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Wenyong Chen Date

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

By

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Doctor of Philosophy

Chemistry

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An Abstract of
A dissertation submitted to the Faculty of the
James T. Laney School of Graduate Studies of Emory University
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Abstract

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II. Uncatalyzed Electrophilic C-C Bond Forming Reactions of Pyranyl and Pyridinyl Molybdenum Complexes

By Wenyong Chen

Chapter One A novel homo-S_N2'-like reaction between neutral $TpMo(CO)_2$(5-acyloxy-η^3-pyranyl) and $TpMo(CO)_2$(5-acyloxy-η^3-pyridinyl) scaffolds and a variety of stabilized carbonanion nucleophiles provided a powerful methodology to construct C-C bonds stereoselectively. Moreover, it proceeded through an interesting anionic mechanism and preliminary mechanistic study was reported. Based on the Mo complex produced in the reaction, a mechanistically related annulative demetallation was developed to furnish the framework of 2,7-dioxabicyclo[4.3.0]nonane and 2-aza-7-oxabicyclo[4.3.0]nonane in good to excellent yields. In order to demonstrate the power of this new reaction sequence, (+)-isofebrifugine was synthesized in a concise route by employing the homo-S_N2'-like-annulative demetallation sequence.

Chapter Two Neutral $TpMo(CO)_2$(5-trifluoroacetate-η^3-pyranyl) and $TpMo(CO)_2$(5-trifluoroacetate-η^3-pyridinyl) scaffolds underwent an uncatalyzed Friedel-Crafts-like reaction with a variety of electron-rich arenes and olefins to form substitution products in high yields. A preliminary study of the mechanism showed that $TpMo(CO)_2$(5-trifluoroacetate-η^3-pyranyl) in DMSO rapidly rearranged to $TpMo(CO)_2$(2-trifluoroacetate-η^3-pyranyl) complex first, which then reacted with indole derivatives. By contrast, $TpMo(CO)_2$(5-trifluoroacetate-η^3-pyranyl) in acetonitrile or chloroform reacted with electron-rich arenes and olefins without the initial rearrangement. And, silyl enol ethers and allylsilanes could only react with the unrearranged $TpMo(CO)_2$(5-trifluoroacetate-η^3-pyranyl) complex. Further annulative demetallation proved to be successful with a series of substrates to form oxygen heterocycles and carbocycles in 5 or 6 membered rings in a mild condition. This methodology has been successfully utilized to access the tetracyclic structure of vindoline in a model system.

Chapter Three A short, practical route to a versatile 5-oxo-4-methyl-(η-2,3,4)-allylmolybdenum pyranyl and 5-oxo-4-methyl-(η-2,3,4)-allylmolybdenum pyridinyl scaffold has been developed using the Achmatowicz rearrangement. Further transformation through reduction and dehydration enabled a rapid access to Δ^5-4-methyl-(η-2,3,4)-allylmolybdenum pyridinyl scaffold.

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Dedicated to my family

for their love and support.

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Wenting, John, Matthew Lindale, Biruk, Kassinath, and Angus. It is a great pleasure to work with you all. And I also want to thank my friends here for their long time friendship, especially Yi, Jie and Ye for the joyful memory.

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List of Abbreviations

[α]	specific rotation
Ac	acetyl
anal	analysis
Aq	aqueous
Ar	argon
Bn	benzyl
br	broad
Bu	butyl
^{o}C	degree Celsius
calcd	calculated
Cbz	benzyloxycarbonyl
cod	1,5-cyclooctadiene
Cy	cyclohexyl
δ	chemical shift(s)
d	doublet
DMAP	dimethyl amino pyridine
Decomp	decomposed
DMSO	dimethyl sulfoxide
DMS	dimethyl sulfide
E	entgegen
ee	enantiomeric excess
Et	ethyl
FAB	fast atom bombardment
FT	Fourier transform
g	gram(s)
h	hour(s)
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectroscopy
Hz	hertz
IR	Infrared Spectroscopy
J	coupling constant
LA	Lewis acid
LDA	lithium diisopropylamide
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
MVK	methyl vinyl ketone
nbd	norbornadiene
NMR	nuclear magnetic resonance

NOE	nuclear Overhauser effect
nm	nanometer(s)
PG	protecting group
Ph	phenyl
ppm	parts per million
pr	propyl
py	pyridine
q	quartet
R	retention factor
r.t.	room temperature
s	singlet
SAR	structure activity relationship
t	triplet
t	tertiary
TBME	*tert*-butyl methyl ether
TBS	*tert*-butyl dimethyl silyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
Tp	hydridotris(1-pyrazolyl)borate
Tr	triphenylcarbenium
UV	ultraviolet
Z	zusammen

Chapter One

The Development of Homo-S_N2'-like Reaction/Annulative Demetallation and the Application in the Synthesis of (+)-Isofebrifugine

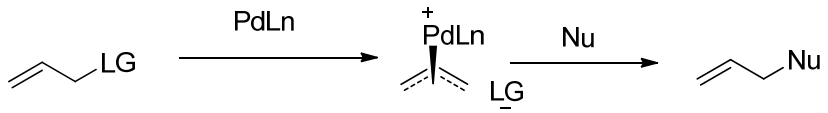
Background

Modern organic synthesis is characterized by high chemo-, regio-, and stereoselectivity. In order to achieve these selectivities, transition metal mediated reactions have been widely applied in synthesis.[1] Among these reactions, asymmetric allylic substitution has been investigated extensively due to its versatility in bond formation.[2] A variety of transition metals, including palladium, molybdenum, iridium, rhodium, tungsten, nickel, copper, and platinum, have been employed in these reactions. Herein are reviewed the latest developments and novel applications in the synthesis of natural products.

Palladium catalyzed allylic substitution

Introduced by Tsuji in 1965, palladium catalyzed allylic substitution has been the most extensively studied transition metal catalyzed allylic substitution (**Figure 1**).[3] Its early development and applications in the total synthesis have been covered by two excellent reviews.[4] Therefore, only the most important developments and applications in recent years will be discussed here.

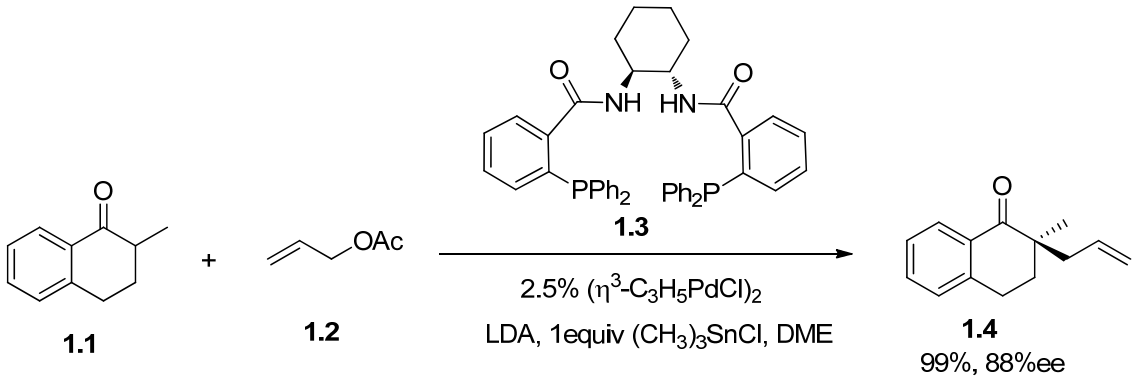
Figure 1. General reaction pathway for Pd catalyzed allylic substitution



One of the most important developments in this area was to control the stereochemistry of the product ketone. Two ways were developed to generate enolates. The first was to preform an enolate by deprotonating a ketone with a strong base. In 1997, Trost reported that when simple ketone enolates were preformed with 2 equiv

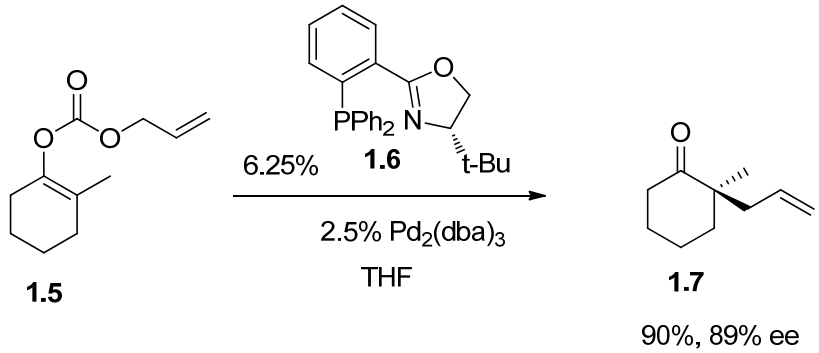
LDA, they could react with an allylpalladium complex to yield alkylation product in high ee (**Scheme 1**).[5] For example, the tetralone **1.1** was deprotonated and reacted with allyl acetate **1.2** in the presence of the ligand **1.3** to furnished allylation product **1.4** in 88%ee. The amount of the base had such a significant effect on the outcome of the reaction that the author proposed the excess base caused a change of the aggregation state of the formed enolates.

Scheme 1. Pd catalyzed asymmetric allylic substitution with simple ketone enolates as nucleophiles



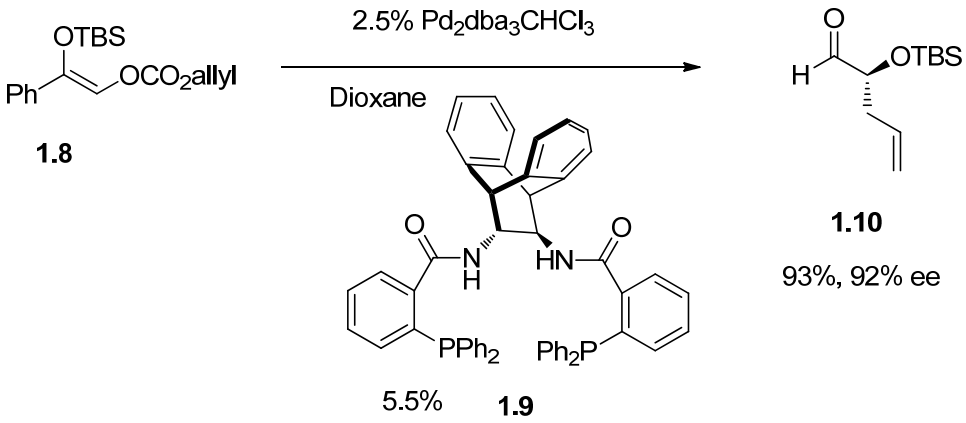
The second method to generate the enolate utilized a decarboxylation to generate the enolate *in situ.* This reaction, known as Tsuji allylation, was made asymmetric by Stoltz (**Scheme 1**).[6] The allyl carboxylate **1.5** was decarboxylated by Pd and reorganized to a chiral ketone in the presence of ligand t-Bu-Phox **1.6**. In this reaction, no base was needed so that the substrate scope was much broader than the previous method.

Scheme 2. Pd catalyzed Tsuji allylation



Recently, Trost published a new development to expand the methodology to synthesize chiral tertiary hydroxyaldehydes (**Scheme 3**).[7] The substrate **1.8** proceeded through the similar Tsuji allylation mechanism to afford tertiary hydroxyaldehyde **1.10** in 93% yield with 92% ee. In this reaction, the ligand **1.9** was a modification of Trost's classical ligand **1.3**.[4b]

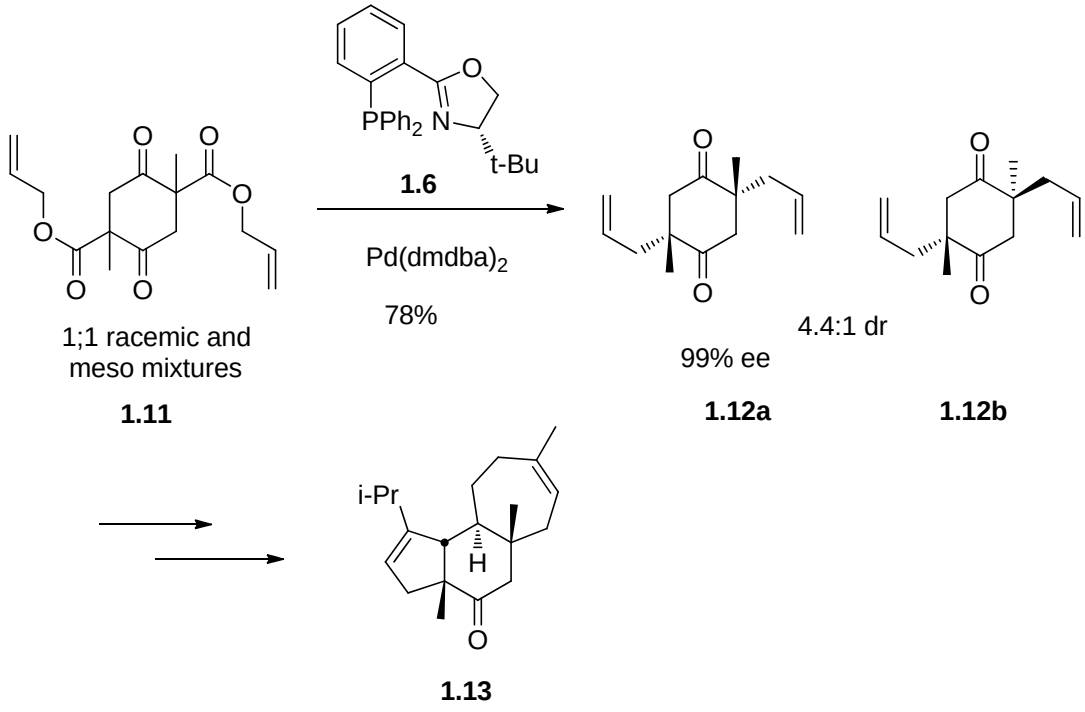
Scheme 3. Pd catalyzed synthesis of chiral tertiary hydroxyaldehyde



Considering that the Tsuji allylation provided a methodology to access enantiopure compounds containing quaternary chiral centers, Stoltz applied it in an elegant synthesis of (-)-cyanthiwigin F (**Scheme 4**).[8] The key step of this synthesis was

the rapid construction of the key intermediate **1.12a** through a double catalytic enantioselective allylic alkylation. In this reaction, the 1:1 racemic and *meso* mixtures **1.11** were converted to high enantiopure products through a one-step Pd catalyzed alkylation in 4.4:1 dr. This result implied that during the course of the reaction the ligand **1.6** controlled the facial selectivity predominantly.

Scheme 4. Synthesis of (-)-cyanthiwigin F through double catalytic enantioselective allylic alkylation

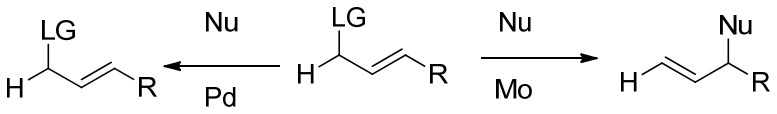


Molybdenum catalyzed asymmetric allylic substitution

Compared to Pd catalyzed asymmetric allylic substitution, Mo catalyzed allylic substitution is much less developed.[9] However, it can be a helpful complement to Pd catalyzed allylic substitution because it usually yields a different regioselectivity in

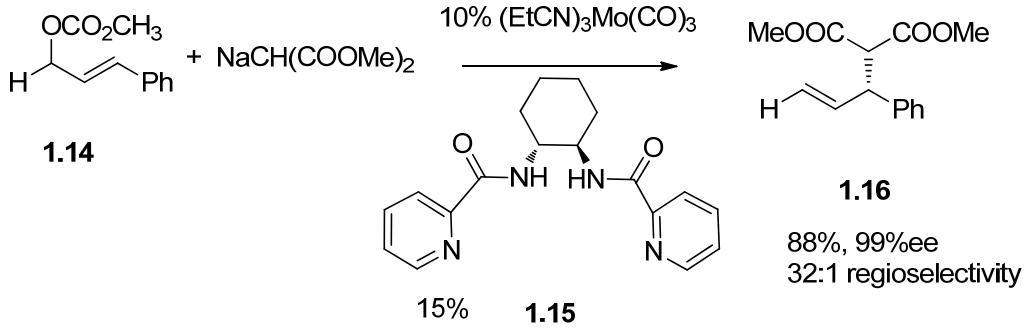
unsymmetrical substrates (**Scheme 5**). Pd catalyzed reactions usually afford linear substituted products; on the contrary, Mo catalyzed reactions often yield branched substituted products.

Scheme 5. Comparison of nucleophilic attack on unsymmetrical substrates



In this area, Trost developed a new chiral pyridylamide ligand which induced excellent enantioselectivity in this reaction (**Scheme 6**).[10] Phenyl substituted unsymmetrical allylic carbonate **1.14** reacted with sodium malonate in the presence of chiral ligand **1.15** to yield the branched substituted product in 99% ee with excellent regioselectivity.

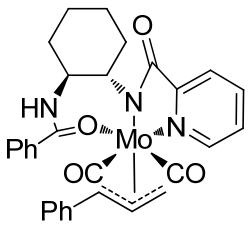
Scheme 6. Chiral pyridylamide controlled Mo catalyzed allylic substitution



Further mechanistic study disclosed more interesting details.[11] A crystal of the intermediate was achieved with an appropriate ligand (**Figure 2**). Complex **1.17**

contained an allyl part, two carbonyl groups, and N,N,O-coordination, showing an octahedral structure.

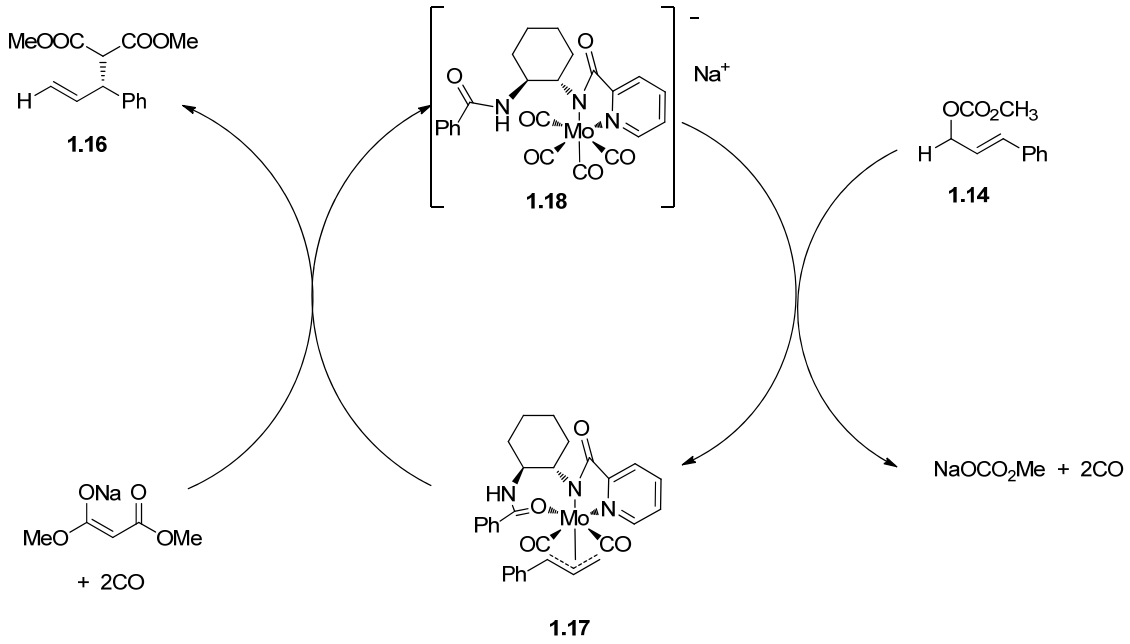
Figure 2 Structure of an intermediate from Mo catalyzed allylic substitution



1.17

However, this isolated intermediate **1.17** failed to react with sodium malonate in solution. Only in the presence of CO or excess $Mo(CO)_6$ could it be attacked by sodium malonate to afford the substitution product. Based on this unexpected observation, the following mechanism was proposed (**Scheme 7**). First, the complex **1.18** reacts with allyl carbonate **1.14** to form the intermediate **1.17**. Then it reacts with sodium malonate in the presence of 2 equiv CO to yield the substitution product **1.16** and to regenerate the Mo complex **1.18**, which is the resting state of the catalyst.

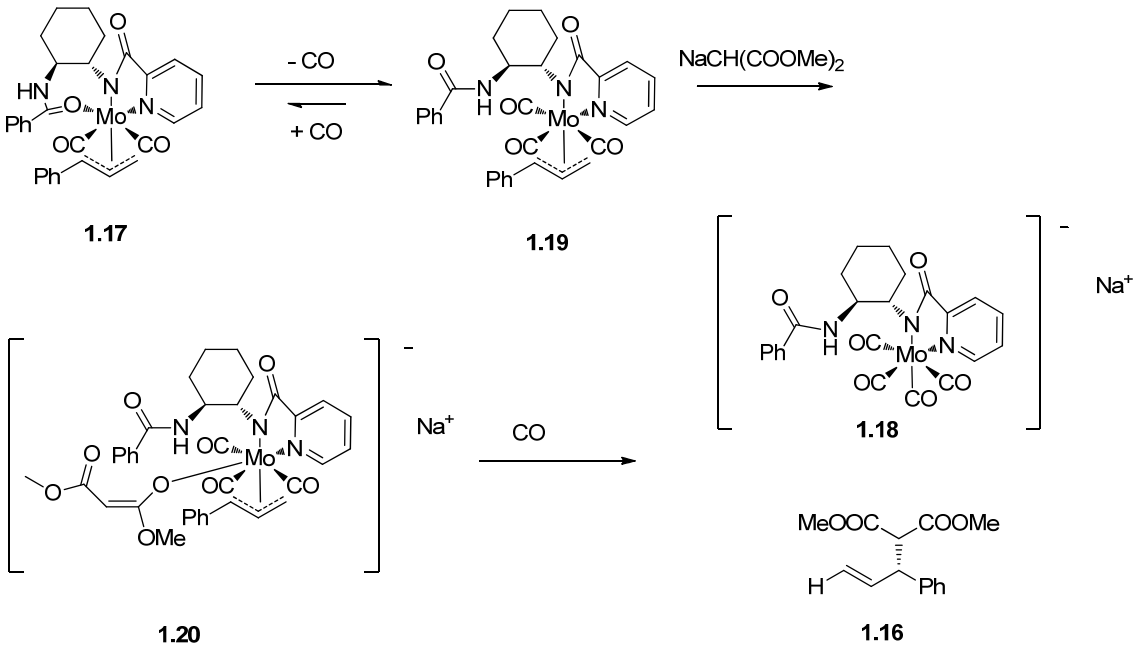
Scheme 7. Proposed mechanism for Mo catalyzed allylic substitution



A recent study on this mechanism disclosed that the reaction proceeded through a retention-retention pathway, which dramatically contrasted with the Pd catalyzed allylic substitution pathway, known as inversion-inversion pathway(**Scheme 8**).[12] Additionally, although the tricarbonyl complex **1.19** was not observed, ^{13}CO rapidly exchanged into the complex **1.17** when it was exposed in a ^{13}CO atmosphere. Based on the above observations, the following detailed mechanism was proposed. The complex **1.17** equilibrates to the tricarbonyl complex **1.19** quickly, though the equilibrium strongly favored the former. Malonate anion can coordinate to molybdenum to form the seven coordinated intermediate **1.20**, which quickly reductively eliminates to the product **1.16**

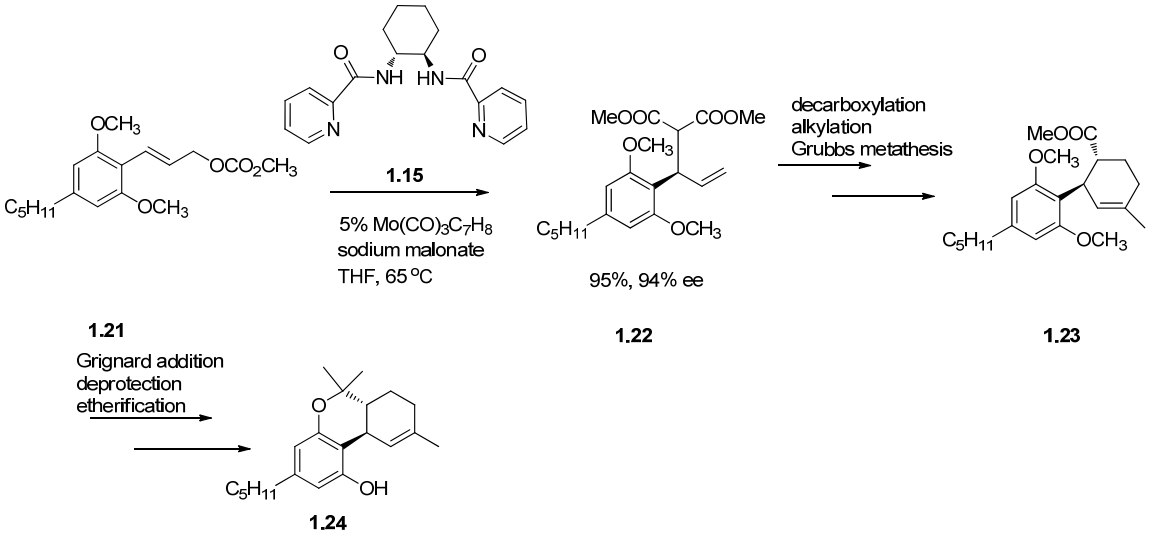
and the resting state of catalyst **1.18**. Nevertheless, it is worth pointing out the putative intermediate **1.20** was a 20-electron complex.

Scheme 8 Further details on the substitution step: tricarbonyl intermediate



Compared with the application of Pd catalyzed allylic substitution, Mo catalyzed substitution is still rarely used in the synthesis of natural products. One recent example comes from the Trost group (**Scheme 9**).[13] The synthesis of (-)-*trans*-tetrahydrocannabinol started from allylic carbonate **1.21**, which was converted into enantiopure **1.22** using Mo catalyzed asymmetric allylic substitution with malonate as the nucleophile. The substitution proceeded in very good yield and enantioselectivity. Further decarboxylation, followed by alkylation and intramolecular metathesis, yielded the *trans* substituted six member ring compound **1.23**. After several steps of functionalization, (-)-*trans*-tetrahydrocannabinol **1.24** was obtained in high enantiopurity.

Scheme 9. Total synthesis of (-)-*trans*-tetrahydrocannabinol employing Mo catalyzed allylic substitution

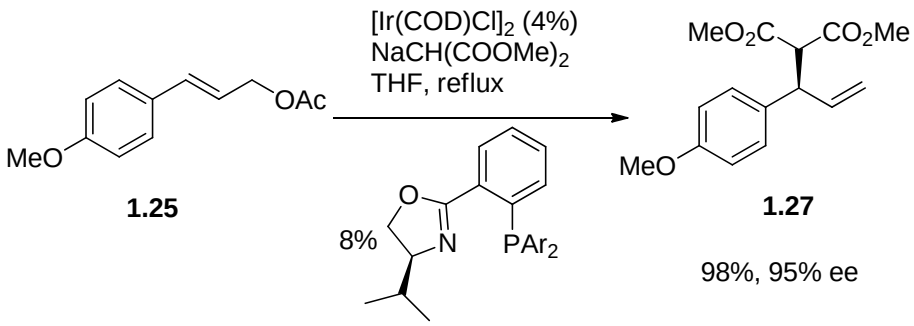


Iridium catalyzed asymmetric allylic substitution

In the last decade, there has been much progress in iridium catalyzed asymmetric allylic substitution. Similar to molybdenum catalyzed allylic substitution, it tends to yield branched products.[14] Moreover, various nucleophiles, such as silyl enol ether, enamine, alkoxide, and sulfonamide, can be used in iridium catalyzed allylic substitution so that it is attracting more and more attention.

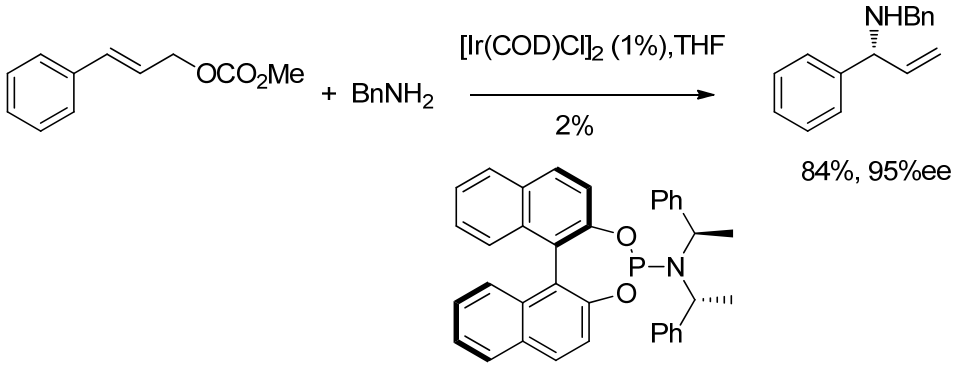
The first enantioselective Ir catalyzed allylic substitution was reported by Helmchen in 1997 (**Scheme 10**).[15] In this reaction, stabilized carbanions reacted with allylic acetate **1.25** to form the branched substitution product **1.27** in 98% yield and 95% ee. A chiral phosphineoxazoline ligand **1.26** was used to control the enantioselectivity for this transformation.

Scheme 10. The first enantioselective Ir catalyzed allylic substitution



Later, Hartwig reported an Ir catalyzed amination employing chiral phophoramidite ligand **1.28**, which proved to be a more general ligand (**Scheme 11**).[16] For example, benzylamine reacted with cinnamyl carbonate to form the branched amination product in 84% yield and excellent enantioselectivity. At a similar time, Helmchen reported the enantiomer of the ligand **1.28** could also be used in the Ir catalyzed allylic alkylation with malonate as a nucleophile to yield highly enantiopure products in good yields and high regioselectivity.[17] Further study in this field disclosed other nucleophiles, such as phenoxides,[18] alkoxides,[19] and silyl enol ethers,[20] could also yield the allylic substitution products in good yields and enantioselectivities.

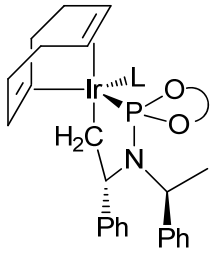
Scheme 11. Chiral phophoramidite ligand controlled Ir catalyzed allylic amination



1.28

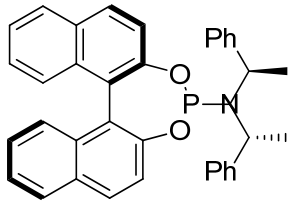
Interestingly, the mechanistic study uncovered an unexpected reactive species (**Figure 3**).[21] The real reactive catalyst was not a simple ligand binding iridium species; instead, it was the cyclometalated species **1.29**.

Figure 3. The cyclometalated reactive species in Ir catalyzed allylic substitution



1.29

L=

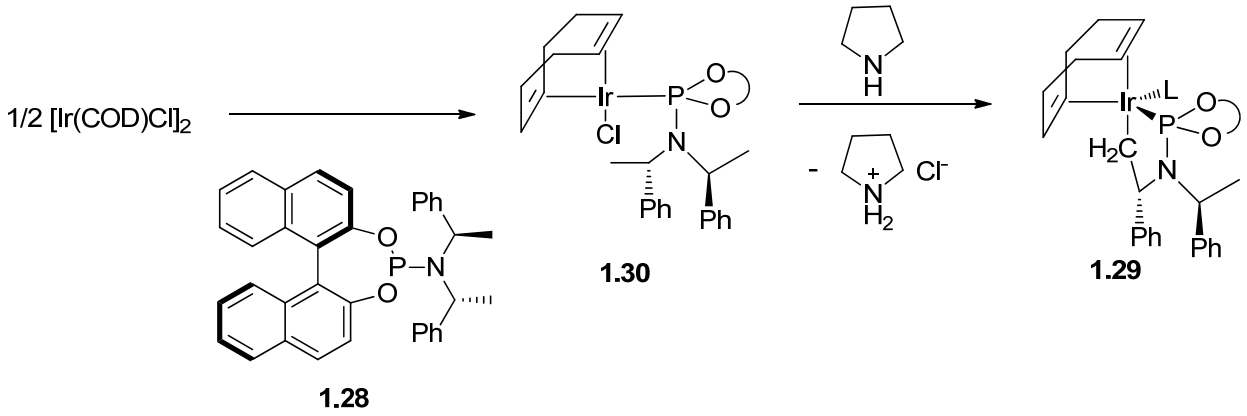


1.28

The complex **1.29** could be prepared by treating the mixtures of $[Ir(COD)Cl]_2$ and the ligand **1.28** with pyrrolidine (**Scheme 12**). When mixing $[Ir(COD)Cl]_2$ and the ligand

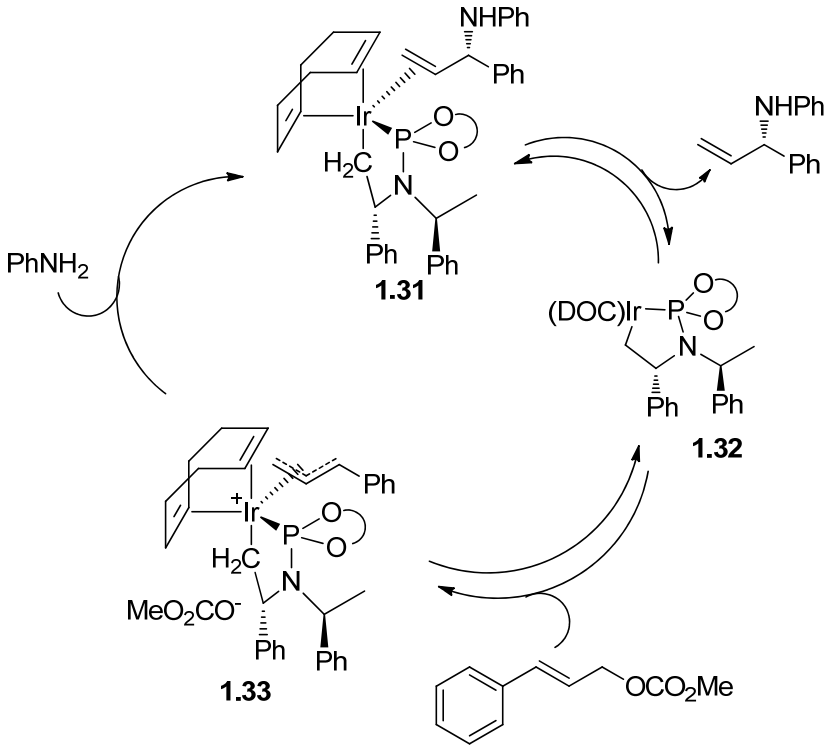
1.28, first a new square complex **1.30** would form. Deprotonation with pyrrolidine led to the formation of the reactive species **1.29**, which demonstrated even higher reactivity than the original catalyst.

Scheme 12. Synthesis of the Ir reactive species 1.29



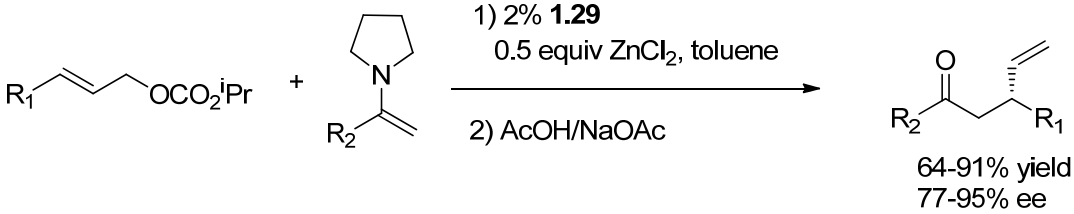
Further mechanistic study disclosed more details about the reaction pathway (**Scheme 13**).[22] The complex **1.31** was shown to be the resting state of the catalyst, which is in equilibrium with the allylic iridium complex **1.33**. The olefin complex **1.31** releases amine substituted product through ligand dissociation to **1.32**, which reacts with allylic carbonate to form the complex **1.33.** Then this complex reacts irreversibly with the amine to yield the complex **1.31** and completes the catalytic cycle.

Scheme 13. Catalytic cycle of Ir catalyzed allylic substitution



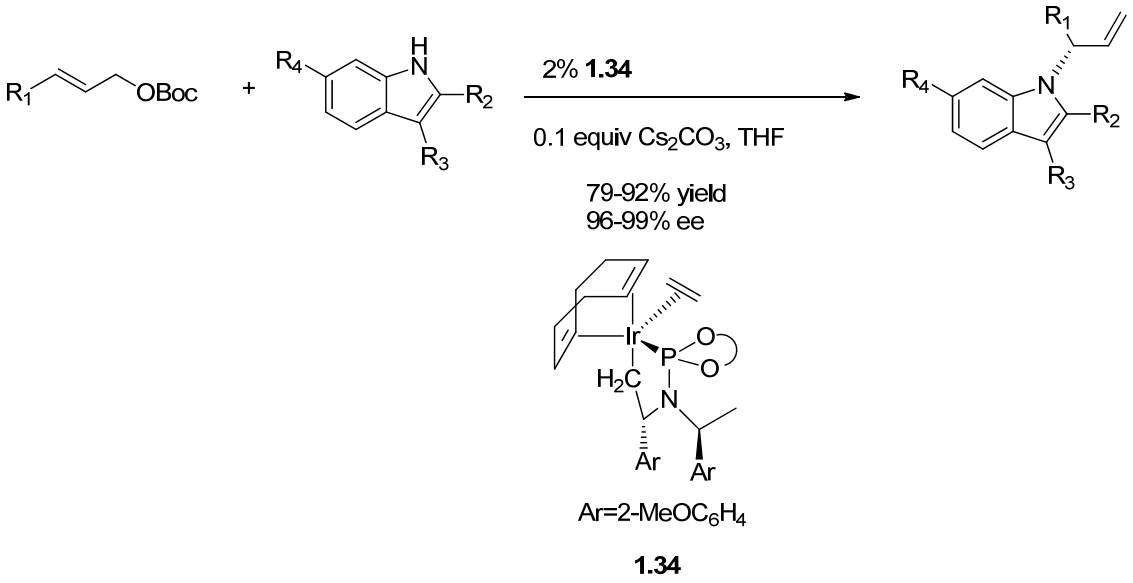
Based on these mechanistic studies, the reaction scope has been expanded to less basic nucleophiles. For example, enamine was successfully used in the allylic alkylation by employing preformed catalyst **1.29** (**Scheme 14**).[23]

Scheme 14. Ir catalyzed reaction of enamine and allylic carbonate



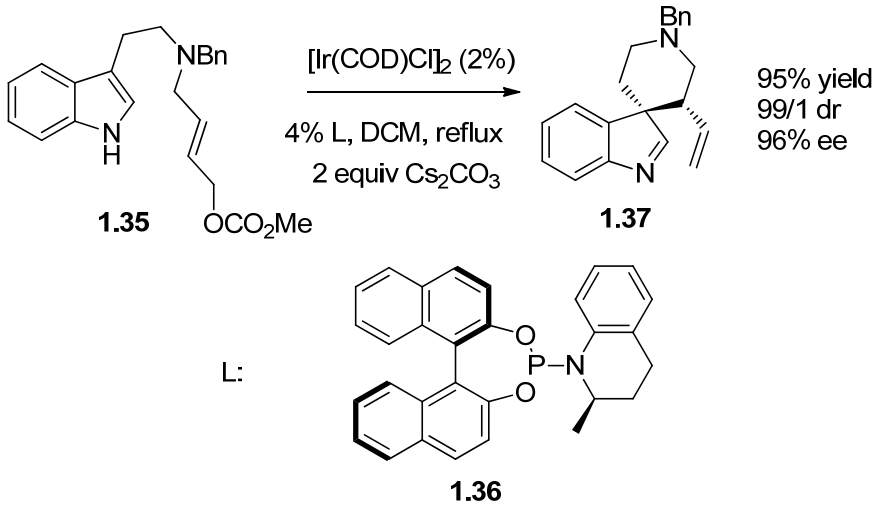
Various indoles could also be employed in the Ir catalyzed allylic substitution. Hartwig's lab successfully achieved *N*-allylation products (**Scheme 15**).[24] Indole derivatives containing an electron-withdrawing group were used as nucleophiles to give the allylic substitution product in good yields and excellent enantioselectivities and regioselectivities when the preformed catalyst **1.34** was used in the reaction.

Scheme 15. N-allylation of indole with electron withdrawing groups



The *C*-alkylation product was reported by You in 2010 (**Scheme 16**).[25] With the modified phosphoramidite ligand **1.36**, indole derivative **1.35** could be converted to spiroindolenine in excellent yield, diastereo- and enantioselectivity.

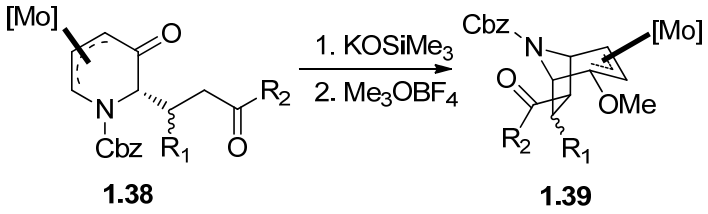
Scheme 16. Ir catalyzed intramolecular C-allylation of indole derivatives



Introduction

In 2006, Zhang in the Liebeskind group reported a novel intramolecular 1,5-Michael-like reaction (**Scheme 17**).[26] An enolate attacked the allylic molybdenum moiety intramolecularly to form an intermediate, which led to a new allyl migration product after being quenched with Meerwein's salt.

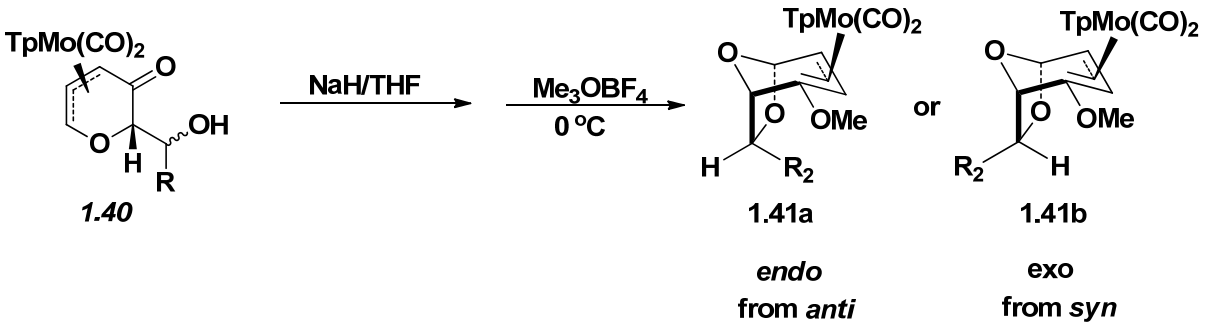
Scheme 17. 1,5-Michael-like reaction



Cheng expanded the scope of this novel reaction to oxygen nucleophiles (**Scheme 18**).[27] The scaffold **1.40**, readily available as a pure diastereomer through a simple Mukaiyama aldol reaction, could be deprotonated and quenched with Meerwein's salt to

form an interesting heterocycle. This methodology was later applied in the synthesis of a member of the brevicomin family.

Scheme 18. 1,5-Michael-like reaction with oxygen nucleophiles



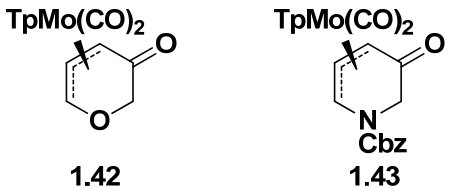
Based on these precedents, a similar intermolecular reaction was envisioned to construct C-C bonds stereoselectively. Herein are reported the results: Homo-S_N2'-like reaction, annulative demetallation, and the application in the synthesis of (-)-isofebrifugine.

Results and Discussion

Initial studies and project design

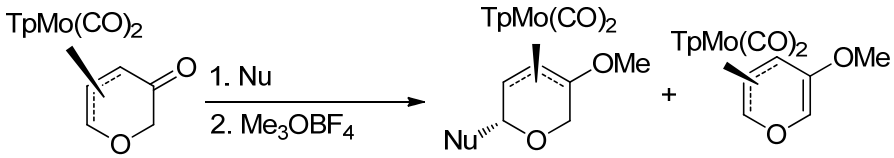
The racemic and enantiopure scaffolds **1.42** and **1.43** were prepared by employing Achmatowicz rearrangement following the reported procedure (**Figure 4**).[28]

Figure 4. 5-oxo pyranyl and pyridinyl scaffold



The pyranyl scaffold was first chosen as the substrate while different nucleophiles such as malonate and phenylacetone were used in the 1,5 Michael-like reaction condition (**Table 1**). Although neither nucleophiles yielded the desired product **1.44**, **1.45** was obtained in low yield when phenylacetone was used in the reaction. This observation showed a competition between an intermolecular 1,5-Michael-like reaction and the enolization of the 5-ketone.

Table 1. Study on the intermolecular 1,5-Michael-like reaction

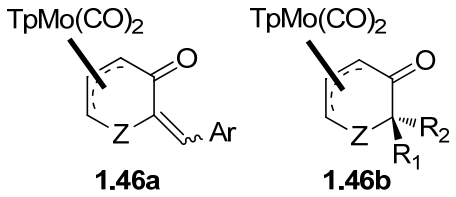


1.42 **1.44** **1.45**

Entry	Nu	**1.44**	**1.45**
1	NaH, $CH_2(COOMe)_2$	0	0
2	NaH, $PhCOCH_3$	0	20%

One solution to avoid the side reaction caused by the acidic proton is blocking the α position of carbonyl group. Two possible substrates could be envisioned, and **1.46a** was easily available through the known procedure: Mukaiyama aldol-dehydration (**Figure 5**). However, this solution would limit the scope of the substrates and the potential application of this methodology. Therefore, we sought a better solution to this problem.

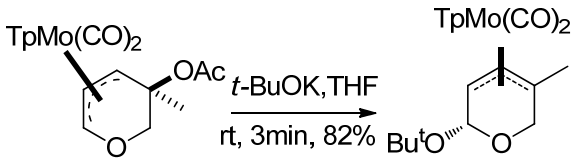
Figure 5. Two possibly useful substrates



1.46a **1.46b**

At that time, we noticed an unpublished result from Yin describing an interesting substitution (**Scheme 19**).[29] In this reaction, KO^{t}Bu was found to act as a nucleophile instead of a base. It attacked the allyl molybdenum moiety directly to displace the OAc. However, the reaction product was not very stable and the reaction was capricious. Moreover, a substantial racemization occurred during the course of the reaction. Yin also studied other nucleophiles, such as Grignard reagents and cuprates, none of which yielded the substitution products.

Scheme 19. An interesting substitution with KO^{t}Bu



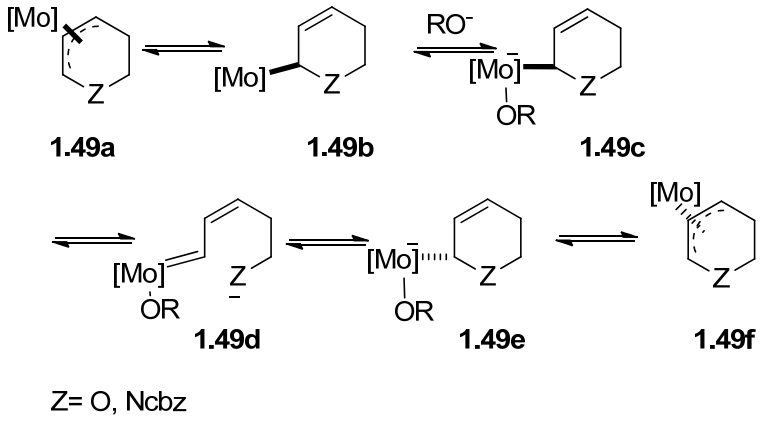
1.47 **1.48**

Both Zhang's 1,5 Michael-like reaction and the above reaction appeared to proceed through a direct nucleophilic attack on allyl molybdenum moiety. Furthermore, the substrate **1.47** would not be easily enolizable due to the absence of the ketone carbonyl group from **1.42**. Therefore, the complex **1.47** could be a promising solution to the difficulties in the intermolecular 1,5-Michael-like reaction. Although Yin's preliminary research work on carbon nucleophiles failed to give promising results, the

importance of constructing C-C bonds stereoselectively prompted us to carry out a more extensive investigation.

For the reported racemization in the *t*-butoxide substitution, a working hypothesis was developed (**Scheme 20**). In this working hypothesis, a general molybdenum heterocyclic complex **1.49a** can slip from η^3 to η^1 and form **1.49b**, which is a 16e complex. In this complex, an alkoxide can coordinate to form **1.49c**, in which molybdenum will be negatively charged and very electron rich. In this case the ring tends to open to form a neutral planar alkylidine carbene **1.49d**, which will racemize to **1.49f** when the ring is closed through intramolecular nucleophilic attack.[30] According to this hypothesis, the alkoxide coordination would be an essential step for the racemization. Therefore, weak coordinative carbon nucleophiles may not coordinate to Mo and will not lead to racemization

Scheme 20. Working hypothesis for the racemization of scaffold in the presence of alkoxide

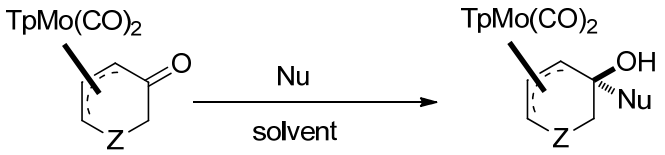


Homo-S_N2'-like reaction

First, a reliable reaction is required to access the complex **1.47** and its' analogues. Yin used Grignard addition followed by quenching with Ac_2O to access **1.47**, which was not general to other Grignard reagents and difficult to purify. Consequently, a stepwise synthesis of the substrate was pursued.

For Grignard addition to the oxygen scaffold **1.42**, Yin's procedure worked well. In the Grignard addition to the nitrogen scaffold **1.43**, Harry Wong's procedure was followed, which required the addition of Grignard reagent at 0 ^oC in toluene to minimize enolization.[31] This protocol provided reproducibly good yields of addition products with recovery of unreacted starting material **1.43**. An alternative protocol provided addition products by employing the cerium reagents, which provided full conversion with slightly higher yield. For the reduction of the scaffold **1.42** and **1.43**, DIBAL proved to be the best choice of reducing agent, which often gave almost quantitative yield. It is worth pointing out that the quality of DIBAL was important to the success of the reaction that an old bottle of DIBAL could diminish the yield to less than 10%. All these results were summarized in **Table 2**.

Table 2. Nucleophilic addition to the complex 1.42 and 1.43



Z= O, NCbz

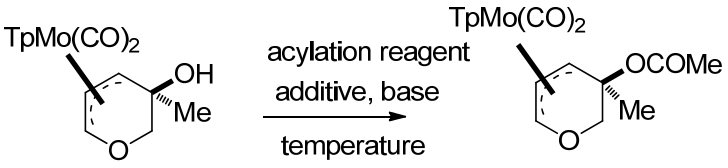
1.42, 1.43

1.50a-e

Entry	Z	Nu	Solvent	Product(yield%)
1	O	MeMgBr	THF	**1.50a**(86)
2	O	PhMgBr	THF	**1.50b**(75)
3	O	DIBAL	THF	**1.50c**(93)
4	NCbz	DIBAL	THF	**1.50d**(93)
5	NCbz	MeMgBr	Toluene	**1.50e**(60% with 27% SM)

Next, using **1.50a** as the substrate, acylation was studied under varying conditions to achieve the best yield (**Table 3**). With a catalytic amount of DMAP, the acylation provided the product **1.47** in 20% yield with the starting material recovered. By changing acylating reagent, temperature, and amount of DMAP, we finally identified the best condition to fully convert the alcohol **1.50a** to acetate substituted product **1.47**. Under the optimal condition, the reaction required excess acetic anhydride, triethylamine, and DMAP at 40^{o}C to achieve a full conversion of starting material to product in 86% yield.

Table 3. The optimization of acylation of the alcohol

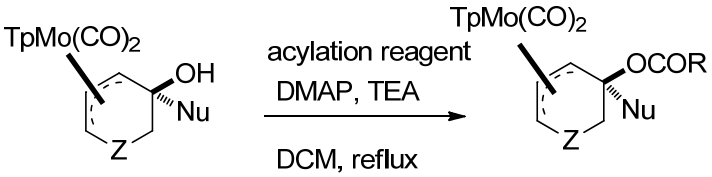


1.50a **1.47**

Entry	Acylation reagent	additive	base	solvent	t	Yield(%)
1	1.5 equiv Ac_2O	0.1 equiv DMAP	1.5 equiv TEA	DCM	rt	20
2	1.5 equiv AcCl	0.1 equiv DMAP	1.5 equiv TEA	DCM	rt	20
3	1.5 equiv Ac_2O	None	None	pyridine	rt	10
4	1.5 equiv Ac_2O	0.1 equiv DMAP	1.5 equiv TEA	DCM	40°C	35
5	3 equiv Ac_2O	3 equiv DMAP	3 equiv TEA	DCM	40°C	86

With this optimized condition in hand, different alcohols **1.50a-e** were acylated successfully to form the desired substrates. These results are summarized in the **Table 4**.

Table 4. Acylation of various substituted scaffold

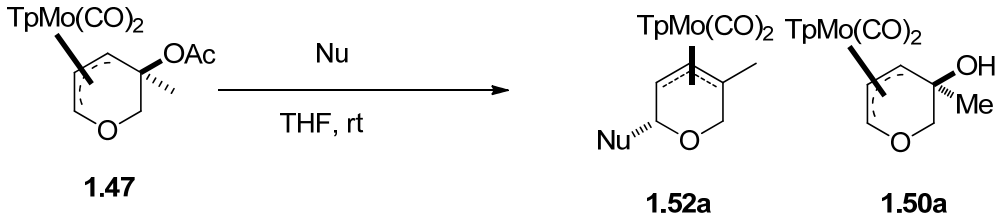


1.50a-e **1.47, 1.51b-g**

Entry	SM	Z	Nu	R	Product(yield%)
1	**1.50a**	O	Me	Me	**1.47** (86)
2	**1.50b**	O	Ph	Me	**1.51b** (85)
3	**1.50c**	O	H	*p*-$NO_2C_6H_4$	**1.51c** (97)
4	**1.50c**	O	H	Me	**1.51d** (97)
5	**1.50d**	NCbz	H	*p*-$NO_2C_6H_4$	**1.51e** (95)
6	**1.50e**	NCbz	Me	Me	**1.51f** (88)
7	**1.50d**	NCbz	H	Me	**1.51g** (95)

Different carbon nucleophiles were studied to investigate the reactivity of the new substrate **1.47** (**Table 5**). Grignard reagents reacted with the ester to yield the corresponding alcohol **1.50a,** while cuprates failed to react with **1.47**. Enolates formed by using NaH or LDA also only yielded the alcohol **1.50a** in low yield with starting material recovered. Gratifyingly, promising results were finally achieved by using sodium malonate as a nucleophile in THF, which furnished the desired substitution product in 70% yield with 30% starting material recovered. Catalytic 15-crown-5-ether was found to be so beneficial that it improved the conversion to 100% in 8 hours.

Table 5. Different nucleophiles studied in the reaction with 1.47



1.47 **1.52a** **1.50a**

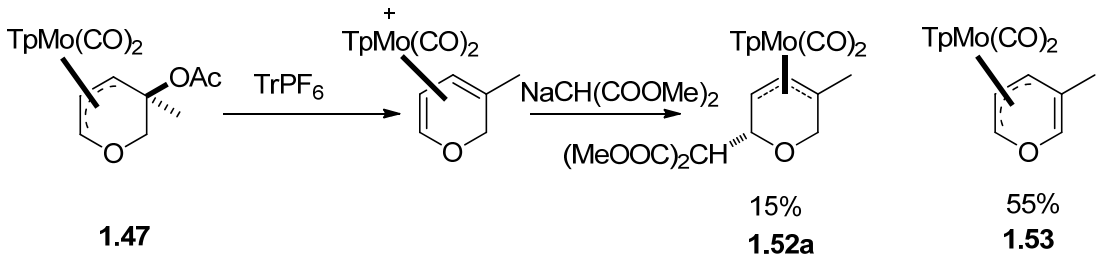
Entry	Nu	**1.52a**(%)	**1.50a**(%)

1	MeMgBr	0	96
2	MeMgBr + CuI	0	0
3	PhCOMe + NaH	0	25
4	PhCOMe + LDA	0	86
5	$CH_2(COOMe)_2$ + NaH	70(30% SM recovery)	0
6	$CH_2(COOMe)_2$ + NaH+ 0.2 equiv 15-C-5	99	0

At this point, it should be noted that the incomplete conversion was not because of a thermodynamic equilibrium. Instead, kinetics was responsible. For example, as showed in the entry 5 and 6 in **Table 5**, the addition of 15-crown-5-ether could promote the malonate substitution to completion. In the absence of 15-crown-5-ether, the reaction would not finish even with 10 equiv. sodium malonate.

With this new reaction, referred to as a Homo-S_N2'-like reaction, we needed to confirm the relative stereochemistry of the substitution product **1.52a** (S**cheme 21**). Therefore, the complex **1.47** was converted to the cation with $TrPF_6$ and then quenched with sodium malonate to provide the substitution product, which showed identical ^{1}HNMR and ^{13}CNMR spectra as **1.52a**. Since experimentation has shown that the nucleophilic attack on molybdenum stabilized carbocation always proceeded through *anti* attack,[32] we could assumed that the homo-S_N2'-like reaction yields the product in *anti* configuration, which was further confirmed by X-ray diffraction later (*vide infra*).

Scheme 21. Nucleophilic attack on Molybdenum stabilized carbocation



1.47

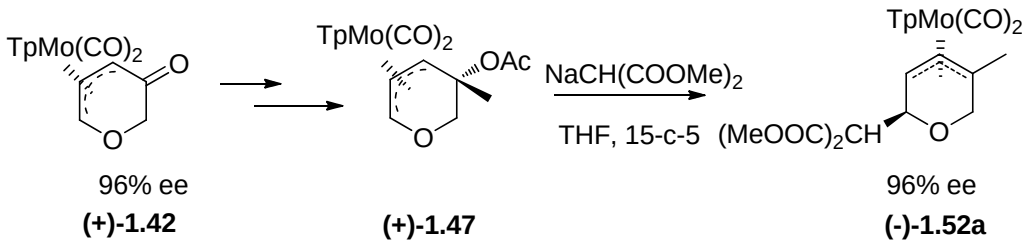
15%
1.52a

55%
1.53

It is also worth noting that the above reaction only yielded 15% nucleophilic attack product **1.52a** with mainly elimination product **1.53**. This result implied that the Homo-S_N2'-like reaction might proceed through a different mechanism than the cationic mechanism (*vide infra*).

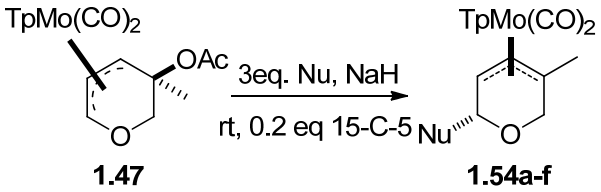
A racemization test was then conducted before moving to other nucleophiles. S**cheme 22** showed the study employing enantiopure oxygen scaffold **1.42** (96% ee) as starting material in the racemization test. HPLC analysis indicated no trace of racemization. This result was encouraging, not only because it proved the Homo-S_N2'-like reaction to be a useful methodology to establish C-C bond stereoselectively, but also because it lent support to the racemization hypothesis for the alkoxide substitution (**Scheme 20**).

Scheme 22. Racemization test on oxygen scaffold



Other nucleophiles were studied to explore the scope and limitation of this new reaction. First, with **1.47** as the substrate, a variety of stabilized nucleophiles were investigated (**Table 6**). They usually provided good to excellent yield of products based on conversion of starting material. However, for individual nucleophiles a careful choice of solvent was necessary to achieve the best conversion, while increasing temperature tended to show a very small effect. In general, THF could be used as a solvent for sodium malonate, while while nucleophiles like acetoacetate usually required a polar solvent, such as acetonitrile or DME, to achieve higher conversions. Interestingly, nitro compounds behaved as sufficient nucleophiles only in DMSO. The nucleophilicity of these stabilized carbonanions could be assessed according to Mayr's N parameters.[33] Nucleophiles with N value greater than 13 usually performed well in the Homo-S_N2'-like reaction. Other nucleophiles, including enamine and silyl enol ether, failed to yield a substitution product.

Table 6. Reaction of 1.47 with a variety of stabilized carbonanions



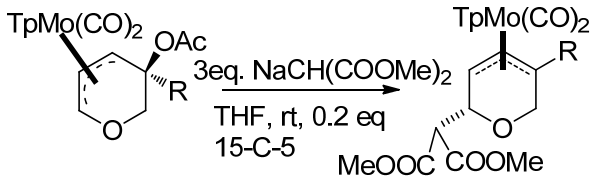
1.47 **1.54a-f**

Entry	Nu	Solvent	Product(yield%)	N parameter
1	CH_3NO_2	DMSO	**1.54a** (80)	N:20.71 S: 0.60(in DMSO)
2	$CH_2(CN)_2$	THF	**1.54b** (94)[1]	N: 18.21 S: 0.69(in 91M 9AN)
3	$CH_2CN(COOEt)$	DME	**1.54c** (94)[2]	N:18.59 S: 0.65(in 91M9AN)
4	$CH_2(COOMe)_2$	THF	**1.52a** (99)	N:18.24 S: 0.64(in91M9AN)
5	$CH_3CH(COOEt)_2$	THF	**1.54d** (66)[3]	
6	CH_3COCH_2COOMe	ACN	**1.54e** (69)[4]	N: 15.99 S: 0.62(in H2O)
7	$CH_3COCH_2COCH_3$	DME	**1.54f** (43)[5]	N: 13.73 S:0.64(in H2O)

[1]Product decomposed very quickly. [2]1.5:1 diastereomers decomposing quickly. [3]Yield based on recovery of starting material up to 94%. [4]Yield based on recovery of starting material up to 99%. The produce was composed of roughly 1.5:1 diastereomers. [5]*p*-nitroboate was used as leaving group. Yield based on recovery of starting material was 66%.

The effect of substitution on pyranyl scaffolds was also studied. **Table 7** summarized related results. The substitution proceeded faster with **1.51d** than with **1.47** (6 hrs vs. 8 hrs); and the complex **1.51b** could not be fully converted to product. These results suggested that this reaction does not proceed through a cationic mechanism because more substituted scaffolds form more stable carbocation intermediates and would lead to faster reactions.

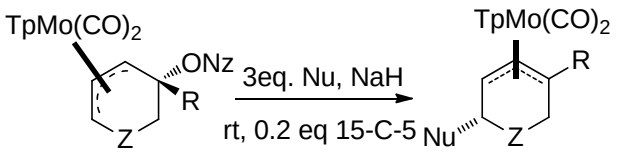
Table 7 The effect of substitution in pyranyl scaffolds



Entry	SM	R	Product (yield%)
1	**1.47**	Me	**1.52a**(99)
2	**1.51b**	Ph	**1.52b**(90+6% SM)
3	**1.51d**	H	**1.52d**(94)

The effect of the substituent was even more obvious when poor nucleophiles and pyridinyl scaffolds were employed in the reaction (**Table 8**). When acetoacetate or acetoacetone were used as nucleophiles in pyranyl scaffolds, higher conversions could be achieved with substrates containing hydrogen instead of methyl. The reaction could also work in pyridinyl scaffolds, but only with strong nucleophiles or unsubstituted scaffolds could high yields be achieved until now.

Table 8. Substitution effect in poor nucleophiles and pyridinyl scaffolds examples



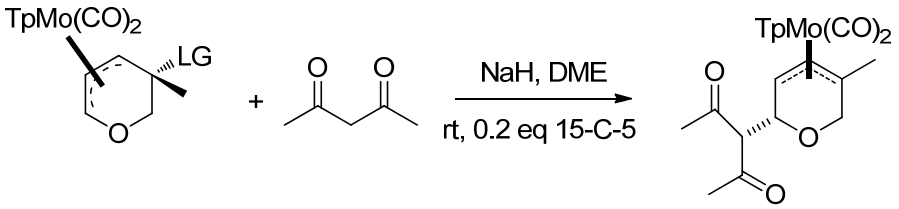
Nz= *p*-nitrobenzoyl

Entry	Z	R	Nu	Solvent	Product(yield%)
1	O	H	CH_3COCH_2COOMe	ACN	**1.55**(94)
2	O	Me	CH_3COCH_2COOMe	ACN	**1.54e**(54)
3	O	H	CH_3COCH_2COMe	ACN	**1.56**(68)
4	O	Me	CH_3COCH_2COMe	ACN	**1.54f**(38)
5[a]	NCbz	H	$CH_{2(}COOMe)_2$	ACN	**1.52e**(90)
6[a]	NCbz	Me	$CH_{2(}COOMe)_2$	ACN	**1.52f**(70+30% SM)
7	NCbz	H	CH_3COCH_2COOMe	ACN	**1.57**(91)
8	NCbz	Me	CH_3COCH_2COOMe	ACN	**1.58**(10+90% SM)

[a] OAc as the leaving group in this example.

The effect of the leaving group was also investigated to optimize the reaction. The poor nucleophile generated from acetoacetone was used to optimize leaving group (**Table 9**). Among studied leaving groups, *p*-nitrobenzoate appeared to be the best choice. Better leaving groups, such as mesylate, led to direct elimination to the complex **1.53**.

Table 9. The effect of leaving group



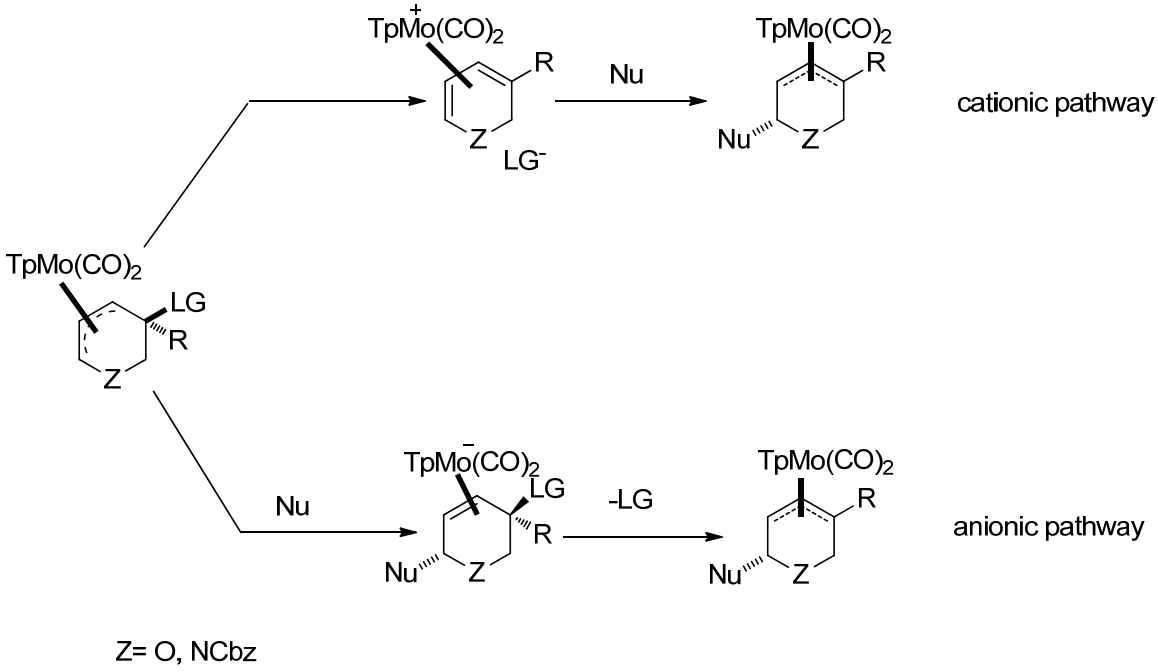
Entry	LG	Yield(%)
1	OAc	22
2	OBz	28
3	ONz	43

Mechanistic consideration

As for the mechanism of the novel Homo-S_N2'-like reaction, there were two possible pathways (**Scheme 23**). The first, the cationic pathway, would proceed through dissociation of the leaving group to form a molybdenum stabilized carbocation that could be quenched by nucleophiles. The second was the anionic pathway, in which the starting material was attacked by nucleophiles directly to form a molybdenum anion intermediate that further kicked out the leaving group to yield substitution product. However, the homo-S_N2'-like process did not appear to proceed via the cationic pathway. Evidence that supported this conclusion consisted of: (1)Exposure of **1.47** to $TrPF_6$ generates the molybdenum-stabilized carbocation, which upon treatment with sodium dimethylmalonate and 15-crown-5-ether showed a different reaction profile from the reactions in homo-S_N2'-like condition (only 18% of nucleophilic addition compound

1.52a is produced). The reaction mostly forms the elimination product **1.53** in 55% yield. (2) compound **1.47** was recovered unchanged after stirring overnight in THF/Et_3N, (3) the homo-S_N2'-like substitution reaction proceeded faster with less substituted substrates (**1.51d** are faster reacting than the more substituted **1.47**), (4) most reactions were significantly accelerated by the use of 15-crown-5-ether.

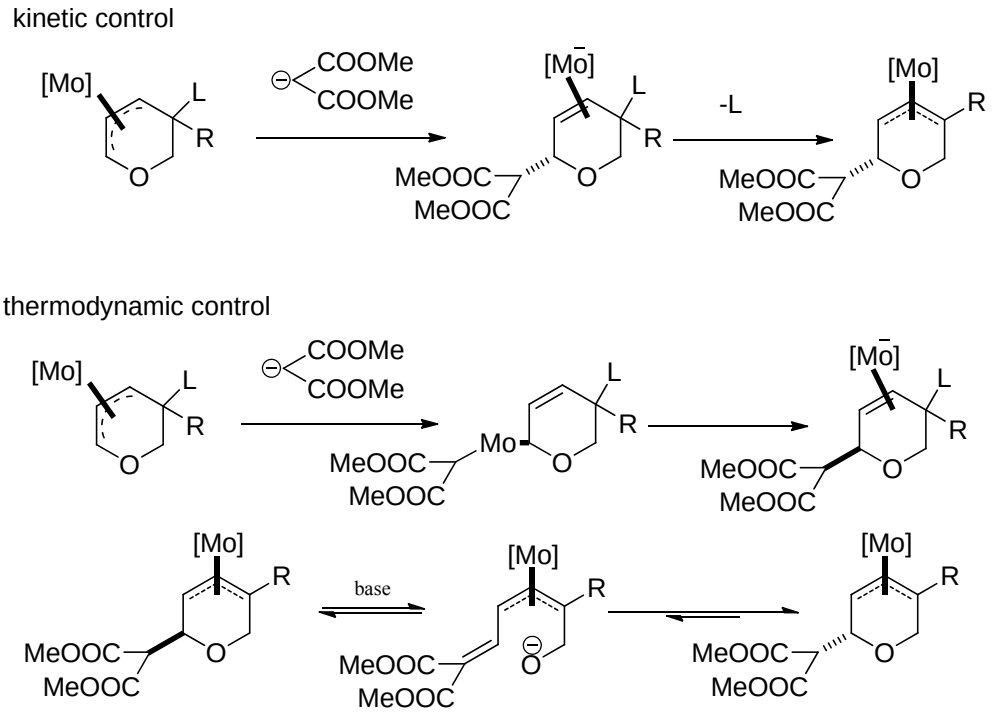
Scheme 23 Two possible pathways leading to the substitution product



There is also an alternative to the anionic pathway that cannot be completely excluded. In this alternative mechanism, no anionic intermediate exists; instead, a transition state involving simultaneous nucleophilic attack and cleavage of the leaving group could be envisioned.

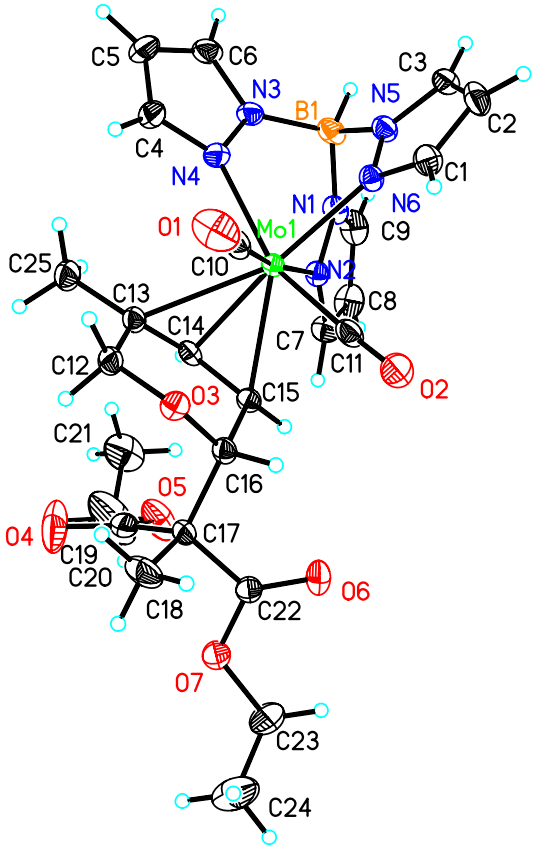
As for the stereochemistry of the nucleophilic attack, both retention[12] and inversion[35] are precedented in molybdenum mediated allylic substitutions. In the homo-S_N2'-like reaction, although we have decided that in the final product the nucleophiles were *anti* to the molybdenum moiety(*vide supra*), there was still a possibility that the configuration was determined by a thermodynamic equilibrium instead of the initial kinetic attack. Consequently, in these cases the final product configuration failed to disclose stereochemical information for the initial nucleophilic attack (**Scheme 24**). Because of the presence of an extra acidic proton and the hereoatom, the final configuration of the nucleophiles could be controlled by either kinetic control or thermodynamic control.

Scheme 24. Retro-Michael-Michael pathway scrambling the stereochemistry



In order to decide the stereochemistry of the initial nucleophilic attack, the methyl diethylmalonate substitution product was crystallized and analyzed by X-ray diffraction (**Figure 6**). In the reaction with sodium methyl diethylmalonate, the thermodynamic equilibrium pathway was excluded due to the absence of an acidic proton. Because of this, the configuration of the final product would represent the stereochemistry of the initial nucleophilic attack. The crystal structure supported that the nucleophilic attack in homo-S_N2'-like reaction proceeded through an inversion process.

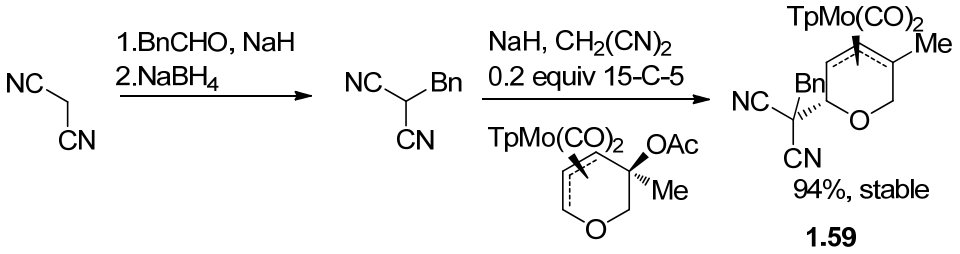
Figure 6. ORTEP view of methyl diethylmalonate substitution product 1.54d



An important side reaction: ring opening

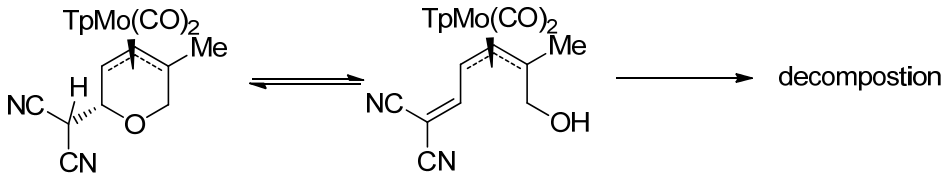
The ring opening side reaction was observed when certain nucleophiles were employed in the homo-S_N2'-like reaction. When carbonanions stabilized by cyanide, such as malononitrile, were used, the substitution product formed very quickly. However, the product was so unstable that it decomposed into a complex mixture within hours. The decomposition mechanism was not well understood until benzylmalononitrile was used as a reaction partner in the homo-S_N2'-like reaction (**Scheme 25**).

Scheme 25 Benzylmalononitrile in homo-S_N2'-like reaction



We suggested the following decomposition pathway (**Scheme 26**), in which the acidic proton was further deprotonated to proceed through a retro-Michael mechanism to yield the ring opening product. This product was unstable and further decomposed to a complex mixture.

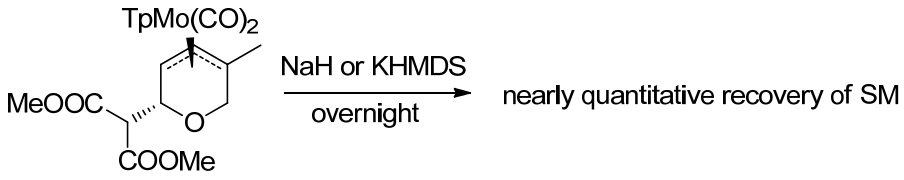
Scheme 26. Hypothesized decomposition pathway for malononitrile substituted product



Control experiments showed that a malonate substitution product was stable, even after stirring with strong base overnight (**Scheme 27**). This interesting comparison

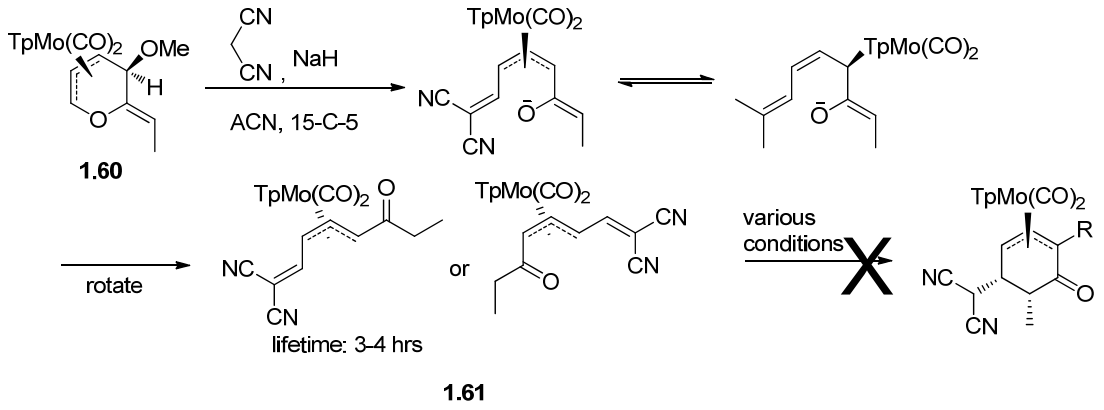
implied that the ring opening pathway would be favored only when the electron withdrawing group was small. Presumably the bulky group forbid the antiperiplanar transtition state required by the elimination.

Scheme 27. Control experiments with malonate substitution product



Further study provided strong evidence to support this working hypothesis (**Scheme 28**). When the compound **1.60** was employed as a substrate, a ring opening product **1.61** could be isolated, presumably through ring opening, η^3-η^1 equilibrium, and C-C bond rotation. Although the configuration of the complex **1.61** was not fully determined, this result strongly supported the existence of a ring opening process. Further investigation attempted to convert the pyranyl heterocycle to a carbocyclic ring using various conditions. The reaction failed possibly due to the low stability of complex **1.61**.

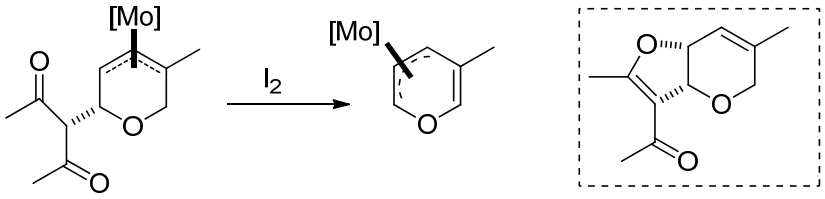
Scheme 28. Ring opening leading to an isolable open chain product



Demetallation

With a variety of molybdenum complexes in hand, a demetallation protocol was needed to convert the complexes to useful organic compounds. Iododemtallation was first tested because it was reported as a successful demetallation in carbocyclic ring system by Pearson.[36] However, it failed to give the desired cyclization product **1.62** in the hetereocyclic system; instead, elimination product **1.53** was isolated and was stable under this condition for 24 hours (**Scheme 29**).

Scheme 29. Iododemetallation of Mo complex 1.54f

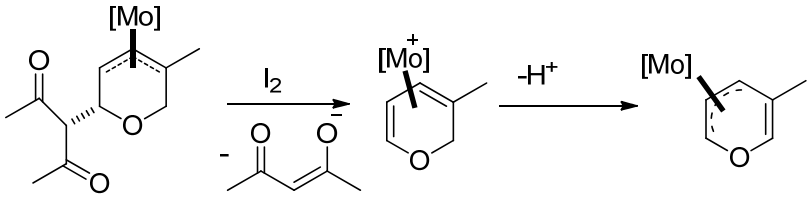


1.54f **1.53** **1.62**

The mechanism for the formation of the complex **1.53** was believed to proceed through the Mo stabilized carbocation deprotonation pathway (**Scheme 1.30**).

Triethylamine was added to suppress the influence of HI, but the same result was achieved.

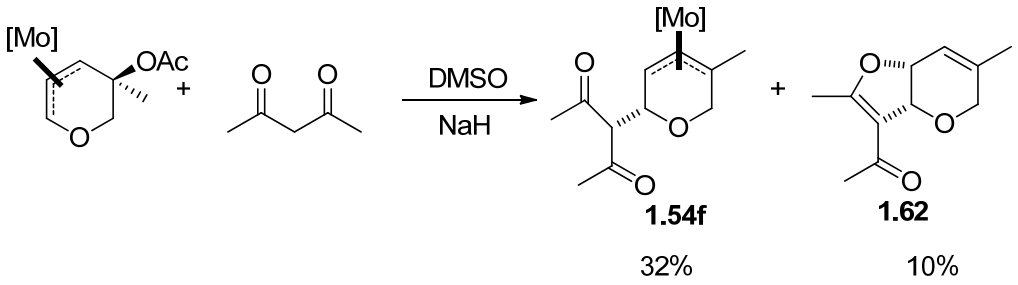
Scheme 30. Working hypothesis of the formation of elimination product 1.53



Other known demetallation methods, such as $NOBF_4/Et_3N$, $NOBF_4/NaCNBH_3$, PDC, Br_2, HCl, and TFAA, were also studied. Unfortunately, none of these yielded any isolable organic compounds and **1.53** was often the isolated product. These failures suggested that new demetallation conditions were desired to convert the metal complexes to useful organic compounds. This new condition would have to be basic in order to avoid the formation of a Mo stabilized carbocation through C-C bond cleavage.

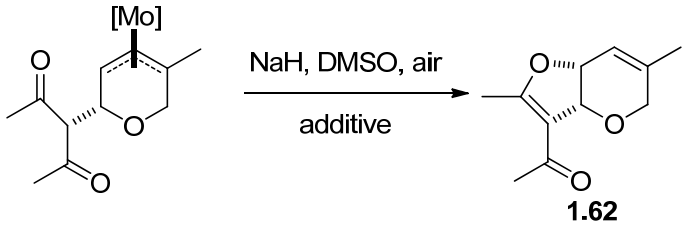
At that time, an unexpected observation provided a vital hint for the search of new demetallation conditions (**Scheme 31**). During the attempt to optimize the homo-S_N2'-like reaction of acetoacetone, we discovered that conducting the reaction in DMSO led to the formation of product in 32% yield with a small amount of inseparable impurities. Careful analysis of the ^{1}HNMR of this mixture indicated the impurity was the elusive demetallation product **1.62**. Although the yield was only 10%, it demonstrated that this reaction could be realized in basic condition. We reasoned that this reaction was caused by trace air dissolved in DMSO.

Scheme 31. Unexpected formation of demetallation product



Further study focusing on exposing the metal complex to air in the presence of NaH showed that this reaction was so inefficient that only around 30-40% conversion could be achieved even after stirring for several days. Realizing that copper salts could be utilized as a catalyst in Wacker reaction, 0.2 equiv $CuCl_2$ was added and the reaction furnished the demetallation product in 89% yield after 3 days. Using 4 equiv $CuCl_2$ accelerated the reaction so full conversion was achieved within 12 hours (**Table 10**).

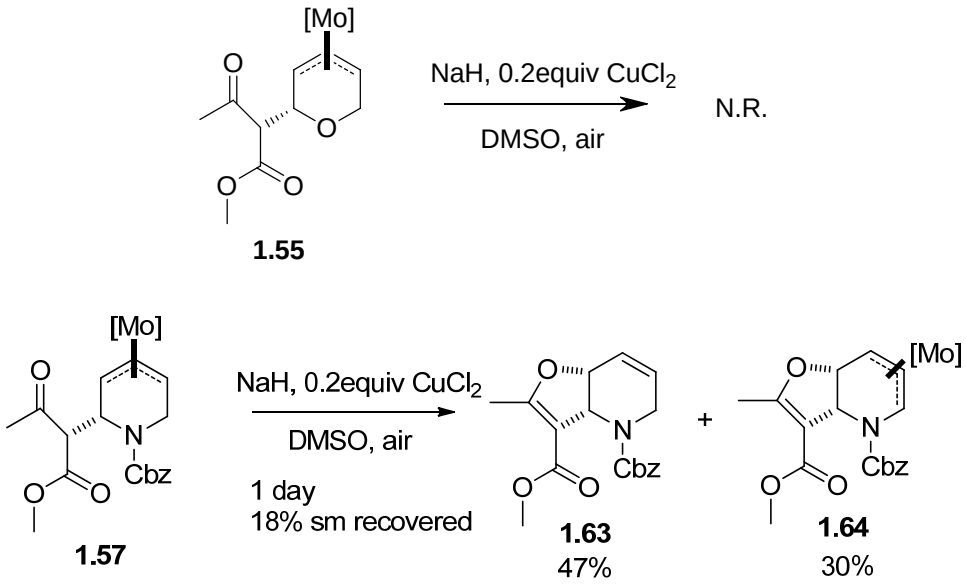
Table 10. Discovery of annulative demetallation



Entry	Additive	Time	Yield(%)
1	None	3 days	30-40
2	0.2 equiv $CuCl_2$	3 days	89
3	4 equiv $CuCl_2$	12 hours	89

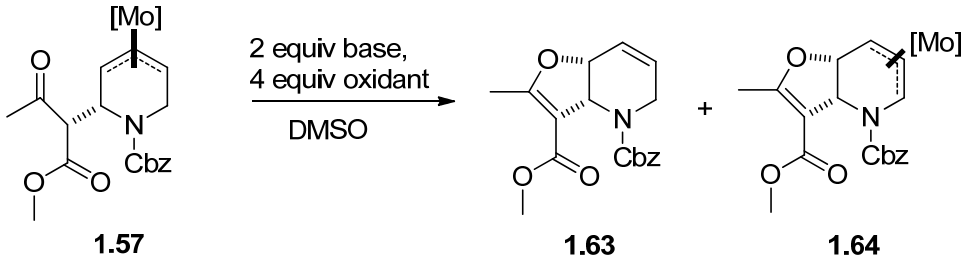
When the reaction was expanded to additional substrates, the results indicated optimization was still needed (**Scheme 32**). In one case, the complex **1.55** containing acetoacetate did not react in the previous condition. In the other case, the complex **1.57** afforded 47% demetallation product **1.63** and 30% **1.64** tentatively assigned as the following structure, with 18% starting material recovered.

Scheme 32. Unsuccessful results with $CuCl_2$



A general condition was still required before this homo-S_N2'-like reaction-annulative demetallation sequence became synthetically useful. Consequently, an extensive screening of bases and oxidants was conducted to solve the problem (**Table 11**). The demetallation of **1.57** was chosen as the model reaction considering its potential application in the synthesis of isofebrifugine. This table showed that in this annulative demetallation the role of oxidants was so crucial that it could totally invert the ratio of products. Finally, copper carboxylate was identified to favor the formation of the full demetallation product **1.63**.

Table 11. Screening of Bases and Oxidants

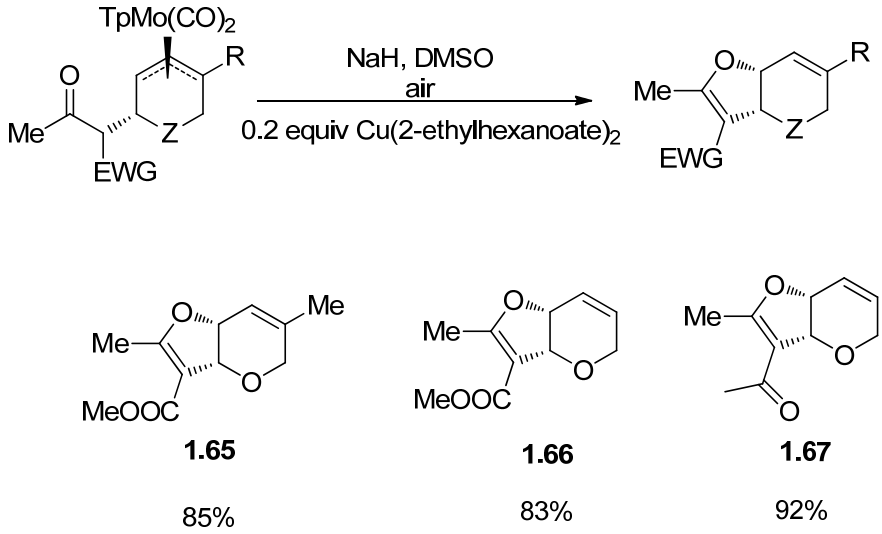


1.57 **1.63** **1.64**

entry	base	oxidant	**1.63** (%)	**1.64** (%)	**1.57** (%)
1	TEA	$CuCl_2$	NR	NR	98
2	DBU	$CuCl_2$	45	30	18
3	NaH	CAN	24	48	19
4	NaH	MnO_2	35	40	20
5	NaH	$Pb(OAc)_4$	29	32	31
6	NaH	$Cu(acac)_2$	25	40	21
7	NaH	$Cu(OAc)_2$	86	1-2	0
8	NaH	$Cu(2\text{-ethylhexanoate})_2$	88	1-2	0

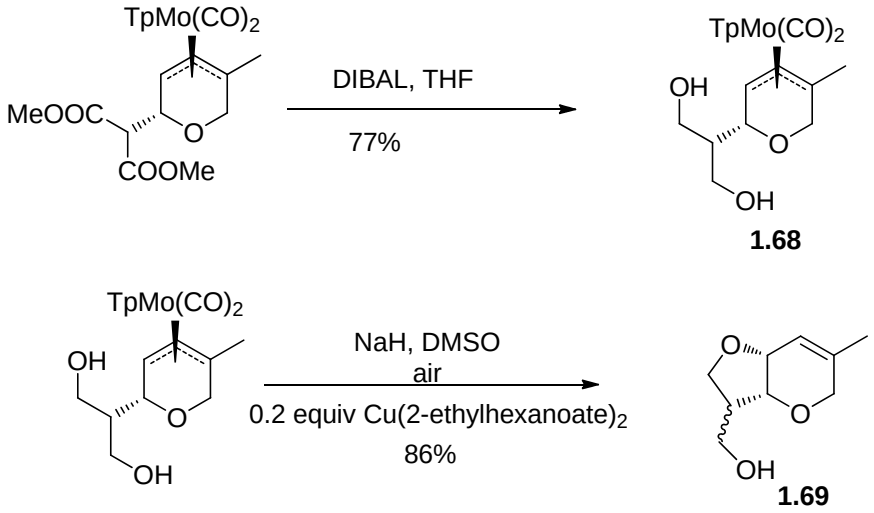
Gratifyingly, this condition did not only work with the complex **1.57**, but also successfully demetallated a wide range of homo-S_N2'-like reaction products (**Scheme 33**). For example, the complex **1.55** was successfully converted to **1.66** in very good yield.

Scheme 33. Demetallation with a variety of substrates



Moreover, not only was an enolate successfully employed in the demetallation, but alkoxide **1.68** was shown to react (**Scheme 34**).

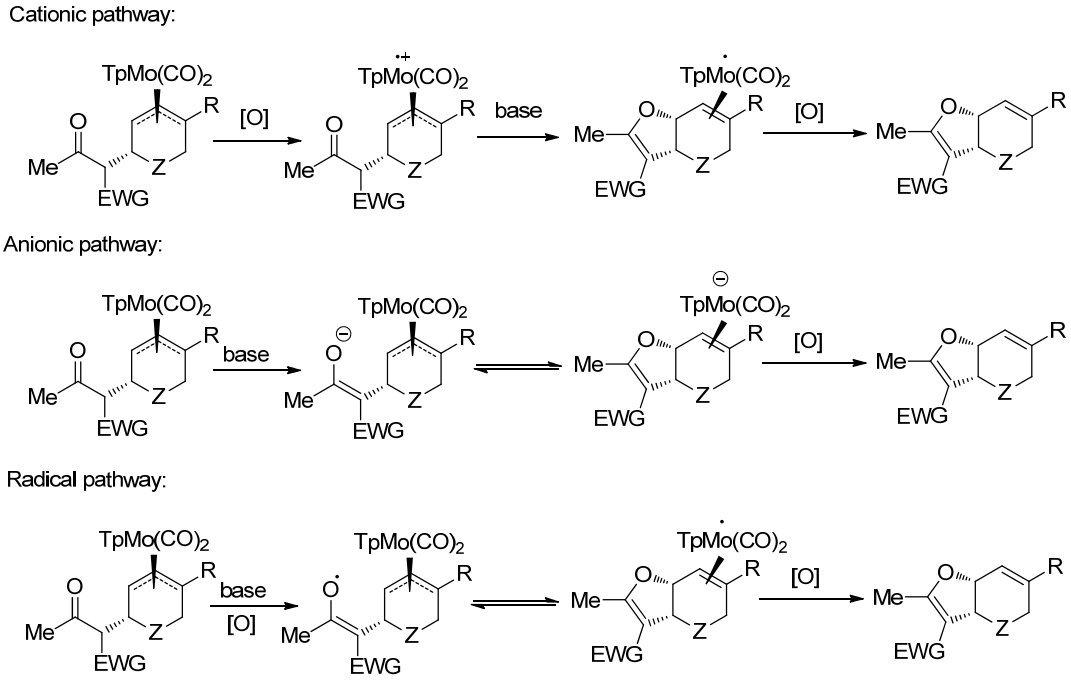
Scheme 34. Demetallation with alkoxide as a nucleophile



For the mechanism of this demetallation, there are three possible pathways (**Scheme 35**). The first is cationic pathway, in which molybdenum is first oxidized to

radical cation quenched by intramolecular nucleophilic attack. This is the most classic demetallation pathway for molybdenum complex. Nevertheless, it was disfavored in this copper mediated demetallation because the complex could be recovered nearly quantitatively in the absence of base or intramolecular nucleophiles, which contradicted with the irreversible oxidation implied by the cationic pathway. The latter two pathways are different only in the sequence of the oxidation, which is difficult to differentiate. Currently, we cannot tell which pathway is the one operating in the system. However, it is worth noting that there may be a mechanistic manifold in which different oxidants and nucleophiles may lead to different pathways.

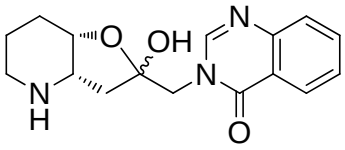
Scheme 35. Three possible mechanism pathways for the demetallation



Total synthesis of (+)-isofebrifugine

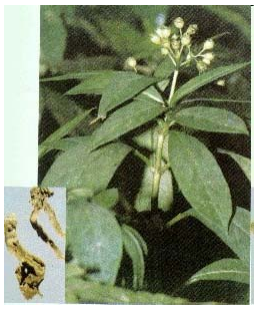
With this novel homo-S_N2'-like reaction-annulative demetallation sequence in hand, we planned to demonstrate its power by applying it in a total synthesis of an interesting natural product. Isofebrifugine was chosen based on two considerations (**Figure 7**). One was that it contained a 2,3-disubstituted piperidine motif, which our methodology could construct enanitioselectively and rapidly. The other was due to its demonstrated high antimalaria activity which required a synthetic route to readily access its analogues in order to lead to the discovery of a new type of antimalaria drug.[37]

Figure 7. Isofebrifugine: antimalarial agent isolated from Chinese plant *Dichroa febrifuga*



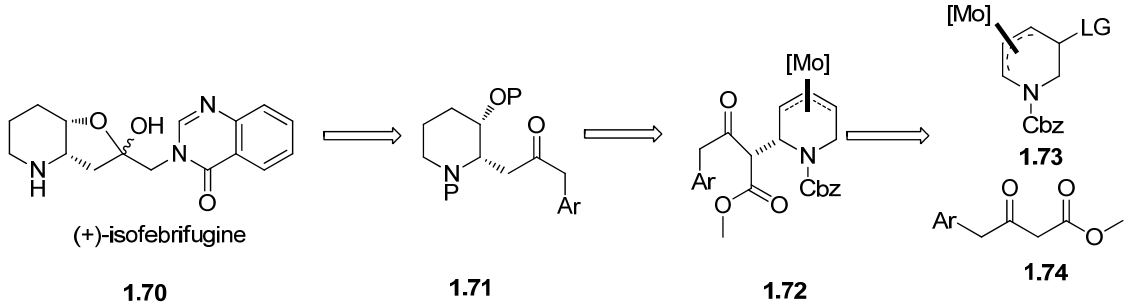
(+)-isofebrifugine

1.70



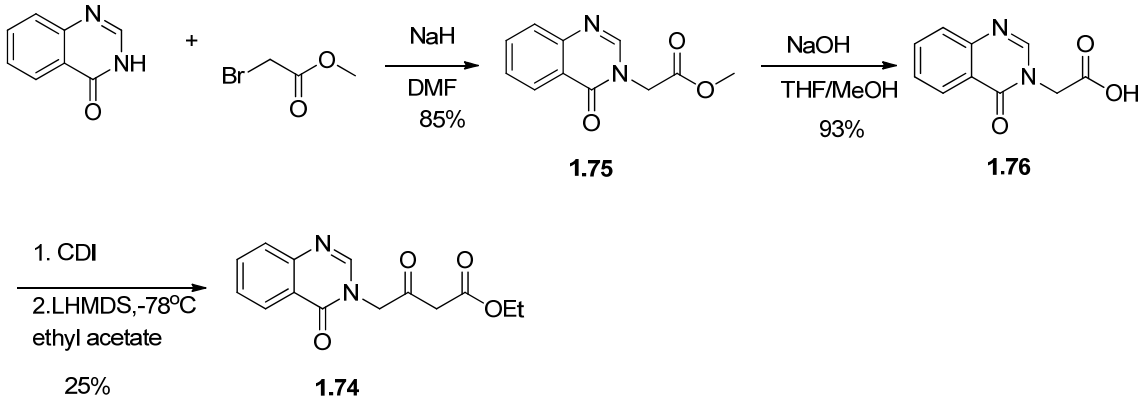
The first retrosynthetic plan was highly convergent (**Scheme 36**). The key intermediate in the synthesis is the 2,3-disubstituted **1.71**, which would be accessed through **1.72** by employing the above methodology. Therefore the synthesis required **1.73**, in which *p*-nitrobenzoate was the leaving group, and **1.74** as the starting material. For efficiency, the racemic complex was initially studied as a model.

Scheme 36. The first retrosynthetic plan for isofebrifugine



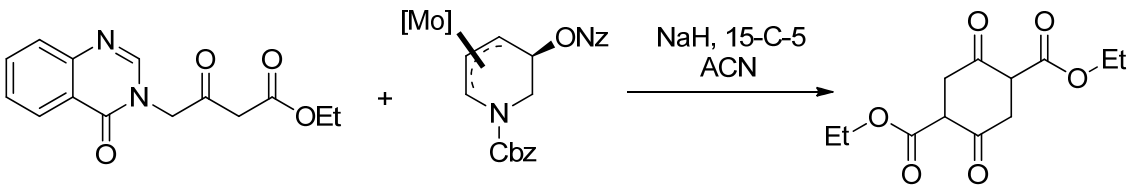
First, the compound **1.74** was prepared by following the route showing in Scheme **37**. Quinazolinone reacted with bromoacetate to form **1.75**, which was hydrolyzed to the acid **1.76** in a good yield. Further acylation of ethyl acetate with activated **1.76** furnished **1.74** in low yield. In order to test the viability of this synthetic route to isofebrifugine, no optimization was attempted at this stage.

Scheme 37. Synthesis of starting material 1.74



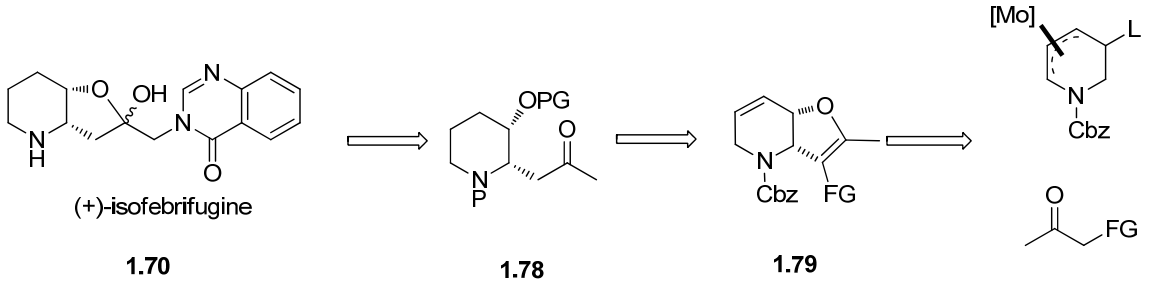
However, the homo-S_N2'-like reaction failed to provide **1.72** with the heterocycle substituted acetoacetate. Only a dimer of acetoacetate **1.77** formed possibly through a double substitution mechanism (**Scheme 38**).

Scheme 38. Homo-S_N2'-like reaction with 1.74



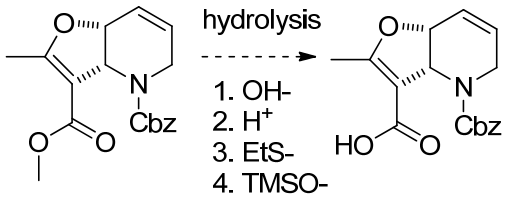
With these results, the synthetic strategy was modified (**Scheme 39**). The hetereocycle was introduced in a late stage so that it would not affect the key step. The intermediate **1.78**, which was envisioned to be the precursor of isofebrifugine, could be converted from **1.79**. It was prepared through the homo-S_N2'-like reaction-annulative demetallation. The most important task in this route was to find an appropriate electron-withdrawing group, which was proved a difficult task.

Scheme 39. Modified retrosynthetic plan for isofebrifugine



Since **1.64** was readily available at that time, we decided to study the decarboxylation to achieve **1.78**. However, a variety of conditions to hydrolyze the ester were studied (**Scheme 40**). All of these conditions failed to yield the hydrolysis product at room temperature, while hydrolysis at high temperature only led to decomposition.

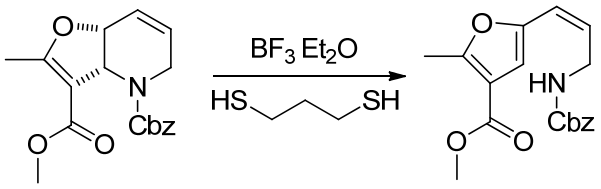
Scheme 40. Hydrolysis efforts to 1.80



1.64 **1.80**

When the compound **1.64** was treated with Lewis acid, an interesting aromatization took place and led to furan **1.81** (**Scheme 41**).

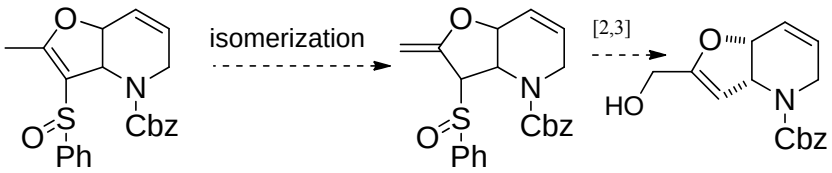
Scheme 41. An unexpected aromatization



1.64 **1.81**

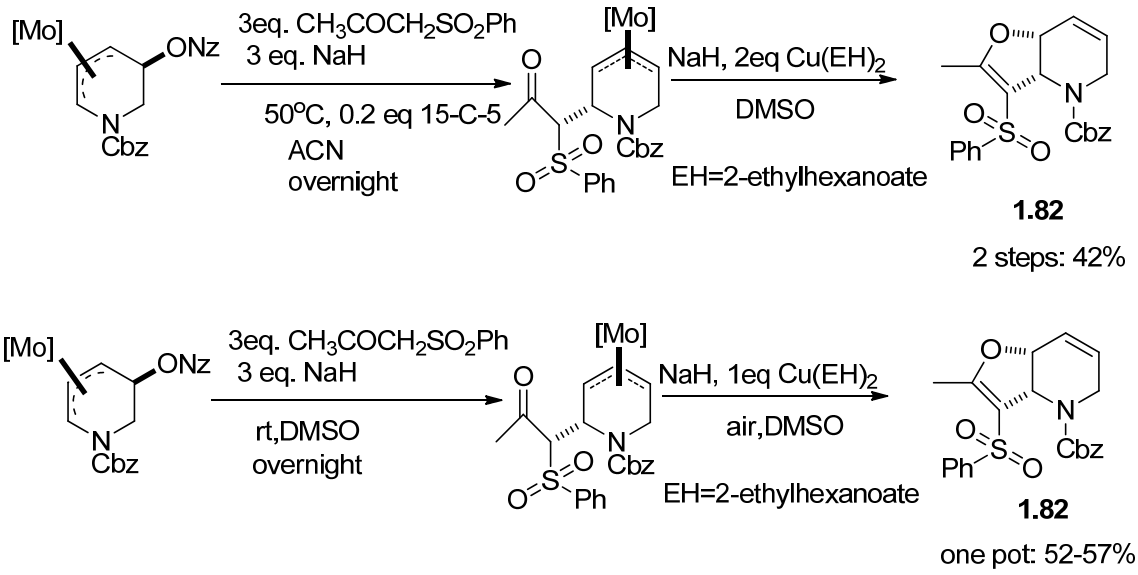
The above results proved that an electron-withdrawing group which was easy to remove was desired. Sulfoxide or sulfonyl groups were proposed to be a good choice. Sulfoxide could be used in a Mislow-Evans rearrangement to functionalize the methyl group so that the heterocycle could be introduced directly (**Scheme 42**). A sulfonyl group should be much easier to remove considering the C-S bond is much easier to cleave than C-C bond.

Scheme 42. Sulfoxide used in Mislow-Evans rearrangement



Although the sulfoxide did not work because the demetallation failed, sulfonyl containing acetone successfully afforded the product **1.82** in a good yield after optimization (**Scheme 43**). The homo-S_N2'-like reaction with phenylsulfonyl acetone worked in ACN at 50 ^oC and DMSO at room temperature. Moreover, in DMSO a one pot demetallation was developed to achieve **1.82** in good yield.

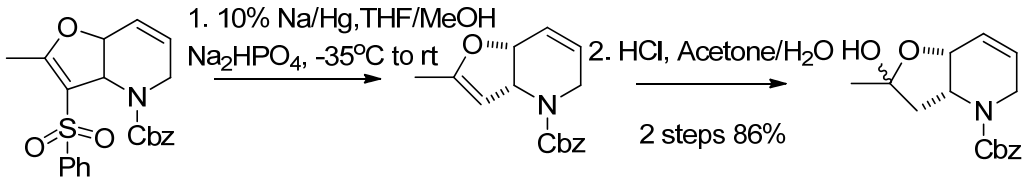
Scheme 43. Phenylsulfonyl acetone as a nucleophile in a one pot reaction



With compound **1.82** in hand, various desulfonyl condition were studied. Different desulfonation methods, including Na/Hg, Raney Ni, Pd/BuMgCl, and Na_2S_2O4, were tested, but only Na/Hg furnished the product **1.83** in a low yield. Consequently, further optimization focused on varying conditions for the reductive desulfonylation with sodium mercury amalgam (**Table 12**). The initial study focused on isolating **1.83** and led

to low yields, although the reaction seemed clean. Thus, we realized that compound **1.83** may be unstable on silica gel due to the existence of the enol ether moiety. As shown in Entry 5, an acidic workup was introduced to achieve **1.84**, which led to a good yield with moderate conversion. Interestingly, as shown in Entry 1 and 2, the conversion was better when the reaction was carried out at a lower temperature. Presumably, the reason was that the reaction between phenylsulfonyl and sodium was not affected so much as the reaction of sodium with the proton source methanol. However, Entry 7 showed that very low temperature only led to decomposition without the formation of product, which was probably caused by the delay of the protonation step. Base on these considerations, the optimal condition for this reaction was found to be conducting the reaction at -35 ^{o}C in a concentrated methanol solution.

Table 12. Optimization of desulfonylation



1.82 **1.83** **1.84**

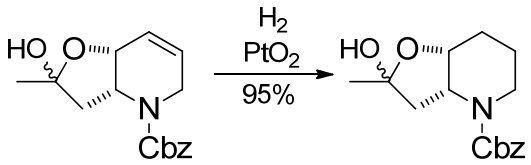
entry	solvent	T^{o}C	additive	conversion(**1.83** Yield)
1	MeOH/THF(0.02M)	20	Na_2HPO_4	50% (<10%)
2	MeOH/THF(0.02M)	-20	Na_2HPO_4	60% (<10%)
3	MeOH/THF(0.02M)	20	NaH_2PO_4	0
4	MeOH/THF(0.02M)	20	none	50% (<10%)

5	MeOH/THF(0.02M)	20	none	50% (40%)*
6	*t*-BuOH(0.02M)	20	none	Complex mixture
7	MeOH/THF(0.02M)	-78	Na_2HPO_4	Complex mixture
8	MeOH/THF(0.02M)	-35	Na_2HPO_4	70% (54%)*
9	MeOH/THF(0.1M)	-35	Na_2HPO_4	>95% (86%)*

* The yield of **1.84** was reported.

Further hydrogenation of **1.84** with PtO_2 as the catalyst proceeded as desired **(Scheme 44**).

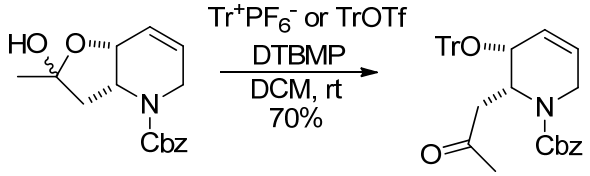
Scheme 44. Hydrogenation of 1.84



1.84 **1.85**

However, the selective protection of the hemiketal as a ketone proved to be difficult. Acylation led to very low conversion even in reflux conditions. Finally, $TrPF_6$ was found to be a good choice for this protection (**Scheme 45**). It furnished the compound **1.86** highly selectively in a 70% yield.

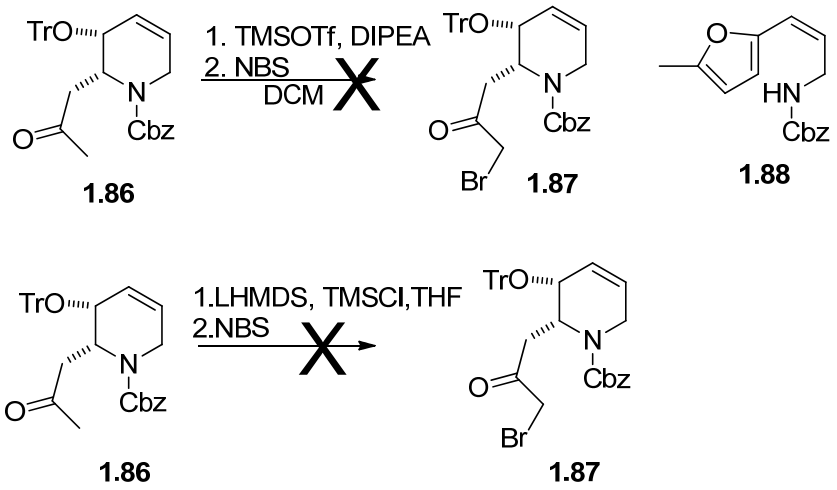
Scheme 45. Protection with the bulky trityl group



1.84 **1.86**

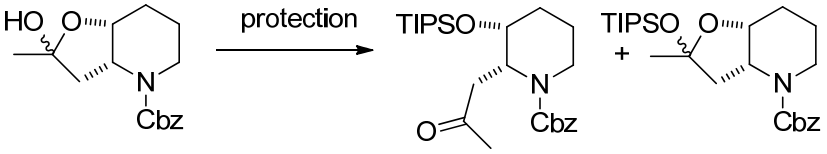
When submitting **1.86** to the bromination conditions, the Lewis acidic condition failed to yield **1.87**; instead, a mixture of deprotection product **1.85** and **1.88** was isolated. The basic enolate formation followed by bromination led only to decomposition to a complex mixture (**Scheme 46**).

Scheme 46. Bromination of 1.86



Considering the successful protection with a trityl group and its failure under acidic bromination conditions, we reasoned that a bulky protective group that was stable to Lewis acid was required for the success of the synthesis. Therefore, TIPS was selected as a protecting group (**Table 13**). When TIPSOTf was used as the reagent, it furnished the desired product **1.89** only in 25% yield with 40% undesired product **1.90**. Fortunately, when conducting this reaction with TIPSCl in DMF, it afforded **1.89** selectively in 75% yield with 20% starting material recovered.

Table 13. TIPS protection

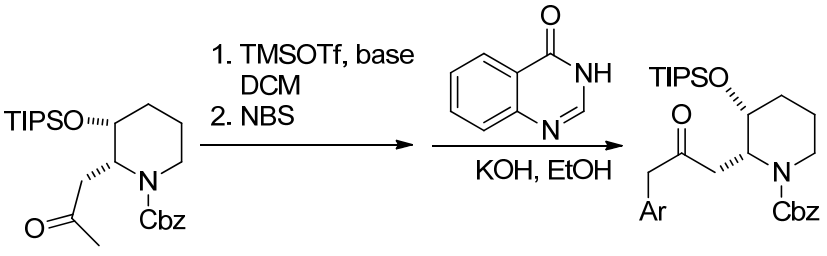


1.85 **1.89** **1.90**

Entry	Condition	**1.89**	**1.90**
1	TIPSOTf, DCM	25%	40%
2	TIPSCl, imidazole, DMF	75% (20% SM)	0

The ketone **1.89** was converted to silyl enol ether with TMSOTf in the presence of DIPEA, then brominated by treating with NBS to afford the bromoketone. Direct substitution of the bromoketone with quinazolinone provided **1.91** in a very low yield (**Table 14**). Interestingly, when switching the base from DIPEA to TEA, the reaction yield was increased to 60%. The reason for this improvement was likely due to the presence of the bulky TIPS group, which required a less encumbered base to deprotonate.

Table 14. Bromination and heterocycle introduction on 1.89

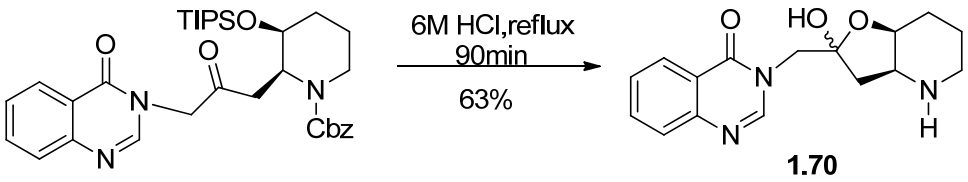


1.89 **1.91**

Entry	base	yield
1	DIPEA	<10%
2	TEA	60%

The final global deprotection was realized by following a known protocol: refluxing the intermediate **1.91** in 6 M HCl for 90 minutes furnished the final natural product **1.70** in 63% yield (**Scheme 47**).

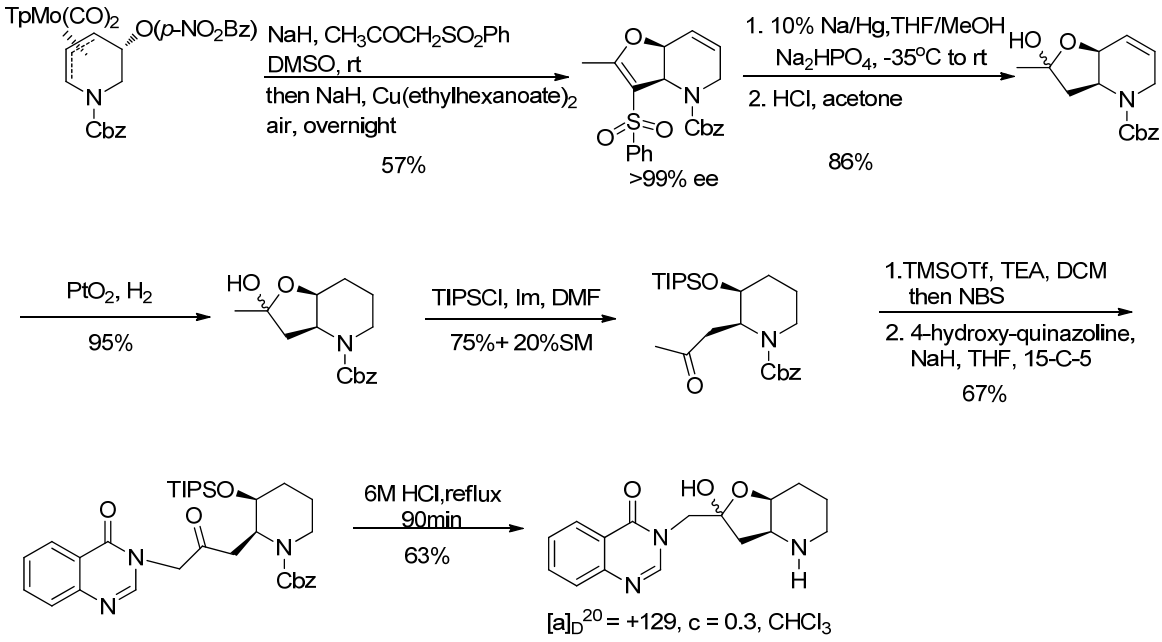
Scheme 47. Global deprotection



1.70

Based on the experience with the racemic compound, the enantiopure scaffold was employed to synthesize (+)-isofebrifugine. The synthetic route is summarized in **Scheme 1.48**. The final product demonstrated the identical ^{1}HNMR, ^{13}CNMR, mass and optical rotation.

Scheme 48. Total synthesis of (+)-isofebrifugine



Conclusion

In this Chapter, we reported a novel homo-S_N2'-like reaction between neutral $TpMo(CO)_2$(5-acyloxy-η^3-pyranyl) and $TpMo(CO)_2$(5-acyloxy-η^3-pyridinyl) scaffolds and a variety of stabilized carbonanion nucleophiles. This reaction provided a powerful methodology to construct C-C bonds stereoselectively. Moreover, it proceeded through an interesting anionic mechanism and preliminary mechanistic study was reported. Based on the Mo complex produced in the reaction, a mechanistically related annulative demetallation was developed to furnish the framework of 2,7-dioxabicyclo[4.3.0]nonane and 2-aza-7-oxabicyclo[4.3.0]nonane in good to excellent yields. In order to demonstrate the power of this new reaction sequence, (+)-isofebrifugine was synthesized in a concise sequence by employing the homo-S_N2'-like-annulative demetallation sequence.

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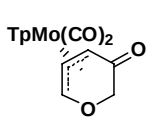
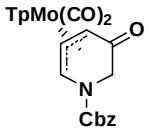
Experimental Section

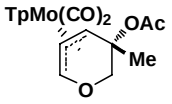


1.42



1.43

(+) and (±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(2R,5R)(η-2,3,4)-5-acetoxy-5methyl-5,6-dihydro-2H-pyran-2-yl]molybdenum, (+)-1.47 and (±)-1.47



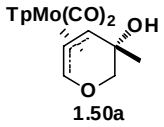
1.47

To a suspension of (±)-**1.42** (500 mg, 1.08 mmol, 1.0 equiv) in THF (25 mL) was added methylmagnesium bromide (3.0 M in Et_2O, 0.54 mL, 1.62 mmol, 1.5 equiv) at -78 °C. The reaction mixture was slowly warmed to 0 °C over 30 minutes, stirred at 0 °C for

40 minutes, and then quenched with Ac_2O (176 mg, 1.73 mmol, 1.6 equiv). After stirring for 1 h at room temperature, the mixture was poured into a separatory funnel containing EtOAc (15 mL) and H_2O (15 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 10 mL), and the combined organic layer were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (3:1) afforded (±)–**1.47** (406 mg, 0.78 mmol, 72%) as a yellow solid.

Similar treatment of (+)-**1.42** (53 mg, 0.11 mmol, 1.0 equiv, 96% ee) in THF (3 mL) with methylmagnesium bromide (3.0 M in Et_2O, 0.06 mL, 0.16 mmol, 1.5 equiv) afforded (2R, 5R)-(+)-**1.47** (34 mg, 0.065 mmol, 60%) {$[\alpha]_D^{20}$ = +256.3, (c = 0.3, CH_2Cl_2)}, TLC (R_f =0.6, 2.5:1 hexanes: EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.51 (d, *J* = 1.6 Hz, 1 H), 7.91 (d, *J* = 2.0 Hz, 1 H), 7.66 (d, *J* = 2.0 Hz, 1 H), 7.58 (d, *J* = 2.0 Hz, 1 H), 7.55 (d, *J* = 1.6 Hz, 1 H), 7.49 (d, *J* = 2.4 Hz, 1 H), 7.01 (dd, *J* = 4.4 Hz, 2.4 Hz, 1 H), 6.28 (t, *J* = 2.0 Hz, 1 H), 6.20 (t, *J* = 2.0 Hz, 1 H), 6.18 (t, *J* = 2.0 Hz, 1 H), 5.25 (d, *J* = 8.0 Hz, 1 H), 3.49 (d, *J* = 11.2 Hz, 1 H), 3.34 (dd, *J* = 8.0 Hz, 3.6 Hz, 1 H), 2.56 (d, *J* = 10.8 Hz, 1 H), 2.02 (s, 3 H), 1.88 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 228.1 (Mo-CO), 224.7 (Mo-CO), 170.9 ($CH_3\underline{C}OO$), 146.7 (CH), 142.9 (CH), 141.5 (CH), 136.01 (CH), 135.96 (CH), 134.4 (CH), 109.7 (CH), 105.9 (CH), 105.6 (CH), 105.4 (CH), 79.1, 71.4, 70.8, 56.4, 29.1 (CH_3), 21.9 (CH_3). IR (cm^{-1}) 2968 (w), 2468 (m), 1945 (s), 1857 (s), 1729 (s). HRMS (FAB) Calcd. for $C_{19}H_{21}BMoN_6O_5$ ($[M+Na]^+$): 545.0618. Found: 545.0632.

Dicarbonyl[hydridotris(1-pyrazolyl)borato][(η-2,3,4)-5-hydroxy-5-methyl-5,6-dihydro-2H-pyran-2-yl]molybdenum, (±)-1.50a

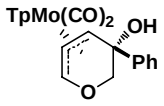


1.50a

To a suspension of (±)-**1.42** (500 mg, 1.08 mmol, 1.0 equiv) in THF (25 mL) was added methylmagnesium bromide (3.0 M in Et_2O, 0.54 mL, 1.62 mmol, 1.5 equiv) at -78 °C. The reaction mixture was slowly warmed to 0 °C over 30 minutes, stirred at 0 °C for 40 minutes, and then quenched with saturated NH_4Cl solution. The mixture was poured into a separatory funnel containing EtOAc (15 mL) and H_2O (15 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 10 mL), and the combined organic layer were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (3:1) afforded (±)–**1.50a** (446 mg, 0.93 mmol, 86%) as a yellow solid.

TLC (R_f = 0.37, 2.5:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 2.0 Hz, 1 H), 7.88 (d, *J* = 2.0 Hz, 1 H), 7.72 (d, *J* = 2.0 Hz, 1 H), 7.59 (d, *J* = 2.4 Hz, 1 H), 7.58 (d, *J* = 2.4 Hz, 1 H), 7.51 (d, *J* = 2.4 Hz, 1 H), 6.99 (dd, *J* = 4.4 Hz, 2.0 Hz, 1 H),6.29 (t, *J* = 2.4 Hz, 1 H), 6.21 (t, *J* = 2.4 Hz, 1 H), 6.20 (t, *J* = 2.4 Hz, 1 H), 4.52 (d, *J* = 7.6 Hz, 1 H), 3.42 (dd, *J* = 7.2 Hz, 4.0 Hz, 1 H), 3.34 (d, *J* = 10.8 Hz, 1 H), 2.82 (s, 1 H), 2.50 (d, *J* = 10.8 Hz, 1 H), 1.60 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 233.1, 223.8, 146.8, 142.0, 141.9, 136.14, 136.09, 134.5, 110.2, 106.0, 105.7, 105.4, 76.4, 73.2, 70.5, 57.6, 32.4. IR (cm^{-1}) 3459 (w), 3150 (w), 2972 (w), 2482 (m), 1934 (s), 1841 (s).

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(η-2,3,4)-5-hydroxy-5-phenyl-5,6-dihydro-2H-pyran-2-yl]molybdenum, (±)-1.50b

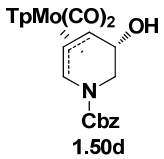


1.50b

To a suspension of (±)-**1.42** (200 mg, 0.43 mmol, 1.0 equiv) in THF (25 mL) was added phenylmagnesium bromide (3.0 M in Et_2O, 0.22 mL, 0.65 mmol, 1.5 equiv) at 0 °C. The reaction mixture stirred at 0 °C for 30 minutes, and then quenched with saturated NH_4Cl. The mixture was poured into a separatory funnel containing EtOAc (15 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 10 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (2:1) afforded (±)–**1.50b**(174 mg, 0.32 mmol, 75%) as an orange solid.

TLC (R_f =0.37, 2.5:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 2.0 Hz, 1 H), 7.86 (d, *J* = 2.0 Hz, 1 H), 7.81 (d, *J* = 1.2 Hz, 1 H), 7.79 (d, *J* = 1.2 Hz, 1 H), 7.74 (d, *J* = 1.6 Hz, 1 H), 7.58 (d, *J* = 2.0 Hz, 1 H), 7.56 (d, *J* = 2.0 Hz, 1 H), 7.51 (d, *J* = 2.0 Hz, 1 H), 7.38-7.42 (m, 2 H), 7.27-7.32 (m, 1 H), 7.13 (dd, *J* = 4.4 Hz, 2.0 Hz, 1 H), 6.31 (t, *J* = 2.0 Hz, 1 H), 6.21 (t, *J* = 2.0 Hz, 1 H), 6.16 (t, *J* = 2.4 Hz, 1 H), 4.63 (d, *J* = 7.6 Hz, 1 H), 3.83 (d, *J* = 11.6 Hz, 1 H), 3.51 (dd, *J* = 8.0 Hz, 4.8 Hz, 1 H), 2.85 (d, *J* = 11.2 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 233.2 (Mo-CO), 224.0 (Mo-CO), 148.7, 146.9, 142.3, 141.7, 136.1, 134.5, 128.5, 127.4, 124.5, 109.5, 106.1, 105.7, 105.3, 77.7, 77.2, 73.1, 72.8, 58.7. IR (cm^{-1}) 3451 (w), 3142 (w), 2482 (m), 1942 (s), 1849 (s), 1505 (s). HRMS (FAB) Calcd. for $C_{22}H_{21}BMoN_6O_4$ ($[M+H]^+$): 543.0844. Found: 543.0849. ($[M-OH]^+$): 525.0739. Found: 525.0739.

(+) and (±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(2R,5R)-(η-2,3,4)-1-benzyloxycarbonyl5-hydroxy-5,6-dihydro-2H-pyridin-2-yl]molybdenum, (+)-1.50d and (±)-1.50d



1.50d

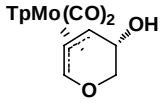
To a solution of (±)-**1.43** (500 mg, 0.84 mmol, 1.0 equiv) in THF (30 mL) was added DIBAL (1.0 M in hexane, 1.3 mL, 1.3 mmol, 1.6 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 20 minutes, and then quenched with potassium sodium tartrate tetrahydrate (740 mg, 2.52 mmol, 3.0 equiv) and H_2O (10 mL). The mixture was poured into a separatory funnel containing EtOAc (15 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 25 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (2:1) afforded (±)–**1.50d** (462 mg, 0.78 mmol, 93%) as an orange solid.

Similar treatment of (+)-**1.43** (500 mg, 0.84 mmol, 1.0 equiv, >99% ee) in THF (30 mL) with DIBAL (1.0 M in hexane, 2.1 mL, 2.10 mmol, 2.5 equiv) afforded (2R, 5R)-(+)-**1.50d** (458 mg, 0.77 mmol, 92%) {$[\alpha]_D^{20}$ = +467, (c = 0.1, CH_2Cl_2)}

TLC (R_f = 0.29, 2.5:1 hexanes:EtOAc). ^{1}H NMR (a mixture of two rotamers) (400 MHz, $CDCl_3$) δ 8.45 (d, *J* = 2.0 Hz, 0.4 H), 8.44 (d, *J* = 1.6 Hz, 0.6 H), 8.20 (d, *J* = 1.6 Hz, 0.6 H), 7.80 (d, *J* = 2.0 Hz, 0.4 H), 7.79 (d, *J* = 2.0 Hz, 0.6 H), 7.63 (d, *J* = 2.0 Hz, 0.6 H), 7.59-7.61 (m, 1.2 H), 7.57 (d, *J* = 2.4 Hz, 0.4 H), 7.56 (d, *J* = 2.0 Hz, 0.4 H), 7.47-7.51 (m, 2.0 H), 7.30-7.41 (m, 4.0 H), 7.14 (dd, *J* = 6.0 Hz, 1.6 Hz, 0.6 H), 6.91 (dd, *J* = 6.0 Hz, 1.2 Hz, 0.4 H), 6.23 (t, *J* = 2.0 Hz, 1.2 H), 6.20 (t, *J* = 2.0 Hz, 0.6 H), 6.16-

6.18 (m, 0.8 H), 5.97 (t, J = 2.0 Hz, 0.4 H), 5.35 (d, J = 11.6 Hz, 0.4 H), 5.23 (d, J = 12.4 Hz, 1.2 H), 5.21 (d, J = 12.0 Hz, 0.4 H), 4.68-4.79 (m, 2 H), 3.80 (dd, J = 12.4 Hz, 6.8 Hz, 0.4 H), 3.74 (dd, J = 12.0 Hz, 6.4 Hz, 0.6 H), 3.42 (t, J = 6.8 Hz, 0.6 H), 3.31 (t, J = 6.4 Hz, 0.4 H), 2.81 (br s, 1 H), 1.91 (t, J = 12.0 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 232.5 (Mo-CO), 231.8 (Mo-CO), 223.8 (Mo-CO), 223.5 (Mo-CO), 155.7 (Cbz carbonyl), 155.2 (Cbz carbonyl), 146.75, 146.68, 143.9, 143.0, 140.8, 140.6, 135.98, 135.96, 135.9, 135.7, 134.4, 128.7, 128.6, 128.4, 128.0, 127.8, 105.9, 105.7, 105.5, 105.4, 92.5, 91.0, 69.0, 68.4, 68.3, 67.7, 67.6, 57.7, 57.4, 47.21 (N-CH_2), 47.20 (N-CH_2). IR (cm^{-1}) 3439 (w), 3127 (w), 2486 (m), 1942 (s), 1841 (s), 1695 (s), 1505 (s). HRMS (ESI) Calcd. for $C_{24}H_{24}BMoN_7O_5$ ($[M+NH_4]^+$): 617.1324. Found: 617.1325.

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(*η*-2,3,4)-5-hydroxy-5,6-dihydro-2H-pyran-2-yl]molybdenum, (±)-1.50c



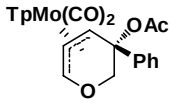
1.50c

To a solution of (±)-**1.42** (500 mg, 1.08 mmol, 1.0 equiv) in THF (30 mL) was added DIBAL (1.0 M in hexane, 1.62 mL, 1.62 mmol, 1.5 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 20 minutes, and then quenched with potassium sodium tartrate tetrahydrate (610 mg, 2.16 mmol, 2.0 equiv) and H_2O (10 mL). The mixture was poured into a separatory funnel containing EtOAc (15 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 15 mL), and the combined organic layer was dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel

with hexanes-EtOAc (2:1) afforded (±)–**1.50c** (464 mg, 1.00 mmol, 93%) as an orange solid.

TLC (R_f = 0.27, 2.5:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (d, *J* = 2.0 Hz, 1 H), 7.88 (d, *J* = 2.0 Hz, 1 H), 7.72 (d, *J* = 2.0 Hz, 1 H), 7.57-7.60 (m, 1 H), 7.51 (d, *J* = 1.6 Hz, 1 H), 6.99 (dd, *J* = 4.4 Hz, 2.4 Hz, 1 H), 6.30 (t, *J* = 2.4 Hz, 1 H), 6.22 (t, *J* = 2.4 Hz, 1 H), 6.20 (t, *J* = 2.4 Hz, 1 H), 4.62-4.72 (m, 2 H), 3.68 (dd, *J* = 11.2 Hz, 6.4 Hz, 1 H), 3.45 (dd, *J* = 7.6 Hz, 4.4 Hz, 1 H), 2.50 (br s, 1 H), 2.37 (t, *J* = 10.4 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 232.4 (Mo-CO), 223.9 (Mo-CO), 146.8 (CH), 142.0 (CH), 141.9 (CH), 136.14 (CH), 136.09 (CH), 134.5 (CH), 110.3 (CH), 106.1 (CH), 105.7 (CH), 105.4 (CH), 71.7, 68.0, 67.2, 57.9. IR (cm^{-1}) 3127 (w), 2957 (w), 2490 (m), 1957 (s), 1872 (s), 1660 (s). HRMS (ESI) Calcd. for $C_{16}H_{17}BMoN_6O_4$ ([M-H]$^-$): 465.0375. Found: 465.0375.

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(η-2,3,4)-5-acetoxy-5-phenyl-5,6-dihydro2H-pyran-2-yl]molybdenum, (±)-1.51b



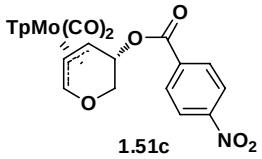
1.51b

To a solution of (±)-**1.50b** (138 mg, 0.26 mmol, 1.0 equiv) in DCM (20 mL) was added DMAP (122 mg, 0.78 mmol, 3.0 equiv), TEA (78 mg, 0.77 mmol, 3.0 equiv) and Ac_2O (85 mg, 0.77 mmol, 3.0 equiv). The reaction mixture was stirred at 40 °C overnight, and then quenched with water. The mixture was poured into a separatory funnel containing EtOAc (15 mL) and H_2O (15mL), and the layers were separated. The aqueous layer was

extracted with EtOAc (2 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (3:1) afforded (±)–**1.51b** (129 mg, 0.22 mmol, 85%) as a yellow solid.

TLC (R_f = 0.57, 2.5:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 2.0 Hz, 1 H), 7.95 (d, *J* = 1.6 Hz, 1 H), 7.65-7.68 (m, 3 H), 7.58-7.60 (m, 2 H),7.52 (d, *J* = 2.4 Hz, 1 H), 7.41 (t, *J* = 7.2 Hz, 2 H), 7.30 (t, *J* = 7.2 Hz, 1 H), 7.13 (dd, *J* = 4.4, 2.0 Hz, 1 H), 6.31 (t, *J* = 2.0 Hz, 1 H), 6.20 (t, *J* = 2.0 Hz, 1 H), 6.19 (t, *J* = 2.0 Hz, 1 H), 4.90 (d, *J* = 7.2 Hz, 1 H), 4.38 (d, *J* = 11.6 Hz, 1 H), 3.50 (dd, *J* = 8.0 Hz, 4.8 Hz, 1 H), 2.96 (d, *J* = 11.6 Hz, 1 H), 2.12 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 228.8 (Mo-CO), 224.9 (Mo-CO), 169.8 ($CH_3\underline{C}OO$), 146.8, 146.1, 142.9, 141.4, 136.0, 134.5, 128.6, 127.4, 124.0, 108.8, 106.0, 105.6, 105.3, 80.3, 77.2, 72.8, 71.2, 57.4, 21.5 (CH_3). IR (cm^{-1}) 3427 (w), 2482 (m), 1945 (s), 1857 (s), 1737 (s), 1710 (s), 1505 (s). HRMS (FAB) Calcd. for $C_{24}H_{23}BMoN_6O_5$ ([M-OAc]$^+$): 525.0739. Found: 525.0745.

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(η-2,3,4)-5-*p*-nitrobenzoyloxy-5,6-dihydro-2Hpyran-2-yl]molybdenum, (±)-1.51c



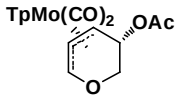
1.51c

To a solution of (±)-**1.50c** (464 mg, 1.00 mmol, 1.0 equiv) in DCM (40 mL) was added DMAP (366 mg, 3.00 mmol, 3.0 equiv), TEA (300 mg, 3.00 mmol, 3.0 equiv) and *p*-nitrobenzoyl chloride (558 mg, 3.00 mmol, 3.0 equiv). The reaction mixture was stirred at 40 °C overnight, and then concentrated to remove DCM and excess TEA. The residue was triturated with EtOAc (60 mL) and then filtered. The organic solution was

concentrated for chromatography. Flash chromatography over silica gel with hexanes-EtOAc (2.7:1) afforded (±)–**1.51c** (594 mg, 0.97 mmol, 97%) as a yellow solid.

TLC (R_f = 0.71, 2.5:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 2.0 Hz, 1 H), 8.24-8.31 (m, 4 H), 7.77 (d, *J* = 2.0 Hz, 1 H), 7.76 (d, *J* = 2.0 Hz, 1 H), 7.61 (d, *J* = 2.4 Hz, 1 H), 7.59 (d, *J* = 2.4 Hz, 1 H), 7.53 (d, *J* = 2.4 Hz, 1 H), 7.10 (dd, *J* = 4.4 Hz, 2.0 Hz, 1 H), 6.29 (t, *J* = 2.0 Hz, 1 H), 6.22 (t, *J* = 2.0 Hz, 1 H), 6.16 (t, *J* = 2.0 Hz, 1 H), 5.97 (ddd, *J* = 10.0 Hz, 6.8 Hz, 2.8 Hz, 1 H), 4.72 (d, *J* = 7.6 Hz, 1 H), 3.81 (dd, *J* = 11.2 Hz, 6.4 Hz, 1 H), 3.54 (dd, *J* = 7.6 Hz, 4.4 Hz, 1 H), 2.69 (t, *J* = 10.4 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 228.6 (Mo-CO), 224.2 (Mo-CO), 164.2 (Ar-COO), 150.5, 146.7, 141.8, 136.13, 136.11, 135.1, 134.5, 131.0, 123.4, 110.3, 106.0, 105.7, 105.3, 77.2, 69.9, 65.2, 64.4, 57.9. IR (cm^{-1}) 3123 (w), 2984 (w), 2486 (m), 1945 (s), 1857 (s), 1722 (s), 1606 (s). HRMS (ESI) Calcd. for $C_{23}H_{20}BMoN_7O_7$ ($[M+H]^+$): 616.0644. Found: 616.0657.

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(η-2,3,4)-5-acetate-5,6-dihydro-2H-pyran-2-yl]molybdenum, (±)-1.51d



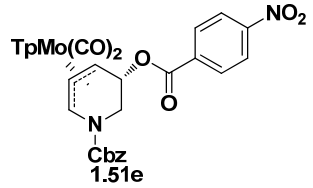
1.51d

To a solution of (±)-**1.50c** (200 mg, 0.43 mmol, 1.0 equiv) in DCM (20 mL) was added DMAP (157 mg, 1.29 mmol, 3.0 equiv), TEA (129 mg, 1.29 mmol, 3.0 equiv) and acetic anhydride (132 mg, 1.29 mmol, 3.0 equiv). The reaction mixture was stirred at 40 °C overnight, and then concentrated to remove DCM and excess TEA. The mixture was poured into a separatory funnel containing EtOAc (15 mL) and H_2O (15mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 10 mL), and the

combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (3:1) afforded (±)–**1.51d** (190 mg, 0.40 mmol, 94%) as a yellow solid.

TLC (R_f = 0.57, 2.5:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (d, *J* = 2.0 Hz, 1 H), 7.76 (d, *J* = 2.0 Hz, 1 H), 7.73 (d, *J* = 2.0 Hz, 1 H), 7.58 (d, *J* = 2.4 Hz, 1 H), 7.57 (d, *J* = 2.0 Hz, 1 H), 7.51 (d, *J* = 2.0 Hz, 1 H), 7.04 (dd, *J* = 4.4 Hz, 2.4 Hz, 1 H), 6.29 (t, *J* = 2.4 Hz, 1 H), 6.20 (t, *J* = 2.0 Hz, 1 H), 6.18 (t, *J* = 2.0 Hz, 1 H), 5.60 (ddd, *J* = 8.8 Hz, 6.4 Hz, 2.8 Hz, 1 H), 4.67 (dt, *J* = 7.6 Hz, 2.4 Hz, 1 H), 3.67 (dd, *J* = 10.8 Hz, 6.8 Hz, 1 H), 3.45 (dd, *J* = 8.0 Hz, 4.0 Hz, 1 H), 2.56 (dd, *J* = 11.2 Hz, 9.6 Hz, 1 H), 2.10 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 227.8 (Mo-CO), 224.6 (Mo-CO), 170.9 ($CH_3\underline{C}OO$), 146.7 (CH), 141.91 (CH), 141.87 (CH), 136.1 (CH), 136.0 (CH), 134.5 (CH), 110.9 (CH), 106.0 (CH), 105.6 (CH), 105.3 (CH), 68.6, 65.1, 64.6, 57.8, 20.9 (CH_3). IR (cm^{-1}) 3146 (w), 2976 (w), 2482 (m), 1945 (s), 1857 (s), 1729 (s). HRMS (ESI) Calcd. for $C_{18}H_{19}BMoN_6O_5$ ($[M]^+$): 508.0559. Found: 508.0569.

(+) and (±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(η-2,3,4)-1-benzyloxycarbonyl5-*p*-nitrobenzoyloxy5,6-dihydro-2H-pyridin-2-yl]molybdenum, (+)-1.51e and (±)-1.51e



1.51e

To a solution of (±)-**1.50d** (500 mg, 0.84 mmol, 1.0 equiv) in DCM (40 mL) was added DMAP (307 mg, 2.52 mmol, 3.0 equiv), TEA (252 mg, 2.52 mmol, 3.0 equiv) and *p*-nitrobenzoyl chloride (469 mg, 2.52 mmol, 3.0 equiv). The reaction mixture was stirred at 40 °C overnight, and then concentrated to remove DCM and excess TEA. The residue

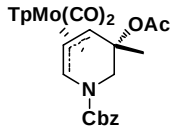
was triturated with EtOAc (60 mL) and then filtered. The organic solution was concentrated for chromatography. Flash chromatography over silica gel with hexanes-EtOAc (3:1) afforded (±)–**1.51e** (597 mg, 0.80 mmol, 95%) as a yellow solid.

Similar treatment of (+)-**1.50d**(500 mg, 0.84 mmol, 1.0 equiv, >99% ee) in DCM (40 mL) with DMAP (307 mg, 2.52 mmol, 3.0 equiv), TEA (252 mg, 2.52 mmol, 3.0 equiv) and *p*-nitrobenzoyl chloride (469 mg, 2.52 mmol, 3.0 equiv) afforded (2R, 5R)-(+)-**1.51e** (574 mg, 0.77 mmol, 92%) {$[\alpha]_D^{20}$ = +242, (c = 0.1, CH_2Cl_2)}

TLC (R_f = 0.58, 2.5:1 hexanes: EtOAc). ^{1}H NMR (a mixture of two rotamers) (400 MHz, $CDCl_3$) δ 8.48 (d, *J* = 2.0 Hz, 1 H), 8.28-8.33 (m, 4 H), 8.25 (d, *J* = 2.0 Hz, 0.6 H), 7.70 (d, *J* = 2.0 Hz, 0.6 H), 7.69 (d, *J* = 2.0 Hz, 0.4 H), 7.66 (d, *J* = 2.0 Hz, 0.4 H), 7.62 (d, *J* = 2.4 Hz, 0.6 H), 7.59 (d, *J* = 2.0 Hz, 0.6 H), 7.57 (d, *J* = 2.4 Hz, 0.4 H), 7.55 (d, *J* = 2.0 Hz, 0.4 H), 7.51 (d, *J* = 2.0 Hz, 1 H), 7.49 (d, *J* = 2.0 Hz, 1 H), 7.29-7.45 (m, 4 H), 7.22 (dd, *J* = 6.4 Hz, 1.6 Hz, 0.6 H), 6.97 (dd, *J* = 6.4 Hz, 1.6 Hz, 0.4 H), 6.26-6.30 (m, 1 H), 6.25 (t, *J* = 2.0 Hz, 0.6 H), 6.16-6.19 (m, 1 H), 6.03-6.11 (m, 1 H), 5.95 (t, *J* = 2.0 Hz, 0.4 H), 5.34 (d, *J* = 12.0 Hz, 0.4 H), 5.23 (d, *J* = 11.6 Hz, 0.4 H), 5.22 (s, 1.2 H), 4.76 (d, *J* = 8.0 Hz, 0.4 H), 4.72 (d, *J* = 7.6 Hz, 0.6 H), 3.82 (t, *J* = 7.6 Hz, 0.4 H), 3.79 (t, *J* = 7.2 Hz, 0.6 H), 3.55 (t, *J* = 6.8 Hz, 0.6 H), 3.47 (t, *J* = 6.4 Hz, 0.4 H), 3.22 (dd, *J* = 12.4 Hz, 9.6 Hz, 0.4 H), 3.20 (dd, *J* = 12.8 Hz, 9.6 Hz, 0.6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 229.7 (Mo-CO), 229.2 (Mo-CO), 224.0 (Mo-CO), 223.7 (Mo-CO), 164.17 (Ar-COO), 164.22 (Ar-COO), 155.6 (Cbz carbonyl), 155.1 (Cbz carbonyl), 150.5, 146.81, 146.76, 144.2, 143.3, 140.7, 140.6, 136.2, 136.1, 135.8, 135.6, 135.14, 135.07, 134.6, 131.1, 128.9, 128.7, 128.51, 128.46, 128.2, 128.1, 123.4, 106.0, 105.8, 105.6, 105.4, 93.4, 92.1, 70.6, 70.5, 68.7, 68.0, 62.1, 62.0, 58.6, 58.1, 43.9 (N-CH_2), 43.8 (N-CH_2). IR (cm^{-1}) 3119

(w), 3061 (w), 2486 (m), 1942 (s), 1853 (s), 1710 (s), 1606 (m), 1529 (s). HRMS (ESI) Calcd. for $C_{31}H_{27}BMoN_8O_8$ ($[M]^+$): 748.1099. Found: 748.1103.

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(η-2,3,4)-1-benzyloxycarbonyl-5-acetoxy5-methyl-5,6-dihydro-2H-pyridin-2-yl]molybdenum, (±)-1.51f



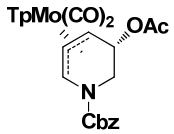
1.51f

To a solution of (±)-**1.50e** (200 mg, 0.34 mmol, 1.0 equiv) in DCM (20 mL) was added DMAP (157 mg, 1.01 mmol, 3.0 equiv), TEA (102 mg, 1.01 mmol, 3.0 equiv) and Ac_2O (111 mg, 1.01 mmol, 3.0 equiv). The reaction mixture was stirred at 40 °C overnight, and then quenched with water. The mixture was poured into a separatory funnel containing EtOAc (15 mL) and H_2O (15mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (3:1) afforded (±)–**1.51f** (195 mg, 0.29 mmol, 88%) as a yellow solid.

TLC (R_f = 0.51, 2.5:1 hexanes:EtOAc). ^{1}H NMR (a mixture of two rotamers) (400 MHz, $CDCl_3$) δ 8.46 (d, *J* = 1.0 Hz, 0.4 H), 8.45 (d, *J* = 0.8 Hz, 0.6 H), 8.13 (d, *J* = 0.8 Hz, 0.6 H), 7.83-7.88 (m, 1 H), 7.55-7.62 (m, 2.4 H), 7.46-7.50 (m, 1.6 H), 7.31-7.43 (m, 4.0 H), 7.20 (d, *J* = 5.2 Hz, 0.6 H), 6.98 (d, *J* = 5.6 Hz, 0.4 H), 6.18-6.24 (m, 2.6 H), 6.00 (br s, 1 H), 5.47 (d, *J* = 7.6 Hz, 0.4 H), 5.39 (d, *J* = 7.2 Hz, 0.6 H), 5.18-5.36 (m, 2 H), 3.63 (d, *J* = 12.8 Hz, 0.4 H), 3.58 (d, *J* = 12.4 Hz, 0.6 H), 3.36 (dd, *J* = 7.6 Hz, 6.4 Hz, 0.6 H), 3.24 (dd, *J* = 7.6 Hz, 6.4 Hz, 0.4 H), 2.02-2.10 (m, 4 H), 1.87 (s, 1.8 H), 1.86 (s,

1.2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ228.8, 228.2, 224.3, 224.1, 171.0, 170.8, 155.9, 155.5, 146.8, 146.7, 143.5, 142.6, 141.9, 141.7, 136.05, 136.00, 135.96, 135.91, 135.9, 135.8, 134.4, 128.6, 128.42, 128.4, 128.1, 127.8, 105.8, 105.7, 105.4, 91.7, 90.1, 80.5, 80.4, 68.7, 68.4, 68.0, 67.8, 56.4, 56.0, 50.6, 50.5, 30.0, 29.9, 22.0, 21.97. IR (cm^{-1}) 3127 (w), 2957 (w), 2482 (m), 1942 (s), 1849 (s), 1729 (s), 1702 (s). HRMS (FAB) Calcd. for $C_{27}H_{28}BMoN_7O_6$ ($[M+NH_4]^+$): 673.1592. Found: 673.1608.

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(η-2,3,4)-1-benzyloxycarbonyl-5-acetoxy-5,6dihydro-2H-pyridin-2-yl]molybdenum, (±)-1.51g



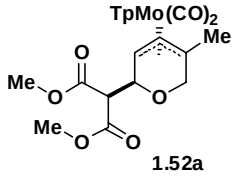
1.51g

To a solution of (±)-**1.50d** (200 mg, 0.34 mmol, 1.0 equiv) in DCM (20 mL) was added DMAP (157 mg, 1.01 mmol, 3.0 equiv), TEA (102 mg, 1.01 mmol, 3.0 equiv) and Ac_2O (111 mg, 1.01 mmol, 3.0 equiv). The reaction mixture was stirred at 40 °C overnight, and then quenched with water. The mixture was poured into a separatory funnel containing EtOAc (15 mL) and H_2O (15mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (3:1) afforded (±)–**1.51g** (204 mg, 0.32 mmol, 95%) as a yellow solid.

TLC (R_f = 0.53, 2.5:1 hexanes:EtOAc). ^1H NMR (a mixture of two rotamers) (400 MHz, $CDCl_3$) δ 8.47 (d, J = 1.2 Hz, 0.6 H), 8.46 (d, J = 2.0 Hz, 0.4 H), 8.24 (d, J = 1.2 Hz, 0.6 H), 7.68 (d, J = 2.0 Hz, 0.6 H), 7.67 (d, J = 2.0 Hz, 0.4 H), 7.64 (d, J = 2.0 Hz, 0.4 H), 7.59 (d, J = 2.4 Hz, 0.6 H), 7.58 (d, J = 2.4 Hz, 0.6 H), 7.55 (d, J = 2.0 Hz, 0.4 H),

7.52 (d, *J* = 2.0 Hz, 0.4 H), 7.45-7.50 (m, 2 H), 7.31-7.42 (m, 4 H), 7.15 (dd, *J* = 6.0 Hz, 1.6 Hz, 0.6 H), 6.89 (dd, *J* = 6.4 Hz, 1.6 Hz, 0.4 H), 6.26 (t, *J* = 2.4 Hz, 1 H), 6.22 (t, *J* = 2.4 Hz, 0.6 H), 6.16-6.19 (m, 1 H), 5.91 (t, *J* = 2.4 Hz, 0.4 H), 5.67-5.77 (m, 1 H), 5.31 (d, *J* = 11.6 Hz, 0.4 H), 5.21 (s, 1.2 H), 5.20 (d, *J* = 11.6 Hz, 0.4 H), 4.69-4.73 (m, 0.4 H), 4.66 (dt, *J* = 8.0 Hz, 2.0 Hz, 0.6 H), 3.64 (quintet, *J* = 6.4 Hz, 1 H), 3.45 (t, *J* = 7.2 Hz, 0.6 H), 3.37 (t, *J* = 6.8 Hz, 0.4 H), 2.18 (dd, *J* = 12.8 Hz, 9.2 Hz, 0.4 H), 2.12 (s, 1.2 H), 2.10 (s, 1.8 H), 2.07 (dd, *J* = 12.4 Hz, 9.6 Hz, 0.6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 228.8 (Mo-CO), 228.5 (Mo-CO), 224.1 (Mo-CO), 223.9 (Mo-CO), 170.8 ($CH_3\underline{C}OO$), 155.7 (Cbz carbonyl), 155.1 (Cbz carbonyl), 146.85, 146.78, 144.4, 143.4, 140.7, 140.6, 136.1, 136.00, 135.95, 135.7, 134.5, 128.9, 128.6, 128.5, 128.1, 128.0, 105.9, 105.8, 105.5, 105.4, 93.8, 92.4, 69.1, 68.9, 68.6, 67.9, 62.1, 61.8, 58.6, 58.1, 43.8 (N-CH_2), 43.7 (N-CH_2), 21.0 ($\underline{C}H_3COO$), 20.9 ($\underline{C}H_3COO$). IR (cm^{-1}) 3127 (w), 3034 (w), 2482 (m), 1942 (s), 1849 (s), 1729 (s), 1702 (s), 1505 (s). HRMS (ESI) Calcd. for $C_{26}H_{26}BMoN_8O_8$ ($[M]^+$): 641.1092. Found: 641.1101. ($[M+NH_4]^+$): 659.1435. Found: 659.1442.

(-) and (±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(*η*-3,4,5)-2-(1´-methoxycarbonyl)methoxycarbonylmethyl-5-methyl-5,6-dihydro-2H-pyran-2-yl]molybdenum, (-)-1.52a and (±)-1.52a



1.52a

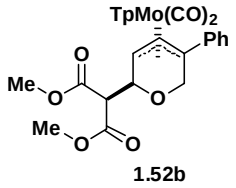
To a solution of (±)-**1.47** (50 mg, 0.096 mmol, 1.0 equiv) in THF (5 mL) was added dimethyl malonate (39.6 mg, 0.30 mmol, 3.1 equiv), 60% NaH dispension (11.6 mg, 0.29 mmol, 3.0 equiv) and 15-crown-5-ether (4.23 mg, 0.019 mmol, 0.2 equiv). The reaction mixture was stirred at room temperature for 8 hours, and then quenched with water. The

mixture was poured into a separatory funnel containing EtOAc (5 mL) and H_2O (5 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (2:1) afforded (±)–**1.52a** (56 mg, 0.095 mmol, 99%) as a yellow solid.

Similar treatment of (+)-**1.47** (34 mg, 0.065 mmol, 1.0 equiv, 96% ee) in THF (3 mL) with malonate (26.6 mg, 0.20 mmol, 3.1 equiv), 60% NaH dispension (7.8 mg, 0.20 mmol, 3.0 equiv) and 15-crown-5-ether (2.86 mg, 0.013 mmol, 0.2 equiv) afforded (2S, 3R)-(-)-**1.52a** (38 mg, 0.065 mmol, 99%, 96% ee) $\{[\alpha]_D^{20} = -375.0, (c = 1.25, CH_2Cl_2)\}$

TLC (R_f = 0.41, 2.5:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 1.2 Hz, 1 H), 7.73 (s, 1 H), 7.61 (m, 3 H), 7.48 (d, *J* = 1.6 Hz, 1 H), 6.24 (br s, 1 H), 6.22 (br s, 1 H), 6.15 (br s, 1 H), 4.52 (dd, *J* = 10.0 Hz, 2.0 Hz, 1 H), 4.16 (t, *J* = 7.2 Hz, 1 H), 3.92 (d, *J* = 7.2 Hz, 1 H), 3.90 (d, *J* = 13.6 Hz, 1 H), 3.84 (s, 3 H), 3.82 (d, *J* = 10.0 Hz, 1 H), 3.75 (s, 3 H), 3.68 (d, *J* = 14.0 Hz, 1 H), 1.87 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 229.8 (Mo-CO), 227.1 (Mo-CO), 167.8 (COOMe), 167.5 (COOMe), 146.9 (CH), 145.3 (CH), 140.2 (CH), 136.6 (CH), 136.0 (CH), 134.3 (CH), 105.7 (CH), 105.6 (CH), 105.1 (CH), 88.5, 70.0, 69.7, 63.4, 59.7, 58.7, 52.8, 52.7, 21.6 (CH_3). IR (cm^{-1}) 3164 (w), 3127 (w), 2957 (m), 2482 (m), 1934 (s), 1841 (s), 1733 (s), 1505 (s). HRMS (FAB) Calcd. for $C_{22}H_{25}BMoN_6O_7$ ($[M+NH_4]^+$): 612.1270. Found: 612.1267. HPLC: Daicel® Chiralcel OJ-RH column, isocratic solvent system: 45 % CH_3CN in H_2O (without TFA), 1.0 mL/min., λ = 254 nm, (2S, 3R)-(-)-**1.52a**: $t_{(-)}$ = 15.9 min; (2R, 3S)-(+)-**1.52a**: $t_{(+)}$ = 18.1 min.

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(η-3,4,5)-2-(1´-methoxycarbonyl)methoxycarbonylmethyl-5-phenyl-5,6-dihydro-2H-pyran-2-yl]molybdenum, (±)-1.52b



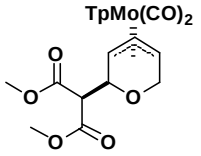
1.52b

To a solution of (±)-**1.51b** (50 mg, 0.084 mmol, 1.0 equiv) in THF (5 mL) was added dimethyl malonate (34 mg, 0.26 mmol, 3.1 equiv), 60% NaH dispension (10 mg, 0.25 mmol, 3.0 equiv) and 15-crown-5-ether (3.7 mg, 0.017 mmol, 0.2 equiv). The reaction mixture was stirred at room temperature for 8 hours, and then quenched with water. The mixture was poured into a separatory funnel containing EtOAc (5 mL) and H_2O (5 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (2:1) afforded (±)–**1.52b** (49 mg, 0.076 mmol, 90%) as a yellow solid.

TLC (R_f = 0.34, 2.5:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 2.0 Hz, 1 H), 7.71 (d, *J* = 2.0 Hz, 1 H), 7.63 (d, *J* = 2.4 Hz, 1 H), 7.44 (d, *J* = 2.0 Hz, 1 H), 7.40 (d, *J* = 2.0 Hz, 1 H), 7.15-7.27 (m, 5 H), 6.27 (t, *J* = 2.0 Hz, 1 H), 6.18 (t, *J* = 2.0 Hz, 1 H), 5.82 (d, *J* = 2.0 Hz, 1 H), 5.58 (t, *J* = 2.0 Hz, 1 H), 4.58-4.64 (m, 2 H), 4.44 (dd, *J* = 8.0 Hz, 2.4 Hz, 1 H), 4.41 (d, *J* = 14.0 Hz, 1 H), 4.14 (d, *J* = 14.0 Hz, 1 H), 3.87 (d, *J* = 7.2 Hz, 1 H), 3.86 (s, 3 H), 3.76 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 230.5 (Mo-CO), 227.2 (Mo-CO), 167.9 (COOMe), 167.5 (COOMe), 147.0, 145.0, 139.9, 137.9, 136.1, 136.0, 134.2, 128.7, 128.1, 126.0, 105.8, 105.6, 104.3, 89.2, 69.9, 65.7, 60.9, 58.9, 58.5,

52.82, 52.78. IR (cm^{-1}) 2957 (w), 2486 (m), 1934 (s), 1853 (s), 1733 (s), 1505 (s). HRMS (FAB) Calcd. for $C_{27}H_{27}BMoN_6O_7$ ($[M+NH_4]^+$): 674.1427. Found: 674.1427.

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(η-3,4,5)-2-(1´-methoxycarbonyl)methoxycarbonylmethyl-5,6-dihydro-2H-pyran-2-yl]molybdenum, (±)-1.52d



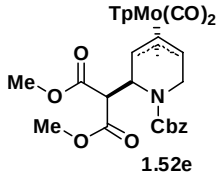
1.52d

To a solution of (±)-**1.51d** (50 mg, 0.098 mmol, 1.0 equiv) in THF (5 mL) was added dimethyl malonate (41 mg, 0.31 mmol, 3.1 equiv), 60% NaH dispension (11.6 mg, 0.29 mmol, 3.0 equiv) and 15-crown-5-ether (4.23 mg, 0.019 mmol, 0.2 equiv). The reaction mixture was stirred at room temperature for 8 hours, and then quenched with water. The mixture was poured into a separatory funnel containing EtOAc (5 mL) and H_2O (5 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (2:1) afforded (±)–**1.52d** (53 mg, 0.092 mmol, 94%) as a yellow solid.

TLC (R_f = 0.31, 2.5:1 hexanes:EtOAc). ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.60 (d, *J* = 1.8 Hz, 1 H), 7.72 (d, *J* = 1.8 Hz, 1 H), 7.65 (d, *J* = 1.2 Hz, 1 H), 7.57 (d, *J* = 1.8 Hz, 2 H), 7.51 (d, *J* = 1.8 Hz, 1 H), 6.30 (t, *J* = 1.8 Hz, 1 H), 6.17 (br s, 2 H), 4.52 (dd, *J* = 11.4 Hz, 1.8 Hz, 1 H), 4.33 (dt, *J* = 7.2 Hz, 1.8 Hz, 1 H), 4.17 (d, *J* = 12.6 Hz, 1 H), 4.09 (d, *J* = 6.6 Hz, 1 H), 3.85 (d, *J* = 11.8 Hz, 1 H), 3.82 (s, 3 H), 3.74-3.77 (m, 4 H), 3.71 (dd, *J* = 12.6 Hz, 1.8 Hz, 1 H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 225.5, 224.4, 167.9, 167.5, 147.3,

142.2, 141.1, 136.02, 135.96, 134.4, 106.0, 105.43, 105.37, 69.8, 68.7, 66.0, 63.2, 58.8, 58.6, 52.8, 52.7. IR (cm^{-1}) 3150 (w), 2957 (m), 2486 (m), 1942 (s), 1857 (s), 1733 (s). HRMS (ESI) Calcd. for $C_{21}H_{23}BMoN_6O_7$. ($[M+NH_4]^+$): 598.1114. Found: 598.1126.

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(*η*-3,4,5)-1-benzyloxycarbonyl-2-(1´-methoxycarbonyl)methoxycarbonylmethyl-5,6-dihydro-2H-pyridin-2-yl]molybdenum, (±)-1.52e



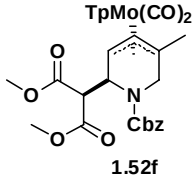
1.52e

To a solution of (±)-**1.51e** (50 mg, 0.078 mmol, 1.0 equiv) in ACN (5 mL) was added dimethyl malonate (32.0 mg, 0.24 mmol, 3.1 equiv), 60% NaH dispension (9.36 mg, 0.23 mmol, 3.0 equiv) and 15-crown-5-ether (3.47 mg, 0.016 mmol, 0.2 equiv). The reaction mixture was stirred at room temperature for 8 hours, and then quenched with water. The mixture was poured into a separatory funnel containing EtOAc (5 mL) and H_2O (5 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (2:1) afforded (±)–**1.52e** (52 mg, 0.073 mmol, 94%) as a yellow solid.

TLC (R_f = 0.28, 2.5:1 hexanes:EtOAc). ^{1}H NMR (a mixture of two rotamers) (400 MHz, $CDCl_3$) δ 8.52-8.54 (m, 1 H), 7.84 (d, *J* = 2.0 Hz, 0.6 H), 7.81 (d, *J* = 2.0 Hz, 0.4 H), 7.67 (d, *J* = 2.0 Hz, 0.4 H), 7.65 (d, *J* = 2.0 Hz, 0.6 H), 7.57 (br s, 2 H), 7.50 (d, *J* = 2.0 Hz, 1 H), 7.28-7.37 (m, 5 H), 6.29 (br s, 1 H), 6.16-6.21 (m, 2 H), 5.05-5.15 (m, 2 H),

4.99-5.04 (m, 1 H), 4.65 (dt, *J* = 7.6 Hz, 2.4 Hz, 0.6 H), 4.52 (dt, *J* = 6.8 Hz, 2.4 Hz, 0.4 H), 4.15-4.31 (m, 2 H), 3.85 (d, *J* = 6.0 Hz, 0.6 H), 3.82 (s, 1.8 H), 3.81 (s, 1.2 H), 3.71-3.76 (m, 2.4 H), 3.67 (s, 1.8 H), 3.49 (s, 1.2 H). ^{13}C NMR (100 MHz, $CDCl_3$): 226.1 (Mo-CO), 225.5 (Mo-CO), 224.4 (Mo-CO), 223.9 (Mo-CO), 168.6 (COOMe), 168.4 (COOMe), 168.1 (COOMe), 167.8 (COOMe), 154.6 (Cbz carbonyl), 154.3 (Cbz carbonyl), 147.2, 142.84, 142.77, 140.99, 140.95, 136.6, 136.3, 136.03, 136.00, 134.39, 128.30, 128.0, 127.8, 127.7, 106.0, 105.6, 105.5, 105.43, 105.41, 69.2, 69.0, 67.4, 67.2, 65.5, 65.0, 64.3, 64.1, 58.0, 57.2, 52.6, 52.5, 52.4, 51.5. 51.3, 39.9 (N-CH_2), 39.4 (N-CH_2). IR (cm^{-1}): 2957 (w), 2486 (w), 1945 (s), 1857 (s), 1733 (s), 1702 (s). HRMS (ESI) Calcd. for $C_{19}H_{30}BMoN_7O_8$ ($[M+Na]^+$): 736.1195. Found: 736.1193.

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(η-3,4,5)-1-benzyloxycarbonyl-2-(1´-methoxycarbonyl)methoxycarbonylmethyl-5-methyl-5,6-dihydro-2H-pyridin-2-yl]molybdenum, (±)-1.52f



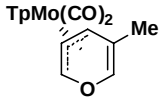
1.52f

To a solution of (±)-**1.51f** (50 mg, 0.077 mmol, 1.0 equiv) in ACN (5 mL) was added dimethyl malonate (32.0 mg, 0.24 mmol, 3.1 equiv), 60% NaH dispension (9.36 mg, 0.23 mmol, 3.0 equiv) and 15-crown-5-ether (3.47 mg, 0.016 mmol, 0.2 equiv). The reaction mixture was stirred at room temperature for 8 hours, and then quenched with water. The mixture was poured into a separatory funnel containing EtOAc (5 mL) and H_2O (5 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated.

Flash chromatography over silica gel with hexanes-EtOAc (2:1) afforded (±)–**1.52f** (39 mg, 0.054 mmol, 70%) as a yellow solid with **1.52f** (15 mg, 0.023 mmol, 30%) recovered.

TLC (R_f = 0.28, 2.5:1 hexanes:EtOAc). ^{1}H NMR (a mixture of two rotamers) (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 2.0 Hz, 0.6 H), 8.46 (d, *J* = 1.6 Hz, 0.4 H), 7.74 (d, *J* = 1.6 Hz, 0.6 H), 7.72 (d, *J* = 2.0 Hz, 1 H), 7.68 (d, *J* = 2.0 Hz, 0.4 H), 7.58-7.62 (m, 2 H), 7.45-7.49 (m, 1 H), 7.26-7.40 (m, 5 H), 6.13-6.24 (m, 3 H), 5.03-5.15 (m, 3 H), 5.45 (dd, *J* = 7.2 Hz, 2.8 Hz, 0.6 H), 4.34 (dd, *J* = 6.8 Hz, 2.8 Hz, 0.4 H), 4.20 (d, *J* = 16.0 Hz, 0.4 H), 4.11 (d, *J* = 16.0 Hz, 0.6 H), 3.88-3.92 (m, 1 H), 3.83 (s, 1.8 H), 3.82 (s, 1.2 H), 3.78 (d, *J* = 7.2 Hz, 0.6 H), 3.70 (d, *J* = 7.8 Hz, 0.4 H), 3.63 (s, 1.8 H), 3.49 (s, 1.2 H), 3.50 (d, *J* = 16.0 Hz, 0.6 H), 3.42 (d, *J* = 16.0 Hz, 0.4 H), 1.99 (s, 1.2 H), 1.95 (s, 1.8 H).

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(η-2,3,4)-5-methyl-2H-pyran-2-yl]-molybdenum, (±)-1.53



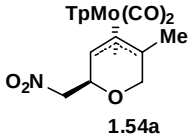
1.53

To a solution of (±)-**1.47** (50 mg, 0.096 mmol, 1.0 equiv) in DCM (5 mL) was added $TrPF_6$ (41 mg, 0.11 mmol, 1.1 equiv). The mixture was stirred at 0 °C for 3 hrs, and dry ether (20 mL) was added to complete the precipitation. The solvents were removed via cannula and the remaining solid was washed with dry ether (3 x 10 mL) then briefly dried under vacuum. The solid was then dissolved in THF (3 mL) and treated with 3.0 equiv sodium malonate solution in 3 mL THF (prepared from 11 mg NaH and 37 mg malonate) and 15-C-5 (4.3 mg, 0.019 mmol, 0.2 equiv). After 1 hr, the reaction was quenched with

water. The mixture was poured into a separatory funnel containing EtOAc (5 mL) and H_2O (5 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (2:1) afforded (±)–**1.53** (24 mg, 0.053 mmol, 55%) as a yellow solid and (±)–**1.52a** (10 mg, 0.017 mmol, 18%) as a side product.

TLC (R_f = 0.70, 2.5:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 2.0 Hz, 1 H), 7.96 (d, *J* = 2.0 Hz, 1 H), 7.83 (d, *J* = 2.0 Hz, 1 H), 7.59-7.61 (m, 2 H), 7.54 (dd, *J* = 4.0 Hz, 2.0 Hz, 1 H), 7.49 (d, *J* = 2.0 Hz, 1 H), 6.25 (t, *J* = 2.0 Hz, 1 H), 6.22 (t, *J* = 2.0 Hz, 1 H), 6.20 (t, *J* = 2.0 Hz, 1 H), 5.76 (br s, 1 H), 4.60 (dd, *J* = 5.2 Hz, 1.2 Hz, 1 H), 2.46 (dd, *J* = 6.0 Hz, 4.0 Hz, 1 H), 1.95 (d, *J* = 1.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 228.9 (Mo-CO), 223.4 (Mo-CO), 145.9, 142.1, 141.1, 136.1, 135.9, 134.4, 130.2, 118.4, 108.7, 105.6, 105.5, 105.3, 65.1, 46.3, 18.1 (CH_3).

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(η-3,4,5)-2-nitromethyl-5-methyl-5,6dihydro-2Hpyran-2-yl]molybdenum, (±)-1.54a



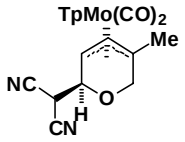
1.54a

To a solution of (±)-**1.47** (50 mg, 0.096 mmol, 1.0 equiv) in DMSO (5 mL) was added nitromethane (18.3 mg, 0.30 mmol, 3.1 equiv), 60% NaH dispension (11.6 mg, 0.29 mmol, 3.0 equiv). The reaction mixture was stirred at room temperature for 5 hours, and then quenched with water. The mixture was poured into a separatory funnel containing EtOAc (5 mL) and H_2O (5 mL), and the layers were separated. The aqueous layer was

extracted with EtOAc (2 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (2:1) afforded (±)–**1.54a** (40 mg, 0.077 mmol, 80%)

TLC (R_f = 0.33, 2.5:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 2.0 Hz, 1 H), 7.72 (d, *J* = 1.6 Hz, 1 H), 7.63 (d, *J* = 2.4 Hz, 1 H), 7.62 (d, *J* = 2.0 Hz, 1 H), 7.57 (d, *J* = 2.0 Hz, 1 H), 7.49 (d, *J* = 2.4 Hz, 1 H), 6.26 (t, *J* = 2.0 Hz, 1 H), 6.24 (t, *J* = 2.4 Hz, 1 H), 6.17 (t, *J* = 2.0 Hz, 1 H), 4.69-4.74 (m, 2 H), 4.59 (ddd, *J* = 8.0 Hz, 4.4 Hz, 2.0 Hz, 1 H), 3.96 (d, *J* = 14.4 Hz, 1 H), 3.92 (d, *J* = 7.6 Hz, 1 H), 3.79 (d, *J* = 14.0 Hz, 1 H), 3.72 (dd, *J* = 7.2 Hz, 2.0 Hz, 1 H), 1.86 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 230.5 (Mo-CO), 225.6 (Mo-CO), 146.9 (CH), 145.6 (CH), 139.5 (CH), 136.8 (CH), 136.1 (CH), 134.4 (CH), 105.8 (CH), 105.7 (CH), 105.3 (CH), 89.2, 78.9, 69.5, 69.1, 62.7, 55.6, 21.8 (CH_3). IR (cm^{-1}) 3146 (w), 2957 (w), 2486 (m), 1934 (s), 1845 (s), 1552 (s). HRMS (FAB) Calcd. for $C_{18}H_{20}BMoN_7O_5$. ($[M+H]^+$): 524.0746. Found: 524.0746.

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(η-3,4,5)-2-malononitrilyl -5-methyl-5,6-dihydro-2H-pyran-2-yl]molybdenum, (±)-1.54b



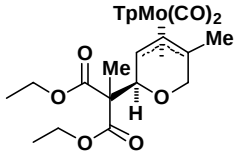
1.54b

To a solution of (±)-**1.47** (50 mg, 0.096 mmol, 1.0 equiv) in THF (5 mL) was added malononitrile (19.8 mg, 0.30 mmol, 3.1 equiv), 60% NaH dispension (11.6 mg, 0.29 mmol, 3.0 equiv) and 15-crown-5-ether (4.23 mg, 0.019 mmol, 0.2 equiv). The reaction mixture was stirred at room temperature overnight, and then quenched with water. The

mixture was poured into a separatory funnel containing EtOAc (5 mL) and H_2O (5 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 5 mL), and the combined organic layer were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (2:1) afforded (±)-**1.54b** (47mg, 0.090mmol, 94%).

TLC (R_f = 0.32, 2.5:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 (brs, 1 H), 7.72 (br s, 1 H), 7.63 (m, 3 H), 7.50 (d, *J* = 2.0 Hz, 1 H), 6.27 (m, 2 H), 6.18 (br s, 1 H), 4.44 (dd, *J* = 6.0, 2.0 Hz, 1 H), 4.12 (d, *J* = 6.8 Hz, 1 H), 3.97-4.04 (m, 3 H), 3.88 (d, *J* = 14.4 Hz, 1 H), 1.88 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 230.3, 225.6, 146.9, 145.6, 139.8, 136.9, 136.3, 134.6, 111.7, 111.4, 105.91, 105.88, 105.4, 88.0, 72.2, 70.1, 63.9, 54.8, 24.5, 21.8. IR (cm^{-1}) 3127 (w), 2957 (w), 2910 (m), 2486 (m), 2235 (m), 1938 (s), 1849 (s), 1606 (m). HRMS (FAB) Calcd. for $C_{20}H_{20}BMoN_8O_3$ ($[M+H]^+$): 529.0800. Found: 529.0787.

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(η-3,4,5)-2-(1´-ethoxycarbonyl-1´-methyl) ethoxycarbonylmethyl -5-methyl-5,6-dihydro-2H-pyran-2-yl]molybdenum, (±)-1.54d



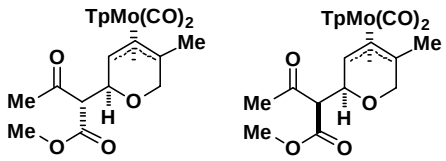
1.54d

To a solution of (±)-**1.47** (50 mg, 0.096 mmol, 1.0 equiv) in THF (5 mL) was added methyl diethylmalonate (52.2 mg, 0.30 mmol, 3.1 equiv), 60% NaH dispension (11.6 mg, 0.29 mmol, 3.0 equiv) and 15-crown-5-ether (4.23 mg, 0.019 mmol, 0.2 equiv). The reaction mixture was stirred at room temperature overnight, and then quenched with

water. The mixture was poured into a separatory funnel containing EtOAc (5 mL) and H_2O (5 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 5 mL), and the combined organic layer were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (2:1) afforded (±)–**1.47** (39 mg, 0.063 mmol, 66%) and the recovered (±)-**1.54d** (14mg, 0.027mmol, 28%).

TLC (R_f = 0.48, 3:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 1.2 Hz, 1 H), 7.84 (d, *J* = 2.0 Hz, 1 H), 7.74 (d, *J* = 1.6 Hz, 1 H), 7.60 (br s, 1 H), 7.49 (d, *J* = 2.0 Hz, 1 H), 6.26 (t, *J* = 2.0 Hz, 1 H), 6.23 (t, *J* = 2.0 Hz, 1 H), 6.15 (t, *J* = 2.0 Hz, 1 H), 4.72 (d, *J* = 1.6 Hz, 1 H), 4.16-4.30 (m, 6 H), 3.98 (d_{AB}, *J* = 14.0 Hz, 1 H), 3.63 (d_{AB}, *J* = 14.0 Hz, 1 H), 1.88 (s, 3 H), 1.67 (s, 3 H), 1.30 (t, *J* = 7.2 Hz, 3H), 1.26 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 229.36 (Mo-CO), 229.32 (Mo-CO), 171.7 (COOEt), 170.6 (COOEt), 147.0 (CH), 144.8 (CH), 141.4 (CH), 136.4 (CH), 135.8 (CH), 134.3 (CH), 105.7 (CH), 105.5 (CH), 105.1 (CH), 84.8, 73.5, 73.0, 65.6, 61.6, 61.39, 61.36, 60.2, 21.4 (CH_3), 18.5 (CH_3), 14.1 (CH_3), 14.0 (CH_3). IR (cm^{-1}) 2988 (w), 2945 (w), 2482 (w), 1934 (s), 1849 (s), 1725 (s). HRMS (FAB) Calcd. for $C_{25}H_{31}BMoN_6O_7$ ($[M+H]^+$): 637.1480. Found: 637.1507. ($[M+NH_4]^+$): 654.1745. Found: 654.1776.

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(*η*-3,4,5)-2-(1´-methoxycarbonyl)acetonyl5-methyl5,6-dihydro-2H-pyran-2-yl]molybdenum, (±)-1.54e



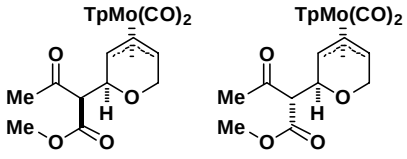
1.54e

To a solution of (±)-**1.47** (50 mg, 0.096 mmol, 1.0 equiv) in ACN (5 mL) was added methyl acetoacetate (34.8 mg, 0.30 mmol, 3.1 equiv), 60% NaH dispension (11.6 mg, 0.29 mmol, 3.0 equiv) and 15-crown-5-ether (4.23 mg, 0.019 mmol, 0.2 equiv). The reaction mixture was stirred at room temperature overnight, and then quenched with water. The mixture was poured into a separatory funnel containing EtOAc (5 mL) and H_2O (5 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (2:1) afforded **(±)–1.54e** (38 mg, 0.066 mmol, 69%) as two diastereomers and the recovered (±)-**1.47** (15mg, 0.029mmol, 30%). The two diastereomers were further purified over silica gel with hexanes-EtOAc (2:1) to provide samples for characterization.

Less polar diastereomer: TLC (R_f = 0.37, 2.5:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 1.6 Hz, 1 H), 7.72 (d, *J* = 1.6 Hz, 1 H), 7.56-7.62 (m, 3 H), 7.48 (d, *J* = 2.4 Hz, 1 H), 6.26 (t, *J* = 2.0 Hz, 1 H), 6.23 (t, *J* = 2.0 Hz, 1 H), 6.16 (t, *J* = 2.0 Hz, 1 H), 4.54 (dd, *J* = 10.4 Hz, 2.0 Hz, 1 H), 4.07 (dd, *J* = 7.2 Hz, 2.4 Hz, 1 H), 3.93 (d, *J* = 7.2 Hz, 1 H), 3.84 (d, *J* = 10.4 Hz, 1 H), 3.84 (s, 3 H), 3.78 (d, *J* = 14.0 Hz, 1 H), 3.64 (d, *J* = 14.0 Hz, 1 H), 2.27 (s, 3 H), 1.86 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 230.0 (Mo-CO), 227.0 (Mo-CO), 201.0 ($CH_3\underline{C}O$), 168.3 (<u>C</u>OOMe), 146.9 (CH), 145.3 (CH), 140.0 (CH), 136.6 (CH), 136.0 (CH), 134.3 (CH), 105.7 (CH), 105.6 (CH), 105.2 (CH), 88.6, 69.9, 69.7, 67.2, 63.2, 59.6, 52.1, 27.4 ($\underline{C}H_3CO$), 21.6 (CH_3). IR (cm^{-1}) 3146 (w), 3127 (w), 2957 (m), 2482 (m), 1930 (s), 1841 (s), 1741 (s), 1714 (s), 1505 (s). HRMS (FAB) Calcd. for $C_{22}H_{25}BMoN_6O_6$ ($[M+NH_4]^+$): 596.1321. Found: 596.1318.

More polar diastereomer: TLC (R_f = 0.35, 2.5:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 1.6 Hz, 1 H), 7.72 (d, *J* = 1.6 Hz, 1 H), 7.56-7.62 (m, 3 H), 7.48 (d, *J* = 2.0 Hz, 1 H), 6.25 (t, *J* = 2.0 Hz, 1 H), 6.21 (t, *J* = 2.0 Hz, 1 H), 6.15 (t, *J* = 2.0 Hz, 1 H), 4.51 (dd, *J* = 10.4 Hz, 2.0 Hz, 1 H), 3.99 (dd, *J* = 7.6 Hz, 1.6 Hz, 1 H), 3.92 (d, *J* = 10.4 Hz, 1 H), 3.87 (d, *J* = 8.0 Hz, 1 H), 3.76 (s, 3 H), 3.75 (d, *J* = 14.0 Hz, 1 H), 3.68 (d, *J* = 14.0 Hz, 1 H), 2.36 (s, 3 H), 1.87 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 229.9 (Mo-CO), 226.9 (Mo-CO), 201.2 (CH_3-<u>C</u>O), 167.9 (<u>C</u>OOMe), 146.9 (CH), 145.3 (CH), 140.2 (CH), 136.6 (CH), 136.0 (CH), 134.3 (CH), 105.7 (CH), 105.6 (CH), 105.1 (CH), 88.5, 69.9, 69.5, 67.2, 63.5, 59.7, 52.8, 25.6 (<u>C</u>H_3CO), 21.7 (CH_3). IR (cm^{-1}) 3146 (w), 3019 (w), 2953 (m), 2482 (m), 1934 (s), 1841 (s), 1741 (s), 1714 (s), 1505 (s). HRMS (FAB) Calcd. for $C_{22}H_{25}BMoN_6O_6$ ($[M+NH_4]^+$): 596.1321. Found: 596.1318.

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(η-3,4,5)-2-(1´-methoxycarbonyl)acetonyl5,6dihydro-2H-pyran-2-yl]molybdenum, (±)-1.55



1.55

To a solution of (±)-**1.51c** (50 mg, 0.081 mmol, 1.0 equiv) in ACN (5 mL) was added methyl acetoacetate (29 mg, 0.25 mmol, 3.1 equiv), 60% NaH dispension (9.7 mg, 0.24 mmol, 3.0 equiv) and 15-crown-5-ether (3.6 mg, 0.016 mmol, 0.2 equiv). The reaction mixture was stirred at room temperature overnight, and then quenched with water. The mixture was poured into a separatory funnel containing EtOAc (5 mL) and H_2O (5 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 5 mL),

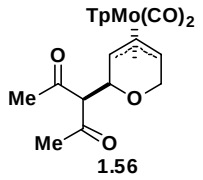
and the combined organic layer were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (2:1) afforded (±)–**1.55** (43 mg, 0.076 mmol, 94%) as two diastereomers. The two diastereomers were further purified over silica gel with hexanes-EtOAc (2:1) to provide samples for characterization.

Less polar diastereomer: TLC (R_f = 0.29, 2.5:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 2.0 Hz, 1 H), 7.70 (d, *J* = 2.0 Hz, 1 H), 7.65 (d, *J* = 1.6 Hz, 1 H), 7.58 (d, *J* = 2.0 Hz, 2 H), 7.52 (d, *J* = 1.6 Hz, 1 H), 6.31 (t, *J* = 2.0 Hz, 1 H), 6.17-6.19 (m, 2 H), 4.54 (dd, *J* = 10.4 Hz, 2.4 Hz, 1 H), 4.05-4.09 (m, 2 H), 3.87 (d, *J* = 10.4 Hz, 1 H), 3.82 (s, 3 H), 3.77 (t, *J* = 7.2 Hz, 1 H), 3.68 (dd, *J* = 12.8 Hz, 2.4 Hz, 1 H), 2.25 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 225.4 (Mo-CO), 224.6 (Mo-CO), 200.9 ($CH_3\underline{C}O$), 168.4 (<u>C</u>OOMe), 147.3 (CH), 142.2 (CH), 141.1 (CH), 136.1 (CH), 136.0 (CH), 134.4 (CH), 106.0 (CH), 105.43 (CH), 105.41 (CH), 69.8, 68.8, 67.0, 65.8, 63.2, 58.4, 52.6, 27.6 ($\underline{C}H_3CO$). IR (cm^{-1}) 3146 (w), 2957 (w), 2486 (m), 1942 (s), 1857 (s), 1741 (s), 1714 (s), 1505 (s). HRMS (FAB) Calcd. for $C_{21}H_{23}BMoN_6O_6$ ($[M+NH_4]^+$): 582.1188. Found:582.1164.

More polar diastereomer: TLC (R_f = 0.27, 2.5:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 1.6 Hz, 1 H), 7.71 (d, *J* = 2.0 Hz, 1 H), 7.65 (d, *J* = 1.6 Hz, 1 H), 7.56-7.58 (m, 2 H), 7.51 (d, *J* = 2.4 Hz, 1 H), 6.31 (t, *J* = 2.4 Hz, 1 H), 6.16-6.18 (m, 2 H), 4.52 (dd, *J* = 10.0 Hz, 2.0 Hz, 1 H), 4.19 (dt, *J* = 7.2 Hz, 2.4 Hz, 1 H), 4.16 (d, *J* = 13.2 Hz, 1 H), 4.06-4.09 (m, 1 H), 3.98 (d, *J* = 10.0 Hz, 1 H), 3.75 (s, 3 H), 3.69-3.75 (m, 2 H), 2.34 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 225.5 (Mo-CO), 224.4 (Mo-CO), 201.2 ($CH_3\underline{C}O$), 167.8 (<u>C</u>OOMe), 147.3 (CH), 142.3 (CH), 141.0 (CH), 136.02 (CH), 135.96 (CH), 134.4 (CH), 106.0 (CH), 105.44 (CH), 105.36 (CH), 69.7, 68.9, 67.1, 66.0, 63.0,

58.6, 52.8, 30.1 ($\underline{C}H_3CO$). IR (cm^{-1}) 3130 (w), 2957 (w), 2486 (m), 1942 (s), 1857 (s), 1733 (s), 1505 (s). HRMS (FAB) Calcd. for $C_{21}H_{23}BMoN_6O_6$ ($[M+NH_4]^+$): 582.1188. Found: 582.1164.

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(*η*-3,4,5)-2-(1´-acetyl)acetonyl-5,6-dihydro2Hpyran-2-yl]molybdenum, (±)-1.56



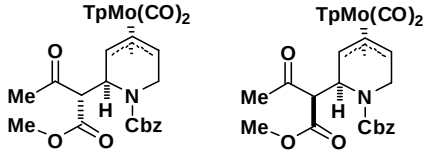
1.56

To a solution of (±)-**1.51c** (50 mg, 0.081 mmol, 1.0 equiv) in ACN (5 mL) was added 2,4-pentadione (25 mg, 0.25 mmol, 3.1 equiv), 60% NaH dispension (9.7 mg, 0.24 mmol, 3.0 equiv) and 15-crown-5-ether (3.6 mg, 0.016 mmol, 0.2 equiv). The reaction mixture was stirred at room temperature overnight, and then quenched with water. The mixture was poured into a separatory funnel containing EtOAc (5 mL) and H_2O (5 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (2:1) afforded (±)–**1.56** (30 mg, 0.055 mmol, 68%) as a yellow solid.

TLC (R_f = 0.33, 2.5:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 1.6 Hz, 1 H), 7.67 (d, *J* = 2.0 Hz, 1 H), 7.64 (d, *J* = 2.0 Hz, 1 H), 7.57-7.58 (m, 2 H), 7.52 (d, *J* = 2.0 Hz, 1 H), 6.31 (t, *J* = 2.0 Hz, 1 H), 6.16-6.18 (m, 2 H), 4.61 (dd, *J* = 10.8 Hz, 2.0 Hz, 1 H), 4.17 (d, *J* = 10.8 Hz, 1 H), 4.02-4.07 (m, 3 H), 3.73 (t, *J* = 7.2 Hz, 1 H), 3.67 (dd, *J* = 12.8 Hz, 1.6 Hz, 1 H), 2.32 (s, 3 H), 2.20 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 225.5 (Mo-CO), 224.4 (Mo-CO), 202.5 ($CH_3\underline{C}O$), 201.8 ($CH_3\underline{C}O$), 147.3 (CH), 142.3

(CH), 141.0 (CH), 136.1 (CH), 136.0 (CH), 134.4 (CH), 106.0 (CH), 105.45 (CH), 105.41 (CH), 76.6, 69.9, 68.9, 65.6, 63.0, 58.4, 31.4 ($\underline{C}H_3CO$), 27.1 ($\underline{C}H_3CO$). IR (cm^{-1}) 3146 (w), 2486 (m), 1942 (s), 1857 (s), 1722 (s), 1698 (s). HRMS (ESI) Calcd. for $C_{21}H_{23}BMoN_6O_5$. ($[M-C_5H_7O_2]^+$): 449.0431 Found: 449.0444.

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(*η*-3,4,5)-1-benzyloxycarbonyl-2(1´-methoxycarbonyl)acetonyl-5,6-dihydro-2H-pyridin-2-yl]molybdenum, (±)-1.57



1.57

To a solution of (±)-**1.51e** (50 mg, 0.067 mmol, 1.0 equiv) in ACN (5 mL) was added methyl acetoacetate (24 mg, 0.21 mmol, 3.1 equiv), 60% NaH dispension (8 mg, 0.20 mmol, 3.0 equiv) and 15-crown-5-ether (2.9 mg, 0.013 mmol, 0.2 equiv). The reaction mixture was stirred at room temperature overnight, and then quenched with water. The mixture was poured into a separatory funnel containing EtOAc (5 mL) and H_2O (5 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (2:1) afforded (±)–**1.57** (42 mg, 0.061 mmol, 91%) as two diastereomers. The two diastereomers were further purified over silica gel with hexanes-EtOAc (2:1) to provide samples for characterization.

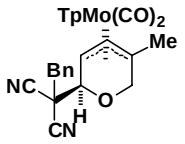
TLC (R_f = 0.27, 2.5:1 hexanes:EtOAc). ^{1}H NMR (a mixture of two rotamers) (400 MHz, $CDCl_3$) δ 8.52-8.54 (m, 1 H), 7.84 (d, *J* = 1.6 Hz, 0.6 H), 7.82 (d, *J* = 2.0 Hz, 0.4 H), 7.66 (d, *J* = 2.0 Hz, 0.4 H), 7.64 (d, *J* = 2.0 Hz, 0.6 H), 7.57 (d, *J* = 2.4 Hz, 1.5 H),

7.50 (d, J = 2.4 Hz, 0.5 H), 7.27-7.36 (m, 5 H), 6.29 (t, J = 2.4 Hz, 1 H), 6.16-6.21 (m, 2 H), 5.15 (d_{AB}, J = 12.4 Hz, 0.4 H), 5.12 (d_{AB}, J = 13.2 Hz, 0.6 H), 5.06 (d_{AB}, J = 12.8 Hz, 0.6 H), 5.02 (d_{AB}, J = 12.4 Hz, 0.4 H), 5.02 (dd, J = 6.8 Hz, 2.8 Hz, 0.6 H), 4.97 (dd, J = 6.4 Hz, 2.8 Hz, 0.4 H), 4.53 (dt, J = 6.8 Hz, 2.8 Hz, 0.6 H), 4.43 (dt, J = 7.6 Hz, 2.8 Hz, 0.4 H), 4.11-4.29 (m, 3 H), 3.84 (s, 1.8 H), 3.80 (s, 1.2 H), 3.62-3.75 (m, 2 H), 2.27 (s, 1.8 H), 1.95 (s, 1.2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 226.1 (Mo-CO), 223.9 (Mo-CO), 201.6 (CH_3CO), 201.2 (CH_3CO), 169.6 (COOMe), 169.4 (COOMe), 154.7 (Cbz carbonyl), 154.1 (Cbz carbonyl), 147.2, 142.9, 140.9, 136.5, 136.1, 136.0, 134.4, 128.4, 128.31, 128.26, 128.0, 127.8, 127.7, 106.0, 105.6, 105.5, 105.4, 69.6, 69.5, 67.4, 67.2, 65.64, 65.56, 65.0. 64.9, 64.1, 52.6, 51.3, 51.0, 39.8 (N-CH_2), 39.5 (N-CH_2), 29.7, 28.93 (CH_3CO), 28.85 (CH_3CO). IR (cm^{-1}) 3127 (w), 2953 (w), 2486 (m), 1945 (s), 1857 (s), 1702 (s), 1505 (s). HRMS (ESI) Calcd. for $C_{29}H_{30}BMoN_7O_7$ ($[M+Na]^+$): 720.1246. Found: 720.1249.

TLC (R_f = 0.25, 2.5:1 hexanes:EtOAc). ^{1}H NMR (a mixture of two rotamers) (400 MHz, $CDCl_3$) δ 8.51-8.54 (m, 1 H), 7.78 (d, J = 2.0 Hz, 0.6 H), 7.75 (d, J = 2.0 Hz, 0.4 H), 7.67 (d, J = 2.0 Hz, 0.4 H), 7.65 (d, J = 2.0 Hz, 0.6 H), 7.56 (d, J = 2.0 Hz, 2 H), 7.50 (d, J = 2.4 Hz, 1 H), 7.26-7.37 (m, 5 H), 6.28-6.30 (m, 1 H), 6.16-6.20 (m, 2 H), 5.01-5.12 (m, 3 H), 4.48 (dt, J = 7.2 Hz, 2.4 Hz, 0.6 H), 4.38 (dt, J = 7.2 Hz, 2.8 Hz, 0.4 H), 4.26-4.32 (m, 1 H), 4.17-4.42 (m, 1 H), 3.78-3.84 (m, 1.4 H), 3.61-3.73 (m, 1.6 H), 3.59 (s, 1.8 H), 3.38 (s, 1.2 H), 2.35 (s, 1.8 H), 2.30 (s, 1.2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 225.3 (Mo-CO), 223.2 (Mo-CO), 221.9 (Mo-CO), 206.0 (CH_3CO), 202.1 (CH_3CO), 168.2 (COOMe), 167.7 (COOMe), 154.5 (Cbz carbonyl), 154.3 (Cbz carbonyl), 147.2, 142.6, 141.1, 136.0, 134.4, 128.3, 128.2, 127.9, 127.83, 127.77, 117.4, 116.2, 112.3,

106.0, 105.5, 105.4, 70.1, 69.6, 67.5, 66.3, 65.8, 65.5, 65.0, 63.7, 63.4, 52.5, 52.3, 51.2, 51.1, 39.0 (N-CH_2),30.8 ($\underline{C}H_3CO$). IR (cm^{-1}) 2957 (w), 2490 (m), 1945 (s), 1861 (s), 1737 (s), 1706 (s). HRMS (ESI) Calcd. for $C_{29}H_{30}BMoN_7O_7$ ($[M+Na]^+$): 720.1246. Found: 720.1249.

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(*η*-3,4,5)-2-benzylmalononitrilyl -5-methyl-5,6-dihydro-2H-pyran-2-yl]molybdenum, (±)-1.59

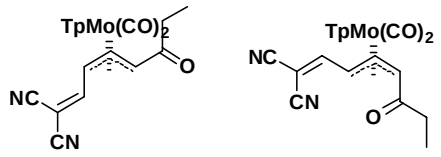


1.59

To a solution of (±)-**1.47** (50 mg, 0.096 mmol, 1.0 equiv) in THF (5 mL) was added benzylmalononitrile (46.8 mg, 0.30 mmol, 3.1 equiv), 60% NaH dispension (11.6 mg, 0.29 mmol, 3.0 equiv) and 15-crown-5-ether (4.23 mg, 0.019 mmol, 0.2 equiv). The reaction mixture was stirred at room temperature overnight, and then quenched with water. The mixture was poured into a separatory funnel containing EtOAc (5 mL) and H_2O (5 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 5 mL), and the combined organic layer were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (2:1) afforded (±)-**1.59** (55 mg, 0.090mmol, 94%).

TLC (R_f = 0.35, 2.5:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 2.0 Hz, 1 H), 7.69 (t, *J* = 2.0 Hz, 2 H), 7.60 (t, *J* = 2.0 Hz, 2 H), 7.54 (d, *J* = 1.6 Hz, 1 H), 7.31-7.45 (m, 5 H), 6.33 (t, *J* = 2.0 Hz, 1 H), 6.21 (t, *J* = 2.4 Hz, 1 H), 6.19 (t, *J* = 2.4 Hz, 1 H), 4.72 (d, *J* = 12.8 Hz, 1 H), 4.21-4.25 (m, 4 H), 3.92 (d, *J* = 12.8 Hz, 1 H), 3.46 (d, *J* = 13.6 Hz, 1 H), 3.32 (d, *J* = 13.6 Hz, 1 H).

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(η-2,3,4)-1-malononitrilene-heptan-5-onyl]molybdenum, (±)-1.61

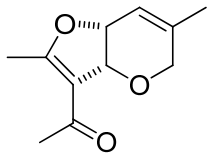


1.61

To a solution of (±)-**1.60** (50 mg, 0.096 mmol, 1.0 equiv) in THF (5 mL) was added malononitrile (20 mg, 0.30 mmol, 3.1 equiv), 60% NaH dispension (11.6 mg, 0.29 mmol, 3.0 equiv) and 15-crown-5-ether (4.23 mg, 0.019 mmol, 0.2 equiv). The reaction mixture was stirred at room temperature overnight, and then quenched with water. The mixture was poured into a separatory funnel containing EtOAc (5 mL) and H_2O (5 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 5 mL), and the combined organic layer were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (2:1) afforded (±)-**1.59** (31 mg, 0.058mmol, 60%).

TLC (R_f = 0.28, 2.5:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (br s, 3 H), 7.60 (s, 3 H), 6.27 (s, 3 H), 5.86 (d, *J* = 12.0 Hz, 1 H), 5.49 (dd, *J* = 10.8, 7.2 Hz, 1 H), 5.30 (dd, *J* = 12.0, 7.2 Hz, 1 H), 3.28 (d, *J* = 10.8 Hz, 1 H), 2.61 (dq, *J* = 11.2, 7.2 Hz, 1 H), 2.24 (dq, *J* = 11.2, 7.2 Hz, 1 H), 1.00 (t, *J* = 7.2 Hz, 3 H).

(±)-1-(2,6-dimethyl-5,7a-dihydro-3aH-furo[3,2-b]pyran-3-yl)ethanone, (±)-1.62

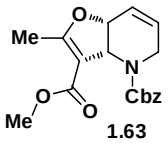


1.62

To a solution of (±)-**1.54f** (50 mg, 0.089 mmol, 1.0 equiv) in DMSO (5 mL) was added 60% NaH dispension (4.3 mg, 0.106 mmol, 1.2 equiv) and copper 2-ethylhexanoate (6.0 mg, 0.018 mmol, 0.2 equiv). The reaction mixture was stirred at room temperature in dry air overnight, and then quenched with water. The mixture was poured into a separatory funnel containing EtOAc (5 mL) and H_2O (5 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 5 mL), and the combined organic layers were washed with 3 M NH_3-H_2O, dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (2:1) afforded (±)–**1.62** (15 mg, 0.080 mmol, 90%) as a colorless oil.

TLC (R_f = 0.32, 2.5:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.82 (br s, 1 H), 4.71 (d, *J*=4.8 Hz, 1 H), 4.47 (br s, 1 H), 3.97 (s, 2 H), 2.31 (s, 3 H), 2.30 (s, 3 H), 1.79 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.0, 173.5, 142.3, 114.5, 114.3, 77.1, 75.9, 66.0, 28.9, 19.6, 15.5. IR (cm^{-1}) 2922 (m), 2829 (m), 1675 (s), 1590 (s). HRMS (FAB) Calcd. for $C_{11}H_{14}O_3$ ($[M+H]^+$): 195.1016. Found: 195.1016.

(±)-4-Benzyl 3-methyl 2-methyl-5,7a-dihydrofuro[3,2-b]pyridine-3,4(3aH)-dicarboxylate, (±)-1.63

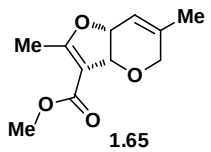


1.63

To a solution of (±)-**1.57** (50 mg, 0.072 mmol, 1.0 equiv) in DMSO (5 mL) was added 60% NaH dispension (3.5 mg, 0.086 mmol, 1.2 equiv) and copper 2-ethylhexanoate (5.0 mg, 0.014 mmol, 0.2 equiv). The reaction mixture was stirred at room temperature in dry air overnight, and then quenched with water. The mixture was poured into a separatory funnel containing EtOAc (5 mL) and H_2O (5 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 5 mL), and the combined organic layers were washed with 3 M NH_3-H_2O, dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (2:1) afforded (±)–**1.63** (20 mg, 0.060 mmol, 83%) as a colorless oil.

TLC (R_f = 0.33, 2.5:1 hexanes:EtOAc). ^{1}H NMR (a mixture of two rotamers) (400 MHz, $CDCl_3$) δ 7.28-7.41 (m, 5 H), 5.99-6.21 (m, 2 H), 5.63 (d, *J* = 8.0 Hz, 1 H), 5.17-5.23 (m, 2 H), 5.03 (d, *J* =8.8 Hz, 1 H), 4.27 (br s, 1 H), 3.53 (s, 3 H), 3.45-3.54 (m, 1 H), 2.18 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 165.6, 155.4, 136.6, 130.3, 129.7, 128.5, 128.1, 122.6, 100.8, 74.6, 67.4, 55.9, 50.8, 39.2 (N-CH_2), 15.1 (CH_3). IR (cm^{-1}) 2926 (w), 1698 (s), 1640 (s). HRMS (ESI) Calcd. for $C_{18}H_{19}NO_5$ ($[M+H]^+$): 330.1336. Found: 330.1335.

(±)-(3aR,7aR)-methyl 2,6-dimethyl-5,7a-dihydro-3aH-furo[3,2-b]pyran-3-carboxylate, (±)-1.65



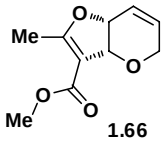
1.65

To a solution of (±)-**1.54e** (50 mg, 0.087 mmol, 1.0 equiv) in DMSO (5 mL) was added 60% NaH dispension (4.0 mg, 0.10 mmol, 1.2 equiv) and copper 2-ethylhexanoate (6.0

mg, 0.017 mmol, 0.2 equiv). The reaction mixture was stirred at room temperature in dry air overnight, and then quenched with water. The mixture was poured into a separatory funnel containing EtOAc (5 mL) and H_2O (5 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 5 mL), and the combined organic layers were washed with 3 M NH_3-H_2O, dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (2:1) afforded (±)–**1.65** (15 mg, 0.071 mmol, 85%) as a colorless oil.

TLC (R_f = 0.34, 2.5:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.79-5.81 (m, 1 H), 4.69 (d, *J* =5.2 Hz, 1 H), 4.46 (br s, 1 H), 3.97 (s, 2 H), 3.76 (s, 3 H), 2.29 (s, 3 H), 1.78 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 165.9, 142.4, 114.2, 105.4, 77.2, 75.2, 66.1, 51.1, 19.6 (CH_3), 14.8 (CH_3). IR (cm^{-1}) 2949 (w), 1698 (s), 1629 (s). HRMS (ESI) Calcd. for $C_{11}H_{14}O_4$ ($[M+H]^+$): 211.0965. Found: 211.0961.

(±)-(3aR,7aR)-Methyl 2-methyl-5,7a-dihydro-3aH-furo[3,2-b]pyran-3-carboxylate, (±)-1.66



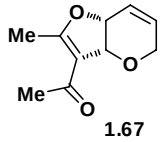
1.66

To a solution of (±)-**1.55** (50 mg, 0.089 mmol, 1.0 equiv) in DMSO (5 mL) was added 60% NaH dispension (4.3 mg, 0.11 mmol, 1.2 equiv) and copper 2-ethylhexanoate (6.3 mg, 0.018 mmol, 0.2 equiv). The reaction mixture was stirred at room temperature in dry air overnight, and then quenched with water. The mixture was poured into a separatory funnel containing EtOAc (5 mL) and H_2O (5 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 5 mL), and the combined organic layers were washed with 3 M NH_3-H_2O, dried over Na_2SO_4, filtered, and concentrated. Flash

chromatography over silica gel with hexanes-EtOAc (2:1) afforded (±)–**1.66** (14.5 mg, 0.074 mmol, 83%) as a colorless oil.

TLC (R_f = 0.34, 2.5:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.30 (ddt, *J* = 10.4 Hz, 4.8 Hz, 1.6 Hz, 1 H), 6.10 (dt, *J* = 10.4 Hz, 2.0 Hz, 1 H), 4.78 (d, *J* = 5.6 Hz, 1 H), 4.42 (br s, 1 H), 4.18 (dd, *J* =16.4 Hz, 2.8 Hz, 1 H), 4.05 (dd, *J* = 16.4 Hz, 2.0 Hz, 1 H), 3.76 (s, 3 H), 2.31 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 165.8, 133.8, 119.8, 105.5, 76.0, 75.8, 62.5, 51.2, 14.8 (CH_3). IR (cm^{-1}) 2949 (w), 1698 (s), 1629 (s). HRMS (ESI) Calcd. for $C_{10}H_{12}O_4$ ($[M+H]^+$): 197.0808. Found: 197.0807.

(±)-1-((3aR,7aR)-2-Methyl-5,7a-dihydro-3aH-furo[3,2-b]pyran-3-yl)ethanone, (±)-1.67



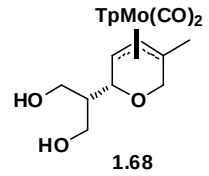
1.67

To a solution of (±)-**1.56** (50 mg, 0.090 mmol, 1.0 equiv) in DMSO (5 mL) was added 60% NaH dispension (4.3 mg, 0.11 mmol, 1.2 equiv) and copper 2-ethylhexanoate (6.4 mg, 0.018 mmol, 0.2 equiv). The reaction mixture was stirred at room temperature in dry air overnight, and then quenched with water. The mixture was poured into a separatory funnel containing EtOAc (5 mL) and H_2O (5 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 5 mL), and the combined organic layers were washed with 3 M NH_3-H_2O, dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (2:1) afforded (±)–**1.67** (15 mg, 0.083 mmol, 92%) as a colorless oil.

TLC (R_f = 0.17, 2.5:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.29-6.33 (m, 1 H), 6.10-6.14 (m, 1 H), 4.80 (d, *J* = 5.6 Hz, 1 H), 4.45 (br s, 1 H), 4.18 (ddd, *J* = 18.2 Hz,

6.0 Hz, 1.6 Hz, 1 H), 4.04 (dq, *J* = 16.8 Hz, 2.0 Hz, 1 H),2.32 (s, 3 H), 2.30 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 195.0 ($CH_3\underline{C}O$), 173.6, 133.7, 120.0, 114.5, 76.5, 75.8, 62.4, 28.9 ($\underline{C}H_3CO$), 15.4 (CH_3). IR (cm^{-1}) 2922 (w), 1668 (s), 1528 (s). HRMS (ESI) Calcd. for $C_{10}H_{12}O_3$ ($[M+H]^+$): 181.0859. Found: 189.0859.

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(*η*-3,4,5)-2-(1´-hydroxymethyl) hydroxyethyl-5-methyl-5,6-dihydro-2H-pyran-3-yl]molybdenum, (±)-1.68



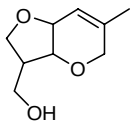
1.68

To a solution of (±)-**1.52a** (50 mg, 0.084 mmol, 1.0 equiv) in THF (5 mL) was added DIBAL (1.0 M in hexane, 0.42 mL, 0.42 mmol, 5 equiv) at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 20 minutes, and then quenched with potassium sodium tartrate tetrahydrate (190mg, 0.84 mmol, 10.0 equiv) and H_2O (10 mL). The mixture was poured into a separatory funnel containing EtOAc (10 mL) and the layers were separated. The aqueous layer was extracted by EtOAc (2 x 5 mL), and the combined organic layer were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (2:1) afforded (±)–**1.68** (35 mg, 0.065 mmol, 77%) as an orange solid.

TLC (R_f =0.21, 1:1 hexanes: EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.54 (d, *J* = 1.6 Hz, 1 H), 7.73 (d, *J* = 1.6 Hz, 1 H), 7.64 (d, *J* = 1.6 Hz, 1 H), 7.61 (br s, 2 H), 7.48 (d, *J* = 2.0 Hz, 1 H), 6.22-6.23 (m, 2 H), 6.15 (t, *J* = 2.0 Hz, 1 H), 4.18 (dd, *J* = 11.6 Hz, 2.8 Hz, 1 H), 4.07-4.12 (m, 2 H), 3.92-4.01 (m, 4 H), 3.83 (d, *J* = 14.0 Hz, 1 H), 3.73 (d, *J* = 14.0 Hz, 1 H), 2.81 (br s, 1 H), 2.69 (br s, 1 H), 1.99-2.07 (m, 1 H), 1.82 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 230.9, 226.8, 146.8, 145.4, 139.7, 136.5, 135.9, 134.2, 105.6, 105.5,

105.1, 88.8, 70.1, 69.0, 64.5, 63.8, 63.3, 59.5, 46.8, 21.8. IR (cm^{-1}) 3385 (s), 3150 (w), 2945 (m), 2899 (m), 2482 (m), 1930 (s), 1841 (s), 1505 (s), 1409 (s). HRMS (ESI) Calcd. for $C_{20}H_{25}BMoN_6O_5$ ($[M]^+$): 538.1028. Found: 538.1033.

(6-methyl-3,3a,5,7a-tetrahydro-2H-furo[3,2-b]pyran-3-yl)methanol, 1.69

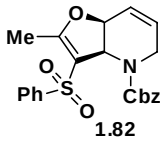


1.69

To a solution of (±)-**1.68** (35 mg, 0.065 mmol, 1.0 equiv) in DMSO (5 mL) was added 60% NaH dispension (3.1 mg, 0.078 mmol, 1.2 equiv) and copper 2-ethylhexanoate (5.0 mg, 0.014 mmol, 0.2 equiv). The reaction mixture was stirred at room temperature in dry air for three days, and then quenched with water. The mixture was poured into a separatory funnel containing EtOAc (5 mL) and H_2O (5 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 5 mL), and the combined organic layers were washed with 3 M NH_3-H_2O, dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (2:1) afforded (±)–**1.69** (9.5 mg, 0.056 mmol, 86%) as a colorless oil.

TLC (R_f = 0.21, 2:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.73 (br s, 1 H), 4.23 (dd, *J* = 9.2 Hz, 8.0 Hz, 0.7 H), 3.86-4.08 (m, 5 H), 3.70-3.73 (m, 1.6 H), 3.56 (dd, *J* = 8.8 Hz, 6.0 Hz, 0.7 H), 2.62-2.71 (m, 0.3 H), 2.53 (quint, *J* = 7.2 Hz, 0.7 H), 2.40 (dd, *J* = 7.2 Hz, 5.2 Hz, 0.3 H), 1.71 (s, 3 H), 1.51 (q, *J* = 5.2 Hz, 0.7 H).

(+) and (±)- (3aS,7aR)-Benzyl 2-methyl-3-(phenylsulfonyl)-5,7a-dihydrofuro[3,2-b]-pyridine4(3aH)-carboxylate, (+) -1.82 and (±)-1.82



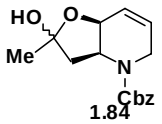
1.82

To a solution of (±)-**1.51e** (500 mg, 0.67 mmol, 1.0 equiv) in DMSO (40 mL) was added phenylsulfonyl acetone (416 mg, 2.1 mmol, 3.1 equiv), 60% NaH dispension (80 mg, 2.0 mmol, 3.0 equiv). The reaction mixture was stirred at room temperature under argon overnight, and then copper 2-ethylhexanoate (50 mg, 0.14 mmol, 0.2 equiv) and 60% NaH dispension (40 mg, 1.0 mmol, 1.5 equiv) were added. The mixture was stirred in dry air for 24 hours, and then quenched with water. The mixture was poured into a separatory funnel containing EtOAc (50 mL) and H_2O (40 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 40 mL), and the combined organic layers were washed with 3 M NH_3-H_2O, dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (2:1) afforded (±)–**1.82** (156 mg, 0.38 mmol, 57%) as light yellow oil.

Similar treatment of (+)-**1.51e** (500 mg, 0.67 mmol, 1.0 equiv, >99% ee) in DMSO (40 mL) with phenylsulfonyl acetone (416 mg, 2.1 mmol, 3.1 equiv) and 60% NaH dispension (80 mg, 2.0 mmol, 3.0 equiv), and further demetalation with copper 2-ethylhexanoate (50 mg, 0.14 mmol, 0.2 equiv) and 60% NaH dispension (40 mg, 1.0 mmol, 1.5 equiv) afforded (3aS, 7aR)-(-)-**1.82** (150 mg, 0.37 mmol, 57%, >99% ee) {$[\alpha]_D^{20}$ = -126.7, (c = 1.1, CH_2Cl_2)}

TLC (R_f = 0.28, 2.5:1 hexanes:EtOAc). ^{1}HNMR (a mixture of two rotamers) (400 MHz, $CDCl_3$) δ 7.92 (d, *J* = 7.2 Hz, 1 H), 7.71 (d, *J* =7.6 Hz, 1 H), 7.30-7.58 (m, 8 H), 6.10 (d, *J* = 9.6 Hz, 1 H), 6.05 (dd, *J* = 10.4 Hz, 4.8 Hz, 1 H), 5.58-5.66 (m, 1 H), 5.23 (AB quartet, *J* = 12.0 Hz, 1.2 H), 5.17 (AB quartet, *J* = 12.0 Hz, 0.8 H), 4.99 (d, *J* = 9.2 Hz, 1 H), 4.22 (dd, *J* = 18.8 Hz, 4.8 Hz, 0.6 H), 4.18 (dd, *J* = 18.4 Hz, 4.4 Hz, 0.4 H), 3.68 (dd, *J* = 18.8 Hz, 2.0 Hz, 0.6 H), 3.05 (d, *J* = 18.4 Hz, 0.4 H), 2.26 (s, 1.2 H), 2.24 (s, 1.8 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 169.6, 155.5, 154.7, 142.3, 142.1, 136.4, 136.0, 132.8, 131.3, 130.3, 129.0, 128.5, 128.4, 128.2, 128.0, 127.9, 127.0, 126.7, 121.7, 121.5, 108.0, 74.4, 74.2, 67.9, 67.6, 56.4, 55.8, 39.3 (NCH_2), 38.8 (NCH_2), 14.6 (CH_3). IR (cm^{-1}) 3065 (w), 1702 (s), 1625 (s). HRMS (ESI) Calcd. for $C_{22}H_{21}NO_5S$ ($[M+H]^+$): 412.1213. Found: 412.1219. ($[M+NH_4]^+$): 429.1479. Found: 429.1484. HPLC: Daicel® Chiralcel OD-RH column, isocratic solvent system: 45 % CH_3CN in H_2O (without TFA), 1.0 mL/min., λ = 254 nm, (3aS, 7aR)-(-)-**1.82**: $t_{(-)}$ = 29.2 min; (3aR, 7aS)-(+)-**1.82**: $t_{(+)}$ = 32.5 min.

(+) and (±)-(3aS,7aS)-Benzyl-2-hydroxy-2-methyl-3,3a,5,7a-tetrahydrofuro[3,2-b]pyridine4(2H)-carboxylate, (+) and (±)-1.84



1.84

To a solution of (±)-**1.82** (130 mg, 0.32 mmol, 1.0 equiv) in THF/methanol (1/2 mL) was added Na_2HPO_4 (683 mg, 4.8 mmol, 15 equiv) and 10% sodium mercury amalgam (1.1 g, 4.8 mmol, 10 equiv) at -35 °C. The reaction mixture was warm to room temperature over 2 hours, and then quenched with water. The mixture was poured into a separatory funnel containing EtOAc (5 mL) and H_2O (4 mL), and the layers were

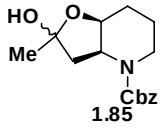
separated. The aqueous layer was extracted with EtOAc (2 x 4 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The residue was dissolved in acetone/water (3/1 mL). The solution was acidified by 1 M HCl to pH = 1, and then stirred for 20 minutes at room temperature. The mixture was neutralized to pH = 7 with saturated sodium carbonate solution, extracted with EtOAc (3 x 5 mL), dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (1:1) afforded (±)–**1.84** (81 mg, 0.28 mmol, 88%) as colorless oil.

Similar treatment of (-)-**1.82** (130 mg, 0.32 mmol, 1.0 equiv, >99% ee) in THF/methanol (1/2 mL) with Na_2HPO_4 (683 mg, 4.8 mmol, 15 equiv) and 10% sodium mercury amalgam (1.1 g, 4.8 mmol, 10 equiv) at -35 °C afforded (3aS, 7aS)-(+)-**1.84** (80 mg, 0.28 mmol, 86%) {$[\alpha]_D^{20}$ = +24.1, (c = 0.5, CH_2Cl_2)}

TLC (R_f = 0.29, 1:1 hexanes:EtOAc). ^{1}HNMR (a mixture of hemiketal, hydroxylketone and corresponding rotamers) (400 MHz, $CDCl_3$) δ 7.27-7.48 (m, 5 H), 5.87 (dd, *J* =10.8 Hz, 2.0 Hz, 0.2 H), 5.62-5.80 (m, 1.8 H), 5.32 (br s, 0.4 H), 4.90-5.16 (m, 2.6 H), 4.60 (d, *J* = 8.0 Hz,0.4 H), 4.51 (br s, 0.6 H), 4.22-4.28 (m, 1 H), 3.65 (dq, *J* = 18.8 Hz, 2.4 Hz, 0.5 H), 3.48-3.59 (m, 0.5 H), 2.90 (dd, *J* = 16.4 Hz, 7.2 Hz, 0.4 H), 2.75 (s, 0.3 H), 3.38 (dd, *J* = 16.0 Hz, 6.0 Hz, 0.6 H), 2.28 (dd, *J* =13.2 Hz, 9.2 Hz, 0.2 H), 2.18 (br s, 1.7 H), 2.01 (dd, *J* =12.8 Hz, 9.6 Hz, 0.2 H), 1.84 (t, *J* =12.0 Hz, 0.4 H), 1.82 (s, 0.7 H), 1.50 (s, 1.5 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.3 (Cbz carbonyl), 136.3, 128.5, 128.2, 128.0, 127.96, 127.92, 127.2, 125.9, 123.9, 105.0, 103.7, 71.7, 70.9, 67.4, 65.6, 52.0, 51.4, 49.3, 41.4, 40.2, 39.4, 39.1, 39.0, 38.5, 30.2, 29.0, 28.4. IR (cm^{-1}) 3424 (br s), 3038 (w), 2984

(w), 1698 (s). HRMS (ESI) Calcd. for $C_{16}H_{19}NO_4$ ($[M+Na]^+$): 312.1206. Found: 312.1209. ($[M+K]^+$): 328.0946. Found: 328.0948.

(+) and (±)-(3aS,7aS)-Benzyl-2-hydroxy-2-methylhexahydrofuro[3,2-b]pyridine-4(2H)carboxylate, (+) and (±)-1.85



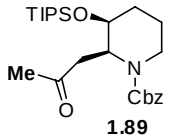
1.85

To a solution of (±)-**1.84** (70 mg, 0.24 mmol, 1.0 equiv) in THF (3 mL) was added PtO_2 (5.5 mg, 0.024 mmol, 0.1 equiv). The reaction mixture was stirred at room temperature for 5 hours in hydrogen with a balloon attached to the flask. The mixture was filtered, and then the filtrate was concentrated. Flash chromatography over silica gel with hexanes-EtOAc (1:1) afforded (±)–**1.85** (67 mg, 0.23 mmol, 95%) as colorless oil.

Similar treatment of (+)-**1.84** (80 mg, 0.24 mmol, 1.0 equiv, >99% ee) in THF (3 mL) with hydrogen in the presence of 10% PtO_2 afforded (3aS, 7aS)-(+)-**1.85** (77 mg, 0.23 mmol, 95%) $\{[\alpha]_D^{20} = +19.8, (c = 0.85, CH_2Cl_2)\}$

TLC (R_f = 0.18, 1:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) (a mixture of hemiketal, hydroxylketone and corresponding rotamers) δ 7.26-7.38 (m, 5 H), 5.07-5.15 (m, 2 H), 4.98 (br s, 1 H), 4.65 (q, *J* = 6.8 Hz, 0.05 H), 4.34 (q, *J* = 6.8 Hz, 0.2 H), 3.98-4.01 (m, 0.75 H), 3.84 (br s, 1 H), 2.96 (dd, *J* = 16.0 Hz, 7.8 Hz, 1 H), 2.69 (br s, 1 H), 2.48 (dd, *J* = 15.6 Hz, 4.8 Hz, 1.3 H), 2.17 (br s, 2 H), 1.80-1.91 (m, 1 H), 1.65-1.75 (m, 1.7 H), 1.39-1.56 (m, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.3 ($CH_3\underline{C}O$), 155.9, 155.2, 136.6, 136.4, 128.5, 128.03, 127.96, 127.8, 103.6, 74.5, 73.4, 68.1, 67.3, 67.1, 53.4, 51.6, 40.9, 40.5, 39.8, 39.5, 38.9, 30.1, 28.0, 27.2, 23.7, 18.7 (CH_3). IR (cm^{-1}) 3443 (s), 2945 (w), 1695 (s). HRMS (ESI) Calcd. for $C_{16}H_{21}NO_4$ ($[M+H]^+$): 292.1543. Found: 292.1544.

(+) and (±)-(2S,3S)-Benzyl 2-(2-oxopropyl)-3-(triisopropylsilyloxy)piperidine-1-carboxylate, (+) and (±)-1.89



1.89

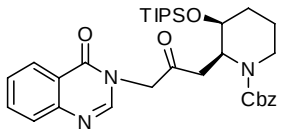
To a solution of (±)-**1.85** (60 mg, 0.21 mmol, 1.0 equiv) in DMF (1 mL) was added imidazole (43 mg, 0.63 mmol, 3 equiv) and TIPSCl (121 mg, 0.63 mmol, 3 equiv). The reaction mixture was stirred at room temperature overnight. The mixture was poured into a separatory funnel containing EtOAc (5 mL) and H_2O (4 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 3 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (6:1) afforded (±)–**1.89** (70 mg, 0.16 mmol, 75%) as colorless oil and (±)-**1.85** (12 mg, 0.042 mmol, 20%) was recovered.

Similar treatment of (+)-**1.85** (60 mg, 0.21 mmol, 1.0 equiv, >99% ee) in DMF (1 mL) with imidazole (43 mg, 0.63 mmol, 3 equiv) and TIPSCl (121 mg, 0.63 mmol, 3 equiv) afforded (2S, 3S)-(+)-**1.89** (70 mg, 0.16 mmol, 75%) and (+)-**1.85** (12 mg, 0.042 mmol, 20%) was recovered. $\{[\alpha]_D^{20} = +34.8, (c = 0.85, CH_2Cl_2)\}$

TLC (R_f = 0.63, 2.5:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) (a mixture of rotamers) δ 7.27-7.37 (m, 5 H), 5.10 (AB quartet, *J* = 12.8 Hz, 1.2 H), 5.09 (s, 0.8 H), 4.99 (br s, 0.4 H), 4.90 (br s, 0.6 H), 4.03 (d, *J* = 12.4 Hz, 0.6 H), 3.78-3.92 (m, 1.4 H), 2.75-2.92 (m, 2 H), 2.56-2.65 (m, 1 H), 2.22 (s, 1.2 H), 2.06 (s, 1.8 H), 1.78-1.84 (m, 1.2 H), 1.61-1.67 (m, 0.8 H), 1.41-1.51 (m, 2 H), 1.08 (s, 8.4 H), 1.01 (s, 12.6). ^{13}C NMR (150 MHz, $CDCl_3$) δ 208.2 ($CH_3\underline{C}O$), 206.9 ($CH_3\underline{C}O$), 165.3, 155.4, 155.1, 136.6, 128.4,

128.02, 127.96, 127.8, 69.4, 69.1, 67.4, 67.3, 53.3, 39.2, 38.8, 38.0, 37.8, 29.9, 29.4, 28.7, 24.3, 23.9, 18.0 ($CH(\underline{C}H_3)_2$), 17.9 ($CH(\underline{C}H_3)_2$), 12.2 ($\underline{C}H(CH_3)_2$), 12.1 ($\underline{C}H(CH_3)_2$). IR (cm^{-1}) 2945 (w), 2868 (w), 1702 (s). HRMS (ESI) Calcd. for $C_{25}H_{41}NO_4Si$ ($[M+H]^+$): 448.2878. Found: 448.2879. ($[M+NH_4]^+$): 465.3143. Found: 465.3145.

(+) and (±)-(2S,3S)-Benzyl 2-(2-oxo-3-(4-oxoquinazolin-3(4H)-yl)propyl)-3-(triisopropylsilyloxy)piperidine-1-carboxylate, (+) and (±)-1.91



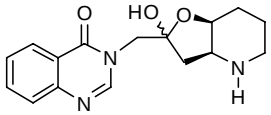
1.91

To a solution of (±)-**1.89** (60 mg, 0.13 mmol, 1.0 equiv) in DCM (2 mL) was added TEA (39 mg, 0.39 mmol, 3 equiv) and TMSOTf (87 mg, 0.39 mmol, 3 equiv) at room temperature. The reaction mixture was stirred 20 minutes. The mixture was loaded onto a plug of silica gel column, and eluted with 20 mL hexanes-EtOAc (2:1) quickly. The solution was concentrated and dissolved again in THF (2 mL). To the solution was added NBS (28 mg, 0.16 mmol, 1.2 equiv). The reaction mixture was stirred at room temperature for 30 minutes. To the reaction mixture was added 4-hydroxy-quinazoline (29 mg, 0.20 mmol, 1.5 equiv), 60% NaH dispension (8 mg, 0.20 mmol, 1.5 equiv) and 15-C-5 (5.8 mg, 0.026 mmol, 0.2 equiv). The reaction mixture was stirred for 2 hours at room temperature, and quenched with water. The mixture was poured into a separatory funnel containing EtOAc (5 mL) and H_2O (4 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 3 mL), and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (1:1) afforded (±)–**1.91** (51.5 mg, 0.087 mmol, 67%) as colorless oil. Similar treatment of (+)-**1.89** (60 mg, 0.13 mmol, 1.0

equiv, >99% ee) in the same sequence afforded (2S, 3S)-(+)-**1.91**52 mg, 0.16 mmol, 67%). {$[\alpha]_D^{20}$ = +48.8, (c = 0.48, $CHCl_3$)}

TLC (R_f = 0.33, 1:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) (a mixture of rotamers) δ 8.27 (d, *J* = 8.0 Hz, 1 H), 8.03 (br s, 1 H), 7.70-7.80 (m, 2 H), 7.47-7.52 (m, 1 H), 7.26-7.33 (m, 5 H), 5.08-5.21 (m, 3 H), 4.90-4.95 (m, 2 H), 3.92-3.96 (m, 2 H), 3.11-3.16 (m, 1 H), 2.88-2.96 (m, 1 H), 2.70-2.80 (m, 1 H), 1.80-1.88 (m, 1 H), 1.66-1.71 (m, 1 H), 1.45-1.56 (m, 2 H), 1.09 (s, 18 H), 1.02 (br s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.8 (CO), 161.0, 156.3, 147.1, 136.2, 134.3, 128.5, 128.1, 127.8, 127.4, 127.1, 126.8, 121.9, 69.2, 67.7, 53.8, 53.3, 38.2, 36.0, 29.7, 28.4, 23.8, 18.1 ($CH(\underline{C}H_3)_2$), 12.2 ($\underline{C}H(CH_3)_2$). IR (cm^{-1}) 2945 (w), 2868 (w), 1687 (s). HRMS (ESI) Calcd. for $C_{33}H_{45}N_3O_5Si$ ($[M+H]^+$): 592.3201. Found: 592.3208.

(+) and (±)-Isofebrifugine, (+) and (±)-1.70



1.70

To (±)-**1.91** (40 mg, 0.068 mmol, 1.0 equiv) was added HCl (1.2 mL, 6 M), and the solution was refluxed for 90 minutes. The mixture was neutralized to pH=10 with solid Na_2CO_3, poured into a separatory funnel containing EtOAc (5 mL) and H_2O (4 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over deactivated alumina with $CHCl_3$-methanol (6:1) afforded (±)–**1.70** (13 mg, 0.043 mmol, 63%). Similar treatment of (+)-**1.91**(40 mg, 0.068 mmol, 1.0 equiv,

>99% ee) with HCl (1.2 mL, 6 M) afforded (+)-**1.70** (13 mg, 0.043 mmol, 63%). {$[\alpha]_D^{20}$ = +129, (c = 0.30, $CHCl_3$)}

TLC (R_f = 0.27, 6:1 chloroform:methanol on alumina). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (dd, *J* = 8.0 Hz, 1.6 Hz, 1 H), 8.30 (s, 1 H), 7.76 (dt, *J* = 6.8 Hz, 1.6 Hz, 2 H), 7.72 (t, *J* = 8.0 Hz, 1 H), 7.50 (dt, *J* = 8.0 Hz, 1.6 Hz, 1 H), 4.46 (d, *J* = 14.4 Hz, 1 H), 4.15 (d, *J* = 14.4 Hz, 1 H), 3.88 (q, *J* =2.8 Hz, 1 H), 3.29 (t, *J* = 3.2 Hz, 1 H), 3.00 (d, *J* = 11.2 Hz, 1 H), 2.53 (dt, *J* = 10.4 Hz, 1.6 Hz, 1 H), 2.05-2.15 (m, 2 H), 1.76-1.89 (m, 2 H), 1.50-1.58 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4 (C=O), 148.2, 148.0, 134.3, 127.5, 127.1, 126.9, 121.9, 105.4 (ketal carbon), 77.8 (CH), 55.7 (CH), 49.8 (CH_2), 44.5 (CH_2), 43.3 (CH_2), 26.8 (CH_2), 20.1 (CH_2). IR (cm^{-1}) 3304 (w), 2926 (w), 2853 (m), 1729 (w), 1675 (s), 1613 (s). HRMS (ESI) Calcd. for $C_{16}H_{19}N_3O_3$ ($[M+H]^+$): 302.1499. Found: 302.1501.

Chapter Two

Uncatalyzed Electrophilic C-C Bond Forming Reactions of Pyranyl and Pyridinyl Molybdenum Complexes. A synthetic Tactic for the Enantioselective Construction of Indole Alkaloids

Background

Stoichiometric transition metal mediated electrophilic reactions

The enantiocontrolled formation of C-C bonds has been the vital task in modern organic synthesis. In recent years, transition metal complexes have been employed widely in organic reactions to construct C-C bonds both catalytically and stoichiometrically. Although numerous efforts have been invested on the catalytic process, much progress has also been achieved in stoichiometric transition metal mediated processes.[1] Various transition metal complexes can be used to stabilize both positive and negative charges on attached ligands. In this Chapter, only those processes in which a stoichiometric metal is used to stabilize carbocations are covered.

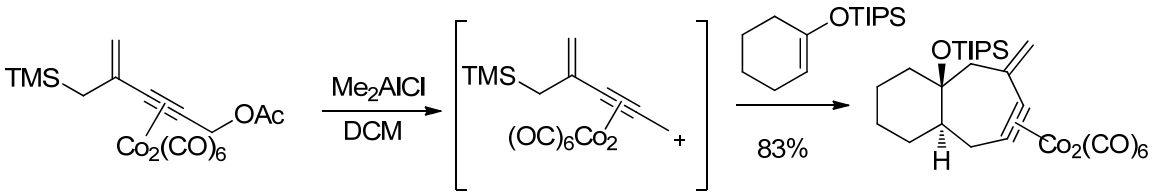
Cobalt Complex

The Nicholas reaction has been a main methodology used to induce electrophilic reactions and has been reviewed extensively since it was discovered in 1972. [2] The required alkyne cobalt intermediates are easily prepared by reacting alkynes with stoichiometric dicobalt octacarbonyl. In a typical Nicholas reaction, stoichiometric Lewis acid or protic acid was used to generate the reactive intermediate, which can be quenched by many kinds of nucleophiles, including hydrides, enol derivatives, allyl metals, aromatics, azides, amines, and alcohols.

A recent example reported by Kuwajima group, who employed dicobalt acetylene complex **2.1** in a novel [5+2] cycloaddition (**Scheme 49**).[3] In the reaction stoichiometric Me_2AlCl was required to generate the reactive intermediate **2.2.** It reacted with a TIPS

enol ether to yield the oxonium ion, which was further trapped by the tethered allyl silane to form the seven membered ring product.

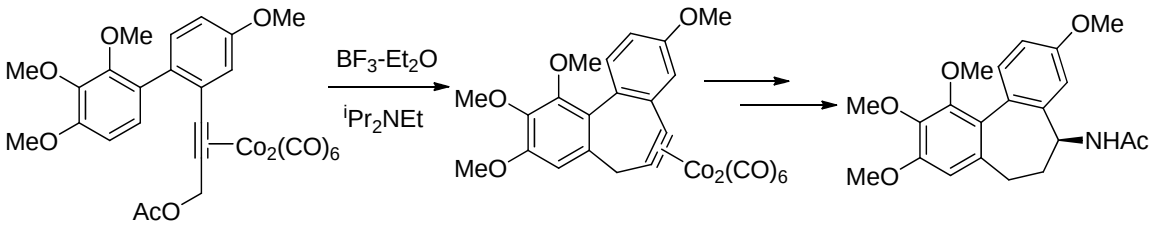
Scheme 49 Dicobalt compounds induced [5+2] reaction



2.1 **2.2** **2.3**

The Nicholas reaction has been widely applied in the total synthesis of natural products in the past two decades. In 2007, an intramolecular Nicholas reaction was applied in the synthesis of NSC 51046(**Scheme 50**). [4] Green reported a synthesis of this bioactive compound starting from dicobalt acetylene complex **2.4,** in which the electron-rich aromatic ring was the nucleophile. The carbocation, which was generated by treating **2.4** with BF_3-Et_2O, was intramolecularly intercepted by the polymethoxy benzene ring to form a cycloheptyne-$Co_2(CO)_6$ complex, a key intermediate to the synthesis of NSC 51046.

Scheme 50 Intramolecular Nicholas reaction in the synthesis of NSC 51046

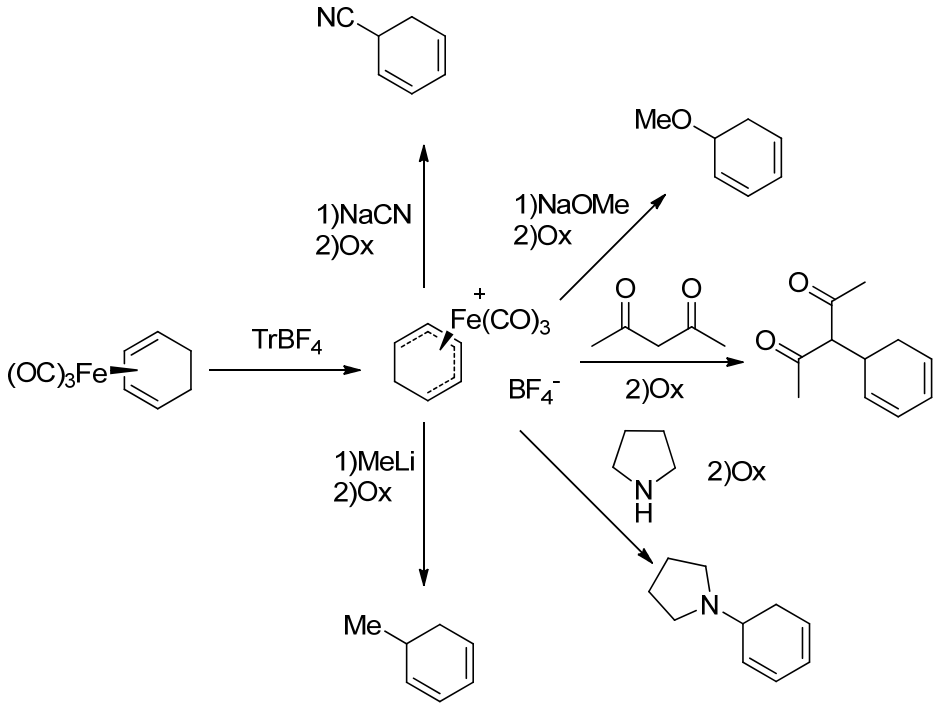


2.4 **2.5** **NSC 51046**

Iron Complex

Dienes can be "protected" as their $Fe(CO)_3$ complexes. Moreover, they have demonstrated powerful capability in the natural product synthesis. [5] As shown in **Figure 8**, $Fe(CO)_3(\eta^4$-cyclohexa-1,3-diene) could be converted to η^5-iron cation complex, which can be functionalized with a variety of nucleophiles.[2a] The new complex was readily oxidized into substituted cyclohexanes.

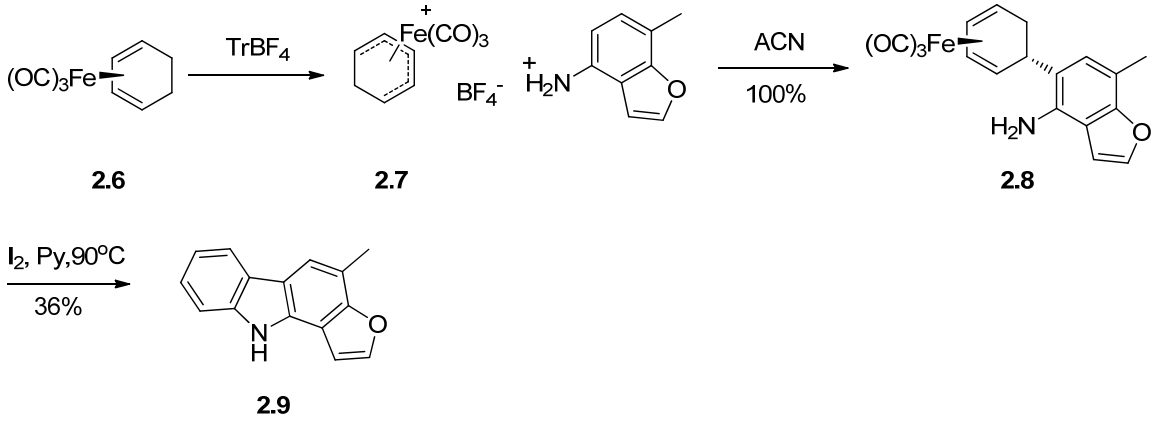
Figure 8 Synthetic applications of iron diene complex



An interesting application of this methodology is the synthesis of carbazole compounds reported by Knolker (**Scheme 51**).[6] In this reaction, the iron salt **2.7** was treated with aminobenzofuran to form a Friedel-Crafts product **2.8** regioselectively. It is

worth noting that there was no *N*-alkylation product observed. After oxidative demetallation with iodine, it afforded the carbazole product **2.9** in a modest yield.

Scheme 51 Iron diene complex in the synthesis of carbazole

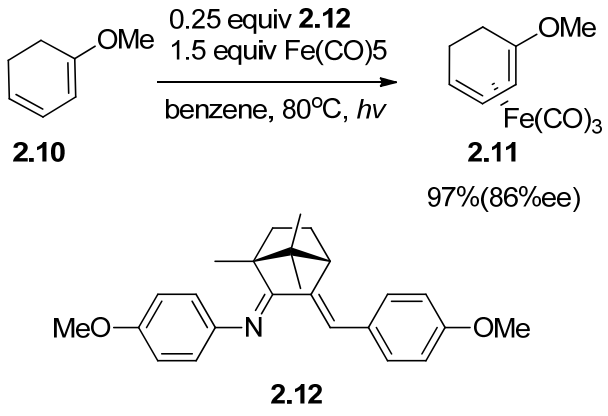


2.6 **2.7** **2.8**

2.9

Different methods have been explored to achieve enantiocontrol in the stoichiometric iron mediated reactions. Knolker developed a catalytic photoinduced reaction to prepare iron diene complex 2.11 in good enantiopurity in the presence of (-)-camphor derived imine 2.12 (**Scheme 52**).[7]

Scheme 52 Catalytic photoinduced preparation of high enantiopurity of iron diene complex



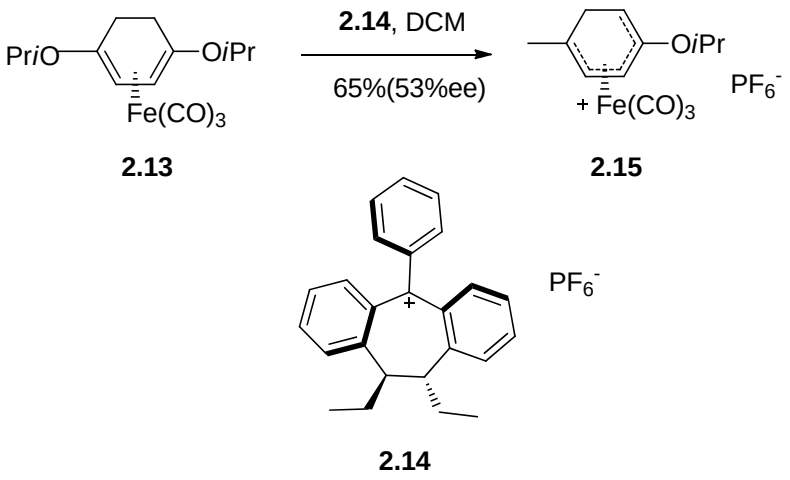
2.10 **2.11**

97%(86%ee)

2.12

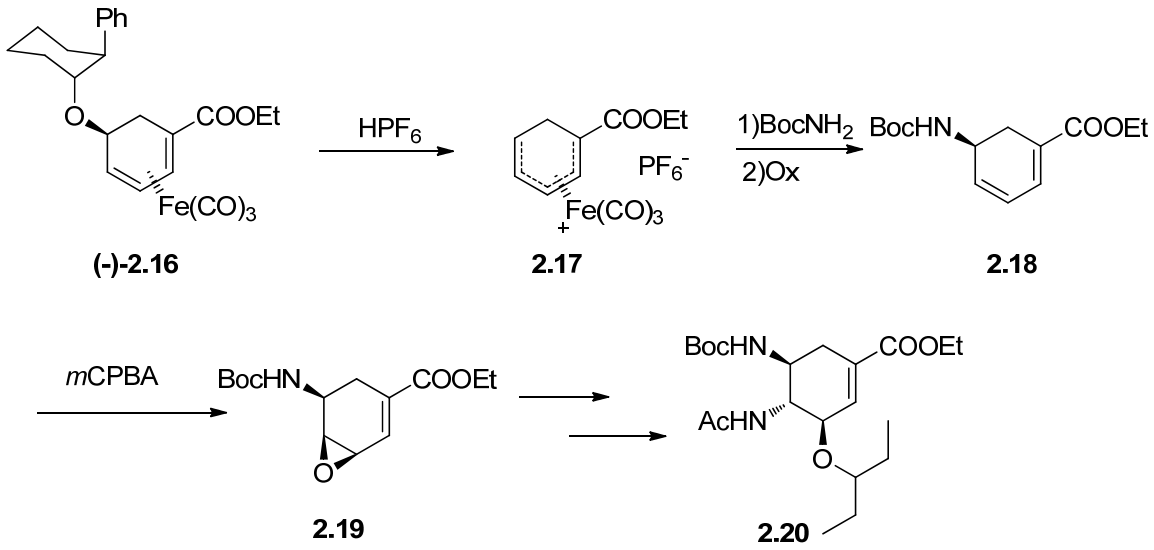
Desymmetrization was also studied to achieve the enantiocontrol in the application of iron complex based methodology. Pettus and coworkers used a chiral trityl cation to abstract the hydride from *meso*-iron diene complex to achieve the cation in a moderate enantiopurity (**Scheme 53**).

Scheme 53 Desymmetrization of iron diene complex



An interesting application of this methodology is the diversity oriented synthesis of oseltamivir by varying different nucleophiles. Kann reported the synthesis of oseltamivir (marketed as Tamiflu) by applying the iron carbonyl complex (**Scheme 54**).[8] The enantiopure **(-)-2.16**, prepared by the preparative HPLC resolution of diastereomers of **2.16**, was treated with hexafluorophosphoric acid to yield the cationic intermediate. Oxidation, following nucleophilic attack of Boc protected amine, afforded the enantiopure amine substituted cyclohexadiene. Regioselective epoxidation and further functional group manipulation led to the key intermediate **2.20**, which had been transformed into Tamiflu. Since different nucleophiles could be used in the nucleophilic attack of **2.17**, analogues of Tamiflu could be easily obtained.

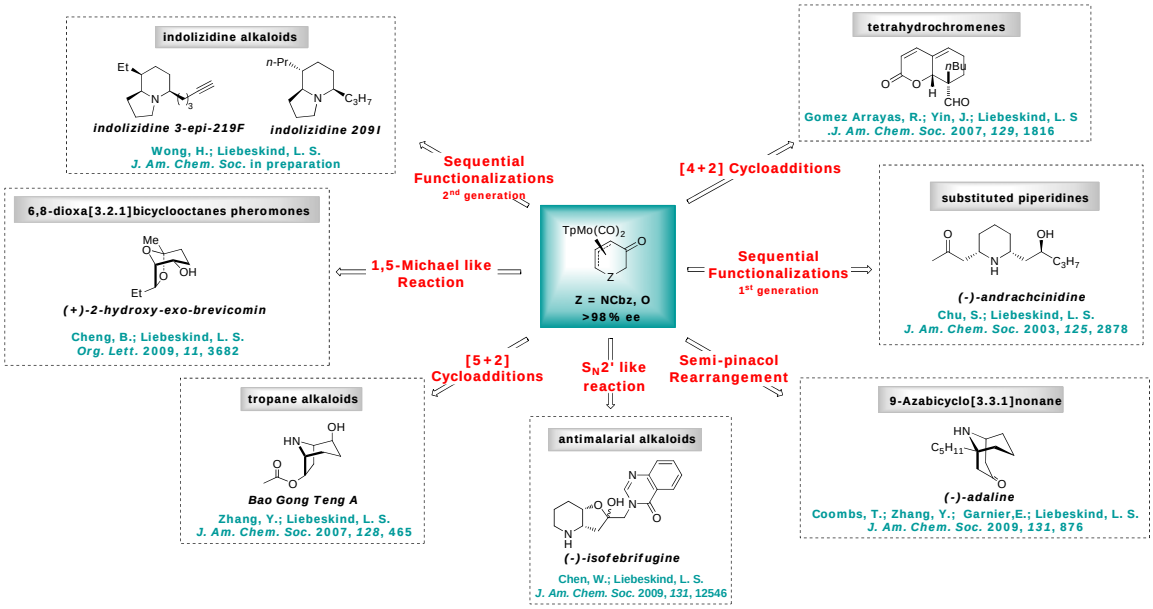
Scheme 54 Total synthesis of oseltamivir



Molybdenum complex

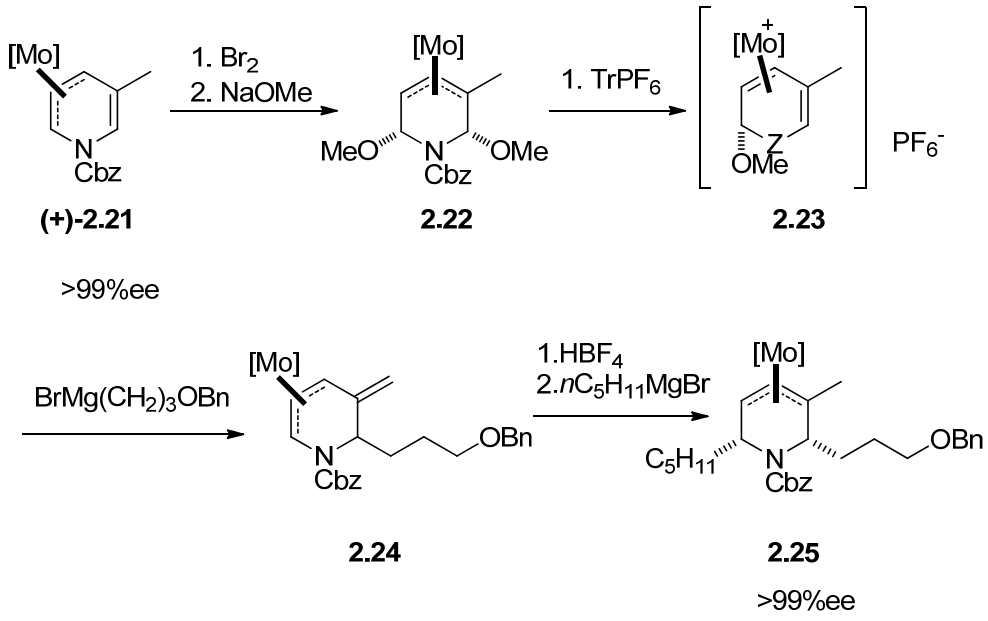
Enantiomerically pure, air and moisture-stable TpMo(CO)$_2$(η^3-pyranyl) and TpMo(CO)$_2$(η^3-pyridinyl) complexes are powerful scaffolds for the enantiocontrolled construction of substituted heterocycles.[9] The Liebeskind group has synthesized a number of natural products enantioselectively utilizing this methodology (**Figure 9**).

Figure 9 Molybdenum mediated organic synthesis



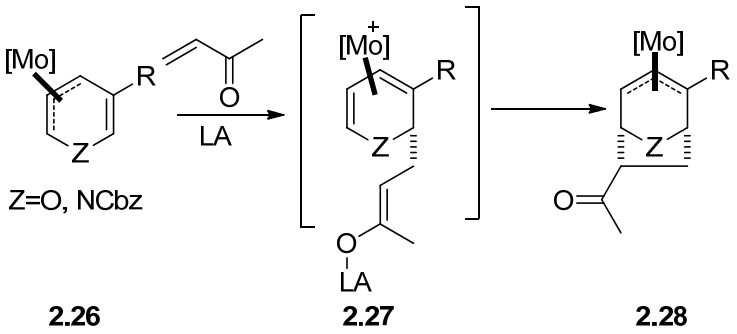
In 2001, Liebeskind and coworker reported a novel sequential functionalization of η^3-pyridinyl complexes (**Scheme 55**).[9k] High enantiopurity **(+)-2.21** was treated with bromine followed by sodium methoxide to produce dimethoxy complex **2.22.** Trityl hexafluorophosphate abstracted one methoxy group regioselectively to generate the molybdenum diene cation **2.23**, which was attacked by a Grignard reagent to introduce an alkyl chain and form **2.24**. Further treatment with HBF_4 led to the formation of a new molybdenum diene cation, which was quenched by another Grignard reagent to afford **2.25** without enantiopurity loss. The novel sequence constituted an efficient method to construct *cis*-2,6-disubstituted piperidine motif.

Scheme 55 Sequential functionalization of molybdenum scaffold



Another interesting reaction was the [5+2] reaction of the molybdenum scaffold (**Scheme 56**).[9d, 9g, 9q] In this reaction, the scaffold **2.26** was converted to the molybdenum diene cationic complex **2.27** in the presence of dienophiles, such as an α,β-unsaturated ketone activated with a Lewis acid. The putative intermediate **2.27** immediately yielded the formal [5+2] product **2.28** via the intramolecular nucleophilic attack of the carbocation. This methodology was successfully applied in the synthesis of (-)-Bao Gong Teng A.[9g]

Scheme 56 [5+2] cycloaddition of molybdenum scaffold

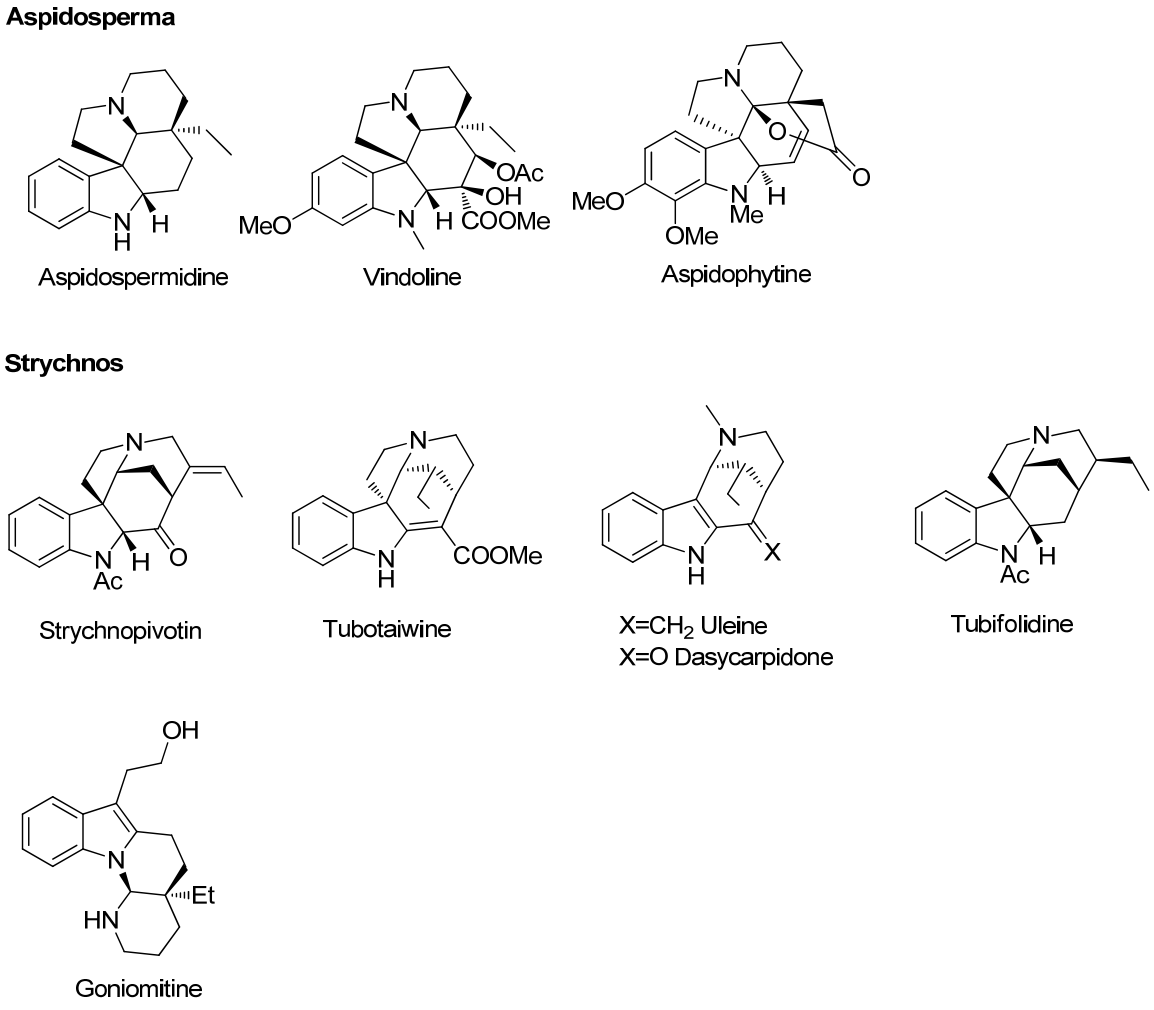


Introduction

Indole alkaloids are an important family of alkaloids in natural product research due to their intriguing structures and interesting biological activities.[10] Among the numerous interesting natural products, there were two families, *strychnos* and *aspidosperma* alkaloids, especially attracting our attention. (**Figure 10**) When examining these complex indole alkaloids carefully, we recognized that the *aspidosperma* alkaloids contain a *cis*-2,3-disubstituted piperidine motif while the *strychnos* alkaloids are composed of a *cis*-2,4-disubstituted piperidine motif. It was also worth pointing out that an indole alkaloid, goniomitine, also includes a *cis*-2,3-disubstituted piperidine motif, within which one of the substitution is a rare C-N substitution. The other reason why these alkaloids intrigued us was the well-known antitumor activity of vinblastine and vincristine, which contained vindoline moiety.[11] Therefore, a novel methodology may

provide an easy access to a large number of analogues of vindoline, which would be helpful to the biological study in this area.

Figure 10 Interesting indole alkaloids



Based on these considerations, the project of introducing indole into the molybdenum scaffold and aiming at the synthesis of the above indole alkaloids was designed. Herein are reported the results of this project, including the discovery of an

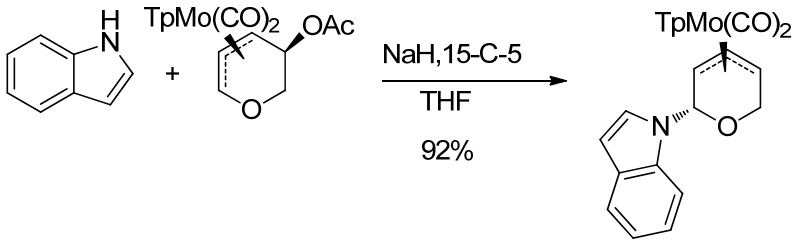
uncatalyzed Friedel-Crafts reaction and related reactions. Furthermore, mechanistic details were investigated to understand the new reactions. In addition, the molybdenum complexes were demetallated with different methods, one of which afforded the tetracyclic structure of vindoline in model system.

Results and discussion

Study in the typical Homo-S_N2'-like reaction condition

The introduction of indole to the molybdenum scaffold was first studied with complex **2.29,** which is readily available according to a known procedure[9a] (**Scheme 57**). Indole successfully functioned as a nucleophile in a homo-S_N2'-like to yield substitution product **2.30** in 92% yield. Interestingly, this reaction provided the *N*-alkylation product selectively. The formation of the product **2.30** showed the possibility that indole could also be used as a nucleophile in $TpMo(CO)_2(\eta^3$-pyridinyl) complexes and this reaction could be applied in the synthesis of goniomitine (**Figure 10**).

Scheme 57 Indole as a nucleophile in a typical Homo-S_N2'-like condition

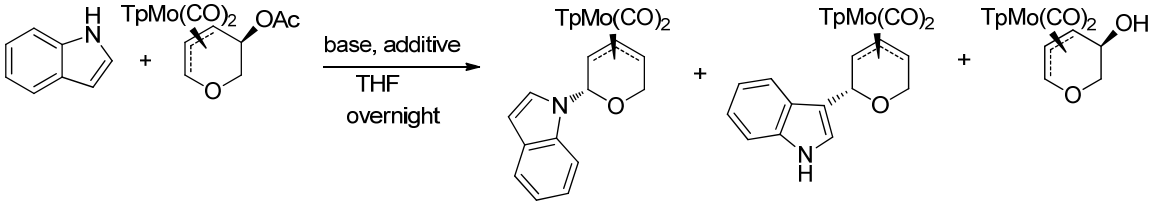


2.29 **2.30**

For the synthesis of most of indole alkaloids, *C*-alkylation of the indole is desired. A search of reaction conditions was carried out by varying additives and bases to achieve

the product **2.31**. (**Table 15**) As shown in **Table 2.1**, the absence of 15-C-5 favored the formation of the *C*-alkylation product **2.31**, but also lowered the conversion of starting material. Varying the counter ion from Na to Mg suppressed the formation of undesired product completely, but led to very poor conversion. Other bases failed to provide the desired product **2.31**; instead, deacetylation product **2.32** was obtained in high yield.

Table 15 Homo-S_N2'-like condition studies with indole as a nucleophile



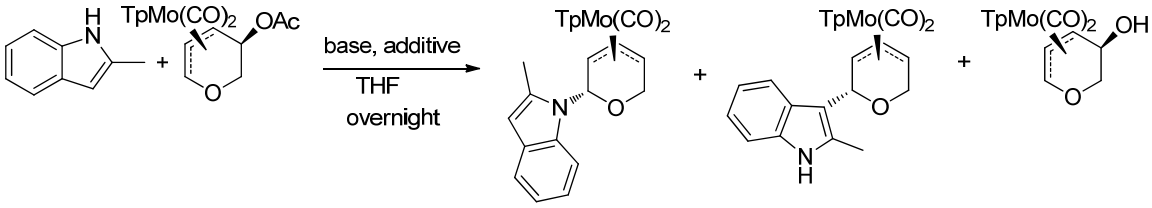
2.29 **2.30** **2.31** **2.32**

Base	Additive	**2.29**	**2.30**	**2.31**	**2.32**
NaH	15-C-5	0	92%	0	0
NaH	None	40%	20%	20%	20%
NaH	MS	40%	20%	20%	20%
MeMgBr	None	80%	0	0	20%
LiO*t*Bu	None	0	0	0	90%
DBU	None	0	0	0	>90%

2-Methylindole was subjected to similar reaction conditions to investigate the effect of the indole substituent. (**Table 16**) The 2-methyl group disfavored the formation

of the *N*-alkylation product, but it showed lower reactivity and failed to afford the product in a synthetically useful yield.

Table 16 Homo-S_N2'-like condition studies with 2-methylindole as an nucleophile



2.29 **2.33** **2.34** **2.32**

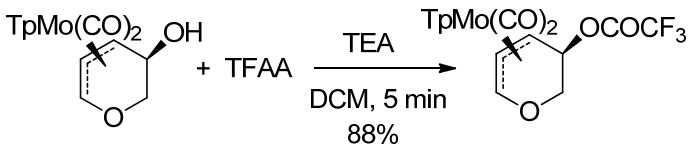
Base	Additive	**2.29**	**2.33**	**2.34**	**2.32**
NaH	15-C-5	40%	10%	0	20%
NaH	None	40%	0	30%	30%
NaH	None(ACN as solvent)	0	0	0	>90%
KH	None	0	0	0	80%

Preparation of new substrate and discovery of an uncatalyzed Friedel-Crafts reaction

The above results suggested that a completely new pathway should be invented to achieve the desired C-alkylation product **2.31** and **2.34**. Therefore, new substrate **2.36**, different from **2.29**, was prepared and studied (**Scheme 58**). The readily available

complex **2.35** was treated with TFAA in the presence of triethylamine to produce the semi-stable 5-trifluoroacetate substituted pyranyl scaffold **2.36** in 88% yield. Compound **2.36** was purified by a quick column chromatography, and it had to be used immediately to avoid decomposition. The trifluoroacetate **2.36** would decompose even stored under vacuum and in the dark as a solid after 12 hours.

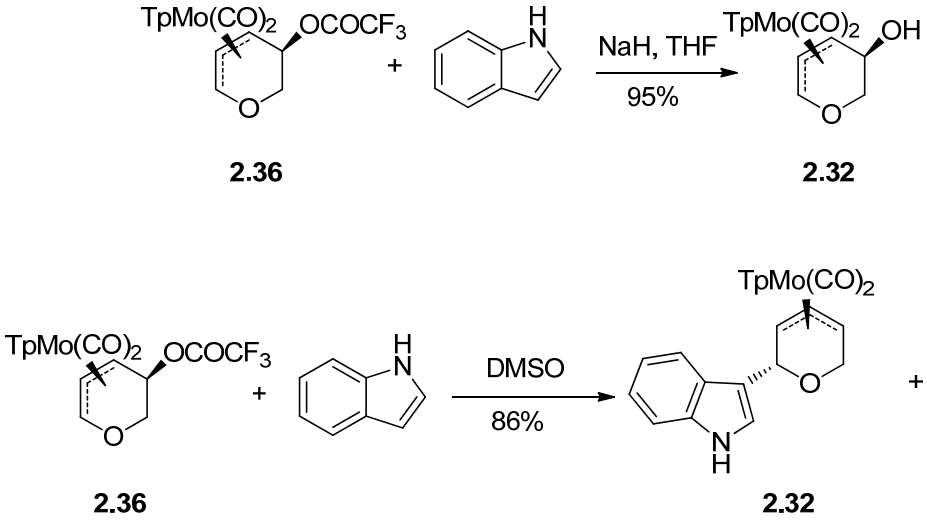
Scheme 58 Preparation of 5-trifluoroacetate substituted pyranyl scaffold



2.35 **2.36**

Complex **2.36** was submitted to the typical Homo-S_N2'-like reaction condition without 15-C-5, which only led in high yield to the deacylation product **2.32**. However, surprisingly, just mixing complex **2.36** with indole in DMSO provided the desired indole substitution product **2.31** in 86% yield with only <5% elimination product **2.37** observed (**Scheme 59**). Moreover, there were no other side product, such as the *N*-alkylation product **2.30** and the deacylation product **2.32**.

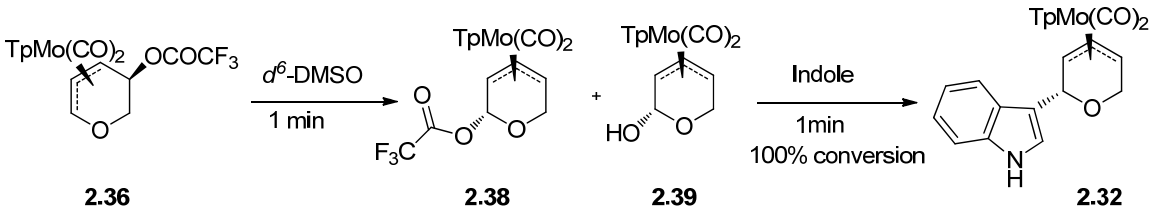
Scheme 59 Complex 2.36 reacted with indole in basic and neutral condition



Mechanistic consideration

d^6-DMSO was used as the reaction solvent in order to understand the mechanism of this reaction. Unexpectedly, complex **2.36** immediately rearranged to the isomeric 2-trifluoroacetate substituted pyranyl scaffold **2.38** along with some of the hydrolysis product **2.39** (**Scheme 60**). After indole was added, total conversion to **2.32** took place in 1 minute.

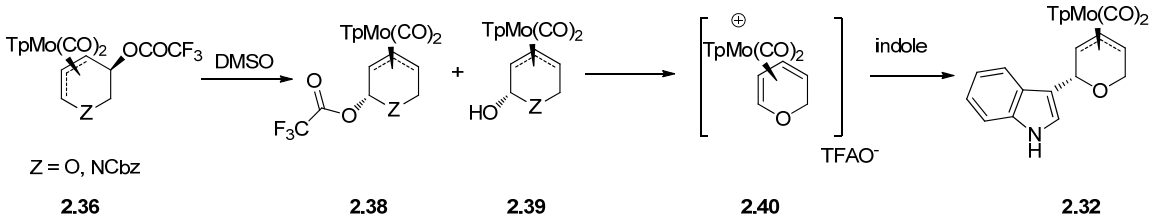
Scheme 60 Rearrangement of complex 2.36 in d^6-DMSO



Stable even after 3 days

Based on the observations above, a Friedel-Crafts–like mechanism was proposed (**Scheme 61**). After complex **2.36** rearranged to **2.38** and **2.39**, dissociation to form a $TpMo(CO)_2$ stabilized carbocation occurs. A Friedel-Crafts-like reaction leads to the product **2.32**.[12] A similar reaction also worked well via this pathway in the pyridinyl scaffold system (*vide infra*).

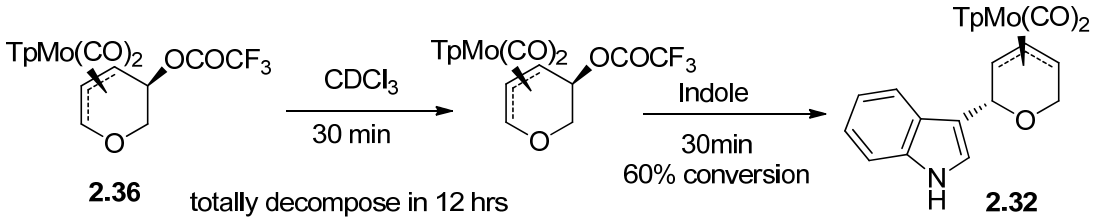
Scheme 61 Proposed mechanism for the uncatalyzed Friedel-Crafts reaction



Compared to complex **2.36**, both **2.38** and **2.39** were very stable. They can stand in DMSO solution for several days without obvious decomposition, while **2.36** decomposed completely after standing overnight in deuterochloroform.

It is worth noting that rearrangement from **2.36** to **2.38** and **2.39** is not a required step for the reaction with indole to occur. When **2.36** was dissolved in deuterochloroform, no rearrangement product was observed after 3 hours while messy signals implied it decomposed in this condition. Nevertheless, indole could also react with complex **2.36** in deuterochloroform to yield **2.32**, though it was slower and somewhat lower yielding (**Scheme 62).** But the reaction between complex **2.36** and indole in acetonitrile could give complex **2.32** in a better yield (80% in ACN *vs.* 61% in $CDCl_3$).

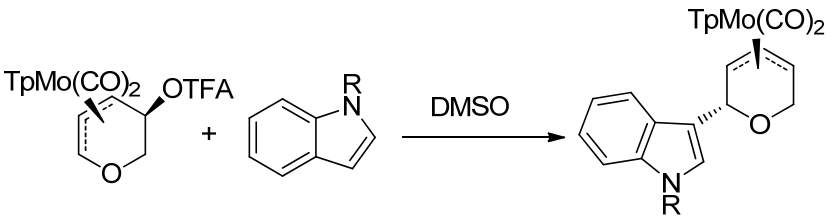
Scheme 62 Uncatalyzed Friedel-Crafts reaction between indole and 2.36 in chloroform



All of these observations suggested that the reaction of complex **2.36** with indole in DMSO could proceed through a different mechanism from that in chloroform or acetonitrile. This suggestion was further corroborated by the fact that silyl enol ether and allylsilane only reacted with complex **2.36** in chloroform or acetonitrile, but not in DMSO (*vide infra*).

Several control experiments were conducted to test the effect of protecting groups on the indole (**Scheme 63**). The results showed that an N-methyl protected indole gave a similar yield to an unprotected indole, while a Cbz protected indole failed to form the product. These observations are consistent with a Friedel-Crafts-like mechanism.

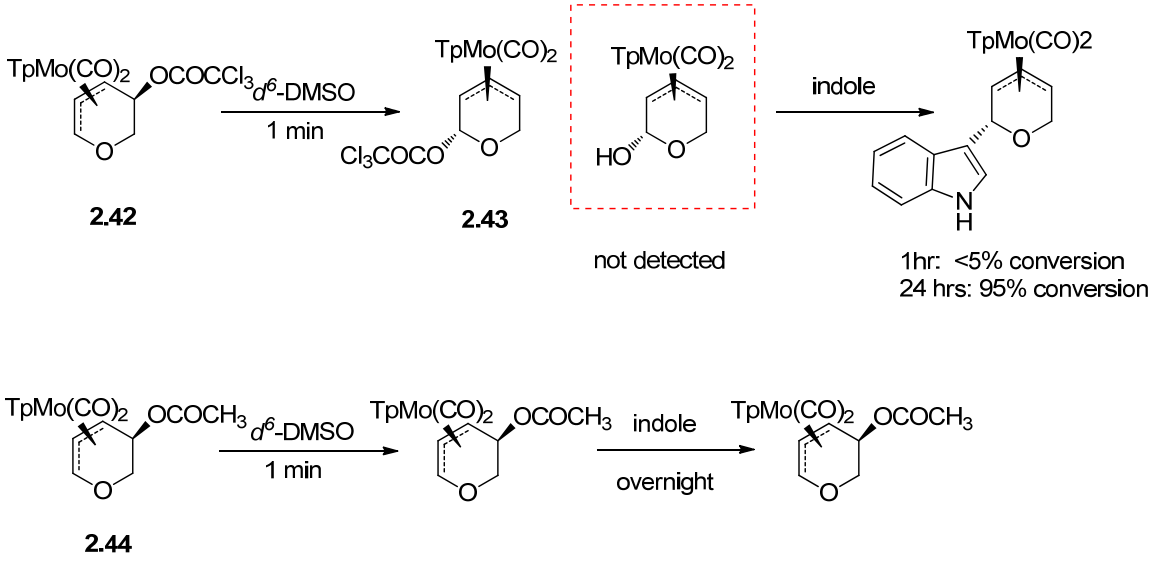
Scheme 63 Control experiments with methyl and Cbz protected indole



Experiments testing the effect of the leaving group were also carried out(**Scheme 64**). Trichloroacetate substituted scaffold **2.42** was prepared in a similar way to **2.36**, although in this reaction DMAP was necessary to promote the acylation step. In DMSO the rearrangement to **2.43** occurred in a similar rate to the trifluoroacetate analogue **2.36**. However, the Friedel-Crafts reaction was much slower: it took 24 hours to achieve 95% conversion. Preparation of a tribromoacetate substituted scaffold was also attempted, but no product was achieved in the similar conditions to those above. Therefore, the acetate analogue **2.44** was used instead to study how a poor leaving group behaved in this reaction. It was found that starting material **2.44** did not rearrange in DMSO; and no reaction took place in the presence of indole with 100% recovery of starting material. Even when a better leaving group such as *p*-nitrobenoate was employed, no reaction was

detected at room temperature, while increasing the temperature to 60 °C led to elimination product **2.37**.

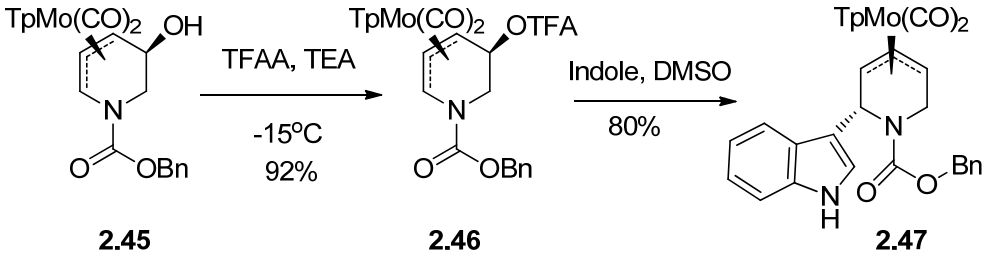
Scheme 64 Control experiments with poor leaving group



Uncatalyzed Friedel-Crafts reaction in pyridinyl molybdenum scaffold

The uncatalyzed Friedel-Crafts reaction was also studied in the pyridinyl scaffold series, which provided mostly successful results with some unexpected discoveries. The Cbz protected pyridinyl scaffold was first studied in the similar conditions to **2.36**. (**Scheme 65**) Complex **2.45** was transformed to trifluoroacetate **2.46** with TFAA in the presence of TEA at -15 °C in an excellent yield. Mixing **2.46** with indole in DMSO furnished the desired indole substitution product **2.47** in good yield in 30 minutes.

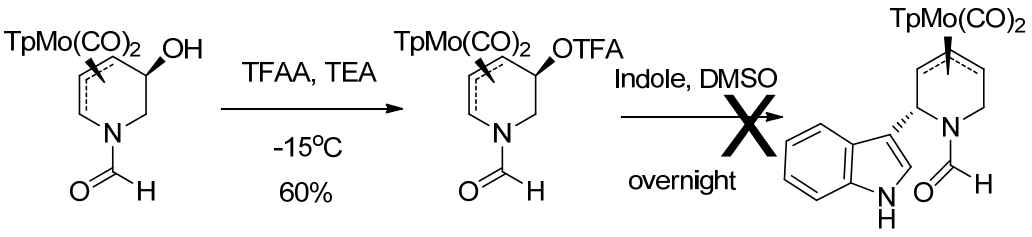
Scheme 65 Uncatalyzed Friedel-Crafts reaction with pyridinyl scaffold



2.45 **2.46** **2.47**

However, when the pyridinyl scaffold was protected with a formyl group, it showed a different reactivity (**Scheme 66**). Although the complex **2.48** could be converted to trifluoroacetate **2.49**, **2.49** was so stable that standing in DMSO with indole overnight did not yield any desired product **2.50**. Furthermore, no rearrangement product was observed with >95% of the starting material recovered. This result strongly suggested that heteroatom assistance is vital to the ionization.

Scheme 66 Unexpected failure with formyl protected pyridinyl scaffold

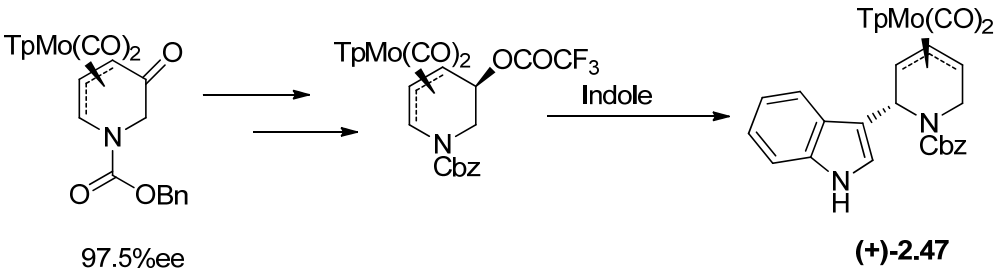


2.48 **2.49** **2.50**

Enantiopure pyridinyl scaffold **(+)-2.47** was also employed to test if there was any racemization during the course of this reaction. (**Table 17**) Starting from 97.5% ee

carbonyl complex, **(+)-2.47** was prepared and studied under three different Friedel-Crafts reaction conditions. Although the reaction in DMSO showed a minimum racemization (0.5% ee loss), the addition of MgO as buffer completely suppressed the enantiopurity loss, and the reaction in acetonitrile did not show any racemization (but contained approximately 10% of an inseparable impurity). Consequently, we conclude that the uncatalyzed Friedel-Crafts reaction can be carried out in the context of enantiocontrolled synthesis.

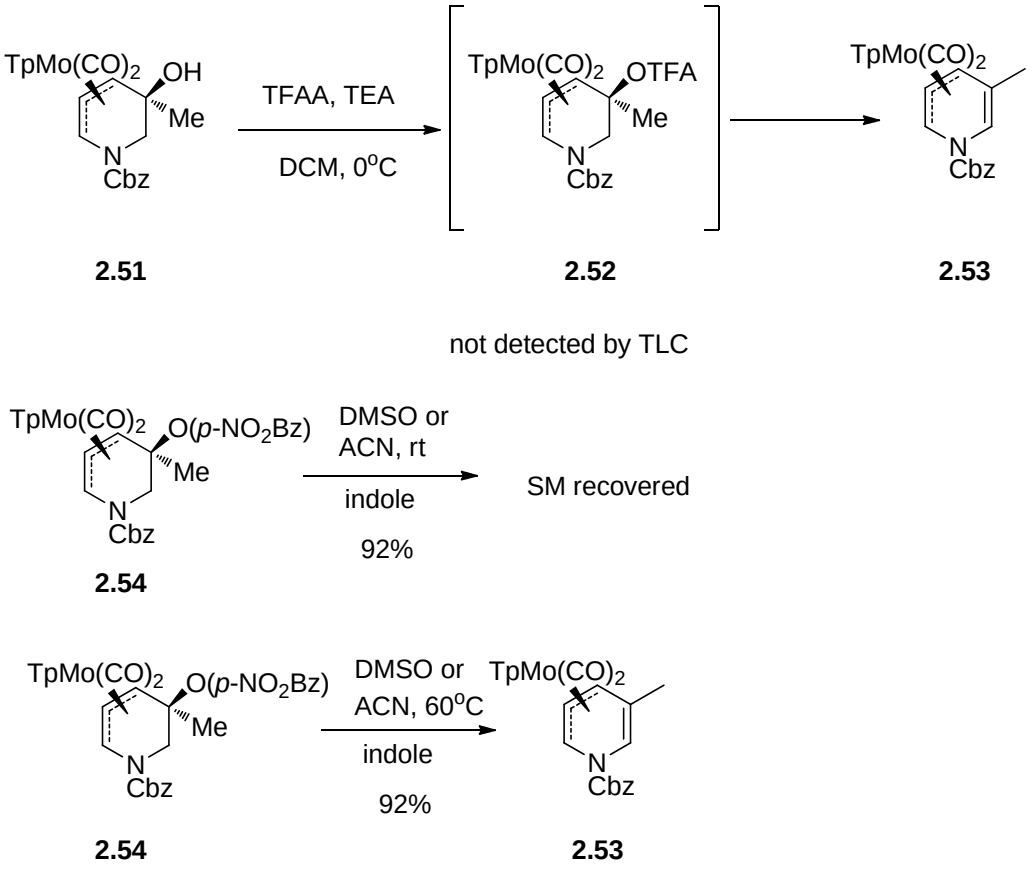
Table 17 Racemization test in different reaction conditions



Condition	Yield	ee
DMSO	80%	97.0%
DMSO, MgO	74%	97.5%
ACN	80%	97.5%

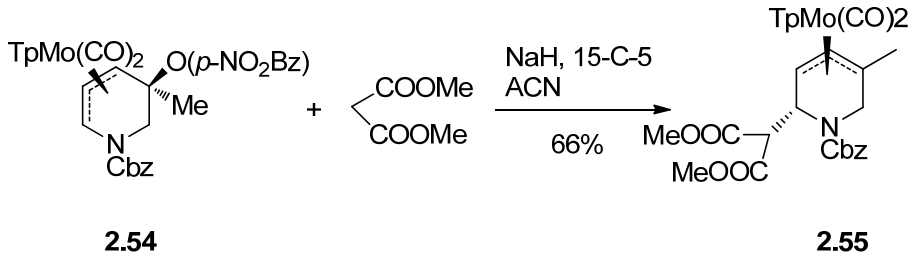
Expansion to the 5-methyl substituted scaffold was also investigated with complex **2.51** as a substrate (**Scheme 67**). However, all these attempts to observe C-C bond formation were fruitless. The trifluoroacetate intermediate **2.52** was never observed because of the rapid formation of elimination product; on the contrary, when the *p*-nitrobenoate was introduced to the substrate **2.51**, the complex **2.54** remained intact at room temperature while elimination to **2.53** took place in harsher conditions.

Scheme 67 Investigation on 5-substituted scaffold



It should be noted that **2.54** is a suitable substrate in homo-S_N2'-like reaction (**Scheme 68**). Malonate reacted with **2.54** to provide the substitution product **2.55** in good yield.

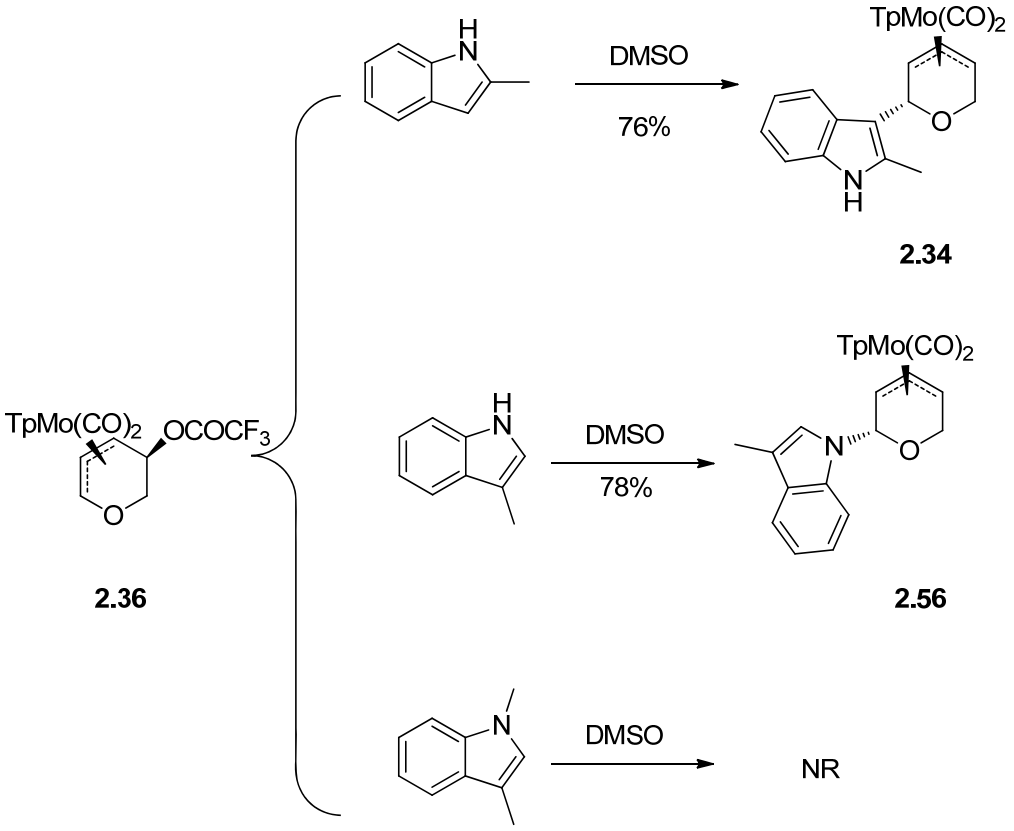
Scheme 68 Successful Homo-S_N2'-like reaction of 2.54



Studies on various indole derivatives

With the successful results of the uncatalyzed Friedel-Crafts-like reaction between indole and pyranyl and pyridinyl scaffolds in hand, various indole derivatives were prepared and studied in the reaction. Firstly, commercially available substituted indoles were studied (**Scheme 69**). 2-methyl indole yielded the *C*-alkylation product **2.34**, while 3-methyl indole provided the *N*-substitution product **2.56**. If both 1 and 3 position of indoles were occupied, no reaction took place. The results shown below clearly indicated that this reaction only occurred on the most electron-rich C-3 or N atom of indole rings with C-3 as the priority.

Scheme 69 Uncatalyzed Friedel-Crafts reaction between pyranyl scaffold and differently substituted indole

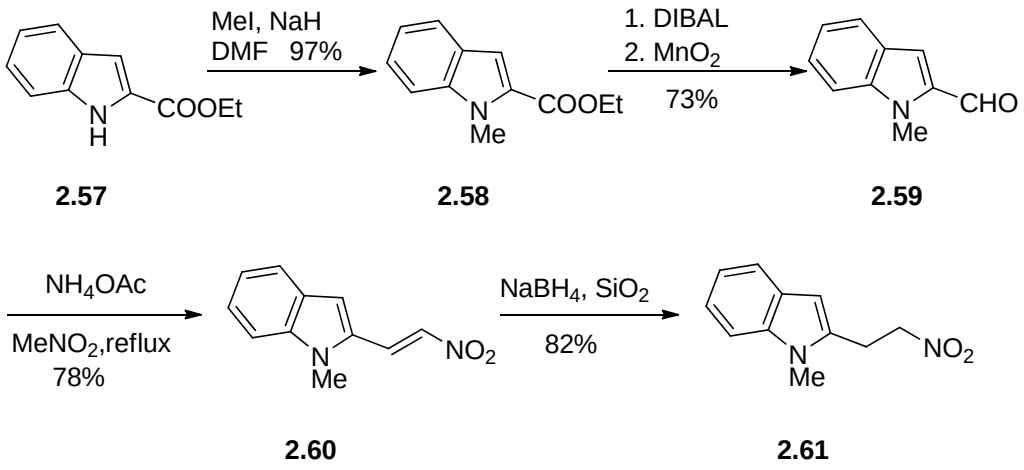


Since 2-substituted indoles worked well in this reaction, a variety of 2-substituted indole derivatives were prepared to study the functional group tolerance of this reaction.

The preparation of 2-nitroethyl indole **2.61** started from ethyl 2-indole carboxylic ester **2.57**. It was converted to **2.58** with methyl iodide by using sodium hydride as the base. Then DIBAL reduction of **2.58** followed by oxidation with MnO_2 led to the aldehyde **2.59**, which was condensed with nitromethane to yield 2-nitroethylene indole

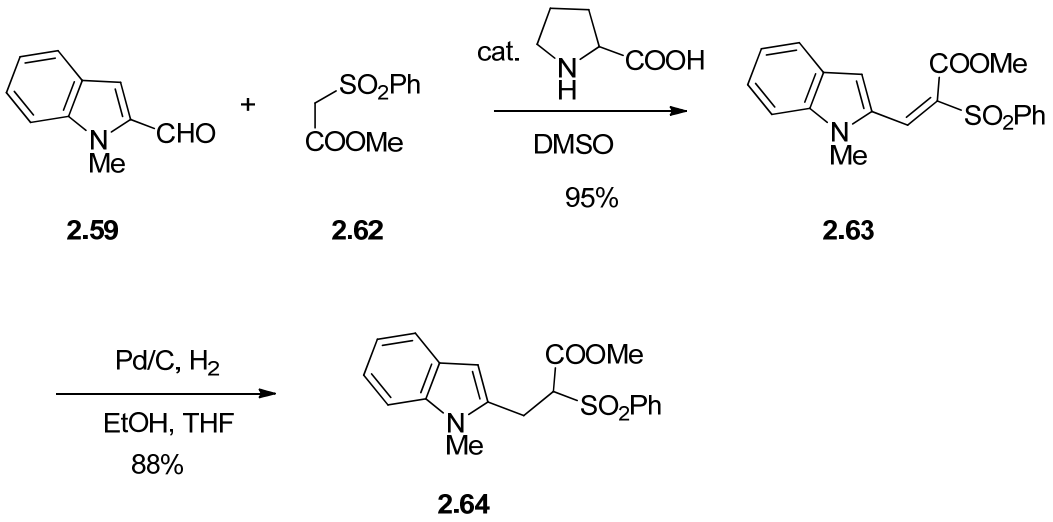
2.60. The reduction with $NaBH_4$ on silica gel furnished the desired 2-nitroethyl indole **2.61**.

Scheme 70 Preparation of 2-nitroethyl indole



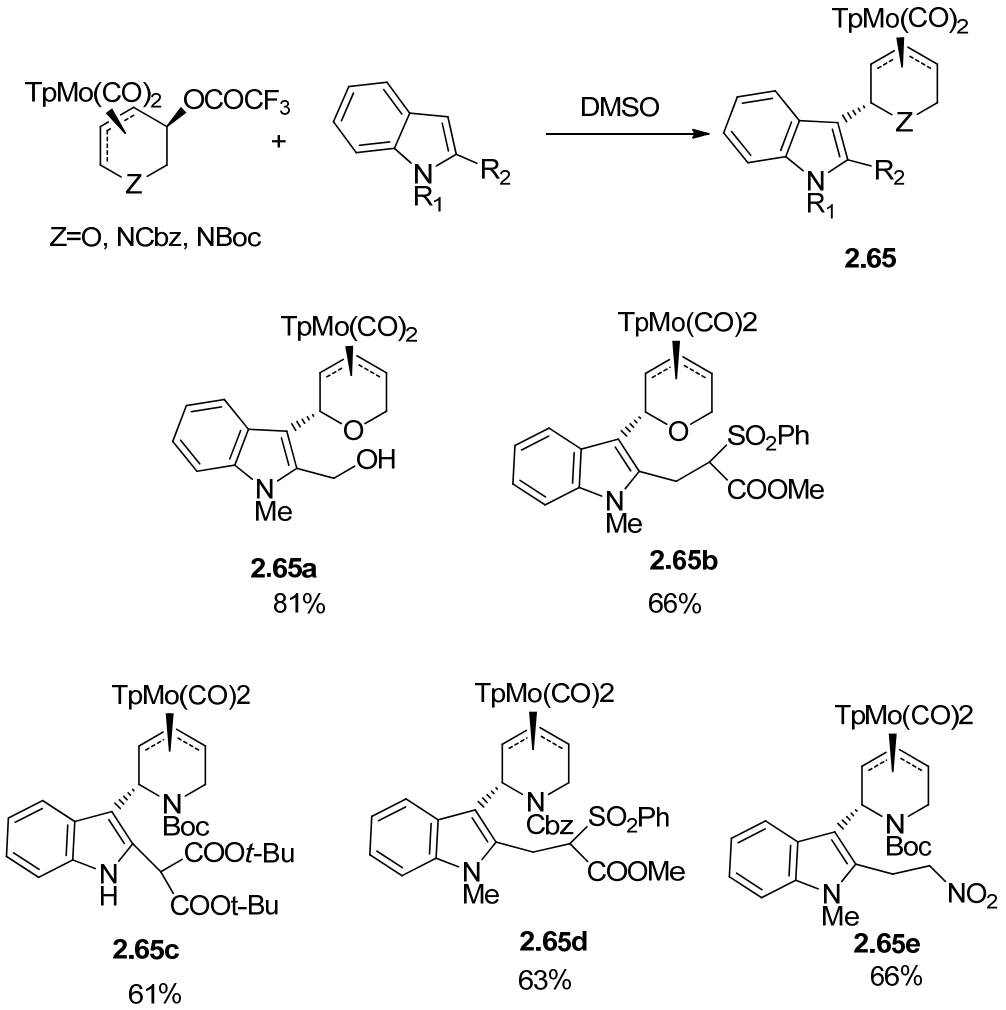
In this case, the synthesis of **2.64** followed a similar route. Proline catalyzed condensation of aldehyde **2.59** with phenylsulfonyl acetate yielded **2.63**, which was hydrogenated to furnish the desired **2.64** in good yield.

Scheme 71 Preparation of phenylsulfonyl acetate methylene indole 2.64



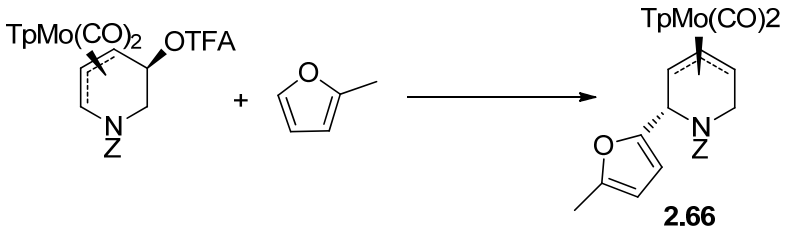
During the course of the study, both pyranyl and pyridinyl scaffolds were used as the substrates. The results of these Friedel-Crafts reactions were shown in the **Scheme 72**. It could be noticed that this reaction tolerated a wide range of functional groups, such as hydroxyl, ester, and sulfonyl. The malonate substituted indole was prepared according to a known procedure.[12a] However, indole carboxylic ester **2.57** failed to react with the molybdenum complex because of its lower nucleophilicity.

Scheme 72 Uncatalyed Friedel-Crafts reaction with 2-substituted indole derivatives



Other electron-rich arenes were also studied in the uncatalyzed Friedel-Crafts-like reaction (**Table 18**). 2-methyl furan was chosen as the reaction partner. The reaction in ACN afforded the substitution product in good yield, while the reaction in DMSO with MgO only produced a poor yield of the desired product **2.66** with a large quantity of elimination product.

Table 18 Friedel-Crafts reaction with 2-methyl furan

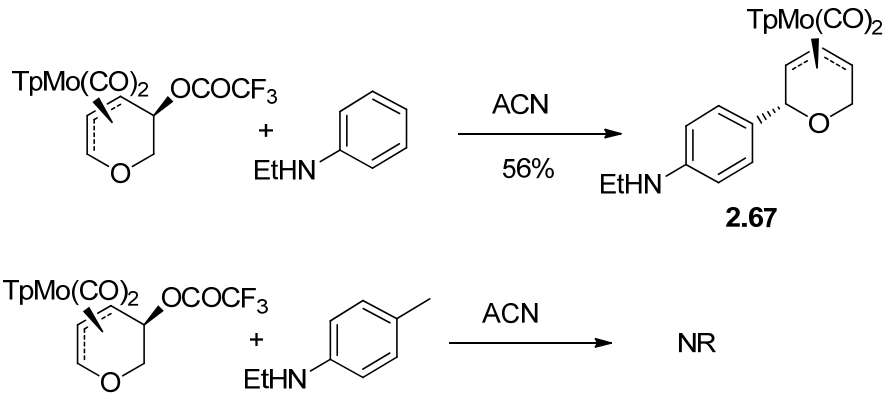


2.66

Conditions	Yield
DMSO, MgO	28%
ACN	84%

Substituted benzenes were also investigated to disclose the scope of the reaction. Ethyl aniline reacted with the pyranyl scaffold and furnished substitution product **2.67** in moderate yield without the *N*-alkylation product (**Scheme 73**). The reaction showed an exclusive *para* selectivity. Interestingly, when the *para* position was blocked, it did not afford any substitution product.

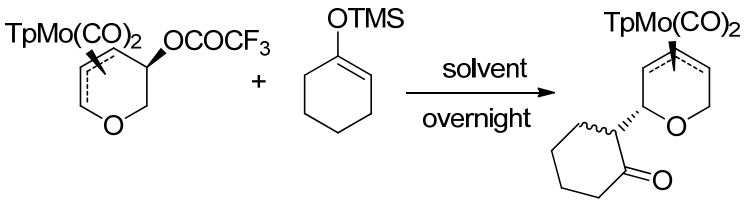
Scheme 73 Friedel-Crafts reaction with substituted aniline



Uncatalyzed Friedel-Crafts reaction with electron-rich olefins

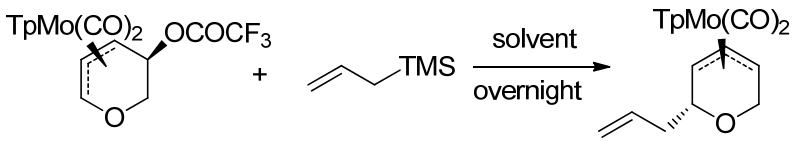
Since various arenes could react through the uncatalyzed Friedel-Crafts-like mechanism, electron-rich olefins as nucleophiles in this reaction were also studied. Silyl enol ether, allyl silane and enamine were first examined (**Scheme 74**). All these olefins failed to react with the complex **2.36** in DMSO; by contrast, silyl enol ether and allyl silane could react with **2.36** in acetonitrile while enamine produced a messy reaction with **2.36** in acetonitrile.

Scheme 74 Uncatalyzed Friedel-Crafts reaction with electron-rich olefins



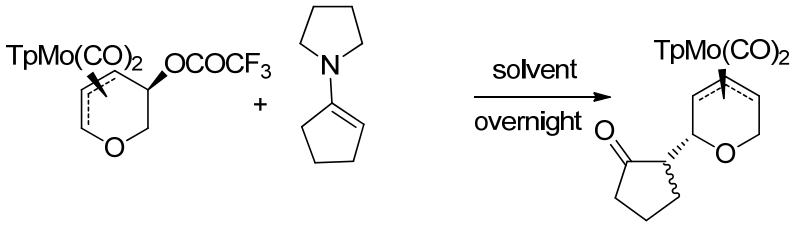
2.36 **2.68**

DMSO NR
ACN 63% (dr: 1:1)



2.36 **2.69**

DMSO NR
ACN 74%

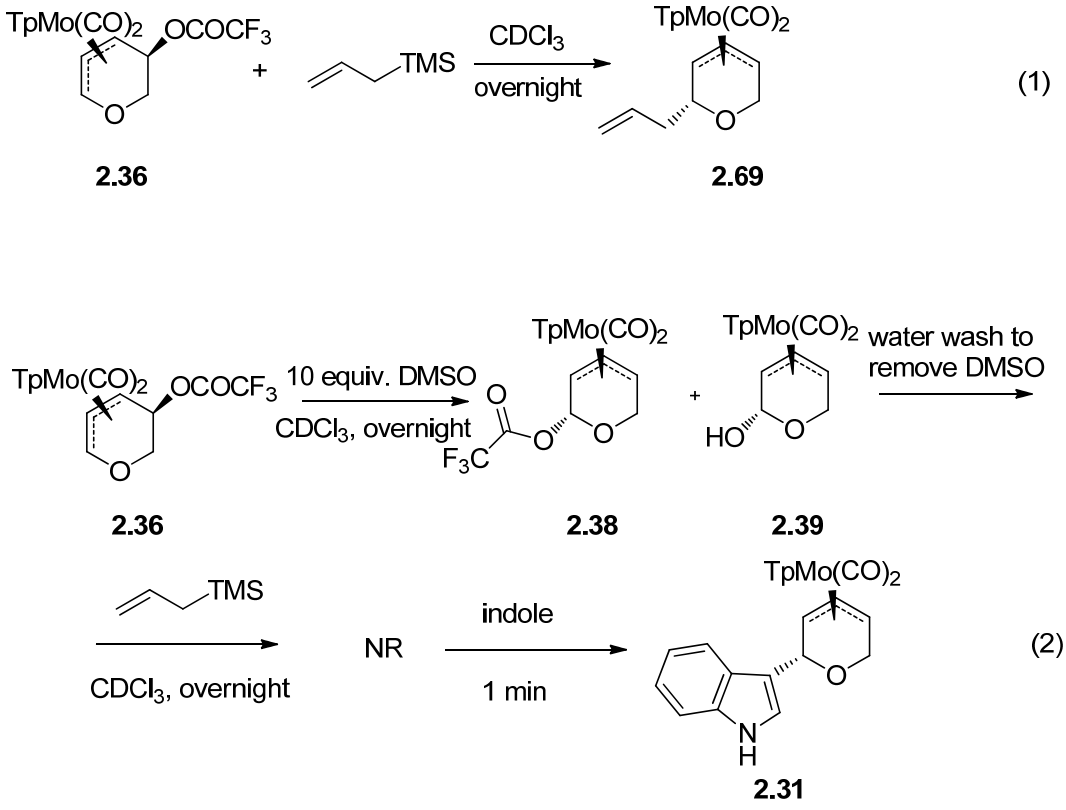


DMSO NR
ACN complex mixture

Since it was known that the complex **2.36** could rearrange to **2.38** and **2.39** in DMSO, the results might suggest that the reaction proceeded through different mechanisms in different solvents. In order to understand the mechanism of these reactions, NMR was used to track the reactions in $CDCl_3$ ($CDCl_3$ was used instead of

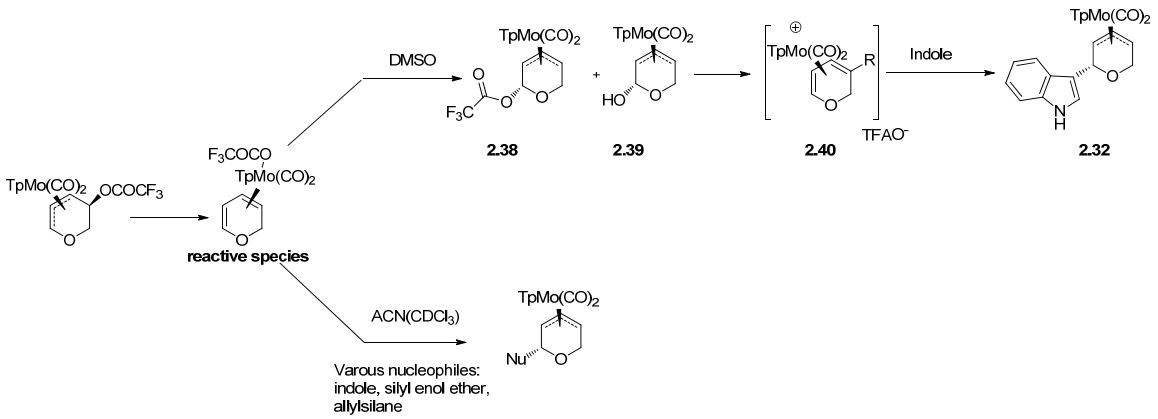
acetonitrile because it was readily available and the reaction performed as well as in acetonitrile). As shown in **scheme 75**, in the equation (1), the complex **2.36** and allyltrimethylsilane was dissolved in $CDCl_3$, standing overnight led to the fully conversion of **2.36** to the product **2.69**. In the equation (2), the complex **2.36** was dissolved in $CDCl_3$ with 10 equivalence of DMSO and stood overnight. The complex **2.36** was fully converted to the complex **2.38** and **2.39,** which was washed with brine to remove DMSO. After adding allyltrimethylsilane for 12 hours, the NMR experiment indicated that the complex **2.38** and **2.39** remained intact and no signal of the product **2.69**. Then indole was added to the mixture, indole substituted product **2.31** formed immediately.

Scheme 75 NMR experiments on the reaction of 2.36 and 2.38



Based on these observations, the following working hypothesis was proposed to describe the mechanistic picture (**scheme 76**). There is an unknown reactive species, which we showed a putative structure here. The reactive species can be promoted by DMSO to rearrange to **2.38** and then react with indole through the intermediate **2.40**, which failed to react with silyl enol ether or allyl silane. However the reactive species would react with various nucleophiles, including indole, silyl enol ether and allyl silane in the absence of DMSO. As for the details of the reaction mechanism, such as the exact structure of the unknown reactive species, further investigation was still needed.

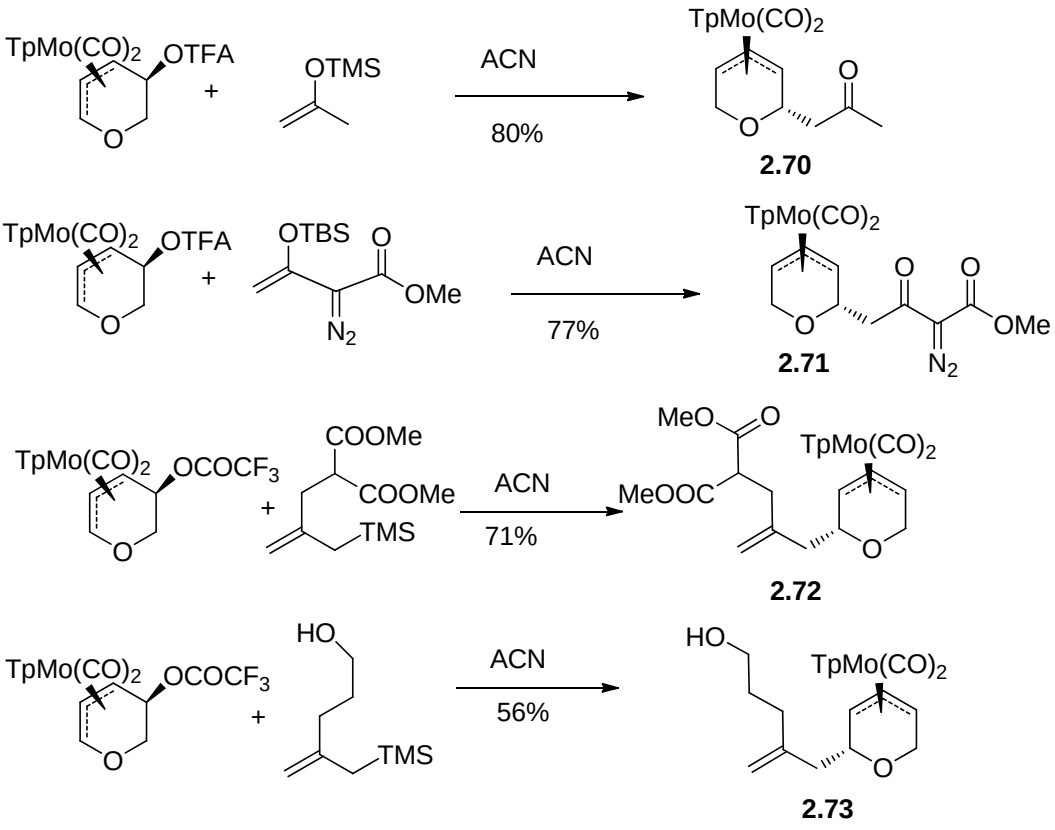
Scheme 76 Mechanism for Friedel-Crafts reaction in DMSO and ACN($CDCl_3$)



With the expansion of the scope of the uncatalyzed Friedel-Crafts-like reaction in hand, more silyl enol ether and silane derivatives were investigated (**scheme 77**). It should be noted that the second example showed not only TMS silyl enol ether but also TBS silyl enol ether could be used in this novel Friedel-Crafts-like reaction. Moreover, the compatibility of this reaction to diazo compounds is important because it allowed an

interesting functional group to be introduced to the scaffold. Although the initial attempts to intramolecular C-H insertion induced by $Rh_2(OAc)_4$ failed due to extensive decomposition, further investigation might disclose some interesting reactions. The reaction in acetonitrile was also compatible with malonate and alcohol group.

Scheme 77 Uncatalyzed F-C reaction with silyl enol ether and allyl silane derivatives

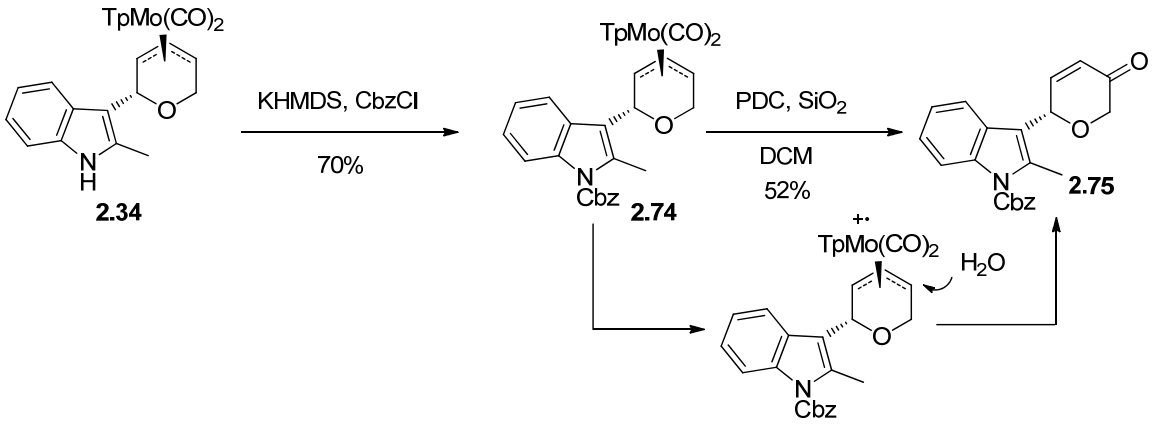


Demetallation

For the simple indole substituted scaffold such as **2.34**, oxidative demetallation with PDC was a good choice to achieve useful organic compounds(**scheme 78**).[9j] Protecting indole with Cbz was necessary in order to realize the demetallation in the

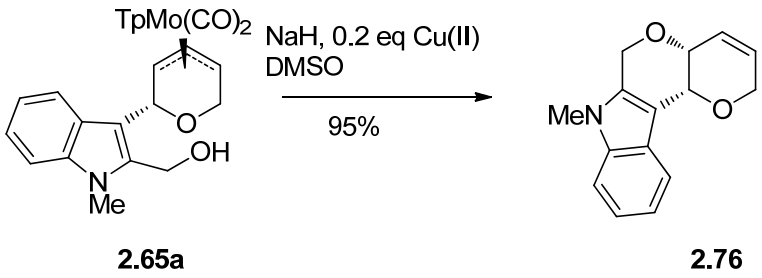
strongly oxidative condition. The reaction showed an excellent regioselectivity possibly because the nucleophilic attack of water from the opposite face of molybdenum moiety occurred on the less steric hindered carbon.

Scheme 78 Oxidative demetallation with PDC



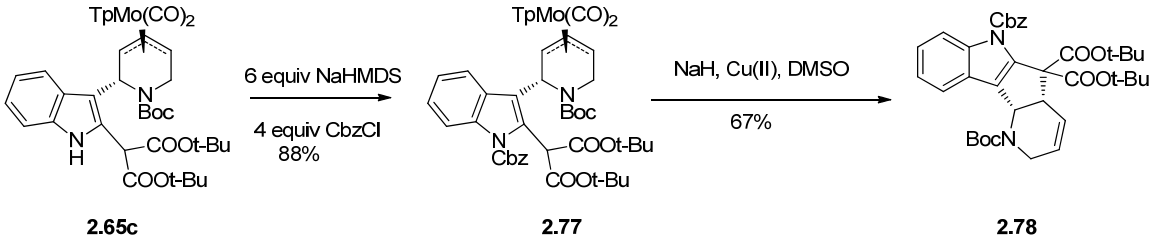
An even more interesting demetallation was the expansion of annulative demetallation, which was originally developed in the context of enolate cyclization.[9a] In the complex **2.65a** the indole alcohol could be deprotonated and then cyclized to yield the product **2.76** (**Scheme 79**). In this case, a six membered oxygen heterocycle formed while Chapter One reported a formation of a five membered ring.

Scheme 79 Annulative demetallation of indole alcohol



This condition not only led to the formation of C-O bond, but also worked well in the formation of C-C bonds when there was an appropriate carbonanion. (**Scheme 80**) Free indole nitrogen had to be protected for this reaction to work. After it was protected with a Cbz group, copper (II) 2-ethylhexanoate was used as the oxidant to cyclize the five membered ring in the pyridinyl scaffold to form **2.78**.

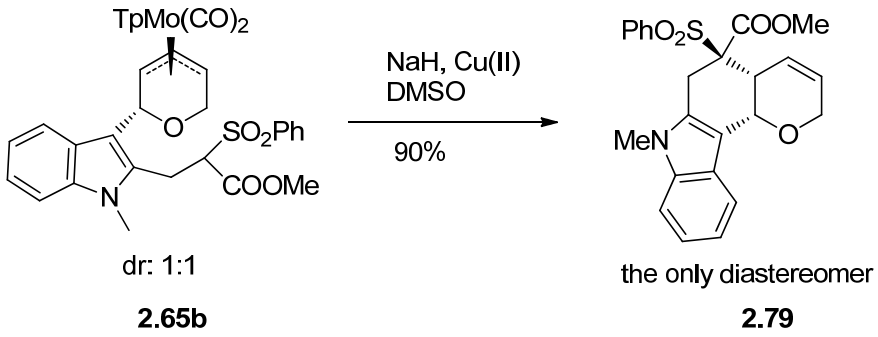
Scheme 80 Annulative demetallation with stabilized carbonanion to form a five membered ring



2.65c **2.77** **2.78**

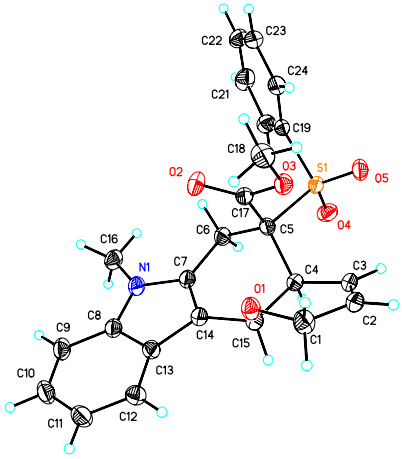
Moreover, the reaction could also lead to the formation of six membered carbocycles (**Scheme 81**). Methyl protected indole can also tolerate the demetallation condition. The diastereomeric mixtures of **2.65b** was treated with NaH and Cu(II) to form a tetracyclic compound **2.79** as a sole diastereomer.

Scheme 81 Annulative demetallation with stabilized carbonanion to form a six membered ring



Furthermore, the structure and relative stereochemistry have been confirmed by X-ray analysis. (**Figure 11**)

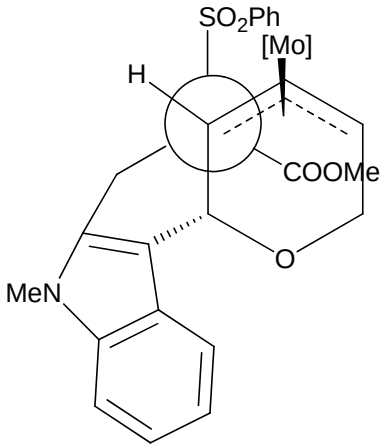
Figure 11 X-ray structure of the demetallation product 2.79



The stereochemistry of the quaternary center was expected to form through the following transition state (**Figure 12**). The carbonanion attacked from the back of

molybdenum moiety through a chair transition state while minimizing the interaction between the phenylsulfonyl group and the pyran ring.

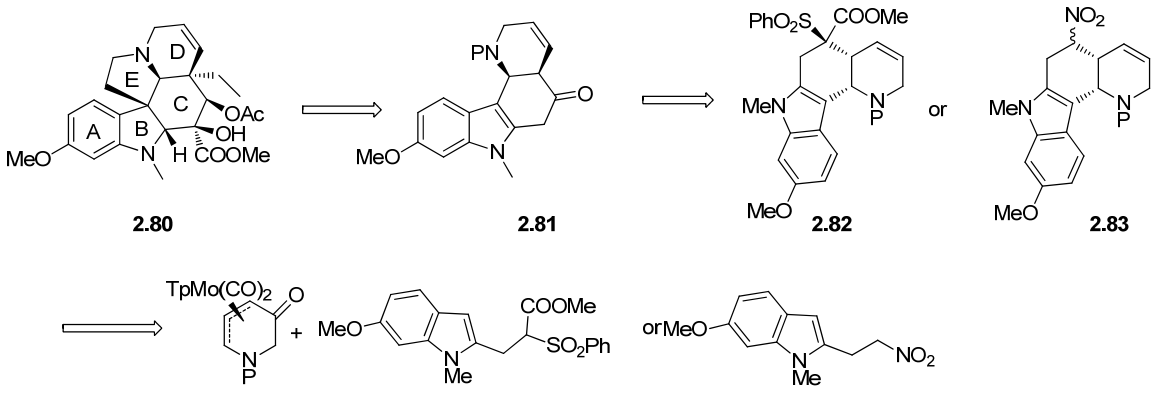
Figure 12 Transition state for the demetallation of the complex 2.65b



Application to the synthesis of natural products

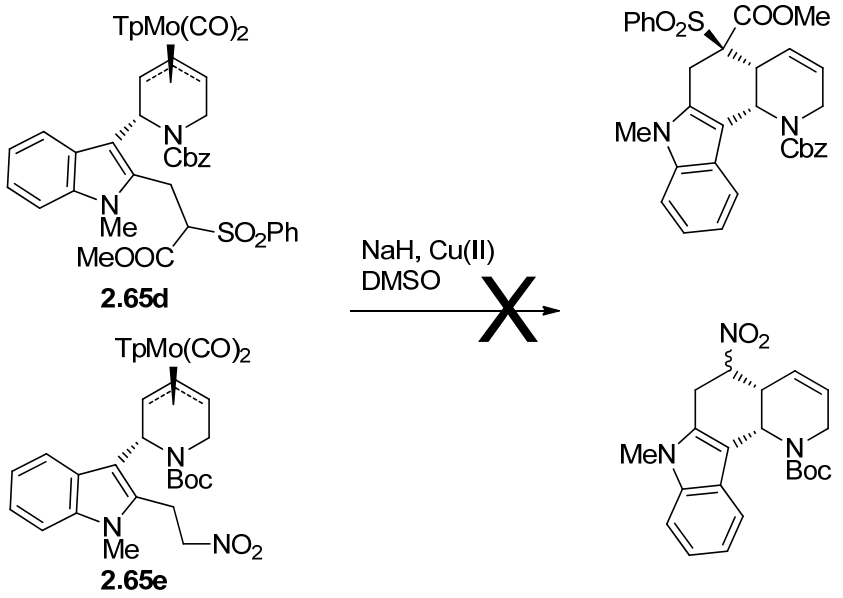
With the successful uncatalyzed Friedel-Crafts reaction and annulative demetallation in hand, this new methodology was applied in the synthesis of natural products. One of the targets was vindoline **2.80**. Here is the retrosynthesis. (**Figure 13**) Compound **2.81** was the key intermediate to the synthesis of vindoline **2.80** because the incorporation of a two-carbon bridge into **2.81** could form ring E and the carbonyl group could be used as a handle to functionalize the ring C and introduce the angular ethyl group. The intermediate **2.82** or **2.83**, which was expected to be readily converted to **2.81** through routine functional group transformations, may be synthesized through the newly developed uncatalyzed Friedel-Crafts-like reaction-annulative demetallation sequence.

Figure 13 Retrosynthesis of vindoline



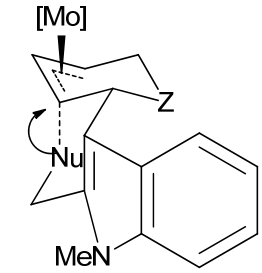
The complex **2.65d** and **2.65e** were chosen as a model to test the demetallation (**Scheme 82**). Unexpectedly, although we tried to demetallate them in many conditions, no desired product has ever been detected. Changing the protecting group on indole nitrogen from methyl to Cbz did not help the reaction either. In addition, deprotecting Cbz or Boc from **2.65d** or **2.65e** proved also troublesome.

Scheme 82 Model study on the synthesis of vindoline



Compared to the successful demetallation of the complex **2.65c**, the current result seemed confusing. These results were rationalized in the term of conformational analysis (**Figure 14**). For this reaction to happen, it requires a chair transition state, in which nucleophilic attack occurs from the axial position so that the indole substitution has to be in the equatorial position. As for this transition state, pyranyl scaffold favors it to form while pyridinyl scaffold disfavors it due to the A(1,3) strain between the carbamate group and the indole.[13] Therefore, in order to promote this reaction, a judicious selection of protecting group might be critical. Further investigation in this area will focus on the fine tuning of the substrate to promote the demetallation.

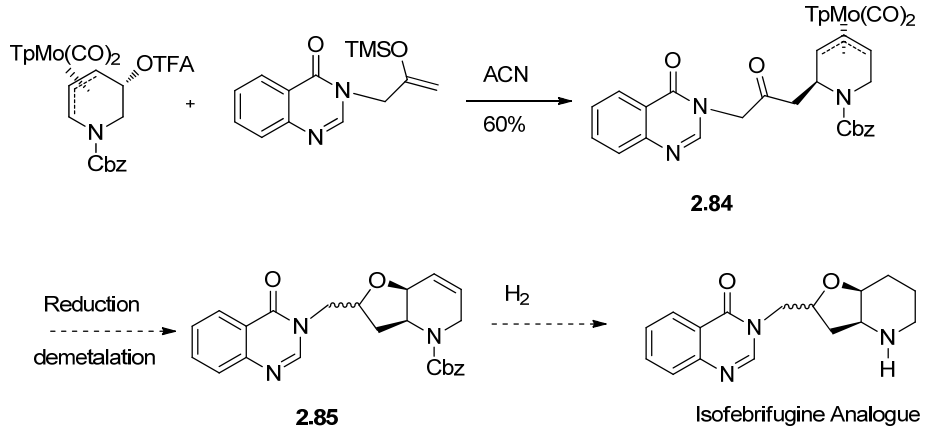
Figure 14 Proposed transition state of annulative demetallation



Z=O	favored
Z=NCbz	disfavored

Besides the synthesis of vindoline, we envisioned the application of this novel methodology to a concise synthesis of isofebrifugine analogue. (**Scheme 83**) By using the uncatalyzed F-C reaction, the quinazolinone substituted ketone could be introduced to the scaffold in one step to form complex **2.84**. And, the reduction to alcohol and annulative demetallation would directly lead to the compound **2.85**, which would yield the isofebrifugine analogue after deprotection. Currently, Greg and Kassinath in the Liebeskind are working on this project and one of the diastereomers of **2.85** has been achieved.

Scheme 83 Proposed synthesis of isofebrifugine analogue



Conclusion

Neutral $TpMo(CO)_2$(5-trifluoroacetate-η^3-pyranyl) and $TpMo(CO)_2$(5-trifluoroacetate-η^3-pyridinyl) scaffolds underwent an uncatalyzed Friedel-Crafts-like reaction with a variety of electron-rich arenes and olefins, such as indole, furan, aniline, silyl enol ether, and allylsilane, to form substitution products in high yields. Moreover, enantiopure starting material was employed in the reaction successfully and no enantiopurity loss was detected. It was worth noting that this reaction demonstrated a superb functional group tolerance, including hydroxyl, amino, ester, sulfonyl, and diazo groups. The preliminary mechanism study showed that the reaction in DMSO underwent a rearrangement first and then probably proceeded through a molybdenum stabilized carbocation intermediate to form substitution product. By contrast, the similar reaction in acetonitrile or chloroform underwent through a completely different mechanism because no rearrangement product has been detected and this reaction showed a higher reactivity. In this case, silyl enol ether and allylsilane can participate the uncatalyzed Friedel-Crafts-like reaction. Further annulative demetallation proved to be successful with a series of

substrates to form oxygen heterocycles and carbocycles in 5 or 6 membered rings in a mild condition. The model study to the synthesis of vindoline was troublesome due to the unexpected difficulty in the demetallation step. Another synthetic application in the synthesis of isofebrifugine analogues has yielded promising results.

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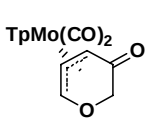
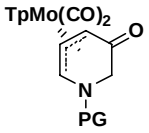
Experimental Section

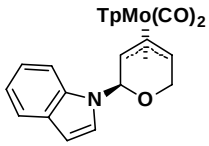


S1



PG=Cbz, S2a
=Boc, S2b

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(*η*-3,4,5)-2-(1′-indolyl)-5,6-dihydro-2H-pyran-3-yl]molybdenum, (±)-2.30



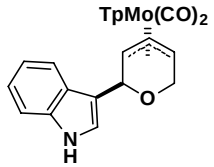
2.30

To a solution of (±)-**2.29** (50 mg, 0.099 mmol, 1.0 equiv) in THF (4 mL) was added NaH (1.2 mg, 0.297 mmol, 3.0 equiv) and indole (38.0 mg, 0.297 mmol, 3.0 equiv). The reaction mixture stirred at room temperature for 2 hours, and then quenched with saturated NH_4Cl. The mixture was poured into a separatory funnel containing EtOAc (5 mL), and the layers were separated. The aqueous layer was extracted by EtOAc (2 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (20:1) afforded (±)–**2.30** (51.3 mg, 0.32 mmol, 92%) as an orange solid.

TLC (R_f =0.65, 3:1 hexanes:EtOAc). ^{1}H NMR (600 MHz, DMSO) δ 8.69 (d, *J* = 1.2 Hz, 1 H), 8.08 (d, *J* = 3.0 Hz, 1 H), 7.75 (s, 1 H), 7.73 (s, 1 H), 7.65 (d, *J* = 7.8 Hz, 1 H), 7.62 (d, *J* = 7.2 Hz, 1 H), 7.61 (d, *J* = 7.2 Hz, 1 H), 7.56 (s, 1 H), 7.55 (d, *J* = 9.0 Hz, 1 H), 7.23 (t, *J* = 7.2 Hz, 1 H), 7.15 (t, *J* = 7.2 Hz, 1 H), 6.59 (d, *J* = 7.2 Hz, 1 H), 6.36 (t, *J* =

3.0 Hz, 1 H), 6.22(t, *J* = 2.4 Hz, 1 H), 6.18 (t, *J* = 2.4 Hz, 1 H), 6.17 (s, 1 H), 4.30 (t, *J* = 7.2 Hz, 1 H), 4.26 (d, *J* = 7.2 Hz, 1 H), 4.18 (d, *J* = 7.2 Hz, 1 H), 3.90 (d, *J* = 13.2 Hz, 1 H), 3.66 (dd, *J* = 13.2 Hz, 1.8 Hz, 1 H). ^{13}C NMR (100 MHz, DMSO) δ 225.5, 224.5, 147.4, 142.1, 141.3, 136.8, 136.2, 136.2, 134.6, 129.3, 125.5, 122.0, 120.7, 120.3, 110.6, 106.2, 105.6, 105.5, 101.8, 77.9, 66.4, 65.1, 63.9, 57.8. IR (cm^{-1}) 3142 (w), 3053 (w), 2930 (w), 2486 (w), 1945 (s), 1861 (s).

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(*η*-3,4,5)-2-(3′-indolyl)-5,6-dihydro-2H-pyran-3-yl]molybdenum, (±)-2.31



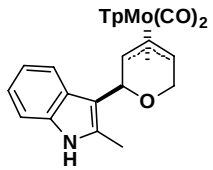
2.31

To a solution of (±)-**2.36** (50 mg, 0.089 mmol, 1.0 equiv) in DMSO (4 mL) was added indole (15.2 mg, 0.13 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature for 1 hour, and then quenched with brine. The mixture was poured into a separatory funnel containing EtOAc (5 mL), and the layers were separated. The aqueous layer was extracted by EtOAc (2 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (2.5:1) afforded (±)–**2.31** (43 mg, 0.077 mmol, 86%) as an orange solid.

TLC (R_f = 0.45, 2:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69(d, *J* = 2.4 Hz, 1 H), 8.17 (br s, 1 H), 7.83 (d, *J* = 8.0 Hz, 1 H), 7.74 (d, *J* = 2.0 Hz, 1 H), 7.72 (d, *J* = 2.0

Hz, 1 H), 7.63 (d, *J* = 2.4 Hz, 1 H), 7.59 (d, *J* = 2.4 Hz, 1 H), 7.58 (d, *J* = 2.4 Hz, 1 H), 7.53 (d, *J* = 2.0 Hz, 1 H), 7.38 (d, *J* = 8.0 Hz, 1 H), 7.21 (t, *J* = 8.0 Hz, 1 H), 7.13 (t, *J* = 7.6 Hz, 1 H), 6.32 (t, *J* = 2.0 Hz, 1 H), 6.17(t, *J* = 2.0 Hz, 1 H), 6.15 (t, *J* = 2.0 Hz, 1 H), 5.32 (d, *J* = 2.0 Hz, 1 H), 4.37 (dt, *J* = 6.8 Hz, 2.4 Hz, 1 H), 4.03-4.11 (m, 2 H), 3.88 (d, *J* = 12.0 Hz, 1 H), 3.62 (dd, *J* = 12.8 Hz, 2.4 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 226.0, 225.8, 147.4, 141.9, 141.4, 136.6, 136.0, 135.9, 134.4, 127.1, 123.8, 122.5, 120.0, 119.9, 116.8, 111.0, 106.0, 105.3, 105.3, 69.8, 67.4, 65.4, 64.2, 57.5. IR (cm^{-1}) 3300 (w), 2482 (w), 1938 (s), 1849 (s), 1505 (s). HRMS (ESI) Calcd. for $C_{24}H_{22}BMoN_7O_3Na$ ($[M+Na]^+$): 588.0823. Found: 588.0829.

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(*η*-3,4,5)-2-(2′-methyl-3′-indolyl)-5,6-dihydro-2H-pyran-3-yl]molybdenum, (±)-2.34

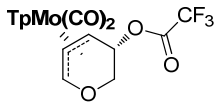


2.34

To a solution of (±)-**2.36** (50 mg, 0.089 mmol, 1.0 equiv) in DMSO (4 mL) was added 2-methylindole (17.1 mg, 0.13 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature for 1 hour, and then quenched with brine. The mixture was poured into a separatory funnel containing EtOAc (5 mL), and the layers were separated. The aqueous layer was extracted by EtOAc (2 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (2.5:1) afforded (±)–**2.34** (39 mg, 0.068 mmol, 76%) as an orange solid.

TLC (R_f=0.48, 2:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, *J* = 2.0 Hz, 1 H), 8.45 (d, *J* = 7.2 Hz, 1 H), 7.97 (br s, 1 H), 7.81 (d, *J* = 2.0 Hz, 1 H), 7.70 (d, *J* = 2.0 Hz, 1 H), 7.60 (d, *J* = 2.4 Hz, 1 H), 7.57 (d, *J* = 2.4 Hz, 1 H), 7.54 (d, *J* = 2.4 Hz, 1 H), 7.32 (d, *J* = 7.2 Hz, 1 H), 7.10-7.17 (m, 2 H), 6.34 (t, *J* = 2.4 Hz, 1 H), 6.22 (t, *J* = 2.4 Hz, 1 H), 6.12(t, *J* = 2.4 Hz, 1 H), 5.24 (d, *J* = 2.4 Hz, 1 H), 4.40-4.43 (m, 1 H), 4.32 (d, *J* = 5.6 Hz, 2 H), 4.30 (d, *J* = 12.0 Hz, 1 H), 3.80 (d, *J* = 12.0 Hz, 1 H), 2.56 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 226.8, 225.8, 147.4, 141.9, 141.5, 135.9, 135.9, 135.2, 134.6, 134.4, 127.8, 121.1, 120.2, 119.7, 111.7, 110.3, 106.0, 105.3, 105.2, 71.2, 67.0, 66.5, 60.1, 12.7. IR (cm-1) 3347 (m), 2957 (w), 2482 (w), 1942 (s), 1853 (s), 1602 (m). HRMS (FAB) Calcd. for $C_{25}H_{24}BMoNaN_7O_3$([M+Na]$^+$): 602.0980. Found: 602.0982.

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(*η*-2,3,4)--5-trifluoroacetoxy-5,6-dihydro-2H-pyran-2-yl]molybdenum, (±)-2.36

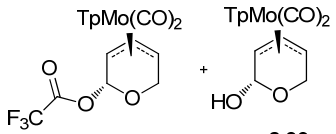


2.36

To a solution of (±)-**2.35** (500 mg, 1.08 mmol, 1.0 equiv) in DCM (25 mL) was added TEA (165 mg, 1.62 mmol, 1.5 equiv) and TFAA (289 mg, 1.40 mmol, 1.3 equiv) at room temperature. The reaction mixture was stirred for 20 minutes, and then loaded on the silica gel directly. Flash chromatography in 5 minutes with hexanes-EtOAc (3:1) afforded (±)–**2.36** (547 mg, 0.95 mmol, 88%) as a yellow solid.

TLC (R_f = 0.62, 3:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 2.0 Hz, 1 H), 7.72 (d, *J* = 2.8 Hz, 1 H), 7.71 (d, *J* = 2.8 Hz, 1 H), 7.59 (d, *J* = 2.0 Hz, 1 H), 7.58 (d, *J* = 2.0 Hz, 1 H), 7.51 (d, *J* = 1.6 Hz, 1 H), 7.05 (dd, *J* = 4.4, 2.0 Hz, 1 H), 6.30 (t, *J* = 2.4 Hz, 1 H), 6.22 (t, *J* = 2.4 Hz, 1 H), 6.20 (t, *J* = 2.0 Hz, 1 H), 5.79 (ddd, *J* = 9.2, 6.0, 2.8 Hz, 1 H), 4.59 (dt, *J* = 7.6, 2.4 Hz, 1 H), 3.75 (dd, *J* = 10.8 Hz, 6.0 Hz, 1 H), 3.54 (dd, *J* = 8.0 Hz, 4.0 Hz, 1 H), 2.64 (dd, *J* = 11.6, 10.0 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 226.9, 224.0, 147.2, 146.8, 142.0, 141.8, 136.2, 134.6, 134.5, 109.7, 106.1, 105.8 105.6, 73.5, 63.7, 62.8, 58.0.

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(*η*-2,3,4)--2-trifluoroacetoxy-5,6-dihydro-2H-pyran-2-yl]molybdenum, (±)-2.38& 2.39



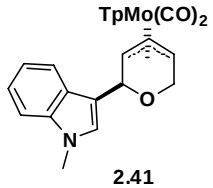
2.38 **2.39**

2.36 (50 mg, 0.08 mmol, 1.0 equiv) was dissolved in 1.2 mL d^6-DMSO for 10 minutes to give a mixture of two compounds **2.38** and **2.39**.

2.38: ^{1}H NMR (400 MHz, d^6-DMSO) δ 8.55 (d, *J* = 2.0 Hz, 1 H), 8.13 (d, *J* = 2.0 Hz, 1 H), 8.03 (d, *J* = 2.0 Hz, 1 H), 7.81-7.87 (m, 3 H), 6.44-6.46 (m, 1 H), 6.24-6.32 (m, 2 H), 4.98 (br s, 1 H), 4.46 (d, *J* = 6.4 Hz, 1 H), 4.24 (d, *J* = 7.2 Hz, 1 H), 4.20 (d, *J* = 12.4 Hz, 1 H), 3.75 (t, *J* = 7.2 Hz, 1 H), 3.47 (d, *J* = 12.0 Hz, 1 H). ^{13}C NMR (100 MHz, d^6-DMSO) δ 227.0, 225.6, 158.4 (*J* = 38 Hz), 146.9, 142.6, 136.6, 135.3, 115.1 (*J* = 288 Hz), 106.7, 105.9, 89.6, 68.7, 68.2, 64.9, 57.0, 55.9.

2.39: ^{1}H NMR (400 MHz, d^{6}-DMSO) δ 8.58 (d, *J* = 2.4 Hz, 1 H), 8.09 (d, *J* = 2.0 Hz, 1 H), 8.01 (d, *J* = 2.0 Hz, 1 H), 7.81-7.87 (m, 3 H), 6.44-6.46 (m, 1 H), 6.24-6.32 (m, 2 H), 4.93 (d, *J* = 2.0 Hz, 1 H), 4.56 (d, *J* = 7.8 Hz, 1 H), 4.39 (d, *J* = 12.4 Hz, 1 H), 4.17 (d, *J* = 8.0 Hz, 1 H), 3.89 (t, *J* = 7.6 Hz, 1 H), 3.57 (d, *J* = 10.0 Hz, 1 H). ^{13}C NMR (100 MHz, d^{6}-DMSO) δ 227.2, 225.3, 146.9, 142.6, 136.5, 135.2, 106.6, 105.8, 92.8, 89.6, 68.7, 68.4, 64.9, 57.0, 56.1.

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(η-3,4,5)-2-(1´-methyl-3´-indolyl)-5,6-dihydro-2H-pyran-3-yl]molybdenum, (±)-2.41

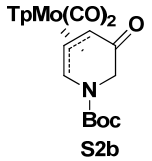


2.41

To a solution of (±)-**2.36** (50 mg, 0.089 mmol, 1.0 equiv) in DMSO (4 mL) was added *N*-methylindole (17.1 mg, 0.13 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature for 1 hour, and then quenched with brine. The mixture was poured into a separatory funnel containing EtOAc (5 mL), and the layers were separated. The aqueous layer was extracted by EtOAc (2 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (2.5:1) afforded (±)–**2.41** (43 mg, 0.075 mmol, 84%) as an orange solid.

TLC (R_f =0.38, 3:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, DMSO) δ 8.62 (d, *J* = 2.0 Hz, 1 H), 8.07 (d, *J* = 2.0 Hz, 1 H), 8.04 (d, *J* = 2.0 Hz, 1 H), 7.89 (d, *J* = 2.4 Hz, 1 H), 7.86 (d, *J* = 2.4 Hz, 1 H), 7.85 (d, *J* = 2.4 Hz, 1 H), 7.81 (s, 1 H), 7.56 (d, *J* = 7.6 Hz, 1 H), 7.45 (d, *J* = 8.4 Hz, 1 H), 7.18 (t, *J* = 7.2 Hz, 1 H), 7.05 (t, *J* = 8.0 Hz, 1 H), 6.49 (t, *J* = 2.0 Hz, 1 H), 6.30 (t, *J* = 2.0 Hz, 1 H), 6.26 (t, *J* = 2.0 Hz, 1 H), 5.11 (d, *J* = 2.4 Hz, 1 H), 4.58 (dt, *J* = 7.2 Hz, 2.4 Hz, 1 H), 4.39 (d, *J* = 6.4 Hz, 1 H), 4.00 (t, *J* = 7.2 Hz, 1 H), 3.84 (s, 3 H), 3.68 (d, *J* = 12.4 Hz, 1 H), 3.43 (dd, *J* = 12.0 Hz, 2.0 Hz, 1 H). ^{13}C NMR (100 MHz, DMSO) δ 226.6, 226.2, 147.0, 142.9, 142.4, 137.1, 136.6, 135.3, 129.6, 127.2, 121.4, 118.9, 113.8, 109.8, 106.6, 105.8, 105.8, 70.2, 68.1, 64.8, 64.6, 56.9, 32.6.
IR (cm^{-1}) 2957 (w), 2922 (m), 2853 (w), 2482 (m), 1942 (s), 1849 (s). HRMS (FAB) Calcd. for $C_{25}H_{25}BMoN_7O_3$([M+H]$^+$): 580.1161. Found: 580.1167.

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(*η*-2,3,4)-1-*t*-butoxycarbonyl-5-oxo-5,6-dihydro-2H-pyridin-2-yl]molybdenum, (±)-S2b



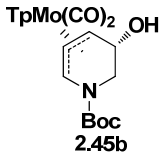
S2b

To a solution of **(±)-S2a** (500 mg, 0.88 mmol, 1.0 equiv) in THF (25 mL) was added 10% $Pd(OH)_2$/C (90 mg, 0.09 mmol, 0.1 equiv). The reaction mixture was stirred at room temperature under hydrogen balloon for 5 hours. The mixture was filtered to give the solution and then concentrated. The solid was dissolved in DCM without purification. To the solution was added Boc_2O (249 mg, 1.14 mmol, 1.3 equiv), DMAP (11 mg, 0.09

mmol, 0.1 equiv)and TEA (138 mg, 1.32 mmol, 1.5 equiv). The mixture was stirred at room temperature overnight, and then the mixture was poured into a separatory funnel containing EtOAc (15 mL) and H_2O (15mL), and the layers were separated. The aqueous layer was extracted by EtOAc (2 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (2:1) afforded **(±)-S2b** (434 mg, 0.77 mmol, 88%) as a yellow solid.

TLC (R_f = 0.28, 2:1 hexanes:EtOAc). ^{1}H NMR (a mixture of two rotamers) (400 MHz, $CDCl_3$) δ 8.41 (d, *J* = 2.0 Hz, 0.3 H), 8.35 (d, *J* = 2.0 Hz, 0.7 H), 8.29 (d, *J* = 1.2 Hz, 0.7 H), 8.01 (d, *J* = 1.6 Hz, 0.3 H), 7.77 (d, *J* = 1.6 Hz, 0.3 H), 7.69 (d, *J* = 1.4 Hz, 0.7 H), 7.65 (d, *J* = 2.0 Hz, 0.3 H), 7.58-7.62 (m, 1.7 H), 7.46-7.49 (m, 1.7 H), 7.32 (dd, *J* = 6.8 Hz, 2.0 Hz, 0.3 H), 6.27 (t, *J* = 1.6 Hz, 0.3 H), 6.17-6.24 (m, 2.7 H), 4.71-4.74 (m, 1 H), 3.99 (t, *J* = 6.0 Hz, 0.7 H), 3.94 (t, *J* = 6.0 Hz, 0.3 H), 3.38 (d, *J* = 20.0 Hz, 0.7 H), 3.36 (d, *J* = 20.0 Hz, 0.3 H), 3.20 (d, *J* = 20.4 Hz, 0.3 H), 3.17 (d, *J* = 20.0 Hz, 0.7 H), 1.57 (s, 2.7 H), 1.46 (s, 6.3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 225.5, 223.0, 222.1, 193.8, 193.6, 153.5, 152.5, 147.3, 147.1, 144.5, 142.7, 141.9, 141.2, 136.5, 136.3, 136.2, 136.1, 134.7, 106.2, 106.0, 105.8, 105.7, 96.2, 93.2, 82.4, 82.0, 64.7, 64.1, 63.7, 62.9, 48.3, 47.5, 28.1, 27.9. IR (cm^{-1}) 3420 (w), 2980 (w), 2482 (w), 1942 (s), 1845 (s), 1695 (s). HRMS (ESI) Calcd. for $C_{21}H_{25}BMoN_7O_5$ ($[M+H]^+$): 564.1059. Found: 564.1061.

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(*η*-2,3,4)-1-*t*-butoxycarbonyl-5-hydroxy-5,6-dihydro-2H-pyridin-2-yl]molybdenum, (±)-2.45b



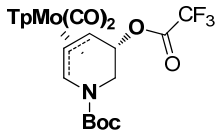
2.45b

To a solution of (±)-**S2b** (500 mg, 0.88 mmol, 1.0 equiv) in THF (20 mL) was added DIBAL (1.0 M in hexane, 2.2 mL, 2.18 mmol, 2.5 equiv) at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 20 minutes, and then quenched with potassium sodium tartrate tetrahydrate (760mg, 2.56mmol, 3.0 equiv) and H_2O (10 mL). The mixture was poured into a separatory funnel containing EtOAc (15 mL) and the layers were separated. The aqueous layer was extracted by EtOAc (2 x 25 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (2:1) afforded (±)–**2.45b** (452 mg, 0.80 mmol, 91%) as an orange solid.

TLC (R_f = 0.27, 2:1 hexanes:EtOAc). ^{1}H NMR (a mixture of two rotamers) (400 MHz, $CDCl_3$) δ 8.42 (d, *J* = 1.2 Hz, 0.4 H), 8.40 (d, *J* = 1.2 Hz, 0.6 H), 8.18 (d, *J* = 1.2 Hz, 0.6 H), 7.96 (d, *J* = 1.2 Hz, 0.4 H), 7.82 (d, *J* = 0.8 Hz, 0.4 H), 7.77 (d, *J* = 1.2 Hz, 0.6 H), 7.62 (d, *J* = 2.0 Hz, 0.4 H), 7.56 (br s, 1.6 H), 7.46 (br s, 1 H), 7.20 (d, *J* = 5.2 Hz, 0.6 H), 7.00 (d, *J* = 5.6 Hz, 0.4 H), 6.23 (br s, 0.4 H), 6.11-6.16 (m, 2.6 H), 4.67-4.79 (m, 2 H), 3.75 (dd, *J* = 12.0 Hz, 7.2 Hz, 0.4 H), 3.63 (dd, *J* = 12.4 Hz, 6.8 Hz, 0.6 H), 3.31 (t, *J* = 6.8 Hz, 0.6 H), 3.25 (t, *J* = 6.8 Hz, 0.4 H), 1.75-1.85 (m, 1 H), 1.59 (s, 3.6 H), 1.47 (s, 5.4 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ232.7, 231.6, 224.1, 223.8, 154.6, 154.0, 146.6, 146.4, 143.8, 142.2, 141.1, 140.6, 136.0, 135.9, 135.82, 135.76, 134.3, 105.8, 105.7, 105.5, 105.4, 105.2, 94.4, 92.2, 81.5, 81.1, 69.5, 67.9, 67.8, 67.6, 57.2, 56.6, 47.4, 46.6, 28.1,

27.9, 27.4. IR (cm^{-1}) 3420 (w), 2980 (w), 2482 (w), 1942 (s), 1845 (s), 1695 (s). HRMS (ESI) Calcd. for $C_{21}H_{26}BMoN_7O_5$ ($[M+Na]^+$): 588.1035. Found: 588.1038.

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(*η*-2,3,4)-1-*t*-butoxycarbonyl-5-trifluoroacetoxy-5,6-dihydro-2H-pyridin-2-yl]molybdenum, (±)-2.46b



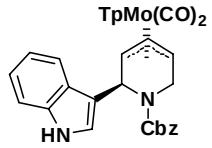
2.46b

To a solution of (±)-**2.45b** (452 mg, 0.80 mmol, 1.0 equiv) in DCM (15 mL) was added TEA (122 mg, 1.20 mmol, 1.5 equiv) and TFAA (218 mg, 1.04 mmol, 1.3 equiv) at -15 ^oC. The reaction mixture was stirred for 20 minutes, and then loaded on the silica gel directly. Flash chromatography in 5 minutes with hexanes-EtOAc (3:1) afforded (±)–**2.46b** (490 mg, 0.74 mmol, 92%) as a yellow solid.

TLC (R_f = 0.63, 3:1 hexanes:EtOAc). ^1H NMR (a mixture of two rotamers) (400 MHz, $CDCl_3$) δ 8.47 (d, *J* = 2.0 Hz, 0.3 H), 8.44 (d, *J* = 2.0 Hz, 0.7 H), 8.21 (d, *J* = 2.0 Hz, 0.7 H), 7.97 (d, *J* = 2.0 Hz, 0.3 H), 7.69 (d, *J* = 1.6 Hz, 0.3 H), 7.66 (d, *J* = 2.4 Hz, 0.7 H), 7.63 (d, *J* = 2.0 Hz, 0.3 H), 7.59 (d, *J* = 2.0 Hz, 0.7 H), 7.58 (d, *J* = 2.0 Hz, 0.3 H), 7.58 (d, *J* = 2.0 Hz, 0.7 H), 7.47-7.49 (m, 1 H), 7.25 (dd, *J* = 6.4 Hz, 2.0 Hz, 0.7 H), 7.06 (dd, *J* = 5.6 Hz, 1.6 Hz, 0.3 H), 6.18-6.27 (m, 3 H), 5.86-5.91 (m, 1 H), 4.60 (d, *J* = 8.8 Hz, 0.3 H), 4.59 (d, *J* = 7.6 Hz, 0.7 H), 3.77 (dd, *J* = 12.8 Hz, 7.2 Hz, 0.3 H), 3.65 (dd, *J* = 12.4 Hz, 7.2 Hz, 0.7 H), 3.46 (t, *J* = 7.2 Hz, 0.7 H), 3.39 (t, *J* = 7.2 Hz, 0.3 H), 2.01-2.10

(m, 1 H), 1.59 (s, 3 H), 1.49 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 228.5, 227.5, 224.0, 223.7, 157.2 (q, J = 43 Hz), 154.4, 153.9, 147.0, 146.8, 144.2, 142.5, 141.2, 140.7, 136.3, 136.2, 136.1, 136.1, 134.5, 114.4 (q, J = 284 Hz), 106.1, 105.9, 105.8, 105.6, 105.5, 94.8, 92.5, 82.1, 81.9, 77.3, 77.0, 76.7, 74.7, 74.5, 60.8, 59.5, 57.5, 57.0, 43.4, 42.6, 34.6, 34.5, 31.6, 29.0, 28.2, 28.0, 25.2, 22.6, 20.7, 14.1, 11.4.

(+) and (±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(*η*-3,4,5)-1-benzyloxycarbonyl-2-(3´-indolyl)-5,6-dihydro-2H-pyridin-3-yl]molybdenum, (+) and (±)-2.47



2.47

To a solution of (±)-**2.46a** (50 mg, 0.072 mmol, 1.0 equiv) in DMSO (4 mL) was added indole (12.6 mg, 0.11 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature for 1 hour, and then quenched with brine. The mixture was poured into a separatory funnel containing EtOAc (5 mL), and the layers were separated. The aqueous layer was extracted by EtOAc (2 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (2.5:1) afforded (±)–**2.47** (40 mg, 0.058 mmol, 80%) as an orange solid.

Similar treatment of (+)-**2.46** (50 mg, 0.072 mmol, 1.0 equiv, 97.5% ee) in DMSO (4 mL) with indole (12.6 mg, 0.11 mmol, 1.5 equiv) afforded (+)–**2.47** (40 mg, 0.058 mmol, 80%, 97% ee).

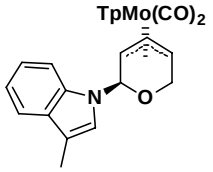
Similar treatment of (+)-**2.46** (50 mg, 0.072 mmol, 1.0 equiv, 97.5% ee) in DMSO (4 mL) with indole (12.6 mg, 0.11 mmol, 1.5 equiv) and MgO (8.8 mg, 0.22 mmol, 3 equiv) afforded (+)–**2.47** (37 mg, 0.054 mmol, 74%, 97.5%ee).

Similar treatment of (+)-**2.46** (50 mg, 0.072 mmol, 1.0 equiv, 97.5% ee) in ACN(4 mL) with indole (12.6 mg, 0.11 mmol, 1.5 equiv) afforded (+)–**2.47** (40 mg, 0.058 mmol, 74%, 97.5%ee). $[\alpha]_D^{20}$ = +121.1, (c = 0.75, CH_2Cl_2)

TLC (R_f = 0.28, 2:1 hexanes:EtOAc). ^{1}H NMR (a mixture of two rotamers) (400 MHz, $CDCl_3$) δ 8.64 (d, *J* = 2.4 Hz,0.5 H), 8.63 (d, *J* = 2.4 Hz,0.5 H), 8.26 (d, *J* = 8.0 Hz,0.5 H), 8.25 (s,0.5 H), 8.21 (s, 0.5 H), 7.81 (d, *J* = 2.0 Hz, 0.5 H), 7.79 (d, *J* = 2.0 Hz, 0.5 H), 7.73 (d, *J* = 8.0 Hz,0.5 H), 7.72 (d, *J* = 2.4 Hz,0.5 H), 7.69 (d, *J* = 2.0 Hz,0.5 H), 7.60 (t, *J* = 2.4 Hz,1 H), 7.57 (d, *J* = 2.0 Hz, 1 H), 7.53 (d, *J* = 2.0 Hz, 1 H), 7.51 (d, *J* = 2.0 Hz,0.5 H), 7.26-7.39 (m, 6.5 H), 7.14-7.23 (m, 1.5 H), 6.94 (t, *J* = 8.0 Hz, 0.5 H), 6.32 (m, 1 H), 6.21 (t, *J* = 2.0 Hz, 1 H), 6.12 (t, *J* = 2.0 Hz,0.5 H), 6.11 (t, *J* = 2.0 Hz,0.5 H), 5.87 (d, *J* = 2.8 Hz, 0.5 H), 5.78 (d, *J* = 2.8 Hz, 0.5 H), 5.15 (d, *J* = 12.4 Hz, 0.5 H), 5.12 (d, *J* = 12.0 Hz, 0.5 H), 5.02 (d, *J* = 12.0 Hz, 0.5 H), 4.98 (d, *J* = 12.0 Hz, 0.5 H), 4.51 (dt, *J* = 7.2 Hz, 2.8 Hz,0.5 H), 4.41-4.46 (m, 1 H), 4.32-4.37 (m, 1 H), 4.26 (dd, *J* = 14.4 Hz, 2.8 Hz,0.5 H), 4.00 (t, *J* = 7.2 Hz, 0.5 H), 3.94 (d, *J* = 7.2 Hz, 0.5 H), 3.71 (d, *J* = 10.0 Hz, 0.5 H), 3.68 (d, *J* = 10.0 Hz, 0.5 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 225.8, 225.3, 225.3, 224.9, 154.7, 154.2, 147.3, 141.9, 141.7, 136.7, 136.6, 136.5, 136.2, 136.0, 134.4, 128.4, 128.2, 128.2, 127.9, 127.8, 127.6, 126.3, 126.0, 123.8, 122.9, 122.2, 122.1, 120.9, 120.1, 119.8, 119.6, 117.7, 117.5, 111.0, 106.0, 105.4, 105.3, 105.3, 105.3, 71.2, 70.8, 67.3, 67.1, 67.0, 64.1, 63.6, 47.3, 47.1, 39.4, 39.2. IR (cm^{-1}) 3358 (m), 3123 (w), 3057 (w), 2482 (m),

1938 (s), 1857 (s), 1679 (s). HRMS (FAB) Calcd. for $C_{32}H_{30}BMoN_8O_4$([M+H]$^+$): 699.1532. Found: 699.1550. HPLC: Daicel® Chiralcel OD-RH column, isocratic solvent system: 65 % CH_3CN in H_2O (without TFA), 1.0 mL/min., λ = 254 nm, (2R, 3R)-(+)-**2.47**: $t_{(+)}$ = 16.6 min; (2S, 3S)-(-)-**2.47**: $t_{(-)}$ = 21.5 min.

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(*η*-3,4,5)-2-(3′-methyl-1′-indolyl)-5,6-dihydro-2H-pyran-3-yl]molybdenum, (±)-2.56



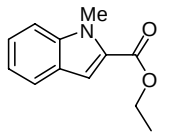
2.56

To a solution of (±)-**2.36** (50 mg, 0.089 mmol, 1.0 equiv) in DMSO (4 mL) was added 3-methylindole (17.1 mg, 0.13 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature for 1 hour, and then quenched with brine. The mixture was poured into a separatory funnel containing EtOAc (5 mL), and the layers were separated. The aqueous layer was extracted by EtOAc (2 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (20:1) afforded (±)–**2.56** (40 mg, 0.075 mmol, 78%) as an orange solid.

TLC (R_f =0.61, 6:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, DMSO) δ 8.65 (d, *J* = 2.4 Hz, 1 H), 8.19 (d, *J* = 2.0 Hz, 1 H), 8.09 (d, *J* = 2.0 Hz, 1 H), 8.00 (s, 1 H), 7.91 (d, *J* = 2.4 Hz, 1 H), 7.89 (d, *J* = 2.4 Hz, 1 H), 7.86 (d, *J* = 2.0 Hz, 1 H), 7.53 (d, *J* = 2.0 Hz, 1 H), 7.33 (d, *J* = 8.0 Hz, 1 H), 7.16 (t, *J* = 8.0 Hz, 1 H), 7.08 (t, *J* = 8.0 Hz, 1 H), 6.50 (t, *J* = 2.0 Hz,

1 H), 6.33 (t, *J* = 2.0 Hz, 1 H), 6.26(t, *J* = 2.0 Hz, 1 H), 6.02 (d, *J* = 2.0 Hz, 1 H), 4.59 (d, *J* = 7.6 Hz, 1 H), 4.49 (d, *J* = 6.8 Hz, 1 H), 4.30 (t, *J* = 7.2 Hz, 1 H), 3.68 (d, *J* = 12.8 Hz, 1 H), 3.48 (dd, *J* = 12.4 Hz, 2.0 Hz, 1 H), 2.32 (s, 3 H). ^{13}C NMR (100 MHz, DMSO) δ 226.2, 225.6, 147.0, 143.6, 142.3, 136.7, 136.7, 135.4, 129.4, 124.0, 121.5, 119.3, 118.7, 110.2, 109.5, 106.8, 106.0, 105.8, 77.3, 66.6, 65.8, 65.1, 57.5, 9.7. IR (cm^{-1}) 2957 (w), 2482 (w), 1949 (s), 1864 (s), 1505 (w). HRMS (FAB) Calcd. for $C_{25}H_{25}BMoN_7O_3$([M+H]$^+$): 580.1161. Found: 580.1167.

ethyl 1-methyl-1H-indole-2-carboxylatemethyl, 2.58

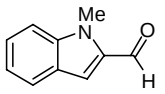


2.58

To a solution of **2.37** (2 g, 10.6 mmol, 1.0 equiv) in DMF (50 mL) was added NaH (636 mg, 15.9 mmol, 1.5 equiv) and methyliodie (2.26 g, 15.9 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature for 5 hours, and then was added NaH (218 mg, 5.3 mmol, 0.5 equiv) and methyliodie (0.75 g, 5.3 mmol, 1.5 equiv). The mixture was left to stir at room temperautre overnight and the quenched with brine. The mixture was poured into a separatory funnel containing EtOAc (25 mL), and the layers were separated. The aqueous layer was extracted by EtOAc (2 x 25 mL), and the combined organic layers were washed by brine, dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (6:1) afforded **2.58** (2.1 g, 10.3 mmol, 97%) as a white solid.

TLC (R_f = 0.33, 6:1 hexanes:EtOAc). m. p. 60-61°C ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 8.0 Hz, 1 H), 7.33-7.41 (m, 2 H), 7.32 (s, 1 H), 7.16 (ddd, *J* = 8.0 Hz, 6.4 Hz, 1.6 Hz, 1 H), 4.38 (q, *J* = 7.6 Hz, 2 H), 4.09 (s, 3 H), 1.42 (t, *J* = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2, 139.6, 128.0, 125.8, 124.9, 122.5, 120.5, 110.2, 110.0, 60.5, 31.6, 14.3. IR (cm^{-1}) 3053 (w), 2984 (w), 1706 (s), 1613 (w), 1517 (m). HRMS (ESI) Calcd. for $C_{12}H_{14}NO_2$ ($[M+H]^+$): 204.1019. Found: 204.1019.

1-methyl-1H-indole-2-carbaldehyde, 2.59



2,59

To a solution of **2.58** (2.1 g, 10.3 mmol, 1.0 equiv) in THF (25 mL) was slowly added DIBAL (1.0 M in hexane, 25.8 mL, 25.8 mmol, 2.5 equiv) at -78°C. The reaction mixture was stirred at -78°C for 30 minutes, and then was slowly warmed up to room temperature. The reaction was quenched with potassium sodium tartrate tetrahydrate (9.2 g, 31 mmol, 3.0 equiv) and H_2O (10 mL). The mixture was poured into a separatory funnel containing EtOAc (40 mL) and the layers were separated. The aqueous layer was extracted by EtOAc (2 x 35 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (2:1) afforded the alcohol (1.6 g, 9.78 mmol, 95%) as a white solid.

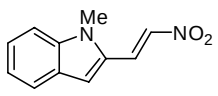
To a solution of the alcohol (1.6 g, 9.78 mmol, 1.0 equiv) in ACN (40 mL) was added MnO_2 (6.3 g, 78.24 mmol, 8 equiv). The reaction mixture was stirred at room temperature

overnight, and then filtered to remove the solid. The mixture was concentrated to give the product. Flash chromatography over silica gel with hexanes-EtOAc (6:1) afforded **2.59** (1.2 g, 7.53 mmol, 77%) as a white solid.

The alcohol: TLC (R_f = 0.34, 2:1 hexanes:EtOAc). m. p. 100-101°C ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.6 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.25 (t, *J* = 8.0 Hz, 1H), 7.12 (t, *J* = 8.0 Hz, 1H), 6.45 (s, 1H), 4.79 (d, *J* = 5.6 Hz, 2H), 3.79 (s, 3H), 1.69 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6, 138.0, 127.1, 121.9, 120.8, 119.5, 109.2, 101.3, 57.4, 29.8. IR (cm^{-1}) 3354 (s), 3053 (m), 2934 (s), 1613 (w), 1548 (m). HRMS (ESI) Calcd. for $C_{10}H_{12}NO$ ($[M+H]^+$): 162.0913. Found: 162.0912.

TLC (R_f = 0.64, 3:1 hexanes:EtOAc). m. p. 82-84°C ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (s, 1 H), 7.74 (d, *J* = 8.0 Hz, 1 H), 7.39-7.46 (m, 2 H), 7.26 (s, 1 H), 7.18 (ddd, *J* = 8.0 Hz, 6.0 Hz, 1.6 Hz, 1 H), 4.11 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.0, 182.9, 140.8, 135.6, 126.9, 126.3, 123.3, 120.9, 117.5, 110.4, 31.5. IR (cm^{-1}) 2837 (w), 1671 (s), 1613 (m), 1521 (m). HRMS (ESI) Calcd. for $C_{10}H_{10}NO$ ($[M+H]^+$): 160.0757. Found: 160.0756.

(E)-1-methyl-2-(2-nitrovinyl)-1H-indole, 2.60

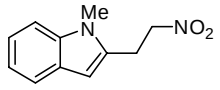


2.60

To a solution of **2.59** (500 mg, 3.14 mmol, 1.0 equiv) in nitromethane (15 mL) was added NH_4OAc (60 mg, 0.77 mmol, 0.25 equiv). The reaction mixture was stirred at reflux for 3 hours. The mixture was poured into a separatory funnel containing EtOAc (10 mL) and the layers were separated. The aqueous layer was extracted by EtOAc (2 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (6:1) afforded **2.60** (494 mg, 2.45 mmol, 78%) as a yellow solid.

TLC (R_f = 0.31, 3:1 hexanes:EtOAc). m. p. 134-136 ^oC ^1H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 13.2 Hz, 1 H), 7.68 (d, *J* = 13.2 Hz, 1 H), 7.64 (d, *J* = 8.0 Hz, 1 H), 7.35 (d, *J* = 3.6 Hz, 2 H), 7.14-7.18 (m, 1 H), 7.10 (s, 1 H), 3.87 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 140.2, 135.7, 129.9, 127.8, 127.3, 125.4, 122.1, 121.2, 110.0, 107.6, 30.3.
IR (cm^{-1}) 3111 (w), 2941 (w), 2049 (w), 1938 (w), 1621 (s). HRMS (ESI) Calcd. for $C_{11}H_{11}N_2O_2$ ($[M+H]^+$): 203.0815. Found: 203.0815.

methyl-2-(2-nitroethyl)-1H-indole, 2.61



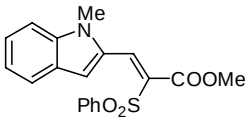
2.61

To a solution of **2.60** (494 mg, 2.45 mmol, 1.0 equiv) in $CHCl_3$(20 mL) and *i*PrOH (3 mL) was added $NaBH_4$ (367 mg, 9.7 mmol, 4 equiv) and silica gel (3.65 g). The reaction mixture was stirred at room for 15 minutes. The reaction was quenched by HOAc, and then the mixture was filtered to yield the solution. It was poured into a separatory funnel

containing EtOAc (10 mL) and the layers were separated. The aqueous layer was extracted by EtOAc (2 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (6:1) afforded **2.61** (320 mg, 1.59 mmol, 65%) as a yellow solid.

TLC (R_f = 0.28, 2:1 hexanes:EtOAc). m. p. 64-66°C ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, *J* = 7.6 Hz, 1 H), 7.24-7.33 (m, 2 H), 7.16 (dt, *J* = 7.2 Hz, 0.8 Hz, 1 H), 6.30 (d, *J* = 0.8 Hz, 1 H), 4.68 (t, *J* = 7.2 Hz, 2 H), 3.66 (s, 2 H), 3.43 (dt, *J* = 7.2 Hz, 0.8 Hz, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.3, 134.1, 127.3, 121.4, 120.1, 119.6, 109.0, 99.5, 73.4, 29.3, 24.3. IR (cm^{-1}) 3030 (w), 1552 (s), 1471 (m). HRMS (ESI) Calcd. for $C_{11}H_{13}N_2O_2$ ($[M+H]^+$): 205.0972. Found: 205.0970

methyl 3-(1-methyl-1H-indol-2-yl)-2-(phenylsulfonyl)acrylate, 2.63



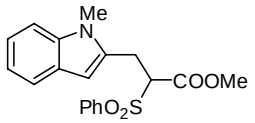
2.63

To a solution of **2.59** (500 mg, 3.14 mmol, 1.0 equiv) in DMSO (20 mL) was added proline (75 mg, 0.62 mmol, 0.2 equiv) and methyl phenylsulfonyl acetate (1 g, 4.71 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature overnight. The mixture was poured into a separatory funnel containing EtOAc (20 mL) and the layers were

separated. The aqueous layer was extracted by EtOAc (2 x 15 mL), and the combined organic layers were washed by brine, dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (1:1) afforded **2.63** (1.06 g, 2.98 mmol, 95%) as a yellow solid.

TLC (R_f = 0.30, 2:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (s, 1 H), 7.97 (d, *J* = 7.2 Hz, 2H), 7.54-7.66 (m, 4 H), 7.34 (d, *J* = 4.0 Hz, 1H), 7.19 (s, 1H), 7.10-7.15 (m, 1 H), 3.88 (s, 3H), 3.81 (s, 3H) . ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.3, 140.1, 139.3, 133.5, 132.4, 130.8, 130.1, 129.0, 128.3, 127.9, 127.3, 125.5, 122.3, 120.9, 110.0, 109.7, 52.8, 30.0. IR (cm^{-1}) 3061 (w), 2953 (w), 1725 (s), 1602 (s), 1517 (s). HRMS (ESI) Calcd. for $C_{19}H_{18}NO_4S$ ($[M+H]^+$): 356.0951. Found: 356.0954.

methyl 3-(1-methyl-1H-indol-2-yl)-2-(phenylsulfonyl)propanoate, 2.64

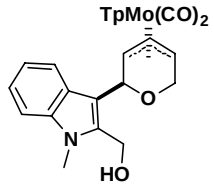


2.64

To a solution of **2.63** (250 mg, 0.7 mmol, 1.0 equiv) in EtOH (10 mL) and THF (5 mL) was added Pd/C (75 mg, 0.07 mmol, 0.1 equiv). The reaction mixture was stirred at room temperature under hydrogen balloon for 5 hours. The mixture was filtered to give the solution and then concentrated. Flash chromatography over silica gel with hexanes-EtOAc (2:1) afforded **2.64** (1.06 g, 2.98 mmol, 88%) as a yellow solid.

TLC (R_f = 0.28, 2:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.4 Hz, 2H), 7.74 (t, *J* = 7.2 Hz, 1H), 7.62 (t, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.0 Hz, 1 H), 7.27 (d, *J* = 8.8 Hz, 1H), 7.20 (dt, *J* = 6.8, 1.2 Hz, 1H), 7.08 (dt, *J* = 8.0 Hz, 0.8 Hz, 1H), 6.19 (s, 1H), 4.36 (dd, *J* = 9.2 Hz, 6.0 Hz, 1H), 3.67 (s, 3H), 3.57 (s, 3H), 3.51-3.56 (m, 2 H) . ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 137.5, 136.7, 134.6, 134.0, 129.3, 129.2, 127.4, 121.5, 120.1, 119.6, 109.0, 100.2, 69.7, 53.2, 29.5, 23.9. IR (cm^{-1}) 3053 (w), 2953 (w), 1741 (s), 1471 (m). HRMS (ESI) Calcd. for $C_{19}H_{18}NO_4S$ ([M-H]$^-$): 356.0962. Found: 356.0962.

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(η-3,4,5)-2-(1′-methyl-2′-hydroxymethyl-3′-indolyl)-5,6-dihydro-2H-pyran-3-yl]molybdenum, (±)-2.65a

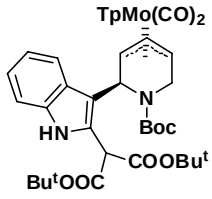


2.65a

To a solution of (±)-**2.36** (50 mg, 0.089 mmol, 1.0 equiv) in DMSO (4 mL) was added the indolyl alcohol (20.9 mg, 0.13 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature for 1 hour, and then quenched with brine. The mixture was poured into a separatory funnel containing EtOAc (5 mL), and the layers were separated. The aqueous layer was extracted by EtOAc (2 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (2.5:1) afforded (±)–**2.65a** (44 mg, 0.072 mmol, 81%) as an orange solid.

TLC (R_f=0.38, 2:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, *J* = 2.0 Hz, 1 H), 8.58 (d, *J* = 8.4 Hz, 1 H), 7.78 (d, *J* = 1.6 Hz, 1 H), 7.72 (d, *J* = 2.0 Hz, 1 H), 7.61 (d, *J* = 2.0 Hz, 1 H), 7.59 (d, *J* = 2.0 Hz, 1 H), 7.55 (d, *J* = 2.0 Hz, 1 H), 7.38 (d, *J* = 8.4 Hz, 1 H), 7.28 (dt, *J* = 7.2 Hz, 1.2 Hz, 1 H), 7.16 (dt, *J* = 7.2 Hz, 1.2 Hz, 1 H), 6.34 (t, *J* = 2.0 Hz, 1 H), 6.22 (t, *J* = 2.0 Hz, 1 H), 6.13(t, *J* = 2.0 Hz, 1 H), 5.34 (d, *J* = 2.0 Hz, 1 H), 4.92 (d, *J* = 14.0 Hz, 1 H), 4.86 (d, *J* = 13.2 Hz, 1 H), 4.56 (dt, *J* = 6.4 Hz, 2.4 Hz, 1 H), 4.31-4.37 (m, 2 H), 4.22 (dd, *J* = 12.4 Hz, 1.6 Hz, 1 H), 3.84 (s, 3 H), 3.74 (dd, *J* = 12.4 Hz, 1.6 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 226.8, 225.9, 147.4, 142.0, 141.4, 138.6, 137.0, 136.0, 134.4, 126.3, 121.9, 121.1, 119.6, 113.3, 109.5, 106.0, 105.4, 105.3, 71.1, 67.4, 67.3, 66.7, 60.1, 54.2, 29.7. IR (cm^{-1}) 3377 (m), 3146 (w), 3053 (w), 2945 (w), 2482 (m), 1942 (s), 1845 (s), 1505 (m). HRMS (FAB) Calcd. for $C_{26}H_{27}BMoN_7O_4$([M+H]$^+$): 610.1266. Found: 610.1271.

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(*η*-3,4,5)-1-*t*-butoxycarbonyl- 2-(2´-malonyl-3´-indolyl)-5,6-dihydro-2H-pyridin-3-yl]molybdenum, (±)-2.65c



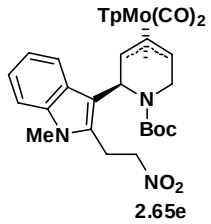
2.65c

To a solution of (±)-**2.46b** (50 mg, 0.076 mmol, 1.0 equiv) in DMSO (4 mL) was added indolyl malonate (37.8 mg, 0.11 mmol, 1.5 equiv) and MgO (8.8 mg, 0.22 mmol, 3.0 equiv). The reaction mixture was stirred at room temperature for 1 hour, and then quenched with brine. The mixture was poured into a separatory funnel containing EtOAc (5 mL), and the layers were separated. The aqueous layer was extracted by EtOAc (2 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (2.5:1) afforded (±)–**2.65c** (41 mg, 0.046 mmol, 61%) as an orange solid.

TLC (R_f = 0.26, 2:1 hexanes:EtOAc). ^{1}H NMR (a mixture of two rotamers) (400 MHz, $CDCl_3$) δ 9.46 (s, 0.5 H), 9.35 (s, 0.5 H), 8.64 (d, *J* = 1.6 Hz,1 H), 8.37 (d, *J* = 8.0 Hz,0.5 H), 8.16 (d, *J* = 8.0 Hz,0.5 H), 7.88(br s, 1 H), 7.82 (d, *J* = 2.0 Hz, 0.5 H), 7.73 (d, *J* = 2.0 Hz, 0.5 H), 7.58-7.60 (m, 1.5 H), 7.50-7.53 (m, 2.5 H), 7.41 (s, 0.5 H), 7.39 (s, 0.5 H),7.17-7.22 (m, 1H), 7.12-7.16(m, 1 H), 6.29-6.31 (m, 1 H), 6.20-6.23 (m, 1 H), 6.03-6.05 (m, 1 H), 5.93 (s, 0.5 H), 5.58 (d, *J* = 2.0 Hz, 0.5 H), 5.52 (d, *J* = 2.8 Hz, 0.5 H), 5.38 (s, 0.5 H), 4.54-4.46 (m, 1 H), 4.45-4.50 (m, 1 H), 4.30-4.38 (m, 1 H), 4.27-4.31 (m, 1 H), 3.93-4.10 (m ,1 H), 1.56 (s, 4.5 H), 1.53 (s, 4.5 H), 1.46 (s, 4.5 H), 1.45 (s, 9 H), 1.36 (s, 4.5 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 226.3, 225.8, 225.2, 168.3, 167.7, 167.1, 166.1, 154.3, 153.8, 147.3, 147.3, 142.2, 142.1, 141.9, 141.8, 136.0, 136.0, 135.8, 134.3, 129.3, 128.8, 128.6, 128.5, 128.4, 128.3, 128.3, 127.0, 126.1, 125.6, 121.9, 121.6, 121.0, 119.6, 119.3, 116.9, 115.3, 111.4, 105.9, 105.8, 105.3, 105.1, 105.0, 83.2, 83.0, 82.5, 82.4, 80.3, 79.1, 70.9, 70.4, 67.0, 66.5, 66.0, 64.9, 50.8, 47.2, 46.0, 41.3, 41.0, 28.5, 28.3, 27.9,

27.9. IR (cm^{-1}) 3358 (m), 3123 (w), 3057 (w), 2482 (m), 1938 (s), 1857 (s), 1679 (s). HRMS (FAB) Calcd. for $C_{40}H_{49}BMoNaN_8O_8$([M+Na]$^+$): 901.2724. Found: 901.2712.

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(*η*-3,4,5)-1-*t*-butoxycarbonyl- 2-(1´-methyl-2´-nitroethyl-3´-indolyl)-5,6-dihydro-2H-pyridin-3-yl]molybdenum, (±)-



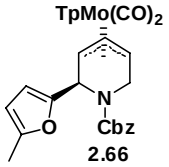
2.65e

To a solution of (±)-**2.46b** (50 mg, 0.076 mmol, 1.0 equiv) in DMSO (4 mL) was added **2.61** (22.4 mg, 0.11 mmol, 1.5 equiv) and MgO (8.8 mg, 0.22 mmol, 3.0 equiv). The reaction mixture was stirred at room temperature for 1 hour, and then quenched with brine. The mixture was poured into a separatory funnel containing EtOAc (5 mL), and the layers were separated. The aqueous layer was extracted by EtOAc (2 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (2.5:1) afforded (±)–**2.65e** (41 mg, 0.046 mmol, 66%) as an orange solid.

TLC (R_f = 0.23, 2:1 hexanes:EtOAc). ^{1}H NMR (major rotamer) (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 2.0 Hz,1 H), 8.30 (d, *J* = 8.0 Hz,1 H), 7.87 (d, *J* = 2.0 Hz, 1 H), 7.82 (d, *J* = 2.0 Hz, 1 H), 7.60 (d, *J* = 2.4 Hz, 1 H), 7.53 (d, *J* = 2.4 Hz, 1 H), 7.51 (d, *J* = 2.0 Hz, 1 H), 7.33 (d, *J* = 8.0 Hz, 1 H), 7.26 (t, *J* = 7.2 Hz, 1 H), 6.30 (t, *J* = 2.0 Hz, 1 H), 6.23 (t, *J* =

2.0 Hz, 1 H), 6.08 (t, *J* = 2.0 Hz, 1 H), 5.58 (d, *J* = 2.8 Hz, 1 H), 4.96 (dt, *J* = 12.8 Hz, 6.8 Hz, 1 H), 4.64 (dt, *J* = 13.2 Hz, 6.4 Hz, 1 H), 4.47 (d, *J* = 4.4 Hz, 1 H), 4.22-4.35 (m, 3 H), 4.08 (t, *J* = 7.6 Hz, 1 H), 3.97 (d, *J* = 15.2 Hz, 1 H), 3.73 (s, 3 H), 3.62 (dt, *J* = 15.6 Hz, 6.8 Hz, 1 H), 1.37 (s, 9 H). ^{13}C NMR (100 MHz, $CDCl_3$)) δ 225.8, 225.7, 153.8, 147.4, 142.4, 141.6, 137.6, 136.0, 135.8, 134.3, 133.0, 125.6, 121.5, 120.9, 119.5, 115.1, 109.3, 105.9, 105.3, 79.4, 75.2, 71.4, 65.8, 65.4, 46.5, 41.5, 29.7, 28.3, 22.9. IR (cm^{-1}) 2976 (w), 2930 (w), 2482 (w), 1942 (s), 1853 (s), 1679 (m). HRMS (FAB) Calcd. for $C_{32}H36BMoNaN_9O_6$([M+Na]$^+$): 774.1828. Found: 774.1835.

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(*η*-3,4,5)-1-benzyloxycarbonyl- 2-(5′-methyl-2′-furanyl)-5,6-dihydro-2H-pyridin-3-yl]molybdenum, (±)-

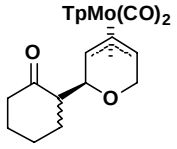


2.66

To a solution of (±)-**2.46a** (50 mg, 0.072 mmol, 1.0 equiv) in ACN (4 mL) was added 2-methylfuran (9.1 mg, 0.11 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature for 1 hour, and then quenched with brine. The mixture was poured into a separatory funnel containing EtOAc (5 mL), and the layers were separated. The aqueous layer was extracted by EtOAc (2 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (2.5:1) afforded (±)–**2.66** (40 mg, 0.060 mmol, 84%) as an orange solid.

TLC (R_f = 0.34, 3:1 hexanes:EtOAc). ^{1}H NMR (a mixture of two rotamers) (400 MHz, $CDCl_3$) δ 8.58 (br s, 1 H), 7.77 (d, *J* = 2.0 Hz, 0.4 H), 7.75 (br s, 1 H), 7.72 (d, *J* = 2.0 Hz, 0.6 H), 7.56-7.58 (m, 2 H), 7.51 (d, *J* = 2.0 Hz, 1 H), 7.27-7.34 (m, 5 H), 6.31 (t, *J* = 2.0 Hz, 1 H), 6.26 (d, *J* = 3.2 Hz, 0.4 H), 6.17-6.19 (m, 1 H), 6.14-6.16 (m, 1 H), 6.14 (d, *J* = 2.8 Hz, 0.6 H), 5.92 (d, *J* = 2.0 Hz, 0.4 H), 5.89 (d, *J* = 2.4 Hz, 0.6 H), 5.43 (d, *J* = 2.8 Hz, 0.4 H), 5.38 (d, *J* = 3.2 Hz, 0.6 H), 5.19 (d, *J* = 13.2 Hz, 0.6 H), 5.13 (d, *J* = 12.4 Hz, 0.4 H), 5.06 (d, *J* = 12.8 Hz, 0.4 H), 5.05 (d, *J* = 12.8 Hz, 0.6 H), 4.19-4.38 (m, 3 H), 3.87 (t, *J* = 7.2 Hz, 1 H), 3.75 (d, *J* = 13.2 Hz, 0.4 H), 3.67 (d, *J* = 13.2 Hz, 0.6 H), 2.31 (s, 1.2 H), 2.27 (s, 1.8 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 225.7, 225.5, 225.3, 225.0, 154.8, 153.6, 153.6, 151.8, 151.7, 147.3, 141.9, 141.7, 136.9, 136.7, 136.0, 134.4, 128.3, 128.2, 127.9, 127.7, 127.6, 127.6, 107.6, 107.5, 106.2, 106.0, 106.0, 105.4, 105.3, 68.2, 68.0, 67.2, 67.0, 67.0, 64.0, 63.9, 48.9, 48.5, 39.8, 39.4, 13.8, 13.7. IR (cm^{-1}) 3134 (w), 3030 (w), 2953 (w), 2837 (w), 2486 (m), 1945 (s), 1861 (s), 1698 (s). HRMS (FAB) Calcd. for $C_{29}H_{29}BMoN_7O_5$([M+H]$^+$): 664.1372. Found: 664.1377.

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



2.68

To a solution of (±)-**2.36** (50 mg, 0.089 mmol, 1.0 equiv) in ACN (4 mL) was added the 1-trimethylsiloxy cyclohexene (22.1 mg, 0.13 mmol, 1.5 equiv). The reaction mixture

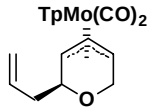
was stirred at room temperature for 1 hour, and then quenched with brine. The mixture was poured into a separatory funnel containing EtOAc (5 mL), and the layers were separated. The aqueous layer was extracted by EtOAc (2 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (2.5:1) afforded (±)–**2.68** (32 mg, 0.056 mmol, 63%, dr 1:1) as an orange solid.

1st diastereomer TLC (R_f =0.37, 2:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 1.6 Hz, 1 H), 7.78 (d, *J* = 2.0 Hz, 1 H), 7.65 (d, *J* = 2.0 Hz, 1 H), 7.56 (d, *J* = 2.0 Hz, 1 H), 7.55 (d, *J* = 2.0 Hz, 1 H), 7.51(d, *J* = 2.0 Hz, 1 H), 6.30 (t, *J* = 2.4 Hz, 1 H), 6.15-6.17 (m, 2 H), 4.56 (dt, *J* = 7.6 Hz, 2.0 Hz, 1 H), 3.96-4.05 (m, 3 H), 3.67-3.71 (m, 2 H), 2.76 (dt, *J* = 10.8 Hz, 4.8 Hz, 1 H), 2.42-2.46 (m, 2 H), 2.25-2.31 (m, 1 H), 2.06-2.11 (m, 1 H), 1.90-1.95 (m, 1 H), 1.58-1.77 (m, 3 H). IR (cm^{-1}) 2934 (m), 2860 (w), 2486 (w), 1938 (s), 1853 (s), 1702 (s), 1505 (m). HRMS (FAB) Calcd. for $C_{22}H_{25}BMoNaN_6O_4$ ($[M+Na]^+$): 569.0977. Found: 569.0976.

1st diastereomer TLC (R_f =0.35, 2:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 1.6 Hz, 1 H), 7.71 (d, *J* = 2.0 Hz, 1 H), 7.68 (d, *J* = 2.0 Hz, 1 H), 7.57-7.59 (m, 2 H), 7.52(dd, *J* = 2.4 Hz, 0.8 Hz, 1 H), 6.31 (t, *J* = 2.0 Hz, 1 H), 6.18 (t, *J* = 2.0 Hz, 1 H), 6.17 (t, *J* = 2.0 Hz, 1 H), 4.30 (dd, *J* = 8.8 Hz, 2.0 Hz, 1 H), 4.22 (d, *J* = 12.4 Hz, 1 H), 4.17 (dt, *J* = 7.2 Hz, 2.4 Hz, 1 H), 4.08 (dd, *J* = 7.2 Hz, 1.6 Hz, 1 H), 3.80 (t, *J* = 7.2 Hz, 1 H), 3.67 (dd, *J* = 12.8 Hz, 2.4 Hz, 1 H), 2.90 (dt, *J* = 9.6 Hz, 5.2 Hz, 1 H), 2.54 (ddd, *J* = 13.6 Hz, 10.4 Hz, 5.6 Hz, 1 H), 2.31 (dt, *J* = 14.0 Hz, 4.8 Hz, 1 H), 2.09-2.19 (m, 2 H),

1.88-2.03 (m, 2 H), 1.74-1.85 (m, 2 H). IR (cm^{-1}) 2937 (m), 2864 (w), 2486 (w), 1938 (s), 1853 (s), 1706 (s), 1505 (m). HRMS (FAB) Calcd. for $C_{22}H_{25}BMoNaN_6O_4$ ($[M+Na]^+$): 569.0977. Found: 569.0976.

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



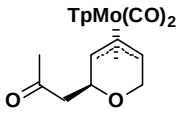
2.69

To a solution of (±)-**2.36** (50 mg, 0.089 mmol, 1.0 equiv) in ACN (4 mL) was added allyl trimethylsilane (14.8 mg, 0.13 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature for 1 hour, and then quenched with brine. The mixture was poured into a separatory funnel containing EtOAc (5 mL), and the layers were separated. The aqueous layer was extracted by EtOAc (2 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (2.5:1) afforded (±)–**2.69** (32 mg, 0.066 mmol, 74%) as an orange solid.

TLC (R_f =0.35, 6:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.63 (d, *J* = 2.0 Hz, 1 H), 7.70 (d, *J* = 2.0 Hz, 1 H), 7.68 (d, *J* = 2.0 Hz, 1 H), 7.57 (d, *J* = 2.0 Hz, 2 H), 7.52 (d, *J* = 2.4 Hz, 1 H), 6.31 (t, *J* = 2.4 Hz, 1 H), 6.17 (t, *J* = 2.0 Hz, 2 H), 5.93 (ddt, *J* =16.8 Hz, 10.0 Hz, 7.2 Hz, 1 H), 5.16 (dd, *J* = 16.8 Hz, 2.0 Hz, 1 H), 5.10 (dd, *J* = 10.0 Hz, 0.8 Hz, 1 H), 4.16 (d, *J* = 12.4 Hz, 1 H), 4.07 (d, *J* = 6.8 Hz, 1 H), 4.06 (d, *J* = 6.8 Hz, 1 H), 3.90 (ddd, *J* = 8.0 Hz, 5.6 Hz, 2.0 Hz, 1 H), 3.78 (t, *J* = 7.2 Hz, 1 H), 3.72 (dd, *J* = 12.4 Hz, 1.6

Hz, 1 H), 2.60 (dt, *J* = 14.0 Hz, 7.2 Hz, 1 H), 2.50 (dt, *J* = 14.0 Hz, 6.0 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 225.7, 225.3, 147.3, 141.6, 141.5, 135.9, 135.5, 134.3, 116.8, 105.9, 105.3, 71.1, 70.4, 67.4, 63.4, 57.6, 40.8. IR (cm^{-1}) 3146 (w), 2926 (m), 2853 (w), 2482 (w), 1938 (s), 1845 (s), 1640 (w). HRMS (FAB) Calcd. for $C_{19}H_{21}BMoNaN_6O_3$ ($[M+Na]^+$): 513.0715. Found: 513.0723.

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



2.70

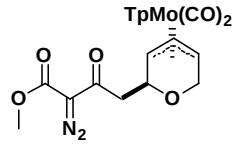
To a solution of (±)-**2.36** (50 mg, 0.089 mmol, 1.0 equiv) in ACN (4 mL) was added 2-trimethyloxypropene (16.9 mg, 0.13 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature for 1 hour, and then quenched with brine. The mixture was poured into a separatory funnel containing EtOAc (5 mL), and the layers were separated. The aqueous layer was extracted by EtOAc (2 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (2.5:1) afforded (±)–**2.70** (36 mg, 0.071 mmol, 80%) as an orange solid.

TLC (R_f=0.20, 2:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 2.0 Hz, 1 H), 7.71 (d, *J* = 2.0 Hz, 1 H), 7.68 (d, *J* = 2.0 Hz, 1 H), 7.58 (br s, 2 H), 7.52 (d, *J* = 2.4 Hz, 1 H), 6.31 (t, *J* = 2.0 Hz, 1 H), 6.17-6.18 (m, 2 H), 4.35 (ddd, *J* = 7.6 Hz, 5.2 Hz, 2.0

Hz, 1 H), 4.14 (d, J = 12.8 Hz, 1 H), 4.06-4.12 (m, 2 H), 3.74 (t, J = 7.6 Hz, 1 H), 3.72 (dd, J = 12.4 Hz, 2.0 Hz, 1 H), 2.99 (dd, J = 14.8 Hz, 8.0 Hz, 1 H), 2.83 (dd, J = 14.8 Hz, 5.2 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 225.3, 225.2, 207.0, 147.3, 141.8, 141.4, 136.0, 134.4, 106.0, 105.3, 70.5, 67.6, 66.8, 62.9, 57.8, 50.6, 30.2.

IR (cm^{-1}) 2957 (m), 2856 (w), 2490 (w), 1948 (s), 1853 (s), 1714 (s), 1625 (s). HRMS (FAB) Calcd. for $C_{19}H_{21}BMoNaN_6O_4$ ($[M+Na]^+$): 529.0675. Found: 529.0664.

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



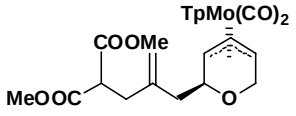
2.71

To a solution of (±)-**2.36** (50 mg, 0.089 mmol, 1.0 equiv) in ACN (4 mL) was added the t-butyldimethyl silyl enol ether of the diazocompound (33.3 mg, 0.13 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature for 1 hour, and then quenched with brine. The mixture was poured into a separatory funnel containing EtOAc (5 mL), and the layers were separated. The aqueous layer was extracted by EtOAc (2 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated.

Flash chromatography over silica gel with hexanes-EtOAc (2.5:1) afforded (±)–**2.71** (39 mg, 0.067 mmol, 77%) as an orange solid.

TLC (R_f=0.41, 2:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 1.6 Hz, 1 H), 7.73 (d, *J* = 2.0 Hz, 1 H), 7.68 (d, *J* = 2.0 Hz, 1 H), 7.57 (t, *J* = 1.6 Hz, 2 H), 7.51 (d, *J* = 2.4 Hz, 1 H), 6.30 (t, *J* = 2.0 Hz, 1 H), 6.17 (t, *J* = 2.4 Hz, 1 H), 4.41 (ddd, *J* = 7.2 Hz, 4.8 Hz, 2.0 Hz, 1 H), 4.24 (d, *J* = 12.8 Hz, 1 H), 4.14 (dt, *J* = 7.2 Hz, 2.4 Hz, 1 H), 4.08 (d, *J* = 7.2 Hz, 1 H), 3.86 (s, 3 H), 3.76 (d, *J* = 7.6 Hz, 1 H), 3.71 (dd, *J* = 12.8 Hz, 2.4 Hz, 1 H), 3.43 (dd, *J* = 14.4 Hz, 8.8 Hz, 1 H), 3.31 (dd, *J* = 14.8 Hz, 4.4 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 225.2, 225.2, 190.0, 161.8, 147.3, 141.9, 141.4, 135.9, 134.4, 105.9, 105.3, 70.7, 68.2, 67.0, 63.0, 57.9, 52.2, 46.5. IR (cm^{-1}) 3130 (w), 2957 (w), 2486 (m), 2138 (s), 1942 (s), 1853 (s), 1718 (s), 1648 (s). HRMS (FAB) Calcd. for $C_{21}H_{21}BMoNaN_8O_6$([M+Na]$^+$): 613.0623. Found: 613.0633.

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



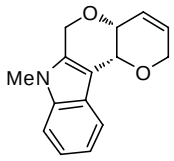
2.72

To a solution of (±)-**2.36** (50 mg, 0.089 mmol, 1.0 equiv) in ACN (4 mL) was added dimethyl 2-(2-((trimethylsilyl)methyl)allyl)malonate (33.5 mg, 0.13 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature for 1 hour, and then quenched with

brine. The mixture was poured into a separatory funnel containing EtOAc (5 mL), and the layers were separated. The aqueous layer was extracted by EtOAc (2 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (2.5:1) afforded (±)–**2.72** (40 mg, 0.063 mmol, 71%) as an orange solid.

TLC (R_f =0.33, 3:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 2.0 Hz, 1 H), 7.73 (d, *J* = 2.0 Hz, 1 H), 7.69 (d, *J* = 2.0 Hz, 1 H), 7.57 (d, *J* = 2.4 Hz, 2 H), 7.52 (d, *J* = 2.0 Hz, 1 H), 6.30 (t, *J* = 2.0 Hz, 1 H), 6.16-6.18 (m, 2 H), 4.98 (s, 1 H), 4.88 (s, 1 H), 4.15 (d, *J* = 12.4 Hz, 1 H), 4.06 (d, *J* = 7.2 Hz, 2 H), 4.00 (t, *J* = 7.2 Hz, 1 H), 3.78 (t, *J* = 7.6 Hz, 1 H), 3.74 (s,6 H), 3,67-3.74(m, 2 H), 2.74 (d, *J* = 7.6 Hz, 2 H), 2.58 (dd, *J* = 14.0 Hz, 8.4 Hz, 1 H), 2.45 (dd, *J* = 14.4 Hz, 4.8 Hz, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 225.5, 225.4, 169.4, 169.4, 147.3, 142.9, 141.8, 141.4, 135.9, 134.3, 113.7, 105.9, 105.3, 71.2, 69.2, 67.1, 63.2, 57.5, 52.6, 52.6, 50.4, 42.6, 34.8. IR (cm^{-1}) 2957 (m), 2926 (m), 2482 (w), 1942 (s), 1853 (s), 1733 (s), 1648 (m). HRMS (FAB) Calcd. for $C_{25}H_{29}BMoNaN_6O_7$ ($[M+Na]^+$): 657.1137. Found: 657.1132.

7-methyl-4a,6,7,11c-tetrahydro-2H-pyrano[2',3':5,6]pyrano[3,4-b]indole



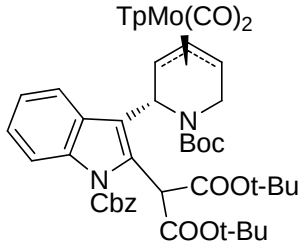
2.76

To a solution of (±)-**2.65a** (44 mg, 0.072 mmol, 1.0 equiv) in DMSO (4 mL) was added 60% NaH dispension (4.32 mg, 0.11 mmol, 1.5 equiv) and copper 2-ethylhexanoate (5

mg, 0.014 mmol, 0.2 equiv). The reaction mixture was stirred at room temperature under dry air for 3 days, and then quenched with brine. The mixture was poured into a separatory funnel containing EtOAc (2 mL), and the layers were separated. The aqueous layer was extracted by EtOAc (2 x 2 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (6:1) afforded (±)–**2.76** (16 mg, 0.068 mmol, 95%) as an orange solid.

TLC (R_f = 0.36, 4:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.0 Hz, 1 H), 7.31 (d, *J* = 8.4 Hz, 1 H), 7.20 (dt, *J* = 8.4 Hz, 1.2 Hz, 1 H), 7.15 (dt, *J* = 8.0 Hz, 0.8 Hz, 1 H), 6.21 (dd, *J* = 10.4 Hz, 1.6 Hz, 1 H), 6.11 (ddt, *J* = 10.4 Hz, 4.0 Hz, 1.6 Hz, 1 H), 5.04 (d, *J* = 14.8 Hz, 1 H), 4.83 (dd, *J* = 14.8 Hz, 1.2 Hz, 1 H), 4.68 (s, 1 H), 4.32-4.43 (m, 2 H), 3.92 (dd, *J* = 4.4 Hz, 2.4 Hz, 1 H), 3.62 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.4, 135.7, 132.7, 126.5, 123.6, 121.7, 119.9, 118.4, 108.9, 106.8, 68.8, 67.4, 65.3, 62.6, 29.6. IR (cm^{-1}) 3042 (w), 2926 (m), 2853 (m), 1471 (s). HRMS (ESI) Calcd. for $C_{15}H_{16}NO_2$ ($[M+H]^+$): 242.1175. Found: 242.1176.

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(*η*-3,4,5)-1-*t*-butoxycarbonyl- 2-(2´-malonyl-3´-*N*-benzyloxycarbonyl-indolyl)-5,6-dihydro-2H-pyridin-3-yl]molybdenum, (±)-2.77



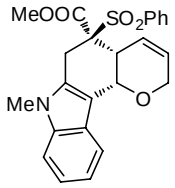
2.77

To a solution of (±)-**2.65c** (50 mg, 0.051 mmol, 1.0 equiv) in THF (4 mL) was added NaHMDS (1.0 M in THF, 0.10 mL, 0.10 mmol, 2 equiv) and CbzCl(14 mg, 0.092 mmol, 1.8 equiv). The reaction mixture was stirred at room temperature for 30 minutes, and then quenched with brine. The mixture was poured into a separatory funnel containing EtOAc (5 mL), and the layers were separated. The aqueous layer was extracted by EtOAc (2 x 5 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel with hexanes-EtOAc (2.5:1) afforded (±)–**2.77** (45 mg, 0.045 mmol, 88%) as an orange solid.

TLC (R_f = 0.27, 2:1 hexanes:EtOAc). ^{1}H NMR (a mixture of two rotamers) (400 MHz, $CDCl_3$) δ 8.59-8.61 (m, 1 H), 8.26 (dd, *J* = 8.8, 1.6 Hz,0.7 H), 8.19 (dd, *J* = 8.8, 0.8 Hz,0.7 H), 8.08 (d, *J* = 7.2 Hz,0.3 H), 8.01 (d, *J* = 8.0 Hz, 0.3 H), 7.88 (d, *J* = 2.0 Hz, 0.7 H), 7.85 (d, *J* = 8.0 Hz, 0.3 H), 7.55-7.61 (m, 1 H), 7.46-7.54 (m, 4 H), 7.23-7.42 (m, 6 H), 6.32 (t, *J* = 2.4 Hz, 1 H), 6.21 (t, *J* = 2.0 Hz, 1 H), 6.10 (s, 0.7 H), 6.03 (t, *J* = 2.4 Hz, 1 H), 5.59 (d, *J* = 12.4 Hz, 0.7 H), 5.56 (d, *J* = 12.4 Hz, 0.3 H), 5.35-5.53 (m, 1.6 H), 5.21

(d, J = 12.4 Hz, 0.7 H), 4.47-4.54 (m, 1.3 H), 4.38 (dd, J = 15.2, 2.4 Hz, 1.0 H), 4.07-4.19 (m, 2.7 H), 4.00 (d, J = 15.6 Hz, 0.7 H), 3.89 (t, J = 6.8 Hz, 0.3 H), 1.47 (s, 2.7 H), 1.44 (s, 9 H), 1.38 (s, 6.3 H), 1.36 (s, 2.7 H), 1.35 (s, 6.3 H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 227.1, 226.8, 224.6, 224.1, 166.2, 165.9, 165.6, 165.3, 154.2, 153.9, 151.7, 151.6, 147.4, 142.4, 142.2, 141.4, 141.1, 140.8, 136.5, 136.1, 136.0, 135.9, 135.8, 135.5, 135.1, 134.4, 131.4, 129.7, 128.6, 128.5, 128.4, 128.3, 127.6, 127.5, 127.0, 125.5, 124.6, 124.0, 122.8, 122.5, 122.2, 121.1, 120.9, 120.4, 115.6, 115.3, 106.0, 105.3, 105.2, 105.1, 82.2, 82.1, 81.5, 81.4, 80.8, 79.5, 68.8, 68.4, 68.1, 67.9, 67.7, 66.5, 65.4, 64.8, 51.7, 51.2, 47.5, 46.8, 41.7, 41.1, 28.3, 28.0, 27.7.

methyl 7-methyl-5-(phenylsulfonyl)-2,4a,5,6,7,11c-hexahydropyrano [3,2-c]carbazole-5-carboxylate



2.79

To a solution of (±)-**2.65b** (50 mg, 0.062 mmol, 1.0 equiv) in DMSO (4 mL) was added 60% NaH dispension (3.74 mg, 0.094 mmol, 1.5 equiv) and copper 2-ethylhexanoate (34 mg, 0.094 mmol, 1.0 equiv). The reaction mixture was stirred at room temperature under dry air overnight, and then quenched with brine. The mixture was poured into a separatory funnel containing EtOAc (2 mL), and the layers were separated. The aqueous layer was extracted by EtOAc (2 x 2 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel

with hexanes-EtOAc (6:1) afforded (±)–**2.79** (24 mg, 0.056 mmol, 90%) as an orange solid.

TLC (R_f = 0.36, 2:1 hexanes:EtOAc). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, *J* = 8.0 Hz, 1.2 Hz, 2 H), 7.68 (d, *J* = 8.0 Hz, 1 H), 7.52 (t, *J* = 7.6 Hz, 1 H), 7.36 (t, *J* = 8.0 Hz, 2 H), 7.14-7.17 (m, 2 H), 7.10 (ddd, *J* = 7.8 Hz, 5.6 Hz, 3.2 Hz, 1 H), 5.86 (dq, *J* = 10.4 Hz, 2.8 Hz, 1 H), 5.68 (d, *J* = 9.6 Hz, 1 H), 5.62 (d, *J* = 4.8 Hz, 1 H), 4.11 (dq, *J* = 16.8 Hz, 2.8 Hz, 1 H), 3.94 (dq, *J* = 16.8 Hz, 2.8 Hz, 1 H), 3.80 (s, 3 H), 3.78-3.80 (m, 1 H), 3.43 (s, 3 H), 3.26 (s, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.5, 137.4, 136.4, 134.0, 132.7, 130.4, 129.5, 128.5, 126.0, 122.5, 121.6, 119.8, 118.9, 108.7, 107.0, 78.0, 68.0, 61.5, 53.5, 37.4, 29.2, 24.7. IR (cm^{-1}) 3057 (w), 2930 (w), 2845 (w), 1737 (s). HRMS (ESI) Calcd. for $C_{24}H_{24}NO_5S$ ($[M+H]^+$): 438.1370. Found: 438.1371.

X-Ray Diffraction Study of 2.79

A suitable crystal of **2.79** was obtained by diffusion recrystallization from Et_2O and hexanes. The crystal was coated with Paratone N oil, suspended in a small fiber loop and placed in a cooled nitrogen gas stream at 173 K on a Bruker D8 SMART APEX CCD sealed tube diffractometer with graphite monochromated MoK (0.71073Å) radiation. Data were measured using a series of combinations of phi and omega scans with 10 s frame exposures and 0.3o frame widths. Data collection, indexing and initial cell refinements were all carried out using SMART5 software. Frame integration and final cell refinements were done using SAINT6 software. The final cell parameters were

determined from least-squares refinement on 5664 reflections. The SADABS7 program was used to carry out absorption corrections.

The structure was solved using Direct methods and difference Fourier techniques (SHELXTL, V6.12).8 Hydrogen atoms were placed their expected chemical positions using the HFIX command and were included in the final cycles of least squares with isotropic Uij ‘s related to the atom’s ridden upon. The C-H distances were fixed at 0.93 Å(aromatic and amide), 0.98 Å (methine), 0.97 Å (methylene), or 0.96 Å (methyl). All non-hydrogen atoms were refined anisotropically. Scattering factors and anomalous dispersion corrections are taken from the International Tables for X-ray Crystallography9. Structure solution, refinement, graphics and generation of publication materials were performed by using SHELXTL, V6.12 software.

Table 19 Crystal data and structure refinement for **2.79**.

Identification code	wyc_06_044	
Empirical formula	C24 H23 N O5 S	
Formula weight	437.49	
Temperature	173(2) K	
Wavelength	1.54178 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 8.0781(2) Å	α= 72.6870(10)°.
	b = 9.0667(2) Å	β= 84.4040(10)°.
	c = 14.8527(4) Å	γ = 82.763(2)°.
Volume	1028.21(4) $Å^3$	
Z	2	
Density (calculated)	1.413 Mg/m^3	
Absorption coefficient	1.719 mm^{-1}	

F(000)	460
Crystal size	0.29 x 0.26 x 0.11 mm^3
Theta range for data collection	3.12 to 66.57°.
Index ranges	-8<=h<=9, -10<=k<=10, -16<=l<=17
Reflections collected	9521
Independent reflections	3306 [R(int) = 0.0174]
Completeness to theta = 66.57°	90.9 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.8335 and 0.6356
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3306 / 0 / 280
Goodness-of-fit on F^2	1.027
Final R indices [I>2sigma(I)]	R1 = 0.0369, wR2 = 0.1005
R indices (all data)	R1 = 0.0406, wR2 = 0.1052
Largest diff. peak and hole	0.406 and -0.315 e.$Å^{-3}$

Table 20 Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **2.79**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	1095(3)	-91(2)	1229(1)	36(1)
C(2)	405(2)	1524(2)	731(1)	32(1)
C(3)	320(2)	2688(2)	1099(1)	28(1)
C(4)	779(2)	2445(2)	2098(1)	25(1)
C(5)	2427(2)	3085(2)	2240(1)	24(1)
C(6)	2475(2)	2981(2)	3296(1)	27(1)
C(7)	2196(2)	1368(2)	3871(1)	26(1)
C(8)	2329(2)	-831(2)	5060(1)	28(1)
C(9)	2642(2)	-1986(2)	5910(1)	35(1)
C(10)	2234(3)	-3452(2)	5982(1)	40(1)
C(11)	1516(3)	-3775(2)	5251(1)	38(1)
C(12)	1183(2)	-2624(2)	4415(1)	32(1)
C(13)	1594(2)	-1122(2)	4313(1)	27(1)
C(14)	1511(2)	312(2)	3566(1)	26(1)
C(15)	825(2)	700(2)	2624(1)	27(1)
C(16)	3306(2)	1471(2)	5386(1)	33(1)
C(17)	4027(2)	2218(2)	1920(1)	26(1)
C(18)	5509(3)	1399(2)	695(1)	38(1)
C(19)	4159(2)	5820(2)	1814(1)	25(1)
C(20)	4046(2)	6666(2)	2454(1)	32(1)
C(21)	5463(3)	7300(2)	2575(2)	40(1)
C(22)	6946(3)	7058(2)	2071(2)	39(1)
C(23)	7044(3)	6203(2)	1436(1)	37(1)
C(24)	5647(2)	5579(2)	1291(1)	31(1)
N(1)	2691(2)	692(2)	4780(1)	28(1)
O(1)	1840(2)	-186(1)	2078(1)	31(1)

O(2)	5112(2)	1566(2)	2443(1)	36(1)
O(3)	4080(2)	2278(2)	1015(1)	30(1)
O(4)	903(2)	5901(2)	2000(1)	36(1)
O(5)	2379(2)	5352(2)	579(1)	35(1)
S(1)	2322(1)	5161(1)	1577(1)	26(1)

Table 21 Bond lengths [Å] and angles [°] for **2.79**.

C(1)-O(1)	1.425(2)	C(11)-C(12)	1.387(3)
C(1)-C(2)	1.494(3)	C(11)-H(11A)	0.9500
C(1)-H(1A)	0.9900	C(12)-C(13)	1.403(3)
C(1)-H(1B)	0.9900	C(12)-H(12A)	0.9500
C(2)-C(3)	1.316(3)	C(13)-C(14)	1.435(2)
C(2)-H(2A)	0.9500	C(14)-C(15)	1.482(2)
C(3)-C(4)	1.511(2)	C(15)-O(1)	1.438(2)
C(3)-H(3A)	0.9500	C(15)-H(15A)	1.0000
C(4)-C(15)	1.540(2)	C(16)-N(1)	1.453(2)
C(4)-C(5)	1.574(2)	C(16)-H(16A)	0.9800
C(4)-H(4A)	1.0000	C(16)-H(16B)	0.9800
C(5)-C(17)	1.537(2)	C(16)-H(16C)	0.9800
C(5)-C(6)	1.547(2)	C(17)-O(2)	1.203(2)
C(5)-S(1)	1.8414(16)	C(17)-O(3)	1.326(2)
C(6)-C(7)	1.490(2)	C(18)-O(3)	1.442(2)
C(6)-H(6A)	0.9900	C(18)-H(18A)	0.9800
C(6)-H(6B)	0.9900	C(18)-H(18B)	0.9800
C(7)-C(14)	1.367(2)	C(18)-H(18C)	0.9800
C(7)-N(1)	1.382(2)	C(19)-C(20)	1.377(3)
C(8)-N(1)	1.379(2)	C(19)-C(24)	1.396(3)
C(8)-C(9)	1.400(3)	C(19)-S(1)	1.7704(17)
C(8)-C(13)	1.413(3)	C(20)-C(21)	1.393(3)
C(9)-C(10)	1.380(3)	C(20)-H(20A)	0.9500
C(9)-H(9A)	0.9500	C(21)-C(22)	1.378(3)
C(10)-C(11)	1.400(3)	C(21)-H(21A)	0.9500
C(10)-H(10A)	0.9500	C(22)-C(23)	1.380(3)

C(22)-H(22A)	0.9500	C(5)-C(6)-H(6B)	110.0
C(23)-C(24)	1.385(3)	H(6A)-C(6)-H(6B)	108.4
C(23)-H(23A)	0.9500	C(14)-C(7)-N(1)	109.90(16)
C(24)-H(24A)	0.9500	C(14)-C(7)-C(6)	125.58(16)
O(4)-S(1)	1.4410(14)	N(1)-C(7)-C(6)	124.41(16)
O(5)-S(1)	1.4369(13)	N(1)-C(8)-C(9)	129.13(18)
		N(1)-C(8)-C(13)	108.52(15)
O(1)-C(1)-C(2)	112.69(15)	C(9)-C(8)-C(13)	122.32(18)
O(1)-C(1)-H(1A)	109.1	C(10)-C(9)-C(8)	116.94(19)
C(2)-C(1)-H(1A)	109.1	C(10)-C(9)-H(9A)	121.5
O(1)-C(1)-H(1B)	109.1	C(8)-C(9)-H(9A)	121.5
C(2)-C(1)-H(1B)	109.1	C(9)-C(10)-C(11)	121.93(18)
H(1A)-C(1)-H(1B)	107.8	C(9)-C(10)-H(10A)	119.0
C(3)-C(2)-C(1)	123.07(16)	C(11)-C(10)-H(10A)	119.0
C(3)-C(2)-H(2A)	118.5	C(12)-C(11)-C(10)	121.06(19)
C(1)-C(2)-H(2A)	118.5	C(12)-C(11)-H(11A)	119.5
C(2)-C(3)-C(4)	121.69(17)	C(10)-C(11)-H(11A)	119.5
C(2)-C(3)-H(3A)	119.2	C(11)-C(12)-C(13)	118.59(19)
C(4)-C(3)-H(3A)	119.2	C(11)-C(12)-H(12A)	120.7
C(3)-C(4)-C(15)	108.28(14)	C(13)-C(12)-H(12A)	120.7
C(3)-C(4)-C(5)	117.90(14)	C(12)-C(13)-C(8)	119.14(17)
C(15)-C(4)-C(5)	110.01(13)	C(12)-C(13)-C(14)	134.66(17)
C(3)-C(4)-H(4A)	106.7	C(8)-C(13)-C(14)	106.14(16)
C(15)-C(4)-H(4A)	106.7	C(7)-C(14)-C(13)	107.29(16)
C(5)-C(4)-H(4A)	106.7	C(7)-C(14)-C(15)	122.78(16)
C(17)-C(5)-C(6)	109.61(14)	C(13)-C(14)-C(15)	129.93(16)
C(17)-C(5)-C(4)	113.42(14)	O(1)-C(15)-C(14)	108.37(15)
C(6)-C(5)-C(4)	108.78(13)	O(1)-C(15)-C(4)	109.93(13)
C(17)-C(5)-S(1)	109.87(11)	C(14)-C(15)-C(4)	112.26(14)
C(6)-C(5)-S(1)	106.86(11)	O(1)-C(15)-H(15A)	108.7
C(4)-C(5)-S(1)	108.08(11)	C(14)-C(15)-H(15A)	108.7
C(7)-C(6)-C(5)	108.36(14)	C(4)-C(15)-H(15A)	108.7
C(7)-C(6)-H(6A)	110.0	N(1)-C(16)-H(16A)	109.5
C(5)-C(6)-H(6A)	110.0	N(1)-C(16)-H(16B)	109.5
C(7)-C(6)-H(6B)	110.0	H(16A)-C(16)-H(16B)	109.5

N(1)-C(16)-H(16C)	109.5	O(5)-S(1)-O(4)	118.34(8)
H(16A)-C(16)-H(16C)	109.5	O(5)-S(1)-C(19)	107.71(8)
H(16B)-C(16)-H(16C)	109.5	O(4)-S(1)-C(19)	108.40(8)
O(2)-C(17)-O(3)	124.23(17)	O(5)-S(1)-C(5)	110.30(8)
O(2)-C(17)-C(5)	122.92(16)	O(4)-S(1)-C(5)	105.82(8)
O(3)-C(17)-C(5)	112.85(14)	C(19)-S(1)-C(5)	105.56(8)
O(3)-C(18)-H(18A)	109.5		
O(3)-C(18)-H(18B)	109.5		
H(18A)-C(18)-H(18B)	109.5		
O(3)-C(18)-H(18C)	109.5		
H(18A)-C(18)-H(18C)	109.5		
H(18B)-C(18)-H(18C)	109.5		
C(20)-C(19)-C(24)	121.93(16)		
C(20)-C(19)-S(1)	118.89(14)		
C(24)-C(19)-S(1)	118.96(14)		
C(19)-C(20)-C(21)	118.65(18)		
C(19)-C(20)-H(20A)	120.7		
C(21)-C(20)-H(20A)	120.7		
C(22)-C(21)-C(20)	120.1(2)		
C(22)-C(21)-H(21A)	120.0		
C(20)-C(21)-H(21A)	120.0		
C(21)-C(22)-C(23)	120.70(18)		
C(21)-C(22)-H(22A)	119.6		
C(23)-C(22)-H(22A)	119.6		
C(22)-C(23)-C(24)	120.36(19)		
C(22)-C(23)-H(23A)	119.8		
C(24)-C(23)-H(23A)	119.8		
C(23)-C(24)-C(19)	118.27(18)		
C(23)-C(24)-H(24A)	120.9		
C(19)-C(24)-H(24A)	120.9		
C(8)-N(1)-C(7)	108.13(15)		
C(8)-N(1)-C(16)	124.87(15)		
C(7)-N(1)-C(16)	126.64(16)		
C(1)-O(1)-C(15)	111.66(14)		
C(17)-O(3)-C(18)	114.94(14)		

Symmetry transformations used to generate equivalent atoms:

Table 22 Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 2.79. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	50(1)	35(1)	28(1)	-12(1)	-8(1)	-8(1)
C(2)	33(1)	39(1)	25(1)	-6(1)	-8(1)	-11(1)
C(3)	26(1)	32(1)	24(1)	-2(1)	-8(1)	-6(1)
C(4)	24(1)	26(1)	24(1)	-6(1)	-5(1)	-4(1)
C(5)	27(1)	22(1)	23(1)	-4(1)	-6(1)	-4(1)
C(6)	29(1)	29(1)	24(1)	-8(1)	-6(1)	-5(1)
C(7)	24(1)	32(1)	23(1)	-5(1)	-4(1)	-2(1)
C(8)	24(1)	34(1)	24(1)	-4(1)	-2(1)	-1(1)
C(9)	31(1)	44(1)	24(1)	-3(1)	-4(1)	2(1)
C(10)	39(1)	38(1)	31(1)	6(1)	-1(1)	2(1)
C(11)	39(1)	30(1)	40(1)	-1(1)	1(1)	-3(1)
C(12)	30(1)	33(1)	31(1)	-6(1)	0(1)	-4(1)
C(13)	24(1)	31(1)	24(1)	-4(1)	-1(1)	-2(1)
C(14)	25(1)	29(1)	24(1)	-5(1)	-4(1)	-3(1)
C(15)	28(1)	28(1)	25(1)	-6(1)	-4(1)	-6(1)
C(16)	32(1)	44(1)	26(1)	-12(1)	-8(1)	-4(1)
C(17)	27(1)	23(1)	26(1)	-4(1)	-6(1)	-6(1)
C(18)	39(1)	37(1)	36(1)	-11(1)	3(1)	2(1)
C(19)	24(1)	22(1)	26(1)	-1(1)	-6(1)	-4(1)
C(20)	30(1)	31(1)	35(1)	-10(1)	-4(1)	-4(1)
C(21)	45(1)	34(1)	47(1)	-15(1)	-15(1)	-6(1)
C(22)	32(1)	32(1)	50(1)	-1(1)	-14(1)	-10(1)
C(23)	27(1)	38(1)	39(1)	1(1)	-3(1)	-6(1)
C(24)	32(1)	31(1)	27(1)	-4(1)	-3(1)	-3(1)
N(1)	29(1)	35(1)	21(1)	-6(1)	-5(1)	-3(1)
O(1)	37(1)	29(1)	27(1)	-9(1)	-8(1)	-2(1)

O(2)	30(1)	43(1)	34(1)	-10(1)	-13(1)	4(1)
O(3)	29(1)	34(1)	25(1)	-7(1)	-3(1)	0(1)
O(4)	26(1)	29(1)	50(1)	-9(1)	-5(1)	-2(1)
O(5)	41(1)	32(1)	29(1)	0(1)	-15(1)	-7(1)
S(1)	24(1)	23(1)	28(1)	-3(1)	-8(1)	-3(1)

Table 23 Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **2.79**.

	x	y	z	U(eq)
H(1A)	182	-776	1382	43
H(1B)	1942	-473	801	43
H(2A)	10	1721	120	38
H(3A)	-39	3706	726	34
H(4A)	-162	2981	2410	29
H(6A)	3573	3237	3417	32
H(6B)	1593	3729	3469	32
H(9A)	3114	-1771	6412	42
H(10A)	2446	-4265	6546	48
H(11A)	1253	-4799	5327	46
H(12A)	687	-2848	3923	38
H(15A)	-340	393	2709	32
H(16A)	3463	2545	5025	50
H(16B)	4375	927	5621	50
H(16C)	2493	1465	5922	50
H(18A)	5446	1505	23	57
H(18B)	5516	301	1058	57
H(18C)	6537	1792	788	57
H(20A)	3023	6814	2804	38

H(21A)	5407	7900	3006	48
H(22A)	7910	7484	2163	47
H(23A)	8076	6041	1095	44
H(24A)	5701	5003	848	37

Table 24 Torsion angles [°] for **2.79**.

O(1)-C(1)-C(2)-C(3)	-7.7(3)
C(1)-C(2)-C(3)-C(4)	-5.5(3)
C(2)-C(3)-C(4)-C(15)	-15.8(2)
C(2)-C(3)-C(4)-C(5)	109.8(2)
C(3)-C(4)-C(5)-C(17)	-68.04(19)
C(15)-C(4)-C(5)-C(17)	56.74(18)
C(3)-C(4)-C(5)-C(6)	169.71(15)
C(15)-C(4)-C(5)-C(6)	-65.51(18)
C(3)-C(4)-C(5)-S(1)	54.04(18)
C(15)-C(4)-C(5)-S(1)	178.82(11)
C(17)-C(5)-C(6)-C(7)	-72.83(17)
C(4)-C(5)-C(6)-C(7)	51.69(18)
S(1)-C(5)-C(6)-C(7)	168.15(12)
C(5)-C(6)-C(7)-C(14)	-18.6(2)
C(5)-C(6)-C(7)-N(1)	157.34(17)
N(1)-C(8)-C(9)-C(10)	-176.20(18)
C(13)-C(8)-C(9)-C(10)	1.5(3)
C(8)-C(9)-C(10)-C(11)	-0.9(3)
C(9)-C(10)-C(11)-C(12)	0.0(3)
C(10)-C(11)-C(12)-C(13)	0.5(3)
C(11)-C(12)-C(13)-C(8)	0.0(3)
C(11)-C(12)-C(13)-C(14)	176.9(2)
N(1)-C(8)-C(13)-C(12)	177.08(16)
C(9)-C(8)-C(13)-C(12)	-1.0(3)
N(1)-C(8)-C(13)-C(14)	-0.6(2)
C(9)-C(8)-C(13)-C(14)	-178.71(17)
N(1)-C(7)-C(14)-C(13)	-0.9(2)
C(6)-C(7)-C(14)-C(13)	175.54(17)
N(1)-C(7)-C(14)-C(15)	178.56(16)
C(6)-C(7)-C(14)-C(15)	-5.0(3)
C(12)-C(13)-C(14)-C(7)	-176.3(2)
C(8)-C(13)-C(14)-C(7)	0.9(2)

C(12)-C(13)-C(14)-C(15)	4.3(3)
C(8)-C(13)-C(14)-C(15)	-178.48(18)
C(7)-C(14)-C(15)-O(1)	114.48(18)
C(13)-C(14)-C(15)-O(1)	-66.2(2)
C(7)-C(14)-C(15)-C(4)	-7.1(2)
C(13)-C(14)-C(15)-C(4)	172.21(17)
C(3)-C(4)-C(15)-O(1)	50.69(18)
C(5)-C(4)-C(15)-O(1)	-79.45(17)
C(3)-C(4)-C(15)-C(14)	171.39(15)
C(5)-C(4)-C(15)-C(14)	41.25(19)
C(6)-C(5)-C(17)-O(2)	0.5(2)
C(4)-C(5)-C(17)-O(2)	-121.33(18)
S(1)-C(5)-C(17)-O(2)	117.60(16)
C(6)-C(5)-C(17)-O(3)	-179.17(13)
C(4)-C(5)-C(17)-O(3)	59.04(18)
S(1)-C(5)-C(17)-O(3)	-62.03(16)
C(24)-C(19)-C(20)-C(21)	0.2(3)
S(1)-C(19)-C(20)-C(21)	-174.33(14)
C(19)-C(20)-C(21)-C(22)	-0.9(3)
C(20)-C(21)-C(22)-C(23)	0.7(3)
C(21)-C(22)-C(23)-C(24)	0.3(3)
C(22)-C(23)-C(24)-C(19)	-1.0(3)
C(20)-C(19)-C(24)-C(23)	0.7(3)
S(1)-C(19)-C(24)-C(23)	175.27(14)
C(9)-C(8)-N(1)-C(7)	178.01(18)
C(13)-C(8)-N(1)-C(7)	0.1(2)
C(9)-C(8)-N(1)-C(16)	-8.5(3)
C(13)-C(8)-N(1)-C(16)	173.63(17)
C(14)-C(7)-N(1)-C(8)	0.5(2)
C(6)-C(7)-N(1)-C(8)	-175.97(16)
C(14)-C(7)-N(1)-C(16)	-172.88(17)
C(6)-C(7)-N(1)-C(16)	10.6(3)
C(2)-C(1)-O(1)-C(15)	44.1(2)
C(14)-C(15)-O(1)-C(1)	169.55(14)
C(4)-C(15)-O(1)-C(1)	-67.43(18)

O(2)-C(17)-O(3)-C(18)	4.1(2)
C(5)-C(17)-O(3)-C(18)	-176.28(14)
C(20)-C(19)-S(1)-O(5)	139.60(14)
C(24)-C(19)-S(1)-O(5)	-35.12(16)
C(20)-C(19)-S(1)-O(4)	10.45(16)
C(24)-C(19)-S(1)-O(4)	-164.27(14)
C(20)-C(19)-S(1)-C(5)	-102.56(15)
C(24)-C(19)-S(1)-C(5)	82.72(15)
C(17)-C(5)-S(1)-O(5)	57.58(14)
C(6)-C(5)-S(1)-O(5)	176.42(11)
C(4)-C(5)-S(1)-O(5)	-66.65(13)
C(17)-C(5)-S(1)-O(4)	-173.30(11)
C(6)-C(5)-S(1)-O(4)	-54.46(13)
C(4)-C(5)-S(1)-O(4)	62.46(13)
C(17)-C(5)-S(1)-C(19)	-58.50(13)
C(6)-C(5)-S(1)-C(19)	60.34(13)
C(4)-C(5)-S(1)-C(19)	177.26(11)

Symmetry transformations used to generate equivalent atoms:

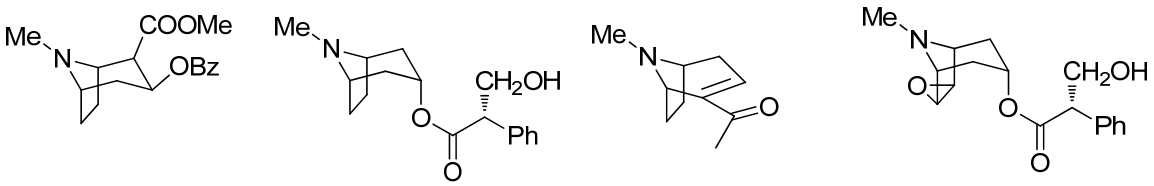
Chapter Three

Synthesis of 4-Methyl Substituted Pyranyl and Pyridinyl Scaffold

Background

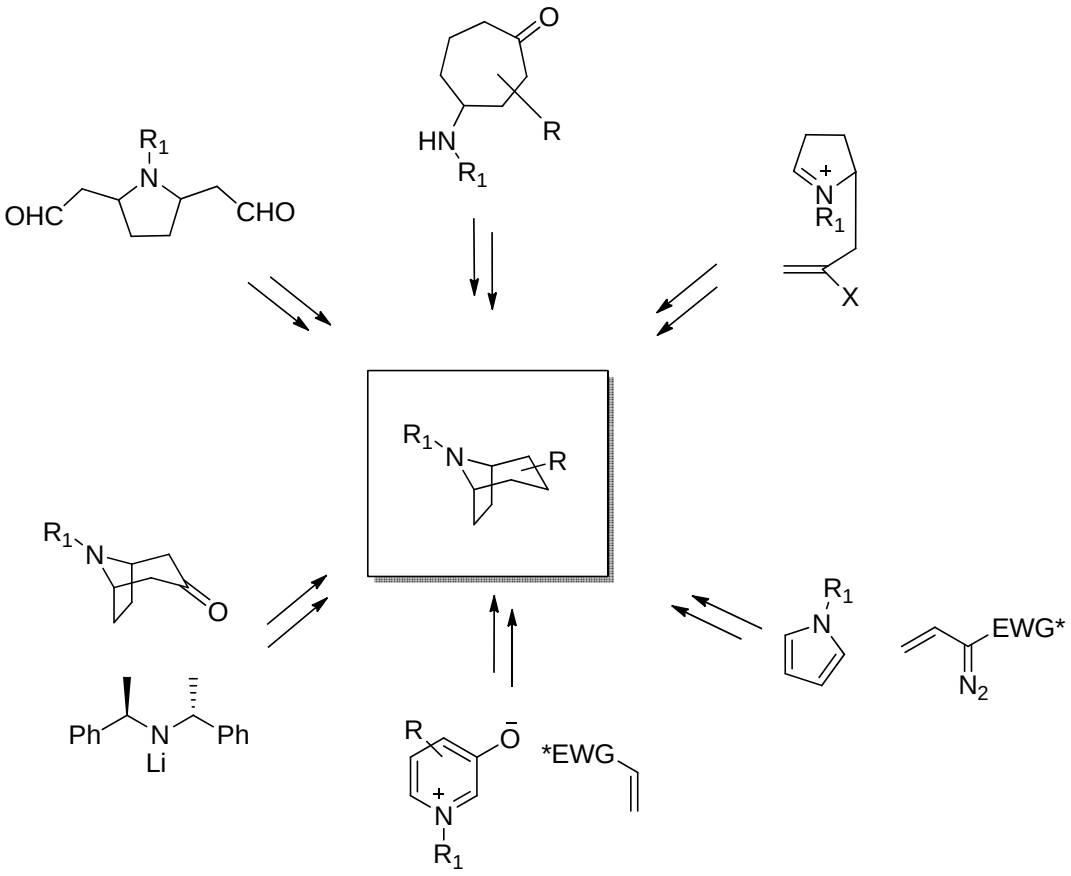
Tropane alkaloids (**Figure 15**) have attracted extensive attention in chemistry, pharmacology, and biology due to their unique 8-azabicyclo[3.2.1]octane skeleton and various biological activities.[1, 2]

Figure 15 A few typical tropane alkaloids



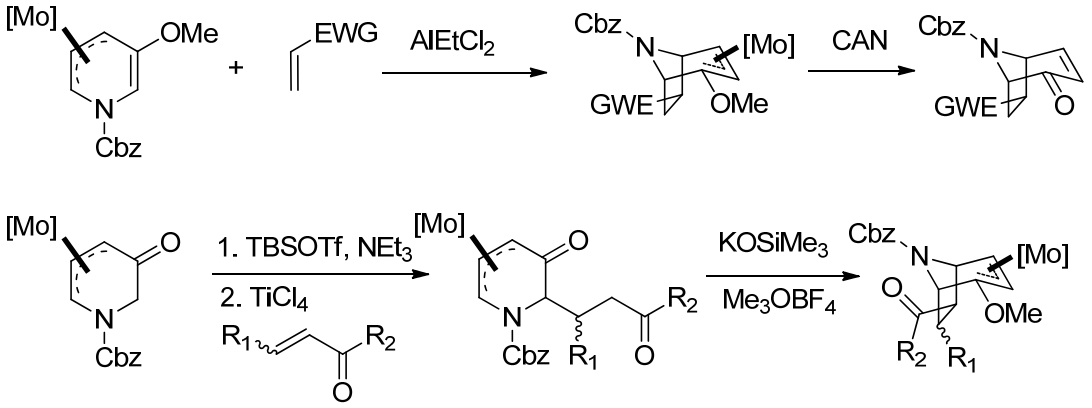
The tropane alkaloids have been enantioselectively synthesized (**Figure 1**) by intramolecular nucleophilic attack of the nitrogen on a carbonyl of a seven member ring derived from sugar,[3-5] intramolecular iminium ion cyclization from an amino acid such as glutamic acid,[6, 7] [4+3] cycloadditions of pyrroles with chiral vinyldiazomethanes,[8] [5+2] cycloadditions between chiral dienophiles and the betain of N-benzyl-3-hydroxypyridinium chloride,[9, 10] and the desymmetrization of tropinone with chiral base[11, 12] or the organocatalytic intramolecular aldol reaction of a *meso*-dialdehyde.[13]

Figure 16 Synthetic methods for tropane alkaloids



Recently, stoichiometric metal mediated reactions have been applied to the synthesis of tropane alkaloids. In 1995, Rigby's group first reported that Cr(0)-mediated [6+2] cycloadditions between azepine and chiral dienophiles followed by a ring contraction led to the synthesis of (+)-ferruginine.[14] The Liebeskind group has developed a chiral molybdenum scaffold for the construction of tropane alkaloids (**scheme 84**) by using a novel [5+2] reaction or a Mukaiyama aldol followed by a 1,5-Michael like reaction.[15-18]

Scheme 84 Construction of tropanes via [5+2] or Mukaiyama aldol followed by 1,5-Michael like reaction

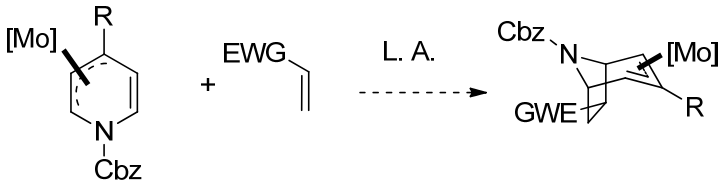


[Mo] = $TpMo(CO)_2$, Tp = hydridotrispyrazolylborate

Introduction

These scaffolds only led to the tropanes with 3-substituent. Since natural tropane alkaloids usually contain substituents on 4-carbon, a series of new scaffolds (**3.1 & 3.2, Scheme 85**) with a substituent on 4-carbon were designed to explore their reactivity and application in the synthesis of tropane alkaloids.

Scheme 85 [5+2] cycloaddition of the scaffolds 3.1 and 3.2



3.1: R = Me
3.2: R = OMe

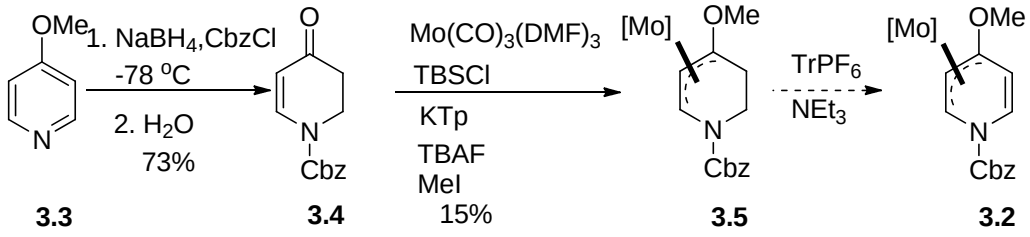
Herein are reported the synthesis of the scaffold **3.1** and the preliminary results of [5+2] cycloadditions.

Results and discussion

Synthesis of 4-methoxy scaffold 3.2

The synthesis of **3.2** (**Scheme 86**) started with the preparation of unsaturated ketone **3.4** from commercially available 4-methoxy pyridine **3.3**. At -78 ^{o}C in THF, $NaBH_4$ and CbzCl were used to transform **3.3** to **3.4** in 73%.[19] However, the metallation step provided **3.5** in a yield of 15% due to low conversion. Different protecting groups on nitrogen, such as ethoxycarbonyl and phenyloxycarbonyl, were investigated; but none showed improvement. Furthermore, a problem appeared in the dehydrogenation step. The common protocol failed to give the desired product **3.2,** leading instead to the demetallation and the regeneration of **3.4** .

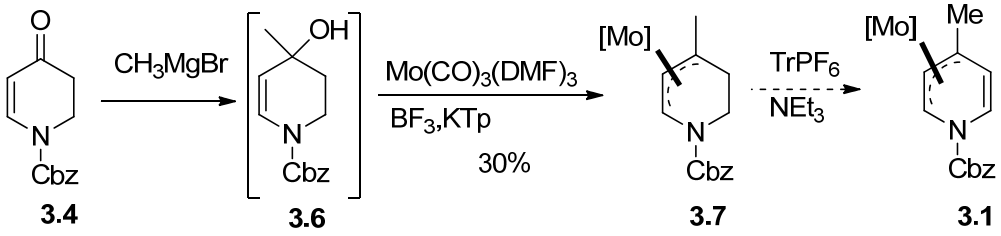
Scheme 86 Synthesis of 4-methoxy substituted scaffold 3.2



The first route to scaffold 3.1

Considering the possible complication caused by methoxy group, the 4-methyl scaffold **3.1**, which could be prepared from the same starting material **3.4** (**Scheme 87**), was chosen as a model. First the 1,2-addition of methyl Grignard reagent followed by acylation and metallation was investigated. Unfortunately, attempts at purification of the intermediate **3.6** led to complex mixtures due to its instability. Therefore, metallation without isolation and acylation of the intermediate **3.6** was studied, and proved to be effective. After extensive investigation, BF_3 was found to be a helpful additive increasing the yield from 18% to 30% for the two steps, presumably by increasing the leaving ability of hydroxyl group.

Scheme 87 Synthesis of 4-methyl substituted scaffold 3.1



With the scaffold **3.7** in hand, the dehydrogenation was carefully studied (**Table 25**). The reaction was found to proceed above -20 ^{o}C, leading only to the decomposition of the starting material. Varying bases and addition sequence of reactants provided no desired product **3.1**.

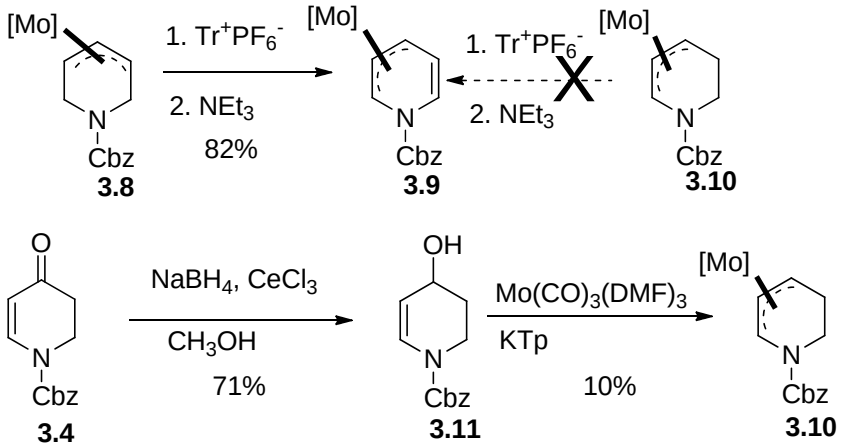
Table 25 Dehydrogenation with different reaction conditions[a]

Entry	Temp	Reagent	base	Yield
1	0 °C	$TrPF_6$	NEt_3	decompose
2	-78 °C	$TrPF_6$	NEt_3	N. R.
3	-20 °C	$TrPF_6$	NEt_3	decompose
4	0 °C	$TrPF_6$[b]	NEt_3	decompose
5	0 °C	$TrPF_6$	DABCO	decompose

[a] The scaffold **7** was dissolved in CH_2Cl_2, and then $TrPF_6$ was added at the indicated temperature. After the resulted mixture was stirred for 30 min, it was raised to room temperature. The base was added and stirred for another 1hour. [b] The scaffold **7** was added into the solution of $TrPF_6$.

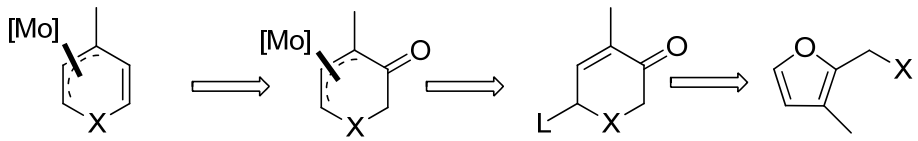
These results prompted an investigation into the effect of the methyl group at carbon 4. Consequently, scaffolds **3.8** and **3.10** were utilized to study dehydrogenation (**Scheme 88**). The scaffold **3.10** was synthesized via the Luche reduction of **3.4**, followed by the metallation. Although the scaffold **3.8** was readily dehydrogenized to yield **3.9,** the scaffold **3.10** unexpectedly failed under the same conditions. These results suggested that the failure of the transformation of **3.7** to **3.1** was caused by the position of allyl moiety instead of that of 4-methyl group.

Scheme 88 Examination of the effect of the 4-methyl



Given that the Achmatowicz reaction has also been used in the synthesis of scaffolds, a new route was chosen to construct the scaffold (**Scheme 89**). In order to explore the feasibility of the application of the Achomatowicz reaction to this system, both the oxygen and nitrogen scaffolds were established.

Scheme 89 Retrosynthesis of the scaffold 3.1



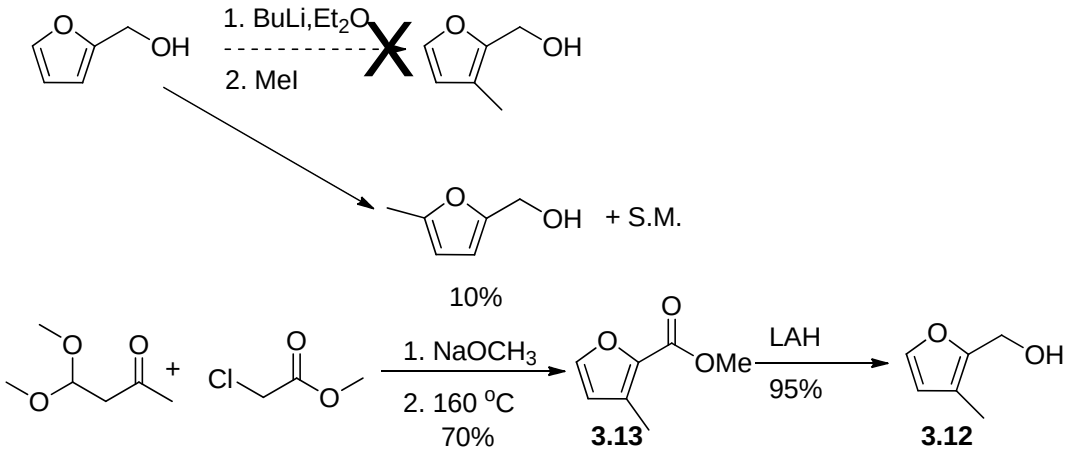
3.14: X=O
3.17: X=NCbz

Synthesis of the oxygen scaffold 3.14

At first, lithiation followed by methylation was examined to introduce the methyl to carbon 3 of the furan (**Scheme 90**).[20, 21] However, these experiments yielded mainly 5-methyl furfuryl alcohol with the desired 2-methyl derivative as a minor product. This

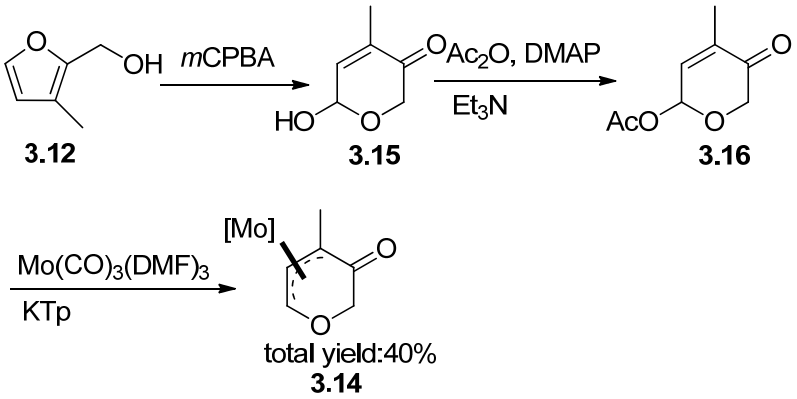
result is probably due to the strong directing effect of the furan oxygen. Therefore, the introduction of the methyl group had to be incorporated during the formation of the furan. Following the formation of **3.13**, a reduction cleanly led to the desired substituted furan **3.12**.

Scheme 90 Synthesis of 3-methyl substituted furfuryl alcohol 3.12



The synthesis of the oxygen scaffold **3.14** (**Scheme 91**) started with the Achmatowicz reaction of **3.12**. The intermediate **3.15** was directly acylated by Ac_2O/DMAP/Et_3N without purification to provide **3.16;** and, **3.16** was immediately converted into the oxygen scaffold **3.14** in 40% total yield.

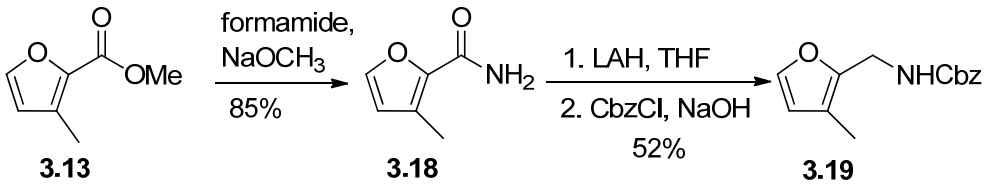
Scheme 91 Synthesis of oxygen scaffold 3.14



Synthesis of the scaffold 3.17

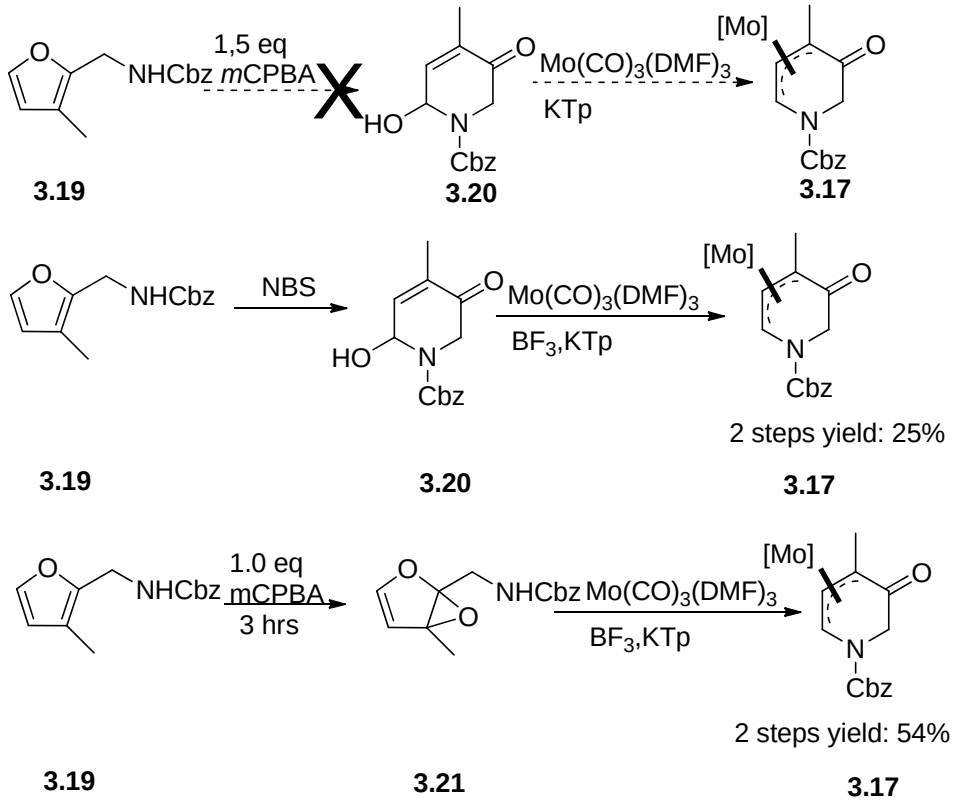
The desired metallation precursor **3.19** was prepared via the aminolysis of the intermediate **3.13** followed by reduction and protection with Cbz (**Scheme 92**).[22]

Scheme 92 Synthesis of N-Cbz-3-methyl furfuryl amine 3.19



The synthesis of **3.17** was first explored by using 1.5 eq *m*CPBA as the oxidant of the aza-Achmatowicz reaction of **3.19**. Metallation of the intermediate led to a complex mixture without desired **3.17**. This might be the result of the excess *m*CPBA, which converted the hydroxyl group into a good leaving group and led to aromatization. On the other hand, when intermediate **3.19** was subjected to oxidation by NBS, the desired intermediate **3.20** formed. However, the crude NMR implied the yield of **3.20** was so low that the total yield was only 25% after the metallation. During the study of *m*CPBA as the oxidant, 0.7 eq *m*CPBA was discovered to lead to the epoxidation of furan without rearrangement. We envisioned that the epoxide could be the potential precursor of the desired scaffold **3.17**. Moreover, the following study proved that it produced **3.17** after metallation. After carefully screening a variety of conditions, the yield was optimized to 54%.

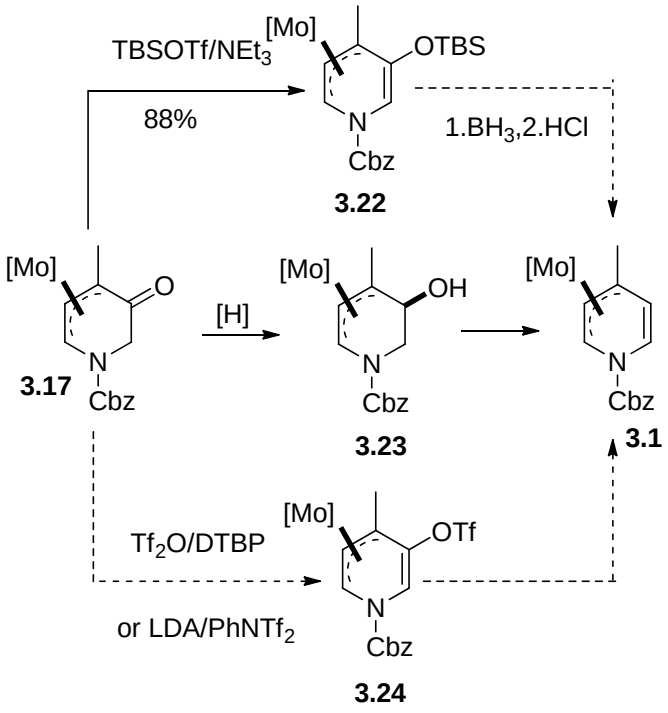
Scheme 93 Synthesis of the scaffold 3.17



Synthesis of the scaffold 3.1

In order to achieve the desired scaffold **3.1**, the following three routes were explored (**Scheme 94**). The scaffold **3.17** could be easily transformed to the corresponding silyl enol ether **3.22** by using TBSOTf/NEt_3.[18] However, the hydroboration-elimination failed in the next step.[23] Another route, which tried to transform **3.17** to the corresponding enol triflate **3.24** that could be reduced by a palladium catalyzed reaction, failed in the first step, where Tf_2O/DTBP caused extensive decomposition of **3.17** while LDA/$PhNTf_2$ could not effect the transformation.

Scheme 94 Possible route of transforming 17 to 1



The third route was the reduction of **3.17** followed by elimination. The results of different reducing agents were shown in **Table 26**. Common reducing agents, such as $NaBH_4$ and $LiAlH_4$, failed to reduce the carbonyl. SmI_2 successfully initiated a reaction, but the product had such a complicated HNMR that it could not be identified. Fortunately, a low yield of the desired compound **3.23** was obtained by using 10 eq BH_3-Me_2S, which led to the discovery of a better reducing agent for this reaction. After a series of experiments, DIBAL, which afforded a yield of 83%, was identified as the best reagents for the reduction.

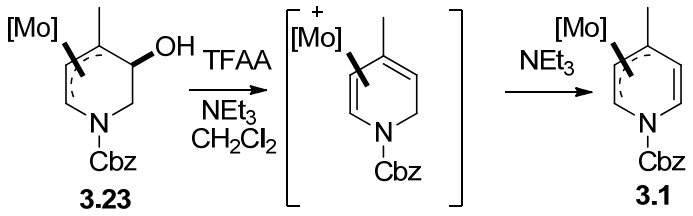
Table 26 Different reducing reagent for the reduction of 3.17[a]

Entry	Reagent	Yield of **3.23**
1	$NaBH_4$	N. R.
2	$LiAlH(t\text{-}BuO)_3$	N. R.
3	$LiAlH_4$	N. R.
4	3 eq BH_3-THF	N.R.
5	10 eq BH_3-Me_2S	14%
6	SmI_2/H_2O/TMEDA	Unknown product
7	1.6 eq DIBAL	83%

[a] The reactions were executed in THF.

The next step was to eliminate the hydroxyl group to provide the desired scaffold **3.1**. Unexpectedly, the elimination (**Scheme 95**), which had worked well in other systems, furnished **3.1** in a yield of 10%.[24] This low yield was probably caused by the low stability of the intermediate molybdenum cation.

Scheme 95 Synthesis of Scaffold 3.1



As shown in **Table 27**, different acylating reagents were investigated to effect the elimination. However, neither Ac_2O nor MsCl served to eliminate the hydroxyl group effectively. Thus, different conditions, including base and solvent, were investigated to tune up the reaction. Finally, CH_3CN, which raised the yield to 51%, was found effective

for the reaction, possibly because it was able to stabilize the necessary intermediate molybdenum cation.

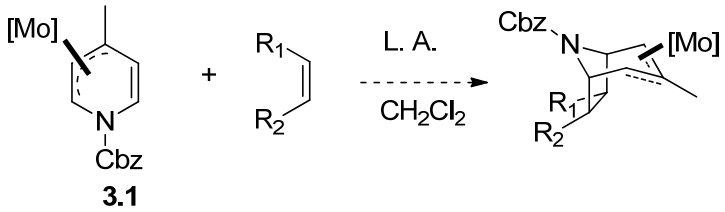
Table 27 Screening of the different conditions for elimination

Entry	Acylating Reagent	Base	Solvent	Yield of **3.1**(recovery of S.M.)
1	TFAA	NEt_3	CH_2Cl_2	10 % (40 %)
2	Ac_2O/DMAP	NEt_3	CH_2Cl_2	N. R.
3	MsCl/DMAP	NEt_3	CH_2Cl_2	N. R.
4	TFAA/DMAP	NEt_3	CH_2Cl_2	10 % (40%)
5	TFAA/DMAP	DABCO	CH_2Cl_2	12 % (40 %)
6	TFAA/DMAP	NEt_3	CH_3CN	51% (10%)
7	TFAA/DMAP	NEt_3	DMF	23%(30%)

Study on the [5+2] reaction of scaffold 3.1

With the scaffold **3.1** available, the [5+2] cycloaddition was explored with some common dienophiles. The results are summarized in **Table 28**. Such Lewis acid as $AlEt_2Cl$ and $AlEtCl_2$ failed to catalyze the cycloaddition while TMSOTf led to the decomposition of the scaffold **3.1.** Secondary amine catalyzed [5+2] cycloaddition was also examined because a Lewis acid might also coordinate to the Cbz protecting group in the scaffold so that the reactivity decreased, but this attempt also failed.

Table 28 Study on the [5+2] cycloaddition of scaffold 3.1



Entry	R1	R2	L.A.(eq)	Yield
1	CH_3CO	H	$AlEt_2Cl$(1.0)	N. R.
2	CH_3CO	H	$AlEtCl_2$(1.0)	N. R.
3	CH_3CO	H	TMSOTf(1.0)	Decomposition
4	OCN(Me)CO		$AlEt_2Cl$(1.0)	N. R.
5	OCN(Me)CO		$AlEtCl_2$(1.0)	N. R.
6	OCN(Me)CO		TMSOTf(1.0)	Decomposition
7[a]	HCO	H		N. R.

[a] It was executed in CH_3OH catalyzed by proline (0.5eq).

Conclusion

A practical synthesis of the scaffold **3.1** was established from inexpensive starting material, while the synthesis **3.2** was explored. The synthesis of scaffold **3.1** demonstrated epoxide **3.21** as a novel, effective metallation precursor and DIBAL was an especially useful reducing reagent. Preliminary study was conducted on the reactivity of scaffold **3.1**, though [5+2] cycloadditions failed in this system.

References

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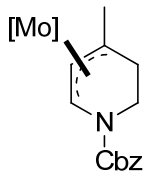
Experimental Section

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(η-2,3,4)-1-benzyloxycarbonyl-4-methyl-5,6-dihydro-2*H*-pyridin-2-yl]molybdenum, (±)-**3.7**

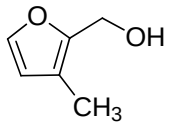


3.7

To a solution of **3.4**(1 g, 4.3 mmol, 1 equiv.) was added MeMgBr(1.73 mL, 5.2 mmol, 1.2 equiv.) at room temperature. The mixture was stirred for 2 hours, quenched with saturated NH_4Cl solution, extracted with EtOAc and dried with Na_2SO_4. After concentration, the product was dissolved in 5 mL DCM directly without purification. The solution was added via syringe to a solution of $Mo(CO)_3(DMF)_3$ (2.1 g, 5.2 mmol, 1.2 equiv) in 15 mL dry, degassed CH_2Cl_2 in a Schlenk flask under dry argon. Then BF_3-OEt (0.81 g, 5.2 mmol, 1.2 equiv) was added. After stirring overnight, potassium hydridotris(1-pyrazolyl)borate (KTp) (1.44 g, 5.6 mmol, 1.3 equiv) was added to the solution in portions, and stirring was continued for 40 minutes. 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 (1:2.3) afforded the pure molybdenum complex **3.7** (770 mg, 30%) as a yellow solid.

(±)-**3.7:** TLC: R_f= 0.30 (EtOAc/hexane, 1:4). IR (cm^{-1}): 1922 (s), 1837 (s), 1698 (s), 1490 (m), 1447 (s), 1409 (s). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8,44-8.48 (m, 1 H), 8.19-8.20 (m, 0.5 H), 7.75-7.77 (m, 1 H), 7.70-7.74 (m, 0.5 H), 7.57-7.62 (m, 2, H), 7.42-7.47 (m, 1 H), 7.28-7.38 (m, 4 H), 7.16 - 7.22 (m, 1 H), 6.91 (d, *J* = 6.0 Hz, 0.5 H), 6.74 (d, *J* = 6.6 Hz, 0.5 H), 6.21 – 6.27 (m, 1.5 H), 6.12-6.16 (m, 1 H), 6.06-6.09 (m, 0.5 H), 5.28 (d, *J* = 12.3 Hz, 0.5 H), 5.20 (d, *J* = 12.3 Hz, 0.5 H), 5.19 (s, 1 H), 3.78 (d, *J* = 6.3 Hz, 0.5 H), 3.67 (d, *J* = 6.0 Hz, 0.5 H), 3.30 – 3.43 (m, 1 H), 2.14-2.39 (m, 3 H), 2.08 (s, 1.5 H), 2.06 (s, 1.5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 229.6, 228.84, 228.6, 228.80, 156.3, 156.0, 147.2, 147.1, 145.2, 145.0, 142.3, 141.3, 137.1, 136.8, 136.76, 136.67, 136.56, 136.2, 136.1, 134.4, 128.7, 128.6, 128.4, 128.3, 128.13, 128.09, 128.03, 128.00, 127.96, 118.3, 117.7, 105.8, 105.7, 105.23, 105.20, 89.6, 87.9, 80.5, 78.4, 68.0, 67.6, 64.6, 63.9, 43.6, 43.4, 40.9, 40.6, 39.00, 38.97, 32.2, 31.9, 30.0, 29.7, 26.9, 26.8. HRMS (ESI) Calcd for $C_{25}H_{27}BMoN_7O_4$ $[M + H]^+$: 598.1266. Found: 598.1268.

(3-Methylfuran-2-yl)methanol, 3.12



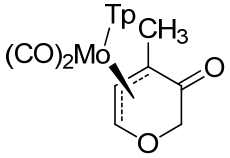
3.12

A solution of methyl 3-methylfuran-2-carboxylate (3.50 g, 25 mmol, 1.0 equiv) in THF (80 mL) was added slowly to a solution of $LiAlH_4$ (0.797 g, 21 mmol, 0.84 equiv) in THF (40 mL) in a three-neck flask fitted with a reflux condenser. After stirring the reaction mixture at room temperature for 3 hours, 25 mL of H_2O was carefully added into

the mixture at 0 °C, which led to the immediate appearance of a white precipitate. The mixture was filtered, and the white precipitate was washed with EtOAc three times. The layers were separated and the aqueous layer was extracted with EtOAc three times. The organic layer was collected, washed with brine, dried on Na_2SO_4 and concentrated under reduced pressure to afford the product **3.12** (2.66 g, 95%) as colorless oil, which was used without further purification.

3.12: TLC: R_f= 0.45 (25% EtOAc in hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (d, *J* = 1.6Hz, 1 H), 7.20 (d, *J* = 1.6 Hz, 1 H), 4.55 (s, 2 H), 2.04 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.2, 141.5, 117.5, 113.0, 55.1, 9.6.

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(η-2,3,4)-4-methyl-5-oxo-5,6-dihydro-2*H*-pyran-2-yl]molybdenum, (±)-**3.14**



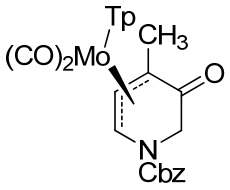
(±)-**3.14**

(3-methylfuran-2-yl)methanol (2.62 g, 23.4 mmol, 1.0 equiv) was dissolved in 20 mL of CH_2Cl_2 and cooled to 0 °C. Then, 77% *m*-CPBA (5.49 g, 24.5 mmol, 1.05 equiv) was added in portions to keep the temperature below 5 °C. 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 °C, 4-(Dimethylamino)-pyridine (0.86 g, 7.02 mmol, 0.3 equiv), triethylamine (3.55 g, 35.1 mmol, 1.5 equiv), and Ac_2O (3.58 g, 35.1 mmol, 1.5 equiv) were added in succession. The mixture was stirred at 0 °C for 20 minutes, and then

warmed to room temperature for 40 minutes. The mixture was washed with brine, dried on Na_2SO_4, and degassed for 20 minutes with dry argon. This solution was added via syringe to a solution of $Mo(CO)_3(DMF)_3$ (11.21g, 28.1 mmol, 1.2 equiv) in 75 mL dry, degassed CH_2Cl_2 in a Schlenk flask under dry argon. After stirring for 1 hour, potassium hydridotris(1-pyrazolyl)borate (KTp) (7.67 g, 30.42 mmol, 1.3 equiv) was added to the solution in portions, and stirring was continued for 40 minutes. 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 (1:2.3) afforded the pure molybdenum complex **3.14** (4.57 g, 41% over 3 steps) as an orange solid.

(±)-**3.14:** TLC: R_f = 0.31 (EtOAc/hexane, 1:2.3). IR (cm^{-1}): 3123 (w), 2964 (w), 2922 (w), 2490 (m), 1949 (s), 1864 (s), 1737 (m), 1637 (s), 1505(m). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (d, *J* = 1.6 Hz, 1 H), 7.72 (d, *J* = 2.4 Hz, 1 H), 7.65 (d, *J* = 2.0 Hz, 1 H), 7.63 (d, *J* = 2.0 Hz, 1 H), 7.47 (d, *J* = 2.0 Hz, 1 H), 7.45 (d, *J* = 1.6 Hz, 1 H), 7.22 (d, *J* = 4.8 Hz, 1 H), 6.28 (t, *J* = 2.0 Hz, 1 H), 6.24 (t, *J* = 2.0 Hz, 1 H), 6.21 (t, *J* = 2.0 Hz, 1 H), 4.50 (d, *J* = 4.8 Hz, 1 H), 3.65 (d, *J* = 18.0 Hz, 1 H), 3.50 (d, *J* = 18.0 Hz, 1 H), 1.80 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 230.4, 223.8, 188.2, 146.8, 146.7, 140.9, 136.9, 136.3, 134.6, 106.1, 106.0, 105.7, 101.4, 86.3, 76.8, 66.6, 17.3. HRMS (ESI) Calcd for $C_{17}H_{18}BMoN_6O_4$ $[M + H]^+$: 479.0531. Found 479.0528.

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(η-2,3,4)-1-benzyloxycarbonyl-4-methyl-5-oxo-5,6-dihydro-2*H*-pyridin-2-yl]molybdenum, (±)-**3.17**



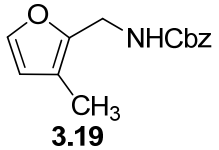
(±)-**3.17**

Benzyl (3-methylfuran-2-yl)methylcarbamate **3.19** (1.00 g, 4.08 mmol, 1.0 equiv) was dissolved in 20 mL CH_2Cl_2 and cooled to 0 ^oC. *m*-CPBA (77% purity, 894 mg, 4.08 mmol, 1.0 equiv) was added in 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 removed *via* filtration and the filtrate was degassed for 20 minutes with dry argon. This solution was added *via* syringe to a solution of $Mo(CO)_3(DMF)_3$ (1.95 g, 4.90 mmol, 1.2 equiv) in 75 mL dry, degassed CH_2Cl_2 in a Schlenk flask under dry argon. After stirring at room temperature for 1 hour, potassium hydridotris(1-pyrazolyl)borate (KTp) (1.31 g, 5.2 mmol, 1.3 equiv) was added to the solution in portions, and stirring was continued for 40 minutes. The reaction mixture was filtered through a short plug of silica gel, eluting with EtOAc. Purification by flash chromatography eluting with EtOAc/hexane (1:2.3) afforded the pure molybdenum complex **3.17** (1.34 g, 54%) as an orange solid.

(±)-**3.17:** TLC: R_f= 0.34 (EtOAc/hexane, 1:2.3). IR (cm^{-1}): 1953 (s), 1868 (s), 1710 (s), 1640 (m), 1505 (m), 1432 (m), 1409 (s). ^1H NMR (400 MHz, $CDCl_3$): δ 8.40 (s, 0.33 H), 8.39 (d, *J* = 2.0 Hz, 0.67 H), 7.80 (d, *J* = 2.0 Hz, 0.67 H), 7.71 (s, 0.33 H), 7.70 (d, *J* =1.6 Hz, 0.67 H), 7.66 - 7.62 (m, 2H), 7.54 (s, 1 H), 7.46 - 7.31 (m, 6.33 H), 7.18 (d, *J* = 6.8 Hz, 0.67 H), 6.30 (t, *J* =2.0 Hz, 0.67 H), 6.23 – 6.20 (m, 2.33 H), 5.31 – 5.16 (m, 2 H), 4.54 (d, *J* = 6.4 Hz, 0.67 H), 4.47 (d, *J* = 6.8 Hz, 0.33 H), 3.53 (d, *J* = 19.2 Hz, 0.67

H), 3.50 (d, J = 20.0 Hz, 0.33 H), 3.33 (d, J = 19.6 Hz, 0.33 H), 3.30 (d, J =19.2 Hz, 0.67 Hz), 1.83 (s, 2 H), 1.80 (s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 229.4 (230.5), 224.1 (223.6), 187.5 (187.7), 154.4 (153.7), 146.7 (146.5), 146.3 (146.6), 141.3 (140.8), 136.9, 136.3, 134.6 (135.7), 128.7 (128.9), 128.4 (128.5), 128.3, 127.8 (128.1), 126.0, 106.1, 105.9, 105.6 (105.7), 86.4 (87.0), 78.4 (77.5), 67.9 (68.2), 48.1 (48.2), 17.8 (17.7). HRMS (ESI) Calcd for $C_{25}H_{25}BMoN_7O_5$ $[M + H]^+$: 612.1059. Found: 612.1066.

Benzyl (3-methylfuran-2-yl)methylcarbamate, 3.19



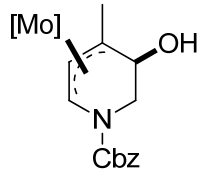
3.19

A solution of methyl 3-methylfuran-2-carboxylate**Error! Bookmark not defined.** (3.50 g, 25 mmol, 1.0 equiv) and NaOMe (5.4 g, 100 mmol, 4.0 equiv) in formamide (125 mL) was heated to 100 ^{o}C and stirred for 45 min. The reaction mixture was poured into ice-water (50 mL) and extracted with EtOAc. The extract was dried and concentrated to give a slightly yellow solid. The solid and $LiAlH_4$ (2.40 g, 62.5 mmol, 2.5 equiv) were dissolved in THF (100 mL) and stirred at 60 ^{o}C for 6 hours. After cooling, 50 mL EtOAc and 50 mL water were added to quench the reaction at 0 ^{o}C. The resulting precipitate was removed by filtration, the layers were separated and the aqueous layer was extracted with EtOAc three times. The combined organic layers were dried over MgSO4, filtered and concentrated down to approximately 50 mL of solution. Into this was added 18 mL of 5% NaOH solution. The mixture was cooled to 0 ^{o}C and CbzCl (5.54 g, 32.5 mmol, 1.3 equiv) was added dropwise. The reaction mixture was warmed to room temperature and

stirred for 30 min. After washing with brine, the mixture was dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography, eluting with 15% EtOAc in hexanes to afford the product (2.94 g, 48%) as a colorless oil.

3.19: TLC: R_f = 0.28 (15% EtOAc in hexanes). IR (cm^{-1}): 3416 (w), 3331 (m), 2930 (m), 1698 (s), 1513 (s), 1455 (s). ^1H NMR (400 MHz, $CDCl_3$) δ 7.38 - 7.32 (m, 5 H), 7.26 (s, 1 H), 6.19 (d, *J* = 0.9 Hz, 1 H), 5.11 (br, s, 3 H), 4.32 (d, *J* = 5.4 Hz, 2 H), 2.04 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 156.1, 146.6, 141.2, 136.4, 128.4, 128.0, 116.9, 113.0, 66.7, 35.9, 9.6. HRMS (ESI) Calcd for $C_{14}H_{16}NO_3$ [M + H^+]: 246.1124. Found 246.1121.

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(η-2,3,4)-1-benzyloxycarbonyl-4-methyl-5-hydroxy-5,6-dihydro-2*H*-pyridin-2-yl]molybdenum, (±)-**3.23**



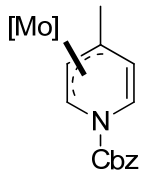
3.23

To a solution of (±)-**3.17** (500 mg, 0.84 mmol, 1.0 equiv) in THF (30 mL) was added DIBAL (1.0 M in hexane, 1.3 mL, 1.3 mmol, 1.6 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 20 minutes, and then quenched with potassium sodium tartrate tetrahydrate (740 mg, 2.52 mmol, 3.0 equiv) and H_2O (10 mL). The mixture was poured into a separatory funnel containing EtOAc (15 mL) and the layers were separated. The aqueous layer was extracted with EtOAc (2 x 25 mL), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Flash chromatography over silica gel

with hexanes-EtOAc (2:1) afforded (±)–**3.23** (416 mg, 0.71 mmol, 83%) as an orange solid.

(±)-**3.23:** TLC: R_f = 0.32 (EtOAc/hexane, 1:2.2). IR (cm^{-1}): 3459 (w), 2961 (w), 2482(m), 1930 (s), 1845 (s), 1695 (s), 1505 (m). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.39-8.41 (m, 1 H), 7.89-7.91 (m, 1.6 H), 7.58-7.64 (m, 2.4 H), 7.30 - 7.46 (m, 6 H), 6.99 (d, *J* = 6.0 Hz, 0.6 H), 6.83 (d, *J* =6.4 Hz, 0.4 H), 6.18 – 6.27 (m, 3 H), 5.19 – 5.30 (m, 2 H), 4.24-4.34 (m, 1 H), 3.90 (dd, *J* = 12.8, 7.2 Hz, 0.4 H), 3.83 (dd, *J* = 12.8, 7.2 Hz, 0.4 H), 3.70 (d, *J* = 6.0 Hz, 0.6 H), 3.61 (d, *J* = 6.0 Hz, 0.4 H), 2.54-2.61 (m, 1 H), 2.16 (s, 1.8 H), 2.13 (s, 1.2 H), 1.95-2.05 (m, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 233.0, 232.3, 228.5, 228.3, 155.6, 155.4, 146.6, 146.5, 146.2, 146.0. 140.9, 140.1, 136.8, 136.2, 128.47, 128.53, 128.2, 128.1, 128.1, 127.9, 105.8, 105.7, 105.31, 105.26, 96.9, 95.5, 78.0, 77.2, 76.6 72.1, 71.9, 68.0, 67.8, 66.1, 46.5, 46.4, 23.5, 23.4. HRMS (ESI) Calcd for $C_{25}H_{25}BMoN_7O_5$ $[M - H]^+$: 612.1059. Found: 612.1073.

(±)-Dicarbonyl[hydridotris(1-pyrazolyl)borato][(η-2,3,4)-1-benzyloxycarbonyl-4-methyl-2*H*-pyridin-2-yl]molybdenum, (±)-**3.1**



3.1

To a solution of (±)-**3.23** (500 mg, 0.84 mmol, 1.0 equiv) in ACN (20 mL) was added TEA (126 mg, 1.26 mmol, 1.5 equiv) and TFAA (206 mg, 1.00 mmol, 1.2 equiv). The reaction mixture was stirred at 0 °C for 1 hour, and then concentrated to remove ACN

and excess TEA. The organic solution was concentrated for chromatography. Flash chromatography over silica gel with hexanes-EtOAc (3:1) afforded (±)–**3.1** (249 mg, 0.43 mmol, 51%) as a yellow solid with (±)-**3.23** (50 mg).

(±)-**3.1:** TLC: R_f = 0.62 (EtOAc/hexane, 1:2.5). IR (cm^{-1}): 2957 (w), 2926 (m), 2474(m), 1918 (s), 1833 (s), 1710 (s), 1621 (s). ^1H NMR (400 MHz, $CDCl_3$): δ 8.77 (br s, 0.7 H), 8.23 (br s, 0.7 H), 8.21 (br s, 0.3 H), 7.99 (br s, 0.3 H), 7.81 (br s, 1 H), 7.63 (m, 1 H), 7.60 (m, 0.7 H), 7.33-7.53 (m, 6.3 H), 7.18 (d, *J* = 5.6 Hz, 0.7 H), 6.99 (d, *J* = 6.0 Hz, 0.3 H), 6.53 (d, *J* = 8.4 Hz, 0.3 H), 6.40 (d, *J* = 7.2 Hz, 0.7 H), 6.29 (br s, 0.7 H), 6.15 – 6.19 (m, 2 H), 5.81 (br s, 0.3 H), 5.68 (d, *J* = 7.2 Hz, 0.3 H), 5.52 (d, *J* = 7.6 Hz, 0.7 H), 5.38 (s, 0.7 H), 5.33 (d, *J* = 16.0 Hz, 1.3 H), 3.20 (d, *J* = 6.4 Hz, 0.7 H), 3.06 (d, *J* = 5.6 Hz, 0.3 H), 2.48 (s, 2.1 H), 2.44 (s, 0.9 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 236.3, 235.1, 224.9, 224.1, 153.2, 153.0, 146.3, 145.4, 143.8, 143.5, 143.4, 136.3, 136.2, 135.8, 135.6, 135.1, 134.2, 129.1, 128.7, 128.7, 128.6, 128.3, 128.0, 117.6, 116.9, 116.5, 115.8, 105.7, 105.3, 105.1, 90.2, 87.9, 84.7, 82.5, 69.3, 68.5, 58.7, 57.6, 23.9, 23.7.