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Synthesis of 3-Methyl-TpMo$(CO)_2$(5-Oxo-Pyranyl) Organometallic Scaffold and Its Application in Forming Quaternary Center at a Ring Junction *via* an Oxidative Annulation-Demetalation Cascade

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An Abstract of
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Abstract

Due to their versatility, π-allylmolybdenum complexes have become common organometallic enantiomeric scaffolds for the construction of a variety of natural- and non-natural biologically important heterocyclic compounds. Recently, the Liebeskind group has developed a concise, high throughput methodology that is based on oxo- and aza-Achmatowicz reactions, to access both racemic and enantiopure $TpMo(CO)_2(\eta^3$-pyranyl) and $TpMo(CO)_2(\eta^3$-pyridinyl) scaffolds respectively. To probe the use of Achmatowicz reaction in the synthesis of substituted scaffolds and for greater synthetic versatility, 3-methyl substituted $TpMo(CO)_2(\eta^3$-pyranyl) organometallic scaffold has been prepared.

The direct nucleophilic functionalization of charge neutral $TpMo(CO)_2(\eta^3$-pyranyl) and $TpMo(CO)_2(\eta^3$-pyridinyl) complexes complement the nucleophilic functionalization of cationic, highly electrophilic molybdenum complexes. The 3-methyl substituted $TpMo(CO)_2(\eta^3$-pyranyl) scaffold underwent an uncatalyzed Friedel-Crafts-like direct nucleophilic functionalization with silyl enol ether to form a 2,3-disubstituted η^3-allylmolybdenum complex. In addition, 2,3-disubstituted η^3-allylmolybdenum complexes were obtained in modest yields by addition of organometallic reagents to a cationic molybdenum complex.

Mild and efficient demetalation of η^3-allymolybdenum complexes is a key step to convert the intermediate into useful organic compounds. Expanding the scope of annulative demetalation of η^3-allymolybdenum to 2,3-disubstituted η^3-allylmolybdenum complexes led to the formation of a quaternary center at the ring junction of *cis*-fused heterocyclic ring system.

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Table of Contents

Chapter One: Introduction to Organometallic Enantiomeric Scaffolding and Synthesis of 3-Methyl Substituted Pyranyl Organometallic Scaffold

Background……..…….....2

Organic Enantiomeric Scaffolding……...2

Organometallic Enantiomeric Scaffolding……...5

Hydrotris(pyrazolyl)borate (Tp) Ligand in η^3-allylic molybdenum complexes……..6

Preparation of η^3-Allyl Molybdenum Complexes……7

Results and Discussions……13

Synthetic Route to 4-Methyl Furfuryl Alcohol……...13

Synthesis of 3-Methyl-5-Oxo-Pyranyl Molybdenum Scaffold……...15

Conclusions……...15

Experimental…….……16

Chapter Two: Nucleophilic Functionalization of $TpMo(CO)_2(\eta^3$-pyranyl) Complexes

Background……...……...…26

Nucleophilic Functionalization of Cationic Molybdenum Complexes…….26

Direct Nucleophilic Functionalization of η^3-Allylmolybdenum Complexes……....27

Results and Discussions……..30

Conclusions…….…36

Experimental…….……...36

References…….…...43

Chapter Three: Quaternary Center Formation *via* Oxidative Annulative Demetalation Cascade

Background……..……45

Demetalation Approaches Involving Cationic Molybdenum Complexes……..……45

Demetalation Approaches Involving Charge Neutral Molybdenum Complexes..….47

Results and Discussions……...49

Conclusions……..52

Experimental……53

References……....59

List of Figures

Figure 1.1 Principal examples of organic scaffolds…….3

Figure 1.2 Comins' chiral auxiliary and possible reactions with the enantiopure dihydro-pyridinone……...3

Figure 1.3 Comins' organic scaffold in alkaloid synthesis……..4

Figure 1.4 Related Bosch and Husson/Royer scaffolds in alkaloid synthesis…….4

Figure 1.5 Metal π-complexes in Enantiocontrolled heterocycle synthesis……6

Figure 1.6 Liebeskind core organometallic Scaffolds……..…8

Figure 1.7 Organometallic scaffolding in natural product synthesis…….11

Figure 2.1 Aspidosperma Alkaloids……..29

List of Schemes

Scheme 1.1 Preparation of "Tp" ligand……...7

Scheme 1.2 π-allyl metal complexes from allyl bromides and acetates…….8

Scheme 1.3 π-allyl metal complexes from enals and enones……..8

Scheme 1.4 Preparation of racemic Scaffolds 1.3 and 1.4 from allyl bromides…….9

Scheme 1.5 Achmatowicz and aza-Achmatowicz reaction based scaffold synthesis…...10

Scheme 1.6 Synthesis of high enantiopure 5-oxo-pyranyl scaffold…..……....10

Scheme 1.7 Synthesis of high enantiopure 5-oxo-pyridinyl scaffold……....11

Scheme 1.8 Previously prepared substituted scaffolds……..…....12

Scheme 1.9 Retrosynthetic plan for the synthesis of 3-methyl-substituted scaffold…….13

Scheme 1.10 Preparation of 4-methyl furfuryl alcohol……..…...14

Scheme 1.11 Thermodynamic equilibrium of lithio species……..…...14

Scheme 1.12 Achmatowicz reaction based Synthesis of 3-methyl substituted scaffold...15

Scheme 2.1 Nucleophilic functionalization of cationic molybdenum complexes…….....27

Scheme 2.2 "1,5-Michael-like" reaction……28

Scheme 2.3 "Homo-S_N2-like" reaction……..…28

Scheme 2.4 Uncatalyzed Friedel-Crafts reaction……...29

Scheme 2.5 Nucleophilic addition and annulative demetalation overview……...30

Scheme 2.6 Preparation of 5-acyl substarate…….30

Scheme 2.7 Preparation of 5-fluoroacetate substrate for uncatalyzed Friedel-Crafts reaction……..……32

Scheme 2.8 Preparation of cationic molybdenum complex……..33

Scheme 2.9 Study on addition of Grignard reagent to cationic molybdenum complex…33

Scheme 2.10 Study on lithiate addition to cationic molybdenum complex……..33

Scheme 2.11 Study on directed ortho lithiation ……...34

Scheme 2.12 Study on lithium-halogen exchange……....35

Scheme 3.1 Demetalation protocol using $NOBF_4$……....45

Scheme 3.2 Demetalation protocol using I_2…….46

Scheme 3.3 Demetalation Protocol using $CuCl_2$ ……47

Scheme 3.4 Possible annulative demetalation pathway……...48

Scheme 3.5 Annulative demetalation using oxygen and nitrogen nucleophiles……..49

Scheme 3.6 Preparation of precursor alcohol for demetalation……...50

Scheme 3.7 Study on annulative demetalation using phenoxide as a nucleophile…..…51

Scheme 3.8 Study on annulative demetalation using nitrogen nucleophile.……..….52

List of Tables

Table 2.1 Study on "homo-S_N2'-like" reaction……..….31

Table 2.2 Study on uncatalyzed Friedel-Crafts reaction…….32

Table 2.3 Study on alternative lithium-halogen exchange approach……..35

Table 3.1 Demetalation protocol using PDC/Silica……47

Table 3.2 Annulative demetalation with a variety of substrates…….48

Table 3.3 Study on demetalation using an internal alkoxide nucleophile……..50

List of Abbreviations

Ac	acetyl
ACN	acetonitrile
Aq	aqueous
Ar	argon
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br	broad
bu	butyl
^{o}C	degree Celsius
calcd	calculated
Cbz	benzyloxycarbonyl
Cp	cyclopentadienyl
Cy	cyclohexyl
δ	chemical shift(s)
d	doublet
DMAP	4-dimethylamino pyridine
DMSO	dimethyl sulfoxide
Et	ethyl
FAB	fast atom bombardment
g	gram(s)
hr(s)	hour(s)
HRMS	high resolution mass spectroscopy
Hz	hertz
IR	Infrared Spectroscopy
J	coupling constant
mol	mole
m	multiplet
m-CPBA	meta-chloroperbenzoic acid
Me	methyl
mg	milligram(s)
MHz	megahertz
min	minute(s)
mL	milliliter(s)
μL	microliter(s)
mmol	millimole(s)
mp	melting point
NMR	nuclear magnetic resonance
PCC	pyridinium chlorochromate
PG	protecting group
Ph	phenyl
ppm	parts per million
pr	propyl
py	pyridine
q	quartet
rt	room temperature
s	singlet

t	triplet
t	tertiary
tert	tertiary
TBME	*tert*-butyl methyl ether
TBS	*tert*-butyl dimethyl silyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Tp	hydrotris(pyrazolyl)borate
Tr	triphenylcarbenium
UV	ultraviot

Chapter One

Introduction to *Organometallic Enantiomeric Scaffolding* and Synthesis of 3-Methyl Substituted Pyranyl Organometallic Scaffold

Background

A concise strategy for the enantiocontrolled construction of bonds in complex molecules remains a challenge to the synthetic organic community as the demand for enantiomerically pure compounds continues to increase. Three distinct approaches have been used traditionally to address this challenge in organic synthesis: (1) incorporation of "chirons"[1,2] or auxiliaries,[3,4] (2) enzymatic transformations,[5] and (3) metallo-[6-8] or organo-catalytic[9,10] asymmetric transformations. While catalytic asymmetric transformations in complex organic synthesis have been the major focus recently, the development of scaffolding approach serves as a 4th strategy for the enantiocontrolled construction of complex molecules. An early strategy that uses chiral templates in enantiocontrolled construction of bonds is the "chiron" approach. This strategy developed by Hanessian[1,2] involves the organic synthesis of complex enantiopure organic compounds from a readily available enantiopure substances such as carbohydrates, amino acids, and hydroxy acids. The "chiron" approach has been extensively used in the synthesis of many classes of natural products and is especially advantageous if the desired molecule has a great similarity to the readily available enantiopure starting material. However, not all desired molecules display such close similarity to their respective starting materials. To address this drawback, others envisioned an enantiomeric scaffolding approach.

Organic Enantiomeric Scaffolding

In the enantiomeric scaffolding approach to the enantiocontrolled construction of bonds, a simple core molecule of high enantiopurity is constructed. The core structure is

then transformed into a wide range of biologically important natural- and non-natural products by the introduction of different substituents in a regio- and diastereocontrolled manner.

Comins,[11-15] Bosch,[16-19] and Husson and Royer[20,21] have been the principal leaders in developing and demonstrating the use of nitrogen based *organic* enantiomeric scaffolds in the synthesis of diverse families of molecules (**Figure 1.1**).

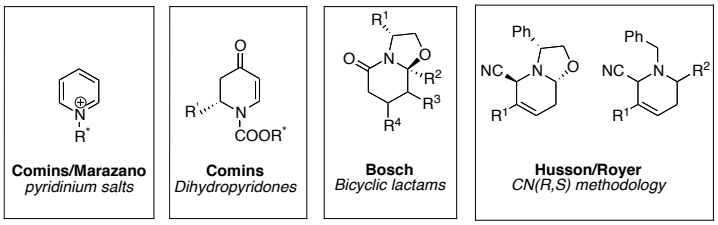


Figure 1.1 Principal Examples of Organic Scaffolds

A chiral auxiliary developed by Comins and coworkers enabled stereo- and regio-selective addition of nucleophiles to 1-acylpyridinium salts.[13] As shown in **Figure 1.2** the chiral auxiliary, when used on a 3-silyl-4-methoxypyridine results in high diastereoselectivity because the bulky TIPS group directs addition to C_6 over C_2, and the C_4-methoxy group blocks addition to C_4, and the chiral auxiliary forces addition to one face of the pyridinium salts.

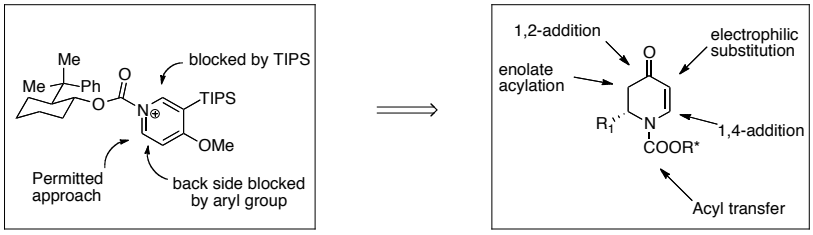


Figure 1.2 Comins' Chiral Auxiliary and Possible Reactions with the Enantiopure Dihydropyridinone

The resulting enantiopure dihydropyridinones are useful tools in the synthesis of complex alkaloids (**Figure 1.3**) by participating in a number of reactions including 1,2-/1,4-addition, enolate acylation, and electrophilic substitutions (**Figure 1.2**).

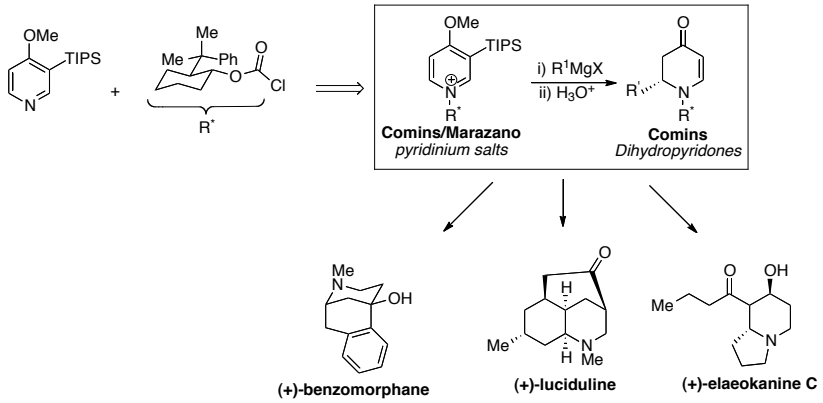


Figure 1.3 Comins' Organic Scaffold in Alkaloid Synthesis

Bosch and coworkers have demonstrated that organic enantiomeric scaffolds of phenylglycinol-derived oxalopiperidone lactams, readily available in both enantiomeric series by a cyclocondensation of phenylglycinol and the methyl ester of 5-oxo-pentanoic acid, are versatile building blocks for the enantioselective synthesis of structurally diverse piperidine-containing natural products and non-natural bioactive compounds. The conformational rigidity of the bicyclic lactam system controls the introduction of different substituents on different ring positions in a regio- and stereocontrolled manner.

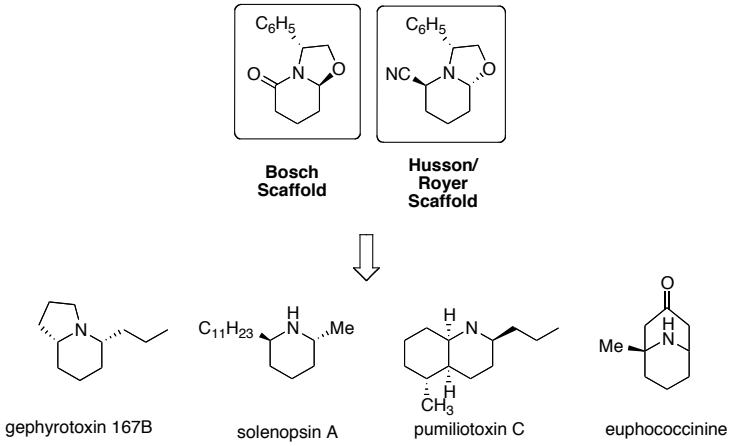


Figure 1.4 Related Bosch and Husson /Royer Scaffolds in Alkaloid Synthesis

Husson and Royer have utilized a similar cyclocondensation of phenylglycinol and glutaraldehyde to access chiral, non-racemic *N*-cyanomethyloxazolidines ring scaffolds.[20] By further functionalizing the *N*-cyanomethyloxazolidines, they have

demonstrated the utility of these scaffolds in regio- and stereocontrolled synthesis of piperidine-containing natural products (**Figure 1.4**).

Although Comins, Bosch, and Husson/Royer have all developed practical methods to access elaborated heterocycles and highlighted their respective utilities by introducing substituents in a regio- and stereocontrolled manner leading to the synthesis of a variety of alkaloids, they are limited by design to the synthesis of nitrogen-based heterocyclic compounds. An alternative and complementary approach to the strategies mentioned above is *organometallic enantiomeric scaffolding*. Unlike the scaffolding approaches taken by other laboratories that are limited to nitrogen-based heterocycles, the Liebeskind laboratory has developed and demonstrated the use of *organometallic* enantiomeric scaffolding strategy to the regio- and stereocontrolled construction of not only nitrogen-based but also oxygen-based heterocycles.

Organometallic Enantiomeric Scaffolding

The Liebeskind laboratory has designed transition-metal-based scaffolds for the enantiocontrolled synthesis of complex heterocyclic compounds and coined the term *organometallic enantiomeric scaffolds* to describe these scaffolds. In this approach, diverse families of important molecules can be obtained in high enantiopurity from simple, readily available, single enantiomers of air-stable organometallic π-complexes of key unsaturated ligands.

Organometallic scaffolding in enantiocontrolled synthesis takes advantage of planar chirality that can be introduced by complexation of an achiral, unsymmetrical π-ligand to a transition metal. The racemic mixture formed during complexation can then

be resolved to generate two separate enantiomers that can further undergo several metal mediated transformations followed by demetalation to generate functionalized heterocyclic compounds (**Figure 1.5**).

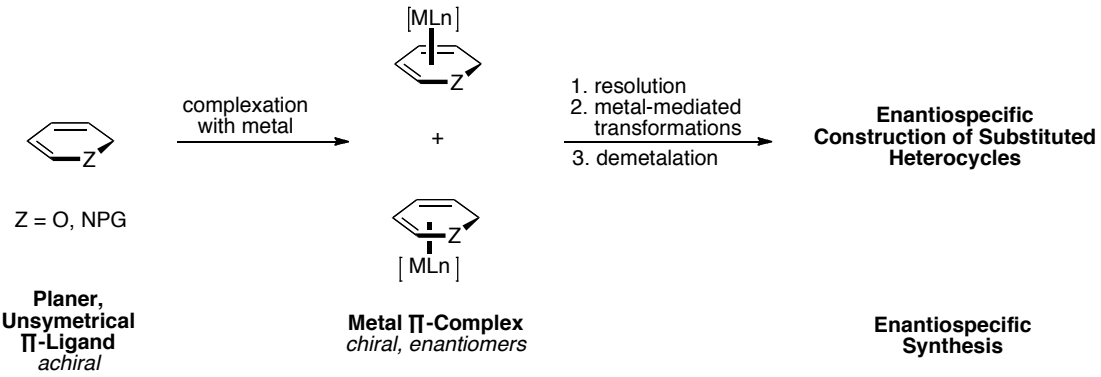


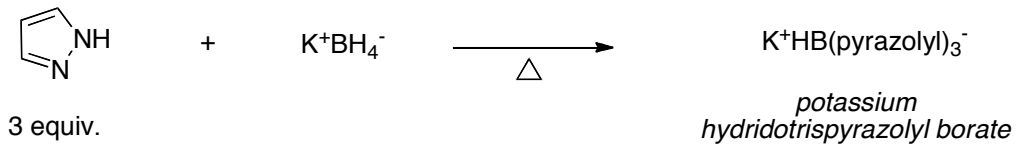
Figure 1.5 Metal π-Complexes in Enantiocontrolled Heterocycle Synthesis

In contrast to metal-based catalytic stereocontrolled transformations in which one metal controls and introduces asymmetry at one step, in organometallic scaffolding, a single metal and its ligands influence novel reactions, control selectivities, and provides a dominant regio- and stereo-control element over several steps. Since a single source of planar chirality controls the regio- and stereo-controlled introduction of substituents in a predictable fashion leading to a variety of chiral, non-racemic compounds, the scaffolding approach avoids the need to develop individual asymmetric routes to each desired heterocyclic compound. In addition, the ease of preparation, and the moisture and air stability make routine synthetic manipulations practical.

Hydrotris(pyrazolyl)borate (Tp) Ligand in η^3-Allylmolybdenum Complexes

The organic chemistry of transition metal based π-allyl complexes of molybdenum has been a powerful tool not only in catalytic synthetic transformations but

also in stoichiometric synthetic transformations.[16-18,22-36] The metal complexes were prepared with auxiliary ligands to enhance their stabilities toward moisture and air and to allow routine handling. Historically, the Liebeskind laboratory incorporated a η^5-cyclopentadienyl (Cp) ligand when developing methods and investigating π-allyl complexes of molybdenum.[37] However, its strong basicity and high nucleophilicity limited the use of the Cp ligand with π-allylic substrates with sensitive functional groups in the preparation of the η^5-$CpMo(CO)_2(\eta^3$-allyl) species. To overcome this problem, the hydrotris(pyrazoyl)borate (Tp)[38,39] ligand was investigated as an isoelectronic, non-basic and less nucleophilic alternative.



Scheme 1.1 Preparation of "Tp" Ligand

The Tp ligand can be incorporated using KTp, an air stable, free flowing white solid that may be prepared in large scale by heating pyrazole and potassium borohydride (**Scheme 1.1**).[39,40] The ease of preparation and air stability of the Tp ligand overcame the above mentioned limitations and resulted in the replacement of the $CpMo(CO)_2$ with $TpMo(CO)_2$ complexes in the investigation of π-allyl complexes of molybdenum.

Preparation of η^3-Allyl Molybdenum Complexes

Using Tp as a stabilizing ligand, the Liebeskind laboratory has developed different strategically functionalized η^3-allylic molybdenum complexes (**Figure 1.6**).[41-43]

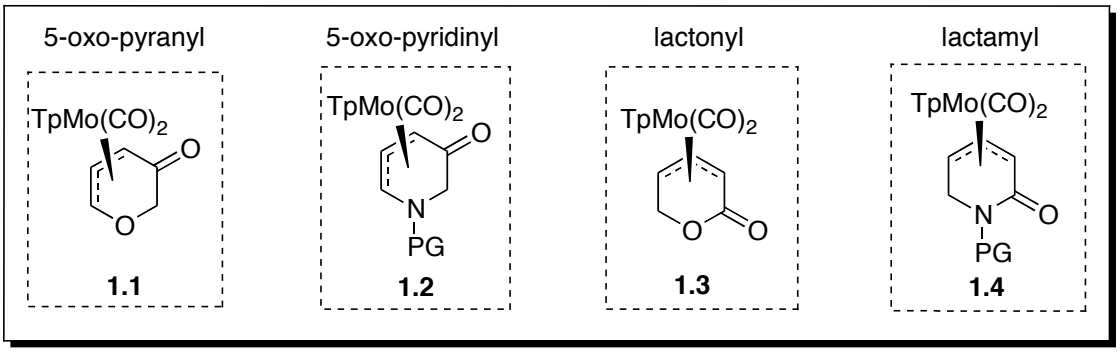
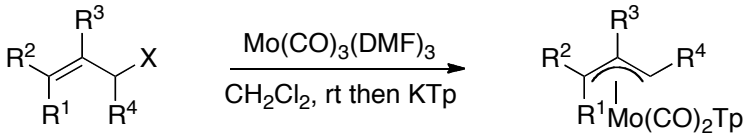


Figure 1.6 Liebeskind Core Organometallic Scaffolds

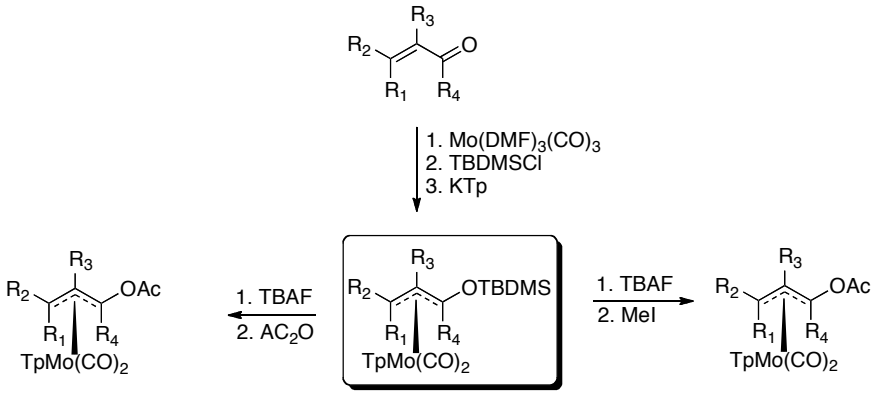
In 1996, the Liebeskind laboratory generalized the preparation of η^3-allylic molybdenum from allylic bromides to include allylic acetates using CH_2Cl_2 as a non-coordinating solvent, $Mo(CO)_3(DMF)_3$ as a zerovalent molybdenum source, and Tp as a stabilizing ligand (**Scheme 1.2**).[42]



X = Br, OAc

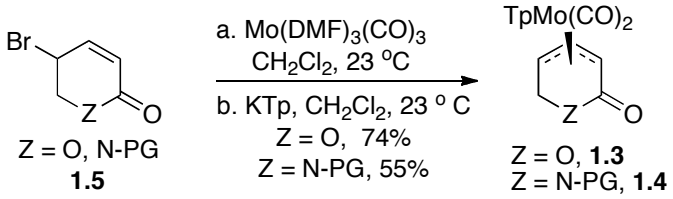
Scheme 1.2 π-Allyl Metal Complexes from Allyl Bromides and Acetates

In addition to allylic bromides and acetates as organic precursors, the generalized procedure included α,β-unsaturated ketones and aldehydes as organic precursors. Treatment of a variety of α,β-unsaturated ketones and aldehydes with $Mo(CO)_3(DMF)_3$ followed by addition of TBDMSCl and subsequent ligand exchange with KTp formed a π-allylmolybdenum complex that underwent desilylative alkylation and acylation to produce various alkoxy or acetoxy π-allyl complexes of molybdenum.[42]



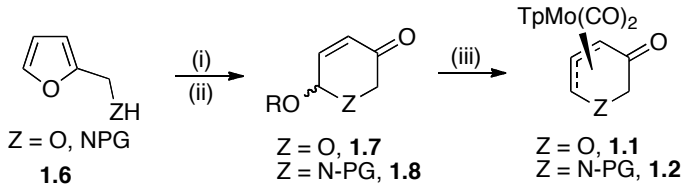
Scheme 1.3 π-Allyl Metal Complexes from Enals and Enones

As mentioned above, treatment of a variety of various allylic acetates or bromides with $Mo(CO)_3(DMF)_3$ followed by ligand exchange with KTp provides the desired π-allyl complexes of molybdenum. The core lactonyl and lactamyl scaffolds were prepared using this established and generalized procedure.[41] Metalation of 5-bromo-5,6-dihydro-2*H*-pyran-2-one[44] and Boc-protected 5-bromo-5,6-dihydro-2*H*-pyridin-2-one derivative with $Mo(DMF)_3(CO)_3$ and ligand exchange with KTp led to the formation racemic lactonyl scaffold **1.3** and lactamyl scaffold **1.4** respectively (**Scheme 1.4**). In addition to the racemic lactonyl **1.3** and lactamyl **1.4** scaffolds, **1.3** and **1.4** have been prepared in high enantiopurity.



Scheme 1.4 Preparation of Racemic Scaffolds 1.3 and 1.4 from Allylic Bromides

Recently, the Liebeskind group reported a unified strategy for the practical, scalable, and high-throughput synthesis of air and moisture stable $TpMo(CO)_2(\eta^3$-pyranyl) **1.1** and $TpMo(CO)_2(\eta^3$-pyridinyl) **1.2** organometallic enantiomeric scaffolds that are based on the oxo- and aza-Achmatowicz oxidative ring expansion.[43]

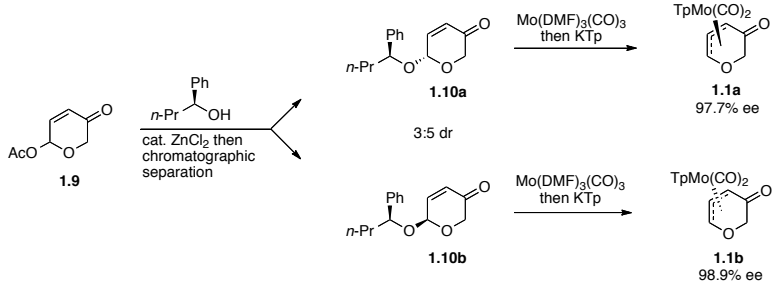


(i) *m*-CPBA, CH_2Cl_2; (ii) Ac_2O, Et_3N, cat. DMAP; (iii) $Mo(CO)_3(DMF)_3$ then KTp

Scheme 1.5 Achmatowicz and aza-Achmatowicz Reaction Based Scaffold Synthesis

In this unified strategy, treatment of furfuryl alcohols and *N*-protected furfuryl amines **1.6** with *m*-CPBA oxidatively rearranged to hydroxypyranones and hydroxypyridinones **1.7** and **1.8**, respectively. Metalation of these intermediates using $Mo(DMF)_3(CO)_3$ followed by ligand exchange with KTp provided racemic $TpMo(CO)_2(\eta^3$-pyranyl) and $TpMo(CO)_2(\eta^3$-pyridinyl) organometallic enantiomeric scaffolds **1.1** and **1.2** respectively.

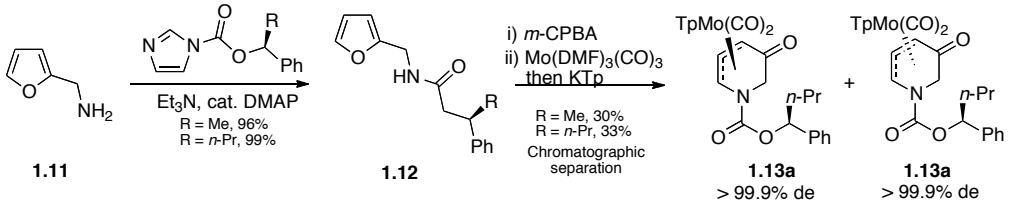
The Liebeskind laboratory has also synthesized $TpMo(CO)_2(\eta^3$-pyranyl) and $TpMo(CO)_2(\eta^3$-pyridinyl) organometallic enantiomeric scaffolds in high enantiopurity using similar strategy. The high enantiopurity $TpMo(CO)_2(\eta^3$-pyranyl) organometallic enantiomeric scaffolds **1.1a** and **1.1b** were prepared from racemic 6-acetoxy-pyranone **1.9** using (*S*)-1-phenylbutanol to form **1.10a** and **1.10b** as diastereomers (**Scheme 1.6**).



Scheme 1.6 Synthesis of High Enantiopure 5-Oxo-pyranyl Scaffold

These diastereomers were separated and subjected to metalation and subsequent ligand exchange separately to give **1.1a** and **1.1b** $TpMo(CO)_2(\eta^3$-pyranyl) in high enantiopurity.[43]

Similarly, aza-Achmatowicz oxidative rearrangement of urethane protected furfural amine derivative **1.12** followed by metalation with $Mo(DMF)_3(CO)_3$ and ligand exchange with KTp provided a diastereomeric mixture of *N*-protected $TpMo(CO)_2(\eta^3$-pyridinyl) organometallic enantiomeric scaffolds **1.13a** and **1.13b** that were separated on silica gel (**Scheme 1.7**).



Scheme 1.7 Synthesis of High Enantiopurity 5-Oxo-pyridinyl Scaffold

Through the development and application of new reactions, these high enantiopurity $TpMo(CO)_2(\eta^3$-pyranyl) and $TpMo(CO)_2(\eta^3$-pyridinyl) complexes have been used in the diastereocontrolled construction of a diverse families of heterocyclic organic systems demonstrated in **Figure 1.6**.[26,27,45-47]

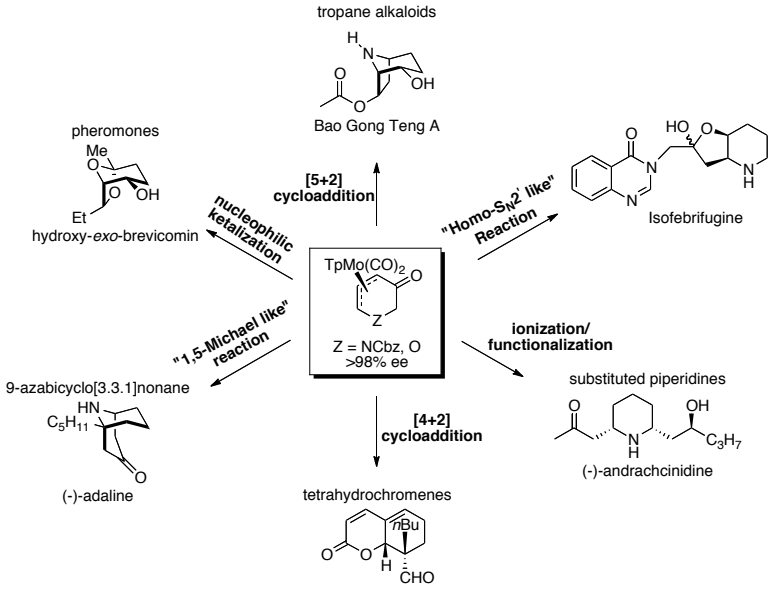
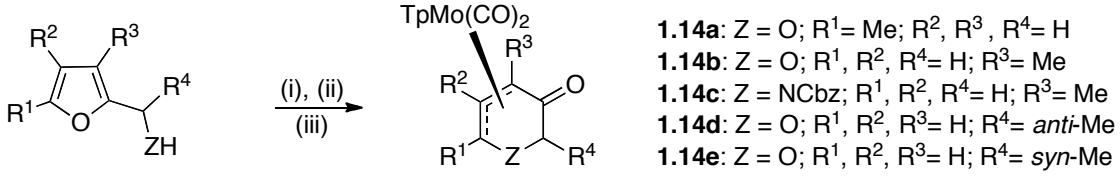


Figure 1.7 Organometallic Scaffolding in Natural Product Synthesis

To probe the use of oxo- and aza-Achmatowicz reactions in the synthesis of substituted scaffolds and for greater synthetic versatility, the Liebeskind laboratory has developed pyranyl and pyridinyl organometallic scaffolds bearing additional substitution patterns about the heterocyclic ring.[43] Methyl-substituted pyranyl scaffolds were prepared by analogy to the unsubstituted pyranyl scaffolds, where by the appropriately methyl substituted furfuryl alcohol underwent Achmatowicz ring rearrangement and the intermediate was acetylated. Metalation of the acetate intermediate with $Mo(DMF)_3(CO)_3$ followed by ligand exchange with KTp provided the appropriately methyl substituted pyranyl scaffolds. Similarly, the substituted pyridinyl scaffold was prepared by oxidative rearrangement of the Cbz-protected furfuryl amine derivative followed by metalation of the hydroxypyridinone with $Mo(DMF)_3(CO)_3$ and subsequent ligand exchange with KTp (**Scheme 1.8**).

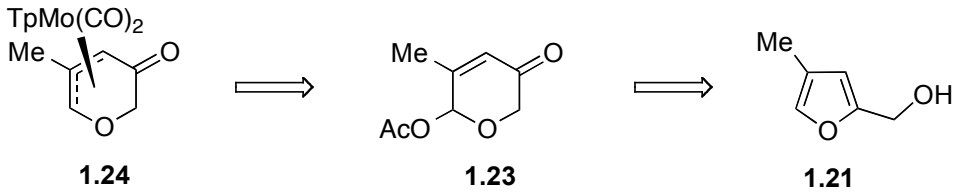


Z = O; (i) = *m*-CPBA; (ii) Ac_2O, Et_3N, cat. DMAP;
(iii) = $Mo(CO)_3(DMF)_3$ then KTp
Z = NCbz; (i) = *m*-CPBA; (iii) = $Mo(CO)_3(DMF)_3$ then KTp

Scheme 1.8 Previously Prepared Substituted Scaffolds

As shown in **Scheme 1.8**, the Liebeskind laboratory has synthesized 2-methyl-substituted scaffold **1.14a**, 4-methyl-substituted scaffolds **1.14b** and **1.14c**, and 6-methyl-substituted scaffolds **1.14d** and **1.14e** from the appropriately substituted furan derivatives. Based on this precedent, 4-substituted furfuryl alcohol and 4-substituted furfuryl amine derivatives were expected to undergo oxidative rearrangement with *m*-CPBA, metalation,

and subsequent ligand exchange to give their respective 3-substituted organometallic scaffolds.



1.24 **1.23** **1.21**

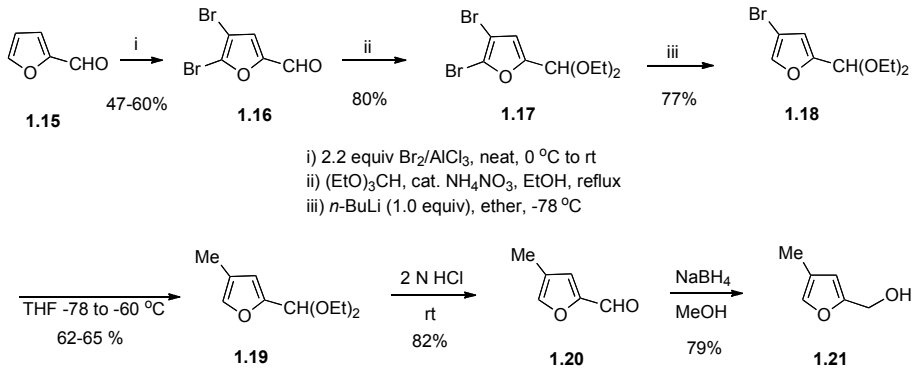
Scheme 1.9 Retrosynthetic Plan for the Synthesis of 3-methyl-Substituted Scaffold

As a model study, this thesis describes the synthesis of 3-methyl-5-oxo-pyranyl molybdenum scaffold using the three-step protocol that is based on Achmatowicz ring expansion (**Scheme 1.9**). In addition, from an exploratory perspective, this thesis describes: In Chapter 2, the nucleophilic functionalization of the 3-methyl substituted molybdenum complexes and in Chapter 3, the application of annulative demetalation of 2,3-disubstituted molybdenum complexes in quaternary center generation at the ring junction of *cis*-fused ring system.

Results and Discussions

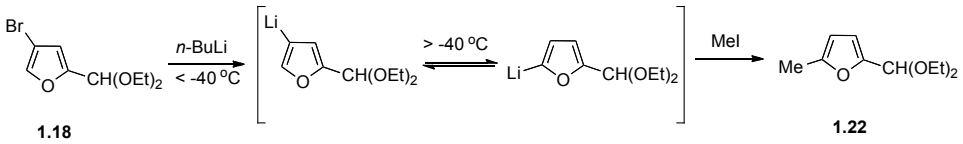
Synthetic Route to 4-Methyl Furfuryl Alcohol

The precursor alcohol, 4-methyl furfuryl alcohol **1.21** was prepared following the route shown in **Scheme 1.10**[48] for two related reasons. First, the relative high cost of 4-substituted furfural and its derivatives (for example: 4-bromo-2-furfural, 1g = $ 101.50) present a challenge of getting these compounds in large scale. Second, all Liebeskind scaffolds must meet the criteria that they must be prepared from an inexpensive and readily available material.[43]



Scheme 1.10 Preparation of 4-methyl Furfuryl Alcohol

Furfural **1.15** was treated with bromine in the presence of aluminum chloride to give 4,5-dibromofurfural **1.16** as a yellow solid in 47-60% yield. 4,5-dibromofurfural **1.16** was protected as diethyl acetal in good yield using catalytic ammonium nitrate as a mild proton source. Slow addition of *n*-BuLi to **1.17** selectively removed the bromine at the 5-position to give a lithiated species which upon acidic workup led to the formation of 4-bromo-2-(diethoxymethyl)furan **1.18** in good yield. Submitting compound **1.18** for additional halogen metal exchange using *n*-BuLi followed by addition of MeI provided the desired compound **1.19**. Here, it is worth mentioning that this step is very temperature dependent. Even if the halogen metal exchange reaction takes place at -78 °C, the reaction mixture must warm to –60 °C in order to obtain **1.19.** However heating above -40 °C must be avoided due to the 4-lithio species of furan equilibrating to the thermodynamically favored 5-lithio species leading to 5-substituted product **1.22** instead of the desired 4-substituted product **1.19 (Scheme 1.11)**.

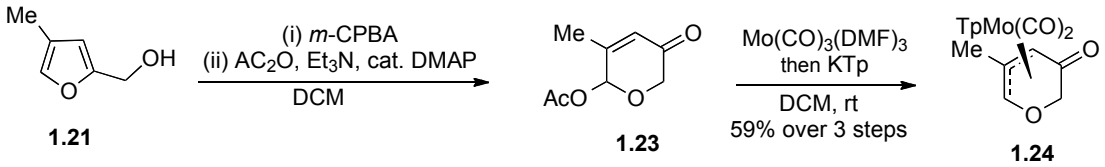


Scheme 1.11 Thermodynamic Equilibrium of Lithio Species

Deprotection of the diethyl acetal in **1.19** with 2 N HCl (aq) and subsequent reduction of the aldehyde **1.20** with $NaBH_4$ in methanol afforded **1.21** in 79%.

Synthesis of 3-Methyl-5-Oxo-Pyranyl Molybdenum scaffold

The reported synthetic route to the 3-methyl-5-oxo-pyranyl molybdenum scaffold **1.24** is based on Achmatowicz[49] ring expansion of 4-methyl furfuryl alcohol as shown in **Scheme 1.12**.



1.21 **1.23** **1.24**

Scheme 1.12 Achmatowicz Reaction Based Synthesis of 3-methyl Substituted Scaffold

In this three-step protocol, oxidation of furfuryl alcohol **1.21** with *m*-CPBA provided the 5-methyl-6-hydroxypyranone intermediate, which, was cooled down to –20 ^{o}C and filtered to remove the precipitated 3-chlorobenzoic acid by-product. The filtrate was then used directly in the acetylation step and the acetylated crude reaction mixture **1.23** was passed through a pad of silica gel before it was used in the metalation step. Metalation of the allylic acetate **1.23** with $Mo(CO)_3(DMF)_3$ followed by ligand exchange with potassium hydridotris(1-pyrazolyl)borate (KTp) provided a crude reaction mixture. A single chromatographic purification followed by trituration with ether provided the racemic scaffold **1.24** in 59% yield over three steps.

Conclusion

In summary, 4-methyl furfuryl alcohol **1.21** was prepared from furfural in 6 steps and it underwent Achmatowicz oxidative ring expansion when treated *m*-CPBA. Acetylation under standard acetylation conditions followed by metalation of the acetate with $Mo(DMF)_3(CO)_3$ and subsequent ligand exchange with KTp afforded the racemic 3-methyl-5-oxopyranyl scaffold **1.24**.

Experimental

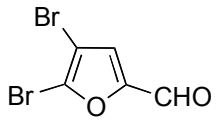
General Methods

Unless otherwise specified, all reactions were carried out under a positive pressure of argon using flame-dried, argon purged glassware. Solvents were dried over activated 4 Å molecular sieves or dispensed directly from a Seca Solvent System purchased from Glass Contour. Thin-layer chromatography (TLC) was performed using commercial Merck KGaA aluminum-supported silica gel plates with fluorescent indicator (F-254). Visualization was accomplished using UV light, 5 % phosphomolybdic acid in ethanol, or $KMnO_4$ (aq). Flash column chromatography was carried out using 32-63 μm silica gel, with compressed air as a source of pressure. All reagents were used as received from Sigma-Aldrich, with the exception of furfural, which was distilled prior to use.

^1H and ^{13}C NMR spectra were recorded on a Varian INOVA (400 MHz ^1H, 100 MHz ^{13}C) instrument in $CDCl_3$, with $CHCl_3$ as an internal reference (7.27 ppm for ^1H and 77.23 ppm for ^{13}C). Infrared spectra were recorded on a Nicolet™ 380 FT-IR spectrometer, equipped with a diamond plate. Peaks are reported with the following relative intensities: s (strong, 65-100 %), m (medium, 40-65 %), w (weak, 20-40 %), br

(broad). *Since nearly all of the Tp molybdenum complexes decompose over 180-200 °C, melting points are not significant and are not shown in the experimental section for these compounds.*

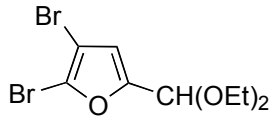
4,5-Dibromofuran-2-carbaldehyde, 1.16[48]



1.16

Freshly distilled furfural **1.15** (15.0 g, 156.0 mmol, 1.0 equiv) was added *via* syringe pump to aluminum chloride (46.0 g, 346.0 mmol, 2.2 equiv) at 0 °C under argon over a period of 2 hr. Bromine (50.5 g, 315.0 mmol, 2.01 equiv) was then added to the reaction mixture *via* syringe over a 2 hrs period. Stirring was then discontinued and the reaction mixture was allowed to stand overnight at room temperature. The reaction mixture was cooled to 0 °C and ice was added until gas formation ceased followed by dilution with diethyl ether. The organic layer was separated, the aqueous layer was then extracted with diethyl ether (2 x 40 mL), and the organic layers were combined, dried over Na_2SO_4, filtered and concentrated. The crude reddish residue was purified by flash chromatography over silica gel with hexanes-EtOAc (9:1) to give 4,5-dibromofural **1.16** (23.8 g, 93.7 mmol, 60 %) as a yellow solid. TLC: R_f = 0.40 (hexanes-EtOAc = 9:1). MP = 34-35 °C [Lit[48] = 36-37 °C]. IR (neat, cm^{-1}): 3123 (w), 2412 (w), 1690 (s), 1592 (s), 1497 (s). ^1H NMR (400 MHz, $CDCl_3$) δ: 9.52 (s, 1H), 7.22 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 176.0, 154.9, 126.2, 125.0, 104.9.

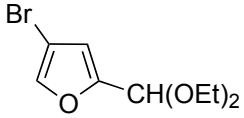
4,5-Dibromo-2-(diethoxymethyl)-furan, 1.17[48]



1.17

Triethyl orthoformate (23.2 g, 157.4 mmol, 4.0 equiv) and ammonium nitrate (0.40 g, 5.0 mmol, 0.13 equiv) were added to a stirred solution of aldehyde **1.16** (10.0 g, 39. 4 mmol, 1.0 equiv) in ethanol (100 mL) and refluxed for 16 hrs under argon. The solution was cooled to room temperature, concentrated *in vacuo* and the residue was dissolved in diethyl ether (50 mL). The mixture was transferred into a separatory funnel containing ether (50 mL) and water (50 mL). The layers were separated and the organic layer was washed with ether (2 x 25 mL). The organic phases were combined, washed with brine, dried over Na_2SO_4 and concentrated. The crude residue was further purified by flash chromatography over silica gel with hexanes-EtOAc (9:1) to afford **1.17** (10.4 g, 31.7 mmol, 80 %). TLC: R_f = 0.62 (Hexanes-EtOAc = 9:1). IR (neat, cm^{-1}): 2993 (m), 2960 (m), 1515 (w), 1304 (w), 1050 (s). ^1H NMR (400 MHz, $CDCl_3$): δ 6.52 (s, 1H), 5.48 (s, 1H) 3.62 -3.61 (m, 4H) 1.26 (t, *J* = 7.4 Hz, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.7, 122.1, 117.0, 105.9, 103.6, 63.3, 16.9.

4-bromo-2-(diethoxymethyl)-furan, 1.18[48]

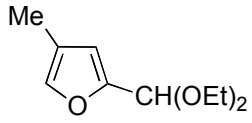


1.18

To a stirred solution of compound **1.17** (8.5 g, 25.8 mmol, 1.0 equiv) in dry ether (50 mL) was added a solution of *n*-BuLi (2.0 M in hexanes, 12.9 mL, 25.8 mmol, 1.0

equiv) *via* syringe pump at -78 °C. The solution was stirred for 2 hr and then quenched with water and acidified to a pH of 5.0 with 5% HCl (aq). The ether layer was separated, dried over Na_2SO_4 and concentrated. The crude residue was purified by flash chromatography over silica gel with hexanes-EtOAc (9:1) to afford **1.18** (4.9 g, 19.7 mmol, 77 %). TLC: R_f = 0.53 (hexanes-EtOAc = 9:1). IR (neat, cm^{-1}): 2976 (m), 2930 (m), 1513 (w), 1304.7 (w), 1050 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (s, 1H), 6.50 (s, 1H), 5.49 (s, 1H), 3.62-3.61 (m, 4H), 1.26 (t, *J* = 7.2, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 157.9, 141.1, 115.0, 105.7, 104.2, 63.3, 16.9.

2-(diethoxymethyl)-4-methylfuran, 1.19[48]

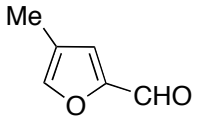


1.19

A solution of *n*-BuLi (2 M in hexanes, 7.5 mL, 15.0 mmol, 1.0 equiv) was added dropwise at -78 °C to compound **1.18** (3.74 g, 15.0 mmol, 1.0 equiv) in dry THF (60 mL). After stirring for 1 hr, MeI (8.6 g, 60.0 mmol, 4 equiv) in dry THF (2 mL) was added dropwise to the mixture. The solution was allowed to warm slowly warm to -60 °C and stirred for 4 hr. The reaction mixture was diluted with ether (50 mL), quenched with saturated solution of NH_4Cl. The layers were separated and the aqueous layer was extracted with diethyl ether (2 x 10 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo.* The product was purified by flash chromatography over silica gel with hexane-EtOAc (9:1) to give **1.19** (1.71 g, 9.2 mmol, 62 %) as yellow oil. TLC: R*f* = 0.65 (hexanes-EtOAc = 9:1). IR (neat, cm^{-1}): 2976 (m), 2930 (m), 1551 (m), 1465 (m), 1156.7 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.43 (s,

1H), 6.50 (s, 1H), 5.49 (s, 1H), 3.62-3.61 (m, 4H), 2.05 (s, 3H), 1.26 (t, J = 8.1, 6H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.7, 141.1, 115.0, 105.9, 63.3, 16.9.

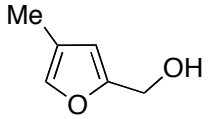
4-methylfuran-2-carbaldehyde 1.20[48]



1.20

Compound **1.19** (8.0 g, 43.2 mmol, 1.0 equiv) was added to HCl (aq) (2N, 40 mL) solution at room temperature and allowed to stir for 15 minutes. The reaction mixture was diluted with diethyl ether (50 mL) and the layers were separated. The aqueous layer was extracted with diethyl ether (2 x 10 mL) and the combined organic phases were washed with sat. $NaHCO_3$ (aq) (2 x 10 mL) followed by brine (10 mL), dried over Na_2SO_4, concentrated *in vacuo* and purified by flash chromatography (10% EtOAc-hexanes) to yield **1.20** (3.9 g, 35.5 mmol, 82 %). TLC: R*f* = 0.55 (hexanes-EtOAc = 9:1). IR (neat, cm^{-1}): 2974 (m), 2930 (m), 1667 (s), 1556 (m), 1472 (m), 1017.7 (w). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.55 (s, 1H), 7.44 (s, 1H), 7.07 (s, 1H), 2.08 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 179.7, 152.1, 141.0, 121.5, 119.9, 9.7.

(4-methylfuran-2-yl) methanol, 1.21

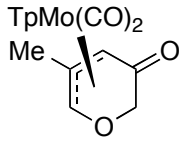


1.21

To a stirred solution of **1.20** (1.3 g, 11.8 mmol, 1.0 equiv) in methanol (10 mL) at 0 ^{o}C was added $NaBH_4$ (0.44 g, 11.8 mmol, 1.0 equiv). The reaction mixture was stirred for 2 hrs at 0 ^{o}C and quenched with water. The mixture was transferred into a separatory

funnel equipped with EtOAc (50 mL) and water (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (2 x 15 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and purification by flash chromatography (10% EtOAc-hexanes) afforded **1.21** (1.01 g, 9.3 mmol, 79 %). TLC: R*f* = 0.45 (hexanes-EtOAc = 9:1). IR (neat, cm^{-1}): 2976 (m), 2930 (m), 1513 (w), 1305 (w), 1050 (s). ^1H NMR (400 MHz, $CDCl_3$): δ 7.15 (s, 1H), 6.18 (s, 1H), 4.55 (s, 2H), 1.99 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.2, 140.0, 120.6, 111.9, 59.3, 9.9.

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(η-2,3,4)-3-methyl-5-oxo-5,6-dihydro-2*H*-pyran-2-yl]molybdenum, (±)-1.24



1.24

(4-methylfuran-2-yl)methanol (0.65 g, 5.8 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (10 mL) and cooled to 0 ^oC. Then, 77% *m*-CPBA (1.57 g, 7.0 mmol, 1.2 equiv) was added in two portions to keep the temperature below 5 ^oC. After 30 minutes, a white precipitate appeared, and the mixture was stirred at room temperature for 3 hours. The white precipitate was filtered, and the filtrate was transferred into a 100 mL round bottom flask. After cooling to 0 ^oC, 4-Dimethylaminopyridine (DMAP) (0.22 g, 1.8 mmol, 0.3 equiv), triethylamine (0.88 g, 8.7 mmol, 1.5 equiv), and Ac_2O (0.89 g, 8.7 mmol, 1.5 equiv) were added in succession. The mixture was stirred at 0 ^oC for 15 minutes, and then warmed to room temperature for 30 minutes. The mixture was washed with brine, dried over Na_2SO_4, and degassed for 20 minutes with dry argon. This solution was added *via* syringe to a solution of $Mo(CO)_3(DMF)_3$ (2.8 g, 7.0 mmol, 1.2 equiv) in 12 mL dry,

degassed CH_2Cl_2 in a Schlenk flask under dry argon. After stirring for 3 hrs, potassium hydridotris(1-pyrazolyl)borate (KTp) (1.9 g, 7.6 mmol, 1.3 equiv) was added to the solution in one portion, and stirring was continued for 1 hr. The reaction mixture was filtered through a short plug of silica, eluting with ethyl acetate. Purification by flash chromatography on silica gel eluting with EtOAc/hexane (1:2) and subsequent trituration with diethyl ether afforded the pure molybdenum complex **1.15** (1.64 g, 59% over 3 steps) as an orange solid. TLC: R_f = 0.30 (hexanes-EtOAc = 2:1). IR (neat, cm^{-1}): 2487 (w), 2158 (w), 1963 (s), 1876 (s), 1653 (m), 1504 (w), 1407 (m), 1050 (m). ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 1.6 Hz, 1H), 7.90 (d, *J* = 2.0 Hz, 1H), 7.88 (d, *J* = 2.0 Hz, 1H), 7.63 (d, *J* = 2.4 Hz, 1H), 7.61 (d, *J* = 2.4 Hz, 1H), 7.44 (d, *J* = 2.0 Hz, 1H), 7.09 (d, *J* = 2 Hz, 1H), 6.24 (t, *J* = 2.0 Hz, 1H), 6.20-6.18 (m, 2H), 4.58 (d, *J* = 2.0 Hz, 1H), 3.51 (d, *J* = 18 Hz, 1H), 3.39 (d, *J* = 18 Hz, 1H), 1.41 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 223.9, 222.0, 194.9, 147.1, 143.1, 142.8, 137.2, 136.9, 134.9, 108.6, 106.3, 106.2, 105.9, 72.3, 68.7, 65.8, 16.4. HRMS (ESI): calcd for $C_{17}H_{18}BMoN_6O_4$ ($[M + H]^+$): 479.0531. Found: 479.0528.

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Chapter Two

Nucleophilic Functionalization of $TpMo(CO)_2(\eta^3$-pyranyl) Complexes

Background

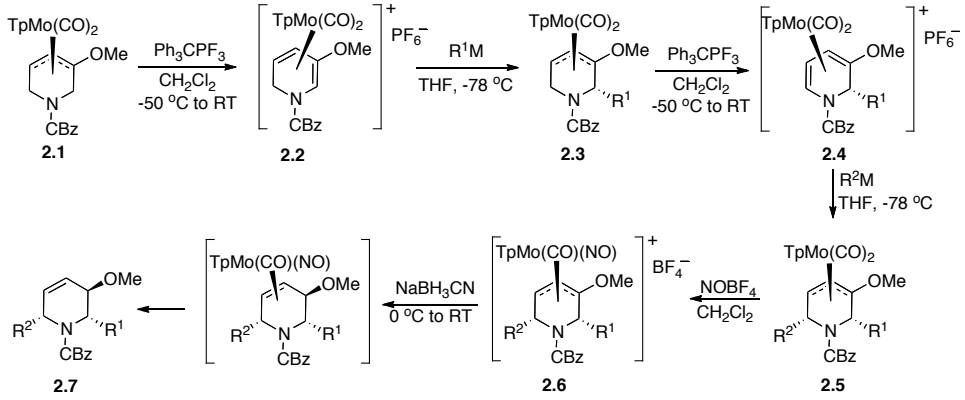
Enantiomerically pure, air- and moisture-stable $TpMo(CO)_2(\eta^3$-pyranyl) and $TpMo(CO)_2(\eta^3$-pyridinyl) complexes are powerful tools for the enantiocontrolled construction of complex heterocycles. Since 1999, the Liebeskind laboratory has synthesized a number of structurally diverse molecules using molybdenum-mediated transformations. Until recent discoveries by the Liebeskind laboratory,[1,2] in most of these enantiocontrolled transformations, neutral $TpMo(CO)_2(\eta^3$-pyranyl) and $TpMo(CO)_2(\eta^3$-pyridinyl) complexes are stable 18-electron species and unreactive toward direct nucleophilic addition. This chapter discusses approaches to nucleophilic functionalization of η^3-allylmoybdenum complexes.

Nucleophilic Functionalization of Cationic Molybdenum Complexes

Traditionally, neutral η^3-allylmolybdenum complexes bearing $TpMo(CO)_2$ auxiliaries do not engage in direct nucleophilic functionalization. However, activation of the η^3-allylmoybdenum complexes to a highly electrophilic complex either by transforming into a cationic η^4-diene molybdenum complex or by $CO \rightarrow NO^+$ exchange to generate cationic η^3-allylmolybdenum complex allows for nucleophilic functionalization of η^3-allylmoybdenum complexes.

Both modes of activation of η^3-allylmolybdenum complexes bearing TpMo(CO) can be demonstrated by the synthesis of 2,3,6-trisubstituted piperidine rings *via* sequential nucleophilic functionalization **Scheme 2.1**.[1] Hydride abstraction from molybdenum complex **2.1** gave a cationic η^4-diene molybdenum species **2.2**, which underwent nucleophilic addition when treated with various nucleophiles. Further

functionalization of the scaffold was achieved by converting compound **2.3** into the corresponding cationic diene **2.4** followed by addition of nucleophiles.



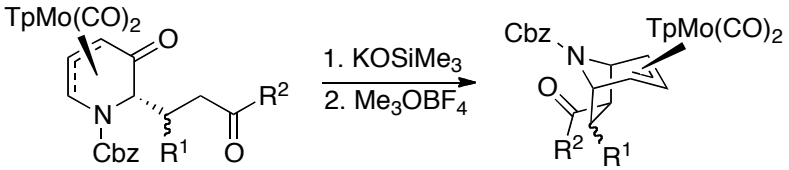
Scheme 2.1 Nucleophilic Functionalization of Cationic Molybdenum Complexes

Treatment of $TpMo(CO)_2$(dihydropyridinyl) complex **2.5** with nitrosonium tetrafluoro-borate generated a cationic TpMo(CO)(NO)(η^3-allyl) complex **2.6** that underwent nucleophilic attack with $NaBH_3CN$ followed by spontaneous demetalation to generate a 2,3,6-trisubstituted piperidine ring **2.7**.

Direct Nucleophilic Functionalization of η^3-Allylmolybdenum Complexes

Recent discoveries by the Liebeskind lab provide a new reaction path for the direct nucleophilic functionalization of a neutral 5-oxo-η^3-pyranyl and 5-oxo-η^3-pyridinyl complexes.

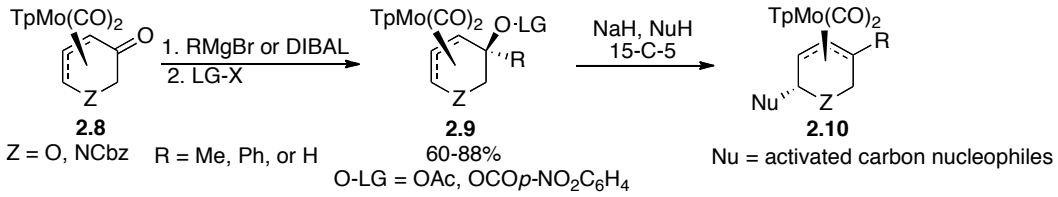
For example, the development of the "1,5-Michael-like" reaction not only served as a novel route for direct nucleophilic functionalization of η^3-allylmolybdenum complexes by an internal enolate without the necessity of converting them into cationic complexes but also proved to be a powerful tool to access oxo- and aza[3.2.1] and [4.3.1]bicyclics in high enantiomeric excess.[2]



Scheme 2.2 "1.,5-Michael-like" Reaction

This novel, non-cationic direct nucleophilic functionalization was explained by a combination of steric and electronic effects that strongly favor octahedral coordination in $TpMo(CO)_2$ over higher coordination numbers.[3] In addition, it could be explained by the presence the two terminal CO ligands and η^2-enone ligand to act as π-back bonding ligands and stabilize the anionic $TpMo(CO)_2$ intermediate generated during the nucleophilic addition. The scope of this novel reaction was expanded to include oxygen nucleophiles.[4]

In addition to the "1,5-Michael-like" reaction, Liebeskind's laboratory also reported the first examples of a "homo-S_N2'-like" intermolecular direct nucleophilic functionalization of charge neutral η^3-allylmoybdenum complexes.[5]

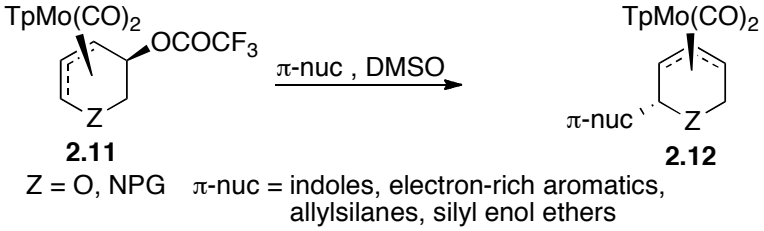


Scheme 2.3 "Homo-S_N2'-like" reaction

In this novel reaction, addition of stabilized anionic carbon nucleophiles to enantiopure charge neutral $TpMo(CO)_2(\eta^3$-allyl) complexes that are less activated than the 5-oxo-η^3-pyranyl and 5-oxo-η^3-pyridinyl complexes led to carbon-carbon bond formation enantiospecifically with *anti* stereoselectivity to the $TpMo(CO)_2$ moiety.[5] The application of this direct nucleophilic functionalization of charge neutral η^3-

allylmolybdenum complexes was demonstrated by an asymmetric synthesis of an antimalarial alkaloid (+)-isofebrifugine.[5-7]

Another interesting discovery in Liebeskind's laboratory for the direct nucleophilic functionalization of charge neutral η^3-allylmolybdenum complexes is the uncatalyzed Friedel-Crafts reaction. In these unpublished results by Dr. Wenyong Chen, addition of π-nucleophiles such as indoles, electron-rich aromatics, allylsilanes, and silyl enol ethers to the 5-trifluoroacetate substituted pyranyl/pyridinyl scaffold led to the formation of C-C bond in an enantiocontrolled manner.



Scheme 2.4 Uncatalyzed Friedel-Crafts reaction

Based on these precedents, Dr. Wenyong Chen proposed that similar nucleophilic addition reaction to a 3-substituted η^3-allylmoylbdenum complexes would provide a 2,3-disubstituted scaffold that could be further functionalized and demetalated to provide a *cis*-2,3-disubstituted heterocyclic motif with a quaternary center at a ring junction. Dr. Chen noted that *aspidosperma* alkaloids **Figure 2.1** contain *cis*-2,3-disubstituted heterocyclic motif with a quaternary center at a ring junction.

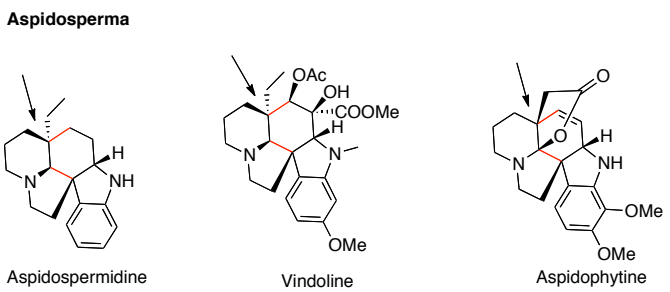
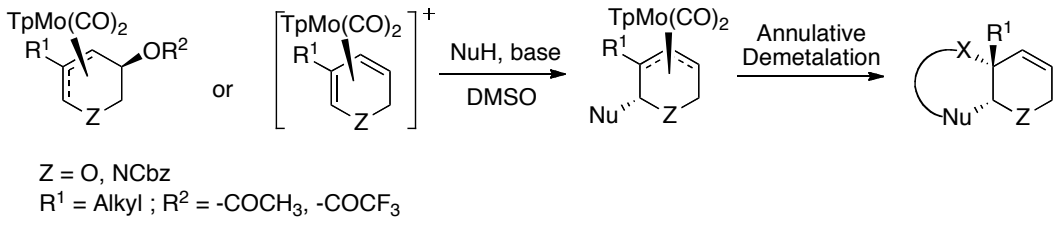


Figure 2.1 *Aspidosperma* Alkaloids

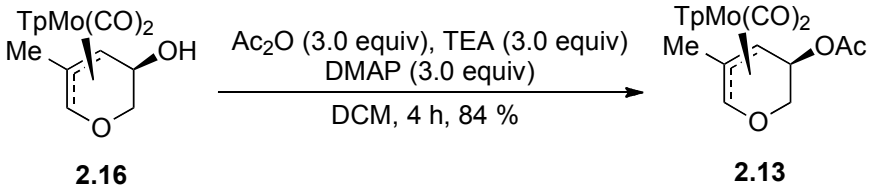
Therefore, as shown in **Scheme 2.5**, nucleophilic functionalization of 3-substituted η^3-allylmolybdenum complexes and subsequent annulative demetalation[5] would provide access to aspidosperma and structurally related alkaloids. As a model study nucleophilic addition to 3-methyl-5-oxo-pyranyl η^3-allylmolybdenum complexes was investigated and the results are reported here. Further functionalization and demetalation of the nucleophilic addition product to generate a *cis*-2,3-disubstituted heterocyclic motif with a quaternary center at a ring junction will be discussed in Chapter 3.



Scheme 2.5 Nucleophilic Addition and Annulative Demetalation Overview

Results and discussion

The introduction of nucleophiles to the 3-methyl-substituted scaffold was first investigated with complex **2.13,** which was available according to a known acetylation procedure[5] (**Scheme 2.6)**.

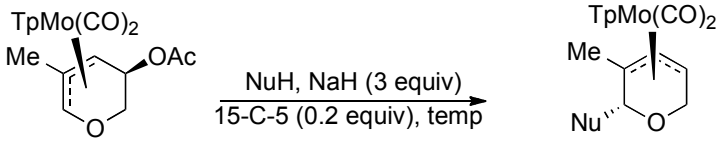


2.16 **2.13**

Scheme 2.6 Preparation of the 5-Acyl Substrate

Different carbon nucleophiles were studied to investigate the reactivity of the 3-methyl substituted molybdenum complex in a "Homo-S_N2'-like" reaction.

Table **2.1** indicates that the "Homo-S_N2'-like" nucleophilic functionalization attempts on η^3-allylmolybdenum complex **2.13** failed to provide the desired substitution product **2.14** when using different stabilized nucleophiles. Entries **1**,**3**, and **5** represent similar reaction conditions to the previously optimized conditions developed by Dr. Wenyong Chen,[5] a former group member in Liebeskind laboratory. These reaction conditions led to the recovery of starting material. Entries **4** and **6** indicate that increasing the reaction temperature led to the formation of traces of the desired product and decomposition of the starting material.

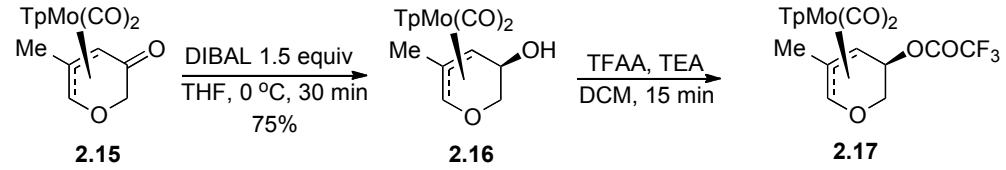


2.13 **2.14**

entry	NuH	solvent	temp (^oC)	**2.14** (%)
1	$CH_2(COOMe)_2$	THF	rt	0
2	$CH_2(COOMe)_2$	THF	60	0
3	$CH_3COCH_2CO_2Me$	ACN	rt	0
4	$CH_3COCH_2CO_2Me$	ACN	60	traces
5	CH_3NO_2	DMSO	rt	0
6	CH_3NO_2	DMSO	60	traces

Table 2.1 Study on "homo-S_N2'-like" reaction

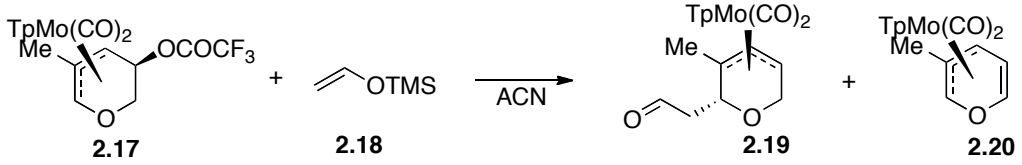
Next, nucleophilic functionalization of η^3-allylmolybdenum complex **2.17** by an uncatalyzed Friedel-Crafts reaction was investigated. The substrate **2.17** for the uncatalyzed Friedel-Crafts reaction was prepared from η^3-allylmolybdenum complex **2.15** by DIBAL reduction followed by treatment of alcohol **2.16** with TFAA in the presence of triethylamine. Complex **2.17** was passed through a pad of silica gel and used immediately to avoid decomposition.



2.15 **2.16** **2.17**

Scheme 2.7 Preparation of 5-Fluoroacetate Substrate for Uncatalyzed Friedel-Crafts Reaction

When the trifluoroacetate **2.17** was dissolved in acetonitrile (ACN) and treated with five equivalents of commercially available silyl enol ether **2.18** the desired product **2.19** was formed along with an elimination product **2.20**.



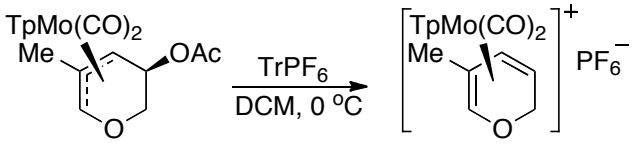
2.17 **2.18** **2.19** **2.20**

entry	temp (°C)	**2.19**	**2.20**
1	rt	39%	52%
2	0	55%	34%
3	-20	61%	29%

Table 2.2 Study on Uncatalyzed Friedel-Crafts Reaction

When submitting complex **2.17** to the Friedel-Crafts condition at lower temperature, the yield of the desired complex was improved and the formation of the undesired elimination product was suppressed (**Table 2.2)**. Further manipulation of **2.17** will be discussed in Chapter 3.

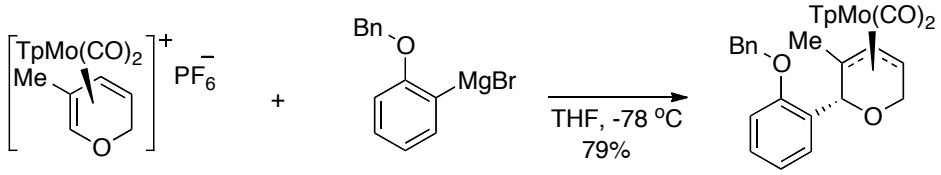
The nucleophilic functionalization of the 3-methyl substituted scaffold with a functionalized Grignard reagent was investigated next. The required molybdenum complex **2.21** for the Grignard addition was prepared by converting the neutral η^3-allylmolybdenum complex **2.13** into a cationic η^4-diene complex **2.21** as shown in **Scheme 2.8**.



2.13 **2.21**

Scheme 2.8 Preparation of Cationic Molybdenum Complex

Treatment of complex **2.13** with solid Ph_3CPF_6 at 0 °C followed by addition of methyl *tert*-butyl ether precipitated a brown solid molybdenum complex. After trituration of the brown solid with *tert*-butyl methyl ether, the disappearance of the C=O IR stretch at 1728 cm^{-1} and the shift from 1946 cm^{-1} and 1855 cm^{-1} to 2034 cm^{-1} and 1938 cm^{-1} confirmed the formation of the cationic diene complex **2.21**. The Grignard reagent was prepared by addition of a commercially available 2-benzyloxybromobenzene to a flask containing magnesium turnings in THF.[8]

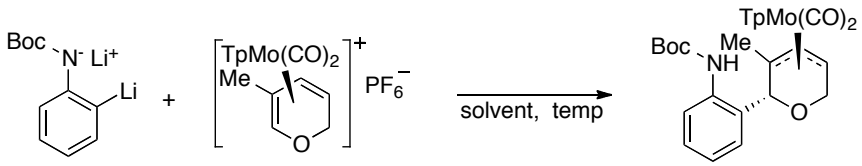


2.21 **2.23** **2.24**

Scheme 2.9 Study on Addition of Grignard Reagent to Cationic Molybdenum Complex

Drop wise addition of Grignard reagent **2.23** to the cationic diene **2.21** at -78 °C gave the desired nucleophilic addition product in good yield **(Scheme 2.9)**. Deprotection of **2.24** and subsequent annulative demetalation will be discussed in Chapter 3.

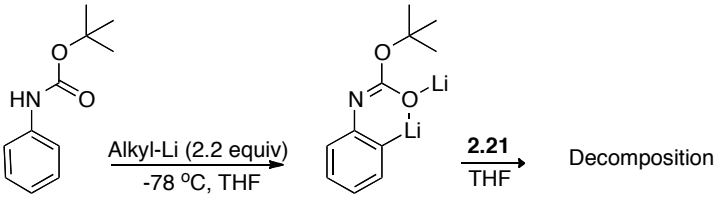
Next the nucleophilic functionalization of η^3-allylmolybdenum complexes with *bis*-lithiated aniline derivative as a nucleophile was investigated (**Scheme 2.10**).



2.25 **2.21** **2.26**

Scheme 2.10 Study on Lithiate Addition to Cationic Molybdenum Complex

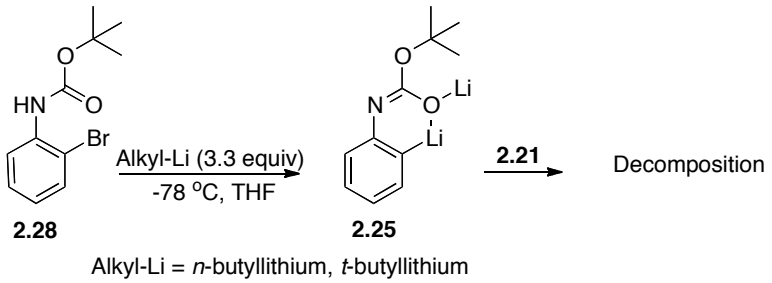
In order to prepare the nucleophilic *bis*-lithiated *N*-*t*-Boc-aniline **2.25**, different conditions were studied. First, attempts were made to directly *ortho*-lithiate *N*-*t*-Boc-aniline.[9] When compound **2.27** was treated with alkyllithium reagents followed by quenching with the electrophilic molybdenum complex **2.21** a complete decomposition was observed (**Scheme 2.11**).



Scheme 2.11 Study on Directed Ortho-Lithiation

A control experiment performed by quenching the reaction mixture with methyl iodide showed the formation of *tert*-butyl *O*-tolylcarbamate and the starting material was recovered in 65%. This may be due to the incomplete the transformation of **2.27** to **2.25** than the addition of **2.25** to the electrophilic species. Therefore, halogen-metal exchange was considered as an alternative to the formation of **2.25**.

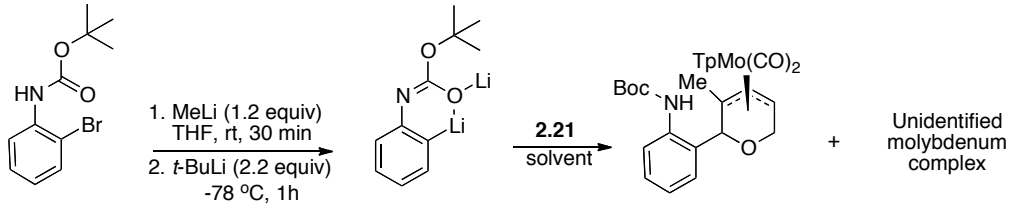
Second, lithium-halogen exchange was investigated for the preparation of the *bis*-lithiated *N*-*t*-Boc-aniline.[9,10] Treatment of compound **2.28** with either *n*-butyllithium or *t*-butyllithium followed by quenching with molybdenum complex **2.21** failed to give the desired product. This may be caused by the faster lithium-halogen exchange with *n*-butyllithium or *t*-butyllithium than deprotonation of the Boc-protected amine, resulting in proton transfer.[11] Therefore, deprotonation of the Boc-protected amine with another base before addition of *n*-butyllithium or *t*-butyllithium was considered.



Scheme 2.12 Study on Lithium-halogen Exchange

Similarly, the preparation of the nucleophilic *bis*-lithiate by first abstraction of the -NH proton with MeLi followed by lithium-halogen exchange with either *n*-BuLi or *t*-BuLi and subsequent quenching with an electrophilic molybdenum complex in THF or THF/ether did not provide the desired product.[11] However, decomposition of the starting material was minimized and unidentified molybdenum complex was isolated (**Table 2.3**).

Based on unpublished results from Dr. Angus Lamar, a postdoctoral associate in the Liebeskind Laboratory, who noted that the addition of MeLi to the 5-position of 5-oxo-η^3-TzMo(CO)$_2$ complexes in dichloromethane occurs in good yield, the reaction was performed in dichloromethane (**entry 3**) and the desired product was obtained in 21% yield along with an unidentified molybdenum complex. Attempts to improve the yield by changing either the order of addition or the rate of addition were not successful.



entry	solvent	temp (°C)	**2.29**	**2.30**
1	THF	-78	0%	38%
2	THF/Ether	-78	0%	41%
3	DCM	-78	21%	33%

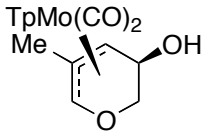
Table 2.3 Study on Alternative Lithium-Halogen Exchange Approach

Conclusions

In summary, model studies on the nucleophilic functionalization of charge neutral 3-methyl substituted scaffold under previously optimized "homo-S_N2'-like" reaction conditions were not successful. In contrast, the 3-methyl substituted scaffold underwent an uncatalyzed Friedel-Crafts-like reaction with silyl enol ether to form a 2,3-disubstituted η^3-allylmolybdenum complex. In addition, 2,3-disubstituted scaffolds were obtained in modest yields by addition of organometallic reagents to a cationic molybdenum complex.

Experimental

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(η-2,3,4)-3-methyl-5-*syn*-hydroxy-2,6-dihydro-2*H*-pyran]molybdenum, (±)-**2.16**

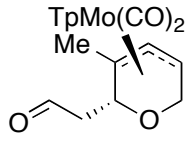


(±)-**2.16**

To a solution of 5-oxo-pyranyl scaffold (±)-**2.15** (1.00 g, 2.09 mmol, 1.0 equiv) in THF (35.0 mL) was added DIBAL (3.35 mL, 6.7 mmol, 1.5 equiv) at 0 ^oC. The reaction solution was stirred for 30 min at 0 ^oC then a sat. sodium potassium tartrate (aq) (35 mL) was added at ambient temperature and the solution was stirred for 30 min at ambient temperature. The solution was then transferred to a separatory funnel and the aqueous layer was extracted once with EtOAc (50 mL). The organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated. The crude residue was further purified by flash chromatography over silica gel with hexanes-EtOAc (1:1) to afford (±)-

2.16 (1.57 g, 3.35 mmol, 75 %) as a yellow solid. TLC: R_f = 0.59 (hexanes-EtOAc = 1:1). IR (neat, cm^{-1}): 3587 (w), 3139 (w), 2962 (w), 2492 (w), 1918 (s), 1808 (s), 1504 (m), 1408 (s), 1394 (m), 1302 (m), 1203 (s), 1120 (s), 1048 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (d, *J* = 2.0 Hz, 1H), 7.92 (d, *J* = 2.0 Hz, 1H), 7.83(d, *J* = 2.0 Hz, 1H), 7.59 (t, *J* = 2.4 Hz, 2H), 7.49 (d, *J* = 2.4 Hz, 1H), 6.66 (d, *J* = 2.4 Hz, 1H), 6.22 (t, *J* = 2.4 Hz, 2H) 6.20 (dt, *J* = 5.6, 2.0 Hz, 2H), 4.58-4.55 (m, 1H) 4.38 (t, *J* = 2.0 Hz) 3.58 (ddd, *J* = 10.8, 6.4 Hz, 1H), 2.51 (d, *J* = 10.4 Hz, 1H), 2.34 (t, *J* = 10.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 232.0, 222.9, 146.5, 142.7, 136.6, 134.5, 108.7, 106.0, 105.8, 105.5, 71.3, 68.3, 67.4, 66.1, 16.9. HRMS (ESI) Calcd for $C_{17}H_{17}O_4N_6BMoNa$ ($[M + 23]^+$): 501.0350. Found: 501.0351.

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(η-3,4,5)-2-(2-ethanal)-3-methyl-2,6-dihydro-2*H*-pyran]molybdenum. (±)-**2.19**

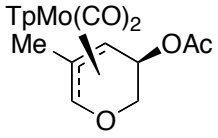


(±)-**2.19**

To a solution of 5-hydroxy pyranyl molybdenum complex, (±)-**2.16** (481 mg, 1.00 mmol, 1.0 equiv) in DCM (15.0 mL) was added Et_3N (0.16 mL, 1.20 mmol, 1.2 equiv) followed by TFAA (0.17 mL, 1.20 mmol, 1.2 equiv). The reaction solution was stirred for 15 min at ambient temperature before being passed through a small plug of silica using DCM as an eluent. The solution was collected and concentrated *in vacuo.* The crude oil was immediately dissolved in CH_3CN (15 mL). To the reaction solution was added trimethyl(vinyloxy)silane (0.15 mL, 2.00 mmol, 2.0 equiv). The reaction was stirred for 4 hrs at -20 ^{o}C before it was transferred to a separatory funnel containing sat.

$NaHCO_3$ (aq). The aqueous layer was separated and extracted with EtOAc (10 mL). The organic phase was washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated. The crude residue was further purified by flash (silica gel) chromatography column with hexanes-EtOAc (7:3) to afford (±)-**2.19** (308 mg, 0.61 mmol, 61 %) as a yellow solid. TLC: R_f = 0.60 (hexanes-EtOAc = 1:1). IR (cm^{-1}): 2470 (w), 1927 (s), 1845 (s), 1721 (m), 1406 (m), 1309 (m), 1205 (m), 1045 (s). ^1H NMR (400 MHz, $CDCl_3$): δ 9.75 (dd, *J* = 5.8, 1.6 Hz, 1H), 8.55 (d, *J* = 1.2 Hz, 1H), 7.73 (d, *J* = 1.3 Hz, 1H), 7.62 (d, *J* = 1.9 Hz, 2H), 7.59 (br s, 1H), 7.49 (d, *J* = 1.7 Hz, 1H), 6.24 (d, *J* = 2.0 Hz, 2H) 6.18 (t, *J* = 1.9 Hz, 1H), 4.49 (dd, *J* = 10.4, 3.6 Hz, 1H), 3.97 (d, *J* = 12.0 Hz, 1H), 3.93 (d, *J* = 7.2 Hz, 1H), 3.87-3.83 (m, 1H), 3.66 (dd, *J* = 12.3, 2.1 Hz, 1H), 2.94 (dd, *J* = 3.9, 1.5 Hz, 1H), 2.74-2.66 (m, 1H), 1.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 231.4, 226.8, 201.2, 146.9, 139.9, 136.9, 136.1, 134.4, 105.9, 105.5, 91.1, 71.9,70.8, 57.5, 57.19, 47.9, 29.9 22.9. HRMS (ESI) Calcd for $C_{19}H_{21}O_4N_6BMoNa$ ($[M + 23]^+$): 529.0663. Found: 529.0663.

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(η-2,3,4)-3-methyl-5-acetate-5,6-dihydro-2Hpyran-2-yl]molybdenum. (±)-**2.13.**

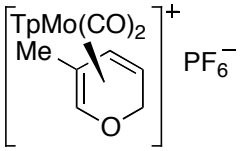


(±)-**2.13**

To a solution of 5-hydroxy pyranyl molybdenum complex (±)-**2.16** (721.5 mg, 1.50 mmol, 1.0 equiv) in DCM (15.0 mL) was added Et_3N (0.62 mL, 4.50 mmol, 3.0 equiv), DMAP (549 mg, 4.50 mmol, 3.0 equiv) followed by Ac_2O (0.62 mL, 4.50 mmol, 3 equiv). The reaction solution was refluxed for 4 hrs then quenched with sat. $NaHCO_3$

(aq) (15 mL). The aqueous layer was separated and extracted with additional DCM (10 mL). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated. The resulting residue was subjected to flash chromatography over silica gel with hexanes-EtOAc (3:1) to afford (±)-**2.13** (659 mg, 1.23 mmol, 84 %) as a yellow solid. TLC: R_f = 0.85 (hexanes-EtOAc = 1:1). IR (cm^{-1}): 2484 (w), 1940 (s), 1848 (s), 1725 (m), 1504 (m), 1407 (m), 1303 (m), 1121 (m), 1048 (m). ^1H NMR (400 MHz, $CDCl_3$): δ 8.42 (d, *J* = 1.8 Hz, 1H), 7.85 (d, *J* = 1.8 Hz, 1H), 7.81 (d, *J* = 1.8 Hz, 1H), 7.61 (d, *J* = 2.4 Hz, 1H), 7.59 (d, *J* = 2.4 Hz, 1H), 7.45 (d, *J* = 1.8 Hz, 1H), 6.71 (d, *J* = 2.4 Hz, 1H), 6.24 (t, *J* = 1.8 Hz, 1H), 6.22 (t, *J* = 1.8 Hz, 1H), 6.19 (t, *J* = 2.4 Hz, 1H), 5.57 (ddd, *J* = 9.9, 6.3, 3.0 Hz, 1H), 4.41 (t, *J* = 2.4 Hz, 1H), 3.57 (dd, *J* = 10.8, 6.6 Hz, 1H), 3.42 (dd, *J* = 7.6, 4.4 Hz, 1H), 2.67 (s, 1H), 2.50 (t, *J* = 10.8 Hz, 1H), 2.09 (s, 3H), 1.25 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 227.4, 223.7, 171.2, 146.4, 142.8, 142.6, 136.7, 136.5, 134.5, 108.9.2, 105.9, 105.8, 105.5, 69.7, 65.6, 63.9, 58.1, 21.2, 16.9. HRMS (ESI) Calcd for $C_{18}H_{19}O_5N_6BMoNa$ ($[M + 23]^+$): 545.0618. Found: 545.0615.

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(η-2,3,4,5)-3-methyl-2,6-dihydro-2*H*-pyran]molybdenum hexafluorophosphate.

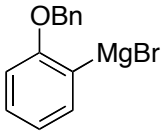


(±)-**2.15**

To a solution of 5-acetoxy pyranyl molybdenum complex (±)-**2.13** (247.5 mg, 0.46 mmol, 1.0 equiv) in DCM (8 mL) was added Ph_3CPF_6 (355.0 mg, 0.92 mmol, 2 equiv) at -20 °C. The reaction solution was allowed to slowly warm to room temperature over 2 hrs at which time FT-IR indicated the disappearance of CO stretch at 1725 cm^{-1}

and the shift of CO stretches at 1940, 1848 cm^{-1} shift to 2025, 1954 cm^{-1}, respectively. *Tert*-butyl methyl ether (10 mL) was added and the reaction mixture was stirred for 10 min at which time the solvent was removed *in vacuo.* The brown solid was triturated with *tert*-butyl methyl ether (2 x 10 mL) to yield the desired cationic molybdenum complex (±)-**2.15**. IR (cm^{-1}): 2480 (w), 2025 (s), 1954 (s), 1502 (m).

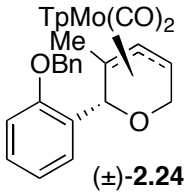
2-benzyloxy benzene magnesium bromide.



2.23

To a mixture of magnesium metal turnings (0.45 g, 18.5 mmol, 3.0 equiv) in THF (6.0 mL) was added 2-benzyloxybromobenzene (1.63 g, 6.19 mmol, 1.0 equiv). The reaction mixture was stirred at ambient temperature for approximately 2 hrs. *Reaction is complete when gas bubbling stops.* The solution was then transferred *via* cannula into a flamed dried, argon purged flask and the Grignard solution was titrated to 0.87 M according to a known literature procedure.[12]

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(η-3,4,5)-2-(2-benzyloxy-benzene)-3-methyl -2,6-dihydro-2*H*-pyran]molybdenum. (±)-**2.24.**

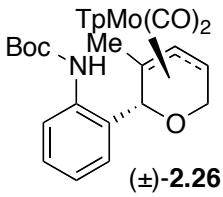


(±)-**2.24**

To a solution of molybdenum cation complex (±)-**2.15** (133.7 mg, 0.22 mmol, 1.0 equiv) in THF (4.0 mL, 0.05 M) was added 2-benzyloxybenzene magnesium bromide **2.23 (**0.87 M in THF, 0.49 mL, 0.43 mmol, 2.0 equiv) at -78 ^{o}C. The reaction solution

was stirred at -78 °C for 1 hr then quenched with sat. NH_4Cl (aq) (10 mL). The aqueous phase was extracted with EtOAc (4 mL). The combined organic phases were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated. The resulting residue was subjected to flash chromatography over silica gel with hexanes-EtOAc (2:1) to afford (±)-**2.24** (0.133 g, 0.211 mmol, 98 %) as a yellow solid. TLC: R_f = 0.75 (hexanes-EtOAc = 1:1). IR (cm^{-1}): 1944 (s), 1852 (s), 1504 (m), 1407 (m), 1307 (m). ^1H NMR (400 MHz, $CDCl_3$): 8.59 (br s, 1H), 7.74 (br s, 2H), 7.63 (d, *J* = 1.6 Hz, 1H), 7.61 (d, *J* = 1.6 Hz, 1H), 7.49-7.47 (m, 3H), 7.36 (t, *J* = 7.2 Hz, 2H), 7.29 (dt, *J* = 7.8, 1.6 Hz, 2H), 7.06-7.00 (m, 2H), 6.24-6.23 (m, 2H), 6.13 (t, *J* = 2.0 Hz, 1H), 5.71 (br s, 1H), 5.27-5.15 (m, 2H), 4.35-4.29 (m, 2H), 3.90-3.87(m, 2H), 3.66 (dd, *J* = 12.0, 2.0 Hz, 1H), 1.54 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 232.2, 227.0, 157.9, 147.0, 146.2, 139.6, 136.7, 136.0, 134.4, 129.4, 128.7, 127.8, 127.0, 120.7, 114.0, 105.8, 105.3, 70.8, 57.4, 56.9, 23.9.

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(η-3,4,5)-2-(2-*N*-(*tert*-butoxycarbonyl) benzene)-3-methyl-2,6-dihydro-2*H*-pyran]molybdenum (±)-**2.26**



(±)-**2.26**

Methyllithium 1.6 M in ether (0.075 mL, 0.12 mmol)) was added dropwise to 2-bromo-*N*-(*tert*-butoxycarbonyl)aniline (27.0 mg, 0.10 mmol) in ether (2 mL) at room temperature and stirred for 15 min. The reaction mixture was then cooled to -78 °C and *tert*-butyllithium 2.0 M in pentane (0.11 mL, 0.22 mmol) was added dropwise. The mixture was allowed to stir for 1 hr at -78 °C and transferred to a solution of molybdenum cation complex (±)-**2.15** (77 mg, 0.12 mmol) in DCM (2.0 mL) *via* cannula.

The reaction mixture was stirred at -78 ^{o}C for 30 min then quenched with sat. NH_4Cl (aq) (4 mL). The aqueous phase was extracted with EtOAc (4 mL). The combined organic phases were washed with brine (5 mL), dried over Na_2SO_4, filtered and concentrated. The resulting residue was subjected to flash chromatography over silica gel with hexanes-EtOAc (2:1). Further purification by chromatotron with hexane-EtOAc (9:1) was required to get (±)-**2.26** (16 mg, 0.024 mmol, 21 %) as a yellow solid. TLC: R_f = 0.75 (hexanes-EtOAc = 3:1). IR (cm^{-1}): 3402 (w), 3012 (w), 2471 (w), 1929 (s), 1841 (s), 1688 (s), 1406 (m), 1303 (m), 1215 (m), 1050 (s). ^{1}H NMR (400 MHz, $CDCl_3$): d 8.57 (br s, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.77-7.75 (m, 2H), 7.66-7.63 (m, 3H), 7.49 (br s, 1H), 7.33 (dt, *J* = 7.8, 1.6 Hz, 1H), 7.14 (dt, *J* = 7.8, 1.2 Hz, 1H), 7.01 (br s, 1H), 6.24 (br s, 2H), 6.15 (br s, 1H), 4.97 (s, 1H), 4.37 (d, *J* = 7.2 Hz, 1H), 3.81 (d, *J* = 7.2 Hz, 1H), 3.54 (br s, 1H), 3.50 (d, *J* = 1.2 Hz, 1H), 1.70 (s, 3H), 1.50 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 232.4, 227.2, 153.7, 146.9, 146.2, 139.6, 138.8, 137.0, 136.2, 134.5, 128.7, 127.8, 127.4, 123.5, 123.0, 105.8, 105.5, 90.8, 80.6, 72.8, 57.7, 56.9, 23.9. HRMS (ESI) Calcd for $C_{28}H_{32}O_5N_7BMoNa$ ($[M + 23]^+$): 678.1510. Found: 678.1519

References

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Chapter Three

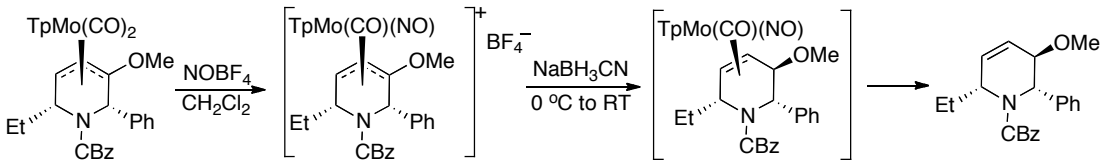
Quaternary Center Formation *via* Oxidative Annulative Demetalation Cascade

Background

Enantiomerically pure, air and moisture-stable π-allylmolybdenum complexes are powerful scaffolds for the enantiocontrolled construction of substituted heterocycles. During the enantiocontrolled construction of the substituted heterocycles, a single metal and its ligands influence novel reactions, control selectivities, and provide a dominant regio- and stereocontrol element over several steps. Once all the metal mediated transformations have occurred, mild and efficient demetalation of η^3-allymolybdenum complexes is a key step to convert the intermediate into useful organic compounds. Therefore, this chapter discusses different demetalation protocols used in converting molybdenum complexes into organic compounds.

Demetalation Approaches Involving Cationic Molybdenum Complexes

Faller reported that $[CpMo(CO)(NO)(\pi\text{-allyl})]^+$ can be obtained by replacement of one of the CO ligand in $CpMo(CO)_2(\pi\text{-allyl})$ with NO^+ using $NOBF_4$.[1] These activated cationic molybdenum complexes can undergo nucleophilic functionalization to give η^2-alkene complexes, which can be demetalated by oxidation to afford the corresponding olefins. This demetalation protocol was extended by the Liebeskind laboratory to analogous $TpMo(CO)_2(\pi\text{-allyl})$ complexes.[2-4]

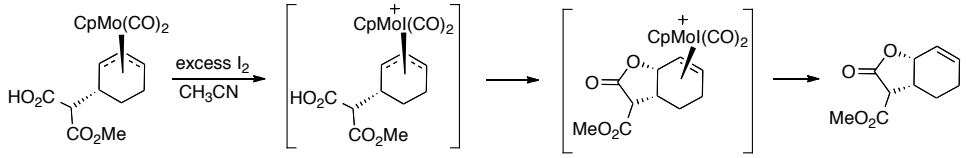


3.1 3.2 3.3

Scheme 3.1 Demetalation Protocol Using $NOBF_4$

For example, as shown in **Scheme 3.1**, treatment of a $TpMo(CO)_2(\eta^3$-allyl) complex **3.1** with nitrosonium tetrafluoroborate generates a cationic $TpMo(CO)(NO)(\eta^3$-allyl) complex **3.2** that is susceptible to nucleophilic attack. Reduction of this cationic intermediate with $NaBH_3CN$ provided the corresponding η^2-alkene complex that underwent spontaneous oxidative demetalation to provide a tri-substituted heterocyclic compound.

Another demetalation protocol that is conceptually related to $CO \rightarrow NO^+$ ligand exchange was reported by Pearson.[5,6] In Pearson's protocol, the cationic intermediate $CpMo(CO)_2(X)(\eta^3$-allyl) complex can be formed by treating $CpMo(CO)_2(\eta^3$-allyl) complexes with Iodine or bromine. The resulting cationic $CpMo(CO)_2(X)(\eta^3$-allyl) complexes undergo demetalation to form iodo- or bromo- alkenes. When the formation of the cationic $CpMo(CO)_2(X)(\eta^3$-allyl) complexes is combined with internal nucleophiles such as carboxylate or hydroxyl group, Pearson's demetalation protocol provides access to cyclization products with high regio- and enantiocontrol (**Scheme 3.2**).



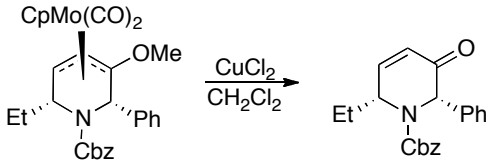
3.4 **3.5** **3.6** **3.7**

Scheme 3.2 Demetalation Protocol using I_2

Pearson explained the presence of the intermediates **3.5** and **3.6** by the gradual disappearance of $CpMo(CO)_2$ carbonyl band at ca. 1950 and 1860 cm^{-1} and the $-CO_2H$ carbonyl band at ca. 1730 cm^{-1} and the appearance of two new peaks at 2082 and 2050 cm^{-1} and then γ-lactone absorption at 1790 cm^{-1}. In the presence of iodine, intermediated **3.6** is oxidized and demetalated to give a bicyclic lactone **3.7**.[5,6]

Demetalation Approaches Involving Charge Neutral Molybdenum Complexes

In addition to the demetalation of cationic $CpMo(CO)_2(X)(\eta^3$- allyl) demetalation, Pearson also described a method for the direct oxidative demetalation of $CpMo(CO)_2(\eta^3$-allyl) complexes using ceric ammonium nitrate in buffered wet acetone.[5] This strategy has been extended by Liebeskind to cyclic $TpMo(CO)_2(\eta^3$-allyl) complexes with a methoxy group at a terminus of the π-allylic system **Scheme 3.3**.[7]

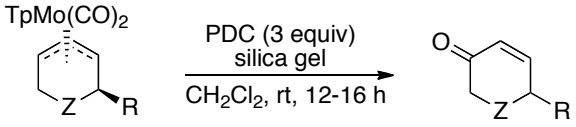


3.8 **3.9**

Scheme 3.3 Demetalation Protocol Using $CuCl_2$

In this extended methodology, oxidative demetalation of $TpMo(CO)_2(\eta^3$-allyl) complexes such as complex **3.8** with either cupric chloride or ceric ammonium nitrate provided the corresponding α,β-unsaturated ketone **3.9**.[7]

Liebeskind also reported a novel oxidative demetalation protocol for the formation of α,β-unsaturated ketones.[7] When various non-electron-deficient carbocyclic and heterocyclic η^3- allylmolybdenum complexes **3.10** were treated with pyridinium dichromate PDC/silica gel, demetalation occurred with the introduction of a carbonyl group at an allylic terminus of the π-system (**Scheme 3.4)**.[7]



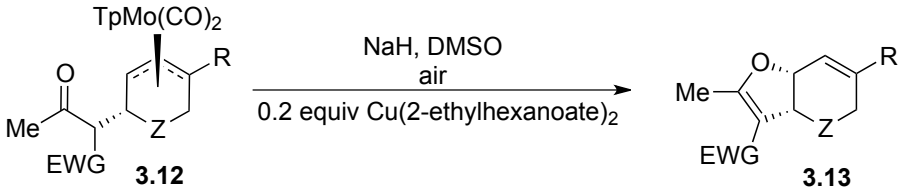
3.10 **3.11**

$Z=C(Me)_2$	R = H	73%
$Z=NCO_2Me$	R = H	70%
$Z=NCO_2Me$	R = Bn	73%
Z=O	R = Ph	75%

Table 3.1 Demetalation Protocol Using PDC/Silica

In contrast to non-electron deficient η^3-allylmolybdenum complexes, when electron deficient η^3-allylmolybdenum complexes were exposed to a similar PDC/silica gel demetalation protocol, β,γ-unsaturated lactones were obtained in good yield.[4]

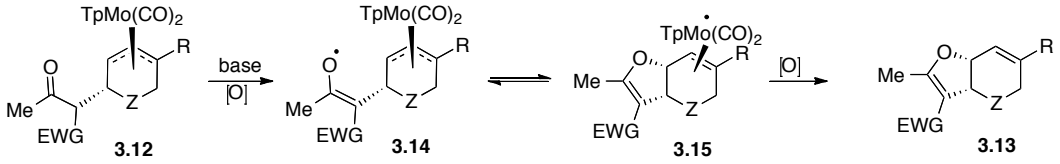
More recently, Liebeskind reported an annulative demetalation protocol of η^3-allylmolybdenum complexes. In this new protocol, treatment of a wide range of "homo-S_N2'-like" reaction products with NaH in DMSO in the presence of a catalytic amount of copper (II) 2-ethylhexanoate open to air provided the corresponding annulation products (**Table 3.1**).[8]



entry	Z	EWG	R	% yield
1	O	COOMe	Me	85
2	O	COOMe	H	83
3	O	COMe	H	92
4	NCbz	COOMe	H	83

Table 3.2 Annulative Demetalation with a Variety of Substrates

Mechanistically, this new annulative demetalation was suggested to proceed through one electron oxidation of the stabilized enolate to a radical that then reacts with the adjacent η^3-allylmolybdenum complexes (**Scheme 3.4**).[8]



Scheme 3.4 Possible Annulative Demetalation Pathway

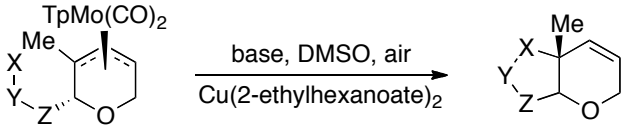
In addition to stabilized enolates, unpublished results in the Liebeskind laboratory indicate that other oxygen, nitrogen, and carbon nucleophiles can be employed in this

new annulative demetalation protocol. Furthermore, the scope was expanded to the formation of six membered rings.

Based on these precedents, a similar demetalation of the 2,3-di-substituted η^3-allylmolybdenum complexes was envisioned to generate a quaternary center at the ring junction of *cis*-fused bicyclic heterocycles. Here are the results for quaternary center generation *via* annulative demetalation.

Results and Discussion

To expand the scope of the oxidative demetalation and to generate a quaternary center at the ring junction of *cis*-fused bicyclic ring system, investigation of the use of nitrogen and oxygen nucleophiles were carried out (**Scheme 3.5**).



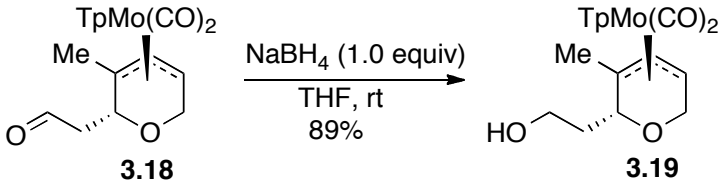
3.16
X = OH, NHR
Y= Z = sp^2C, sp^3C

3.17

Scheme 3.5 Annulative Demetalation Using Oxygen and Nitrogen Nucleophiles

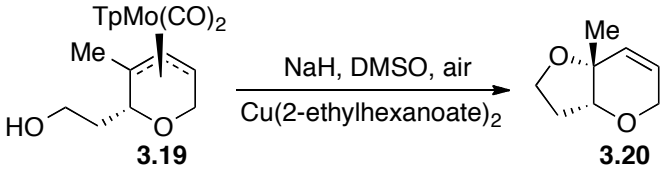
Dr. Wenyong Chen, a previous group member showed that not only an enolate but also an alkoxide would successfully engaged in nucleophilic, oxidative demetalation.[1] Based on this precedent, the η^3-allylmolybdenum complex **3.19**, which can be easily prepared from complex **3.18** by reduction with $NaBH_4$, was exposed to the demetalation conditions.

[1] Chen, W. Organometallic Enantiomeric Scaffolds in the synthesis of Alkaloids: I. Homo-S_N2'-like Reaction/ Annulative Demetallation and the Application in the Synthesis of (+)-Isofebrifugine II. Uncatalyzed Electrophilic C-C Bond Forming Reactions of Pyranyl and Pyridinyl Molybdenum Complexes. Ph.D. Dissertation, Emory University, Atlanta, 2011.



Scheme 3.6 Preparation of Precursor Alcohol for Demetalation

When complex **3.19** was treated with NaH in DMSO in the presence of 1.2 equivalents Cu (II) 2-ethylhexanoate open to air at 40 ^{o}C, the complex was demetalated with the formation of the desired quaternary center at the ring junction of the *cis*-fused bicyclic heterocyclic compound **3.20** in good yield.



entry	Cu(II) (equiv)	Temp (^{o}C)	Yield (%)
1	0.2	rt	sm
2	0.2	40	11
3	1.2	rt	43
4	1.2	40	76

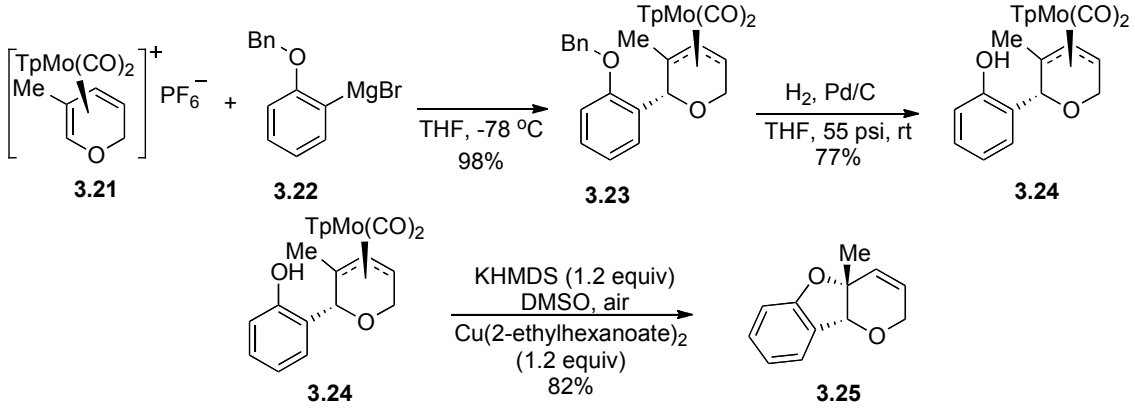
Table 3.3 Study on Demetalation Using an Internal Alkoxide Nucleophile

An attempt to demetalate complex **3.19** at room temperature was very sluggish even after 2 days. In addition, the use of catalytic amount of Cu (II) 2-ethylhexanoate proved to be unsuccessful.

Next, the annulative demetalation of η^3-allylmolybdenum complexes using a phenoxide as a nucleophile, which was first demonstrated by Liebeskind's laboratory group member Mr. John Wiseman, was extended to the formation of quaternary center at a ring junction.

As discussed in Chapter two, the intermediate **3.23** was prepared by addition of Grignard reagent **3.22** to complex **3.21**. The substrate (η^3-allyl) molybdenum complex

3.24 was prepared from **3.23** by hydrogenation over palladium-on-carbon to remove the benzyl-protecting group (**Scheme 3.7**).

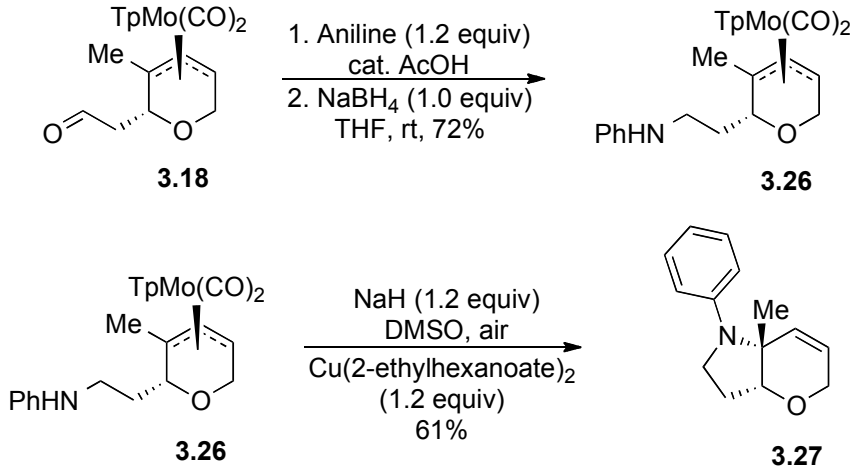


Scheme 3.7 Study on Annulative Demetalation Using Phenoxide as a Nucleophile

Treatment of complex **3.24** with potassium hexamethyldisilazide in DMSO open to dry air in the presence of Cu (II) 2-ethylhexanoate led to the formation to the tricyclic heterocyclic compound **3.25** with a quaternary center at the ring junction of the *cis*-fused rings. Unlike the annulative demetalation using an internal alkoxide as nucleophile as in complex **3.19** that required higher temperature, the annulative demetalation using a phenoxide as a nucleophile proceeded at room temperature in a better yield.

In addition to the above annulative demetalations that used oxygen nucleophile in the generation of a quaternary center, annulative demetalation with nitrogen nucleophiles were investigated.

The precursor complex **3.26** for the annulative demetalation was prepared by following a standard reductive amination protocol.[9] Aniline reacted with complex **3.18** in the presence of catalytic amount of glacial acetic acid to form compound **3.26** after reduction with $NaBH_4$ (**Scheme 3.7**).



Scheme 3.8 Study on Annulative Demetalation Using Nitrogen Nucleophile

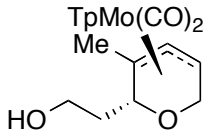
When compound **3.26** was treated with NaH in DMSO in the presence of Cu (II) 2-ethylhexanoate open to air, the desired demetalation product **3.27** was formed in good yield with a quaternary center at the ring junction.

Conclusions

In this chapter, we reported the use of annulative demetalation of η^3-allyl molybdenum complex to generate a quaternary center at the ring junction of a *cis*-fused - bicyclic ring. Annulative demetalations using internal oxygen nucleophiles provided the desired quaternary center at the ring junction. In addition, nitrogen nucleophile was able to participate in the generation of a quaternary center. Although not investigated here, future work may lead to the formation of quaternary center using internal carbon nucleophiles in annulative demetalation.

Experimental

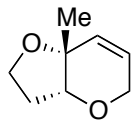
(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(η-3,4,5)-2-(2-ethanol)-3-methyl-2,6-dihydro-2*H*-pyran]molybdenum. (±)**-3.19.**



(±)-**3.19**

To a solution of (±)-**3.18** (126.5 mg, 0.25 mmol, 1.0 equiv) in THF (12 mL) was added $NaBH_4$ (10 mg, 0.27 mmol, 1.1 equiv) at 0 ^oC. The reaction mixture was stirred at room temperature for 2 hrs and then quenched with water. The mixture was transferred to a separatory funnel containing EtOAc (15 mL) and H_2O (8 mL). The phases were separated and the aqueous layer was extracted once with EtOAc (2 x 5 mL). The combined organic phases were washed with brine (10 mL), dried over Na_2SO_4, filtered and concentrated. The crude residue was further purified by flash chromatography over silica gel with hexanes-EtOAc (3:1) to afford (±)-**3.19** (113 mg, 0.22 mmol, 89 %) as a yellow solid. TLC: R_f = 0.52 (hexanes-EtOAc = 1:1). IR (cm^{-1}): 3485 (w), 2919 (w), 1925 (s), 1836 (s), 1405 (m), 1304 (m), 1217 (m). ^1H NMR (400 MHz, $CDCl_3$): 8.51 (s, 1H), 7.69 (br s, 1H), 7.60 (s, 2H), 7.58 (br s, 1H), 7.46 (d, *J* = 1.6 Hz, 1H), 6.21 (t, *J* = 1.8 Hz, 1H), 6.15 (s, 1H), 4.09-4.03 (m, 3H), 3.94 (d, *J* = 7.2 Hz, 1H), 3.82-3.78 (m, 3H), 3.67 (dd, *J* = 12.0, 2.0 Hz, 1H), 2.11-2.04 (m, 1H), 1.89-1.80 (m, 1H), 1.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 232.0, 227.4, 146.9, 146.2, 139.6, 136.8, 136.1, 134.5, 105.8, 105.7, 105.5, 95.0, 74.4, 72.3, 62.0, 57.8, 56.9, 35.1, 23.5. HRMS (ESI) Calcd for $C_{19}H_{23}O_4N_6BMo$ ($[M]^+$): 508.0923 Found: 508.0927.

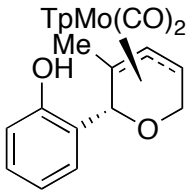
(±)-(3a*R*,7a*R*)-7a-Methyl-3,3a,5,7a-tetrahydro-2*H*-furo[3,2-*b*]pyran, (±)-3.20.



(±)-3.20

To a solution of (±)-**3.19** (67 mg, 0.13 mmol, 1.0 equiv) in DMSO (3.0 mL) was added NaH (60 % dispersion in oil, 6.4 mg, 0.16 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature for 15 min then Cu (II) 2-ethylhexanoate (56.5 mg, 0.16 mol, 1.2 equiv) was added and the reaction mixture was stirred at 40 ^{o}C for 20 hrs in dry air before it was transferred to a separatory funnel containing EtOAc (10 mL) and sat. $NaHCO_3$ (aq) (5 mL). The aqueous layer was separated and extracted with EtOAc (5 mL). The combined organic phases were washed with 3 M NH_3-H_2O (5 mL), dried over Na_2SO_4, filtered and concentrated. The resulting residue was subjected to flash chromatography over silica gel with hexanes-EtOAc (3:1) to afford (±)-**3.20** (14 mg, 0.10 mmol, 76 %) as colorless oil. TLC: R_f = 0.79 (hexanes-EtOAc = 2:1). IR (cm^{-1}): 2895 (s), 1597 (s), 1339 (m), 1154 (s), 1085 (s). ^{1}H NMR (400 MHz, $CDCl_3$): 5.97 (dd, *J* = 10.2, 1.8 Hz, 0.5 H), 5.94 (dd, *J* = 10.2, 1.6 Hz, 0.5 H), 5.58 (br d, *J* = 10.2 Hz, 1H), 4.18 (dd, *J* = 3.9, 1.6 Hz, 0.3H), 4.12 (dd, *J* = 3.9, 1.6 Hz, 0.7H), 3.85 (d, *J* = 5.4 Hz, 1H), 4.08-3.92 (m, 3H), 2.32-2.23 (m, 1H), 2.07-1.99 (m, 1H), 1.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 143.6, 135.2, 129.9, 129.2, 127.7, 127.6, 124.2, 75.9, 75.7, 64.0, 56.2, 56.1, 47.3, 31.7, 21.7. HRMS (ESI) Calcd for $C_8H_{13}O_2$ ([M + 1]$^+$): 140.0835. Found: 140.0840.

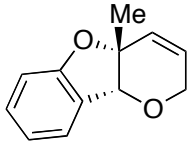
(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(η-3,4,5)-2-(2-hydroxyl-benzene)-2,6-dihydro-2*H*-pyran]molybdenum, (±)-**3.24.**



(±)-**2.24**

To a solution of (±)-**3**.**23** (120 mg, 0.18 mmol, 1.0 equiv) in THF (3.0 mL) was added 10 % Pd/C (3.6 mg, 20 % by weight). The mixture was shaken under a positive pressure of H_2 (55 psi) for 14 hrs, after which the mixture was filtered through packed celite to remove Pd/C and the solvent was evaporated. The resulting residue was subjected to flash chromatography over silica gel with hexanes-EtOAc (3:1) to afford (±)-**3**.**24** (80 mg, 0.14 mmol, 77 %) as a yellow solid. TLC: R_f = 0.49 (hexanes-EtOAc = 4:1). IR (cm^{-1}): 3302 (w), 2928 (w), 2178 (w), 1925 (s), 1836 (s), 1408 (m), 1309 (m), 1207 (m), 1125 (m), 1041 (m). ^{1}H NMR (400 MHz, $CDCl_3$): 8.59 (br s, 1H), 7.79 (br s, 1H), 7.67-7.64 (m, 4H), 7.49 (d, *J* = 1.5 Hz, 1H), 7.29-7.25 (m, 1H), 7.01 (dd, *J* = 7.5, 0.9 Hz, 1H), 6.96 (dd, *J* = 7.5, 1.2 Hz, 1H), 6.26 (br t, *J* = 1.8 Hz, 1H), 6.17 (br s, 1H), 6.06 (s, 1H), 5.14 (s, 1H), 4.37 (br d, *J* = 7.2 Hz, 1H), 3.83 (d, *J* = 6.6 Hz, 1H), 3.64 (br d, *J* = 12.3 Hz, 1H), 3.56 (dd, *J* = 12.1, 2.1 Hz, 1H), 1.81 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 232.1, 227.2, 157.0, 147.6, 142.1, 141.6, 136.4, 136.3, 134.7, 129.9, 128.8, 127.0, 119.8, 116.7, 106.3, 105.7, 70.4, 66.9, 66.5, 57.2, 56.9, 23.7. HRMS (ESI) Calcd for $C_{23}H_{23}O_4N_6BMoNa$ ($[M + 23]^+$): 579.0824. Found: 579.0819.

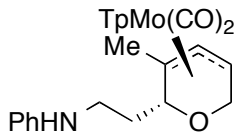
(±)-(4a*R*,9b*R*)-4a-Methyl-4a,9b-dihydro-2*H*-pyrano[3,2-*b*]benzofuran, (±)-3.25.



(±)-**3.25**

To a solution of (±)-**3.24** (68mg, 0.12 mmol, 1.0 equiv) in DMSO (3.0 mL, 0.05 M) was added KHMDS (0.14 mL, 0.14 mmol, 1M in THF, 1.2 equiv). The reaction mixture was stirred for 15 min then Cu (II) 2-ethylhexanoate (50 mg, 0.14 mol, 1.2 equiv) was added and the reaction mixture was stirred at room temperature in dry air for 10 hrs before it was transferred to a separatory funnel containing EtOAc (10 mL) and sat. $NaHCO_3$ (aq) (5 mL). The aqueous layer was separated and extracted with EtOAc (5 mL). The combined organic phases were washed with 3 M NH_3-H_2O, dried over Na_2SO_4, filtered and concentrated. The resulting residue was subjected to flash chromatography over silica gel with hexanes-EtOAc (3:1) to afford (±)-**3.20** (19 mg, 0.10 mmol, 82 %) as colorless oil. TLC: R_f= 0.82 (hexanes-EtOAc = 3:1). IR (cm^{-1}): 2905 (s), 1592 (s), 1339 (m), 1149 (s), 1085 (s). ^{1}H NMR (400 MHz, $CDCl_3$): 7.42 (d, *J* = 7.8 Hz, 1H), 7.25 (dt, *J* = 8.2, 1.2 Hz, 1H) 6.94 (dt, *J* = 7.6, 0.6 Hz, 1H), 6.83 (d, *J* = 8.2 Hz, 1H), 6.12-6.06 (m, 1H), 6.03-5.97 (m, 1H), 4.89 (s, 1H), 4.18 (dd, *J* = 3.9, 1.6 Hz, 0.3H), 4.12 (dd, *J* = 3.9, 1.6 Hz, 0.7H), 3.85 (d, *J* = 5.4 Hz, 1H), 1.42 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 159.3, 130.8, 129.6, 126.7, 126.2, 126.0, 120.9, 111.2, 81.7, 81.3, 61.8, 24.6. HRMS (ESI) Calcd for $C_{12}H_{12}O_2$ ($[M]^+$): 189.0910 Found: 189.0906.

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(η-3,4,5)-2-(2-aniline-ethyl)-3-methyl-2,6-dihydro-2*H*-pyran]molybdenum, (±)-**3.26.**

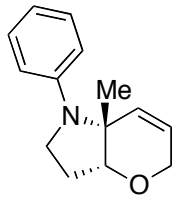


(±)-**3.26**

To a solution of (±)-**3.18** (30 mg, 0.06 mmol, 1.0 equiv) and aniline (6.6 mg, 0.07 mmol, 1.2 equiv) in THF (3.0 mL) was added glacial acetic acid (1.0 μL, 0.017 mmol,

0.28 equiv). The reaction mixture was stirred for 2 hrs and then $NaBH_4$ (3 mg, 0.08 mol, 1.3 equiv) was added. The reaction mixture was stirred at room temperature for 2 hrs before it was transferred to a separatory funnel containing EtOAc (5 mL) and water (3 mL). The aqueous layer was separated and extracted with EtOAc (2 x 3 mL). The combined organic phases were washed with brine, dried over Na_2SO_4, filtered and concentrated. The resulting residue was subjected to flash chromatography over silica gel with hexanes-EtOAc (3:1) to afford (±)-**3.26** (26 mg, 0.04 mmol, 72 %) as yellow solid. TLC: R_f = 0.82 (hexanes-EtOAc = 3:1). IR (cm^{-1}): 2905 (s), 1592 (s), 1339 (m), 1149 (s), 1085 (s). ^1H NMR (400 MHz, $CDCl_3$): 8.55 (br s, 1H), 7.70 (br s, 1H), 7.61 (s, 2H), 7.58 (s, 1H), 7.47 (s, 1H), 7.18 (t, *J* = 8.4 Hz, 2H), 6.69 (t, *J* = 7.5 Hz, 1H), 6.63 (d, *J* = 8.4 Hz, 2H), 6.23 (br s, 2H), 6.15 (s, 1H), 4.04 (d, *J* = 12.0 Hz, 1H), 3.98 (dd, *J* = 11.1, 1.8 Hz, 2H), 3.93 (d, *J* = 10.5 Hz, 1H), 3.82 (d, *J* = 10.5 Hz, 1H), 3.69 (d, *J* = 12.0 Hz, 1H), 3.35-3.32 (m, 1H), 2.22-2.13 (m, 1H), 1.92-1.79 (m, 1H), 1.75 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 231.6, 226.7, 147.6, 142.9, 141.3, 136.9, 136.3, 134.7, 129.7, 127.3, 113.1, 106.3, 105.7, 71.4, 69.9, 66.5, 63.6, 57.9, 38.7, 34.9, 23.7. HRMS (ESI) Calcd for $C_{25}H_{29}O_4N_7BMo$ ($[M + 1]^+$): 600.1423. Found: 600.1427

(±)-(3a*R*,7a*R*)-7a-methyl-1-phenyl-1,2,3,3a,5,7a-hexahydropyrano[3,2-*b*]pyrrole, (±)-3.27.



(±)-**3.27**

To a solution of (±)-**3.26** (25 mg, 0.04 mmol, 1.0 equiv) in DMSO (2.0 mL, 0.02 M) was added NaH (60 % dispersion in oil, 2.0 mg, 0.05 mmol, 1.2 equiv). The reaction

mixture was stirred for 15 min then Cu (II) 2-ethylhexanoate (17.6 mg, 0.16 mol, 1.2 equiv) was added and the reaction mixture was stirred at room temperature in dry air for 10 hrs and then, quenched with water. The mixture was poured into a separatory funnel containing EtOAc (10 mL) and water (5 mL). The aqueous layer was separated and extracted with EtOAc (2 x 5 mL). The combined organic phases were washed with 3 M NH_3-H_2O, dried over Na_2SO_4, filtered and concentrated. The resulting residue was subjected to flash chromatography over silica gel with hexanes-EtOAc (3:1) to afford (±)-**3.27** (14 mg, 0.10 mmol, 61%) as colorless oil. TLC: R_f = 0.71 (hexanes-EtOAc = 1:1). IR (cm^{-1}): 2895 (s), 1597 (s), 1339 (m), 1154 (s), 1085 (s). ^{1}H NMR (400 MHz, $CDCl_3$): 7.17 (dd, *J* = 8.4, 7.2 Hz, 2H), 6.72 (d, *J* = 8 Hz, 2H), 6.64 (t, *J* = 7.2 Hz, 1H), 6.40 (dt, *J* = 12.4, 2.4 Hz, 1H), 5.84-5.79 (m, 1H), 4.18 (dd, *J* = 3.9, 1.6 Hz, 1H), 4.17-4.05 (m, 1H), 3.80 (dd, 4.4, 1.6 Hz, 1H) 3.64 (dt, *J* = 9.6, 2.0 Hz 1H), 3.31 (dt, *J* = 8.2, 2.4 Hz, 1H), 2.28-2.18 (m, 1H), 2.07-1.99 (m, 1H), 1.40 (s, 3H). ^{13} C NMR (100 MHz, $CDCl_3$): 129.1, 127.8, 126.9, 116.1, 113.7, 84.1, 63.9, 60.0, 47.9, 30.1, 28.4, 23.9. HRMS (ESI) Calcd for $C_{14}H_{17}NO$ ($[M]^+$): 215.1309. Found: 215.1306.

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