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Gregory Nicholas Goschy Date

I. A New Approach to the Synthesis of a Key 5-Oxo-Pyridinyl Molybdenum Scaffold.

II. Oxidative Demetalation of η^3-Allylmolybdenum Complexes with an Oxygen Nucleophile; Application to the Synthesis of (+)-Isofebrifugine Analogs

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B.S., College of Charleston, 2008

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An Abstract of
A thesis submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
in partial fulfillment of the requirements for the degree of
Master of Science
in Chemistry
2010

Abstract

I. A New Approach to the Synthesis of a Key 5-Oxo-Pyridinyl Molybdenum Scaffold.

II. Oxidative Demetalation of η^3-Allylmolybdenum Complexes with an Oxygen Nucleophile; Application to the Synthesis of (+)-Isofebrifugine Analogs
By Gregory Nicholas Goschy

Due to their versatility, molybdenum π-complexes have become common organometallic enantiomeric scaffolds for the construction of a variety of enantiopure heterocycles. A concise, high throughput method was developed to access both racemic and chiral, non-racemic $TpMo(CO)_2(\eta^3$-pyridinyl) complexes in an efficient manner. In recent years, the use of a key 5-oxo-pyridinyl scaffold has become a major focus for the Liebeskind laboratory. Although there have been many improvements to the preparation of this key scaffold, recent increases in the chiral auxiliary precursor price has hindered widespread use of this chemistry. Further exploration and screening of the "chiral pool" has led to the construction of a variety of inexpensive chiral auxiliaries, as well as a different method to incorporate them.

Oxidative demetatalation of η^3-allylmolybdenum complexes is a key step in the synthesis of numerous biologically active compounds. Expanding the scope of this reaction by incorporating oxygen as the nucleophile will provide a better route towards the synthesis of (+)-isofebrifugine and its analogs.

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II. Oxidative Demetalation of η^3-Allylmolybdenum Complexes with an Oxygen Nucleophile; Application to the Synthesis of (+)-Isofebrifugine Analogs

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List of Schemes

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List of Abbreviations

Δ	heat
(±)	racemic
Ac_2O	acetic anhydride
Ag_2CO_3	silver carbonate
AgCl	silver chloride
AcOH	acetic acid
ACN	acetonitrile
Aq	aqueous
BH_3	borane
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br	broad
calcd	calculated
cat	catalytic
Cbz	carboxybenzyl
CDI	1,1'-carbonyldiimidazole
CH_2Cl_2	methylene chloride
Cp	cyclopentadienyl
d	doublet
de	diastereomeric excess
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
ESI	electrospray ionization
Et	ethyl
FT	Fourier transform
g	gram(s)
h	hour(s)
HPLC	high performance liquid chromatography
^{1}H NMR	proton nuclear magnetic resonance
HRMS	high resolution mass spectroscopy
Hz	hertz
IR	infrared spectroscopy
J	coupling constant
kcal	kilocalorie(s)
KTp	potassium trispyrazolylborate
LAH	lithium aluminum hydride
m-CPBA	meta-chloroperbenzoic acid
m	multiplet
Me	methyl
mg	milligram(s)
min	minute(s)

mL	milliliter(s)
mmol	millimole(s)
mol	mole(s)
mp	melting point
MsCl	methanesulfonyl chloride
NMR	nuclear magnetic resonance
Ph	phenyl
ppm	parts per million
q	quartet
quant	quantitative
R	group
rt	room temperature
s	singlet
SAR	structure activity relationship
TBDMS	tert-butyldimethylsilyl
TEA	triethylamine
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
TLC	thin layer chromatography
TMSI	iodotrimethylsilane
Tp	trispyrazolylborate
t	triplet
Ts	tosyl
UV	ultraviolet

Chapter One

An Introduction to *Organometallic Enantiomeric Scaffolding*

Introduction

Enantiocontrolled construction of complex organic molecules has been one of the primary challenges for modern synthetic chemists. Three unique methodologies have been developed to address the control of absolute stereochemistry in organic synthesis: (1) syntheses that incorporate "chirons"[1-3] or auxiliaries[4,5] originating from the "chiral pool" (2) enzymatic transformations,[6-8] and (3) metallo-[9] or organo-catalytic[10-12] asymmetric transformations. While catalytic approaches to enantiocontrolled bond construction in complex organic syntheses have been the major focus in recent decades, the development of *enantiomeric scaffolds* provides a strategic alternative approach to these complex organic systems. The goal of this scaffolding strategy is to construct a simple core molecule of high enantiopurity that is tactically versatile. The resident functionality of the core molecule enables general transformations to a wide range of interesting molecules including a variety of natural- and non-natural products.

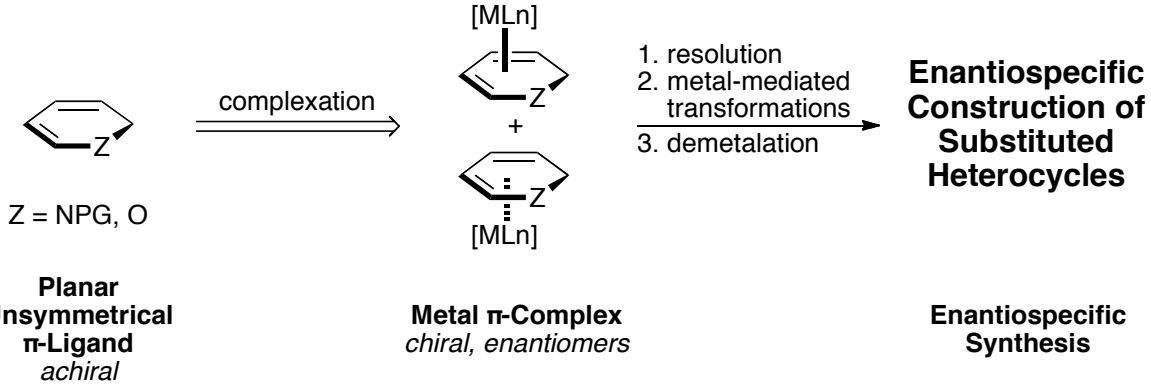
---

[1] Hanessian, S. *Pure Appl. Chem.* **1993**, *65*, 1189-1204.
[2] Hanessian, S. *Aldrichim. Acta* **1989**, *22*, 3-14.
[3] Hanessian, S. In *Total Synthesis of Natural Products: The "Chiron" Approach*; Pergamon Press: Oxford, UK, 1983.
[4] Blaser, H. U. *Chem. Rev.* **1992**, *92*, 935-952.
[5] Krohn, K. Chiral Building Blocks from Carbohydrates. In *Organic Synthesis Highlights*; Mulzer, J., Altenbach, H. J., Braun, M., Krohn, K., Reissig, H. U., Eds.; VCH Verlagsgesellschaft: Weinheim, Germany, 1991; pp 251-260.
[6] Shaw, N. M.; Robins, K. T.; Kiener, A. Biocatalytic Approaches for the Large-Scale Production of Asymmetric Synthons. In *Asymmetric Catalysis on Industrial Scale*; Blaser, H.-U., Schmidt, E., Eds.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, Germany, 2004; pp 105-115.
[7] Mulzer, J. Enzymes in Organic Synthesis. 2. In *Organic Synthesis Highlights*; Mulzer, J., Altenbach, H. J., Braun, M., Krohn, K., Reissig, H. U., Eds.; VCH Verlagsgesellschaft: Weinheim, Germany, 1991; pp 216- 223.
[8] Mulzer, J. Enzymes in Organic Synthesis. 1. In *Organic Synthesis Highlights*; Mulzer, J., Altenbach, H. J., Braun, M., Krohn, K., Reissig, H. U., Eds.; VCH Verlagsgesellschaft: Weinheim, Germany, 1991; pp 207- 215.
[9] Ojima, I. *Catalytic Asymmetric Synthesis*, 2nd ed.; Wiley: New York, 2000; p 864.
[10] Seayad, J.; List, B. *Org. Biomol. Chem.* **2005**, *3*, 719-724.
[11] Dalko, P. I.; Moisan, L. *Angew. Chem., Int. Ed. Engl.* **2004**, *43*, 5138-5175.
[12] Clarke, M. L. *Lett. Org. Chem.* **2004**, *1*, 292-296.

Concept: Transition Metal Complexes in Organic Synthesis

Organometallic enantiomeric scaffolding is another approach that can be implemented in the enantiocontrolled synthesis of complex organic molecules. Our group describes organometallic enantiomeric scaffolds as, "simple, readily available, *single enantiomers* of air-stable organometallic π-complexes of key unsaturated ligands from which *diverse families* of important molecular structures can be obtained in high enantiopurity."[13] These complexes exhibit novel reactivity and remarkable stereo- and regiocontrol on the organic ligand substate.[14] These organometallic enantiomeric

Figure 1.1 Metal π-Complexes in Enantiospecific Heterocyclic Synthesis



scaffolds can be synthesized by complexation of an achiral, unsymmetrical π-ligand to a transition metal which forms a racemic mixture of a metal π-complex bearing planar chirality (Figure 1.1). The racemic mixture can then be resolved to furnish two facial enantiomers, which can undergo metal-mediated transformations, followed by

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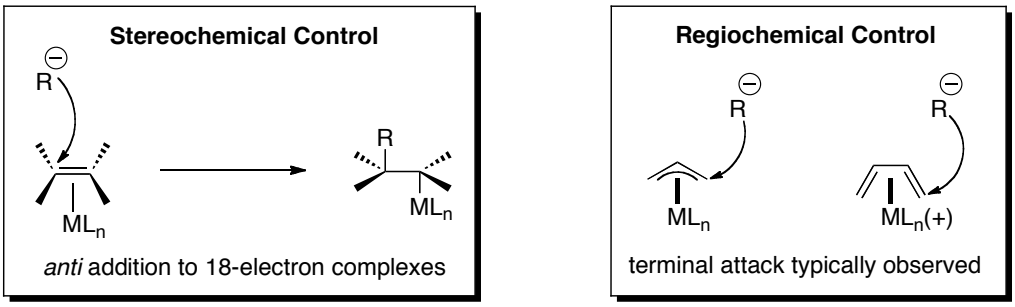
[13] Coombs, T. C.; Lee; Wong, H.; Armstrong, M.; Cheng, B.; Chen, W.; Moretto, A. F.; Liebeskind, L. S. *J. Org. Chem*. **2008,** *73*, 882-888.

[14] (a) Pearson, A. J. In *Advances in Metal-Organic Chemistry*; Liebeskind, L. S., Ed.; JAI: Stanford, CT, 1989; Vol. 1, p. 1. (b) Harmon, W. D. *Chem Rev*. **1997**, *97*, 1953-1978. (c) Li, C. L.; Liu, R. S. *Chem Rev.* **2000**, *100*, 3127-3162. (d) Pape, A. R.; Kaliappan, K. P.; Kündig, E. P. *Chem Rev.* **2000**, *100*, 2917-2940.

demetalation, to generate multi-functionalized heterocyclic compounds of high enantiopurity. Consequently, these scaffolds have proven to be powerful synthetic tools for the construction of complex organic molecules with high enantiopurity.

As previously stated, metal π-complexes exhibit novel reactivity in terms of stereo- and regiocontrol. Nucleophilic functionalization of the complexes takes place at the terminal positions of the η^3-allyl and cationic diene ligands and is typically directed *anti* to the metal-ligand moiety (Figure 1.2).

Figure 1.2 Nucleophilic Functionalization of Metal π-Complexes



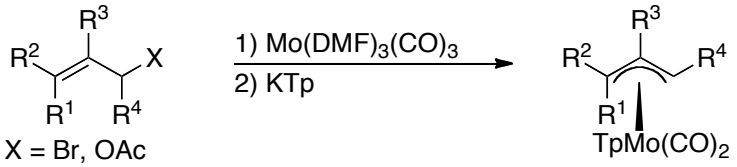
Preparation of η^3-Allyl Molybdenum π-Complexes

Liebeskind *et al.*[15] generalized the preparation of π-allyl molybdenum complexes from allylic bromides to include allylic acetates, enals, and enones using $Mo(CO)_3(DMF)_3$[16] as the Mo(0) source, tris(1-pyrazolyl) borate (Tp)[17] as the spectator ligand, and methylene chloride as a non-coordinating solvent (Scheme 1.1).

---

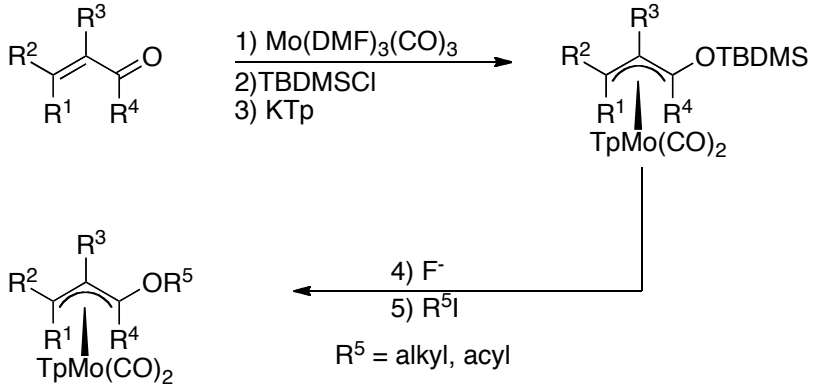
[15] Ward, Y. D.; Villanueva, L. A.; Allred, G. D.; Payne, S. C.; Semones, M. A.; Liebeskind, L. S. *Organometallics* **1995,** *14*, 4132-4156.
[16] Paquali, M.; Leoni, P.; Sabatino, P.; Brage, D. *Gazz. Chim. Ital.* **1992**, *122*, 275-277.
[17] a) Trofimenko, S. *Chem. Rev.* **1993**, *93*, 943-980. b) Trofimenko, S. *Chem. Rev.* **1972,** *72,* 497-509. c) Trofimenko, S. *Acc. Chem. Res.* **1971,** *4,* 17-22.

Scheme 1.1 π-Allyl Molybdenum Complexes from Allylic Bromides and Acetates



Another route to obtain π-allyl molybdenum complexes involves using α,β-unsaturated ketones or aldehydes as organic precursors.[15] Complexation of $Mo(CO)_3(DMF)_3$ with the enal or enone followed by quenching with TBDMSCl and subsequent ligand exchange with KTp forms a π-allyl molybdenum intermediate that was transformed into various alkoxy or acetoxy molybdenum π-complexes (Scheme 1.2).

Scheme 1.2 π-Allyl Molybdenum Complexes from Enals and Enones



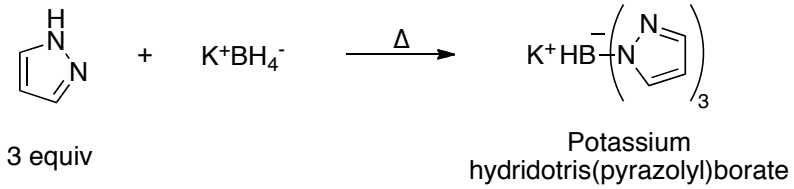
The Hydridotrispyrazolylborate (Tp) Ligand

When initially developing methods for obtaining π-allyl molybdenum complexes, our group incorporated η^5-cyclopentadienyl (Cp) as the stabilizing ancillary ligand.[18] However, limitations arose due to the strong basicity and nucleophilicity of the Cp anion

[18] Liebeskind, L. S.; Welker, M. E.; Fengl, R. W. *Organometallics.* **1986**, *108*, 6328-6343.

used to prepare the $CpMo(CO)_2$ moiety. As a result, the hyridotris(pyrazoyl)borate (Tp)[19] ligand was investigated as an isoelectronic alternative. Incorporation of the 6-electron, monoanionic "Tp" ligand, overcame the drawbacks relative to the "Cp" ligand, which resulted in the replacement of the more common $CpMo(CO)_2$ complexes with $TpMo(CO)_2$ complexes in the study of stoichiometric molybdenum π-complexes. The "Tp" ligand can be introduced using potassium hydridotris(pyrazoyl)borate (KTp), an air- and moisture stable, free-flowing solid that is easily prepared on kilogram scale from pyrazole and potassium borohydride (Scheme 1.3).[20]

Scheme 1.3 Preparation of the "Tp" Ligand



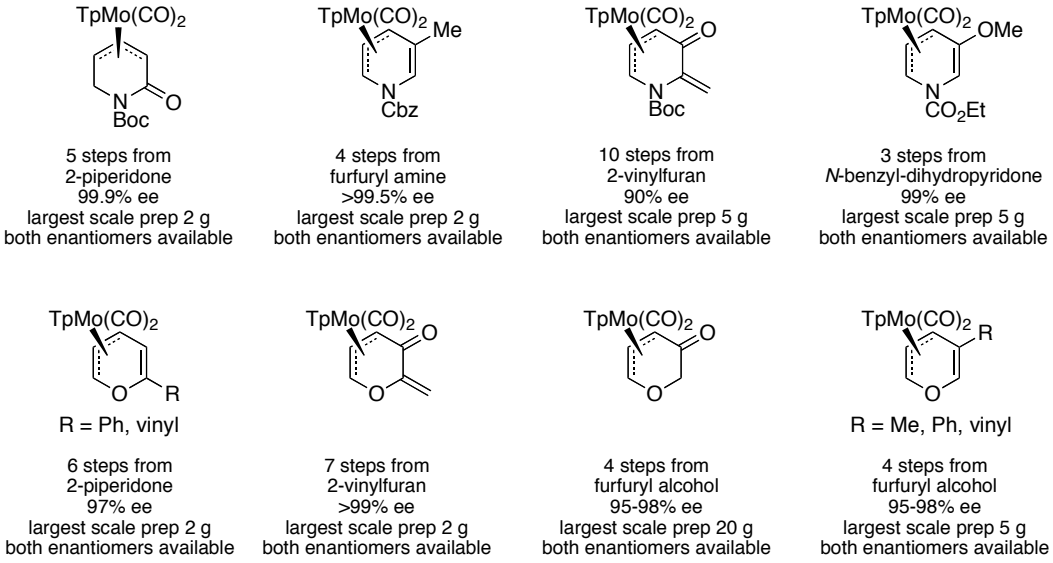
Utilization of $TpMo(CO)_2$ Complexes in Organic Synthesis

The Liebeskind laboratory has developed a versatile methodology utilizing stoichiometric molybdenum π-complexes to access a variety of functionalized η^3-allyl $TpMo(CO)_2$-based heterocyclic scaffolds (Figure 1.3), and highlighted their importance through the synthesis of numerous structurally intriguing heterocycles.[21-34] All of these

[19] a) Trofimenko, S. *Chem. Rev.* **1993**, *93*, 943-980. b) Trofimenko, S. *Chem. Rev.* **1972,** *72,* 497-509. c) Trofimenko, S. *Acc. Chem. Res.* **1971,** *4,* 17-22.
[20] Trofimenko, S. *J. Am. Chem. Soc.* **1967,** *89,* 3170-3177.
[21] Shu, C.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2003**, *125*, 2878–2879.
[22] Shu, C.; Alcudia, A.; Yin, J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2001**, *123*, 12477–12487.
[23] Yin, J.; Llorente, I.; Villanueva, L. A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2000**, *122*, 10458–10459.
[24] Moretto, A. F.; Liebeskind, L. S. *J. Org. Chem.* **2000**, *65*, 7445–7455.
[25] Rubio, A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 891–901.

molybdenum scaffolds are air-stable solids, and are easily prepared on multi-gram scale in high enantiopurity.

Figure 1.3 Previously Developed Organometallic Enantiomeric Scaffolds



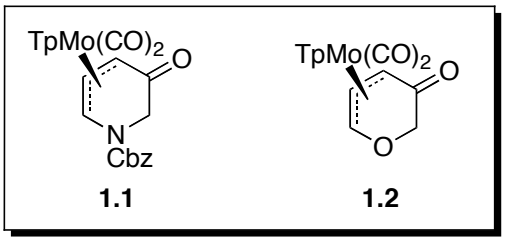
Preparation of a Key 5-Oxo Pyridinyl Molybdenum Scaffold

While there have been many different $TpMo(CO)_2(\eta^3$-pyridinyl) complexes developed by the Liebeskind group (Figure 1.3), a lack of general reactivity hindered synthetic application.[21-34] Consequently, a more universal $TpMo(CO)_2(\eta^3$-pyridinyl) complex was needed to accommodate the construction of compounds with various frameworks and functionalities. This resulted in the development of enantiopure

[26] Moretto, A. F.; Liebeskind, L. S. *J. Org. Chem.* **2000**, *65*, 7445–7455.
[27] Arrayás, R. G.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2003**, *125*, 9026–9027.
[28] Arrayás, R. G.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2001**, *123*, 6185–6186.
[29] Arrayás, R. G.; Yin, J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2007**, *129*, 1816–1825.
[30] Zhang, Y.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2006**, *128*, 465–472.
[31] Zhang, Y.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2005**, *127*, 11258–11259.
[32] Malinakova, H. C.; Liebeskind, L. S. *Org. Lett.* **2000**, *2*, 3909–3911.
[33] Malinakova, H. C.; Liebeskind, L. S. *Org. Lett.* **2000**, *2*, 4083–4086.
[34] Yin, J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1999**, *121*, 5811–5812.

$TpMo(CO)_2(\eta^3$-pyridinyl) scaffold **1.1** (Figure 1.5) as a key "enantiomeric scaffold" for the synthesis of a wide range of piperidine based alkaloids. The basis for the development of this particular scaffold originated from $TpMo(CO)_2(\eta^3$-pyranyl) scaffold **1.2** (Figure 1.4), which is used as an "enantiomeric scaffold" for the synthesis of enantiopure pyranyl heterocycles .[35]

Figure 1.4 Key 5-Oxo-Pyridinyl and Pyranyl scaffolds



1.1 **1.2**

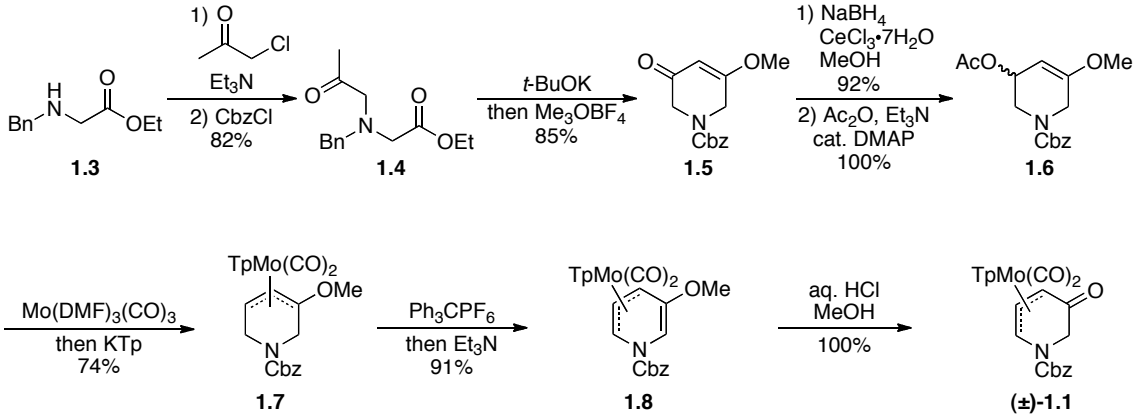
While the versatility of the 5-oxo-pyridinyl scaffold has been extensively demonstrated, a significant drawback to its use lies in the rather lengthy synthesis from commercial materials (Scheme 1.4).[22,26,32] The previously employed synthesis has evolved over the past years,[36] but has not been optimized to the point where it would be considered appealing to other synthetic chemists.

The initial synthesis of the 5-oxo-pyridinyl scaffold started with commercially available *N*-benzyl glycine ethyl ester **1.3**, alkylation with chloroacetone and exchange of the benzyl protecting group for Cbz, afforded compound **1.4**. Treating **1.4** with potassium *t*-butoxide induced Dieckmann cyclization and the β-diketone product was trapped with

[35] (a) Arrayás, R. G.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2001**, *123*, 6185-6186. (b) Yin, J.; Llorente, I.; Villanueva, L. A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2000**, *122*, 10458-10459.
[36] Wong, H. Design, Synthesis and Resolution of a Chiral, Non-Racemic Organometallic Chiron: Asymmetric Total Syntheses of Tetrahydropyridine-Based Alkaloids. Ph.D. Dissertation, Emory University, Atlanta, 2006.

Meerwein's reagent, giving methoxyenone **1.5**. Luche reduction of the enone followed by acylation of the resulting allylic alcohol afforded allylic acetate **1.6**, which underwent oxidative addition to $Mo(DMF)_3(CO)_3$. Ligand exchange with KTp provided complex **1.7**. Two-step migration of the $TpMo(CO)_2$ moiety by hydride abstraction with Ph_3CPF_6 and deprotonation with Et_3N led to fully-unsaturated complex **1.8**, which underwent acid-mediated hydrolysis of the enol ether to afford the desired 5-oxo-pyridinyl scaffold **1.1**. Overall, eight steps were required to synthesize the racemic scaffold.

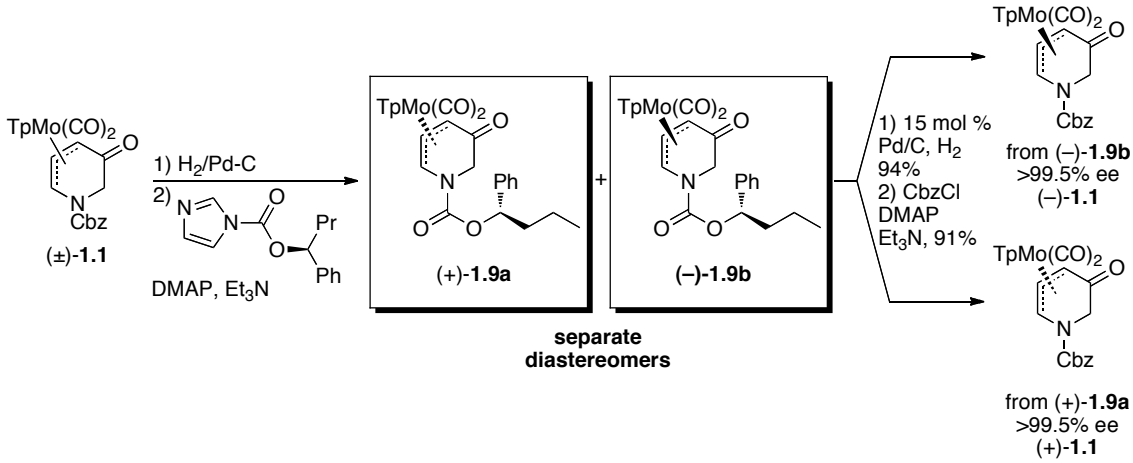
Scheme 1.4 Synthesis of (±)- 5-Oxo-Pyridinyl Scaffold



In order to access single enantiomers of scaffold **1.1**, additional steps were necessary.[13] Compound (±)-**1.1** was subjected to hydrogenolytic removal of the Cbz group, followed by reprotection of the free amine with a chiral auxiliary to afford a mixture of diastereomers (+)-**1.9a** and (–)-**1.9b** (Scheme 1.5). The diastereomers were separated using chromatographic resolution, followed by hydrogenolysis of the chiral auxiliary and reprotection of the enantiopure free amine with CbzCl to give (+)-**1.1** and (–)-**1.1**. The identity of the chiral auxiliary was important for minimizing racemization

during its removal. After extensive optimization, it was found that phenylbutanol-derived carbamates led to no racemization upon removal of the chiral auxiliary.[13]

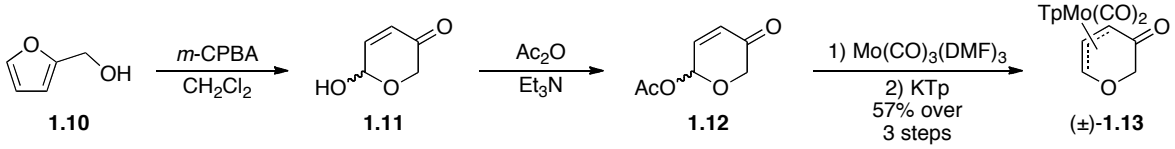
Scheme 1.5 Diasteremeric Scaffold Resolution



The Aza-Achmatowicz Approach to a Key 5-Oxo-Pyridinyl Molybdenum Scaffold

The aza-Achmatowicz approach to 5-oxo-pyridinyl scaffolds evolved from the Achmatowicz-based synthesis of 5-oxo-pyranyl scaffolds (Scheme 1.6).[37]

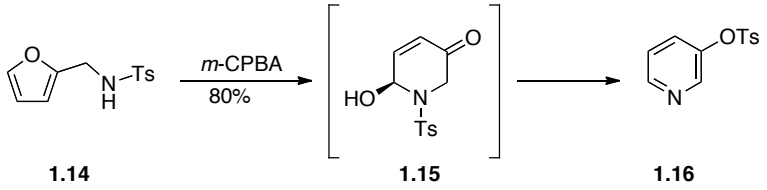
Scheme 1.6 Achmatowicz-Based Synthesis of 5-Oxo-Pyranyl Scaffold



[37] Moretto, A. F. The Utilization of Stoichiometric Molybdenum π-Complexes for the Synthesis of Substituted Piperidines. Ph.D. Dissertation, Emory University, Atlanta, 1999.

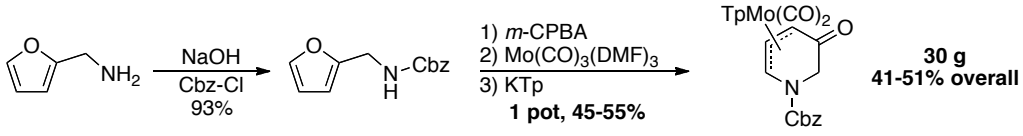
Initial attempts of the aza-Achmatowicz approach to 5-oxo-pyridinyl scaffolds resulted in facile aromatization of the 2,6-dihydro-1*H*-pyridin-5-one intermediate, which is consistent with previous literature reports (Scheme 1.7).[38-41] Further investigation of the aza-Achmatowicz reaction sequence revealed that the most efficient route to access $TpMo(CO)_2(\eta^3$-pyridinyl) complex **1.1** was *via* a "two-pot" route where the only intermediate that was isolated and purified was the *N*-protected furfuryl amine (Scheme 1.8).[42] This "two-pot" route circumvents aromatization of the oxidatively rearranged intermediate, where benzoic acid by-products are removed before addition of Mo(0) source.

Scheme 1.7 Aromatization of 2,6-dihydro-1*H*-pyridin-5-one



1.14 **1.15** **1.16**

Scheme 1.8 "Two-Pot" Synthesis of Racemic $TpMo(CO)_2(\eta^3$-pyridinyl) Complex



1.17 **1.18** (±)-**1.1**

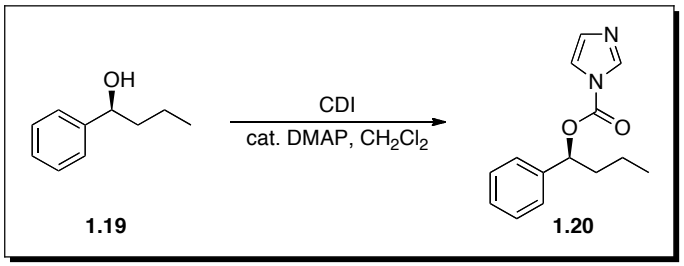
[38] McKillop, A.; Boulton, A. J. In *Comprehensive Heterocyclic Chemistry*; Katritzsky, A. R.; Rees, C. W., Eds.; Pergamon Press: Oxford, U.K. 1984; V. 2A, P. 90 ff.
[39] Shono, T.; Matsumura, Y.; Tsubata, K.; Inoue, K.; Nishida, R. *Chem. Lett.* **1983**, 21-24.
[40] Shono, T.; Matsumura, Y.; Tsubata, K.; Inoue, K.; Tanaka, J. *Chem. Lett.* **1981**, 1121-1124.
[41] Ciufolini, M. A.; Hermann, C. Y. W.; Dong, Q.; Shimizu, T.; Swaminathan, S.; Xi, N. *Synlett* **1998**, 105-114.
[42] Armstrong, M. A. Synthesis and Resolution of Chiral, Non-Racemic $TpMo(CO)_2(\eta^3$-pyridinyl) Complexes. Master Dissertation, Emory University, Atlanta, 2007.

Overall, a "two-pot" approach to $TpMo(CO)_2(\eta^3$-pyridinyl) complex **1.1** was achieved where the rearrangement/metalation/ligand exchange sequence is run under mild conditions (0 °C - rt, 1-1.5 h) for each step.

Exploration of the "Chiral Pool" for Asymmetric *N*-Protection

A major issue during previous resolutions and enantiocontrolled syntheses of chiral, non-racemic molybdenum π-complexes was racemization during cleavage of the chiral auxiliary. Various chiral alcohols were screened as potential precursors to chiral auxiliaries with certain criteria in mind: (1) inexpensive for use in large-scale preparation (2) easily removable with sufficient functional group compatability (3) easy separation of diastereomers on large scale. As stated above, it was found that (*S*)-(-)-1-phenyl-1-butanol was the best precursor to a carbamate chiral auxiliary of $TpMo(CO)_2(\eta^3$-pyridinyl) complex **1.1**. In order to attach the chiral auxiliary, (*S*)-(-)-1-phenyl-1-butanol is treated with CDI and catalytic DMAP to afford carbamate **1.20** (Scheme 1.9), which can then be introduced to the $TpMo(CO)_2(\eta^3$-pyridinyl) complex.

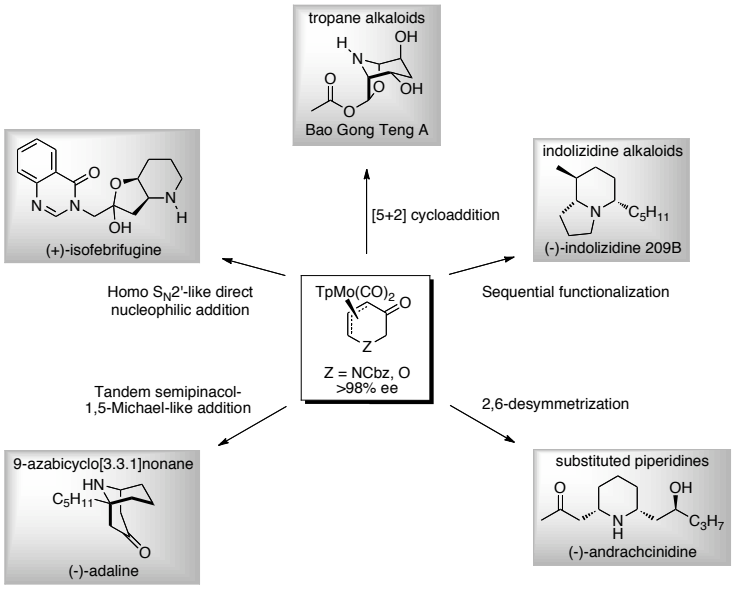
Scheme 1.9 (*S*)-(-)-1-Phenyl-1-Butanol Chiral Auxiliary Precursor



Synthesis of Enantiopure Substituted Alkaloids from a Key 5-Oxo-Pyridinyl Molybdenum Scaffold

There are a variety of naturally occurring and biologically active alkaloids, which possess a piperidine skeletal framework. The versatility of molybdenum π-complexes in organic syntheses allows the enantiocontrolled construction of these complex polycyclic compounds. The Liebeskind laboratory has been successful in synthesizing many interesting alkaloids by utilizing molybdenum π-complexes as enantiomeric scaffolds (Figure 1.5). A variety of reactions have been incorporated into these syntheses including, but not limited to, [5+2], [5+3], and [4+2] cycloadditions,[26,32] 2,6-desymmetrizations,[21] 2,6-difunctionalizations,[21] 1,5-Michael-like additions,[30] semipinacol rearrangements,[43] and most recently, homo S_N2'-like direct nucleophilic additions.[44]

Figure 1.5 Moybdenum π-Complexes as Enantiomeric Scaffolds



[43] Coombs, T. C.; Zhang, Y.; Garnier-Amblard, E. C.; Liebeskind, L. S. *J. Am. Chem. Soc.*, **2009**, *131*, 876–877.
[44] Chen, Wenyong; Liebeskind, L. S. *J. Am. Chem. Soc.*, **2009**, *131*, 12546–12547.

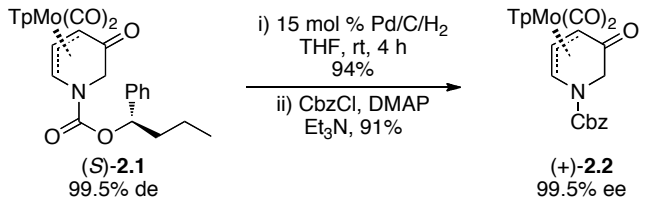
Chapter Two

Racemization-Free Removal of the Methyl Mandelate Chiral Auxiliary

Introduction

Developing efficient methodologies is an important aspect of synthetic chemistry. The Liebeskind laboratory has demonstrated that $TpMo(CO)_2(\eta^3$-pyridinyl) complexes are versatile and powerful synthetic tools for enantiocontrolled bond construction. However, a recent price increase in the chiral auxiliary precursor has hindered the widespread use of this chemistry up to date: The price of (*S*)-(-)-1-phenyl-1-butanol has increased from $10/g to $115/g over the past three years.[1] While this alcohol can be synthesized, insufficient enantiopurity proves this to be an ineffective alternative. The chiral auxiliary of (*S*)-(-)-1-phenyl-1-butanol has proven to be the most effective up to this point (Scheme 2.1).

Scheme 2.1 Racemization-Free Hydrogenolysis



(*S*)-**2.1**
99.5% de

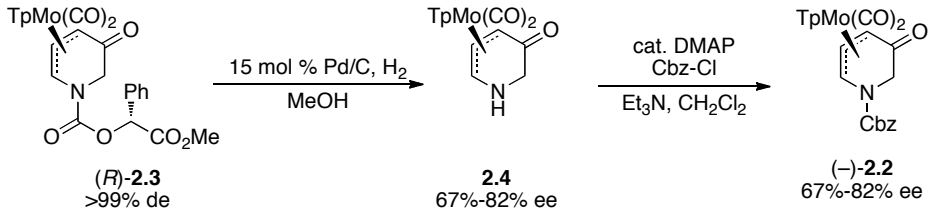
(+)-**2.2**
99.5% ee

As a result, the incorporation of other chiral auxiliaries has been explored. A major advantage to using the (*S*)-(-)-1-phenyl-1-butanol chiral auxiliary is that it can be removed by hydrogenolysis due to the benzyl moiety, which is a much milder removal than the previous method using SmI_2 for the α-deoxygenation of enantiopure carbamate.[2] Also, hydrogenolysis conditions tolerate more functional groups and avoid racemization in certain systems. When exploring the "chiral pool" for other potential auxiliaries, it

[1] Aldrich catalog
[2] Malinkova, H.C.; Liebeskind, L. S. *Org. Lett.* **2000**, *2*, 2909-3911.

was apparent that compounds possessing a benzyl group would be a good place to start. An initial investigation by former Liebeskind group member Dr. Heilam Wong introduced the idea of using mandelates as precursors to the auxiliary. This was based on previous work done by Inanaga and coworkers, who reported a highly efficient resolution of a chiral pyrrolidine using a mandelate carbamate as a stoichiometric chiral, non-racemic auxiliary.[3] The use of methyl-(*R*)-(–)mandelate was investigated and was found to meet all the criteria of an ideal chiral non-racemic auxiliary: (1) inexpensive for large scale preparation, $14.64/g (2) easily separable diastereomers (3) easy removal for better functional group compatibility. However, upon hydrogenolysis, it was observed that partial racemization of the metal complex was taking place (Scheme 2.2). Even though the complex racemizes during hydrogenolysis, there is enough potential in this system to pursue another method of removal in order to circumvent racemization.

Scheme 2.2 Cleavage of Mandelate Protected Carbamate: Partial Racemization



(*R*)-**2.3**
>99% de

2.4
67%-82% ee

(–)-**2.2**
67%-82% ee

Results and Discussion

Optimization of Hydrogenolysis

Racemization-free hydrogenolysis of the methyl mandelate chiral auxiliary to form free amine intermediate **2.4** is the crux of this reaction sequence. As a result,

[3] Hanamoto, T.; Shimomoto, N.; Kikukawa, T.; Inanaga, J. *Tetrahedron Asymmetry* **1999**, *10*, 2951-2959.

various hydrogenolysis conditions were investigated which include variations in: (1) reaction time, (2) catalyst, (3) temperature, and (4) solvent.

The first variant that was explored was the hydrogenolysis catalyst (Table 2.1). The catalyst 15 mol % Pd/C used in the past that led to partial racemization. This reaction was repeated under standard conditions[4] with a lower catalyst loading, and was found to provide an improved % ee, but drastically decreased yield (Table 2.1, entry 1). The next catalyst that was investigated was 20 mol % $Pd(OH)_2$, also known as Pearlman's catalyst (Table 2.1, entry 4). The catalyst loading was increased from 10 mol % to 20 mol % to increase overall yield. This system was found to be the best catalyst and catalyst loading for removal of the auxiliary. Other palladium catalysts were investigated, but proved to be less effective or ineffective by comparison.

Table 2.1 Optimization of Hydrogenolysis: Catalyst, THF, 23 °C, 24 h

entry	(mol %) catalyst	% yield	% ee
1	(10) Pd/C	32	89.9
2	(10) $Pd_2(dba)_3$	55	89.4
3	(10) $Pd(PPh_3)_4$	---	---
4	(20) $Pd(OH)_2$	81	89.6

The second variant considered was the solvent (Table 2.2). Utilization of numerous solvents was investigated with the differing catalysts. Solvent had little to no effect when varied with 10 mol % $Pd_2(dba)_3$. It was found that THF and EtOAc were the best solvent choices for use with $Pd(OH)_2$. While EtOAc yielded slightly better results (Table 2.2, entry 5), these conditions proved to be more difficult to reproduce than those

[4] Standard conditions: solvent: THF, temperature: 23 °C, reaction time: 24 h.

with THF as the solvent (Table 2.2, entry 1). Since there was no apparent reason for the irreproducibility of the reaction using EtOAc, THF was chosen as the preferred hydrogenolysis solvent.

Table 2.2 Optimization of Hydrogenolysis: Solvent, 23 °C, 24 h

entry	(mol%) catalyst	solvent	% yield	% ee
1	(20) $Pd(OH)_2$	THF	81	89.6
2	(20) $Pd(OH)_2$	THF/AcOH	---	---
3	(20) $Pd(OH)_2$	MeOH	46	87.2
4	(20) $Pd(OH)_2$	EtOH	71	89.1
5	(20) $Pd(OH)_2$	EtOAc	80	90.7
6	(20) $Pd(OH)_2$	AcOH	---	---

The third variant considered was the reaction time (Table 2.3). Time intervals starting from 0.5 hours up to 24 h were investigated. Reaction time was initially thought to have played a major part in the racemization process, but after investigation it was found that only the yields were time dependent. While the four hour reaction showed slightly higher yields, there was a slight decrease in enantiomeric excess, which cannot be fully explained at this time. Thus the 24-hour reaction time was found to be the optimum time interval.

Table 2.3 Optimization of Hydrogenolysis: Time, THF, 23 °C

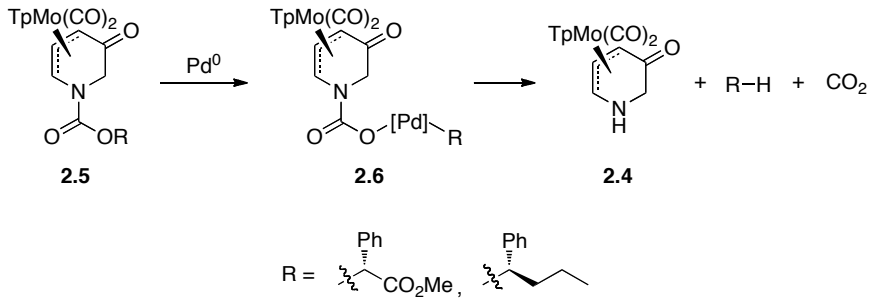
entry	(mol %) catalyst	time (h)	% yield	% ee
1	(20) $Pd(OH)_2$	0.5	---	---
2	(20) $Pd(OH)_2$	1	62	90.2
3	(20) $Pd(OH)_2$	2	78	89.7
4	(20) $Pd(OH)_2$	4	84	85.4
5	(20) $Pd(OH)_2$	24	81	89.6

After rigorous optimization, it was clear that even under the optimized conditions (Table 2.3, entry 5) partial racemization was still taking place. Varying the reaction temperature was investigated and was found to not be critical. The % ee was increased from 67-82% ee to 85-91% ee, unfortunately an enantiomeric excess of ~99% is required for *organometallic enantiomeric scaffolding* if the concept is to be useful for the total synthesis of high enantiopurity molecules.

Control Experiments and Mechanistic Insight

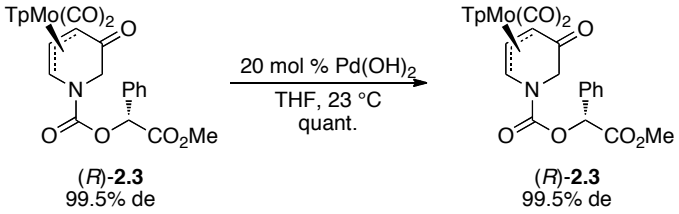
Understanding the mechanistic properties of removal of the methyl mandelate chiral auxiliary is an important part of circumventing the issue of racemization. An interesting point in this reaction series is that no racemization occurs when R = 1-phenylbutane, but when R = methylphenylacetate partial racemization will occur (Scheme 2.3). This indicates that the methyl ester moiety is responsible for the racemization. A number of control experiments were conducted in order to gain more insight about the reaction mechanism.

Scheme 2.3 Mechanistic Insight: Difference in Groups



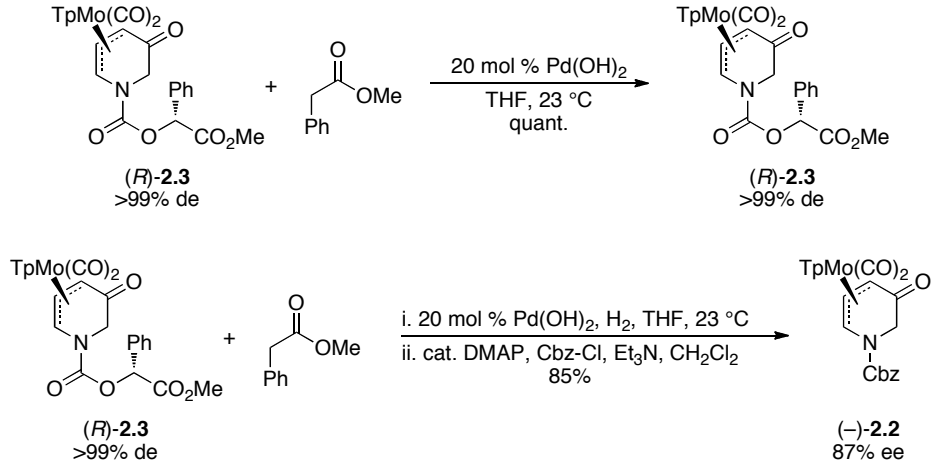
The first control experiment tested the effect of the palladium catalyst on the methyl mandelate system in the absence of hydrogen (Scheme 2.4). The result was that Pearlman's catalyst does not racemize the complex in the absence of hydrogen gas.

Scheme 2.4 Control Experiment: Effect of Palladium Catalyst



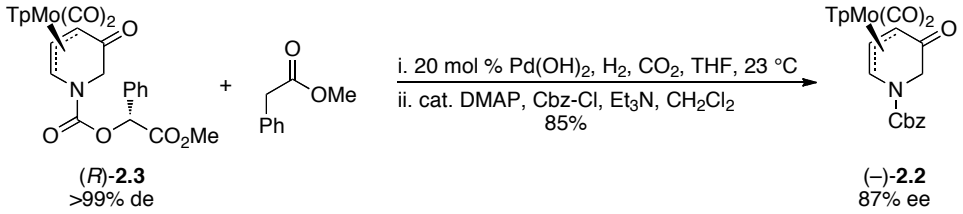
The next control experiments involved the addition of by-products during the hydrogenolysis to see if they had an effect on the racemization process. The first by-product to be tested on the methyl mandelate system was methylphenylacetate in both the presence and absence of hydrogen (Scheme 2.5).

Scheme 2.5 Control Experiments: Addition of Methylphenylacetate



It was found that the addition of methylphenylacetate did not change any of the previous results for these reactions. The other by-product, carbon dioxide, was also tested to see if there was an effect during hydrogenolysis. It was found that the addition of CO_2 during removal of the methyl mandelate auxiliary did not have an effect (Scheme 2.6).

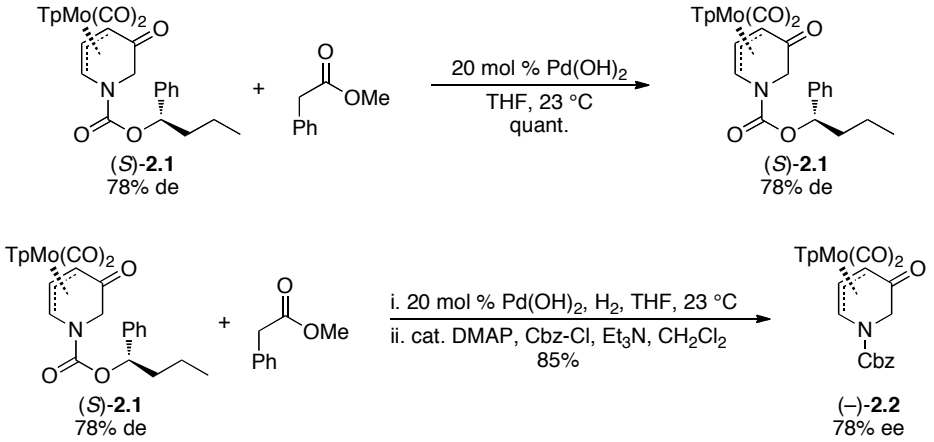
Scheme 2.6 Control Experiment: Addition of Carbon Dioxide



(*R*)-**2.3**
>99% de

(–)-**2.2**
87% ee

Scheme 2.7 Control Experiment Comparisons



(*S*)-**2.1**
78% de

(*S*)-**2.1**
78% de

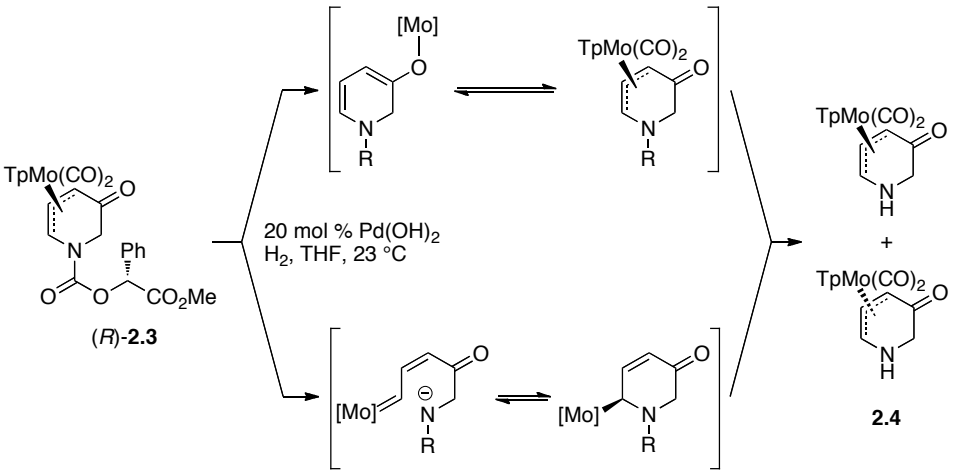
(*S*)-**2.1**
78% de

(–)-**2.2**
78% ee

To give these control experiments actual worth, they needed to be directly compared to the series that did not racemize (Scheme 2.7). These control experiments showed that the starting material **2.3** is stable to the $Pd(OH)_2$ catalyst. Also the addition of either by-product has no effect on the enantiomeric excess of the product. Thus, racemization must take place while the active Pd species is coordinated to the complex. The reasoning for

racemization is not clear at this point, but certain factors have been ruled out as the cause of racemization.

Scheme 2.8 Possible Pathways to Racemization



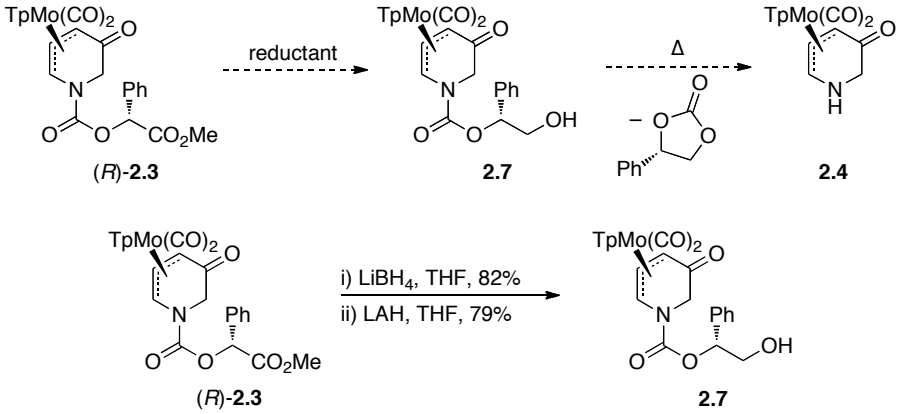
Possible Pathways to Racemization

There are two reasonable pathways that would explain the racemization in this reaction sequence (Scheme 2.8). The first possibility involves formation of a diene with molybdenum slipping out on to the oxygen to form an oxomolybdate complex. By doing so, the metal will lose facial selectivity when moving back to the η^3 position creating a mixture of enantiomers. The second possibility involves the metal slipping to the η^1 position adjacent to the protected nitrogen causing the ring to open. When the ring opens, a metal carbene is formed which lacks chirality and thus lacks facial selectivity upon closing of the ring. Either of these pathways is feasible, but neither has been proven. To date, we do not know how the Pd/H_2 would induce such plausible mechanisms (Scheme 2.8).

Other Methods to Remove the Chiral Auxiliary

Since optimization of the hydrogenolysis proved to be ineffective, other methods for removing carbamates were investigated. The first option was to reduce the methyl ester to an alcohol, which could then be heated to close the alcohol on the carbonyl carbon of the carbamate yielding both the free amine as well as the corresponding carbonate (Scheme 2.9). Both $LiBH_4$ and LAH were investigated as reducing agents, unfortunately both reagents caused over reduction of the ketone located on the ring.

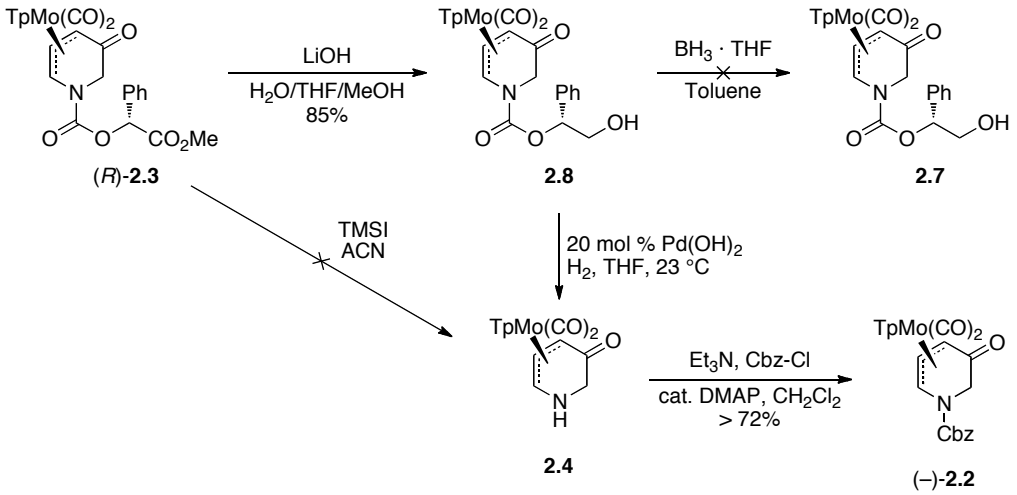
Scheme 2.9 Cleavage of Methyl Mandelate Auxiliary: Reduction



The next options that were explored began with hydrolysis of the methyl ester with LiOH to afford the carboxylic acid in 85% yield, followed by standard borane reduction. Unfortunately, the corresponding alcohol that could then undergo the same type of removal as above (Scheme 2.10), was not obtained. The carboxylic acid was also subjected to the standard hydrogenolysis without success: This reaction led to co-eluting impurities, which could not be separated and thus could not be purified to give an

accurate result or comparison. Finally, a modified Cbz-removal involving TMSI in ACN was explored, but this reaction did not afford any desired product either (Scheme 2.10).

Scheme 2.10 Cleaveage of Methyl Mandelate Chiral Auxiliary Attempts



Conclusion

After extensive optimization of removal of the methyl mandelate chiral auxiliary *via* hydrogenolysis, the enantiopure desired product could not be obtained using this method. While ee was increased from previous results, it was not satisfactory enough to be considered synthetically useful. Other methods of removal were also investigated, but proved to be ineffective as well. Greater efforts were brought to find a new class of chiral auxiliaries that might avoid racemization during the deprotection step.

Chapter Three

A New Approach to a Key 5-Oxo-Pyridinyl Organometallic Enantiomeric Scaffold *via* Novel Sulfenamide Chiral Auxiliaries

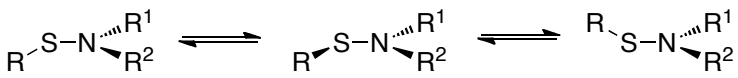
Introduction

After realizing that the candidates with the most potential for a new carbamate-based chiral auxiliary fell short of the overall goal, it was obvious that a different approach was necessary. As a result, sulfenamide-based chiral auxiliaries derived from inexpensive chiral alcohols were considered as a new method for introducing chirality to the key 5-oxo-pyridinyl molybdenum scaffold. The basis for this new concept developed from previous work done by Kellogg,[1] where a number of optically active thiols were synthesized from chiral alcohols. Interestingly, there is no report of using sulfenamides as chiral auxiliaries to date.

Background

Sulfenamides are compounds that contain divalent sulfur bonded to trivalent nitrogen. They are typically derived from sulfenic acids, RSOH, but can be obtained through different methods as well.[2] Stereochemical interest in the chirality of sulfenamides is usually attributed to the S-N bond, which acts as a chiral axis (Figure 3.1).[2] Using dynamic NMR techniques, Raban and co-workers found that a significant torsional barrier around the S-N bond exists, ranging from 12 to 18 kcal/mole.[3]

Figure 3.1 Axial Chirality in Sulfenamides



[1] Strijtveen, B.; Kellogg, R. M. *J. Org. Chem.* **1986**, *51*, 3664-3671.
[3] Craine, L.; Raban, M. *Chem. Rev.* **1989**, *89*, 689-709.
[3] Raban, M.; Jones, F. B., Jr.; Kenney, G. W. J., Jr. *J. Am. Chem. Soc.***1969,** *91***,** 6677**.**

Due to these substantial torsional barriers of the S-N bond, no rotamers are observed in the ^{1}H NMR spectrum of molybdenum sulfenamide complexes, which is advantageous since the traditional carbamate chiral auxiliaries display rotamers in the ^{1}H NMR specta making them difficult to interpret.

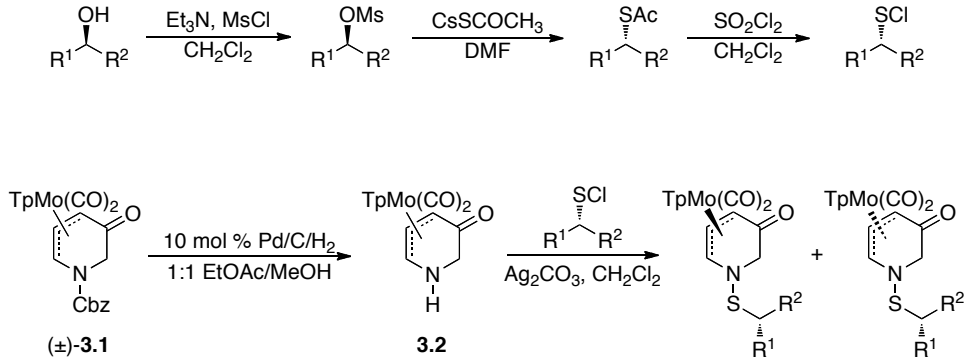
The reactivity profile of sulfenamides is particularly interesting due to the fact that polarization of the S-N bond allows attack of nucleophiles at sulfur and electrophiles at nitrogen.[2] They can also be oxidized at sulfur or nitrogen, and reductively cleaved.[2] While there has been extensive work done in the field of sulfenamide chemistry, there has been no report of introducing sulfenamides as chiral auxiliaries.

Results and Discussion

General Preparation of Sulfenamides

It has been demonstrated that sulfenamide chiral auxiliaries can be introduced to $TpMo(CO)_2(\eta^3$-pyridinyl) complexes through a 3-step process (Scheme 3.1).

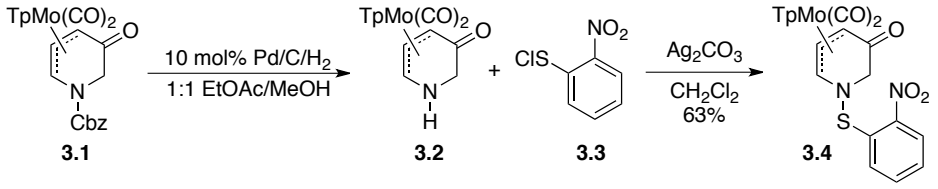
Scheme 3.1 Synthesis of Molybdenum Complex with Sulfenamide Auxiliary



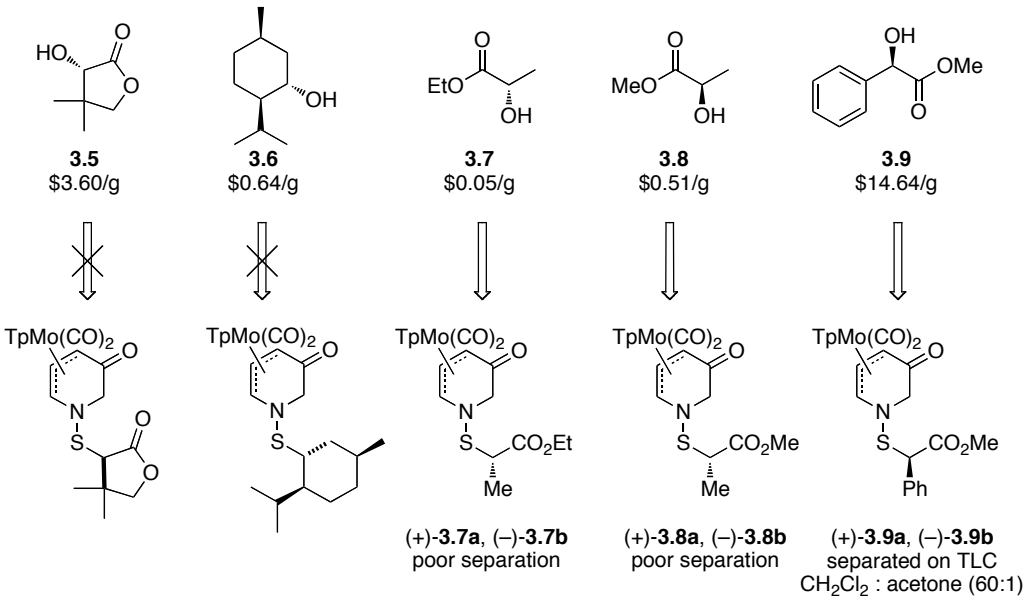
Initially, the chiral alcohol is converted to the mesylate using methanesulfonyl chloride. The mesylate is then displaced using freshly prepared cesium thioacetate to give the corresponding thioacetate with inversion of stereochemistry. This step required heating for more sterically hindered systems. The thioacetate is then treated with sulfuryl chloride to afford the corresponding sulfenyl chloride, which is directly engaged with *N*-unprotected scaffold to afford the corresponding $TpMo(CO)_2(\eta^3$-pyridinyl) complex.

The first example of the $TpMo(CO)_2(\eta^3$-pyridinyl) complex bearing a sulfenamide moiety was achieved using racemic starting material, 2-nitrophenylsulfenyl chloride (Scheme 3.2).[1] Beginning with the racemic $TpMo(CO)_2(\eta^3$-pyridinyl) complex **3.1**, the Cbz group is removed under standard hydrogenolysis conditions to afford free amine **3.2**. Treatment of the free amine with compound **3.3** and Ag_2CO_3 provided sulfenamide **3.4** in moderate yield. Various amine and metal bases were screened during optimization, but Ag_2CO_3 proved to be the most effective for this system. In fact, AgCl precipitates out of the reaction making sulfur more electrophilic and more susceptible to attack by the free amine. This provided a basis for the construction of a variety of sulfenamide complexes, which will be described in the next section.

Scheme 3.2 Preparation of 2-Nitrophenylsulfenamide



Scheme 3.3 Chiral Auxiliary Candidates and $TpMo(CO)_2(\eta^3$-pyridinyl) Complexes



Preparation of Sulfenamide Complexes from Inexpensive Chiral, Non-Racemic Alcohols

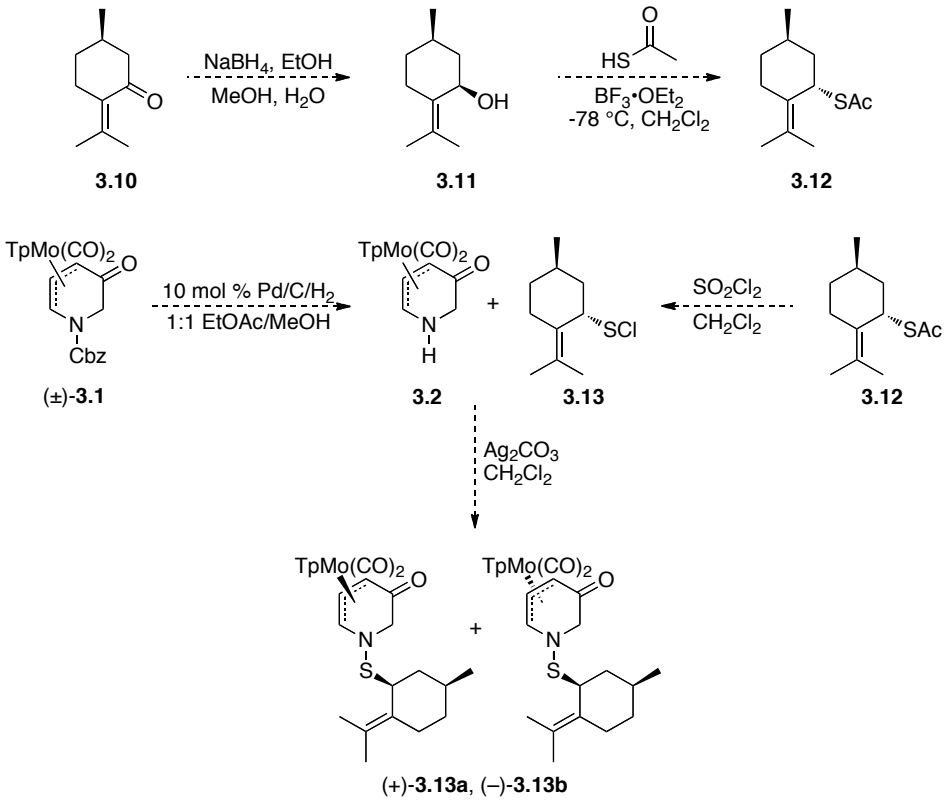
Several inexpensive chiral, non-racemic alcohols were chosen to expand the scope of moybdenum sulfenamide complex chemistry (Scheme 3.3). Neither of the cyclic chiral auxiliary candidates **3.5** and **3.6** could be attached to the molybdenum complex to form the sulfenamide. Both lactic acid derivatives **3.7** and **3.8** could be transformed to the corresponding molybdenum sulfenamide complexes, but after screening numerous resolution conditions it was found that the diastereomers were not easily separable. Once again, methyl mandelate **3.9** proved to be the most promising candidate for this series. The two diastereomers could be cleanly separated on TLC, but issues arose when attempting to translate this resolution to large-scale column chromatography. Severe decomposition was observed during the attempts to resolve the two diastereomers by gravity chromatography. It was initially believed that the increased

amount of time the complex spent on the column compared to the time taken to resolve on a TLC plate was the issue, so measures were taken to mimic the conditions of a TLC plate. The silica was deactivated using water, which increased the rate at which the complex moved down the column. Unfortunately, this did not prove to be an effective method of circumventing decomposition. The other likely cause of decomposition was instability of the complex to the acidic silica, so the silica was deactivated with Et_3N. Unfortunately, this led to decomposition as well.

Investigation of Sulfenamide Complexes from Inexpensive Chiral, Non-Racemic Terpenes

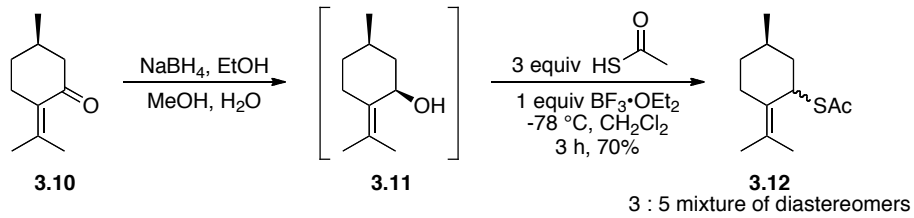
After exhausting the "chiral pool" for inexpensive alcohols, other compounds such as terpenes were considered as potential chiral auxiliary candidates. Only terpenes that could be easily and selectively reduced to chiral, non-racemic alcohols were considered. After screening various chiral, non-racemic terpenes, it was determined that (1*R*)-(+)-Pulegone **3.10** was the most promising (Scheme 3.4).

Scheme 3.4 Proposed Synthesis of (1*R*)-(+)-Pulegone Sulfenamide Complex



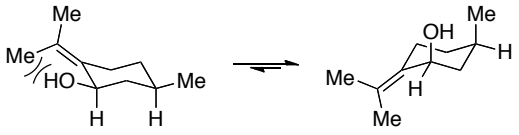
(1*R*)-(+)-Pulegone was selectively reduced to alcohol **3.11** using sodium borohydride, but Lewis acid-catalyzed displacement of the alcohol unexpectedly yielded a 3:5 mixture of diastereomers **3.12** (Scheme 3.5).

Scheme 3.5 Synthesis of (1*R*)-(+)-Pulegone Thioacetate



We suspect that 1,3-strain between the hydroxyl and methyl groups of conformer **3.11a** makes the preferred conformer **3.11b** (Scheme 3.6), which is not suitable for nucleophilic attack. As a result of the two undesirable conformers, the addition of thioacetic acid proceeds unselectively. The formation of both diastereomers could also be due to the fact that allylic alcohols tend to ionize under Lewis acidic conditions causing thioacetic acid to add unselectively as well. Since the diastereomers were not easily separable by column chromatography, this route was discarded.

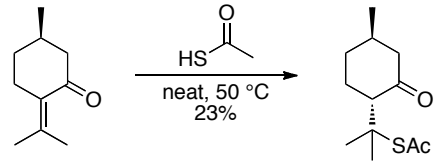
Scheme 3.6 Conformational Restraints of Alcohol 3.11



3.11a **3.11b**

Another option for converting (1*R*)-(+)-pulegone to a chiral auxiliary was to introduce the thioacetate by a 1,4-Michael addition (Scheme 3.7). This can be achieved by treating compound **3.10** with thioacetic acid at 50 °C in the absence of solvent (Scheme 3.7). While thioacetate **3.14** was obtained, the corresponding molybdenum sulfenamide complex could not be synthesized.

Scheme 3.7 Synthesis of Thioacetate 3.14 *via* 1,4-Michael Addition



3.10 **3.14**

Conclusion

Extensive investigation towards the development of novel molybdenum sulfenamide complexes for the resolution of enantiopure $TpMo(CO)_2(\eta^3$-pyridinyl) complexes was carried out. A number of chiral, non-racemic alcohols and terpenes were explored as potential chiral auxiliaries. Three molybdenum sulfenamide complexes were successfully synthesized, but none could be resolved to the corresponding diastereomers on large scale. A new class of moybdenum complexes were synthesized with efforts towards the resolution of enantiopure $TpMo(CO)_2(\eta^3$-pyridinyl) complexes.

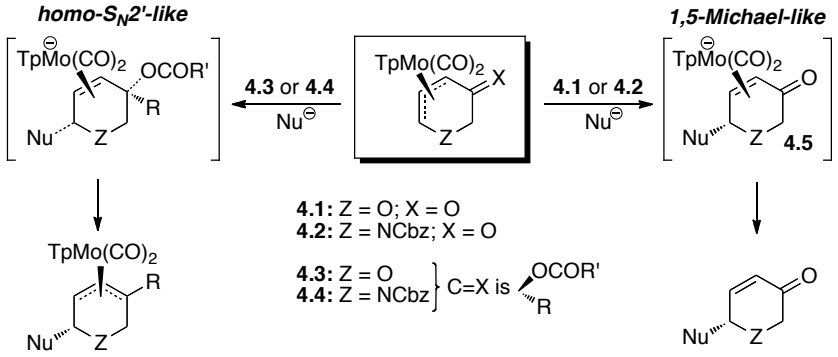
Chapter Four

Oxidative Demetalation of η^3-Allylmolybdenum Complexes with an Oxygen Nucleophile; Application to the Synthesis of (+)-Isofebrifugine Analogs

Introduction

The Liebeskind laboratory has demonstrated various reaction profiles pertaining to $TpMo(CO)_2(\eta^3$-pyranyl) and $TpMo(CO)_2(\eta^3$-pyridinyl) complexes. Surveying the literature shows that in most cases a $TpMo(CO)_2$-stabilized carbocation is the requisite intermediate for nearly all synthetic transformations of these scaffolds.[1a-i,k,l,n] Recently, Liebeskind group members Yongjang Zhang and Wenyong Chen discovered a new, noncationic reaction path, which takes place through the direct nucleophilic addition of an internal enolate to a terminal π-carbon of a neutral 5-oxo-η^3-pyranyl (and pyridiniyl) complex (Scheme 4.1).[1j,o]

Scheme 4.1 Nucleophilic Functionalization of Neutral $TpMo(CO)_2(\eta^3$-pyranyl/pyridinyl) Complexes[3]



[1] (a) Yin, J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1999**, *121*, 5811–5812. (b) Malinakova, H. C.; Liebeskind, L. S. *Org. Lett.* **2000**, *2*, 3909–3911. (c) Malinakova, H. C.; Liebeskind, L. S. *Org. Lett.* **2000**, *2*, 4083–4086. (d) Moretto, A. F.; Liebeskind, L. S. *J. Org. Chem.* **2000**, *65*, 7445–7455. (e) Yin, J.; Llorente, I.; Villanueva, L. A.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2000**, *122*, 10458–10459. (f) Arrayás, R. G.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2001**, *123*, 6185–6186. (g) Shu, C.; Alcudia, A.; Yin, J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2001**, *123*, 12477–12487. (h) Arrayás, R. G.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2003**, *125*, 9026–9027. (i) Shu, C.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2003**, *125*, 2878–2879. (j) Zhang, Y.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2005**, *127*, 11258–11259. (k) Zhang, Y.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2006**, *128*, 465–472. (l) Arrayás, R. G.; Yin, J.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2007**, *129*, 1816–1825. (m) Coombs, T. C.; Lee, M. D., IV; Wong, H.; Armstrong, M.; Cheng, B.; Chen, W.; Moretto, A. F.; Liebeskind, L. S. *J. Org. Chem.* **2008**, *73*, 882–888. (n) Garnier, E. C.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2008**, *130*, 7449–7458. (o) Coombs, T. C.; Zhang, Y.; Garnier-Amblard, E. C.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2009**, *131*, 876–877.

This synthetically useful 1,5-Michael-like functionalization mode can be explained, in part, by the tendency of $TpMo(CO)_2$ systems to favor six-coordinate structures over seven-coordinate.[2] This could also be explained by the characterizable anionic $TpMo(CO)_2$ intermediate generated by the nucleophilic addition, which possesses three good π-back-bonding ligands to delocalize the anionic charge: η^2-enone ligand and the two terminal CO ligands.[1o] These observations led to the investigation of a more general nucleophilic addition to less activated $TpMo(CO)_2$ complexes than the 5-oxo-η^3-pyranyl/pyridinyl complexes.

Following these considerations, Liebeskind and Chen reported the first examples of an "homo-S_N2'-like" intermolecular nucleophilic substitution of charge neutral $TpMo(CO)_2$(5-acyloxy-η^3-pyranyl) and $TpMo(CO)_2$(5-acyloxy-η^3-pyridinyl) complexes (Table 4.1).[3] Substrates **4.3a-c** and **4.4a,b** were prepared in high yields from readily available $TpMo(CO)_2$(η^3-pyranyl) and $TpMo(CO)_2$(η^3-pyridinyl) complexes **4.1** and **4.2** by hydride or Grignard reagent addition to the carbonyl followed by acylation. Treatment of **4.3a-c, 4.4a,b** with anionic carbon nucleophiles (pK_a range = 13.3-18.0 in DMSO) in the presence of 15-crown-5 ether afforded the corresponding products in good to excellent yields (Table 4.1). When incorporating carbanions generated from precursors more acidic than that of dimethyl malonate, the reaction benefitted from the use of acetonitrile instead of THF as solvent (Table 4.1, entries 2 and 3). The use of high enantiopurity scaffold will result in the formation of the corresponding substitution product with no loss of enantiopurity. When R is H on the scaffold, higher product yields were obtained using *p*-nitrobenzoate instead of acetate as the leaving group.

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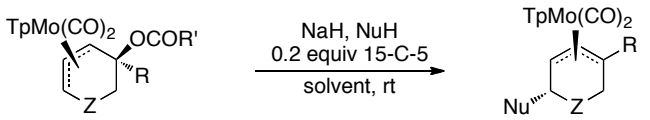
[2] Curtis, M. D.; Shiu, K. B.; Butler, W. M. *Organometallics* **1983**, *2*, 1475–1477.
[3] Chen, W., Liebeskind, L. S. *J. Am. Chem. Soc.* **2009**, *131*, 12546-12547.

Table 4.1 "Homo S_N2'-Like" Substitution Reactions[3]



4.6 - 4.14

entry	reactant	NuH	solvent	% yield
1	**4.3a** (R = R' = Me)	$CH_2(COOMe)_2$	THF	**4.6**, 99[a]
2	**4.3a** (R = R' = Me)	CH_3COCH_3COOM	ACN	**4.7**,
3	**4.3a** (R = R' = Me)	CH_3COCH_3COOM	THF	**4.7**,
4	**4.3a** (R = R' = Me)	$CH_2(COOEt)_2$	THF	**4.8**,
5	**4.3a** (R = R' = Me)	CH_3NO_2	DMSO	**4.9**, 80[d]
6	**4.3b** (R = H, R' = *p*-	CH_3COCH_3COOM	ACN	**4.10**, 94[c]
7	**4.3b** (R = H, R' = *p*-	CH_3COCH_3COMe	ACN	**4.11**, 68
8	**4.3c** (R = Ph, R' = Me)	$CH_2(COOMe)_2$	THF	**4.12**, 90
9	**4.4a** (R = H, R' = Me	$CH_2(COOMe)_2$	ACN	**4.13**, 94
10	**4.4b** (R = H, R' = *p*-	CH_3COCH_3COOM	ACN	**4.14**, 91[c]

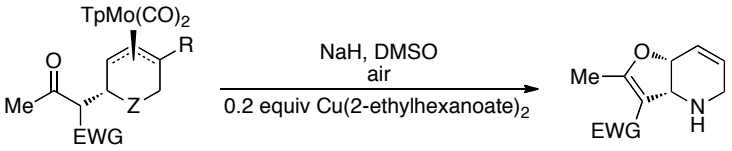
[a] 96% ee product from 96% ee starting material. The enantiopurity was determined by chiral HPLC. [b] The number in the parentheses is the yield based on the recovery of starting material. [c] An approximate 1.5:1 ratio of diastereomers was observed according to crude NMR. [d] No 15-crown-5 ether was added.

This mechanistically new enantiocontrolled carbon-carbon bond formation occurs enantiospecifically with excellent *anti* stereoselectivity.[3]

A variety of molybdenum complex products were cleanly converted to bicyclic annulative products in high yields with excellent stereoselectivity. For example, treatment of **4.7**, **4.10**, **4.11**, and **4.14** with NaH in DMSO in the presence of catalytic copper(II) 2-ethylhexanoate open to air provided the corresponding annulation products **4.15-4.18** in 83-92% isolated yields (Table 4.2). It was suggested that the mechanism for the reactions in Table 4.2 proceed through one-electron oxidation of the stabilized enolate to a radical[4] which then reacts with the adjacent η^3-allylmolybdenum moiety. The synthetic potential

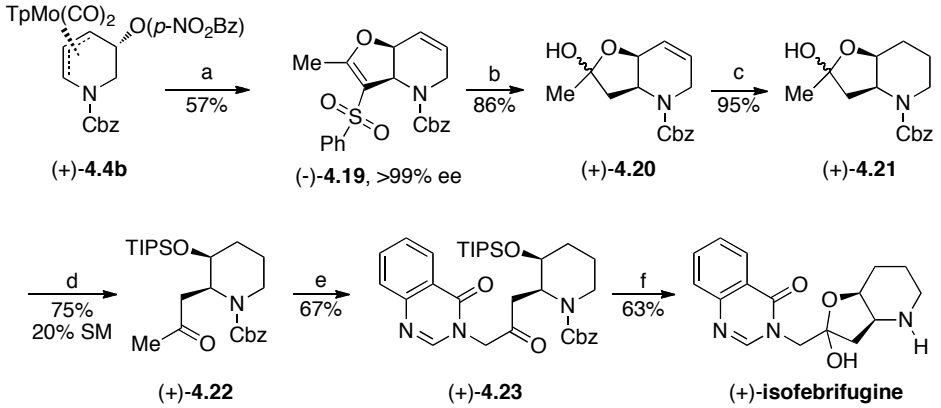
of this methodology was demonstrated by the asymmetric synthesis of the alkaloid (+)-isofebrifugine (Scheme 4.2), known for its antimalarial activity.[5]

Table 4.2 Cu-Catalyzed Aerobic Annulative Demetalation[3]



entry	reactant	Z	EWG	R	% yield
1	**4.7**	O	COOMe	Me	**4.15**, 85
2	**4.10**	O	COOMe	H	**4.16**, 83
3	**4.11**	O	COMe	H	**4.17**, 92
4	**4.14**	NCbz	COOMe	H	**4.18**, 83

Scheme 4.2 Enantiocontrolled Synthesis of (+)-Isofebrifugine[3]



[a] (a) NaH, $CH_3COCH_2SO_2Ph$, DMSO, rt, overnight then NaH, Cu(ethylhexanoate)$_2$, air, overnight. (b) (i) 10 mol % Na/Hg, THF/MeOH, Na_2HPO_4, -35 °C to rt; (ii) HCl, acetone. (c) PtO_2, H_2. (d) TIPSCl, imidazole, DMF. (e) (i) TMSOTf, TEA, DCM then NBS; (ii) 4-hydroxyquinazoline, NaH, THF, 15-C-5. (f) 6 M HCl, reflux, 90 min.

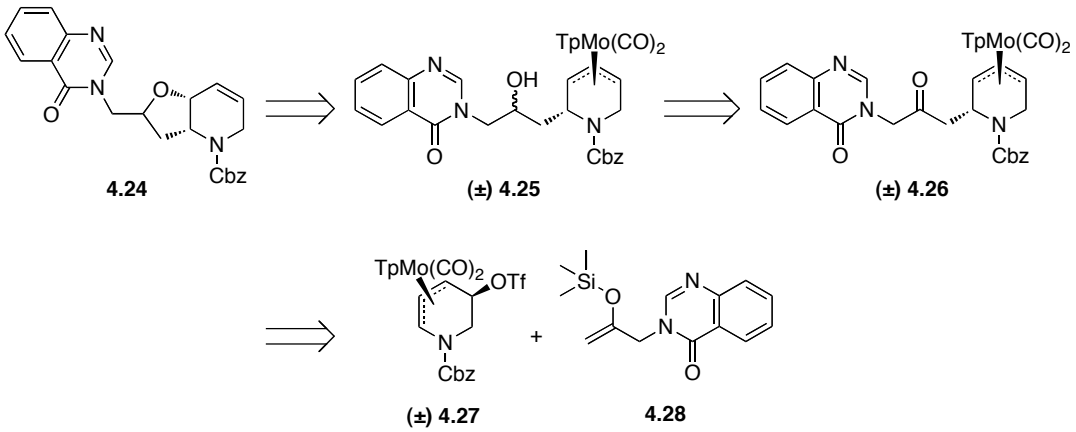
[4] (a) Jahn, U.; Hartmann, P.; Dix, I.; Jones, P. G. *Eur. J. Org. Chem.* **2001**, 3333–3355. (b) Jahn, U.; Hartmann, P. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2277–2282. (c) Jahn, U. *J. Org. Chem.* **1998**, *63*, 7130–7131.

[5] (a) Koepfly, J. B.; Mead, J. F.; Brockman, J. A., Jr. *J. Am. Chem. Soc.* **1949**, *71*, 1048–1054. (b) Kobayashi, S.; M., U.; Suzuki, R.; Ishitani, H.; Kim, H.; Wataya, Y. *J. Org. Chem.* **1999**, *64*, 6833–6841. (c) Wee, A. G. H.; Fan, G.-J. *Org. Lett.* **2008**, *10*, 3869–3872.

Results and Discussion

To expand the scope of the oxidative demetalation of η^3-allylmolybdenum complexes, investigation of the use of an oxygen nucleophile was carried out. Liebeskind group member Wenyong Chen initially probed this method, which was then followed by the application to the synthesis of (+)-isofebrifugine analogs.

Scheme 4.3 Retrosynthesis of (±)-Isofebrifugine Analog

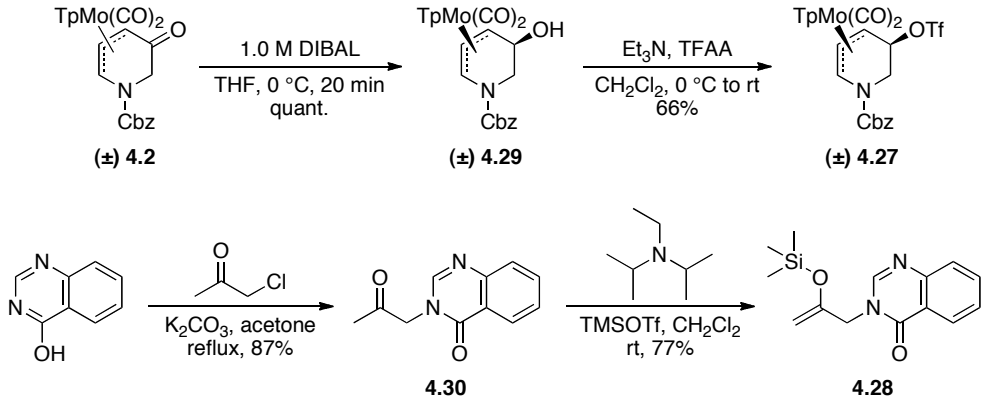


4.24 **(±) 4.25** **(±) 4.26**

(±) 4.27 **4.28**

Silyl enol ether **4.28** was prepared in two steps from commercially available 4-hydroxyquinazoline (Scheme 4.4). Due to its instability, triflate **4.27** was prepared fresh right before subjection to the corresponding silyl enol ether of ketone **4.28** (Scheme 4.4).

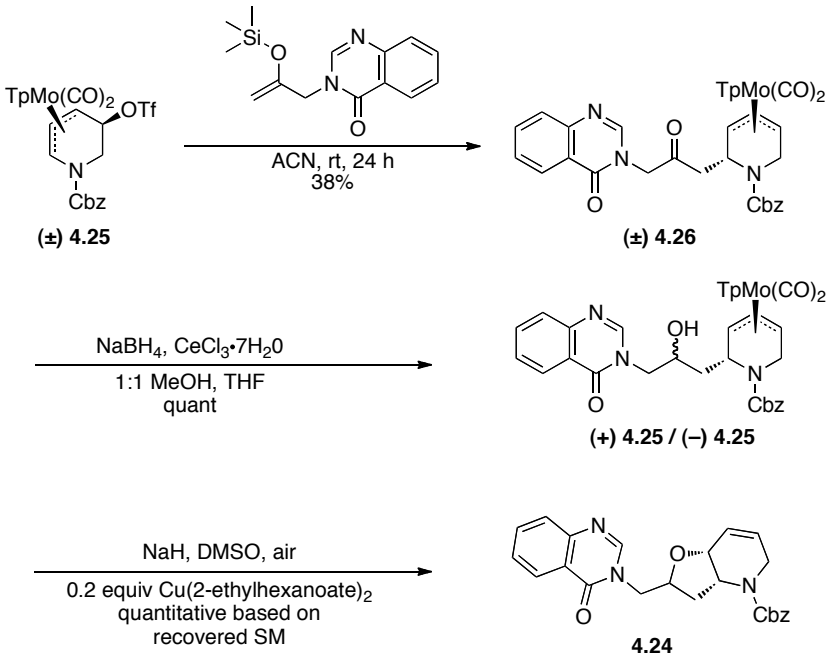
Scheme 4.4 Preparation of Silyl Enol Ether and Triflate



Addition of silyl enol ether **4.28** to triflate **4.27** in acetonitrile at room temperature afforded the corresponding ketone **4.26** in 38% yield (Scheme 4.5). The low yield can be attributed to formation of molybdenum decomposition products. Reduction of ketone **4.26** using sodium borohydride and cerium chloride heptahydrate in a 1:1 methanol/THF solution afforded the corresponding alcohols (+) and (–)-**4.25** in high yield. The two diasteromers are difficult to separate by chromatography. A mixture of alcohols (+)-**4.25** and (–)-**4.25** was subjected to sodium hydride and stoichiometric copper(II) 2-ethylhexanoate in DMSO open to air to afford annulation product **4.24** and the less polar diastereomer **4.25**. The absolute stereochemistry of each diastereomer **4.25** being unknown, they will be referred to with regard to their polarity on TLC. Interestingly, based on ^{1}H NMR it was found that only the more polar diastereomer of alcohols **4.25** reacted under the oxidative/demetalation conditions. This was further proven by subjecting each single diastereomer to the reaction conditions, which showed that the more polar compound gave the desired product in quantitative yield based on recovered starting material, while the less polar compound did not react at all giving full recovery of starting material. Because we know which compound reacts, it would be beneficial in the

future to subject the unreactive diastereomer to Mitsunobu conditions to invert the alcohol affording the reactive diastereomer.

Scheme 4.5 Synthesis of Isofebrifugine Analog 4.24



Conclusion

Incorporating oxygen as the nucleophile for oxidative demetalation of η^3-allylmolybdenum complexes expanded the scope of this class of reactions. Determining the reactive diastereomer of compounds **4.25** made it reasonable to assume that subjection of the unreactive diastereomer to Mitsunobu conditions would afford a significant amount of the reactive alcohol. A more convergent route towards synthesis of analogs of (+)-isofebrifugine was developed providing a better entry for SAR studies.

Experimental Section

General Methods

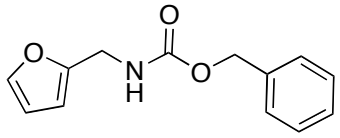
Reagents were obtained from Aldrich Chemical (www.sigma-aldrich.com) and used without further purification. Optima grade solvents were obtained from Fisher Scientific, degassed with argon, and purified on a solvent drying system as described[1] unless otherwise specified. Dry diethyl ether was purchased from Mallinckrodt and used as received, unless otherwise specified. Sparging with argon or using freeze-thaw-pump method degassed solvents. Unless otherwise specified, all reactions were performed in flame-dried glassware under positive Ar pressure with magnetic stirring. Cold baths were generated as follows: 0 °C, wet ice/water; -40 °C, dry ice/CH3CN; -78 °C, dry ice/acetone.

Analytical thin-layer chromatography (TLC) was carried out on commercial Merck Silica gel 60 plates, 0.25 thickness, with fluorescent indicator (F-254). Visualization was accomplished by UV light or stained with 5% phosphomolybdic acid (PMA) in ethanol or 0.75% potassium permanganate ($KMnO_4$) in H_2O. Column chromatography was performed by the method of Still[2] with 32-63 μm silica gel (Woelm).

Unless otherwise indicated, all ^1H and ^{13}C NMR spectra were recorded on a Varian Inova 400 MHz (400 MHz ^1H, 100 MHz ^{13}C) at room temperature in $CDCl_3$ with internal $CHCl_3$ as the reference (7.27 ppm for ^1H and 77.23 ppm for ^{13}C). Chemical shifts are expressed in ppm, coupling constants are expressed in Hertz. The letters m, s, d, t, and q stand for multiplet, singlet, doublet, triplet, and quartet, respectively. The

[1] Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520.
[2] Still, W.C.; Khan, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.

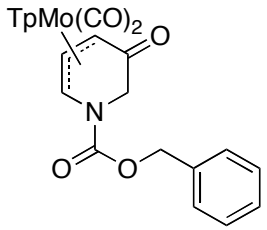
letters br indicate that the signal is broad. IR spectra were recorded on a Nicolet™ 380 FT-IR spectrometer, equipped with a diamond plate. Peaks are reported (cm^{-1}) with the following relative intensities: s (strong, 67-100%), m (medium, 40-67%), w (weak, 20-40%) and br (broad). Melting points (m.p.) are uncorrected and were taken in open capillary tubes on a Thomas Hoover capillary melting point apparatus. *Since almost all of the Tp molybdenum complexes decompose at about 180-200 ºC melting points are not significant and are not shown in the experimental section*. Optical rotations were measured with a Perkin-Elmer 241MC polarimeter. HPLC analyses were carried out at room temperature using an Agilent 1100 system with a quaternary pump. Separations were achieved on DAICEL chiral CHIRALPAK AS reversed phase columns using a Waters™ 486 UV detector (HPLC grade acetonitrile and water were used).



Benzyl (2-furylmethyl)carbamate (1.18)[1] To a round bottom flask charged with furfuryl amine (19.05 mL, 0.206 mol, 1.00 equiv.) in CH_2Cl_2 (1030 mL) was added NaOH (9.06 g, 0.227 mol, 1.10 equiv.) in H_20 (180 mL) and benzyl chloroformate (31.88 mL, 0.227 mol, 1.10 equiv.) at ambient temperature. The red-orange suspension was stirred at room temperature for 23 hours. The reaction mixture was quenched with $NaHCO_3$ (100 mL), then diluted with EtOAc (300 mL). The organic and aqueous layers were separated, and the organic layer was washed with brine (3 x 300 mL), dried over

[1] Coombs, T. C.; Lee; Wong, H.; Armstrong, M.; Cheng, B.; Chen, W.; Moretto, A. F.; Liebeskind, L. S. *J. Org. Chem*. **2008,** *73*, 882-888.

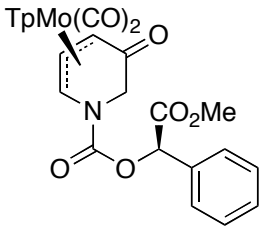
$MgSO_4$, and the solvent was removed under reduced pressure to provide the crude product. The crude product was purified by flash chromatography (SiO_2, 6.5 cm x 23.0 cm, hexanes: EtOAc = 3:1) to afford the product **1.18** (4 g, 93 %) as a pale yellow oil, which solidified at low temperature. TLC: R_f = 0.59 (hexanes: EtOAc = 1:1). IR (cm^{-1}): 3327 (w), 1703 (s), 1519 (m), 1241 (s), 729 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34-7.32 (m, 6 H), 6.30 (dd, *J* = 3.1, 1.9 Hz, 1 H), 6.22 (d, *J* = 2.6 Hz, 1 H), 5.60 (br s, 1 H), 5.11 (s, 2 H), 4.34 (d, *J* = 5.4 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.3, 151.7, 142.4, 136.6, 128.7, 128.4, 110.6, 107.5, 67.2, 38.3. HRMS (ESI) calcd for $C_{13}H_{14}NO_3$ ([M + H]$^+$): 232.0974 Found: 232.0965.



(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(2*R*,6*R*)-(η^3-2,3,4)-1-benzyloxycarbonyl]-5-oxo-5,6-dihydro-2*H*-pyridin-2-yl]-molybdenum (1.1)[1] The residue **1.18** (10.0 g, 43.2 mmol, 1.0 equiv.) was dissolved in CH_2Cl_2 (63 mL) and cooled to 0 °C. To the solution was added *m*CPBA (~77 % purity, 11.19 g, 65.0 mmol, 1.50 equiv.) portionwise. After holding the temperature at 0 °C for 1.5 hours, the white solids were removed by vacuum filtration. The filtrate was degassed with argon for 30 minutes. To the degassed solution at 0 °C was added solid $Mo(DMF)_3(CO)_3$ (17.17 g, 42.8 mmol, 0.99 equiv.). After stirring for 5 minutes at 0 °C, the reaction was warmed to room temperature and stirred for 1.0 hour. To the reaction mixture was added KTp (12.1 g, 48.0 mmol, 1.11 equiv.). The reaction mixture was stirred at room temperature for 1

hour, filtered over a pad of Celite®, and concentrated under reduced pressure. The crude product was subjected to short filter chromatography (SiO_2, 5.0 cm x 20.0 cm, hexanes: EtOAc = 9:1 ramping gradually to hexanes: EtOAc = 2:1). Fractions overlapping with impurities were collected and subjected to a second chromatography (SiO_2, 5.0 cm x 20.0 cm, hexanes: EtOAc = 4:1) to afford the product **(±)-1** (10.23 g, 39.6 %) as an orange solid. TLC: R_f = 0.62 (hexanes: EtOAc = 1:1). IR (cm^{-1}) 1968 (s), 1875 (s), 1696 (s), 1654 (s). ^{1}H NMR (mixture of two rotamers- 400 MHz, $CDCl_3$): δ 8.45 (d, *J* = 1.9 Hz, 0.4 H), 8.42 (d, *J* = 1.9 Hz, 0.6 H), 8.31 (d, *J* = 1.9 Hz, 0.6 H), 7.76 (d, *J* = 1.9 Hz, 0.4 H), 7.74 (d, *J* = 1.9 Hz, 0.6 H), 7.70 (d, *J* = 1.9 Hz, 0.4 H), 7.65 (d, *J* = 1.9 Hz, 0.6 H), 7.62 (d, *J* = 1.9 Hz, 0.6 H), 7.60 (d, *J* = 1.9 Hz, 0.4 H), 7.58 (d, *J* = 1.9 Hz, 0.4 H), 7.47-7.52 (m, 1.6 H), 7.40-7.44 (m, 2 H), 7.27-7.38 (m, 3 H), 7.22 (dd, *J* = 6.4, 1.9 Hz, 0.4 H), 6.28-6.30 (m, 1.6 H), 6.22-6.24 (m, 1 H), 5.97 (t, *J* = 2.2 Hz, 0.4 H), 5.27 (AB quartet, *J* = 11.4 Hz, 0.4 Hz, 2 H), 5.24 (s, 0.6 H), 4.74-4.77 (m, 1 H), 4.09 (t, *J* = 6.4 Hz, 0.6 H), 3.98 (t, *J* = 6.4 Hz, 0.4 H), 3.41 (AB quartet, *J* = 20.0 Hz, 0.4 H), 3.39 (AB quartet, *J* = 19.7 Hz, 0.6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 224.9, 224.5, 222.6, 221.9, 193.3, 192.6, 154.4, 153.6, 147.1, 147.0, 144.2, 143.3, 141.3, 141.2, 136.33, 136.31, 136.2, 136.1, 135.4, 135.1, 134.6, 128.7, 128.5, 128.4, 128.3, 128.0, 127.6, 106.0, 105.8,105.6, 93.7, 92.2, 68.7, 67.9, 64.4, 64.0, 63.7, 63.3, 47.7, 47.6. HRMS (ESI) calcd. for $C_{24}H_{23}BMoN_7O_5$ ($[M+H]^+$): 598.0908 Found: 598.0905. HPLC: Daicel® Chiralcel AS-RH, CH_3CN: H_2O = 50: 50, 1.0 mL/min., λ = 254 nm, **(+)-1** t_R = 15.74 min., **(-)-1** t_R = 22.87 min.

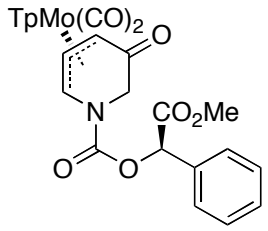
Procedure for the Synthesis of Diastereomers (*S*)-2.5a and (*R*)-2.5b.[2] The residue **1.1** (2.68 g, 4.48 mmol, 1.0 equiv.) was dissolved in 1:5 methanol/EtOAc (80 mL) and added Pd/C (10 wt. %, 477 mg, 0.45 mmol, 0.1 equiv.). A balloon of hydrogen was attached and flushed with vacuum to remove any remaining air. After stirring for 24 h at room temperature, the reaction mixture was filtered through a short plug of Celite® and concentrated under reduced pressure. The resulting residue was dissolved in CH_2Cl_2 (60 mL) then added triethylamine (0.87 mL, 6.27 mmol, 1.4 equiv.) and catalytic DMAP. A solution of compound **2.4** (1.40 g, 5.38 mmol, 1.2 equiv.) in CH_2Cl_2 (4 mL) was then added to the mixture. After stirring 24 h at room temperature, the reaction mixture was concentrated under reduced pressure. The crude product was subjected to column chromatography (SiO_2, 7.5 cm x 6.0 cm, hexanes: EtOAc = 1:1) to afford a mixture of diastereomers. Chromatography (gravity flow, SiO_2, 18.0 cm x 35.0 cm, CH_2Cl_2: EtOAc = 6:1) afforded (*S*)-**2.5a** (0.97 g, 33%) and (*R*)-**2.5b** (1.14 g, 39%) diastereomers each as orange solids with complete diastereoseparation (>99.9% de for each isomer).



TLC: R_f = 0.30 (hexanes: EtOAc = 1:1). IR (cm^{-1}) 1962 (s), 1866 (s), 1754 (w), 1706 (m). ^1H NMR (mixture of two rotamers- 400 MHz, $CDCl_3$): δ 8.46 (d, *J* = 1.6 Hz, 0.4 H), 8.38 (d, *J* = 1.6 Hz, 0.6 H), 8.24 (d, *J* = 1.6 Hz, 0.6 H), 7.76 (d, *J* = 1.6 Hz, 0.4 H), 7.74

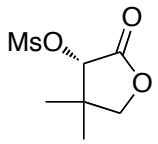
[2] Wong, H. Design, Synthesis and Resolution of a Chiral, Non-Racemic Organometallic Chiron: Asymmetric Total Syntheses of Tetrahydropyridine-Based Alkaloids. Ph.D. Dissertation, Emory University, **2006**.

(d, *J* = 1.6 Hz, 0.6 H), 7.66 (d, *J* = 1.6 Hz, 0.4 H), 7.63 (d, *J* = 2.4 Hz, 0.6 H), 7.61 (d, *J* = 2.4 Hz, 0.6 H), 7.58 (d, *J* = 2.4 Hz, 0.4 H), 7.56 (d, *J* = 2.4 Hz, 0.4 H), 7.51 (d, *J* = 2.0 Hz, 0.4 H), 7.50 (d, *J* = 2.0 Hz, 0.6 H), 7.37-7.44 (m, 5 H), 7.35 (d, *J* = 6.4, 0.4 H), 7.33 (d, *J* = 6.4, 0.6 H), 6.29 (t, *J* = 2.4 Hz, 1.0 H), 6.25-6.27 (m, 1.4 H), 6.22 (t, *J* = 2.4 Hz, 0.6 H), 5.93 (s, 1 H), 4.77 (d, *J* = 6.0 Hz, 0.6 H), 4.75 (d, *J* = 6.0 Hz, 0.4 H), 4.13 (t, *J* = 6.4 Hz, 0.6 H), 4.01 (t, *J* = 6.4 Hz, 0.4 H), 3.76 (s, 0.6 H), 3.73 (s, 0.4 H), 3.70 (AB quartet, *J* = 20.0 Hz, 0.6 H), 3.42 (AB quartet, *J* = 19.6 Hz, 0.4 H), 3.29 (AB quartet, *J* = 19.6 Hz, 0.6 H), 3.28 (AB quartet, *J* = 20.0 Hz, 0.4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 224.7, 222.0, 192.9, 169.7, 169.1, 154.1, 152.8, 147.7, 147.5, 144.5, 144.4, 141.7, 136.8, 136.5, 135.0, 134.7, 133.4, 129.7, 129.5, 129.2, 129.0, 127.9, 127.6, 106.5, 106.0, 91.8, 90.9, 76.2, 76.1, 65.1, 64.3, 64.0, 52.9, 52.8, 48.1. HRMS (ESI) calcd. for $C_{26}H_{25}BMoN_7O_7$ ($[M+H]^+$): 656.0963 Found: 656.0968. HPLC: Daicel® Chiralcel AS-RH, CH_3CN: H_2O = 50: 50, 1.0 mL/min., λ = 254 nm, 18.83 min, >99.9% de.



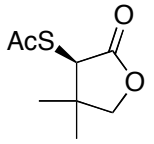
TLC: R_f = 0.30 (hexanes: EtOAc = 1:1). IR (cm^{-1}) 1967 (s), 1873 (s), 1756 (w), 1712 (w). ^{1}H NMR (mixture of two rotamers- 400 MHz, $CDCl_3$): δ 8.46 (d, *J* = 1.6 Hz, 0.5 H), 8.37 (d, *J* = 1.6 Hz, 0.5 H), 8.20 (d, *J* = 1.6 Hz, 0.5 H), 7.77 (d, *J* = 1.6 Hz, 0.5 H), 7.72 (d, *J* = 1.6 Hz, 0.5 H), 7.64 (d, *J* = 1.6 Hz, 0.5 H), 7.62 (d, *J* = 1.6 Hz, 0.5 H), 7.51-7.58 (m, 3.0 H), 7.38-7.48 (m, 5 H), 7.31 (d, *J* = 6.4, 0.4 H), 7.29 (d, *J* = 6.4, 0.6 H), 6.29 (t, *J* = 2.0 Hz, 0.5 H), 6.27 (t, *J* = 2.0 Hz, 0.5 H), 6.25 (t, *J* = 2.0 Hz, 0.6 H), 6.21-6.23 (m, 1.4 H),

5.99 (s, 0.5 H), 5.96 (s, 0.5 H), 5.84 (d, *J* = 2.4 Hz, 0.6 H), 5.83 (d, *J* = 2.4 Hz, 0.4 H), 4.76 (d, *J* = 3.2 Hz, 0.5 H), 4.75 (d, *J* = 3.2 Hz, 0.5 H), 4.12 (t, *J* = 2.4 Hz, 0.5 H), 3.99 (t, *J* = 2.4 Hz, 0.5 H), 3.79 (s, 0.6 H), 3.69 (s, 0.4 H), 3.56 (AB quartet, *J* = 19.6 Hz, 0.6 H), 3.47 (AB quartet, *J* = 19.2 Hz, 0.4 H), 3.46 (AB quartet, *J* = 19.6 Hz, 0.6 H), 3.33 (AB quartet, *J* = 19.2 Hz, 0.4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 224.7, 222.0, 192.9, 169.7, 169.1, 154.1, 152.8, 147.7, 147.5, 144.5, 144.4, 141.7, 136.8, 136.5, 135.0, 134.7, 133.4, 129.7, 129.5, 129.2, 129.0, 127.9, 127.6, 106.5, 106.0, 91.8, 90.9, 76.2, 76.1, 65.1, 64.3, 64.0, 52.9, 52.8, 48.1. HRMS (ESI) calcd. for $C_{26}H_{25}BMoN_7O_7$ ($[M+H]^+$): 656.0963 Found: 656.0963. HPLC: Daicel® Chiralcel AS-RH, CH_3CN: H_2O = 50: 50, 1.0 mL/min., λ = 254 nm, 16.42 min, >99.9% de.

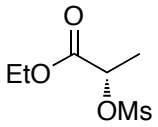


(*S*)-4,4-Dimethyl-2-oxotetrahydrofuran-3-yl methanesulfonate (3.5c) To a solution of (*R*)-(-)-pantolactone (1.0 g, 7.68 mmol, 1.0 equiv) in CH_2Cl_2 (7.7 mL) at 0 °C was added triethylamine (3.2 mL, 23.05 mmol, 3.0 equiv). A solution of methanesulfonyl chloride (1.19 mL, 15.37 mmol, 2.0 equiv) in CH_2Cl_2 (7.7 mL) was added to the reaction flask via syringe pump over 0.5 h. The solution stirred at 0 °C for 0.5 h, warmed to room temperature over 1.5 h, and stirred at room temperature for 0.5 h. The solution was diluted with water (12 mL), extracted with CH_2Cl_2 (3 x 10 mL), washed with brine (3 x 10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, 3.0 cm x 23.0 cm, hexanes: EtOAc = 2:1) to afford the product **3.5c** (1.58 g, 99 %) as a white solid (mp 46-48 °C). TLC: R_f = 0.51

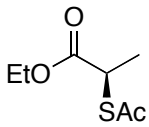
(hexanes: EtOAc = 1:1). IR (cm^{-1}) 2972 (w), 2940 (w), 1738 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.99 (s, 1 H), 4.09 (AB quartet, J = 16.4 Hz, 8.8 Hz, 2 H), 3.30 (s, 3 H), 1.29 (s, 3 H), 1.18 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171, 81.3, 76.1, 40.3, 39.4, 31.6, 22.0, 19.5. HRMS (ESI) Calcd. for $C_7H_{13}O_5S$ ([M + H]): 209.0484. Found: 209.0477.



(*R*)-*S*-(4,4-Dimethyl-2-oxotetrahydrofuran-3-yl) ethanethioate (3.5d) To a solution of the mesylate of (*R*)-(-)-pantolactone (1.44 g, 6.89 mmol, 1.0 equiv) in DMF (14 mL) was added cesium ethanethioate (1.51 g, 7.24 mmol, 1.05 equiv). The solution was heated to 110 °C and stirred for 24 h while keeping temperature constant, diluted with water (10 mL), extracted with Et_2O (3 x 8 mL), washed with brine (3 x 8 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, 5.0 cm x 23.0 cm, hexanes: EtOAc = 4:1) to afford the product **3.5d** (1.09 g, 84 %) as a dark yellow liquid. TLC: R_f = 0.47 (hexanes: EtOAc = 2:1). IR (cm^{-1}) 2965 (w), 1776 (m), 1699 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.34 (s, 1 H), 3.25 (AB quartet, J = 94.4 Hz, 11.2 Hz, 2 H), 2.45 (s, 3 H), 1.25 (s, 3 H), 1.09 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.7, 174.2, 52.5, 40.7, 30.3, 23.2, 22.5. HRMS (ESI) Calcd. for $C_8H_{13}O_3S$ ([M + H]): 189.0585. Found: 189.0579.



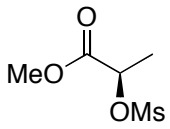
(*S*)-Ethyl 2-((methylsulfonyl)oxy)propanoate (3.7c)[3] To a solution of ethyl (*S*)-lactate (1.0 g, 8.91 mmol, 2.0 equiv) in CH_2Cl_2 (6 mL) at 0 °C was added triethylamine (2.5 mL, 18.06 mmol, 3.0 equiv). A solution of methanesulfonyl chloride (0.69 mL, 8.91 mmol, 2.0 equiv) in CH_2Cl_2 (6 mL) was added to the reaction flask via syringe pump over 15 min. The solution stirred at 0 °C for 0.5 h, warmed to room temperature over 1.5 h, and stirred at room temperature for 0.5 h. The solution was diluted with water (12 mL), extracted with CH_2Cl_2 (3 x 4 mL), washed with brine (3 x 8 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, 3.0 cm x 23.0 cm, hexanes: EtOAc = 5:1) to afford the product **3.7c** (1.46 g, 99 %) as a white solid. TLC: R_f = 0.48 (hexanes: EtOAc = 1:1). IR (cm^{-1}) 2988 (w), 1744 (m), 1352 (m); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.11 (q, *J* = 7.2 Hz, 6.8 Hz, 1 H), 4.25 (q, *J* = 7.2 Hz, 6.8 Hz, 2 H), 3.15 (s, 3 H), 1.61 (d, *J* = 7.2 Hz, 3 H), 1.31 (t, *J* = 7.2 Hz, 3 H);^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 74.3, 62.0, 38.9, 18.3, 14.0. HRMS (ESI) Calcd. for $C_6H_{13}O_5S$ ([M + H]): 197.0484. Found: 197.0488.



(*R*)-Ethyl 2-(acetylthio)propanoate (3.7d)[4] To a solution of (*R*)-methyl 2-(methylsulfonyloxy)-2-phenylacetate (1.0 g, 4.09 mmol, 1.0 equiv) in DMF (8.2 mL) was added cesium ethanethioate (0.89 g, 4.30 mmol, 1.05 equiv). The solution stirred at room

[3] Hillis, L. R.; Ronald, R. C. *J. Org. Chem.* **1981**, *46*, 3348-3349.
[4] Strijtveen, B.; Kellogg, R. M. *J. Org. Chem.* **1986**, *51*, 3664-3671.

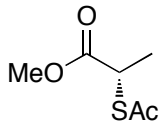
temperature for 24 h, diluted with water (8 mL), extracted with Et_2O (3 x 6 mL), washed with brine (5 x 6 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, 3.0 cm x 23.0 cm, hexanes: EtOAc = 10:1) to afford the product **3.7d** (0.844 g, 92 %) as a light orange oil. TLC: R_f = 0.43 (hexanes: EtOAc = 2:1). IR (cm^{-1}) 2983 (w), 1733 (s), 1694 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 4.20 (m, 4 H), 2.38 (s, 3 H), 1.49 (d, J = 7.2 Hz, 3 H), 1.25 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.6, 171.8, 61.5, 40.9, 30.1, 17.6, 14.0. HRMS (ESI) Calcd. for $C_7H_{13}O_3S$ ([M + H]): 177.0585. Found: 177.0587.



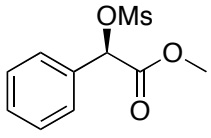
(*R*)-Methyl 2-((methylsulfonyl)oxy)propanoate (3.8c)[5] To a solution of (-)-methyl L-lactate (3.0 g, 28.8 mmol, 1.0 equiv) in CH_2Cl_2 (29 mL) at 0 °C was added triethylamine (12.0 mL, 86.5 mmol, 3.0 equiv). A solution of methanesulfonyl chloride (4.5 mL, 57.6 mmol, 2.0 equiv) in CH_2Cl_2 (29 mL) was added to the reaction flask via syringe pump over 1 h. The solution stirred at 0 °C for 0.5 h, warmed to room temperature over 1.5 h, and stirred at room temperature for 0.5 h. The solution was diluted with water (30 mL), extracted with CH_2Cl_2 (3 x 15 mL), washed with brine (3 x 15 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, 5.0 cm x 23.0 cm, hexanes: EtOAc = 4:1) to afford the product **3.20** (4.64 g, 88 %) as a colorless oil. TLC: R_f = 0.42 (hexanes: EtOAc = 1:1). IR (cm^{-1}) 2959 (w), 1748 (m); ^1H NMR (400 MHz, $CDCl_3$) δ 5.14 (q, J = 7.2 Hz, 6.8 Hz, 1 H),

[5] Bridger, G. *et al*. *PCT Int. Appl.* **2005**, 2005059107.

3.81 (s, 3 H), 3.16 (s, 3 H), 1.62 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 74.0, 52.4, 38.4, 17.9. HRMS (ESI) Calcd. for $C_5H_{11}O_5S$ ([M + H]): 183.0327. Found: 183.0321.



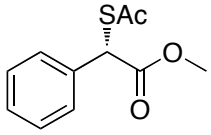
(*S*)-Methyl 2-(acetylthio)propanoate (3.8d)[6] To a solution of the mesylate of (-)-methyl L-lactate (3.0 g, 16.5 mmol, 1.0 equiv) in THF (33 mL) was added cesium ethanethioate (3.6 g, 17.3 mmol, 1.05 equiv). The solution stirred at room temperature for 24 h, diluted with water (30 mL), extracted with Et_2O (3 x 10 mL), washed with brine (3 x 10 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, 5.0 cm x 23.0 cm, hexanes: EtOAc = 5:1) to afford the product **3.21** (0.84 g, 92 %) as an orange liquid. TLC: R_f = 0.42 (hexanes: EtOAc = 4:1). IR (cm^{-1}) 2954 (w), 1736 (s), 1693 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.23 (q, J = 7.6 Hz, 7.2 Hz, 1 H), 3.72 (s, 3 H), 2.34 (s, 3 H), 1.49 (d, J = 7.2 Hz, 3 H). HRMS (ESI) Calcd. for $C_6H_{11}O_3S$ ([M + H]): 163.0429. Found: 163.0423.



(*R*)-Methyl-2-(methylsulfonyloxy)-2-phenylacetate (3.9c)[7] To a solution of methyl (*R*)-(-)-mandelate (1.0 g, 8.91 mmol, 2.0 equiv) in CH_2Cl_2 (6 mL) at 0 °C was added

[6] Owen, L. N.; Rahman, M. B. *J. Chem. Soc.* **1971**, *13*, 2432-2440.
[7] Creary, X.; Geiger, C. C. *J. Am. Chem. Soc.* **1982**, *104*, 4151-4162.

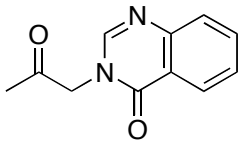
triethylamine (2.5 mL, 18.06 mmol, 3.0 equiv). A solution of methanesulfonyl chloride (0.69 mL, 8.91 mmol, 2.0 equiv) in CH_2Cl_2 (6 mL) was added to the reaction flask via syringe pump over 15 min. The solution stirred at 0 °C for 0.5 h, warmed to room temperature over 1.5 h, and stirred at room temperature for 0.5 h. The solution was diluted with water (12 mL), extracted with CH_2Cl_2 (3 x 4 mL), washed with brine (3 x 8 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, 3.0 cm x 23.0 cm, hexanes: EtOAc = 5:1) to afford the product **3.9c** (1.46 g, 99 %) as a white solid (mp 113-114 °C). TLC: R_f = 0.11 (hexanes: EtOAc = 4:1). IR (cm^{-1}) 3330 (w), 2958 (w), 1697 (s), 1506 (m), 1241 (s), 698 (s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35-7.26 (m, 6 H), 6.31 (s, 1 H), 6.19 (d, *J* = 3.2 Hz, 1 H), 5.69 (t, J) 7.0 Hz, 1 H), 5.18 (br s, 1 H), 4.37 (dd, J) 15.3, 6.0 Hz, 1 H), 4.28 (dd, J) 15.6, 5.5 Hz, 1 H), 1.89 (m, 1 H), 1.75 (m, 1 H), 1.33 (m, 2 H), 0.93 (t, J) 7.3 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 132.8, 130.1, 129.2, 127.8, 79.0, 53.1, 39.4. HRMS (ESI) Calcd. for $C_{10}H_{13}O_5S$ ([M + H]): 245.0484. Found: 245.0487.



(*S*)-Methyl-2-(acetylthio)-2-phenylacetate (3.9d)[8] To a solution of (*R*)-methyl 2-(methylsulfonyloxy)-2-phenylacetate (1.0 g, 4.09 mmol, 1.0 equiv) in DMF (8.2 mL) was added cesium ethanethioate (0.89 g, 4.30 mmol, 1.05 equiv). The solution stirred at room temperature for 24 h, diluted with water (8 mL), extracted with Et_2O (3 x 6 mL), washed with brine (5 x 6 mL), dried over $MgSO_4$, and concentrated under reduced pressure. The

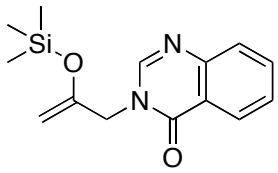
[8] Hughes, D. L. In *Organic Reactions*; Wiley: Hoboken, NJ, 1992.

crude product was purified by flash chromatography (SiO_2, 3.0 cm x 23.0 cm, hexanes: EtOAc = 10:1) to afford the product **3.9d** (0.844 g, 92 %) as a dark orange oil. TLC: R_f = 0.33 (hexanes: EtOAc = 4:1). IR (cm^{-1}) 1741 (w), 1694 (w); ^1H NMR (400 MHz, $CDCl_3$) δ 7.35-7.26 (m, 5 H), 5.27 (s, 1 H), 3.69 (s, 3 H), 2.30 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.1, 170.6, 135.0, 129.1, 128.7, 128.5, 53.3, 51.2, 30.1. HRMS (ESI) Calcd. for $C_{11}H_{13}O_3S$ ([M + H]): 225.0585. Found: 225.0584.



3-(2-Oxopropyl)quinazolin-4(3*H*)-one (4.30)[9] To a solution of 4-hydroxyquinazoline (1.0 g, 6.84 mmol, 1.0 equiv) in acetone (45.6 mL) was added potassium carbonate (1.13 g, 8.21 mmol, 1.2 equiv) and chloroacetone (1.22 mL, 7.52 mmol, 1.1 equiv). The solution stirred at reflux for 24 h, then concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, 3.0 cm x 23.0 cm, hexanes: EtOAc = 1:5 ramping gradually to 100% EtOAc) to afford the product **4.30** (1.20 g, 87%) as a white solid (mp 157-159 °C). TLC: R_f = 0.14 (CH_2Cl_2: Et_2O = 2:1). IR (cm^{-1}) 1721 (m), 1668 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, J = 8 Hz, 1 H), 7.89 (s, 1 H), 7.78 (m, 2 H), 7.53 (app t, J = 7.2 Hz, 1 H), 4.81 (s, 2 H), 2.37 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ . HRMS (ESI) Calcd. for $C_{11}H_{11}N_2O_2$ ([M + H]): 203.0821. Found: 203.0822.

[9] Burgess, L. E. *et al. Tet. Lett.* **1996**, *37*, 3255-3258.



3-(2-((Trimethylsilyl)oxy)allyl)quinazolin-4(3*H*)-one (4.28)[10] To a solution of 3-(2-oxopropyl)quinazolin-4(3*H*)-one (1 g, 4.95 mmol, 1.0 equiv) in CH_2Cl_2 (24.7 mL) was added Hunig's base (0.95 mL , 5.44 mmol, 1.1 equiv). After stirring 15 min at rt, TMSOTf (0.94 mL, 5.19 mmol, 1.05 equiv) was added. The reaction stirred 20 min at rt, then concentrated under reduced pressure. The crude product was purified by flash chromatography (SiO_2, 3.0 cm x 23.0 cm, hexanes:EtOAc = 5:1 deactivated with 1% Et_3N) to afford the product **4.28** (1.05 g, 77%) as a colorless oil. TLC: R_f = 0.63 (CH_2Cl_2: Et_2O = 2:1). IR (cm^{-1}) 2955 (w), 2930 (w), 2957 (w), 1681 (s), 1610 (s); ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (dd, *J* = 7.2 Hz, 1.2 Hz, 1 H), 8.04 (s, 1 H), 7.74-7.67 (m, 2 H), 7.46 (app t, *J* = 7.2 Hz, 1 H), 4.51 (s, 2 H), 4.32 (d, *J* = 1.6 Hz, 1 H), 4.28 (d, *J* = 1.6 Hz, 1 H), 0.82 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.9, 152.5, 148.1, 146.9, 146.8, 134.3, 127.6, 127.3, 127.0, 126.9, 122.2, 93.2, 49.8, 25.9, 25., 25.6, 18.0. HRMS (ESI) Calcd. for $C_{14}H_{19}N_2O_2Si$ ([M + H]): 275.1216. Found: 275.1220.

[10] Sugiura, M. *et. al. J. Am. Chem. Soc.* **2001**, *123*, 12510-12517.