Kugelrohr distillation	short path bulb-to-bulb evaporative distillation
lit	literature
LDA	lithium diisopropylamide
LNMP	lithium N-methylpiperazide

LTMDA	lithium N,N,N′-trimethylethylenediamine
m	meter
m(NMR)	multiplet
M	molar
Me	methyl
MeMgX	methylmagnesium halide
MHz	megahertz
min	minute(s)
ml	milliliter(s)
mm	millimeter(s)
mmol	millimole(s)
mp	melting point
N	normal
Nu	nucleophile(s)
Ph	phenyl
ppm	parts per million
q	quartet
R	alkyl group
RMgX	alkylmagnesium halide
radial PLC	radial preparative-layer chromatography
rt	room temperature
s	singlet

t	triplet
TEA	triethylamine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMEDA	N,N,N',N'-tetramethylethylenediamine
TMS	tetramethylsilane
TMS(bonded)	trimethylsilane
TMSCl	chlorotrimethylsilane
V	volts

ABSTRACT

New Synthetic Methods

A. *Lithiation of Methoxypyridines and N-Methylindoles*

Directed by α-Amino Alkoxides

B. Synthetic Methods using N-Acyliminium Ions and

1-Acylpyridinium Salts

by

Michael O. Killpack, Doctor of Philosophy

Utah State University, 1990

Major Professor: Dr. Daniel L. Comins

Department: Chemistry and Biochemistry

Directed lithiation-alkylation of several methoxypyridinecarboxaldehydes was achieved in a one-pot reaction via α–amino alkoxide intermediates. The α–amino alkoxides were prepared by the addition of methoxypyridine-carboxaldehydes to certain lithiated secondary amines at cold temperatures. Several examples are cited where the regioselectivity of alkylation was changed by simply varying the lithiated amine used to form the α–amino

alkoxide. Interestingly, there were no cases found where the α–amino alkoxides directed lithiation into the 2-position on the pyridine ring. Directed N-methyl lithiation-alkylation by α-amino alkoxides on 1-methylindole-2-carboxaldehyde was accomplished using a C-3 blocking group strategy. Preparation of 3-chloro-1-methylindole-2-carboxaldehyde was achieved in high yields. The subsequent metalation, alkylation with various electrophliles, and removal of the chloro blocking group makes the overall procedure an attractive method for preparation of useful N-substituted indoles. Substituted pyridines were prepared by anodic oxidation of 1-acyldihydropyridines. Yields were moderate to good, and this methodology gives an alternative to chemical oxidations. The addition of triphenylsilylmagnesium bromide to 1-acyl salts of 4-methoxypyridines gave optically active 1-acyl-2,3-dihydro-4-pyridones in high yields. Preparation of (-)-1-((1R,2S,5R)-8-phenylmenthoxy)-(S)-2-triphenylsilyl-2,3-dihydro-4-pyridone was achieved in 82% yield and 96% diastereomeric excess. This unique molecule was further studied by subjecting it to stereoselective addition and reduction reactions. Chiral 1-acyl-α-methoxy-pyrrolidines, -2-pyrrolidinones, and -2-piperidones were prepared in good yield. They were treated with Lewis acids in the presence of nucleophiles in an attempt to form optically active pyrrolidines, pyrrolidinones, and piperidones. These reactions gave low diastereomeric excess or low product yields.

(153 pages)

INTRODUCTION

Nitrogen heterocycles have been widely studied and used in the synthesis of numerous alkaloids. Their importance as precursors to many biologically active compounds has focused a tremendous amount of attention on developing methods to functionalize these systems. In this study we investigated novel synthetic methods for regio- and/or stereoselective carbon-carbon bond formation on the pyridine, indole, pyrrolidine, pyrrolidinone, and piperidone ring systems. In part A we report the regioselective metalation of several methoxypyridinecarboxaldehydes and 1-methylindole-2-carboxaldehydes using α-amino alkoxides as both a protecting and directing group. In part B we report the use of N-acyliminium ions and 1-acylpyridinium ions for the preparation of substituted pyridines and the asymmetric synthesis of dihydropyridones, pyrrolidines, pyrrolidinones, and piperidones.

PART A. LITHIATION OF METHOXYPYRIDINES AND N-METHYLINDOLES DIRECTED BY α-AMINO ALKOXIDES

I. INTRODUCTION

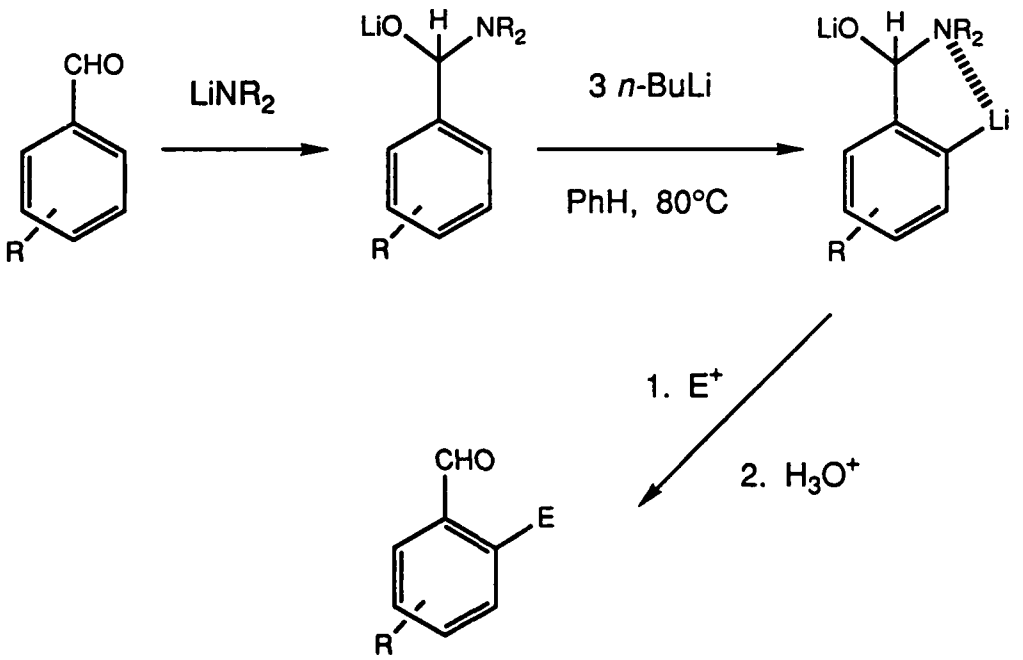
Heteroatom-facilitated lithiation is recognized as an important synthetic tool for the elaboration of aromatic systems.[1] The ability to direct lithiation in a regioselective manner, the accessability of inexpensive organolithium reagents, and the high reactivity of the newly formed organolithium species make directed metalation synthetically attractive and have motivated continued research and development of various ortho directing groups. The purpose of this study was to investigate the alkylation of 1-methyl-2-indole-carboxaldehyde and several isomeric methoxypyridinecarboxaldehydes by using lithiated secondary amines to form α-amino alkoxide directing groups in situ. The α-amino alkoxides were investigated as both protecting groups for the electrophilic aldehydes and as regioselective directors for metalation using various alkyllithium bases. This methodology has the advantage of being a one-pot reaction, and by varying the amine component of the α-amino alkoxide, one may change the position of metalation on the aromatic compound. The lithiation-alkylation of methoxypyridinecarboxaldehydes using α-amino alkoxides is the first reported study of carbonyl-derived directing groups prepared from pyridinecarboxaldehydes. The methodology developed provides a new synthetic route to substituted alkoxypyridines, which are valuable precursors to pyridones and pyridinols[2] as well as dihydropyridones.[3] Our primary interest in 1-methyl-2-indolecarboxaldehyde was to develop a novel methodology for N-

methyl lithiation, thus enabling various substituents to be added to the methyl group of the 1-methylindole ring system.

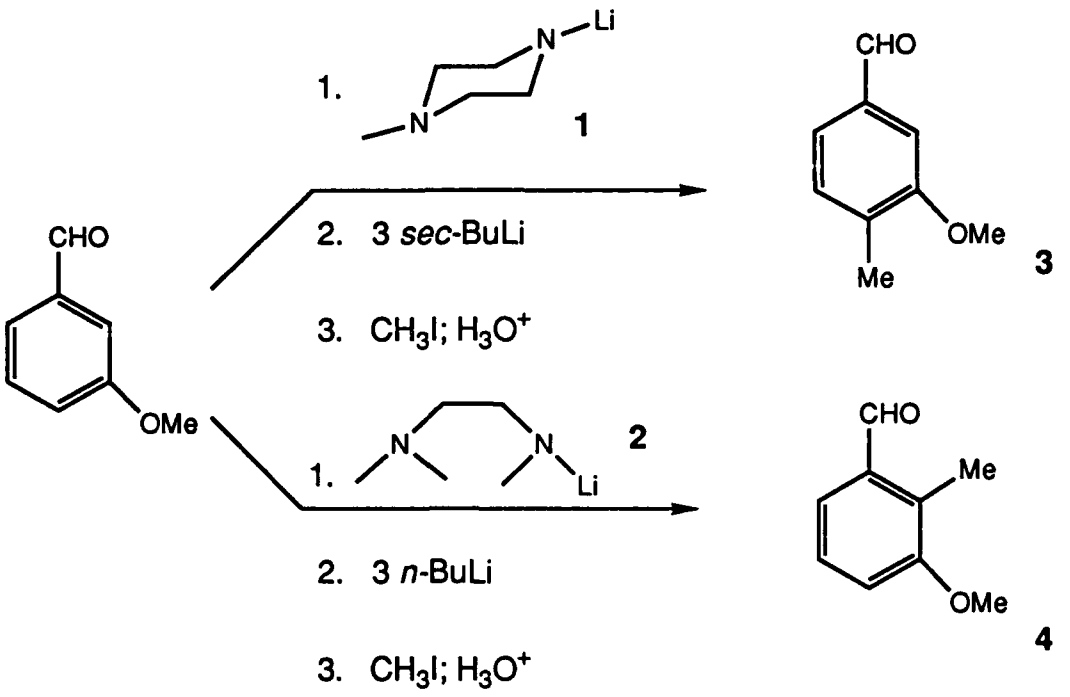
II. REVIEW OF THE LITERATURE

Numerous examples of ortho-metalations have been reported, and several reviews are available.[1] A variety of heteroatom directing groups have been employed and include $CONR_2$,[4] CONHR,[4] oxazolines,[5] pivaloylamino,[6] $OCONEt_2$,[7] OR,[8] OCH_2OR,[9] halogen,[10] and SO_2NR_2.[11]

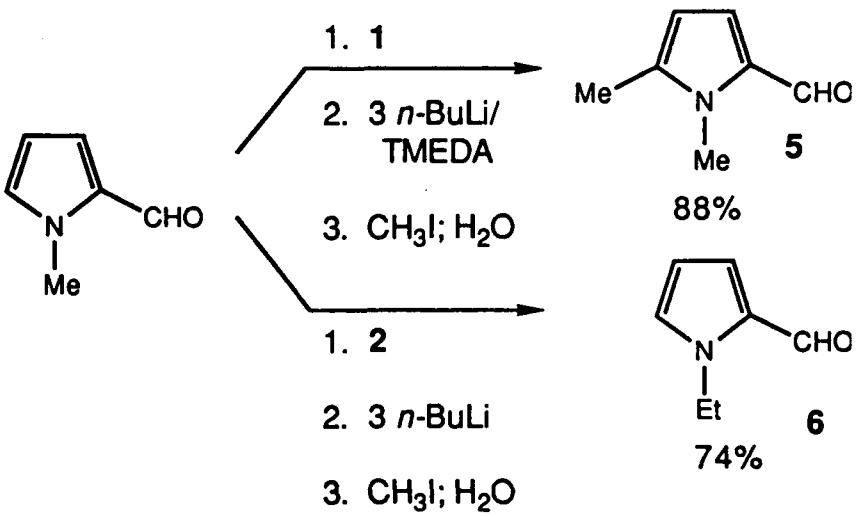
α-Amino Alkoxides as Protecting and Directing Groups for Alkylation of Aromatic Aldehydes Via Directed Lithiation. In the past, metalation of aromatic aldehydes has had the disadvantage of requiring multiple steps. First, the electrophilic aldehydes were protected as either acetals,[12] oxathiolanes,[13] or imidazolidines.[14] Subsequently, metalation and



alkylation were carried out followed by removal of the protecting group. Comins and Brown[15] demonstrated that the addition of aromatic aldehydes to lithiated secondary amines formed α-amino alkoxides in situ, which are effective protecting groups for lithiation even under such vigorous conditions as excess *n*-BuLi in refluxing benzene. A major advantage of the α-amino alkoxide protecting group is its ease of removal. As shown above, aqueous acidic workup provides ring substituted aldehydes via a one-pot procedure. Another advantage of this methodology is the directing ability of the α-amino alkoxide, which is primarily due to the chelating properties of the amine component and not to strong inductive effects. This allows one to vary the regioselectivity of metalation by simply changing the lithiated amine used to form the α-amino alkoxide. Of the lithiated amines studied, the two which have demonstrated the greatest difference in chelating ability are N,N,N′-trimethylethylenediamine (**2**) and N-methylpiperazine (**1**). For example, Comins and Brown found that 3-methoxybenzaldehyde gave 4-substituted product **3** when lithiated amine **1** was used and the 2-alkylated product **4** when lithiated amine **2** was used to form the α-amino alkoxide.[15]



The use of α-amino alkoxides as *in situ* protecting and directing groups also works well for five-membered heterocyclic aromatic aldehydes[16] such as

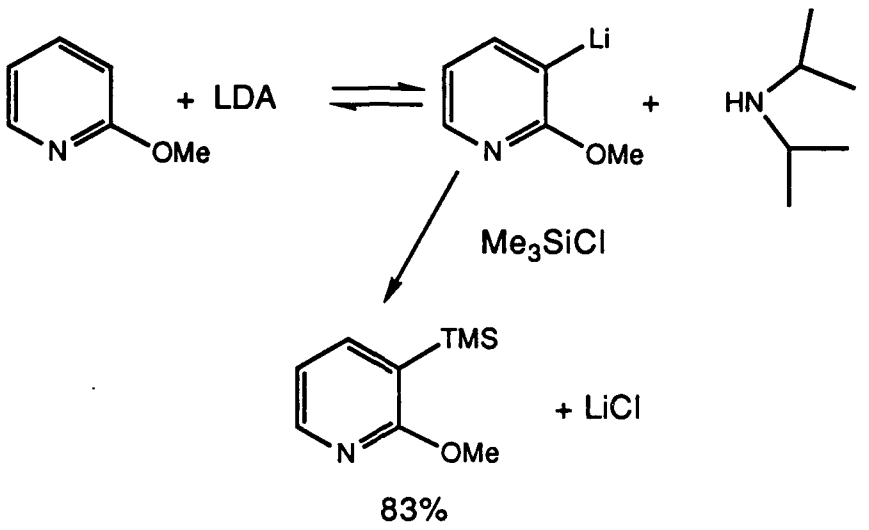


thiophene-, furan-, pyrrole-, and indolecarboxaldehydes. These reaction also

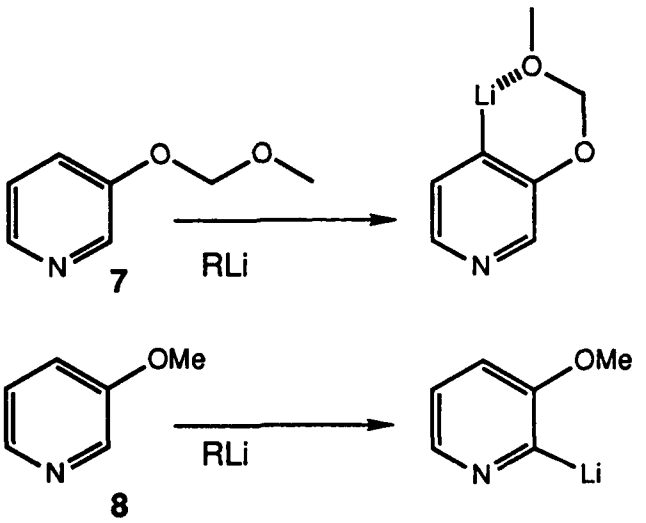
demonstrate the versatility of changing the amine component to affect the regioselectivity of the reaction. Of particular interest to our study is the novel N-methyl alkylation of N-methyl-2-pyrrolecarboxaldehyde to give **6**.

Lithiation of Substituted Pyridines. Susceptibility to nucleophilic attack has made directed metalation of the pyridine ring system difficult.[1b] The first reported lithiation of a substituted pyridine was in 1969 by Cook and Wakefield[17] of 2,3,5,6-tetra-chloropyridine. Since that time several others have successfully lithiated the pyridine ring using ortho-directing groups. Meyers and Gabel[5] utilized oxazolines to direct lithiation of 4-(2-oxazolinyl)pyridine into the 3 position. Katritzky, Rahimi-Rastgoo, and Ponskshe[18] used a carbonyl-derived ortho-directing group, CONHR, to direct metalation into the 3 position of 2-aminocarbonylpyridines. Miah and Snieckus[7] reported directed metalation of 2-, 3-, and 4-pyridyl diethylcarbamates with *sec*-BuLi /TMEDA at -78°C. Lithiation occurred at C-3 as expected for both 2- and 4-pyridyl diethylcarbamates and at C-4 for 3-pyridylcarbamate.

Recently, the lithiation of the three isomeric methoxypyridines were reported in two independent studies, one by Comins and LaMunyon[8c] and the other by Queguiner and coworkers.[8d] Both groups found strong alkyl lithium bases too nucleophilic to affect lithiation, and both found that LDA was not basic enough to give complete deprotonation of the methoxypyridines. However, when an electrophile was used which reacted with the lithiated



methoxypyridines and not with LDA, the reaction went to completion in high yield as shown in the above reaction scheme. Both studies suggest ways to achieve full lithiation of the methoxypyridines so that a variety of electrophiles may be used. The best results were obtained by Comins and LaMunyon.[8c] They found mesityllithium[19] greatly reduced nucleophilic side reactions but was still basic enough to lithiate methoxypyridines. Both research groups reported the 3 position was lithiated on 2- and 4-methoxypyridine, and 3-methoxypyridine (**8**) directed lithiation to C-2. Interestingly, Winkle and Ronald[20] reported 3-(methoxymethoxy)pyridine (**7**) directed lithiation to the 4 position rather than C-2 (see scheme below).

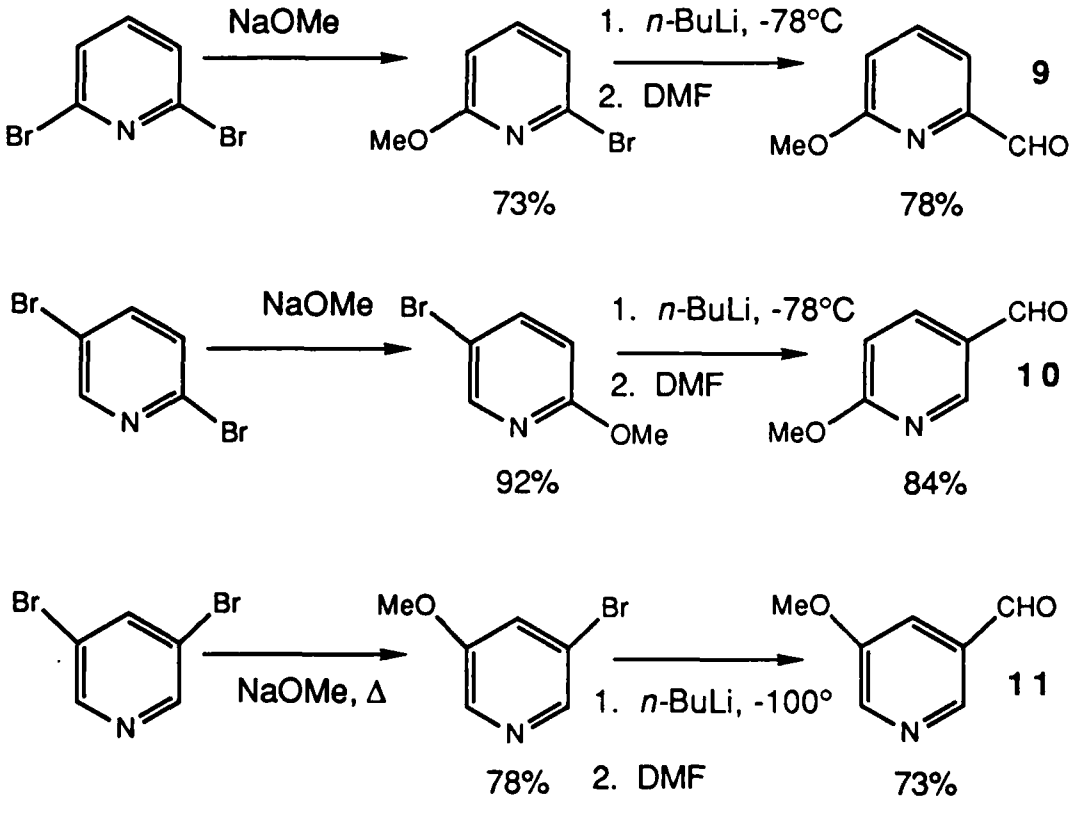


Lithiation of N-Substituted Indoles. Even with excess alkyl lithium, only deprotonation of the nitrogen atom on N-unsubstituted indoles has been achieved.[1b] It has been reported that lithiation occurs at the α position on N-alkylindoles;[21] however, it should be noted that rates are slow and THF/TMEDA is usually required for improved results. Lithiation of the α-position has also been achieved by protecting the nitrogen with methoxymethyl[22] or arylsulfonyl[23] protecting groups. These protecting groups have the advantage of possible removal, and their inherent heteroatom directing influence improve rates and yields over their alkyl counter parts. The utility of lithiation of indoles has been used as the initial step in the synthesis of several indole alkaloids and related compounds.[24]

Several useful results have been reported for the directed lithiation of N-methyl and N-(methoxymethyl)indolcarboxaldehydes using α-amino alkoxide chemistry.[16] Lithiation-alkylation at the α-position of 1-methyl-3-indole-carboxaldehyde and 1-(methoxymethyl)-3-indolecarboxaldehyde was accomplished in good yield. The analogous reaction occurred at the β-position of 1-methyl-2-indolecarboxaldehyde when lithiated N-methylpiperizide was used to form the α-amino alkoxide. However, when 1-methyl-2-indolecarboxaldehyde was lithiatied using N,N,N′-trimethylethylenediamine and *n*-BuLi, an undesirable mixture of N-methyl- and β-lithiation occurred.

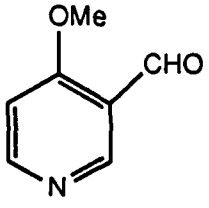
III. RESULTS AND DISCUSSION

Synthesis of Methoxypyridinecarboxaldehydes. The first three methoxypyridinecarboxaldehydes studied were prepared in two steps from dibromopyridine precursors. Nucleophilic substitution of bromide by sodium methoxide on 2,6-dibromopyridine in methanol gave 6-bromo-2-methoxypyridine in good yield. Treatment with *n*-BuLi at -78°C affected



lithium-halogen exchange, and subsequent formylation with dimethylformamide

(DMF) gave 6-methoxy-2-pyridinecarboxaldehyde (**9**). Using analogous procedures, 6-methoxy-3-pyridinecarboxaldedhyde (**10**) was prepared starting from 2,5-dibromopyridine. Nucleophilic substitution of bromide by sodium methoxide on 3,5-dibromopyridine required more vigorous (sodium methoxide in DMF at 63-68°C) conditions to give 5-bromo-3-methoxypyridine, and the subsequent lithium-halogen exchange required colder temperatures (-100°C) to reduce side reactions. Formylation with DMF gave 5-methoxy-3-pyridinecarboxaldehyde (**11**). Lithiation of 2-, 3-, and 4-methoxypyridines using mesityllithium as the base followed by formylation with DMF gave



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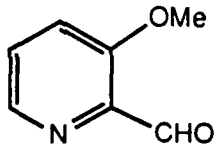

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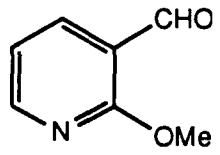


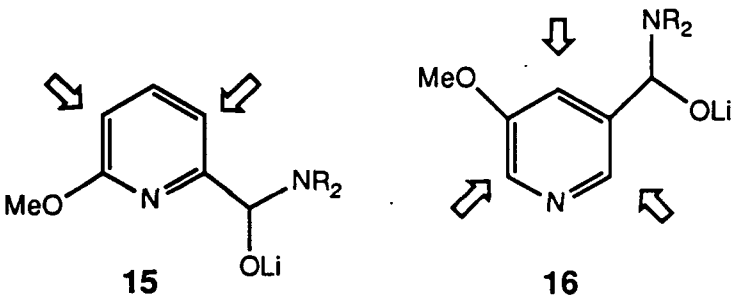
14

2-methoxy-3-pyridinecarboxaldehyde (**14**), 3-methoxy-2-pyridinecarboxaldehyde (**13**), and 4-methoxy-3-pyridinecarboxaldehyde (**12**), respectively.[8c]

Regioselective Alkylation of Methoxypyridinecarboxaldehydes. Preparation of α-amino alkoxides was accomplished by the addition methoxypyridinecarboxaldehydes to lithiated N-methylpiperazide (LNMP) or lithium N,N,N′-trimethylethylenediamine (LTMDA) at -78°C in THF.

After 15 min the α-amino alkoxides were completely formed and the alkyllithium reagent was added. Since both the methoxy and α-amino alkoxide groups are effective ortho directors, a possibility existed that lithiation could occur at more than one site on the ring. For example, α-amino alkoxide **15**, prepared from pyridinecarboxaldehyde **9**, has two sites, C-3 and C-5, where ortho metalation

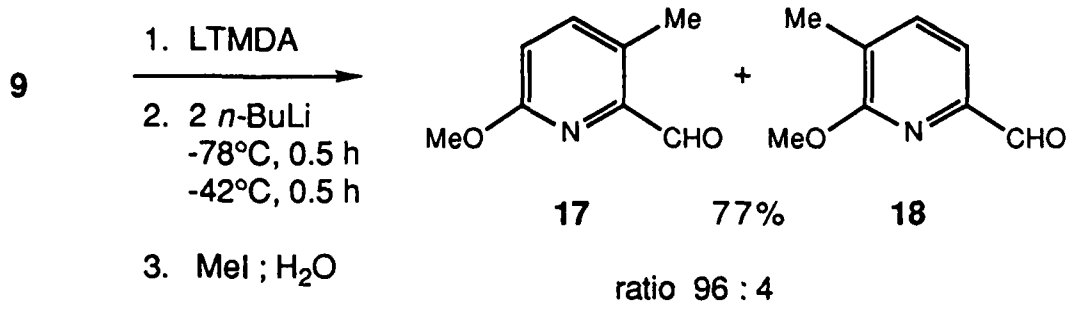
Metalation

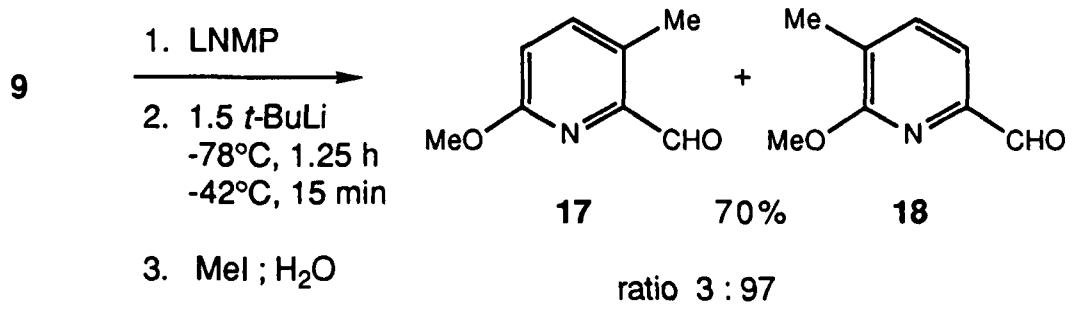


15 **16**

might occur, and α-amino alkoxide **16** has three sites, C-1, C-4, and C-6, next to directing groups. Based on previous studies,[15,16] we believed high regioselectivity at more than one site might be achieved by varying the amine component of the α-amino alkoxide. This turned out to be the case with methoxypyridinecarboxaldehyde **9**. When treated with LTMDA followed by

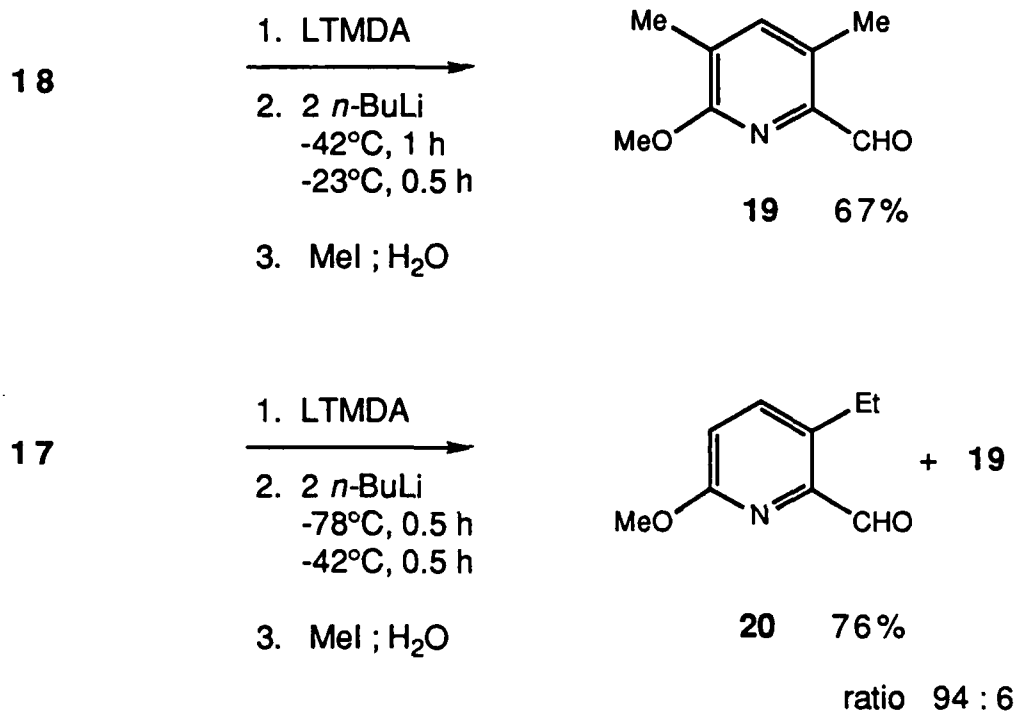
metalation with *n*-BuLi and methylation with methyl iodide, **9** gave trisubstituted pyridines **17** and **18** in 77% yield. The TMEDA-like directing ability of the α-amino alkoxide accounts for the 96 : 4 ratio of isomers. Reaction of **9** with LNMP, *t*-BuLi, and methyl iodide gave a 3:97 ratio of **17** and **18** in 70% yield. The reversal of regioselectivity demonstrates the large difference in chelating ability between the two α-amino alkoxides. To further demonstrate





the utility of α-amino alkoxides in funtionalizing the pyridine ring, both **17** and

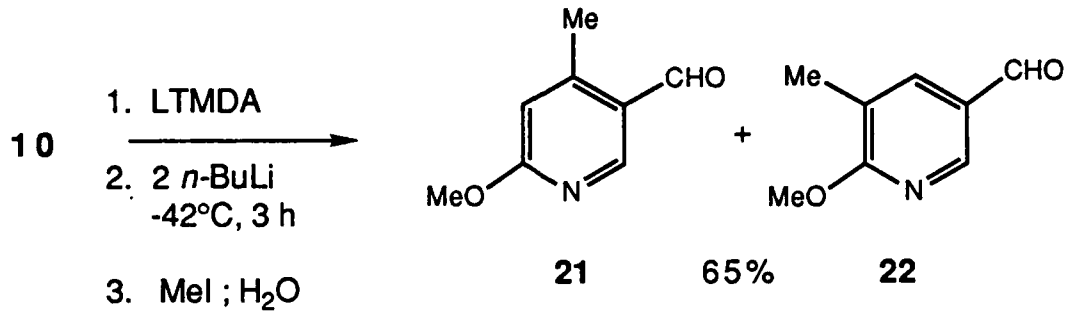
18 were alkylated using LTMDA as the amine component of the α-amino alkoxide. As shown below, **18** gave the tetra substituted product, while

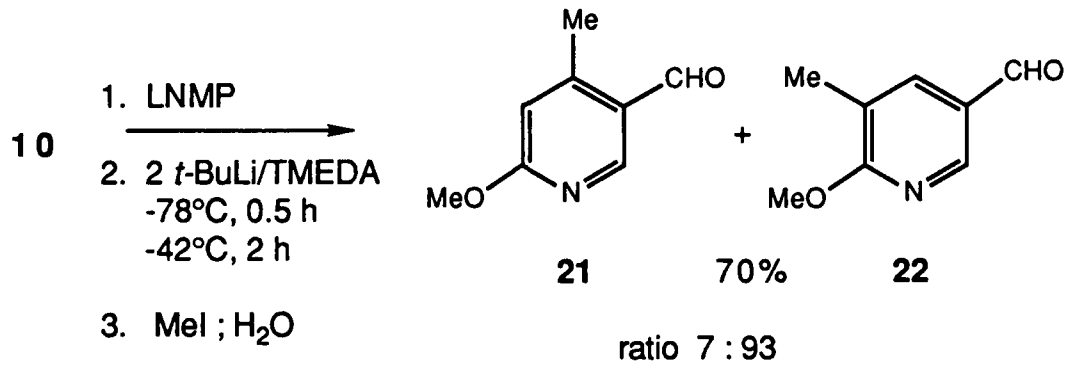


alkylation of **17** gave a mixture of **20** and **19.** The large ratio of **20** to **19** demonstrates the ability of α-amino alkoxides to direct lateral metalation as well as ring lithiation.

We next studied methoxypyridinecarboxaldehyde **10** using LTMDA and *n*-BuLi . The possibility existed that the α-amino alkoxide formed from the addition of **10** to LTMDA might direct metalation to either C-2 or C-4. As shown

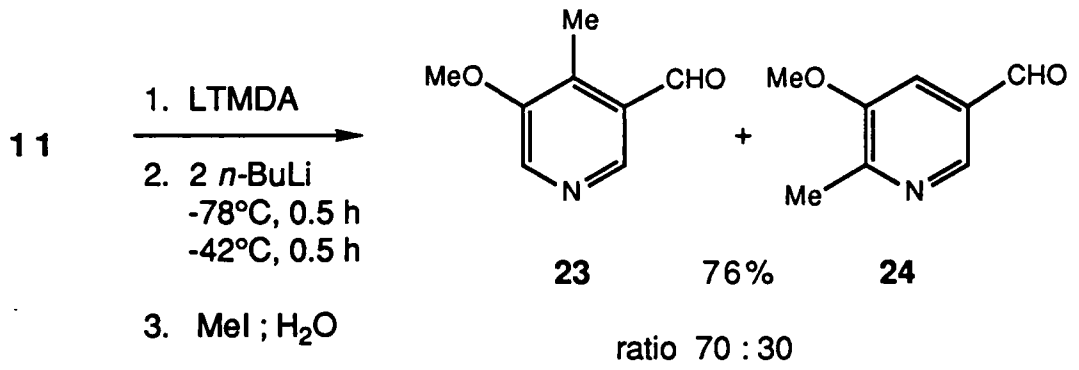
below, we found a high ratio of **21** vs **22** and lithiation-metalation was not observed at C-2. We found metalation-alkylation of **10**, using LNMP, *t*-BuLi, and methyl iodide, gave primarily the C-5 alkylated product **21** with an overall yield of 70%.

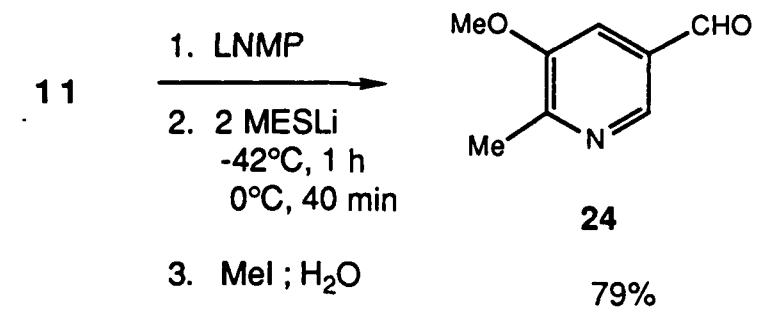




When we investigated the lithiation-methylation of methoxypyridinecarboxaldehyde **11** using LTMDA to form the α-amino alkoxide, we were disappointed

in the selectivity for lithiation-alkylation ortho to the protected aldehyde functionality. The best result was achieved using *n*-BuLi at -78°C. This gave a 70:30 ratio of the C-4 to C-6 methylated product as shown below. Again, we



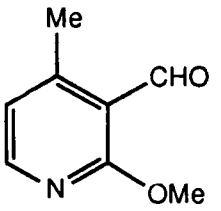


were unable to detect any C-2 alkylated product. When **11** was treated with LNMP, mesityllithium, and methyl iodide, **24** was isolated as the sole product in 79% yield.

Methylation of methoxypyridinecarboxaldehyde **12** using LTMDA, *n*-BuLi, and methyl iodide gave **25** as the sole product in 82% yield. In an analogous

reaction, **13** was lithiated-methylated using LNMP and MESLi to give **26** as the only isolated product. The last methoxypyridinecarboxaldehyde we investigated proved to be of particular interest. We found that **14** gave substituted pyridine **27** when either lithiated amine, LTMDA or LNMP, was

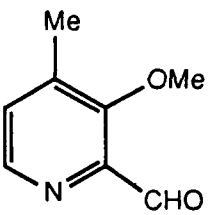
12 → 1. LTMDA; 2. 2 *n*-BuLi, -42°C, 1.5 h, -23°C, 0.5 h; 3. MeI ; H_2O



25

82%

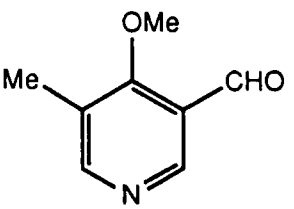
13 → 1. LNMP; 2. 2 MESLi, -23°C, 2 h, 0°C, 1 h; 3. MeI ; H_2O



26

67%

14 → 1. LNMP; 2. 1.5 MESLi, -23°C, 4 h; 3. MeI ; H_2O

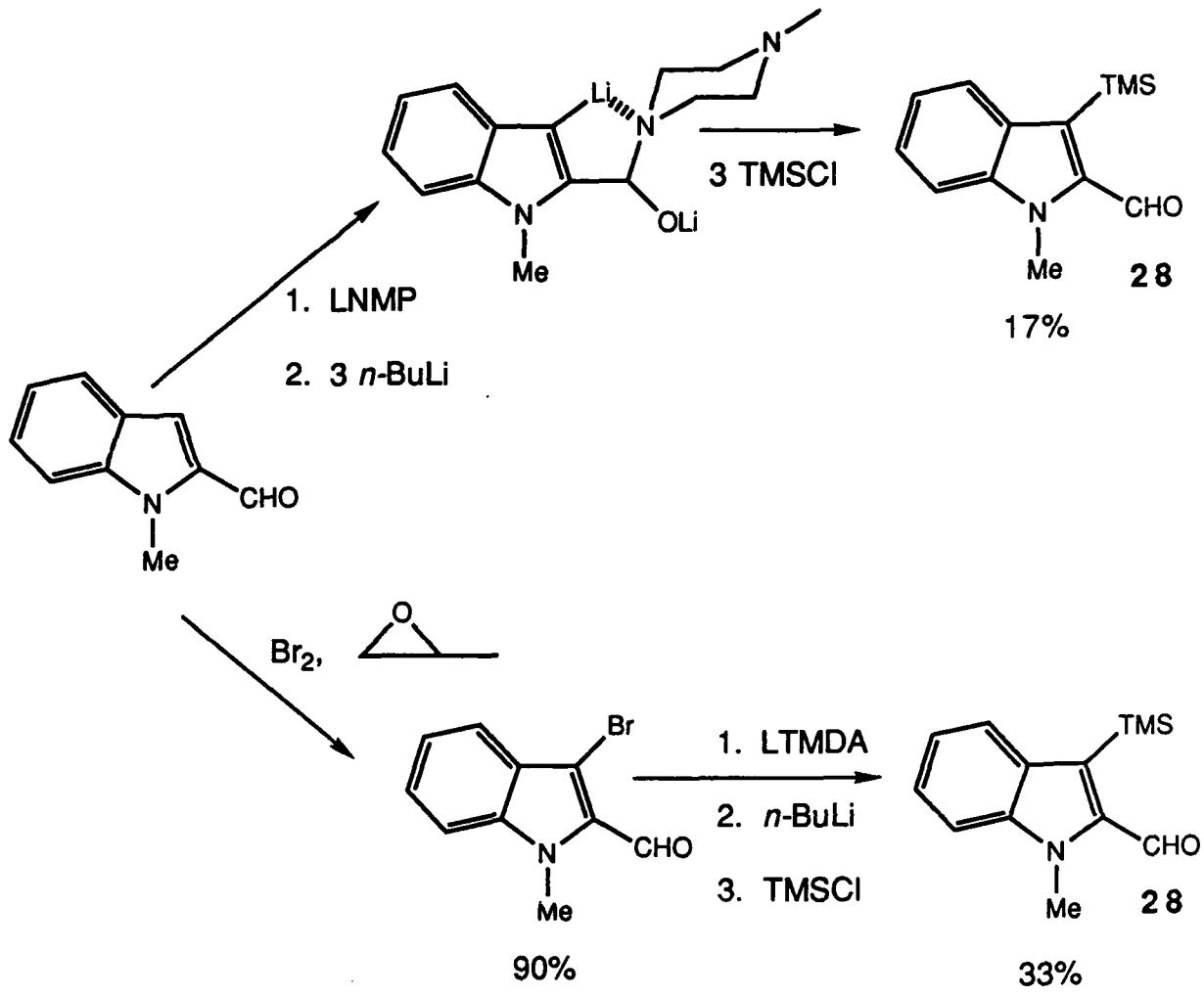


27

82%

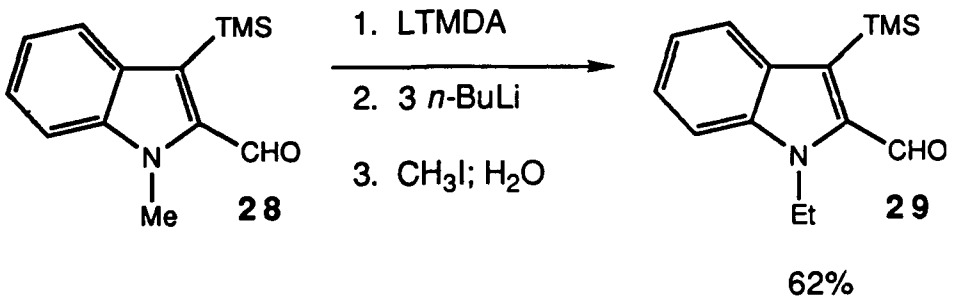
used as the amine component of the α-amino alkoxide, and regardless of reaction conditions. Surprisingly, we were unable to detect any C-2 substituted product. This is the only case where C-2 was the only ortho position available to the α-amino alkoxide for directed metalation. All other examples either had the option to direct to C-4, or C-2 was already substituted. The highest yield for methylation at C-5, 82%, was achieved using LNMP, MESLi, and methyl iodide.

N-Methyl Lithiation of N-Methylindoles. In a previous study[16] we were surprised to find that 1-methyl-2-pyrrolecarboxaldehyde was lithiated at the N-methyl position. The only reported directed lithiation of 2-substituted N-methylpyrroles was using the oxazoline directing group and it directed lithiation to the β position.[25] We attempted to utilize this novel reaction on 1-methylindole-2-carboxaldehyde, but lithiation-methylation of the α-amino alkoxide prepared from LTMDA gave a 2 to 1 mixture of 1-ethylindole-2-carboxaldehyde vs 1,3-dimethylindole-2-carboxaldehyde. We were unable to improve the ratio of N-methyl lithiation, but when the α-amino alkoxide was prepared from LNMP, lithiation occurred solely at C-3. To develop a potentially useful method for N-methyl lithiation we decided to try a strategy of blocking C-3 prior to metalation. Our first attempt at this strategy was to add a trimethylsilyl group at C-3. We prepared the 3-trimethylsilylindole **28** by the



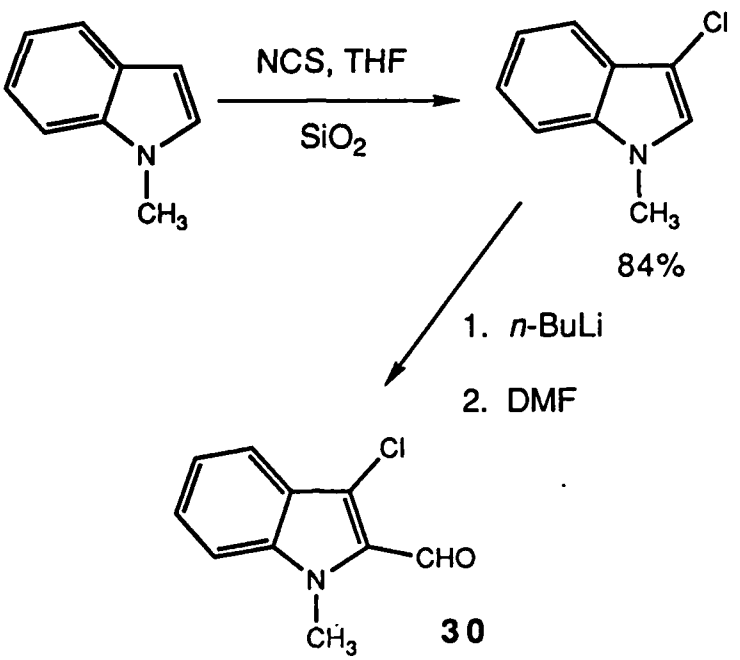
addition of TMSCl to the lithium anion, prepared from 1-methyl-2-indolecarboxaldehyde by either direct lithiation using the α-amino alkoxide protecting group with excess *n*-BuLi or by bromination at C-3 followed by addition of LTMDA and lithium halogen exchange with *n*-BuLi. Treatment of **28** with LTMDA, excess *n*-BuLi, and methyl iodide gave N-methyl substituted

product **29** in 62% yield. This reaction demonstrated our strategy to block C-3 was effective, but the low yields achieved in preparing **28** made the TMS group unattractive as a blocking group.



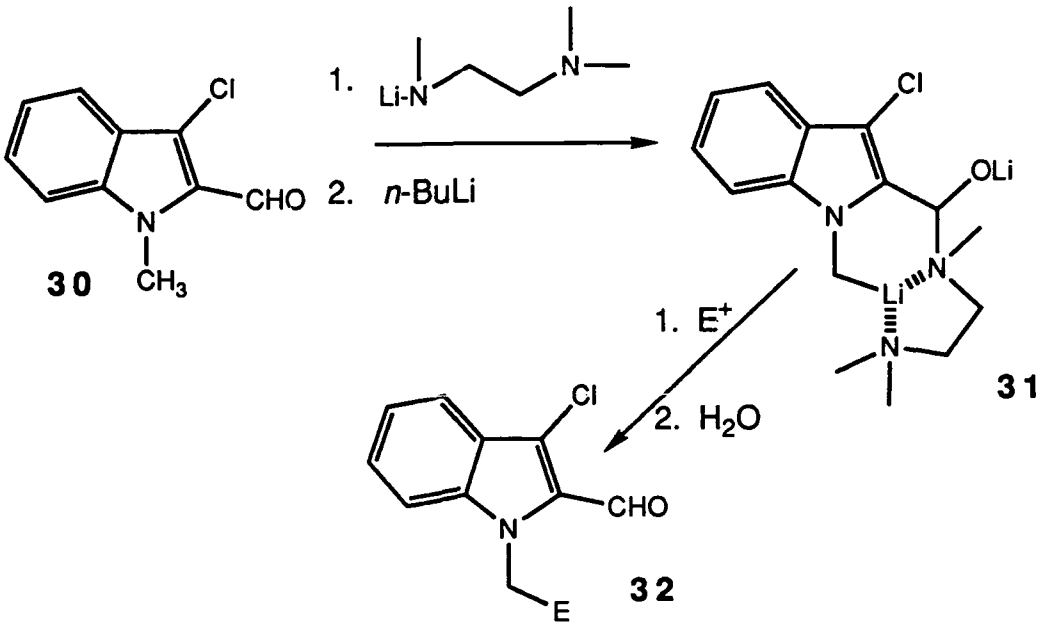
Since aryl chlorides are not susceptible to lithium-halogen exchange,[1a] we next studied the possibility of using a chloro group to block C-3. Our first attempts at chlorination of N-methylindole with N-chlorosuccinimide gave a mixture of products with poor yields (25-65%), and purification required both chromatography and distillation. However, by utilizing silica gel as a proton source and changing solvents from CH_2Cl_2 to THF, the yield was improved to 84% and purification was accomplished by a simple Kugelrohr distillation. The inductive effect and directing ability of the 3-chloro group drastically increased the rate and ease by which C-2 was lithiated with *n*-BuLi. Fomylation of the resulting anion with DMF gave the target aldehyde (**30**) in 92% yield. Reaction

of **30** with lithiated N,N,N′-trimethylethylenediamine formed α-amino alkoxide



30

31. Lithiation with *n*-BuLi followed by reaction with electrophiles gave N-substituted indoles **32** as listed in Table I.



To further demonstrate the utility of the 3-chloro protecting group, we treated **30** with 10% Pd/C, EtOH, triethylamine, and formic acid. As shown below, the chloro group was cleanly removed in 81% yield.[26]

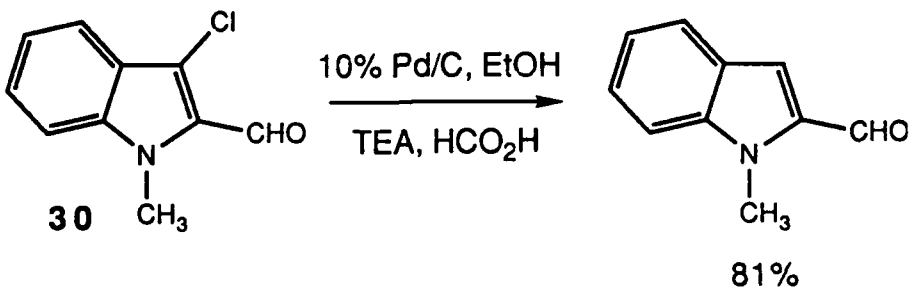
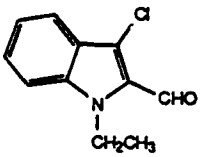
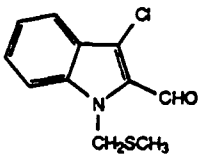
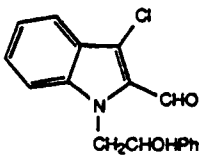
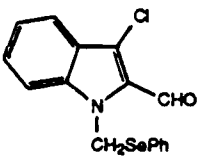
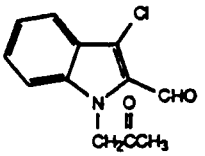
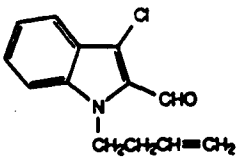


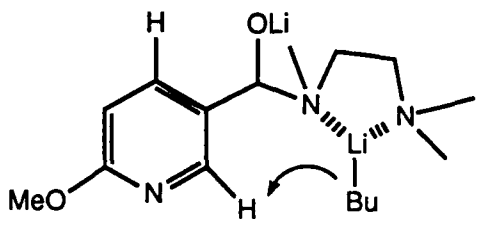
Table I. Reactions of Dianion 31 with Electrophiles

Entry	Electrophile [a]	Product	Yield, %	mp,°C
a	MeI		94	58-59.5
b	MeSSMe		85	95-97
c	PhCHO		84	130.5-132.5
d	PhSeSePH		73	119.5-120.5
e	EtOAc [b]		55	152.5-154
f	Ac_2O [c]		43	152.5-154
g	 [d]		75	30-31

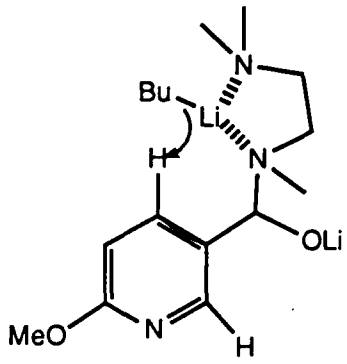
[a] Unless indicated, the electrophile was added at -78°C and the mixture was allowed to come to room temperature. [b] The dianion was added to neat EtOAc (50 ml). [c] Inverse addition and 30 mmol of Ac_2O were used. [d] A large excess of electrophile (18 mmol) was used.

IV. SUMMARY AND CONCLUSIONS

In this study we report the utility of using α-amino alkoxides in directed lithiation reactions of several methoxypyridinecarboxaldehydes and 3-chloro-1-methylindole-2-carboxaldehyde. The convenience of in situ protection and one-pot procedure makes the use of these reactions synthetically attractive. We found several examples where regioselectivity was altered by simply changing the lithiated amine used to form the α-amino alkoxide. This study also suggests that the α-amino alkoxides, formed from LTMDA with C-3 substituted pyridinecarboxaldehydes, may direct lithiation to C-4 but not C-2. An advantage of this selectivity is that one may predict the regioselectivity for lithiation of C-3 pyridinecarboxaldehydes, but the obvious disadvantage is the inaccessibility of substitution at C-2 ortho to the aldehyde functionality. As discussed earlier, the C-3 methoxy or ethoxy group directs lithiation to C-2,[8] while the C-3 chelating groups[5,7,18,20] direct metalation to C-4. A possible rationale for this selectivity could involve the angle of intramolecular attack. In the pyridine ring the bond lengths of the C-N bonds are shorter than the C-C bonds. This distorts the C-4, C-3, H-3 bond angle to 121.36°, while the C-2, C-3, H-3 bond angle is 120.11°.[27] These small distortions may affect the angle of intramolecular attack as **33** and **34** depict.[28]



Less favorable
33



More favorable
34

Directed N-methyl lithiation-alkylation by α-amino alkoxides on 1-methyl-indole-2-carboxaldehyde was accomplished using a C-3 protecting group strategy. Preparation of 3-chloro-1-methylindole-2-carboxaldehyde was achieved in high yields. The subsequent metalation-alkylation with various electrophiles and the removal of the chloro protecting group, makes the overall procedure an attractive method for preparation of useful N-substituted indoles.

V. Experimental Section

All reactions were performed in oven dried glassware under a N_2 atmosphere. Tetrahydrofuran (THF) was dried by distillation from sodium benzophenone ketyl prior to use. N,N,N′-Trimethylethylenediamine, N-methylpiperazine, and dimethylformamide (DMF) were distilled from calcium hydride and stored over 3 Å molecular sieves under N_2. Other solvents and reagents from commercial sources were generally stored over 3 Å molecular sieves and used without further purification. The *n*-butyllithium used in this study was purchased (Alfa Products) as a 2 M solution in hexane. Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were recorded on a Varian XL-300 or an IBM AF 80 spectrometer. Radial preparative-layer chromatography (radial PLC) was carried out by using a chromatotron (Harris Associates, Palo Alto, CA). Elemental analysis were carried out by M-H-W Laboratories, Phoenix, AZ. Infrared spectra were recorded on a Perkin-Elmer model 7500 spectrometer. Gas-liquid chromatography (GC) was performed on a Hewlett Packard Model 5880A gas chromatograph equipped with a 30 m 0.25 mm FSOT column packed with OV-101. The 2,4-dinitrophenylhydrazones were prepared by using a modified method published by Behforouz.[29] 4-Methoxy-3-pyridinecarboxaldehyde and 2-methoxy-3-pyridinecarboxaldehyde were prepared by literature procedure.[8c]

6-Bromo-2-methoxypyridine. 6-Bromo-2-methoxypyridine was prepared by a variation of the literature procedure.[30] To a stirred solution of 2,6-dibromopyridine (17.42 g,74 mmol) in anhydrous MeOH (50 mL) was added NaOMe (28.6 mL of 25% NaOMe in MeOH, 125 mmol). The mixture was refluxed for 25 h, then poured into cold 5% $NaHCO_3$ (50 mL). The mixture was extracted with ether (3x30 mL) and the organic layers were concentrated. Ether (50 mL) was added to the remaining liquid and the mixture was washed with brine (40 mL).The organic layer was dried (K_2CO_3) and concentrated, and the residue was Kugelrohr distilled (85-95°C/15 mmHg) to give 10.11 g (73%) of 6-bromo-2-methoxypyridine as a clear liquid: IR (neat) 2953, 1596, 1582, 1558, 1472, 1413, 1298, 1022, 857 cm^{-1}; ^1H NMR (80 MHz, $CDCL_3$) δ 3.89 (s,3 H), 6.63 (d, 1 H, *J*=8 Hz), 6.99 (d, 1 H, *J*=8 Hz), 7.37 (t, 1 H, *J*=8 Hz); ^{13}C NMR (20 MHz, $CDCl_3$) δ 54.3, 109.5, 120.3, 138.8, 140.5, 163.9.[30]

6-Methoxy-2-pyridinecarboxaldehyde (9). To a stirred solution of 6-bromo-2-methoxypyridine (1.01 g, 5.40 mmol) in THF (20 mL) at -78°C was added *n*-BuLi (5.61 mmol). After 1 h, DMF (0.472 g, 6.00 mmol) was added and the mixture was allowed to stir for 30 min at -78°C. The cold mixture was poured directly into a stirred aqueous solution of 5% $NaHCO_3$ (50 mL) and extracted with ether (3x25 mL). The combined organic layers were washed with brine and dried (K_2CO_3). The mixture was filtered and concentrated. The crude product was purified by radial PLC (silica gel, 5% EtOAc/hexanes)

Kugelrohr distillation (bp 99-105°C/20 mmHg (lit[31] bp 103-104°C/20 mmHg)) to give 5-Bromo-2-methoxypyridine 574 mg (78%) of **2** as an oil: IR (neat) 2955, 2829, 1719, 1704, 1600, 1474, 1333, 1276 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 4.03 (s, 3 H), 6.98 (d, 1 H, *J*=8.4 Hz), 7.57 (d,1 H, *J*=7.2 Hz), 7.74 (dd, 1 H, *J*=8.4, 7.2 Hz), δ 9.97(s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.15, 115.01, 115.92, 138.71, 150.08, 164.02, 192.50; DNP mp 216-219°C.

5-Bromo-2-methoxypyridine. 5-Bromo-2-methoxypyridine was prepared by a variation of the literature procedure.[30] To a stirred solution of 2,5-dibromopyridine (10.94 g, 46 mmol) in anhydrous MeOH (25 mL) was added NaOMe (50 mL of 25% NaOMe in MeOH, 210 mmol). The mixture was refluxed for 7 h, then the solution was poured into cold stirred 5% $NaHCO_3$ (75 mL). The mixture was extracted with ether (4x30 mL) and washed with brine (3x30 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by Kugelrohr distillation (65-70°C/3.5 mmHg) to give 7.96 g (92%) of a clear liquid: IR (neat) 2984, 2946, 1572, 1451, 1339, 1293, 1262, 1009, 799 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 3.88 (s, 3 H), 6.59 (d, 1 H, *J*=8.8 Hz), 7.56 (d, 1 H, *J*=8.8 Hz), 8.18 (s, 1 H); ^{13}C NMR (20 MHz, $CDCl_3$) δ 53.76, 111.79, 112.69, 141.00, 147.70, 163.10.

6-Methoxy-3-pyridinecarboxaldehyde (10). To a stirred solution of 5-bromo-2-methoxypyridine (1.63 g, 8.69 mmol) in THF (25 mL) at -78°C was added *n*-BuLi (9.10 mmol). After 1 h, DMF (1.27 g, 17.4 mmol) was added and

stirring was continued for 30 min at -78°C. The cold mixture was poured directly into a stirred aqueous solution of 5% $NaHCO_3$ (50 mL) and extracted with ether (3x25 mL). The combined organic layers were washed with brine and dried (K_2CO_3). The mixture was filtered and concentrated to give a yellow solid (1.212 g). The crude product was recrystallized from hexanes to give 1.00 g (84%) of **10** as a light yellow solid: mp 50.5-51.5°C; IR (neat) 2993, 2952, 2837, 1696, 1605, 1568, 1495, 1363, 1291, 1222, 1016, 838 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.04 (s, 3 H), 6.85 (d, 1 H, *J*=9 Hz), 8.07 (d, 1 H, *J*=9 Hz), 8.64 (s, 1 H), 9.96 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.07, 111.84, 126.50, 137.20, 152.63, 167.47, 189.26; Our data are in agreement with reported spectra.[32]

5-Bromo-3-methoxypyridine. Sodium methoxide in MeOH (20.5 mL, 95 mmol) was stirred under reduced pressure (15 mmHg) at 65°C for 30 min. The remaining solid was placed under a N_2 atmosphere and dissolved in DMF (60 mL). Solid 3,5-dibromopyridine (15 g, 63 mmol) was added and the mixture was stirred at 63-68°C. After 4 h, additional NaOMe/MeOH solution (7 mL, 32 mmol) was added. The reaction mixture was allowed to stir at 63-68°C for 12 h, then poured into H_2O (80 mL) and extracted with ether (6x20 mL). The combined organic layers were washed with brine (50 mL) and dried ($MgSO_4$). The mixture was filtered and concentrated to give a yellow solid. The crude product was purified by radial PLC (silica gel, 10% EtOAc/hexanes) followed by recrystallization (hexanes) to give 8.78 g (78%) of 5-bromo-3-methoxypyridine

as a light yellow solid. The residue from the mother liquid was purified by radial PLC (silica gel, 5% EtOAc/hexanes)to give an additional 1.27 g (11%) of product: IR (neat) 3045,3010, 2940, 1577, 1557, 1457, 1418, 1313, 1266, 1009, 858 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.86 (s, 3 H), 7.36 (s, 1 H), 8.25 (s, 1 H), 8.29 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.45, 120.02, 122.78, 142.46, 135.85, 155.64; mp 34-35°C. Anal. Calcd for C_6H_6BrNO: C, 38.33; H, 3.22; N, 7.45. Found: C, 38.18; H, 3.26; N, 7.28.

5-Methoxy-3-pyridinecarboxaldehyde (11). To a stirred solution of 5-bromo-3-methoxypyridine (4.09 g, 22.9 mmol) in THF (100 mL) at -100°C was added *n*-BuLi (25.2 mmol) over 10 min. The solution was allowed to stir for an additional 20 min at -100°C, and then DMF (2.3 mL, 29.8 mmol) was added. The mixture was stirred for 30 min, allowing the temperature to slowly warm to -60°C. The cold mixture was then poured directly into brine (100 mL) and extracted with ether (3x40 mL). The combined organic layers were dried (K_2CO_3), filtered, and concentrated. The crude product was purified by radial PLC (silica gel, 10% EtOAc/hexanes) to give 2.19 g (73%) of **11** as a light yellow solid: IR (neat) 2943, 2844, 1708, 1693, 1588, 1473, 1428, 1321, 1282, 1253, 1175 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.93 (s, 3 H), 7.62 (s, 1 H), 8.56 (s, 1 H), 8.67 (s, 1 H), 10.11 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.59, 116.16, 131.86, 144.86, 144.53, 156.00, 199.51; mp 33-34°C (hexanes/CCl_4). Anal. Calcd for $C_7H_7NO_2$: C, 61.51; H, 5.15; N, 10.21. Found: C, 67.17; H, 5.22;

N, 10.35.

General Procedure for Methylation of Methoxypyridinecarboxaldehydes. To a stirred solution of the secondary amine (N,N,N′-trimethylethylenediamine or N-Methylpiperazine)(2.4 mmol) in 10 mL of THF was added *n*-BuLi (2.2 mmol) at -78°C. After 15 min, the appropriate methoxypyridinecarboxaldehyde (2 mmol) was added and the mixture was stirred at -78°C for 15 min. The indicated base was added and stirred at the indicated temperatures and times. Methyl iodide (10 mmol) was added at -78°C and the mixture was allowed to come to room temperature (30 min). The solution was poured into vigorously stirred cold brine (25 mL) and extracted with ether (3x25 mL). The organic extracts were dried (K_2CO_3) and concentrated. The crude products were purified by radial PLC (EtOAc/ hexanes).

Spectral Data. **6-Methoxy-3-methyl-2-pyridinecarboxaldehyde (17).** IR (neat) 2945, 2820, 1711, 1606, 1483, 1341, 1272, 796 cm^{-1}; ^1H NMR (80 MHZ, $CDCl_3$) 2.55 (s, 3 H), 3.99 (s, 3 H), 6.83 (d, 1 H, *J*=8.4 Hz), 7.47 (d, 1 H, 8.4 Hz), 10.06 (s, 1 H); ^{13}C NMR (20 MHz, $CDCl_3$) 18.03, 53.87, 115.57, 129.14, 143.28, 146.92, 162.79, 195.38; mp 52.5-54°C. Anal. Calcd for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.53; H, 6.08; N, 9.12.

6-Methoxy-5-methyl-2-pyridinecarboxaldehyde (18). IR (KBr) 3011, 2955, 2841, 1695, 1597, 1463, 1277, 1243, 1027 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.28 (s,3 H), 4.05 (s,3 H), 7.49 (d, 1 H, *J*=7.2 Hz), 7.54 (d, 1 H,

J=7.2 Hz), 9.94 (s, 1 H); ^{13}C NMR (20 MHz, $CDCl_3$) δ 16.50, 53.83, 116.04, 127.65, 138.96, 148.82, 162.96, 193.06; DNP mp 222-224°C. Anal. Calcd for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.21; H, 5.83; N, 9.12.

3,5-Dimethyl-6-methoxy-2-pyridinecarboxaldehyde (19). IR (KBr)2961, 2924, 2832, 1696, 1561, 1478, 1416, 1356, 1277, 1117 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 2.21 (s, 3 H), 2.50 (s, 3 H), 4.00 (s, 3 H), 7.23 (s, 1 H), 10.01 (s, 1 H); ^{13}C NMR (20 MHz, $CDCl_3$) δ 16.09, 17.74, 53.66, 126.38, 129.17, 142.76, 144.76, 160.84, 194.92; mp 84.5-85.5°C (hexanes). Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.21; H, 6.79; N, 8.35.

3-Ethyl-6-methoxy-2-pyridinecarboxaldehyde (20). IR (neat) 2975, 1711, 1603, 1482, 1337, 1271, 1030 cm-1; ^1H NMR (80 MHz, $CDCl_3$) δ 1.19 (t, 3 H, *J*=7.5 Hz), 3.01 (q, 3 H, *J*=7.5 Hz), 3.99 (s, 3 H), 6.86 (d, 1 H, *J*=8.4 Hz), 7.53 (d, 1 H, *J*=8.4 Hz), 10.06 (s, 1 H); ^{13}C NMR (20 MHz, $CDCl_3$) δ 15.58, 24.24, 53.86, 115.84, 135.54, 141.85, 146.50, 162.70, 195.12; DNP mp 180-184°C. Anal Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.45; H, 6.66; N, 8.57.

6-Methoxy-4-methyl-3-pyridinecarboxaldehyde (21). IR (KBr) 3026, 1695, 1613, 1554, 1446, 1362, 1255, 1147 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 2.61 (s, 3 H), 4.01 (s, 3 H), 6.60 (s, 1 H), 8.51 (s, 1 H), 10.07 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) 19.85, 53.85, 112.90, 125.38, 151.42, 155.25,

166.60, 190.58; mp 91-92°C (hexanes). Anal. Calcd for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.31; H, 6.02; N, 9.13.

6-Methoxy-5-methyl-3-pyridinecarboxaldehyde (22). IR (neat) 2989, 2953, 1694, 1605, 1484, 1408, 1381, 1268, 1141, 1016 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 2.24 (s, 3 H), 4.06 (s, 3 H), 7.88 (s, 1 H), 8.47 (s, 1 H), 9.93 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.79, 54.30, 122.10, 126.73, 136.35, 150.39, 166.19, 189.81; mp 56-56.5°C (hexanes). Anal. Calcd for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.69; H, 5.94; N, 9.30.

5-Methoxy-4-methyl-3-pyridinecarboxaldehyde (23). IR (KBr) 2960, 1692, 1585, 1489, 1422, 1294, 1270, 1011, 909, 713 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.56 (s, 3 H), 3.98 (s, 3 H), 8.37 (s, 1 H), 8.62 (s, 1 H), 10.33 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) 10.51, 56.50, 129.85, 136.45, 137.57, 146.04, 154.18, 191.82; mp 70.5-71.5°C. Anal. Calcd for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.66; H, 6.06; N, 9.27.

5-Methoxy-6-methyl-3-pyridinecarboxaldehyde (24). IR (KBr) 2978, 2860, 1689, 1595, 1392, 1152 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.57 (s, 3 H), 3.91 (s, 3 H), 7.51 (s, 1 H), 8.52 (s, 1 H), 10.05 (s, 1 H); ^{13}C NMR (80 MHz, $CDCl_3$) 20.10, 55.40, 112.32, 130.81, 144.56, 154.27, 156.30, 190.58; mp 75.5-76.5°C (hexanes). Anal. Calcd for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.38; H, 6.02; N, 9.19.

3-Methoxy-4-methyl-2-pyridinecarboxaldehyde(26). IR (neat)

2933, 2832, 1715, 1585, 1561, 1473, 1263, 1224, 1002 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.30 (s, 3 H), 3.84 (s, 3 H), 7.28 (d, 1 H, *J*=4.8 Hz), 8.35 (d, 1 H, *J*=4.8 Hz), 10.15 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.19, 62.34, 130.09, 142.80, 144.78, 145.24, 157.33, 191.04; mp 42.5-44°C (hexanes). Anal. Calcd for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.76; H, 6.00; N, 9.18.

4-Methoxy-5-methyl-3-pyridinecarboxaldehyde (27). IR (KBr) 2897, 1703, 1678, 1574, 1480, 1404, 1269, 1228, 1153, 996, 821 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.34 (s, 3 H), 4.01 (s, 3 H), 8.57 (s, 1 H), 8.83 (s, 1 H), 10.38 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.09, 62.61, 123.84, 126.88, 150.32, 157.09, 166.77, 189.07; mp 64.5-66°C (hexanes). Anal. Calcd for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.51; H, 6.04; N, 9.29.

2-Methoxy-4-methyl-3-pyridinecarboxaldehyde (25). IR (neat) 2988, 2953, 2869, 1686, 1590, 1564, 1476, 1377, 1302, 1083 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.59 (s, 3 H), 4.04 (s, 3 H), 6.77 (d, 1 H, *J*=5.1 Hz), 8.16 (d, 1 H, *J*=5.1 Hz), 10.54 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.79, 53.84, 117.16, 120.87, 150.79, 152.42, 165.78, 191.47; mp 29.5-30°C (hexanes). Anal. Calcd for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.68; H, 5.89; N, 9.15.

3-Chloro-1-methylindole. We used a modified method reported for the preparation of 3-chloro-1-methylpyrrole.[33] To a 50 mL flask was added

1.75 g silica gel (60 Å pore size, 35-70 Å particle size), 1-methylindole (1.01 g, 7.70 mmol), and THF (20 mL). The mixture was cooled to 0°C and N-chlorosuccinimide (1.05 g, 7.8 mmol) was added slowly. The solution was allowed to come to room temperature and, after stirring for 0.5 h, filtered through a fritted funnel into a stirred aqueous solution of saturated sodium thiosulfate (20 mL) and H_2O (20 mL). The aqueous layer was extracted with ether (2x30 mL) and the combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), and concentrated. The light yellow crude product was purified by bulb to bulb distillation (110-125°C/ 2 mmHg) to give 1.073 g (84%) of 3-chloro-1-methylindole as a clear colorless oil: bp 92°C/0.5 mmHg; IR (neat) 3122, 3056, 2937, 1486, 1466, 1362, 1325, 1241, 1110, 968 cm^{-1}; ^1H NMR (300 MHz, $CDCL_3$) δ 3.76 (s, 3 H), 7.02 (s, 1 H), 7.15-7.35 (m, 3 H), 7.62 (d, 1 H, J=8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) 32.87, 104.28, 109.44, 118.28, 119.83, 122.53, 125.18, 125.65, 135.75; Anal. Calcd for C_9H_8ClN: C, 65.26; H, 4.87; N, 8.46. Found: C, 65.18; H, 5.00; N, 8.68.

3-Chloro-1-methylindole-2-carboxaldehyde (30). To a stirred solution of 3-chloro-1-methylindole (10.34 g, 62.5 mmol) in THF (100 mL) at -42°C was added *n*-BuLi (65.6 mmol). After 1 h DMF (5.47 g, 5.80 mL, 74.8 mmol) was added and the mixture was stirred for an additional 20 min. The ice bath was removed and 50 mL of H_2O was added. The solution was placed in a separatory funnel and the aqueous layer was extracted with ether (3 x 40 mL). The combined organic layers were washed with brine, dried, and concentrated

to give 12.55 g of a yellow solid. The crude product was recrystallized (hexanes) to give 8.14 g of product. The mother liquor was Kugelrohr distilled (125-140°C/ 2 mmHg) followed by recrystallization to give an additional 2.95 g of **30** as a white solid. Total yield was 11.09 g (92%): mp 88-89°C; IR (KBr) 3316, 2826, 1669, 1614, 1511, 1472, 1399, 1351, 1334, 1189, 887 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.99 (s, 3 H), 7.20 (t, 1 H, *J*=6.9 Hz) 7.30 (d, 1 H, *J*=8.4 Hz), 7.43 (t, 1 H, *J*=6.9 Hz), 7.68 (d, 1 H, *J*=8.1 Hz), 10.11 (s, 1 H); ^{13}C NMR (75 MHz, $CDCL_3$) 31.65, 110.35, 119.04, 120.36, 121.35, 124.08, 127.96, 128.90, 138.49, 181.08; Anal. calcd for $C_{10}H_8ClNO$: C, 62.03; H, 4.16; N, 7.23. Found: C, 62.23; H, 4.38; N, 7.23.

1-Methylindole-2-carboxaldehyde. 3-Chloro-1-methylindole-2-carboxaldehyde (0.290 g, 1.5 mmol) and 10% Pd/C (0.040 g, 0.038 mmol) were placed in a 25-mL three-neck flask fitted with a condenser and flushed with N_2. After 15 min, EtOH (10 mL), triethylamine (2.1 mL, 15 mmol), and 96% acetic acid (0.45 mL, 12 mmol) were added and the solution was refluxed for 7.5 h. The mixture was filtered and concentrated. The concentrate was dissolved in ether (50 mL), washed with water (20 mL) and then brine (20 mL). The organic layer was dried ($MgSO_4$) and concentrated to give 0.220 g of a yellow solid. The crude product was purified by radial PLC (10% EtOAc/hexanes) to give 0.193 g (81%) of product as a white solid: mp 84-85°C, (hexanes)(lit.[34] mp 84-85 °C); ^1H NMR (300 MHz, $CDCl_3$ 4.06 (s, 3 H), 7.15-7.80 (m, 5 H), 9.86 (s, 1 H).

General procedure for the metalation and addition of electrophiles to 3-chloro-1-methylindole-2-carboxaldehyde (30). To a solution of N,N,N′-trimethylethylenediamine (0.23 mL, 1.8 mmol) in THF (10 mL) at -42°C was added *n*-BuLi (1.7 mmol). After 15 min, 2.90 g of 3-chloro-1-methyl-indole-2-carboxaldehyde (1.5 mmol) was added, and the mixture was stirred for 15 min at -42°C followed by the addition of *n*-BuLi (4.5 mmol). After stirring the solution for 3 h at -42°C, the reaction flask was sealed and placed in a freezer (-20°C) for 15 h. The reaction mixture was cooled to -78°C and the electrophile was added. The mixture was then allowed to warm to room temperature (for quantity of electrophile and length of time stirred at room temperature see Table I). The solution was poured into cold, stirring H_2O (30 mL). The aqueous layer was extracted with ether (3 x 20 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), and concentrated to give the crude products which were purified by radial PLC (silica gel, 10-30% EtOAC/hexanes).

Spectral Data for Table 1. 3-Chloro-1-ethylindole-2-carboxaldehyde. IR (KBr) 3067, 1667, 1615, 1509, 1354, 1338, 1236, 1178 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.37 (t, 3 H, *J*=7.2 Hz), 4.59 (q, 2 H, *J*=7.2 Hz), 7.20-7.29 (m, 1 H), 7.38-7.50 (m, 2 H), 7.75 (d, 1 H, *J*=8.1 Hz), 10.18 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.46, 39.84, 110.39, 119.41, 120.54, 121.34, 124.30, 127.97, 128.28, 137.58, 180.8; mp 58.0-59.5°C (hexanes). Anal. Calcd

for $C_{11}H_{10}ClNO$: C, 63.62; H, 4.85; N, 6.75. Found: C, 63.67; H, 4.81; N, 6.81.

3-Chloro-1-(methylthiomethyl)-indole-2-carboxaldehyde. IR (KBr) 2914, 1658, 1611, 1512, 1456, 1428, 1335, 1283, 1253, 924 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.06 (s, 3 H), 5.73 (s, 2 H), 7.20-7.35 (m, 1 H), 7.44-7.56 (m, 2 H), 7.75 (d, 1 H, *J*=8.4 Hz), 10.16 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.47, 47.17, 111.39, 120.78, 121.19, 122.12, 124.81, 128.40, 128.55, 138.03, 180.98; mp 95.0-97.5°C (hexanes). Anal. Calcd for $C_{11}H_{10}ClNOS$: C, 55.12; H, 4.20; N, 5.84. Found: C, 55.12; H, 4.35; N, 5.88.

3-Chloro-1-(2-phenyl-2-ethanol)-indole-2-carboxaldehyde. IR (KBr) 3419(b), 3035, 1645, 1614, 1511, 1461, 1408, 1354, 1335, 1308, 1173, 915 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.75-2.80 (m, 1 H), 4.51 (dd, 1 H, *J*=14.4 Hz, *J*=9.0 Hz), 4.68 (dd, 1 H, *J*=14.4 Hz, *J*=3.3 Hz), 5.00-5.08 (m, 1 H), 7.10-7.70 (m, 8 H), 7.70 (d, 1 H, *J*=8.1 Hz) 10.09 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) 52.40, 74.20, 111.37, 120.39, 120.73, 121.65, 124.15, 125.72, 128.01, 128.35, 128.54, 128.82, 139.08, 141.14, 181.48; mp 130.5-132.5°C (EtOAc/hexanes). Anal. Calcd for $C_{17}H_{14}ClNO_2$: C, 68.12; H, 4.71; N, 4.67. Found: C, 68.17; H, 4.73; N, 4.70.

3-Chloro-1-(methylselenylphenyl)-indole-2-carboxaldehyde. IR (CH_2Cl_2) 3049, 1670, 1516, 1456, 1405, 1170 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.96 (s, 2 H), 6.93 (d, 1 H, *J*=8.4 Hz), 7.01-7.36 (m, 7 H), 7.67 (d, 1 H,

J=7.5 Hz), 9.96 (s, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 41.76, 111.19, 120.42, 120.93, 121.94, 124.54, 127.38, 127.91, 127.93, 128.60, 128.81, 136.52, 137.69, 180.53; mp 119.5-120.5°C (hexanes). Anal. Calcd for $C_{16}H_{12}ClNOSe$: C, 55.11; H, 3.47; N, 4.02. Found: C, 54.92; H, 3.71; N, 3.84.

3-Chloro-1-(methylmethylketone)-indole-2-carboxaldehyde. IR (KBr) 3063, 1729, 1662, 1615, 1514, 1424, 1373, 1356, 914 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.25 (s, 3 H), 5.28, (s, 2 H), 7.15-7.29 (m, 2 H), 7.42-7.49 (m, 1 H), 7.76 (d, 1 H, *J*=8.4 Hz), 10.09 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 26.85, 53.87, 109.76, 120.36, 120.73, 121.89, 124.38, 128.56, 138.37, 181.09, 201.72; mp 152.5-154.0°C (EtOAc/hexanes). Anal. Calcd for $C_{12}H_{10}ClNO_2$: C, 61.16; H, 4.28; N, 5.94. Found: C, 61.18; H, 4.32; N, 5.85.

2-Chloro-1-(3-butene)-indole-2-carboxaldehyde. IR (neat) 3065, 1668, 1615, 1511, 1465, 1411, 1353, 1336, 1174 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.24 (m, 2 H), 4.52-4.63 (m, 2 H), 4.80-5.08 (m, 2 H), 5.72-5.86 (m, 1 H), 7.20-7.50 (m, 3 H), 7.74 (d, 1 H, *J*=8.1 Hz), 10.18 (s, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 34.64, 44.21, 110.64, 117.38, 119.47, 120.40, 121.31, 124.12, 127.89, 128.39, 134.15, 137.86, 180.71; mp 30-31°C (EtOAc/hexanes). Anal. Calcd for $C_{13}H_{12}NOCl$: C, 66.81; H, 5.18; N, 5.99. Found: C, 66.68; H, 5.36; N, 5.94.

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PART B. SYNTHETIC METHODS USING N-ACYLIMINIUM IONS AND 1-ACYLPYRIDINIUM SALTS

I. INTRODUCTION

The preparation of substituted pyridines, pyrrolidines, and piperidines via highly reactive N-acyliminium ions and 1-acylpyridinium salts is an important area of research.[1-3] Excellent regioselectivity and high yields for carbon-carbon bond formation makes these reactions synthetically useful and widely studied. Since direct addition of nucleophiles to the pyridine ring is often unachievable or gives a mixture of products, preparation of substituted pyridines via 1-acylpyridinium salts has been an attractive synthetic route.[3-4] Several techniques to prepare 1-acyldihydropyridines in high yields and excellent regioselectivity have been developed[4] and the oxidation back to pyridines has generally been accomplished using elemental sulfur or *o*-chloronil. In an effort to improve the yields and convenience of these reactions, we investigated the anodic oxidation of dihydropyridines as an alternative to sulfur or *o*-chloronil oxidation. In addition to preparation of pyridines, 1-acyldihydropyridines have been utilized for the synthesis of several alkaloids.[4j,9-12] In an effort to expand the use of this methodology to encompass asymmetric synthesis, we treated chiral 1-acyl-4-methoxypyridinium salts with triphenylsilylmagnesium bromide to give optically active 1-acyl-2-triphenylsilyl-2,3-dihydropyridones in good yield. The ability to further elaborate these novel molecules was investigated. We applied similar

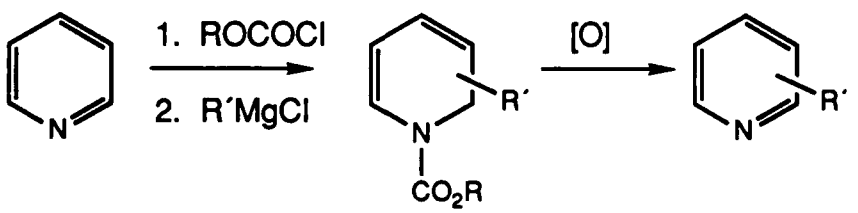
methodology to chiral 1-acyl-α-methoxy -pyrrolidines, -pyrrolidinones, and -piperidones. Our strategy was to prepare optically active pyrrolidines, pyrrolidinones, and piperidones via 1-acyliminium ion intermediates.

II. REVIEW OF THE LITERATURE

The use of 1-acyliminium ion intermediates is an important method for regioselective carbon-carbon bond formation and several reviews are available.[1-3] Almost all 1-acyliminium ion intermediates are generated in situ and are highly reactive towards nucleophiles. The method by which nucleophiles are added to 1-acyliminium ions is reaction dependent. Examples of intramolecular nucleophilic attack, addition of nucleophiles to preformed 1-acyliminium ions, and the reverse addition of nucleophiles prior to the formation of the 1-acyliminium ion intermediates are well known.[1-3]

Preparation of Substituted Pyridines by Oxidation of 1-Acyldihydropyridines. The ability to add a substituent regioselectively to the pyridine ring presents special challenges to the synthetic chemist. One versatile and powerful method which has been developed for the preparation of substituted pyridines is nucleophilic substitution via 1-acylpyridinium salts. Several techniques have been reported for regioselective substitution at either the 2- or 4-position on the pyridine ring of 1-acylpyridinium salts.[2,4] The

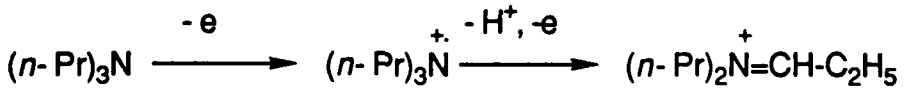
Scheme I



general methodology (Scheme I) requires preparation of the substituted 1-acyldihydropyridines and subsequent oxidation to give the substituted pyridine. Preparation of the substituted dihydropyridines is accomplished by first generating in situ a 1-acylpyridinium salt by reaction of pyridines with alkyl chloroformates. The addition of nucleophiles to the highly electrophilic 1-acylpyridinium salt is rapid and is usually carried out at cold temperatures. The second step, which involves oxidation of the substituted dihydropyridines, is of particular interest to this study. The most widely used oxidizing agents have been elemental sulfur in refluxing decalin[4] or *o*-chloranil;[4] however, silver nitrate and oxygen have also been used.[5] The preparation of dihydropyridines from 1-acylpyridinium salts is generally reported in good to high yields (50-99), whereas, the oxidation step is known to reduce the overall two step yield by greater than 25%.[4,5]

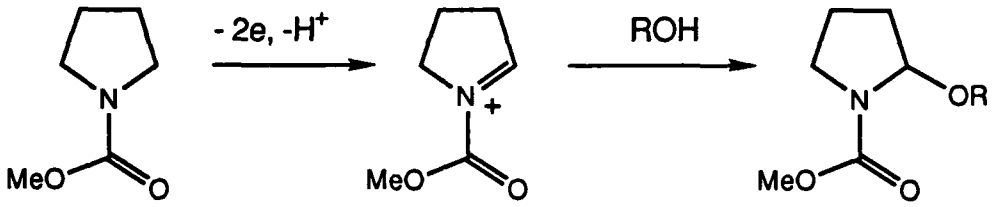
Anodic Oxidation of Amines and N-Acylamines. Anodic oxidation of amines and *N*-acylamines is well known and Shono has proposed a general mechanism (Scheme II).[3] The oxidation is initiated by the direct removal of one electron from the lone pair electrons of nitrogen.[6] The

Scheme II



formation of the cation radical has been observed by ESR in the oxidation of 1,4-diazabicyclo[2.2.2]octane.[7] The loss of a proton and the removal of a second electron gives a highly reactive iminium ion . These iminium ions react readily with mild nucleophiles such as alcohols as shown in Scheme III.[8]

Scheme III



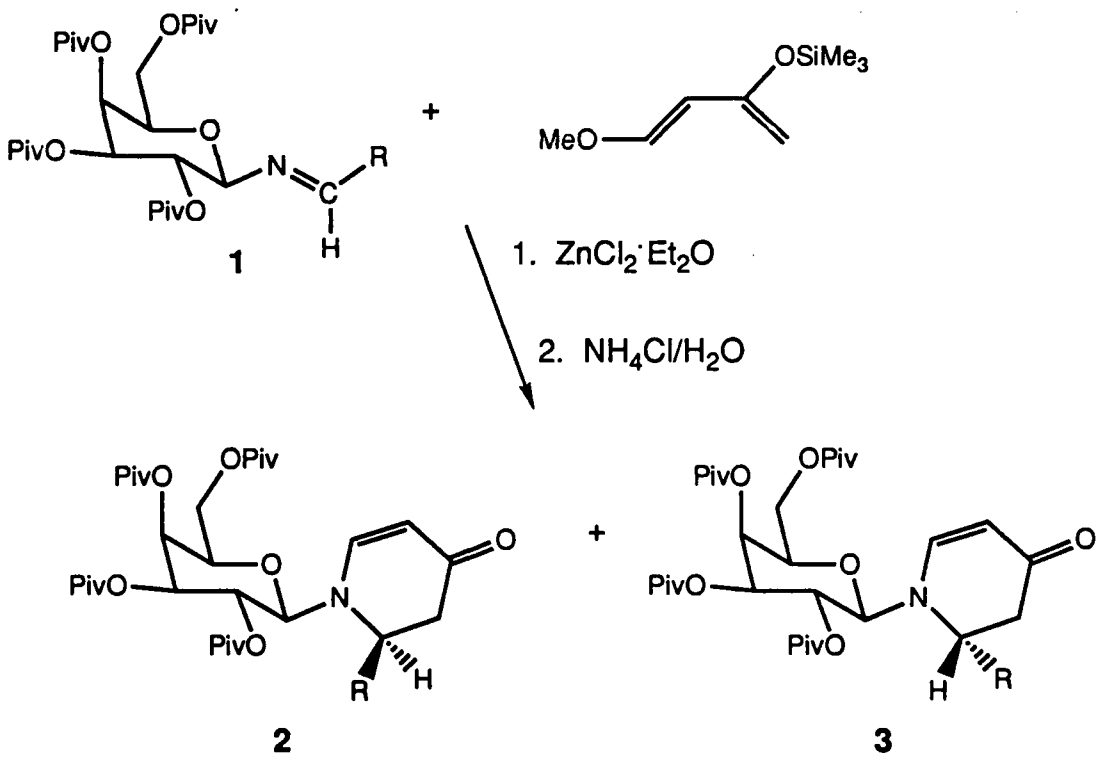
Preparation of Dihydropyridones. In recent years 2,3-dihydropyridones have been utilized as synthetic intermediates for the synthesis of several alkaloids.[9-12,14] In spite of the importance of these key intermediates there have only been a few methods reported for their preparation.

The first reported methods for the preparation of 2,3-dihydropyridones were condensation reactions of Schiff bases with β-diketones or partial reduction of pyridones.[13]

Danishefsky and Kerwin reported the preparation of dihydropyridones via a Lewis acid cyclocondensation between imines with siloxydienes.[14] This methodology has recently been expanded by Kunz and Pfrengle using tetra-O-

pivaloyl-β-galactopyranosylamine derivatives.[12] Chiral imines **1** were prepared from substituted aldehydes and tetra-O-pivaloyl-β-galactopyranosylamine (Scheme IV). The Lewis acid catalyzed reaction of **1** with Danishefsky's diene gave diastereomers **2** and **3**. Stereoselectivity is somewhat dependent on R and diastereomeric excess varied between 38 and 96%. The diasteriomers were separated by flash chromatography to give two

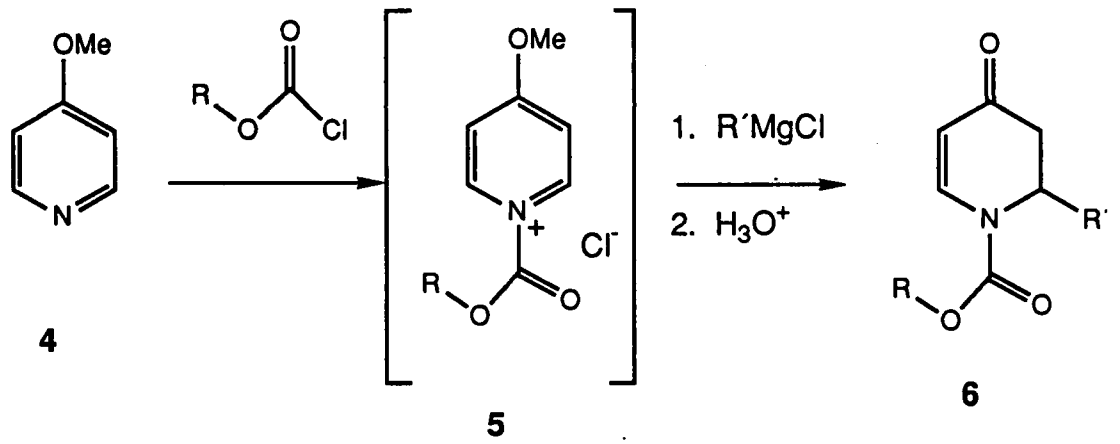
Scheme IV



enantiomerically pure isomers. Utilizing this methodology as the key step, enatiomerically pure (S)-conine and (S)-anabasine were prepared in 6 steps.[12]

Another method for the preparation of 1-acyl-2,3-dihydropyridones which has received considerable attention in recent years is the addition of nucleophiles to 1-acyl-4-methoxypyridinium salts.[9-11] The methodology gives 2-substituted 1-acyl-2,3-dihydro-4-pyridones in a one-pot procedure (Scheme V). Addition of 4-methoxypyridine to an alkyl chloroformate gives 1-acyl-4-methoxy-

Scheme V



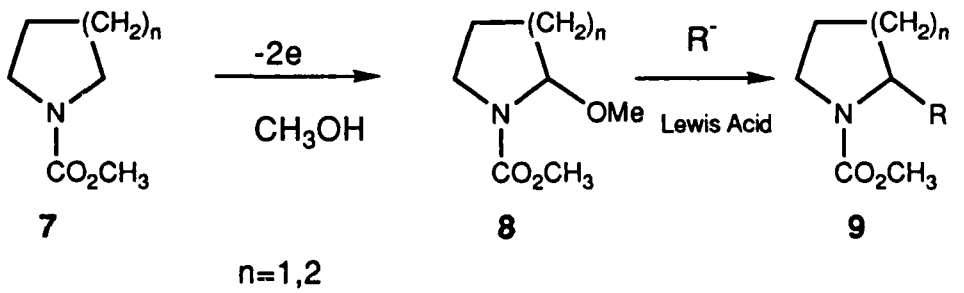
4 **5** **6**

pyridinium salts **5**, which upon addition of a Grignard reagent and acidic workup gives substituted 1-acyl-2,3-dihydropyridones **6** in high yields. Using this approach (±)-lasubine II[10] was prepared in four steps and the synthesis of (±)-myrtine[11] was achieved in five steps. To expand this methodology to include asymmetric synthesis, Comins and coworkers have recently explored

the use of chiral chloroformates ((-)-menthyl chloroformate or (-)-8-phenylmenthyl chloroformate) to prepare optically active pyridinium salts, which, when treated with alkyl Grignards followed by acidic workup, give optically active 2-substituted 1-acyl-2,3-dihydropyridones in moderate to high diastereomeric excess (34-94%).[15]

Carbon-Carbon Bond Formation at the α-Position of Piperidine and Pyrrolidine Rings Utilizing N-Acyliminium Ions. Carbon-carbon bond formation at the α-position of pyrrolidine and piperidine by means of N-acyliminium ions has received considerable attention.[1,3] The preparation of N-acyliminium ions has been accomplished by several methods. One important method for generating acyliminium ions has been developed by Shono and coworkers (Scheme VI).[3,16] The key step involves the anodic

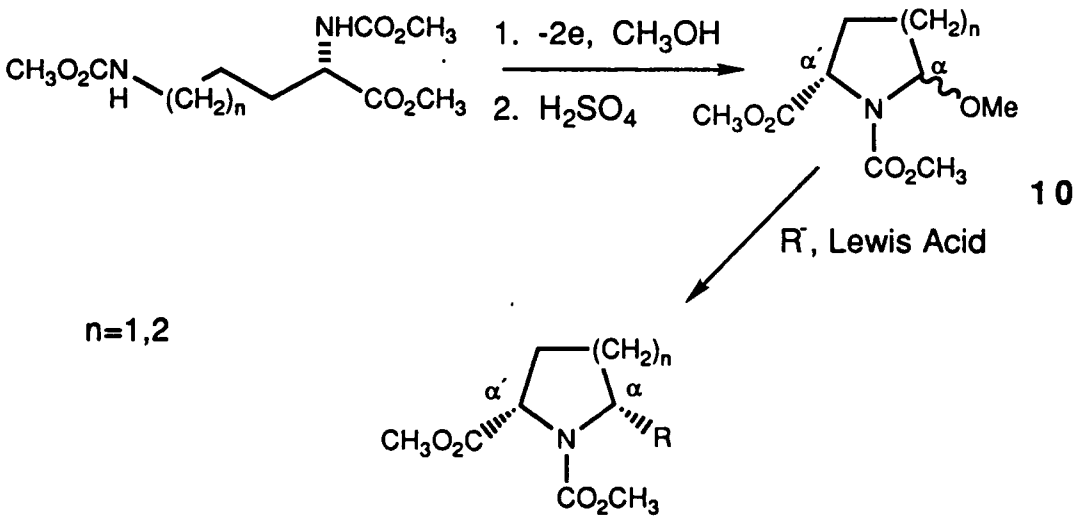
Scheme VI



oxidation of carbamates **7** in methanol to give α-methoxylated product **8**.

Treatment with Lewis acids catalyze the formation of 1-acyl-iminium ions which react with nucleophiles to give the desired α-substituted products **9**. Shono and coworkers have utilized this chemistry to prepare several optically active piperidine and pyrrolidine alkaloids from amino acids (Scheme VII).[17,18] The key step was the anodic preparation of optically active compounds **10** from α-amino acids. Addition of Lewis acid to **10** catalyzed the formation of an acyliminium ion and the nucleophile (R⁻) was diastereoselectively introduced into the α-position by the influence of the substituent on the α′-position. The

Scheme VII

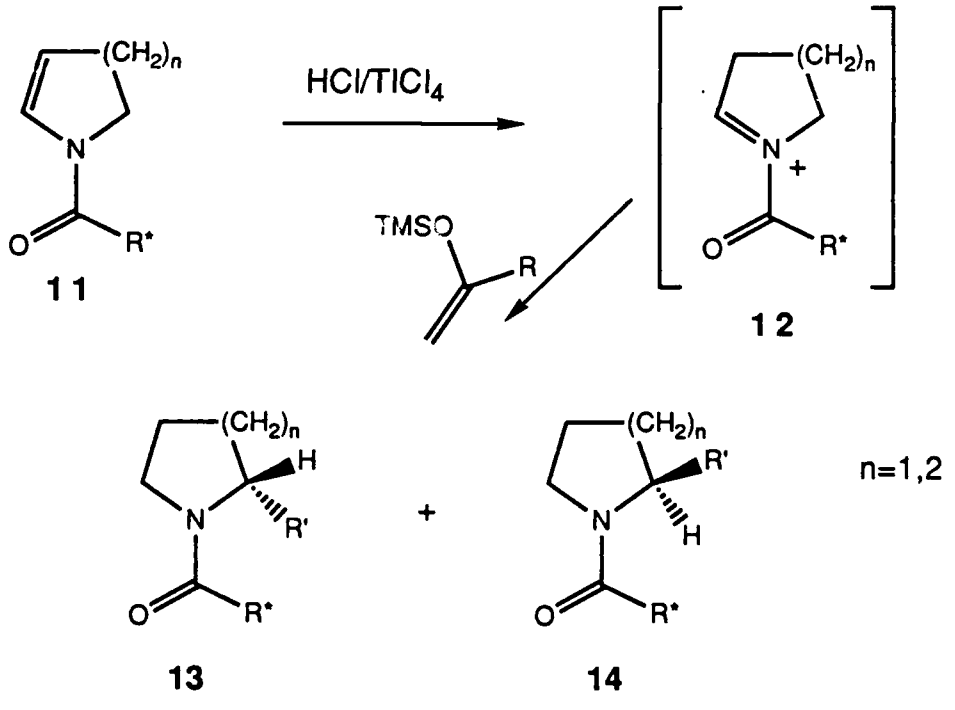


diastereomers were separated by chromatography and were further elaborated to give optically active (+)-*N*-methylconine (96% pure),[17] (+)-hygroline (43%

pure),[17] and (+)-*N*- methylpseudoconhydrydrine (90% pure).[18] It should be noted that the optical purity was much higher for substituted piperidines than the pyrrolidine analogues.

Wanner and coworkers have utilized a different approach to the synthesis of optically active α-substituted piperidines and pyrrolidines (Scheme VIII).[19] They initially prepared enamides **11** followed by the addition of acid to

Scheme VIII



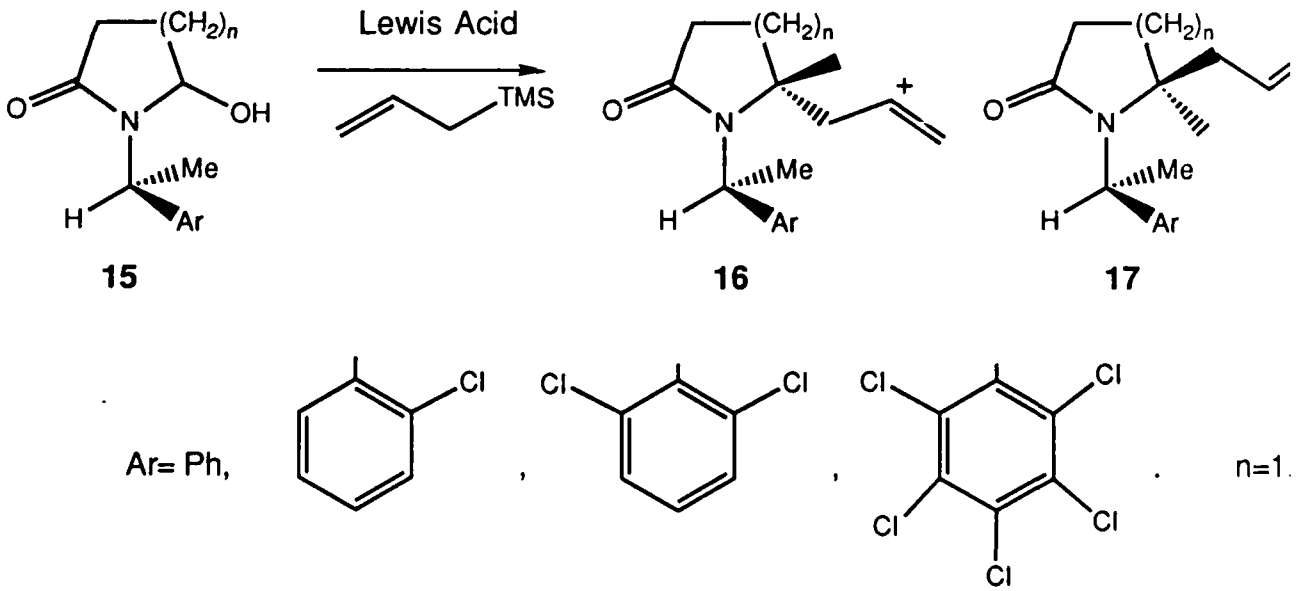
11 **12** **13** **14**

generate acyliminium ion **12**. Nucleophilic attack by silylenol ethers gave

substituted products **13** and **14** in high yield and varying diastereomeric excess (30-88%). Again, the diastereomers were separated by chromatography. The best results were obtained when R* was a champhor derivative. This methodology has been employed in the synthesis of 1-substituted terahydroisoquinolines including the alkaloid (-)-homolaudanosine.[19]

Polniaszek, Belmont, Alverez, and Kaufman have recently reported another method for the stereoselective nucleophilic addition of allylsilanes to chiral acyliminium ions.[20,21] Their procedure is based on the multistep

Scheme IX



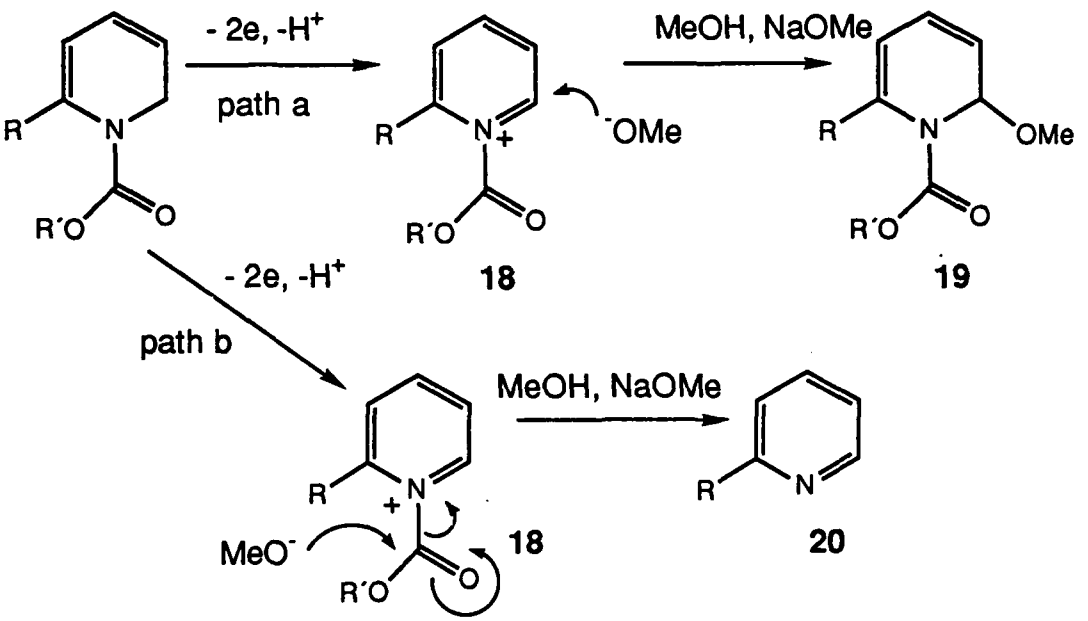
synthesis of chiral hydroxy lactams **15** from succinic or glutaric anhydride (Scheme IX). Addition of Lewis acid followed by the allylation with allyltrimethylsilane gave allyl substituted lactams **16** and **17** in high yields. Stereoselectivity ranged from poor to moderate. The best results were achieved (92% overall yield and 66% de) when Ar was phenyl and tin tetrachloride was used as the Lewis acid.[20]

III. RESULTS AND DISCUSSION

Anodic Oxidation of 1-Acyldihydropyridines. Preparation of 4-substituted 1-acyl-1,4-dihydropyridines for this study was accomplished by the copper-catalyzed regioselective addition of Grignard reagents to 1-acylpyridinium salts.[4a] Using similar methodology, substituted 1-acyl-1,2-dihydropyridines were prepared by addition of Grignard reagents to 4-substituted 1-acylpyridinium salts.[4a,22]

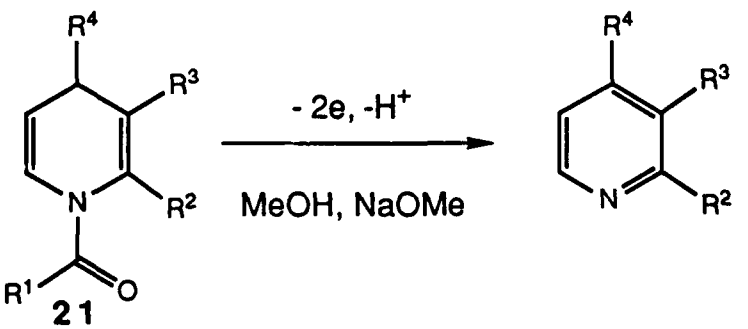
The oxidation of 1-acyldihydropyridines to substituted pyridines has been achieved in varying yields using a variety of oxidizing agents.[4,5] Frequently the crude products are contaminated with by-products derived from the oxidizing agents, causing purification problems. In an attempt to improve this two-step synthetic procedure for the preparation of substituted pyridines, we decided to explore the anodic oxidation of 1-acyldihydropyridines. Based on Shono's mechanism for the anodic oxidation of amines and 1-acylamines (Scheme II), we believed the anodic oxidation of 1-acyldihydropyridines would give the aromatic 1-acylpyridinium salt **18** as shown in Scheme X. The possibility exits that nucleophilic attack might occur on either the pyridine ring (path a) to give 2-methoxylated 1-acyldihydropyridine **19** or at the N-acyl carbonyl (path b) to give the desired substituted pyridine **20**.

Scheme X



We first investigated anodic oxidation of 1-acyl-1,4-dihydropyridines **21** in

Scheme XI



methanol using sodium methoxide as an electrolyte and nucleophile (Table II). As shown in entries 1-3, the anodic oxidation of 1,4-dihydropyridines gave yields of substituted pyridines (path b) comparable to reported literature values. Entry 5 represents the highest reported two-step yield for the preparation of a substituted pyridine via a 1-acyldihydropyridine intermediate. Oxidation of 4-alkyl-3-halo-1,4-dihydropyridines has been carried out in moderate to good yields but required *o*-chloranil.[4b,4d] We had hoped anodic oxidation would be

Table II. Oxidation of 1-Acyl-1,4-dihydropyridines

entry[a]	R_1	R_2	R_3	R_4	oxidation yield (%)	overall yield (%)[b]	literature yield (%)[c]
1.	Et	H	H	Ph	65	47	62
2.	Et	H	H	*n*-Bu	79	52	62
3.	Ph	H	H	*n*-Bu	60	59	62
4.	Et	Me	H	*n*-Bu	60	49	--
5.	Et	H	Me	Ph	90	89	67
6.	Ph	H	Cl	Ph	--	24	55

[a] Reactions were run on a 10-12 mmol scale. The 1-acyl-1,2-dihydropyridines were prepared by literature procedure and were used without purification. Oxidation was achieved using 0.40 amps with a voltage reading between 18-22 V. Six F/Mol of electricity was passed through the solution. [b] The overall yield was obtained for the two-step preparation. [c] Entries 1,2,3, and 5 were obtained from reference 4a and entry 6 was reported in reference 4d.

an alternative to oxidation with *o*-chloranil procedure but found the yields too low to be useful (entry 6).

We next oxidized 1-acyl-1,2-dihydropyridines **22** using the same

Scheme XII

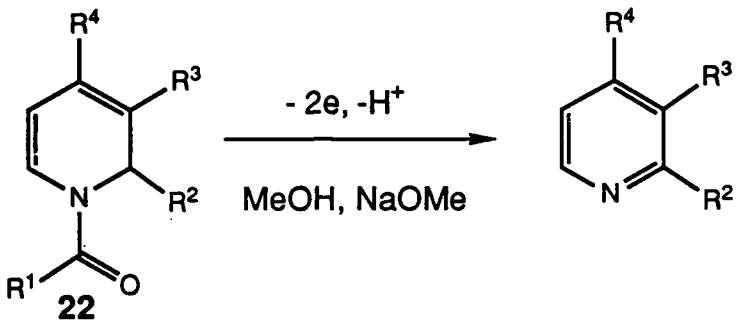


Table III. Oxidation of 1-Acyl-1,2-dihydropyridines

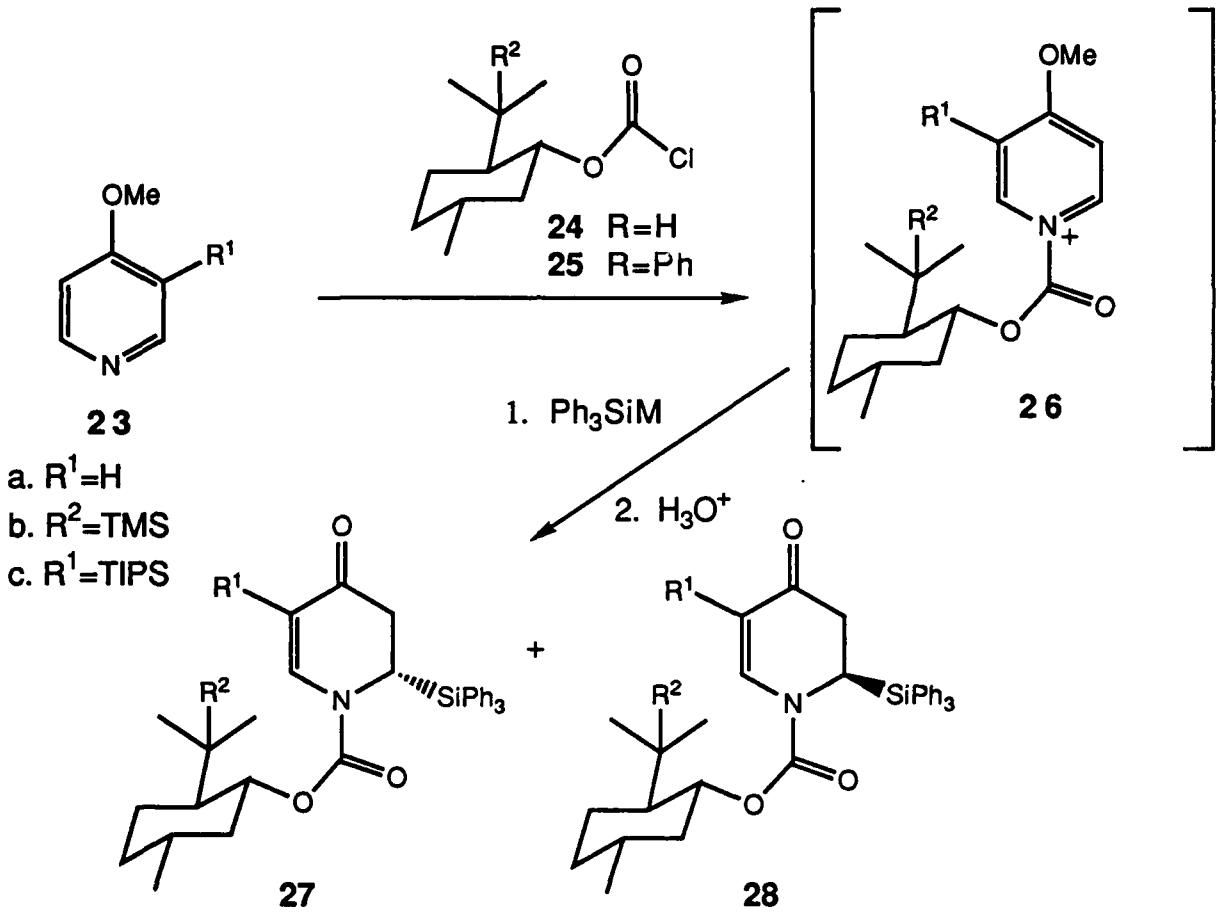
entry[a]	R_1	R_2	R_3	R_4	oxidation yield (%)	overall yield (%)[b]	literature yield (%)
1.	Et	Ph	H	Me	38	36	--
2.	Et	*n*-Bu	H	Me	31	30	--

[a] Reactions were run on a 10-12 mmol scale. The 1-acyl-1,2-dihydropyridines were prepared by literature procedure and were used without purification. Oxidation was achieved using 0.40 amps with a voltage reading between 18-22 V. Six F/Mol of electricity was passed through the solution. [b] The overallyield was obtained for the two-step preparation.

anodic oxidation technique (Scheme XII). These reaction mixtures turned dark brown and were only moderately successful as can be seen in Table III. Literature oxidation values were unavailable for comparisons.

Preparation of Optically Active 1-Acyl-2-triphenylsilyl-2,3-dihydro-4-pyridones. The importance of 1-acyl-2,3-dihydro-4-pyridones as synthetic intermediates was discussed earlier. To further develop the utility of these heterocycles in synthesis, we set out to add a large, removable group to the 2-position of a 1-acyl-2,3-dihydro-4-pyridone via asymmetric synthesis. This molecule could then be further functionalized for use in alkaloid synthesis. Our strategy was to prepare 1-acyl-2-triphenylsilyl-2,3-dihydro-4-pyridones **27** and **28** via chiral 1-acylpyridinium salts formed from (-)-menthyl chloroformate or (-)-8-phenylmenthyl chloroformate, and 4-methoxypyridine or 4-methoxy-3-(trialkylsilyl)pyridines (**25b,25c**) (Scheme XIII). We felt the addition of a `triphenylsilyl anion to **26** would give a high diastereomeric ratio of either **27** or **28**. Results of this study are listed in Table IV. Using a literature procedure, we first prepared triphenylsilyllithium[23] and added it to the acyl salt prepared from 4-methoxypyridine and (-)-menthyl chloroformate (**24**) (entry 1). Based on ^{1}H NMR, it appeared that the silyllithium anion attacked the acyl carbonyl rather than an α-carbon on the pyridine ring, and we were unable to detect any of the

Scheme XIII



desired 2-substituted product. Next, we tried the same reaction except we formed a softer nucleophile formed by transmetalation of triphenylsilyllithium with magnesium bromide (entry 2). The yield was reasonable but diastereoselectivity was poor.

Table IV. Preparation of 1-Acyl-2-triphenylsilyl-2,3-dihydropyridones

entry[a]	M	R^1	R^2	solvent	diastereomer ratio[b] 27 : 28	yield %
1	Li	H	H	THF	--	--
2	MgBr	H	H	THF	56 : 42	63
3	MgBr	TMS	H	THF	63 : 37	65
4	MgBr	TIPS	H	THF	73 : 27	68
5	MgBr	TMS	Ph	THF	93 : 7	62
6	MgBr	TIPS	Ph	THF	58 : 42	65
7	MgBr	TMS	Ph	Toluene/THF	98 : 2	73
8	MgBr	Bu_3Sn	Ph	Toluene/THF	92 : 8[c]	40
9	MgBr	H	Ph	Toluene/THF	98 : 2	88

[a] All reactions were performed on a 1 mmol scale. [b] Ratio was determined by HPLC analysis of the crude product. [c] Acidic workup removed the Bu_3Sn group to give the same diastereomeric products as entry 9.

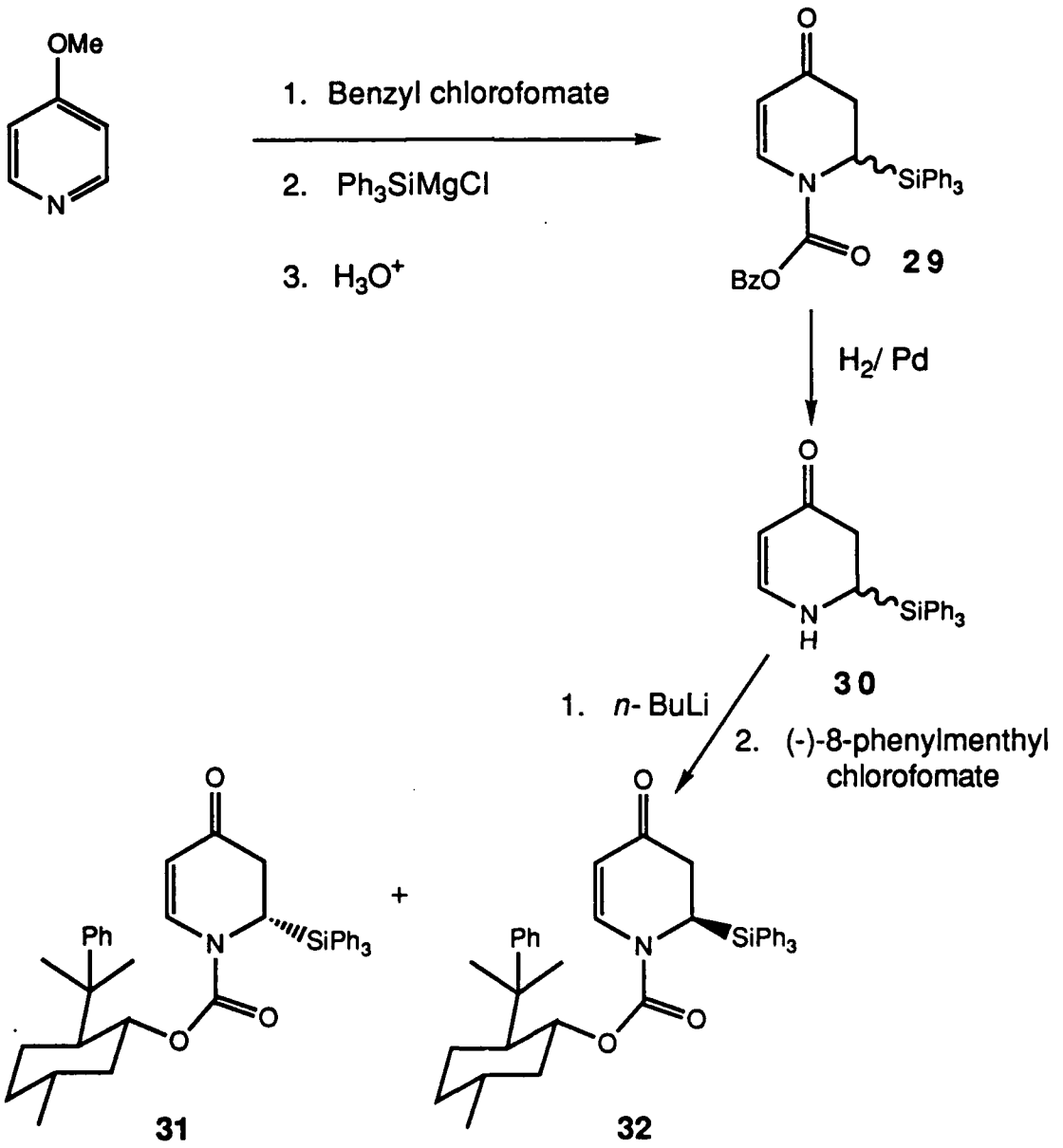
Diastereoselectivity was improved when the reaction was carried out on the chiral 1-acyl salts formed from 4-methoxy-3-(trialkylsilyl)pyridines and (-)-menthyl chloroformate (entries 3 and 4). Surprisingly, when (-)-8-phenylmenthyl chloroformate (**25**) was reacted with 4-methoxy-3-(triisopropylsilyl)pyridine followed by treatment with triphenylsilylmagnesium

bromide (entry 6), diastereoselectivity was reduced. This is in sharp contrast with the analogous reactions using alkyl or aryl Grignard reagents.[15] Reactions carried out on the chiral 1-acyl salt formed from 4-methoxypyridine or 4-methoxy-3-(trimethylsilyl)pyridine and (-)-8-phenylmenthyl chloroformate in toluene gave the best results (entries 7 and 9).

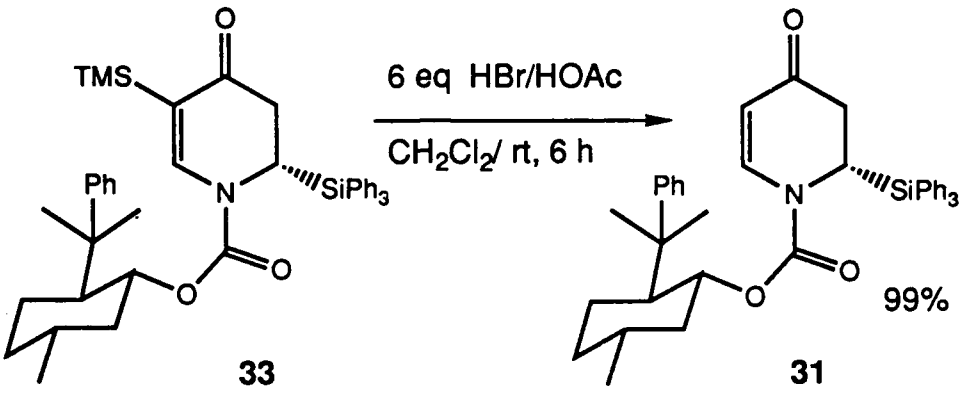
We were unable to isolate the minor diastereomer from entry 9, so a 50:50 mixture was prepared as shown in Scheme XIV. Racemic **29** was prepared from benzyl chloroformate, 4-methoxypyridine, and triphenylsilylmagnesium bromide in 61% yield. Hydrogenation of **29** gave racemic **30** which was deprotonated with *n*- BuLi and treated with (-)-8-phenylmenthyl chloroformate to give a 54:46 mixture of diastereomers **31** and **32** in 52% yield. The HPLC data, spectral data, and elemental *analysis confirmed* our previous results listed in entrys 8 and 9 of Table IV.

Single crystal X-ray structure analysis of the major diastereomer from entry 9 revealed **31**, which has the S-configuration at the newly formed stereogenic center, to be the correct structural assignment (see Appendix A). To determine the correct structural assignment of the major diastereomer of entry 7 (**33**) we removed the C-5 trimethylsilyl group with HBr/HOAc in methylene chloride. The resulting product gave spectral data matching that of **31**. The S-configuration has been tentatively assigned for the newly formed stereogenic centers of the major diastereomers for entries 2-6.

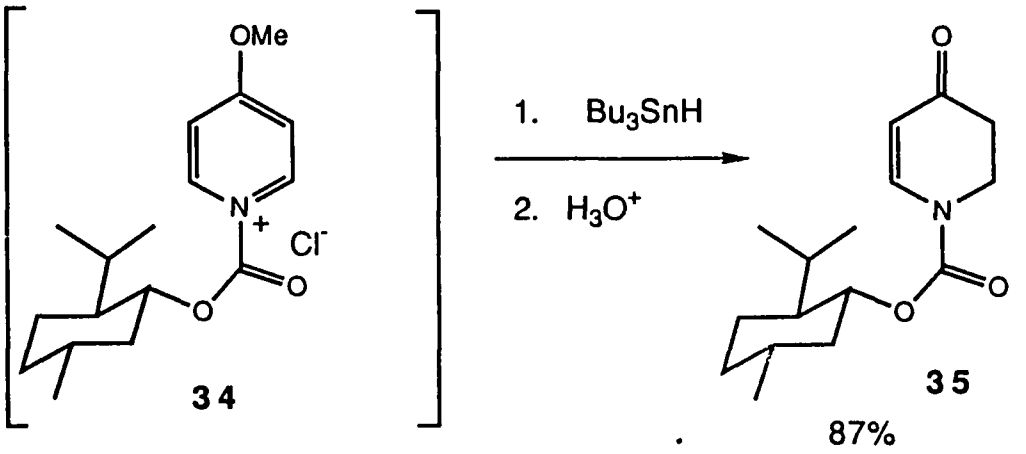
Scheme XIV



Ratio 54:46

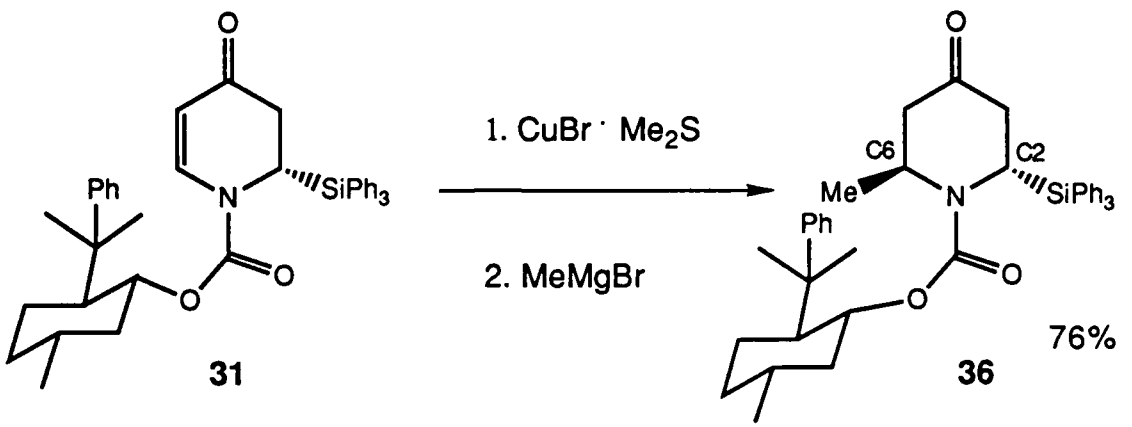


We also explored the use of a tributyltin anion as a nucleophile for addition to acyl salt **34.** When tributyltinmagnesium bromide, prepared from cyclohexylmagnesium bromide and tributyltinhydride,[24] was added to **34**, we were unable to detect any of the expected 2-substituted product. However, a small amount of reduced product **35** was isolated. Tributyltin hydride has been used to reduce N-acylquinolinium salts[25] and widely studied as a reducing agent for alkyl, vinyl, and aryl halides.[26] With this in mind, 1-acyl-4-methoxypyridinium salt **34** was treated with tributyltinhydride. The reaction gave reduced product **35** in 87% yield. Previously reported reductions of 1-acylpyridines using sodium borohydride ranged from 35 to 56% yield.[27,4g]



Reactivity of (-)-1-((1R,2S,5R)-8-Phenylmenthoxycarbonyl)-5-trimethylsilyl-(S)-2-triphenylsilyl-2,3-dihydro-4-pyridone (33) and (-)-1-((1R,2S,5R)-8-Phenylmenthoxycarbonyl)-(S)-2-triphenylsilyl-2,3-dihydro-4-pyridone (31). To investigate the utility of the newly formed chiral 1-acyl-2,3-dihydropyridones **31** and **33**, we first isolated them in isomerically pure form by recrystallization.

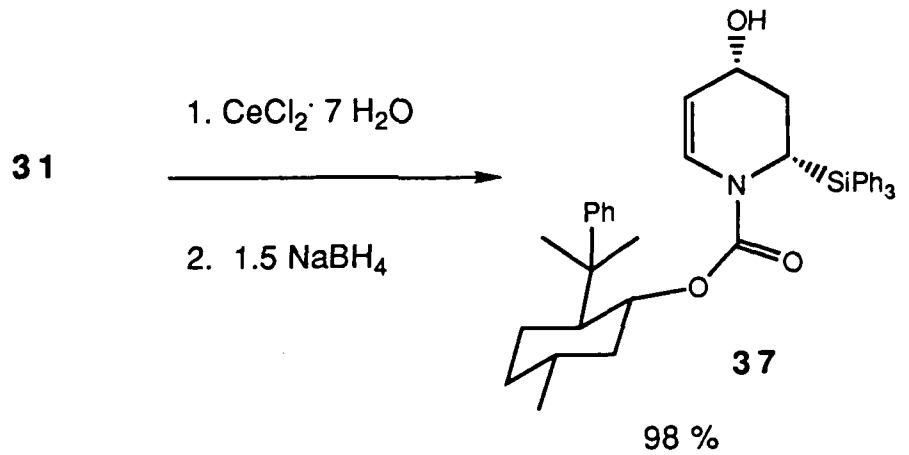
Conjugate addition was accomplished by the addition of **31** to a solution containing copper bromide and methyl Grignard. Only one isomer was isolated in 78% yield along with 10% starting material. We attempted to eleminate starting material by use of longer reaction times and lower temperatures, but we were unsuccessful. A probable cause for the remaining starting material is the



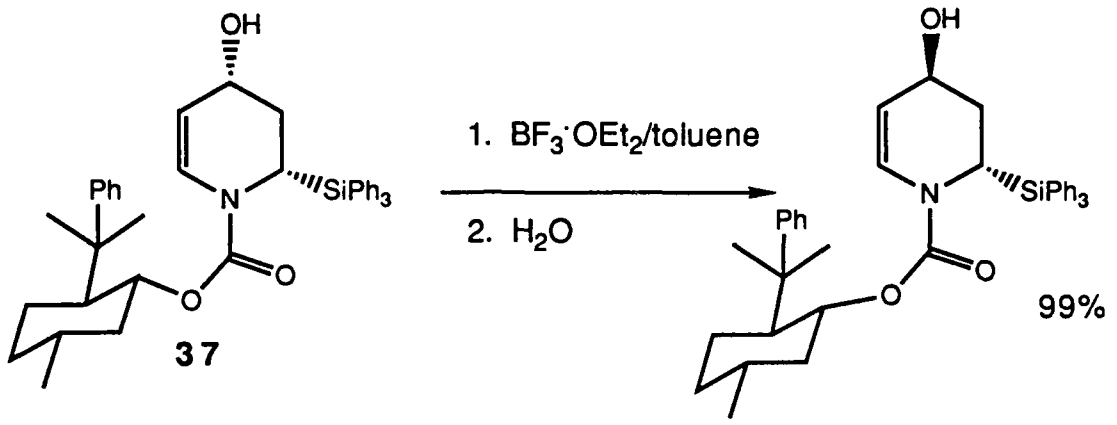
formation of an enolate anion. We attempted to transform **36** into a known structure by protecting the ketone as a dimethyl ketal followed by the anodic oxidation of the triphenylsilyl group. The formation of the ketal was achieved in 98% yield by using *p*-toluenesulfonic acid in methanol, but the anodic oxidation was unsuccessful. To date we have been unable to make a positive stereochemical assignment for **36**; however, the ^{1}H NMR indicates coupling constants for a trans product (the C-6 proton had an gauche coupling constant of 6.6 Hz and the C-2 proton had an axial-axial coupling constant of 13.6 Hz). We tentatively assigned the newly formed stereogenic center as the S-configuration. To verify these results, crystals of **36** have been submitted for single crystal X-ray structure analysis.

To expand the reactions available to functionalize **31** we next reduced the α–β unsaturated carbonyl to allylic alcohol **37**. This was accomplished by forming a complex with $CeCl_3$ in refluxing ethanol/methanol followed by treatment with sodium borohydride.[28] The reaction was very clean and the

resulting product was used without further purification. Only one diastereomer was isolated and it was tentatively assigned as the cis isomer.



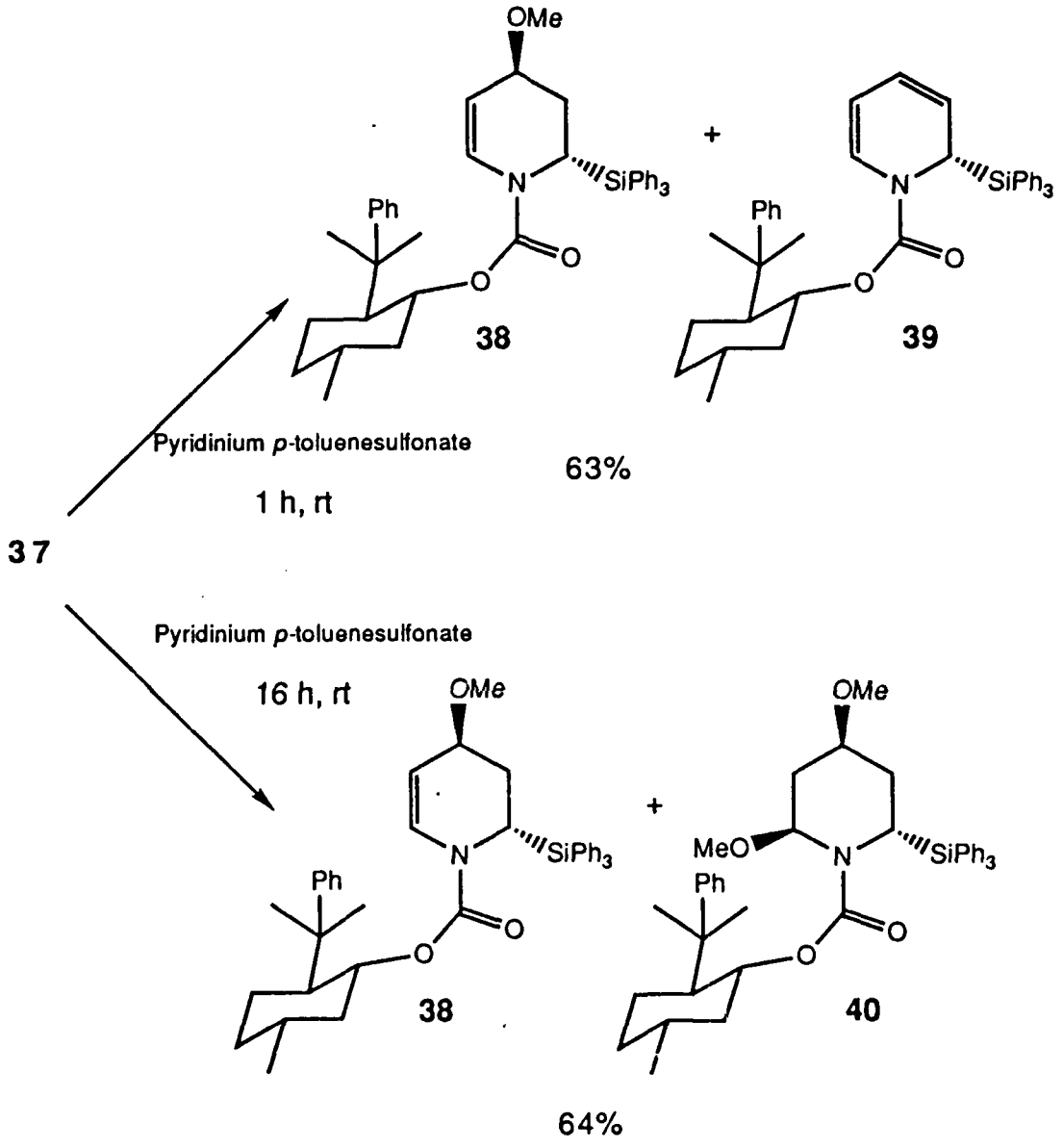
This is reasonable since steric interactions of the large triphenylsilyl group should block axial attack, causing the hydride to be delivered into the equatorial position to give **37**. The trans diastereomer was prepared by the formation of an acyliminium ion on treatment of **37** with $BF_3 \cdot OEt_2$ in toluene for 30 min,



followed by the direct addition of water. Again, the stereoselectivity may be rationalized by the steric blocking effect of the triphenylsilyl group which forces equatorial attack by the nucleophile (H_2O). Evidence to support our structural assignment is based on ^1H NMR data and molecular modeling studies. The molecular modeling studies were accomplished on a Macintosh II computer using PC Model software from Serena Software (Appendix B). The results obtained indicate a larger coupling constant should exist between an equatorial proton at C-4, rather than an axial proton, and the C-5 vinyl proton. By ^1H NMR data (see Appendix C) the coupling constant between the C-4 and C-5 protons was determined to be 3.6 Hz for **37** and 2.4 Hz for the trans isomer.

We next attempted to protect the alcohol **37** by deprotonation and the addition of iodomethane. The reaction was unsuccessful and no methoxylated product was detected. However, preparation of 4-methoxytetrahydropyridine **38** was achieved by treatment of **37** with pyridinium *p*-toluenesulfonate in methanol for one hour at room temperature. This gave a mixture of the desired product and the elimination product **39.** Radial preparative-layer chomato-

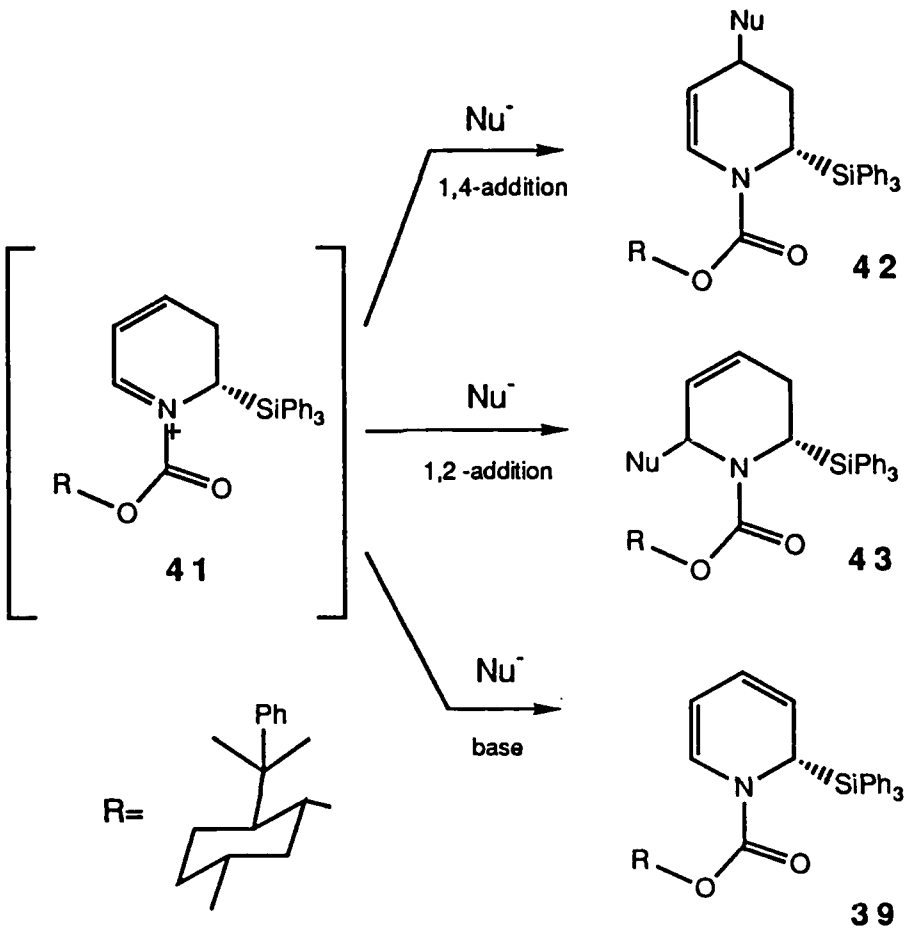
graphy was used to isolate both products, but the net yield of **38** was a



disappointing 40%. By using the same reaction conditions, but letting the reaction mixture stir over night (16 hours) at room temperature, both the methoxy tetrahydropyridine **38** and dimethoxy piperidine **40** were isolated in a

64% combined yield with a ratio of 1 to 2. The products were separated by chromatography and fully characterized. Additionally, by ^1H NMR we could only detect one diastereomer of each. We tentatively assigned all methoxy groups a trans configuration in relationship to the triphenylsilyl group.

The addition of Lewis acids to **37**, **38**, or **40** forms acyliminium ion **41**. Addition of nucleophiles to this highly reactive intermediate gives one of three products as depicted in Scheme XV. The nucleophile can react by means of a 1,4-addition to give product **42**, it can add to the α-carbon to give the 6-substituted product **43**, or the nucleophile can act as a Bronsted-Lowry base to give the deprotonated product **39**. This is the first reported synthesis of a chiral 1,2-dihydropyridine. In this study we investigated the addition of several nucleophiles to 1-acyliminium ion **41** prepared from **37**, **38**, and **40** (Table V). It should be noted that only one diastereomer of each product was isolated. At cold temperatures, allyltrimethylsilane gave a mixture of both 1,4- and 1,2-addition products as shown in entries 1 and 2. However, high regioselectivity was achieved by using allyltrimethylsilane when the reaction was carried out at temperatures above -42°C as shown in entries 3 and 4. The use of allyltributyltin as the nucleophile gave only the 1,2-addition product in high yield (entry 5). Grignard reagents acted primarily as bases to give deprotonated product **39**. The best result of 1,2-addition was achieved by the addition of Grignard reagents at warmer temperatures (-23°C, entry 6). Similar results were found using trialkylaluminum nucleophiles (entries 7 and 8). At -23°C a



good ratio of 1,2-addition to elimination product was achieved, but by lowering the temperature to -42°C elimination was the favored reaction.

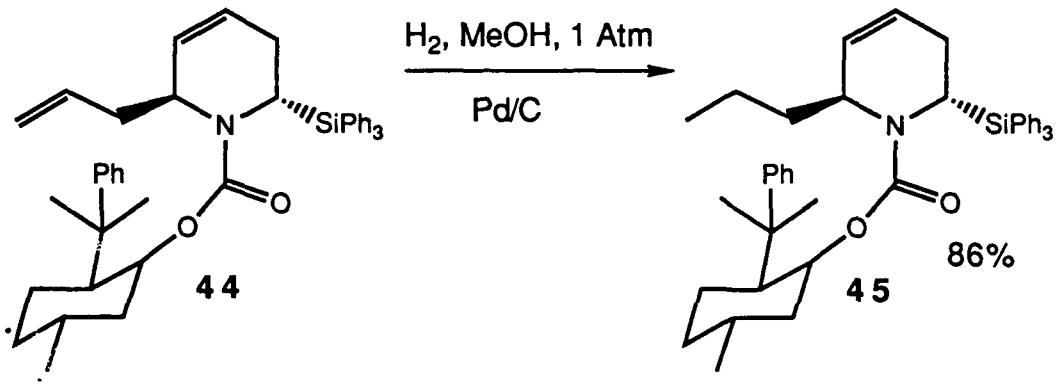
We next attempted to reduce **44**, the product from 1,2-addition of allyltrimethylsilane to **41**. As shown below, the terminal alkene was easily reduced under one atm of hydrogen by a catalytic amount of palladium on carbon. However, reduction of the C4-C5 double bond of tetrahydropyridine

Table V. Nucleophilic Addition to N-Acyliminium Ion 41

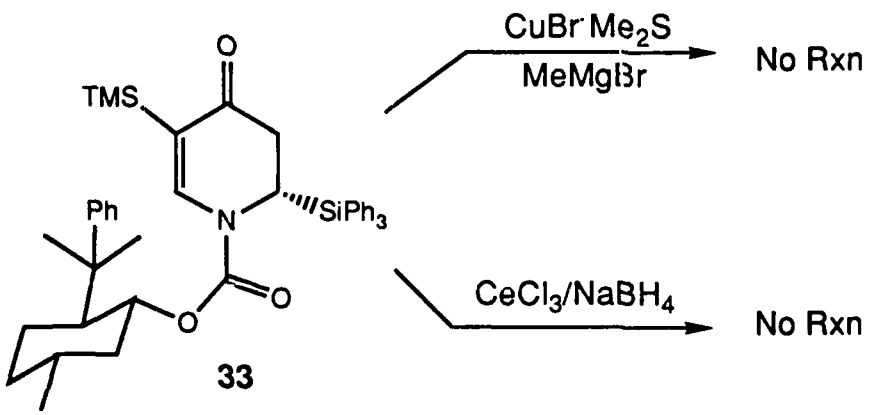
entry	starting [b] material	Lewis acid	nucleophile	rxn temp °C	product ratio[d] **42 : 43 : 39**	yield[e] %
1.	**37**	$SnCl_4$	Allyltrimethylsilane	-78	50 : 50 : --	62
2.	**37**	$BF_3{\cdot}OET_2$	Allyltrimethylsilane	-78-rt[c]	13 : 87 : --	66
3.	**37**	$BF_3{\cdot}OET_2$	Allyltrimethylsilane	-42-rt[c]	--: >98 : --	85
4.	**37**	$BF_3{\cdot}OET_2$	Allyltrimethylsilane	-23	--: >98 : --	83
5.	**37**	$BF_3{\cdot}OET_2$	Allyltributyltin	-78-rt[c]	--: >98 : --	83
6.	**37**	$BF_3{\cdot}OET_2$	*n*-propylmagnesium Bromide[b]	-23	-- : 60 : 40	--
7.	**37**	$BF_3{\cdot}OET_2$	Allylmagnesium Bromide[b]	-78	-- : -- : >98	82
8.	**37**	$BF_3{\cdot}OET_2$	*n*-Propylmagnesium Chloride/$AlCl_3$[b]	-23	-- : 77 : 23	75
9.	**37**	$BF_3{\cdot}OET_2$	*n*-Propylmagnesium Chloride/$AlCl_3$[b]	-42	-- : 25 : 75	--
10.	**38**	$BF_3{\cdot}OET_2$	Allyltrimethylsilane	-42-rt[c]	-- : >98 : --	78
11.	**40**	$BF_3{\cdot}OET_2$	Allyltrimethylsilane	-42-rt[c]	-- : >98 : --	71

[a] Compounds **37**, **38**, or **40** were disolved in toluene followed by the addition of nucleophiles and the dropwise addition of 1.5 equivilants of Lewis acid. Water was added to the reaction at temperatures listed unless noted. [b] *N*-Acyliminium ion was preformed for 30 min prior to addition of the nucleophile. [c] The reaction was allowed to warm to room temperature prior to workup. [e] Product ratios were determined by NMR. [e] Yields of isolated material by radial PLC.

45 turned out to be very difficult. Even after 16 hours under 40 psi of hydrogen gas and excess Pd/C, the reaction only went to 50% completion and it looked like, by ^1H NMR, that epimerization was taking place at the C-2 carbon.

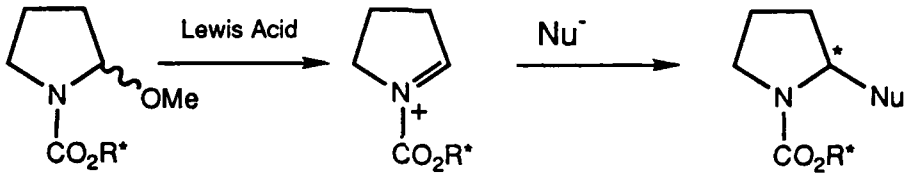


We also investigated the reactivity of **33** by following the same procedures used for the conjugate addition of copper reagents and reduction by $CeCl_3/NaBH_4$ as applied to **31**. As shown below **33** was recovered quantitatively and there was no isolated product.



Asymmetric Synthesis of 2-Alkylpyrrolidines by Addition of Nucleophiles to Chiral N-Acyliminium Ions. Based on the high diastereoselectivity found from the addition of Grignard reagents to 1-acyl-4-methoxypyridinium salts to give 2-alkyl-2,3-dihydro-4-pyridones,[15] we decided to investigate the use of similar procedures for the preparation of chiral 2-substituted pyrrolidines. Our strategy for accomplishing the desired asymmetric synthesis was to first prepare chiral 1-acyl-2-methoxypyrrolidines

Scheme XV.

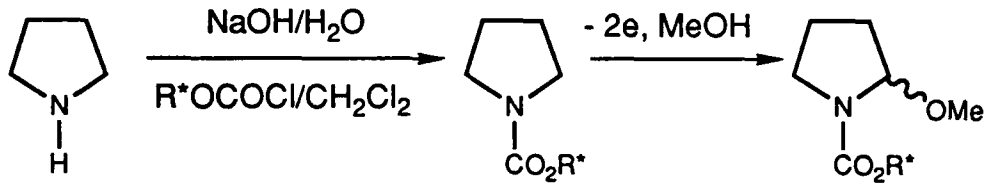


46 **47** **48**

46, which would be treated with a Lewis acid to give acyliminium ion intermediates **47**. We envisioned that nucleophiles would be diastereoselectively introduced into the α-position by the influence of the 1-acyl chiral auxiliary (Scheme XV).

We first prepared chiral 1-acylpyrrolidines by treating pyrrolidine (**49**) with (-)-menthyl chloroformate or (-)-8-phenylmenthyl chloroformate under basic conditions to give **50a** and **50b** in high yields (91% and 85%). Next we used Shono's [8] methodology for anodic oxidation of carbamates on **50a** which gave

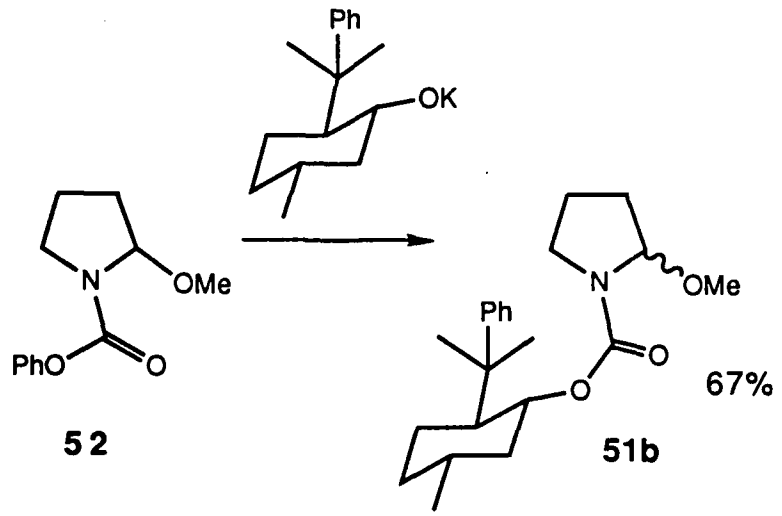
51a in 95% yield. However. when we attempted the anodic oxidation of **50b** we were unable to achieve satisfactory results. The best result for anodic oxidation of **50b** gave a 50:50 mixture of starting material to α-methoxy carbamate **51b**. Unfortunately, we were unable to cleanly separate the starting material from the product.



49 **50** **51**

a. R*= (-)-menthyl
b. R*= (-)-8-phenylmenthyl

We developed a better procedure for the preparation of **51b** by treatment

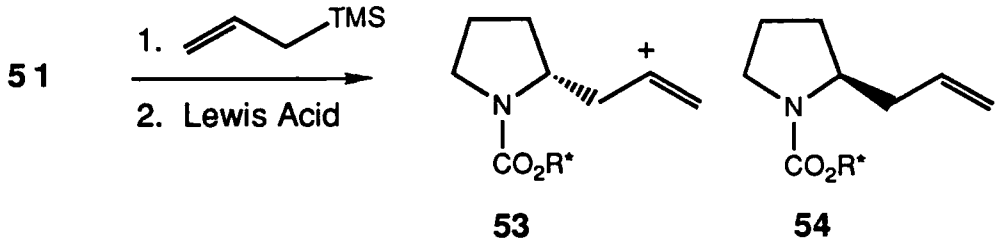


52 **51b**

of 2-methoxy-1-(phenoxycarbonyl)pyrrolidine (**52**) with the potassium salt of

(-)-8-phenylmenthol as shown above.

The results of our study on the addition of nucleophiles to **51** via acyliminium ions is outlined in Table VI. Treatment of **51** with Lewis Acids



53 **54**

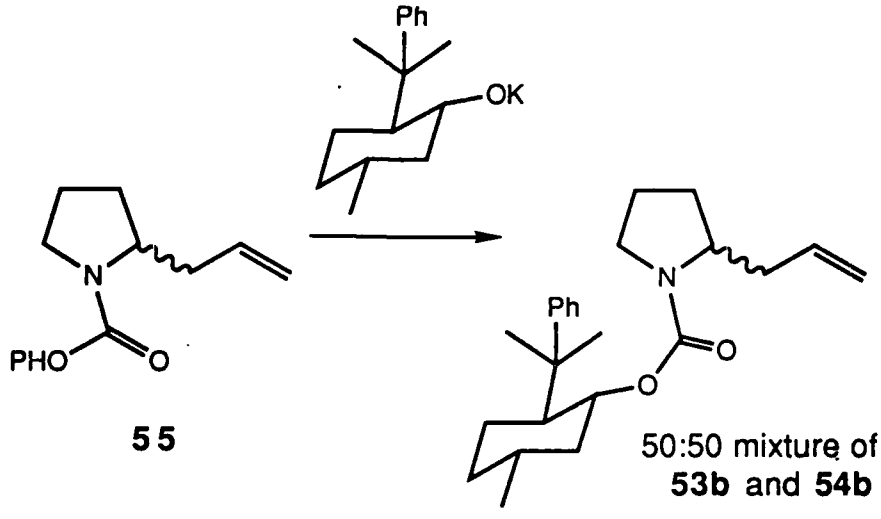
a. R*= (-)-menthyl
b. R*= (-)-8-phenylmenthyl

Table VI. Addition of Allyltrimethylsilane to Chiral N-Acyliminium Ions

entry[a]	pyrrolidine	Lewis acid	solvent	diastereomeric excess	yield[d] %
1.	**51a**	BF_3OEt_2	CH_2Cl_2	0[b]	91
2.	**51b**	BF_3OEt_2	CH_2Cl_2	4[b]	74
3.	**51b**	$SnCl_4$	CH_2Cl_2	8[b]	53
4.	**51b**	BF_3OEt_2	toluene	8[c]	--
5.	**51b**	$SnCl_4$	toluene	30[c]	55

[a] All reaction were run on a 0.5-2 mmol scale. Addition of allyltrimethylsilane and Lewis acids were carried out at -78°C and allowed to warm to room temperature before workup. [b] The de was determined by HPLC and ^1H NMR. [c] The de was determined by ^1H NMR. [d] Purified yields by radial PLC.

readily formed acyliminium ions; however, the only successful nucleophile was allyltrimethylsilane. The use of Grignard reagents led to very low yields and poor results. As can be seen by entry 1, the desired product was isolated in excellent yield, but there was no diastereoselectivity. Changing the chiral auxiliary to (-)-8-phenylmenthyl introduced a small diastereomeric excess. The best result was achieved by the addition of allyltrimethylsilane to the acyliminium ion formed from the treatment of **51b** with $SnCl_4$ in toluene (entry 5). To confirm our results we prepared a 50:50 mixture of **53** and **54** as depicted below. Due to low yields and only moderate diastereoselectivity, we decided to investigate other routes for the asymmetric synthesis of pyrrolidines.



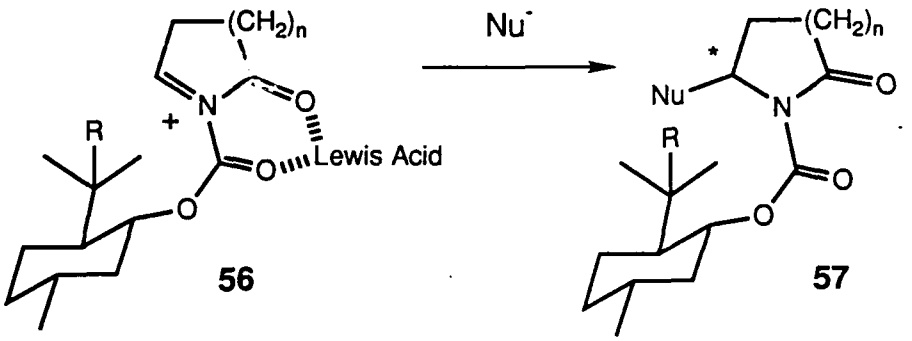
55

50:50 mixture of **53b** and **54b**

Addition of Nucleophiles to Chiral Acyliminium Ions Derived From 1-Acyl-2-pyrrolidinone and 1-Acyl-2-piperidone. To further investigate the effect of 1-acyl chiral auxiliaries on acyliminium ion reactions,

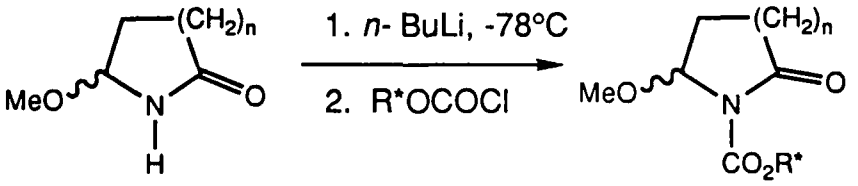
we developed a strategy for the addition of nucleophiles to chiral 1-acyliminium ions derived from 1-acyl-2-pyrrolidinone and 1-acyl-2-piperidone. Scheme XVI shows how the chelation of a Lewis acid to both the ring carbonyl and the acylcarbonyl (**56**) might lock the chiral auxiliary into a fixed position. The chiral auxiliary could then influence the diastereoselectivity of the nucleophilic reaction.

Scheme XVI



56 **57**

To generate the acyliminium ion we first needed to prepare methoxylated



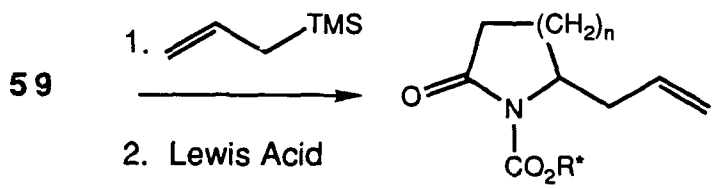
58 **59**

a. n=1, R*= (-)-menthyl
b. n=1, R*= (-)-8-phenylmenthyl
c. n=2, R*= (-)-menthyl
d. n=2, R*= (-)-8-phenylmenthyl

1-acyl-2-pyrrolidinones and 1-acyl-2-piperidones. This was accomplished by using literature procedures for the preparation of α-methoxylated lactams **58** from 2-pyrrolidinone and δ-valerolactam.[3] Deprotonation of **58** by *n*-BuLi followed by the addition of the appropriate chlorofomate gave **59 a-d** in good yields (69-74%).

We attempted to prepare α-substituted products via nucleophilic addition to acyliminium ions prepared from **59 a-d**. The results of treating **59** with

Scheme XVII



60

a. n=1, R*= (-)-menthyl
b. n=1, R*= (-)-8-phenylmenthyl
c. n=2, R*= (-)-menthyl
d. n=2, R*= (-)-8-phenylmenthyl

several Lewis acids in the presence of allyltrimethylsilane are outlined in Table VII. As can be seen by the poor results, we were unable to find suitable reaction conditions to trigger the formation of the iminium ion. As discussed earlier, our initial strategy was to use Lewis acids to chelate with both the acyl and ring carbonyls. It appears that a strong chelation does occur with Lewis

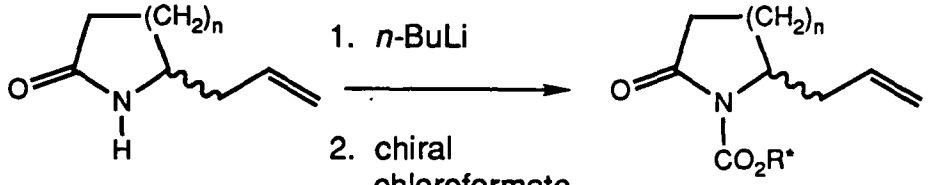
acids which have more than one binding site available ($SnCl_4$ and $TiCl_4$). The strong interactions between the chelating Lewis acid and the carbonyl oxygens reduce the electron density on the nitrogen which greatly inhibits the formation of acyliminium ions.

Table VII. Reactions of Lewis Acids with 59.

entry[a]	pyrridinone/ piperidone	Lewis acid	rxn time hours	temp °C	reaction completion[b] %
1.	**59a**	BF_3OEt_2	1	rt	30
2.	**59a**	BF_3OEt_2	20	rt	100[c]
3.	**59a**	$SnCl_4$	0.5	rt	30
4.	**59a**	$TiCl_4$	0.5	-78	--[d]
4.	**59b**	BF_3OEt_2	15	rt	100[c]
5.	**59b**	$TiCl_4$	16	-20	--[d]
6.	**59b**	$SnCl_4$	18	-20	--[d]
7.	**59c**	BF_3OEt_2	16	0	30
8.	**59c**	$TiCl_4$	2	rt	--[d]
9.	**59d**	BF_3OEt_2	16	rt	100[c]

[a] All reactions were run on a 1 mmol scale. Addition of allyltrimethylsilane (6 mmol) and Lewis acids (3 mmol) were carried out at -78°C and allowed to warm to listed temperature. [b] The yield was determined by ^1H NMR. [c] Although starting material was absent, the reactions were messy and isolated yields were low (less than 40%). [d] Over 90% recovery of starting material was obtained.

To confirm our results we prepared 50:50 mixtures of the expected products **60.** Deprotonation of **61** by *n*-BuLi followed by the addition of the appropriate chlorofomate gave **60** as a 50:50 mixture of diastereomers.



61 **60**

a. n=1, R*= (-)-menthyl
b. n=1, R*= (-)-8-phenylmenthyl
c. n=2, R*= (-)-menthyl
d. n=2, R*= (-)-8-phenylmenthyl

IV. SUMMARY AND CONCLUSIONS

The anodic oxidation of 1-acyldihydropyridines to pyridines is feasible and synthetically useful. In this study we found examples which gave moderate to excellent yields. The major advantages of this procedure are the lack of by-products, as compared to the oxidation with sulfur and *o*-chloranil, and the use of inexpensive and non-toxic reagents. It is apparent from the low yields for the oxidation of chloro-substituted 1-acyl-1,4-dihydropyridines and substitituted 1-acyl-2,3-dihydropyridines that the utility of this procedure is substrate dependent.

The addition of triphenylsilylmagnesium bromide to (-)-4-methoxy-1-((1R,2S,5S)-8-phenylmenthoxy)pyridinium salt gave (-)-1-((1R,2S,5R)-8-phenylmenthoxy)-(S)-2-triphenylsilyl-4-pyridone in 88% yield and 96% de. The utility of this interesting compound was investigated by studying the stereoselective copper mediated addition of methylmagnesium chloride and the stereoselective reduction of the ring carbonyl by $CeCl_3/NaBH_4$. We also broadened the range of nucleophiles which could be added to the piperidine ring structure by forming acyliminium ions by treatment of the reduced 4-hydroxy products with Lewis acids. The highly reactive acyliminium ions proved to be excellent electrophiles for stereoselective addition of allyltrimethylsilyl nucleophiles. It should be noted that additional studies are required before (-)-1-((1R,2S,5R)-8-phenylmenthoxy)-(S)-2-triphenylsilyl-4-

pyridone can be utilized effectively in natural product synthesis. Reaction conditions for the removal of the triphenylsilyl group and the removal and recovery of the (-)-8-phenylmenthyl chiral auxiliary needs investigation.

Our strategy for the addition of nucleophiles to chiral N-acyliminium ions derived from chiral α-methoxy N-acylpyrrolidines, N-acylpyrrolidinones, and N-acylpiperidones proved to be a disappointment. Studies for the preparation of chiral 2-methoxy-1-acylpyrrolidines gave excellent results. Also, good yields were achieved for the addition of allyltrimethylsilane to acyliminium ions from 2-methoxy-1-acylpyrrolidines, but these reactions gave such low diastereoselectivity further studies on the project were abandoned. We used a similar strategy on chiral 1-acyl-α-methoxy-2-pyrrolidinones and -2-piperidones. We had hoped chelation between the acyl and ring carbonyls with Lewis acids would improve diastereoselectivity. Preparation of chiral 1-acyl-α–methoxypyrroidinones and 1-acyl-α–methoxypiperidones was achieved in good yield, but subsequent addition of Lewis acids to trigger iminium ion formation proved unsuccessful. It appears that the our strategy for chelation of Lewis acids to the ring and acyl carbonyls not only locks the chiral auxiliary into a more rigid position, but it sufficiently reduces nitrogen electron density so that iminium ions are no longer easily formed or stabilized.

V. EXPERIMENTAL SECTION

All reactions were performed in oven-dried glassware under a N_2 atmosphere. Tetrahydrofuran (THF) was dried by distillation from sodium/benzophenone ketyl prior to use. Pyridine and substituted pyridines were distilled from calcium hydride and stored over 4 Å molecular sieves under N_2. Other solvents and reagents from commercial sources were generally stored over 3 Å molecular sieves and used without further purification. The alkyl Grignards used in this study were purchased (Aldrich Chemical Co.) as a 2 M or 3 M solution in ether or THF. Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were recorded on a Varian XL-300 spectrometer. Radial preparative-layer chromatography (Radial PLC) was carried out by using a chromatotron (Harris Associates, Palo Alto, CA). Infrared spectra were recorded on a Perkin-Elmer model 7500 spectrometer. The 1,4-dihydropyridines,[4a,4d] (-)-8-phenylmenthol,[29] and 5-methoxy-2-pyrrolidone[8] were prepared using literature procedures.

2-*n*-Butyl-4-methyl-1-(ethoxycarbonyl)-1,2-dihydropyridine. General Procedure for the Preparation of 1,2-Dihydropyridines. 2-*n*-Butyl-4-methyl-1,2-dihydropyridine was prepared by a variation of literature procedures.[4a,4d] A solution of 4-methylpyridine (0.96 g, 10.3 mmol) in THF (25 mL) was cooled to -78°C and *n*-butylmagnesium chloride (10.27 mmol, 5.12 mL) in THF was added followed by the dropwise addition of ethyl chloroformate

(0.98 mL, 10.3 mmol). The ice bath was removed and the solution was allowed to warm to room temperature. After 0.5 h, ether (40 mL) was added and the solution was washed successively with 10% HCl (40 mL), H_2O (20 mL), and brine (20 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give 2.20 g (96%) of product as an oil. The crude product was oxidized by electrolysis without further purification.

4-*n*-Butylpyridine. General Procedure for the Oxidation of Dihydropyridines by Anodic Oxidation. A solution of crude 4-*n*-butyl-1-(phenoxycarbonyl)-1,4-dihydropyridine (3.16 g, 12.3 mmol) in methanol (80 mL) was placed in an electrolysis cell[8] equipped with carbon electrodes and a magnetic stirrer. Sodium methoxide (4.35 M/MeOH) was added dropwise as an electrolyte until a constant current (0.4 A) could be maintained with a voltage reading between 18 V and 22 V. The cell was cooled with an external water bath (18°C) while 6 F/mol of electricity was passed through the solution with stirring. The solvent was removed under reduced pressure at room temperature and ether was added (40 mL). The solution was extracted with 10% HCL (3x20 mL) and the organic layer was discarded. To the aqueous layer was added CH_2Cl_2 (50 mL) and the mixture was cooled to 0°C. The mixture was made basic with 25% NaOH and extracted with CH_2Cl_2 (2x20 mL). The combined organic extracts were washed with brine (20 mL), dried (K_2CO_3), and concentrated. The crude product was purified by radial PLC (30% EtOAc/hexane, 1% MeOH) to give 0.981 g (59%) of 4-*n*-butylpyridine as a clear

yellow oil: IR (neat) 2958, 2932, 2872, 1713, 1603, 1466, 1416, 1071 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.93 (t, 3 H, *J*=7.4 Hz), 1.22-1.42 (m, 2 H), 1.55-1.71 (m, 2 H), 2.60 (t, 2 H, *J*=7.8 Hz), 7.10 (d, 2 H, *J*=4.5 Hz), 8.48 (d, 2 H, *J*=4.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.58, 21.99, 32.16, 34.66, 123.64, 149.32, 151.44. Picrate mp 112-113.5°C (lit.[1] picrate mp 112.8-113.8°C).

Spectral Data. **4-Phenylpyridine.** IR (CH_2Cl_2) 3037, 2978, 1484, 1411, 831 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.40-7.55 (m, 5 H), 7.65 (d, 2 H, *J*=4.5 Hz), 8.67 (d, 2 H, *J*=4.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 121.41, 126.78, 128.87, 128.92, 137.88, 148.08, 150.05; mp 73-74°C (hexanes) (lit.[2] mp 73-74°C).

3-Methyl-4-phenylpyridine. IR (neat) 3028, 1708, 1591, 1479, 1444, 1405, 771, 703 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.29 (s, 3 H), 7.15 (d, 1 H, *J*=5.0 Hz), 7.25-7.50 (m, 5 H), 8.47 (d, 1 H, 5.0 Hz), 8.51 (s, 1 H); ^{13}C NMR (75 MHz, $CDCL_3$) δ 17.09, 123.83, 127.81, 128.29, 128.39, 130.43, 138.91, 147.23, 148.98, 151.16. Picrate mp 162-163°C (lit.[2] picrate mp 162-163°C).

2-Methyl-4-phenylpyridine. IR (neat) 3061, 3030, 1606, 1598, 1548, 1106, 1077, 763 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.63 (s, 3 H), 7.32 (d, 1 H, *J*=5.4 Hz). 7.35-7.52 (m, 4 H), 7.63 (d, 2 H, *J*=7.5 Hz), 8.54 (d, 1 H, 5.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.44, 118.76, 121.09, 126.88, 128.79, 128.92, 138.29, 148.59, 149.43, 158.71. Picrate mp 218-220°C (lit.[2] picrate mp

219-220°C).

3-Chloro-4-phenylpyridine. IR (neat) 3056, 1581, 1489, 1397, 1106, 771 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, 1 H, *J*=4.8 Hz), 7.32-7.55 (m, 5 H), 8.49 (d, 1 H, *J*=4.8 Hz), 8.66 (s, 1 H); ^{13}C (75 MHz, $CDCl_3$) δ 125.11, 128.21, 128.66, 128.70, 130.12, 136.25, 147.29, 147.63, 149.90. Mp 35-37°C (lit.[3] mp 35-37°C). Picrate mp 160-161.5 °C.

2-*n*-Butyl-4-methylpyridine. IR (neat) 2958, 2931, 1606, 1563, 1456, 1378, 821 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.94 (t, 2 H, *J*=7.5 Hz), 1.33-1.42 (m, 2 H), 1.66-1.80 (m, 2 H), 2.28 (s, 3 H), 2.73 (t, 2 H, *J*=7.8 Hz), 6.88 (d, 1 H, *J*=4.8 Hz), 6.94 (s, 1 H), 8.36 (d, 1 H, *J*=4.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.43, 20.35, 22.02, 31.59, 37.48, 121.30, 122.98, 146.53, 148.38, 161.66. Picrate mp 94-95°C (lit.[4] picrate mp 98.6-99.0°C).

4-Methyl-2-phenylpyridine. IR (neat) 3059, 1605, 1559, 1447, 776, 736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.36 (s, 3 H), 7.01 (d, 1 H, *J*=5.1 Hz), 7.33-7.48 (m, 3 H), 7.51 (s, 1 H), 7.97 (d, 2 H, *J*=6.9 Hz), 8.53 (d, 1 H, *J*=5.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.08, 121.36, 123.00, 126.79, 128.55, 128.67, 139.40, 147.57, 149.29, 157.20. Picrate mp 185-187°C (lit.[5] mp 186-187°C).

Preparation of Triphenylsilylmagnesium Chloride. Freshly cut lithium metal (8 mmol, .05 g) (excess lithium may be added to reduce the reaction time) was placed in a 25-mL flask under N_2 and washed with hexanes (10 mL). THF (10 mL) was added followed by the addition of

chlorotriphenylsilane (1.5 mmol, 0,442 g). The solution was stirred for 4-12 h at room temperature (the solution first forms a white precipitate then a brown milky mixture and finally a homogeneous, dark black solution of triphenylsilyllithium). When prepared on a more concentrated scale it may take as long as 2 days for the reaction to turn black.[23] In a separate 50-mL flask containing THF (10 mL) and magnesium turnings (4 mmol, 0.10 g) was added 1,2-dibromoethane (0.16 mL, 2.5 mmol), and the mixture was refluxed for 3 h. The heating mantle was removed and the black solution of triphenylsilyllithium was transfered by syringe into the solution of $MgBr_2$/THF at room temperature forming a purple solution. The mixture was stirred for 30 min at room temperature and added directly to the 1-acylpyridinium salts via a syringe.

Preparation of (-)-8-Phenylmenthyl Chloroformate. This procedure was developed by Comins and O'Connor but the experimental procedure is unpublished. To a 250-mL flask containing (-)-8-phenylmenthol (7.00 g, 30.1 mmol), quinoline (11 mL, 93 mmol), and toluene (120 mL) at 0°C was added phosgene (32 mL of a 1.93 M solution in toluene, 62 mmol), and the mixture was stirred for 30 min at 0°C. The solution turned yellow and a yellow precipitate formed. The mixture was stirred overnight at room temperature after which the precipitate was removed by vacuum filtration through a fritted funnel, and the solvent was removed under reduced pressure. Ether (100 mL) was added to the concentrate and the solution was washed with 10% aqueous HCl (2x40 mL). The aqueous layers were then extracted with Et_2O (2x30 mL) and the combined organic layers were washed with brine, dried

($MgSO_4$), and concentrated to give 10.7 g of product as a red oil. The product was used without further purification.

Preparation of (-)-1-((1R,2S,5R)-8-Phenylmenthoxycarbonyl)-(S)-2-triphenylsilyl-2,3-dihydro-4-pyridone (31). General Procedure for the Preparation of Chiral 2-Triphenylsilyl-2,3-dihydropyridones. To a 100-mL flask equiped with a mechanical stirrer was added (-)-8-phenylmenthyl chloformate (2.19 g, 7.44 mmol), toluene (40 mL), and 4-methoxypyridine (0.89 mL, 8.2 mmol) at -23°C. After 15 min, the solution was cooled to -85°C (Et_2O/CO_2) and $Ph_3SiMgCl$ (prepared from 3.30 g of Ph_3SiCl, 11.1 mmol) was added dropwise over 15 min. The mixture was stirred for an additional 30 min at -85°C and the cooling bath was removed. The mixture was allowed to come to room temperature over 30 min followed by the addition of a saturated aqueous solution of oxalic acid (40 mL). The mixture was stirred at room temperature for 5 min, and then extracted with Et_2O (2x50 mL). The combined organic layers were washed with H_2O (2x30 mL) and brine (30 mL). The solution was dried, concentrated, and checked by HPLC (10% EtOAc/hexanes) for diasteriomeric excess (96%). The crude product was purified by radial PLC (5-30% EtOAc/hexanes) to give 4.03 g (88%) of a white foam. The product was further purified by recrystallization from 5% EtOAc/hexanes to give clear colorless crystals (mp 163.5-164.5°C): IR (neat) 2959, 2922, 1712, 1672, 1595, 1429, 1362, 1260, 1107 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.40-2.10 (m, 17 H), 2.61 (d, 1 H, *J*=17.1 Hz), 2.83 (dd, 1 H,

J=8.4 Hz, *J*=17.1 Hz), 4.53 (dt, 1 H, *J*=4.5 Hz, *J*=10.5 Hz), 4.74 (d, 1 H, *J*=8.4 Hz), 5.02 (d, 1 H, *J*= 8.1 Hz), 6.43 (d, 1 H, *J*=8.1 Hz), 7.00-7.55 (m, 20 H); ^{13}C NMR (75 MHz, $CDCL_3$) 21.58, 22.12, 26.05, 29.96, 29.96, 30.98, 34.27, 37.49, 39.03, 41.06, 43.41, 50.47, 77.37, 107.00, 124.69, 125.25, 127.89, 129.95, 131.56, 136.26, 142.84, 150.75, 151.81, 191.82; mp 163.5-164.5°C (EtOAc/hexanes). Anal. Calcd for $C_{40}H_{43}NO_3Si$: C, 78.26; H, 7.06; N, 2.28. Found: C, 78.40; H, 6.98; N, 2.30. $[\alpha]^{20}$ -60.0° (c=1, CH_2Cl_2).

Spectral Data. **(-)-1-((1R,2S,5R)-8-Phenylmenthoxycarbonyl)-(R)-2-triphenylsilyl-2,3-dihydro-4-pyridone (32).** IR (neat) 3049, 2958, 1709, 1672, 1601, 1427, 1321, 1261, 1190, 1107 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.20-2.20 (m, 17 H), 2.26 (d, 1 H, *J*=17.4 Hz), 2.64 (dd, 1 H, *J*=8.4 Hz, *J*=17.4 Hz), 3.70 (d, 1 H, *J*=8.4 Hz), 4.68 (dt, 1 H, *J*=4.5 Hz, *J*=10.5 Hz), 4.98 (d, 1 H, *J*=8.1 Hz), 6.95-7.70 (m, 20 H), 7.81 (d, 1 H, *J*=8.1 Hz); ^{13}C NMR (75 Mhz, $CDCl_3$) δ 21.55, 22.13, 26.27, 30.52, 30.52, 30.97, 34.12, 38.16, 39.26, 39.76, 42.69, 50.05, 78.02, 108.48, 125.03, 128.00, 128.26, 130.14, 131.35, 136.42, 143.21, 152.06, 152.47, 192.35. Anal. Calcd for $C_{40}H_{43}NO_3Si$: C, 78.26; H, 7.06; N, 2.28. Found: C, 78.16; H, 7.21; N, 2.29. $[\alpha]^{20}$ -18.7° (c=1, CH_2Cl_2).

1-((-)-Menthoxycarbonyl)-(S)-2-triphenylsilyl-2,3-dihydro-4-pyridone. IR (neat) 2956, 1717, 1673, 1599, 1337, 1312, 1260, 1194 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.40-2.00 (m, 18 H), 2.71 (d, 1 H, *J*=17.1 Hz), 3.01

(dd, 1 H, J=8.4 Hz, J=17.1 Hz), 4.41 (dt, 1 H, J=3.6 Hz, J=10.5 Hz), 5.09 (d, 1 H, J=5.09 Hz), 5.29 (d, 1 H, J=7.8 Hz) 7.00-7.80 (m, 16 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.44, 20.61, 21.85, 23.33, 26.30, 31.16, 31.99, 37.79, 40.57, 43.73, 46.80, 77.89, 107.80, 128.02, 130.11, 136.36, 142.85, 192.08. Analysis was performed on a mixture of both (R) and (S) isomers (56:42 ratio by HPLC). Anal. Calcd for $C_{34}H_{39}NO_3Si$: C, 75.94; H, 7.31; N, 2.60. Found: C, 75.97; H, 7.47; N, 2.69.

(-)-1-((1R,2S,5R)-Menthoxycarbonyl)-(R)-2-triphenylsilyl-2,3-dihydro-4-pyridone. IR (neat) 2957, 2870, 1718, 1673, 1601, 1429, 1329, 1317, 1263, 1242, 1192 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.40-2.10 (m, 18 H), 2.70 (d, 1 H, J=17.4 Hz), 3.00 (dd, 1 H, J=8.7 Hz, J=17.4 Hz), 4.42 (dt, 1 H, J=4.2 Hz, J=10.5 Hz), 4.9-5.3 (m, 2 H), 7.2-8.0 (m, 16 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.46, 20.83, 21.78, 23.40, 26.68, 31.00, 33.88, 37.84, 39.00, 41.80, 43.95, 46.92, 77.96, 108.50, 128.03, 130.13, 133.55, 136.32, 143.52, 192.07.

(-)-1-((1R,2S,5R)-Menthoxycarbonyl)-5-trimethylsilyl-(S)-2-triphenylsilyl-2,3-dihydro-4-pyridone. IR (neat) 2954, 2870, 1718, 1658, 1574, 1429, 1300, 1255, 1109 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03 (s, 9 H), 0.60-2.40 (m, 17 H), 2.95 (d, 1 H, J=16.8 Hz), 3.20 (dd, 1 H, J=8.7 Hz, J=16.8 Hz), 4.5-4.8 (m, 1 H), 5.20-5.50 (m, 1H), 7.5-8.1 (m, 16 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -1.7, 16.6, 20.8, 21.8, 23.5, 26.6, 31.1, 33.9, 38.4, 40.5, 44.0, 46.9, 77.8, 127.9, 130.0, 131.6, 136.4, 147.5, 194.8. Anal. Calcd for $C_{37}H_{47}NO_3Si_2$:

C, 72.86; H, 7.76; N 2.30. Found: C, 73.04; H, 7.82; N, 2.36.

(-)-1-((1R,2S,5R)-Menthoxycarbonyl)-5-triisopropylsilyl-(S,R)-2-triphenylsilyl-2,3-dihydro-4-pyridone. IR (neat) 2958, 2866, 1718, 1661, 1567, 1462, 1370, 1333, 1303, 1258, 1110 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.40-2.20 (m, 39 H), 2.8-3.1 (m, 2 H), 4.2-4.5 (m, 1 H), 5.0-5.2 (m,1 H), 7.0-8.1 (m, 16 H); ^{13}C (300 MHz, $CDCl_3$) δ 11.12, 16.49, 18.76, 20.94, 21.81, 23.25, 26.40, 31.06, 33.89, 38.14, 41.00, 43.92, 46.91, 77.60, 111.00, 127.93, 130.01, 131.48, 136.43, 148.50, 152.25, 194.87. Anal. Calcd for $C_{43}H_{59}NO_3Si_2$: C, 74.37; H, 8.56; N, 2.02. Found: C, 74.41; H, 8.59; N, 1.91.

(-)-1-((1R,2S,5R)-8-Phenylmenthoxycarbonyl)-5-trimethylsilyl-(S)-2-triphenyl-silyl-2,3-dihydro-4-pyridone. IR (neat) 2953, 1710, 1656, 1571, 1362, 1305, 1256, 1109 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.02 (s, 9 H), 0.40-2.00 (m, 17 H), 2.61 (d, 1 H, *J*=16.8 Hz), 2.79 (dd, 1 H, *J*=8.4 Hz, *J*=16.8 Hz), 4.58 (dt, 1 H, *J*=4.5 Hz, *J*=10.5 Hz), 4.98 (d, 1 H, *J*=7.8 Hz), 6.70 (s, 1 H), 6.90-7.90 (m, 20 H); ^{13}C (75 MHz, $CDCl_3$) δ -1.64, 14.10, 21.60, 22.31, 22.61, 26.10, 29.71, 31.02, 31.54, 34.17, 38.14, 39.12, 41.20, 43.82, 50.77, 76.89, 114.50, 124.73, 125.25, 127.87, 129.92, 131.56, 134.96, 136.37, 147.26, 150.96, 151.77, 194.69. Anal. Calcd for $C_{43}H_{51}NO_3Si_2$: C, 75.28; H, 7.49; N, 2.04. Found: C, 75.33; H, 7.44; N, 1.89. $[\alpha]^{20}$ -48.9° (c=1, CH_2Cl_2).

(-)-1-((1R,2S,5R)-8-Phenylmenthoxycarbonyl)-5-trimethylsilyl-(R)-2-triphenylsilyl-2,3-dihydro-4-pyridone. IR (neat) 2956, 2924, 1713,

1656, 1575, 1457, 1386, 1324, 1300, 1256, 1227, 1109 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ -0.80 (s, 9 H), 0.50 -2.15 (m, 17 H), 2.25 (d, 1 H, *J*=16.8 Hz), 2.60 (dd, 1 H, *J*=8.4 Hz, *J*=16.8 Hz), 3.65 (d, 1 H, 8.4 Hz), 4.70 (dt, 1 H, *J*= 4.5 Hz, *J*=10.5 Hz), 7.05-7.65 (m, 20 H), 7.78 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ -1.59, 21.58, 22.41, 26.37, 29.70, 30.33, 31.05, 34.14, 38.88, 39.33, 39.74, 42.98, 49.94, 78.05, 116.93, 125.09, 128.01, 128.31, 130.04, 131.58, 136.52, 148.02, 152.48, 195.41; M+, found 685.3407, $C_{43}H_{51}NO_3Si_2$ requires 685.3407.

(-)-1-((1R,2S,5R)-8-Phenylmenthoxycarbonyl)-5-triisopropylsilyl-(S)-2-triphenylsilyl-2,3,-dihydro-4-pyridone. IR (neat) 2949, 2865, 1713, 1660, 1563, 1361, 1304, 1258, 1110 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.40-2.40 (m, 38 H), 2.78 (d, 1 H, *J*=16.5 Hz), 2.93 (dd, 1 H, *J*=8.1 Hz, *J*=16.5 Hz), 4.57 (dt, 1 H, *J*=4.2 Hz, *J*=10.5 Hz), 5.03 (d, 1 H, *J*=8.1 Hz), 7.00-7.60 (m, 21 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.32, 18.88, 21.61, 25.89, 26.73, 27.42, 31.09, 34.14, 38.01, 39.83, 41.33, 44.05, 50.96, 72.91. Anal. Calcd for $C_{49}H_{63}NO_3Si_2$: C, 76.41; H, 8.24; N, 1.82. Found: C, 76.27; H, 8.21; N, 1.78.

(-)-1-((1R,2S,5R)-8-Phenylmenthoxycarbonyl)-5-triisopropylsilyl-(R)-2-triphenylsilyl-2,3,-dihydro-4-pyridone. IR (neat) 2949, 2865, 1713, 1660, 1571, 1385, 1298, 1259, 1227, 1109 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.60-2.20 (m, 38 H), 2.34 (d, 1 H, *J*=15.6 MHz), 2.66 (dd, 1 H, *J*=8.4 Hz, *J*=15.3 Hz), 3.80 (d, 1 H, *J*=8.4 Hz), 4.74 (dt, 1 H, *J*=4.8 Hz, *J*=10.5

Hz), 7.00-7.40 (m, 20 H), 7.85 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.09, 14.08, 18.75, 21.51, 22.57, 26.33, 30.08, 31.03, 31.54, 34.09, 38.30, 39.34, 40.01, 42.43, 50.21, 77.92, 111.20, 125.16, 127.94, 130.02, 131.48, 136.52, 149.24, 152.15, 195.20. Anal Calc. for $C_{49}H_{63}NO_3Si_2$: C, 76.41; H, 8.24; N, 1.82. Found : C, 76.55; H, 8.06; N, 1.65.

(-)-1-((1R,2S,5R)-8-Phenylmenthoxycarbonyl)-5-triisopropylsilyl-(S)-2-triphenylsilyl-2,3,-dihydro-4-pyridone. IR (neat) 2949, 2865, 1713, 1660, 1563, 1361, 1304, 1258, 1110 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.40-2.40 (m, 38 H), 2.78 (d, 1 H, 16.5 Hz), 2.90 (dd, 1 H, *J*=8.1 Hz, *J*=16.5 Hz), 4.58 (dt, 1 H, *J*=4.2 Hz, *J*=10.5 Hz), 5.03 (d, 1 H, *J*=8.1 Hz), 7.05-7.60 (m, 21 H); ^{13}C (75 MHz, $CDCl_3$) δ 11.32, 18.88, 21.61, 25.89, 26.73, 27.42, 31.09, 31.24, 38.01, 39.83, 41.33, 44.05, 50.96, 54.15, 72.91, 110.08, 125.35, 127.91, 129.97, 131.66, 136.53, 148.36, 150.51, 151.10, 194.84. Anal. Calcd for $C_{49}H_{63}NO_3Si_2$: C, 76.41; H, 8.24; N, 182. Found: C, 76.27; H, 8.21; N, 1.78.

1-(Benzyloxycarbonyl)-2-triphenylsilyl-2,3-dihydro-4-pyridone (29). This compound was prepared on a 5.3 mmol scale from **4** as described for the preparation of **31** from **4**. Purification by radial PLC (5-30% EtOAC/hexanes) gave **29** in 61% yield. IR (neat) 3068, 3051, 1720, 1670, 1599, 1427, 1386, 1319, 1261 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 2.70 (d, 1 H, *J*=17.4 Hz), 3.01 (dd, 1 H, *J*=8.7 Hz, *J*=17.4 Hz), 4.78-4.92 (m, 1 H), 5.08 (d, 1

H, *J*=5.08), 7.05-7.60 (m, 20 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 37.56, 44.16, 68.91, 108.64, 128.01, 128.59, 128.68, 130.19, 131.19, 136.29, 142.73, 192.04. mp 111.5-113°C (EtOAc/ hexanes). Anal. Calcd for $C_{31}H_{27}NO_3Si$: C, 76.04; H, 5.56; N, 2.86. Found: C, 76.14; H, 5.66; N, 2.89.

Preparation of a 50:50 Mixture of (31) and (32). To a 25-mL flask containing MeOH (15 mL), dihydropyridone **32** (0.334 g, 0.68 mmol), and 10% palladium on carbon (0.205 g) was attached a balloon containing H_2 and the solution was stirred under a H_2 atmosphere at room temperature for 7 h. The mixture was filtered through a pad of celite and concentrated to give 0.210 g (96%) of **30** as an oil. In another 25-mL flask, a solution of 0.130 g of crude **30** in THF (8 mL) and cooled to -78°C followed by the dropwise addition of *n*-BuLi (0.40 mmol). After 5 min, (-)-8-phenylmenthyl chlorofomate (0.120 g in 5 mL THF, 0.40 mmol) was slowly added and the solution was allowed to come to room temperature over 30 min. Water (40 mL) was added and the mixture was extracted with Et_2O (40 mL). The organic layer was washed with brine, dried ($MgSO_4$), and concentrated to give a viscous yellow oil. The crude product was analyzed by HPLC (5% EtOAc/hexanes) and found to contain a 54:46 ratio of diastereomers. The crude product was purified by preparative radial chromatography to give 0.120 g (52%) of **31** and **32** as a foam.

Preparation of (-)-1-((1R,2S,5R)-Menthoxycarbonyl)-2,3-dihydro-4-pyridone (35). 4-Methoxypyridine (0.055 g, 0.5 mmol) and tributyltinhydride (0.17 mL, 0.6 mmol) were added to THF (8 mL) and cooled to

0°C. (-)-Menthyl chloroformate (0.11 mL, 0.5 mmol) was added dropwise and the mixture was stirred for 5 min at 0°C and 0.5 h at room temperature. Saturated aqueous oxalic acid was added and stirred for 5 min followed by extraction with ether (2x30 mL). The combined organic layers were washed with H_2O (30 mL) and brine (30 mL), then dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by radial PLC (30% EtOAc/ hexanes) to give 0.122 g (87%) of **35** as a clear viscous oil. IR (neat) 2959, 2870, 1724, 1675, 1605, 1422, 1386, 1304, 1213, 1181, 1124 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.70-2.18 (m, 18 H), 2.57 (t, 1 H, *J*=7.8 Hz), 4.03 (t, 1 H, *J*=7.8 Hz), 4.72 (dt, 1 H, *J*=4.5 Hz, *J*=10.8 Hz), 5.33 (d, 1 H, *J*=8.4 Hz), 7.86 (d, 1 H, *J*=8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.35, 20.61, 21.83, 23.36, 26.34, 31.28, 33.95, 35.55, 40.89, 42.31, 47.04, 77.93, 107.07, 143.51, 152.15, 193.29; mp 78.5-80.5°C (hexanes). Anal. Calcd for $C_{16}H_{25}NO_3$: C, 68.79; H, 9.02; N, 5.01. Found: C, 68.85; H, 8.96, N, 4.84.

Preparation of (+)-(S)-2-Methyl-1-((1R,2S,5R)-8-phenyl-menthoxycarbonyl)-(S)-6-triphenylsilyl-4-oxopiperidine (36). To a 50-mL flask containing **31** (0.613 g, 1.00 mmol) was added CuBr·Me_2S (0.615 g, 3.0 mmol) and THF (20 mL). The heterogeneous mixture was cooled to -78°C and $BF_3{\cdot}OEt_2$ (0.42 mL, 3 mmol) was added. After stirring for 5 min, MeMgCl (1.00 mL. 3.0 mmol) was added dropwise. The solution turned brown then a golden yellow. The solution was stirred for 4 h at -78°C and poured directly into an aqueous solution of 20% NH_4OH/NH_4Cl (50:50)(50 mL) and

Et_2O (50 mL). The organic layer was washed with H_2O (30 mL) and brine (30 mL). The mixture was dried (K_2CO_3) and concentrated under reduced pressure to give 0.710 g of a viscous foam as a crude product. Purification by radial PLC (5-30% EtOAc/hexanes) gave 0.476 g (76%) of **36** and 0.062 g (10%) of starting material (**31**). IR (neat) 2955, 2922, 1709, 1655, 1570, 1305, 1255, 1109 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.80-1.68 (m, 20 H), 2.19 (d, 1 H, *J*=14.4 Hz), 2.47 (dd, 1 H, *J*=6.6 Hz, *J*=14.4 Hz), 2.54 (d, 1H, *J*=14.4 Hz), 2.76 (dd, 1 H, *J*= 13.2 Hz, *J*=14.4 Hz), 3.73 (d, 1 H, *J*=13.2 Hz), 4.10-4.24 (m, 1 H), 4.60 (dt, 1 H, *J*=4.2 Hz, *J*=10.8 Hz), 7.10-7.70 (m, 20 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.99, 19.29, 21.72, 22.24, 26.25, 26.34, 26.55, 30.96, 34.01, 34.40, 39.58, 40.14, 42.22, 43.10, 47.09, 49.38, 50.37, 76.17, 124.91, 125.24, 127.51, 128.85, 135.83, 136.19, 151.68, 154.68, 207.81. mp 164-165°C. Anal. Calcd for $C_{41}H_{47}NO_3Si$: C, 78.18; H, 7.52; N, 2.22. Found: C, 78.20; H, 7.61; N, 2.16. $[\alpha]^{20}$+52.9° (c=1, CH_2Cl_2).

Preparation of (-)-4,4-Dimethoxy-2-methyl-1-((1R,2S,5R)-8-phenylmenthoxycarbonyl)-(S)-6-triphenylsilylpiperidine. To MeOH (10 mL) in a 25-mL flask was added 3 Å powdered seives (0.30 g), **36** (0.095 g, 0.15 mmol), and *p*-toluenesulfonic acid (0.06 g). The mixture was stirred at room temperature for 2.5 h and poured into a solution of 5% aqueous $NaHCO_3$ (20 mL). The solution was extracted with CH_2Cl_2 (2x40 mL) and the combined extracts were dried (K_2CO_3), filtered through a pad of silica gel, and concentrated to give 0.100 g (98%) of product as a white solid. The product was

sent for analysis without further purification. IR (neat) 2957, 2920, 1678, 1429, 1303, 1278, 1112 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.60-2.00 (m, 23 H), 2.16 (d, 1 H, *J*=13.8 Hz), 2.61 (s, 3 H), 3.13 (s, 3 H), 3.35 (d, 1 H, *J*=12.9 Hz), 4.38-4.55 (m, 2 H), 7.10-7.70 (m, 20 H); ^{13}C (75 MHz, $CDCl_3$) δ 18.48, 21.82, 23.45, 27.03, 30.02, 30.98, 33.71, 34.47, 37.28, 37.40, 40.25, 42.53, 47.10, 47.46, 50.62, 75.65, 99.29, 125.11, 125.59, 127.46, 127.88, 128.58, 135.95, 137.30, 151.24, 154.54. Anal. Calcd for $C_{43}H_{52}NO_4Si$: C, 76.52; H, 7.77; N, 2.08. Found: C, 76.51; H, 7.73; N, 2.02.

Preparation of (+)-(R)-4-Hydroxy-1-((1R,2S,5R)-8-phenyl-menthoxycarbonyl)-(S)-2-triphenylsilyl-1,2,3,4-tetrahydropyridine (37). In a 25-mL flask was placed **31** (0.495 g, mmol), EtOH (10 mL), and $CeCl_3 \cdot 7\ H_2O$ (3.3 mL of a 0.3 molar solution in MeOH). The mixture was refluxed until the starting material was completely dissolved. After cooling to 0°C, $NaBH_4$ (3 eq, 0.110 g) was slowly added over a 5 min period. The solution was stirred for an additional 30 min at 0°C and 30 min at room temperature. The solvent was removed under reduced pressure and to the residue was added CH_2Cl_2 (50 mL), H_2O (40 mL), and 10% aqueous HCl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (40 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to give 0.486 g (98%) of **37** as a white foam. By NMR only one diastereomer was detected and no further purification was required for elemental analysis. IR (neat) 2955, 2920, 1691, 1649, 1427, 1390, 1109 cm^{-1}; ^1H NMR (300 MHz,

$CDCl_3$) δ 0.40-2.25 (m, 19 H), 3.95 (s, 1 H), 4.35-4.05 (m, 2 H), 4.59 (dd, 1 H, *J*=3.6 Hz, *J*=8.4 Hz), 5.90 (d, 1 H, *J*=8.4 Hz), 7.00-7.64 (m, 20 H); ^{13}C NMR (75 Mhz, $CDCl_3$) δ 21.58, 25.08, 26.41, 27.79, 30.85, 33.58, 34.38, 39.43, 40.01, 41.08, 50.40, 62.35, 76.13, 108.66, 124.96, 127.50, 127.77, 129.21, 134.61, 136.34, 151.48, 151.91. Anal. Calcd for $C_{40}H_{45}NO_3Si$: C,78.01; H, 7.36; N, 2.27. Found: C, 78.11; H, 7.42; N, 1.99. $[\alpha]^{20}+7.1°$ (c=1, CH_2Cl_2).

Preparation of (-)-(S)-4-Hydroxy-1-((1R,2S,5R)-8-phenylmenthoxycarbonyl)-(S)-2-triphenylsilyl-1,2,3,4-tetrahydropyridine. To a solution of **37** (.109 g, 0.18 mmol) in toluene (3 mL) at -23°C was added BF_3·OEt (0.05 mL, 0.36 mmol). After stirring for 5 min, H_2O (20 mL) was added and the mixture was allowed to come to room temperature over 15 min. The solution was extracted with Et_2O (40 mL) and the organic layer was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to give 0.108 g (99%) of (-)-(S)-4-Hydroxy-1-((1R,2S,5R)-8-phenylmenthoxycarbonyl)-(S)-2-triphenylsilyl-1,2,3,4-tetrahydropyridine as an viscous oil. The product was used without further purification. A small sample was recrystallized (hexanes) for elemental analysis. IR (Neat) 2957, 2920, 1693, 1647, 1427, 1390, 1109 cm^{-1}; ^1H NMR (300 Mhz, $CDCl_3$) δ 0.20-1.82 (m, 19 H), 2.83 (s, 1 H), 4.01 (dd, 1 H, *J*=2.4 Hz, *J*=8.1 Hz), 4.17-4.25 (m, 1 H), 4.76 (dt, 1 H, *J*=4.2 Hz, *J*=10.5 Hz), 5.87 (d, 1 H, *J*=8.1 Hz), 7.00-7.60 (m, 20 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.64, 26.23, 26.67, 26.89, 30.12, 30.94, 34.43, 39.74, 40.58, 41.31,

50.65, 65.72, 76.12, 106.91, 125.24, 126.99, 127.70, 127.97, 129.34, 134.36, 136.23, 151.36, 151.83; mp 149-150.5°C (hexanes). Anal. Calcd for $C_{40}H_{45}NO_3Si$: C, 78.01; H, 7.36; N, 2.27. Found: C, 78.07; H, 7.38; N, 2.28. $[\alpha]^{20}$ -155.5° (c=1, CH_2Cl_2).

Preparation of (-)-4,6-Dimethoxy-1-((1R,2S,5R)-8-phenylmenthoxycarbonyl)-(S)-2-triphenylsilylpiperidine (40). To a solution of **37** (0.484 g, 0.79 mmol) in MeOH (10 mL) was added pyridinium *p*-tosylate (0.30 g) and the solution was stirred for 16 h at room temperature. Methylene chloride (60 mL) and saturated aqueous $NaHCO_3$ (30 mL) were added to the solution. The organic layer was washed with brine, dried (K_2CO_3), and concentrated under reduced pressure. The crude product was purified by radial PLC to give 0.210 g (40%) of **40** as a viscous oil and an additional 0.120 g (24%) of (-)-4-methoxy-1-((1R,2S,5R)-8-phenylmenthol-carbonyl)-(S)-2-triphenylsilyl-1,2,3,4-tetrahydropyridine (**38**). IR (neat) 1682, 1456, 1410, 1325, 1263, 1101 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.64-2.35 (m, 20 H), 2.50 (s, 3 H), 2.74 (s, 3 H), 2.80-3.00 (m, 1 H), 3.23 (d, 1 H, *J*=28.8 Hz), 4.29 (s, 1 H), 4.75 (dt, 1 H, *J*=4.2 Hz, *J* =10.5 Hz), 5.31 (d, 1 H, *J*=7.2 Hz), 7.00-7.70 (M, 20 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.78, 24.67, 26.60, 28.47, 31.21, 32.22, 34.55, 37.19, 38.06, 39.43, 42.02, 49.94, 55.18, 55.79, 69.73, 76.45, 82.59, 124.85, 127.29, 127.57, 128.06, 129.21, 134.41, 136.27, 152.04, 154.17; mp 209-211°C (EtOAc/hexanes). Anal. Calcd for $C_{42}H_{51}NO_4Si$: C, 76.21; H, 7.77; N, 2.12. Found: C, 76.07; H, 7.75; N, 1.99. $[\alpha]^{20}$ -67.1° (c=1, CH_2Cl_2).

Preparation of (-)-(R)-4-Methoxy-1-((1R,2S,5R)8-phenylmenthoxycarbonyl)-(S)-2-triphenylsilyl-1,2,3,4-tetrahydropyridine (38). To a solution of **37** (1.13 g) in MeOH (20 mL) was added pyridinium *p*-toluenesulfonate (0.35 g) and the solution was stirred for 1 h at room temperature. MeOH was removed under reduced pressure and the remaining thick oil was dissolved in CH_2Cl_2 (50 mL) and passed through a pad of silica gel. The solvent was removed under reduced pressure and the crude product was purified by radial PLC to give 0.400 g (34%) of **38** as a white foam. IR (neat) 2957, 2920, 1693, 1651, 1427, 1388, 1330, 1109, 1080 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.20-1.95 (m, 18 H), 2.25-2.40 (m, 1 H), 2.90 (s, 3 H), 2.93-3.06 (m, 1 H), 4.45 (dt, 1 H, *J*=4.5 Hz, *J*=10.8 Hz), 4.53 (d, 1 H, *J*=8.4 Hz), 4.62-4.67 (m, 1 H), 5.97 (d, 1 H, *J*=8.4 Hz), 7.05-7.70 (m, 20 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.11, 21.63, 22.63, 25.69, 26.54, 27.24, 29.03, 30.92, 31.56, 34.46, 39.56, 41.10, 50.70, 55.46, 70.21, 75.96, 105.63, 125.10, 125.23, 126.64, 127.79, 127.96, 129.57, 133.39, 136.36, 151.53, 151.68. Anal. Calcd for $C_{41}H_{47}NO_3Si$: C, 78.18; H, 7.52; N, 2.22. Found: C, 78.29; H, 7.62; N, 2.20. $[\alpha]^{20}$ -95.4° (c=1, CH_2Cl_2).

Preparation of (-)-1-((1R,2S,5R)-8-phenylmenthoxycarbonyl)-(S)-2-triphenylsilyl-1,2,-dihydropyridine (39). To a 25-mL flask containing **37** (0.234 g, 0.38 mmol) in toluene (10 mL) at -78°C was added $BF_3{\cdot}OEt_2$ (0.10 ml, 0.76 mmol). The solution was stirred at -78°C for 1.5 h

followed by the addition of allylmagnesiumchloride (0.57 mL, 1.14 mmol). After 15 min, the mixture was poured into a flask containing cold H_2O (40 mL) and the mixture was extracted with Et_2O (2x30 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give a thick yellow oil. The crude product was purified by radial PLC (5-30% EtOAc/hexanes) to give 0.185 g (82%) of **39** as a viscous foam. IR (neat) 2955, 2920, 1693, 1427, 1325, 1265, 1111 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.48-1.90 (m, 17 H), 4.52 (dt, 1 H, *J*=4.2 Hz, *J*=10.5 Hz), 4.72-4.80 (m, 1 H), 5.52-5.66 (m, 3 H), 7.96 (d, 1 H, *J*=7.5 Hz), 7.00-7.72 (m, 20 H); ^{13}H NMR (75 MHz, $CDCl_3$) δ 21.74, 26.13, 26.84, 27.08, 31.13, 34.51, 39.77, 41.77, 47.04, 50.76, 76.20, 108.72, 120.70, 122.00, 125.13, 126.06, 127.62, 127.88, 129.55, 132.58, 136.47, 151.24, 151.55. Anal. Calcd. for $C_{40}H_{43}NO_2Si$: C, 80.36; H, 7.25; N, 2.34. Found: C, 80.12; H, 7.30; N, 2.20.

Preparation of (-)-2-Allyl-1-((1R,2S,5R)-8-phenylmenthyl-carbonyl)-(S)-6-triphenylsilyl-1,2,5,6-tetrahydropyridine (44). To **37** (0.470 g, 0.760 mmol) and allyl-trimethylsilane (0.48 mL, 3.0 mmol) in CH_2Cl_2 (8 mL) at -42°C was added BF_3·OEt (0.18 mL, 1.5 mmol) and the solution was allowed to come to room temperature over 30 min. Water (30 mL) was added and the mixture was extracted with CH_2Cl_2 (40 mL). The organic layer was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to give 0.512 g of a viscous foam as the crude product. Purification by radial PLC (5% EtOAc/hexanes) gave 0.364 g (74%) of **44** as a white solid. IR (neat)

2920, 2881, 1678, 1427, 1410, 1309, 1107 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.80-2.10 (m, 17 H), 2.30 (dd, 1 H, *J*=6.0 Hz, *J*=17.4 Hz), 2.45-2.50 (m, 2 H), 4.51 (d, 1 H, *J*=17.4 Hz), 4.76-4.88 (m, 2 H), 5.08 (d, 1 H, *J*=7.8 Hz), 5.16 (d, 1 H), *J*=7.8 Hz), 5.20-5.40 (m, 1 H), 5.42-5.56 (m, 1 H), 6.84-7.53 (m, 20 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.00, 22.55, 25.87, 26.42, 29.95, 31.30, 34.67, 38.00, 39.31, 42.42, 49.93, 50.97, 75.23, 116.69, 122.96, 124.86, 126.72, 127.65, 127.95, 129.46, 134.14, 135.18, 136.44, 152.63; mp 158.5-159.5°C. Anal. Calcd for $C_{43}H_{51}NO_2Si$: C, 80.70; H, 7.72; N, 2.19. Found: C, 80.59; H, 7.74; N, 2.10. $[\alpha]^{20}$ -15.7° (c=1, CH_2Cl_2).

Preparation of (-)-1-((1R,2S,5R)-8-Phenylmenthoxycarbonyl)-2-propyl-(S)-6-triphenylsilyl-1,2,5,6-tetrahydropyridine (45). To a 25-mL flask containing MeOH (10 mL) was added **44** (0.150 g, 0.23 mmol) and 10% palladium on carbon (0.050 g, 0.05 mmol). The mixture was stirred under one atm of H_2 for 2 h, then filtered through a pad of celite and concetrated. The crude product was purified by radial PLC (5-30% EtOAc/hexanes) to give 0.129 g (86%) of **45** as a colorless foam. IR (neat) 2955, 2924, 1672, 1427, 1411, 1307, 1107 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.50-2.08 (m, 24 H), 2.27 (dd, 1 H, *J*=6.3 Hz, *J*=17.4 Hz), 2.42-2.70 (m, 2 H), 4.83 (dt, 1 H, *J*=4.2 Hz, *J*=10.8 Hz), 5.13 (d, 1 H, *J*=10.2 Hz), 5.21 (d, 1H, *J*=8.1 Hz), 5.42-5.51 (m, 1 H), 6.90-7.70 (m, 20 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.80, 19.21, 21.96, 23.14, 25.88, 26.48, 29.34, 31.27, 34.63, 36.94, 37.73,

39.34, 42.34, 50.01, 50.86, 75.21, 122.72, 124.76, 124.89, 127.53, 127.87, 129.29, 134.33, 136.34, 152.44, 155.06. Anal. Calcd for $C_{43}H_{51}NO_2Si$: C, 80.45; H, 8.02; N, 2.18. Found: C, 80.18; H, 8.02; N, 2.12.

Preparation of (-)-1-((1R,2S,5R)-menthoxycarbonyl)-pyrrolidine (50a). To a solution of pyrrolidine (5.70 mL, 4.86 g, 68 mmol) , CH_2Cl_2 (100 mL), and 1 N aqueous NaOH (100 mL) at 0°C was added (-)-menthyl chloroformate (9.80 mL, 45.7 mmol). The mixture was stirred for 10 min at 0°C and at room temperature for 1 h. The mixture was placed in a separatory funnel and the organic layer was removed. The aqueous layer was extracted with CH_2Cl_2 (40 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated. The crude product was distilled (115-117°C, 3 mmHg) to give 10.54 g (91%) of **50a** as a thick clear oil. IR (neat) 2958, 2931, 1685, 1423, 1271, 1260, 1180, 1106 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.70-2.18 (m, 22 H), 3.32 (d, 2 H, *J*=6 Hz), 3.38 (d, 2 H, *J*=6.3 Hz), 4.56 (dt, 1 H, *J*=5 Hz, *J*=10.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) .δ 16.45, 20.73, 21.96, 23.47, 24.83, 25.59, 26.19, 31.23, 34.27, 41.69, 45.50, 45.88, 47.27, 74.32, 154.87; mp 40-41°C (hexanes). Anal. Calcd for $C_{15}H_{27}NO_2$: C, 71.10; H, 10.74; N, 5.52. Found: C, 71.30; H, 10.69; N, 5.60.

Preparation of 1-(Phenoxycarbonyl)pyrrolidine. This compound was prepared on a 78.4 mmol scale from **49** as described for the preparation of **50a** from **49**. Purification was accomplished by Kugelrohr distillation (bp 135-140°C 1.5 mmHg) to give 14.52 g (97%) of 1-(Phenoxycarbonyl)pyrrolidine as a

clear colorless oil. IR (CH_2Cl_2) 2981, 2957, 2883, 1717, 1595, 1493, 1402, 1213, 1194, 1163, 1056 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.85-2.05 (m, 4 H), 3.48 (d, 2 H, *J*=6.6 Hz), 3.56 (d, 2 H, *J*=6.6 Hz), 7.05-7.40 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.81, 25.64, 46.17, 46.27, 121.60, 124.87, 129.01, 151.28, 152.98; mp 72.5-73.5°C (hexanes). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.20; H, 6.91; N, 7.48.

Preparation of (-)-1-((1R,2S,5R)-8-Phenylmenthoxycarbonyl)-pyrrolidine (50b). This compound was prepared on a 30.1 mmol scale from **49** as described for the preparation of **50a** from **49**. Purification was accomplished by Kugelrohr distillation (bp 135-140°C/1.5 mmHg) to give 9.75 g (98%) of **50b** as a clear colorless oil. IR (neat) 2953, 2921, 1696, 1600, 1495, 1413, 1390, 1371, 1345, 1178, 1127, 1103 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.80-2.05 (m, 21 H), 2.16-2.28 (m, 1 H), 2.76-2.88 (m, 1 H), 3.16-3.34 (m, 1 H), 4.78 (dt, 1 H, *J*=4.5 Hz, *J*=10.5 Hz), 7.05-7.35 (m, 5 H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 21.75, 24.54, 24.71, 25.36, 26.53, 28.16, 31.21, 34.54, 39.57, 42.68, 44.58, 45.69, 50.84, 74.09124.52, 125.25, 127.56, 152.23, 153.92. Anal. Calcd for $C_{21}H_{31}NO_2$: C, 72.70; H, 7.41; N, 6.15. Found: C, 72.62; H, 7.41; N, 6.15.

Preparation of 1-(-)-1-((1R,2S,5R)-Menthoxycarbonyl)-2-methoxypyrrolidine (51a). Methanol (70 mL) and **50a** (10.40 g, 41.0 mmol) were placed in an electrolysis cell equipped with carbon electrodes and a magnetic stirrer. Tetraethylammonium *p*-toluenesulfonate (~ 0.5 g) was

added slowly as an electrolite until a constant current (0.30 A) could be maintained with a voltage reading between 18 and 22 V. The cell was cooled with an external water bath (18°C) while 2.4 F/mol of electricity was passed through the solution. The solvent was removed under reduced pressure and Et_2O (100 mL) was added and the orgasnic solution was washed with H_2O (50 mL). The aqueous layer was extracted with Et_2O (2x20 mL) and the combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), filtered through a pad of silica, and concentrated to give 11.06 g (95%) of **51a** as a thick oil. The product was used without further purification. IR (neat) 2954, 2871, 1703, 1401, 1319, 1181, 1086 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ .070-2.20 (m, 22 H), 3.20-3.55 (m, 5 H), 4.50-4.72 (m, 1 H), 7.00-7.30 (m, 1 H). Anal. Calcd for $C_{16}H_{29}NO_3$: C, 67.81; H, 10.31; N, 4.94. Found: C, 67.64; H, 10.10; N, 5.01.

Preparation of 2-Methoxy-1-(phenoxycarbonyl)pyrrolidine (52). Methanol (60 mL) and 1-phenoxycarbonyl)pyrrolidine (12.00 g, 62.7 mmol) were placed in an electrolysis cell[8] equipped with carbon electrodes and a magnetic stirrer. Tetraethylammonium *p*-toluenesulfonate (~ 0.4 g) was added slowly as an electrolite until a constant current (0.30 A) could be maintained with a voltage reading between 18 and 23 V. The cell was cooled with an external water bath (18°C) while 2.4 F/mol of electricity was passed through the solution. The solvent was removed under reduced pressure and CH_2Cl_2 (70 mL) and brine (50 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (2x30 mL) and the combined organic layers were dried

($MgSO_4$), filtered through a pad of silica, and concentrated to give 13.202 g (95%) of **52** as a viscous oil. The product used without further purification. IR (neat) 2981, 2942, 2896, 1728, 1594, 1386, 1211, 1180 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.80-2.22 (m, 4 H), 3.44 (m, 3 H), 3.40-3.60 (m, 2 H), 5.28 (d, 0.6 H, *J*=4.8 Hz), 5.34 (d, 0.4 H, *J*=4.5 Hz), 7.05-7.40 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.50, 22.55, 31.91, 32.46, 45.83, 45.99, 55.42, 56.16, 88.74, 89.23, 121.36, 121.50, 125.13, 129.02, 150.90, 152.87, 154.06. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.19; H, 6.77; N, 6.32.

Preparation of 2-Methoxy-(-)-1-((1R,2S,5R)-8-phenylmenthoxy-carbonyl)pyrrolidine (51b). To (-)-8-phenylmenthol (0.63 g, 2.71 mmol) in THF (40 mL) at -42°C was added potassium *t*-butoxide (0.28 g, 2.5 mmol). The solution was warmed to room temperature over 30 min and then recooled to -42°C followed by the addition of **52** (0.35mL, 0.39 g, 1.8 mmol). After stirring at room temperature for 23 h, H_2O (30 mL) was added and the solution was extracted with Et_2O (3x30 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), and concentrated under reduced pressure to give 0.98 g of a clear oil. The crude product was purified by radial PLC (0-5% EtOAc/hexanes) to give 0.413 g (67%) of **51b** as a clear colorless oil. IR (neat) 2952, 2920, 1701, 1600, 1456, 1327, 1097, 1086 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.75-2.18 (m, 21 H), 2.80 (m, 1 H), 3.32 (s, 3 H), 3.35-3.60 (m, 1 H), 4.82 (dt, 1 H, *J*=4.5 Hz, *J*=10.8 Hz), 5.08 (d, 1 H, *J*=4.5 Hz), 7.20-7.35 (m, 5 H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 21.76, 22.01, 23.64, 26.46, 29.07, 31.28, 31.73, 34.52, 39.52, 42.42, 44.19, 50.59, 55.83, 74.63, 88.76, 124.59, 125.24, 127.63, 152.45, 154.82. Anal. Calcd for $C_{22}H_{33}NO_3$: C, 76.55; H, 9.48; N, 4.25. Found: C, 76.67; H, 9.58; N, 4.22.

Preparation of 2-Allyl-(-)-1-((1R,2S,5R)-menthoxycarbonyl)-pyrrolidine (53a/54a). To **51a** (0.505 g, 1.78 mmol) and allyltrimethylsilane (0.57 mL, 3.59 mmol) in CH_2Cl_2 (10 mL) at -78°C was added $BF_3{\cdot}EtO_2$ (0.32 mL, 2.57 mmol). After stirring for 30 min at -78°C, the solution was allowed to come to room temperature for 1.5 h and poured into brine (30 mL). The mixture was extracted with CH_2Cl_2 (3x30 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated to give 4.95 g of a yellow oil. The crude product was analyzed by HPLC (5% EtOAc/hexanes) and showed no diastereomeric excess. The product was purified by Kugelrohr distillation (bp 132-136°C, 1.0 mmHg) to give 0.473 g (90%) of **53a/54a** as a clear colorless oil. IR (neat) 2955, 2871, 1698, 1455, 1407, 1372, 1319 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.72-2.25 (m, 23 H), 2.30-2.62 (m, 1 H), 3.25-3.50 (m, 2 H), 2.75-3.98 (m, 1 H), 4.48-4.65 (m, 1 H), 5.00-5.18 (m, 2 H), 5.65-5.85 (m, 1 H). Anal. Calcd for $C_{18}H_{31}NO_2$: C, 73.67; H, 10.65; N, 4.77. Found: C, 73.53; H, 10.47; N, 4.89.

Preparation of 2-Allyl-1-(phenoxycarbonyl)-pyrrolidine (55). To **52** (1.00 g, 4.50 mmol) and allyltrimethylsilane (2.0 mL, 12.5 mmol) in CH_2Cl_2 (10 mL) at -78°C, was added $SnCl_4$ (0.70 mL, 5.85 mmol). After stirring

for 10 min at -78°C the solution was allowed to come to room temperature for 0.5 h and poured into H_2O (30 mL). The mixture was extracted with CH_2Cl_2 (3x30 mL) and the combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated to give 0.95 g of a yellow oil as the crude product. The product was purified by radial PLC to give 0.473 g (53%) of **55** as a clear colorless oil. IR (neat) 2981, 2942, 2896, 1728, 1594, 1386, 1211, 1180 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 1.75-2.10 (m, 4 H), 2.15-2.35 (m, 1H), 2.50-2.70 (m, 1 H), 3.40-3.65 (m, 2 H), 3.89-4.18 (m, 1H), 5.00-5.18 (m, 1H), 5.70-5.18(m, 1 H), 7.05-7.45 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 22.55, 23.41, 28.95, 29.79, 37.47, 38.73, 46.71; 56.83, 57.30, 117.20, 121.43, 121.73, 124.74, 128.88, 134.42, 151.09, 152.69. Anal. Calcd for $C_{14}H_{17}NO_2$: C, 65.19; H, 6.83; N, 6.33. Found: C, 65.19; H, 6.77; N, 6.32.

Preparation of 2-Allyl-(-)-1-((1R,2S,5R)-8-phenylmenthoxy-carbonyl)pyrrolidine (53b/54b). To **51b** (0.400 g, 1.15 mmol) and allyltrimethylsilane (0.37 mL, 2.27 mmol) in CH_2Cl_2 (20 mL) at -78°C was added $SnCl_4$ (0.18 mL, 1.50 mmol). After stirring for 1 h at -78°C, the solution was allowed to come to room temperature for 0.5 h and poured into brine (30 mL). The mixture was extracted with CH_2Cl_2 (3x30 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated to give 4.95 g of a yellow oil. The crude product was analyzed by HPLC (5% EtOAC/hexanes) and showed 8% diastereomeric excess. The product was purified by radial PLC to give 0.139 g of one diastereomer and 0.85 g of a second diasteriomer for a combined yeild

of 53%. Diastereomer 1. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.70-2.20 (m, 22 H), 2.40-2.60 (m, 1 H), 2.70-2.90 (m, 1 H), 3.25-3.90 (m, 1 H), 4.80 (dt, 1 H, *J*=4.5 Hz, *J*=10.5 Hz), 5.00-5.15 (m, 2 H), 5.60-5.81 (m, 1 H), 7.03-7.32 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.66, 21.81, 22.05, 23.24, 24.30, 26.59, 28.51, 29.03, 31.31, 34.34, 34.61, 38.02, 39.63, 42.67, 45.17, 50.77, 56.93, 74.09, 117.00, 124.62, 125.31, 127.68, 135.19, 152.44, 153.83. $[\alpha]^{20}$+9.9°(c=1, CH_2CL_2). Diastereomer 2. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.70-2.60 (m, 24 H), 3.20-3.85 (m, 1 H), 3.70-3.85 (m, 1 H), 4.60-5.15 (m, 3 H), 5.45-5.85 (m, 1 H), 7.00-7.40 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.79, 22.71, 23.07, 23.31, 24.79, 26.39, 26.62, 28.05, 28.93, 29.40, 31.25,34.64, 38.18, 38.60, 39.39, 39.59, 42.32, 42.71, 45.43, 46.34, 50.81, 50.92, 54.83, 56.79, 74.22, 116.66, 116.82, 124.49, 125.15, 127.68, 135.28, 152.36, 152.74, 153.77. $[\alpha]^{20}$-29.3°(c=1, CH_2Cl_2).

Preparation of a 50:50 Mixture of 53b and 53a. To a solution of (-)-8-phenylmenthol (0.60 g, 2.42 mmol) in THF (10 mL) at -42°C was added potassium *t*-butoxide (0.27 g, 2.42 mmol). After stirring for 30 min the solution was transfered via a cannula into a flask containing **55** (0.400 g, 1.73 mmol) in THF (10 mL) at -42°C. The mixture was allowed to warm and stir at room temperature for 19 h followed by the addition of H_2O (20 mL). The aqueous layer was extracted with ether (2x30 mL) and the combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to give 0.80 g of a crude product. The crude product was anaylized by HPLC (5% EtOAC/hexanes) to

verify the 50:50 mixture of diastereomers. Purification by preparative radial chromatography (5-20% EtOAc/hexanes) gave 0.459 g of **53b/54b** as a mixture of diastereomers. IR (neat) 2952, 2920, 1701, 1600, 1456, 1327, 1097, 1086 cm^{-1}. Anal. Calcd for $C_{24}H_{35}NO_2$: C, 78.01; H, 9.55; N, 3.79. Found: C, 78.31; H, 9.28; N, 3.86.

Preparation of 5-Methoxy-(-)-1-((1R,2S,5R)-menthoxy-carbonyl)-2-pyrrolidinone (59a). To 5-methoxy-2-pyrrolidinone (1.85 g, 16.0 mmol) at -78°C was added *n*-BuLi (6.80 mL, 16 mmol) and the solution was allowed to stir for 10 min followed by the dropwise addition of (-)-menthyl chloroformate (3.44 mL, 16 mmol). The mixture was stirred at -78°C for 30 min, allowed to warm to room temperature, filtered through a pad of silica, and concentrated to give 5.11 g of a yellow liquid. The crude product was purified by Kugelrohr distillation (180-190°C/1.2 mmHg) to give 3.28 g (69%) of **59a** as a clear liquid. IR (neat) 2953, 2871, 1794, 1762, 1719, 1353, 1293, 1204, 1088, 1035 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.70-2.20 (m, 19 H), 2.30-2.50 (m, 1 H), 2.70-2.80 (m, 1 H), 3.42 (s, 3 H), 4.77 (dt, 1 H, *J*=4.5 Hz, *J*=10.5 Hz), 5.41-5.45 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.85, 16.18, 20.67, 20.79, 21.87, 22.91, 23.25, 25.09, 25.58, 25.81, 26.12, 30.45, 30.31, 33.97, 40.55, 40.63, 46.90, 55.87, 56.32, 77.12, 77.21, 151.06, 173.50. Anal. Calcd for $C_{16}H_{27}NO_3$: C, 64.62; H, 9.15; N, 4.71. Found: C, 64.80; H, 9.40; N, 4.73.

Preparation of 5-Methoxy-(-)-1-((1R,2S,5R)-8-phenyl-menthoxycarbonyl)-2-pyrrolidinone (59b). This compound was

prepared on a 3.32 mmol scale from **58b** as described for the preparation of **59a** from **58a**. Purification was accomplished by radial PLC (5-30% EtOAc/hexanes) to give 0.768 g (74%) of **59b** as a viscous oil. Diastereoisomers were separated by radial PLC (5-30% EtOAc/hexanes). Diastereoisomer 1: IR (neat) 2960, 2925, 2871, 1792, 1782, 1713, 1497, 1373, 1348, 1294, 1205, 1088 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.70-2.35 (m, 20 H), 2.50-2.65 (m, 1 H), 3.38 (m, 3 H), 4.96 (t, 1 H, *J*=4.8 Hz, *J*=10.5 Hz), 5.20-5.26 (m, 1 H), 7.05-7.35 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.57, 25.23, 25.85, 26.56, 27.00, 30.32, 31.24, 34.06, 39.70, 41.51, 50.06, 56.13, 76.84, 88.93, 124.68, 125.44, 127.57, 150.70, 151.33, 172.10. Diastereoisomer 2: IR (neat) 2963, 2252, 1790, 1714, 1600, 1445, 1317, 1263, 1087, 1018 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.80-2.35 (m, 20 H), 2.50-2.65 (m, 1 H), 3.13 (t, 3 H), 3.71 (dd, 1 H, *J*=3.3 Hz, *J*=4.5 Hz), 4.93 (dt, 1 H, *J*=4.5 Hz, *J*=10.8 Hz), 7.10-7.38 (m, 5 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.70, 21.84, 24.99, 26.15, 30.07, 30.45, 31.19, 34.39, 39.27, 41.43, 50.48, 56.02, 76.28, 88.15, 124.65, 125.23, 127.92, 149.24, 152.67, 174.07.

Preparation of 1-((-)-1-((1R,2S,5R)-Menthoxycarbonyl)-6-methoxy-2-piperidone (59c). This compound was prepared on a 4.41 mmol scale from **58c** as described for the preparation of **59a** from **58a**. Purification was accomplished by radial PLC (5-30% EtOAc/hexanes) to give 0.970 g (74%) of **59c** as a viscous oil. IR (neat) 2956, 2871, 1776, 1718,

1204, 1170, 1080 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.70-2.20 (m, 22 H), 2.40-2.50 (m, 1 H) 2.60-2.75 (m, 1 H), 3.37 (s, 3 H), 4.75 (dt, 1 H, *J*=4.2 Hz, *J*=10.8 Hz), 5.50 (d, 1 H, *J*=1.5 Hz); Anal. Calcd for $C_{17}H_{28}NO_4$: C, 65.57; H, 9.38; N, 4.50. Found: C, 65.39; H, 27; N, 4.31.

Preparation of 6-Methoxy-(-)-1-((1R,2S,5R)-8-phenylmenthoxycarbonyl)-2-piperidone (59d). This compound was prepared on a 8.60 mmol scale from **58d** as described for the preparation of **59a** from **58a**. Purification was accomplished by radial PLC (20% EtOAc/hexanes) to give 0.768 g (73%) of **59d** as a viscous oil. IR (neat)2953, 1772, 1713, 1393, 1357, 1278, 1204, 1138 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 0.80-2.50 (m, 25 H), 3.33 (s, 3H), 4.88 (dt, 1 H, *J*=4.5 Hz, *J*=10.8 Hz), 5.29 (s, 1H), 7.10-7.35 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.47, 21.70, 25.27, 26.56, 27.59, 31.34, 34.01, 34.29, 39.68, 41.25, 517, 55.88, 77.42, 85.06, 124.86, 125.46, 127.72, 151.27, 154.37, 171.72. Anal. Calcd for $C_{23}H_{35}NO_4$: C, 70.37; H, 8.86; N, 3.73. Found: C, 70.10; H, 8.63; N, 3.80.

Preparation of a 50:50 mixture of 60b. To a solution of 5-allyl-2-pyrrolidinone (0.164 g, 1.31 mmol) in THF (10 mL) was added *n*-BuLi (0.49 mL, 1.6 mmol) at -78°C. After 15 min, (-)-8-phenylmenthyl chloroformate was added and the mixture was allowed to warm to room temperature for 30 min. The solution was filtered through a pad of silica, and concentrated under reduced pressure to give a viscous yellow oil. The crude product was purified by radial PLC (5-20% EtOAC/hexanes) to give 0.175 g of one diastereoisomer

and 0.188 g of the other diastereomer with an overall yield of 87%. HPLC (5% EtOAc/hexanes) of the crude product indicated a 49:51 ratio of diastereoisomers. IR (neat) 2956, 2870, 1782, 1752, 1708, 1299, 1284, 1235 cm^{-1}; ^1H NMR for **51** (300 MHz, $CDCl_3$) δ 0.80-2.55 (m, 23 H), 4.00-4.11 (m, 1 H), 4.96 (dt, 1 H, *J*=4.5 Hz, *J*=10.5 Hz), 5.06-5.17 (m, 2H), 5.65-6.80 (m, 1H), 7.10-7.45 (m, 5 H); ^1H NMR for **52** (300 MHz, $CDCl_3$) δ 0.80-2.50 (m, 23 H), 2.70-2.80 (m, 1 H), 4.85-5.70 (m, 3 H), 5.50-5.70 (m, 1 H), 7.05-7.45 (m, 5 H).

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APPENDICES

APPENDIX A.

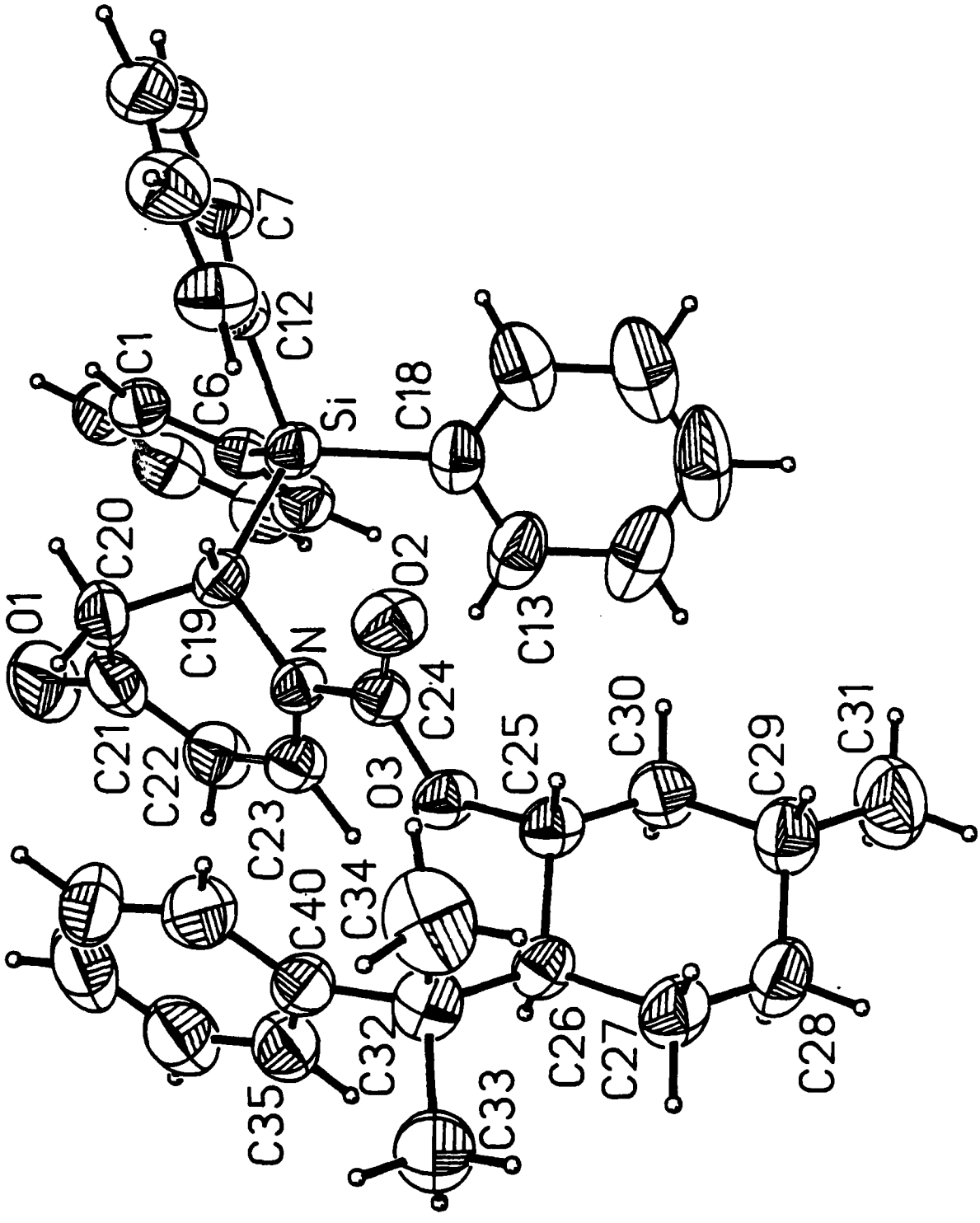
C7
C12
C1
C6
Si
C18
C20
O2
O1
C19
N
C13
C24
C21
C22
C23
O3
C25
C30
C29
C31
C40
C34
C32
C26
C27
C28
C35
C33

Table. Crystal Data for $C_{40}H_{43}NO_3Si$

formula	$C_{40}H_{43}NO_3Si$
mol wt, g mol^{-1}	613.88
crystal size, mm	0.55 x 0.44 x 0.43
λ (Mok_α), Å	0.71069
a , Å	10.516 (4)
b, Å	14.693 (5)
c, Å	22.582 (8)
α, deg	90
β, deg	90
γ, deg	90
V, $Å^3$	3489
space group	$P2_12_12_1$
Z	4
D_{calc}, g cm^{-3}	1.17
F (000), e^-	1312
temp, K	298
scan type	ω
scan range	2° + dispension
scan speed, deg min^{-1}	variable between 4 and 29.3
2θ range, deg	$3 \leq 2\theta \leq 55$
background	stationary on each side of a peak for1/2 of scan time
octants measured	h k l

standards	2 measured after every 48 reflections
no. measured	4501
no. used, NO	3182 with $\underline{F_o} \geq 4\,\sigma\,(\underline{F_o})$
sec. extinction coeff	3.2×10^{-6}
μ, cm^{-1}	1.00 cm^{-1}
R^a	0.0491
$R_w{}^b$	0.0674
goodness of fit, S^c	1.3
max shift/σ	0.5
no. variables, NV	415
difference peak excursion, $eÅ^{-3}$	+0.25, -0.18

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a $R = \Sigma(||F_o| - |F_c||)/\Sigma |F_o|$

b $R_w = [\Sigma w(||F_o| - |F_c||)^2/\Sigma w |F_o|^2]^{1/2}$,

c $S = [\Sigma w(|F_o|-|F_c|)^2/(NO-NV)]^{1/2}$

Table 2. Bond lengths (Å) and Bond angles (°)

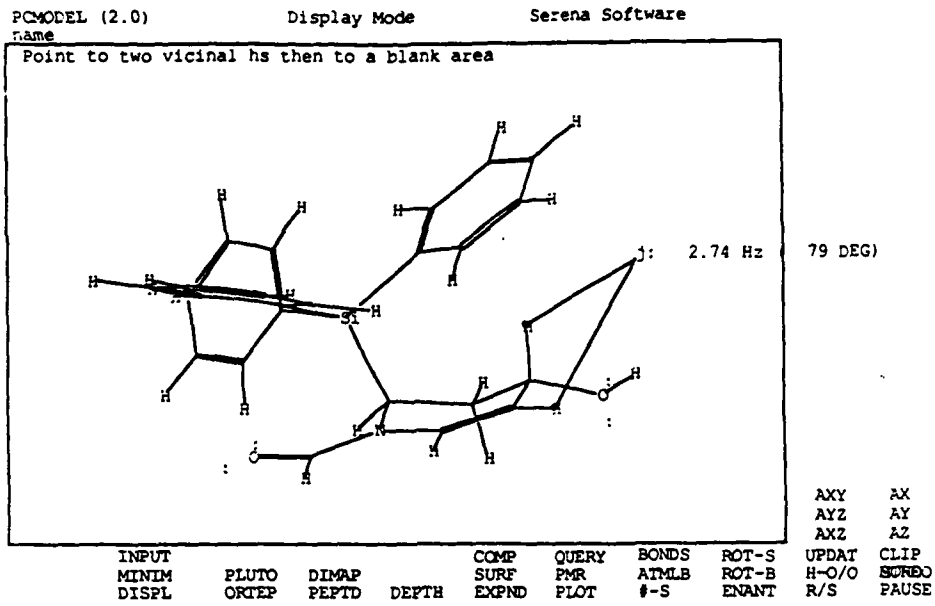
Si-C(6)	1.887(4)	Si-C(12)	1.875(4)
Si-C(18)	1.881(4)	Si-C(19)	1.926(4)
C(1)-C(2)	1.394(5)	C(1)-C(6)	1.401(5)
C(2)-C(3)	1.393(6)	C(3)-C(4)	1.360(7)
C(4)-C(5)	1.381(6)	C(5)-C(6)	1.389(5)
C(7)-C(8)	1.387(6)	C(7)-C(12)	1.387(5)
C(8)-C(9)	1.363(6)	C(9)-C(10)	1.368(7)
C(10)-C(11)	1.383(6)	C(11)-C(12)	1.397(6)
C(13)-C(14)	1.410(6)	C(13)-C(18)	1.390(6)
C(14)-C(15)	1.385(10)	C(15)-C(16)	1.356(10)
C(16)-C(17)	1.365(8)	C(17)-C(18)	1.383(7)
C(19)-C(20)	1.529(6)	C(19)-N	1.479(4)
C(20)-C(21)	1.503(6)	C(21)-O(1)	1.221(6)
C(21)-C(22)	1.450(7)	C(22)-C(23)	1.346(5)
C(23)-N	1.388(5)	N-C(24)	1.380(4)
C(24)-O(2)	1.208(5)	C(24)-O(3)	1.326(4)
O(3)-C(25)	1.461(4)	C(25)-C(26)	1.534(5)
C(25)-C(30)	1.502(5)	C(26)-C(27)	1.533(5)
C(26)-C(32)	1.563(5)	C(27)-C(28)	1.511(5)
C(28)-C(29)	1.521(6)	C(29)-C(30)	1.517(6)
C(29)-C(31)	1.532(6)	C(32)-C(33)	1.541(6)
C(32)-C(34)	1.542(6)	C(32)-C(40)	1.533(5)
C(35)-C(36)	1.367(7)	C(35)-C(40)	1.392(6)
C(36)-C(37)	1.379(8)	C(37)-C(38)	1.348(8)
C(38)-C(39)	1.381(7)	C(39)-C(40)	1.388(6)

C(6)-Si-C(12)	109.1(2)	C(6)-Si-C(18)	112.0(2)
C(12)-Si-C(18)	109.4(2)	C(6)-Si-C(19)	109.7(2)
C(12)-Si-C(19)	105.8(2)	C(18)-Si-C(19)	110.6(2)
C(2)-C(1)-C(6)	121.9(4)	C(1)-C(2)-C(3)	119.0(4)
C(2)-C(3)-C(4)	120.0(4)	C(3)-C(4)-C(5)	120.4(4)
C(4)-C(5)-C(6)	122.2(4)	Si-C(6)-C(1)	120.7(3)
Si-C(6)-C(5)	122.9(3)	C(1)-C(6)-C(5)	116.4(3)
C(8)-C(7)-C(12)	121.9(4)	C(7)-C(8)-C(9)	120.1(4)
C(8)-C(9)-C(10)	120.1(4)	C(9)-C(10)-C(11)	119.5(4)
C(10)-C(11)-C(12)	122.3(4)	Si-C(12)-C(7)	122.4(3)
Si-C(12)-C(11)	121.6(3)	C(7)-C(12)-C(11)	116.0(4)
C(14)-C(13)-C(18)	121.0(5)	C(13)-C(14)-C(15)	119.3(5)
C(14)-C(15)-C(16)	119.6(6)	C(15)-C(16)-C(17)	120.9(6)
C(16)-C(17)-C(18)	122.4(5)	Si-C(18)-C(13)	122.3(3)
Si-C(18)-C(17)	120.8(3)	C(13)-C(18)-C(17)	116.9(4)
Si-C(19)-C(20)	113.8(2)	Si-C(19)-N	113.6(2)
C(20)-C(19)-N	108.6(3)	C(19)-C(20)-C(21)	113.4(3)
C(20)-C(21)-O(1)	121.8(4)	C(20)-C(21)-C(22)	115.5(4)
O(1)-C(21)-C(22)	122.4(4)	C(21)-C(22)-C(23)	121.0(4)
C(22)-C(23)-N	122.8(4)	C(19)-N-C(23)	118.7(3)
C(19)-N-C(24)	118.5(3)	C(23)-N-C(24)	122.5(3)
N-C(24)-O(2)	123.3(3)	N-C(24)-O(3)	110.1(3)
O(2)-C(24)-O(3)	126.5(3)	C(24)-O(3)-C(25)	120.3(3)
O(3)-C(25)-C(26)	107.4(3)	O(3)-C(25)-C(30)	106.4(3)
C(26)-C(25)-C(30)	114.9(3)	C(25)-C(26)-C(27)	108.1(3)
C(25)-C(26)-C(32)	114.0(3)	C(27)-C(26)-C(32)	113.5(3)
C(26)-C(27)-C(28)	113.9(3)	C(27)-C(28)-C(29)	111.0(3)
C(28)-C(29)-C(30)	108.2(3)	C(28)-C(29)-C(31)	112.4(4)
C(30)-C(29)-C(31)	112.2(3)	C(25)-C(30)-C(29)	113.8(3)
C(26)-C(32)-C(33)	109.5(3)	C(26)-C(32)-C(34)	110.2(3)
C(33)-C(32)-C(34)	108.2(3)	C(26)-C(32)-C(40)	111.3(3)
C(33)-C(32)-C(40)	106.4(3)	C(34)-C(32)-C(40)	111.1(3)
C(36)-C(35)-C(40)	122.3(4)	C(35)-C(36)-C(37)	120.0(5)
C(36)-C(37)-C(38)	119.1(5)	C(37)-C(38)-C(39)	121.2(5)
C(38)-C(39)-C(40)	121.3(5)	C(32)-C(40)-C(35)	120.0(4)
C(32)-C(40)-C(39)	123.8(4)	C(35)-C(40)-C(39)	116.1(4)

Table 1. Atomic coordinates ($\times 10^4$) and isotropic thermal parameters ($A^2 \times 10^3$)

	x	y	z	U*
Si	4360(1)	4818(1)	10948(1)	43(1)
C(1)	3091(4)	5826(3)	11863(2)	50(1)
C(2)	2973(4)	6480(3)	12307(2)	61(1)
C(3)	4026(5)	7009(3)	12454(2)	69(2)
C(4)	5154(4)	6874(3)	12173(2)	65(1)
C(5)	5265(4)	6212(3)	11742(2)	57(1)
C(6)	4244(4)	5675(2)	11568(1)	44(1)
C(7)	2919(4)	3598(3)	11682(2)	56(1)
C(8)	2052(4)	2908(3)	11796(2)	64(1)
C(9)	1506(4)	2445(3)	11338(2)	66(2)
C(10)	1851(5)	2633(3)	10767(2)	69(2)
C(11)	2706(4)	3327(3)	10656(2)	63(1)
C(12)	3247(4)	3847(3)	11110(2)	49(1)
C(13)	7031(4)	4934(4)	10709(2)	69(2)
C(14)	8266(4)	4578(5)	10637(2)	95(2)
C(15)	8461(6)	3651(5)	10704(2)	111(3)
C(16)	7464(6)	3103(5)	10838(2)	101(3)
C(17)	6273(5)	3453(3)	10914(2)	74(2)
C(18)	6013(3)	4371(3)	10850(2)	54(1)
C(19)	3743(3)	5356(3)	10224(2)	44(1)
C(20)	2763(4)	6111(3)	10317(2)	63(1)
C(21)	3341(4)	6996(3)	10514(2)	65(2)
O(1)	2742(4)	7548(2)	10807(2)	96(1)
C(22)	4602(4)	7185(3)	10286(2)	61(1)
C(23)	5197(4)	6591(2)	9926(2)	48(1)
N	4768(3)	5708(2)	9838(1)	41(1)
C(24)	5331(3)	5122(3)	9439(1)	41(1)
O(2)	5009(3)	4338(2)	9378(1)	57(1)
C(3)	6244(2)	5548(2)	9144(1)	46(1)
C(25)	7075(3)	5043(2)	8743(1)	44(1)
C(26)	7181(3)	5595(3)	8168(1)	44(1)
C(27)	8298(4)	5207(3)	7805(2)	61(1)
C(28)	9519(4)	5129(3)	8147(2)	64(1)
C(29)	9361(4)	4516(3)	8685(2)	61(1)
C(30)	8306(4)	4905(3)	9067(2)	55(1)
C(31)	10604(5)	4395(4)	9030(2)	94(2)
C(32)	5910(4)	5666(3)	7813(2)	53(1)
C(33)	6157(5)	6148(4)	7218(2)	77(2)
C(34)	5383(5)	4707(3)	7682(2)	85(2)
C(35)	5223(4)	7137(3)	8303(2)	61(1)
C(36)	4367(5)	7695(3)	8578(2)	80(2)
C(37)	3155(5)	7386(4)	8696(2)	95(2)
C(38)	2836(5)	6530(4)	8541(2)	89(2)
C(39)	3699(4)	5961(4)	8266(2)	69(2)
C(40)	4928(4)	6247(3)	8143(2)	49(1)

APPENDIX B.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name
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j: 2.74 Hz (79 DEG)
AXY AX
AYZ AY
AXZ AZ
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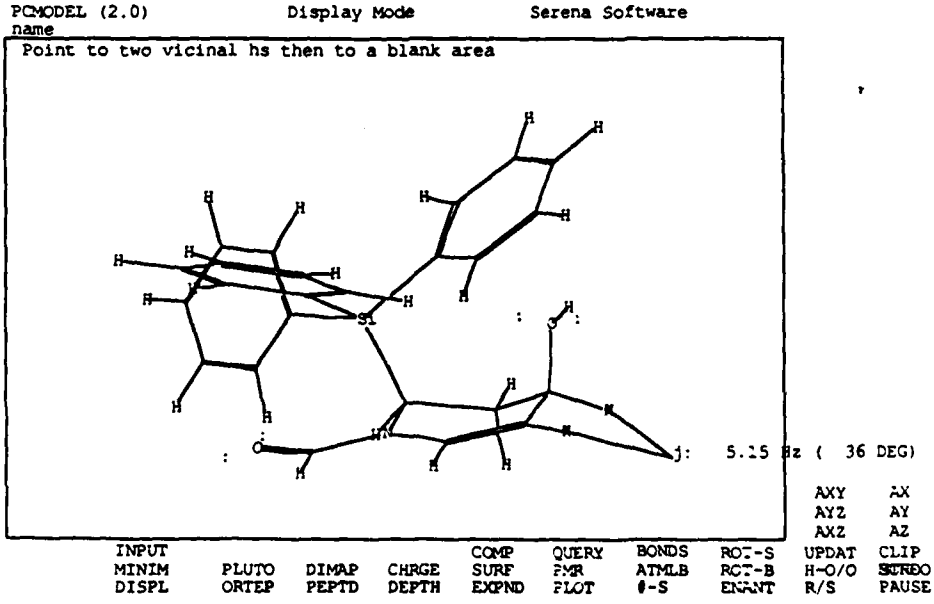
MINIM PLUTO DIMAP SURF PMR ATMLB ROT-B H-O/O SCRDO
DISPL ORTEP PEPTD DEPTH EXPND PLOT #-S ENANT R/S PAUSE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AYZ AY
AXZ AZ
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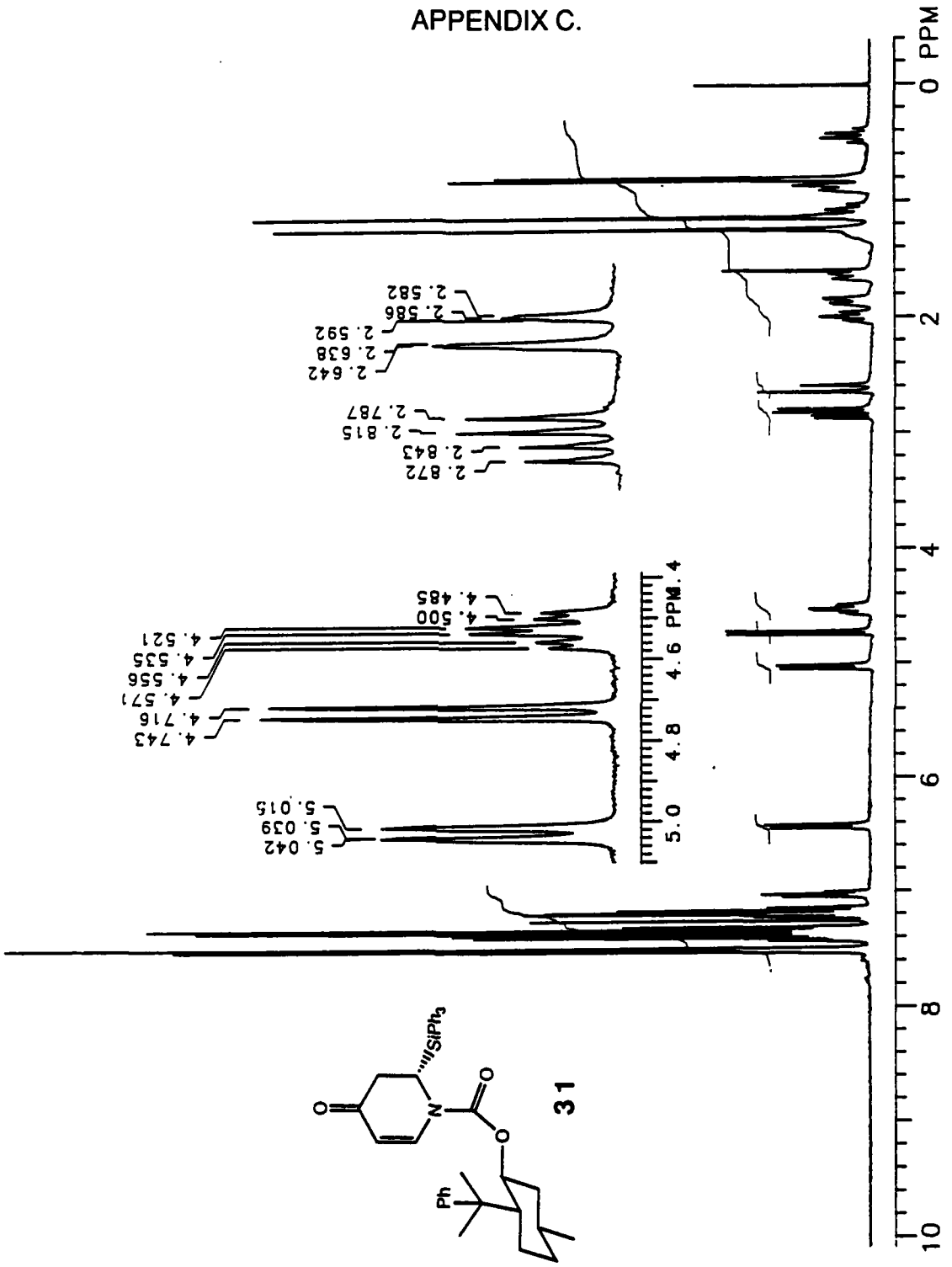
MINIM PLUTO DIMAP CHRGE SURF PMR ATMLB ROT-B H-O/O SCRDO
DISPL ORTEP PEPTD DEPTH EXPND PLOT #-S ENANT R/S PAUSE

APPENDIX C.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2
4
6
8
10
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4.8
4.6 PPM.4
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5.039
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4.716
4.571
4.556
4.535
4.521
4.500
4.485
2.872
2.843
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2.638
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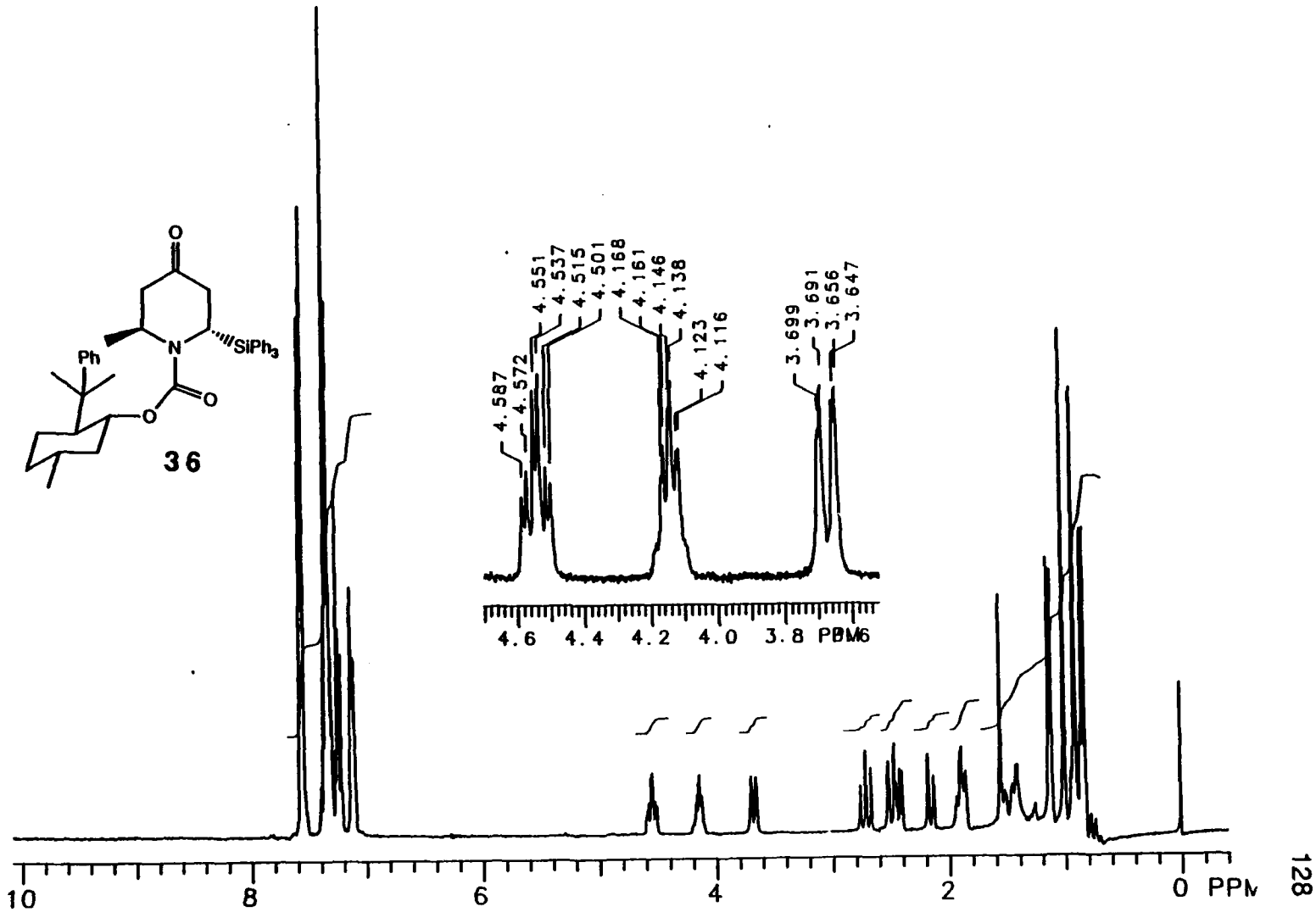
2.586
2.582
SiPh3
N
O
O
O
Ph
31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Ph
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O
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4.515
4.501
4.168
4.161
4.146
4.138
4.123
4.116
3.699
3.691
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4.4
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4.0
3.8
PPM
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8
6
4
2
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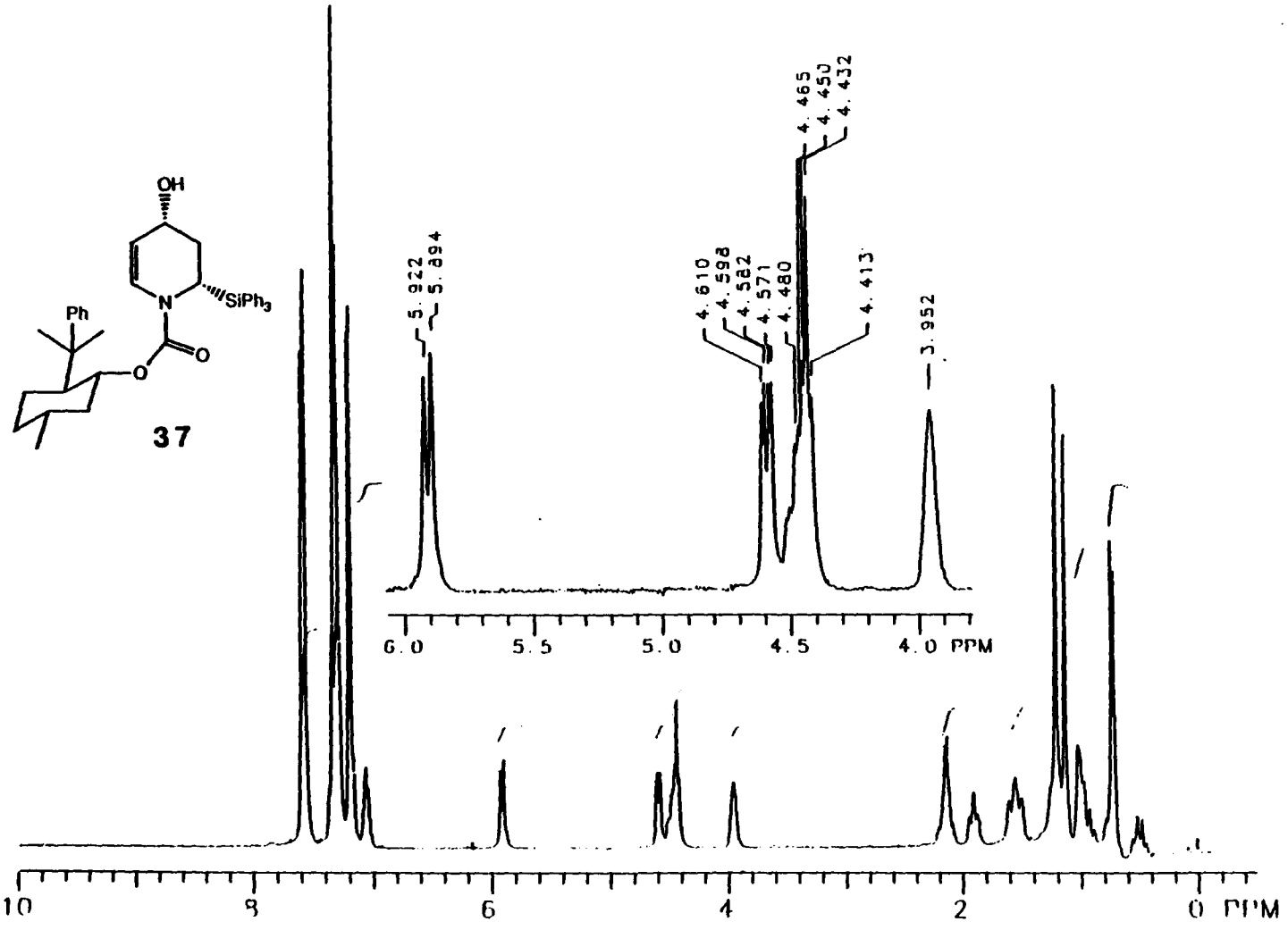
PPM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4.450
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6.0
5.5
5.0
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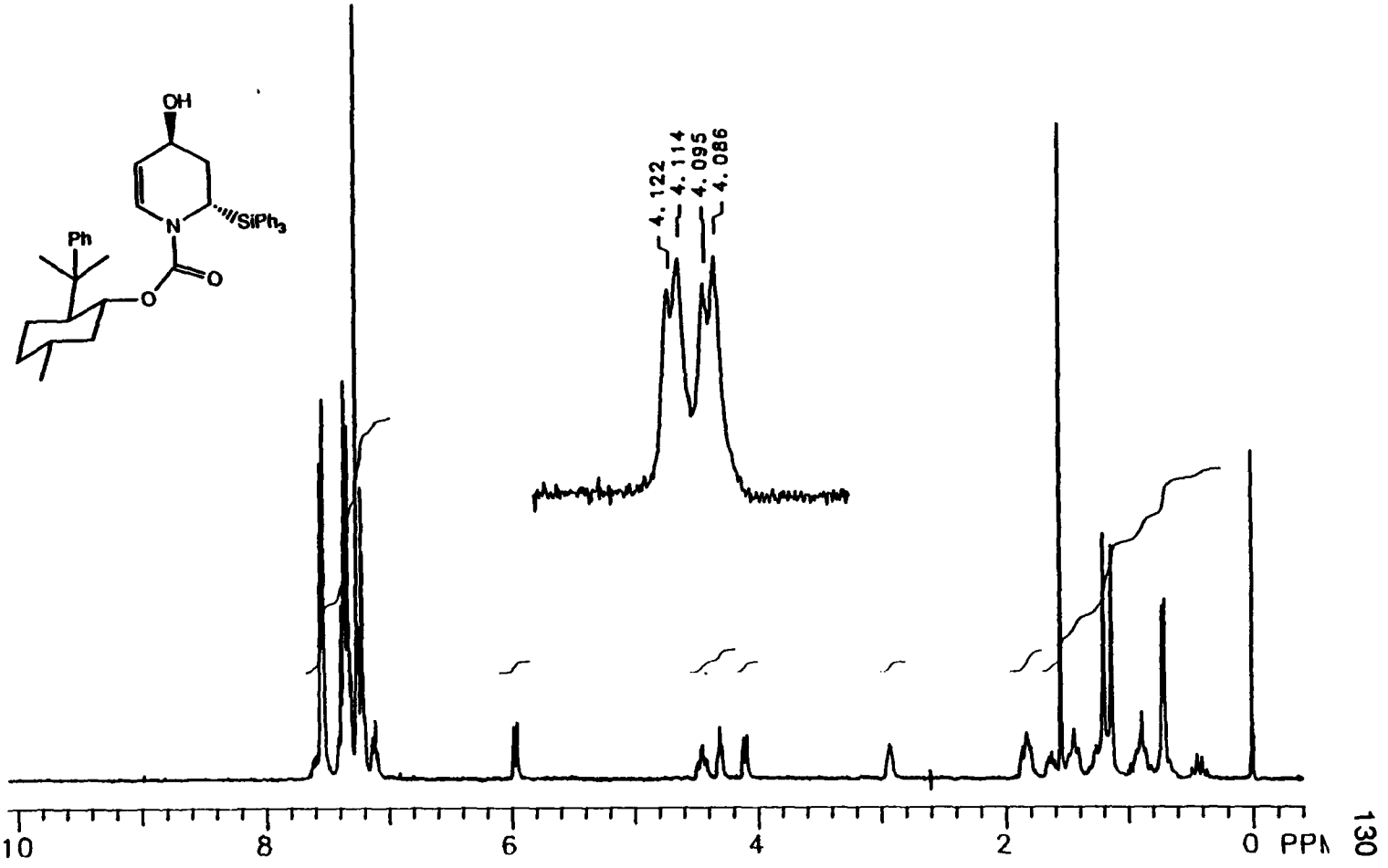
6
4
2
0 PPM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4.086
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4
2
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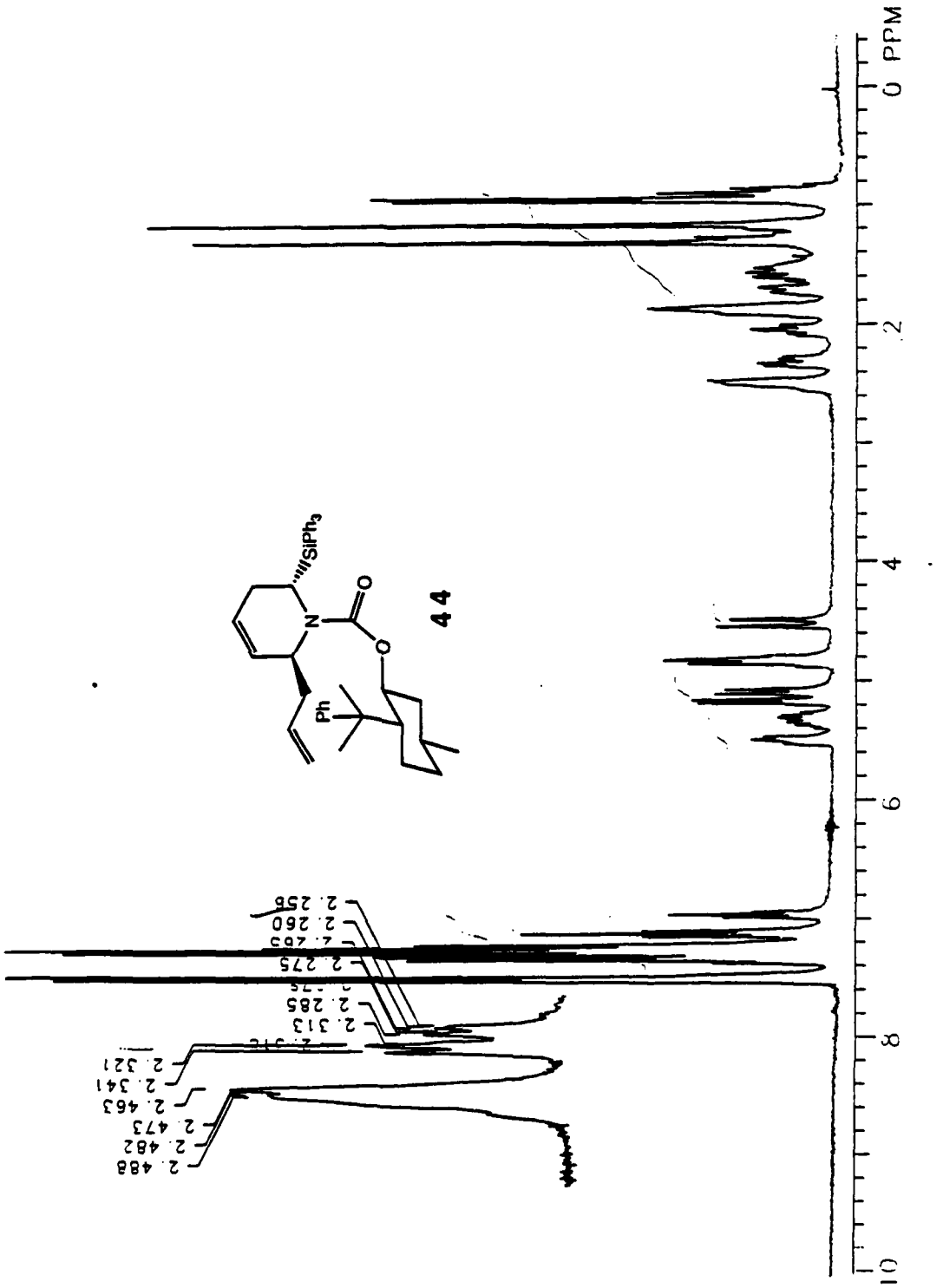
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6
8
10
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2.265
2.275
2.285
2.313
2.321
2.341
2.463
2.473
2.482
2.488
SiPh3
Ph
O
N
O
44

APPENDIX D.

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N-METHYL LITHIATION OF N-METHYLINDOLES DIRECTED BY α-AMINO ALKOXIDES

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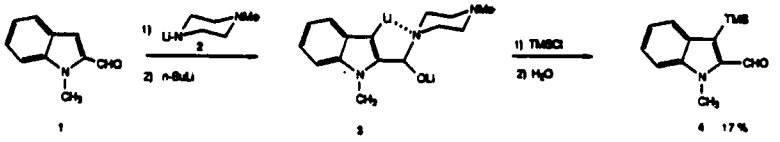
Summary: *A novel N-methyl lithiation-alkylation of an α-amino alkoxide derived from 3-chloro-N-methylindole-2-carboxaldehyde is described.*

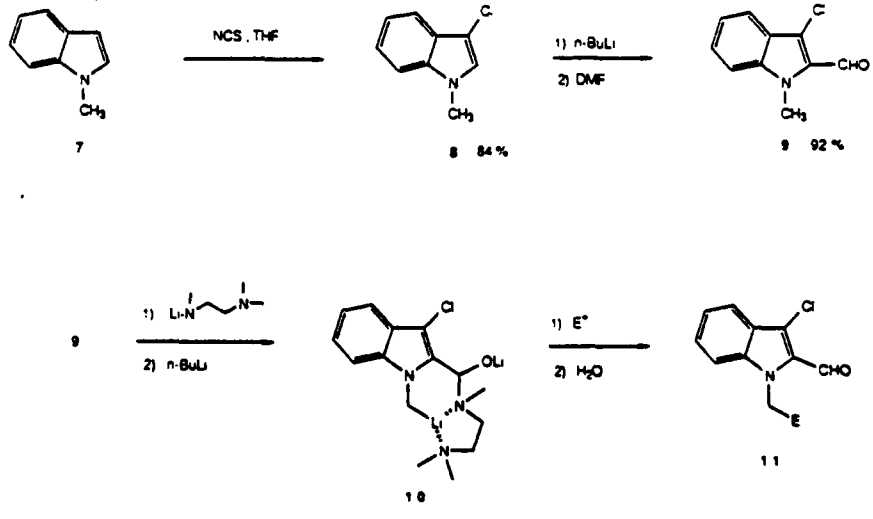
The reaction of aromatic aldehydes with certain lithium dialkylamides gives α-amino alkoxides in situ that can be ring lithiated with alkyllithiums. Alkylation and hydrolysis on workup provides ortho-substituted aryl aldehydes via a one-pot reaction.[2,3] This methodology works well for the one-pot substitution of heterocyclic aromatic aldehydes[3] as well as for benzaldehyde derivatives[2]. We previously reported that attempted C-3 lithiation of the α-amino alkoxide derived from N-methyl-2-pyrrolecarboxaldehyde and lithiated N,N,N′-trimethylethylenediamine gave metalation solely on the N-methyl group. When we tried to extend this novel directed lithiation to N-methylindole-2-carboxaldehyde, lithiation-methylation of the α-amino alkoxide prepared from N,N,N′-trimethylethylenediamine gave a mixture of 1-ethylindole-2-carboxaldehyde and 1,3-dimethylindole-2-carboxaldehyde in a ratio of 42/58. We were unable to find conditions to improve the ratio of products in favor of N-methyl substitution.[3] It appeared that a removable blocking group at C-3 was needed to effect a synthetically useful N-methyl substitution of N-methylindole-2-carboxaldehydes. We report herein our progress toward developing this potentially useful directed lithiation methodology.

Initially we explored the use of a trimethylsilyl group to block the C-3 position. Treatment of N-methylindole-2-carboxaldehyde (1) with lithium N-methylpiperizide (2) followed by n-BuLi gave the dianion 3 in situ.[3] Addition of TMSCl and aqueous workup gave only a 17% yield of the desired aldehyde 4. In an effort to find a more efficient method to prepare 4, we brominated 1 to give 3-bromo-1-methylindole-2-carboxaldehyde 5 in 90% yield.[4] In situ protection as an α-amino alkoxide[5], followed by lithium-halogen exchange and silylation gave a disappointing 33% yield of 4. Treatment of 4 with lithiated N,N,N′-trimethylethylenediamine, n-butyllithium, and methyl iodide provided a 62% yield of the N-methyl alkylated product 6. This result demonstrated that the C-3 blocking group strategy is effective, but the low yield obtained for the preparation of 4 makes the use of a C-3 TMS group unattractive.[6]



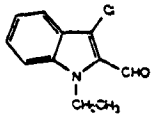
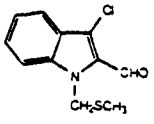
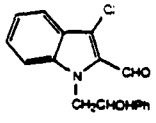
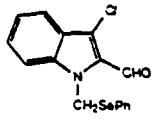
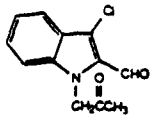
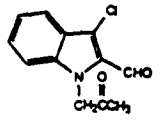
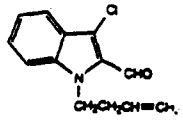
4338

Since an aryl chloride is not prone to lithium-chloride exchange[7], we explored the possibility of using a chlorine as a C-3 blocking group. Chlorination of N-methylindole (7) with NCS in THF gave an 84% yield of 3-chloro-1-methylindole (8) (bp 92°C/0.5 mm). Lithiation of 8 with n-BuLi and addition of DMF provided the desired aldehyde 9 in 92% yield (mp 88-89°C). In situ α-amino alkoxide formation



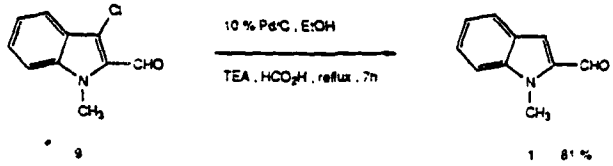
and lithiation with n-BuLi (3 equiv, THF, 3h at -42°C, 15h at -20°C) gives dianion 10, which on reaction with electrophiles and aqueous workup provides N-methyl substituted indoles 11 as shown in the Table.

Table. Reactions of Dianion **10** with Electrophiles

Entry [a]	Electrophile	Product [e]	yield,[f] %	mp,[g] °C
a	MeI		94	58-59.5
b	MeSSMe		85	95-97
c	PhCHO		84	130.5-132.5
d	PhSeSePh		73	119.5-120.5
e	EtOAc[b]		55	152.5-154
f	Ac_2O[c]		43	152.5-154
g	Br[d]		75	30-31

[a] Reactions were performed on a 1.5 mmol scale in 10 ml of THF. Unless indicated, electrophile (4-6 equiv) was added at -78°C and allowed to warm to room temperature. The workup consisted of pouring the reaction mixture into cold water followed by extraction with ether. [b] The dianion was added to EtOAc (50 mL). [c] Inverse addition and 30 mmol of Ac_2O were used. [d] A large excess of electrophile (18 mmol) was utilized. [e] All products gave the expected IR and NMR spectra and elemental analysis. [f] Yields are for isolated, pure material obtained from radial PLC (silica gel, EtOAc/hexanes). [g] Melting points are for material recrystallized from hexanes or EtOAc hexanes.

To demonstrate that the C-3 chloro blocking group could be removed if required, we treated 3-chloro-1-methylindole-2-carboxaldehyde (9) with 10% Pd/C, EtOH, Et_3N, and formic acid to give an 81% yield of N-methylindole-2-carboxaldehyde (1).[8]



9 1 81 %

Acknowledgement

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References and Notes.

1. Address correspondence to this author at Department of Chemistry, North Carolina State University, Raleigh, NC 27695-8204.

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Lithiation of Methoxypyridines Directed by α-Amino Alkoxides

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The addition of methoxypyridinecarboxaldehydes to certain lithium dialkylamides gave α-amino alkoxides in situ that were ring-lithiated with alkyllithium bases. Alkylation and hydrolysis on workup provided ring-substituted methoxypyridinecarboxaldehydes via a one-pot reaction. The one-pot methylation of isomeric methoxypyridinecarboxaldehydes was examined. The regioselectivity of the lithiation–methylation was dependent on the aldehyde, the amine component of the α-amino alkoxide, and the metalation conditions. When lithiated *N,N,N'*-trimethylethylenediamine was used as the amine component of the α-amino alkoxide, methylation generally occurred ortho to the aldehyde function. The analogous reactions using lithium *N*-methylpiperazide as the amine component gave substitution next to the methoxy group. Several new methylated methoxypyridinecarboxaldehydes were prepared in a regioselective manner by using this one-pot procedure.

Despite the susceptibility of pyridines to nucleophilic attack by alkyllithium bases, directed lithiation has recently evolved as a useful method for regioselective substitution of the pyridine ring.[2] A variety of ortho-directing groups have been utilized to effect regiospecific metalation into an ortho position of pyridine. Directing groups include $CONR_2$,[3] CONHR,[3] oxazolines,[4] pivaloylamino,[5] $OCONEt_2$,[6] OR,[7] OCH_2OR,[8] halogen,[9] and SO_2NR_2.[10] Carbonyl-derived directing groups prepared from pyridinecarboxaldehydes have not been investigated. Due to a need for substituted methoxypyridinecarboxaldehydes in our laboratories, we decided to study the lithiation of methoxypyridines directed by α-amino alkoxides.

The addition of aromatic aldehydes to certain lithium dialkylamides gives α-amino alkoxides that can be ring-lithiated with alkyllithiums. Alkylation and hydrolysis on workup provides ortho-substituted aryl aldehydes via a one-pot reaction. This methodology works well for the one-pot substitution of benzaldehyde derivatives[11] as well

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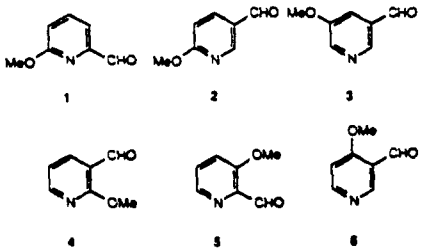
as for heterocyclic aromatic aldehydes,[12] i.e., various thiophene-, furan-, pyrrole-, and indolecarboxaldehydes. The directing power of an α-amino alkoxide group can be altered by simply varying the amine component, allowing regioselective control during the lithiation of a diactivated aromatic ring.[11,12] Since an α-amino alkoxide's ortho-directing ability is due to a chelation effect and not a strong inductive effect, it was not clear that the regioselective control inherent in this methodology could be utilized in the pyridine series, as competing nucleophilic attack of the alkyllithium base on the pyridine nucleus may occur. In this report we describe our studies on the directed lithiation of various α-amino alkoxides prepared in situ from methoxypyridinecarboxaldehydes.

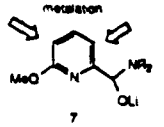
Results and Discussion

Synthesis of Methoxypyridinecarboxaldehydes. The required methoxypyridinecarboxaldehydes were prepared in two steps from commercially available dibromopyridines or from methoxypyridines in one step via directed lithiation. Treatment of 2,6-dibromopyridine with sodium methoxide in methanol gave 6-bromo-2-methoxypyridine, which on lithium–halogen exchange and formylation with dimethylformamide (DMF) provided 6-methoxy-2-pyridinecarboxaldehyde (1). In an analogous

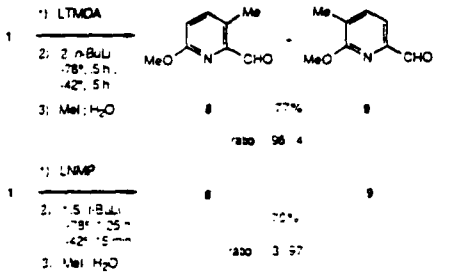


fashion, 2,5-dibromopyridine was converted to 5-bromo-2-methoxypyridine, which was treated with *n*-butyllithium and DMF to give 6-methoxy-3-pyridinecarboxaldehyde (2). Monosubstitution of 3,5-dibromopyridine was achieved using sodium methoxide in DMF. Subsequent lithium–halogen exchange at −100 °C and formylation gave 5-methoxy-3-pyridinecarboxaldehyde (3) in good yield. Directed lithiation of 2-, 3-, and 4-methoxypyridine using mesityllithium as the base and subsequent formylation with DMF gave 2-methoxy-3-pyridinecarboxaldehyde (4), 3-methoxy-2-pyridinecarboxaldehyde (5), and 4-methoxy-3-pyridinecarboxaldehyde (6), respectively.[7c]

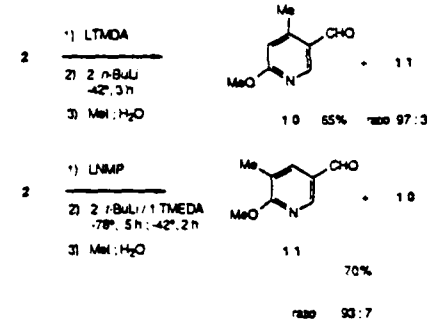
Directed Lithiation Studies. The α-amino alkoxides were prepared by addition of the pyridinecarboxaldehyde to lithiated *N,N,N'*-trimethylethylenediamine (LTMDA) or lithium *N*-methylpiperazide (LNMP) in tetrahydrofuran (THF) at −78 °C. The α-amino alkoxide 7, formed



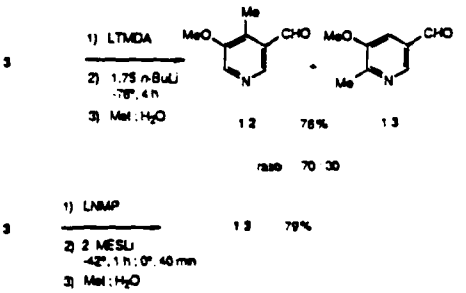
in situ from pyridinecarboxaldehyde 1, has two sites, C-3 and C-5, where lithiation may occur. We anticipated that regioselective metalation could be achieved at either position by varying the amine component of the α-amino alkoxide. Reaction of 1 with LTMDA followed by lithiation with *n*-butyllithium and methylation gave a 77% yield of aldehydes 8 and 9 in a ratio of 96:4. The regioselectivity can be reversed by changing the amine component. Treatment of 1 with LNMP, *tert*-butyllithium, and methyl iodide gave a 70% yield of 8 and 9 in a ratio of 3:97.



We next investigated the methylation of pyridinecarboxaldehyde 2. The α-amino alkoxide formed from 2 and LTMDA was lithiated and methylated to give the C-4 and C-5 substituted pyridines 10 and 11 in a ratio of 97:3. The analogous reaction of 2 with LNMP and *tert*-butyllithium gave mainly C-5 methylated pyridine 11. Lithiation–methylation at C-2 was not observed.



The metalation of pyridinecarboxaldehyde 3 using LTMDA and *n*-butyllithium led to a 70:30 mixture of C-4 and C-6 methylated pyridines 12 and 13. We were unable to find conditions to improve the ratio of products in favor of C-4 substitution. A highly regioselective C-6 methylation was obtained, however, by using LNMP as the amine component and mesityllithium[13] (MESLi) as the base. In this manner pyridinecarboxaldehyde 13 was isolated as the sole product in 79% yield. Substitution at C-4 occurred when pyridinecarboxaldehyde 4 was treated with LTMDA,



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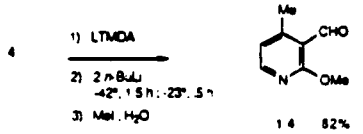
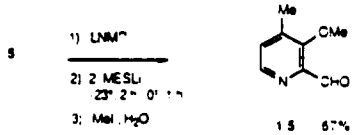
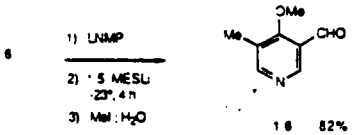
n-butyllithium, and methyl iodide. An 82% yield of substituted pyridine 14 was isolated as the sole product.



14 82%



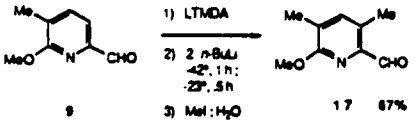
15 67%



16 82%

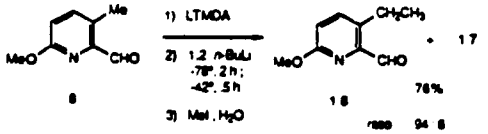
Mesityllithium was effective at lithiating the C-4 position of the α-amino alkoxide derived from pyridine 5 and LNMP. Methylation and workup gave 3-methoxy-4-methyl-2-pyridinecarboxaldehyde (15) in 67% yield. Regiospecific substitution of pyridinecarboxaldehyde 6 at C-5 was achieved using LNMP and mesityllithium. We were unable to induce metalation at C-2 by using LTMDA as the amine component.

To determine if methylated methoxypyridinecarboxaldehydes could be further substituted using this methodology, we prepared an α-amino alkoxide from pyridine 9 and LTMDA. Lithiation with *n*-butyllithium and methylation gave a 67% yield of the tetrasubstituted pyridine 17.



9 17 67%

The analogous reaction of the α-amino alkoxide derived from pyridinecarboxaldehyde 8 and LTMDA gave alkylation mainly on the C-3 methyl group. A mixture of products 18 and 17 were obtained in a ratio of 94:6, demonstrating the α-amino alkoxide's ability to direct lateral metalation as well as ring lithiation.



8 18 76%

ratio 94:6

Conclusion

Lithiation of pyridines directed by α-amino alkoxides has been shown to be effective for the substitution of various methoxypyridinecarboxaldehydes. The procedure utilizes a convenient one-pot reaction, which has an obvious advantage over the more classical multistep ortho-directing methodologies. A high degree of regioselective control is achieved in many cases by simply changing the amine component of the α-amino alkoxide. The lack of success in obtaining an α-amino alkoxide directed lithiation at C-2 is interesting. A C-3 methoxy or ethoxy group directs lithiation to C-2,[7] while chelating C-3 ortho-directing groups such as $-OCH_2OMe$ and $-OCONR_2$ effect metalation at C-4.[6,8] Because the C–N bonds of a pyridine ring are shorter than the ring C–C bonds, some of the bond angles are distorted from 120°. In pyridine, for example, the C-4, C-3, H-3 bond angle is 121.36°, whereas the C-2, C-3, H-3 angle is 120.11°.[14] This small distortion might affect the angle of intramolecular attack onto the C-2 or C-4 hydrogen by the alkyllithium base, which is chelated to a C-3 directing group (i.e., 19 and 20). This may cause C-2 lithiation via complex 19 to be less favorable than the analogous attack at the C-4 hydrogen via complex 20.[15] Further study is needed to support this hypothesis.

19 20

The methodology presented in this paper is useful for the regioselective preparation of substituted alkoxypyridines, which are valuable precursors to pyridones and pyridinols,[16] as well as synthetically useful dihydropyridones.[17]

Experimental Section

All reactions were performed in oven-dried glassware under a N_2 atmosphere. Tetrahydrofuran (THF) was dried by distillation from sodium benzophenone ketyl prior to use. *N,N,N'*-Trimethylethylenediamine, *N*-methylpiperazine, and dimethylformamide (DMF) were distilled from calcium hydride and stored over 3-Å molecular sieves under N_2. Other solvents and reagents from commercial sources were generally stored over 3-Å molecular sieves and used without further purification.

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were recorded on a Varian XL-300 or an IBM AF 80 spectrometer. Radial preparative-layer chromatography (Radial PLC) was carried out by using a Chromatotron (Harris Associates, Palo Alto, CA). Elemental analyses were carried out by M-H-W laboratories, Phoenix, AZ. Infrared spectra were recorded on a Perkin-Elmer Model 7500 spectrometer. Gas–liquid chromatography (GC) was performed on a Hewlett-Packard Model 5880A gas chromatograph equipped with a 30 m × 0.25 mm FSOT column packed with OV-101. The 2,4-dinitrophenylhydrazones were prepared by using a modified method published by Behforouz.[18]

6-Bromo-2-methoxypyridine. 6-Bromo-2-methoxypyridine was prepared by a variation of the literature procedure.[19] To

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a stirred solution of 2,6-dibromopyridine (17.42 g, 74 mmol) in anhydrous MeOH (50 mL) was added NaOMe (28.6 mL of 25% NaOMe in MeOH, 125 mmol). The mixture was refluxed for 25 h and then poured into cold 5% $NaHCO_3$ (50 mL). The mixture was extracted with ether (3 × 30 mL), and the organic layer was concentrated. Ether (50 mL) was added to the remaining liquid, and the mixture was washed with brine (40 mL). The organic layer was dried (K_2CO_3) and concentrated, and the residue was Kugelrohr distilled (85–95 °C/15 mmHg) to give 10.11 g (73%) of 6-bromo-2-methoxypyridine as a clear liquid: IR (neat) 2953, 1596, 1582, 1558, 1472, 1413, 1298, 1022, 857 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 3.89 (s, 3 H), 6.63 (d, 1 H, J = 8 Hz), 6.99 (d, 1 H, J = 8 Hz), 7.37 (t, 1 H, J = 8 Hz); ^{13}C NMR (20 MHz, $CDCl_3$) δ 54.3, 109.5, 120.3, 138.8, 140.5, 163.9.

6-Methoxy-2-pyridinecarboxaldehyde (1). To a stirred solution of 6-bromo-2-methoxypyridine (1.01 g, 5.40 mmol) in THF (20 mL) at −78 °C was added *n*-BuLi (5.61 mmol). After 1 h, DMF (0.472 g, 6.09 mmol) was added, and the mixture was allowed to stir for 30 min at −78 °C. The cold mixture was poured directly into a stirred aqueous solution of 5% $NaHCO_3$ (50 mL) and extracted with ether (3 × 25 mL). The combined organic extracts were washed with brine and dried (K_2CO_3). The mixture was filtered and concentrated. The crude product was purified by radial PLC (silica gel, 5% EtOAc–hexanes) followed by Kugelrohr distillation (bp 99–105 °C/20 mmHg (lit.[20] bp 103–104 °C/20 mmHg)] to give 574 mg (78%) of 1 as an oil: IR (neat) 2955, 2929, 1719, 1704, 1600, 1474, 1333, 1276 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.03 (s, 3 H), 6.98 (d, 1 H, J = 8.4 Hz), 7.57 (d, 1 H, J = 7.2 Hz), 7.74 (dd, 1 H, J = 8.4, 7.2 Hz), 9.97 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.15, 115.01, 115.92, 138.71, 150.08, 164.02, 192.50; DNP mp 216–219 °C.

5-Bromo-2-methoxypyridine. 5-Bromo-2-methoxypyridine was prepared by a variation of the literature procedure.[19] To a stirred solution of 2,5-dibromopyridine (10.94 g, 46 mmol) in anhydrous MeOH (25 mL) was added NaOMe (50 mL of 25% NaOMe in MeOH, 210 mmol). The mixture was refluxed for 7 h and then poured into cold stirred 5% $NaHCO_3$ (75 mL). The mixture was extracted with ether (4 × 30 mL) and washed with brine (3 × 30 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated. The crude product was purified by Kugelrohr distillation (65–70 °C/3.5 mmHg) to give 7.96 g (92%) of a clear liquid: IR (neat) 2984, 2946, 1572, 1451, 1339, 1293, 1262, 1009, 799 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ 3.88 (s, 3 H), 6.59 (d, 1 H, J = 8.8 Hz), 7.56 (d, 1 H, J = 8.8 Hz), 8.18 (s, 1 H); ^{13}C NMR (20 MHz, $CDCl_3$) δ 53.76, 111.79, 112.69, 141.00, 147.70, 163.10.

6-Methoxy-3-pyridinecarboxaldehyde (2). To a stirred solution of 5-bromo-2-methoxypyridine (1.63 g, 8.69 mmol) in THF (25 mL) at −78 °C was added *n*-BuLi (9.10 mmol). After 1 h, DMF (1.27 g, 17.4 mmol) was added and stirring was continued for 30 min at −78 °C. The cold mixture was poured directly into a stirred aqueous solution of 5% $NaHCO_3$ (50 mL) and extracted with ether (3 × 25 mL). The combined organic extracts were washed with brine and dried (K_2CO_3). The mixture was filtered and concentrated to give a yellow solid (1.21 g). The crude product was recrystallized from hexanes to give 1.00 g (84%) of 2 as a light yellow solid: mp 50.5–51.5 °C (hexanes); IR (neat) 2993, 2952, 2837, 1698, 1605, 1568, 1495, 1363, 1291, 1222, 1016, 838 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.04 (s, 3 H), 6.85 (d, 1 H, J = 9 Hz), 8.07 (d, 1 H, J = 9 Hz), 8.64 (s, 1 H), 9.96 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.07, 111.84, 126.50, 137.20, 152.63, 167.47, 189.26.

5-Bromo-3-methoxypyridine. Sodium methoxide in MeOH (20.5 mL, 95 mmol) was stirred under reduced pressure (15 mmHg) at 65 °C for 30 min. The remaining solid was placed under a N_2 atmosphere and dissolved in DMF (60 mL). Solid 3,5-dibromopyridine (15 g, 63 mmol) was added, and the mixture was stirred at 63–68 °C. After 4 h, additional NaOMe/MeOH solution (7 mL, 32 mmol) was added. The reaction mixture was allowed to stir at 63–68 °C for 12 h, then poured into H_2O (80 mL), and extracted with ether (6 × 20 mL). The combined organic extracts were washed with brine (50 mL) and dried ($MgSO_4$). The mixture was filtered and concentrated to give a yellow solid. The crude product was purified by radial PLC (silica gel, 10% EtOAc–hexanes) followed by recrystallization (hexanes) to give 5.75 g (78%) of 5-bromo-3-methoxypyridine as a light yellow solid. The residue from the mother liquid was purified by radial PLC (silica gel, 5% EtOAc–hexanes) to give an additional 1.27 g (11%) of product: IR (neat) 3045, 3010, 2940, 1577, 1557, 1457, 1418, 1313, 1266, 1009, 858 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.86 (s, 3 H), 7.36 (s, 1 H), 8.25 (s, 1 H), 8.29 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.45, 120.02, 122.78, 135.85, 142.46, 155.64; mp 34–35 °C (hexanes). Anal. Calcd for C_6H_6BrNO: C, 38.33; H, 3.22; N, 7.45. Found: C, 38.18; H, 3.26; N, 7.28.

5-Methoxy-3-pyridinecarboxaldehyde (3). To a stirred solution of 5-bromo-3-methoxypyridine (4.09 g, 22.9 mmol) in THF (100 mL) at −100 °C was added *n*-BuLi (25.2 mmol) over 10 min. The solution was allowed to stir for an additional 20 min at −100 °C, and then DMF (2.3 mL, 29.8 mmol) was added. The mixture was stirred for 30 min, allowing the temperature to slowly warm to −60 °C. The cold mixture was then poured directly into brine (100 mL) and extracted with ether (3 × 40 mL). The combined organic extracts were dried (K_2CO_3), filtered, and concentrated. The crude product was purified by radial PLC (silica gel, 10% EtOAc–hexanes) to give 2.19 g (73%) of 3 as a light yellow solid: IR (neat) 2943, 2844, 1708, 1693, 1585, 1473, 1429, 1321, 1282, 1253, 1175 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.93 (s, 3 H), 7.82 (s, 1 H), 8.56 (s, 1 H), 8.67 (s, 1 H), 10.11 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 55.59, 116.16, 131.86, 144.53, 144.86, 156.00, 199.51; mp 33–34 °C (hexanes CCl_4). Anal. Calcd for $C_7H_7NO_2$: C, 61.31; H, 5.15; N, 10.21. Found: C, 61.17; H, 5.22; N, 10.35.

2-Methoxy-3-pyridinecarboxaldehyde (4). To a stirred solution of *tert*-butyllithium (8.19 mmol, 4.96 mL of a 1.65 M solution in pentane) in 20 mL of THF at −78 °C was added dropwise 2-bromomesitylene (0.60 mL, 3.9 mmol). After this stirred for 1 h, 2-methoxypyridine (0.32 mL, 3.0 mmol) was added dropwise, and the mixture was warmed to 0 °C and stirred for 1 h. The homogeneous solution was warmed to room temperature and stirred for an additional 1 h. This solution was cooled to −78 °C and *N,N*-dimethylformamide (0.35 mL, 4.5 mmol) was added in one portion and stirred for 1 h. Acetic acid (6.0 mmol, 0.35 mL) was added, and the solution was warmed to room temperature. Saturated aqueous $NaHCO_3$ (20 mL) was added, and the mixture was extracted with three 20-mL portions of diethyl ether. The combined organic layers were washed with brine, dried over $MgSO_4$ for 15 min, filtered through Celite, and concentrated in vacuo. The crude product was purified by radial PLC (silica gel, EtOAc–hexanes) to give 0.257 g (63%) of 4 as an oil: ^1H NMR (300 MHz, $CDCl_3$) δ 10.38 (s, 1 H), 8.39 (dd, 1 H, J = 5.0 and 2.0 Hz), 8.12 (dd, 1 H, J = 8.0 and 2.0 Hz), 7.02 (m, 1 H, J = 8.0, 5.0 and 1.0 Hz), 4.08 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.1, 164.4, 152.8, 137.5, 118.8, 117.2, 53.8; IR (neat) 3004, 2964, 2869, 1684, 1654, 1584, 1474, 1422, 1394, 1114, 1269, 1204, 1115, 1034, 883, 824, 794, 692 cm^{-1}. Anal. Calcd for $C_7H_7O_2N$: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.40; H, 5.14; N, 10.28.

3-Methoxy-2-pyridinecarboxaldehyde (5). To a stirred solution of *tert*-butyllithium (8.01 mmol, 4.40 mL of a 1.82 M solution in pentane) in 20 mL of THF at −78 °C was added dropwise 2-bromomesitylene (0.60 mL, 3.9 mmol). After this stirred for 1 h, 3 methoxypyridine (0.30 mL, 3.0 mmol) was added dropwise. The solution was warmed to −23 °C, stirred for 3 h, and then cooled again to −78 °C. *N,N*-Dimethylformamide (0.35 mL, 4.5 mmol) was added, and the resulting solution was stirred at −78 °C for 1 h. The reaction was quenched at −78 °C with 20 mL of brine and extracted with ether. The combined organic layers were washed with brine, dried over K_2CO_3, and concentrated. The crude product was purified by radial PLC (silica gel, EtOAc/EtOH) to give 0.350 g (85%) of 5, which was subsequently recrystallized (benzene/cyclohexane) to give a white solid: mp 67–68 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 10.35 (s, 1 H), 8.41 (d, 1 H, J = 4.0 Hz), 7.55–7.35 (m, 2 H), 3.98 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 190.3, 157.8, 141.9, 140.9, 128.7, 120.1, 55.7; IR (KBr) 3077, 2991, 2960, 2876, 1694, 1577, 1470, 1432, 1395, 1297, 1255, 1189, 1158, 1114, 1066, 1007, 925, 857, 807, 738, 658 cm^{-1}. Anal. Calcd for $C_7H_7NO_2$: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.36; H, 5.16; N, 10.24.

4-Methoxy-3-pyridinecarboxaldehyde (6). To a stirred solution of *tert*-butyllithium (8.01 mmol, 4.40 mL of a 1.82 M solution in pentane) in 20 mL of THF at −78 °C was added dropwise 2-bromomesitylene (0.60 mL, 3.9 mmol). After this

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stirred for 1 h, 4-methoxypyridine (0.30 mL, 3.0 mmol) was added dropwise. This solution was warmed to −23 °C, stirred for 3 h, and then cooled again to −78 °C. *N,N*-Dimethylformamide (0.35 mL, 4.5 mmol) was added, and the solution was stirred at −78 °C for 1 h. The reaction was quenched at −78 °C with 20 mL of brine and extracted with ether. The combined organic layers were dried over K_2CO_3. Concentration gave the crude product which was purified by radial PLC (silica gel, EtOAc, EtOH) to give 0.317 g (77%) of **6** as a solid, which was further purified for elemental analysis by recrystallization (CCl_4) to give white crystals: mp 65.5–67.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.46 (s, 1 H), 8.90 (s, 1 H), 8.65 (d, 1 H, J = 6.0 Hz), 6.95 (d, 1 H, J = 6.0 Hz), 4.01 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.6, 166.6, 155.9, 150.7, 120.4, 107.1, 55.8; IR (KBr) 3105, 3079, 2985, 2951, 2886, 2849, 2770, 1679, 1586, 1500, 1488, 1439, 1396, 1314, 1278, 1205, 1170, 1061, 1018, 932, 841, 822, 745, 660 cm^{-1}. Anal. Calcd for $C_7H_7NO_2$: C, 61.31; H, 5.14; N, 10.21. Found: C, 61.11; H, 5.09; N, 10.01.

General Procedure for Methylation of Methoxypyridinecarboxaldehydes. To a stirred solution of the secondary amine (*N,N,N'*-trimethylethylenediamine or *N*-methylpiperazine, 2.4 mmol) in 10 mL of THF was added *n*-BuLi (2.2 mmol) at −78 °C. After 15 min, the appropriate methoxypyridinecarboxaldehyde (2 mmol) was added, and the mixture was stirred at −78 °C for 15 min. The indicated base was added and stirred at the indicated temperatures and times. Methyl iodide (10 mmol) was added at −78 °C, and the mixture was allowed to come to room temperature (30 min). The solution was poured into vigorously stirred cold brine (25 mL) and extracted with ether (3 × 25 mL). The organic extracts were dried (K_2CO_3) and concentrated. The crude products were purified by radial PLC (EtOAc-hexanes).

Spectral Data. 6-Methoxy-3-methyl-2-pyridinecarboxaldehyde (8): IR (neat) 2945, 2820, 1711, 1606, 1483, 1341, 1272, 796 cm^{-1}; ^{1}H NMR (60 MHz, $CDCl_3$) δ 2.55 (s, 3 H), 3.99 (s, 3 H), 6.83 (d, 1 H, J = 8.4 Hz), 7.47 (d, 1 H, J = 8.4 Hz), 10.06 (s, 1 H); ^{13}C NMR (20 MHz, $CDCl_3$) δ 18.03, 53.87, 115.57, 129.14, 143.28, 146.92, 162.79, 195.38; mp 52.5–54 °C (hexanes). Anal. Calcd for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.53; H, 6.08; N, 9.12.

6-Methoxy-5-methyl-2-pyridinecarboxaldehyde (9): IR (KBr) 3011, 2955, 2841, 1695, 1597, 1463, 1277, 1243, 1027 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.28 (s, 3 H), 4.05 (s, 3 H), 7.49 (d, 1 H, J = 7.2 Hz), 7.54 (d, 1 H, J = 7.2 Hz), 9.94 (s, 1 H); ^{13}C NMR (20 MHz, $CDCl_3$) δ 16.50, 53.83, 116.04, 127.65, 138.96, 148.82, 162.96, 193.06; DNP mp 222–224 °C (EtOH). Anal. Calcd for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.21; H, 5.83; N, 9.12.

6-Methoxy-4-methyl-3-pyridinecarboxaldehyde (10): IR (KBr) 3028, 1695, 1613, 1554, 1446, 1362, 1255, 1147 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.61 (s, 3 H), 4.01 (s, 3 H), 6.60 (s, 1 H), 8.51 (s, 1 H), 10.07 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 19.85, 53.85, 112.90, 125.38, 151.42, 155.25, 166.60, 190.58; mp 91–92 °C (hexanes). Anal. Calcd for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.31; H, 6.02; N, 9.13.

6-Methoxy-5-methyl-3-pyridinecarboxaldehyde (11): IR (neat) 2989, 2953, 1694, 1605, 1484, 1408, 1381, 1268, 1141, 1016 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.24 (s, 3 H), 4.06 (s, 3 H), 7.88 (s, 1 H), 8.47 (s, 1 H), 9.93 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.79, 54.30, 122.10, 126.73, 136.35, 150.39, 166.19, 189.81; mp 56–56.5 °C (hexanes). Anal. Calcd for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.69; H, 5.94; N, 9.30.

5-Methoxy-4-methyl-3-pyridinecarboxaldehyde (12): IR (KBr) 2960, 1692, 1565, 1489, 1422, 1294, 1270, 1011, 909, 713 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.56 (s, 3 H), 3.98 (s, 3 H), 8.37 (s, 1 H), 8.62 (s, 1 H), 10.33 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 10.51, 56.50, 129.85, 136.45, 137.37, 146.04, 154.18, 191.82; mp 70.5–71.5 °C (hexanes). Anal. Calcd for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.66; H, 6.06; N, 9.27.

5-Methoxy-6-methyl-3-pyridinecarboxaldehyde (13): IR (KBr) 2978, 2860, 1689, 1595, 1392, 1152 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.57 (s, 3 H), 3.91 (s, 3 H), 7.51 (s, 1 H), 8.52 (s, 1 H), 10.05 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.10, 55.40, 112.32, 130.81, 144.56, 154.27, 156.30, 190.58; mp 75.5–76.5 °C (hexanes). Anal. Calcd for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.38; H, 6.02; N, 9.19.

2-Methoxy-4-methyl-3-pyridinecarboxaldehyde (14): IR (neat) 2988, 2953, 2869, 1686, 1590, 1564, 1476, 1377, 1302, 1083 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.59 (s, 3 H), 4.04 (s, 3 H), 6.77 (d, 1 H, J = 5.1 Hz), 8.16 (d, 1 H, J = 5.1 Hz), 10.54 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.79, 53.84, 117.16, 120.87, 150.79, 152.42, 165.78, 191.47; mp 29.5–30 °C (hexanes). Anal. Calcd for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.68; H, 5.89; N, 9.15.

3-Methoxy-4-methyl-2-pyridinecarboxaldehyde (15): IR (neat) 2933, 2832, 1715, 1585, 1561, 1473, 1263, 1224, 1002 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.30 (s, 3 H), 3.84 (s, 3 H), 7.28 (d, 1 H, J = 4.8 Hz), 8.35 (d, 1 H, J = 4.8 Hz), 10.15 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 15.19, 62.34, 130.09, 142.80, 144.78, 145.24, 157.33, 191.04; mp 42.5–44 °C (hexanes). Anal. Calcd for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.76; H, 6.00; N, 9.18.

4-Methoxy-5-methyl-3-pyridinecarboxaldehyde (16): IR (KBr) 2897, 1703, 1678, 1574, 1480, 1404, 1269, 1228, 1153, 996, 821 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.34 (s, 3 H), 4.01 (s, 3 H), 8.57 (s, 1 H), 8.83 (s, 1 H), 10.38 (s, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.09, 62.61, 123.84, 128.88, 150.32, 157.09, 166.77, 189.07; mp 64.5–66 °C (hexanes). Anal. Calcd for $C_8H_9NO_2$: C, 63.57; H, 6.00; N, 9.27. Found: C, 63.51; H, 6.04; N, 9.29.

3,5-Dimethyl-6-methoxy-2-pyridinecarboxaldehyde (17): IR (KBr) 2961, 2924, 2832, 1696, 1561, 1478, 1416, 1356, 1277, 1117 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ 2.21 (s, 3 H), 2.50 (s, 3 H), 4.00 (s, 3 H), 7.23 (s, 1 H), 10.01 (s, 1 H); ^{13}C NMR (20 MHz, $CDCl_3$) δ 16.09, 17.74, 53.66, 125.38, 129.17, 142.76, 144.76, 160.84, 194.92; mp 84.5–85.5 °C (hexanes). Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.21; H, 6.79; N, 8.35.

3-Ethyl-6-methoxy-2-pyridinecarboxaldehyde (18): IR (neat) 2975, 1711, 1603, 1482, 1337, 1271, 1030 cm^{-1}; ^{1}H NMR (80 MHz, $CDCl_3$) δ 1.19 (t, 3 H, J = 7.5 Hz), 3.01 (q, 2 H, J = 7.5 Hz), 3.99 (s, 3 H), 6.86 (d, 1 H, J = 8.4 Hz), 7.53 (d, 1 H, J = 8.4 Hz), 10.06 (s, 1 H); ^{13}C NMR (20 MHz, $CDCl_3$) δ 15.58, 24.24, 53.86, 115.84, 135.54, 141.85, 146.50, 162.70, 195.12; DNP mp 180–184 °C (EtOH). Anal. Calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.45; H, 6.66, N, 8.57.

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Doctor of Philosophy

Dissertation: New Synthetic Methods

A. Lithiation of Methoxy Pyridines and N-Methyl Indoles Directed by α-Amino Alkoxides.
B. Synthetic Methods Using N-Acyliminium Ions and 1-Acylpyridinium salts.

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Publications:

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