NIOBIUM TRICHLORIDE-MEDIATED COUPLING REACTIONS OF IMINES WITH ELECTROPHILES

by

Darren John McMurtrie

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APPROVAL

Name: Darren John McMurtrie

Degree: M.Sc. Chemistry

Title of Thesis: Niobium Trichloride-Mediated Coupling Reactions of Imines with Electrophiles

Examining Committee:

Chairperson: Dr. G.R. Agnes, Associate Professor

Dr. P.D. Wilson, Assistant Professor
(Senior Supervisor)

Dr. A.J. Bennet, Professor
(Committee Member)

Dr. J.A. Clyburne, Assistant Professor
(Committee Member)

Dr. V.E. Williams, Assistant Professor
(Internal Examiner)

Date Approved: 1/August/2003

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ABSTRACT

The cross-coupling reaction of imines with ketone and aldehyde electrophiles, mediated by a niobium trichloride complex ($NbCl_3$.DME), is known to afford predominantly *syn* 1,2-amino alcohols. The intermediate in these reactions is thought to be a metallaaziridine that functions as a *C,N*-dianion. The more reactive carbon centre of the dianion reacts with electrophiles to form new carbon-carbon bonds. Our research objective was to prepare a variety of small, functionalized molecules through the cross-coupling of imines with a variety of electrophiles. After screening many different electrophiles as reaction candidates, epoxides and alkyl glyoxylates (or pyruvates) were used to prepare 1,2-amino alcohols and β-amino-α-hydroxy alkyl esters, respectively.

Three 1,2-amino alcohols were prepared with good diastereoselectivities through the $NbCl_3$.DME-mediated coupling reactions of imines with epoxides. These results have been rationalized in terms of epoxide rearrangement, upon coordination to the metallaaziridine, that produces a metal coordinated aldehyde intermediate that in turn reacts to afford the observed reaction products.

Five β-amino-α-hydroxy methyl esters were synthesized using the $NbCl_3$.DME-mediated coupling reaction of a variety of imines with methyl glyoxylate. These reactions allowed for the formation of a new carbon-carbon bond and two stereogenic centres as well as the installation of three functional groups. These reactions showed notable chemoselectivity as the metallaaziridine complexes reacted only at the aldehydic centre of methyl glyoxylate. One of the products of these reactions was used to prepare the side chain of Taxol. In a similar fashion, two β-amino-α-hydroxy *tert*-butyl esters

were synthesized using the $NbCl_3$.DME-mediated coupling reaction of two imines with *tert*-butyl glyoxylate. As anticipated, increasing the steric bulk of the glyoxylate electrophile allowed for improved diastereoselection in these reactions.

A series of fluorinated derivatives of the side chain of Taxol were prepared, using methyl 3,3,3-trifluoropyruvate as an electrophile, in an effort to further examine the synthetic potential of this chemical reaction. The metallaaziridine complexes reacted at the carbonyl centre adjacent to the electron-withdrawing trifluoromethyl substituent to afford the corresponding β-amino-α-hydroxy alkyl ester products. Impressive levels of diastereoselectivity were observed with this particular pyruvate electrophile.

DEDICATION

My graduate research is dedicated to my good friend and mentor, Cory Jay Owen (1976-2002). You were always there for me and I think of you every day of my life. Vicariously, I will carry on for both of us.

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I am greatly indebted to my supervisor, Dr. Peter D. Wilson, for providing me with a stimulating research project. I thank him for providing invaluable guidance on this work, financial support, and for allowing me to gain independence in the lab. I take great pride in being the first student to graduate from Dr. Wilson's research group. Such pride will follow me as I further my career in organic chemistry.

I also appreciate the assistance from Dr. Jason A. Clyburne with regards to the chemical literature and development of the transition metal chemistry described herein. Dr. Clyburne's enthusiasm, encouragement, and research group were of valuable assistance to our project.

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LIST OF ABBREVIATIONS AND SYMBOLS

AcOH	acetic acid
Anal	analysis (elemental)
Å	Ångstrom
aq.	aqueous
Ar	aromatic
amu	atomic mass units
C_6H_6	benzene
BzCl	benzoyl chloride
Bn	benzyl
br	broad
t-BuOH	*tert*-butanol
t-Bu	*tert*-butyl
Calcd	calculated
^{13}C NMR	carbon-13 nuclear magnetic resonance spectroscopy
C.I.	chemical ionization
δ	chemical shift (NMR)
COSY	^{1}H-^{1}H correlation spectroscopy
J	coupling constant
CD_3COCD_3	deuterated acetone (acetone-d_6)
C_6D_6	deuterated benzene (benzene-d_6)
$CDCl_3$	deuterated chloroform (chloroform-d)
NaOD	deuterated sodium hydroxide

ds	diastereoselectivity
DCM	dichloromethane
Et_2O	diethyl ether
DME	1,2-dimethoxyethane
DMAP	4-(*N*,*N*-dimethylamino)pyridine
d	doublet
dd	doublet of doublets
dq	doublet of quartets
Et	ethyl
EtOAc	ethyl acetate
ef	evaporated film
g	gram
Hz	Hertz
HMQC	^{1}H-^{13}C heteronuclear multiple quantum correlation spectroscopy
h	hour(s)
HCl(aq.)	hydrochloric acid
IR	infrared
$MgSO_4$	anhydrous magnesium sulfate
m/*z*	mass to charge ratio
MS	mass spectrum
mp	melting point
m	*meta*
*m*CPBA	*meta*-chloroperoxybenzoic acid

MeOH	methanol
Me	methyl
μL	microlitre
mL	millilitre
mmol	millimole
min	minute(s)
M	molarity
m	multiplet
$NbCl_3$.DME	niobium trichloride dimethoxyethane complex
$NbCl_5$	niobium pentachloride
NOE	nuclear Overhauser effect
o	*ortho*
$Pd(OH)_2$	palladium hydroxide
p	*para*
M	molecular ion (mass spectroscopy, C.I.)
H_5IO_6	hydrated periodic acid
Ph	phenyl
^{31}P NMR	phosphorus-31 nuclear magnetic resonance
KBr	potassium bromide
KOH	potassium hydroxide
^{1}H NMR	proton nuclear magnetic resonance
q	quartet
R_f	retention factor

rt	room temperature
s	singlet
$NaBH_4$	sodium borohydride
Na_2SO_4	anhydrous sodium sulfate
THF	tetrahydrofuran
TLC	thin layer chromatography
Bu_3SnCl	tributyltin chloride
Bu_3SnH	tributyltin hydride
Et_3N	triethylamine
CF_3	trifluoromethyl
t	triplet
cm^{-1}	wavenumber
w/v	weight per volume

CHAPTER 1. INTRODUCTION

1.1 Introduction

This thesis concerns the development and application of synthetic methods based on use of the niobium trichloride dimethoxyethane complex ($NbCl_3$.DME). $NbCl_3$.DME has been reported to mediate a coupling reaction between imines and aldehydes or ketones to afford predominantly *syn* 1,2-amino alcohols.[1] This synthetic method appeals to our research programme as it has been shown to: 1) generate two stereogenic centres and two functional groups in a single operation; 2) form a new carbon-carbon bond; and 3) involve a novel reagent and organometallic intermediates.

Our primary objective was to expand the scope of the existing synthetic method that involved the use of aldehydes and ketones as electrophiles. Thus, the study of the direct one-pot synthesis of a variety of small, functionalized molecules through the cross-coupling of imines with other electrophiles was proposed.

1.2 Niobium

Niobium has an atomic mass of 93 and is located in Group V of the periodic table, below vanadium and above tantalum. The most common source of niobium is the *columbite-tantalite* series of ores and minerals that have the general composition $(Fe/Mn)(Nb/Ta)_2O_6$, with variable ratios of Fe/Mn and Nb/Ta.[2] Niobium is 10 to 12 times more abundant than tantalum in the earth's crust and the separation and production

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[1] Roskamp, E. J.; Pedersen, S. F. *J. Am. Chem. Soc.* **1987**, *109*, 6551-6553.

[2] Cotton, F. A.; Wilkinson, G. *Advanced Inorganic Chemistry*, 5th Ed., John Wiley & Sons, New York, **1988**, Chapter 19-B.

of these metals is complex. Niobium forms many compounds in oxidation states II, III, IV, and V.[2] The V oxidation state of niobium is the most common and has a stable d^0 electron configuration. The oxides of niobium are numerous and geometrically diverse. For instance, the oxides $NbOCl_3$ and Nb_2O_5 are octahedral whereas $ScNbO_4$ is tetrahedral.

$NbCl_3$.DME can be made synthetically from the direct reduction of niobium pentachloride ($NbCl_5$) using tributyltin hydride in 1,2-dimethoxyethane (DME) and it is also commercially available.[3] $NbCl_5$ has shown versatility as a Lewis acid catalyst. It has been shown to be effective in the diastereoselective allylation of aldehydes and in the ring opening of epoxides.[4, 5] $NbCl_5$ is commercially available and is prepared by the direct reaction of the metal with excess chlorine gas.[2] $NbCl_5$ is soluble in some organic solvents such as ethers and carbon tetrachloride.[2] It has a dimeric structure in the solid state with a distorted octahedral configuration. A distance of 3.95 Å between the niobium centres suggests that there is no metal-metal bonding (**Figure 1**).[2] $NbCl_5$, a bright yellow solid, should be stored under an inert atmosphere as it can be hydrolyzed readily to niobium pentoxide (Nb_2O_5), an inert white solid.[2]

---

[3] Pedersen, S. F.; Hartung, J. B., Jr.; Roskamp, E. J.; Dragovich, P. S.; Ruffing, C. J.; Klein, B. A. *Inorg. Syn.* **1992**, *29*, 119-123.

[4] Andrade, C. K. Z.; Azevedo, N. R. *Tetrahedron Lett.* **2001**, 42, 6473-6476.

[5] Constantino, M. G.; Lacerda, V.; Aragao, V. *Molecules* **2001**, *6*, 770-776.

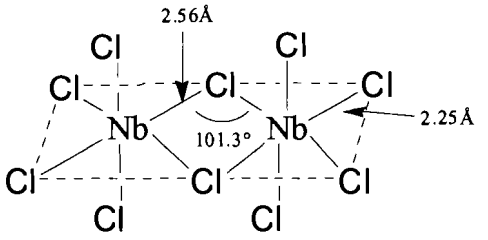


Figure 1 Chemical Structure of $NbCl_5$.

$NbCl_3$.DME is a brick red solid and has an unknown molecular structure.[3] However, the molecular structure of $NbCl_3$.DME is most likely monomeric due to the presence of the dimethoxyethane ligand that can provide a stabilizing interaction with the niobium metal centre.[2] The 3+ oxidation state of niobium is highly reactive and can act as a two electron reductant in the cross-coupling reaction of an imine with an aldehyde or ketone.[1] Also, the reductive coupling of oxo amides to afford indoles has been reported using $NbCl_3$.DME that was generated by the reduction of $NbCl_5$ with metallic zinc *in situ*.[6] Vanadium in the 2+ oxidation state has been shown to be an effective mediator (in the complex $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$) for the reductive pinacol coupling of aldehydes.[7] $NbCl_3$.DME is unlike other Group V transition metal complexes in that it can selectively cross-couple an imine to an aldehyde or ketone to afford 1,2-amino alcohols.

1.3 Application of $NbCl_3$.DME in Organic Synthesis

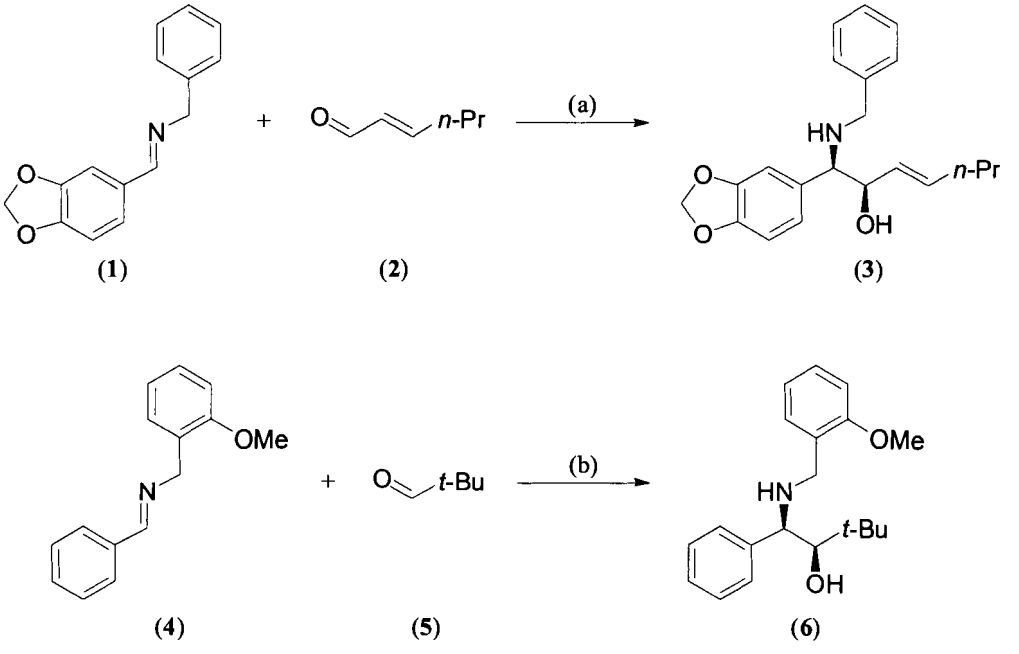
It was reported by Pedersen in 1987 that $NbCl_3$.DME mediated a coupling reaction between imines (*e.g.* **1** and **4**) and aldehydes (*e.g.* **2** and **5**) to afford predominantly *syn* 1,2-amino alcohols (*e.g.* **3** and **6**) (**Scheme 1**).[1] In this scheme and in the following schemes in this thesis, only one of the enantiomers of the reaction products

---

[6] Fürstner, A.; Hupperts, A.; Ptock, A.; Janssen, E. *J. Org. Chem.* **1994**, *59*, 5215-5229.

[7] Kammermeier, B.; Beck, G.; Holla, W.; Jacobi, D.; Napierski, B.; Jendralla, H. *Chem.-Eur. J.* **1996**, *2*, 307-315.

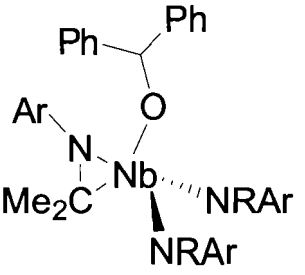
is depicted. For each example, the imines were allowed to complex with $NbCl_3$.DME and after subsequent addition of the aldehydes the amino alcohols were isolated from these one-pot reactions. Of note, a new carbon-carbon bond was formed, two chiral centres were created and two functional groups are installed in this process. The diastereoselectivity of the reaction was much improved in the second example and this may be attributed to the large *tert*-butyl substituent of the aldehyde electrophile that is adjacent to the carbon atom where the new carbon-carbon bond is formed. An additional control element, the presence of the methoxy substituent on the imine that could chelate to the metal centre may also be responsible for this improvement in diastereoselectivity.



Scheme 1 **Niobium Trichloride-Mediated Reactions.**
Reagents and conditions: a) $NbCl_3$.DME, THF, 0.5 h, rt, 73 % (ds = 6.5:1 *syn*:*anti*); b) $NbCl_3$.DME, THF, 0.5 h, rt, 79 % (ds = 83:1 *syn*:*anti*).

It has been suggested by Pedersen that the intermediate in the above reaction is a metallaaziridine.[1] The isolation and characterization of a metallaaziridine derived from an imine and $NbCl_3$.DME has not yet been reported to our knowledge. However, the

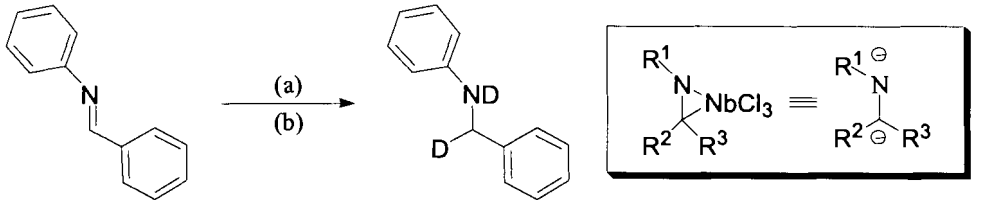
synthesis and crystal structure of the metallaaziridine **7** has been reported recently (**Figure 2**).[8] The metallaaziridine **7** does not contain any chlorine atom substituents. However, they are replaced by two isoelectronic imido ligands and an alkoxy ligand in this complex.



(7, R = $CHMe_2$, Ar = 3,5-$C_6H_3Me_2$)

Figure 2 Structure of Metallaziridine 7.

Hydrolysis of the proposed metallaaziridine intermediate derived from *N*-benzylidene-aniline **8** and $NbCl_3$.DME, with deuterated sodium hydroxide (NaOD) afforded the corresponding deuterated amine **9** (**Scheme 2**). This suggests that the $NbCl_3$.DME-imine complex functions as a *C,N*-dianion in subsequent reactions.[1]



(8) (9)

Scheme 2 Hydrolysis of $NbCl_3$.DME-*N*-Benzylidene-Aniline Complex with Deuterated Sodium Hydroxide.[1]
Reagents and conditions: a) $NbCl_3$.DME, THF, 0.5 to 12 h, rt; b) NaOD.

[8] Mindiola, D. J.; Cummins, C. C. *Organometallics* **2001**, *20*, 3626-3628.

We have rationalized the diastereoselectivity of these cross-coupling reactions in terms of the transition state **10** (**Figure 3**). Here, the large R^1 and R^3 substituents of the imine and aldehyde substrates would be expected to adopt an *anti*-relationship which would minimize the steric interactions and lead to the production of *syn* 1,2-amino alcohols. In addition, an intramolecular formyl hydrogen bond to one of the chloride ligands may restrict the rotation of the aldehyde and therefore create an additional organizational element in the transition state of the reaction.[9]

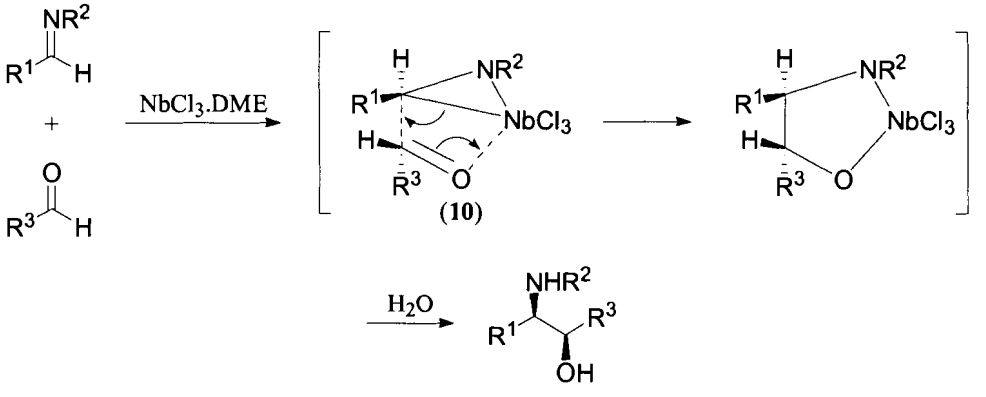


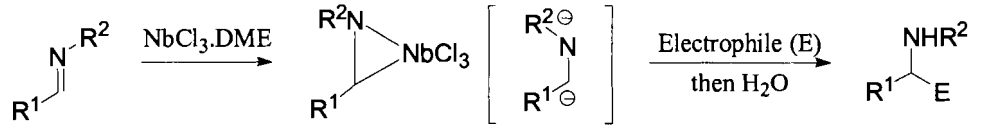
Figure 3 Reaction Mechanism and Stereochemical Rational.

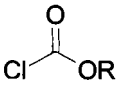
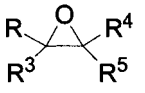
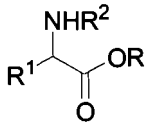
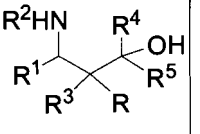
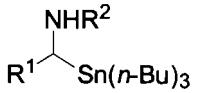
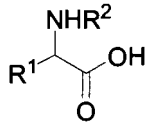
1.4 Project Objective

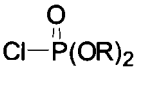
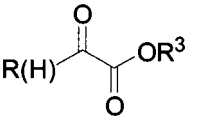
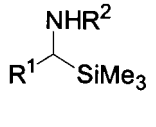
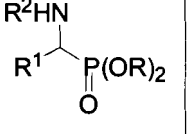
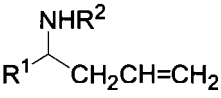
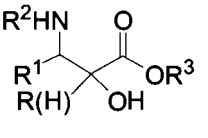
The initial study by Pedersen was limited to aldehydes and ketones as the electrophilic components.[1] Our project objective was to use $NbCl_3$.DME to mediate the cross-coupling reaction of imines with other electrophiles in order to synthesize a series of small, multi-functionalized molecules. We planned to examine the reactivity of $NbCl_3$.DME-imine complexes with a variety of electrophiles that included: chloroformates **11**, epoxides **12**, tributyltin chloride **13**, carbon dioxide **14**, chlorotrimethylsilane **19**, chlorophosphonates **20**, allyl iodide **21**, alkyl glyoxylates and

[9] Corey, E. J.; Lee, T. W. *Chem. Commun.* **2001**, 1321-1329.

pyruvates **22**. These reactions should afford directly: α-amino esters **15**, 1,3-amino alcohols **16**, aminoorganostannanes **17**, α-amino acids **18**, amino silanes **23**, amino phosphonates **24**, amines **25** and β-amino-α-hydroxy esters **26**, respectively (**Scheme 3**).



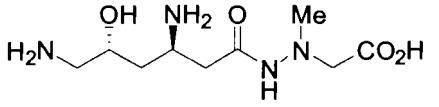
Electrophile	 (**11**)	 (**12**)	$ClSn(n\text{-}Bu)_3$ (**13**)	CO_2 (**14**)
Product	 (**15**)	 (**16**)	 (**17**)	 (**18**)

Electrophile	$ClSiMe_3$ (**19**)	 (**20**)	$I-CH_2CH=CH_2$ (**21**)	 (**22**)
Product	 (**23**)	 (**24**)	 (**25**)	 (**26**)

Scheme 3 Potential Scope of Niobium Trichloride-Mediated Reactions.

The products of these reactions have great potential as precursors in the preparation of natural products and designed structural derivatives in medicinal chemistry. α-Amino esters can be used as building blocks for the synthesis of α-amino acids by the simple hydrolysis of the ester functional group. 1,3-Amino alcohols are important target structures because they are found in several antibiotics and numerous

biologically active compounds (**Figure 4**).[10, 11, 12, 13] This difunctional structural unit requires extensive effort to install and existing methods include the reduction of 1,3-amino ketones or the reduction of isoxazolines.[10, 14, 15]



Negamycin

Figure 4 The 1,3-Amino Alcohol Moiety in a Biologically Active Compound.

Aminoorganostannanes can serve as valuable precursors for the production of aminoorganolithiums that have potential use in organic synthesis.[16] Amino silanes are useful in organic chemistry as they can be deprotonated and used in further synthetic transformations.[17] α-Amino phosphonates are of great synthetic interest in medicinal chemistry as they are structural analogues of α-amino acids and have been incorporated in peptide mimics, enzyme inhibitors, and antibiotics.[18, 19] The use of alkyl glyoxylates

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[10] Nogradi, M. *Stereoselective Synthesis*; VCH, Wienheim, Germany, **1987**; Chapters 3, 5, 6.

[11] Barluenga, J.; Aguilar, E.; Fustero, S.; Olano, B.; Viado, A. L. *J. Org. Chem.* **1992**, *57*, 1219-1223.

[12] Wang, Y. F.; Izawa, T.; Kobayashi, S.; Ohno, M. *J. Am. Chem. Soc.* **1982**, *104*, 6465-6466.

[13] Wovkulich, P. M.; Uskokovic, M. R. *J. Am. Chem. Soc.* **1981**, *103*, 3956-3958.

[14] Keck, G.E.; Truong, A.P. *Org. Lett.* **2002**, *4*, 3131-3134.

[15] Jaeger, V.; Schwab, W.; Buss, V. *Angew. Chem.-Int. Edit. Engl.* **1981**, *93*, 576-578.

[16] Burchat, A. F.; Chong, J. M.; Park, S. B. *Tetrahedron Lett.* **1993**, *34*, 51-54.

[17] Ruwisch, L.; Klingebiel, U.; Rudolph, S.; HerbstIrmer, R.; Noltemeyer, M. *Chem. Ber.* **1996**, *129*, 823-828.

[18] Yadav, J. S.; Reddy, B. V. S.; Madan, C. *Synlett* **2001**, 1131-1133.

as electrophiles in cross-coupling reactions with imines could afford β-amino-α-hydroxy alkyl esters. These products are of medical interest as, for example, they can be used as precursors for the construction of the Taxol side chain and structural analogues.

1.5 Towards the Diastereoselective Synthesis of the Taxol Side Chain

Taxol (Paclitaxel), a complex highly oxygenated diterpene isolated from the Pacific Yew, *Taxus brevifolia*, is highly effective against lung, ovarian, and breast cancers (**Figure 5**).[20] However, the natural supply of Taxol is limited in quantity and so over the last few decades many research groups have undertaken the considerable synthetic challenge of its total synthesis.[21, 22, 23, 24, 25, 26, 27] The side chain of Taxol, *N*-

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[19] Yadav, J. S.; Reddy, B. V. S.; Raj, K. S.; Reddy, K. B.; Prasad, A. R. *Synthesis* **2001**, 2277-2280.

[20] Nicolaou, K. C.; Dai, W. M.; Guy, R. K. *Angew. Chem.-Int. Edit. Engl.* **1994**, *33*, 15-44.

[21] Holton, R. A.; Somoza, C.; Kim, H. B.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S. C.; Nadizadeh, H.; Suzuki, Y.; Tao, C. L.; Vu, P.; Tang, S. H.; Zhang, P. S.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1597-1598.

[22] Holton, R. A.; Kim, H. B.; Somoza, C.; Liang, F.; Biediger, R. J.; Boatman, P. D.; Shindo, M.; Smith, C. C.; Kim, S. C.; Nadizadeh, H.; Suzuki, Y.; Tao, C. L.; Vu, P.; Tang, S. H.; Zhang, P. S.; Murthi, K. K.; Gentile, L. N.; Liu, J. H. *J. Am. Chem. Soc.* **1994**, *116*, 1599-1600.

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[24] Nicolaou, K. C.; Yang, Z.; Liu, J. J.; Ueno, H.; Nantermet, P. G.; Guy, R. K.; Claiborne, C. F.; Renaud, J.; Couladouros, E. A.; Paulvannan, K.; Sorensen, E. J. *Nature* **1994**, *367*, 630-634.

[25] Wender, P. A.; Badham, N. F.; Conway, S. P.; Floreancig, P. E.; Glass, T. E.; Granicher, C.; Houze, J. B.; Janichen, J.; Lee, D. S.; Marquess, D. G.; McGrane, P. L.; Meng, W.; Mucciaro, T. P.; Muhlebach, M.; Natchus, M. G.; Paulsen, H.; Rawlins, D. B.;

benzoyl-(2*R*,3*S*)-3-phenylisoserine, has been identified to be essential to the biological function of the antitumor agent.[20]

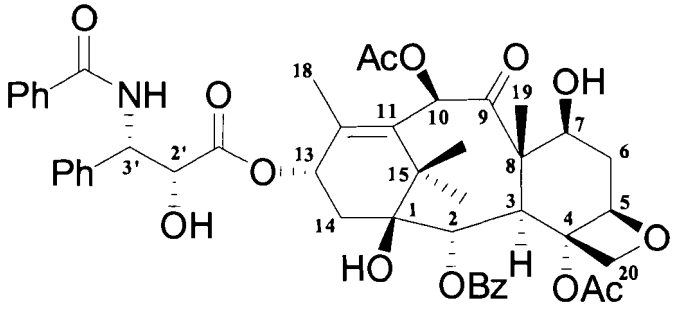

Figure 5 Chemical Structure of Taxol (Paclitaxel).

More recently, the synthesis of (2′*S*,3′*R*)-2′-methyldocetaxel, a semi-synthetic analogue of Taxol has been reported.[28] The 1(*S*)-phenylethylamine-derived imine **27** afforded the required (2*S*,3*R*) *syn* 1,2-amino alcohol **28** with good stereoselectivity on treatment with $NbCl_3$.DME and methyl pyruvate (**Scheme 4**). The *syn*:*syn* ratio of 4:1 refers to the diastereoselectivity of the reaction relative to the methyl substituent of the chiral auxiliary. The *syn*:*anti* ratio of 9:1 refers to the diastereoselectivity of the reaction relative to the amino alcohol substituents. The (2*S*,3*R*) amino alcohol isomer **28** was isolated from this mixture of diastereomers in 35 % yield. The amino alcohol **28** was

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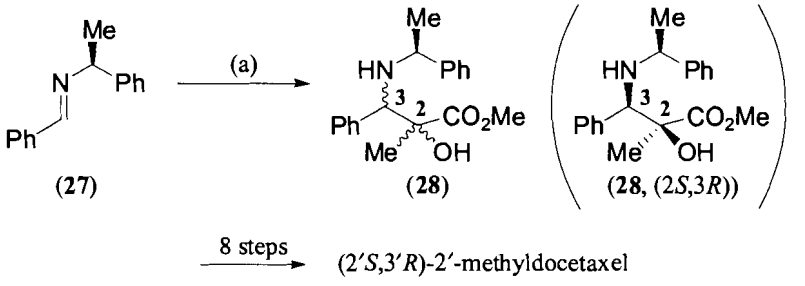
Satkofsky, J.; Shuker, A. J.; Sutton, J. C.; Taylor, R. E.; Tomooka, K. *J. Am. Chem. Soc.* **1997**, *119*, 2755-2756.

[26] Wender, P. A.; Badham, N. F.; Conway, S. P.; Floreancig, P. E.; Glass, T. E.; Houze, J. B.; Krauss, N. E.; Lee, D. S.; Marquess, D. G.; McGrane, P. L.; Meng, W.; Natchus, M. G.; Shuker, A. J.; Sutton, J. C.; Taylor, R. E. *J. Am. Chem. Soc.* **1997**, *119*, 2757-2758.

[27] Mukaiyama, T.; Shiina, I.; Iwadare, H.; Saitoh, M.; Nishimura, T.; Ohkawa, N.; Sakoh, H.; Nishimura, K.; Tani, Y.; Hasegawa, M.; Yamada, K.; Saitoh, K. *Chem.-Eur. J.* **1999**, *5*, 121-161.

[28] Denis, J. N.; Fkyerat, A.; Gimbert, Y.; Coutterez, C.; Mantellier, P.; Jost, S.; Greene, A. E. *J. Chem. Soc.-Perkin Trans. 1* **1995**, 1811-1815.

then converted to an *N,O*-cyclic acetal, hydrolyzed to the corresponding carboxylic acid, and attached to a semi-synthetic derivative of Taxol to afford (2′*S*,3′*R*)-2′-methyldocetaxel following deprotection.



(27) (28) (28, (2*S*,3*R*))

Scheme 4 **Synthesis of 1,2-Amino Alcohol 28.**[28]
Reagents and conditions: a) $NbCl_3$.DME, THF, 1 h at -15 °C to 20 °C, 2 h at 0 °C; *syn*:*anti* ca. 9:1; *syn*:*syn* ca. 4:1, combined yield, 68 %, isolated yield of (2*S*,3*R*) *syn* 1,2-amino alcohol **28**, 35 %.

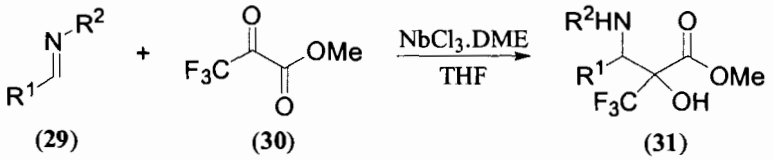
In this work to prepare a derivative of the Taxol side chain, methyl pyruvate was used as the electrophile which introduced a methyl substituent at carbon-2′. We planned to use alkyl glyoxylates as the electrophiles in the niobium trichloride-mediated coupling reactions of imines to prepare the natural ester side chain of Taxol. It was hoped that variation of the alkyl substituent of the glyoxylate would allow for stereochemical control of these reaction.

1.6 Preparation of Fluorinated Taxol Side Chain Derivatives

The introduction of fluorine atom substituents in analogues of biologically active compounds is of medicinal interest. This may have a major effect on drug disposition, in terms of distribution, drug clearance, and extent of drug metabolism.[29] Thus, we also proposed to prepare fluorinated derivatives of the Taxol side chain by the niobium

[29] Park, B. K.; Kitteringham, N. R. *Drug Metab. Rev.* **1994**, *26*, 605-643.

trichloride-mediated coupling reaction of imines with the commercially available fluorinated pyruvate derivative **30** (**Scheme 5**).



(29) (30) (31)

Scheme 5 Proposed Synthesis of Fluorinated Taxol Side Chain Derivatives.

CHAPTER 2. Results and Discussion: Optimization of Reaction Conditions

2.1 Introduction

$NbCl_3$.DME is a moisture sensitive reagent that must be stored and handled under an inert atmosphere at all times. In the presence of oxygen and moisture $NbCl_3$.DME is oxidized and hydrolyzed to give the more stable niobium (V) oxides and niobium (V) oxohalides.[2] $NbCl_3$.DME initially was purchased from the Aldrich chemical company (Aldrich) and we decided to duplicate one of the known reactions to prepare a 1,2-amino alcohol.[1] This was rationalized to be a logical step since if a comparable yield could be obtained then our reaction conditions would be suitable for the development of the reaction's potential with other electrophiles.

2.2 Preparation of Imine Precursors

A variety of imines were prepared before any transition-metal coupling reactions were performed. The imine starting materials **29** were prepared by simple condensation reactions of amines **32** and aldehydes **33** (**Scheme 6**). The experimental conditions used included room temperature reactions in dichloromethane using either anhydrous magnesium sulfate or anhydrous sodium sulfate to absorb water with the use of activated molecular sieves, and heating in benzene using a Dean-Stark trap to remove water.[30, 31] The imines were purified either by distillation (for oils) or by recrystallization (for solids).

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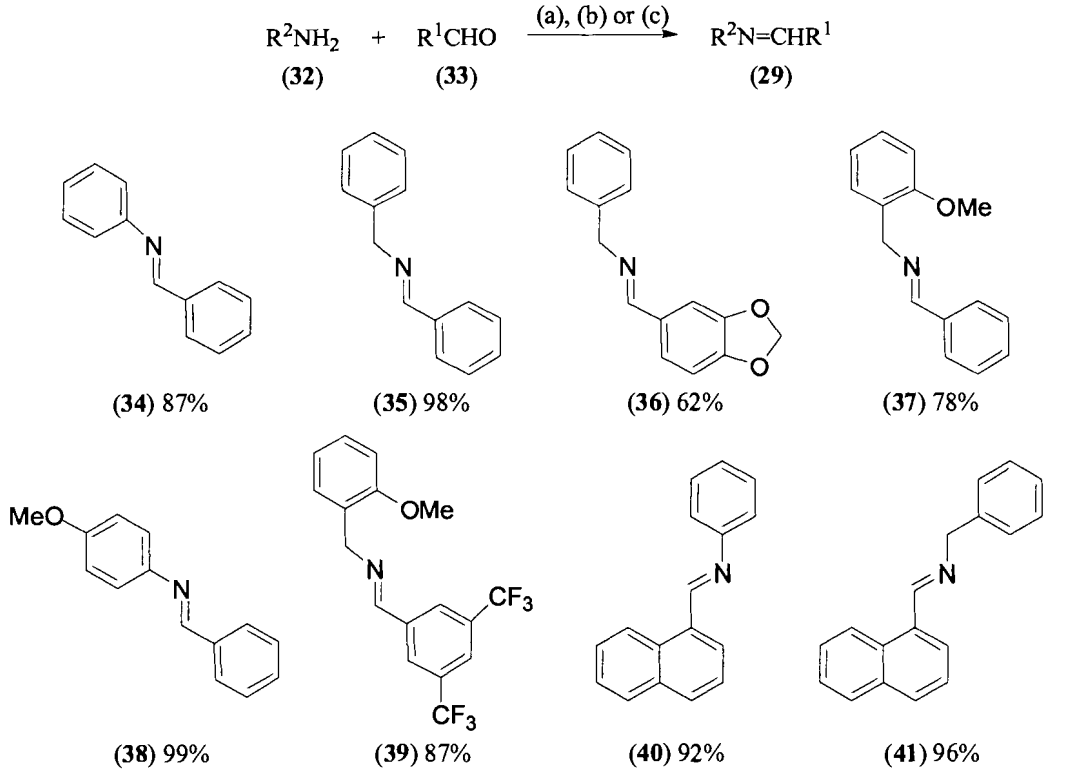
[30] Grigg, R.; McMeekin, P.; Sridharan, V. *Tetrahedron* **1995**, *51*, 13331-13346.

[31] Higashiyama, K.; Inoue, H.; Takahashi, H. *Tetrahedron* **1994**, *50*, 1083-1092.



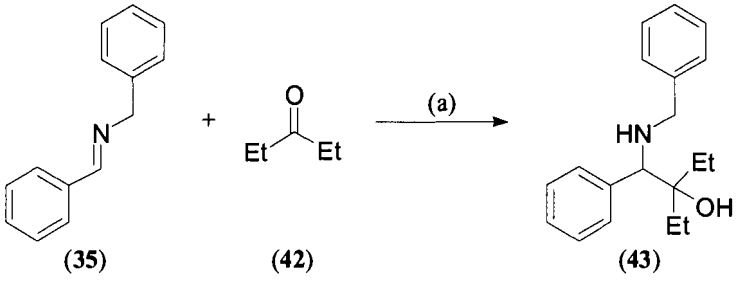
Scheme 6 **Synthesis of Imines.**
Reagents and conditions: a) DCM, $MgSO_4$, 4 Å molecular sieves, rt; b) DCM, Na_2SO_4, 4 Å molecular sieves, rt; c) C_6H_6, reflux.

Aromatic imines were selected for use in our cross-coupling studies as they are more stable than aliphatic imines. Imines **34** and **38** were chosen as they are both solids that can be purified by recrystallization. The latter compound has a 4-methoxy substituent that could possibly exert an electronic effect in cross-coupling reactions with electrophiles. Imines **35**, **36**, **37**, **39** and **41** were selected as they contain a benzyl substituent that can be readily deprotected for further use in synthesis.[28] The presence of a 2-methoxy substituent on the benzyl substituent of imines **37** and **39** could allow for the possibility of chelation to the niobium centre in $NbCl_3$.DME which could enhance the stereochemical control of the cross-coupling reactions. Imines **36** and **39** were selected for our studies in order to examine the effect of electron-donating and electron-withdrawing substituents on the imine. It was hoped that the presence of the sterically

demanding 1-naphthyl group of imines **40** and **41** would further influence stereochemical control in subsequent cross-coupling reactions.

2.3 Optimization of Reaction Conditions

The model reaction selected involved the coupling of imine **35** (*N*-benzylidene-benzylamine) with diethyl ketone **42**, mediated by $NbCl_3$.DME in THF which had been reported to afford the 1,2-amino alcohol **43** in high yield (**Scheme 7**).[1] We chose to optimize this reaction due to the reported high yield (97%) and that no diastereomeric 1,2-amino alcohols would be produced which would simplify product analysis.



Scheme 7 **Synthesis of 1-Benzylamino-2-ethyl-1-phenyl-butan-2-ol 43.**
Reagents and conditions: a) $NbCl_3$.DME, THF, 0.5 h, rt, 97 %.[1]

The reaction was performed following the reported experimental conditions and the amino alcohol **43** was isolated in a poor 20 % yield (**Table 1**, Entry 1).[1] The literature procedure involved the addition of 1.5 equivalents of imine **35** to 1.5 equivalents of $NbCl_3$.DME in THF at room temperature. The resultant solution should have appeared green in color, that would have suggested the formation of the metallaaziridine complex, but we did not observe this color change.[1] After stirring at room temperature for approximately 2 min, an equivalent of ketone **42** was added again without any noticeable color change. After stirring for a further 30 min at room temperature, an aqueous solution of potassium hydroxide was added and the product was

isolated in the usual manner. The poor yield obtained could have resulted from our handling of the air sensitive reagent or the quality of the commercial sample of $NbCl_3$.DME.

Entry	Eq. of Imine **35**	Eq. of $NbCl_3$.DME	Reaction Time to form Metallaaziridine / minutes	Eq. of Ketone **42**	Reaction Time / minutes	Yield **43** / %
1	1.5	1.5 (Aldrich)	2 (rt)	1.0	30 (rt)	20
2	1.5	1.5 (Aldrich)	10 (rt)	1.0	60 (rt)	28
3	1.5	1.5 (Aldrich)	30 (rt)	1.0	30 (rt)	21
4	1.5	1.5 (Aldrich)	90 from -20 °C to 10 °C	1.0	180 from -10 °C to rt	14

Table 1 Initial Attempts to Synthesize 1,2-Amino Alcohol 43.

A considerable amount of imine **35** was unreacted from this cross-coupling reaction, and so the period of time to form the metallaaziridine complex at room temperature was extended (Entry 2). The yield of the reaction increased to 28 % which suggested more time was required for the imine to form a complex with the niobium reagent. Increasing the reaction time to form the metallaaziridine to 30 min decreased the yield to 21 % (Entry 3). A diamine byproduct was isolated from this reaction as indicated by analysis of the mass spectrum. A molecular ion (C.I., M+1) at 395 amu was observed. This suggested that a longer reaction time eventually lead to the metallaaziridine reacting with any unreacted imine that caused a decrease in yield of the required amino alcohol product **43**.

Next, we altered the temperature of the metallaaziridine formation reaction to –20 °C and allowed it to warm to 10 °C over the course of 90 min (Entry 4). The cross-coupling step of the reaction was also performed at a lower temperature and for a longer period of time in an attempt to suppress a pinacol coupling reaction of ketone **42**.

$NbCl_3$.DME has been shown to act as a two-electron reductant in the pinacol coupling reaction of aldehydes and ketones.[6, 32] The yield of the reaction dropped to 14 % under these conditions.

The low yields obtained thus far indicated that the $NbCl_3$.DME was either of poor quality or we were having difficulties handling the reagent using our standard laboratory techniques. To gauge how sensitive the reaction was to the presence of moisture and oxygen we decided to conduct the entire reaction in a glove box. In this case, using the same conditions as Entry 1 (**Table 1**), we obtained an improved yield of 62 %. As the yield was still lower than reported in the literature (97 %), we decided to prepare $NbCl_3$.DME.[1]

$NbCl_3$.DME can be synthesized by the reduction of $NbCl_5$ with tributyltin hydride.[3] $NbCl_3$.DME was prepared successfully and in good yields by adding solid $NbCl_5$ to a solution of tributyltin hydride in DME at -78 °C (**Scheme 8**). The order of addition in this preparation was very important as $NbCl_5$ reacted exothermically with the solvent (DME) in the absence of tributyltin hydride.

$$NbCl_5 + 2Bu_3SnH \xrightarrow{(a)} NbCl_3.DME + 2Bu_3SnCl + H_2$$

Scheme 8 **Synthesis of Niobium Trichloride Dimethoxyethane Complex ($NbCl_3$.DME).**
Reagents and conditions: a) DME, THF, 4 h at -78 °C to -60 °C, 16 h at -78 °C to rt, 93 %.

The $NbCl_3$.DME reagent was characterized by melting point and IR spectroscopy which were found to be consistent with literature values.[3] The quality of the batches of

[32] Szymoniak, J.; Besancon, J.; Moise, C. *Tetrahedron* **1992**, *48*, 3867-3876.

$NbCl_3$.DME that were synthesized throughout this project was later determined by repeating successful cross-coupling experiments.

2.4 Final Optimization of Reaction Conditions

With the $NbCl_3$.DME reagent that we had prepared, it was found that good yields of the amino alcohol **43** could be obtained, outside of a glove box, using a variety of reaction conditions (**Table 2**). A 50 % yield was obtained on using the same reaction times and equivalents of reagents as in the original literature reference (Entry 1).[1] Increasing the reaction time to prepare the metallaaziridine and the number of equivalents did not improve this yield (Entry 2). Increasing the number of equivalents of $NbCl_3$.DME greatly improved the yield of the reaction (Entries 3 and 4). A modest increase in yield resulted when using lower temperatures for the formation of the metallaaziridine and the subsequent cross-coupling reaction (Entry 5). The final entry showed the use of more $NbCl_3$.DME reagent can further increase the yield for this specific reaction, but not significantly (Entry 6). The yields in Entries 3, 4, 5 and 6 are very similar and we selected the conditions listed in Entry 4 for subsequent cross-coupling reactions with other electrophiles. These experimental conditions (Entry 4) minimized the amount of $NbCl_3$.DME used, allowed for a sufficient period of time for the metallaaziridine complex formation (30 min) and was conducted entirely at room temperature.

Entry	Eq. of Imine **35**	Eq. of $NbCl_3$.DME	Reaction Time to form Metallaaziridine / minutes	Eq. of Ketone **42**	Reaction Time / minutes	Yield **43** / %
1	1.5	1.5	2 (rt)	1.0	30 (rt)	50
2	1.5	1.0	30 (rt)	2.0	30 (rt)	50
3	1.5	3.0	2 (rt)	1.0	30 (rt)	79
4	1.5	3.0	30 (rt)	1.0	30 (rt)	78
5	1.5	3.0	30 at 0 °C	1.0	120 from 0 °C to rt	80
6	1.5	4.5	30 (rt)	1.0	30 (rt)	84

Table 2 Optimized Results for the Synthesis of 1,2-Amino Alcohol 43.

The 1,2-amino alcohol **43** showed a molecular ion (C.I., M+1) of 284 amu by mass spectroscopy and also gave satisfactory elemental analysis. Two, broad IR bands at 3452 and 3333 cm^{-1} were characteristic of a 1,2-amino alcohol. In the ^1H NMR spectrum, two 3H triplets at δ = 0.81 (J = 7.3 Hz) and 0.91 (J = 7.3 Hz) ppm were indicative of two diastereotopic methyl groups being coupled to methylene protons. Two doublets at δ = 3.38 (J = 12.9 Hz) and 3.60 (J = 12.9 Hz) ppm corresponded to the diastereotopic benzylic methylene protons. A singlet at δ = 3.60 ppm was observed for the isolated benzylic methine proton.

2.5 Conclusions

$NbCl_3$.DME complex was synthesized successfully by adaptation of a literature method which proved to be superior to commercially available material. This reagent was then used in the cross-coupling reaction of imine **35** with ketone **42** and afforded the 1,2-amino alcohol **43** in good yields. Although our yields did not approach the value of 97 % quoted in the literature, we decided that our conditions were sufficiently optimized

for the study of $NbCl_3$.DME-mediated cross-coupling reactions of imines with a wider range of electrophiles.

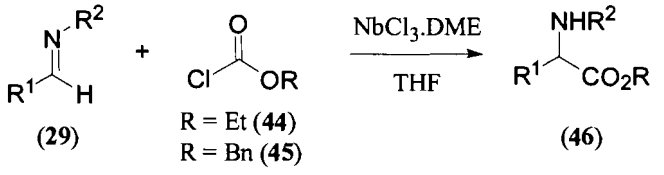
CHAPTER 3. Results and Discussion: Reactions of Niobium Trichloride-Imine Complexes with Various Electrophiles

3.1 Introduction

The $NbCl_3$.DME mediated cross-coupling reactions of imines with a variety of electrophiles, that included chloroformates, epoxides, tributyltin chloride, carbon dioxide (and ethylene carbonate), chlorotrimethylsilane, chlorophosphonates and allyl iodide, were studied. These one-pot reactions were considered to be potential new methods for the preparation of α-amino esters, 1,3-amino alcohols, aminoorganostannanes, amino acids (esters), amino silanes, amino phosphonates and amines, respectively.

3.2 Attempted Synthesis of Amino Esters

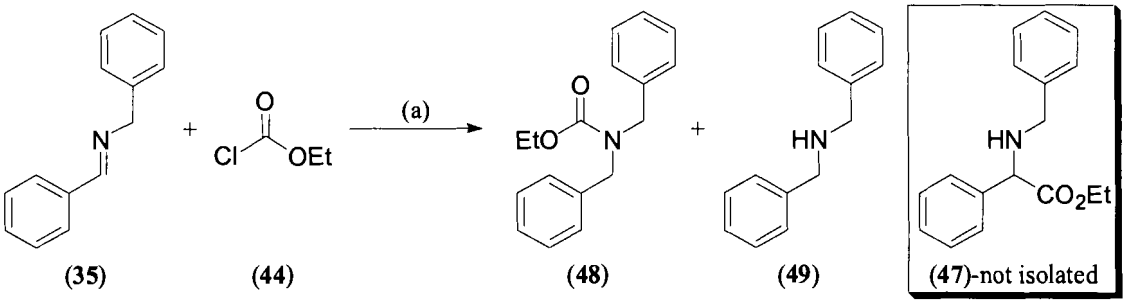
The $NbCl_3$.DME mediated cross-coupling of imines **29** with ethyl chloroformate **44** and benzyl chloroformate **45** as electrophiles were studied to develop a direct one-step synthesis of α-amino esters **46** (**Scheme 9**). If successful, this reaction would result in the formation of a new carbon-carbon bond and a new stereocentre as well as and the installation of two functional groups.



Scheme 9 **Direct One-Step Synthesis of α-Amino Esters.**

We first attempted to prepare α-amino ester **47** using imine **35** and ethyl chloroformate **44**. Unfortunately, the α-amino ester **47** was not formed under a series of

different reaction conditions. The major product of the reaction was carbamate **48** and a minor product was dibenzylamine **49** (**Scheme 10, Table 3**).



(35) (44) (48) (49)

Scheme 10 **Attempted Synthesis of α-Amino Ester 47.**
Reagents and conditions: a) See **Table 3**.

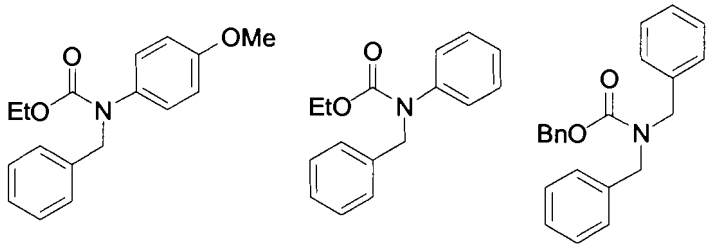
Entry	Eq. of Imine **35**	Eq. of $NbCl_3$.DME	Reaction Time to form Metallaaziridine / minutes (rt)	Eq. of **44**	Reaction Time / minutes (rt)	Yield **48** / %
1	1.5	1.5	30	1.0	30	40
2	1.5	3.0	30	1.0	30	38
3	1.0	2.0	30	1.3	30	54
4	1.0	2.0	30	5.0	30	58
5	1.0	2.0	30	5.0	120	48

Table 3 **Reaction Conditions for the Synthesis of Carbamate 48.**

The carbamate **48** would most likely have formed during a noticeable exothermic workup using an aqueous solution of potassium hydroxide. This would have formed the corresponding amine, dibenzylamine **49**, which in turn reacted with the chloroformate electrophile **44** to form a nitrogen-carbon bond. There was no apparent color change upon the addition of the chloroformate electrophile **44** to the reaction mixtures, thus it appeared that the imine-niobium complex did not react with this electrophile.

Other imines were examined to see if the structure of the imine had any effect on the outcome of the reaction. In addition, benzyl chloroformate **45** was also employed as

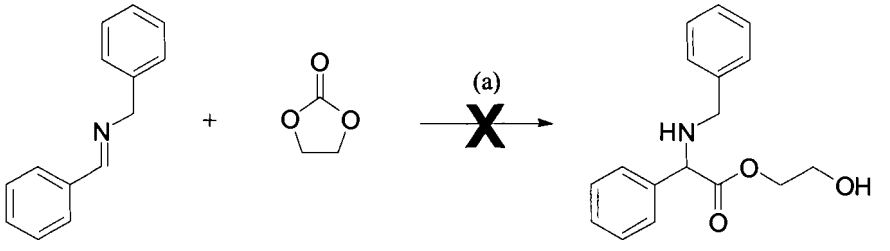
the electrophilic species. In an attempt to make α-amino esters, three additional carbamates **50**, **51** and **52** were synthesized (**Scheme 11**). As in the attempted preparation of α-amino ester **47**, no color change occurred when the chloroformate electrophiles were added to the reaction mixtures.



(**50**) 51% (**51**) 53% (**52**) 47%

Scheme 11 Synthesis of Carbamates 50, 51 and 52.

Using ethylene carbonate **53** as an electrophile, we attempted to synthesize the hydroxy amino ester derivative **54** (**Scheme 12**). This electrophile **53** proved to be unreactive under our optimized experimental conditions, affording dibenzylamine **49** as the major product. There was no color change after carbonate **53** was added.



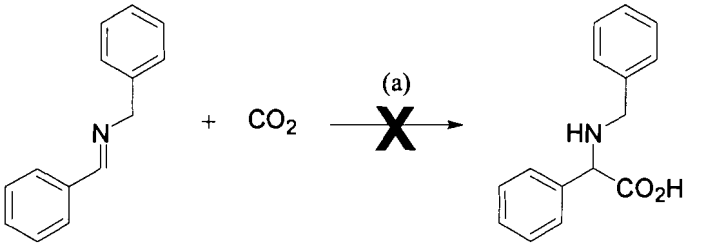
(**35**) (**53**) (**54**)

Scheme 12 Attempted Synthesis of Hydroxy Amino Ester Derivative 54.
Reagents and conditions: a) $NbCl_3$.DME, THF, 0.5 h, rt.

3.3 Attempted Synthesis of Amino Acids

We attempted to form an amino acid **56** in a one-pot reaction using carbon dioxide **55** as an electrophile (**Scheme 13**). Anhydrous carbon dioxide **55** was bubbled

over the course of 3.5 hours into the reaction, at room temperature, that caused a color change of the solution from dark green to dark blue.[33] Upon examination of the organic and aqueous fractions following the workup, the desired product was not identified by either ^{1}H NMR or mass spectroscopy.[34]



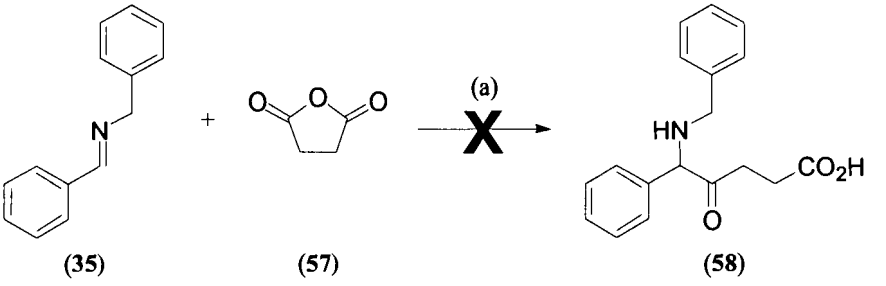
(35) (55) (56)

Scheme 13 **Attempted Synthesis of α-Amino Acid 56.**
Reagents and conditions: a) $NbCl_3$.DME, THF, 3.5 h, rt.

Using succinic anhydride **57** as an electrophile, we attempted to synthesize the amino acid derivative **58** (**Scheme 14**). The electrophile **57** proved to be unreactive when using our optimized experimental conditions, and afforded dibenzylamine **49** as the major product of the reaction. There was no color change after anhydride **57** was added to the reaction mixture.

[33] Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*, 5th Ed., John Wiley & Sons, New York, **1989**, Chapter 4.2.

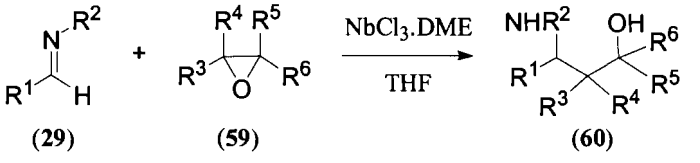
[34] Beers, S. A.; Schwender, C. F.; Loughney, D. A.; Malloy, E.; Demarest, K.; Jordan, J. *Bioorg. Med. Chem.* **1996**, *4*, 1693-1701.



Scheme 14 **Attempted Synthesis of Amino Acid Derivative 58.**
Reagents and conditions: a) $NbCl_3$.DME, THF, 2.0 h, rt.

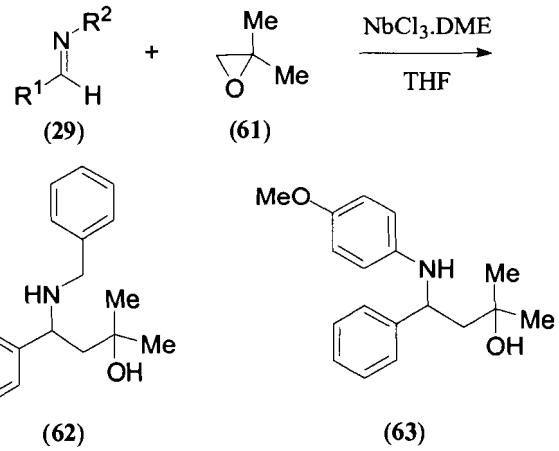
3.4 Attempted Synthesis of 1,3-Amino Alcohols

The reaction of imine-niobium complexes with epoxides **59** as electrophiles was studied in an attempt to develop a method for the direct one-pot synthesis of 1,3-amino alcohols **60** (**Scheme 15**). This would have allowed for the formation of a new carbon-carbon bond and the installation of two functional groups as well as products that could contain up to three stereogenic centres.



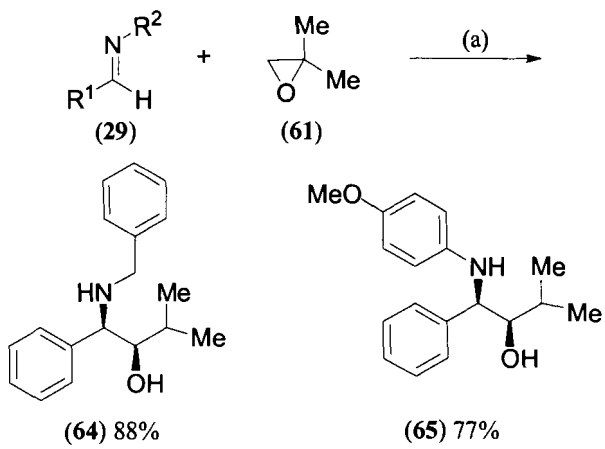
Scheme 15 **Attempted Synthesis of 1,3-Amino Alcohols.**

In the first instance, we chose 2,2-dimethyloxirane **61** as the electrophilic component of the reaction (**Scheme 16**). In **Scheme 16**, general imine **29** refers to imines **35** and **38** (Section 2.2). We had hoped that the metallaaziridine complexes would react regioselectively with the less sterically hindered methylene carbon of the epoxide to form the 1,3-amino alcohols **62** and **63** as single regioisomeric products.[5]



Scheme 16 Synthesis of 1,3-Amino Alcohols from Epoxide 61.

The 1,3-amino alcohols **62** and **63** were not formed under our optimized experimental conditions. However, the 1,2-amino alcohols **64** and **65** were isolated in high yield and as single diastereomers (**Scheme 17**). The crude ^{1}H NMR spectra of 1,2-amino alcohols **64** and **65** contained many unidentifiable peaks, and so the diastereoselectivity of the reactions could not be determined.



Scheme 17 Synthesis of 1,2-Amino Alcohols 64 and 65.
Reagents and conditions: a) $NbCl_3$.DME, THF, 0.5 h, rt.

Our rationalization of the observed outcome of the reactions is that the oxygen atom of the epoxide can coordinate to the niobium metal centre in the metallaaziridine complex (**Figure 6**). Once the epoxide is coordinated to the metal, a carbon-oxygen bond

can cleave regioselectively to afford a tertiary carbocation. Lewis acids are known to help promote the rearrangement of epoxides and epoxide bonds are known to cleave preferentially at the more substituted carbon atom.[5] A 1,2-hydride shift can then occur to form a metallaaziridine intermediate that is coordinated to isobutyraldehyde. The stereochemistry of these reactions in not definitive, however, known from the work of Pedersen using aldehydes as the electrophilic component, *syn*-1,2-amino alcohols are the major products on reaction of this resultant intermediate.

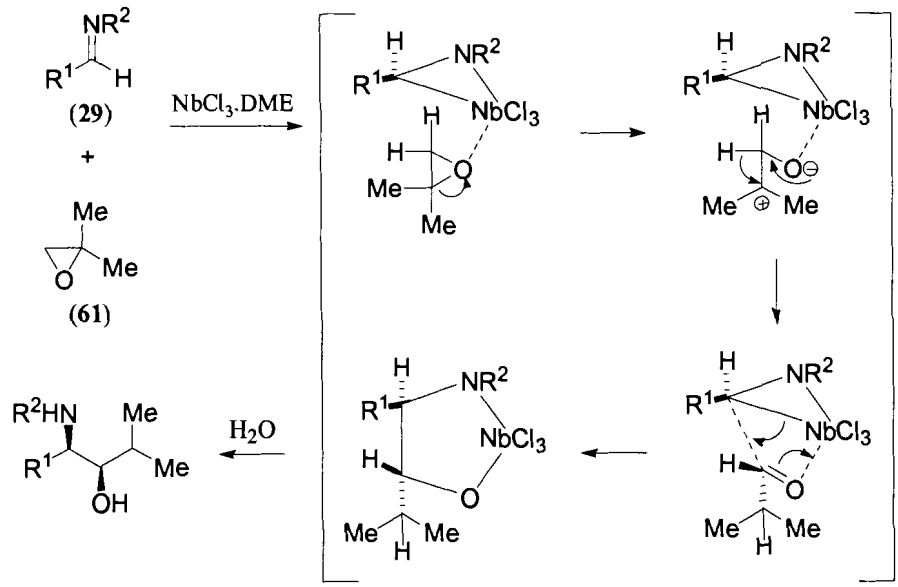


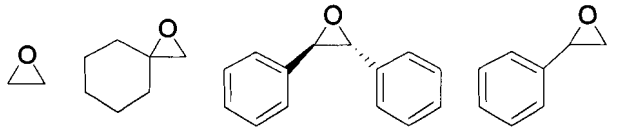
Figure 6 Possible Reaction Mechanism and Stereochemical Outcome.

The 1,2-amino alcohol **64** gave satisfactory elemental analysis with a molecular ion (C.I., M+1) of 270 amu. In the ^{1}H NMR spectrum, two 3H doublets at δ = 0.84 (J = 6.9 Hz) and 0.94 (J = 6.9 Hz) ppm were indicative of two methyl groups being coupled to a methine proton. A 1H multiplet at δ = 1.38-1.46 ppm corresponded to a methine proton being coupled to two methyl groups and another methine proton. A 2H multiplet at δ = 3.50-3.55 ppm correlated to the methine protons adjacent to the oxygen and nitrogen atoms.

The 1,2-amino alcohol **65** was fully characterized. The mass spectrum revealed a molecular ion (C.I., M+1) of 286 amu. In the ^{1}H NMR spectrum, two 3H doublets at δ = 0.94 (J = 6.7 Hz) and 1.04 (J = 6.7 Hz) ppm were characteristic of two methyl groups being coupled to a methine proton. A 1H multiplet at δ = 1.80-1.89 ppm was observed for a methine proton being coupled to two methyl groups and another methine proton. A 1H multiplet at δ = 3.28-3.32 ppm correlated to the methine proton adjacent to the oxygen atom. A 1H doublet at δ = 4.35 (J = 4.9 Hz) ppm related to the methine proton adjacent to the nitrogen atom that was coupled to the methine proton adjacent to the oxygen atom.

A further attempt was made to synthesize 1,2-amino alcohol **64** using isobutyraldehyde as an electrophile instead of epoxide **61**. In this case the reaction afforded a mixture of products, in low yield, that could not be separated *via* flash column chromatography. It was difficult to determine if the *syn* isomer of amino alcohol **64** was the major product of the reaction. Thus, it appeared that epoxide **61** was a better electrophile than isobutyraldehyde in the preparation of 1,2 amino alcohols **64** and **65**.

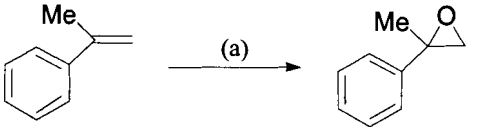
Ethylene oxide **66**, 1-oxaspiro[2,5]octane **67**, *trans*-stilbene epoxide **68** and styrene oxide **69** were also examined as electrophiles in order to synthesize either the desired 1,3-amino alcohols or 1,2-amino alcohols (**Figure 7**). Unfortunately, the reactions with these epoxides did not yield any of the desired products. Polymerization of epoxides **66** and **69** occurred under the standard reaction conditions. Epoxides **67** and **68** proved to be unreactive.



(66) (67) (68) (69)

Figure 7 Examining the Scope of the Reaction with Other Epoxides.

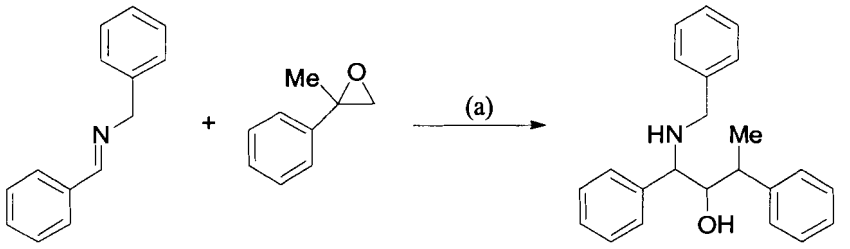
The only effective epoxide in our cross-coupling reactions was epoxide **61**. The presence of two methyl substituents at one carbon atom of epoxide **61** and its relative small size may have facilitated the formation of a tertiary carbocation in the coupling reactions (**Figure 6**). To test this hypothesis, epoxide **71** was synthesized from its corresponding styrene precursor **70** (**Scheme 18**). The presence of both a methyl and a phenyl substituent at one carbon atom of this epoxide could allow for the formation of a tertiary carbocation.



(70) (71)

Scheme 18 Synthesis of Epoxide 71.
Reagents and conditions: a) *m*CPBA, $NaHCO_3$, DCM, 80 min, 0 °C, 39 %.

The cross-coupling reaction of epoxide **71** with imine **35** was successful, and resulted in the formation of 1,2-amino alcohol **72** (**Scheme 19**). This reaction was highly stereoselective in that of the four possible diastereomers that could form as a result of the creation of the three stereogenic centres, only one diastereomer could be isolated and identified.



(35) (71) (72)

Scheme 19 **Synthesis of 1,2-Amino Alcohol 72.**
Reagents and conditions: a) $NbCl_3$.DME, THF, 0.5 h, rt, 23 %.

The 1,2-amino alcohol **72** exhibited a molecular ion (C.I., M+1) of 332 amu and gave satisfactory elemental analysis. In the ^1H NMR COSY spectrum (**Figure 8**), a 3H doublet at δ = 1.26 (J = 7.0 Hz) ppm was assigned to the methyl substituent (H^1) which was coupled to a benzylic methine proton (H^2). The benzylic methine proton (H^2), a 1H doublet of quartets at δ = 2.64 (J = 7.0, 4.0 Hz) ppm, was coupled to both the methine proton (H^3) and the methyl substituent (H^1). A 1H doublet of doublets at δ = 3.80 (J = 7.0, 4.0 Hz) ppm represented the methine proton (H^3) that was coupled to two different benzylic methine protons (H^2 and H^4). A 1H doublet at δ = 3.55 (J = 7.6 Hz) ppm corresponded to the benzylic methine proton (H^4) that in turn was coupled to the methine proton (H^3).

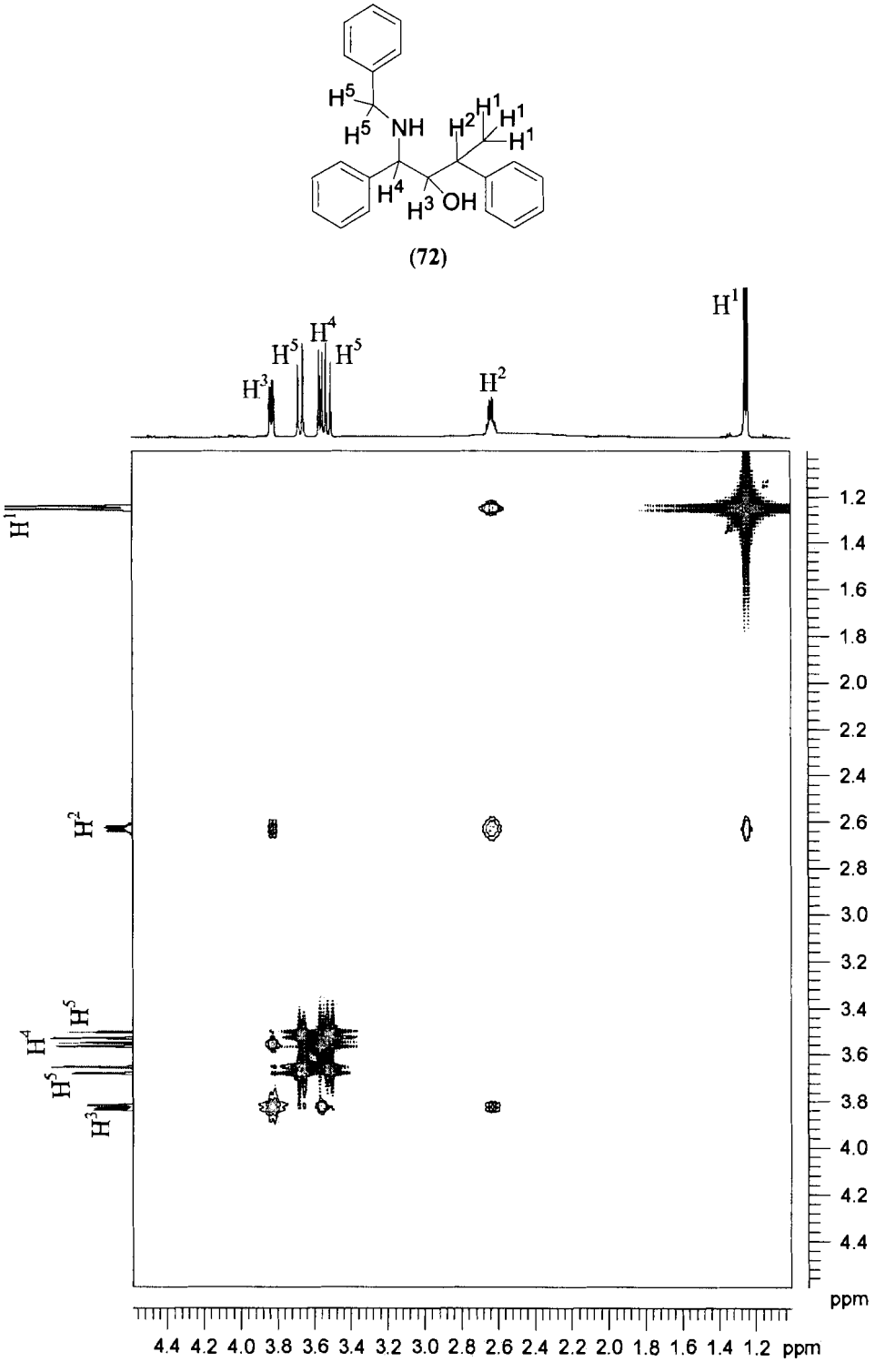
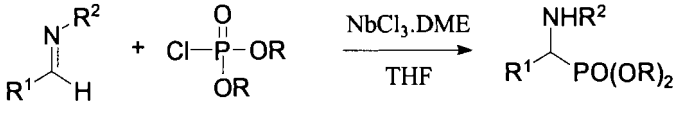


Figure 8 **COSY Spectrum of 1,2-Amino Alcohol 72 in $CDCl_3$.**

3.5 Attempted Synthesis of α-Amino Phosphonates

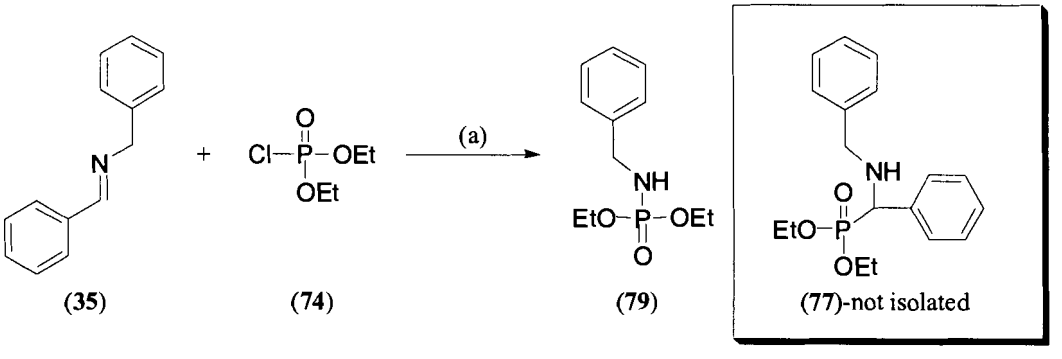
The reactions of $NbCl_3$.DME-imine complexes with a variety of chlorophosphonates that included: dimethyl chlorophosphonate **73**, diethyl chlorophosphonate **74** and diphenyl chlorophosphonate **75**, were studied. This could have allowed for the direct one-step synthesis of α-amino phosphonates **76**, **77**, and **78** **(Scheme 20)**.



(29) R = Me (73), R = Et (74), R = Ph (75) → R = Me (76), R = Et (77), R = Ph (78)

Scheme 20 Towards the One-Step Synthesis of α-Amino Phosphonates.

Using diethyl chlorophosphonate **74** as an electrophile we were unable to isolate the intended α-amino phosphonate **77** but instead obtained the phosphoramide **79** **(Scheme 21)**.



(35) (74) (79) (77)-not isolated

Scheme 21 Synthesis of Diethyl-*N*-benzylamino-phosphoramide 79.
Reagents and conditions: a) $NbCl_3$.DME, THF, 0.5 h, rt, 41 %.

The use of 1.5 equivalents of $NbCl_3$.DME and 1.5 equivalents of imine to 1.0 equivalent of diethyl chlorophosphonate afforded the phosphoramide **79** in 41 % yield. Using our optimized conditions for the metallaaziridine complex formation that involved

doubling the number of equivalents of $NbCl_3$.DME, the yield of product **79** fell to 11 %. Therefore, phosphoramide **79** was produced by hydrolysis of the uncoupled imine, to afford on workup, benzylamine which in turn reacted with the chlorophosphonate **74**. The spectral data recorded for phosphoramide **79** was consistent with the literature values.[35] No color changes were observed when the imine-niobium complexes were reacted with the chlorophosphonate electrophiles **73** and **75**. These results suggested that the metallaaziridine complexes were unreactive towards this class of electrophile.

3.6 Further Reactions with other Electrophiles

The reaction of the $NbCl_3$.DME-imine complexes with other electrophiles that included tributyltin chloride, chlorotrimethylsilane and allyl iodide, were also studied. This could have afforded in one-pot reactions aminoorganostannanes, amino silanes and amines, respectively. We were unsuccessful in obtaining our intended products in each of these cases. No color change took place when each of these electrophiles were added to the reaction mixture. These results suggested that the metallaaziridine complexes were unreactive towards these classes of electrophiles.

3.7 Conclusions

The examination of the reactivity of the imine-niobium complexes with a variety of electrophiles led to an important discovery, specifically when using epoxides **61** and **71** as electrophiles. This allowed for the preparation and isolation of 1,2 amino alcohols **64**, **65** and **72**, as single diastereomers. These results have been rationalized in terms of epoxide rearrangement, upon coordination to the metallaaziridine that forms a niobium

[35] Willeit, A.; Mueller, E. P.; Peringer, P. *Helv. Chim. Acta* **1983**, *66*, 2467-2480.

coordinated aldehyde intermediate that in turn reacts to afford the observed reaction products.

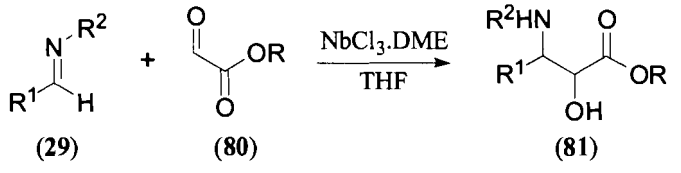
Chloroformates, ethylene carbonate, succinic anhydride, chlorophosphonates, tributyltin chloride, chlorotrimethylsilane and allyl iodide proved to be unreactive with the imine-niobium complexes. The major isolated products for these examples were the reduced amine and decomposition products of the imine starting material.

In terms of the reactivity of imine-niobium complexes, it is apparent that the electrophile should be highly reactive and contain a carbonyl oxygen (*e.g.* aldehydes and ketones) or an epoxide to coordinate to the metal centre in order to facilitate the cross-coupling reaction.

CHAPTER 4. Results and Discussion: Synthesis of the Methyl Ester Side Chain of Taxol and Derivatives

4.1 Introduction

To further expand our study of the cross-coupling of imines with other electrophiles, we focused our attention on alkyl glyoxylates. Alkyl glyoxylates are functionalized aldehydes with two carbonyl sites available for reaction with nucleophiles. Esters are poor electrophiles as compared to aldehydes and so glyoxylates would be expected to show chemoselectivity in $NbCl_3$.DME-mediated cross-coupling reactions with imines. The use of alkyl glyoxylates **80** as electrophiles in cross-coupling reactions with imines **29** could lead to the formation of β-amino-α-hydroxy alkyl esters **81** (**Scheme 22**). These reaction products have applicability as precursors for the synthesis of the Taxol side chain and its structural analogues.



(29) (80) (81)

Scheme 22 Proposed Synthesis of β-Amino-α-hydroxy Alkyl Esters 81.

Our retrosynthetic analysis of the side chain of Taxol **83** is shown in **Figure 9**. One of the most efficient ways to introduce the Taxol side chain onto the parent taxane ring system is to convert the *syn* β-benzoylamino-α-hydroxy methyl ester **83** (R = Me) to the carboxylic acid **82**.[27] This compound is much more reactive than its corresponding open chain form in condensation with 7-TES baccatin III which is a key step in the semi-synthesis of Taxol.[27]

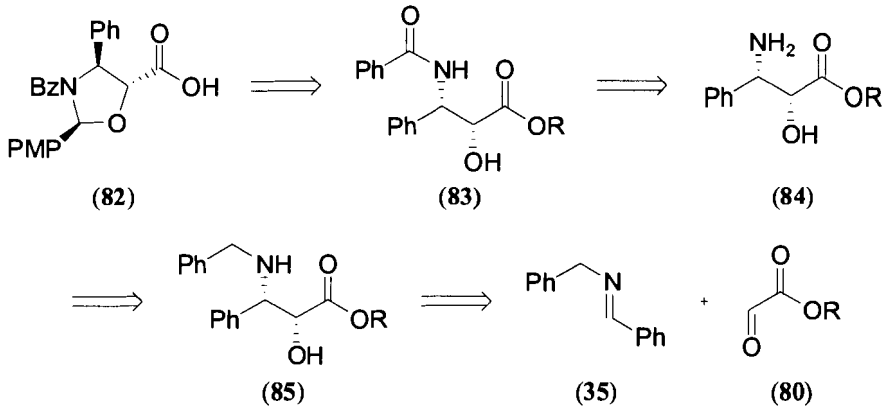


Figure 9 Retrosynthetic Analysis of the Taxol Side Chain.

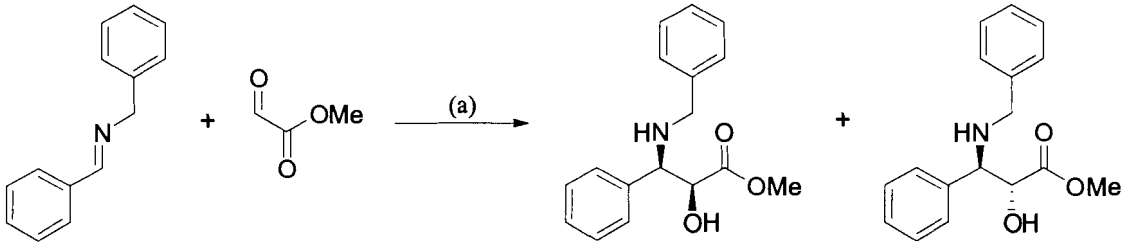
Ester **83** could be synthesized from amino alcohol **84** by reaction of the primary amine with benzoyl chloride.[36] Amino alcohol **84** could be obtained by hydrogenolysis of the benzyl protecting group of the β-amino-α-hydroxy alkyl ester **85**.[28] It was apparent that our key reaction would be the $NbCl_3$.DME-mediated coupling of the imine **35** and the alkyl glyoxylate **80**. The alkyl substituent, R, could be varied since the ester **83** is eventually hydrolyzed to the corresponding carboxylic acid **82**. Variation of the R substituent could be used to influence the stereochemical control of the cross-coupling reaction (**Figure 3**). Also, substituent variation on the benzyl protecting group can be tolerated as this substituent is eventually cleaved to obtain the primary amino alcohol **84**.

4.2 Synthesis of β-Amino-α-hydroxy Methyl Ester 87

Our first attempt to synthesize β-amino-α-hydroxy methyl ester **87** was successful from imine **35** with methyl glyoxylate **86** (**Scheme 23**, **Table 4**, Entry 1). In this one-pot reaction, a carbon-carbon bond was formed, two new stereocentres were created and three functional groups were installed. The ratio of *syn*:*anti* diastereomers was

[36] Barco, A.; Benetti, S.; DeRisi, C.; Pollini, G. P.; Spalluto, G.; Zanirato, V. *Tetrahedron* **1996**, *52*, 4719-4734.

determined to be approximately 1:1 by integration of the ^{1}H NMR spectrum of the crude reaction mixture.



(35) (86) (87-*syn*) (87-*anti*)

Scheme 23 **Synthesis of the β-Amino-α-hydroxy Methyl Ester 87.**
Reagents and conditions: a) See **Table 4**.

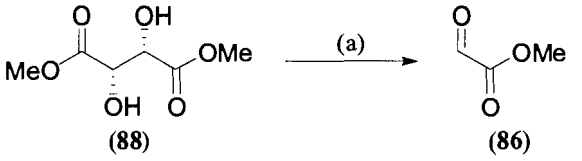
Entry	Eq. of Imine **35**	Eq. of $NbCl_3$.DME	Reaction Time to form Metallaaziridine / minutes (rt)	Eq. of **86**	Reaction Time / hours	Yield **87** / %
1	1.5	1.5	2	1.0	0.5 (rt)	48
2	1.5	3.0	30	1.0	0.5 (rt)	65
3	1.5	3.0	30	1.0	8.5 from -78 °C to rt	22

Table 4 **Optimized Reaction Conditions for the Synthesis of β-Amino-α-hydroxy Methyl Ester 87.**

Doubling the amount of $NbCl_3$.DME used in the reaction and increasing the reaction time for metallaaziridine complex formation increased the reaction yield to 65 % (Entry 2). This result was reproducible on a larger scale. The diastereomers were separated using flash column chromatography. The spectral data of these compounds was in agreement with the literature values.[37] An attempt to induce diastereoselectivity of the reaction by performing it a lower temperature was made without any success and was accompanied by a decrease in the yield of the reaction (Entry 3).

[37] Andersson, P. G.; Guijarro, D.; Tanner, D. *J. Org. Chem.* **1997**, *62*, 7364-7375.

Methyl glyoxylate **86** was freshly prepared from the oxidative cleavage of dimethyl L-tartrate **88** and was immediately distilled over activated molecular sieves (**Scheme 24**).[38] Care had to be taken in the preparation and handling of glyoxylate **86** for use in the air-sensitive $NbCl_3$.DME-mediated cross-coupling reaction, as glyoxylate **86** is known to rapidly hydrate and polymerize.[39]



(88) (86)

Scheme 24 **Oxidative Cleavage of Dimethyl L-Tartrate.**
Reagents and conditions: a) H_5IO_6, Et_2O, 0.5 h, rt, 77 %.

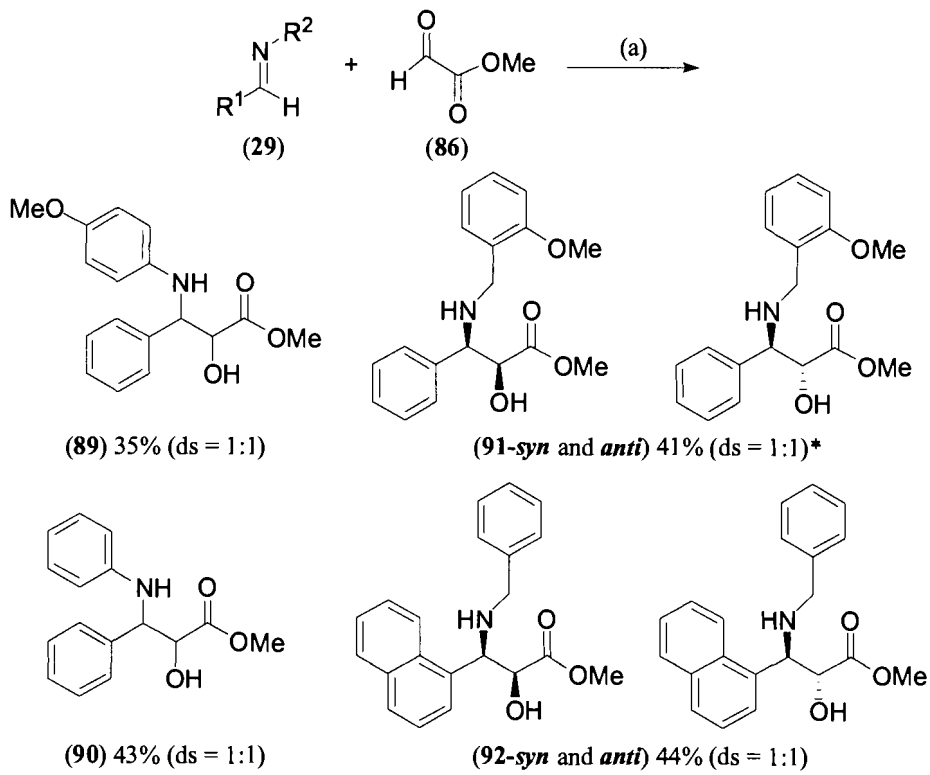
4.3 Synthesis of β-Amino-α-hydroxy Methyl Esters

Using our optimized conditions, four additional β-amino-α-hydroxy methyl esters were synthesized (**Scheme 25**). In **Scheme 25**, general imine **29** refers to imines **34**, **37**, **38** and **41** (Section 2.2). The diastereoselectivity of each of the reactions was 1:1. The yields for these reactions were good when one considers the instability of the electrophile and that amine byproducts from reduction of the imines were also isolated. β-Amino-α-hydroxy methyl esters **89** and **90** were synthesized from imines **38** and **34**, respectively. The *ortho*-methoxy substituent on the benzyl protecting group of imine **37** was employed to provide diastereoselective control of the reaction, on chelation to the niobium metal centre of the reagent, in the preparation of β-amino-α-hydroxy methyl ester **91**. The large 1-naphthyl substituent of imine **41** was employed to provide a steric effect in the

[38] Schuda, P. F.; Ebner, C. B.; Potlock, S. J. *Synthesis* **1987**, 1055-1057.

[39] Vairon, J. P.; Muller, E.; Bunel, C. *Macromol. Symp.* **1994**, *85*, 307-312.

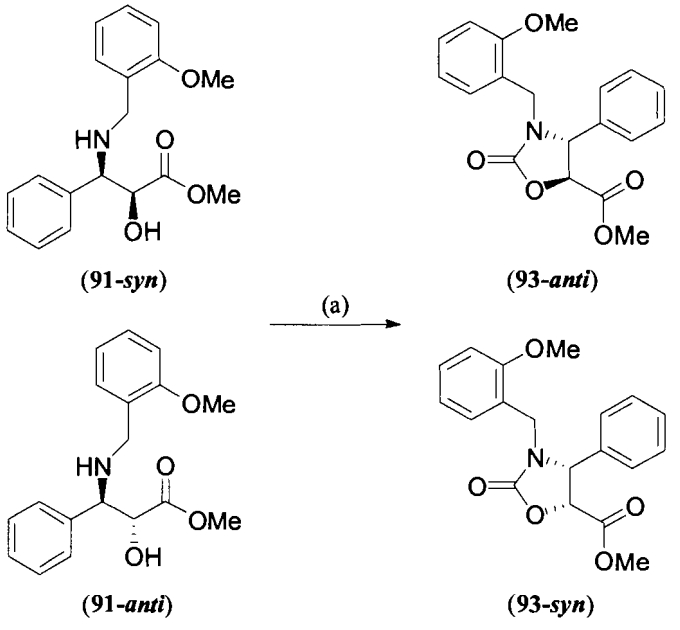
$NbCl_3$.DME cross-coupling reaction in the preparation of β-amino-α-hydroxy methyl ester **92**. β-Amino-α-hydroxy methyl ester **92** could also serve as a Taxol side chain analogue with a naphthyl group replacing the phenyl substituent. A C-3′ aryl group is required, as replacement by a methyl group or a proton will cause a dramatic decrease in biological activity.[20]



Scheme 25 **Synthesis of β-Amino-α-hydroxy Methyl Esters.**
Reagents and conditions: a) $NbCl_3$.DME, THF, 0.5 h, rt.
* Yields of products after protection and isolation of the corresponding oxazolidinones.

The β-amino-α-hydroxy methyl esters **91** were protected as their corresponding oxazolidinone derivatives **93**, using a known literature procedure, as one of the diastereomers of β-amino-α-hydroxy methyl ester **91** co-eluted with a reaction

byproduct.[40] Thus, both diastereomers were derivatized to less polar compounds that could be purified by flash column chromatography (**Scheme 26**).



Scheme 26 **Derivatization of a *β*-Amino-*α*-hydroxy Methyl Ester 91.** Reagents and conditions: a) *N,N*-carbonyldiimidazole, THF, 2.5 h, rt, 41 % (two-steps from **86**).

We were unable to separate the two diastereomers of *β*-amino-*α*-hydroxy methyl esters **89** by flash column chromatography, so they were characterized as a mixture. The *β*-amino-*α*-hydroxy methyl esters **89** exhibited a molecular ion (C.I., M+1) of 302 amu and passed elemental analysis. In the ^{1}H NMR spectrum, four 3H singlets at δ = 3.68, 3.69, 3.72 and 3.78 ppm were indicative of two different methoxy groups on each of the diastereomers. Four 1H doublets at δ = 4.49, 4.67, 4.79 and 4.86 ppm corresponded to methine protons.

[40] Williams, R. M.; Ehrlich, P. P.; Zhai, W. X.; Hendrix, J. *J. Org. Chem.* **1987**, *52*, 2615-2617.

It also was not possible to separate the two diastereomers of β-amino-α-hydroxy methyl esters **90** by flash column chromatography, so they were again analyzed together. The β-amino-α-hydroxy methyl esters **90** exhibited a molecular ion (C.I., M+1) of 272 amu and passed elemental analysis. In the ^{1}H NMR spectrum, two 3H singlets at δ = 3.74 and 3.78 ppm were indicative of the methoxy substituent of each diastereomer.

The *anti* isomer of oxazolidinone **93**, exhibited a molecular ion of 342 amu and was fully characterized. The absence of broad IR bands in the O-H and N-H stretching region indicated that the β-amino-α-hydroxy methyl ester precursor **91** had been protected. In the ^{1}H NMR spectrum, two 3H singlets at δ = 3.68 and 3.76 ppm corresponded to the two methoxy substituents (H^{15} and H^7) (**Figures 10** and **11**). Two 1H doublets at δ = 3.95 (J = 15.1 Hz) and 4.75 (J = 15.1 Hz) ppm were indicative of the two benzylic protons (H^8) on the same carbon (C^8) that are coupled to one another. A 1H doublet at δ = 4.58 (J = 5.1 Hz) ppm represented the methine proton (H^4) adjacent to the nitrogen atom, that is coupled to the other methine proton (H^5) adjacent to the oxygen atom, that exhibited a 1H doublet at δ = 4.66 (J = 5.1 Hz) ppm. On examining similar oxazolidinone ring systems that have been reported, a methine proton coupling constant of 5.1 Hz indicated an *anti* relationship between the two methine protons.[41, 42] From 3D modeling studies (CS Chem3D Pro), the dihedral angle between these two methine protons was found to be approximately 120 °. Thus, an NOE contact should not be

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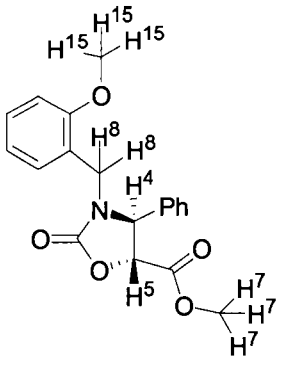
[41] Deutsch, H. M.; Glinski, J. A.; Hernandez, M.; Haugwitz, R. D.; Narayanan, V. L.; Suffness, M.; Zalkow, L. H. *J. Med. Chem.* **1989**, *32*, 788-792.

[42] Merino, P.; Castillo, E.; Franco, S.; Merchan, F. L.; Tejero, T. *Tetrahedron* **1998**, *54*, 12301-12322.

observed on irradiation of one of the protons. The NOE spectrum ($CDCl_3$, 400 MHz, **Figure 12**), showed no positive enhancement of proton (H^5) at δ = 4.66 ppm, on irradiation of the proton (H^4) at δ = 4.58 ppm. Of note, the *anti* isomer of oxazolidinone **93** corresponded to the *syn* isomer of the β-amino-α-hydroxy methyl ester **91** precursor.



(93-*anti*)

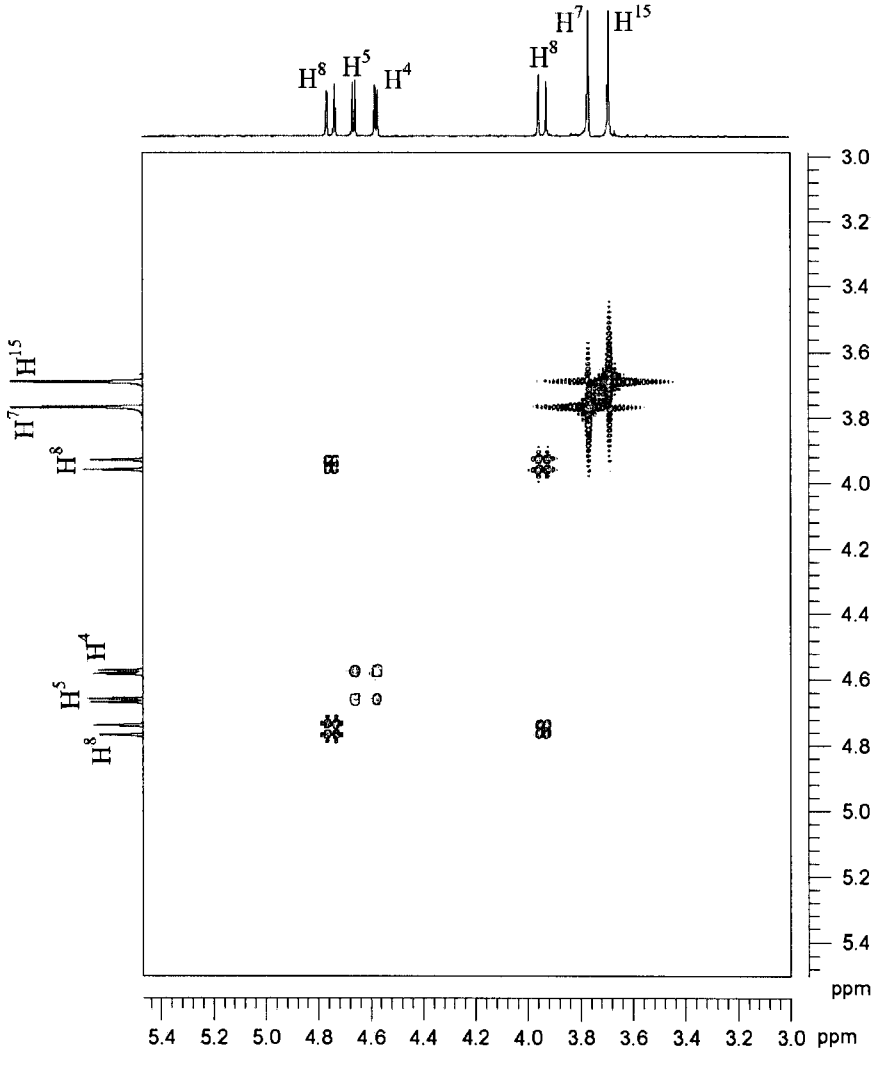
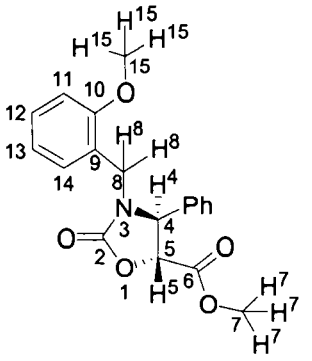


Figure 10 COSY Spectrum of the *Anti* Isomer of Oxazolidinone 93 in $CDCl_3$.



(**93-*anti***)

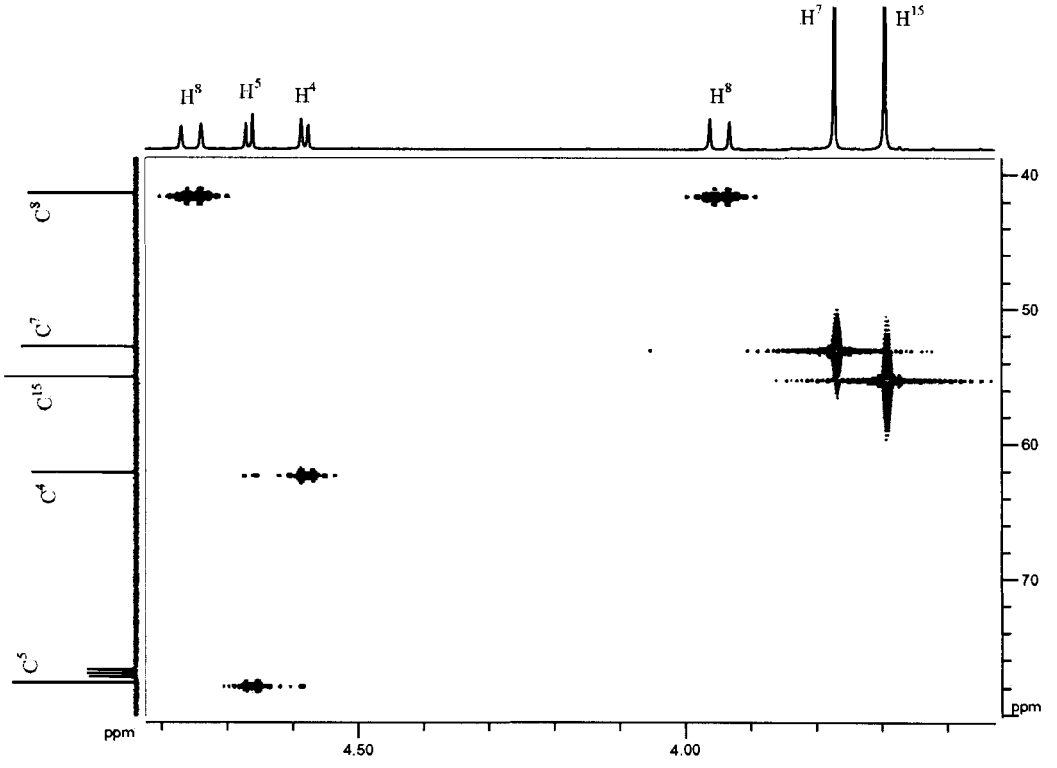
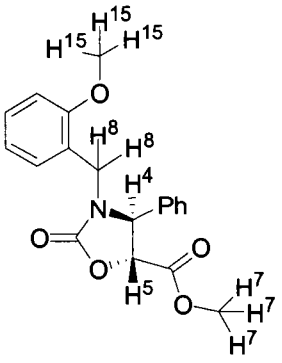


Figure 11 HMQC Spectrum of the *Anti* Isomer of Oxazolidinone 93 in $CDCl_3$.



(93-*anti*)

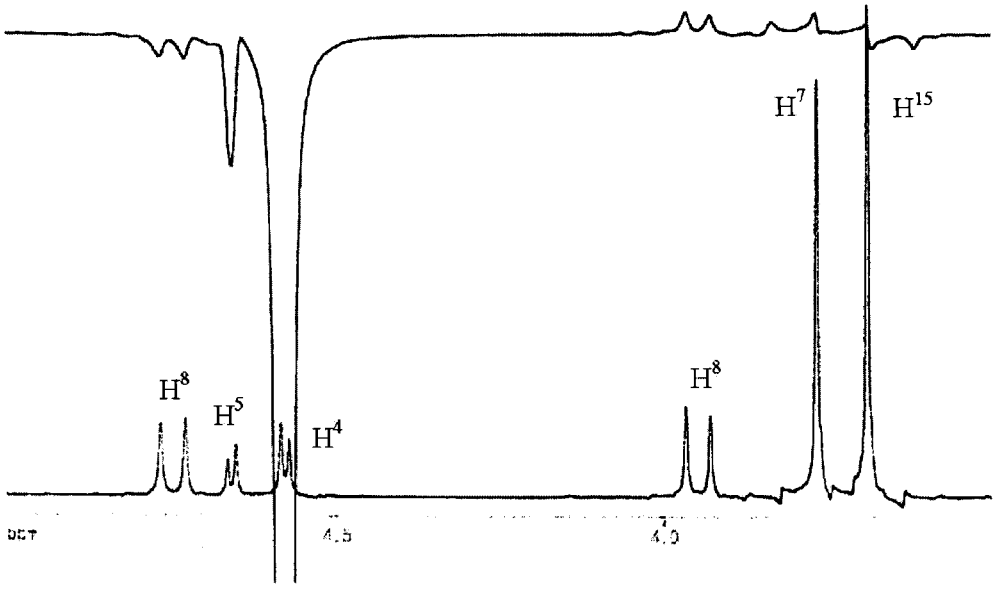
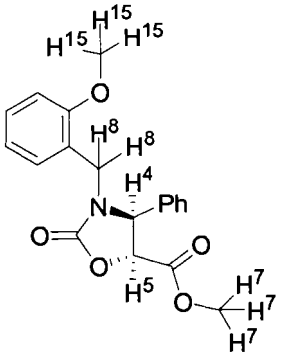


Figure 12 NOE Spectrum of the *Anti* Isomer of Oxazolidinone 93 in $CDCl_3$.

The *syn* isomer of oxazolidinone **93** exhibited a molecular ion (C.I., M+1) of 342 amu and again was fully characterized. In the ^1H NMR spectrum, two 3H singlets at δ = 3.23 and 3.67 ppm corresponded to the two methoxy substituents (H^7 and H^{15}) (**Figures 13** and **14**). Two 1H doublets at δ = 3.93 (J = 14.7 Hz) and 4.78 (J = 14.7 Hz) ppm corresponded to the two benzylic protons (H^8) on the same carbon (C^8) that are coupled to one another. A 1H doublet at δ = 4.86 (J = 9.6 Hz) ppm related to the methine proton (H^4) adjacent to the nitrogen atom, that is coupled to the other methine proton (H^5)

adjacent to the oxygen atom, that exhibited a 1H doublet at δ = 5.09 (J = 9.6 Hz) ppm. The coupling constant of 9.6 Hz suggested a *syn* relationship between these two protons.[41, 42] From 3D modeling studies (CS Chem3D Pro), the two methine protons have a dihedral angle of approximately 3 °. An NOE contact should be evident in this case and a positive enhancement for the proton (H^4) at δ = 4.86 ppm, on irradiation of proton (H^5) at δ = 5.09 ppm, was observed. Of note, the *syn* isomer of oxazolidinone **93** corresponded to the *anti* isomer of the β-amino-α-hydroxy methyl ester **91** precursor.



(93-*syn*)

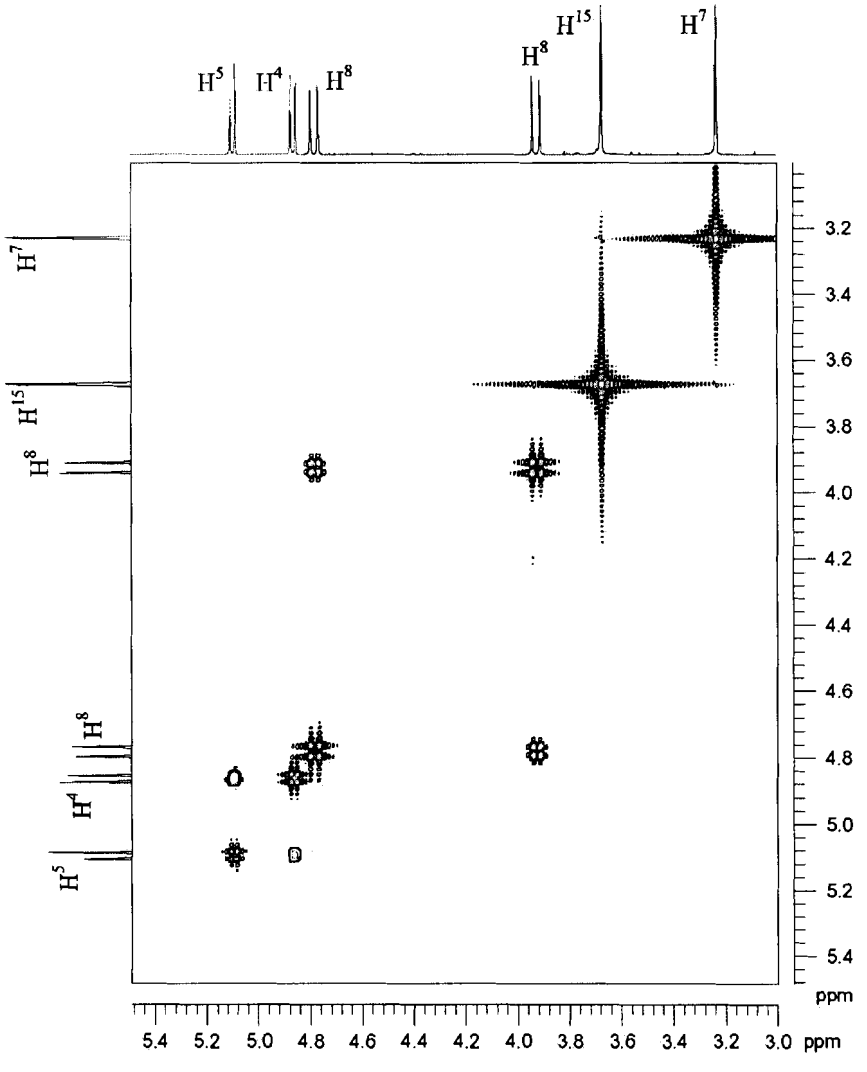
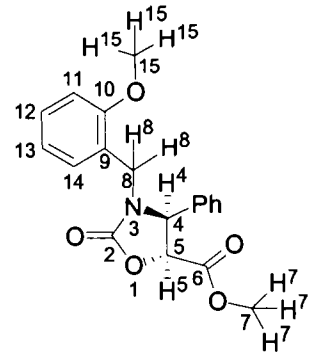


Figure 13 COSY Spectrum of the *Syn* Isomer of Oxazolidinone 93 in $CDCl_3$.



(93-*syn*)

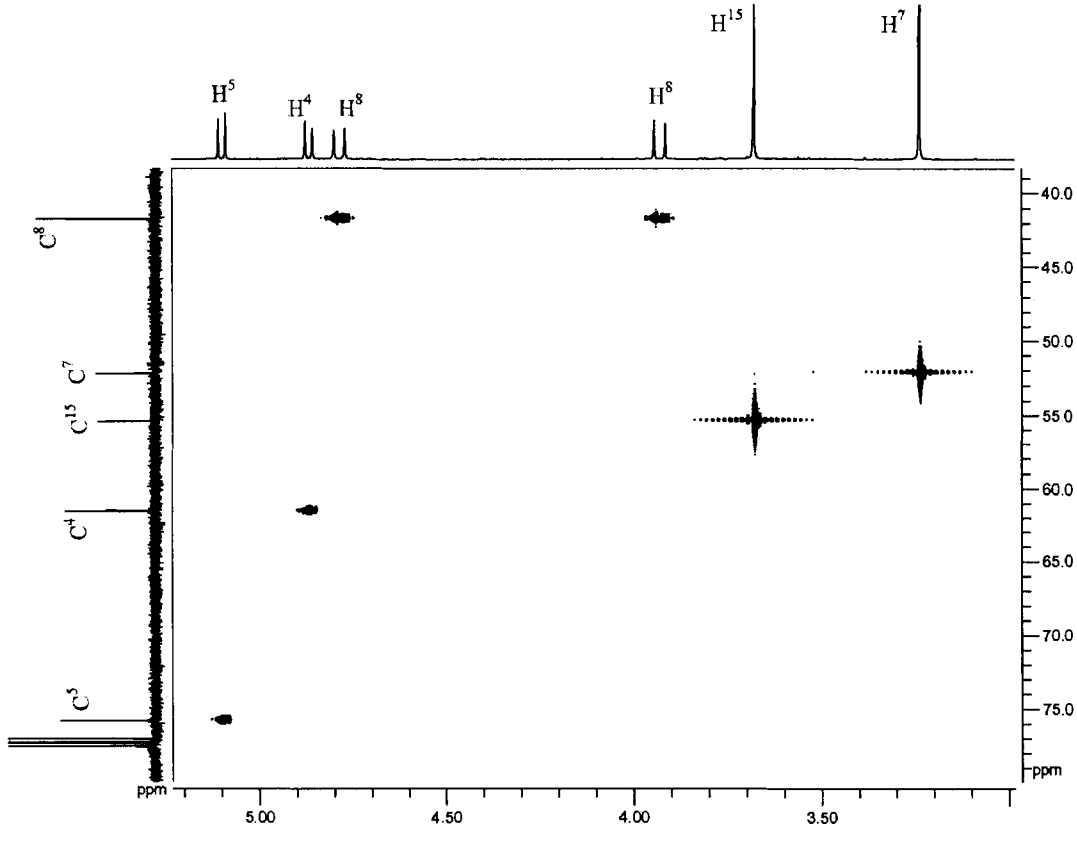
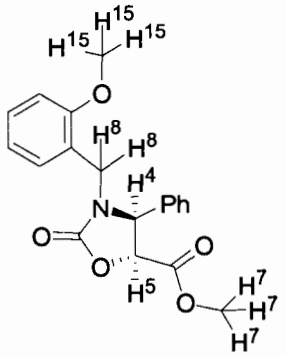


Figure 14 HMQC Spectrum of the *Syn* Isomer of Oxazolidinone 93 in $CDCl_3$.



(93-*syn*)

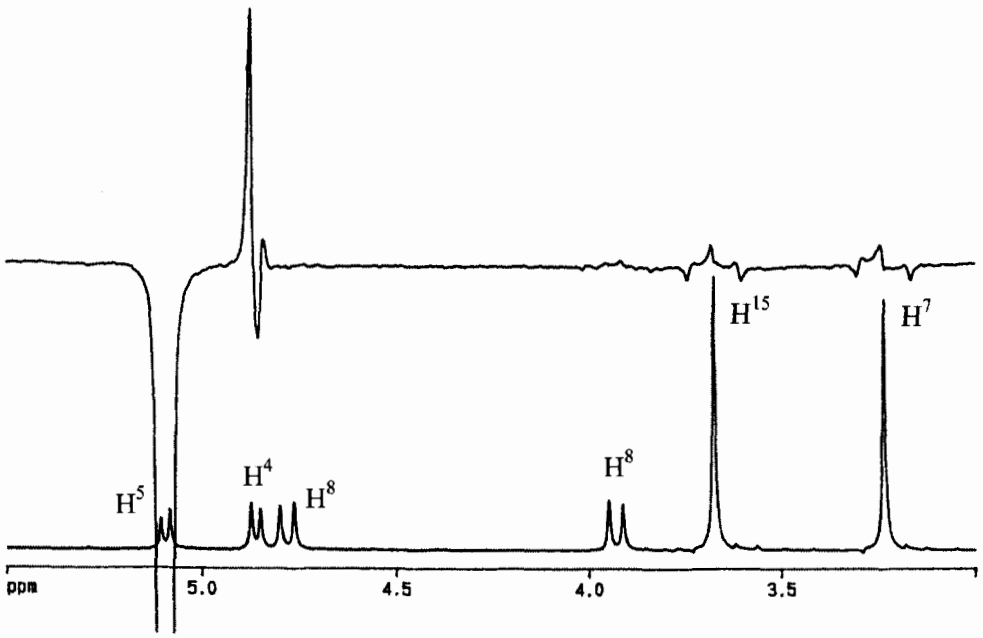


Figure 15 NOE Spectrum of the *Syn* Isomer of Oxazolidinone 93 in $CDCl_3$.

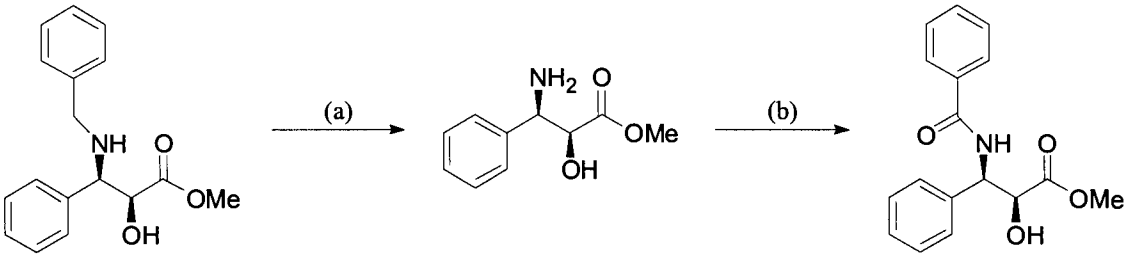
The *syn* isomer of β-amino-α-hydroxy methyl ester **92** exhibited a molecular ion (C.I., M+1) of 336 amu and gave satisfactory elemental analysis. In the ^1H NMR spectrum, two 1H doublets at δ = 4.43 (J = 3.1 Hz) and 4.96 (J = 3.1 Hz) ppm were indicative of two methine protons that are *syn* to one another.

The *anti* isomer of β-amino-α-hydroxy methyl ester **92** exhibited a molecular ion (C.I., M+1) of 336 amu and also gave satisfactory elemental analysis as well. In the ^1H

NMR spectrum, two 1H doublets at δ = 4.69 (J = 4.3 Hz) and 5.00 (J = 4.3 Hz) ppm represented the two methine protons that are *anti* to one another. The stereochemistry of the two isomers was tentatively assigned by analogy with a known compound, β-amino-α-hydroxy methyl ester **87**.

4.4 Synthesis of the *Syn* Methyl Ester Side Chain of Taxol

In order to complete the synthesis of the *syn* methyl ester side chain of Taxol, the diastereomers of the β-amino-α-hydroxy methyl esters **87** were separated chromatographically.[37] The diastereomer **87-*syn*** was then deprotected by hydrogenolysis and the resultant amine was reacted with benzoyl chloride to afford the *syn* methyl ester side chain of Taxol **95** in a 23 % yield over three steps from methyl glyoxylate **86** **(Scheme 27)**.[28, 36]



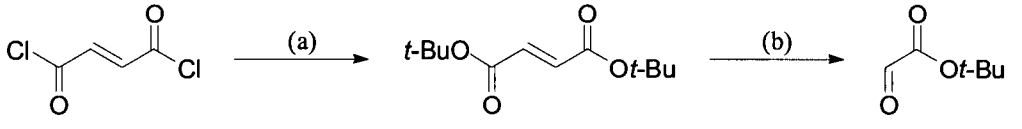
(87-*syn*) (94) (95)

Scheme 27 **Synthesis of the *Syn* Methyl Ester Side Chain of Taxol 95.**
Reagents and conditions: a) H_2, 20 % $Pd(OH)_2$ on carbon, MeOH/AcOH (50/1), 30 h, rt; b) BzCl, NEt_3, DMAP, DCM, 0.5 h, rt, 72 % from **87-*syn***.

4.5 Synthesis of β-Amino-α-hydroxy *tert*-Butyl Esters

Since our research goal was to develop a diastereoselective synthesis of the Taxol side chain, we investigated the use of *tert*-butyl glyoxylate **98** instead of methyl glyoxylate **86** as an electrophile. From Pedersen's work, we expected that larger alkyl glyoxylates would give rise to better diastereoselectivities.[1] *tert*-Butyl glyoxylate **98** was

prepared using a literature procedure (**Scheme 28**).[43] This involved treatment of fumaryl chloride **96** with *tert*-butanol in the presence of *N,N*-dimethylaniline which afforded di-*tert*-butyl fumarate **97**. The spectral data for fumarate **97** was found to be identical to literature values.[43] Ozonolysis of fumarate **97** provided the desired glyoxylate **98** which was distilled and used immediately in the following niobium-promoted cross-coupling reactions.

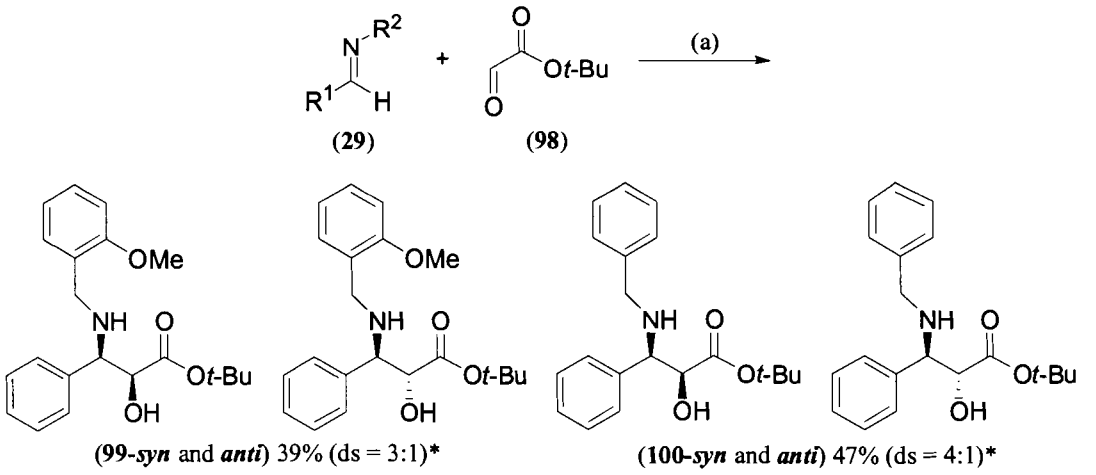


(96) (97) (98)

Scheme 28 **Preparation of *tert*-Butyl Glyoxylate 98.**
Reagents and conditions: a) *t*-BuOH, *N,N*-dimethylaniline, Et_2O, 2.5 h, reflux, 32 %; b) O_3, DCM, 3.0 h, -78 °C, 24 %.

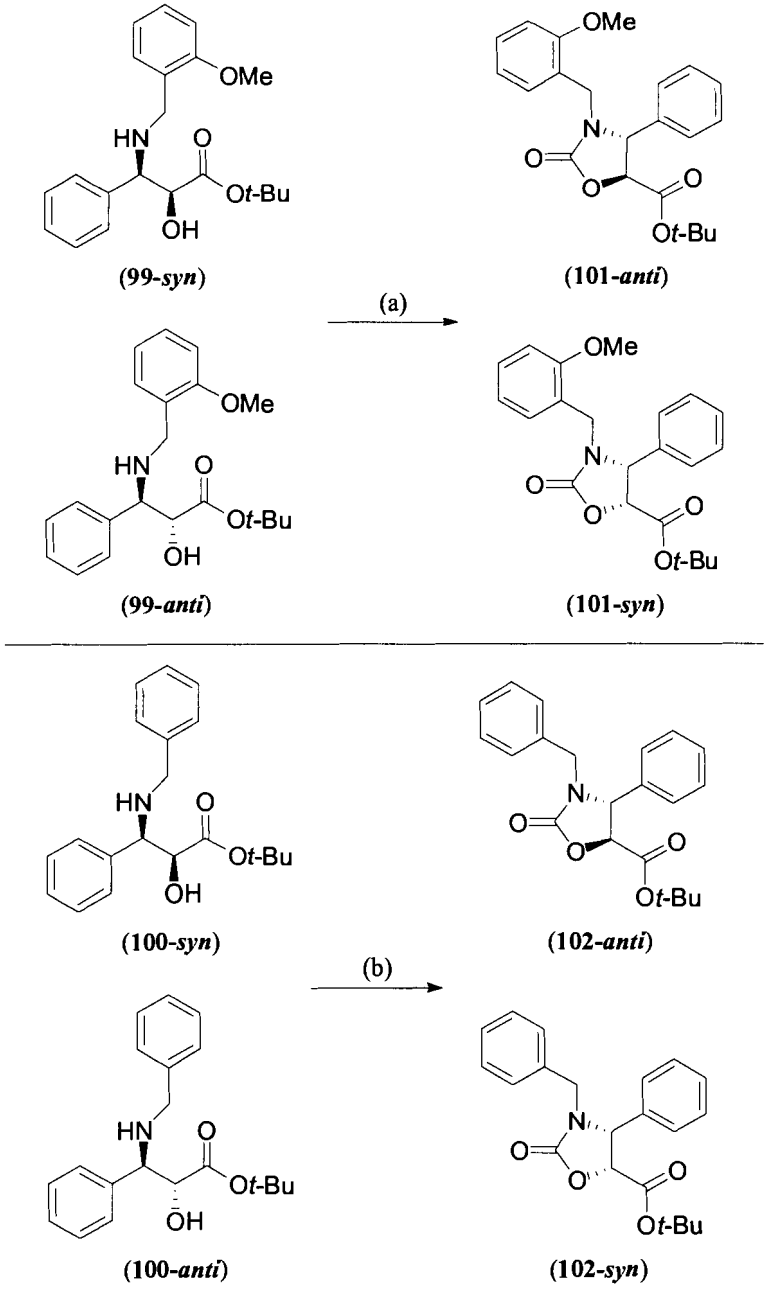
As intended, we were able to achieve improved diastereoselectivities in the $NbCl_3$.DME-mediated coupling of two imines, **35** and **37**, with *tert*-butyl glyoxylate **98** (**Scheme 29**). The *β*-amino-*α*-hydroxy *tert*-butyl esters **99** and **100** were synthesized with *syn* diastereoselectivities of 3:1 and 4:1.

[43] Subasinghe, N.; Schulte, M.; Chan, M. Y. M.; Roon, R. J.; Koerner, J. F.; Johnson, R. L. *J. Med. Chem.* **1990**, *33*, 2734-2744.



Scheme 29 **Synthesis of β-Amino-α-hydroxy *tert*-Butyl Esters 99 and 100.**
Reagents and conditions: a) $NbCl_3$.DME, THF, 0.5 h, rt.
* Yields of products after protection and isolation of the corresponding oxazolidinones.

The presence of an *ortho*-methoxy substituent on imine **37**, that could chelate to the niobium reagent, did not seem to have an effect in determining the stereochemical control of the reaction. Both β-amino-α-hydroxy *tert*-butyl esters **99** and **100** could serve as Taxol side chain precursors since the *N*-benzyl and ester functionalities could be modified before attachment to the taxane ring skeleton by standard deprotection methods.[27] These compounds were protected as their corresponding oxazolidinones in a similar fashion to β-amino-α-hydroxy methyl esters **91** in order to determine the stereochemistry of the major and minor isomers (**Scheme 30**).[40]



Scheme 30 **Derivatization of β-Amino-α-hydroxy *tert*-Butyl Esters 99 and 100.** Reagents and conditions: a) *N,N*-carbonyldiimidazole, THF, 2.5 h, rt; b) *N,N*-carbonyldiimidazole, THF, 2.5 h, rt.

The major *anti* isomer of oxazolidinone **101** which corresponded to the *syn* β-amino-α-hydroxy *tert*-butyl ester **99,** exhibited a molecular ion (C.I., M+1) of 384 amu and gave satisfactory elemental analysis. The lack of broad IR bands in the O-H and N-H

stretching region indicated that the *β*-amino-*α*-hydroxy *tert*-butyl ester precursor **99** had been protected to the oxazolidinone **101**. In the ^{1}H NMR spectrum, a 2H singlet at δ = 4.51 ppm corresponded to the two *anti* methine protons. This was consistent with the reported results that the *syn* isomer of 1,2-amino alcohols is the predominant product in the $NbCl_3$.DME cross-coupling reactions of imines with aldehydes.[1]

The minor *syn* isomer of oxazolidinone **101** which corresponded to the *anti β*-amino-*α*-hydroxy *tert*-butyl ester **99,** exhibited a molecular ion (C.I., M+1) of 384 amu and gave satisfactory elemental analysis. In the ^{1}H NMR spectrum, two 1H doublets at δ = 4.80 (J = 9.6 Hz) and 4.99 (J = 9.6 Hz) ppm corresponded to the two *syn* methine protons that are coupled to one another.

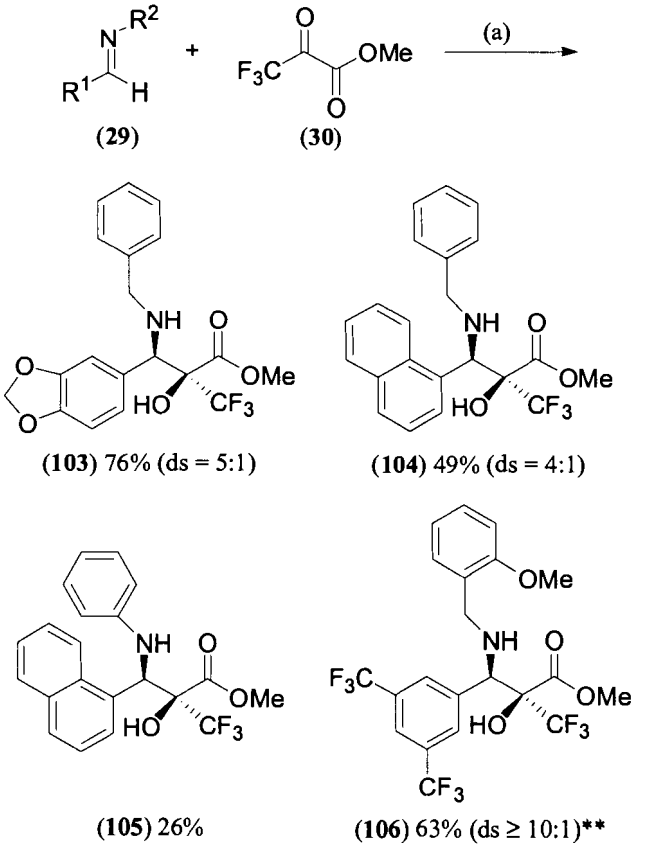
The major *anti* isomer of oxazolidinone **102** exhibited a molecular ion (C.I., M+1) of 354 amu and was fully characterized. The lack of broad IR bands in the O-H and N-H stretching region correlated with the protection of the *β*-amino-*α*-hydroxy *tert*-butyl ester precursor **100** as the oxazolidinone **102**. In the ^{1}H NMR spectrum, two 1H doublets at δ = 4.42 (J = 5.0 Hz) and 4.57 (J = 5.0 Hz) ppm corresponded to the two *anti* methine protons that are coupled to one another.

The minor *syn* isomer of oxazolidinone **102** exhibited a molecular ion (C.I., M+1) of 354 amu and was fully characterized. In the ^{1}H NMR spectrum, two 1H doublets at δ = 4.71 (J = 9.6 Hz) and 4.92 (J = 9.6 Hz) ppm were assigned as two *syn* methine protons that are coupled to one another.

4.6 Synthesis of Fluorinated Taxol Side Chain Derivatives

The use of methyl pyruvate as an electrophile by Greene and co-workers afforded the 1,2-amino alcohol **28** as the major product from a 9:1 mixture of diastereomers, that was used to prepare a Taxol analogue (Section 1.5).[28] We wanted to examine the possibility of incorporating fluorine atoms in an effort to synthesize Taxol side chain derivatives by cross-coupling imines with the commercially fluorinated pyruvate **30**. The fluorinated structural analogues of the Taxol side chain **103, 104, 105** and **106** were synthesized using methyl 3,3,3-trifluoropyruvate **30** as the electrophile (**Scheme 31**). In **Scheme 31**, general imine **29** refers to imines **36, 39, 40** and **41** (Section 2.2). The high diastereoselectivities of these reactions may be the result of both steric and electronic effects caused by incorporating the trifluoromethyl group. It has been suggested that the trifluoromethyl group is isosteric with an isopropyl group.[44] Based on the observations of Pedersen and Greene, it is believed that the *syn* isomer for the fluorinated compounds **103, 104, 105** and **106** was predominant.[1, 28]

[44] Bott, G.; Field, L.D.; Sternhell, S. *J. Am. Chem. Soc.* **1980**, *102*, 5618-5626.



Scheme 31 **Synthesis of Fluorinated Taxol Side Chain Analogues.**
Reagents and conditions: a) $NbCl_3$.DME, THF, 0.5 h, rt.
** Estimated ds by the ^1H NMR spectrum of the crude mixture.

These reactions were compatible with imines that are derived from bulky aldehydes and contain both electron-donating (methylenedioxy) and electron-withdrawing (trifluoromethyl) substituents.

It was not possible to separate the two diastereomers of the *β*-amino-*α*-hydroxy methyl esters **103** by flash column chromatography, so they were analyzed together. The *β*-amino-*α*-hydroxy methyl esters **103** exhibited a molecular ion (C.I., M+1) of 398 amu and were fully characterized. In the ^1H NMR spectrum ($CDCl_3$), two 3H singlets at δ = 3.65 and 3.87 ppm corresponded to the methoxy substituents of each diastereomer. Two 1H signals at δ = 4.03 and 4.28 ppm represented the isolated benzylic (ArC*H*) proton of

each diastereomer. In the ^{13}C NMR spectrum, two quartets at $\delta = 80.50$ ($^{2}J_{C\text{-}F} = 28.9$ Hz) and 81.30 ($^{2}J_{C\text{-}F} = 28.9$ Hz) ppm corresponded to the quaternary carbon adjacent to the trifluoromethyl carbon of each diastereomer. A quartet at $\delta = 123.21$ ($^{1}J_{C\text{-}F} = 287.5$ Hz) ppm related to the trifluoromethyl carbon of the major diastereomer that is coupled to the three fluorine atoms.

Again we were unable to separate the two diastereomers of β-amino-α-hydroxy methyl esters **104** by flash column and preparative liquid chromatography, so they were analyzed together. The β-amino-α-hydroxy methyl esters **104** exhibited a molecular ion (C.I., M+1) of 404 amu and were fully characterized. In the ^{1}H NMR spectrum, two 3H singlets at $\delta = 3.09$ and 3.94 ppm corresponded to the methoxy substituents of each diastereomer. Two 1H peaks at $\delta = 5.15$ and 5.28 ppm corresponded to the isolated benzylic (ArC*H*) proton of each diastereomer. In the ^{13}C NMR spectrum, four quartets at $\delta = 80.22$ ($^{2}J_{C\text{-}F} = 27.5$ Hz), 81.26 ($^{2}J_{C\text{-}F} = 29.0$ Hz), 122.43 ($^{1}J_{C\text{-}F} = 286.9$ Hz) and 123.52 ($^{1}J_{C\text{-}F} = 288.4$ Hz) ppm related to the coupling of the fluorine atoms to the two different carbons atoms of each diastereomer.

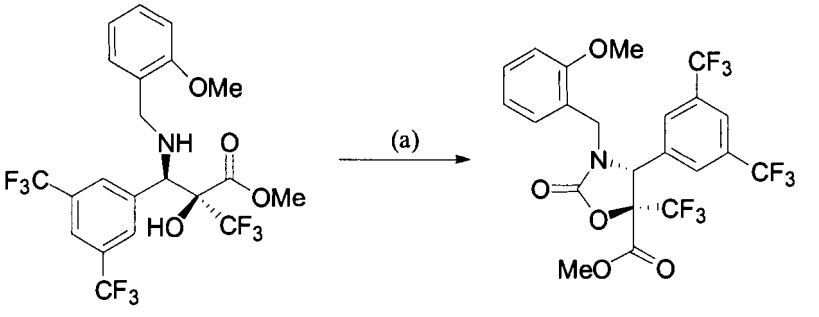
For β-amino-α-hydroxy methyl ester **105** the crude ^{1}H NMR spectrum was complicated. Measuring the diastereoselectivity of the reaction was not possible, however, the yield reported is that of a pure single stereoisomer. The single stereoisomer of β-amino-α-hydroxy methyl ester **105** exhibited a molecular ion (C.I., M+1) of 390 amu and passed elemental analysis. In the ^{1}H NMR spectrum, a 1H peak at $\delta = 6.10$ ppm corresponded to the isolated benzylic proton as evidenced by a separate ^{1}H NMR

spectrum that was recorded on adding deuterium oxide that exchanged with the amine and hydroxy protons at $\delta = 4.15$ and 5.11 ppm.

β-Amino-α-hydroxy methyl ester **106** exhibited a molecular ion (C.I., M+1) of 520 amu and was fully characterized. In the ^{1}H NMR (C_6D_6) spectrum, two 3H singlets at $\delta = 2.96$ and 3.18 ppm were indicative of the two methoxy substituents. A 1H singlet peak at $\delta = 4.36$ ppm corresponded to the isolated benzylic (ArC*H*) proton of the major diastereomer. In the ^{13}C NMR spectrum, a quartet at $\delta = 80.00$ ($^2J_{C\text{-}F} = 27.5$ Hz) ppm corresponded to the aliphatic quaternary carbon adjacent to a trifluoromethyl substituent. Two quartets at $\delta = 123.04$ ($^1J_{C\text{-}F} = 286.9$ Hz) and 123.12 ($^1J_{C\text{-}F} = 273.1$ Hz) ppm related to the two different types of trifluoromethyl carbons that are coupled to three fluorine atoms. A quartet at $\delta = 131.35$ ($^2J_{C\text{-}F} = 33.6$ Hz) ppm corresponded to the two aromatic carbons adjacent to the trifluoromethyl substituents.

We also derivatized β-amino-α-hydroxy methyl ester **106** to the corresponding oxazolidinone **107** in anticipation that a solid product would result. This would have provided an opportunity to obtain a crystal structure in order to confirm the relative stereochemistry of this compound (**Scheme 32**).[40] Oxazolidinone **107** exhibited a molecular ion (C.I., M+1) of 546 amu and was fully characterized. The lack of broad IR bands in the O-H and N-H stretching region indicated that the ester precursor **106** had been protected as the oxazolidinone **107**. In the ^{1}H NMR spectrum, two 3H singlets at $\delta = 3.36$ and 3.64 ppm corresponded to the two methoxy substituents. A 1H peak at $\delta = 4.88$ ppm represented the isolated benzylic (ArC*H*) proton. In the ^{13}C NMR spectrum, the presence of fluorine atoms in the derivatized product was confirmed.

Although a white solid was obtained with a melting point (mp) of 52-54 °C, attempts to obtain suitable crystals for analysis were unsuccessful. Nevertheless, the spectral analysis of β-amino-α-hydroxy methyl ester **106** and oxazolidinone **107** both confirm that only one diastereomer was formed.



(106) (107)

Scheme 32 **Derivatization of a β-Amino-α-hydroxy Methyl Ester 106.**
Reagents and conditions: a) *N,N*-carbonyldiimidazole, THF, 24 h at rt, 24 h at reflux, 53 %.

4.7 Conclusions

Using methyl glyoxylate as an electrophile in the $NbCl_3$.DME cross-coupling reactions, five β-amino-α-hydroxy methyl esters **87**, **89**, **90**, **91** and **92** were synthesized. No diastereoselectivity was observed in these reactions and the products were isolated as a 1:1 mixture of the *syn* and *anti* isomers. The synthesis of the *syn* methyl ester side chain **95** of Taxol was completed, in a non-diastereoselective fashion, following the separation of the two diastereomers of β-amino-α-hydroxy methyl ester **87**, in three steps with an overall yield of 23 % from the corresponding glyoxylate precursor **86**. Increasing the steric bulk of the glyoxylate electrophile led to diastereoselective control of the reaction favoring the formation of the *syn* isomer in the synthesis of two β-amino-α-hydroxy *tert*-butyl esters **99** and **100**. These two β-amino-α-hydroxy *tert*-butyl esters

99 and **100** are suitable for use in a diastereoselective synthesis of a *syn tert*-butyl side chain of Taxol. The use of a fluorinated pyruvate electrophile **30** afforded the fluorinated Taxol side chain analogues **103**, **104**, **105** and **106**, diastereoselectively. This synthetic method was found to be compatible with both electron-withdrawing and electron-donating substituents on the imine precursors.

CHAPTER 5. Experimental.

5.1 General Experimental

Unless otherwise specified, all non-aqueous reactions were performed under an inert atmosphere of nitrogen using oven-baked glassware. Reaction temperatures listed were those of the external bath.

Anhydrous tetrahydrofuran (THF 99.9 %, inhibitor free) was purchased from the Aldrich chemical company unless otherwise noted. Benzene, dichloromethane, and triethylamine were dried over calcium hydride and distilled under an atmosphere of nitrogen. Diethyl ether (ether) was dried over sodium/benzophenone and distilled under an atmosphere of nitrogen. Methanol was dried over magnesium methoxide and distilled under an atmosphere of nitrogen. All other organic solvents were dried according to standard literature procedures and distilled before use.[45] All commercially available reagents were used as received unless otherwise noted. Brine refers to a saturated aqueous solution of sodium chloride. Molecular sieves were activated by heating over a Bunsen burner for 4 h.

Yields listed for diastereomers represent the total yield before further separation to the individual stereoisomers by repeated chromatography. Melting points (mp) measurements were performed on a Gallenkamp apparatus and are uncorrected. Nuclear magnetic resonance (NMR) spectra for ^{1}H and ^{13}C were recorded on a Bruker Model AMX 400 Spectrometer using operating frequencies of 400.1 and 100.6 MHz, respectively. Nuclear magnetic resonance (NMR) spectra for COSY and HMQC were

[45] Armarego, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*, 4th Ed., The Bath Press, Great Britain, **1998**.

recorded on a Varian Model AS 500 Spectrometer using operating frequencies of 499.8 and 125.8 MHz, respectively. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal reference (acetone: δ 2.05 ppm, benzene: δ 7.16 ppm, chloroform: δ 7.26 ppm and water: δ 4.79 ppm).[46] NMR data is reported as follows: chemical shift, multiplicity (s=singlet, d=doublet, t=triplet, q=quartet and m=multiplet), integration, coupling constants (Hz) and assignment. Infrared (IR) spectra were recorded on a Perkin-Elmer IR spectrophotometer. IR spectra were either recorded as a neat film, KBr disc, nujol mull, or as an evaporated film (ef). Mass spectra (MS) were recorded on a Hewlett Packard 5985 GC-mass spectrometer using chemical ionization. Elemental analyses for carbon, hydrogen and nitrogen (C, H and N) were conducted using a Carlo Erba Model 1106 elemental analyzer.

Analytical thin layer chromatography (TLC) was performed on precoated EM Science Silica Gel 60 F-254 plates with aluminum backing and visualization was accomplished with ultraviolet light. Compounds on the plates were further identified with either an ethanolic solution of *p*-anisaldehyde or an acidic solution of cerium molybdate. Flash chromatography on silica gel was performed using a pressurized flow of the desired solvent system on Merck Silica Gel 60 (230-400 Mesh).[47]

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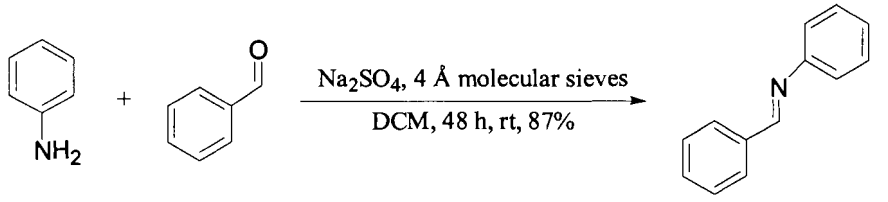
[46] Gottlieb, H. E.; Kotlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512-7515.

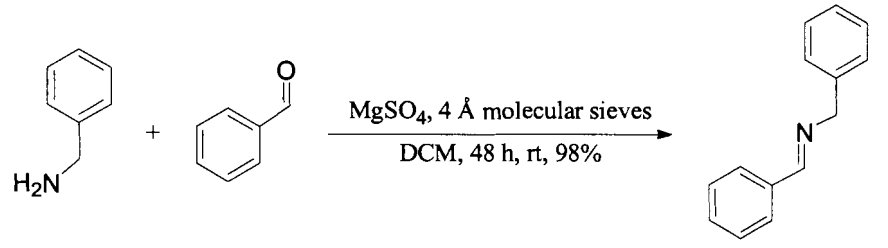
[47] Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.

5.2 Experimental Section Concerning Chapter 2



(108) (109) (34)

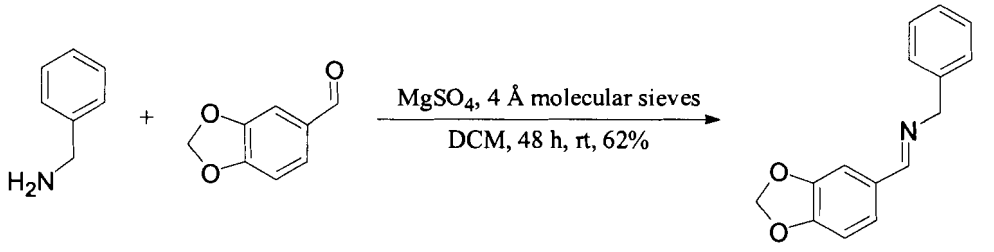
***N*-Benzylidene-aniline 34** was prepared based on a literature procedure.[30] A solution of aniline **108** (1.95 mL, 21.4 mmol) in dichloromethane (86 mL) was treated in succession with benzaldehyde **109** (2.20 mL, 21.6 mmol), anhydrous sodium sulfate (10.7 g, 75.3 mmol) and activated molecular sieves (4 Å, 1.00 g). The mixture was stirred at room temperature for 48 h. After filtering off the solid, the solution was concentrated under vacuum. Recrystallization of the residue from ethanol afforded the title compound **34** as a yellow solid (3.38 g, 18.7 mmol, 87 %): mp: 51-52 °C (ethanol) (lit.[48] mp 52 °C, ethanol); R_f 0.84 (hexanes:ether, 7:3); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.76-6.86 (m, 1H, Ar*H*), 7.16-7.28 (m, 3H, Ar*H*), 7.38-7.50 (m, 4H, Ar*H*), 7.90-7.94 (m, 2H, Ar*H*), 8.45 (s, 1H, NC*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 120.86, 125.96, 128.77, 129.14, 129.36, 129.73, 131.42, 131.45, 160.44; IR (KBr, cm^{-1}) 3060, 2990, 1626, 1590, 1484, 1451, 1193, 761, 693; MS (C.I.) *m/z* 182 [M+1].



(110) (109) (35)

[48] Kuder, J.E.; Gibson, H.W.; Wychick, D. *J. Org. Chem.* **1975**, *40*, 875-878.

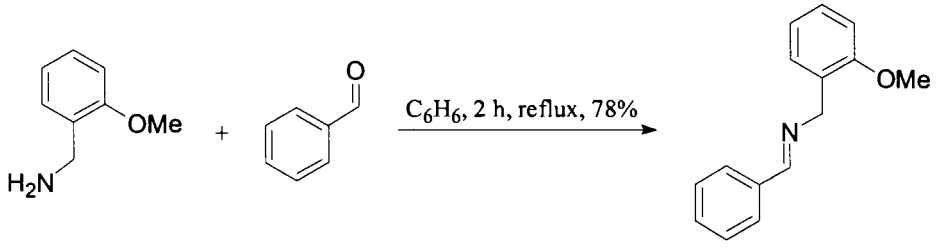
***N*-Benzylidene-benzylamine 35** was prepared based on a literature procedure.[30] A solution of benzylamine **110** (2.05 mL, 18.8 mmol) in dichloromethane (75 mL) was treated in succession with benzaldehyde **109** (1.90 mL, 18.7 mmol), anhydrous magnesium sulfate (11.2 g, 93.0 mmol) and activated molecular sieves (4 Å, 1.00 g). The mixture was stirred at room temperature for 48 h. After filtering off the solid residue, the solution was concentrated under vacuum. Purification of the residue by kugelrohr distillation afforded the title compound **35** as a clear oil (3.57 g, 18.3 mmol, 98 %): R_f 0.71 (hexanes:ethyl acetate, 4:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.88 (s, 2H, ArC*H*$_2$), 7.31-7.50 (m, 8H, Ar*H*), 7.85 (m, 2H, Ar*H*), 8.44 (s, 1H, NC*H*); ^{13}C NMR (C_6D_6, 100 MHz) δ 64.87, 126.76, 127.15, 127.25, 127.61, 128.33, 128.42, 130.39, 136.74, 161.08; IR (neat, cm^{-1}) 3062, 3027, 2839, 1644, 1601, 1580, 1496, 1451, 1311, 1292, 1027, 858, 749, 693; MS (C.I.) *m/z* 196 [M+1], 107.



(110) **(111)** **(36)**

***N*-(3,4-Methylenedioxy)-benzylidene-benzylamine 36** was prepared based on a literature procedure.[30] A solution of benzylamine **110** (2.05 mL, 18.8 mmol) in dichloromethane (75 mL) was treated in succession with piperonal **111** (2.80 g, 18.7 mmol), anhydrous magnesium sulfate (11.2 g, 93.0 mmol) and activated molecular sieves (4 Å, 1.00 g). The mixture was stirred at room temperature for 48 h. After filtering off the solid, the solution was concentrated under vacuum. Recrystallization of the residue from hexanes:dichloromethane (4:1) afforded the title compound **36** as a white solid

(2.78 g, 11.6 mmol, 62 %): mp: 65-66 °C (hexanes:dichloromethane) (lit.[49] mp 69-70 °C); R_f 0.49 (hexanes:ethyl acetate, 4:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.75 (s, 2H, ArCH_2), 6.00 (s, 2H, OCH_2O), 6.84 (d, 1H, J = 7.7 Hz, ArH), 7.15-7.17 (dd, 1H, J = 8.1, 1.5 Hz, ArH), 7.26-7.31 (m, 1H, ArH), 7.32-7.37 (m, 4H, ArH), 7.43 (s, 1H, ArH), 8.28 (s, 1H, NCH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 64.70, 101.42, 106.71, 108.01, 124.58, 126.93, 127.91, 128.47, 130.96, 139.40, 148.25, 149.94, 161.09; IR (KBr, cm^{-1}) 3027, 2860, 2831, 1641, 1442, 1256, 924; MS (C.I.) *m/z* 240 [M+1].

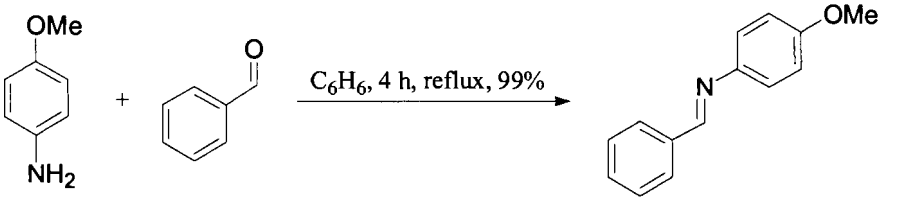


(112) **(109)** **(37)**

Benzylidene-(2-methoxybenzyl)-amine 37 was prepared based on a literature procedure.[31] A solution of 2-methoxybenzylamine **112** (4.40 mL, 33.7 mmol) in benzene (120 mL) was treated with benzaldehyde **109** (3.45 mL, 33.9 mmol). The mixture was heated at reflux in a round-bottom flask equipped with a Dean-Stark trap for 2 h. After allowing the mixture to cool to room temperature, the solution was concentrated under vacuum. Purification of the residue by kugelrohr distillation afforded the title compound **37** as a clear colorless oil (5.95 g, 26.4 mmol, 78 %): R_f 0.76 (dichloromethane:ether, 9:1); ^{1}H NMR (C_6D_6, 400 MHz) δ 3.38 (s, 3H, ArOCH_3), 4.97 (s, 2H, ArCH_2), 6.62 (d, 1H, J = 8.1 Hz, ArH), 6.98 (t, 1H, J = 7.4 Hz, ArH), 7.13-7.22 (m, 4H, ArH), 7.54 (m, 1H, J = 7.4 Hz, ArH), 7.78-7.84 (m, 2H, ArH), 8.18 (s, 1H, NCH); ^{13}C NMR (C_6D_6, 100

[49] Strumberg, D.; Pommier, Y.; Paull, K.; Jayaraman, M.; Nagafuji, P.; Cushman, M. *J. Med. Chem.* **1999**, *42*, 446-457.

MHz) δ 54.60, 59.29, 110.05, 120.61, 127.52, 127.76, 127.89, 128.63, 129.31, 130.29, 136.94, 157.16, 161.37; IR (neat, cm^{-1}) 2836, 1646, 1601, 1493, 1463, 1243, 1030, 753; MS (C.I.) *m/z* 226 [M+1]. Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.70; H, 6.66; N, 6.46.



(113) **(109)** **(38)**

***N*-Benzylidene-4-methoxy-aniline 38** was prepared based on a literature procedure.[31] A solution of *p*-anisidine **113** (10.0 g, 81.2 mmol) in benzene (150 mL) was treated with benzaldehyde **109** (8.25 mL, 81.2 mmol). The mixture was heated at reflux in a round-bottom flask equipped with a Dean-Stark trap for 4 h. After allowing the mixture to cool to room temperature, the solution was concentrated under vacuum. Recrystallization of the residue from ethanol afforded the title compound **38** as a shiny grey solid (17.1 g, 81.0 mmol, 99 %): mp: 64-66 °C (ethanol) (lit.[50] mp 71-72 °C, ethanol); R_f 0.86 (ethyl acetate:hexanes, 4:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.84 (s, 3H, ArOC*H*$_3$), 6.91-6.96 (m, 2H, Ar*H*), 7.23-7.28 (m, 2H, Ar*H*), 7.44-7.49 (m, 3H, Ar*H*), 7.86-7.92 (m, 2H, Ar*H*), 8.46 (s, 1H, NC*H*); ^{13}C NMR (C_6D_6, 100 MHz) δ 54.68, 114.42, 122.40, 128.53, 128.64, 130.62, 137.06, 145.23, 157.51, 158.58; IR (KBr, cm^{-1}) 2956, 1623, 1506, 1249, 873; MS (C.I.) *m/z* 212 [M+1]. Anal. Calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.39; H, 6.26; N, 6.59.

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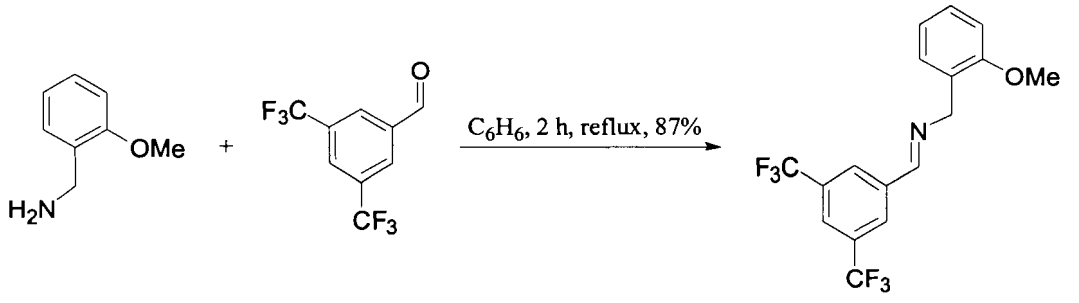
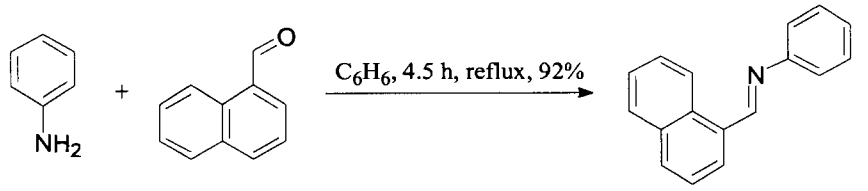
[50] Ojima, I.; Habus, I.; Zhao, M.; Zucco, M.; Park, Y. H.; Sun, C. M.; Brigaud, T. *Tetrahedron* **1992**, *48*, 6985-7012.



(112) (114) (39)

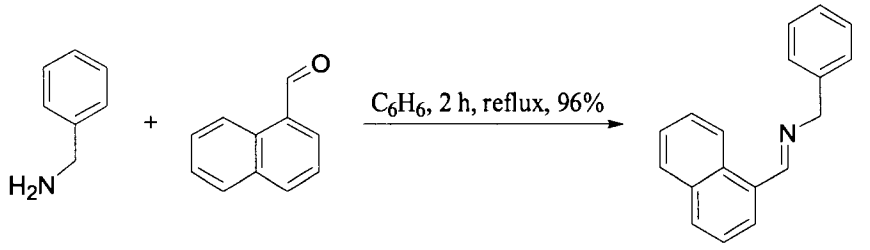
***N*-(3,5-*Bis*-trifluoromethyl)-benzylidene-(2-methoxybenzyl)-amine 39** was prepared based on a literature procedure.[31] A solution of 2-methoxybenzylamine **112** (550 μL, 4.21 mmol) in benzene (25 mL) was treated with 3,5-*bis*(trifluoromethyl)benzaldehyde **114** (680 μL, 4.13 mmol). The mixture was heated at reflux in a round-bottom flask equipped with a Dean-Stark trap for 2 h. After allowing the mixture to cool to room temperature, the solution was concentrated under vacuum. Purification of the residue by kugelrohr distillation afforded the title compound **39** as a yellow oil (1.30 g, 3.59 mmol, 87 %): R_f 0.80 (pentane:ether, 4:1); ^{1}H NMR (C_6D_6, 400 MHz) δ3.39 (s, 3H, OCH_3), 4.90 (s, 2H, ArCH_2), 6.62 (d, 1H, J = 8.9 Hz, Ar*H*), 6.96 (dt, 1H, J = 7.5, 1.1 Hz, Ar*H*), 7.15-7.20 (m, 1H, Ar*H*), 7.38 (dd, 1H, J = 7.5, 1.8 Hz, Ar*H*), 7.70-7.75 (m, 2H, Ar*H*), 7.95 (s, br, 2H, Ar*H* and NC*H*); ^{13}C NMR (C_6D_6, 100 MHz) δ 54.56, 59.03, 110.23, 120.69, 123.18, 123.40 (q, $^1J_{C\text{-}F}$ = 273.1 Hz, CCF_3), 126.95, 128.24, 128.45, 129.61, 131.60 (q, $^2J_{C\text{-}F}$ = 34.2 Hz, CCF_3), 138.54, 157.23, 157.97; IR (neat, cm^{-1}) 2840, 1651, 1603, 1494, 1281, 1132, 898, 845, 755, MS (C.I.) *m/z* 362 [M+1], 256, 138, 121. Anal. Calcd for $C_{17}H_{13}F_6NO$: C, 57.43; H, 4.57; N, 3.53. Found: C, 57.38; H, 4.61; N, 3.63.



(108) (115) (40)

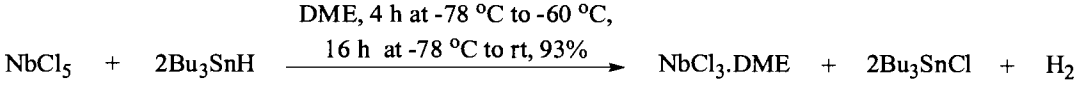
***N*-(1-Napthylidene)-aniline 40** was prepared based on a literature procedure.[31] A solution of aniline **108** (9.60 mL, 105 mmol) in benzene (150 mL) was treated with 1-napthaldehyde **115** (14.6 mL, 108 mmol). The mixture was heated at reflux in a round-bottom flask equipped with a Dean-Stark trap for 4.5 h. After allowing the mixture to cool to room temperature, the solution was concentrated under vacuum. Recrystallization of the residue from hexanes afforded the title compound **40** as a yellow solid (22.2 g, 96.1 mmol, 92 %): mp: 68-69 °C (hexanes) (lit.[51] mp 71 °C, hexanes); R_f 0.92 (dichloromethane:ether, 9:1); ^{1}H NMR (C_6D_6, 400 MHz) δ7.08-7.36 (m, 7H, Ar*H*), 7.39-7.46 (m, 1H, Ar*H*), 7.62-7.68 (m, 2H, Ar*H*), 7.95-8.00 (d, 1H, J = 7.0 Hz, Ar*H*), 8.84 (s, 1H), 9.24-9.28 (d, 1H, J = 8.5 Hz); ^{13}C NMR (C_6D_6, 100 MHz) δ121.05, 124.93, 125.11, 125.72, 126.10, 126.33, 126.61, 126.72, 128.62, 129.11, 130.51, 131.75, 134.09, 153.19, 159.96; IR (neat, cm^{-1}) 3064, 1588, 1484, 1335, 1236, 1199, 1162, 803; MS (C.I.) *m/z* 232 [M+1]. Anal. Calcd for $C_{17}H_{13}N$: C, 88.28; H, 5.67; N, 6.06. Found: C, 88.13; H, 5.75; N, 5.88.

[51] Schulze, vJ.; Gerson, F.; Murrell, J.N.; Heilbronner, E. *Helv. Chim. Acta* **1961**, *44*, 428-438.



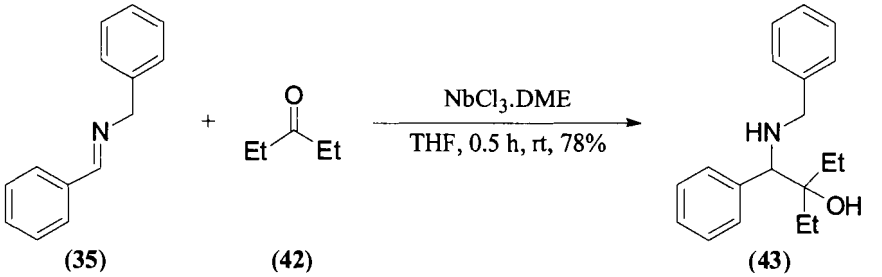
(110) (115) (41)

***N*-(1-Napthylidene)-benzylamine 41** was prepared based on a literature procedure.[31] A solution of benzylamine **110** (10.2 mL, 93.4 mmol) in benzene (150 mL) was treated with 1-napthaldehyde **115** (12.8 mL, 94.3 mmol). The mixture was heated at reflux in a round-bottom flask equipped with a Dean-Stark trap for 2 h. After allowing the mixture to cool to room temperature, the solution was concentrated under vacuum. Purification of the residue by kugelrohr distillation afforded the title compound **41** as an orange oil (21.0 g, 89.8 mmol, 96 %): R_f 0.81 (dichloromethane:ether, 9:1); ^{1}H NMR (C_6D_6, 400 MHz) δ 4.75 (s, 2H, ArC*H*$_2$), 7.12-7.34 (m, 5H, Ar*H*), 7.38-7.45 (m, 3H, Ar*H*), 7.63 (t, 2H, J = 8.6 Hz, Ar*H*), 7.81 (dd, 1H, J = 7.3, 1.3 Hz, Ar*H*), 8.68 (s, 1H), 9.36 (d, 1H, J = 8.6 Hz); ^{13}C NMR (C_6D_6, 100 MHz) δ 66.21, 125.31, 125.52, 126.25, 127.07, 127.41, 128.16, 128.71, 128.77, 130.27, 131.30, 131.88, 131.95, 134.34, 140.31, 161.92; IR (neat, cm^{-1}) 3060, 2828, 1643, 1510, 1495, 1453, 1337, 1237, 1066, 1027, 801, 775, MS (C.I.) *m/z* 246 [M+1], 108. Anal. Calcd for $C_{18}H_{15}N$: C, 88.13; H, 6.16; N, 5.71. Found: C, 88.00; H, 6.31; N, 5.81.



Niobium trichloride dimethoxyethane complex (NbCl$_3$.DME) was prepared by the modification of a known procedure.[3] A two-neck 500-mL Schlenk flask with a nitrogen inlet adapter was charged with 1,2-dimethoxyethane (270 mL) and tributyltin

hydride (50 g, 170 mmol). A 100 mL round-bottomed flask containing niobium pentachloride (22.5 g, 83.3 mmol) was attached to the Schlenk flask *via* a piece of Teflon tubing (30 cm long, 2 cm in diameter) that was configured with two male 19/24 joints on each end. The reaction mixture was then cooled to -78 °C with vigorous stirring and the niobium pentachloride was added slowly over 90 min. After the addition was complete, the bath temperature was maintained between -78 °C and -60 °C for 4 h. At this point, the reaction was cooled to -78 °C and allowed to slowly warm to room temperature overnight. After stirring overnight, the solution was allowed to stand for 4 h, allowing the product to settle. The reaction product was isolated by first removing a large portion of the supernatant using a cannula, followed by washing the solid with 1,2-dimethoxyethane (3 x 30 mL) and pentane (3 x 30 mL). Residual solvents were removed under vacuum to afford the title compound as a brick red solid (22.5 g, 77.7 mmol, 93 %): mp (sealed capillary): 118-125 °C (lit.[3] mp 116-130 °C); IR (nujol mull, cm^{-1}) 2923, 2854, 1305, 1239, 1178, 1170, 1154, 1069, 1027, 1007, 892, 846.

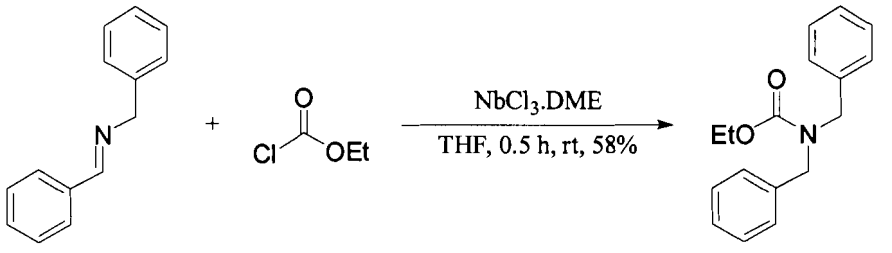


(35) (42) (43)

1-Benzylamino-2-ethyl-1-phenyl-butan-2-ol 43. To a solution of niobium trichloride dimethoxyethane complex (868 mg, 3.00 mmol) in tetrahydrofuran (16 mL) at room temperature was added a solution of *N*-benzylidene-benzylamine **35** (292 mg, 1.50 mmol) in tetrahydrofuran (1.5 mL). A color change from maroon to dark green over the course of 30 min was observed while stirring at room temperature. After 30 min, diethyl

ketone **42** (105 μL, 1.00 mmol) was added dropwise to the reaction mixture. After stirring for 30 min the reaction mixture was poured into a separatory funnel containing an aqueous solution of potassium hydroxide (10 % w/v, 20 mL) and extracted with ether (2 x 20 mL). The combined ether layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford a yellow oil. After dissolving the oil in ether (15 mL), the resultant solution was extracted with hydrochloric acid (1 *M*, 3 x 15 mL) after which the aqueous layers were combined and basified with potassium hydroxide pellets at 0 °C to pH 12. The aqueous fraction was then extracted with ether (3 x 45 mL) and the combined ether layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. Purification by silica gel chromatography using hexanes:ethyl acetate (9:1) as the eluent afforded the title compound **43** as a yellow oil (221 mg, 0.781 mmol, 78 %): R_f 0.35 (hexanes:ethyl acetate, 6:1); ^{1}H NMR (C_6D_6, 400 MHz) δ 0.81 (t, 3H, J = 7.3 Hz, CH_2CH_3), 0.91 (t, 3H, J = 7.3 Hz, CH_2CH_3), 1.10-1.34 (m, 2H, CH_2CH_3), 1.46-1.56 (m, 1H, CH_2CH_3), 1.73-1.84 (m, 1H, CH_2CH_3), 3.38 (d, 1H, J = 12.9 Hz, ArCHH), 3.60 (d, 1H, J = 12.9 Hz, ArCHH), 3.60 (s, 1H, ArCH), 7.00-7.33 (m, 10H, ArH); ^{13}C NMR (C_6D_6, 100 MHz) δ 7.39, 7.90, 27.71, 27.76, 51.61, 67.04, 75.72, 126.90, 127.00, 128.05, 128.24, 128.34, 128.76, 140.63, 140.68; IR (ef, cm^{-1}) 3452, 2967, 2937, 1575, 1494, 1454, 1117, 1028, 956, 852; MS (C.I.) *m/z* 284 [M+1], 266, 196. Anal. Calcd for $C_{19}H_{25}NO$: C, 80.52; H, 8.61; N, 5.20. Found: C, 80.40; H, 8.68; N, 5.37.

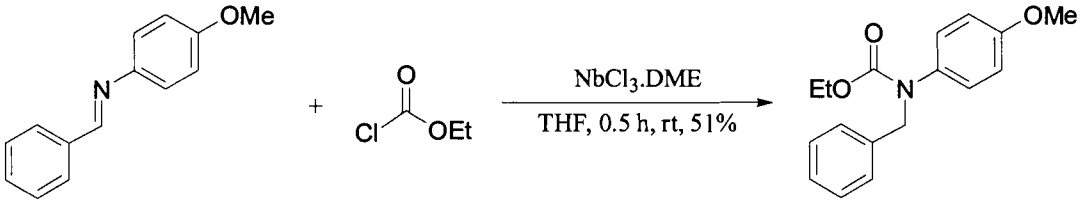
5.3 Experimental Section Concerning Chapter 3



(35) (44) (48)

Ethyl *N,N*-dibenzyl-carbamate 48. To a solution of niobium trichloride dimethoxyethane complex (434 mg, 1.50 mmol) in tetrahydrofuran (6 mL) at room temperature was added a solution of *N*-benzylidene-benzylamine **35** (146 mg, 0.748 mmol) in tetrahydrofuran (2 mL). A color change from maroon to dark green over the course of 30 min was observed while stirring at room temperature. After 30 min, ethyl chloroformate **44** (360 μL, 3.77 mmol) was added dropwise to the reaction mixture. After stirring for 30 min the reaction mixture was cooled to 0 °C followed by the dropwise addition of an aqueous solution of potassium hydroxide (10 % w/v, 10 mL). The mixture was then poured into a separatory funnel and extracted with ether (2 x 10 mL). The combined ether layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford a yellow oil. Purification by silica gel chromatography using hexanes:ethyl acetate (30:1) as the eluent afforded the title compound **48** as a clear oil (117 mg, 0.434 mmol, 58 %): R_f 0.50 (hexanes:ethyl acetate, 6:1); ^{1}H NMR (C_6D_6, 400 MHz) δ 1.05 (t, 3H, J = 7.3 Hz, CH_2CH_3), 4.19 (q, 2H, J = 7.3 Hz, CH_2CH_3), 4.24-4.40 (s, br, 2H, $ArCH_2$), 4.44-4.60 (s, br, 2H, $ArCH_2$), 7.00-7.30 (m, 10H, Ar*H*); ^{13}C NMR (C_6D_6, 100 MHz) δ 14.46, 48.77, 49.36, 61.33, 127.19, 127.97, 138.01, 156.55; IR (neat, cm^{-1}) 3030, 2981, 1698, 1454, 1422, 1235, 1117, 1075, 1027,

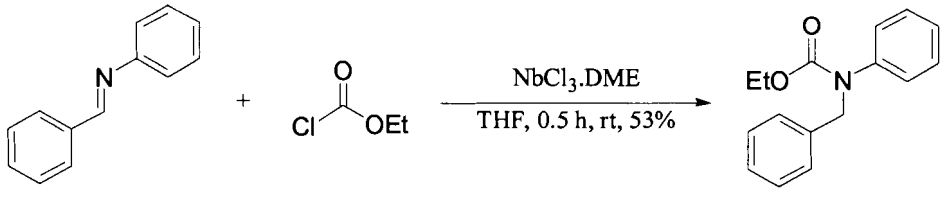
965, 885; MS (C.I.) *m/z* 270 [M+1]. Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81, H, 7.11, N, 5.20. Found: C, 76.01; H, 7.14; N, 5.38.



(38) (44) (50)

Ethyl *N*-benzyl-*N*-(4-methoxy-phenyl)-carbamate 50. To a solution of niobium trichloride dimethoxyethane complex (651 mg, 2.25 mmol) in tetrahydrofuran (6 mL) at room temperature was added a solution of *N*-benzylidene-4-methoxy-aniline **38** (158 mg, 0.748 mmol) in tetrahydrofuran (2 mL). A color change from maroon to dark yellow over the course of 2.5 h was observed while stirring at room temperature. After 2.5 h, ethyl chloroformate **44** (360 μL, 3.77 mmol) was added dropwise to the reaction mixture. After stirring for 30 min the reaction mixture was cooled to 0 °C followed by the dropwise addition of an aqueous solution of potassium hydroxide (10 % w/v, 10 mL). The mixture was then poured into a separatory funnel and extracted with ether (2 x 10 mL). The combined ether layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford a red oil. Purification by silica gel chromatography using hexanes:ethyl acetate (30:1) as the eluent afforded the title compound **50** as an orange oil (108 mg, 0.378 mmol, 51 %): R_f 0.71 (hexanes:ethyl acetate, 3:1); ^{1}H NMR (C_6D_6, 400 MHz) δ 0.99 (t, 3H, J = 7.3 Hz, CH_2CH_3), 3.21 (s, 3H, $ArOCH_3$), 4.13 (q, 2H, J = 6.9 Hz, CH_2CH_3), 4.83 (s, br, 2H, $ArCH_2$), 6.54-6.68 (m, 2H, Ar*H*), 6.80-7.40 (m, 7H, Ar*H*); ^{13}C NMR (C_6D_6, 100 MHz) δ 14.38, 54.47, 61.33, 113.96, 126.79, 127.19, 128.35, 129.20, 129.39, 135.20, 138.68, 155.83, 158.06; IR (neat, cm^{-1}) 2979, 2934,

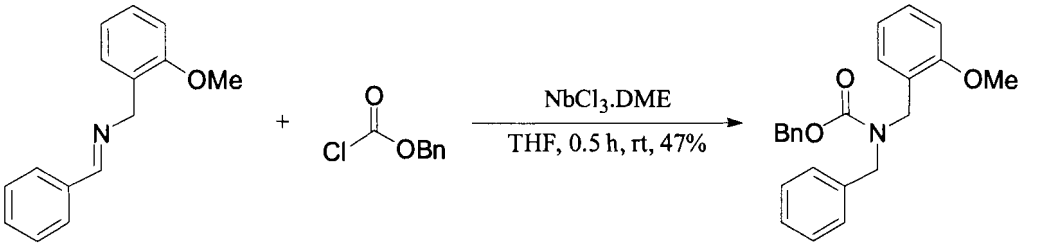
1702, 1513, 1406, 1380, 1247, 1133, 1028, 835; MS (C.I.) *m/z* 286 [M+1]. Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56, H, 6.71, N, 4.91. Found: C, 71.28; H, 6.65; N, 5.09.



(34) (44) (51)

Ethyl *N*-benzyl-*N*-phenyl-carbamate 51. To a solution of niobium trichloride dimethoxyethane complex (651 mg, 2.25 mmol) in tetrahydrofuran (6 mL) at room temperature was added a solution of *N*-benzylidene-aniline **34** (136 mg, 0.751 mmol) in tetrahydrofuran (2 mL). A color change from maroon to dark yellow over the course of 30 min was observed while stirring at room temperature. After 30 min, ethyl chloroformate **44** (360 μL, 3.77 mmol) was added dropwise to the reaction mixture. After stirring for 30 min the reaction mixture was cooled to 0 °C followed by the dropwise addition of an aqueous solution of potassium hydroxide (10 % w/v, 10 mL). The mixture was then poured into a separatory funnel and extracted with ether (2 x 10 mL). The combined ether layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford a yellow oil. Purification by silica gel chromatography using hexanes:ethyl acetate (30:1) as the eluent afforded the title compound **51** as a yellow oil (102 mg, 0.400 mmol, 53 %): R_f 0.34 (hexanes:ethyl acetate, 8:1); ^{1}H NMR (C_6D_6, 400 MHz) δ0.95 (t, 3H, J= 6.9 Hz, CH_2CH_3), 4.09 (q, 2H, J = 6.9 Hz, CH_2CH_3), 4.81 (s, 2H, ArCH_2), 6.89-6.94 (m, 1H, Ar*H*), 6.99-7.15 (m, 6H, Ar*H*), 7.20 (s, 1H, Ar*H*), 7.24-7.28 (m, 2H, Ar*H*); ^{13}C NMR (C_6D_6, 100 MHz) δ 14.27, 54.06, 61.40, 125.97, 126.96, 127.14, 128.35, 128.61, 128.90, 138.55, 142.61, 155.45; IR

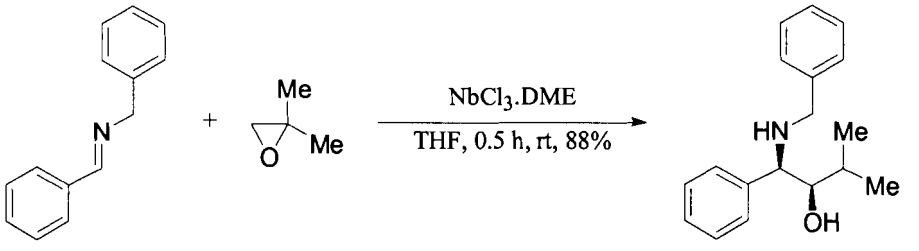
(ef, cm^{-1}) 2981, 1704, 1598, 1498, 1404, 1380, 1276, 1223, 1136, 1022, 767; MS (C.I.) *m/z* 256 [M+1], 166. Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27, H, 6.71, N, 5.49. Found: C, 75.07; H, 6.84; N, 5.38.



(37) (45) (52)

Benzyl *N*-(2-methoxybenzyl)-*N*-phenyl-carbamate 52. To a solution of niobium trichloride dimethoxyethane complex (434 mg, 1.50 mmol) in tetrahydrofuran (6 mL) at room temperature was added a solution of benzylidene-(2-methoxy-benzyl)-amine **37** (169 mg, 0.750 mmol) in tetrahydrofuran (2 mL). A color change from maroon to dark green over the course of 30 min was observed while stirring at room temperature. After 30 min, benzyl chloroformate **45** (535 μL, 3.75 mmol) was added dropwise to the reaction mixture. After stirring for 30 min the reaction mixture was cooled to 0 °C followed by the dropwise addition of an aqueous solution of potassium hydroxide (10 % w/v, 10 mL). The mixture was then poured into a separatory funnel and extracted with ether (2 x 10 mL). The combined ether layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford a yellow oil. Purification by silica gel chromatography using hexanes:ethyl acetate (20:1) as the eluent followed by recrystallization in hexanes:ether afforded the title compound **52** as a white solid (128 mg, 0.355 mmol, 47 %): mp: 54-56 °C; R_f 0.40 (hexanes:ethyl acetate, 6:1); ^{1}H NMR (CD_3COCD_3, 400 MHz) δ 3.76 (s, 3H, ArOC*H*$_3$), 4.43-4.54 (m, 4H, 2ArC*H*$_2$N), 5.19 (s, 2H, ArC*H*$_2$O), 6.86-6.97 (m, 2H, Ar*H*), 7.10-7.37 (m, 12H, Ar*H*); ^{13}C NMR

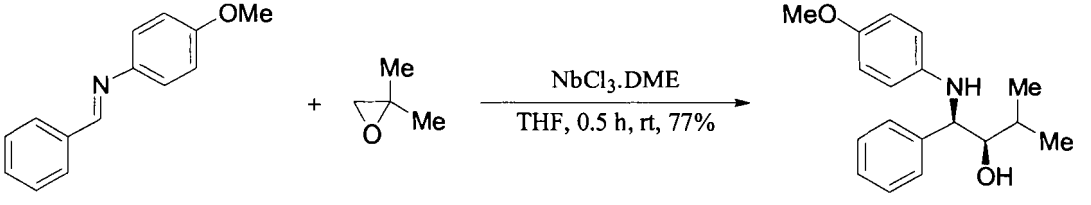
(CD_3COCD_3, 100 MHz) δ 49.53, 55.10, 59.91, 71.89, 115.59, 125.51, 130.77, 132.29, 132.48, 132.92, 133.29, 133.50, 133.58, 133.85, 134.21, 134.35, 142.51, 143.49, 162.56; IR (neat, cm^{-1}) 3031, 2940, 1700, 1494, 1463, 1419, 1235, 1122, 1029; MS (C.I.) *m/z* 362 [M+1], 266, 121. Anal. Calcd for $C_{23}H_{23}NO_3$: C, 76.43, H, 6.41, N, 3.88. Found: C, 76.36; H, 6.39; N, 3.67.



(35) **(61)** **(64)**

***Syn*-1-Benzylamino-3-methyl-1-phenyl-butan-2-ol 64.** To a solution of niobium trichloride dimethoxyethane complex (868 mg, 3.00 mmol) in tetrahydrofuran (16 mL) at room temperature was added a solution of *N*-benzylidene-benzylamine **35** (292 mg, 1.50 mmol) in tetrahydrofuran (1.5 mL). A color change from maroon to dark green over the course of 30 min was observed while stirring at room temperature. After 30 min, 2,2-dimethyloxirane **61** (90 μL, 1.0 mmol) was added dropwise to the reaction mixture. After stirring for 30 min the reaction mixture was poured into a separatory funnel containing an aqueous solution of potassium hydroxide (10 % w/v, 20 mL) and extracted with ether (2 x 20 mL). The combined ether layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford a yellow oil. After dissolving the oil in ether (15 mL), the resultant solution was extracted with hydrochloric acid (1 *M*, 3 x 15 mL) after which the aqueous layers were combined and basified with potassium hydroxide pellets at 0 °C to pH 12. The aqueous fraction was then extracted with ether (3 x 45 mL) and the combined ether layers were dried over anhydrous sodium

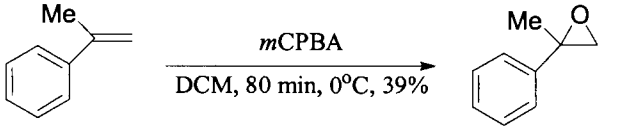
sulfate, filtered and concentrated under vacuum. Purification by silica gel chromatography using dichloromethane:ether:triethylamine (100:5:1) as the eluent followed by recrystallization from ethanol afforded the title compound **64** as a white solid (236 mg, 0.878 mmol, 88 %): mp: 50-52 °C (ethanol); R_f 0.56 (hexanes:ethyl acetate, 1:1); ^{1}H NMR (C_6D_6, 400 MHz) δ0.84 (d, 3H, J = 6.9 Hz, C*H*$_3$), 0.94 (d, 3H, J = 6.9 Hz, C*H*$_3$), 1.38-1.46 (m, 1H, (CH$_3$)$_2$C*H*), 3.50-3.55 (m, 2H, *H*CN and *H*CO), 3.55 (d, 1H, J = 13.1 Hz, ArCH*H*), 3.67 (d, 1H, J = 13.1 Hz, ArC*H*H), 6.88-7.36 (m, 10H, Ar*H*); ^{13}C NMR (C_6D_6, 100 MHz) δ 14.86, 20.67, 29.10, 51.01, 65.63, 78.48, 126.94, 127.09, 127.19, 128.12, 128.29, 128.57, 140.22, 141.57; IR (KBr, cm^{-1}) 3200, 2960, 1602, 1493, 1453, 1357, 1201, 1141, 1100, 1054, 1000, 915; MS (C.I.) *m/z* 270 [M+1], 196. Anal. Calcd for $C_{18}H_{23}NO$: C, 80.26; H, 8.61; N, 5.20. Found: C, 80.08; H, 8.66; N, 5.29.



(38) **(61)** **(65)**

***Syn*-3-Methyl-1-(4-methoxy-phenylamino)-1-phenyl-butan-2-ol 65.** To a solution of niobium trichloride dimethoxyethane complex (1.30 g, 4.50 mmol) in tetrahydrofuran (16 mL) at room temperature was added to a solution of *N*-benzylidene-4-methoxy-aniline **38** (317 mg, 1.50 mmol) in tetrahydrofuran (1.5 mL). A color change from maroon to dark yellow over the course of 2.5 h was observed while stirring at room temperature. After 2.5 h, 2,2-dimethyloxirane **61** (90 μL, 1.0 mmol) was added dropwise to the reaction mixture. After stirring for 30 min the reaction mixture was poured into a separatory funnel containing an aqueous solution of potassium hydroxide (10 % w/v, 20

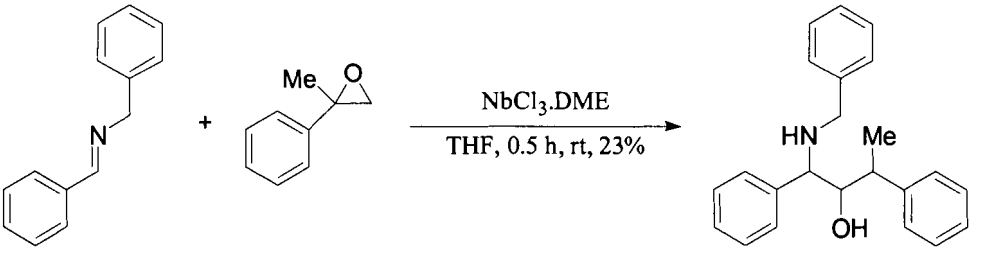
mL) and extracted with ether (2 x 20 mL). The combined ether layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford a yellow oil. After dissolving the oil in ether (15 mL), the resultant solution was extracted with hydrochloric acid (1 *M*, 3 x 15 mL) after which the aqueous layers were combined and basified with potassium hydroxide pellets at 0 °C to pH 12. The aqueous fraction was then extracted with ether (3 x 45 mL) and the combined ether layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. Purification by silica gel chromatography using hexanes:ethyl acetate (12:1) as the eluent afforded the title compound **65** as a brown oil (219 mg, 0.767 mmol, 77 %): R_f 0.22 (hexanes:ethyl acetate, 6:1); ^{1}H NMR (C_6D_6, 400 MHz) δ 0.94 (d, 3H, J = 6.7 Hz, C*H*$_3$), 1.04 (d , 3H, J = 6.7 Hz, C*H*$_3$), 1.80-1.89 (m, 1H, $(CH_3)_2$C*H*), 3.28-3.32 (m, 1H, *H*CO), 3.34 (s, 3H, ArOC*H*$_3$), 4.35 (d, 1H, J = 4.9 Hz, *H*CN), 6.47 (m, 2H, J = 8.9 Hz, Ar*H*), 6.71 (m, 2H, J = 9.2 Hz, Ar*H*), 7.04-7.10 (m, 1H, Ar*H*), 7.13-7.22 (m, 4H, Ar*H*); ^{13}C NMR (C_6D_6, 100 MHz) δ 17.45, 19.78, 29.92, 54.90, 61.16, 80.62, 114.87, 115.30, 127.06, 127.13, 128.56, 141.56, 142.25, 152.67; IR (neat, cm^{-1}) 3426, 2958, 2929, 1731, 1619, 1505, 1241, 1042, 821; MS (C.I.) *m/z* 286 [M+1], 212. Anal. Calcd for $C_{18}H_{23}NO_2$: C, 75.76; H, 8.12; N, 4.91. Found: C, 75.30; H, 8.20; N, 5.16.



(70) (71)

2-Methyl-2-phenyloxirane 71. To a suspension of sodium bicarbonate (2.13 g, 25.4 mmol) in dichloromethane (50 mL) at room temperature was added α-methylstyrene **70** (3.30 mL, 25.4 mmol). The solution was then cooled to 0 °C and then *m*CPBA (68 %,

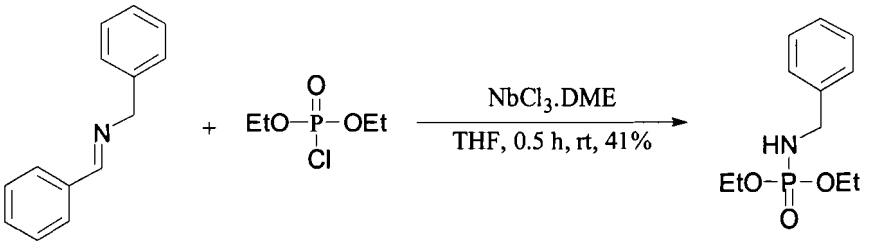
2.00 g, 7.88 mmol) was added. After stirring for 45 min at 0 °C, more *m*CPBA (68 %, 3.00 g, 11.8 mmol) was added. After stirring for 35 min at 0 °C, the reaction mixture was poured into a separatory funnel containing an aqueous solution of potassium hydroxide (40 % w/v, 50 mL), diluted with water (100 mL), and extracted with dichloromethane (3 x 100 mL). The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. Purification by silica gel chromatography using hexanes:ether:triethylamine (100:10:1) as the eluent followed by kugelrohr distillation, afforded the title compound **71** as a clear colorless oil (1.02 g, 7.63 mmol, 39 %): R_f 0.45 (hexanes:ether, 10:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.73 (s, 3H, C*H*$_3$), 2.81 (d, 1H, J = 5.5 Hz, C*H*H), 2.98 (d, 1H, J = 5.5 Hz, CH*H*), 7.25-7.40 (m, 5H, Ar*H*); ^{13}C NMR (C_6D_6, 100 MHz) δ 21.79, 56.72, 56.99, 125.28, 127.43, 128.30, 141.17; IR (neat, cm^{-1}) 3037, 2985, 1686, 1447, 1266, 1062, 860; MS (C.I.) *m/z* 135 [M+1], 121, 105. Anal. Calcd for $C_9H_{10}O$: C, 80.56; H, 7.51. Found: C, 80.33; H, 7.61.



(35) (71) (72)

1-Benzylamino-1,3-diphenyl-butan-2-ol 72. To a solution of niobium trichloride dimethoxyethane complex (1.30 g, 4.50 mmol) in tetrahydrofuran (16 mL) at room temperature was added to a solution of *N*-benzylidene-benzylamine **35** (292 mg, 1.50 mmol) in tetrahydrofuran (1.5 mL). A color change from maroon to dark green over the course of 30 min was observed while stirring at room temperature. After 30 min, 2-

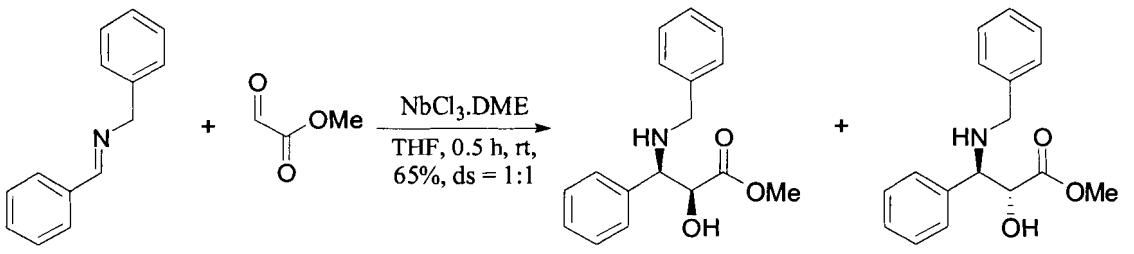
methyl-2-phenyloxirane **71** (130 μL, 1.00 mmol) was added dropwise to the reaction mixture. After stirring for 30 min the reaction mixture was poured into a separatory funnel containing an aqueous solution of potassium hydroxide (10 % w/v, 20 mL) and extracted with ether (2 x 20 mL). The combined ether layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford a yellow oil. After dissolving the oil in ether (15 mL), the resultant solution was extracted with hydrochloric acid (1 *M*, 3 x 15 mL) after which the aqueous layers were combined and basified with potassium hydroxide pellets at 0 °C to pH 12. The aqueous fraction was then extracted with ether (3 x 45 mL) and the combined ether layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum. Purification by silica gel chromatography using hexanes:ethyl acetate (6:1) as the eluent afforded the title compound **72** as a white crystalline solid as a single diastereomer (75.2 mg, 0.227 mmol, 23 %): mp: 101-102 °C; R_f 0.15 (hexanes:ethyl acetate, 4:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (d, 3H, J = 7.0 Hz, C*H*$_3$), 2.64 (dq, 1H, J = 7.0, 4.0 Hz, ArC(*H*)CH$_3$), 3.52 (d, 1H, J = 12.8 Hz, ArC*H*H), 3.55 (d, 1H, J = 7.6 Hz, *H*CN), 3.66 (d, 1H, J = 12.8 Hz, ArCH*H*), 3.80 (dd, 1H, J = 7.9, 4.0 Hz, *H*CO), 7.12-7.20 (m, 3H, Ar*H*), 7.22-7.35 (m, 10H, Ar*H*), 7.36-7.42 (m, 2H, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 13.96, 40.94, 51.20, 64.81, 78.75, 126.15, 127.02, 127.54, 127.66, 128.18, 128.25, 128.36, 128.80, 129.10, 139.95, 141.13, 145.36; IR (ef, cm^{-1}) 3296, 3025, 1493, 1453, 1092, 927; MS (C.I.) *m/z* 332 [M+1], 196. Anal. Calcd for $C_{23}H_{25}NO$: C, 83.34; H, 7.60; N, 4.23. Found: C, 83.60; H, 7.55; N, 4.26.



(35) (74) (79)

Diethyl-*N*-benzylamino-phosphoramide 79. To a solution of niobium trichloride dimethoxyethane complex (434 mg, 1.50 mmol) in tetrahydrofuran (16 mL) at room temperature was added to a solution of *N*-benzylidene-benzylamine **35** (292 mg, 1.50 mmol) in tetrahydrofuran (1.5 mL). A color change from maroon to dark green over the course of 30 min was observed while stirring at room temperature. After 30 min, ethyl chlorophosphonate **74** (145 μL, 1.00 mmol) was added dropwise to the reaction mixture. After stirring for 30 min the reaction mixture was poured into a separatory funnel containing an aqueous solution of potassium hydroxide (10 % w/v, 20 mL) and extracted with ether (2 x 20 mL). The combined ether layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford a yellow oil. Purification by silica gel chromatography using hexanes:ethyl acetate (1:1) as the eluent afforded the title compound **79** as a yellow oil (100 mg, 0.411 mmol, 41 %): R_f 0.05 (hexanes:ethyl acetate, 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.25 (t, 6H, J = 7.0 Hz, 2CH_2CH_3), 3.18-3.25 (s, br, 1H, N*H*), 3.95-4.11 (m, 6H, ArCH_2 and CH_2CH$_3$), 7.22-7.34 (m, 5H, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 16.08, 16.16, 42.28, 62.30, 62.36, 127.29, 128.50, 139.64, 139.71; ^{31}P NMR ($CDCl_3$, 162 MHz, coupled) δ 8.80-9.24 (m, 1*P*); ^{31}P NMR ($CDCl_3$, 162 MHz, decoupled) δ 9.10 (s, 1*P*); IR (neat, cm^{-1}) 3263, 2983, 1455, 1237, 1029, 965; MS (C.I.) *m/z* 244 [M+1]. Anal. Calcd for $C_{11}H_{18}NO_3P$: C, 54.32; H, 7.46; N, 5.76. Found: C, 54.75; H, 7.64; N, 5.65.

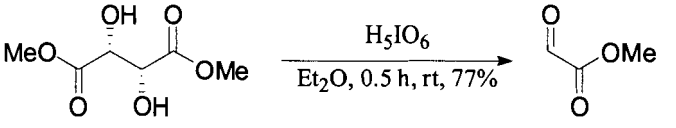
5.4 Experimental Section Concerning Chapter 4



(35) (86) (87-*syn*) (87-*anti*)

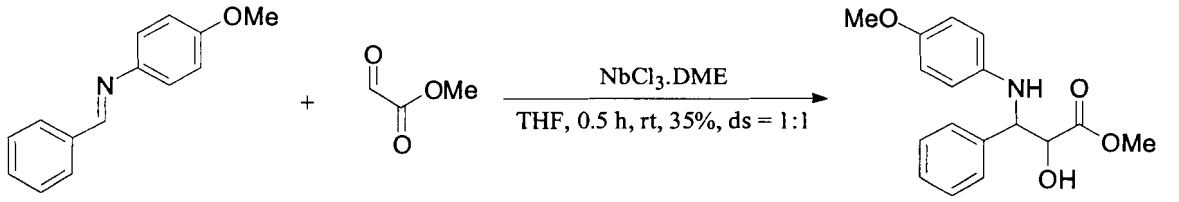
Syn* and *Anti*-Methyl-3-benzylamino-2-hydroxy-3-phenyl-propanoate 87.** To a solution of niobium trichloride dimethoxyethane complex (868 mg, 3.00 mmol) in tetrahydrofuran (16 mL) at room temperature was added to a solution of *N*-benzylidene-benzylamine **35** (292 mg, 1.50 mmol) in tetrahydrofuran (1.5 mL). A color change from maroon to dark green over the course of 30 min was observed while stirring at room temperature. After 30 min, methyl glyoxylate **86** (90 mg, 1.0 mmol) was added dropwise to the reaction mixture. After stirring for 30 min the reaction mixture was poured into a separatory funnel containing an aqueous solution of potassium hydroxide (10 % w/v, 20 mL) and extracted with ether (2 x 20 mL). The combined ether layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford a yellow oil. Purification by silica gel chromatography using pentane:ether (1:1) as the eluent afforded the title compounds **87-*syn and **87-*anti*** as a 1:1 mixture of diastereomers (185 mg, 0.649 mmol, 65 %): **87-*syn*** (2*R*,3*S* and 2*S*,3*R*) (yellow solid); mp: 105-107 °C (lit.[37] mp 107-108 °C); R_f 0.57 (pentane:ether, 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.49 (d, 1H, J = 13.4 Hz, ArC*H*H), 3.71 (s, 3H, OCH_3), 3.76 (d, 1H, J = 13.4 Hz, ArCH*H*), 3.95 (d, 1H, J = 3.7 Hz, *H*CN), 4.25 (d, 1H, J = 3.7 Hz, *H*CO), 7.21-7.41 (m, 10H, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 50.59, 52.43, 63.30, 74.90, 127.00, 127.62, 127.76, 128.20, 128.24, 128.56, 139.50, 139.92, 173.87; IR (KBr, cm^{-1}) 3509, 3371, 3024, 1725, 1494, 1458, 1256, 1104,

1028, 933; MS (C.I.) *m/z* 286 [M+1], 196. Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.34; H, 6.78; N, 5.09. **87-*Anti*** (2*R*,3*R* and 2*S*,3*S*) (yellow solid); mp: 97-99 °C (lit.[37] mp 98-99 °C); R_f 0.32 (pentane:ether 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.40-3.20 (s, br, 1H, O*H*, or N*H*), 3.60 (s, 3H, OCH_3), 3.62 (d, 1H, J = 13.1 Hz, ArC*H*H), 3.78 (d, 1H, J = 13.1 Hz, ArCH*H*), 4.07 (d, 1H, J = 4.0 Hz, *H*CN), 4.54 (d, 1H, J = 4.0 Hz, *H*CO), 7.23-7.37 (m, 10H, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 50.91, 52.08, 63.73, 73.52, 127.10, 127.67, 127.92, 128.23, 128.24, 128.47, 137.68, 139.66, 173.01; IR (KBr, cm^{-1}) 3466, 3334, 3030, 2920, 1719, 1488, 1454, 1434, 1281, 1124, 1083, 1024, 875; MS (C.I.) *m/z* 286 [M+1], 196. Anal. Calcd for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.90; H, 6.79; N, 5.13.



(88) **(86)**

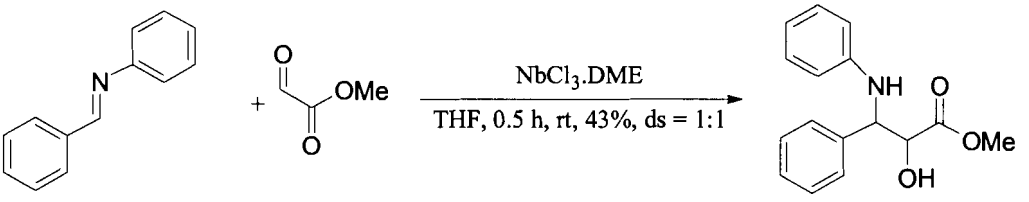
Methyl glyoxylate 86 was prepared based on a literature procedure.[38] A solution of dimethyl L-tartrate **88** (3.27 g, 18.4 mmol) in ether (16.5 mL) was treated with hydrated periodic acid (4.18 g, 18.3 mmol) over a 30 min period. The mixture was then stirred at room temperature for 30 min. After filtering off the solid residue, the filtrate was dried over anhydrous magnesium sulfate and concentrated under vacuum. The oily residue was distilled from activated molecular sieves (4 Å, 200 mg) under high vacuum using a 5 cm Vigreux column to afford the title compound **86** as a colorless oil (2.49 g, 28.3 mmol, 77 %): R_f 0.23 (ethyl acetate:hexanes, 2:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ diagnostic peak 9.40 (s, 1H, C*H*O); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 53.16, 169.27, 183.38.



(38) (86) (89)

Methyl-2-hydroxy-3-(4-methoxy-phenylamino)-3-phenyl-propanoate 89. To a solution of niobium trichloride dimethoxyethane complex (434 mg, 1.50 mmol) in tetrahydrofuran (16 mL) at room temperature was added a solution of *N*-benzylidene-4-methoxy-aniline **38** (317 mg, 1.50 mmol) in tetrahydrofuran (1.5 mL). A color change from maroon to dark yellow over the course of 2.5 h was observed while stirring at room temperature. After 2.5 h, methyl glyoxylate **86** (90 mg, 1.0 mmol) was added dropwise to the reaction mixture. After stirring for 30 min the reaction mixture was poured into a separatory funnel containing an aqueous solution of potassium hydroxide (10 % w/v, 20 mL) and extracted with ether (2 x 20 mL). The combined ether layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford a brown oil. Purification by silica gel chromatography using pentane:ether (1:1) as the eluent afforded the title compound **89** as a yellow oil as a 1:1 mixture of diastereomers (106 mg, 0.352 mmol, 35 %): R_f 0.26 (pentane:ether, 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.68 (s, 3H, OC*H*$_3$), 3.69 (s, 3H, OC*H*$_3$), 3.72 (s, 3H, OC*H*$_3$), 3.78 (s, 3H, OC*H*$_3$), 4.49 (d, 1H, J = 2.5 Hz, C*H*), 4.67 (d, 1H, J = 3.4 Hz, C*H*), 4.79 (d, 1H, J = 3.9 Hz, C*H*), 4.86 (d, 1H, J = 3.0 Hz, C*H*), 6.50-6.61 (m, 4H, Ar*H*), 6.63-6.79 (m, 4H, Ar*H*), 7.22-7.38 (m, 10H, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 52.43, 53.01, 55.63, 59.91, 60.49, 73.48, 74.66, 114.72, 114.78, 115.36, 116.48, 126.96, 127.33, 127.57, 128.00, 128.47, 128.58, 137.21, 139.40, 140.18, 140.38, 152.34, 152.46, 172.67, 173.36; IR (neat, cm^{-1}) 3402, 2952, 2833, 1740,

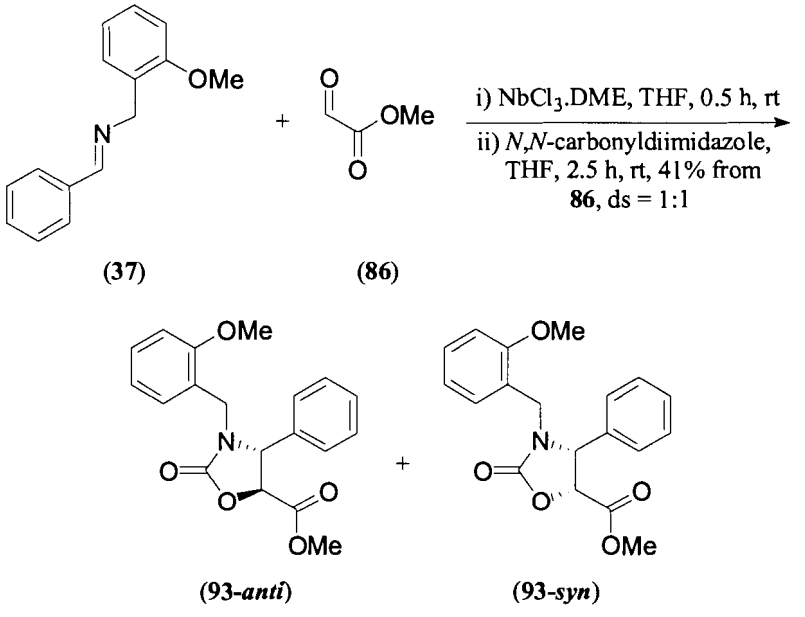
1732, 1515, 1242, 1100, 1033, 822; MS (C.I.) *m/z* 302 [M+1], 212. Anal. Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.48; H, 6.46; N, 4.91.



(34) (86) (90)

Methyl-2-hydroxy-3-phenyl-3-phenylamino-propanoate 90. To a solution of niobium trichloride dimethoxyethane complex (434 mg, 1.50 mmol) in tetrahydrofuran (16 mL) at room temperature was added a solution of *N*-benzylidene-aniline **34** (272 mg, 1.50 mmol) in tetrahydrofuran (1.5 mL). A color change from maroon to dark yellow over the course of 30 min was observed while stirring at room temperature. After 30 min, methyl glyoxylate **86** (90 mg, 1.0 mmol) was added dropwise to the reaction mixture. After stirring for 30 min the reaction mixture was poured into a separatory funnel containing an aqueous solution of potassium hydroxide (10 % w/v, 20 mL) and extracted with ether (2 x 20 mL). The combined ether layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford a colorless oil. Purification by silica gel chromatography using pentane:ether (4:1) as the eluent afforded the title compound **90** as a white solid and as a 1:1 mixture of diastereomers (116 mg, 0.428 mmol, 43 %): mp: 74-76 °C; R_f 0.27 (pentane:ether, 1:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.88 (s, br, 1H, N*H* or O*H*), 3.12 (s, br, 1H, N*H* or O*H*), 3.74 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.52 (s, br, 1*H*), 4.67-4.96 (m, 5*H*), 6.55-6.72 (m, 6H, Ar*H*), 7.21-7.41 (m, 4H, Ar*H*), 7.24-7.41 (m, 10H, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 52.51, 53.07, 58.91, 59.49, 73.58, 74.60, 113.62, 113.84, 113.96, 117.93, 118.00, 126.92,

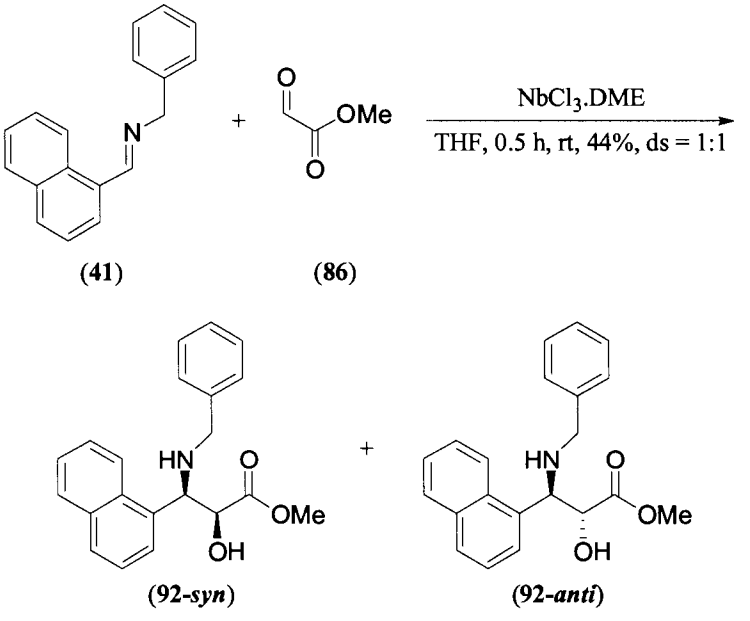
127.35, 127.64, 128.07, 128.52, 128.64, 129.14, 137.09, 139.24, 146.17, 146.33, 172.53, 173.28; IR (KBr, cm^{-1}) 3492, 3377, 3025, 1736, 1602, 1521, 1498, 1285, 1094, 986, 943, 871; MS (C.I.) *m/z* 272 [M+1], 182. Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32; N, 5.16. Found: C, 70.61; H, 6.36; N, 5.22.



***Anti* and *Syn*-5-Carboxymethyl-3-(2-methoxybenzyl)-4-phenyl-oxazolidinone 93.** To a solution of niobium trichloride dimethoxyethane complex (868 mg, 3.00 mmol) in tetrahydrofuran (16 mL) at room temperature was added to a solution of benzylidene-(2-methoxybenzyl)-amine **37** (338 mg, 1.50 mmol) in tetrahydrofuran (1.5 mL). A color change from maroon to dark green over the course of 30 min was observed while stirring at room temperature. After 30 min, methyl glyoxylate **86** (90 mg, 1.0 mmol) was then added dropwise to the reaction mixture. After stirring for 30 min the reaction mixture was then poured into a separatory funnel containing an aqueous solution of potassium hydroxide (10 % w/v, 20 mL) and extracted with ether (2 x 20 mL). The combined ether layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum

to afford a yellow oil. The yellow oil was then dissolved in tetrahydrofuran (15 mL) and *N,N*-carbonyldiimidazole (309 mg, 1.90 mmol) was added.[40] The resultant solution was stirred at room temperature for 2.5 h, and then the solvent was removed under vacuum to produce a yellow oil. The resultant oil was dissolved in dichloromethane (20 mL), washed with hydrochloric acid (1 M, 3 x 5 mL), water (2 x 5 mL) and brine (1 x 5 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and the solution was concentrated under vacuum. Purification by silica gel chromatography using dichloromethane:ether (50:1) as the eluent afforded the title compounds **93-*anti*** and **93-*syn*** as a 1:1 mixture of diastereomers (139 mg, 0.407 mmol, 41 %): **93-*anti*** (4*R*,5*S* and 4*S*,5*R*) (yellow oil); R_f 0.74 (dichloromethane:ether, 9:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.68 (s, 3H, OC*H*$_3$), 3.76 (s, 3H, OC*H*$_3$), 3.95 (d, 1H, *J* = 15.1 Hz, ArC*H*H), 4.58 (d, 1H, *J* = 5.1 Hz, *H*CN), 4.66 (d, 1H, *J* = 5.1 Hz, *H*CO), 4.75 (d, 1H, *J* = 15.1 Hz, ArCH*H*), 6.80 (d, 1H, *J* = 8.1 Hz, Ar*H*), 6.88 (t, 1H, *J* = 7.7 Hz, Ar*H*), 7.10 (m, 1H, *J* = 7.4 Hz, Ar*H*), 7.20-7.28 (m, 3H, Ar*H*), 7.36-7.44 (m, 3H, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 41.41, 52.86, 55.06, 62.13, 76.73, 110.25, 120.52, 122.99, 126.74, 129.11, 129.18, 129.42, 130.22, 137.47, 156.51, 157.52, 168.94; ^{13}C NMR (C_6D_6, 100 MHz) δ 41.31, 51.77, 54.42, 62.09, 77.54, 110.20, 120.53, 123.63, 126.75, 128.59, 129.00, 129.09, 130.01, 138.03, 156.33, 157.57, 168.81; IR (ef, cm^{-1}) 2955, 1770, 1494, 1459, 1438, 1411, 1247, 1119, 1070, 1027, 757; MS (C.I.) *m/z* 342 [M+1], 121. Anal. Calcd for $C_{19}H_{20}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.93; H, 5.70; N, 4.36. **93-*Syn*** (4*R*,5*R* and 4*S*,5*S*) (yellow solid); mp: 85-87 °C; R_f 0.70 (dichloromethane:ether, 9:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.23 (s, 3H, OC*H*$_3$), 3.67 (s, 3H, OC*H*$_3$), 3.93 (d, 1H, *J* = 14.7 Hz, ArC*H*H), 4.78 (d, 1H, *J* = 14.7 Hz, ArCH*H*), 4.86 (d, 1H, *J* = 9.6 Hz, *H*CN), 5.09 (d,

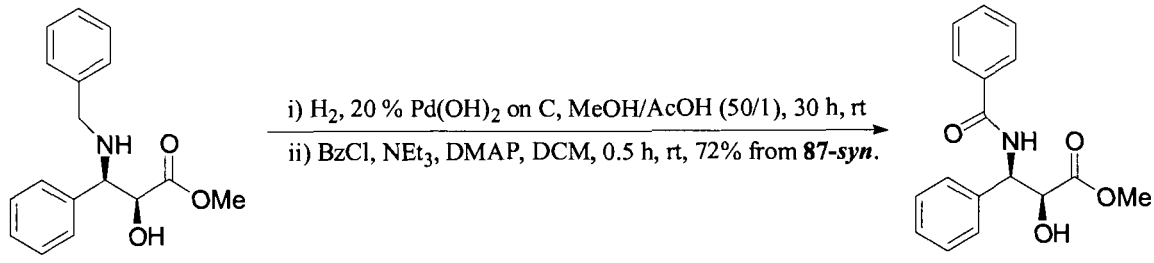
1H, J = 9.6 Hz, *H*CO), 6.82 (d, 1H, J = 8.5 Hz, Ar*H*), 6.87 (t, 1H, J = 6.6 Hz, Ar*H*), 7.10-7.18 (m, 3H, Ar*H*), 7.24-7.30 (m, 1H, Ar*H*), 7.32-7.40 (m, 3H, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 41.44, 51.84, 55.09, 61.26, 75.51, 110.33, 120.59, 123.26, 127.58, 128.56, 129.14, 129.58, 130.91, 133.99, 156.85, 157.62, 167.00; ^{13}C NMR (C_6D_6, 100 MHz) δ 41.19, 50.80, 54.37, 61.13, 75.23, 110.23, 120.63, 124.08, 127.04, 128.21, 128.51, 129.23, 130.86, 134.68, 156.73, 157.70, 167.70; IR (ef, cm^{-1}) 2951, 2840, 1764, 1602, 1494, 1459, 1438, 1411, 1289, 1249, 1216, 1120, 1073, 757; MS (C.I.) *m/z* 342 [M+1], 152, 121. Anal. Calcd for $C_{19}H_{20}NO_5$: C, 66.85; H, 5.61; N, 4.10. Found: C, 66.58; H, 5.86; N, 4.21.



***Syn* and *Anti*-Methyl-3-(Benzylamino)-2-hydroxy-3-(1-naphthyl)-propanoate 92.** To a solution of niobium trichloride dimethoxyethane complex (868 mg, 3.00 mmol) in tetrahydrofuran (16 mL) at room temperature was added to a solution of *N*-(1-napthylidene)-benzylamine **41** (368 mg, 1.50 mmol) in tetrahydrofuran (1.5 mL). A color change from maroon to dark green over the course of 30 min was observed while

stirring at room temperature. After 30 min, methyl glyoxylate **86** (90 mg, 1.0 mmol) was added dropwise to the reaction mixture. After stirring for 30 min the reaction mixture was poured into a separatory funnel containing an aqueous solution of potassium hydroxide (10 % w/v, 20 mL) and extracted with ether (2 x 20 mL). The combined ether layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford a yellow oil. Purification by silica gel chromatography using pentane:ether (1:1) as the eluent afforded the title compounds **92-*syn*** and **92-*anti*** as a 1:1 mixture of diastereomers (148 mg, 0.440 mmol, 44 %): **92-*syn*** (2*R*,3*S* and 2*S*,3*R*) (white solid); mp: 64-65 °C; R_f 0.19 (pentane:ether, 2:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.80-3.30 (s, br, 1H, N*H* or O*H*), 3.58 (d, 1H, J = 13.4 Hz, ArC*H*H), 3.71 (s, 3H, OCH_3), 3.97 (d, 1H, J = 13.4 Hz, ArCH*H*), 4.43 (d, 1H, J = 3.1 Hz, *H*CN), 4.96 (d, 1H, J = 3.1 Hz, *H*CO), 7.22-7.36 (m, 5H, Ar*H*), 7.50-7.60 (m, 3H, Ar*H*), 7.68 (d, 1H, J = 7.0 Hz, Ar*H*), 7.86 (d, 1H, J = 7.9 Hz, Ar*H*), 7.90-7.95 (m, 1H, Ar*H*), 7.98-8.04 (m, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 50.68, 52.54, 58.15, 73.82, 122.28, 124.10, 125.45, 125.54, 126.31, 127.07, 127.91, 127.98, 128.26, 129.16, 131.58, 134.08, 134.51, 139.93, 174.07; IR (ef, cm^{-1}) 3469, 3366, 2951, 1741, 1454, 1270, 1211, 1106, 782; MS (C.I.) *m/z* 336 [M+1], 246. Anal. Calcd for $C_{21}H_{21}NO_3$: C, 75.20; H, 6.31; N, 4.18. Found: C, 75.29; H, 6.50; N, 4.09. **92-*Anti*** (2*R*,3*R* and 2*S*,3*S*) (opaque white oil); R_f 0.13 (pentane:ether, 2:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.37 (s, 3H, OCH_3), 3.65 (d, 1H, J = 13.1 Hz, ArC*H*H), 3.85 (d, 1H, J = 13.1 Hz, ArCH*H*), 4.69 (d, 1H, J = 4.3 Hz, *H*CN), 5.00 (d, 1H, J = 4.3 Hz, *H*CO), 7.24-7.36 (m, 5H, Ar*H*), 7.48-7.54 (m, 3H, Ar*H*), 7.63 (d, 1H, J = 7.0 Hz, Ar*H*), 7.84 (d, 1H, J = 8.3 Hz, Ar*H*), 7.88-7.92 (m, 1H, Ar*H*), 7.98-8.03 (m, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 51.07, 51.72, 58.66, 72.85, 122.44, 124.05, 125.23, 125.57,

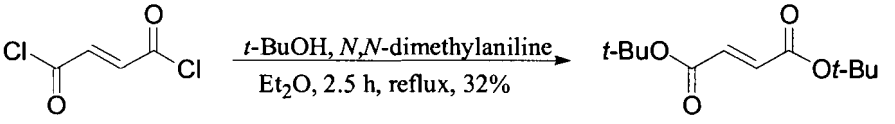
126.19, 127.18, 128.35, 128.44, 128.77, 129.08, 131.81, 133.32, 133.95, 139.94, 173.00; IR (KBr, cm^{-1}) 3449, 3333, 2950, 1739, 1453, 1438, 1208, 1119, 1028, 910, 799, 778; MS (C.I.) *m/z* 366 [M+1], 246, 229. Anal. Calcd for $C_{21}H_{21}NO_3$: C, 75.20; H, 6.31; N, 4.18. Found: C, 75.01; H, 6.74; N, 3.96.



(87-*syn*) **(95)**

Syn*-Methyl-3-(benzoylamino)-2-hydroxy-3-phenyl-propanoate 95** was prepared based on literature procedures.[28, 36] To a solution of the *syn*-methyl-3-(benzylamino)-2-hydroxy-3-phenyl-propanoate **87-*syn (250 mg, 0.876 mmol) in methanol/acetic acid (1.5 mL, 50/1) was added palladium hydroxide (20 % on carbon, 100 mg). The resultant mixture was stirred under a hydrogen atmosphere (balloon) for 30 h. The reaction mixture was then filtered through a pad of celite and sodium bicarbonate with methanol (50 mL). The filtrate was concentrated under vacuum to yield a yellow oil. A solution of the resultant yellow oil in dichloromethane (2.5 mL) at 0 °C was then treated in succession with benzoyl chloride (100 μL, 0.861 mmol), triethylamine (120 μL, 0.861 mmol) and 4-(*N*,*N*-dimethylamino)pyridine (100 mg, 0.819 mmol). The mixture was stirred at room temperature for 30 min, diluted with dichloromethane (10 mL) and then it was transferred to a separatory funnel and washed with brine (5 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford a yellow oil. Purification by silica gel chromatography using petroleum ether:ethyl acetate (3:2) as the eluent afforded the title

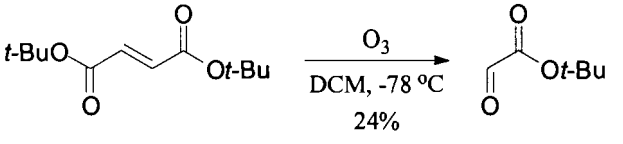
compound **95** as a white solid (189 mg, 0.631 mmol, 72 %): mp: 164-166 °C (lit.[36] mp 164 °C); R_f 0.30 (petroleum ether:ethyl acetate, 3:2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.41 (s, br, 1H, O*H*), 3.82 (s, 3H, OCH_3), 4.62 (s, br, 1H, *H*CO), 5.74 (dd, 1H, J = 9.2, 2.1 Hz, *H*CN), 7.04 (d, br, 1H, J = 8.9 Hz, N*H*), 7.27-7.54 (m, 8H, Ar*H*), 7.74-7.79 (m, 2H, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 53.26, 54.84, 73.21, 126.89, 127.06, 127.94, 128.63, 128.72, 131.77, 134.03, 138.66, 166.90, 173.38; IR (KBr, cm^{-1}) 3359, 1721, 1638, 1533, 1435, 1323, 1231, 1214, 1095, 981, 800; MS (C.I.) *m/z* 300 [M+1], 210. Anal. Calcd for $C_{17}H_{17}NO_4$: C, 68.21; H, 5.72; N, 4.68. Found: C, 68.31; H, 5.83; N, 4.75.



(96) (97)

Di-*tert*-butyl fumarate 97.[43] To a solution of *tert*-butanol (31.0 g, 418 mmol) in ether (90 mL) at 0 °C was added *N,N*-dimethylaniline (33.7 mL, 266 mmol) in a three-necked 500 mL round bottomed flask that was equipped with a reflux condenser, a pressure equalizing dropping funnel, and a mechanical stirrer. Fumaryl chloride **96** (14.1 mL, 130 mmol) in ether (15 mL) was then added slowly *via* the dropping funnel. The temperature of the reaction mixture was maintained below 30 °C during the addition process. After all of the fumaryl chloride had been added, the mixture was heated at reflux for 2.5 h. The reaction mixture was then cooled and washed with a solution of aqueous sulfuric acid (6 *M*, 50 mL), a saturated aqueous solution of sodium carbonate (50 mL) and saturated brine (50 mL). The ether layer was dried, filtered and concentrated under vacuum to afford a black solid. Purification by recrystallization from acetone

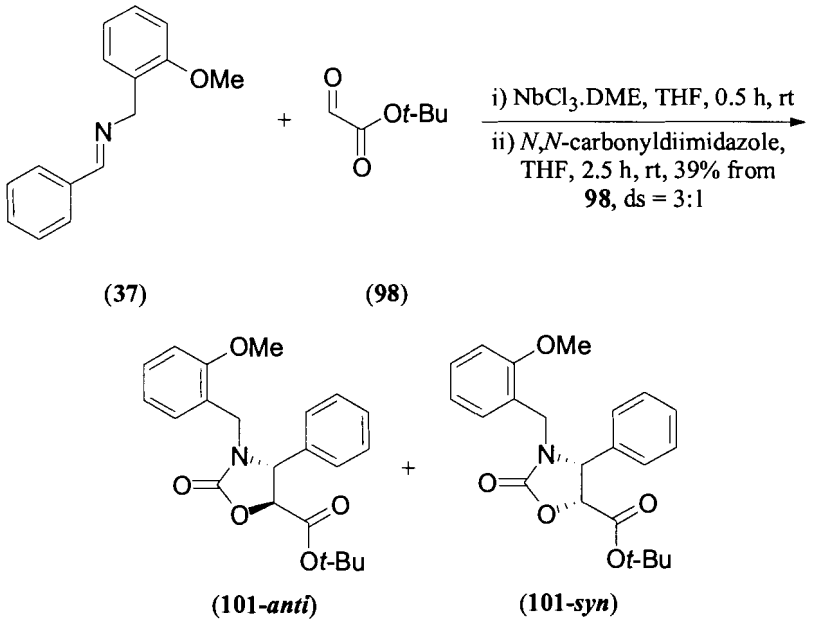
afforded the title compound (**97**) as light purple crystals (9.52 g, 41.7 mmol, 32 %): mp: 68-70 °C (acetone) (lit.[43] mp 71-71.5 °C, acetone); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49 (s, 18H, 6C*H*$_3$), 6.66 (s, 2H, 2C*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.95, 81.62, 134.55, 164.40; IR (KBr, cm^{-1}) 2982, 1707, 1370, 1315, 1257, 1143, 975, 847; MS (C.I.) *m/z* 229 [M+1], 197, 173. Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.14; H, 8.83. Found: C, 63.02; H, 8.79.



(**97**) (**98**)

***tert*-Butyl glyoxylate 98.**[43] A solution of Di-*tert*-butyl fumarate **97** (9.52 g, 41.7 mmol) in dichloromethane (50 mL) was added to a two-neck 250 mL round bottomed flask that was equipped with a drying tube and a stir bar. The resultant solution was cooled at -78 °C and was purged with oxygen for 30 min. During the course of the next 3 hours, ozone was bubbled through the solution which caused the solution to change color from purple to orange. The reaction mixture was then transferred to a dropping funnel and added dropwise to dimethyl sulfide (3.50 mL, 47.6 mmol) at 0 °C in a three-necked flask equipped with a reflux condenser, a stir bar, and a nitrogen inlet adapter. After the addition process was complete, the reaction was allowed to warm to room temperature overnight while stirring under nitrogen. The dimethyl sulfide and dichloromethane were then distilled out of the reaction flask at atmospheric pressure. The resultant orange oily residue was distilled under high vacuum, from activated molecular sieves (4 Å, 200 mg), using a 5 cm Vigreux column that afforded the title compound **98** as a clear colorless oil

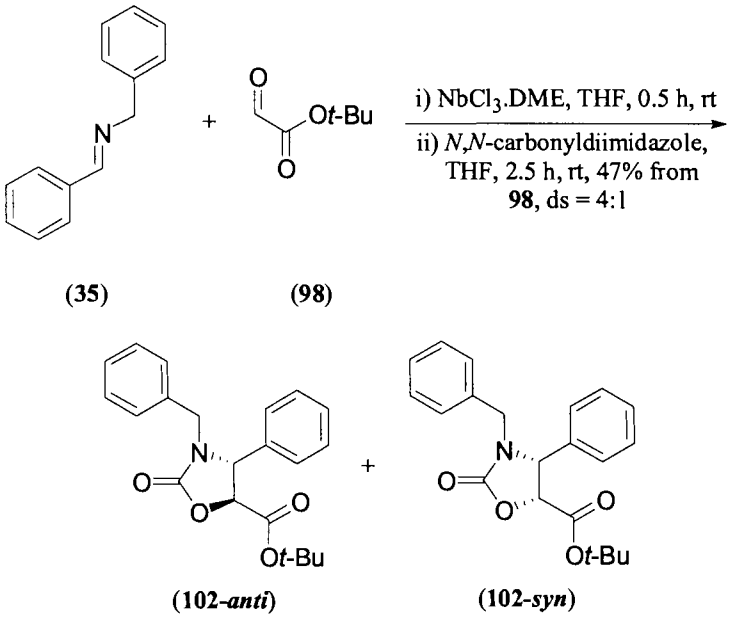
(2.60 g, 20.0 mmol, 24 %): ^{1}H NMR ($CDCl_3$, 100 MHz) δ diagnostic peak 9.30 (s, 1H, C*H*O).



***Anti* and *Syn* -5-Carboxy*tert*-butyl-3-(2-methoxybenzyl)-4-phenyl-oxazolidinone 101.** To a solution of niobium trichloride dimethoxyethane complex (868 mg, 3.00 mmol) in tetrahydrofuran (16 mL) at room temperature was added to a solution of benzylidene-(2-methoxybenzyl)-amine **37** (338 mg, 1.50 mmol) in tetrahydrofuran (1.5 mL). A color change from maroon to dark green over the course of 30 min was observed while stirring at room temperature. After 30 min, *tert*-butyl glyoxylate **98** (130 mg, 1.00 mmol) was added dropwise to the reaction mixture. After stirring for 30 min the reaction mixture was poured into a separatory funnel containing an aqueous solution of potassium hydroxide (10 % w/v, 20 mL) and extracted with ether (2 x 20 mL). The combined ether layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford an orange oil. The orange oil was then dissolved in tetrahydrofuran (11 mL) and *N*,*N*-carbonyldiimidazole (243 mg, 1.50 mmol) was added.[40] The resultant solution

was stirred at room temperature for 2.5 h. The solvent was then removed under vacuum to produce a yellow oil. The resultant oil was then dissolved in dichloromethane (20 mL), washed with hydrochloric acid (1 *M*, 3 x 5 mL), water (2 x 5 mL) and brine (1 x 5 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and the solution was concentrated under vacuum. Purification by silica gel chromatography using dichloromethane:ether (50:1) as the eluent afforded the title compounds **101-*anti*** and **101-*syn*** as a 3:1 mixture of diastereomers (149 mg, 0.389 mmol, 39 %): **101-*anti*** (4*R*,5*S* and 4*S*,5*R*) (yellow oil); R_f 0.74 (dichloromethane:ether, 9:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.40 (s, 9H, 3CH_3), 3.69 (s, 3H, OCH_3), 3.94 (d, 1H, J = 15.1Hz, ArC*H*H), 4.51 (s, 2H, *H*CN and *H*CO), 4.74 (d, 1H, J = 15.1Hz, ArCH*H*), 6.81 (d, 1H, J = 8.1 Hz, Ar*H*), 6.88 (t, 1H, J = 8.5 Hz, Ar*H*), 7.10-7.20 (m, 1H, Ar*H*), 7.18-7.32 (m, 3H, Ar*H*), 7.36-7.42 (m, 3H, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.78, 41.14, 55.09, 62.30, 78.04, 83.24, 110.23, 120.51, 123.27, 126.66, 128.96, 129.12, 129.30, 129.99, 137.80, 156.82, 157.47, 167.52; IR (ef, cm^{-1}) 2979, 2936, 1770, 1494, 1459, 1411, 1370, 1247, 1157, 1070, 839, 755; MS (C.I.) *m/z* 384 [M+1], 328, 121. Anal. Calcd for $C_{22}H_{25}NO_5$: C, 68.91; H, 6.57; N, 3.65. Found: C, 68.69; H, 6.65; N, 3.69. **101-*syn*** (4*R*,5*R* and 4*S*,5*S*) (yellow oil); R_f 0.72 (dichloromethane:ether, 9:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.00 (s, 9H, 3CH_3), 3.68 (s, 3H, OCH_3), 3.85 (d, 1H, J = 14.7 Hz, ArC*H*H), 4.75 (d, 1H, J = 14.7 Hz, ArCH*H*), 4.80 (d, 1H, J = 9.6 Hz, *H*CN), 4.99 (d, 1H, J = 9.6 Hz, *H*CO), 6.82 (d, 1H, J = 8.5 Hz, Ar*H*), 6.88 (m, 1H, J = 7.4 Hz, Ar*H*), 7.10-7.14 (m, 1H, Ar*H*), 7.18-7.23 (m, 2H, Ar*H*), 7.24-7.30 (m, 1H, Ar*H*), 7.33-7.40 (m, 3H, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.29, 41.25, 55.11, 61.19, 75.40, 82.78, 110.34, 120.55, 123.56, 128.29, 128.56, 129.05, 129.46, 130.75, 134.52, 156.87, 157.62, 165.12; IR (ef, cm^{-1}) 2977, 2922,

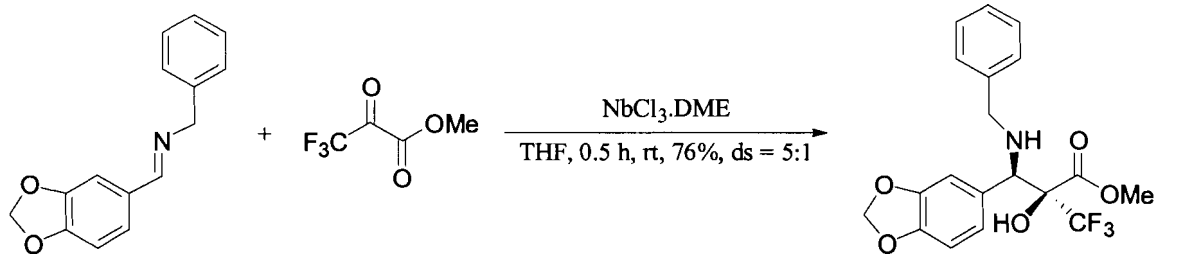
1765, 1602, 1495, 1460, 1412, 1370, 1249, 1158, 1073, 839, 756; MS (C.I.) *m/z* 384 [M+1], 328, 121. Anal. Calcd for $C_{22}H_{25}NO_5$: C, 68.91; H, 6.57; N, 3.65. Found: C, 68.75; H, 6.69; N, 3.81.



***Anti* and *Syn*-5-Carboxy*tert*-butyl-3-benzyl-4-phenyl-oxazolidinone 102.** To a solution of niobium trichloride dimethoxyethane complex (868 mg, 3.00 mmol) in tetrahydrofuran (16 mL) at room temperature was added a solution of *N*-benzylidene-benzylamine **35** (292 mg, 1.50 mmol) in tetrahydrofuran (1.5 mL). A color change from maroon to dark green over the course of 30 min was observed while stirring at room temperature. After 30 min, *tert*-butyl glyoxylate **98** (130 mg, 1.00 mmol) was added dropwise to the reaction mixture. After stirring for 30 min the reaction mixture was poured into a separatory funnel containing an aqueous solution of potassium hydroxide (10 % w/v, 20 mL) and extracted with ether (2 x 20 mL). The combined ether layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford an orange oil. The orange oil was then dissolved in tetrahydrofuran (11 mL) and

N,N-carbonyldiimidazole (243 mg, 1.50 mmol) was added.[40] The resultant solution was stirred at room temperature for 2.5 h, and then the solvent was removed under vacuum to produce a yellow oil. The resultant oil was then dissolved in dichloromethane (20 mL), washed with hydrochloric acid (1 *M*, 3 x 5 mL), water (2 x 5 mL) and brine (1 x 5 mL). The organic layer was then dried over anhydrous magnesium sulfate, filtered and the solution was concentrated under vacuum. Purification by silica gel chromatography using dichloromethane:ether (50:1) as the eluent afforded the title compounds **102-*anti*** and **102-*syn*** as a 4:1 mixture of diastereomers (167 mg, 0.473 mmol, 47 %): **102-*anti*** (4*R*,5*S* and 4*S*,5*R*) (yellow oil); R_f 0.75 (dichloromethane:ether, 9:1); ^{1}H NMR ($CDCl_3$, 400 MH) δ 1.42 (s, 9H, 3C*H*$_3$), 3.66 (d, 1H, *J* = 15.3 Hz, ArCH*H*), 4.42 (d, 1H, *J* = 5.0 Hz, *H*CN), 4.57 (d, 1H, *J* = 5.0 Hz, *H*CO), 4.91 (d, 1H, J = 15.3 Hz, ArCH*H*), 7.10-7.14 (m, 2H, Ar*H*), 7.19-7.23 (m, 2H, Ar*H*), 7.27-7.33 (m, 3H, Ar*H*), 7.38-7.45 (m, 3H, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ27.77, 45.77, 61.75, 78.10, 83.51, 126.85, 127.97, 128.18, 128.75, 129.30, 129.37, 135.01, 136.89, 156.75, 167.28; IR (ef, cm^{-1}) 2980, 1770, 1413, 1370, 1240, 1156, 1085, 703; MS (C.I.) *m/z* 354 [M+1], 298, 253. Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.62; H, 6.57; N, 4.08. **102-*Syn*** (4*R*,5*R* and 4*S*,5*S*) (white solid); mp: 103-104 °C; R_f 0.67 (dichloromethane:ether, 9:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.00 (s, 9H, 3C*H*$_3$), 3.59 (d, 1H, *J* = 14.9 Hz, ArC*H*H), 4.71 (d, 1H, *J* = 9.6 Hz, *H*CN), 4.92 (d, 1H, *J* = 14.9 Hz, ArCH*H*), 5.01 (d, 1H, *J* = 9.6 Hz, *H*CO), 7.09-7.14 (m, 2H, Ar*H*), 7.16-7.24 (m, 2H, Ar*H*), 7.28-7.34 (m, 3H, Ar*H*), 7.36-7.42 (m, 3H, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 27.30, 46.11, 60.57, 75.40, 82.92, 128.08, 128.34, 128.60, 128.79, 128.88, 129.38, 133.72, 135.14, 156.89, 164.90; IR (ef, cm^{-1}) 2980, 1767, 1459, 1412, 1370, 1228, 1157, 1083, 703; MS (C.I.) *m/z* 354

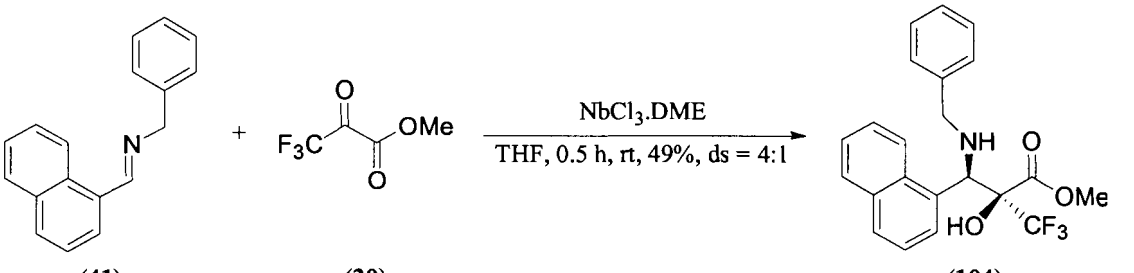
[M+1], 298. Anal. Calcd for $C_{21}H_{23}NO_4$: C, 71.37; H, 6.56; N, 3.96. Found: C, 71.29; H, 6.55; N, 3.78.



(36) (30) (103)

***Syn*-Methyl-3-benzylamino-2-(3,3,3,-trifluoromethyl)-2-hydroxy-3-(3,4-methylenedioxy)phenyl-propanoate 103.** To a solution of niobium trichloride dimethoxyethane complex (1.30 g, 4.50 mmol) in tetrahydrofuran (16 mL) at room temperature was added to a solution of *N*-(3,4-methylenedioxy)-benzylidene-benzylamine **36** (359 mg, 1.50 mmol) in tetrahydrofuran (1.5 mL). A color change from maroon to dark green over the course of 30 min was observed while stirring at room temperature. After 30 min, methyl-3,3,3-trifluoropyruvate **30** (100 μL, 0.98 mmol) was added dropwise to the reaction mixture. After stirring for 30 min the reaction mixture was then poured into a separatory funnel containing an aqueous solution of potassium hydroxide (10 % w/v, 20 mL) and extracted with ether (2 x 20 mL). The combined ether layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford a yellow oil. Purification by silica gel chromatography using dichloromethane:ether (30:1) as the eluent afforded the title compounds **103** as a yellow oil and as a 5:1 mixture of diastereomers (297 mg, 0.747 mmol, 76 %): R_f 0.88 (dichloromethane:ether, 9:1); Major *syn* isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.45 (d, 1H, J = 13.3 Hz, ArC*H*H), 3.65 (s, 3H, OCH_3), 3.73 (d, 1H, J = 13.3 Hz, ArCH*H*), 4.16 (s, 1H, *H*CN), 5.96-5.99 (m, 2H, OCH_2O), 6.61-6.65 (m, 1H, Ar*H*), 6.72-6.75 (m, 1H,

Ar*H*), 6.78-6.84 (m, 1H, Ar*H*), 7.24-7.34 (m, 5H, Ar*H*); ^{1}H NMR (C_6D_6, 400 MHz) δ 3.02 (s, 3H, OCH_3), 3.33 (d, 1H, J = 13.6 Hz, ArC*H*H), 3.59 (d, 1H, J = 13.6 Hz, ArCH*H*), 4.28 (s, 1H, *H*CN), 5.28 (d, 1H, J = 1.1 Hz, OC*H*HO), 5.32 (d, 1H, J = 1.5 Hz, OCH*H*O), 6.35 (dd, 1H, J = 7.9, 1.5 Hz, Ar*H*), 6.56 (d, 1H, J = 7.9 Hz, Ar*H*), 6.75 (d, 1H, J = 1.5 Hz, Ar*H*), 7.10-7.16 (m, 2H, Ar*H*), 7.18-7.24 (m, 1H, Ar*H*), 7.36 (d, 2H, J = 7.2 Hz, Ar*H*); Minor *anti* isomer: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.35 (d, 1H, J = 13.3 Hz, ArC*HH*), 3.66 (d, 1H, ArCH*H*), 3.87 (s, 3H, OCH_3), 4.03 (s, 1H, *H*CN), 5.96-5.99 (m, 2H, OCH_2O), 6.61-6.65 (m, 1H, Ar*H*), 6.72-6.75 (m, 1H, Ar*H*), 6.78-6.84 (m, 1H, Ar*H*), 7.24-7.34 (m, 5H, Ar*H*); Both Isomers: ^{13}C NMR ($CDCl_3$, 100 MHz) δ 49.72, 50.30, 53.67, 54.22, 60.60, 61.57, 80.50 (q, $^2J_{C\text{-}F}$ = 28.9 Hz, *C*CF_3), 81.30 (q, $^2J_{C\text{-}F}$ = 28.9 Hz, *C*CF_3), 101.10, 101.22, 107.87, 107.98, 108.19, 108.54, 122.26, 122.86, 123.21 (q, $^1J_{C\text{-}F}$ = 287.5 Hz, C*C*F_3), 124.68, 126.71, 127.08, 127.44, 127.54, 127.70, 128.16, 128.31, 128.47, 130.26, 139.43, 147.57, 147.70, 147.88, 147.99, 168.88, 170.18; IR (neat, cm^{-1}) 3463, 2898, 1751, 1506, 1440, 1037, 913, 811, 781; MS (C.I.) *m/z* 398 [M+1], 291, 240. Anal. Calcd for $C_{19}H_{18}F_3NO_5$: C, 57.43; H, 4.57; N, 3.53. Found: C, 57.38; H, 4.61; N, 3.63.



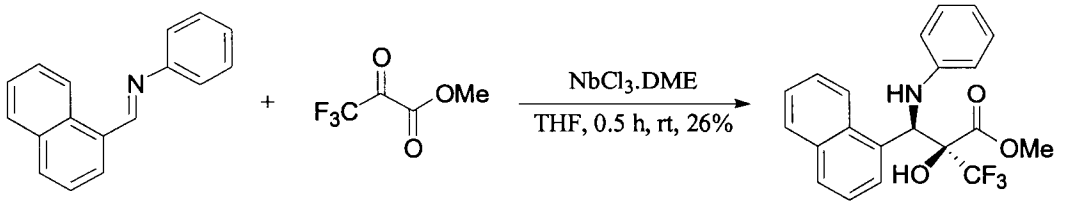
(41) **(30)** **(104)**

***Syn*-Methyl-3-benzylamino-2-(3,3,3,-trifluoromethyl)-2-hydroxy-3-(1-naphthyl)-propanoate 104**. To a solution of niobium trichloride dimethoxyethane complex (1.30 g, 4.50 mmol) in tetrahydrofuran (16 mL) at room temperature was added

to a solution of *N*-(1-napthylidene)-benzylamine **41** (368 mg, 1.50 mmol) in tetrahydrofuran (1.5 mL). A color change from maroon to dark green over the course of 30 min was observed while stirring at room temperature. After 30 min, methyl-3,3,3-trifluoropyruvate **30** (100 μL, 0.98 mmol) was added dropwise to the reaction mixture. After stirring for 30 min the reaction mixture was poured into a separatory funnel containing an aqueous solution of potassium hydroxide (10 % w/v, 20 mL) and extracted with ether (2 x 20 mL). The combined ether layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford a yellow oil. Purification by silica gel chromatography using hexanes:ethyl acetate (8:1) as the eluent followed by liquid chromatography on a cellulose triacetate column[52] afforded the title compound **104** as a yellow oil and as a 4:1 mixture of diastereomers (195 mg, 0.484 mmol, 49 %): R_f 0.38 (hexanes:ethyl acetate, 6:1); Both isomers: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.09 (s, 3H, OC*H*$_3$), 3.27 (d, 1H, J = 13.1 Hz, ArC*H*H), 3.50 (d, 1H, J = 13.4 Hz, ArCH*H*), 3.61 (d, 1H, J = 13.4 Hz, ArC*H*H), 3.74 (d, 1H, J = 13.4 Hz, ArCH*H*), 3.94 (s, 3H, OC*H*$_3$), 4.40 (s, br, 1H, N*H* or O*H*), 5.15 (s, 1H, *H*CN), 5.28 (s, 1H, *H*CN), 7.06-7.96 (m, 24H, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 50.02, 50.71, 53.09, 53.48, 54.26, 54.41, 80.22 (q, $^2J_{C\text{-}F}$ = 27.5 Hz, *C*CF$_3$), 81.26 (q, $^2J_{C\text{-}F}$ = 29.0 Hz, *C*CF$_3$), 122.43 (q, $^1J_{C\text{-}F}$ = 286.9 Hz, C*C*F$_3$), 122.70, 123.54 (q, $^1J_{C\text{-}F}$ = 288.4 Hz, C*C*F$_3$), 125.42, 125.51, 125.58, 125.80, 126.03, 126.42, 126.57, 126.71, 127.16, 127.36, 127.75, 127.83, 127.93, 128.13, 128.30, 128.37, 128.69, 128.92, 129.03, 129.68, 131.73, 132.68, 133.41, 133.55, 133.65, 139.40, 139.51, 168.56, 170.43; IR (ef, cm^{-1}) 3474, 3061, 3030, 2955, 2850, 1749, 1454, 1440,

[52] Keeling, C. I.; Ngo, H. T.; Benusic, K. D.; Slessor, K. N. *J. Chem. Ecol.* **2001**, *27*, 487-497.

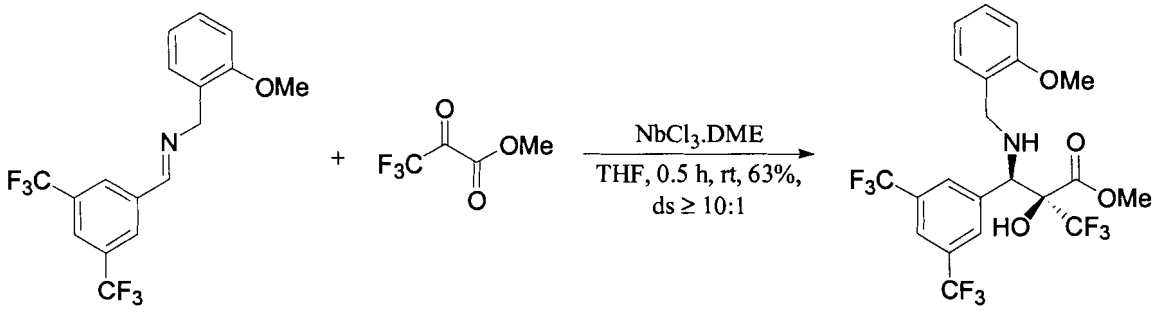
1243, 1149, 1082, 910, 861, 784; MS (C.I.) *m*/z 404 [M+1], 246, 159. Anal. Calcd for $C_{22}H_{20}F_3NO_3$: C, 65.50; H, 5.00; N, 3.47. Found: C, 65.90; H, 4.93; N, 3.69.



(40) **(30)** **(105)**

***Syn*-Methyl-2-(3,3,3,-trifluoromethyl)-2-hydroxy-3-(1-naphthyl)-3-phenylamino-propanoate 105**. To a solution of niobium trichloride dimethoxyethane complex (1.30 g, 4.50 mmol) in tetrahydrofuran (16 mL) at room temperature was added to a solution of *N*-(1-napthylidene)-aniline **40** (347 mg, 1.50 mmol) in tetrahydrofuran (1.5 mL). A color change from maroon to dark green over the course of 30 min was observed while stirring at room temperature. After 30 min, methyl-3,3,3-trifluoropyruvate **30** (100 μL, 0.98 mmol) was added dropwise to the reaction mixture. After stirring for 30 min the reaction mixture was poured into a separatory funnel containing an aqueous solution of potassium hydroxide (10 % w/v, 20 mL) and extracted with ether (2 x 20 mL). The combined ether layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum to afford a yellow oil. Purification by silica gel chromatography using hexanes:ethyl acetate (16:1) as the eluent afforded the title compound **105** as a yellow solid and as a single stereoisomer (100 mg, 0.257 mmol, 26 %): mp: 120-121 °C; R_f 0.29 (hexanes:ethyl acetate, 6:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ3.20 (s, 3H, OC*H*$_3$), 4.15 (s, 1H, N*H* or O*H*), 5.11 (d, 1H, J = 7.6 Hz, N*H* or O*H*), 6.10 (s, br, 1H, *H*CN), 6.56-6.68 (m, 3H, Ar*H*), 7.04 (t, 2H, J = 7.9 Hz, Ar*H*), 7.44 (t, 1H, J = 7.9 Hz, Ar*H*), 7.52 (t, 1H, J = 7.9 Hz, Ar*H*), 7.64 (t, 1H, J = 7.3 Hz, Ar*H*), 7.77 (t, 2H, J

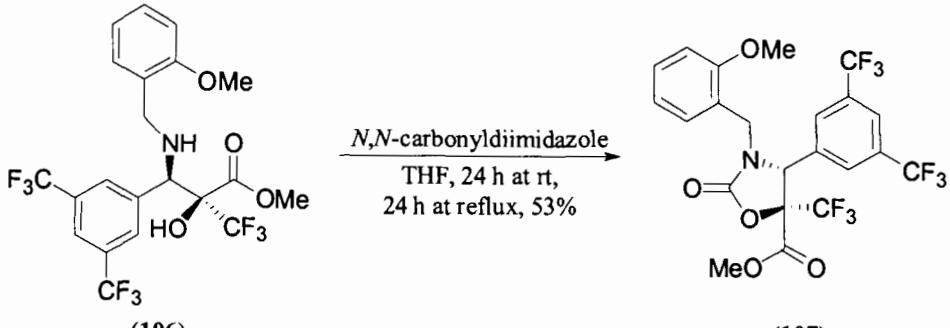
= 7.9 Hz, Ar*H*), 7.87 (t, 1H, *J* = 8.2 Hz, Ar*H*), 8.40 (d, 1H, *J* = 8.5 Hz Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 51.21, 53.65, 79.89 (q, $^2J_{C\text{-}F}$ = 27.5 Hz, *C*CF_3), 113.48, 118.02, 122.25, 123.17 (q, $^1J_{C\text{-}F}$ = 286.9 Hz, C*C*F_3), 125.48, 125.60, 126.29, 126.40, 127.72, 129.17, 129.27, 130.92, 132.41, 133.68, 145.65, 168.17; IR (ef, cm^{-1}) 3436, 3051, 2918, 1752, 1603, 1436, 1284, 1239, 1181, 1145, 782, 749; MS (C.I.) *m/z* 390 [M+1], 297, 232. Anal. Calcd for $C_{21}H_{18}F_3NO_3$: C, 64.78; H, 4.66; N, 3.60. Found: C, 65.09; H, 4.82; N, 3.44.



(39) (30) (106)

***Syn*-Methyl-3-(3,5-*Bis*-trifluoromethylphenyl)-2-(3,3,3-trifluoromethyl)-2-hydroxy-3-(2-methoxybenzylamino)-propanoate 106**. To a solution of niobium trichloride dimethoxyethane complex (868 mg, 3.00 mmol) in tetrahydrofuran (16 mL) at room temperature was added to a solution of *N*-(3,5-*bis*-trifluoromethyl-benzylidene)-(2-methoxybenzyl)-amine **39** (542 mg, 1.50 mmol) in tetrahydrofuran (1.5 mL). A color change from maroon to dark green over the course of 30 min was observed while stirring at room temperature. After 30 min, methyl-3,3,3-trifluoropyruvate **30** (100 μL, 0.98 mmol) was added dropwise to the reaction mixture. After stirring for 30 min the reaction mixture was poured into a separatory funnel containing an aqueous solution of potassium hydroxide (10 % w/v, 20 mL) and extracted with ether (2 x 20 mL). The combined ether layers were dried over anhydrous sodium sulfate, filtered and concentrated under vacuum

to afford a yellow oil. Purification by silica gel chromatography using pentane:ether (16:1) as the eluent afforded the title compound **106** as a colorless oil as a single stereoisomer (319 mg, 0.613 mmol, 61 %): R_f 0.62 (pentane:ether, 4:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ3.58 (d, 1H, J = 13.7 Hz, ArC*H*H), 3.64 (s, 3H, OCH_3), 3.71 (d, 1H, ArCH*H*), 3.73 (s, 3H, OCH_3), 4.34 (s, 1H, *H*CN), 6.74 (d, 1H, J = 8.2 Hz, Ar*H*), 6.85 (dt, 1H, J = 7.3, 0.9 Hz, Ar*H*), 7.00 (dd, 1H, J = 7.3, 1.8 Hz, Ar*H*), 7.20 (dt, 1H, J = 8.2, 1.8 Hz, Ar*H*), 7.65 (s, 2H, Ar*H*), 7.78 (s, 1H, Ar*H*); ^{1}H NMR (C_6D_6, 400 MHz) δ2.96 (s, 3H, OCH_3), 3.18 (s, 3H, OCH_3), 3.53 (s, 2H, ArCH_2), 4.36 (s, 1H, *H*CN), 6.34 (d, 1H, J = 8.2 Hz, Ar*H*), 6.77 (t, 1H, J = 7.3 Hz, Ar*H*), 6.96-7.04 (m, 2H, Ar*H*), 7.61-7.70 (m, 3H, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ47.51, 53.63, 54.84, 62.08, 80.00 (q, $^2J_{C\text{-}F}$ = 27.5 Hz, *C*CF_3), 110.07, 120.34, 122.18, 123.04 (q, $^1J_{C\text{-}F}$ = 286.9 Hz, C*C*F_3), 123.11 (q, $^1J_{C\text{-}F}$ = 273.1 Hz, C*C*F_3) 126.51, 128.90, 130.00, 131.35 (q, $^2J_{C\text{-}F}$ = 33.6 Hz, Ar*C*CF_3), 139.84, 157.51, 168.14; IR (neat, cm^{-1}) 3479, 2961, 2843, 1755, 1748, 1603, 1495, 1469, 1442, 1373, 1279, 1170, 1029, 902, 845; MS (C.I.) *m/z* 520 [M+1], 362, 270. Anal. Calcd for $C_{21}H_{18}F_9NO_4$: C, 48.56; H, 3.49; N, 2.70. Found: C, 48.63; H, 3.54; N, 2.92.



(106) **(107)**

***Anti*-5-Carboxymethyl-4-(3,5-*bis*-trifluoromethylphenyl)-5-trifluoromethyl-3-(2-methoxybenzyl)-oxazolidinone 107**. β-amino-α-hydroxy methyl ester **106** (202 mg, 0.389 mmol) was dissolved in tetrahydrofuran (7.5 mL) and *N,N*-carbonyldiimidazole

(94.6 mg, 0.583 mmol) was added.[40] The resultant solution was stirred at room temperature for 24 h, after which the solution was heated at reflux for 24 h. The solvent was then removed under vacuum to produce a yellow residue. The yellow residue was dissolved in dichloromethane (20 mL), washed with hydrochloric acid (1 *M*, 3 x 5 mL) water (2 x 5 mL) and brine (1 x 5 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered and the solution was concentrated under vacuum. Purification by silica gel chromatography using hexanes:ether (9:1) as the eluent followed by recrystallization from hexanes afforded the title compound **107** as a white solid (112 mg, 0.204 mmol, 53 %): mp: 52-54 °C (hexanes); R_f 0.62 (pentane:ether, 4:1); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.36 (s, 3H, OC*H*$_3$), 3.64 (s, 3H, OC*H*$_3$), 4.04 (d, 1H, J = 14.3 Hz, ArC*H*H), 4.81 (d, 1H, J = 14.3 Hz, ArCH*H*), 4.88 (s, 1H, *H*CN), 6.78 (d, 1H, J = 8.2 Hz, Ar*H*), 6.86 (d, 1H, J = 7.3 Hz, Ar*H*), 7.03 (d, 1H, J = 7.3 Hz, Ar*H*), 7.25-7.31 (m, 1H, Ar*H*), 7.50-7.64 (s, br, 2H, Ar*H*), 7.89 (s, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 42.79, 53.20, 54.92, 61.48, 81.91 (q, $^2J_{C\text{-}F}$ = 32.0 Hz, *C*CF$_3$), 110.30, 120.96, 121.81 (q, $^1J_{C\text{-}F}$ = 283.8 Hz, C*C*F$_3$), 122.66 (q, $^1J_{C\text{-}F}$ = 273.1 Hz, C*C*F$_3$), 123.55, 124.02, 130.62, 131.15, 132.29 (q, $^2J_{C\text{-}F}$ = 33.6 Hz, Ar*C*CF$_3$), 136.11, 154.46, 157.31 162.18; IR (neat, cm^{-1}) 2969, 2841, 1778, 1758, 1496, 1437, 1359, 1277, 1141, 1057, 1019, 907, 758; MS (C.I.) *m/z* 546 [M+1], 161, 121. Anal. Calcd for $C_{22}H_{16}F_9NO_5$: C, 48.45; H, 2.96; N, 2.57. Found: C, 48.19; H, 2.92; N, 2.67.