NEW CHIRAL MOLYBDENUM METATHESIS CATALYSTS; APPLICATION TO THE ENANTIOSELECTIVE PREPARATION OF CYCLIC AMINES.

by

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Submitted to the Department of Chemistry in Partial Fulfillment of the Requirements for the Degree of

DOCTOR OF PHILOSOPHY at the

MASSACHUSETTS INSTITUTE OF TECHNOLOGY June 2004

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“…la chimie est aussi un art. De fait elle façonne des mondes entièrement nouveaux qui n'existaient pas avant d'avoir été mis en forme par la main du chimiste…”

– J. M. Lehn
sigh... you know things are bad when you confuse your lab key with your apartment key...
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ABSTRACT

CHAPTER 1:
Optically pure (R)-5,5',6,6',7,7',8,8'-octahydro-1,1'-bi-2-napthol was derivatized with mesityl groups in the 3 and 3' positions to give (R)-MES2BtetH2 1.43. Addition of the dipotassium salt of 1.43 to (Ar,F,N)Mo(CHCMe2Ph)(OTf)2(DME) yielded [(Ar,F,N)Mo((R)-MES2Btet)(CHCMe2Ph)(THF)], (R)-1.44a. This material was studied in detail by variable temperature 1H NMR spectroscopy with and without solvent additives (THF, DMF and MeCN). An X-ray study of (R)-1.44a showed it to crystallize as the THF adduct of an anti-alkylidene, in a distorted trigonal bipyramid. Complex (R)-1.44a was shown to be an active and selective catalyst for olefin metathesis for representative ARCM transformations to form dihydrofurans.

CHAPTER 2:
The first catalytic asymmetric ring-closing metathesis (ARCM) method for the synthesis of nitrogen-containing heterocycles was developed; this was accomplished via Mo-catalyzed desymmetrization of unsaturated prochiral amines to afford tetrahydropyridines (2.68a-e). The selectivity of this transformation was sensitive to the olefin substitution pattern of the prochiral amine. However, this novel method was also applicable for the formation seven- (2.84), and eight-membered (2.84) rings in high yield, with exceptional enantioselectivity. Importantly, this method remained highly effective when performed without solvent. Several chiral benzoazepines (2.95a-c) were also prepared via Mo-catalyzed ARCM. In these latter cases, the steric size of groups attached to the prochiral carbon was observed to affect both the rate and selectivity of ARCM. Related benzoazocine precursors (2.97 and 2.100) could not be successfully desymmetrized to cyclic amines. A prochiral tetaene (2.101) was rapidly transformed into a spirocyclic-benzazepine (2.103) by tandem ARCM/RCM with good enantioselectivity. Carbocyclic amines (2.105a-f) were also efficiently synthesized via ARCM with good enantioselectivity. Several of these enantioselective transformations were equally effective when catalyzed by catalysts prepared in situ.
CHAPTER 3:

Three new poly(styrene) supported chiral Mo-based catalysts were prepared. Two of the supported complexes were biphenolate-based ((S)-3.75 and (S)-3.76) while the third was binaptholate-based ((R)-3.77). Additionally, a new support was developed, wherein the Mo–alkylidene could be supported in tandem with polymer generation. Several poly(norbornene) supported catalysts were also prepared, with various cross-linking levels. It was found that the activity and selectivity of these poly(norbornene) supported systems was greatest with low cross-linking levels (8 %), such as for (S)-3.88d. Two more lightly cross-linked poly(norbornene) complexes were prepared with distinct imido groups, (S)-3.89 and (S)-3.90. The ability of these polymer-bound chiral complexes to promote an assortment of asymmetric ring-closing (ARCM) and ring-opening (AROM) metathesis reactions was studied. In many instances, the levels of reactivity and enantioselectivity observed were competitive with the analogous homogeneous catalysts. In all cases, the optically enriched products obtained through the use of the above supported complexes, after simple filtration and removal of the polymeric chiral Mo complexes, were found to contain significantly lower levels of metal impurities compared to products synthesized with the corresponding homogeneous catalysts.

APPENDIX A:

Several N-alkenyl-7-aza-norbornobenzodienes were prepared (A.28 – A.30) and studied in the context of AROM/RCM transformations. Complete consumption of these materials was only obtained with unusually high catalyst loadings (≥ 20 mol %). All products obtained (A.31 – A.33) were highly unstable and efforts to characterize and/or derivatize these products failed. Various N-alkenyl-8-aza-bicyclo[3.2.1]oct-6-enes (A.37 – A.39, A.45 – A.47, A.53 and A.54) were also prepared. However, as yet no successful application of AROM/RCM to these substrates has been achieved.

Thesis Supervisor: Dr. Richard R. Schrock
Title: Frederick G. Keyes Professor of Chemistry
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LIST OF ABBREVIATIONS

Ac  acetyl, -C(O)CH₃
Ad  1-adamantyl
Allyl -CH₂CH=CH₂
Anal Analysis
Ar  aryl
Ar_C₃  2,6-Cl₂C₆H₃
Ar_pr  2,6-(i-Pr)₂C₆H₃
b  broad
Bn  benzyl, -CH₂(C₆H₅)
BOC tert-butylcarboxylate, -CO₂C(CH₃)₃
BSA N,O-bis(trimethylsilyl)acetamide
n-Bu  n-butyl, -CH₂CH₂CH₂CH₃
t-Bu  tert-butyl, -(CH₃)₃
BuLi  n-butyllithium
t-BuLi  t-butyllithium
Calcd calculated
CBz  benzylcarboxylate, -CO₂CH₂Ph
conv conversion
Cy  cyclohexyl, -C₆H₁₁
d  doublet
dba  dibenzylideneacetone, (C₆H₅CH=CH)₂CO
DCC  dicyclohexylcarbodiimide
DCU  dicyclohexylurea
deg, °  degree(s)
DMF  dimethylformamide
equiv equivalent(s)
eq  equation(s)
EI  Electron Impact
Et  ethyl
ESI  Electro-Spray Ionization
g  gram(s)
GC  Gas Chromatography
h  hour(s)
HPLC High Performance Liquid Chromatography
HRMS High Resolution Mass Spectrometry
IMES 1,3-bis-(2,4,6-trimethyl-phenyl)-imidazolene
J  coupling constant in Hertz
m  multiplet
Me  methyl
MeCN  acetonitrile
MES  mesityl, 2,4,6-trimethyl-phenyl, -2,4,6-Me₃C₆H₂
MeLi  methyl lithium
min  minute(s)
MOM methoxymethylene, -CH₂OCH₃
nd not determined
Nf nonfluorobutanesulfonyl, -SO₂(CF₂)₃CF₃
NMR Nuclear Magnetic Resonance
Ns nosyl, -SO₂-p-(NO₂)C₆H₄
Ph phenyl, -C₆H₅
PMB para-methoxybenzyl, -CH₂(C₆H₄)OCH₃
ppm parts per million
i-Pr iso-propyl
n-Pr n-propyl
q quartet
(rac) racemic
s singlet
sep septet
SES trimethylsilylethylsulfonyl, -SO₂CH₂CH₂SiMe₃
TBS tert-butyldimethylsilyl, -SiMe₂(CMe₃)
TBDPS tert-butyldiphenylsilyl, -SiPh₂(CMe₃)
TES triethylsilyl, -SiEt₃
Tf triflate, -SO₂CF₃
TFA trifluoroacetyl, -C(O)CF₃
TIPS tri-iso-propylsilyl, -Si(i-Pr)₃
TMEDA tetramethylethylenediamine
TMSE trimethylsilylethylene, -CH₂CH₂SiMe₃
THF tetrahydrofuran
TMS trimethylsilyl, -SiMe₃
TMSCI trimethylsilylchloride
Tr trityl, -C(C₆H₅)₃
TRIP 2,4,6-triiso-propylphenyl, -2,4,6-(i-Pr)₃C₆H₂
TROC trichloroethylcarboxylate, -CO₂CH₂CCl₃
Ts tosyl, -SO₂-p-(CH₃)C₆H₄
wt weight
δ chemical shift downfield from tetramethylsilane in ppm
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CHAPTER I: Preparation, Characterization and Utility of a Novel Chiral Molybdenum–Alkylidene for Olefin Metathesis.

A portion of this work has appeared in print:

1.1 INTRODUCTION

1.1.1 Catalyst construct and preparation.

Although Mo–based catalysts are significantly more sensitive than their Ru–counterparts, they have provided a fruitful basis for the development of myriad asymmetric metathesis catalysts and methods. These complexes possess a modular design wherein both imido and alkoxide groups are variable ligands that remain attached to the metal throughout the catalytic cycle. Structural or electronic modification of these ligands has been used to tune the reactivity and selectivity of these catalysts.

In order to prepare 1.1a and similar complexes, a short synthesis was developed from readily available starting materials, as shown in Scheme 1.1. The divergent nature of this route allows for preparation of multiple alkoxide variations from “universal precursor” complex 1.4. In order to modify the imido-ligand, the entire synthetic sequence must be repeated, beginning with a different amine. This route has allowed the systematic study of the properties and reactivity of various Mo–based catalysts. In most cases, isolable complexes required a sterically protected (2,6–disubstituted) phenylimido–ligand, however one alkylimido (1-adamantyl) ligand has also been successfully used. The alkoxide ligands are also subject to variability and in general, more electron–deficient alkoxides generate more reactive metathesis catalysts.
Scheme 1.1 Synthetic route to Mo-based metathesis catalysts.

Four coordinate Mo–alkylidenes possess a unique, yet diagnostic attribute: the Mo–Cₐ double bond is weak enough that complexes exist in equilibrium between two stereoisomeric forms in solution. In general the syn–alkylidene, wherein the alkyl substituent on Cₐ is cis to the imido ligand (Scheme 1.2), dominates the equilibrium (generally, $K_{eq} = \frac{[\text{syn}]}{[\text{anti}]}$ lies between 20 and 2000). However, the anti–alkylidene is usually accessible at room temperature (rate of syn to anti conversion, $k_{\text{syn\textrightarrowanti}}$, varies greatly upon the ligand set). It should be noted that steric influences from both the alkoide and imido ligands also affect the value of $K_{eq}$. The thermodynamic preference for the syn–alkylidene is rationalized by a proposed α–agostic interaction between the syn–Cₐ–Hₐ, σ-orbital and Mo–N σ*–orbital (Figure 1.1). This interaction would transfer electron density out of the Cₐ–Hₐ bond and thereby increase the triple-bond character of the Mo–Cₐ bond. Accumulated crystallographic data supports this proposition: syn–alkylidene structures generally exhibit larger Mo–Cₐ–Cₐ bond angles and shorter Mo–Cₐ bond lengths than their anti–alkylidene brethren. While the anti–alkylidene is generally the minor species in solution, in one example it has been shown to be orders of
magnitude more reactive toward metathesis. One possible explanation for this observation is the greater Lewis acidity of anti–alkylidene species, which is demonstrated by stronger binding of basic additives, such as trimethylphosphine, quinuclidine and THF.

1.1.2 Kinetic resolution with chiral hexafluoro–Mo catalysts.

The first chiral Mo–based metathesis catalyst used in the context of asymmetric organic chemistry, 1.6, was reported by Fujimura and Grubbs in 1996. The ability of this system to kinetically resolve racemic dienes through ring–closing metathesis (RCM) was tested on several silyl and acyl ethers. However, as indicated by the selected examples in Scheme 1.3, the enantioselectivity of this catalyst was poor, at best. While these studies proved the feasibility of asymmetric ring–closing metathesis (ARCM), selectivities were substantially below synthetically useful levels ($k_{rel} \approx 10$).
1.1.3 **Highly tactic polymers via ROMP with racemic binaphtholate–Mo catalysts.**

Studies in the area of ring-opening metathesis polymerization (ROMP) had shown that C$_2$ symmetric biphenolate and binaphtholate ligands could be used to afford highly stereoselective complexes. For example, 1.9 provided a highly cis–isotactic polymer from the ROMP of optically pure 1.10 (Scheme 1.4)\textsuperscript{15,16}. Such high tacticity indicated enantiomorphic site control, wherein the substrate adds preferentially to one CNO–face of the Mo–alkylidene, regardless of the metal–bound polymer chain’s local orientation. In contrast to chain–end control, where an error is propagated, in this case the metal center directs the mode of addition and therefore a higher degree of selectivity is obtained. Gel permeation chromatography indicated two distinct chain lengths were present in polymer samples obtained with 1.9. This result was attributed to “matched–mismatched behaviour”. The racemic catalyst would form two diastereomeric intermediates with the enantiopure monomer; one of these diastereomers was much more reactive (“matched”) and therefore led to longer polymer chains.
1.1.4 Kinetic resolution with chiral biphen–Mo catalysts.

Given the high selectivity obtained with 1.9 for ROMP, it was decided to develop enantiopure biphenolates for use as chiral Mo–catalysts for organic synthesis. The enantiopure biphenolate–ligated Mo–alkylidene (S)-1.11a was prepared and shown to exhibit excellent enantioselectivity for ARCM of various racemic dienes,\textsuperscript{17,18} as shown in Scheme 1.5. In many cases $k_{rel} > 20$, and in all cases, $k_{rel}$ was at a synthetically useful level.
The hypothesized source of enantioselectivity in each of the above transformations is illustrated by the key transition states shown in Figure 1.2. As discussed earlier (section 1.1.1), although the anti-alkylidene is the minor species in solution, it is significantly more Lewis acidic than the syn-alkylidene and therefore believed to be more reactive. As an anti-alkylidene, the Mo-bound substrate may adopt two different transition states to lead to the observed product. In both cases, the tethered diene adopts a pseudo–chair conformation, with the R–group in an equatorial position. In transition state I, the pendant olefin is shown approaching the back CNO–face of the anti Mo–alkylidene, whereas in transition state diast-I the olefin is shown approaching the front CNO–face. Attack of the olefin via this latter mode is believed to be less accessible because of the proximity of the t-butyl groups on the biphenolate ligand, as determined by X-ray crystallography of (S)-1.11a.19

![Diagram](image)

**Figure 1.2 Proposed transition states leading to observed stereochemistry.**

1.1.5 Catalyst modularity and optimization of ARCM efficiency.

Although catalyst (S)-1.11a was extremely selective for the transformations shown in Scheme 1.3, the biphenolate ligand required a classical resolution. Furthermore, this catalyst system did not uniformly provide high reactivity and selectivity, *vide infra*. New classes of C₂ symmetric diolates for use in Mo–catalysts were therefore synthesized.
from binaphthol, which is commercially available enantiopure. As illustrated in Figure 1.3, both 3,3’-bis-alkylphenolates\textsuperscript{4,20} and 3,3’-bis-arylnaphthalates\textsuperscript{9,21} have been combined with four distinct imido\textsuperscript{22} ligands to provide active Mo-based catalysts.

![Imido- and diolate ligand variation in chiral Mo-alkylidene complexes.](image)

With a library of chiral catalysts in hand, a high degree of catalyst–substrate specificity was observed for several transformations. The kinetic resolution of several silyl ether 1,7-dienes, as depicted in Scheme 1.6, constitute early examples of this specificity.\textsuperscript{21} For dienes 1.19a-b, catalyst (R)-1.15a exhibited excellent enantioselection, (S)-1.11a showed little to no selectivity for both substrates, and yet (S)-1.11b displayed appreciable selectivity. In contrast, dienes 1.20a-b were efficiently resolved by (S)-1.11a
Scheme 1.6 Catalyst–substrate specificity exhibited by various kinetic resolutions.

Only. Examples such as these prove that no one catalyst is optimal in every instance; however, with the available library of chiral Mo–complexes, a variety of transformations can be achieved with good selectivity.

Desymmetrization of readily available achiral molecules is significantly more efficient than kinetic resolution, as all of the material is converted to product. Several ARCM examples of this process have been developed, as depicted in Scheme 1.7. ARCM of prochiral trienes 1.21 and 1.23 proceeded to afford enantiopure dihydrofuran 1.22 and dihydropyran 1.24, respectively.18,23 Desymmetrization of silyl ethers, such as 1.25 and 1.27, allowed for subsequent transformation to chiral acyclic dienes.21,24 Many of these transformations could even be carried out with equal selectivity in the absence of solvent. The transformations depicted in Scheme 1.7 again show a high degree of substrate to catalyst specificity. This data, in combination with that depicted in Scheme 1.6, highlights the advantages inherent in an available class of chiral metathesis catalysts.
In addition to simple ring-closure, desymmetrization may be the result of tandem metatheses. Some excellent desymmetrizations proceed via asymmetric ring-opening metathesis tandem ring-closing metathesis (AROM/RCM), which is essentially an isomerization. Both carbacyle 1.30 and pyran 1.32 were prepared in high enantiomeric excess via AROM/RCM, as depicted in Scheme 1.8.\textsuperscript{25} The enantioselective preparation of pyran 1.32, was particularly noteworthy, as 1.32 is a key portion of the anti-HIV agent tipranavir.\textsuperscript{26-28}
Scheme 1.8 Desymmetrization of achiral pentenes via AROM/RCM.

Selectivity in the desymmetrizations detailed above is believed to arise from selective ring-opening metathesis (Scheme 1.9). In this case, even if both diastereomeric products are equally accessible, (i.e., have similar activation energies) ring–closure may follow more rapidly for one diastereomer than the other. Final ring–closure must be irreversible; the products obtained from these transformations do not racemize upon exposure to achiral metathesis catalysts.
Desymmetrizations have also been successfully carried out on *meso*-polyenes such as 1.33 and 1.35, illustrated in Scheme 1.10. For each of these examples, enantioselection arises in a different manner. In the case of 1.33, the enantiotopic terminal olefins are thought to be equally accessible for metathesis to generate two diastereomeric species (Scheme 1.11). However since metathesis is reversible, the “matched” diastereomer will undergo subsequent metathesis to lead to the product rapidly, whereas the “mismatched” diastereomer is more likely to revert to starting
meso-tetraene. A similar mechanism of reversible metathesis followed by irreversible metathesis is invoked to explain selectivity for substrate 1.23 (vide supra).

Scheme 1.10 Desymmetrization of meso-polyenes via ARCM and AROM/RCM.

The results described above clearly point to the diversity of activity and reactivity afforded by distinct ligand combinations. The modular design of these Mo–based imido alkylidene complexes can be exploited to afford a variety of efficient and selective catalysts for olefin metathesis. The products accessed by these new catalysts are typically unavailable, or tedious to prepare, by other known methods.

1.2 RESULTS AND DISCUSSION

1.2.1 Objective.

Each chiral Mo–alkylidene catalyst previously prepared exhibited a unique reactivity and selectivity profile. It was difficult to ascertain whether these distinctions arose from differences in steric or electronic properties, or some combination of both. While complexes (S)-1.11a-d, (R)-1.16a-c, and (R)-1.18a-c are all ligated by bis-alkylbiphenolates, complexes (R)-1.15a-c and (R)-1.17a-b possess bis-arylbinaphtholate ligands (Figure 1.2). The data in Table 1.1 illustrates some of the disparities between these catalyst systems in terms of reactivity and selectivity.
At the outset of this project, only catalysts \((S)-1.11a, (R)-1.16a, (R)-1.15a\) and \((R)-1.17a\) had been prepared. In order to diversify the available catalyst library, we began a program aimed at the development of novel ligands for these Mo–based catalysts. We chose to investigate a ligand that combined the electronics of the \textit{bis}-alkylbiphenolate systems (such as \((S)-1.11a\) and \((R)-1.16a\)) with the sterics of the \textit{bis}-arylbinaaphtholate systems (such as \((R)-1.15a\) and \((R)-1.17a\)): a \textit{bis}-alkylbiphenolate ligand system, \(3,3'\)-\textit{bis}-mesityl-1,1'-bitetralin-2,2'-dil. We hoped this amalgamation of steric and electronic properties could clarify which was of greater importance to the selectivity and reactivity of a catalyst system.

\[
\text{Me} \quad \overset{\text{O}}{\text{-}} \quad \overset{\text{R}^*}{\text{Me}} \\
\overset{\text{N}}{\text{Mo}} \quad \overset{\text{O}}{\text{-}} \quad \overset{\text{G}}{\text{Me}} \\
\text{Me} \quad \overset{\text{O}}{\text{-}} \quad \overset{\text{R}^*}{\text{Me}} \\
\overset{\text{N}}{\text{Mo}} \quad \overset{\text{O}}{\text{-}} \quad \overset{\text{G}}{\text{Me}} \\
\text{Me} \quad \overset{\text{O}}{\text{-}} \quad \overset{\text{R}^*}{\text{Me}} \\
\overset{\text{N}}{\text{Mo}} \quad \overset{\text{O}}{\text{-}} \quad \overset{\text{G}}{\text{Me}} \\
\text{Me} \quad \overset{\text{O}}{\text{-}} \quad \overset{\text{R}^*}{\text{Me}} \\
\overset{\text{N}}{\text{Mo}} \quad \overset{\text{O}}{\text{-}} \quad \overset{\text{G}}{\text{Me}} \\
\text{Me} \quad \overset{\text{O}}{\text{-}} \quad \overset{\text{R}^*}{\text{Me}} \\
\overset{\text{N}}{\text{Mo}} \quad \overset{\text{O}}{\text{-}} \quad \overset{\text{G}}{\text{Me}} \\
\text{Me} \quad \overset{\text{O}}{\text{-}} \quad \overset{\text{R}^*}{\text{Me}} \\
\overset{\text{N}}{\text{Mo}} \quad \overset{\text{O}}{\text{-}} \quad \overset{\text{G}}{\text{Me}} \\
\text{Me} \quad \overset{\text{O}}{\text{-}} \quad \overset{\text{R}^*}{\text{Me}} \\
\overset{\text{N}}{\text{Mo}} \quad \overset{\text{O}}{\text{-}} \quad \overset{\text{G}}{\text{Me}} \\
\text{Me} \quad \overset{\text{O}}{\text{-}} \quad \overset{\text{R}^*}{\text{Me}} \\
\overset{\text{N}}{\text{Mo}} \quad \overset{\text{O}}{\text{-}} \quad \overset{\text{G}}{\text{Me}} \\
\text{Me} \quad \overset{\text{O}}{\text{-}} \quad \overset{\text{R}^*}{\text{Me}} \\
\overset{\text{N}}{\text{Mo}} \quad \overset{\text{O}}{\text{-}} \quad \overset{\text{G}}{\text{Me}}
\]

\((S)-1.11a\) \(R = \text{i-Pr}\)  \\
\((S)-1.11c\) \(R = -\text{Cl}\)  \\
\((R)-1.16a\) \(R = \text{i-Pr}\)  \\
\((R)-1.15a\) \(R = \text{i-Pr}, R' = \text{i-Pr}\)  \\
\((R)-1.15c\) \(R = \text{i-Pr}, R' = -\text{Cl}\)  \\
\((R)-1.17a\) \(R = \text{i-Pr}, R' = \text{Me}\)

\[
\overset{\text{Me}}{\text{Me}} \quad \overset{\text{H}}{\text{-}} \quad \overset{\text{H}}{\text{-}} \\
\overset{\text{Me}}{\text{Me}} \quad \overset{\text{H}}{\text{-}} \quad \overset{\text{H}}{\text{-}} \\
\overset{\text{Me}}{\text{Me}} \quad \overset{\text{H}}{\text{-}} \quad \overset{\text{H}}{\text{-}} \\
\overset{\text{Me}}{\text{Me}} \quad \overset{\text{H}}{\text{-}} \quad \overset{\text{H}}{\text{-}} \\
\overset{\text{Me}}{\text{Me}} \quad \overset{\text{H}}{\text{-}} \quad \overset{\text{H}}{\text{-}} \\
\overset{\text{Me}}{\text{Me}} \quad \overset{\text{H}}{\text{-}} \quad \overset{\text{H}}{\text{-}} \\
\overset{\text{Me}}{\text{Me}} \quad \overset{\text{H}}{\text{-}} \quad \overset{\text{H}}{\text{-}} \\
\overset{\text{Me}}{\text{Me}} \quad \overset{\text{H}}{\text{-}} \quad \overset{\text{H}}{\text{-}} \\
\overset{\text{Me}}{\text{Me}} \quad \overset{\text{H}}{\text{-}} \quad \overset{\text{H}}{\text{-}} \\
\overset{\text{Me}}{\text{Me}} \quad \overset{\text{H}}{\text{-}} \quad \overset{\text{H}}{\text{-}} \\
\overset{\text{Me}}{\text{Me}} \quad \overset{\text{H}}{\text{-}} \quad \overset{\text{H}}{\text{-}} \\
\overset{\text{Me}}{\text{Me}} \quad \overset{\text{H}}{\text{-}} \quad \overset{\text{H}}{\text{-}} \\
\overset{\text{Me}}{\text{Me}} \quad \overset{\text{H}}{\text{-}} \quad \overset{\text{H}}{\text{-}} \\
\overset{\text{Me}}{\text{Me}} \quad \overset{\text{H}}{\text{-}} \quad \overset{\text{H}}{\text{-}}
\]

**Table 1.1 Comparison of reactivity & selectivity by chiral metathesis catalysts incorporating \textit{bis}-alkylbiphenolate and \textit{bis}-arylbinaaphtholate ligands.**

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Catalyst</th>
<th>Conv (%)a</th>
<th>E.e.(%)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.22</td>
<td>((S)-1.11a)</td>
<td>81; - 93</td>
<td></td>
</tr>
<tr>
<td></td>
<td>((S)-1.11c)</td>
<td>99; - 90</td>
<td></td>
</tr>
<tr>
<td></td>
<td>((R)-1.15a)</td>
<td>93; +95</td>
<td></td>
</tr>
<tr>
<td></td>
<td>((R)-1.15c)</td>
<td>99; +86</td>
<td></td>
</tr>
<tr>
<td></td>
<td>((R)-1.16a)</td>
<td>72; +96</td>
<td></td>
</tr>
<tr>
<td></td>
<td>((R)-1.17a)</td>
<td>90; +92</td>
<td></td>
</tr>
<tr>
<td>1.37</td>
<td>((S)-1.11a)</td>
<td>32; - 94</td>
<td></td>
</tr>
<tr>
<td></td>
<td>((S)-1.11c)</td>
<td>99; - 97</td>
<td></td>
</tr>
<tr>
<td></td>
<td>((R)-1.15a)</td>
<td>&lt;5; ND</td>
<td></td>
</tr>
<tr>
<td></td>
<td>((R)-1.15c)</td>
<td>99; +91</td>
<td></td>
</tr>
<tr>
<td></td>
<td>((R)-1.16a)</td>
<td>93; +95</td>
<td></td>
</tr>
<tr>
<td></td>
<td>((R)-1.17a)</td>
<td>95; +94</td>
<td></td>
</tr>
</tbody>
</table>

\(a.\) Conv determined by analysis of the 500 MHz \(^1\text{H}\) NMR spectrum of the unpurified reaction mixture. \(b.\) Enantioselectivity determined by chiral GC analysis (CDGTA); e.e. for entry 1 arbitrarily assigned as \((-\)); all other assignments are relative and used for comparison only.
1.2.2 Ligand Synthesis: \((R)-3,3'\text{-bis-mesityl-1,1'}\text{-bitetralin-2,2'}\text{-dil}\).

The difficult step of the synthesis of \((R)-3,3'\text{-bis-mesityl-1,1'}\text{-bitetralin-2,2'}\text{-dil}\) proved to be aryl–aryl coupling; all other transformations proceeded smoothly in good to excellent yield. Hydrogenation, protection and bromination of \((+)-(R)\text{-binaphthol}\) each proceeded in greater than 85 % yield (72 % overall) to afford dibromide 1.40, as shown in Scheme 1.11. Although it was possible to carry out a Kumada-Corriu coupling between dibromide 1.40 and mesitylmagnesium bromide, it was found that diiodide 1.41 afforded significantly improved conversions to 1.42. Deprotection of 1.42 was straightforward and proceeded in excellent yield to afford \((R)\text{-MES}_2\text{BitetH}_2\) (1.43).

Scheme 1.11 Synthesis of \((R)\text{-MES}_2\text{BitetH}_2\), 1.43, from \((+)-(R)\text{-binaphthol}\).

1.2.3 Synthesis and Characterization of \([(\text{Ar}_p\text{N})\text{Mo}((R)\text{-MES}_2\text{Bitet})(\text{CHCMe}_2\text{Ph})(\text{THF})], \text{ (R)-1.44a}\)

Addition of the di-potassium salt of 1.43 to \((\text{Ar}_p\text{N})\text{Mo(OTf)}_2(\text{CHCMe}_2\text{Ph})(\text{DME})_2\) (1.4a) allowed the successful isolation of
[(Ar₆,N)Mo((R)-MES₂Bitet)(CHMe₂Ph)(THF)], (R)-1.44a, isolated as an analytically pure yellow powder from pentane, in 69 % yield, eq 1.1. Although the $^1$H and $^{13}$C spectra of 1.44a were too complex to completely assign, characteristic alkylidene resonances were observed at 13.80 and 11.57 ppm at 22 °C.

X-Ray quality crystals of (R)-1.44a were grown from ether at – 35 °C. The structure was obtained and solved by Dr. Peter J. Bonitatebus Jr.'4 This new catalyst was found to be an anti–THF adduct, as shown in Figure 1.4, along with selected bond lengths and angles. The bond angles are quite similar to those found for (R)-1.17a (see Table 1.4 at the end of this chapter for comparison).⁹

<table>
<thead>
<tr>
<th>Selected Bond</th>
<th>Bond Length (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mo(1)-N(1)</td>
<td>1.721(9)</td>
</tr>
<tr>
<td>Mo(1)-C(1)</td>
<td>1.882(1)</td>
</tr>
<tr>
<td>Mo(1)-O(1)</td>
<td>2.005(5)</td>
</tr>
<tr>
<td>Mo(1)-O(2)</td>
<td>2.000(7)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Selected Bond</th>
<th>Bond Angle (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N(1)-Mo(1)-C(1)</td>
<td>100.5(4)</td>
</tr>
<tr>
<td>N(1)-Mo(1)-O(1)</td>
<td>103.8(4)</td>
</tr>
<tr>
<td>N(1)-Mo(1)-O(2)</td>
<td>131.9(3)</td>
</tr>
<tr>
<td>C(11)-O(1)-Mo(1)</td>
<td>114.2(6)</td>
</tr>
<tr>
<td>C(14)-O(2)-Mo(1)</td>
<td>131.2(6)</td>
</tr>
<tr>
<td>O(2)-Mo(1)-O(1)</td>
<td>91.1(3)</td>
</tr>
<tr>
<td>C(2)-C(1)-Mo(1)</td>
<td>128.4(9)</td>
</tr>
<tr>
<td>C(11)-C(12)-C(13)-C(14)</td>
<td>-73.8(16)</td>
</tr>
</tbody>
</table>

Figure 1.4 ORTEP diagram of (R)-1.44a with tables of selected bond lengths and angles.
1.2.4 Variable Temperature $^1$H NMR Study, with Chelating–Solvent Additives, of 
[(Ar$_{2}$P$_{3}$N)Mo((R)-MES$_{2}$Bitet)(CHCM$_{2}$Ph)(THF)], (R)-1.44a

Variable temperature $^1$H NMR studies, Figure 1.5, of (R)-1.44a showed the 
alkylidene resonance at 13.80 ppm to remain essentially constant from −80 to 60 °C, 
while the upfield resonance shifted from 12.54 to 11.47 ppm over the same range. 
Unfortunately, due to limited solubility, the $J_{CH}$ value of these resonances could not be 
determined within 40 h on a 500 MHz spectrometer. However, based on previous imido-
molybdenum-alkylidene systems,$^{9,17,20,21}$ we assigned the resonance at 13.80 ppm to the 
THF-bound anti-alkylidene. The upfield resonance (from 11.47 ppm to 12.54 ppm) was 
seen to coalesce, indicating rapid equilibrium on the $^1$H NMR time–scale, between −20 
and 0 °C. This upfield resonance was assigned to the syn-alkylidene, which presumably 
must be THF-bound at lower temperatures (12.54 ppm). However, because syn-alkylidenes are generally significantly less basic (due to an α-agostic interaction, as 
discussed in Section 1.1.1) they may exist adduct-free at higher temperatures (11.47 
ppm). Upon the addition of 10 equivalents of THF, the syn-alkylidene resonance at 12.54

![Figure 1.5 Variable temperature $^1$H NMR of (R)-1.44a in toluene-$d_6$.](image)
Figure 1.6 Variable temperature $^1$H NMR of (R)-1.44a with 10 equiv of THF in toluene-$d_6$.

Scheme 1.12 Alkylidene species observed by variable temperature $^1$H NMR of (R)-1.44a.
ppm only began to broaden at 40 °C (Figure 1.6) which supports the assignment of this resonance as the THF–bound syn–alkylidene. These assignments are summarized in Scheme 1.12.

Variable temperature $^1$H NMR studies of (R)-1.44a with added DMF and acetonitrile were also performed. Spectra in the presence of DMF are shown in Figure 1.7. At – 40 °C it is clear that a base is bound to the metal on the NMR time scale to give primarily one anti-adduct with an alkylidene resonance at 13.90 ppm and two syn–adducts with resonances at 12.95 and 12.43 ppm. Again, $J_{CH}$ values could not be obtained within 40 h on a 500 MHz spectrometer, and therefore it is difficult to comment as the exact identity of the observed alkylidene species. While it is clear that no base–free species are observed, the chemical shifts are quite close, but not identical to those observed for THF–bound species (vide supra). However, the differences are < 0.2 ppm, and could be the result of solvent effects. As DMF is a much more basic, tightly binding

![Figure 1.7 Variable temperature $^1$H NMR of (R)-1.44a with 10 equiv of DMF in toluene-d$_8$.](image-url)
solvent, we postulate all three resonances to be indicative of DMF-bound species: an anti-DMF-adduct, (13.90 ppm) and two diastereomeric syn-DMF-adducts (12.95 ppm and 12.43 ppm) as shown in Scheme 1.13. Upon warming the sample to 80 °C the two diastereomeric syn-adducts interconvert, presumably via loss of DMF. However, little or no base-free alkylidene is present, judging from the position of the syn adduct average resonance at ~ 12.6 ppm. This postulate is supported by solvent additive studies discussed in Section 1.2.6 (vide infra).

Spectra in the presence of acetonitrile (Figure 1.8) are similar to those of the DMF-bound species, and we postulate all resonances to be indicative of MeCN-ligated species: one anti-$1.47$ (13.98 ppm) and two diastereomeric syn-$1.47$ species (13.03 ppm and 12.30 ppm). However, in this case the average resonance for the two interconverting syn adducts moves upfield with increasing temperature, which suggests some loss of acetonitrile to yield a base-free species. Consistent with this observation is the fact that $(R)-1.44a$ is active for metathesis in the presence of acetonitrile (vide infra). All evidence suggests that loss of a coordinated base is a prerequisite for metathesis activity.$^{30}$
Figure 1.8 Variable temperature $^1$H NMR of (R)-1.44a with 10 equiv of MeCN in toluene-$d_4$.

Scheme 1.14 Possible alkylidene species observable in solution of (R)-1.44a with 10 equiv of MeCN.
Attempts to grow crystals from cold ether solutions of (R)-1.44a in the presence of either DMF or acetonitrile failed.

1.2.5 Synthesis and Characterization of (Ar\text{Cl, N})\text{Mo}[(R)-\text{MES}_2\text{Bitet}](\text{CHt-Bu})(\text{THF})

As part of the collaborative nature of this project, Dr. Jennifer Y. Jamieson prepared the more Lewis–acidic 2,6-dichlorophenylimido variant of this Mo–catalyst, (R)-1.44b, as shown in eq 1.2. Interestingly, this species existed solely as the THF–bound syn–isomer in solution. The alkylidene resonance was observed at 12.89 ppm ($J_{CH} = 121$ Hz) at room temperature for species (R)-1.44b. While no variable temperature or solvent additive studies were carried out on this material, its efficacy in ARCM was tested and is useful for comparison.

\[
\begin{align*}
\text{1.44b } &
\text{Ar} & = 2,6-\text{Cl}_2\text{C}_{6}\text{H}_3 \\
(R)-1.44b &
\text{R} & = \text{Cl}
\end{align*}
\]

1.2.6 Desymmetrization Ring-Closing Metathesis Reactions with [(Ar_{Pr, N})\text{Mo}((R)-\text{MES}_2\text{Bitet})(\text{CHCMe}_2\text{Ph})(\text{THF})], (R)-1.44a, and [(Ar_{Cl, N})\text{Mo}((R)-\text{MES}_2\text{Bitet})(\text{CHtBu})(\text{THF})], (R)-1.44b.

The new bis-arylbinaphtholate-imido-molybdenum-alkylidenedes, (R)-1.44a and (R)-1.44b have been shown to be active and selective catalysts for ARCM of various ethers (Table 1.2). The rate and enantioselectivity of these transformations is comparable to that of (R)-1.17 for the preparation of dihydrofurans 1.22 and 1.37. Both 1.44a and
1.44b resulted in low levels of conversion of siloxane 1.25 to cyclic siloxane 1.26, even at elevated temperatures.

Table 1.2 Comparison of desymmetrization ARCM via (R)-1.44a and (R)-1.44b with (S)-1.11a, (S)-1.11c, (R)-1.15a, (R)-1.15c, (R)-1.16a and (R)-1.17a.

<table>
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<tr>
<th>Substrate</th>
<th>Catalyst</th>
<th>Conv (%)</th>
<th>E.e. (%)</th>
</tr>
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<tbody>
<tr>
<td>Me</td>
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<td>81</td>
<td>-93</td>
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</tr>
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<tr>
<td>Me</td>
<td>Me</td>
<td>99</td>
<td>+96</td>
</tr>
</tbody>
</table>

\( a \). Conv determined by analysis of the 500 MHz \( ^1 \text{H} \) NMR spectrum of the unpurified reaction mixture. \( ba \). Enantioselectivity determined by chiral GC analysis (CDGTA); e.e. for entry 1 arbitrarily assigned as (−); all other assignments are relative and used for comparison only.

Solvent additive studies reaffirmed the reversible binding of basic molecules (vide supra), which resulted in a decrease of reaction rate (see entries 2 – 7, Table 1.3). In all cases, the rate decrease was accompanied by a slight increase in enantioselectivity, which suggests that olefins must compete with other basic species to bind Mo–alkyldienes. In the case of THF, solvent binding becomes reversible at \( \sim 40 \, ^\circ \text{C} \) (vide supra, Figure 1.6),
and therefore the rate of reaction improves significantly at elevated temperature (entry 3, Table 1.3). Significantly greater rate reduction was observed in the presence of DMF or acetonitrile (entries 4 – 7) both of which required temperatures over ~ 60 °C (vide supra, Figures 1.7 and 1.8), for solvent-adduct free species to become accessible.

<table>
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<th>entry</th>
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<th>conv (%); e.e. (%)</th>
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<td></td>
<td>none</td>
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<tr>
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<td></td>
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<td>24; 22 0; nd</td>
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</tr>
<tr>
<td>7</td>
<td>1.21</td>
<td>1.22</td>
<td></td>
<td>24; 50 0; nd</td>
<td></td>
</tr>
</tbody>
</table>

a. Conditions: 5 mol % (R)-1.44a, 1 equiv of solvent additive and 1.21 in C₆D₆. b. Conv determined by analysis of the 500 MHz ¹H NMR spectrum of the unpurified reaction mixture. c. Enantioselectivity determined by chiral GC analysis (CDGTA).

1.3 CONCLUSIONS

The bis-arylbinaphenolate ligand system, 1.43, has been prepared and successfully used to prepare two novel, chiral Mo-based metathesis catalysts, (R)-1.44a and (R)-1.44b. Structurally, complex (R)-1.44a is nearly identical to bis-arylbinaphatholate system, (R)-1.17a⁹ (see Table 1.4); both these complexes hold little structural similarity to bis-alkylbiphenolate systems (R)-1.11a¹⁹ and (R)-1.16a.²⁰ The reactivity of (R)-1.44a toward trienes such as 1.22 holds more in common with (R)-1.17a (Table 1.2). However the culmination of these and related studies on various asymmetric metathesis transformations has repeatedly shown that over-arching conclusions cannot be drawn from one or two examples. Each specific combination of imido- and diolate ligands
results in unique properties for all catalysts. Even so, two new catalysts were prepared, characterized, and added to the available library of chiral Mo–based metathesis catalysts.

Table 1.4 Table of selected bond lengths (Å) and angles (°) for Mo-alkylidenes ligated with bis-alkylbiphenolates, a bis-arylbinaphtholate and a bis-arylbiphenolate.

<table>
<thead>
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<th>Selected Bond</th>
<th>(S)-1.11a Bond Length</th>
<th>(R)-1.16a Bond Length</th>
<th>(R)-1.17a Bond Length</th>
<th>(R)-1.44a Bond Length</th>
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</table>

<table>
<thead>
<tr>
<th>Selected Bond</th>
<th>Bond Angle</th>
<th>Bond Angle</th>
<th>Bond Angle</th>
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<td>N(1)-Mo(1)-O(1)</td>
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<td>105.9(5)</td>
<td>102.18(18)</td>
<td>103.8(4)</td>
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<tr>
<td>N(1)-Mo(1)-O(2)</td>
<td>110.2(2)</td>
<td>115.0(5)</td>
<td>132.67(19)</td>
<td>131.9(3)</td>
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<tr>
<td>C(11)-O(1)-Mo(1)</td>
<td>-97.1(4)</td>
<td>102.8(7)</td>
<td>113.6(3)</td>
<td>114.2(6)</td>
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<td>C(14)-O(2)-Mo(1)</td>
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<td>102.0(8)</td>
<td>134.6(3)</td>
<td>131.2(6)</td>
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<td>O(2)-Mo(1)-O(1)</td>
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<td>119.9(5)</td>
<td>88.94(15)</td>
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<td>C(2)-C(1)-Mo(1)</td>
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<td>146.4(11)</td>
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<tr>
<td>C(11)-C(12)-C(13)-C(14)</td>
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<td>-88.6(15)</td>
<td>-68.1(7)</td>
<td>-73.8(16)</td>
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</tbody>
</table>
1.4 EXPERIMENTAL DETAILS

GENERAL

$^1$H NMR spectra were recorded on Varian VXR 500 (500 MHz) or Unity 300 (300 MHz) spectrometers. Chemical shifts are reported in ppm from tetramethylsilane with the residual protio-solvent resonance as the internal standard ($\text{C}_6\text{D}_6$: $\delta$ 7.16, CDCl$_3$: $\delta$ 7.26). Data are reported as follows: chemical shift, multiplicity ($s = $ singlet, $d = $ doublet, $t = $ triplet, $q = $ quartet, $br = $ broad, $m = $ multiplet), coupling constants (Hz), integration, and assignment. $^{13}$C NMR spectra were recorded on Varian VXR 500 (125 MHz) spectrophotometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the residual protio-solvent resonance as the internal standard ($\text{C}_6\text{D}_6$: $\delta$ 128.39, CDCl$_3$: $\delta$ 77.7). Enantiomer ratios were determined by chiral GC (CDGTA column) in comparison with authentic racemic materials. High-resolution mass spectrometry was performed at the Massachusetts Institute of Technology, Department of Chemistry Instrumentation Facility (Cambridge, MA).

All reactions were conducted in oven-dried (135 °C) glassware under an inert atmosphere of dry $\text{N}_2$. All metathesis substrates were dried by vacuum distillation over calcium hydride, followed by storing over molecular sieves under a $\text{N}_2$ atmosphere for a minimum of 12 hours prior to use. Handling of all Mo catalysts was performed in a drybox. Benzene, DME, THF, Et$_2$O, and toluene were sparged with $\text{N}_2$ and then passed through an activated alumina column or distilled from sodium/benzophenone ketyl under $\text{N}_2$. Pentane was washed with concentrated acid to remove olefinic impurities, then sparged with $\text{N}_2$ and then passed through an activated alumina column. CH$_2$Cl$_2$ was distilled from calcium hydride under $\text{N}_2$. Benzyl potassium was prepared by the literature method. All reagents were used as received from Aldrich Chemical Co., Lancaster Synthesis, or Strem Chemicals, Inc. unless otherwise stated. Mo catalyst precursor (Ar$_p$N)Mo(CHCMe$_2$Ph)(OTf)$_2$DME, 1.4a, and desymmetrizations substrates such as 1.21 were prepared according to published procedures.
(+)-(R)-2,2’-Dihydroxy-5,5’,6,6’,7,7’,8,8’-octahydro-1,1’-dinaphthyl (1.38): A solution of (+)-(R)-binaphthol (30 g, 100 mmol) and platinum oxide (2.5 g, 11 mmol) in glacial acetic acid (250 mL) was sparged with hydrogen gas three times. The vessel was then placed under an atmosphere of hydrogen at 40 psi overnight. The reaction mixture was poured onto 300 mL of water, stirred vigorously over CH₂Cl₂ and filtered to recover the platinum catalyst. The organic layer was separated, and the aqueous layer extracted three times with CH₂Cl₂. Organic layers were combined, washed with saturated NaHCO₃ solution and brine, then dried over MgSO₄, and concentrated in vacuo to 24.9 g (85 mmol, 85 % yield) of beige solid, judged to be acceptably pure by ¹H NMR (300 MHz, CDCl₃): δ 7.1 (d, 2H), 6.8 (d, 2H), 4.6 (s, 2H, OH), 2.8 (t, 4H), 2.25 (m, 4H), 1.75 (m, 8H). No further spectral data obtained as this matches previously reported ¹H NMR spectra.²⁰

(+)-(R)-2,2’-Dimethoxy-5,5’,6,6’,7,7’,8,8’-octahydro-1,1’-dinaphthyl (1.39): A three-neck flask, equipped with condenser, was charged with 1.38 (10 g, 34 mmol) K₂CO₃ (23.5 g, 170 mmol) and acetone (300 mL). This mixture was heated to 70 °C, and methyl iodide (8 mL, 128 mmol) was added. After 20 hours, more methyl iodide was added (7 mL, 112 mmol) and the mixture was kept at 70 °C for another 14 hours. The reaction mixture was cooled to room temperature, and then poured onto water (300 mL) to produce a white slurry. This slurry was filtered to afford a white solid, which was dried under vacuum to 10.54 g (33 mmol, 96 % yield). The crude material was judged to be acceptably pure by ¹H NMR (300 MHz, CDCl₃): δ 7.1 (d, 2H), 6.8 (d, 2H), 3.7 (s, 6H), 2.8 (br t, 4H), 2.2 (m, 4H), 1.75 (m, 8H). ¹³C NMR not obtained as insufficiently soluble in the readily available deuterated solvents (benzene, CD₂Cl₂, CD₃Cl, DMSO).

(+)-(R)-3,3’-Dibromo-2,2’-dimethoxy-5,5’,6,6’,7,7’,8,8’-octahydro-1,1’-dinaphthyl (1.40): Bromine (6.75 mL, 131 mmol) was added to a solution of 1.39 (16.9 g, 52 mmol) in CH₂Cl₂ (500 mL) at 0 °C. After 1 hour, the red solution was poured onto a saturated
solution of NaHSO₃ (600 mL) and stirred for 1 hour. The resultant biphasic mixture was extracted three times with DCM (600 mL), dried over MgSO₄, and concentrated in vacuo to 22.1 g (46 mmol, 88 % yield) of white, crystalline solid, judged to be clean by ¹H NMR (300 MHz, CDCl₃): δ 7.4 (s, 2H), 3.6 (s, 6H), 2.8 (br t, 4H), 2.2 (m, 4H), 1.75 (m, 8H). ¹³C NMR (75 MHz, CDCl₃): δ 151.5, 135.9, 134.7, 132.9, 131.9, 113.8, 60.4, 29.3, 27.4, 22.7, 22.7.

(+)-(R)-3,3′-Diiodo-2,2′-dimethoxy-5,5′,6,6′,7,7′,8,8′-octahydro-1,1′-dinaphthyl (1.41): tert-Butyllithium (25 mL, 1.7M in hexanes) was added at – 78°C to a clear, colourless solution of 1.40 (5 g, 10 mmol) in ether (250 mL) under N₂, and the reaction mixture turned bright orange. The mixture was warmed to 0°C for 30 minutes, then a solution of iodine (5.8 g, 23 mmol) in ether (50 mL) added to the reaction mixture via cannula. The reaction mixture turned pale yellow, then brown, and was left to warm to room temperature overnight. The reaction mixture was poured onto saturated NaHSO₃ solution, stirred for 2 hours, and then extracted twice with ether (300 mL). The ethereal solution was dried over MgSO₄, and concentrated under vacuum to a pale yellow foam, (5.04 g, 8.4 mmol, 84 % yield) which was used without further purification. ¹H NMR (300 MHz, CDCl₃): δ 7.6 (s, 2H), 3.5 (s, 6H), 2.8 (br t, 4H), 2.2 (m, 4H), 1.75 (8H). ¹³C NMR (75 MHz, CDCl₃): δ 154.2, 139.1, 137.2, 135.5, 131.4, 88.3, 60.4, 29.0, 27.4, 25.7, 22.6, 22.6.

1,3,5-Trimethylphenyl-2-magnesium bromide (MESMgBr): 1,2-dibromoethane (250 μL) was added to magnesium turnings (3.8 g, 157 mmol) in dry ether (100 mL), and the resulting mixture heated to reflux. 2-Bromomesitylene (20 mL, 131 mmol) was added to the mixture drop-wise, after which the cloudy solution was refluxed overnight. The mixture was filtered to afford a yellow solution, and found to be 2.1 M by titration against cumylphenol with 1,10-phenanthroline as indicator.
(+-)(R)-3,3’-Bis-2”’,4”,6”-trimethylphenyl-2,2’-dimethoxy-5,5’6,6’,7,7’,8,8’-
octahydro-1,1’-dinaphthyl (1.42): To a dark green mixture of 1.41
(4 g, 6.97 mmol) and bis-triphenylphosphinonickel (II) chloride
(1.83 g, 2.8 mmol) in ether (200 mL) was added mesitylmagnesium
bromide (10 mL, 2.1M) under N₂, to create a dark black mixture.
The mixture was heated to reflux overnight, then quenched with 10
% HCl (250 mL) to create a red biphasic mixture, which was stirred for 20 minutes. This
mixture was extracted three times with ether (400 mL) washed with saturated NaHCO₃,
then brine, dried over MgSO₄ and concentrated in vacuo to an orange solid. Purified via
column chromatography, eluting with 750 mL of toluene : hexanes (1:4) mix to obtain on
off-white solid. This was washed with pentane, to afford 1.54 g of white powder, (2.8
mmol) in a 40% isolated yield. ¹H NMR (400 MHz, CDCl₃): δ 6.93 (s, 2H), 6.92 (s, 2H),
6.76 (s, 2H), 3.13 (s, 6H), 2.78 (br t, 4H), 2.32 (m, 4H), 2.32 (s, 6H), 2.12 (s, 6H), 2.10 (s,
6H), 1.77 (m, 8H). ¹³C NMR (100 MHz, CDCl₃): δ 152.5, 136.5, 136.2, 135.2, 132.1,

(+-)(R)-3,3’-Bis-2”’,4”,6”-trimethylphenyl-2,2’-dihydroxy-5,5’6,6’,7,7’,8,8’-
octahydro-1,1’-dinaphthyl (1.43): To a clear, colourless solution of
1.42 (1.34 g, 2.4 mmol) in dry CH₂Cl₂ (70 mL) at 0 °C was added
boron tribromide (9.6 mL, 1.0M) to produce a dark-red solution. The
resultant mixture was stirred for 2 hours, slowly warming to room
temperature. The reaction was quenched on cooled water (100 mL)
then extracted three times with CH₂Cl₂ (200 mL) dried over MgSO₄, and concentrated in
vacuo to 1 g of brown, crystalline solid. The crude product was purified via a short silica
plug with 250 mL ether:hexanes (1:4) to obtain 700 mg of off-white foam. (1.3 mmol, 55
% yield) ¹H NMR (300 MHz, CDCl₃): δ 7.00 (s, 2H), 6.99 (s, 2H), 6.87 (s, 2H), 4.53 (s,
2H, OH), 2.82 (br t, 4H), 2.36 (m, 10H), 2.15 (s, 6H), 2.08 (s, 6H), 1.82 (m, 8H). ¹³C
NMR (75 MHz, CDCl₃): δ 147.8, 137.0, 135.9, 133.6, 131.1, 129.7, 128.3, 128.2, 124.5,
(MES₂Biet)⁺²K⁺: Solid potassium hydride (362 mg, 9.0 mmol) was added in small portions to a solution of 1.43 (2.4 g, 4.5 mmol) in THF (30 mL). The resultant white suspension was stirred for 40 minutes at room temperature, then filtered over a fine frit to isolate an off-white powder, which was dried under vacuum to 1.5 g (2.5 mmol, 56% yield) and used without characterization or further purification.

[(Ar₃p,N)Mo((R)-MES₂Biet)(CHCMₑPh)(THF)], [(R)-1.44a]: [Biet(MES)₂]⁺²K⁺ (500 mg, 0.8 mmol) was added portion-wise to a cold, THF solution of (2,6-Ar₃p,N)Mo(OTf)₂(CHNp)(DME) (652 mg, 0.8 mmol) in THF (15 mL). The reaction mixture turned from yellow to deep red after fifteen minutes, and was stirred for another 4 hours. THF was removed in vacuo, and the resultant yellow-brown solid dissolved in toluene, filtered over celite, and re-concentrated under vacuum. The crude product was then taken up in pentane, whereupon a yellow powder crashed out. The powder was isolated by filtration, washing with cold pentane. The filtrate was concentrated to half the original volume and cooled to produce a second crop of product. After drying under high vacuum, 570 mg (0.5 mmol, 69 % yield) of yellow powder was obtained. ¹H NMR (400 MHz, C₆D₆): δ 13.8 (s, 1H, anti-CH, 56% of alkylidene CH), 11.6 (s, 1H, syn-CH, 44% of alkylidene CH), 7.2-6.9 (m, 4H), 6.8 (s, 2H), 6.77 (s, 2H), 6.69 (s, 2H), 3.42 (m, 4H), 3.25 (m), 3.14 (m), 2.84-2.75 (m), 2.60 (dd), 2.32 (dd), 2.16 (d), 2.1 (s), 1.8-0.9 (m). ¹³C NMR (125 MHz, C₆D₆): δ 313.8, 287.5, 161.3, 159.9, 154.6, 154.0, 151.6, 150.5, 138.8, 138.3, 138.1, 137.8, 136.7, 136.4, 136.1, 136.0, 135.7, 135.6, 135.3, 135.1, 134.4, 133.3, 131.9, 130.3, 127.8, 127.2, 126.9, 126.8, 126.7, 126.1, 126.0, 125.8, 125.7, 123.1, 72.0, 53.8, 51.4, 33.0, 31.0, 30.3, 30.0, 29.9, 29.5, 28.8, 28.6, 28.5, 25.1, 24.4, 24.1, 23.8, 23.7, 23.5, 23.0, 22.8, 21.8, 21.5, 21.4, 21.3, 21.2, 21.1, 20.9, 20.8, 20.7, 20.5, 14.3. Anal Calcd for MoC₆₀H₇O₃N: C, 76.54; H, 7.73; N, 1.39; Found: C, 76.63; H, 7.67; N, 1.33. To obtain diffraction quality crystals, a small sample was dissolved in ether, and stored at –35°C for three days. These
crystals, when viewed under a microscope, though yellow to the naked eye, appeared as red rods.

Figure 1.9 Fully labeled ORTEP representation of complex (R)-1.44a.
Table 1.5 Crystal data and structure refinement for complex (R)-1.44a.

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<td>Limiting indices</td>
<td>-13 $\leq$ h $\leq$ 11, -19 $\leq$ k $\leq$ 10, -17 $\leq$ l $\leq$ 19</td>
</tr>
<tr>
<td>Reflections collected</td>
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</tr>
<tr>
<td>Independent reflections</td>
<td>5333 [R$_{int}$ = 0.0861]</td>
</tr>
<tr>
<td>Completeness to $\theta$ = 20.00</td>
<td>97.7%</td>
</tr>
<tr>
<td>Absorption correction</td>
<td>Empirical</td>
</tr>
<tr>
<td>Max. and min. transmission</td>
<td>0.2662 and 0.2041</td>
</tr>
<tr>
<td>Refinement method</td>
<td>Full-matrix least-squares on $F^2$</td>
</tr>
<tr>
<td>Data / restraints / parameters</td>
<td>5333 / 0 / 658</td>
</tr>
<tr>
<td>Goodness-of-fit on $F^2$</td>
<td>1.028</td>
</tr>
<tr>
<td>Final R indices [I$&gt;2\sigma(I)$]</td>
<td>$R_1 = 0.0663$, $wR_2 = 0.1101$</td>
</tr>
<tr>
<td>R indices (all data)</td>
<td>$R_1 = 0.1126$, $wR_2 = 0.1261$</td>
</tr>
<tr>
<td>Absolute structure parameter</td>
<td>-0.08(7)</td>
</tr>
<tr>
<td>Extinction coefficient</td>
<td>0.0000(2)</td>
</tr>
</tbody>
</table>
Largest diff. peak and hole 0.394 and -0.287 eÅ⁻³

Further data may be obtained by referring to the Cambridge Crystallographic Database.

Representative procedure for variable temperature ¹H NMR studies of (R)-1.44a: Complex (R)-1.44a (46 mg, 46 μmol) and THF (37 μL, 460 μmol) were dissolved in toluene-­d₈ (1 mL) and transferred to a sealed J. Young NMR tube. ¹H NMR spectra of the sample were obtained at 20 °C intervals while cooling the sample down to −80 °C, then re-obtained upon warming to 20 °C, (same as obtained upon cooling) and finally while heating to 60 °C.

Representative procedure for ARCM: In all cases, substrates were prepared as previously described.¹⁷²¹ Trialkenyl ether 1.21 (61 mg, 400 μmol) was diluted in benzene-­d₆ to give a ~ 0.2 M solution to which (R)-1.44a, 7 (20 mg, 20 μmol) was then added. The solution was stirred for ~ 1 h at room temperature under dinitrogen in a loosely capped vial. The conversion was then determined by ¹H NMR spectroscopy (500 MHz) of the unpurified reaction mixture. The % e.e. was determined by gas chromatography on chiral column (CDGTA) as compared to an authentic (rac)-sample prepared with 1.1a.

2-Isopropenyl-3-methyl-2,5-dihydro-furan (1.22) ¹H NMR (300 MHz, C₆D₆): δ 5.2 (m, 1H, CH=C), 5.0 (s, 1H, CH₂C=CH₂H), 4.9 (s, 1H, CH₃C=CH₂H), 4.8 (m, 1H, CH), 4.5 (d, 2H, J = 1.8 Hz, OCH₂), 1.6 (s, 3H, CH₃), 1.4 (s, 3H, CH₃).

No further spectral data obtained as this matches previously reported ¹H NMR spectra.¹⁸ GC: (CDGTA, 70 °C, 15 psi) (authentic rac appears at 9.1 and 9.8 minutes).

3-Methyl-2-(1-methyl-propenyl)-2,5-dihydro-furan (1.37) ¹H NMR (300 MHz, C₆D₆): δ 5.6 (m, 1H, CH=C), 5.6 (s, 1H, CH₂C=CH₃H), 4.9 (s, 1H, CH), 4.6 (m, 2H, OCH₂), 1.7 (s, 3H, CH₃), 1.6 (s, 3H, CH₃), 1.5 (s, 3H, CH₃). No further
spectral data obtained as this matches previously reported $^1$H NMR spectra.\textsuperscript{18} GC: (CDGTA, 70 °C, 15 psi) (authentic rac appears at 16.7 and 17.2 minutes).

**Representative procedure for solvent additive effect on ARCM:** Trialkenyl ether \textbf{1.21} (61 mg, 400 μmol) and THF (29 mg, 400 μmol) were diluted in benzene-$d_6$ to give a ~ 0.2 M solution to which \textbf{(R)-1.44a} (20 mg, 20 μmol) was then added. The solution was then transferred to a J. Young NMR tube, and periodically monitored by $^1$H NMR spectroscopy. The conversion was then determined by $^1$H NMR spectroscopy (500 MHz) of the unpurified reaction mixture. The % e.e. was determined by gas chromatography on chiral column (CDGTA) as compared to an authentic (rac)-sample prepared analogously with \textbf{1.1a}. 
CHAPTER 2: Preparation of Chiral Small- and Medium-Ring Cyclic Amines via Asymmetric Ring-Closing Metathesis.

A portion of this work has appeared in print:


2.1 INTRODUCTION

2.1.1 Ring–closing metathesis in organic chemistry prior to well–defined catalysts.

The first examples of ring–closing metathesis used in synthetic organic chemistry appeared in 1980.\textsuperscript{32,33} Both reports detail macrolide–lactone preparation via 'classical' catalysts, which were prepared \textit{in situ} from tungsten hexachloride and an organometallic alkylating agent, such as tetramethylditin (Scheme 2.1). However, few other metathesis applications outside the area of polymerization appeared prior to the development of well–defined catalysts.

\begin{center}
\includegraphics[width=0.8\textwidth]{Scheme_2.1.png}
\end{center}

\textit{Scheme 2.1} Macrolide formation \textit{via} RCM with classical metathesis catalysts.

2.1.2 Discrete catalysts for olefin metathesis.

The first well–defined catalysts for olefin metathesis (Figure 2.1, 1.1a and 1.1b) were reported in the late 1980s. However, the high oxygen and moisture sensitivity of these systems required the use of rigorous Schlenk or dry–box techniques.\textsuperscript{34,35} The report of 2.1a, (Figure 2.1) an olefin metathesis catalyst significantly more stable to air, was met with much enthusiasm.\textsuperscript{36} Nevertheless, not only was 2.1a less sensitive but also significantly less reactive than 1.1a. Therefore many still considered metathesis a non–ideal approach toward complex molecule synthesis. Only recently, with the report of
highly active, yet bench–stable catalysts,\textsuperscript{37,38} (2.1b and 2.1d) has olefin metathesis truly been embraced by the synthetic organic community.\textsuperscript{39-42}

![Chemical structures](image)

**Figure 2.1** Well-defined catalysts for olefin metathesis.

### 2.1.3 Early application of olefin metathesis to organic synthesis: Macrolide ring–closing metathesis and total synthesis.

In most RCM applications, in addition to the newly formed ring, a volatile byproduct (ethylene or propylene) is generated. The resulting entropic gain is sufficient to drive the reaction, provided that the enthalpic cost of ring–formation is relatively small.\textsuperscript{43-45} Therefore, it is not surprising that many early applications of metathesis involved the preparation of highly flexible macrocycles. One example is the preparation of commercial olfactory ingredient 2.3 (eq 2.1).\textsuperscript{44} Although diene 2.2 lacks conformational constraints to encourage ring–closure, significant homodimerization was not observed. The reversible nature of olefin metathesis was invoked to explain the lack of homodimeric byproducts.\textsuperscript{46}
One of the earliest applications of olefin metathesis in complex natural product synthesis was the preparation of fluvirucin B\(_1\) (SCH 38516 Scheme 2.2).\(^{47}\) This synthesis marked the first time a highly functionalized diene was successfully subjected to a Mo–based RCM catalyst. Substantial homodimeric contamination was observed when the stereogenic centers in 2.4 were removed.\(^{48}\)

**Scheme 2.2** A key step in the total synthesis of fluvirucin B\(_1\): Mo–catalyzed RCM.

The majority of RCM macrolide formation continues to be reported via Ru–based catalysts. Some examples include SCH 351448 (Scheme 2.3)\(^{49}\) and woodrosin 1 (Scheme 2.4).\(^{50}\) It is interesting to note that although the high functional group tolerance of 2.1–type catalysts is often touted, acidic and basic moieties of RCM substrates (such as 2.6 and 2.8) are frequently masked with protecting groups or introduced after metathesis by synthetic workers. Various epothilones have also been prepared utilizing Ru–catalyzed RCM, however May and Greico have shown that Mo–based 1.1\(a\) is equally effective (Scheme 2.5).\(^{51-54}\) More examples of macrolide formation via RCM with Mo–based catalysts may be found elsewhere.\(^{6,45,55}\)
Scheme 2.3 A key step in the total synthesis of woodrosin 1: Ru-catalyzed RCM.
Scheme 2.4 A key step in the total synthesis of SCH 351448: Ru-catalyzed RCM.

Scheme 2.5 A key step in the total synthesis of (-)-epothilone B: Mo-catalyzed RCM.
The preparation of the macrocyclic core of cytotrienins A–D highlights the dissimilarity of the various Ru–based catalysts. While Panek and coworkers first subjected 2.11 to 2.1b, only (E,E)-diene 2.12 was obtained (Scheme 2.6). In contrast, the less reactive 2.1a successfully provided the desired (E,E,E)-triene 2.13 in good yield.

Scheme 2.6 A key step in the synthesis of the macrocyclic core of cytotrienins A–D: RCM.

Since the report of catalysts 2.1c and 2.1d, the number of syntheses which incorporate RCM as a key step has grown exponentially. The vast majority of these metatheses have been carried out with Ru–based catalysts. The rapid growth in the area of macrolide formation as well as smaller ring–systems has recently been reviewed.
2.1.4 Small and medium rings via ring-closing olefin metathesis.

Fu and Grubbs were the first to closely study the selective formation of small-ring systems via RCM. Simple five-, six-, seven- and eight-membered carba- and oxacycles were all successfully prepared with catalyst 1.1a (Scheme 2.7). Later work showed that Ru-based 2.1a, although also highly effective at ring-closure, suffered from poorer reactivity with non-terminal olefins.

![Scheme 2.7 Systematic study of RCM by Fu and Grubbs.](image)

Since these preliminary investigations, RCM to access small oxacyclic carbacycles has been used in the context of total synthesis by several researchers. For example, cyclopentene 2.19 was efficiently prepared with 1.1a to gain access to carba-D-fructofuranose (Scheme 2.8).

![Scheme 2.8 A key step in the synthesis of carba-D-fructofuranose: Mo-catalyzed RCM.](image)
Another example of small-ring preparation via RCM appeared in the context of the synthesis of \((-\)-agelastatin A). In this case, highly functionalized diene \textbf{2.20} was treated with Ru-based \textbf{2.1d} to afford cyclopentene \textbf{2.21}. This RCM transformation established the central ring of the target molecule (Scheme 2.9), with several key stereocenters already in place.

\begin{center}
\includegraphics[width=0.8\textwidth]{Scheme_2.9.png}
\end{center}

Scheme 2.9 A key step in the synthesis of \((-\)-agelastatin A: Ru-catalyzed RCM.

Natural products containing small oxacycles are also accessible via RCM. In one example, chiral pyran \textbf{2.23} (Scheme 2.10) was prepared using the first generation Ru-catalyst \textbf{2.1a}, and subsequently used to enantioselectively access \((+)-\)ambructin. This is another example wherein several stereocenters have been installed in the diene prior to RCM.

An interesting example of regioselective RCM has recently been reported by Denmark and coworkers, wherein the highly active \textbf{1.1a} was used to convert triene \textbf{2.24} to siloxane \textbf{2.25} in excellent yield (Scheme 2.11). The presence of an \(\alpha,\beta\)-disubstituted olefin, which remained unchanged by the catalyst, is significant. Siloxane \textbf{2.25} was then subjected to palladium catalyzed cross-coupling to generate 9-membered ring \textbf{2.26}, which accessed antifeedant \((+)-\)brasilenyene. No mention of an attempt at the direct formation of the 9-membered ring via RCM is made.
Scheme 2.10 A key step in the synthesis of (+)-ambructicin: Ru–catalyzed RCM.

Scheme 2.11 A key step in the synthesis of (+)-brasilenyne: Mo–catalyzed RCM.

Small–lactones have also been prepared via RCM. A representative example is the preparation of 2.27 with catalyst 2.1a, in the context of the total synthesis of (+)-methynolide. In this case, Cossy et al. reported the use of titanium iso–propoxide as a co–catalyst, presumably to deactivate the proximal Lewis–basic ester moiety.
Medium rings have frequently presented difficulties for synthetic applications. For example, diene 2.28 was shown to be prone to oligomerization over RCM with 2.1a.\textsuperscript{65} However, Crimmins \textit{et al.} have reported that when vicinal stereogenic centers are in place, such as for dienes 2.29a-b, RCM occurred in good yield.\textsuperscript{66} The authors suggest that this observation is the result of the \textit{gauche effect},\textsuperscript{67} which contributes to significant stabilization of the conformations that facilitate ring-closure. Similar conformational bias introduced by a tributylstannyl group placed $\alpha$ to the heteroatom has also been observed to facilitate RCM.\textsuperscript{68}
Not surprisingly, conformational restriction imparted by existing ring–systems also encourages ring–closure. Several applications of RCM to annulation strategies, such as those disclosed by Delgado and Martin (Scheme 2.14), have appeared in the literature. \(^{69,70}\)

![Diagram of RCM reactions](image)

**Scheme 2.14 RCM to afford [6,7] and [6,8] bicyclic systems.**

Medium–ring RCM has been used to access complex natural products, such as (±)-mycoepoxydiene, and (+)-laurencin (Scheme 2.15). In the first example, RCM was used to annulate 2.33, simultaneously creating both 7– and 8–membered rings. \(^{71}\) In the latter example, a single ring was created, facilitated by vicinal stereocenters. \(^{66}\)
2.1.5 Ring–closing metathesis to generate nitrogen–containing heterocycles.

The first examples of RCM to afford nitrogen–containing heterocycles were reported by Fu and Grubbs in the early 1990s, utilizing 1.1a as the catalyst for metathesis.\textsuperscript{58,59,72} As shown in Scheme 2.16, 5-, 6- and 7–membered rings were accessible from both trialkyl amines, 2.37, as well as dialkyl amides, 2.39. Later work showed that Ru–based 2.1a was also effective at the preparation of small azacycles, although it frequently suffered from poorer reactivity with more highly substituted olefins.\textsuperscript{59}
After this initial work, a myriad of studies on the application of RCM to heterocycles appeared. One early application was reported by Schoemaker and co–workers, wherein catalyst 2.1a was used for the preparation of non–natural amino–acids, such as 2.42 (Scheme 2.17).73

![Scheme 2.17 Preparation of non–natural amino–acids via RCM.](image)

The preparation of various natural products has also been reported. For example, (−)-coniine has been prepared via RCM utilizing the amino acid L–norvaline as a chiral starting material (Scheme 2.18).74

![Scheme 2.18 Synthesis of (−)-coniine from L–norvaline via Ru–catalyzed RCM.](image)

In contrast to medium oxacycles, medium azacycles have repeatedly been accessed without vicinal stereogenic centers (2.46, Scheme 2.19).65,75 Applications to complex natural products have also been reported, such as the preparation of (−)-balanol. This product was accessed via RCM of diene 2.47 with Ru–based catalyst 2.1a (Scheme 2.19).76
Scheme 2.19 A key step in the total synthesis of (-)-balanol: Ru-catalyzed RCM.

Most medium-sized cyclic amines prepared via RCM have been part of annulation strategies. For example, Martin and coworkers have disclosed the preparation of numerous bicyclic alkaloid-cores via RCM (Scheme 2.20).\textsuperscript{77} In this manner, 5-, 6-, 7- and 8-membered rings were successfully annulated onto pyrrolidinone and piperidinones. It should be noted that such annulation strategies are not unlimited; the related 12-membered ring precursor was prone to homodimerization under the same conditions.

Scheme 2.20 Medium rings can be annulated onto small rings via RCM.

Several applications to total synthesis with similar ring-annulation strategies were developed. The total synthesis of manzamine A, (Scheme 2.21) was one of the earliest examples of medium ring preparation via RCM.\textsuperscript{78-80}
Scheme 2.21 Medium ring RCM as part of the total synthesis of manzamine A.

Antitumor antibiotic (+)-FR900482 was also prepared via an annulation RCM. This study demonstrates the complementary nature of Mo- and Ru-based catalyst systems. When 2.53 was protected as a TBS-ether (as for 2.53a) catalyst 1.1a outperformed Ru-based 2.1a. However, when the alcohol was left unprotected, as in 2.53b, catalyst 1.1a was subject to complete decomposition, while 2.1a provided good conversion to the ring-closed system 2.54b. Both of 2.54a and 2.54b could be carried forward to access (+)-FR900482.

Scheme 2.22 Variation in the yield of RCM transformations catalyzed by 1.1a vs. 2.1a.
Various other syntheses utilizing annulation strategies have been reported. One example is the preparation of the alkaloid (±)-tabersonine from diene 2.55 (Scheme 2.22). It should be noted that in this example, Kozmin et al. reported significantly lower conversions with Ru–based 2.1a than with Mo–based 1.1a.

![Scheme 2.23 Small ring RCM as a key step in the synthesis of (±)-tabersonine.](image)

2.1.6 Diastereoselective ring–closing metathesis to generate nitrogen–based heterocycles.

A particularly interesting series of papers by Huwe and Blechert detail diastereoselective RCM of various chiral trialkenyl amines (Scheme 2.24). Interestingly, 1.1a and 2.1a gave the opposite sense of diastereoselectivity for RCM for both (rac)-2.57 and (S)-2.59 to afford 5– and 6–membered cyclic amines. The authors attribute the catalyst specificity observed to the different spatial arrangements of the respective ligands of 1.1a and 2.1a during cyclization.
Scheme 2.24 Diastereoselective RCM of amino–triienes by Mo– and Ru–based catalysts.

2.1.7 Other methods of enantioselective preparation of cyclic amines.

The methods for enantioselective preparation of amines are too numerous to detail here; however there are several reviews in the literature that adequately describe this ongoing area of research. A short overview of the methods that are applicable to cyclic amine preparation is provided for comparison with the asymmetric ring–closing metathesis (ARCM) methods described in this thesis.

Perhaps the most facile route to chiral amines is the use of readily available amino acids; however, this method is practical only for the naturally occurring enantiomers. Also, temporarily attached groups, used as chiral auxiliaries, have been reported in numerous applications. For example, diastereoselective Diels–Alder transformations have been reported with various amino acid derivatives. However, methods which
transform an achiral molecule into a chiral one via one transformation introduce complexity most efficiently.

Chiral boronic–ester 2.61 has been reported by Yamamoto and coworkers to effectively mediate aza–Diels–Alder reactions to provide chiral piperidinones (Scheme 2.25).\(^\text{101}\) This method provides good yields and enantioselectivity for several N–benzyl imines, however it is less selective with N–aryl imines.

![Scheme 2.25 Asymmetric aza–Diels–Alder reaction catalyzed by a chiral boronic ester.](image)

Reduction or alkylation of imines is the most common method of enantioselective amine preparation. Nakamura et al. have reported the use of chiral allylic zinc reagent 2.62, which is generated from an enantiopure lithiated bis–oxazoline and allylzinc bromide.\(^\text{102}\) This reagent effectively reduces various cyclic aldimines in moderate to good yield with high to excellent enantioselectivity (Scheme 2.26). However, the reagent affords poor enantioselectivity in the reduction of ketimines and acyclic–imines.

![Scheme 2.26 Asymmetric imine alkylation with a bis–oxazoline ligated allylzinc reagent.](image)
The use of chiral catalysts in lieu of stoichiometric reagents is generally considered more elegant methodology. Acyclic imine allylation has been reported by Yamamoto and coworkers with chiral bis-π-allyl palladium complex 2.63 and allyl tributylstannane.\textsuperscript{103-105} However, when the method is applied to cyclic imines, enantioselectivity is drastically reduced (Scheme 2.27).

![Scheme 2.27 Asymmetric aldilmine allylation with a chiral π-allylpalladium catalyst.](image)

Asymmetric reduction of cyclic ketimines has been successfully carried out by Buchwald and coworkers in the presence of chiral titanocene catalyst 2.64.\textsuperscript{106} In this case, acyclic imines are reduced with less selectivity by 2.64 than their cyclic counterparts. This method allows access to cyclic 5-, 6- and 7- membered cyclic amines in good yield and excellent enantioselectivity. However, one drawback of this method is the need for relatively high pressures of hydrogen (80 psi).

![Scheme 2.28 Asymmetric ketimine reduction with a chiral titanocene catalyst.](image)
Asymmetric cyclization via intramolecular allylic alkylation of \( \omega,5 \)-unsaturated alkyl amines has been reported by Trost et al.\textsuperscript{107} Chiral bis–phosphine 2.65, when combined with allylpalladium chloride, catalyzes enantioselective nucleophilic attack by nitrogen on the distal olefin to generate a cyclic amine (Scheme 2.29). This method generates 5- and 6-membered azacycles with good enantioselectivity, however a substantial loss of selectivity is observed for the 7-membered case.

Scheme 2.29 Asymmetric allylic alkylation with a chiral bis–phosphine ligand and palladium.

Another intramolecular cyclization was recently described by Yamamoto and coworkers, again involving palladium catalysis.\textsuperscript{108} In this example, RENORPHOS (2.66) is used as a chiral ligand for Pd–catalyzed intramolecular hydroamination. This method has been used to afford 5- and 6-membered rings (Scheme 2.30), however the method is limited to nonafluorobutanesulfonyl–protected amines. When other protective groups are placed on nitrogen, enantioselectivities are adversely affected.

Scheme 2.30 Asymmetric cyclization with RENORPHOS and palladium.
2.2 RESULTS AND DISCUSSION

2.2.1 Enantioselective synthesis of tetrahydropyridines \textit{via} desymmetrization ARCM.

Chiral cyclic amines constitute an important class of compounds because this functional group is present in the vast majority of drugs and drug candidates. Based on the success of our chiral metathesis catalysts for oxygen–based heterocycles and the accumulated data of cyclic amine preparation \textit{via} RCM, we began a program of research dedicated to the application of asymmetric ring-closing metathesis (ARCM) to cyclic amine products. The ability of various chiral Mo–complexes to promote ARCM of trialkenyl amine 2.67a was examined. As the data in Table 2.1 indicate, these studies pointed to chiral \textit{bis}–alkylbiphenolate complexes as the most active (entries 1–3, 5–6) complexes, with (R)-1.11a as the most enantioselective catalyst.

We next studied the influence of different electronic and steric properties of the \textit{N}-aryl substituents on this transformation. Aryl amines bearing phenyl, \textit{p}–methoxy or \textit{p}–bromo phenyl groups, 2.67a–c, were all readily converted to \textit{N}–aryl–tetrahydropyridines 2.68a–c in > 97 % e.e. and > 78 % isolated yield within 20 min at 22 °C (entries 1–3, Table 2.2) with 5 mol % (R)-1.11a. When arylamines that bear an \textit{ortho} substituent were examined (entries 4–5, Table 2.2), < 5 % conversion was observed with (R)-1.11a. However, catalyst screening established that chiral \textit{bis}–alkylbiphenolate complex (R)-1.18a effectively transformed 2.67d and 2.67e within 20 min to > 98 % conversion to afford 2.68d and 2.68e in 84 % and 82 % e.e respectively. ((S)-1.11c performed similarly for substrates 2.67d and 2.67e.)
Table 2.1 Catalyst screening for desymmetrization of unsaturated amines.\textsuperscript{a}

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<th>product</th>
<th>catalyst</th>
<th>conv (%)\textsuperscript{b}</th>
<th>time (h)</th>
<th>e.e. (%)\textsuperscript{c}</th>
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<tbody>
<tr>
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<td>+98</td>
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</tr>
<tr>
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<td><img src="image4" alt="Product image" /></td>
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<td>+61</td>
<td></td>
</tr>
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<td>95; 23</td>
<td>+80</td>
<td></td>
</tr>
</tbody>
</table>

\textsuperscript{a} Conditions: 5 mol % catalyst, C\textsubscript{6}H\textsubscript{6}, 22 °C. \textsuperscript{b} Conv determined by analysis of the 500 MHz \textsuperscript{1}H NMR spectrum of the unpurified reaction mixture. \textsuperscript{c} Enatioselectivity determined by chiral HPLC analysis (Chiralcel OJ column); e.e. for entry 1 arbitrarily assigned as (+); all other assignments are relative and used for comparison only.
Single-crystals of \textbf{2.68c} were grown from a concentrated methanolic solution. A crystal was harvested, mounted and solved by James P. Araujo. Due to the presence of a heavy atom (atomic weight > 35), the absolute stereochemistry of this crystal could be determined by examination of the absolute structure (Flack) parameter.\textsuperscript{111} This parameter should be approximately zero for the correct configuration, and one for the inverted configuration. Using this technique, as implemented in the SHELXTL suite of programs,\textsuperscript{112} we were able to determine the absolute stereochemical identity of cyclic amine \textbf{2.68c}. (Other stereochemical assignments in this study are by inference.) The Flack parameter was found to be $-0.002(16)$, for the enantiomer shown in Figure 2.2 ((\textit{R})- at C7). When the absolute configuration was inverted, and the data refined separately, the Flack parameter was found to be $0.9407(325)$, confirming that (\textit{R})- at C7 is the correct absolute configuration.
Figure 2.2 X–Ray of 2.68c indicated the new stereogenic center at C7 have (R)-configuration.

The stereochemical induction of all ARCM transformations detailed herein are inferred by analogy to 2.68c (*vide supra*). Based upon the determined absolute stereochemistry of 2.68c, some discussion of key transition states involved in the ARCM mechanism is possible. Metathesis between (R)-1.11a and 2.67c must first result in 2.69, which can exist in either the syn– or anti–form (Scheme 2.31). Both syn–2.69 and anti–2.69 could lead to the observed product through metathesis with the appropriate olefin on diastereomeric CNO–faces. Thus, four distinct transition states are possible (syn– and anti–2.70 and 2.71). Of the four transition state depicted in Scheme 2.31, those which invoke an anti–alkylidene are expected to possess higher energies of activation, yet also be more reactive. However, none of these species are observable. Even at low temperatures under ethylene pressure, the resting state of this catalyst is an unsubstituted metallacycle. It is therefore difficult to comment as to the exact identity of catalytic species involved in these desymmetrizations.
Scheme 2.31 Possible key transition states leading to the observed stereochemistry of 2.68c.
2.2.2 Effect of olefin substitution pattern and replacement of α–methyl group with α–trimethylsilyl.

The reactivity and selectivity levels of catalytic desymmetrizations shown in Table 2.2 are sensitive to the pattern of olefin substitution. As illustrated in eq 2.2, all–terminal triene 2.72 (similar to trienes 2.67 of Table 2.2) readily underwent ring–closure in the presence of 5 mol % of all chiral catalysts; however, 2.73 was obtained in < 10 % e.e. in all cases. The low level of enantioselectivity observed for substrate 2.72 was not unexpected; in this case all olefins are equally reactive toward metathesis, and therefore a statistical mixture of diene–tethered alkylidene intermediates (2.74a–c, Scheme 2.32) was expected. Although \( \frac{1}{3} \) of 2.72 may undergo ARCM to 2.73 (path a, Scheme 2.32), the remainder would be converted in equal parts to 2.74b and 2.74c, for which RCM to afford the 6–membered ring is no longer an asymmetric process (Scheme 2.32, paths b and c). Therefore we expect \( \frac{2}{3} \) of 2.72 to generate rac–2.73, and the expected enantioselectivity would be \( \sim 32 \% \) e.e. (assuming path a proceeds with similar enantioselectivity to ARCM of substrates 2.67).

![Diagram](image)

Given that the enantioselectivities observed were even lower (< 10 % e.e.) than predicted above, we considered another possible intermediate, cyclopentenyl–amine 2.75 (path d, Scheme 2.32). Although this byproduct was never observed, it could be subject to rapid asymmetric ring–opening metathesis (AROM) to preferentially generate one of 2.74b or 2.74c.
To test this hypothesis, we examined substrates 2.76 and 2.78 (Scheme 2.33). Substrate 2.76 was subject to rapid AROM/RCM with moderate levels of enantioselectivity (20 – 35 % e.e.). This observation lends support to the postulate of equilibrium between 2.74b–c and 2.75, which may account for the very low levels of enantioselectivity observed for eq 2.1. However, as the best level of enantioselectivity obtained was only 35 % e.e. (using catalyst (R)-1.11a), 2.76 was not considered a successful candidate for AROM/RCM. In reactions involving triene 2.78, ring closure was significantly slower than for 2.72 and the product mixture was often contaminated with cyclopentene 2.80. The most appreciable enantioselectivity observed for the formation of 2.79 was a modest 50 % e.e. (using catalyst (R)-1.44a). Clearly, neither of these substrates would provide a selective route to unsubstituted azacycles.
Another potential route to unsubstituted azacycles involves the use of a temporary α-substituent. We chose trimethylsilyl (TMS) as an electronically neutral, yet removable (Lewis acid,\textsuperscript{115,116} fluoride\textsuperscript{46} or protodesilylation\textsuperscript{117}) substituent. Unfortunately, bis-α-TMS substituted 2.81 caused significant catalyst decomposition with 5% loading for all chiral catalysts, as shown in eq 2.3. No more than 40% conversion was observed for any catalyst, including achiral 1.1a. This result was not unanticipated, as decomposition of Mo\textsuperscript{VI}–alkylidenes to Mo\textsuperscript{IV}–complexes by vinyl–TMS species had previously been observed.\textsuperscript{118} We had hoped that the presence of N–allyl olefin would negate that tendency; however it was ineffective.

\[ \text{eq 2.3} \]
2.2.3 Enantioselective synthesis of pentahydroazepines and hexahydroazocines.

Catalytic asymmetric synthesis of medium ring unsaturated amines was also accomplished efficiently and with excellent enantioselectivity. As depicted in Scheme 2.34, chiral catalyst \((R)-1.11a\) promoted the formation of pentahydroazepine 2.84 in 95 % e.e. and 90 % isolated yield. Perhaps more importantly, the Mo-catalyzed ARCM of 2.85, effected in the presence of 5 mol % \((S)-1.11c\), delivered optically pure (> 98 % e.e.) eight-membered cyclic amine 2.86 in 93 % yield after chromatography. Catalytic ARCM of both 2.83 and 2.85 (Scheme 2.34) were expectedly faster with the more Lewis acidic complex \((S)-1.11c\) (20 min vs. 7 – 8 h for > 95 % conversion at 22 °C with \((R)-1.11a\)). However, whereas formation of 2.84 was more selective with \((R)-1.11a\) (95 % e.e. vs. 87 % e.e. with \((S)-1.11c\)), 2.86 was formed as a single enantiomer when either \((R)-1.11a\) or \((S)-1.11c\) was used. These observations, in addition to those depicted in Table 2.2 (\textit{vide supra}), underline the importance of a modular catalyst design.

![Scheme 2.34 Enantioselective synthesis of medium ring amines by catalytic ARCM.](image)
2.2.4 Enantioselective synthesis of tetrahydropyridines via kinetic resolution ARCM.

As part of the collaborative nature of this research, once the above results in the area of desymmetrization ARCM had been obtained, studies on the kinetic resolution of related systems were begun by Elizabeth S. Sattely. Her work is detailed in Table 2.3 and is discussed for comparison to the desymmetrization processes previously outlined (Sections 2.2.1 – 2.2.4). As shown in Table 2.3, chiral catalyst (S)-1.11a promoted

Table 2.3 Kinetic resolution, catalyzed by (S)-1.11a, of acyclic amines by ARCM. Studies performed by Elizabeth S. Sattely.\textsuperscript{a}

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>Ar</th>
<th>additive</th>
<th>conv (%)\textsuperscript{,b}</th>
<th>time (h)</th>
<th>(k_{\text{rel}})\textsuperscript{c}</th>
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\textsuperscript{a} Conditions: 5 mol % (S)-1.11a, C\textsubscript{6}H\textsubscript{6}, 22 °C. \textsuperscript{b} Conv determined by analysis of the 400 MHz \(^1\text{H}\) NMR spectrum of the unpurified reaction mixture. \textsuperscript{c} Enantioselectivity determined by chiral HPLC analysis (Chiralpak AD for entries 1–3, & 6–7; Chiralcel OJ for entries 4, 5 & 8; Chiralcel OD for entry 9). Calculation of \(k_{\text{rel}}\) values (based upon the method of Kagan and Fiaud\textsuperscript{119} and is only an approximation of the relative rates of reactions of the two enantiomers, as it is based on a first-order equation, where a simultaneous process (such as homodimerization) does not occur.
efficient ring closure of 2.87a, with a measurable amount of asymmetric induction (entry 1, \( k_{rel} = 3 \)). On the basis of previous studies, the effect of diallyl ether and ethylene on the rate and selectivity of the ARCM was also examined\(^{120,121}\). Both additives led to more facile ring–closure and significant improvement in the efficiency of kinetic resolution (entries 2 – 3, \( k_{rel} = 8 \) and 17, respectively). A similar trend was observed for diene 2.87b, bearing the more electron–rich \( p \)-(MeO) aryl group. At this point, the importance of the amine substituent’s identity became evident, as the reaction of 2.87b proved to be noticeably less facile than that of 2.87a. Transposition of the terminal and 1,1–disubstituted olefin (entries 6 – 7) of the substrate gave rise to significant reduction in the efficiency of the resolution. As illustrated in entries 8 and 9, medium ring systems were also accessible with high degrees of selectivity. Both 2.91 and 2.93 underwent efficient kinetic resolution (\( k_{rel} = 13 \) and > 50, respectively). In these later examples, catalytic ARCM proceeded with high selectivity without diallyl ether or ethylene additives. In contrast to previous examples, the aforementioned additives caused significant reduction in reaction efficiencies.

Later studies indicated that although the corresponding benzylamine and tosylamide variants of 2.87 reacted readily with achiral Mo–complex 1.1a, none of the available chiral catalysts provided high reactivity or selectivity. These observations highlight the importance of the nature of the amine substituent.

### 2.2.5 Enantioselective synthesis of secondary, tertiary and spirocyclic benzoazepines.

Although there is the potential for rupture of M–O bonds and removal of alkoxide ligands within metathesis catalysts (in the case of Mo– and W–based complexes) through protonation by an NH moiety\(^{122,123}\), we next looked to secondary amines (e.g., \( RR’NH \)). We began with the investigation of enantioselective synthesis of polycyclic secondary amines. Toward this end, we prepared trienes 2.95a–c, illustrated in Table 2.4, and
screened our library of chiral Mo complexes to afford 2.96a–c. These studies indicated that complexes (R)-1.44a (Chapter 1) and (R)-1.15a promoted the most efficient and enantioselective desymmetrizations.

As the data in entries 1–2 of Table 2.4 indicate, both (R)-1.44a and (R)-1.15a efficiently converted (> 98 % conversion in 3 h at 55 °C) triene 2.95a (R = H) to unsaturated azepine 2.96a in 93 % e.e. However, when 2.95b was used as the substrate (entries 3–4), ring closures became significantly slower, particularly with (R)-1.15a (entry 4). Further, the product 2.96b was formed in only 22 – 24 % e.e. Complex (R)-1.15a was equally ineffective for transformation of amine 2.95c (entry 6) to bicyclic amine 2.96c (only 30 % conversion after 20 h). In stark contrast, however, as depicted in entry 5, chiral catalyst (R)-1.44a promoted the formation of 2.96c efficiently (> 98 % conversion in 3 h) to deliver the desired amine in quantitative yield and 80 % e.e. It should be noted that reactions in Table 2.4 were significantly slower when carried out at 22 °C. As an example, ARCM of 2.96a with either 5 mol % (R)-1.44a or (R)-1.15a proceeded to < 56 % conversion after 24 h at 22 °C (still 93 % e.e. in both cases); longer

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate R</th>
<th>catalyst</th>
<th>time (h); conv (%);</th>
<th>yield (%);</th>
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<tr>
<td>1</td>
<td>2.95a H</td>
<td>(R)-1.44a</td>
<td>3; &gt;98</td>
<td>75; 93</td>
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<td>3; &gt;98</td>
<td>80; 93</td>
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<tr>
<td>3</td>
<td>2.95b Et</td>
<td>(R)-1.44a</td>
<td>24; 90</td>
<td>71; 24</td>
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<tr>
<td>4</td>
<td></td>
<td>(R)-1.15a</td>
<td>24; 20</td>
<td>nd; 22</td>
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<td>5</td>
<td>2.95c Ph</td>
<td>(R)-1.44a</td>
<td>3; &gt;98</td>
<td>98; 80</td>
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<td>6</td>
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<td>(R)-1.15a</td>
<td>30; 20</td>
<td>nd; nd</td>
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a. Conditions: 5 mol % catalyst, C₆H₆, 55 °C, 3 – 30 hr. b. Conv determined by analysis of the 500 MHz 1H NMR spectrum of the unpurified reaction mixture. c. Isolated yields after purification by chromatography. d. Enantioselectivity determined by chiral HPLC analysis (Chiralcel OD).
reaction times did not result in additional conversion. The enantioselectivity trend in this system parallels that observed for the preparation of 7–membered siloxacycles bearing quaternary carbon centers α to the heteroatom.\textsuperscript{24}

All attempts to prepare analogous polycyclic secondary amines incorporating a benzoazocine unit failed (Scheme 2.35). When the substrate was modified such that the most reactive olefin was no longer styrenyl (2.97), homodimerization of the substrate (2.99) predominated over ring–closure (2.98) with all catalysts. In contrast to other systems (\textit{vide infra}), reversion\textsuperscript{46,48,124} of acyclic 2.99 to a monomeric species, which may eventually afford the desired cyclic amine 2.98, did not occur, even with prolonged reaction times. Redesign of the substrate to retain the styrenyl moiety, 2.100, resulted in an extremely unreactive species, for which no Mo–based catalyst showed any RCM activity.

![Scheme 2.35 Attempts at the preparation of benzoazocines.](image)

The complete failure of 2.100 to undergo metathesis inspired us to prepare tetaene 2.101, (Scheme 2.36) the design of which is an amalgamation of 2.95 and 2.100. Previous examples of tetaenens that can undergo tandem RCM have frequently shown a high level of enantioselectivity.\textsuperscript{23} In the case of 2.101, treatment with 5 mol % (\textit{R})-1.18a first led to the formation of cyclohexenylamine 2.102 within 20 min. After 6 h,
intermediate 2.102 was converted to 2.103 in quantitative yield and 79 % e.e. As conversion to 2.102 was complete prior to any formation of 2.103, all enantioselectivity must have occurred during the formation of cyclohexenyl–amine intermediate 2.102.

Scheme 2.36 ARCM–tandem–RCM to afford a chiral spirocycle.

2.2.6 Enantioselective synthesis of secondary cyclohexenylamines.

We examined the ability of (R)-1.18a to desymmetrize cyclohexenyl–aniline precursors 2.104a–e; data from catalytic ARCM are summarized in Table 2.5. All transformations proceeded readily to > 98 % conversion (as judged by 1H NMR spectra of the unpurified products) within 25 min at 22 °C in the presence of 2 mol % (R)-1.18a. No significant rate difference between reactions of less hindered amines (2.104a–b and 2.104e, entries 1 – 2 and entry 5) and ortho–substituted arylamines 2.104c–d (entries 3 – 4) was observed. Nor was any notable variation in reaction rate observed between electron rich arylamine 2.104a (bearing a p-(MeO)C₆H₄ group) and its electron deficient variant 2.104e (bearing a m-(CF₃)C₆H₄ group). These findings suggest that internal chelation between the Mo–alkylidene derived from the more reactive terminal olefin in 2.104 and the neighboring Lewis basic heteroatom⁷²  (six–membered chelate) is not a significant effect. Nonetheless, catalytic ARCM of 2.104c–d occured with higher levels of enantiodifferentiation (79 – 81 % e.e.) than 2.104a–b and 2.104e (64 – 67 % e.e.). These results underline the value of local steric in determining the degree of enantioselectivity. As illustrated in entry 6 of Table 2.5, the derived benzyl amine 2.104f also underwent ARCM to afford the derived cyclic amine in 65 % e.e.; however, in this
instance, it was Mo complex (R)-1.15a that delivered the highest enantioselectivity (> 98 % conversion in 0.5 h and 59 % e.e. with (R)-1.18a).

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Table 2.5 Enantioselective synthesis of secondary amines through Mo-catalyzed ARCM. a</th>
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<tr>
<td>entry</td>
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a. Conditions: 2 mol % catalyst, C_6H_6, 22 °C, 20 – 25 min. b. Conv determined by analysis of the 500 MHz ¹H NMR spectrum of the unpurified reaction mixture. c. Isolated yields after purification by chromatography. d. Enantioselectivity determined by chiral HPLC analysis (Chiralpak AS column for entries 1 – 2, Chiralcel OD for entries 3 – 5). Enantioselectivity for entry 6 was determined by analysis of the derived (S)-MTPA ester. e. Catalyst (R)-1.15a used.

Not surprisingly, all-terminal variant 2.106 showed no enantioselectivity when subjected to chiral metathesis catalysts (eq 2.4). This result parallels previous studies (Section 2.2.2).
2.2.7 Practical aspects: In–Situ catalysts; solvent–free reactions.

Several additional factors render the present catalytic enantioselective method of particular utility in asymmetric synthesis:

(1) Several reactions could be carried out in the absence of solvent and with lower catalyst loading to afford products of high optical purity in an efficient and environmentally friendly manner. Particularly impressive is the efficient Mo–catalyzed ARCM that deliver medium ring amines (Scheme 2.37) in high optical purity and excellent yields without contamination by homodimeric or oligomeric products (< 2 %). It is noteworthy that monitoring of the reaction progress indicated that homodimeric products were formed initially during formation of 2.84 and 2.86. Prolonged reaction times, however, allowed for reversion\(^{46-48,124}\) of such acyclic compounds to monomeric entities that eventually underwent ring closure to afford the cyclic trisubstituted alkenes. The final products, due to the lack of reactivity of trisubstituted alkenes, were not prone to ring–opening metathesis. Evidently, cyclic species 2.84 and 2.86 are thermodynamically favored over the acyclic intermediates observed.

![Scheme 2.37 Products from ARCM performed without solvent.](image)

(2) The non–racemic cyclic secondary amines obtained from ARCM can be functionalized and converted to a variety of polycyclic amines, without loss of enantiomeric excess. A representative example is illustrated in Scheme 2.38. Subjection of optically enriched 2.96a (93 % e.e.) to benzylpotassium and allylbromide, followed by
treatment of the derived allylamine with achiral 1.1a, led to the formation of tricyclic amine 2.108 in 93 % e.e.

Scheme 2.38 Enantioselective tricycle formation via RCM of enantioenriched diene.

It should be noted that attempts to make the above process more efficient, through alkylation of starting triene 2.95a prior to metathesis, failed. When tetrane 2.109 was subjected to metathesis catalysts (Scheme 2.39), only dihydroquinone 2.110 was produced. Prolonged reaction times, as well as the use of ethylene or diallyl ether additives, failed to access 2.108. These results stand in contrast to the highly effective desymmetrization of tetrane 2.101 (vide supra).

Scheme 2.39 Failed ARCM of tetrane to directly afford a tricycle.

(3) Chiral catalysts are easily prepared and used in situ – without isolation and purification – to promote efficient asymmetric metathesis with levels of enantioselectivity analogous to those obtained with the isolated and purified catalysts (compare data in Scheme 2.40 with entry 3, Table 2.2 and entry 4, Table 2.5). Various bis(alkoxides) were easily prepared by treatment of the parent diols with potassium hydride (or any other suitable base). When the appropriate bis(alkoxides) was added to commercially available complex 1.4a (Strem), the in situ prepared catalyst acted as a selective and efficient catalyst for ARCM.
Scheme 2.40 In situ prepared and used catalysts equally effective for various ARCM to prepare chiral cyclic amines.

2.3 CONCLUSIONS

The catalytic ARCM protocols detailed herein provide an effective method for enantioselective synthesis of otherwise difficult-to-access cyclic amines. A variety of small and medium ring unsaturated azacycles have been synthesized through Mo-catalyzed asymmetric metathesis efficiently and with exceptional levels of enantioselectivity. From an environmental point of view, the ability to carry out many of these transformations in the absence of solvent makes this method particularly attractive. Furthermore, the ease and equivalent reactivity and selectivity of in situ prepared catalysts, increases the practicality of this method.
2.4 EXPERIMENTAL DETAILS

GENERAL

$^1$H NMR spectra were recorded on Varian VXR 500 (500 MHz) or Unity 300 (300 MHz) spectrometers. Chemical shifts are reported in ppm from tetramethylsilane with the residual protio-solvent resonance as the internal standard ($C_6D_6$: $\delta$ 7.16, CDCl$_3$: $\delta$ 7.26). Data are reported as follows: chemical shift, multiplicity ($s$ = singlet, $d$ = doublet, $t$ = triplet, $q$ = quartet, $br$ = broad, $m$ = multiplet), coupling constants (Hz), integration, and assignment. $^{13}$C NMR spectra were recorded on Varian VXR 500 (125 MHz) or Unity 300 (75 MHz) spectrometers with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the residual protio-solvent resonance as the internal standard ($C_6D_6$: $\delta$ 128.39, CDCl$_3$: $\delta$ 77.7). Infrared (IR) spectra were recorded on ThermoNicolet Avatar 360 spectrophotometer, $\mu_{\text{max}}$ in cm$^{-1}$. Bands were characterized as broad (br), strong (s), medium (m), and weak (w). Enantiomer ratios were determined by chiral HPLC (Chiral Technologies Chiralpak AD (4.6 mm $\theta \times$ 250 mm), Chiralpak AS (4.6 mm $\theta \times$ 250 mm), Chiralcel OJ (4.6 mm $\theta \times$ 250 mm) or Chiralcel OD (4.6 mm $\theta \times$ 250 mm)) in comparison with authentic racemic materials. High-resolution mass spectrometry was performed at the Massachusetts Institute of Technology, Department of Chemistry Instrumentation Facility (Cambridge, MA). Elemental analyses were carried out by Robertson–Microlit Labs (Madison, NJ).

All reactions were conducted in oven– (135 °C) or flame–dried glassware under an inert atmosphere of dry N$_2$. All metathesis substrates were dried by vacuum distillation over calcium hydride, followed by storing over molecular sieves under a N$_2$ atmosphere for a minimum of 12 h prior to use. Handling of all Mo catalysts was performed in a drybox. Benzene, DME, THF, Et$_2$O, and toluene were sparged with N$_2$ and then passed through an activated alumina column or distilled from sodium/benzophenone ketyl under N$_2$. Pentane was washed with concentrated acid to remove olefinic impurities, then sparged with N$_2$ and then passed through an activated alumina column. CH$_2$Cl$_2$ was distilled from
calcium hydride under N\textsubscript{2}. All reagents were used as received from Aldrich Chemical Co., Lancaster Synthesis, or Strem Chemicals, Inc. unless otherwise stated. Several Mo–based catalysts were synthesized as previously described\textsuperscript{9,19,21} however certain catalysts used were the generous donation of coworkers Dr. J. Y. Jamieson (1.11c), Dr. W. C. P. Tsang (1.17a), S. L. Aeilts (1.16a) and Dr. S. A. Miller (1.18a).

**Representative procedure 2.1:** Used for the preparation of ethyl–N–arylimidates. The procedure for the condensation of aniline with triethyl orthoformate using para–toluenesulfonic acid to form the following ethyl–N–arylimidates is based upon a known general method.\textsuperscript{125} The desired ethyl–N–arylimidates were purified by vacuum distillation.

**Ethyl–N–paramethoxyphenylformimidate:** (Used in the synthesis of 2.67b, 2.76, 2.78 and 2.81.) Prepared via procedure 2.1 in 58 % yield (22 g, 120 mmol). \textsuperscript{1}H NMR (500 MHz, C\textsubscript{6}D\textsubscript{6}): \( \delta \) 7.53 (s, 1H, ArN=CH(OCH\textsubscript{2}CH\textsubscript{3})), 6.90 (d, \( J = \) 8.7 Hz, 2H, ArH), 6.75 (d, \( J = \) 8.7 Hz, 2H, ArH), 4.21 (q, \( J = \) 7.1 Hz, 2H, OCH\textsubscript{2}CH\textsubscript{3}), 3.32 (s, 3H, CH\textsubscript{3}O), 1.10 (t, \( J = \) 7.1 Hz, 3H, OCH\textsubscript{2}CH\textsubscript{3}); \textsuperscript{13}C NMR (125 MHz, C\textsubscript{6}D\textsubscript{6}): \( \delta \) 157.7, 154.8, 142.3, 122.9, 115.9, 62.5, 55.3, 14.6. HRMS (El+) Calcd for C\textsubscript{10}H\textsubscript{13}NO\textsubscript{2} [M + H]: 179.0941. Found: 179.0939.

**Ethyl–N–parabromophenylformimidate:** (Used in the synthesis of 2.67c.) Prepared via procedure 2.1 in 46 % yield (8.9 g, 46 mmol). \textsuperscript{1}H NMR (500 MHz, C\textsubscript{6}D\textsubscript{6}): \( \delta \) 7.19 (m, 2H, ArH), 6.53 (m, 2H, ArH), 4.09 (q, \( J = \) 7.0 Hz, 2H, OCH\textsubscript{2}CH\textsubscript{3}), 1.04 (t, \( J = \) 7.0 Hz, 3H, OCH\textsubscript{2}CH\textsubscript{3}); \textsuperscript{13}C NMR (125 MHz, C\textsubscript{6}D\textsubscript{6}): \( \delta \) 155.5, 148.0, 132.7, 123.8, 117.9, 62.8, 14.5. HRMS (El+) Calcd for C\textsubscript{8}H\textsubscript{10}BrNO [M + H]: 226.9940. Found: 226.9949.
**Ethyl–N–orthomethoxyphenylformimidate:** *(Used in the synthesis of 2.67d.)* Prepared via procedure 2.1 in 71 % yield (28 g, 160 mmol). $^1$H NMR (500 MHz, C$_6$D$_6$): $\delta$ 7.69 (s, 1H, ArN=CH(OCH$_2$CH$_3$)), 6.92 (m, 2H, ArH), 6.85 (t, $J = 6.1$ Hz, 1H, ArH), 6.62 (d, $J = 7.1$ Hz, 1H, ArH), 4.25 (q, $J = 7.1$ Hz, 2H, OCH$_2$CH$_3$), 3.31 (s, 3H, CH$_3$O), 1.09 (t, $J = 7.1$ Hz, 3H, OCH$_2$CH$_3$); $^{13}$C NMR (125 MHz, C$_6$D$_6$): $\delta$ 156.1, 152.8, 138.6, 125.2, 123.7, 121.6, 112.4, 62.3, 55.6, 14.6. HRMS (EI$^+$) Calcd for C$_{19}$H$_{13}$NO$_2$ [M + H]: 179.0941. Found: 129.0937.
**Ethyl-\textsuperscript{N}-orthobromophenylformimidate:** (Used in the synthesis of 2.67e.) Prepared via procedure 2.1 in quantitative yield (19 g, 100 mmol). \textsuperscript{1}H NMR (500 MHz, C\textsubscript{6}D\textsubscript{6}): \(\delta\) 7.45 (d, \(J = 7.9\) Hz, 1H, ArN=CH(OCH\textsubscript{2}CH\textsubscript{3})), 7.17 (d, \(J = 7.9\) Hz, 1H, ArH), 6.85 (t, \(J = 7.6\) Hz, 1H, ArH), 6.60 (t, \(J = 7.6\) Hz, 1H, ArH), 6.50 (d, \(J = 7.6\) Hz, 1H, ArH), 4.21 (q, \(J = 7.0\) Hz, 2H, OCH\textsubscript{2}CH\textsubscript{3}), 1.10 (t, \(J = 7.0\) Hz, 3H, OCH\textsubscript{2}CH\textsubscript{3}); \textsuperscript{13}C NMR (125 MHz, C\textsubscript{6}D\textsubscript{6}): \(\delta\) 155.9, 155.8, 147.7, 133.6, 125.7, 122.0, 118.9, 63.1, 14.5. HRMS (EI\textsuperscript{+}) Calcd for C\textsubscript{9}H\textsubscript{16}BrNO \([M + H]\): 226.9940. Found: 226.9935.

**Methallyl-magnesium bromide:** Magnesium turnings (24.0 g, 990 mmol) in THF (125 mL) were cooled to 0 °C in a 3-neck flask equipped with an addition funnel charged with a 3-bromo-2-methyl-propene solution (99.0 mmol in 100 mL THF). Approximately 3 mL of the halide solution was added to the stirring magnesium suspension to initiate the reaction. After stirring for 15 min, the solution had become cloudy and dark. The mixture was then cooled to –35 °C, and the remaining halide solution was added drop-wise over 3 h. Subsequently, the reaction mixture was allowed to warm to room temperature, and then stirred for an additional 30 minutes. The mixture was then transferred through a teflon cannula to a bomb and stored in an N\textsubscript{2} glovebox. Before each use, the Grignard was titrated against a stock solution of 4-cumylphenol in THF using 1,10-phenanthroline as indicator.

**Representative procedure 2.2:** Used for preparation of [3-Methyl-1-(2-methyl-allyl)-but-3-enyl]-aryl-amines. Ethyl-N-phenylformimidate (2.55 g, 14.4 mmol) was added to a solution of methylallyl magnesium bromide (100 mL, 0.35 M in THF), to produce a mild exotherm. The mixture was stirred for 30 min and then quenched by the slow addition of 200 mL water. The resulting aqueous layer was washed three times with 70 mL portions of Et\textsubscript{2}O. The combined organic extracts were washed first with 200 mL of a saturated solution of ammonium chloride and then with 200 mL of a saturated solution of sodium chloride. After drying over MgSO\textsubscript{4}, the organic extract was filtered and
concentrated *in vacuo* to a brown oil. The product was purified by silica gel chromatography (5 % Et₂O in pentane) to give [3-methyl-1-(2-methyl-allyl)-but-3-enyl]-phenyl-amine as a clear, colorless oil.

**[3-Methyl-1-(2-methyl-allyl)-but-3-enyl]-phenyl-amine:** *(Used in the synthesis of 2.67a, 2.83 and 2.85.)* Prepared via procedure 2.2 in 97 % yield (3 g, 14 mmol). ¹H NMR (500 MHz, C₆D₆): δ 7.17 (m, 2H, ArH), 6.75 (t, J = 7.3 Hz, 1H, ArH), 6.54 (d, 7.6 Hz, 2H, ArH), 4.80 (d, J = 0.9 Hz, 2H, C=CH₂H₃), 4.75 (d, J = 0.9 Hz, 2H, C=CH₂H₃), 3.60 (sextet, J = 6.7 Hz, 1H, NHCH₂(CH₂C(CH₃)=CH₂)₂), 3.20 (d, J = 6.7 Hz, 1H, NH), 2.10 (d, J = 6.7 Hz, 4H, CH(CH₂C(CH₃)=CH₂)₂), 1.58 (s, 6H, CH(CH₂C(CH₃)=CH₂)₂). ¹³C NMR (100 MHz, C₆D₆): δ 148.5, 143.6, 130.1, 117.9, 113.6, 113.4, 49.7, 43.7, 22.8. IR (Neat): 3407 (s), 3073 (s), 2933 (s), 1647 (s), 1601 (s), 1506 (s), 1435 (s), 1375 (s), 1259 (s), 1181 (m), 1074 (m), 1031 (m). HRMS (EL⁺) Calcd for C₁₅H₂₁N [M + H]: 215.1669. Found: 215.1670.

**[3-Methyl-1-(2-methyl-allyl)-but-3-enyl]-paramethoxyphenyl-amine:** *(Used in the synthesis of 2.67b, 2.76, and 2.78.)* Prepared via procedure 2.2 in 84 % yield (1.2 g, 4.7 mmol). ¹H NMR (500 MHz, C₆D₆): δ 6.82 (d, J = 8.9 Hz, 2H, ArH), 6.50 (d, J = 8.9, 2H Hz, ArH), 4.83 (s(br), 2H, C=CH₂H₃), 4.79 (s(br), 2H, C=CH₂H₃), 3.55 (s, 1H, NHCH₂(CH₂C(CH₃)=CH₂)₂), 3.41 (s, 3H, CH₃O), 3.02 (s(br), 1H, NH), 2.15 (m, 4H, CH(CH₂C(CH₃)=CH₂)₂), 1.62 (s, 6H, CH(CH₂C(CH₃)=CH₂)₂). ¹³C NMR (125 MHz, C₆D₆): δ 153.1, 143.8, 142.7, 115.7, 115.0, 113.3, 55.7, 50.8, 43.9, 22.9. IR (Neat): 3396 (m), 3073 (s), 2934 (s), 2831 (s), 1647 (s), 1575 (s), 1442 (s), 1375 (s), 1239 (s), 1180 (s), 1041 (s). HRMS (EL⁺) Calcd for C₁₆H₂₃NO [M + H]: 245.1774. Found: 245.1783.
[3-Methyl-1-(2-methyl-allyl)-but-3-enyl]-parabromophenyl-amine: (Used in the synthesis of 2.67c.) Prepared via procedure 2.2 in 76 % yield (3.7 g, 12 mmol). 1H NMR (500 MHz, C6D6): δ 7.21 (dd, J = 6.7, 2.1 Hz, 2H, ArH), 6.15 (dd, J = 6.7, 2.1 Hz, 2H, ArH), 4.78 (s(br), 2H, CCH3=CH2H3), 4.70 (s(br), 2H, CCH3=CH2H3), 3.41 (sextet, J = 6.7 Hz, 1H, NHCH(C6H2CCH2=CH2)2), 3.08 (s(br), 1H, NH), 2.00 (m, 4H, NHCH(C6H2CCH2=CH2)2), 1.54 (s, 6H, NHCH(C6H2CCH2=CH2)2). 13C NMR (125 MHz, C6D6): δ 147.3, 143.3, 132.8, 115.0, 113.6, 109.3, 49.8, 43.5, 22.8. IR (Neat): 3409 (s), 3073 (s), 2933 (s), 1647 (s), 1595 (s), 1496 (s), 1443 (m), 1375 (m), 12929 (s), 1180 (m), 1674 (s). HRMS (EI+) Calcd for C15H20BrN [M + H]: 293.0774. Found: 293.0770.

[3-Methyl-1-(2-methyl-allyl)-but-3-enyl]-orthomethoxyphenyl-amine: (Used in the synthesis of 2.67d.) Prepared via procedure 2.2 in 79 % yield (4.1 g, 17 mmol). 1H NMR (500 MHz, C6D6): δ 7.00 (t, J = 7.6 Hz, 1H, ArH), 6.77 (d, J = 7.9 Hz, 1H, ArH), 6.73 (t, J = 7.6 Hz, 1H, ArH), 6.57 (d, J = 7.9 Hz, 1H, ArH), 4.80 (m, 4H, C=CH2H3), 4.33 (d(br), J = 7.0 Hz, 1H, NH), 3.72 (d, J = 7.0 Hz, 1H, NHCH(C6H2C(CH3)=CH2)2), 3.32 (s, 3H, CH3O), 2.25 (dd, J = 14.2, 7.0 Hz, 2H, CH(C6H2C(CH3)=CH2)2), 2.17 (dd, J = 14.2, 6.4 Hz, 2H, CH(CH2C(CH3)=CH2)2), 1.61 (s, 6H, CH(CH2C(CH3)=CH2)2). 13C NMR (125 MHz, C6D6): δ 147.7, 143.7, 138.4, 122.2, 116.7, 113.3, 110.5, 110.1, 55.4, 49.6, 43.7, 22.9. IR (Neat): 3421 (m), 3073 (m), 2935 (s), 1648 (m), 1602 (s), 1515 (s), 1457 (s), 1375 (m), 1228 (s), 1176 (m), 1124 (m), 1031 (m). HRMS (EI+) Calcd for C16H23NO [M + H]: 245.1774. Found: 245.1779.

[3-Methyl-1-(2-methyl-allyl)-but-3-enyl]-orthobromophenyl-amine: (Used in the synthesis of 2.67e.) Prepared via procedure 2.2 in 80 % yield (4.8 g, 17 mmol). 1H NMR (500 MHz, C6D6): δ 7.38 (d, J = 7.9 Hz, 1H, ArH), 7.01 (t, J = 7.3 Hz, 1H, ArH), 6.59 (d, J = 7.9 Hz, 1H, ArH), 6.37 (t, J = 7.3 Hz, 1H, ArH), 4.81 (s, 2H, C=CH2H3), 4.78 (s, 2H, C=CH2H3), 4.39 (s(br), 1H, NH), 3.59 (pentet, J = 6.7 Hz, 1H, NHCH(C6H2C(CH3)=CH2)2), 2.12 (m, 4H, CH(CH2C(CH3)=CH2)2), 1.62 (s, 6H
CH(CH₂C(CH₃)=CH₂)₂. ¹³C NMR (100 MHz, C₆D₆): δ 145.0, 143.1, 133.5, 129.2, 118.1, 113.9, 111.6, 110.9, 50.0, 43.4, 22.8. IR (Neat): 3401 (m), 3073 (s), 2933 (s), 1791 (w), 1648 (s), 1597 (s), 1510 (s), 1433 (s), 1375 (s), 1286 (s), 1018 (s). HRMS (El⁺) Calcd for C₁₅H₂₀BrN [M + H]: 293.0774. Found: 293.0789.

**Representative procedure 2.3:** *Used for the preparation of Allyl-[3-Methyl-1-(2-methyl-allyl)-but-3-enyl]-arylamines.* Benzyl potassium (1.5 g, 12 mmol) was added to a stirring solution of [3-methyl-1-(2-methyl-allyl)-but-3-enyl]-phenyl-amine (3.5 g, 12 mmol) in THF (125 mL) at −35 °C to afford a yellow solution. After 15 min, allyl bromide (1.1 mL, 13 mmol) was added by syringe. The mixture was then allowed to warm to room temperature (22 °C). 100 mL of water was then added to quench the reaction. The resulting aqueous layer was washed three times with 80 mL portions of Et₂O. The organic extracts were combined and washed with 200 mL of a saturated solution of ammonium chloride, followed by 200 mL of a saturated solution of sodium chloride. After drying over MgSO₄, the organic extract was filtered and concentrated *in vacuo* to an orange oil. The product was purified by silica gel chromatography (2 % Et₂O in pentane) to give allyl-[3-methyl-1-(2-methyl-allyl)-but-3-enyl]-phenyl-amine (2.67a) as a colorless oil.

**Allyl-[3-methyl-1-(2-methyl-allyl)-but-3-enyl]-phenyl-amine (2.67a): Prepared via procedure 2.3 in 42% yield (1.5 g, 5.8 mmol).* ¹H NMR (500 MHz, C₆D₆): δ 7.24 (t, J = 7.3 Hz, 2H, ArH), 6.91 (d, J = 7.8 Hz, 2H, ArH), 6.77 (t, J = 7.3 Hz, 1H, ArH), 5.71 (m, 1H, NCH₂CH=CH₂), 5.11 (dd, J = 17.4, 1.7 Hz, 1H, NCH₂CH=CH₂H₆), 5.00 (dd, J = 10.3, 1.7 Hz, 1H, NCH₂CH=CH₂H₈), 4.77 (s(br), 4H, CH(CH₂C(CH₃)=CH₂)₂), 4.26 (pentet, J = 7.2 Hz, 1H, CH(CH₂C(CH₃)=CH₂)₂), 3.62 (m, 2H, NCH₂CH=CH₂), 2.13 (m, 4H, CH(CH₂C(CH₃)=CH₂)₂), 1.60 (s, 6H, CH(CH₂C(CH₃)=CH₂)₂). ¹³C NMR (100 MHz, C₆D₆): δ 149.7, 143.7, 137.6, 129.8, 117.7, 116.1, 114.8, 113.2, 55.5, 47.0, 41.3, 22.8. IR
(Neat): 3074 (s), 2932 (s), 1647 (s), 1598 (s), 1447 (s), 1281 (s), 1039 (m). HRMS (EI\textsuperscript{+})
Calcd for C\textsubscript{18}H\textsubscript{23}N [M + H]: 255.1982. Found: 255.1990.

**Allyl-[3-Methyl-1-(2-methyl-allyl)-but-3-enyl]-paramethoxyphenyl-amine (2.67b):** Prepared via procedure 2.3 in 67 % yield (0.72 g, 2.5 mmol). \textsuperscript{1}H NMR (300 MHz, C\textsubscript{6}D\textsubscript{6}): \( \delta \) 6.86 (m, 4H, ArH), 5.76 (m, 1H, NCH\textsubscript{2}CH=CH\textsubscript{2}), 5.16 (dd, \( J = 17.3, 1.8 \) Hz, 1H, CH\textsubscript{2}CH=CH\textsubscript{2}H\textsubscript{b}), 5.02 (dd, \( J = 10.3, 1.8 \) Hz, 1H, CH\textsubscript{2}CH=CH\textsubscript{2}H\textsubscript{a}), 4.82 (s(br), 4H, CH(CH\textsubscript{2}C(CH\textsubscript{3})=CH\textsubscript{2})), 4.06 (pentet, \( J = 7.3 \) Hz, 1H, CH(CH\textsubscript{2}C(CH\textsubscript{3})=CH\textsubscript{2})), 3.61 (s(br), 2H, NCH\textsubscript{2}CH=CH\textsubscript{2}), 3.39 (s, 3H, CH\textsubscript{3}O), 2.22 (dd, \( J = 14.3, 7.5 \) Hz, 2H, CH(CH\textsubscript{3}H\textsubscript{b}C(CH\textsubscript{3})=CH\textsubscript{2})), 2.09 (dd, \( J = 14.3, 6.8 \) Hz, 2H, CH(CH\textsubscript{3}H\textsubscript{a}C(CH\textsubscript{3})=CH\textsubscript{2})), 1.64 (s, 6H, CH(CH\textsubscript{3}C(CH\textsubscript{3})=CH\textsubscript{2})). \textsuperscript{13}C NMR (100 MHz, C\textsubscript{6}D\textsubscript{6}): \( \delta \) 153.3, 144.0, 138.0, 118.1, 116.1, 115.2, 113.1, 57.7, 55.5, 47.6, 41.2, 22.8. IR (Neat): 3073 (s), 2934 (s), 1837 (w), 1646 (s), 1373 (m), 1242 (s), 1043 (s). HRMS (EI\textsuperscript{+}) Calcd for C\textsubscript{19}H\textsubscript{25}NO [M + H]: 285.2087. Found: 285.2089.

**Allyl-[3-Methyl-1-(2-methyl-allyl)-but-3-enyl]-parabromophenyl-amine (2.67c):** Prepared via procedure 2.3 in 80 % yield (3.3 g, 9.6 mmol). \textsuperscript{1}H NMR (500 MHz, C\textsubscript{6}D\textsubscript{6}): 7.25 (m, 2H, ArH), 6.54 (m, 2H, ArH), 5.57 (m, 1H, NCH\textsubscript{2}CH=CH\textsubscript{2}), 4.98 (m, 2H, NCH\textsubscript{2}CH=CH\textsubscript{2}), 4.75 (dd, \( J = 2.1, 1.5 \) Hz, 2H, NCH(CH\textsubscript{2}C(CH\textsubscript{3})=CH\textsubscript{2}H\textsubscript{b})), 4.70 (dd, \( J = 1.8, 0.9 \) Hz, 2H, NCH(CH\textsubscript{2}C(CH\textsubscript{3})=CH\textsubscript{2}H\textsubscript{a})), 4.06 (pentet, \( J = 7.3 \) Hz, 1H, NCH(CH\textsubscript{2}C(CH\textsubscript{3})=CH\textsubscript{2})), 3.47 (m, 2H, NCH\textsubscript{2}CH=CH\textsubscript{2}), 2.04 (dd, \( J = 14.7, 7.6 \) Hz, 2H, NCH(CH\textsubscript{3}H\textsubscript{b}C(CH\textsubscript{3})=CH\textsubscript{2})), 2.00 (dd, \( J = 14.7, 6.7 \) Hz, 2H, NCH(CH\textsubscript{3}H\textsubscript{a}C(CH\textsubscript{3})=CH\textsubscript{2})), 1.54 (s, 6H, NCH(CH\textsubscript{2}C(CH\textsubscript{3})=CH\textsubscript{2})). \textsuperscript{13}C NMR (125 MHz, C\textsubscript{6}D\textsubscript{6}): \( \delta \) 148.6, 143.3, 136.7, 132.5, 116.2, 113.4, 109.4, 107.1, 55.6, 46.9, 41.3, 22.8. IR (Neat): 3075 (s), 2932 (s), 1647 (s), 1374 (s), 1248 (m), 1083 (m). HRMS (EI\textsuperscript{+}) Calcd for C\textsubscript{18}H\textsubscript{24}NBr [M + H]: 333.1087. Found: 333.1072.
Allyl-[3-Methyl-1-(2-methyl-allyl)-but-3-enyl]-orthomethoxyphenyl-amine (2.67d): Prepared via procedure 2.3 in 58 % yield (2.5 g, 8.7 mmol). $^1$H NMR (500 MHz, C$_6$D$_6$): $\delta$ 6.99 (s, 1H, ArH), 6.86 (m, 2H, ArH), 6.60 (m, 1H, ArH), 5.77 (m, 1H, NCH$_2$CH=CH$_2$), 5.16 (dd, $J = 18.3$, 0.9 Hz, 1H, NCH$_2$CH=CH$_2$H$_3$), 4.96 (dd, $J = 11.9$, 0.9 Hz, 1H, NCH$_2$CH=CH$_2$H$_3$), 4.84 (m, 4H, NCH(=C(=CH$_2$)=CCH$_3$)$_2$), 4.84 (pentet, $J = 7.3$ Hz, 1H, NCH(=C(=CH$_2$)=CCH$_3$)$_2$), 3.77 (m, 2H, NCH$_2$CH=CH$_2$), 3.35 (s, 3H, CH$_3$O), 2.44 (dd, $J = 13.7$, 7.0 Hz, 2H, NCH(=C=CH$_2$H$_3$)(=C=CH$_2$)H$_3$), 2.20 (dd, $J = 13.7$, 7.3 Hz, 2H, NCH(=C(=CH$_2$)=CCH$_3$)$_2$), 1.65 (s, 6H, NCH(=C(=CH$_2$)=CCH$_3$)$_2$). $^{13}$C NMR (100 MHz, C$_6$D$_6$): $\delta$ 154.2, 144.8, 140.0, 138.0, 123.8, 122.5, 121.2, 116.2, 113.0, 58.0, 55.4, 47.5, 42.1, 22.6. IR (Neat): 3072 (s), 2935 (s), 1782 (w), 1646 (s), 1373 (s), 1238 (s), 1031 (s). Anal Calcd for C$_{19}$H$_{27}$NO: C, 79.95; H, 9.53; N, 4.91. Found: C, 79.69; H, 9.51; N, 5.20.

Allyl-[3-Methyl-1-(2-methyl-allyl)-but-3-enyl]-orthobromophenyl-amine (2.67e): Prepared via procedure 2.3 in 98 % yield (3.9 g, 12 mmol). $^1$H NMR (500 MHz, C$_6$D$_6$): $\delta$ 7.45 (dd, $J = 7.9$, 1.5 Hz, 1H, ArH), 6.97 (dd, $J = 8.2$, 1.5 Hz, 1H, ArH), 6.89 (dt, $J = 8.2$, 1.5 Hz, 1H, ArH), 6.50 (dt, $J = 7.9$, 1.5 Hz, 1H, ArH), 5.66 (m, 1H, NCH$_2$CH=CH$_2$), 5.15 (m, 1H, NCH$_2$CH=CH$_2$H$_3$), 4.93 (m, 1H, NCH$_2$CH=CH$_2$H$_3$), 4.82 (s(br), 2H, NCH(=C(=CH$_2$)=CCH$_3$)$_2$), 4.76 (s(br), 2H, NCH(=C(=CH$_2$)=CCH$_3$)$_2$), 3.90 (pentet, $J = 7.0$ Hz, 1H, NCH(=C(=CH$_2$)=CCH$_3$)$_2$), 3.69 (m, 2H, NCH$_2$CH=CH$_2$), 2.55 (dd, $J = 13.7$, 6.7 Hz, 2H, CH(=C=CH$_2$H$_3$)(=C=CH$_2$)H$_3$), 2.18 (dd, $J = 13.7$, 7.3 Hz, 2H, CH(=C=CH$_2$H$_3$)(=C=CH$_2$)H$_3$), 1.52 (s, 6H). $^{13}$C NMR (125 MHz, C$_6$D$_6$): $\delta$ 149.5, 144.3, 136.9, 134.5, 127.3, 126.6, 124.2, 121.7, 116.9, 113.6, 58.2, 47.7, 42.2, 22.5. IR (Neat): 3072 (s), 2936 (s), 1646 (s), 1474 (s), 1274 (m), 1026 (m). HRMS (EI') Calcd for C$_{18}$H$_{24}$NBr [M + H]: 333.1087. Found: 333.1089.

**Representative procedure 2.4:** Used to desymmetrize trialkylamines via ARCM to produce 4-methyl-2-(2-methyl-allyl)-1-aryl-1,2,3,6-tetrahydro-pyridines. Catalyst
(R)-1.11a (38 mg, 36 μmol) was added in a single portion to a benzene (1.0 mL) solution of amine 2.67b (285 mg, 1 mmol) in a loosely capped vial, and stirred under N₂ atmosphere. After 20 min, ¹H NMR of an aliquot indicated the reaction to be complete. The reaction mixture was exposed to ambient atmosphere, and concentrated in vacuo to a brown oil. The crude material was purified via column chromatography on silica, eluting with ether in pentane (1:9) to afford an off-white solid.

4-Methyl-2-(2-methyl-allyl)-1-phenyl-1,2,3,6-tetrahydro-pyridine (2.68a):

Prepared via procedure 2.4 using catalyst (R)-1.11a in 78% yield (177 mg, 0.78 mmol). ¹H NMR (500 MHz, C₆D₆): δ 7.3 (m, 2H), 6.8 (m, 3H), 5.3 (m, 1H), 4.8 (s, 1H), 4.7 (s, 1H), 4.2 (m, 1H), 3.6 (ddd, 1H, J = 0.9 Hz, 1.2 Hz, 16.8 Hz), 3.3 (ddd, 1H, J = 0.9 Hz, 1.2 Hz, 16.8 Hz), 2.3 (d, 1H, J = 16.8 Hz), 2.2 (dd, 1H, J = 13.3 Hz, 10.1 Hz), 2.1 (dd, 1H, J = 13.2 Hz, 4.0 Hz), 1.9 (d, 1H, J = 16.8 Hz), 1.6 (s, 3H), 1.5 (s, 3H). ¹³C NMR (75 MHz, C₆D₆): δ 150.2, 144.2, 130.5, 129.9, 118.8, 118.4, 115.1, 113.1, 50.8, 44.1, 37.3, 32.6, 23.8, 22.7. IR (KBr): 3070 (m), 2834 (s), 1597 (s), 1498 (s), 1339 (m), 1234 (s), 1008 (m). HRMS (El⁺) Calcd for C₁₆H₂₁N [M + H]: 227.1669. Found: 227.1682. HPLC (Chiralcel OJ, 0.2% iPrOH in hexane, 1.0 mL/min, 254 nm) 98% e.e. [α]D = + 18.1 ± 0.1° (c = 0.95, CHCl₃).

4-Methyl-2-(2-methyl-allyl)-1-paramethoxyphenyl-1,2,3,6-tetrahydro-pyridine (2.68b): Prepared via procedure 2.4 using catalyst (R)-1.11a in 81% yield (208 mg, 0.8 mmol). ¹H NMR (500 MHz, C₆D₆): δ 6.9 (d, 2H, J = 9.2 Hz), 6.8 (d, 2H, J = 9.2 Hz), 5.3 (m, 1H), 4.8 (m, 1H), 4.7 (m, 1H), 4.0 (m, 1H), 3.5 (m, 1H), 3.4 (s, 3H), 3.3 (m, 1H), 2.4 (m, 1H), 2.2 (m, 1H), 2.1 (m, 1H), 1.9 (m, 1H), 1.7 (s, 3H), 1.6 (s, 3H). ¹³C NMR (125 MHz, C₆D₆): δ 153.6, 144.7, 144.4, 130.7, 119.1, 117.6, 115.4, 113.0, 55.5, 52.6, 44.9, 37.0, 32.9, 23.9, 22.8. IR (KBr): 3078 (m), 2912 (m), 1644 (m), 1512 (s), 1384 (s), 1230 (s), 1175 (s), 1039 (s). HRMS (El⁺) Calcd for C₁₇H₂₃NO [M + H]: 257.1774. Found: 257.1777. Anal Calcd. for C₁₇H₂₃NO: C, 79.33; H, 9.01; N, 5.44. Found: C, 79.86; H,
9.54; N, 5.18. HPLC (Chiralcel OJ, 10 % iPrOH in hexane, 1.0 mL/min, 235 nm) 94 % e.e. \([\alpha]D^0 = +15.2 \pm 0.1^\circ \) (c = 1.15, CHCl₃).

4-Methyl-2-(2-methyl-allyl)-1- *para* bromophenyl -1,2,3,6-tetrahydro-pyridine (2.68c): Prepared via procedure 2.4 using catalyst (R)-1.11a in 81 % yield (200 mg, 0.66 mmol). \(^1\)H NMR (500 MHz, C₆D₆): \(\delta\) 7.30 (dd, 2H, J = 7.0, 2.1 Hz, aryl CH), 6.43 (dd, 2H, J = 7.0, 2.1 Hz, aryl CH), 5.21 (m, 1H, CH=CH₃), 4.73 (s, 2H, CCH₃=CH₉H₅), 4.64 (s, 2H, CCH₃=CH₉H₅), 3.92 (pentet, 1H, J = 4.5 Hz, NCHCH₂), 3.35 (br d, 1H, J = 16.8 Hz, NCH₉H₅CH), 3.11 (br d, 1H, J = 16.8 Hz, NCH₉H₅CH), 2.20 (br d, 1H, J = 16.8 Hz, CCH₃H₅C), 2.05 (dd, 1H, J = 10.1, 13.4 Hz, CCH₃H₅C), 1.93 (dd, 1H, J = 4.6, 13.4 Hz, CCH₃H₅C), 1.82 (br d, 1H, J = 16.8 Hz, CCH₃H₅C), 1.60 (s, 3H, CH₃), 1.50 (s, 3H, CH₃). \(^{13}\)C NMR (125 MHz, C₆D₆): \(\delta\) 150.0, 143.8, 132.6, 130.5, 118.3, 116.5, 113.4, 110.2, 50.7, 44.0, 37.4, 32.5, 23.8, 22.7. IR (Neat): 3069 (m), 2926 (m), 1592 (m), 1497 (s), 1457 (m), 1388 (m), 1238 (m), 1176 (m). HRMS (EI): Calcd for C₁₆H₂₀NBr [M + H]: 305.0774. Found: 305.0763. HPLC (Chiralpak AD, 0.1 % iPrOH in hexane, 1.0 mL/min, 254 nm) 97 % e.e. \([\alpha]D^0 = +15.4 \pm 0.1^\circ \) (c = 1.0, CHCl₃). X-ray quality crystals (white rods) were grown from a methanol solution.

Figure 2.10 Fully labeled ORTEP representation of C₁₆H₂₀NBr, 2.68c.
Table 2.5 Crystal data and structure refinement for C\textsubscript{16}H\textsubscript{26}NBr, 2.68c.

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Data / restraints / parameters 1755 / 1 / 166

Goodness-of-fit on $F^2$ 1.122

Final R indices [I>2σ(I)] $R_I = 0.0416, wR_2 = 0.1176$

R indices (all data) $R_I = 0.0426, wR_2 = 0.1188$

Absolute structure parameter $-0.002(16)$

Extinction coefficient 0.003(4)

Largest diff. peak and hole 0.640 and $-0.617$ e.$Å^{-3}$

Further data may be obtained by referring to the Cambridge Crystallographic Database.

4-Methyl-2-(2-methyl-allyl)-1- orthomethoxyphenyl -1,2,3,6-tetrahydro-pyridine (2.68d): Prepared via procedure 2.4 using catalyst (R)-1.18a in 77 % yield (181 mg, 0.7 mmol). $^1$H NMR (500 MHz, C$_6$D$_6$): δ 7.0 (m, 3H), 6.7 (m, 1H), 5.4 (m, 1H), 4.8 (m, 2H), 4.3 (m, 1H), 3.8 (m, 1H), 3.4 (s, 3H), 3.3 (m, 1H), 2.6 (m, 1H), 2.3 (m, 2H), 1.9 (m, 1H), 1.7 (s, 3H), 1.6 (s, 3H). $^{13}$C NMR (125 MHz, C$_6$D$_6$): δ 153.8, 144.7, 141.6, 131.4, 122.7, 121.9, 121.3, 119.8, 113.1, 112.8, 55.7, 52.6, 45.8, 38.7, 33.4, 24.1, 22.7. IR (NaCl): 3068 (s), 2910 (s), 1644 (s), 1500 (s), 1294 (s). (El$^+$) Calcd for C$_{17}$H$_{23}$NO [M + H]: 257.1774. Found: 257.1784. HPLC (Chiralcel OJ, 0.1 % iPrOH in hexane, 1.0 mL/min, 245 nm) 90 % e.e. [α]$^D = +6.6 \pm 0.1^\circ$ (c = 1.0, CHCl$_3$).

4-Methyl-2-(2-methyl-allyl)-1- orthobromophenyl -1,2,3,6-tetrahydro-pyridine (2.68e): Prepared via procedure 2.4 using catalyst (R)-1.18a in 90 % yield (250 mg, 0.8 mmol). $^1$H NMR (500 MHz, C$_6$D$_6$): δ 7.5 (m, 2H), 7.0 (m, 1H), 6.9 (m, 1H), 6.6 (m, 1H), 5.3 (m, 1H), 4.7 (m, 2H), 4.0 (m, 1H), 3.7 (m, 1H), 3.2 (m, 1H), 2.5 (m, 1H), 2.3 (m, 2H), 1.8 (m, 1H), 1.6 (s, 3H), 1.5 (s, 3H). $^{13}$C NMR (125 MHz, C$_6$D$_6$): δ 150.8, 144.1, 134.6, 131.8, 124.4, 123.7, 121.0, 119.3, 113.3, 107.1, 54.0, 46.3, 38.3, 32.0, 24.0, 22.6. IR
(Neat): 3068 (m), 2910 (s), 1645 (m), 1473 (s), 1387 (m), 1224 (w), 1067 (w). Anal Calcd. for C₁₆H₂₀NBr: C, 62.75; H, 6.58; N, 4.57. Found: C, 63.02; H, 6.55; N, 4.36. HPLC (Chiralcel OJ, 0.2 % iPrOH in hexane, 1.0 mL/min, 265 nm) 78 % e.e. [α]D = +3.3 ± 0.1° (c = 1.0, CHCl₃).

**Representative procedure 2.5: Used for the preparation of (1-allyl-but-3-enyl)-aryl-amines.** Ethyl-N-phenylformimidate (5.9 g, 33 mmol) was slowly added to commercial allyl magnesium chloride (50 mL, 2.0 M in THF) to produce an exotherm. The mixture was stirred for 12 h and then quenched by the slow addition of 100 mL of water. The resulting aqueous layer was washed three times with 60 mL portions of Et₂O. The organic extracts were combined and washed with 180 mL of a saturated solution of ammonium chloride, followed by 180 mL of a saturated solution of sodium chloride. After drying over MgSO₄, the organic extract was filtered and concentrated *in vacuo* to a brown oil. The product was purified by silica gel chromatography (5 % Et₂O in pentane) to give (1-allyl-but-3-enyl)-phenyl-amine as a colorless oil.

**(1- Allyl-but-3-enyl)-phenyl-amine: (Used in the synthesis of 2.72.)** Prepared via procedure 2.5 in 97% yield (6.0 g, 32 mmol). ¹H NMR (500 MHz, C₆D₆): δ 7.17 (m, 2H, ArH), 6.74 (m, 1H, ArH), 6.46 (m, 1H, ArH), 5.65 (m, 2H, CH(CH₂CH=CH₂)₂), 5.00 (m, 4H, CH(CH₂CH=CH₂)₂), 3.30 (m, 1H, CH(CH₂CH=CH₂)₂), 3.20 (s(br), 1H, NH), 2.07 (m, 4H, CH(CH₂CH=CH₂)₂). ¹³C NMR (100 MHz, C₆D₆): δ 148.2, 135.6, 130.0, 117.9, 117.7, 114.1, 52.4, 38.8. IR (Neat): 3408 (m), 3076 (m), 2924 (m), 1832 (w), 1640 (m), 1602 (s), 1506 (s), 1432 (s), 1319 (s), 1264 (s), 1180 (m), 1030 (s). HRMS (El⁺) Calcd for C₁₃H₁₇N [M + H]: 187.1356. Found: 187.1360.
(1- Allyl-but-3-enyl)-para-methoxyphenyl-amine: (Used in the synthesis of 2.76 and 2.78.) Prepared via procedure 2.5 in 80% yield (5.8 g, 26 mmol). $^1$H NMR (500 MHz, CD$_2$Cl$_2$): δ 6.81 (m, 2H, ArH), 6.43 (m, 2H, ArH), 5.70 (m, 2H, CH=CH$_2$), 5.00 (m, 4H, CH=CH$_2$), 3.41 (s, 3H, CH$_3$O), 3.27 (m, 1H, CH(CH$_2$CH=CH$_2$)$_2$), 3.01 (s(br), 1H, NH), 2.16–2.08 (m, 4H, CH(CH$_2$CH=CH$_2$)$_2$). $^{13}$C NMR (125 MHz, CD$_2$Cl$_2$): δ 153.1, 142.3, 135.8, 117.7, 115.6, 55.7, 53.5, 38.8. IR (Neat): 3397 (m), 3075 (m), 2909 (m), 2832 (m), 1841 (w), 1640 (s), 1514 (s), 1440 (s), 1241 (s), 1180 (m), 1040 (s). HRMS (EI$^+$) Calcd for C$_{14}$H$_{19}$NO [M + H]: 217.1416. Found: 217.1466.

**Allyl-(1-allyl-but-3-enyl)-phenyl-amine (2.72):** Prepared via procedure 2.3, in 82% yield (2.9 g, 13 mmol). $^1$H NMR (300 MHz, CD$_2$Cl$_2$): δ 7.17 (m, 2H, ArH), 6.74 (m, 3H, ArH), 5.61 (m, 3H, CH=CH$_2$), 5.05–4.85 (m, 6H, CH=CH$_2$), 3.79 (pentet, J = 7.7 Hz, 1H, CH(C$_2$H$_2$CH=CH$_2$)$_2$), 3.57 (m, 2H, NCH$_2$CH=CH$_2$), 2.07 (m, 4H, CH(CH$_2$CH=CH$_2$)$_2$). $^{13}$C NMR (75 MHz, CD$_2$Cl$_2$): δ 150.1, 137.2, 136.7, 129.7, 117.7, 117.0, 116.1, 114.8, 59.0, 47.1, 37.9. IR (Neat): 3076 (m), 2977 (m), 1640 (m), 1598 (s), 1503 (s), 1392 (m), 1230 (m), 1167 (m), 1039 (m). HRMS (EI$^+$) Calcd for C$_{16}$H$_{21}$N [M + H]: 227.1669. Found: 227.1673.

**2- Allyl-1-phenyl-1,2,3,6-tetrahydro-pyridine (2.73):** Precooled (−35 °C) solutions of amine 2.72 (90 mg, 0.39 mmol) and various chiral Mo–catalysts (i.e., catalyst (R)-1.11a) were combined in a J. Young tube; which was then allowed to warm to room temperature over 5 minutes. $^1$H NMR of the reaction mixture indicated no starting amine remained. The reaction was diluted with ether, stirred with charcoal, then filtered over celite with copious ether washing. The crude mixture was concentrated in vacuo, then purified via column chromatography (silica gel), eluting with 4% ether in pentane to isolate a clear, colorless oil. $^1$H NMR (500 MHz, CD$_2$Cl$_2$): δ 7.25 (m, 2H, aryl CH), 6.83 (t, 1H, J = 7.5 Hz, aryl CH), 6.76 (d, 2H, J = 7.5 Hz, aryl CH), 5.62 – 5.49 (m, 3H, CH=CH$_2$), 4.91 (m, 2H, CH=CH$_2$), 3.92 (m, 1H, NCHCH)
3.52 (br dd, 1H, J = 2.5, 17.5 Hz, NCH₄H₆CH), 3.25 (br dd, 1H, J = 2.5, 17.5 Hz, NCH₄H₆CH), 2.30 (br d, 1H, J = 17.0 Hz, CCH₄H₆C), 2.20 – 2.07 (m, 2H, CCH₂C), 1.91 (br d, 1H, J = 17.0 Hz, CCH₄H₆C). ¹³C NMR (125 MHz, C₆D₆): δ 137.0, 129.9, 128.7, 125.1, 123.2, 118.5, 116.9, 115.2, 52.4, 44.0, 33.9, 28.4. IR (Neat): 3036 (m), 2922 (m), 1639 (m), 1598 (s), 1502 (s), 1390 (m), 1237 (m), 1036 (m). HRMS (EI⁺) Calcd for C₁₄H₁₇N [M + H]: 199.1356. Found: 199.1360. HPLC (Chiralpak AD, 0.1 % iPrOH in hexane, 0 °C, 1.0 mL/min, 254 nm).

**Cyclopent–3–enyl–(4–methoxy–phenyl)–amine:** (Used in the synthesis of 2.76.)

Catalyst 1.1a (200 mg, 276 µmol) was added to a yellow solution of (1–Allyl–but–3–neyl)–para–methoxyphenyl–amine (2 g, 9.2 mmol) in benzene (40 mL) under an N₂ atmosphere, whereupon the mixture turned ruby–red. After 2 hours, the reaction was exposed to air, then concentrated in vacuo. The crude material was purified by column chromatography (silica gel), eluting with 20 % ether in pentane, to afford 1.57 g (8.6 mmol, 93 % yield) of a dark–orange oil. ¹H NMR (500 MHz, C₆D₆): δ 6.83 (d, 2H, J = 8.9 Hz, aryl CH), 6.40 (d, 2H, J = 8.9 Hz, aryl CH), 5.54 (m, 2H, CH=CH), 3.86 (m, 1H, NCH(CH₂CH=)₂), 3.42 (s, 3H, CH₃O), 3.12 (br, 1H, NH), 2.50 (dd, J = 7.3 Hz, 15.3 Hz, NCH(CH₄H₆CH=)₂), 2.02 (dd, J = 3.8 Hz, 18.6 Hz, NCH(CH₄H₆CH=)₂). ¹³C NMR (125 MHz, C₆D₆): δ 153.0, 142.6, 129.6, 128.7, 115.6, 115.3, 55.7, 53.5, 40.9. IR (Neat): 3391 (m), 3055 (m), 2832 (s), 1616 (m), 1511 (s), 1464 (s), 1350 (m), 1236 (s), 1180 (s), 1039 (s). HRMS (ESI) Calcd for C₁₂H₁₅NO [M + H]: 190.1226. Found: 190.1235.

**Allyl–cyclopent–3–enyl–(4–methoxy–phenyl)–amine (2.76):** Prepared via procedure

2.3, in > 98 % yield (1.5 g, 6.3 mmol). ¹H NMR (500 MHz, C₆D₆): δ 6.84 (d, 2H, J = 9.0 Hz, aryl CH), 6.76 (d, 2H, J = 9.0 Hz, aryl CH), 5.76 (m, 1H, CH₂CH=CH₂), 5.58 (m, 2H, CH=CH), 5.20 (dd, 1H, J = 0.9 Hz, 17.1 Hz, CH=CH₄H₆), 5.03 (dd, 1H, J = 0.9 Hz, 10.1 Hz, CH=CH₄H₆), 4.26 (m, 1H,
NCH(CH₂CH=)=₂), 3.54 (m, 2H, CH₂CH=CH₂), 3.41 (s, 3H, CH₃O), 2.45 (dd, J = 8.9 Hz, 15.0 Hz, NCH(CH₄H₅CH=)=₂), 2.31 (dd, J = 8.9 Hz, 15.0 Hz, NCH(CH₄H₅CH=)=₂). ¹³C NMR (125 MHz, C₆D₆): δ 153.6, 144.8, 137.4, 130.2, 118.2, 115.6, 115.2, 59.1, 55.6, 52.4, 37.5. IR (Neat): 3052 (m), 2907 (m), 1642 (w), 1512 (s), 1464 (m), 1387 (w), 1287 (m), 1243 (s), 1205 (s), 1181 (m), 1042 (s). HRMS (El⁺) Calcd for C₁₅H₁₉NO [M + H]: 229.1462. Found: 229.1459.

2- Allyl-1-(4-methoxy-phenyl)-1,2,3,6-tetrahydro-pyridine (2.77): Precooled (−35°C) solutions of amine 2.76 (61 mg, 0.26 mmol) and various chiral Mo-catalysts (i.e., catalyst (R)-1.11a, 10 mg, 13 μmol) were combined in a J. Young tube; which was then allowed to warm to room temperature over 5 minutes. ¹H NMR of the reaction mixture indicated no starting amine remained, therefore the reaction was diluted with ether, stirred with charcoal, then filtered over celite with copious ether washing. The crude mixture was concentrated in vacuo, then purified via column chromatography (silica gel), eluting with 20% ether in pentane to isolate a clear, colorless oil. ¹H NMR (500 MHz, C₆D₆): δ 6.88 (d, 2H, J = 9.2 Hz, aryl CH), 6.77 (d, 2H, J = 9.2 Hz, aryl CH), 5.66 – 5.52 (m, 3H, CH=CH & CH=CH₂), 4.97 – 4.92 (m, 2H, CH=CH₂), 3.79 (m, 1H, NCH(CH₂CH=)=₂), 3.48 – 3.44 (m, 1H, NCH₃H₆), 3.42 (s, 3H, CH₃O) 3.34 – 3.30 (m, 1H, NCH₃H₆), 2.40 – 1.92 (m, 4H, NCH(CH₄H₅CH=)=₂). ¹³C NMR (75 MHz, C₆D₆): δ 153.8, 144.9, 137.3, 125.5, 123.5, 117.8, 116.8, 115.3, 55.5, 45.0, 33.6, 28.7.

(1-Allyl-but-3-enyl)-(4-methoxy-phenyl)-(2-methyl-allyl)-amine (2.78): Prepared via procedure 2.3 (using 3-bromo-2-methyl-propene as the alkylation agent) in 65% yield (1.2 g, 4.5 mmol). ¹H NMR (500 MHz, C₆D₆): δ 6.82, (m, 4H, ArH), 5.78 (m, 1H, CH=CH₂), 5.04–4.86 (m, 6H, C=CH₂), 3.65 (pentet, J = 7.6 Hz, 1H, CH(CH₂CH=CH₂), 3.47 (s, 2H, NCH₂C), 3.38 (s, 3H, CH₃O), 2.27–2.05 (m, 4H, CH(CH₂CH=CH₂)), 1.59 (s, 3H, (CH₃)C=CH₂). ¹³C NMR (125
MHz, C₆D₆): δ 153.7, 144.3, 143.7, 137.3, 119.2, 116.8, 115.0, 112.5, 62.3, 55.5, 51.7, 37.6, 20.9. IR (Neat): 3075 (m), 2932 (m), 1640 (m), 1511 (s), 1464 (m), 1242 (s), 1041 (m). HRMS (El⁺) C₁₈H₂₅NO [M + H]: 271.1931. Found: 271.1938.

2-Allyl-1-(4-methoxy-phenyl)-5-methyl-1,2,3,6-tetrahydro-pyridine (2.79) and Cyclopent-3-enyl-(4-methoxy-phenyl)-2(2-methyl-allyl)-amine (2.80): Catalyst (R)-1.11a (14 mg, 14 µmol) was added in a single portion to a benzene (1.0 mL) solution of amine 2.78 (100 mg, 0.3 mmol) in a loosely capped vial, and stirred under N₂ atmosphere. After 12 hours, ¹H NMR of an aliquot indicated the reaction to be a mixture of two species. The reaction mixture was exposed to ambient atmosphere, and concentrated in vacuo to a brown oil. The crude material was purified via column chromatography on silica, eluting with ether in pentane (1:19) to afford an off-white solid. The first material to come of the column was identified as 2.80, (25 mg, 84 µmol) in 28 % yield, the second was identified as 2.79, (25 mg, 84 µmol) also in 28 % yield. Spectral data are given below.

2-Allyl-1-(4-methoxy-phenyl)-5-methyl-1,2,3,6-tetrahydro-pyridine (2.79): ¹H NMR (500 MHz, C₆D₆): δ 6.89 (m, 2H, aryl CH), 6.79 (m, 2H, aryl CH), 5.66 (m, 1H, CH=CH₂), 5.37 (m, 1H, CH₂CH=CH(CH₃)), 4.98 – 4.93 (m, 2H, CH=CH₂), 3.79 (m, 1H, NCH₂CH₂), 3.43 (s, 3H, CH₃O), 3.37 (br d, 1H, J = 16.8 Hz, NCH₃H₆CH), 3.26 (br d, 1H, J = 16.8 Hz, NCH₃H₆CH), 2.38 (br m, 1H, CCH₃H₆C), 2.20 (dt, 1H, J = 13.7, 3.1 Hz, CCH₃H₆C), 2.11 (dt, 1H, J = 13.7, 8.9 Hz, CCH₃H₆C), 1.98 (br dd, 1H, J = 3.1, 16.8 Hz, CCH₃H₆C), 1.54 (s, 3H, CH₃C). ¹³C NMR (125 MHz, C₆D₆): δ 153.8, 144.8, 137.3, 131.8, 118.4, 118.0, 116.8, 115.3, 55.5, 54.1, 49.1, 33.7, 28.5, 21.1. IR (Neat): 3074 (m), 2927 (s), 1639 (m), 1511 (s), 1394 (m), 1245 (s), 1181 (m), 1041 (s). HRMS (El⁺) Calcd for C₁₆H₂₁NO [M + H]: 243.1618. Found: 243.1614. HPLC (Chiralcel OJ, 10 % iPrOH in hexane, 1.0 mL/min, 254 nm).
Cyclopent-3-enyl-(4-methoxy-phenyl)-2(2-methyl-allyl)-amine (2.80): \(^1\)H NMR (500 MHz, CD\(_2\)Cl\(_2\)): \(\delta\) 6.86 (m, 2H, aryl CH), 6.73 (m, 2H, aryl CH), 5.59 (m, 2H, CH=CH), 5.11 (m, 1H, CH\(_2\)C(CH\(_3\))=CH\(_2\)H\(_b\)), 4.88 (m, 1H, CH\(_2\)C(CH\(_3\))=CH\(_2\)H\(_b\)), 4.33 (m, 1H, NCH\(_2\)CH\(_2\)), 3.42 (s, 3H, CH\(_3\)O), 3.41 (s, 2H, NCH\(_2\)C), 2.45 (m, 2H, NCH\(_2\)H\(_b\)CH), 2.36 (m, 2H, NCH\(_2\)H\(_b\)CH), 1.56 (s, 3H, CH\(_3\)C). \(^{13}\)C NMR (125 MHz, CD\(_2\)Cl\(_2\)): \(\delta\) 153.3, 144.9, 143.9, 130.3, 117.1, 115.2, 111.3, 58.9, 55.6, 55.4, 37.2, 30.2, 20.5. IR (Neat): 3052 (m), 2930 (s), 1656 (m), 1512 (s), 1464 (s), 1387 (s), 1242 (s), 1042 (s). HRMS (EI\(^+\)) Calcd for C\(_{19}\)H\(_{21}\)NO [M + H]: 243.1618. Found: 243.1625.

2-Trimethyl-silyl-propenyl magnesium bromide: (Used in the synthesis of 2.81.)

\(n\)-BuLi (31 mL, 1.6 M) was added over 10 min to a suspension of isopropenyl-trimethyl-silane (10.4 g, 49 mmol) and potassium tert-butoxide (5.98 g, 49 mmol) in ether (100 mL) at -35 °C. The suspension was warmed to room temperature over 1 hour, then filtered and washed with ether to afford a bright yellow powder, 5.0 g (67 % yield). This powder (4.5 g, 29 mmol) was stirred in THF (100 mL) with magnesium dibromide (5.4 g, 29 mmol) for 18 hours. The suspension was then filtered over celite, to afford a pale yellow solution, which was titrated against cumylphenol, and found to be 1.08 M.

(4-Methoxy-phenyl)-[3-trimethylsilyl-1-(2-trimethylsilyl-allyl)-but-3-enyl]-amine: (Used in the synthesis of 2.81.)

Ethyl-N-\(\text{para-}\)methoxyphenylformimidate (2.58 g, 14.4 mmol) was added to a solution of 2-trimethylsilyl-propenyl magnesium bromide (30 mL, 1.08 M in THF), to produce a mild exotherm. The mixture was stirred overnight and then quenched by the slow addition of 200 mL water. The resulting aqueous layer was washed three times with 70 mL portions of Et\(_2\)O. The combined organic extracts were washed first with 200 mL of a saturated solution of ammonium chloride and then
with 200 mL of a saturated solution of sodium chloride. After drying over MgSO₄, the organic extract was filtered and concentrated in vacuo to a brown oil. The product was purified by silica gel chromatography (10 % Et₂O in pentane) to give a clear, colorless oil, 1.25 g, (3.5 mmol) 24 % yield. ¹H NMR (500 MHz, C₆D₆): δ 6.82 (m, 2H, aryl CH), 6.58 (m, 2H, aryl CH), 5.75 (m, 2H, C(TMS)=CH₃H₆), 5.50 (m, 2H, C(TMS)=CH₃H₈), 3.70 (pentet, 1H, J = 6.1 Hz, CH(CH₂R)₂), 3.38 (s, 3H, CH₃O), 3.12 (br, 1H, NH), 2.41 (d, 4H, J = 6.7 Hz, CH(CH₂R)₂), 0.11 (s, 9H, (CH₃)₃Si). ¹³C NMR (125 MHz, C₆D₆): δ 153.1, 150.5, 142.5, 127.3, 115.7, 115.2, 55.6, 53.0, 42.5, −0.7. IR (Neat): 3399 (m), 3048 (m), 2954 (s), 2832 (m), 1618 (w), 1512 (s), 1466 (m), 1247 (s), 1180 (m), 1042 (s). HRMS (ESI⁺) Calcd for C₃₀H₅₅NSi₂O [M + H]: 362.2330. Found: 362.2315.

**Allyl-(4-methoxy-phenyl)-[3-trimethylsilanyl-1-(2-trimethylsilanyl-allyl)-but-3-enyl]-amine (2.81):** Prepared via procedure 2.3 in 22 % yield (0.3 g, 0.7 mmol). ¹H NMR (500 MHz, C₆D₆): δ 6.95 (m, 2H, aryl CH), 6.88 (m, 2H, aryl CH), 5.81 (m, 1H, CH=CH₂), 5.79 (m, 2H, C(TMS)=CH₃H₆), 5.52 (m, 2H, C(TMS)=CH₃H₇), 5.19 (dd, 1H, J = 1.8 Hz, 17.4 Hz, CH=CH₃H₆), 5.04 (dd, 1H, J = 1.8 Hz, 10.4 Hz, CH=CH₃H₇), 4.17 (pentet, 1H, J = 7.0 Hz, CH(CH₂R)₂), 3.70 (m, 2H, NCH₂), 3.38 (s, 3H, CH₃O), 2.49 (dd, 2H, J = 7.0 Hz, J = 15.0 Hz, CH(CH₃H₆R)₂), 2.37 (dd, 2H, J = 6.7 Hz, J = 15.0 Hz, CH(CH₃H₇R)₂), 0.12 (s, 18H, (CH₃)₃Si). ¹³C NMR (125 MHz, C₆D₆): δ 153.5, 150.1, 143.9, 138.0, 128.9, 127.0, 118.4, 116.2, 115.2, 113.2, 59.5, 55.5, 48.1, 38.1, −0.9. IR (Neat): 3048 (m), 2954 (s), 2903 (s), 1642 (w), 1511 (s), 1464 (w), 1247 (s), 1181 (m), 1044 (m). HRMS (ESI⁺) Calcd for C₃₂H₅₉NSi₂O [M + H]: 402.2643. Found: 402.2630.

**1-(4-Methoxy-phenyl)-4-trimethylsilanyl-2-(2-trimethylsilanyl-allyl)-1,2,3,6-tetrahydro-pyridine (2.82):** Prepared via procedure 2.4 with catalyst 1.1a (2.0 mg, 2.6 μmol) and 2.81 (20 mg, 53 μmol); isolated 2.82 (5 mg, 13 μmol) in 25 % yield. ¹H NMR (500 MHz, C₆D₆): δ 6.92 (m, 4H,
aryl CH), 5.98 (m, 1H, C(TMS)=CH₂Hₓ), 5.63 (m, 1H, C(TMS)=CH₂Hₓ), 5.44 (m, 1H, CH=C(TMS)), 4.18 (m, 1H, CH(CH₂R)₂), 3.51 (m, 2H, NCH₂), 3.42 (s, 3H, CH₃O), 2.51 – 2.32 (m, 4H, CH(CH₂HₓR)₂, CH(CH₂HₓR)₂), 0.14 (s, 9H, (CH₃)₃Si), 0.06 (s, 9H, (CH₃)₃Si). ¹³C NMR (125 MHz, C₆D₆): δ 153.9, 150.7, 144.7, 134.8, 133.7, 127.3, 118.0, 115.4, 55.5, 53.3, 46.1, 35.1, 30.2, 29.3, –0.7, –1.7. IR (Neat): 2955 (s), 2832 (m), 1511 (s), 1454 (m), 1247 (s), 1181 (m), 1045 (m).

Representative procedure 2.6: Used for preparation of But–3– and Pent–4–enoic acid [3–methyl–1–(2–methyl–allyl)–but–3–enyl]–phenyl–amides. 4–Pentenoyl chloride (1.10 mL, 10.2 mmol) was added to a stirring solution of [3–methyl–1–(2–methyl–allyl)–but–3–enyl]–phenyl–amine (2.00 g, 9.30 mmol), pyridine (0.95 mL, 10.2 mmol), and 4–dimethylamino–pyridine (58.0 mg, 0.500 mmol) in 200 mL of CH₂Cl₂ at 0 °C. The resulting mixture was allowed to warm to room temperature (22 °C) over 2 h, and then quenched by the slow addition of 300 mL water. The resulting aqueous layer was washed three times with 175 mL portions of CH₂Cl₂. The organic extracts were combined, washed with 500 mL of a saturated solution of ammonium chloride, followed by 500 mL of a saturated solution of sodium chloride. After drying over MgSO₄, the organic extract was filtered and concentrated in vacuo to a brown oil. The product was purified by silica gel chromatography (20 % Et₂O in pentane) to give but–3–enoic acid [3–methyl–1–(2–methyl–allyl)–but–3–enyl]–phenyl–amide as a clear yellow oil.

But–3–enoic acid [3–methyl–1–(2–methyl–allyl)–but–3–enyl]–phenyl–amide: (Used in the synthesis of 2.83.) Prepared via procedure 2.6 in 57 % yield (1.0 g, 3.7 mmol). ¹H NMR (500 MHz, C₆D₆): δ 7.0 (m, 5H, ArH), 6.1 (m, 1H, C(O)CH₂CH=CH₂), 5.6 (br s, 1H, CH(CH₂CCH₃=CH₂)₂), 5.0–4.8 (m, 6H, CH=CH₂), 2.8 (m, 2H, C(O)CH₂CH=CH₂), 2.2–1.9 (m, 4H, CH(CH₂CCH₃=CH₂)₂), 1.8 (s, 6H, CH(CH₂CCH₃=CH₂)₂). ¹³C NMR (125 MHz, C₆D₆): δ 170.3, 143.6, 133.6, 131.1, 129.5, 117.2, 113.2, 41.9, 41.8, 40.8, 23.1. IR (Neat): 3074
(m), 2971 (m), 1658 (s), 1595 (s), 1495 (s), 1376 (s), 1242 (s), 1029 (m). HRMS (EI')
C_{19}H_{25}NO [M + H]: 283.1931. Found: 283.1937.

**Pent-4-enoic acid [3-methyl-1-(2-methyl-allyl)-but-3-ethyl]-phenyl-amide:** *(Used in the synthesis of 2.85.)* Prepared via procedure 2.6 in 96% yield (2.7 g, 8.9 mmol). $^1$H NMR (500 MHz, C$_6$D$_6$): δ 7.02 (m, 5H, ArH), 5.74 (m, 1H, C(O)CH$_2$ CH$_2$CH=CH$_2$), 5.60 (s(br), 1H, CH(CH$_2$CCH$_3$=CH$_2$)$_2$), 4.99–4.85 (m, 6H, CH=CH$_2$), 2.44 (m, 2H, C(O)CH$_2$CH$_2$CH=CH$_2$), 2.18–2.02 (m, 4H, CH(CH$_2$CCH$_3$=CH$_2$)$_2$), 1.96 (t, 2H, C(O)CH$_2$ CH$_2$CH=CH$_2$), 1.76 (s, 6H, CH(CH$_2$CCH$_3$=CH$_2$)$_2$). $^{13}$C NMR (125 MHz, C$_6$D$_6$): δ 171.6, 143.7, 138.5, 131.1, 129.6, 128.7, 115.2, 113.1, 41.9, 35.3, 30.4, 23.1. IR (Neat): 3295 (w), 3074 (s), 2917 (s), 1818 (w), 1654 (s), 1595 (s), 1495 (s), 1377 (s), 1269 (s), 1172 (m), 1029 (m). HRMS (EI') C$_{20}$H$_{27}$NO [M + H]: 297.2087. Found: 297.2081.

**Representative procedure 2.7:** *Used for preparation of But-3- and Pent-4-ethyl-[3-methyl-1-(2-methyl-allyl)-but-3-ethyl]-phenyl-amine.* Lithium aluminum hydride (654 mg, 17.0 mmol) was added to a solution of but-3-enoic acid [3-methyl-1-(2-methyl-allyl)-but-3-ethyl]-phenyl-amide (6.90 mmol in 125 mL Et$_2$O). A reflux condenser was affixed to the top of the flask, and the mixture was then heated at reflux for 12 h. The reaction was allowed to cool to room temperature (22 °C) and then quenched by the slow addition of 125 mL of water. The resulting aqueous layer was washed with three 70 mL portions of Et$_2$O. The combined organic layers were dried over MgSO$_4$, filtered, and concentrated to give but-3-ethyl-[3-methyl-1-(2-methyl-allyl)-but-3-ethyl]-phenyl-amine (2.83) as a cloudy, colorless oil.

**But-3-ethyl-[3-methyl-1-(2-methyl-allyl)-but-3-ethyl]-phenyl-amine (2.83):**

Prepared via procedure 2.7, in 61% yield (0.5 g, 1.9 mmol). $^1$H NMR (500 MHz, C$_6$D$_6$): δ 7.24 (m, 2H, ArH), 6.87 (d, J = 8.9 Hz, 2H, ArH),
6.77 (t, \( J = 7.3 \) Hz, 1H, ArH), 5.73 (m, 1H, NCH\(_2\)CH\(_2\)CH=CH\(_2\)), 5.03 (m, 2H, NCH\(_2\)CH\(_2\)CH=CH\(_2\)), 4.77 (s(br), 4H, NCH(CH\(_2\)CCH\(_3\)=CH\(_2\))), 4.18 (pentet, 1H, \( J = 7.3 \) Hz, NCH(CH\(_2\)CCH\(_3\)=CH\(_2\))), 3.12 (m, 2H, NCH\(_2\)CH\(_2\)CH=CH\(_2\)), 2.29 (m, 2H, NCH\(_2\)CH\(_2\)CH=CH\(_2\)), 2.19 (dd, \( J = 14.3 \), 7.6 Hz, 2H, NCH(CH\(_4\)H\(_6\)CCH\(_3\)=CH\(_2\))), 2.09 (dd, \( J = 14.3 \), 6.7 Hz, 2H, NCH(CH\(_4\)H\(_6\)CCH\(_3\)=CH\(_2\))), 1.59 (s, 6H, NCH(CH\(_2\)CCH\(_3\)=CH\(_2\))).

\(^{13}\)C NMR (125 MHz, C\(_6\)D\(_6\)): \( \delta \) 149.4, 143.7, 136.8, 130.0, 117.8, 116.3, 115.2, 113.2, 56.5, 43.4, 41.5, 33.3, 22.8. IR (Neat): 3074 (s), 2968 (s), 1646 (m), 1598 (s), 1502 (s), 1261 (m), 1039 (m). Anal Calcd. for C\(_{19}\)H\(_{25}\)N: C, 84.70; H, 10.10; N, 5.20. Found: C, 84.97; H, 10.40; N, 5.08.

**Pent-4-enyl-[3-methyl-1-(2-methyl-allyl)-but-3-enyl]-phenyl-amine (2.85):**
Prepared via procedure 2.7, in quantitative yield (2.0 g, 6.9 mmol). \(^1\)H NMR (500 MHz, C\(_6\)D\(_6\)): \( \delta \) 7.25 (m, 2H, ArH), 6.88 (d, \( J = 8.9 \) Hz, 2H, ArH), 6.78 (t, \( J = 7.3 \) Hz, 1H, ArH), 5.73 (m, 1H, NCH\(_2\)CH\(_2\)CH\(_2\)CH=CH\(_2\)), 4.99 (m, 2H, NCH\(_2\)CH\(_2\)CH\(_2\)CH=CH\(_2\)), 4.80 (m, 4H, NCH(CH\(_2\)CCH\(_3\)=CH\(_2\))), 4.19 (pentet, \( J = 7.3 \) Hz, 1H, NCH(CH\(_2\)CCH\(_3\)=CH\(_2\))), 3.04 (m, 2H, NCH\(_2\)CH\(_2\)CH\(_2\)CH=CH\(_2\)), 2.22 (dd, \( J = 14.3 \), 7.6 Hz, 2H, NCH(CH\(_4\)H\(_6\)CCH\(_3\)=CH\(_2\))), 2.12 (dd, \( J = 14.3 \), 7.0 Hz, 2H, NCH(CH\(_4\)H\(_6\)CCH\(_3\)=CH\(_2\))), 1.93 (m, 2H, NCH\(_2\)CH\(_2\)CH\(_2\)CH=CH\(_2\)), 1.61 (m, 8H, NCH(CH\(_2\)CCH\(_3\)=CH\(_2\)) & NCH\(_2\)CH\(_2\)CH\(_2\)CH=CH\(_2\)). \(^{13}\)C NMR (125 MHz, C\(_6\)D\(_6\)): \( \delta \) 143.8, 138.8, 129.4, 117.8, 115.4, 115.2, 113.2, 56.6, 43.5, 41.6, 32.2, 27.8, 22.8. IR (Neat): 3074 (m), 2969 (m), 1644 (m), 1598 (s), 1502 (s), 1442 (m), 1348 (m), 1266 (w), 1038 (w). Anal Calcd. for C\(_{20}\)H\(_{29}\)N: C, 84.75; H, 10.31; N, 4.94. Found: C, 84.56; H, 10.40; N, 5.02.

**4-Methyl-2-(2-methyl-allyl)-1-phenyl-2,3,6,7-tetrahydro-1H-azepine (2.84):**
Prepared via procedure 2.4, (catalyst (R)-1.11a, 95 % yield, 140 mg, 0.63 mmol). \(^1\)H NMR (500 MHz, C\(_6\)D\(_6\)): \( \delta \) 7.3 (m, 2H), 6.7 (m, 3H), 5.2 (m, 1H), 4.8 (m, 2H), 4.0 (m, 1H), 3.4 (m, 1H), 3.3 (m, 1H), 2.5 – 2.0 (m, 6H), 1.9 (m, 1H), 1.6 (s, 3H), 1.6 (s, 3H). \(^{13}\)C NMR (125 MHz, C\(_6\)D\(_6\)): \( \delta \) 149.4, 143.6,
133.6, 130.4, 123.8, 116.6, 113.2, 112.7, 55.9, 41.4, 41.3, 36.8, 28.9, 27.5, 23.0. IR (Neat): 3511 (m), 3071 (s), 2964 (s), 1910 (w), 1646 (s), 1380 (s), 1236 (s), 1034 (s). Anal Calcd for C_{19}H_{27}N: C, 84.70; H, 10.1; N, 5.20. Found: C, 84.97; H, 10.4; N, 5.08. HPLC (Chiralcel OD, 2.0 % iPrOH in hexane, 1.0 mL/min, 254 nm) 95 % e.e. [α]^D = -20.9 ± 0.1° (c = 1.0, CHCl_3).

**6-Methyl-8-(2-methyl-allyl)-1-phenyl-1,2,3,4,7,8-hexahydro-azocine (2.86):**

![Molecular structure of 6-Methyl-8-(2-methyl-allyl)-1-phenyl-1,2,3,4,7,8-hexahydro-azocine](image)

Prepared via procedure 2.7, (catalyst (S)-1.11c, 99 % yield, 82 mg, 0.35 mmol). ^1H NMR (500 MHz, C_6D_6): δ 7.3 (m, 2H), 6.7 (m, 3H), 5.4 (m, 1H), 4.8 (m, 2H), 4.2 (m, 1H), 3.3 (m, 1H), 3.0 (m, 1H), 2.3 (m, 1H), 2.0 – 1.8 (m, 3H), 1.7 (s, 3H), 1.6 (s, 3H). ^13C NMR (125 MHz, C_6D_6): δ 149.3, 143.6, 135.4, 130.1, 127.0, 116.2, 113.1, 112.2, 54.2, 41.2, 36.6, 30.2, 28.0, 22.7. IR (Neat): 3070 (m), 2963 (s), 1596 (s), 1503 (s), 1346 (s), 1232 (s), 1047 (s). HRMS (EI^+ ) Calcd for C_{19}H_{25}N [M + H]: 255.1982. Found: 255.1992. HPLC (Chiralcel OD, 0.1 % iPrOH in hexane, 1.0 mL/min, 254 nm) > 98 % e.e. [α]^D = + 9.0 ± 0.1° (c = 1.15, CHCl_3).

**2-Vinyl-phenylamine: (Used in the synthesis of substrates 2.95a–c, 2.100 and 2.101.)**

2-Amino-phenethylalcohol (18 g, 131 mmol) and potassium hydroxide (7.36 g, 131 mmol) were combined in a distillation apparatus, then heated to 180 °C under vacuum. A clear, colorless oil was distilled over 4 h at 55 – 60 °C at 0.25 Torr, 12.1 g (102 mmol, 78% yield). ^1H NMR (500 MHz, C_6D_6): δ 7.27 (dd, 1H, J = 1.5 Hz, 7.6 Hz, aryl CH), 6.99 (dt, 1H, J = 1.5 Hz, 7.3 Hz, aryl CH), 6.71 (dt, 1H, J = 1.2 Hz, 7.3 Hz, aryl CH), 6.57 (dd, 1H, J = 11.2 Hz, 17.4 Hz, ArCH=CH_2), 6.31 (dd, 1H, J = 0.9 Hz, 7.9 Hz, aryl CH), 5.50 (dd, 1H, J = 1.5 Hz, 17.4 Hz, CH=CH=CH_2=H), 5.09 (dd, 1H, J = 1.5 Hz, 11.2 Hz, CH=CH_2H_3), 3.00 (br, 2H, NH_2). This spectrum matches published material^{126–128} on this compound, therefore no further spectral data were obtained.
Representative procedure 2.8: Used for preparation of N-styrenylimidate esters.
2-Vinyl-phenylamine (2.15 g, 18 mmol), triethyl orthoformate (3.9 mL, 23 mmol) and
p-toluenesulfonic acid (20 mg, 90 μmol) were heated to 130 °C to remove 2 equivalents
of ethanol in a Dean–Stark condenser. After the mixture was cooled, residual orthoester
was removed at room temperature under Schlenk vacuum. Subsequently, the crude
material was distilled at reduced pressure with heating to afford of clear, colorless oil.

N-(2-Vinyl-phenyl)-formic acid ethyl ester: (Used in the synthesis of substrate
2.95a.) Prepared via procedure 2.8; distilled at 50 °C at 100 mTorr, in 68 %
yield (2.16 g, 12 mmol). 1H NMR (500 MHz, C6D6): δ 7.52 (dd, 1H, J = 1.5
Hz, 7.6 Hz, aryl CH), 7.37 (dd, 1H, J = 11.0 Hz, 17.7 Hz, aryl CH), 7.27 (s,
1H, N=CH), 6.99 (m, 2H, aryl CH + CH=CH2), 6.57 (dd, 1H, J = 1.5 Hz, 7.6 Hz, aryl
CH), 5.71 (dd, 1H, J = 17.7 Hz, 1.4 Hz, CH=CHtrans), 4.22 (dd, 1H, J = 11.1 Hz, 1.4
Hz, CH=CHcis, 3Htrans), 4.11 (q, 2H, J = 7.0 Hz, OCH2CH3), 1.06 (t, 3H, J = 7.0 Hz,
OCH2CH3). 13C NMR (125 MHz, C6D6): δ 154.8, 146.6, 134.4, 131.8, 129.2, 126.2,
125.0, 120.9, 114.1, 62.6, 14.6. IR (Neat): 3065 (m), 2932 (s), 1646 (s), 1594 (s), 1481
(s), 1390 (s), 1281 (s), 1201 (s), 1097 (s), 1054 (m). HRMS (El+) Calcd for C11H13NO [M + H]: 175.0992. Found: 175.0997.

N-(2-Vinyl-phenyl)-propionimidic acid ethyl ester: (Used in the synthesis of substrate
2.95b.) Prepared via procedure 2.8; distilled at 65 °C at 100 mTorr, 76 % yield (7.6 g, 38
mmol). 1H NMR (500 MHz, C6D6): δ 7.52 (dd, 1H, J = 1.2 Hz, J = 7.6 Hz, aryl CH), 7.05
(m, 2H, aryl CH & CH=CH2), 6.93 (td, 1H, J = 7.3 Hz, J = 0.6 Hz, aryl CH), 6.69 (dd,
1H, J = 1.2 Hz, 7.9 Hz, aryl CH), 5.65 (dd, 1H, J = 1.5 Hz, 17.7 Hz, CH=CHtrans), 5.15
(dd, 1H, J = 1.5 Hz, 11.0 Hz, CH=CHtrans), 3.14 (q, 2H, J = 7.1 Hz, OCH2CH3), 1.98 (q,
2H, J = 7.6 Hz, CCH2CH3), 1.14 (t, 3H, J = 7.1 Hz, OCH2CH3), 0.90 (t, 3H, J = 7.6 Hz,
CCH2CH3). 13C NMR (125 MHz, C6D6): δ 164.6, 147.8, 134.4, 129.7, 129.1, 126.4,
123.6, 122.0, 113.9, 61.9, 24.2, 14.7, 11.0. IR (Neat): 3086 (w), 2978 (s), 2897 (m), 1668
N-(2-Vinyl-phenyl)-benzimidic acid ethyl ester: (Used in the synthesis of substrate 2.95c.) Prepared via procedure 2.8; distilled at 90 – 100 °C, at 100 mTorr, 56 % yield. (4.5 g, 19 mmol). $^1$H NMR (500 MHz, C$_6$D$_6$): $\delta$ 7.50 (dd, 1H, $J = 7.3$ Hz, $J = 1.2$ Hz, aryl CH), 7.39 (dd, 1H, $J = 7.9$ Hz, $J = 1.5$ Hz, aryl CH), 7.25 (dd, 1H, $J = 17.7$, $J = 11.0$ Hz, CH=CH$_2$), 6.85 (m, 5H, aryl CH), 6.52 (dd, 1H, $J = 1.5$ Hz, 7.6 Hz, aryl CH), 5.71 (dd, 1H, $J = 1.5$ Hz, 17.7 Hz, CH=CH$_2$H$_a$H$_b$), 5.19 (dd, 1H, $J = 2.2$ Hz, 11.0 Hz, CH=CH$_2$H$_b$), 3.76 (s, 3H, OCH$_3$). $^{13}$C NMR (125 MHz, C$_6$D$_6$): $\delta$ 147.2, 134.4, 132.2, 130.5, 130.0, 129.8, 129.1, 126.4, 123.6, 122.2, 114.2, 54.1, 13.0. IR (Neat): 3085 (m), 3014 (m), 2943 (m), 2837 (w), 1665 (s), 1625 (s), 1595 (s), 1493 (m), 1413 (w), 1270 (s), 1192 (m), 1119 (s), 1074 (m), 1029 (m). HRMS (ESI') Calcd for C$_{16}$H$_{19}$NO [M + H]: 238.1226. Found: 238.1228.

Representative procedure 2.9: Used for preparation of [3-Methyl-1-(2-methyl-allyl)-alkenyl]-(2-vinyl-phenyl)-amines. Styrenyl imidate ester (1.62 g, 9.2 mmol) was added via syringe to methallyl Grignard (58 mL, 0.34 M) at −78 °C. After 1 min, TLC of an aliquot indicated the reaction to be complete, and it was quenched by addition of 1 mL of methanol. After the mixture had warmed to room temperature, 10% HCl$_{(aq)}$ was added. The biphasic mixture was extracted three times with ether. All organic extracts were combined, washed with saturated NaHCO$_3$ solution (50 mL), then NaCl solution (50 mL), dried over MgSO$_4$ and concentrated in vacuo to a yellow oil. The product was purified by column chromatography over silica gel, eluting with 1 % ether in pentane to afford a clear, bright yellow oil.
[3-Methyl-1-(2-methyl-allyl)-but-3-enyl]-(2-vinyl-phenyl) amine (2.95a): Prepared via procedure 2.9 in 82 % yield (1.8 g, 7.5 mmol). \(^1\)H NMR (500 MHz, C\(_6\)D\(_6\)): \(\delta\) 7.32 (dd, 1H, J = 1.5 Hz, 7.3 Hz, aryl CH), 7.19 (m, 1H, aryl CH), 6.79 (dd, 1H, J = 11.0 Hz, 17.4 Hz, CH=CH\(_2\)), 6.73 (m, 1H, aryl CH), 5.56 (dd, 1H, J = 1.5 Hz, 17.4 Hz, CH=CH\(_a\)H\(_b\)), 5.17 (dd, 1H, J = 1.5 Hz, 11.0 Hz, CH=CH\(_b\)H\(_a\)), 4.79 (m, 2H, CH\(_3\)C=CH\(_a\)H\(_b\)), 4.75 (m, 2H, CH\(_3\)C=CH\(_b\)H\(_a\)), 3.76 (br, 1H, NH), 3.65 (pentet, 1H, J = 6.7 Hz, CH(CH\(_2\)R\(_2\))), 2.15 (m, 4H, CH(CH\(_2\)R\(_2\))), 1.56 (s, 6H, CH\(_3\)C=CH\(_2\)). \(^13\)C NMR (125 MHz, C\(_6\)D\(_6\)): \(\delta\) 145.4, 143.6, 134.0, 129.8, 128.7, 125.3, 117.9, 116.3, 113.6, 111.3, 49.6, 43.7, 22.7. IR (Neat): 3420 (m), 3074 (m), 2933 (m), 1647 (m), 1602 (s), 1509 (s), 1459 (s), 1375 (m), 1317 (s), 1260 (m), 1186 (m). HRMS (El\(^+\)) Calcd for C\(_{17}\)H\(_{23}\)N [M + H]: 241.1825. Found: 241.1822.

[1-Ethyl-3-methyl-1-(2-methyl-allyl)-but-3-enyl]-(2-vinyl-phenyl) amine (2.95b): Prepared via procedure 2.9 in 15 % yield (0.4 g, 1.6 mmol). \(^1\)H NMR (500 MHz, C\(_6\)D\(_6\)): \(\delta\) 7.31 (dd, 1H, J = 7.6 Hz, J = 1.5 Hz, aryl CH), 7.13 (t, 1H, J = 8.2 Hz, aryl CH), 6.88 (d, 1H, J = 8.2 Hz, aryl CH), 6.73 (m, 2H, aryl CH & CH=CH\(_2\)), 5.50 (dd, 1H, J = 1.8 Hz, J = 17.4 Hz, CH=CH\(_a\)H\(_b\)), 5.12 (dd, 1H, J = 1.5 Hz, J = 11.0 Hz, CH=CH\(_b\)H\(_a\)), 4.89 (m, 2H, C=CH\(_a\)H\(_b\)), 4.79 (m, 2H, C=CH\(_b\)H\(_a\)), 3.90 (br s, 1H, NH), 2.50 (d, 2H, J = 14.4 Hz, CH\(_a\)H\(_b\)), 2.28 (d, 2H, J = 14.4 Hz, CH\(_b\)H\(_a\)), 1.68 (s, 6H, CH\(_3\)), 1.64 (q, 2H, J = 7.5 Hz, CH\(_2\)CH\(_2\)), 0.80 (t, 3H, J = 7.5 Hz, CH\(_3\)CH\(_3\)). \(^13\)C NMR (125 MHz, C\(_6\)D\(_6\)): \(\delta\) 143.2, 134.5, 129.3, 129.0, 117.5, 116.9, 115.9, 114.2, 43.9, 30.8, 25.1, 9.2. IR (Neat): 3416 (m), 3073 (m), 2968 (s), 1640 (m), 1603 (s), 1514 (s), 1461 (s), 1374 (m), 1317 (s), 1283 (m), 1162 (m), 1027 (w). HRMS (ESI\(^+\)) Calcd for C\(_{19}\)H\(_{27}\)N [M + Na]: 292.2036. Found: 292.2032.

[3-Methyl-1-(2-methyl-allyl)-1-phenyl-but-3-enyl]-(2-vinyl-phenyl) amine (2.95c): Prepared via procedure 2.9 in 11 % yield (0.15 g, 0.46 mmol). \(^1\)H NMR (500 MHz, C\(_6\)D\(_6\)): \(\delta\) 7.33 (dd, 1H, J = 1.5 Hz, 7.3 Hz, aryl CH), 7.27 (m, 2H, aryl CH), 7.07
(m, 3H, aryl CH), 6.95 (dd, 1H, J = 17.4 Hz, J = 10.7 Hz, CH=CH₂), 6.81 (dt, 1H, J = 1.5 Hz, J = 7.8 Hz, aryl CH), 6.64 (d, 1H, J = 8.3 Hz, aryl CH), 6.34 (d, 1H, J = 8.3 Hz, aryl CH), 5.62 (dd, 1H, J = 1.7 Hz, 17.4 Hz, CH=CH₂Hₙ), 5.25 (dd, 1H, J = 1.7 Hz, 10.7 Hz, CH=CH₂Hₙ), 4.89 (m, 2H, C=CH₄Hₙ), 4.78 (m, 2H, C=CH₄Hₙ), 4.65 (s, 1H, NH), 2.82 (d, 2H, J = 13.4 Hz, CH₄Hₙ), 2.73 (d, 2H, J = 13.4 Hz, CH₂Hₙ), 1.36 (s, 6H, CH₃). ¹³C NMR (125 MHz, C₆D₆): δ 144.8, 143.7, 143.1, 134.4, 128.8, 127.9, 125.9, 117.6, 116.9, 116.7, 116.1, 61.1, 47.7, 24.8. IR (Neat): 3419 (m), 3070 (m), 2964 (s), 2280 (s), 1639 (m), 1602 (s), 1578 (m), 1511 (s), 1447 (s), 1375 (w), 1261 (s), 1186 (w), 1076 (s), 1025 (s). HRMS (ESI⁺) Calcd for C₂₃H₂₇N [M + H]: 318.2216. Found: 318.2217.

**Representative procedure 2.10:** Used for preparation of 2-alkyl-4-methyl-2-(2-methyl-allyl)-3-1H-benzo[b]azepines.

[3-Methyl-1-(2-methyl-allyl)-but-3-enyl]-2-(vinyl-phenyl)-amine 2.95a (300 mg, 1.2 mmol) and (R)-1.15a (72 mg, 62 μmol) were dissolved in benzene (15 mL) and heated to 55 °C under N₂ atmosphere for 5 h. The reaction was cooled to room temperature, then stirred over charcoal and filtered through celite and washed with ether. Solvents were removed in vacuo to afford a brown solid. This product was purified by column chromatography (silica gel), eluting with 1% ether in pentane to afford a white solid.

**4-Methyl-2-(2-methyl-allyl)-2,3-1H-benzo[b]azepine (2.96a):** Prepared via procedure 2.10 in 80 % yield (catalyst (R)-1.15a, 215 mg, 240 μmol).

¹H NMR (500 MHz, C₆D₆): δ 7.12 (dd, 1H, J = 1.2 Hz, 7.6 Hz, aryl CH), 6.93 (dt, 1H, J = 1.5 Hz, 7.6 Hz, aryl CH), 6.80 (dt, 1H, J = 1.2 Hz, 7.3 Hz, aryl CH), 6.47 (d, 1H, J = 7.6 Hz, aryl CH), 6.27 (s, 1H, ArCH=CCH₃), 4.80 (s, 1H, CH₃C=CH₄Hₙ), 4.70 (s, 1H, CH₃C=CH₄Hₙ), 3.92 (br, 1H, NH), 3.18 (m, 1H, NHCH), 2.31 (dd, 1H, J = 9.2 Hz, 17.4 Hz, CH(CH₄HₙR)(CH₃R’)), 1.98 (m, 3H, CH(CH₄HₙR)(CH₃R’)), 1.78 (s, 3H, CH₃), 1.43 (s, 3H, CH₃). ¹³C NMR (125 MHz, C₆D₆): δ 148.4, 143.4, 136.1, 133.3, 128.7, 127.5, 127.3, 125.3, 120.1, 118.0, 114.3, 51.1, 45.7,
45.1, 27.7, 22.0. IR (KBr): 3368 (s), 3055 (m), 2881 (m), 1646 (m), 1601 (s), 1580 (m), 1491 (s), 1442 (s), 1283 (s), 1199 (m), 1050 (m). HRMS (EI') Calcd for C₁₇H₂₃N [M + H]: 242.1903. Found: 242.1906. (Chiralcel OJ, 0.1 % iPrOH in hexane, 1.0 mL/min, 254 nm) 93 % e.e. [α]D = −22.5 ± 0.1° (c = 1.0, CHCl₃).

2-Ethyl-4-methyl-2-(2-methyl-allyl)-2,3-dihydro-1H-benzo[b]azepine (2.96b): Prepared via procedure 2.10 in 71 % yield (catalyst (R)-1.44a, 32 mg, 132 μmol). ¹H NMR (500 MHz, C₆D₆): δ 7.07 (dd, 1H, J = 1.4 Hz, 7.6 Hz, aryl CH), 6.97 (dt, 1H, J = 1.5 Hz, 7.6 Hz, aryl CH), 6.77 (dt, 1H, J = 1.2 Hz, 7.4 Hz, aryl CH), 6.34 (dd, 1H, J = 0.6 Hz, 8.1 Hz, aryl CH), 6.30 (s, 1H, ArCH=CR₂), 4.88 (m, 1H, C=CH₁₇H₁₅), 4.74 (m, 1H, C=CH₃H₂), 3.81 (s, 1H, NH), 2.22 (m, 3H, CH₂ & CH₃H₂), 2.04 (d, 1H, J = 13.6 Hz, CH₃H₂), 1.81 (s, 3H, CH₃), 1.64 (s, 3H, CH₃), 1.44 (m, 2H, CH₂CH₃), 0.72 (t, 3H, J = 7.5 Hz, CH₂CH₃). ¹³C NMR (125 MHz, C₆D₆): δ 145.5, 143.1, 133.9, 133.1, 127.9, 127.7, 124.1, 119.3, 118.9, 116.0, 105.0, 56.5, 46.2, 45.9, 31.9, 28.4, 25.2. IR (Neat): 3379 (m), 3071 (m), 2967 (s), 1640 (m), 1602 (s), 1485 (s), 1448 (m), 1324 (m), 1276 (m), 1160 (w), 1060 (w). HRMS (EI') Calcd for C₁₇H₂₅N [M + H]: 242.1903. Found: 242.1906. (Chiralcel OJ, 1 % iPrOH in hexane, 1.0 mL/min, 254 nm) 24 % e.e.

4-Methyl-2-(2-methyl-allyl)-2-phenyl-2,3-dihydro-1H-benzo[b]azepine (2.96c): Prepared via procedure 2.10 in 98 % yield (catalyst (R)-1.44a, 55 mg, 189 μmol). ¹H NMR (500 MHz, C₆D₆): δ 7.18 (m, 2H, aryl CH), 7.02 (m, 3H, aryl CH), 6.96 (m, 2H, aryl CH), 7.74 (dt, 1H, J = 1.2 Hz, 7.4 Hz, aryl CH), 6.66 (dd, 1H, J = 0.6 Hz, 8.1 Hz, aryl CH), 6.08 (s, 1H, ArCH=CR₂), 4.84 (m, 1H, C=CH₁₇H₁₅), 4.80 (s, 1H, NH), 4.74 (m, 1H, C=CH₃H₂), 2.54 (s, 2H, CH₂), 2.41 (d, 2H, J = 5.5 Hz, CH₂), 1.57 (s, 3H, CH₃), 1.11 (s, 3H, CH₃). ¹³C NMR (125 MHz, C₆D₆): δ 146.2, 145.6, 143.2, 134.3, 132.9, 128.7, 127.9, 127.1, 126.7, 123.9, 118.7, 118.4, 116.8, 100.5, 63.5, 53.9, 47.9, 27.8, 24.2. IR (Neat): 3392 (m), 3057 (m), 2917 (m), 1639 (m), 1601 (s), 1487 (s), 1445 (s), 1375 (m),
1278 (m), 1186 (w), 1031 (w). HRMS (El+) Calcd for C_{21}H_{23}N [M + H]: 290.1903. Found: 290.1905. (Chiralcel OJ, 1 % iPrOH in hexane, 1.0 mL/min, 254 nm) 80 % e.e.

**N–Allyl–phenyl–amine:** *(Used in the synthesis of substrate 2.97.)* Allyl bromide (16 mL, 187 mmol) was added to aniline (17 mL, 187 mmol) and triethylamine (26 mL, 187 mmol) in ether at 0 °C. After 24 h, the resultant suspension was filtered over a frit to remove ammonium salts, then concentrated *in vacuo* to a yellow oil. The product was not successfully purified *via* distillation, however column chromatography over silica gel, eluting with 5 % ether in pentane afforded 10.77 g of a clear, colorless oil (80 mmol, 43% yield). ¹H NMR (300 MHz, C₆D₆): δ 7.13 (m, 2H, aryl CH), 6.71 (tt, 1H, J = 1.0 Hz, 7.3 Hz, aryl CH), 6.38 (d, 2H, J = 7.7 Hz, aryl CH), 5.59 (m, 1H, NHCH=CH₂), 5.02 (m, 1H, CH=CH₂H₃), 4.91 (m, 1H, CH=CH₂H₃), 3.30 (m, 2H, NHCH₂CH=CH₂), 3.08 (br s, 1H, NH). No further spectral data obtained as this matches previously reported ¹H NMR spectra.¹²⁹

**2–Allyl–phenylamine:** *(Used in the synthesis of substrate 2.97.)* Allyl–phenyl–amine (9.6 g, 72 mmol) and zinc chloride (9.8 g, 72 mmol) were refluxed in xylene (25 mL) for 8 h. After the mixture had cooled to room temperature, ether and 3M NaOH(aq) were added. The biphasic mixture was extracted with ether three times (100 mL), then dried over MgSO₄ and concentrated *in vacuo* to an orange oil. The product was isolated by column chromatography over silica gel with a gradient: 1.0 L pentane to remove xylene; 1.0 L of 5 % ether in pentane to remove residual starting material; 1.0 L of 10 % ether in pentane to obtain 4.77 g of the product as a clear, yellow oil (50 % yield). ¹H NMR (300 MHz, C₆D₆): δ 7.05 (dt, 1H, J = 1.4 Hz, 7.6 Hz, aryl CH), 6.97 (dd, 1H, J = 1.4 Hz, 7.4 Hz, aryl CH), 6.76 (dt, 1H, J = 1.1 Hz, 7.4 Hz, aryl CH), 6.39 (dd, 1H, J = 1.1 Hz, 7.6 Hz, aryl CH), 5.76 (m, 1H, CH=CH₂), 4.96 (m, 1H, CH=CH₂), 3.05 (m, 4H, CH₂ & NH₂). No further spectral data obtained as this matches previously reported ¹H NMR spectra.¹³⁰
**N-(2-Allyl-phenyl)-formic acid ethyl ester:** *(Used in the synthesis of substrate 2.97.)*

Prepared via procedure 2.1, distilled at 50 °C, 30 mTorr, as a clear, colorless oil (3.5 g, 18 mmol) in 81 % yield. ¹H NMR (500 MHz, C₆D₆): δ 7.35 (s, 1H, N=CH(OEt)), 7.15 (m, 1H, aryl CH), 7.02 (m, 2H, aryl CH), 6.61 (m, 1H, aryl CH), 6.01 (m, 1H, CH=CH₂), 5.05 (m, 2H, CH=CH₂), 4.14 (q, 2H, J = 7.0 Hz, OCH₂CH₃), 3.50 (d, 2H, J = 6.7 Hz, CH₂CH=CH₂), 1.08 (t, 3H, J = 7.0 Hz, OCH₂CH₃). ¹³C NMR (125 MHz, C₆D₆): δ 154.5, 147.3, 138.2, 133.8, 130.3, 127.8, 125.1, 120.3, 115.7, 62.5, 36.8, 14.6. IR (Neat): 3423 (br), 3074 (m), 2979 (m), 1648 (s), 1596 (s), 1487 (m), 1390 (w), 1255 (s), 1200 (s), 1094 (m). HRMS (EI⁺) Calcd for C₁₂H₁₅NO [M + H]: 190.1226. Found: 190.1222.

*(2-Allyl-phenyl)-[3-methyl-1-(2-methyl-allyl)-but-3-enyl]-amine (2.97):* Prepared via procedure 2.2 (2.2 g, 8.5 mmol) in 65 % yield. ¹H NMR (500 MHz, C₆D₆): δ 7.22 (dt, 1H, J = 1.5 Hz, 7.8 Hz, aryl CH), 7.05 (dd, 1H, J = 1.5 Hz, 7.6 Hz, aryl CH), 6.78 (m, 2H, aryl CH), 5.84 (m, 1H, CH=CH₂), 5.01 (m, 2H, CH=CH₂), 4.81 (m, 2H, C=CH₂H₃), 4.77 (m, 2H, C=CH₂H₃), 3.70 (septet, 1H, J = 6.4 Hz, CH(CH₃)₂), 3.65 (d, 1H, J = 5.5 Hz, NH), 3.17 (d, 2H, J = 6.1 Hz, ArCH₂CH=CH₂), 2.26 (dd, 2H, J = 6.7 Hz, 14.3 Hz, CH(CH₃)₂H₃), 2.18 (dd, 2H, J = 6.7 Hz, 14.3 Hz, CH(CH₃)₂H₃), 1.59 (s, 6H, CH₃). ¹³C NMR (125 MHz, C₆D₆): δ 146.2, 143.6, 136.8, 131.0, 124.5, 117.7, 116.6, 113.6, 110.9, 49.3, 43.7, 37.2, 22.8. IR (Neat): 3419 (m), 3074 (s), 2933 (s), 1646 (s), 1604 (s), 1513 (s), 1452 (s), 1375 (s), 1261 (s), 1181 (w), 1074 (w). HRMS (ESI⁻) Calcd for C₁₈H₂₁N [M+Na]: 278.1879. Found: 278.1871.

**4-Iodo-2-methyl-but-1-ene:** *(Used in the synthesis of substrate 2.100.)* Imidazole (4.08 g, 60 mmol) and iodine (15.24 g, 60 mmol) were sequentially added to a solution of triphenylphosphine (15.72 g, 60 mmol) in CH₂Cl₂ at 0 °C. The resultant orange mixture
was stirred five minutes, then 3-methyl-3-buten-1-ol (5.05 mL, 50 mmol) was added via syringe over 5 min. The reaction was stirred overnight, then concentrated in vacuo to yield an orange slurry. The mixture was filtered over celite, washed with pentane, then concentrated in vacuo to an orange solid. The crude material was purified by flash–chromatography through a short plug of silica gel, eluting with 100 % pentane. The product thus obtained was used without further purification. $^1$H NMR (300 MHz, C$_6$D$_6$): δ 4.72 (m, 1H, C=CH$_a$H$_b$), 4.57 (m, 1H, C=CH$_2$H$_b$), 2.76 (t, 2H, J = 7.5 Hz, CH$_2$CH$_3$I), 2.19 (t, 2H, J = 7.5 Hz, CH$_2$CH$_2$I), 1.37 (s, 3H, CH$_3$). No further spectral data obtained as this matches previously reported $^1$H NMR spectra.$^{13}$(

**[4-Methyl-1-(3-methyl-but-3-enyl)-pent-4-enyl]-(2-vinyl-phenyl)-amine (2.100):**

[Diagram]

4-Iodo-2-methyl-but-1-ene (2.46 g, 12.6 mmol) was added dropwise to a solution of t-BuLi (15.1 mL, 1.7 M) in pentane and ether at −78 °C. The resultant solution was warmed to −45 °C over 45 min, then re-cooled to −78 °C. N-styrenylimidate ester (1.0 g, 5.71 mmol) was added to the solution via syringe, which turned the mixture from yellow to deep purple, then red. After 5 min, methanol (2 mL) was added to quench the reaction. After the solution had warmed to room temperature, water (20 mL) was added. The biphasic solution was extracted with ether three times (50 mL). All organic extracts were combined, then washed with saturated NH$_4$Cl(aq) and NaCl(aq) solutions, dried over MgSO$_4$, and concentrated in vacuo, to a yellow oil. Column chromatography on silica gel, eluting with 1 % ether in pentane afforded 920 mg (3.4 mmol, 60 % yield) of a cloudy yellow oil. $^1$H NMR (500 MHz, C$_6$D$_6$): δ 7.32 (dd, 1H, J = 1.5 Hz, 7.6 Hz, aryl CH), 7.15 (m, 1H, aryl CH), 6.72 (m, 3H, aryl CH & CH=CH$_2$), 5.54 (dd, 1H, J = 1.5 Hz, 17.4 Hz, CH=CH$_a$H$_b$), 5.15 (dd, 1H, J = 1.5 Hz, 11.0 Hz, CH=CH$_a$H$_b$), 4.78 (m, 2H, C=CH$_a$H$_b$), 4.74 (m, 2H, C=CH$_a$H$_b$), 3.47 (d, 1H, J = 8.5 Hz, NH), 3.25 (m, 1H, CH), 1.98 (m, 4H, CH(CH$_2$CH$_3$R)$_2$), 1.59 (s, 6H, CH$_3$), 1.57 – 1.40 (m, 4H, CH(CH$_2$CH$_3$R)$_2$).

$^{13}$C NMR (125 MHz, C$_6$D$_6$): δ 145.9, 134.0, 129.8, 128.7, 124.8, 117.7, 116.2, 112.0,
110.9, 52.9, 34.7, 33.6, 23.0. IR (Neat): 3427 (m), 3075 (m), 2938 (s), 1649 (m), 1602 (s), 1577 (m), 1508 (s), 1458 (s), 1374 (m), 1317 (s), 1259 (m), 1186 (w), 1056 (w), 1026 (w). HRMS (ESI⁺) Calcd for C₁₉H₂₈N [M + H]: 270.2216. Found: 270.2218.

**Representative Procedure 2.11:** *Used for the preparation of pent-4-enoic acid (N-aryl)-amides.* To a solution of 2-vinylaniline, (5 g, 42 mmol) pyridine (4.3 mL, 46 mmol) and N,N-dimethylaminopyridine (256 mg, 2.1 mmol) in dichloromethane at 0 °C was added drop-wise 4-pentenoyl chloride (5.1 mL, 46 mmol). After warming to room temperature, 10 % HCl$_{(aq)}$ (100 mL) was added to the solution. This mixture was extracted three times with dichloromethane (200 mL). All organic extracts were combined, washed with saturated NaHCO$_3$ solution, then NaCl solution, dried over MgSO$_4$ and concentrated *in vacuo* to an off-white solid. The solid was tritertated in pentane for 1 h, then filtered to afford a white powder.

**Pent-4-enoic acid (2-vinyl-phenyl)-amide:** * (Used in the synthesis of substrate 2.101.)

Prepared via procedure 2.11 in 82 % yield (6.94 g, 34 mmol). $^1$H NMR (500 MHz, C$_6$D$_6$): δ 7.95 (d, 1H, J = 7.9 Hz, aryl CH), 7.25 (d, 1H, J = 7.6 Hz, aryl CH), 7.08 (br, 1H, NH), 7.01 (m, 1H, aryl CH), 6.86 (t, 1H, J = 7.9 Hz, aryl CH), 6.64 (dd, 1H, J = 11.0 Hz, 17.4 Hz, ArCH=CH$_2$), 5.67 (m, 1H, CH$_2$CH=CH$_2$), 5.42 (dd, 1H, J = 1.5 Hz, 17.4 Hz, ArCH=CH$_2$), 5.07 (d, 1H, J = 10.7 Hz, ArCH=CH$_2$H$_2$), 4.94 (d, 1H, J = 17.4 Hz, CH$_2$CH=CH$_2$H$_2$), 4.90 (d, 1H, J = 10.7 Hz, CH$_2$CH=CH$_2$H$_2$), 2.27 (m, 2H, C(O)CH$_2$CH$_2$), 1.94 (t, 2H, J = 7.5 Hz, C(O)CH$_2$CH$_2$). $^{13}$C NMR (125 MHz, C$_6$D$_6$): δ 170.5, 137.8, 135.8, 133.3, 131.0, 129.0, 128.7, 127.0, 125.6, 124.9, 117.1, 115.9, 36.5, 30.1. IR (KBr): 3272 (s), 3078 (w), 2977 (w), 1827 (w), 1652 (s), 1529 (s), 1450 (s), 1373 (m), 1291 (m), 1197 (m), 1022 (w). HRMS (ESI⁻) Calcd for C$_{13}$H$_{13}$NO [M + Na]: 224.1046. Found: 224.1050.
[1,1-Bis-(2-methyl-allyl)-pent-4-enyl]-(2-vinyl-phenyl)-amine (2.101): Prepared via procedure 2.12 (vide infra) in 22% yield (0.64 g, 2.2 mmol). \(^1\text{H} \text{NMR} (500 \text{ MHz, } \text{C}_6\text{D}_6): \delta \) 7.30 (dd, 1H, J = 1.5 Hz, 7.3 Hz, aryl CH), 7.11 (dt, 1H, J = 1.8 Hz, 7.8 Hz, aryl CH), 6.88 (d, 1H, J = 8.2 Hz, aryl CH), 6.72 (m, 2H, aryl CH + ArCH=CH), 5.73 (m, 1H, CH\_2CH\_2CH=CH), 5.49 (dd, 1H, J = 1.8 Hz, 17.1 Hz, ArCH=CH\_2), 5.14 (dd, 1H, J = 1.8 Hz, 10.6 Hz, ArCH=CH\_2H\_b), 5.01 (dd, 1H, J = 1.8 Hz, 17.1 Hz, CH\_2CH\_2CH=CH\_2H\_b), 4.95 (dd, 1H, J = 1.2 Hz, 10.6 Hz, CH\_2CH\_2CH=CH\_2H\_b), 4.89 (m, 2H, CH\_3C=CH\_2H\_b), 4.78 (m, 2H, CH\_3C=CH\_2H\_b), 3.94 (s, 1H, NH), 2.47 (d, 2H, J = 14.0 Hz, C(CH\_3H\_bR)\_2), 2.29 (d, 2H, J = 14.0 Hz, C(CH\_3H\_bR)\_2), 2.07 (m, 2H, CH\_2), 1.79 (m, 2H, CH\_2), 1.68 (s, 6H, CH\_3). \(^{13}\text{C} \text{NMR} (125 \text{ MHz, } \text{C}_6\text{D}_6): \delta \) 144.4, 143.0, 138.9, 134.5, 129.4, 129.1, 126.4, 117.6, 117.0, 116.1, 115.0, 114.0, 58.9, 44.7, 37.7, 29.2, 25.1. IR (Neat): 3415 (m), 3074 (m), 2946 (s), 1640 (s), 1602 (s), 1579 (s), 1514 (s), 1454 (s), 1374 (m), 1318 (s), 1260 (m), 1163 (m), 1059 (m). HRMS (ESI\(^+\)) Calcd for C\(_{21}\)H\(_{29}\)N [M + H]: 296.2373. Found: 296.2381.

8,4'-Dimethyl-5,7-dihydropirol[6H-benzo-5-aza-cycloheptene-6,1'-cyclohex-3'-ene] (2.103): Catalyst (R)-1.18c (2 mg, 2 \mu\text{mol}) was added to a solution of 2.100 (12 mg, 40 \mu\text{mol}) in benzene-\text{d}_6 (1 mL), and the resultant mixture placed in a J. Young tube. The reaction was monitored by \(^1\text{H} \text{NMR analysis. After 1 h, the ratio of (2.100 : 2.101 : 2.102) was (0 : 4 : 1); after 6 h, only 2.102 was observable. The mixture was exposed to air, stirred over charcoal, filtered through celite and concentrated in vacuo to give 98 mg (360 \mu\text{mol}, > 99 \% yield). \(^1\text{H} \text{NMR} (500 \text{ MHz, } \text{C}_6\text{D}_6): \delta \) 7.08 (dd, 1H, J = 1.5 Hz, 7.3 Hz, aryl CH), 6.94 (dt, 1H, J = 1.5 Hz, 7.6 Hz, aryl CH), 6.79 (dt, 1H, J = 1.2 Hz, 7.3 Hz, aryl CH), 6.35 (dd, 1H, J = 1.2 Hz, 7.9 Hz, aryl CH), 6.32 (m, 1H, ArCH=CH\_2), 5.35 (m, 1H, CH\_2CH=CH\_2), 3.85 (s, 1H, NH), 2.43 (d, 1H, J = 17.1 Hz, CH\_2H\_b), 2.04 (d, 1H, J = 17.1 Hz, CH\_2H\_b), 1.88 - 1.71 (m, 5H, CH\_2), 1.81 (s, 3H, CH\_3), 1.52 (s, 3H, CH\_3), 1.24 (m, 1H, CH). \(^{13}\text{C} \text{NMR} (125 \text{ MHz, } \text{C}_6\text{D}_6): \delta \) 145.7, 134.0, 132.9, 131.4, 128.7, 127.6,
127.4, 125.3, 121.9, 119.6, 119.5, 52.2, 49.0, 43.9, 30.4, 28.4, 24.1, 23.0. IR (Neat): 3369 (m), 3051 (m), 2911 (s), 1601 (s), 1482 (s), 1447 (s), 1376 (m), 1278 (s), 1160 (m), 1083 (m), 1016 (m). HRMS (ESI⁺) Calcd for C₁₇H₂₁N [M + H]: 240.1747. Found: 240.1756. HPLC: (Chiralcel OJ, 1.0% Isopropanol in Hexane, 1.0 mL/min, 254 nm) – 79% e.e.

**Pent-4-enoic acid (4-methoxy-phenyl)-amide:** *(Used in the synthesis of substrate 2.104a.)* Prepared via procedure 2.11 in 73 % yield (12.2 g, 59 mmol). H NMR (500 MHz, C₆D₆): δ 7.52 (d, 2H, J = 9 Hz, aryl CH), 6.76 (d, 2H, J = 9 Hz, aryl CH), 5.74 (m, 1H, CH=CH₂), 4.97 (m, 2H, CH=CH₂), 3.27 (s, 3H, CH₃O), 2.36 (m, 2H, C(O)CH₂CH₂), 1.97 (t, 2H, J = 7.5 Hz, C(O)CH₂CH₂). ¹³C NMR (125 MHz, C₆D₆): δ 170.3, 157.0, 138.0, 132.5, 122.1, 115.8, 114.6, 55.3, 55.2, 36.8, 30.2. IR (KBr): 3309 (s), 3082 (w), 2952 (m), 1875 (w), 1653 (s), 1602 (m), 1542 (s), 1516 (s), 1410 (s), 1247 (s), 1174 (m), 1030 (s). HRMS (ESI⁺) Calcd for C₁₂H₁₅NO₂ [M + Na]: 228.0995. Found: 228.0999.

**Pent-4-enoic acid (4-bromo-phenyl)-amide:** *(Used in the synthesis of substrate 2.104b.)* Prepared via procedure 2.11 in 98 % yield (8.45 g, 40 mmol). H NMR (500 MHz, CD₂Cl₂): δ 7.86 (br, 1H, NH), 7.41 (m, 4H, aryl CH) 5.86 (m, 1H, CH=CH₂) 5.09 (dd, 1H, J = 17.1 Hz, 0.9 Hz, CH=CH₂H), 5.02 (dd, 1H, J = 10.7 Hz, 0.9 Hz, CH=CH₂H), 2.43 (s, 4H, CH₂CH₂). ¹³C NMR (125 MHz, CD₂Cl₂): δ 171.5, 137.9, 137.8, 132.3, 122.0, 116.9, 116.0, 37.1, 29.8. IR (KBr): 3285 (s), 2979 (w), 1656 (s), 1589 (m), 1530 (s), 1488 (s), 1395 (m), 1299 (w), 1189 (w), 1072 (m). HRMS (ESI⁺) Calcd for C₁₁H₁₂NOBr [M + Na]: 275.9994. Found: 275.9997.

**Pent-4-enoic acid (2-methoxy-phenyl)-amide:** *(Used in the synthesis of substrate 2.104c.)* Prepared via procedure 2.11 in 98 % yield (8.2 g, 40 mmol). H NMR (500
MHz, CD₂Cl₂): δ 8.31 (d, 1H, J = 7.9 Hz, aryl CH), 7.79 (br, 1H, NH), 7.02 (dt, 1H, J = 7.9 Hz, J = 1.2 Hz, aryl CH), 6.92 (dd, 1H, J = 7.9 Hz, 1.2 Hz, aryl CH), 6.89 (dd, 1H, J = 8.2 Hz, J = 1.2 Hz, aryl CH), 5.88 (m, 1H, CH=CH₂), 5.10 (d, 1H, J = 17.1 Hz, CH=CH₃H₆), 5.02 (d, 1H, J = 10.7 Hz, CH=CH₂H₆), 3.86 (s, 3H, CH₃O), 2.45 (m, 2H, CH₂). ¹³C NMR (125 MHz, CD₂Cl₂): δ 170.7, 137.7, 128.4, 123.9, 121.3, 120.0, 115.8, 110.5, 56.2, 37.5, 29.9. IR (KBr): 3325 (s), 2939 (m), 1679 (s), 1600 (s), 1524 (s), 1460 (s), 1434 (w), 1356 (s), 1253 (m), 1176 (m), 1047 (m). HRMS (ESI⁺) Calcd for C₁₂H₁₅NO₂ [M + Na]: 228.0995. Found: 228.0996.

**Pent-4-enoic acid (2-bromo-phenyl)-amide:** *(Used in the synthesis of substrate 2.104d.)* Prepared via procedure 2.11 in 70 % yield (6.1 g, 24 mmol). ¹H NMR (500 MHz, CD₂Cl₂): δ 8.29 (d, 1H, J = 7.9 Hz, aryl CH), 7.66 (br, 1H, NH), 7.55 (dd, 1H, J = 7.9 Hz, J = 1.5 Hz, aryl CH), 7.31 (dt, 1H, J = 7.8 Hz, 1.2 Hz, aryl CH), 6.99 (dt, 1H, J = 7.8 Hz, J = 1.5 Hz, aryl CH), 5.91 (m, 1H, CH=CH₂), 5.14 (d, 1H, J = 17.1 Hz, CH=CH₃H₆), 5.06 (d, 1H, J = 10.1 Hz, CH=CH₂H₆), 2.51 (m, 2H, CH₂). ¹³C NMR (125 MHz, CD₂Cl₂): δ 170.9, 137.4, 136.4, 132.8, 128.7, 125.6, 122.7, 116.1, 114.0, 37.4, 29.8. IR (KBr): 3273.7 (s), 1659.8 (s), 1579.6 (m), 1526.9 (s), 1438.3 (m), 1414.3 (m), 1374.5 (w), 1291.7 (m), 1186.3 (m), 1027.3 (m). HRMS (ESI⁺) Calcd for C₁₁H₁₂NOBr [M + Na]: 275.9994. Found: 275.9992.

**Pent-4-enoic acid (3-trifluoromethyl-phenyl)-amide:** *(Used in the synthesis of substrate 2.104e.)* Prepared via procedure 2.11 in > 99 % yield (10 g, 41 mmol). ¹H NMR (500 MHz, CDCl₃): δ 7.87 (d, 1H, J = 8.2 Hz, aryl CH), 7.33 (br, 1H, aryl CH), 7.05 (d, 1H, J = 7.9 Hz, aryl CH), 6.89 (t, 1H, J = 7.9 Hz, aryl CH), 6.23 (br, 1H, NH), 5.71 (m, 1H, CH=CH₂), 4.98 (m, 1H, CH=CH₂H₆), 4.95 (m 1H, CH=CH₂H₆), 2.29 (m, 2H, CH₂), 1.83 (m, 2H, CH₂). ¹³C NMR (125 MHz, CDCl₃): δ 139.5, 137.5, 130.1, 127.1, 123.3, 120.8, 116.6, 116.1, 36.8, 29.8. IR (KBr): 3302 (s), 2982 (m), 1667 (s), 1558 (s), 1494
(s), 1448 (s), 1335 (s), 1282 (m), 1167 (s), 1071 (s). HRMS (ESI\textsuperscript{+}) Calcd for C\textsubscript{12}H\textsubscript{12}NO\textsubscript{3} [M + Na]: 266.0763. Found: 266.0762.

**Pent-4-enoic acid (benzyl)-amide:** *(Used in the synthesis of substrate 2.104f.)* Prepared *via* procedure 2.11 in 90 % yield (9.35 g, 50 mmol). \textsuperscript{1}H NMR (500 MHz, C\textsubscript{6}D\textsubscript{6}): \textdelta 7.09 (m, 5H, aryl CH), 5.73 (m, 1H, CH\textsubscript{2}CH=CH\textsubscript{2}), 5.10 (br, 1H, NH), 4.95 (m, 2H, CH=CH\textsubscript{2}), 4.21 (s, 2H, CH\textsubscript{2}Ar), 2.32 (m, 2H, C(O)CH\textsubscript{2}CH\textsubscript{3}), 1.86 (t, 2H, J = 7.6 Hz, C(O)CH\textsubscript{2}CH\textsubscript{2}). \textsuperscript{13}C NMR (125 MHz, C\textsubscript{6}D\textsubscript{6}): \textdelta 173.1, 139.6, 137.9, 190.0, 127.7, 115.7, 43.9, 35.7, 30.5. IR (Neat): 3289 (s), 3032 (m), 1728 (m), 1641 (s), 1546 (s), 1454 (m), 1380 (m), 1266 (m), 1080 (m), 1028 (m). HRMS (ESI\textsuperscript{+}) Calcd for C\textsubscript{12}H\textsubscript{13}NO [M + Na]: 212.1046. Found: 212.1047.

**Representative procedure 2.12:** *Used for the preparation of [1,1-Bis-(2-methyl-allyl)-pent-4-ynyl]-(aryl)-amines.* Phosphorous pentachloride (2.0 g, 9.7 mmol) was added to a solution of pent-4-enoic acid (4-methoxy-phenyl)-amide (2.0 g, 9.7 mmol) and dichloromethane (20 mL) in a Schlenk flask under vigorous N\textsubscript{2} flow, to produce a mild exotherm. After 20 min, the solvent was removed in vacuo to afford a green oil. \textsuperscript{1}H NMR of the crude product indicated complete conversion to the imidoyl chloride. This material was diluted in THF (20 mL) and added to methallyl Grignard (73 mL, 0.40 M) at room temperature to afford an orange solution. The mixture was quenched with water (150 mL) then extracted three times with ether (200 mL). All organic extracts were combined, washed with saturated solutions of NH\textsubscript{4}Cl\textsubscript{(aq)}, then NaCl\textsubscript{(aq)}, dried (MgSO\textsubscript{4}) and concentrated in vacuo to a brown oil. The crude product was purified by column chromatography (silica gel), eluting with 20 % ether in pentane, to afford a yellow oil.

**[1,1-Bis-(2-methyl-allyl)-pent-4-ynyl]-(4-methoxy-phenyl)-amine (2.104a):** Prepared *via* procedure 2.12 in 77 % yield (2.23 g, 7.5 mmol). \textsuperscript{1}H NMR (500 MHz,
C$_6$D$_8$): $\delta$ 6.76 (d, 2H, J = 9 Hz, aryl CH), 6.55 (d, 2H, J = 9 Hz, aryl CH), 5.76 (m, 1H, CH=CH$_2$), 5.05 (dd, 1H, J = 1.5 Hz, 17.1 Hz, CH=CH$_2$H$_b$), 4.97 (dd, 1H, J = 1.2 Hz, 10.4 Hz, CH=CH$_2$H$_b$), 4.93 (m, 2H, CH$_2$C=CH$_2$H$_b$), 4.85 (m, 2H, CH$_2$C=CH$_2$H$_b$), 3.39 (s, 3H, CH$_3$O), 2.41 (d, 2H, J = 13.9 Hz, C(CH$_2$H$_b$)$_2$), 2.26 (d, 2H, J = 13.9 Hz, C(CH$_2$H$_b$)$_2$), 2.09 (m, 2H, CH$_2$), 1.74 (s, 6H, CH$_3$C=CH$_2$), 1.69 (m, 2H, CH$_2$). $^{13}$C NMR (125 MHz, C$_6$D$_8$): $\delta$ 153.2, 143.3, 140.9, 139.1, 118.3, 115.7, 115.4, 114.9, 59.0, 55.5, 44.6, 37.7, 29.2, 25.4. IR (Neat): 3406 (m), 3073 (m), 2945 (m), 1640 (m), 1510 (s), 1455 (m), 1374 (w), 1241 (s), 1179 (m), 1042 (m). HRMS (ESI$^+$) Calcd for C$_{29}$H$_{39}$NO [M + H]: 300.2322. Found: 300.2318.

[1,1–Bis–(2–methyl–allyl)–pent–4–enyl]–(4–bromo–phenyl)–amine (2.104b): Prepared via procedure 2.12 in 82% yield (2.2 g, 6.5 mmol). $^1$H NMR (500 MHz, C$_6$D$_8$): $\delta$ 7.15 (d, 2H, J = 8.9 Hz, aryl CH), 6.17 (d, 2H, J = 8.9 Hz, aryl CH), 5.70 (m, 1H, CH=CH$_2$), 5.00 (dd, 1H, J = 17.1 Hz, 0.6 Hz, CH=CH$_2$H$_b$), 4.95 (dd, 1H, J = 10.1 Hz, 0.9 Hz, CH=CH$_2$H$_b$), 4.86 (s, 2H, C(CH$_3$)=CH$_2$H$_b$), 4.72 (s, 2H, C(CH$_3$)=CH$_2$H$_b$), 3.29 (s, 3H, CH$_3$O), 2.29 (d, 2H, J = 14.3 Hz, CH$_2$H$_b$), 2.10 (d, 2H, J = 14.4 Hz, CH$_2$H$_b$), 1.97 (m, 2H, CH$_2$), 1.61 (s, 6H, CH$_3$C), 1.57 (m, 2H, CH$_2$). $^{13}$C NMR (125 MHz, C$_6$D$_8$): $\delta$ 146.1, 142.8, 138.7, 132.6, 127.1, 117.3, 115.9, 115.1, 109.4, 58.8, 44.0, 37.2, 29.0, 25.1. IR (Neat): 3417 (m), 3074 (s), 2945 (s), 1640 (s), 1592 (s), 1489 (s), 1452 (m), 1374 (m), 1319 (m), 1254 (m), 1181 (w), 1076 (s). HRMS (ESI$^+$) Calcd for C$_{19}$H$_{26}$NBr [M + H]: 348.1321. Found: 348.1308.

[1,1–Bis–(2–methyl–allyl)–pent–4–enyl]–(2–methoxy–phenyl)–amine (2.104c): Prepared via procedure 2.12 in 25% yield (0.72 g, 2.4 mmol). $^1$H NMR (500 MHz, C$_6$D$_8$): $\delta$ 6.92 (m, 2H, aryl CH), 6.70 (m, 1H, aryl CH), 6.56 (d, 1H, J = 7.6 Hz, aryl CH), 5.76 (m, 1H, CH=CH$_2$), 5.02 (ddd, 1H, J = 17.1 Hz, 1.5 Hz, J = 3.66 Hz, CH=CH$_2$H$_b$), 4.94 (ddd, 1H, J = 10.4 Hz, 1.2 Hz, J = 2.1 Hz, CH=CH$_2$H$_b$), 4.91 (m, 2H, C(CH$_3$)=CH$_2$H$_b$), 4.84 (m, 2H, C(CH$_3$)=CH$_2$H$_b$), 4.63 (s, 1H, NH), 3.30 (s, 3H, CH$_3$O),
2.55 (d, 2H, J = 14.4 Hz, CHaHb), 2.35 (d, 2H, J = 14.4 Hz, CHaHb), 2.14 (m, 2H, CH2),
1.85 (m, 2H, CH2), 1.75 (s, 6H, CH3C). 13C NMR (125 MHz, CD2Cl2): δ 147.9, 143.2,
139.1, 137.3, 127.1, 121.8, 116.6, 115.7, 114.8, 113.1, 110.5, 58.6, 55.5, 44.5, 37.6, 29.2,
25.0. IR (Neat): 3428 (w), 3073 (m), 2946 (s), 2834 (m), 1640 (s), 1602 (s), 1521 (s),
1458 (s), 1374 (m), 1352 (m), 1296 (w), 1251 (s), 1221 (s), 1177 (m), 1125 (m), 1088
(w), 1032 (s). HRMS (ESI+) Calcd for C26H29NO [M + Na]: 322.2141. Found: 322.2139.

[1,1-Bis-(2-methyl-allyl)-pent-4-ethyl]-[2-bromo-phenyl]-amine (2.104d): Prepared
via procedure 2.12 in 86 % yield (2.4 g, 6.8 mmol). 1H NMR (500 MHz, CD2Cl2): δ 7.38
(dd, 1H, J = 7.9 Hz, 1.5 Hz, aryl CH), 6.94 (dt, 1H, J = 7.8 Hz, 1.5 Hz, aryl CH), 6.82
(dd, 1H, J = 8.2 Hz, J = 1.2 Hz, aryl CH), 6.35 (dt, 1H, J = 1.5 Hz, 7.6 Hz, aryl CH), 5.71
(m, 1H, CH=CH2), 5.00 (dd, 1H, J = 17.1 Hz, 1.5 Hz, CH=CH2Hb), 4.95 (dd, 1H, J = 10.1
Hz, 1.5 Hz, H=CHaHb), 4.94 (s, 2H, C(CH3)=CHaHb), 4.89 (m, 2H, C(CH3)=CHaHb),
4.64 (s, 1H, NH), 2.42 (d, 2H, J = 14.3 Hz, CHaHb), 2.29 (d, 2H, J = 14.3 Hz, CHaHb),
2.06 (m, 2H, CH2), 1.80 (m, 2H, CH2), 1.66 (s, 6H, CH3C). 13C NMR (125 MHz, CD2Cl2): δ
144.1, 142.6, 138.7, 133.7, 127.1, 118.0, 116.4, 115.0, 114.2, 112.0, 59.3, 44.6, 37.5,
29.1, 25.0. IR (Neat): 3409 (m), 3074 (m), 2947 (m), 1640 (m), 1593 (s), 1517 (s), 1463
(s), 1374 (w), 1319 (m), 1287 (m), 1261 (w), 1166 (w), 1088 (m), 1018 (s). HRMS (ESI+)

[1,1-Bis-(2-methyl-allyl)-pent-4-ethyl]-[3-trifluoromethyl-phenyl]-amine (2.104e):
Prepared via procedure 2.12 in 90 % yield (2.5 g, 7.4 mmol). 1H NMR (500 MHz, CD2Cl2):
δ 6.89 (m, 3H, aryl CH), 6.49 (m, 1H, aryl CH), 5.69 (m, 1H, CH=CH2), 5.02 (ddd, 1H, J
= 17.1 Hz, 1.5 Hz, J = 3.35 Hz, CH=CH2Hb), 4.96 (ddd, 1H, J = 10.1 Hz, 1.2 Hz, J = 1.8
Hz, CH=CHaHb), 4.84 (m, 2H, C(CH3)=CHaHb), 4.71 (m, 2H, C(CH3)=CHaHb), 3.46 (s,
3H, CH3O), 2.34 (d, 2H, J = 14.3 Hz, CHaHb), 2.13 (d, 2H, J = 14.3 Hz, CHaHb), 1.96 (m,
2H, CH2), 1.62 (m, 2H, CH2), 1.59 (s, 6H, CH3C). 13C NMR (125 MHz, CD2Cl2): δ 147.5,
142.6, 138.6, 130.2, 118.1, 116.1, 115.2, 113.9, 112.1, 58.9, 44.0, 37.3, 28.9, 25.1. IR
(Neat): 3423 (w), 3076 (m), 2947 (s), 1641 (m), 1613 (s), 1526 (s), 1492 (s), 1439 (s), 1350 (s), 1279 (w), 1164 (s), 1097 (m), 1071 (s). HRMS (ESI⁺) Calcd for C₂₀H₂₆NF₃ [M + H]: 338.2090. Found: 338.2110.

**[1,1-Bis-(2-methyl-allyl)-pent-4-enyl]-(benzyl)-amine (2.104f):** Prepared via procedure 2.12 in 33% yield (1.0 g, 3.5 mmol). ¹H NMR (500 MHz, C₆D₆): δ 7.38 (d, 2H, J = 7.5 Hz, aryl CH), 7.22 (t, 2H, J = 7.5 Hz, aryl CH), 7.12 (t, 1H, J = 7.5 Hz, aryl CH), 5.82 (m, 1H, CH=C=CH₂), 5.08 (dd, 1H, J = 1.5 Hz, 17.1 Hz, CH=CH₃H₆), 4.99 (dd, 1H, J = 1.2 Hz, 10.1 Hz, CH=CH₃H₆), 4.92 (m, 2H, CH₂C=CH₃H₆), 4.88 (m, 2H, CH₂C=CH₃H₆), 3.61 (s, 2H, PhCH₂N), 2.11 (s, 1H, NH), 2.10 – 2.06 (m, 6H, CH₂), 1.79 (s, 6H, CH₃), 1.55 (m, 2H, CH₂). ¹³C NMR (125 MHz, C₆D₆): δ 143.4, 142.0, 139.6, 129.0, 128.8, 127.5, 115.2, 114.6, 58.7, 46.7, 43.9, 36.7, 29.1, 25.8. IR (Neat): 3409 (br), 3074 (m), 2941 (s), 1640 (s), 1452 (s), 1373 (m), 1330 (m), 1242 (w), 1029 (m). HRMS (ESI⁺) Calcd for C₂₀H₂₅N [M + H]: 284.2373. Found: 284.2374.

**Representative procedure 2.13:** Used for the preparation of (aryl)-[3-methyl-1-(2-methyl-allyl)-cyclohex-3-enyl]-amines. Catalyst (R)-1.18a (5 mg, 7 μmol) was added to a solution of 2.104a (68 mg, 230 μmol) in benzene-d₆ (1 mL), and the resultant mixture placed in a J. Young tube. The reaction was monitored by ¹H NMR spectral analysis. After 1 h, the reaction was complete. The mixture was exposed to air, stirred over charcoal, filtered through celite and concentrated in vacuo. The crude material was purified by chromatography over silica gel, eluting with 1% ether in pentane to afford a clear, colorless oil.

**(4-Methoxy-phenyl)-[3-methyl-1-(2-methyl-allyl)-cyclohex-3-enyl]-amine (2.105a):** Prepared via procedure 2.13 in 81% yield (50 mg, 186 μmol). ¹H NMR (500 MHz, C₆D₆): δ 6.75 (m, 2H, aryl CH), 6.60 (m, 2H, aryl CH),
5.35 (m, 1H, ArCH=C(CH₃)), 4.96 (m, 1H, CH₃C=CH₃Hₖ), 4.82 (m, 1H, CH₂C=CH₂Hₙ),
3.39 (s, 3H, CH₃O), 3.08 (br, 1H, NH), 2.54 (d, 1H, J = 13.7 Hz, CCH₃HₖC(CH₃)=), 2.23
(d, 1H, J = 13.7 Hz, CCH₃HₖC(CH₃)=), 1.97 – 1.85 (m, 5H), 1.85 (s, 3H, CH₃), 1.56 (s,
3H, CH₃), 1.42 (m, 1H). ¹³C NMR (125 MHz, C₆D₆): δ 153.8, 143.6, 141.1, 131.5, 128.7,
121.3, 119.5, 115.2, 115.1, 55.5, 46.4, 42.9, 31.7, 25.4, 24.2, 23.3. IR (Neat): 3402 (w),
3070 (w), 2926 (s), 1641 (m), 1510 (s), 1442 (m), 1375 (w), 1239 (s), 1179 (m), 1041
(Chiralpak AS, 0.1 % IPA in Hexane, 254 nm, 1.0 mL/min) 64 % e.e.

(4-Bromo-phenyl)-[3-methyl-1-(2-methyl-allyl)-cyclohex-3-enyl]-amine (2.105b):
Prepared via procedure 2.13 in 78 % yield (57 mg, 178 µmol). ¹H NMR (500 MHz,
C₆D₆): δ 7.17 (d, 2H, J = 6.7 Hz, aryl CH), 6.18 (d, 2H, J = 6.7 Hz, aryl CH), 5.30 (m,
1H, CH=C(CH₃)), 4.91 (m, 1H, C(CH₃)=CH₃Hₖ), 4.70 (m, 1H, C(CH₃)=CH₃Hₖ), 3.12 (br,
1H, NH), 2.45 (d, 1H, J = 13.7 Hz, CH₃Hₖ), 2.08 (d, 1H, J = 13.7 Hz, CH₃Hₖ), 1.92 (br d,
1H, J = 15.9 Hz, CH₃Hₖ), 1.83 – 1.77 (m, 3H, CH₂, CH₃Hₖ), 1.82 (br d, 1H, J = 17.8 Hz,
CH₃Hₖ), 1.70 (s, 3H, CH₃), 1.53 (s, 3H, CH₃), 1.26 (m, 1H, CH₃Hₖ). ¹³C NMR (125 MHz,
C₆D₆): δ 146.5, 143.0, 132.5, 130.8, 121.7, 117.4, 115.3, 109.6, 55.2, 45.3, 43.3, 31.1,
25.0, 24.1, 23.0. IR (Neat): 3414 (m), 3072 (m), 2924 (s), 2850 (m), 1641 (m), 1591 (s),
1489 (s), 1444 (m), 1375 (m), 1317 (m), 1256 (m), 1180 (m), 1076 (m). HRMS (ESI⁺)
Calcd for C₁₇H₂₂NBr [M + Na]: 342.0828. Found: 342.0832. HPLC (Chiralpak AS, 0.1 %
IPA in Hexane, 254 nm, 1.0 mL/min) 67 % e.e.

(2-Methoxy-phenyl)-[3-methyl-1-(2-methyl-allyl)-cyclohex-3-enyl]-amine (2.105c):
Prepared via procedure 2.13 in 98 % yield (62 mg, 230 µmol). ¹H NMR (500
MHz, C₆D₆): δ 6.96 (m, 2H, aryl CH), 6.71 (dt, 1H, J = 1.8, J = 7.9 Hz, aryl CH), 6.57
(dd, 1H, J = 1.2 Hz, 7.9 Hz, aryl CH), 5.36 (m, 1H, CH=C(CH₃)), 4.93 (m, 1H, C(CH₃)=CH₃Hₖ), 4.77 (m, 1H, C(CH₃)=CH₃Hₖ), 4.52 (br, 1H, NH), 3.28 (s, 3H, CH₃O),
2.70 (d, 1H, J = 13.7 Hz, CH₃Hₖ), 2.33 (d, 1H, J = 13.7 Hz, CH₃Hₖ), 2.18 – 1.84 (m, 5H,
$\text{CH}_2$, $\text{CH}_2\text{H}_b$, 1.81 (s, 3H, $\text{CH}_3$), 1.54 (s, 3H, $\text{CH}_3$), 1.49 (m, 1H, $\text{CH}_2\text{H}_b$). $^{13}\text{C}$ NMR (125 MHz, $\text{C}_6\text{D}_6$): $\delta$ 148.0, 143.5, 137.6, 131.3, 121.8, 121.5, 116.6, 115.1, 113.1, 110.5, 55.5, 55.0, 45.2, 43.5, 31.7, 24.9, 24.2, 23.3. IR (Neat): 3427 (w), 3070 (m), 2923 (s), 2835 (m), 1641 (m), 1602 (s), 1515 (s), 1457 (s), 1359 (m), 1252 (s), 1176 (m), 1115 (m), 1032 (s). HRMS (ESI+) Calcd for $\text{C}_{15}\text{H}_{25}\text{NO}$ [M + H]: 272.2009. Found: 272.2012. HPLC (Chiralcel OD, 0.1 % IPA in Hexane, 254 nm, 1.0 mL/min) 79 % e.e.

(\text{-Bromo-phenyl})-[3-methyl-1-(2-methyl-allyl)-cyclohex-3-eny]l-amine (2.105d): Prepared via procedure 2.13 in 91 % yield (160 mg, 450 $\mu$mol). Analogous preparation as above, 91 % yield. $^1\text{H}$ NMR (500 MHz, $\text{C}_6\text{D}_6$): $\delta$ 7.39 (dt, 1H, $J = 1$ Hz, 7.9 Hz, aryl CH), 6.96 (dt, 1H, $J = 1.5$ Hz, 8.2 Hz, aryl CH), 6.85 (dd, 1H, $J = 1.5$ Hz, 8.2 Hz, aryl CH), 6.36 (dt, 1H, $J = 1.5$ Hz, 7.9 Hz, aryl CH), 5.33 (m, 1H, CH=C(CH$_3$)), 4.90 (m, 1H, C(CH$_3$)=CH$_2$H$_b$), 4.73 (m, 1H, C(CH$_3$)=CH$_2$H$_b$), 4.50 (br, 1H, NH), 2.55 (d, 1H, $J = 13.7$ Hz, CH$_2$H$_b$), 2.23 (d, 1H, $J = 13.7$ Hz, CH$_2$H$_b$), 2.09 (br d, 1H, $J = 17.4$ Hz, CH$_2$H$_b$), 2.02 – 1.78 (m, 5H, CH$_2$, CH$_2$H$_b$), 1.73 (s, 3H, CH$_3$), 1.54 (s, 3H, CH$_3$), 1.38 (m, 1H, CH$_2$H$_b$). $^{13}\text{C}$ NMR (125 MHz, $\text{C}_6\text{D}_6$): $\delta$ 144.5, 142.8, 133.6, 130.9, 121.6, 118.0, 115.6, 114.2, 112.2, 55.7, 45.2, 43.0, 31.2, 24.8, 24.1, 23.2. IR (Neat): 3407 (m), 3071 (w), 2964 (m), 2924 (m), 2850 (m), 1642 (m), 1593 (s), 1515 (s), 1463 (s), 1375 (w), 1323 (m), 1287 (m), 1099 (m), 1018 (s). HRMS (ESI+) Calcd for $\text{C}_{17}\text{H}_{22}\text{NBr}$ [M + Na]: 342.0828. Found: 342.0838. HPLC (Chiralcel OD, 0.1 % IPA in Hexane, 254 nm, 1.0 mL/min) 81 % e.e.

(3-Trifluormethyl-phenyl)-[3-methyl-1-(2-methyl-allyl)-cyclohex-3-eny]l-amine (2.105e): Prepared via procedure 2.13 in 85 % yield (60 mg, 191 $\mu$mol). $^1\text{H}$ NMR (500 MHz, $\text{C}_6\text{D}_6$): $\delta$ 6.90 (m, 2H, aryl CH), 6.83 (s, 1H, aryl CH), 6.48 (m, 1H, aryl CH), 5.27 (m, 1H, CH=C(CH$_3$)), 4.88 (m, 1H, C(CH$_3$)=CH$_2$H$_b$), 4.68 (m, 1H, C(CH$_3$)=CH$_2$H$_b$), 3.31 (br, 1H, NH), 2.49 (d, 1H, $J = 13.7$ Hz, CH$_2$H$_b$), 2.11 (d, 1H, $J = 13.7$ Hz, CH$_2$H$_b$), 1.93 (m, 1H, CH$_2$H$_b$), 1.85 – 1.7 (m, 4H, CH$_2$), 1.66 (s, 3H, CH$_3$), 1.52 (s, 3H, CH$_3$), 1.29 (m, 1H, CH$_2$H$_b$). $^{13}\text{C}$ NMR (125 MHz, $\text{C}_6\text{D}_6$): $\delta$ 147.9, 142.8, 130.7, 130.1, 121.7, 118.0,
115.5, 113.9, 112.0, 55.3, 45.2, 43.3, 31.1, 25.0, 24.0, 23.0. IR (Neat): 3423 (m), 3074 (m), 2925 (s), 1643 (m), 1613 (s), 1524 (s), 1492 (s), 1440 (s), 1339 (s), 1264 (s), 1164 (s), 1124 (s), 1071 (s). HRMS (ESI') Calcd for C_{18}H_{22}NF_3 [M + H]: 310.1777. Found: 310.1769. HPLC (Chiralcel OD, 0.1 % IPA in Hexane, 254 nm, 1.0 mL/min) 64 % e.e.

**Benzyl-[3-methyl-1-(2-methyl-allyl)-cyclohex-3-enyl]-amine (2.105f):** Prepared via procedure 2.13 in 85 % yield (catalyst (R)-1.15a, 25 mg, 96 µmol). \(^1\)H NMR (500 MHz, C\(_6\)D\(_6\)): \(\delta\) 7.39 (d, 2H, J = 7.3 Hz, aryl CH), 7.20 (t, 2H, J = 7.3 Hz, aryl CH), 7.13 (t, 2H, J = 7.3 Hz, aryl CH), 5.33 (m, 1H, ArCH=CCH=CH(R), 4.95 (m, 1H, CH\(_2\)C=CH\(_2\)Ph), 4.81 (m, 1H, CH\(_3\)=CH\(_2\)Ph), 3.63 (m, 2H, NCH\(_2\)Ph), 2.25 (d, 1H, J = 13.7 Hz, CCH\(_3\)=C=CH\(_3\)C(CH\(_3\))=), 2.05 (d, 1H, J = 13.7 Hz, CCH\(_3\)=C=CH\(_3\)C(CH\(_3\))=), 2.02 – 1.87 (m, 4H), 1.88 (s, 3H, CH\(_3\)), 1.61 (m, 1H), 1.57 (s, 3H, CH\(_3\)), 1.37 (m, 1H), 1.11 (t, 1H, J = 7.0 Hz, CH\(_3\)). \(^1\)^C NMR (125 MHz, C\(_6\)D\(_6\)): \(\delta\) 143.8, 142.4, 132.2, 128.9, 127.4, 120.7, 114.8, 54.5, 46.7, 44.6, 42.0, 31.6, 25.6, 24.3, 23.4. IR (Neat): 3405 (w), 3028 (m), 2924 (s), 1640 (m), 1451 (m), 1375 (m), 1114 (m), 1071 (w), 1029 (m). HRMS (ESI') Calcd for C\(_{18}\)H\(_{23}\)N [M + H]: 256.2060. Found: 256.2056.

**Representative procedure 2.14:** Used to desymmetrize trialkylamines via ARCM in the absence of solvent. Amine 2.67a (255 mg, 1 mmol) was stirred with (R)-1.11a (19 mg, 25 µmol) in a loosely capped vial under N\(_2\) atmosphere. After 20 min, the reaction solidified and was exposed to ambient atmosphere. \(^1\)H NMR of an aliquot, (quenched by the addition of pyridine) indicated the reaction had proceeded to > 98 % conv. The product was purified by column chromatography on silica, eluting with benzene. To give 2.68a as an off–white solid (177 mg, 0.78 mmol) in 78 % yield.

(2-Bromo-phenyl)-(1,1-diallyl-pent-4-enyl)-amine (2.106): Prepared via procedure 2.12, using allyl–magnesium chloride in place of methallyl–magnesium bromide (2.0 g,
6.3 mmol) in 80% yield. $^1$H NMR (500 MHz, C$_6$D$_6$): δ 7.38 (dd, 1H, J = 7.9 Hz, J = 1.5 Hz, aryl CH), 7.11 (dt, 1H, J = 7.3 Hz, J = 1.2 Hz, aryl CH), 6.92 (dt, 1H, J = 1.2 Hz, J = 8.2 Hz, aryl CH), 6.79 (dd, 1H, J = 1.2 Hz, 7.6 Hz, aryl CH), 6.60 (dd, 1H, J = 1.2 Hz, 7.6 Hz, aryl CH), 6.37 (dt, 1H, J = 1.5 Hz, 7.5 Hz, aryl CH), 5.69 (m, 3H, CH=CH$_2$), 5.02 – 4.91 (m, 6H, CH=CH$_2$), 4.44 (br, 1H, NH), 2.31 – 2.18 (m, 4H, CH$_2$), 2.01 – 1.96 (m, 2H, CH$_2$), 1.69 – 1.61 (m, 2H, CH$_2$). $^{13}$C NMR (125 MHz, C$_6$D$_6$): δ 139.0, 134.5, 134.0, 133.6, 129.8, 128.8, 119.2, 118.7, 116.9, 115.0, 114.6, 112.6, 58.9, 41.6, 36.6, 29.4. IR (Neat): 3395 (br m), 3076 (m), 2936 (m), 2861 (w), 1640 (m), 1593 (s), 1515 (s), 1463 (s), 1328 (m), 1166 (w), 1019 (m). HRMS (EI$^+$) Calcd for C$_{15}$H$_{23}$N [M + H]: 321.1008. Found: 321.0096.

(2-Bromo-phenyl)-(1-(allyl)-cyclohex-3-ynyl)-amine (2.107): Precooled (∼35 °C) solutions of amine 2.106 (90 mg, 0.39 mmol) and various chiral Mo–catalysts (i.e., catalyst (R)-1.11a) were combined in a J. Young tube; which was then allowed to warm to room temperature over 5 minutes. $^1$H NMR of the reaction mixture indicated no starting amine remained, therefore the reaction was diluted with ether, stirred with charcoal, then filtered over celite with copious ether washing. The crude mixture was concentrated in vacuo, then purified via column chromatography, eluting with 4% ether in pentane to isolate a clear, colorless oil. $^1$H NMR (500 MHz, C$_6$D$_6$): δ 7.39 (dd, 1H, J = 1.2 Hz, 7.9 Hz, aryl CH), 6.94 (dt, 1H, J = 1.5, J = 7.8 Hz, aryl CH), 6.79 (dd, 1H, J = 1.5 Hz, 8.2 Hz, aryl CH), 6.38 (dt, 1H, J = 1.5 Hz, 7.6 Hz, aryl CH), 5.76 (m, 1H, CH=CH), 5.59 (m, 1H, CH$_a$=CH$_b$), 5.43 (m, 1H, CH$_a$=CH$_b$), 4.98 (m, 2H, CH=CH$_2$H$_b$), 4.49 (br, 1H, NH), 2.43 (dd, 1H, J = 14.5 Hz, J = 7.3 Hz, CH$_a$H$_b$), 2.24 (dd, 1H, J = 14.5 Hz, J = 7.3 Hz, CH$_a$H$_b$), 2.15 (br d, 1H, J = 17.7 Hz, CH$_a$H$_b$), 2.00 – 1.70 (m, 4H, CH$_2$, CH$_a$H$_b$), 1.38 (m, 1H, CH$_a$H$_b$). $^{13}$C NMR (125 MHz, C$_6$D$_6$): δ 134.3, 133.6, 129.7, 127.5, 118.4, 116.9, 114.5, 55.0, 42.2, 37.9, 31.1, 23.2. IR (Neat): 3404 (m), 3073 (m), 2921 (m), 1639 (m), 1594 (s), 1513 (s), 1483 (s),
1326 (m), 1286 (m), 1131 (w), 1018 (m). HPLC (Chiralcel OD, 0.1 % IPA in Hexane, 254 nm, 1.0 mL/min) < 5 % e.e.

1-Allyl-4-methyl-2-(2-methyl-allyl)-2,3-dihydro-1H-benzo[b]azepine: (Used in the preparation of 2.109.) Benzyl potassium (80 mg, 610 µmol) was added to a solution of 4-Methyl-2-(2-methyl-allyl)-
2,3-1H-benzo[b]azepine, 2.96a, (100 mg, 470 µmol) in THF (7 mL) at −35 °C. After warming to room temperature for 35 min, allyl bromide (74 mg, 610 µmol) was added to the solution. The reaction was stirred another 2 h, then quenched on water (2 mL) and 10% HCl\textsubscript{(aq)} (1 mL). The mixture was extracted three times with ether (50 mL). All organic extracts were combined, washed with saturated solutions of NaHCO\textsubscript{3(aq)} and NaCl\textsubscript{(aq)}, then dried (MgSO\textsubscript{4}) and concentrated in vacuo. The product was purified by column chromatography (silica gel), eluting with 1% ether in pentane to obtain 65 mg of clear, colorless oil (260 µmol, 55 % yield). \textsuperscript{1}H NMR (500 MHz, C\textsubscript{6}D\textsubscript{6}): δ 7.14 (dd, 1H, J = 1.5 Hz, 7.6 Hz, aryl CH), 7.08 (dt, 1H, J = 1.8 Hz, 7.6 Hz, aryl CH), 6.87 (dt, 1H, J = 1.2 Hz, 7.3 Hz, aryl CH), 6.83 (d, 1H, J = 8.2 Hz, aryl CH), 6.37 (s, 1H, ArCH=CH\textsubscript{2}CH\textsubscript{2}CH=CH\textsubscript{2}), 5.81 (m, 1H, CH\textsubscript{2}CH=CH\textsubscript{2}), 5.13 (m, 1H, CH\textsubscript{2}CH=CH\textsubscript{2}), 5.02 (m, 1H, CH\textsubscript{2}CH=CH\textsubscript{2}), 4.72 (m, 1H, CH\textsubscript{2}CH=CH\textsubscript{2}), 4.59 (m, 1H, CH\textsubscript{2}CH=CH\textsubscript{2}), 3.64 (m, 2H, NCH\textsubscript{2}CH=CH\textsubscript{2}), 3.49 (m, 1H, NCH), 2.27 (dd, 1H, J = 1.5 Hz, 17.4 Hz, CH(CH\textsubscript{2}H\textsubscript{n})(CH\textsubscript{2}R')), 2.17 (dd, 1H, J = 3.5 Hz, 17.4 Hz, NCH(CH\textsubscript{2}H\textsubscript{n})(CH\textsubscript{2}R')), 2.08 (m, 2H, NCH(CH\textsubscript{2}R')(CH\textsubscript{2}R')), 1.86 (s, 3H, CH\textsubscript{3}), 1.56 (s, 3H, CH\textsubscript{3}). \textsuperscript{13}C NMR (125 MHz, C\textsubscript{6}D\textsubscript{6}): δ 147.9, 143.9, 137.1, 134.9, 133.1, 129.2, 128.7, 127.5, 120.4, 120.3, 117.0, 113.5, 58.3, 54.2, 40.1, 40.0, 28.0, 22.8. IR (Neat): 3071 (m), 2966 (m), 1644 (m), 1595 (m), 1495 (s), 1439 (m), 1374 (m), 1232 (m), 1168 (m). HRMS (El\textsuperscript{+}) Calcld for C\textsubscript{18}H\textsubscript{21}N: 253.1825. Found: 253.1821. [α]\textsuperscript{D} = −0. 6 ± 0.1 °(c = 0.3, CHCl\textsubscript{3}).
6,9-Dimethyl-7,7a,8,11-tetrahydro-11a-aza-dibenzo[a,c]cycloheptene (2.108):

Catalyst 1.1a, (10 mg, 13 μmol) was added to a solution of 1-Allyl-4-methyl-2-(2-methyl-allyl)-2,3-dihydro-1H-benzol[b]-azepine (65 mg, 256 μmol) in benzene-\(d_6\). After 10 min, \(^1\)H NMR indicated the reaction was complete. The solution was stirred over charcoal, filtered through celite and concentrated in vacuo. The product was purified by column chromatography eluting with 1% ether in pentane to afford a white solid, 40 mg (177 μmol, 69 % yield). \(^1\)H NMR (500 MHz, C\(_6\)D\(_6\)): \(\delta\) 7.11 (m, 2H, aryl CH), 6.95 (m, 2H, aryl CH), 6.37 (s, 1H, ArCH=C), 5.24 (m, 1H, NCH\(_2\)CH=CH\(_2\)), 3.68 (m, 1H, NCH\(_2\)H\(_5\)CH), 3.49 (m, 1H CH(CH\(_2\)R)(CH\(_2\)R')), 3.36 (m, 1H, NCH\(_2\)H\(_5\)CH), 2.21 (m, 2H, CH(CH\(_2\)R)(CH\(_2\)R')), 1.82 (s, 3H, CH\(_3\)), 1.81 (m, 2H, CH(CH\(_2\)R)(CH\(_2\)R')). \(^13\)C NMR (125 MHz, C\(_6\)D\(_6\)): \(\delta\) 150.0, 138.8, 133.2, 133.1, 130.6, 128.7, 127.6, 127.4, 121.4, 120.9, 120.0, 65.6, 50.4, 38.1, 37.3, 26.9, 23.5. IR (Neat): 3061 (m), 2926 (s), 1593 (s), 1487 (s), 1442 (s), 1386 (m), 1257 (m), 1225 (s), 1179 (m), 1049 (m). HRMS (El\(^+\)) Calcld for C\(_{18}\)H\(_{39}\)N: 225.1512. Found: 225.1513. HPLC (Chiracel OJ, 100% hexane, 0 °C, 1.0 mL/min, 254 nm) > 90 % e.e. (No baseline.) [\(\alpha\)\(^D\) = +6.5 ± 0.1 °(c = 1.0, CHCl\(_3\)).

Allyl-[3-methyl-1-(2-methyl-allyl)-but-3-enyl]-(2-vinyl-phenyl)-amine (2.109)

Benzyl potassium (350 mg, 2.7 mmol) was added to a solution of amine 2.95a (500 mg, 2.1 mmol) in THF (30 mL) at -35 °C. After stirring for 30 min, allyl bromide (326 mg, 2.7 mmol) was added, which slowly turned the deep red mixture to a white suspension in a yellow solution. After 30 min, the reaction was poured onto water, then extracted three times with ether (60 mL). All organic layers were combined, washed with saturated solutions of NH\(_4\)Cl, NaCl, then dried (MgSO\(_4\)) and concentrated in vacuo to a yellow oil. The crude material was purified by column chromatography, eluting with 0.1% ether in pentane to isolate 160 mg of colorless oil (0.57 mmol, 27 % yield). \(^1\)H NMR (500 MHz, C\(_6\)D\(_6\)): \(\delta\) 7.44 (dd, 1H, J
= 1.5 Hz, 7.9 Hz, aryl CH), 7.26 (dd, 1H, J = 11.0 Hz, 17.4 Hz, ArCH=CH₂), 7.03 (dd, 1H, J = 0.9 Hz, 8.2 Hz, aryl CH), 6.85 (t, 1H, J = 7.9 Hz, aryl CH), 5.62 (m, 1H, CH₂CH=CH₂), 5.57 (dd, 1H, J = 1.5 Hz, 17.7 Hz, ArCH=CH₃H₆), 5.11 (dd, 1H, J = 1.5 Hz, 10.1 Hz, CH₂CH=CH₃H₆), 5.04 (dd, 1H, J = 1.5 Hz, 17.4 Hz, ArCH=CH₃H₆), 4.88 (dd, 1H, J = 1.5 Hz, 10.1 Hz, CH₂CH=CH₃H₆), 4.75 (m, 4H, CH₃C=CH₂), 3.62 (m, 2H, NCH₂CH=CH₂), 3.55 (pentet, 1H, J = 7.0 Hz, CH(CH₂R)₂), 2.31 (dd, 2H, J = 6.7 Hz, 13.7 Hz, CH(CH₃H₆R)₂), 2.72 (dd, 2H, J = 6.7 Hz, 13.7 Hz, CH(CH₃H₆R)₂), 1.47 (s, 6H, CH₃C=CH₂). ¹³C NMR (125 MHz, C₆D₆): δ 149.0, 144.2, 137.2, 136.5, 134.3, 128.0, 127.6, 123.8, 123.1, 116.6, 113.6, 113.0, 59.9, 47.4, 41.5, 22.6. IR (Neat): 3420 (m), 3073 (s), 2933 (s), 1646 (m), 1602 (s), 1509 (s), 1457 (s), 1374 (m), 1316 (s), 1260 (m), 1186 (m), 1029 (w). HRMS (ESI) Calcd for C₂₀H₂₇N [M + H]: 282.2216. Found: 282.2225.

1-[3-Methyl-1-(2-methyl-allyl)-but-3-enyl]-1,2-dihydro-quinoline (2.110)

Catalyst 1.1a (13 mg, 18 μmol) was added to a solution of tetraene 2.107 (100 mg, 355 μmol) in benzene-d₆. After 1.5 h, ¹H NMR indicated the reaction to be complete, so the solution was exposed to air, then stirred over charcoal. The mixture was filtered over celite and concentrated in vacuo. This compound is highly unstable! ¹H NMR (500 MHz, C₆D₆): δ 7.07 (dt, 1H, J = 1.5 Hz, 7.8 Hz, aryl CH), 6.81 (dd, 1H, J = 1.5 Hz, 7.3 Hz, aryl CH), 6.69 (d, 1H, J = 8.2 Hz, aryl CH), 6.62 (dt, 1H, J = 0.9 Hz, 7.3 Hz, aryl CH), 6.20 (d, 1H, J = 9.5 Hz, ArCH=CHR), 5.39 (m, 1H, ArCH=CHR), 4.78 (m, 4H, CH₃C=CH₂), 4.05 (pentet, 1H, J = 7.6 Hz, NCH(CH₂R)₂), 3.68 (m, 2H, NCH₂CH=CH₂), 2.14 (dd, 2H, J = 7.6 Hz, 14.3 Hz, CH(CH₃H₆R)₂), 2.04 (dd, 2H, J = 7.3 Hz, 14.3 Hz, CH(CH₃H₆R)₂), 1.60 (s, 6H, CH₃). ¹³C NMR (125 MHz, C₆D₆): δ 146.5, 143.5, 129.7, 127.5, 124.0, 121.9, 117.4, 113.1, 110.6, 52.7, 41.8, 39.1, 22.7. IR (Neat): 3072 (m), 2931 (s), 1646 (m), 1597 (s), 1493 (s), 1451 (s), 1374 (m), 1265 (m), 1185 (w), 1049 (w). HRMS (ESI') Calcd for C₁₈H₂₅N [M + H]: 254.1903. Found: 254.1910.
**Representative procedure 2.15:** Used to desymmetrize trialkyamines via ARCM with in situ prepared catalysts. A THF solution of the bis–potassium salt of the requisite diol (100 µL, 0.1 M) was added to a THF solution of complex 1.4a (100 µL, 0.1 M) and the resultant solution stirred for 1 h under an N₂ atmosphere. A benzene solution of amine 2.67a (51 mg, 2.0 mmol) was then at once. The mixture was stirred in a loosely capped vial under N₂ atmosphere for 2 h. ¹H NMR of an aliquot, indicated the reaction had proceeded to > 98 % conv, therefore the mixture was exposed to ambient atmosphere and concentrated in vacuo. The product was purified by column chromatography on silica, eluting with benzene, to give 2.68a as an off–white solid (45 mg, 2.0 mmol) in quantitative yield.
CHAPTER 3: Chiral Heterogeneous Molybdenum–Alkylidene Metathesis Catalysts.

A portion of this work has been submitted for publication:

3.1 INTRODUCTION

3.1.1 Solid–phase techniques in organic synthesis.

Solid–phase synthesis was first reported by Letsinger\textsuperscript{132,133} and Merrifield.\textsuperscript{134} Merrifield’s peptide synthesis on a poly(styrene–co–divinylbenzene) solid support (Scheme 3.1) is illustrative. In this seminal paper, various N–CBz protected amino acids were tethered to the resin \textit{via} ester formation (3.2). Following acidic removal of the CBz–protecting group, addition of another N–CBz protected amino acid provided the peptide linkage (3.4). After removal of the terminal CBz–moiety, the substrate was cleaved (basic conditions) from the support to afford clean dipeptide (3.5). Using the intermediate steps of this process iteratively, various tetrapeptides have also been prepared. Forty years later, solid–phase chemistry is considered the standard for oligopeptide synthesis, and is frequently automated.\textsuperscript{135}

![Scheme 3.1 Use of Merrifield’s Resin, poly(styrene–co–divinylbenzene), to prepare peptides.]

Solid–phase synthesis greatly simplifies product purification: undesirable byproducts, and even excess reagent, can be simply washed away from the support prior
to substrate release. However, this technique adds two non-complexity-generating steps: attachment to and release from the resin. Other disadvantages include increased reaction time, greater difficulty in reaction progress monitoring, and potential contamination of the final product with resin components. Regardless, this method constitutes an important and growing area of chemistry, particularly in drug discovery research. More detailed information can be found in several excellent general reviews.\textsuperscript{136,137}

3.1.2 Development of polymer-supported reagents.

The above mentioned disadvantages of solid-phase synthesis can be avoided, and the benefits retained, by moving from solid-supported substrates to solid-supported reagents. Using this method, the extraneous steps of substrate attachment and release are no longer required. However, because the resin-bound reagent is removed by filtration, a large excess can still be used to drive the reaction. Furthermore, the reaction progress may be monitored in real time by examination of solution aliquots. This technique has become so popular that many supported reagents are now commercially available (Figure 3.1). The reader is referred to excellent reviews in the literature.\textsuperscript{138,139}

![Figure 3.1 Some commercially available resin-supported reagents.](image-url)
Typical commercial resin-bound reagents include various oxidation and reduction reagents such as 3.6 and 3.7, respectively. However, the immobilized analogues of highly toxic or hazardous reagents, such as osmium or selenium oxidants, 3.11 and 3.12, respectively, are some of the most attractive resins. Immobilization results in reduced odor, easier handling, and increased safety. Reagents which typically create significant quantities of undesired byproducts also benefit from a heterogeneous variant. An illustrative example is the peptide coupling reagent dicyclohexylcarbodiimide (DCC). While this reagent greatly facilitates acylation of amines (eq 3.1), it also generates an equimolar amount of dicyclohexylurea (DCU), which is often difficult to remove completely.\textsuperscript{140}

\[ \text{RNH}_2 + \text{R'}\text{CO}_2\text{H} + \text{DCC} \rightarrow \text{R}^'\text{NH}_2\text{R}'' + \text{DCU} \] (3.1)

However, when the carbodiimide moiety is resin-bound, the urea byproduct remains resin-bound as well, and can be completely and easily removed by filtration (Scheme 3.2).\textsuperscript{141}

Scheme 3.2 Facilitated product purification \textit{via} heterogeneous reagent.
In addition to product purification, heterogeneous reagents are often more compatible with one another than their discrete counterparts. For instance, an oxidation–reduction sequence could never be carried out in a single flask with traditional reagents. However, it has been shown that periodate and borohydride are rendered mutually inert when attached to separate polymer supports. Hébert et al. have used this effect to improve the yield of various trihydroxy nucleosides (3.16, Scheme 3.3). With traditional reagents, the oxidized intermediate, a highly unstable aldehyde, had to be isolated prior to reduction, which resulted in reduced overall yield of 3.16. However, when the supported oxidant and reductant were used in one–pot, the intermediate dialdehyde was immediately reduced in situ, and thus significantly greater yield was obtained.

![Scheme 3.3 One–pot use of heterogeneous oxidant and reductant.](image)

3.1.3 Development of polymer–supported catalysts.

Polymer supported variants of many catalysts have also been developed. Only a few representative examples are discussed herein; the reader is referred to a recent review by Janda and coworkers for further details.\textsuperscript{138}

Palladium–catalyzed couplings constitute an indispensable class of carbon–carbon bond forming reactions. Therefore, it is not surprising that several researchers have studied the adaptation of palladium catalysts to poly(styrene) supports. Trost and coworkers were the first to show that when 3.9 is modified to incorporate palladium
(3.17, Scheme 3.4), a highly active, removable catalyst is afforded.\textsuperscript{143} In addition to \(\pi\)-allyl chemistry, this resin is an effective catalyst for Suzuki-type couplings (Scheme 3.4).\textsuperscript{144}

Scheme 3.4 Supported Pd-catalyst as an efficient cross-coupling catalyst.

Moburg and coworkers have reported the use of a resin-tethered chiral ligand for asymmetric Pd-catalyzed \(\pi\)-allyl substitutions.\textsuperscript{145} While the efficiency of this system was variable (from 60 – 100 % yield), enantioselectivity was reproducibly around 80 % e.e. (Scheme 3.5).

Scheme 3.5 Supported chiral ligand for Pd-catalyzed \(\pi\)-allyl substitutions.
Another excellent representative of the advantages available from heterogeneous variants of traditional homogeneous catalysts is transition-metal catalyzed asymmetric hydrogenation. Typical asymmetric hydrogenation catalysts have extensive applications\(^{146}\) however the ability to remove, and even reuse, these catalysts would greatly improve commercial viability. Bayston \textit{et al.} have reported the synthesis of a poly(styrene) supported Ru–BINAP hydrogenation catalyst (3.30, Scheme 3.6).\(^{147}\) Asymmetric hydrogenation of olefins and β–keto–esters catalyzed by 3.30 proceeded in good yield, and high enantioselectivity, to afford products with very low metal contamination (less than 1 % of the amount initially loaded). Furthermore, this catalyst retained good levels of activity upon reuse.

![Scheme 3.6 Asymmetric reductions catalyzed by a heterogeneous Ru–BINAP complex.](image)

3.1.4 The first polymer–supported metathesis catalysts.

Many heterogeneous variants of ill–defined metathesis catalysts have been reported.\(^{148-152}\) However, a heterogeneous metathesis catalyst based on a single–component metal carbene was not described until 1995.\(^{153}\) To achieve this, Grubbs and coworkers tethered dicyclopentylphosphine to a poly(styrene) resin (3.35a–b, Scheme 3.7). When treated with 2.1a, displacement of both tricyclopentylphosphine ligands occurred to afford the supported catalysts 3.36a–b. Although supported catalysts 3.36a–b exhibited significantly slower reaction rates for the cross–metathesis of cis–2–pentene,
they also displayed extended catalyst lifetimes and were reusable for several cycles, with minor loss in activity (20 % per cycle).

![Chemical structures](image)

Scheme 3.7 First polymer-supported Ru-based olefin metathesis catalyst.

An alternative method for alkylidene immobilization, first developed by Barrett and coworkers, is often referred to as the "boomerang" method. In this case, the resin is modified to incorporate a terminal olefin, which is used as the site of alkylidene attachment by addition of 2.1a or 2.1b, to afford 3.38a–b (Scheme 3.8). These systems exhibit improved activity compared to 3.36a–b, as the active alkylidene is released into solution for catalysis. Alkylidene return to the resin (the "boomerang" effect) is the

![Chemical structures](image)

Scheme 3.8 Ru-based boomerang–catalysts for olefin metathesis.
crucial feature of this design: it permits recycling of the catalyst and ensures low metal–contamination of unpurified substrates. However, in practice significant activity loss was observed upon catalyst recycling. The inherent instability of the propagating methylene species in solution was cited to explain this deactivation.

The degree of catalyst recapture from solution was vastly improved by using an ortho–alkoxy styrene as the site of Ru-alkylidene attachment to poly( styrene) (3.43, Scheme 3.9). This design is based upon 2.1c, (bearing a bidentate alkyldene). From the recycling data presented, it is clear that the use of a styrene with bidentate capabilities vastly improves catalyst recapture, allowing for a highly recyclable system.

![Scheme 3.9 A Ru-based, boomerang–type catalyst bearing a bidentate carbene.](image)

Blechert and coworkers have reported the preparation of a permanently immobilized variant of 2.1b, wherein attachment to the resin is achieved via the N–heterocyclic carbene ligand 3.44 (Scheme 3.10). This catalyst exhibited good, albeit slow, reactivity in a variety of RCM transformations (Scheme 3.10). Furthermore, catalyst 3.44 retained high activity in a representative RCM transformation for four cycles.
Scheme 3.10 A permanently immobilized Ru–based metathesis catalyst.

Slight modifications to the tether between resin and ligand can have dramatic effects. Even greater changes are observed when a resin other than poly(styrene) is used as the immobilization–platform. A variety of supported catalysts analogous to those discussed above have appeared in the literature. More detailed description of these subtle variations can be found elsewhere.\textsuperscript{159}

3.1.5 The first polymer–supported chiral metathesis catalyst.

Stelzer and coworkers were the first to report a heterogeneous single–component molybdenum carbene catalyst for olefin metathesis.\textsuperscript{160} In this report, diolate–modified alumina was treated with 1.1a to afford a mixed diolate species, which was found to be active for ROMP of various cyclic olefins. However, no other heterogeneous single–component achiral molybdenum carbenes have been reported in the literature.

Previous work in these laboratories was dedicated to the development of heterogeneous chiral Mo–based metathesis catalysts.\textsuperscript{161,162} In order to prepare an immobilized variant of catalyst (S)-1.11a, it was necessary to modify biphenol 3.49 such that it could be tethered to a poly(styrene) resin. It was decided to incorporate styrenyl–moieties so that the ligand could be co–polymerized with styrene directly, rather
than added to a pre-formed resin (Scheme 3.11). Thus, chiral biphenol 3.49 was brominated to afford 3.50, which rearranged in the solid state to afford 3.51. Displacement of the benzylc bromides with $p$-vinylbenzylimagnesium chloride, followed by protection of the phenol groups with ethoxy-chloromethane proceeded smoothly to afford 3.52. This modified ligand was then co-polymerized with styrene and divinylbenzene, and subjected to acidic deprotection conditions, to afford the resin-supported chiral ligand 3.53 (0.225 mmol/g). Deprotonation of the supported ligand, followed by addition of $(\text{Ar}_9\text{N})\text{Mo}$(CHCMe$_2$Ph)(OTf)$_2$DME, 1.4a, afforded $(S)$-3.54 as a dark brown powder. This powder was analyzed for Mo-content by ICP-MS (Robertson-Microlit) and found to be 1.58% Mo by weight, or 0.164 mmol/g; 73% of the potential ligand sites were occupied by a molybdenum-center.

Scheme 3.11 Preparation of a heterogeneous chiral biphenolate Mo-based metathesis catalyst.
Table 3.1 Catalytic Enantioselective Olefin Metathesis Promoted by Poly(styrene)–Supported Biphenolate–Based Chiral Mo Complex (S)-3.54.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>discrete catalyst (S)-1.11a</th>
<th>PS-bound (S)-3.54</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>conv (%)(^b)</td>
<td>yield (%)(^c)</td>
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<tr>
<td>1</td>
<td><img src="3.55a" alt="image" /></td>
<td><img src="3.56a" alt="image" /></td>
<td>&gt; 98; 0.5</td>
<td>89; &gt; 98</td>
</tr>
<tr>
<td>2</td>
<td><img src="3.55b" alt="image" /></td>
<td><img src="3.56b" alt="image" /></td>
<td>&gt; 98; 0.5</td>
<td>88; &gt; 98</td>
</tr>
<tr>
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<td><img src="3.57" alt="image" /></td>
<td><img src="3.58" alt="image" /></td>
<td>93; 24</td>
<td>88; 19</td>
</tr>
<tr>
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<td><img src="3.59" alt="image" /></td>
<td><img src="3.60" alt="image" /></td>
<td>93; 2</td>
<td>84; &gt; 98</td>
</tr>
<tr>
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<td><img src="1.27" alt="image" /></td>
<td><img src="1.28" alt="image" /></td>
<td>&gt; 98; 2</td>
<td>97; 93</td>
</tr>
</tbody>
</table>

\(a\). Conditions: 5 mol % catalyst, \(\text{C}_6\text{H}_6\), 22 °C. \(b\). Conv determined by analysis of the 400 MHz \(^1\text{H}\) NMR spectrum of the unpurified reaction mixture. \(c\). Isolated yields after purification by chromatography. \(d\). Enantioselectivity determined by chiral GC (\(\beta\)-dex for entries 3 & 4) and HPLC (Chiralcel OD for entry 1, Chiralpak AD for entry 2, and Chiralcel OJ for entry 3) analysis.
This novel heterogeneous catalyst, \((S)-3.54\), was tested in various asymmetric metathesis processes (Table 3.1). Although reduced activity was observed for certain transformations (entries 3 – 4), the enantioselectivity was found to be comparable to that obtained with homogeneous catalyst \((S)-1.11a\) in most cases. Importantly, catalyst recovery was greatly improved: simple filtration and solvent removal afforded products contaminated with \(\leq 5\%\) of the Mo initially used. In contrast, 91% of the molybdenum initially loaded was detected in the unpurified products of transformations catalyzed with \((S)-1.11a\). Further, catalyst \((S)-3.54\) was found to be recyclable for representative desymmetrizations; marked loss in activity was only observed upon the third iteration.

3.1.6 Poly(norbornene)–supported chiral metathesis catalyst.

Recently, Buchmeiser and coworkers reported a variation of \((S)-3.54\), utilizing a ring–opening metathesis polymerization (ROMP) generated poly(norbornene) support.\(^{163}\) This modification required norbornylene, as opposed to styrenyl, moieties be tethered to chiral biphenol 3.49. Therefore, sodium norbornylmethoxide was added to 3.51 to generate 3.61. Addition of Ru–based catalyst 2.1d initiated ROMP of 3.61 to generate a poly(norbornene)–like support \(((S)-3.62, \text{ Scheme } 3.12)\) which exhibited an extraordinarily high degree of swelling (solvent uptake of 2000 wt %). Ethyl vinyl ether was added to ensure complete removal of ruthenium from the polymer. This support is distinct from 3.53 not only because a different monomer was used, but also because each monomer represents a possible site of metal coordination. Thus, the theoretical catalyst loading on this support is unusually high.

Resin 3.62 was then treated with potassium hydride, followed by complex 1.4a, to afford \((S)-3.63\), with a Mo–loading of 0.47 mmol/g. Various ARCM transformations proved that \((S)-3.63\) performs with selectivity comparable to both \((S)-1.11a\) and \((S)-3.54\). However, inspection of Table 3.2 reveals that the substantial decrease in reaction rate
often observed for (S)-3.54 was not observed with (S)-3.63. This improved activity was attributed to the increased swelling properties of the poly(norbornene)--like support.

Scheme 3.12 Preparation of a poly(norbornene) supported chiral Mo--based metathesis catalyst.

Similar results for catalyst recycling and metal--contamination were obtained with (S)-3.63 as previously reported for (S)-3.54. After the first cycle, catalyst (S)-3.63 shows marked activity decrease; however the enantiomeric excess of the obtained product remains high. While Buchmeiser and coworkers did not analyze the unpurified products for metal--contamination, examination of the metal--content of the recovered resin indicated < 5 % loss of the initial Mo loading after three cycles.
3.1.7 Second generation polymer–supported chiral metathesis catalyst.

The catalytic activity and selectivity observed for binaphthol–ligated (R)-1.15a often complements that observed for the corresponding biphenol–ligated (S)-1.11a. Accordingly, a heterogeneous variant of (R)-1.15a was recently developed in our laboratories. Optically pure binaphthol 3.64 was synthesized from (+)–(R)–binaphthol as previously reported. Regioselective bromination, followed by Pd–catalyzed Suzuki–coupling with p–vinylphenylboronic acid, gave 3.65 in moderate yield after chromatography (Scheme 3.13). 3.65 was co–polymerized with styrene and divinylbenzene, then subjected to boron tribromide to afford supported chiral ligand 3.66 as an off–white powder (0.166 mmol/g). Deprotonation of the supported ligand,
Scheme 3.13 Preparation of heterogeneous chiral binaphthol–ligated Mo–based metathesis catalyst.

followed by addition of \((\text{Ar}_p\text{N})\text{Mo(CHCM}_{2}\text{Ph})(\text{OTf})_2\text{DME}, 1.4a\), afforded \((R)-3.67\) as a dark brown powder. This powder was analyzed for Mo–content by ICP–MS (Robertson–Microlit) and found to be 0.59 % Mo by weight, or 0.062 mmol/g. This indicated 53 % of the potential ligand sites were occupied by a molybdenum–center.

As the data in Table 3.3 indicate, supported catalyst \((R)-3.67\) efficiently promoted a variety of ARCM (entries 1 – 2) and AROM/RCM (entries 3 – 5) reactions. In most cases, reaction rates and enantioselectivities are comparable to those obtained with the homogeneous system, \((R)-1.15a\). However, there are instances wherein enantioselectivity is markedly worse (entry 2) or improved (entry 3) over that obtained with \((R)-1.15a\). The origin of these variations remains unclear.
Table 3.3 Catalytic Enantioselective Olefin Metathesis Promoted by Poly(styrene)–Supported Binaphthol–Based Chiral Mo Complex (R)-3.67.\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>discrete catalyst (R)-1.15a</th>
<th>PS-bound (R)-3.67</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>conv (%)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>yield (%)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>1</td>
<td>Me(\text{Me}_2\text{Si} )\text{CH}_2\text{CH}_2\text{Me})</td>
<td>Me(\text{Me}_2\text{Si} )\text{CH}_2\text{CH}_2\text{Me})</td>
<td>&gt; 98; 3 86; &gt; 98</td>
<td>98; 3 86; &gt; 98</td>
</tr>
<tr>
<td></td>
<td>(\text{Me})</td>
<td>(\text{Me})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Ph(\text{O} )\text{CH}_2\text{CH}_2\text{Me})</td>
<td>Ph(\text{O} )\text{CH}_2\text{CH}_2\text{Me})</td>
<td>&gt; 98; 6 87; 91</td>
<td>96; 6 85; 65</td>
</tr>
<tr>
<td></td>
<td>(\text{Ph})</td>
<td>(\text{Ph})</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Me(\text{Me}_2\text{Si} )\text{CH}_2\text{CH}_2\text{Me})</td>
<td>Me(\text{Me}_2\text{Si} )\text{CH}_2\text{CH}_2\text{Me})</td>
<td>&gt; 98; 24 75; 80</td>
<td>85; 24 60; 98</td>
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<tr>
<td></td>
<td>(\text{Me})</td>
<td>(\text{Me})</td>
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<td></td>
</tr>
<tr>
<td>4</td>
<td>H(\text{O} )\text{CH}_2\text{CH}_2\text{Me})</td>
<td>H(\text{O} )\text{CH}_2\text{CH}_2\text{Me})</td>
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<td>70; 0.3 62; 84</td>
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</tr>
<tr>
<td>5</td>
<td>Me(\text{Me}_2\text{Si} )\text{CH}_2\text{CH}_2\text{Me})</td>
<td>Me(\text{Me}_2\text{Si} )\text{CH}_2\text{CH}_2\text{Me})</td>
<td>&gt; 98; 2.0 83; 91</td>
<td>98; 2.0 89; 86</td>
</tr>
<tr>
<td></td>
<td>(\text{Me})</td>
<td>(\text{Me})</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\textit{a.} Conditions: 5 mol % catalyst, C\(_6\)H\(_6\), 22 °C. \textit{b.} Conv determined by analysis of the 400 MHz \(^1\text{H}\) NMR spectrum of the unpurified reaction mixture. \textit{c.} Isolated yields after purification by chromatography. \textit{d.} Enantioselectivity determined by chiral GC analysis (CDGTA for entries 1, 3, & 4; \(\beta\)-dex for entries 2 & 5).
3.2 Results and Discussion

3.2.1 Synthesis of poly(styrene) supported 2,6–dichlorophenylimido and 1–adamantylimido Mo–alkyldienes.

The culmination of work on chiral Mo–based metathesis catalysts and asymmetric metathesis transformations has shown that no single catalyst excels for all transformations. We have found that a class of chiral metathesis catalysts (vs. a single catalyst) is necessary for substrate generality to be achieved. Each specific combination of imido– and diolate ligands results in unique properties. Illustrative examples are presented in Table 3.4. In the case of 8–membered ring formation (entry 1) activity, but not selectivity, was affected by a change in the imido–ligand. The product of AROM/CM (CM = cross–metathesis) of 3.74a with allyl pinacolborate (entry 2) was significantly less prone to competitive transformations when catalyst (S)-1.11d was used than with all other catalysts. Finally, AROM/RCM of cyclopentene 1.29a (entry 3) was rapid for all catalysts, but only with catalyst (R)-1.15c could enantioselectivity be improved by the addition of THF.

Based on the above observations, it became clear that an entire class of supported chiral metathesis catalysts was needed to realize the full potential of asymmetric metathesis. Therefore, the 2,6–dichlorophenylimido– and 1–adamantylimido variants of heterogeneous (S)-3.54 were both prepared, according to the procedures previously developed in this lab. After the preparation of additional poly(styrene) supported ligand 3.53, (0.130 mmol/g) chiral catalysts (S)-3.75 and (S)-3.76 (Figure 3.2) were prepared with the requisite Mo–precursor complexes ((ArClN)Mo(CHCMe3)(OTf)2DME and (AdN)Mo(CHCMe2Ph)(OTf)2DME, respectively). Both catalysts were isolated as red–brown powders and analyzed for Mo–content by ICP–MS (Kolbe). Catalyst (S)-3.75 was determined to be 0.95 % Mo, or 0.106 mmol/g, which indicated that 79 % of all ligand sites were occupied by a molybdenum–center.
Table 3.4 Enantioselective Olefin Metathesis Promoted by Biphenol-Based Mo Complexes with Various Imido Ligands.\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>catalyst</th>
<th>conv (%),(^b)</th>
<th>yield (%),(^c)</th>
<th>e.e. (%),(^d)</th>
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<td>nd; 98</td>
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<td><img src="image3" alt="" /></td>
<td><img src="image4" alt="" /></td>
<td>((S)-1.11c)</td>
<td>98; 0.5</td>
<td>98; 98</td>
<td></td>
</tr>
<tr>
<td>3</td>
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<td><img src="image6" alt="" /></td>
<td>((S)-1.11a)</td>
<td>20(^e); 6</td>
<td>nd; nd</td>
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</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="" /></td>
<td><img src="image8" alt="" /></td>
<td>((S)-1.11c)</td>
<td>30(^e); 6</td>
<td>nd; nd</td>
<td></td>
</tr>
<tr>
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<td><img src="image9" alt="" /></td>
<td><img src="image10" alt="" /></td>
<td>((S)-1.11d)</td>
<td>80(^e); 6</td>
<td>78; 94(^f)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td><img src="image11" alt="" /></td>
<td><img src="image12" alt="" /></td>
<td>((R)-1.15c)</td>
<td>98; 24</td>
<td>nd; 78</td>
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<tr>
<td>7</td>
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<td><img src="image14" alt="" /></td>
<td>((R)-1.15c^*)</td>
<td>98; 24</td>
<td>93; 92</td>
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</table>

\(^a\) Conditions: 5 mol % catalyst, \(\text{C}_8\text{H}_8\), 22 °C under \(\text{N}_2\) atm. \(^b\) Conv determined by analysis of the 500 MHz \(^1\text{H}\) NMR spectrum of the unpurified reaction mixture. \(^c\) Isolated yields after purification by chromatography. \(^d\) Enantioselectivity determined by chiral GC (CDGTA for entry 3) and HPLC (Chiralcel OD for entry 1 and Chiralpak AS for entry 2) analysis. \(^e\) Conv to desired product, as opposed to other species. \(^f\) Conditions: 5 mol % catalyst, \(\text{C}_8\text{H}_8\), 4 °C under \(\text{N}_2\) atm.

\* plus 10 equiv THF
A better Mo–alkylidene loading was observed for (S)-3.76, which was determined to be 1.18 % Mo, or 0.123 mmol/g (95 % loading). Also, the 2,6-dichlorophenylimido-variant of supported binaphthol Mo–complex 3.67 was similarly prepared, ((R)-3.77) and found to be 1.09 % Mo, or 0.119 mmol/g (97 % loading).

![Chemical structures of (S)-3.75 and (S)-3.76](image)

Figure 3.2 Poly(styrene) supported chiral molybdenum alkylidenes.

3.2.2 Asymmetric metathesis reactions with poly(styrene) supported Mo–alkylidenes.

The results of catalytic enantioselective metathesis reactions promoted by poly(styrene) bound catalyst (S)-3.75 are presented in Table 3.5 (following page); for comparison, the outcomes of reactions initiated under identical conditions with the homogeneous variant, (S)-1.11c, are presented in the left column. As the data in Table
3.5 indicate, catalyst (S)-3.75 efficiently initiated several ARCM transformations. In all cases, reactions in the presence of homogeneous (S)-1.11c proceeded to > 90 % conversion in a shorter period of time than those carried out with (S)-3.75. In two cases (entries 3 – 4) the reaction arrested after < 77 % conversion with the heterogeneous catalyst. Disappointingly, all products derived from reactions with supported catalyst (S)-3.75 were formed with slightly lower levels of asymmetric induction compared to reactions that employed homogeneous (S)-1.11c. Notwithstanding this shortcoming, these products were still generated in appreciable enantiopurity, all within 10 % of that obtained with homogeneous (S)-1.11c. Furthermore, these products were substantially purer, after simple filtration, than when prepared with homogeneous (S)-1.11c. As a representative example, unpurified 2.86, prepared with (S)-3.75, was analyzed for Mo–contamination (ICP–MS) and found to contain < 1 % of Mo employed for the transformation.

Table 3.6 details both AROM/CM and AROM/RCM transformations catalyzed with homogeneous (S)-1.11d (left column) and heterogeneous (S)-3.76. In these examples, all reactions proceeded to > 95 % conversion with both the homo– and heterogeneous catalysts, however extended reaction times were required with (S)-3.76 in some examples (entries 3 – 4). Interestingly, in contrast to the examples in Table 3.5, the level of asymmetric induction obtained with (S)-3.76 was often greater than that obtained with homogeneous (S)-1.11d (entries 1, 2 & 4). However, in both AROM/CM transformations (entries 1 – 2), poorer trans:cis stereoselectivity was observed with the heterogeneous system. Further, the regioselectivity of AROM/RCM for both 3.78 and 3.80 was significantly reduced when catalyzed by (S)-3.76. Substantially greater quantities of the achiral seven–membered ring ether products 3.82 and 3.83 (Figure 3.3) were observed. Thus, although 3.78 was quickly consumed by (S)-1.11d, the desired tricycle 3.79 comprised only 80 % of the resultant mixture, while the remaining 20 % was achiral 3.82. When catalyst (S)-3.76 was used, byproduct 3.82 comprised 40 % of the resultant material. Similarly, (S)-1.11d generated 3.81 with < 2 % contamination by 3.83, whereas heterogeneous (S)-3.76 resulted in 11 % contamination by 3.83.
Table 3.5 Catalytic Enantioselective Olefin Metathesis Promoted by Poly(styrene)-Supported Dichloro–Imido Biphenol–Based Chiral Mo Complex (S)-3.75.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
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<th>PS-bound (S)-3.75</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>conv (%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>conv (%)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
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<td>yield (%)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>yield (%)&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>e.e. (%)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>e.e. (%)&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>time (h)</td>
<td>time (h)</td>
</tr>
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<td></td>
<td>&gt; 98; 1</td>
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<td>91; 81</td>
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</tr>
<tr>
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<td>98; 0.5</td>
<td>74; 5</td>
</tr>
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<td>Me</td>
<td>Me</td>
<td>98; 98</td>
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<td>98; 0.5</td>
<td>76; 20</td>
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<td></td>
<td>91; 62</td>
<td>76; 54</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>Ar = 2-(MeO)C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;3&lt;/sub&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Conditions: 5 mol % catalyst, C<sub>6</sub>H<sub>6</sub>, 22 °C under N<sub>2</sub> atm. <sup>b</sup> Conv determined by analysis of the 500 MHz ¹H NMR spectrum of the unpurified reaction mixture. <sup>c</sup> Isolated yields after purification by chromatography. <sup>d</sup> Enantioselectivity determined by chiral GC (CDGTA for entries 1 & 2) and HPLC (Chiralcel OD for entries 3 & 4) analysis.
Table 3.6 Catalytic Enantioselective Olefin Metathesis Promoted by Poly(styrene)–Supported Adamantyl–Imido Biphenol–Based Chiral Mo Complex (S)–3.76.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>discrete catalyst (S)–1.11d</th>
<th>PS-bound (S)–3.76</th>
</tr>
</thead>
<tbody>
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<td></td>
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<td>conv (%)(^b), yield (%)(^c)</td>
<td>time (h)</td>
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<td>78; 94</td>
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<tr>
<td>2</td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
<td>&gt; 98; 3</td>
<td>74; 90</td>
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</tr>
<tr>
<td>3</td>
<td><img src="image9.png" alt="Image" /></td>
<td><img src="image10.png" alt="Image" /></td>
<td>98; 3</td>
<td>82; 96(^e)</td>
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<tr>
<td>4</td>
<td><img src="image11.png" alt="Image" /></td>
<td><img src="image12.png" alt="Image" /></td>
<td>&gt; 98; 3</td>
<td>90; 72(^f)</td>
</tr>
</tbody>
</table>

\(^a\) Conditions: 5 mol % catalyst, C\(_6\)H\(_6\), 22 °C under N\(_2\) atm. \(^b\) Conv determined by analysis of the 500 MHz \(^1\)H NMR spectrum of the unpurified reaction mixture. \(^c\) Isolated yields after purification by chromatography. \(^d\) Enantioselectivity determined by chiral GC (CD–BPH for entry 2; CDGTA for entries 3 & 4) and HPLC (Chiralpak AS for entry 1) analysis. \(^e\) Observed 20% RCM to achiral seven–membered ring–ether with (S)–1.11d, vs 40% with (S)–3.75. \(^f\) Observed < 2% RCM to achiral seven–membered ring–ether with (S)–1.11d, vs 11% with (S)–3.75.
Attempts to recycle supported catalyst (S)-3.76 proved that transformations carried out with recycled samples of this catalyst proceeded with excellent levels of enantioselectivity; however, these transformations occurred with increasingly slower rates. As an example, when the sample of (S)-3.76 used for AROM/CM of 3.55a was isolated through filtration (under N₂ atmosphere) and re-subjected to the same reaction conditions, the reaction proceeded to only 65 % conversion in 3 h. The product was isolated in 55 % yield and 98 % e.e. (trans:cis = 10:1). The sample of (S)-3.76 was re-isolated for a third cycle, however < 5 % conversion was observed after 24 h. Somewhat surprisingly, when representative unpurified samples were analyzed for Mo–contamination (ICP–MS) 18 – 38 % of the Mo initially used was found in the crude material. It is difficult to rationalize why so much Mo leached into the crude materials, when compared to (S)-3.75 or (S)-3.54. It is possible that the unique properties of alkyl–imido ligated species²² result in catalytic intermediates particularly prone to decomposition, thus facilitating metal loss by the polymer support.

While the above data suggests that all heterogeneous variants of chiral Mo–based catalysts will compare well with their homogeneous counterparts, the data presented in Table 3.7 is strong evidence to the contrary. For both ARCM (entries 1 – 2) and AROM/RGM (entries 3 – 4) transformations, the levels of asymmetric induction were significantly and uniformly poorer when (R)-3.77 was used as catalyst than with the homogeneous variant, (R)-1.15c. No clear explanation for these results can be offered at
<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>conv (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>yield (%)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>e.e. (%)&lt;sup&gt;d&lt;/sup&gt;</th>
<th>conv (%)&lt;sup&gt;b&lt;/sup&gt;</th>
<th>yield (%)&lt;sup&gt;c&lt;/sup&gt;</th>
<th>e.e. (%)&lt;sup&gt;d&lt;/sup&gt;</th>
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<td>nd</td>
<td>54</td>
</tr>
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<td><img src="image" alt="1.30b&lt;sup&gt;e&lt;/sup&gt;" /></td>
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<td>95; 91</td>
<td>95; 1</td>
<td>90; 75</td>
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<td></td>
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<td><img src="image" alt="1.30c&lt;sup&gt;e&lt;/sup&gt;" /></td>
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<td></td>
</tr>
<tr>
<td>4</td>
<td><img src="image" alt="1.29c" /></td>
<td><img src="image" alt="1.30c&lt;sup&gt;e&lt;/sup&gt;" /></td>
<td>98; 24</td>
<td>85; 85</td>
<td>98; 24</td>
<td>nd; 40</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Conditions: 5 mol % catalyst, C<sub>6</sub>H<sub>6</sub>, 22 °C under N<sub>2</sub> atm.  
<sup>b</sup> Conv determined by analysis of the 500 MHz <sup>1</sup>H NMR spectrum of the unpurified reaction mixture.  
<sup>c</sup> Isolated yields after purification by chromatography.  
<sup>d</sup> Enantioselectivity determined by chiral GC analysis (CDGTA for all entries).  
<sup>e</sup> Conditions: 5 mol % catalyst, 10 equiv THF, C<sub>6</sub>H<sub>6</sub>, 5 °C under N<sub>2</sub> atm.
this time. However, it should be noted that the asymmetric induction obtained with catalyst (R)-1.15c has been shown to greatly improve when THF additives are used. The polymeric support of (R)-3.77 may adversely affect the nature of this solvent effect.

3.2.3 Synthesis of a chiral norbornylene–containing biphenoletate ligand.

A major drawback to the poly(styrene)–supported catalysts discussed above is the need for three transformations (deprotection, deprotonation and alkylidene addition) after the ligand has been supported. Due to the heterogeneous nature of these steps, it is difficult to quantify when these reactions are complete, and impossible to remove any insoluble impurities. In order to address such complications, we have designed an alternative approach where the Mo–alkylidene is supported in the process of creating the polymer support.

\[ \text{3.51} \xrightarrow{4 \text{ equiv } \text{MgCl}_2} \xrightarrow{\text{THF, } 22^\circ\text{C}} \text{93 \% yield} \xrightarrow{\text{3.84}} \]

Alkylation of 3.51 with norbornylmethylene magnesium bromide, afforded 3.84 in excellent yield (eq 3.2). Biphenol 3.84 is highly similar to biphenol 3.61, used by Kroll et al. to synthesize poly(norbornene) supported (S)-3.63. However, Kroll et al. did realize that the bis–potassium salt of biphenols are not only tolerated by Mo-based metathesis catalysts, but can be used to generate metathetically–active Mo-alkylidenes! Thus, using the bis–potassium salt of 3.84 we have been able to prepare various poly(norbornene) supported chiral catalysts in a one-pot procedure.
3.2.4 One-pot preparation of poly(norbornene) supported 2,6-di-iso-propylphenylimido, 2,6-dichlorophenylimido and 1-adamantylimido Mo-alkylidenes.

Treatment of 3.84 with potassium hydride, addition of co-monomers 3.85 and 3.86, and finally addition of 1 equiv of 1.4a at −35 °C, followed by slow warming, provided (S)-3.88a–d as tan–orange solids, via Mo-alkylidene 3.87, in near quantitative yield (Scheme 3.14). Initially, only co-monomer 3.85 was used, to generate a 100 % cross-linked support ((S)-3.88a). However, (S)-3.88a exhibited significantly reduced activity for two representative ARCM reactions (Table 3.8), as compared to either homogeneous (S)-1.11a or the poly(styrene) bound variant (S)-3.54. To address this complication, we decided to enhance catalyst accessibility through the synthesis of less cross-linked supports, by adding various amounts of co-monomer 3.86.

(S)-3.88a  x = 28, y = 0  (100 % cross-linking)
(S)-3.88b  x = 34, y = 35  (50 % cross-linking)
(S)-3.88c  x = 9.4, y = 59  (15 % cross-linking)
(S)-3.88d  x = 5, y = 65  (8 % cross-linking)

Scheme 3.14 One-pot synthesis of heterogeneous chiral Mo-alkylidenes.
As the data in Table 3.8 indicate, as the degree of cross-linking was reduced, reaction efficiencies increased. Thus, the most active and selective catalyst was found to be \((S)-3.88d\), which promoted ARCM of both \(1.21\) and \(2.67c\) to > 90 % conversion within one hour to afford cyclic dienes \(1.22\) and \(2.68c\) in 87 % e.e. and 96 % e.e., respectively (right–most column).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>((S)-1.11a)</th>
<th>((S)-3.88a)</th>
<th>((S)-3.88b)</th>
<th>((S)-3.88c)</th>
<th>((S)-3.88d)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>conv(%)(^b)</td>
<td>conv(%)(^b)</td>
<td>conv(%)(^b)</td>
<td>conv(%)(^b)</td>
<td>conv(%)(^b)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>e.e. (%)(^c)</td>
<td>e.e. (%)(^c)</td>
<td>e.e. (%)(^c)</td>
<td>e.e. (%)(^c)</td>
<td>e.e. (%)(^c)</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>99; 93</td>
<td>22; 84</td>
<td>34; 73</td>
<td>80; 84</td>
<td>99; 87</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 hour</td>
<td>5 hours</td>
<td>6 hours</td>
<td>1 hour</td>
<td>1 hour</td>
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<td></td>
<td>99; 98</td>
<td>15; 60</td>
<td>46; 73</td>
<td>99; 95</td>
<td>93; 96</td>
</tr>
</tbody>
</table>

\(^a\) Conditions: 5 mol % catalyst, \(C_6H_6\), 22 °C. \(^b\) Conv determined by analysis of the 500 MHz \(^1\)H NMR spectrum of the unpurified reaction mixture. \(^c\) Enantioselectivity determined by chiral GC (CDGTA for entry 1) and HPLC (Chiralcel OD for entry 2) analysis. \(^d\) \(Ar = p\)-Br\(C_6H_4\).

Based on these results, related dichlorophenylimido complex \((S)-3.89\) and adamantylimido complex \((S)-3.90\) were also prepared with 8 % cross–linked poly(norbornene) supports (Figure 3.4). The Mo–content of these materials was determined by ICP–MS analysis (Kolbe). Complex \((S)-3.88d\) was found to be contain 0.075 mmol/g of Mo; \((S)-3.89\) possessed 0.089 mmol/g; \((S)-3.90\) held 0.081 mmol/g. These analyses indicated substantially lower Mo–content than expected based upon the amount of complexes \(1.4a-d\) used. The low levels of catalyst loading are likely due to
3.2.5 Asymmetric metathesis reactions with poly(norbornene) supported molybdenum alkylidenes.

The results of studies regarding the ability of the poly(norbornene) supported complexes (S)-3.88d, (S)-3.89 and (S)-3.90 to initiate various catalytic ARCM and AROM/CM processes are summarized in Table 3.9 (following pages). Although in one case the desired product was isolated in significantly lower optical purity (entry 10), in the majority of cases the supported complexes afforded similar reactivity and enantioselectivity as the homogeneous analogues. The above findings are particularly noteworthy since in many cases < 3 % catalyst loading of the supported complex was used. As was mentioned briefly above, the increased activities of the chiral complexes (S)-3.88d, (S)-3.89 and (S)-3.90 were likely due to higher flexibility and degree of swelling of the poly(norbornene) backbone, as compared to poly(styrene). Thus, more appreciable rates of diffusion of substrates to catalyst sites were possible. However, there is also a significant disadvantage to these systems. As illustrated in eq 3.3, “self–cannibalism” through intramolecular metathesis within the polymeric structure, can

Figure 3.4 Poly(norbornene) (8 % cross–linking) supported chiral metathesis catalysts.

smaller, and thus more soluble, polymer chains, which could be washed out of the mixture upon filtration and isolation of the polymer beads.
Table 3.9: Catalytic Enantioselective Olefin Metathesis Promoted by Poly(norbornene)-Supported Biphenol-Based Chiral Mo Complexes 3.88d, 3.89 and 3.90. 

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Product</th>
<th>discrete catalyst</th>
<th>poly(norbornene)-bound</th>
</tr>
</thead>
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<td>catalyst; mol (%)</td>
<td>conv (%); time (h)</td>
</tr>
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<td><img src="image1" alt="" /></td>
<td><img src="image2" alt="" /></td>
<td>(S)-1.11a; 5</td>
<td>91; 1</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3" alt="" /></td>
<td><img src="image4" alt="" /></td>
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<td>&gt;98; 1</td>
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<td><img src="image6" alt="" /></td>
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<td>90; 1</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7" alt="" /></td>
<td><img src="image8" alt="" /></td>
<td>(R)-1.11a; 5</td>
<td>98; 0.5</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9" alt="" /></td>
<td><img src="image10" alt="" /></td>
<td>(R)-1.11a; 5</td>
<td>98; 6</td>
</tr>
<tr>
<td>6</td>
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<td><img src="image12" alt="" /></td>
<td>(S)-1.11c; 5</td>
<td>98; 0.5</td>
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</tbody>
</table>

Ar = p-BrC₆H₄

(S)-3.88d; 2.7 >98; 6 92; -87
(S)-3.89; 2.6 .98; 1 96; -86
(S)-3.89; 2.5 98; 1 95; -96
(S)-3.88d; 2.7 93; 2 88; -96
(S)-3.88d; 5 78; 6 70; -89
(S)-3.89; 5 85; 2 67; -96
<table>
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<th>Entry</th>
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<th>Product</th>
<th>discrete catalyst</th>
<th>poly(norbornene)-bound</th>
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<td></td>
<td></td>
<td>catalyst; mol (%)</td>
<td>conv (%); time (h)</td>
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<td>98; 0.5</td>
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<tr>
<td>8</td>
<td><img src="image5" alt="3.55a" /></td>
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<td>98; 2</td>
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<td>9</td>
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<td><img src="image8" alt="3.74a" /></td>
<td>(S)-1.11a; 5</td>
<td>98; 0.5</td>
</tr>
</tbody>
</table>

\*a. Conditions: C₆H₆, 22 °C, under N₂ atm. \*b. Conv determined by analysis of the 500 MHz ¹H NMR spectrum of an unpurified aliquot of the reaction mixture. \*c. Isolated yields after purification by chromatography. \*d. Enantioselectivity determined by chiral GC (CDGTA for entries 1 – 3) and HPLC (Chiralcel OD for entries 4 – 7; Chiralcel OJ for entry 8; Chiralpak AD for entry 9 and Chiralpak AS for entry 10) analysis.
release oligomeric pieces of the original polymer backbone. Consequently, the unpurified products from Table 3.9 contain detectable amounts of oligonorbornenes. The most reactive dichlorophenyllimido complex (S)-3.89 released organic polymers most readily, even upon simple suspension in pentane, diethyl ether or benzene. Nonetheless, the high activity of the poly(norbornene) supported catalysts, the excellent degrees of asymmetric induction promoted, and the relative ease with which polymeric debris can be removed, (silica chromatography) renders the present class of chiral metathesis catalysts of notable utility in enantioselective organic and combinatorial synthesis.
Despite the propensity of these materials to decompose, per eq 3.3, the crude
materials of these transformations possess significantly lower degrees of metal
contamination. Analysis for metal content of the crude products of these transformations
showed substantially reduced metal content in all cases. However, significantly different
amounts of metal contamination were observed from different poly(norbornene)-
supported catalysts. For example, unpurified 2.86, prepared with (S)-3.89, was analyzed
for Mo–contamination (ICP–MS) and found to contain 1.5 % of Mo that was initially
employed for the transformation. However, when crude 2.68c (prepared with (S)-3.88d)
was analyzed for metal content, Mo was detected that represented 5.4 % of that originally
used. Again, the alkylimido-catalyst resulted in the greatest metal contamination: crude
3.74a was found to contain 16.7 % of the Mo loaded on the sample of (S)-3.90 used for
the transformation.

3.3 CONCLUSIONS

Six distinct chiral Mo-based supported catalysts have been synthesized and tested
as catalyst for enantioselective olefin metathesis. Together, these chiral complexes offer
access to a range of optically enriched small molecules that cannot be easily prepared by
alternative methods. In all cases, simple filtration of the supported catalyst affords
products that contain significantly lower levels of metal impurity than products obtained
with homogeneous chiral complexes. In several cases, the level of metal contamination is
reduced to < 2 %. In many instances the levels of activity and enantioselectivity of these
supported catalysts are comparable to those observed with the analogous homogeneous
catalysts. Also noteworthy are the facility with which these supported complexes are
synthesized, particularly those that are bound to poly(norbornene) structures.
3.4 **Experimental Details**

**General**

$^1$H NMR spectra were recorded on Varian VXR 500, (500 MHz) Unity 300, (300 MHz) or Bruker DPX 400 (400 MHz) spectrometers. Chemical shifts are reported in ppm from tetramethylsilane with the residual *protio*-solvent resonance as the internal standard ($\text{C}_6\text{D}_6$: δ 7.16, CDCl$_3$: δ 7.26). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), integration, and assignment. $^{13}$C NMR spectra were recorded on Varian VXN 500, (125 MHz) Unity 300, (75 MHz) or Bruker DPX 400 (100 MHz) spectrophotometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the residual *protio*-solvent resonance as the internal standard ($\text{C}_6\text{D}_6$: δ 128.39, CDCl$_3$: δ 77.7). Infrared (IR) spectra were recorded on ThermoNicolet Avatar 360 spectrophotometer, $\mu_{\text{max}}$ in cm$^{-1}$. Bands were characterized as broad (br), strong (s), medium (m), and weak (w). High-resolution mass spectrometry was performed at the Massachusetts Institute of Technology, Department of Chemistry Instrumentation Facility (Cambridge, MA). Enantiomer ratios were determined by chiral HPLC (Chiral Technologies Chiralpak AS (4.6 mm θ x 250 mm), Chiralcel OJ (4.6 mm θ x 250 mm) or Chiralcel OD (4.6 mm θ x 250 mm)) or chiral GC (CDGTA, CD-BPH, or β–dex) in comparison with authentic racemic materials. Elemental analysis for trace Mo–content (ICP–MS) was performed by Kolbe Analysis (Manheim, Germany) or Robertson–Microlit (Madison, NJ).

All reactions were conducted in oven– (135 °C) or flame–dried glassware under an inert atmosphere of dry N$_2$. All metathesis substrates were dried by storing over molecular sieves under a N$_2$ atmosphere for a minimum of 12 hours prior to use. Handling of all Mo catalysts was performed in a drybox. Benzene, DME, THF, Et$_2$O, and toluene were sparged with N$_2$ and then passed through an activated alumina column or distilled from sodium/benzophenone ketyl under N$_2$. Pentane was washed with concentrated acid to
remove olefinic impurities, then sparged with N\textsubscript{2} and then passed through an activated alumina column. CH\textsubscript{2}Cl\textsubscript{2} was distilled from calcium hydride under N\textsubscript{2}. All reagents were used as received from Aldrich Chemical Co., Lancaster Synthesis, or Strem Chemicals, Inc. unless otherwise stated. Benzyl potassium was prepared by the literature method.\textsuperscript{31} Mo-complexes (Ar\textsubscript{p,N})Mo(CHMe\textsubscript{2}Ph)(OTf\textsubscript{2})DME, (Ar\textsubscript{Cl,NI})Mo(CHCMe\textsubscript{3})(OTf\textsubscript{2})DME, and (AdN)Mo(CHCMe\textsubscript{2}Ph)(OTf\textsubscript{2})DME were prepared as previously described.\textsuperscript{2,4,19,161,164} Chiral ligands (S)-3.49 and (R)-3.64 were also prepared as previously described.\textsuperscript{19,21} Certain desymmetrization substrates were provided by Dr. Jesper Jernelius (3.55a, 3.55b and 1.27), G. Alex Cortez (3.78 and 3.80), and Dr. Xin Teng (1.29b and 1.29c). All desymmetrization substrates and products have previously been described in this thesis (Chapters 1 and 2) or in the literature.\textsuperscript{17,18,21-26,167-171}

\textbf{(S)-5,5'-Bis-bromomethyl-3,3'-di-tert-buty1-6,6'-dimethyl-biphenyl-2,2'-diol (3.51):} A solution of bromine (17.9 g, 112 mmol) in glacial acetic acid (50 mL) was added dropwise to a suspension of (S)-3.49 (18.1 g, 51 mmol) and sodium acetate (16.9 g, 206 mmol) in glacial acetic acid (450 mL) over 30 min, whereupon (S)-3.49 slowly dissolved. The clear orange–yellow solution was stirred for 15 min, after which ice–water (1.0 L) was added. The resulting suspension was stirred 15 min, then filtered to afford a pale yellow solid. The solid was washed with water (2 x 50 mL) and taken up in ether (200 mL). Once in ether, the material was washed with cold water (50 mL) followed by cold brine (50 mL). The organic extract was dried (MgSO\textsubscript{4}) and concentrated \textit{in vacuo} at 0 °C. At this point, \textsuperscript{1}H NMR spectra of the crude material showed diquinone intermediate 3.50: \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): δ 6.90 (m, 2H, aryl CH), 1.93 (m, 12H, CH\textsubscript{3}), 1.22 (m, 18 H, C(CH\textsubscript{3})\textsubscript{3}). Solid 3.50 rearranged over 5 – 21 days to the desired dibromide 3.51. \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): δ 7.32 (s, 2H, aryl CH), 5.01 (s, 2H, OH), 4.57 (s, 4H, CH\textsubscript{2}Br), 1.94 (s, 6H, CH\textsubscript{3}), 1.39 (s, 18H, C(CH\textsubscript{3})\textsubscript{3}). No further spectra were obtained as this matches the previously reported spectra.\textsuperscript{161,162}
**p-Vinylbenzylmagnesium chloride**: (Used in the synthesis of 3.52): A solution of p-vinylbenzyl chloride (24.7 g, 162 mmol) in ether (100 mL) was added slowly to a magnesium slurry (15.5 g, 647 mmol) in ether (300 mL) at 0 °C. After 35 min, addition was complete; the reaction was allowed to warm to room temperature with stirring over 1 h. The resultant slurry was filtered over celite under an N₂ atmosphere, to afford a yellow solution. The solution was found to be 0.52 M by titration against cumylphenol with 1,10-phenanthroline as indicator.

(S)-3,3'-Di-tert-butyl-6,6'-dimethyl-5,5'--bis-[2-(4-vinyl-phenyl)ethyl]--biphenyl-2,2'-diol: (Used in the synthesis of 3.52): (S)-Br₂BiphenH₂, 3.51, 161 (1.75 g, 3.4 mmol) in ether was added dropwise to p-vinylbenzylmagnesium chloride (40 mL, 0.45 M) at −30 °C, to produce a mild exotherm. After stirring for 2 h, the white suspension was quenched by addition of methanol (5 mL). After warming to room temperature, a solution of saturated NH₄Cl (aq) was added and the mixture extracted three times with ether (200 mL). The organic extracts were combined, washed with saturated NaHCO₃ (aq) and brine, then dried over MgSO₄ and concentrated in vacuo to a yellow oil. The crude material was purified by chromatography over silica gel, eluting with 2% ether in pentane, to afford 1.1 g of a white glassy–solid (1.1 mmol, 60% yield.) ⁱH NMR (300 MHz, CDCl₃): 7.31 (d, J = 8 Hz, 4H, aryl CH), 7.07 (d, J = 8 Hz, 4H, aryl CH), 7.02 (s, 2H, aryl CH) 6.68 (dd, J = 17.6 Hz, J = 10.9 Hz, 2H, CH=CH₂), 5.69 (d, J = 17.6 Hz, 2H, CH=CH₂H₂), 5.18 (d, J = 17.6 Hz, 2H, CH=CH₂H₂), 4.78 (s, 2H, OH), 2.87 (m, 8H, CH₂CH₂), 1.74 (s, 6H, CH₃), 1.36 (s, 18H, C(CH₃)₃). No further spectra were obtained as this matches the previously reported spectrum. 161, 162

(S)-5,5'-Di-tert-butyl-6,6'-bis-ethoxymethoxy-2,2'-dimethyl-3,3'-bis-[2-(4-vinyl-phenyl)ethyl]-biphenyl (3.52): Potassium hydride (182 mg, 4.5 mmol) was added portion-wise to a solution of (S)-3,3'-Di-tert-butyl-6,6'-dimethyl-5,5'-bis-[2-(4-
vinyl–phenyl)ethyl]–biphenyl–2,2′–dil (1.1 g, 2.1 mmol) in THF (50 mL) under N₂ at room temperature. After the addition was complete, the mixture was stirred an additional 30 min, then cooled to −50 °C, whereupon ethoxy chloromethane (420 μL, 4.5 mmol) was added via syringe. The solution was stirred overnight, slowly warming to room temperature. The reaction was quenched by the addition of 10 % HCl(aq), then extracted three times with ether (200 mL). All organic extracts were combined, washed with saturated NaHCO₃(aq), then brine, dried over MgSO₄, and concentrated in vacuo to 1.34 g of a viscous yellow oil (2.1 mmol, 100 % yield). ¹H NMR (300 MHz, CDCl₃): 7.33 (d, J = 8.0 Hz, 2H, aryl CH), 7.31 (s, 2H, aryl CH) 7.12 (d, J = 8.0 Hz, 4H, aryl CH), 6.71 (dd, J = 17.6 Hz, J = 10.9 Hz, 2H, CH=CH₂), 5.71 (d, J = 17.6 Hz, 2H, CH=CH₂H₃), 5.21 (d, J = 10.9 Hz, 2H, CH=CH₂H₃), 4.39 (d, J = 4.1 Hz, 2H, OCH₃H₆O), 4.00 (d, J = 4.1 Hz, 2H, OCH₂H₆O), 3.58 (m, 2H, CH₂), 3.06 (m, 2H, CH₂), 2.90 (m, 8H, CH₂), 1.89 (s, 6H, CH₃), 1.38 (s, 18H, C(CH₃)₃), 1.08 (t, J = 7.0 Hz, 6H, OCH₂CH₂). No further spectra were obtained as this matches the previously reported spectrum.¹⁶¹,¹⁶²

**Polystyrene–supported ligand 3.53:** A suspension of 3.52 (402 mg, 0.62 mmol), styrene (4.68 mL, 40.3 mmol), divinylbenzene (100 μL, 0.35 mmol), benzoyl peroxide (48 mg, 0.14 mmol) and poly(vinyl alcohol) (56 mg), in toluene (5.4 mL) and water (50 mL) was homogenized by vigorous stirring for 1 h at room temperature. Once homogenized, the mixture was heated to 90 °C, with continued stirring, for 48 h. After the sample was cooled, white solid was isolated by filtration, and washed three times with water (20 mL), methanol (20 mL), and pentane (20 mL). The solid was subsequently dried under high vacuum, with heating to 60 °C until a steady vacuum was obtained (8 h, 60 mTorr). In this manner, 6.0 g of white particles were obtained (85 %
yield). IR (KBr): 3060 – 2923 (m) 1941 (w) 1868 (w) 1604 (s) 1493 (m) 1452 (m) 1350 (s) 1262 (m). This matches the previously reported spectrum.\textsuperscript{161,162} This material was then deprotected as follows: the polymer (3.92 g) was treated with concentrated HCl (0.5 mL) in a THF:methanol (5:1) suspension (30 mL). The suspension was agitated by gentle rotation for 48 h, then isolated by filtration. The obtained white solid was washed with THF (20 mL), methanol (20 mL) and finally pentane (20 mL). The solid chunks were lightly crushed in a mortar and pestle, then dried under high vacuum (60 °C, 60 mTorr) for 18 h to afford 3.14 g (80 % yield). IR (KBr): 3511 (s) 3059 (s) 3930 (m) 2790 (s) 2708 (m) 1942 (w) 1868 (w) 1646 (s) 1603 (m). This matches the previously reported spectrum.\textsuperscript{161,162}

**Polystyrene-supported catalyst (S)-3.75:** A suspension of potassium hexamethyldisilazide (82 mg, 0.39 mmol) and polystyrene supported ligand 3.53 (1 g, 0.13 mmol/g) in THF (100 mL) was agitated by slow rotation for 24 h, then filtered, washed with THF (4 x 8 mL) then ether (3 x 7 mL) and dried in vacuo to an orange–brown solid. To this solid was added THF (20 mL) and (Ar\textsubscript{Cl}N)Mo(CHCMe\textsubscript{3})(OTf)\textsubscript{2}DME (93 mg, 0.13 mmol); the suspension was agitated another 24 h. The product was filtered, washed with THF (3 x 20 mL, only very slightly yellow washings) and pentane (3 x 20 mL), then dried in vacuo to a brown powder, 1.04 g. El. Anal. Calcd 1.20 % Mo; Found: 0.95 % Mo, 0.106 mmol/g, 79 % loading (Kolbe).

**Polystyrene-supported catalyst (S)-3.76:** A suspension of potassium hexamethyldisilazide (82 mg, 0.39 mmol) and polystyrene supported ligand PS–(S)BiphenH\textsubscript{2} (1 g, 0.13 mmol/g) in THF (100 mL) was agitated by slow rotation for 24 h, then filtered, washed with THF (3 x 5 mL) and dried in vacuo to
an orange–brown solid. To this solid was added THF (15 mL) and (AdN)Mo(CHCMe₂Ph)(OTf)₃DME (100 mg, 0.13 mmol); the suspension was agitated another 24 h. The product was filtered, washed with THF (3 x 15 mL, only very slightly yellow washings) and pentane (4 x 5 mL), then dried in vacuo to a brown powder, 1.0 g. El. Anal. Calcd 1.25 % Mo; Found: 1.18 % Mo, 0.123 mmol/g, 95 % loading (Kolbe).

Representative Asymmetric Olefin Metathesis Transformation with (S)-3.75: A vial was charged with amine 2.85, (30 mg, 106 μmol) and (S)-3.75 (50 mg, 5.3 μmol) in benzene, and shaken on a Thermolyne (Type 37600) mixer under N₂ atmosphere. After 18 h, a ¹H NMR spectrum of an aliquot indicated the reaction to be at 75 % conversion. The reaction mixture was filtered over celite, washing with pentane. The crude material was then concentrated in vacuo. A sample of the crude material was sent for ICP–MS analysis to determine residual metal content.

Spectral data for all compounds presented in Table 3.5 can be found in either Chapter 1 (1.22, & 1.37) or Chapter 2 (2.86 & 2.105d) of this thesis.

Representative Asymmetric Olefin Metathesis Transformation with (S)-3.76: A vial was charged with benzyl–norbornylether 3.55a, (20.7 mg, 103 μmol) allyl–pinacolborate, (17.3 mg, 103 μmol) and (S)-3.76 (47 mg, 5.2 μmol) in benzene, and shaken on a Thermolyne (Type 37600) mixer under N₂ atmosphere. After 3 h, a ¹H NMR spectrum of an aliquot indicated the reaction to be complete, and it was filtered over celite, washing with pentane. The crude material was concentrated in vacuo, and judged to be clean by ¹H NMR spectral analysis.

2-[3-(2-Benzylxyloxy-3–vinylcyclopentyl)allyl]4,4,5,5–tetramethyl–[1,3,2]dioxaborola ne (3.74a): ¹H NMR (500 MHz, C₆D₆): δ 7.41 (d, 2H, J = 6.7 Hz, ortho–aryl CH) 7.21 (t,
2H, J = 7.6 Hz, \textit{meta}–aryl \textbf{CH}) 7.11 (t, 1H, J = 7.3 Hz, \textit{para}–aryl \textbf{CH}) 6.13 (m, 1H, \textbf{CH}=\textbf{CH}_2) 5.79 (m, 2H, \textbf{CH}=\textbf{CH}) 5.03 (m, 2H, \textbf{CH}=\textbf{CH}_2) 4.61 (d, 1H, J = 11.6 Hz, OCH$_3$H$_3$) 4.51 (d, 1H, J = 11.6 Hz, OCH$_3$H$_3$) 3.54 (t, 1H, J = 3.8 Hz, CHOBO) 2.42 (m, 1H, CHCH=CH$_2$) 2.33 (m, 1H, CHCH=CH$_2$B) 1.90 (m, 4H, CH$_3$CH$_2$) 1.67 (m, 2H, BCH$_2$) 1.03 (s, 12H, 4 x CH$_3$). This matched the reported \textsuperscript{1}H NMR spectrum therefore no further spectra obtained.\textsuperscript{22} In order to determine enantiomeric excess as well as \textit{trans:cis} ratio, \textbf{3.74a} was converted to the allylic alcohol as follows: Crude \textbf{3.74a} was dissolved in THF (0.2 mL) and ethanol (0.2 mL). Then pH 7.00 buffer (sodium & potassium phosphate) (0.2 mL) and H$_2$O$_2$ (30 % in water) (0.2 mL) were added and the mixture stirred 15 min. The mixture was diluted with ether (5 mL) and quenched with NaHCO$_3$. The mixture was extracted with ether, (3 x 5 mL) dried over MgSO$_4$ and concentrated \textit{in vacuo}. The product was purified via column chromatography, eluting with 5 % ether in pentane to afford a clear, colorless oil. \textsuperscript{1}H NMR (500 MHz, C$_6$D$_6$): $\delta$ 7.32 (d, 2H, J = 7.6 Hz, \textit{ortho}–aryl \textbf{CH}) 7.19 (t, 2H, J = 7.3 Hz, \textit{meta}–aryl \textbf{CH}) 7.10 (t, 1H, J = 7.6 Hz, \textit{para}–aryl \textbf{CH}) 6.09 (m, 1H, \textbf{CH}=\textbf{CH}_2) 5.82 (m, 1H, CH=CH) 5.54 (m, 1H, CH=CH) 5.05 (m, 2H, CH=CH$_2$) 4.88 (d, 1H, J = 11.9 Hz, OCH$_3$H$_3$) 4.40 (d, 1H, J = 11.9 Hz, OCH$_3$H$_3$) 3.89 (dd, 2H, J = 5.5 Hz, J = 1.2 Hz, CH$_2$OH) 3.51 (t, 1H, J = 4.0 Hz, CHOBO) 2.33 (m, 2H, 2 x CHCH=CH) 1.83 (m, 2H, CH$_2$) 1.67 (m, 2H, CH$_2$). This matched the reported \textsuperscript{1}H NMR spectrum therefore no further spectra obtained.\textsuperscript{22} HPLC (Chiralpak AS, 1 % IPA / Hexane, 1.0 mL / min, 190 nm) (authentic rac material at 15.3 & 17.3 min): 97 % e.e. Metal–contamination was determined by ICP–MS of a crude sample of \textbf{3.74a} (50 mg) sent to Robertson–Microlit (used 0.643 mg Mo for RCM). Observed 0.28 % Mo; i.e. 0.14 mg, or 22 % of loading.

\textbf{2-[3-(2-Methoxy-3-vinylcyclopentyl)allyl]4,4,5,5-tetramethyl-[1,3,2]dioxaborolane (3.74b):} \textsuperscript{1}H NMR (500 MHz, C$_6$D$_6$): $\delta$ 6.11 (m, 1H, CH=CH$_2$) 5.79 (m, 2H, CH=CH) 5.03 (m, 2H, CH=CH$_2$) 3.29 (s, 3H, OCH$_3$) 3.24 (t, 1H, J = 4.0 Hz, CHOMe) 2.40 – 2.30
(m, 2H, 2 x CHCH=CH₂) 2.00 – 1.75 (m, 4H, CH₂CH₂) 1.69 (m, 2H, BCH₂) 1.05 (s, 12H, 4 x CH₃). This matched the reported ¹H NMR spectrum therefore no further spectra obtained.²² In order to determine enantiomeric excess as well as trans:cis ratio, 3.74b was converted to the allylic alcohol as above. ¹H NMR (500 MHz, C₆D₆): δ 6.04 (m, 1H, CH=CH₂) 5.81 (m, 1H, CH=CH) 5.55 (m, 1H, CH=CH) 5.04 (m, 2H, CH=CH₂) 3.99 (d, 2H, J = 5.8 Hz, CH₂OH) 3.29 (m, 1H, CHOME) 3.20 (s, 3H, OCH₃) 2.82 (m, 2H, 2 x CHCH=CH₂) 2.85 – 1.34 (m, 4H, CH₂CH₂). This matched the reported ¹H NMR spectrum therefore no further spectra obtained.²² GC (CD–BPH): 99 % e.e.

**Spirocycle 3.79:** ¹H NMR (500 MHz, C₆D₆): δ 5.74 (m, 3H, 3 x CH) 5.30 (m, 1H, CH) 4.18 (dq, 1H, J = 17.7 Hz, J = 2.7 Hz, OCH₂H₂b) 4.01 (dq, 1H, J = 17.7 Hz, J = 2.4 Hz, OCH₂H₂b) 2.57 (m, 1H, CH) 2.22 (m, 2H, CH₂) 1.84 (m, 3H CH, CH₂) 1.50 (m, 1H, CH) 1.25 (m, 1H, CH) 1.14 (m, 1H, CH) 1.04 (m, 1H, CH). This matched the reported ¹H NMR spectrum²² therefore no further spectra obtained. GC (CDGTA, 105 °C, 15 psi) (authentic rac at 34.42 & 40.48 min): 89 % e.e. 12 mg of the crude material was sent to Robertson–Microlit for ICP–MS (used 0.726 mg Mo for RCM). Observed 1.11 % Mo: i.e. 0.1332 mg, or 18 % of amount used.

**Spirocycle 3.82:** ¹H NMR (500 MHz, C₆D₆): δ 5.86 (m, 2H, CH=CH) 5.67 (m, 1H, CH=CH) 5.40 (m, 1H, CH=CH) 3.91 (m, 2H, OCH₂) 2.50 (m, 2H, 2 x CH) 2.16 (m, 2H, CH₂) 2.05 (m, 4H, 2 x CH₂) 0.98 (dd, 2H, J = 3.4 Hz, J = 10.7 Hz, CH₂). This matched the reported ¹H NMR spectrum²² therefore no further spectra obtained.

**Spirocycle 3.81:** ¹H NMR (500 MHz, C₆D₆): δ 5.81 – 5.69 (m, 3H, vinyl CH) 5.42 (m, 1H, vinyl CH) 3.94 (br d, 1H, J = 17.1 Hz, OCH₂H₆b) 3.87 (br d, 1H, J = 17.1 Hz, OCH₂H₆b) 2.22 – 2.13 (m, 2H) 2.09 – 1.96 (m, 3H) 1.90 – 1.79 (m, 1H)
1.77 – 1.70 (m, 1H) 1.66 – 1.59 (m, 2H) 1.21 (ddd, 1H, J = 6.7 Hz, J = 13.4 Hz, J = 11.3 Hz). This matched the reported \(^1\)H NMR spectrum\(^{22}\) therefore no further spectra obtained. GC (CDGTA, 70 °C, 15 psi) (authentic rac at 199.35 & 210.64 min): 74 % e.e. 30 mg of the crude material was sent to Robertson–Microlit for ICP–MS (used 0.715 mg Mo for RCM). Observed 0.90 % Mo; i.e. 0.27 mg, or 38 %.

**(R)**–**3,3'–Bis**–(2,4,6–triisopropylphenyl)–6,6'–dibromo–2,2'–dimethoxy–1,1'–binaphthyl \((Used\ in\ the\ synthesis\ of\ 3.65.)\): At 0 °C, a solution of bromine (0.55 mL, 11 mmol) in CH\(_2\)Cl\(_2\) (5 mL) was added drop–wise to a CH\(_2\)Cl\(_2\) solution of 3,3'–bis–(2,4,6–triisopropylphenyl)–2,2'–dimethoxy–1,1'–bina

phthyl, 3.64, (3.5 g, 4.9 mmol). After 5 h at 0 °C, the reaction was quenched by the addition of an aqueous solution of NaHSO\(_3\) (10 %, 5 mL). The organic phase was separated, washed with water and brine and then dried over MgSO\(_4\). The resultant yellow foam was purified via column chromatography on silica, eluting with hexane and CH\(_2\)Cl\(_2\) (9:1) to afford a white foam (600 mg, 2.6 mmol, 54 % yield). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 7.98 (d, J = 2.0 Hz, 2H) 7.65 (s, 2H) 7.36 (dd, J = 9.0 Hz, J = 2.0 Hz, 2H) 7.14 (d, J = 9.0 Hz, 2H) 7.08 (d, J = 4.8 Hz, 4H) 3.05 (s, 6H) 2.94 (septet, J = 6.9 Hz, 2H) 2.72 (septet, J = 6.9 Hz, 4H) 1.30 (d, J = 6.9 Hz, 12 H) 1.24 (d, J = 6.9 Hz, 12 H) 1.18 (d, J = 6.9 Hz, 6H) 1.16 (d, J = 6.9 Hz, 6H) 1.10 (d, J = 6.9 Hz, 6H) 1.06 (d, J = 6.9 Hz, 6H). \(^1^3\)C NMR (75 MHz, CDCl\(_3\)): \(\delta\) 158.4, 155.7, 148.7, 147.7, 147.2, 146.9, 135.8, 132.8, 131.7, 127.6, 124.8, 122.6, 121.1, 119.1, 60.1, 34.6, 27.8, 25.8, 25.6, 24.4, 23.7. HRMS (ESI) Calcd for C\(_{90}\)H\(_{60}\)O\(_2\)Br\(_2\) [M+Na]: 897.2852. Found: 897.2906.

**(R)**–**3,3'–bis**–(2,4,6–triisopropylphenyl)–6,6'–bis–(4–vinyl–phenyl)–2,2'–dimethoxy–1,1'–binaphthyl \((3.65): \) A THF solution (170 mL) of

**(R)**–**3,3'–bis**–(2,4,6–triisopropylphenyl)–6,6'–dibromo–2,2'–dimethoxy–1,1'–binaphthyl, (6.57 g, 7.07 mmol) Pd(PPh\(_3\))\(_4\) (507 mg, 0.49 mmol) and \(p\)–vinylphenylboronic acid (2.6
g, 21 mmol) was added to aqueous K₂CO₃ (35 mL, 1.0 M). The resultant mixture was heated to 70 °C, with vigorous stirring, for 22 h in a teflon–sealed bomb. After cooling, the mixture was diluted with water (100 mL) and ether (200 mL), and the organic phase separated. The aqueous layer was extracted with ether (2 x 100 mL). All organic extracts were combined, washed with water, then brine, and dried over MgSO₄. The crude material was triterated in hexane (200 mL) and filtered over celite to remove palladium salts. The product was purified via column chromatography on silica gel, eluting with hexane and methylene chloride (9:1) to afford a white powder (3.52 g, 3.8 mmol, 54% yield). ³¹H NMR (300 MHz, CDCl₃): δ 8.08 (d, J = 1.8 Hz, 2H) 7.84 (s, 2H) 7.72 (d, J = 8.3 Hz, 4H) 7.61 (dd, J = 8.7 Hz, J = 1.8 Hz, 2H) 7.54 (d, J = 8.3 Hz, 4H) 7.47 (d, J = 8.7 Hz, 2H) 7.13 (d, J = 4.8 Hz, 4H) 6.79 (dd, J = 17.6 Hz, J = 10.9 Hz, 2H) 5.84 (d, J = 17.6 Hz, 2H) 5.29 (d, J = 10.9 Hz, 2H) 3.18 (s, 6H) 2.94 (m, 6H) 1.35 (d, J = 6.9 Hz, 12H) 1.24 (d, J = 6.9 Hz, 6H) 1.17 (d, J = 6.9 Hz, 6H) 1.14 (d, J = 6.9 Hz, 6H).

¹³C NMR (75 MHz, CDCl₃): δ 155.6, 148.5, 147.3, 147.1, 140.7, 137.2, 136.8, 136.7, 135.0, 133.4, 133.3, 131.6, 130.8, 127.6, 127.0, 125.9, 125.8, 124.9, 121.0, 114.2, 70.5, 60.3, 34.6, 31.4, 31.2, 25.7, 25.6, 24.4, 23.7, 23.6. HRMS (ESI⁺) Calcd for C₅₄H₆₀O₂ [M+Na]: 945.5581. Found: 945.5589.

**Polystyrene–supported ligand 3.66:** A 100 mL teflon–sealed bomb was charged with 3.65, (443 mg, 0.48 mmol) styrene, (3.9 mL, 34 mmol) technical–grade divinylbenzene, (240 µL, 0.84 mmol) benzoyl peroxide (50 mg) and poly(vinyl alcohol) (54 mg) in a mixture of toluene and water (6 mL : 50 mL). The suspension was vigorously stirred at 80 °C for 16 h. After cooling, a white powder was isolated by filtration, then washed with water, (2 x 50 mL) THF, (2 x 50 mL) methanol, (3 x 50 mL) and finally pentane (50 mL). The polymer
sample was then dried at 60 °C for 24 h, to afford 3.54 g (90 % yield). A portion of this material was then deprotected as follows: the polymer (1.12 g, theoretical loading: 0.28 mmol/g) was suspended in CH₂Cl₂ and treated with boron tribromide (2.0 mmol, 1.0 M) at room temperature, with vigorous agitation for 48 h. To the reaction was added HClₐq (3 %, 12 mL), THF (10 mL) and methanol (10 mL), and the slurry agitated a subsequent 24 h. After filtration, an off–white polymer was obtained, washed with water (10 mL), THF, (10 mL) methanol, (10 mL) and pentane (10 mL). The polymer sample was then dried at 60 °C for 24 h, to afford 1.03 g (87 % yield). IR (KBr): 3526 (s) 3051 (m) 3021 (m) 2962 (s) 2927 (s) 2871 (m) 1588 (w) 1511 (w) 1487 (m) 1064 (m).

**Polystyrene–supported catalyst (R)-3.77:** A suspension of potassium hexamethyldisilazide (77 mg, 0.36 mmol) and 3.77 (1 g, 0.12 mmol/g) in THF (100 mL) was agitated by slow rotation for 24 h, then filtered, washed with THF (3 x 20 mL), then ether (2 x 25 mL) and dried in vacuo to an orange–brown solid. To this solid was added THF (15 mL) and (Ar₃N)Mo(CHCMe₃)(OTf)₂DME (87 mg, 0.12 mmol); the suspension was agitated another 24 h. The product was filtered, washed with THF (3 x 15 mL, only very slightly yellow washings) and pentane (4 x 15 mL), then dried in vacuo to a brown powder, 1.0 g. El Anal Calcd: 1.12 % Mo; Found: 1.09 % Mo, 97 % loading, 0.119 mmol/g (Kolbe).

**Representative Asymmetric Olefin Metathesis Transformation with (R)-3.77:** A vial was charged with amine 1.21 (20.8 mg, 0.100 mmol) and (R)-3.77 (71.7 mg, 0.00500 mmol) in benzene (3 mL), and shaken on a Thermolyne (Type 37600) mixer under N₂ atmosphere. After 2 hours the reaction mixture was then filtered through a pasteur pipette fitted with a cotton plug and concentrated in vacuo to afford pale yellow oil 1.22 (18.5 mg, 89 %).
Spectral data for certain compounds presented in Table 3.7 can be found in Chapter 1 (1.22, & 1.37) of this thesis.

4- Allyl-4-methoxy-cyclohexene (1.30b): $^1$H NMR (300 MHz, C$_6$D$_6$): $\delta$ 5.90 (m, 1H, CH=CH$_2$) 5.64 – 5.45 (m, 2H, CH=CH) 5.03 (m, 2H, CH=CH$_2$) 3.00 (s, 3H, OCH$_3$) 2.14 (m, 4H, 2 x CH$_2$) 1.84 (m, 2H, CH$_2$) 1.63 (m, 2H, CH$_2$). This matched the reported $^1$H NMR spectrum therefore no further spectra obtained.$^{25}$ GC: (CDGTA, 70 °C, 15 psi) (authentic rac material at 21.2 and 22.2 minutes): 65 % e.e.

(1-Allyl-cyclohex-3-enyloxymethyl)-benzene (1.30c): $^1$H NMR (300 MHz, C$_6$D$_6$): $\delta$ 5.92 (m, 1H, CH=CH$_2$) 5.64 – 5.45 (m, 2H, CH=CH) 5.02 (m, 2H, CH=CH$_2$) 4.34 (s, 1H, OCH$_3$H$_b$Ph) 4.28 (s, 1H, OCH$_2$H$_b$Ph) 2.20 (m, 4H, 2 x CH$_2$) 1.79 (m, 2H, CH$_2$) 1.72 (m, 2H, CH$_2$). This matched the reported $^1$H NMR spectrum therefore no further spectra obtained.$^{25}$ Enantiomeric ratio determined for the debenzylated derivative, afforded by reducing–metal treatment (sodium and catalytic naphthalene). GC: (CDGTA, 70 °C, 15 psi) (authentic rac material at 25.6 and 26.8 minutes): 39 % e.e.

Norbornylmethylene bromide: Synthesized according to a previously published procedure.$^{172,173}$ Dicyclopentadiene, (30 mL, 224 mmol) allyl bromide (46 mL, 537 mmol) and hydroquinone (150 mg) were heated to 170 °C in a Teflon–valve sealed bomb for 20 h. After cooling, excess allyl bromide was removed by heating to 100 °C at atmospheric pressure. The remaining oil was purified by distillation at reduced pressure (40 °C, 300 mTorr) to afford 60 g (71 %) of clear, colourless oil: mixture of exo and endo isomers. $^1$H NMR (500 MHz, C$_6$D$_6$): MAJOR ISOMER (endo) $\delta$ 6.22 (m, 1H, H3), 6.01 (m, 1H, H2), 3.23 (dd, 1H, J = 6.9 Hz, 9.6 Hz,
H8), 3.06 (dd, 1H, J = 6.9 Hz, 9.6 Hz, H8), 3.01 (s, 1H, H4), 2.89 (s, 1H, H1), 2.54 (m, 1H, H5), 1.96 (m, 1H, H6\textsubscript{exo}), 1.50 (m, 1H, H7), 1.31 (d, 1H, J = 8.2 Hz, H7), 0.60 (m, 1H, H6\textsubscript{endo}). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): 138.2, 131.6, 49.6, 45.4 43.1, 42.1, 38.3, 32.7.

**Norbornylmethylene magnesium bromide:** Synthesized according to a previously published procedure.\textsuperscript{174} An ether solution of norbornylmethylene bromide (6.25 g, 33 mmol) was added dropwise to a slurry of magnesium bromide (2 g, 83 mmol) in ether. The mixture proceeded to auto-reflux for 30 min, after which it was filtered over celite to afford a pale yellow solution. The solution was titrated against cumylphenol using 1,10-phenanthroline as indicator and found to be 0.95 M.

**(S)-5,5’-Bis-(2-bicyclo[2.2.1]hept-5-en-2-yl-ethyl)-3,3’-di-tert-butyl-6,6’-dimethylbiphenyl-2,2’-diol (3.84):** (S)-Br\textsubscript{2}BiphenH\textsubscript{2}, 3.51,\textsuperscript{161} (2.3 g, 4.5 mmol) in THF was added dropwise to norbornylmethylene magnesium bromide (19 mL, 0.95 M) at –30 °C, to produce a mild exotherm. After stirring for 2 h, the white suspension was quenched by addition of methanol. After warming to room temperature, water was added and the mixture extracted three times with ether (200 mL). The organic extracts were combined, washed with NH\textsubscript{4}Cl\textsubscript{(aq)}, dried over MgSO\textsubscript{4} and concentrated in vacuo to a cloudy oil. Residual water was removed by lyophilization with benzene, followed by dissolution in THF and storage over sieves for 24 h. The material was then decanted and re-concentrated to a viscous oil, 2.4 g (93 %). \textsuperscript{1}H NMR (500 MHz, CD\textsubscript{3}OD): δ 7.35 (s, 2H, aryl CH), 6.10 (m, 1H), 6.06 (m, 1H), 5.93 (m, 2H), 4.88 (s, 2H, OH), 2.74 – 2.5 (br m, 8H), 1.95 (s, 3H, CH\textsubscript{3}), 1.94 (s, 3H, CH\textsubscript{3}), 1.85 – 1.80 (br m, 3H), 1.56 (s, 18H, C(CH\textsubscript{3})\textsubscript{3}), 1.53 (m, 2H), 1.42 (m 4H), 1.17 (m, 2H), 1.13 (m, 2H), 0.54 (m, 2H). \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): 150.9, 137.4, 137.1, 136.4, 134.0, 133.6, 132.6, 132.5, 132.4, 128.7, 128.5, 127.9, 121.7, 50.0, 49.9, 45.9, 45.8, 42.9, 39.3, 36.8, 34.9, 34.2, 33.5, 32.9, 32.8, 29.8, 15.6.
1,4,4a,5,8,8a-hexahydro-1,4,5,8-exolendo-dimethanonaphthalene (3.85): A Teflon-sealed glass bomb was charged with nobornylene, 3.86, (36 mL, 384 mmol) dicyclopentadiene (20 mL, 164 mmol) and hydroquinone (115 mg, 1.04 mmol) and heated to 180 °C. After 72 h, the vessel was cooled to room temperature and purified by fractional distillation at 60 mTorr with slight heating. The first fraction recovered (25 – 30 °C) was excess nobornylene (12 g, 39 %) and the second fraction (30 – 35 °C) was the desired product (14 g, 30 %). The product was redistilled from sodium prior to use. \(^1\)H NMR (500 MHz, \(C\_8D\_8\)): exo/endo isomer: \(\delta\) 6.20 (t, 2H, \(J = 1.5\) Hz, CH), 5.91 (t, 2H, \(J = 1.5\) Hz, CH), 2.61 (d, 1H, \(J = 8.6\) Hz, CH), 2.57 (m, 2H), 2.44 (m, 2H), 2.14 (m, 2H), 1.69 (m, 1H), 1.42 (m, 1H), 1.16 (d, 1H, \(J = 8.9\) Hz). endo/endo isomer: \(\delta\) 5.23 (m, 4H), 2.54 (m, 2H), 2.5 (m, 4H), 1.61 (d, \(J = 7.0\) Hz, 1H). \(^{13}\)C NMR (100 MHz, \(C\_8D\_8\)): 131.6, 55.8, 44.9, 43.2.

Polynorbornene supported (S)-3.88a: Potassium hydride (50 mg, 1.3 mmol) was added to a solution of 3.84 (230 mg, 0.40 mmol) in THF (25 mL) at room temperature. After 3 h, the ligand solution was filtered over celite and added to a solution of 3.85 (1.78 g, 11.2 mmol) in THF (25 mL) which had been cooled to –35 °C during the previous 3 h. With vigorous stirring, a THF (3 mL) solution of (Ar\(\_f\)N)Mo(CHCM\(\_\)e\(\_\)Ph)(OTf)\(_\_\)DME, 1.4a, (322 mg, 0.40 mmol) was added to the reaction mixture. After approximately 15 min, the clear, deep-red mixture developed a highly gelatinous consistency. The mixture was agitated overnight, warming to room temperature. The material was gently pounded in a mortar and pestle, filtered over a coarse frit, and washed with toluene (50 mL), pentane (50 mL) and ether (3 x 20 mL). After drying in vacuo, 2.12 g of an orange–tan solid was obtained.
Polynorbornene supported (S)-3.88d: Potassium hydride (20 mg, 0.50 mmol) was added to a solution of 3.84 (94 mg, 0.167 mmol) in THF (5 mL) at room temperature. After 3 h, the ligand solution was filtered over celite and added to a solution of norbornylene, 3.86, (1.0 g, 10.6 mmol) and 3.85 (127 mg, 0.8 mmol) in THF (50 mL) which had been cooled to −35 °C during the previous 3 h. With vigorous stirring, a THF (3 mL) solution of (Ar₃N)Mo(CHCMe₂Ph)(OTf)₂DME, 1.4a, (132 mg, 0.167 mmol) was added to the reaction mixture. After approximately 15 min, the clear, deep–red mixture developed a highly gelatinous consistency. The mixture was stirred overnight, warming to room temperature. The material was gently pounded in a mortar and pestle, filtered over a coarse frit, and washed with toluene (20 mL), pentane (20 mL) and ether (3 x 20 mL). After drying in vacuo, 700 mg of a bright–orange solid was obtained. El Anal Calcd: 1.39 % Mo; Found: Kolbe: 0.72 (52 % loading, 0.075 mmol/g); Robertson–Microlit: 0.66 (47 % loading, 0.069 mmol/g).

Polynorbornene supported (S)-3.89: Potassium hydride (22 mg, 0.555 mmol) was added to a solution of 3.84 (105 mg, 0.185 mmol) in THF (5 mL) at room temperature. After 3 h, the ligand solution was filtered over celite and added to a solution of norbornylene, 3.86, (1.15 g, 12.2 mmol) and 3.85 (150 mg, 0.924 mmol) in THF (50 mL) which had been cooled to −35 °C during the previous 3 h. With vigorous stirring, a THF (3 mL) solution of (Ar₃N)Mo(CH₂Bu)(OTf)₂DME, 1.4b, (143 mg, 0.185 mmol) was added to the reaction mixture. After approximately 5 min, the clear, deep–red mixture developed a highly gelatinous consistency. The mixture was stirred overnight, warming to room temperature. The material was gently pounded in a mortar and pestle, filtered over a coarse frit, and washed with toluene (20 mL), pentane (20 mL) and ether (3 x 20
mL). After drying in vacuo, 1.2 g of a dark–brown solid was obtained. El Anal Calcd: 1.21 % Mo; Found: Kolbe: 0.78 (64 % loading, 0.081 mmol/g); Robertson–Microlit: 0.68 (56 % loading, 0.071 mmol/g).

Polynorbornene supported (S)-3.90: Potassium hydride (39 mg, 0.96 mmol) was added to a solution of 3.84 (180 mg, 0.32 mmol) in THF (10 mL) at room temperature. After 3 h, the ligand solution was filtered over celite and added to a solution of norbornylene, 3.86, (1.95 g, 20.7 mmol) and 3.85 (250 mg, 1.58 mmol) in THF (50 mL) which had been cooled to −35 °C during the previous 3 h. With vigorous stirring, a THF (3 mL) solution of (AdN)Mo(CHCMe₂Ph)(OTf)₂DME, 1.4, (245 mg, 0.32 mmol) was added to the reaction mixture. After approximately 5 minutes, the clear, deep–red mixture developed a highly gelatinous consistency. The mixture was stirred overnight, warming to room temperature. The material was gently pounded in a mortar and pestle, filtered over a coarse frit, and washed with toluene (20 mL), pentane (20 mL) and ether (3 x 20 mL). After drying in vacuo, 2.5 g of a bright–orange solid was obtained. El Anal Calcd: 1.23 % Mo; Found: Kolbe: 0.85 (69 % loading, 0.089 mmol/g); Robertson–Microlit: 0.78 (63 % loading, 0.081 mmol/g).

Representative Asymmetric Olefin Metathesis Transformation with (S)-3.88a–d, (S)-3.89 & (S)-3.90: A vial was charged with substrate 2.67c (15 mg, 52 µmol), supported catalyst (S)-3.88d (20 mg, 1.3 µmol) and benzene (3 mL). The vessel was secured with a teflon–lined cap, and shaken on a Thermolyne (Type 37600) mixer under N₂ atmosphere. After 2 hours, a ¹H NMR spectrum of an aliquot indicated 93 % conversion. The reaction mixture was then filtered through a pasteur pipette fitted with a cotton plug and concentrated in vacuo to afford pale yellow oil 2.68c (12 mg, 88 %).
Spectral data for certain compounds presented in Table 3.9 can be found in Chapter 1 (1.22, & 1.37), Chapter 2 (2.68c, 2.84, 2.86, & 2.105d) and earlier parts of Chapter 3 (3.74a) of this thesis.

2,2,5-Trimethyl-7-(2-methyl-allyl)-7-phenyl-2,3,6,7-tetrahydron-[1,2]oxasilepine (1.28): $^1$H NMR (500 MHz, C$_6$D$_6$): $\delta$ 7.37 (dd, 2H, J = 1.2 Hz, J = 7.3 Hz, aryl CH) 7.20 (t, 1H, J = 7.3 Hz, aryl CH) 7.07 (tt, 2H, J = 1.2 Hz, J = 7.3 Hz, aryl CH) 5.57 (q, 1H, J = 7.9 Hz, =CHCH$_3$) 4.77 (m, 1H, =CH$_2$H$_b$) 4.68 (m, 1H, =CH$_2$H$_b$) 2.71 (d, 1H, J = 14.0 Hz, CH$_3$H$_b$) 2.59 (m, 2H, CH$_2$H$_b$) 2.39 (d, 1H, J = 14.0 Hz, CH$_3$H$_b$) 1.60 (s, 3H, CH$_3$) 1.36 (s, 3H, CH$_3$) 1.20 (s, 2H, SiCH$_2$) 0.24 (s, 3H, Si(CH$_3$)) 0.23 (s, 3H, Si(CH$_3$)). This matched the reported $^1$H NMR spectrum therefore no further spectra obtained. In order to determine enantiomeric excess, 1.28 was converted to the allylic alcohol as follows: Oxasilapine, 1.28, (22 mg, 77 μmol) was added to a 1.0 M solution of tetrabutylammonium fluoride in THF (6 mL) and stirred for four hours. The reaction was diluted in water, extracted with ether (3 x 5 mL) and concentrated in vacuo. The crude material was subjected to chromatography over silver-nitrate impregnated (13 % w/w) silica, eluting with ether in pentane (30:70) to remove the undesired regioisomer. $^1$H NMR (500 MHz, C$_6$D$_6$): $\delta$ 7.35 (d, 2H, J = 7.0 Hz, aryl CH) 7.15 (obscured d, 2H, aryl CH) 7.05 (tt, 1H, J = 1.2 Hz, J = 7.3 Hz, aryl CH) 5.30 (q, 1H, J = 6.7 Hz, =CHCH$_3$) 4.78 (m, 1H, =CH$_2$H$_b$) 4.69 (m, 1H, =CH$_2$H$_b$) 2.74 (d, 1H, J = 13.4 Hz, CH$_3$H$_b$) 2.57 (d, 1H, J = 13.4 Hz, CH$_3$H$_b$) 2.53 (d, 1H, J = 13.4 Hz, CH$_3$H$_b$) 2.39 (d, 1H, J = 13.4 Hz, CH$_3$H$_b$) 1.52 (s, 3H, CH$_3$) 1.49 (d, 3H, J = 6.7 Hz, =CHCH$_3$) 1.47 (s, 3H, CH$_3$). HPLC (Chiralcel OJ, 100 % Hexane, 1.0 mL / min, 235 nm) (authentic rac material at 5.2 & 5.8 min): 91 % e.e.

[2-(2-Benzoyloxy-3-vinylcyclopentyl)-vinyl]benzene (3.56a): $^1$H NMR (500 MHz, C$_6$D$_6$): $\delta$ 7.23 7.25 7.07 6.39 (d, 1H, J = 16.5 Hz, PhCH=CH) 6.14 (m, 1H, CH=CH$_2$) 5.61 (dd, 1H, J = 16.5 Hz, J = 0.9 Hz, PhCH=CH) 5.09
(m, 2H, CH=CH₂) 4.49 (d, 1H, J = 11.9 Hz, OCH₆H₆Ph) 4.44 (d, 1H, J = 11.9 Hz, OCH₆H₆Ph) 3.58 (t, 1H, J = 3.8 Hz, CHOBN) 2.45 (m, 2H, 2 x CH) 1.93 (m, 2H, CH₂) 1.75 (m, 2H, CH₂). This matched the reported ¹H NMR spectrum²⁴ therefore no further spectra obtained. HPLC (Chiralpak AD, 0.1 % IPA in Hexane, 1.0 mL / min, 254 nm) (authentic rac material at 6.9 & 7.9 min): > 98 % e.e.

**Oligo(norbornene) (3.92):** Catalyst (S)—3.89 (40 mg, 2.84 µmol) and diallyl ether (9 mg, 90 µmol) were stirred in benzene (5 mL) overnight. The material was then filtered over celite, washing with pentane, and all volatiles removed *in vacuo*. Approximately 20 mg of a sticky off-white gum remained. ¹H NMR (500 MHz, C₆D₆): δ 5.8 (m, CH=CH₂), 5.5 (m, a, CH=CH), 5.0 (m, CH=CH₂), 2.5 (b, CH), 2.0 (c, CH₆H₆), 1.8 (d, CH₂), 1.4 (e, CH₂), 1.2 (f, CH₆H₆).
APPENDIXA: Studies on Asymmetric Ring–Opening Metathesis / Ring–Closing Metathesis of *aza*-Bicyclic Systems.
A.1 INTRODUCTION

A.1.1 Tandem metathesis transformations: Ring-opening metathesis / cross metathesis (ROM/CM) and ring-opening metathesis / ring-closing metathesis (ROM/RCM).

Catalytic ring-opening metathesis (ROM) transformations have been explored less than RCM. However, the applications developed from this process offer powerful new tools to organic synthesis. In particular, when ROM is used in tandem with a second metathesis process, such as cross metathesis (CM), complicated transformations can be achieved in one step. Snapper and coworkers reported the use of such an ROM/CM process to prepare both multifidene and viridine (Scheme A.1).\textsuperscript{175} The use of this tandem metathesis process substantially reduced the number of synthetic steps required. In these examples, the release of strain inherent to the starting \textit{endo}–cyclic olefin is part of the driving force.

![Scheme A.1 ROM/CM of a cyclobutene as a key step in the synthesis of various alkaloids.](image)

When metathesis can occur intramolecularly, as for ROM/RCM, an overall isomerization is obtained. Several examples of this latter process have been reported, in particular for carbocyclic amines. Stapper and Blechert have reported the synthesis of the alkaloid cuscohygrine,\textit{via} ROM/RCM of cycloheptene A.2 (Scheme A.2).\textsuperscript{176}
Scheme A.2 ROM/RCM of a cycloheptene as a key step in the synthesis of cuscohygrine.

The release of a large amount of ring–strain is not necessary for ROM/RCM to be viable. For example, a similar ROM/RCM transformation of cyclopentene A.4 was recently reported by Schaudt and Blechert (Scheme A.3). The product obtained, A.5, was used to access the naturally–occuring alkaloid astrophyline.

Scheme A.3 ROM/RCM of a cycloheptene as a key step in the synthesis of astrophyline.

A.1.2 Asymmetric ring–opening metathesis / cross metathesis (AROM/CM) of strained olefins.

Asymmetric variations of the processes detailed above have also been studied in these laboratories. The intermolecular case (AROM/CM) was one of the first asymmetric processes studied in detail. When catalyst (S)-1.11a was added to norbornene, oligomerization occured, even in the presence of a large excess of styrene. However, more sterically encumbered norbornyl ethers, such as A.6 – A.8, were found to undergo AROM/CM selectively with various styrenes (Table A.1) in the presence of catalyst (S)-1.11a. In all cases, products A.9 – A.11 were obtained as a single olefin stereoisomer (> 98 % trans), frequently in > 96 % e.e. It should be noted that longer reaction times led to greater impurities in products A.9 – A.11, as these products are themselves prone to
Table A.1 Tandem AROM/RCM of norbornyl ethers with various styrenes.\(^a\)

\[
\begin{align*}
\text{H} & \quad \text{OR} \\
\text{+ 2 equiv } & \quad \text{Ar} \\
5 \text{ mol }\% & \quad \text{(S)-1.11a} \\
\text{benzene, } & \quad 22 ^\circ \text{C} \\
\text{A.6 - A.8} & \quad \text{A.9 - A.11}
\end{align*}
\]

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<th>product</th>
<th>time (h)</th>
<th>total conv(%)(^b)</th>
<th>conv to product (%)(^b)</th>
<th>yield (%)(^c)</th>
<th>e.e. (%)(^d)</th>
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<td>64; 91</td>
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<td>A.9c</td>
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<td>&lt; 10; nd</td>
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<td>98; 80</td>
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\(^a\) Conditions: 5 mol \% catalyst, 2 equiv requisite styrene, \(C\(_6\)H\(_6\)\), 22 \(^\circ\)C. \(^b\) Conv determined by analysis of the 400 MHz \(^1\)H NMR spectrum of the unpurified reaction mixture. \(^c\) Isolated yields after purification by chromatography; all products obtained as > 98 \% trans. \(^d\) Enantioselectivity determined by chiral HPLC analysis (Chiralcel OD column for entries 1 – 2, 4 – 7; Chiralpak AD for entries 8 – 9).

Scheme A.4 Functional group tolerance of AROM/RCM process.
metathesis. Thus, extended reaction times led to homodimerization, as well as secondary CM, to result in undesirable byproducts.

A variety of products were successfully prepared via AROM/CM with catalyst (S)-1.11a (Scheme A.4). Various functional groups were tolerated on the norbornene partner (A.12 – A.14), as well as the terminal olefin (A.14, A.17). Frequently, the materials obtained were optically pure.

Similar to results obtained with norbornene, several sterically unprotected norbornyl ethers were found to be prone to oligomerization. For example, norbornyl ethers wherein the heteroatom is anti- to the internal olefin (such as A.18, Scheme A.5) were oligomerized by Mo–based (S)-1.11a. However, it was recently disclosed that chiral Ru–based catalyst A.19 (Scheme A.5) selectively catalyzed AROM/CM of A.18 with excellent enantioselectivity and very little oligomeric contamination. These results highlight, yet again, the complementarity of Ru– and Mo–based metathesis catalysts.

Scheme A.5 Sterically unprotected norbornyl ethers are prone to oligomerization with 1.11a.
A.1.3 Asymmetric ring–opening metathesis / ring–closing metathesis (AROM/RCM).

Asymmetric ring–opening metathesis / ring–closing metathesis (AROM/RCM), an isomerization that generates chirality, is the most atom–efficient metathesis transformation. An early example of AROM/RCM developed in our laboratories was the isomerization of meso–triene A.20, catalyzed by \((S)\text{-1.11a}\), to chiral dihydrofuran A.21 (eq A.1) in high enantioselectivity (92 % e.e.).\(^{171}\) The more reactive cyclobutene moiety was believed to be subject to ROM first; thus enantioselectivity was believed to occur during approach of the endocyclic olefin.

\[\text{A.20} \xrightarrow{5 \text{ mol % } (S)\text{-1.11a}} \text{benzene, 22 \text{ °C}} \text{ A.21} \]

\((A.1)\)

Sterically protected norbornyl ethers were also found to be good candidates for AROM/RCM. For example, methallyl norbornyl ether A.22 was isomerized by \((S)\text{-1.11a}\) to A.23 with excellent enantioselectivity (Scheme A.6).\(^{171}\) In this case, diallyl ether was needed as an additive, to first generate the more reactive Mo-methylidene species \textit{in situ}. In the absence of diallyl ether, the reaction did not proceed.

Scheme A.6 AROM/RCM of a sterically protected norbornyl ether.
However, similar to AROM/CM processes (Section A.1.2), sterically unprotected norbornyl ethers (such as A.24, Scheme A.7) were found to polymerize rapidly upon exposure to (S)-1.11a. In yet another example of the complementarity of Mo- and Ru-based metathesis catalysts, when A.24 was subjected to 2.1a under an ethylene atmosphere, triene A.25 was obtained in high yield. Triene A.25 could then be subjected to ARCM with (S)-1.11a to afford optically pure A.26.

Scheme A.7 AROM/RCM of a sterically unprotected norbornyl ether: Two steps needed!

A.2 RESULTS AND DISCUSSION

A.2.1 Asymmetric ring-opening metathesis / ring-closing metathesis (AROM/RCM) of N-alkenyl-7-aza-norbombenzodienes.

N-Alkyl-7-aza-norbombenzodienes exist as two isomers: the alkyl group may reside over the aryl ring (syn-A.27, Scheme A.8) or over the internal olefin (anti-A.27). Detailed spectroscopic studies of N-methyl- and N-benzyl-7-aza-norbombenzodienes have shown that the syn-isomer is preferred at low temperatures (in both cases, the ratio of syn:anti ≈ 70:30 at – 50 °C). However, the syn- and anti-isomers readily interconvert at room temperature. The energy of activation for this conformational isomerization is
less than 65 kJ/mol, in both the \( N \)-methyl- and \( N \)-benzyl- cases, which indicates frequent and rapid interconversion.\textsuperscript{178-180}

\begin{equation*}
\text{syn-A.27} \quad \leftrightarrow \quad \text{anti-A.27}
\end{equation*}

\begin{align*}
\text{for } R = \text{Me}, \Delta G^\text{rev} &= 64.6 \text{ kJ/mol (25 °C)} \\
\text{for } R = \text{Bn}, \Delta G^\text{rev} &= 61.9 \text{ kJ/mol (25 °C)}
\end{align*}

Scheme A.8 Syn--- to anti-- isomerization of \( N \)-alkyl-7-aza-norbornobenzodienes.

Given the importance of steric protection observed for AROM/CM and AROM/RCM of norbornyl ethers, we became interested in how \( N \)-alkenyl-7-aza-norbornobenzodienes would perform under similar conditions. While we expected the internal olefin to be relatively sterically unprotected, we wondered whether or not the rapid interconversion between syn-- and anti--isomers would be sufficient to prevent polymerization. We therefore prepared and studied \( N \)-allyl--, \( N \)-butenyl--, and \( N \)-pentenyl--7-aza-norbornobenzodienes (A.28 -- A.30, Scheme A.9). It should be noted that these compounds were highly sensitive to mildly acidic conditions, as well as elevated temperatures, and had to be purified via chromatography on alumina gel.

\begin{equation*}
\text{syn-A.28, } n = 1 \quad \leftrightarrow \quad \text{anti-A.28, } n = 1 \\
\text{syn-A.29, } n = 2 \quad \leftrightarrow \quad \text{anti-A.29, } n = 2 \\
\text{syn-A.30, } n = 3 \quad \leftrightarrow \quad \text{anti-A.30, } n = 3
\end{equation*}

Scheme A.9 \( N \)-Alkenyl-7-aza-norbornobenzodienes studied.
Early attempts at AROM/RCM showed that higher catalyst loadings (≥ 20 mol %) were necessary for complete consumption of dienes A.28 – A.30. We suspected the product iso-indoles A.31 – A.33 capable of stabilizing catalyst decomposition pathways, so we looked to $^1$H NMR spectroscopy to identify possible alkylidene species in solution. When 50 mol % 1.1a was used, a substantial amount of residual 1.1a was observed in the alkylidene region. Three new peaks were also present in the alkylidene region: a triplet at 13.21, a doublet at 12.50, and a triplet at 12.31 ppm with coupling constants of 10.9, 7.2 and 6.5 Hz respectively (Figure A.1). At 20 mol % 1.1a, only the triplets at 13.21 and 12.31 remained. Given the presence of one doublet, at higher catalyst loading only, we do not believe any base-adducted methylidenes were present (two distinct doublets would be expected). We postulate these new signals to represent intermediate alkylidene species.

Figure A.1 Alkylidene region of the $^1$H NMR of AROM/RCM of A.30 with catalyst 1.1a.
**A.34 – A.35.** However, **A.34 – A.35** are all presumed intermediates on the path to the desired products, and do not explain the need for higher catalyst loadings.

However, when higher catalyst loadings were used, $^1$H NMR spectra of the crude materials were clearly free of any $N$-alkyl-$7$-$aza$-norbornobenzodienes. However, the crude materials also seemed contaminated, possibly by oligomeric products. Unfortunately, products **A.31 – A.33** could not be purified by chromatography – all were found to rapidly decompose upon exposure to air to afford a black tar (Scheme A.10).

![Diagram](image)

**Scheme A.10** AROM/RCM of $N$-alkyl-$7$-$aza$-norbornobenzodienes led to unstable products.

Not surprisingly, we were unable to analyze highly unstable *iso*-indoles **A.31 – A.33** by either high performance liquid chromatography (HPLC) or gas chromatography (GC). Addition of various chiral derivatizing agents, such as Mosher’s Acid, also failed to provide a handle by which to discern the enantiomeric ratio. Several derivatizations of **A.33** also failed to provide a more stable product (Scheme A.11). Selective hydrogenation of the olefinic moieties of **A.33** did not improve stability or characterizability, nor did quaternization of the nitrogen center as either the HCl or methyl iodide salt.

We also attempted to perform these AROM/RCM reactions in tandem with a final CM (AROM/RCM/CM), by adding 2 equiv of styrene; however the products obtained were equally unstable. We were greatly disappointed at our inability to characterize or analyze these compounds. After careful consideration, it was decided that the utility of the desired *iso*-indoles did not merit continued work on these substrates.
A.2.2 Asymmetric ring-opening metathesis / ring-closing metathesis (AROM/RCM) of N-alkenyl tropanes.

To avoid the instability encountered with of the above systems, we began to look into tropane–based substrates. N-Alkenyl-8-aza-bicyclo[3.2.1]oct-6-enes (A.37 – A.39, Scheme A.12) possess significantly less ring-strain than 7-aza-norbornobenzodienes, and therefore are less prone to ROM. Furthermore, because AROM/RCM is a reversible process, it is possible that the desired products of AROM/RCM (A.40 – A.42) may be disfavored and not isolable. However, successful AROM/RCM of these substrates would lead to a variety of alkaloid–type products. We therefore endeavored to study these systems in regards to AROM/RCM.
Scheme A.12 Proposed AROM/RCM of tropane-based substrates.

Neither A.37 nor A.39 showed any conversion to the desired products (A.40 and A.42, respectively) in the presence of any available metathesis catalyst (1.1a, 2.1d, (S)-1.11a, (S)-1.11c, etc.). We attributed this failure to the reversibility of the AROM/RCM process, and speculated that the desired products were less thermodynamically favored than the starting bicycles.

Scheme A.13 No reaction was observed for A.37 or A.39 with all metathesis catalysts.

In contrast, low conversion was observed for substrate A.38 in the presence of 5 mol % of either 1.1a or (rac)-1.11a (Table A.2). Conversion remained low at elevated temperatures as well as with additives such as ethylene or diallyl ether (entries 2 – 5). Second-generation Ru-based catalyst 2.1d was completely ineffective for this transformation (entry 7). However, a substantial improvement in conversion was catalyst
observed with higher catalyst loading of (rac)-1.11a (entry 6), which suggested that catalyst decomposition was competing with the desired transformation.

Again, we wondered if these bicyclic amines could coordinate to catalytic intermediates, possibly stabilizing a catalyst decomposition pathway. Therefore we treated A.38 with 100 mol % of (rac)-1.11a, and carefully followed all resonances in the alkylidene region (Figure A.2) by 1H NMR spectroscopy. Initially, 4 new doublets were observed at 12.69 ppm (very small) 12.65 ppm (5.5 %, J = 12.0Hz) 11.36 ppm (2.8 %, 7.0 Hz) and 11.24 (2.4 %, 7.5 Hz). At first we believed these doublets could represent base-adducted methyldienes; however, over time the intensity of each signal changed in a distinct manner. This suggests that each doublet represents a distinct alkylidene species. Furthermore, because each resonance was a doublet, we believe all signals represent unique species, each resulting from ROM of the endocyclic olefin (postulated intermediates A.43 – A.44).
However, all new alkylidene resonances observed in Figure A.2 also represent intermediates along a productive catalyst cycle path. Therefore, in both cases (Figure A.1 and Figure A.2), the data from $^1$H NMR spectra cannot explain why reaction turnover was so low. Clearly, in both cases some mode of decomposition has arrested catalyst turn-over, but none of the alkylidenes observed by $^1$H NMR have clarified this reaction path.
The above results contrasted related work by G. Alex Cortez: Complex (S)-1.11d was found to catalyze AROM/CM of related N-methyl tropane A.45 with styrene, to afford A.52 in excellent yield and enantioselectivity (eq A.2).\textsuperscript{182}

We postulated that either the methyl groups or the benzyl ether moiety could have a detrimental effect on the desired AROM/RCM transformation of A.37 – A.39. Therefore, we moved to less–substituted tropanes A.47 – A.49 (Scheme A.14), which are directly related to A.45.

Disappointingly, we found substrates A.47 – A.49 to be equally unreactive with all of our available catalysts (1.1a, 2.1d, (S)-1.11a, (S)-1.11c, (S)-1.11d, etc.). Additives such as diallyl ether, ethylene, even styrene, all failed to facilitate the reaction. We therefore prepared substrates A.53 and A.54 (Figure A.3), wherein the N–alkenyl olefin was designed to be less reactive than the endocyclic olefin. We hoped this would force AROM to occur first, in a manner similar to that observed in eq A.2.
However, when either A.53 or A.54 was subjected to various Mo-based catalysts, no reaction was observed. Again, additives (ethylene, diallyl ether, styrene) failed to facilitate the reaction. These results are summarized in Scheme A.15.

Scheme A.15 Summary of AROM/RCM reactions attempted with A.45 – A.54.
A.3 CONCLUSIONS

The inherent instability of iso-indoles A.31 – A.33, afforded by AROM/RCM of N-alkyl-7-aza-norbornobenzodienes, prevented detailed study of these products. However, when we turned our attention to less strained tropane–based systems (A.37 – A.39, A.47 – A.49, A.53 and A.54) very low reactivity was observed. No explanation for the low reactivity of can be given at this time. However, given the success observed for AROM/CM of A.51 with styrene, we feel that this area warrants further study.
A.4 EXPERIMENTAL DETAILS

GENERAL

$^1$H NMR spectra were recorded on Varian VXR 500 (500 MHz) or Unity 300 (300 MHz) spectrometers. Chemical shifts are reported in ppm from tetramethylsilane with the residual protio-solvent resonance as the internal standard ($^{1}C_{6}D_{6}$: δ 7.16, CDCl$_3$: δ 7.26). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), integration, and assignment. $^{13}$C NMR spectra were recorded on Varian VXR 500, (125 MHz) Unity 300, (75 MHz) or Bruker DPX 400 (100 MHz) spectrophotometer with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the residual protio-solvent resonance as the internal standard ($^{1}C_{6}D_{6}$: δ 128.39, CDCl$_3$: δ 77.7). Infrared (IR) spectra were recorded on ThermoNicolet Avatar 360 spectrophotometer, $\mu_{\text{max}}$ in cm$^{-1}$. Bands were characterized as broad (br), strong (s), medium (m), and weak (w). High-resolution mass spectrometry was performed at the Massachusetts Institute of Technology, Department of Chemistry Instrumentation Facility (Cambridge, MA).

All reactions were conducted in oven- (135 °C) or flame-dried glassware under an inert atmosphere of dry N$_2$. All metathesis substrates were dried by storing over molecular sieves under a N$_2$ atmosphere for a minimum of 12 h prior to use. Handling of all Mo catalysts was performed in a drybox. Benzene, THF, Et$_2$O and toluene were sparged with N$_2$ and then passed through an activated alumina column or distilled from sodium/benzophenone ketyl. Pentane was washed with concentrated acid to remove olefinic impurities, dried over calcium chloride, then sparged with N$_2$ and passed through an activated alumina column. CH$_2$Cl$_2$, was distilled from calcium hydride. Benzyl potassium was prepared by the literature method.$^{31}$ All reagents were used as received from Aldrich Chemical Co., Lancaster Synthesis, or Strem Chemicals, Inc. unless otherwise stated.
1-(1,4-Dihydro-1,4-epiazano-naphthalene-9-carboxylic acid tert-butyl ester: (Used in the synthesis of A.28 – A.30.) 1,2-Dibromoethane (1 mL) was added to a slurry of magnesium turnings (6.9 g, 280 mmol) in THF (300 mL) to activate the metal. N-BOC-pyrrole (45 mL, 270 mmol) was added to the slurry, which was then heated to reflux temperature. A THF solution (50 mL) of 1-bromo-2-fluorobenzene (30 mL, 270 mmol) was added dropwise over 2.5 h with continued refluxing. After the reaction mixture had cooled, saturated NH₄Cl(aq) solution was added, the biphasic mixture extracted three times with CH₂Cl₂ (400 mL). The organic extracts were combined, dried over MgSO₄ and concentrated in vacuo to a tan solid. The crude material was washed with cold pentane to afford 26 g (105 mmol, 39 % yield) of tan solid, used directly in the next reaction. ¹H NMR (300 MHz, C₆D₆): δ 6.96 (m, 2H, aryl CH), 6.76 (m, 2H, aryl CH), 6.53 (br, 2H, vinyl CH), 5.54 (br, bridge CH), 5.30 (br, bridge CH), 1.38 (s, 9H, C(CH₃)₃). No further spectral data obtained as this matched the literature spectrum.¹⁷⁹,¹⁸³,¹⁸⁴

1,4-Dihydro-1,4-epiazano-naphthalene: (Used in the synthesis of A.28 – A.30.) Dry HCl(g) was bubbled through a cold solution (≤ 5 °C) of N-BOC-aza-norbornabenzodiene (25 g, 105 mmol) in nitromethane (400 mL) over 25 min. The resultant solution was kept cold, and stirred a subsequent 3.5 h. Ether (300 mL) was added to afford a slurry, which was filtered to obtain a muddy purple solid. Residual nitromethane was removed in vacuo, to afford a free-flowing powder (16.7 g, 93 mmol, 89 % yield). To a vigorously stirred suspension of this powder in ether (400 mL) was added a solution of potassium hydroxide (13 g, 230 mmol) in water (100 mL). After stirring 30 min, the ether layer was decanted, and the aqueous layer extracted with ether (3 × 50 mL). The organic extracts were combined, dried over MgSO₄, and concentrated in vacuo. The crude oil was distilled with heating under vacuum to afford a clear, colorless oil (45 – 50 °C, 0.03 mTorr) 8.3 g (58 mmol, 55 % yield). ¹H NMR (300 MHz, C₆D₆): δ 7.00 (m, 2H, aryl CH), 6.80 (m, 2H, aryl CH), 6.61 (s, 2H, vinyl CH),
4.53 (s, bridge CH). No further spectral data obtained as this matched the literature spectrum.²⁷⁹,⁺³⁸,⁺³⁴

9-Prop-2-enyl-1,4-dihydro-1,4-epiazano-napthalene (A.28): Allyl bromide (2.4 mL, 26 mmol) was added to 1,4-dihydro-1,4-epiazano-napthalene (3.77 g, 26 mmol) in ether. After stirring overnight, the ammonium salt was removed by filtration, and the product purified by chromatography on alumina. ¹H NMR (500 MHz, C₅D₅): δ 7.03 (m, 2H, aryl CH), 6.85 (m, 2H, aryl CH), 6.50 (br, 2H, vinyl CH), 5.93 (m, 1H, CH=CH₂), 5.00 (m, 2H, CH=CH₂), 4.31 (m, 2H, bridge CH), 2.90 (br, 2H, NCH₂). ¹³C NMR (125 MHz, C₅D₅): δ 144.0, 136.8, 125.2, 123.6, 120.7, 116.9, 71.4, 70.6, 53.6. HRMS (ESI⁺) Calcd for C₁₃H₁₃N [M + H]: 184.1122. Found: 184.1122.

1-(1,4-Dihydro-1,4-epiazano-napthalen-9-yl)-but-3-en-1-one: (Used for the preparation of A.29.) Solutions (CH₂Cl₂) of 3-butenolic acid (0.87 mL, 10.2 mmol), then 7-aza-norbornobenzodienes (1.33 g, 9.3 mmol) were sequentially added to a solution of dicyclohexylcarbodiimide (2.11 g, 10.2 mmol) in CH₂Cl₂ at 0 °C to afford a milky white suspension. After 18 h, the white suspension was filtered to remove the insoluble urea, and the filtrated concentrated in vacuo to a yellow oil, (1.95 g, 100%). The crude material was used without further purification. ¹H NMR (500 MHz, C₅D₅): δ 6.95 (d, 1H, J = 6.7 Hz, aryl CH), 6.92 (d, 1H, J = 6.7 Hz, aryl CH), 6.75 (m, 2H, aryl CH), 6.53 (dd, 1H, J = 2.4 Hz, J = 5.5 Hz, CH=CH), 6.39 (dd, 1H, J = 2.4 Hz, J = 5.5 Hz, CH=CH), 5.90 (m, 1H, CH=CH₂), 5.83 (m, 1H, bridge CH), 4.94 (m, 2H, CH=CH₂), 4.88 (m, 1H, bridge CH), 2.69 (m, 2H, NCH₂). ¹³C NMR (125 MHz, C₅D₅): δ 167.8, 149.6, 149.2, 144.8, 142.6, 132.0, 128.7, 125.6, 125.3, 121.9, 120.7, 118.0, 66.2, 64.5, 39.7. IR (KBr): 3445 (br w), 3291 (w), 3072 (w), 2934 (w), 1641 (s), 1427 (s), 1289 (s), 1228 (s), 1126 (m), 1076 (w), 1001 (m). HRMS (ESI⁺) Calcd for C₁₄H₃NO [M + Na]: 211.0992. Found: 211.0987.
9-But-3-enyl-1,4-dihydro-1,4-epiazano-napthalene (A.29): Lithium aluminum hydride (1.05 g, 27.8 mmol) was added to 1-(1,4-dihydro-1,4-epiazano-napthalen-9-yl)-but-3-en-1-one (1.96 g, 9.3 mmol) in dry ether (150 mL) at room temperature under an N₂ atmosphere. After 12 h, the reaction was cooled to 0 °C, and water (20 mL) was added to destroy excess reducing agent. The mixture was filtered over celite, then dried with MgSO₄ and concentrated in vacuo to a yellow oil, which was distilled under vacuum (0.04 mm Hg, 60 – 65 °C) to afford a clear, colourless oil. The material was further purified via column chromatography over alumina, eluting with 20 % ether in pentane to a clear, colorless oil (1.25 g, 6.3 mmol) in 68 % yield. ^1H NMR (500 MHz, C₆D₆): δ 7.0 (m, 2H, aryl CH), 6.86 (m, 2H, aryl CH), 6.80 – 6.20 (br, 2H, CH=CH), 5.77 (m, 1H, CH=CH₂), 4.96 (m, 2H, CH=CH₂), 4.29 (br, 2H, bridge CH), 2.60 – 2.00 (br, 2H, NCH₂CH₂), 2.17 (m, 2H, CH₂CH=CH₂). ^13C NMR (125 MHz, C₆D₆): δ 143.9 (br), 137.8, 137.7, 126.8, 125.0 (br), 115.7, 115.6, 70.9 (br), 65.9, 49.8 (br), 48.6, 34.7, 33.9. IR (Neat): 3072 (s), 2980 (s), 2838 (m), 1640 (m), 1452 (s), 1365 (w), 1273 (m), 1183 (w), 1107 (m). HRMS (ESI⁺) Calcd for C₁₄H₁₅N [M + H]: 198.1277. Found: 198.1278.

1-(1,4-Dihydro-1,4-epiazano-napthalen-9-yl)-pent-4-en-1-one: (Used for the preparation of A.30.) 4-Pentenoyl chloride (1.13 mL, 10.2 mmol) was added dropwise via syringe to a solution of 1,4-dihydro-1,4-epiazano-napthalene, (1.33 g, 9.3 mmol) pyridine (0.95 mL, 10.2 mmol) and DMAP (57 mg, 0.46 mmol) in CH₂Cl₂ (50 mL) at 0 °C under an N₂ atmosphere. After 2 h, ^1H NMR of an aliquot indicated the reaction was complete. A solution of 10 % HCl(aq) (20 mL) was added to the mixture, which was then extracted three times with CH₂Cl₂ (20 mL), dried over MgSO₄ and concentrated in vacuo to a yellow oil (1.98 g, 95%). The crude material was used without further purification. ^1H NMR (500 MHz, C₆D₆): δ 6.95 (d, 1H, J = 6.7 Hz, aryl CH), 6.91 (d, 1H, J = 6.7 Hz, aryl CH), 6.75 (m, 2H, aryl CH), 6.54 (dd, 1H, J = 2.4 Hz, J = 5.5 Hz, CH=CH), 6.38 (dd,
1H, J = 2.4 Hz, J = 5.5 Hz, CH=CH), 5.85 (m, 1H, bridge CH), 5.71 (m, 1H, CH=CH₂), 4.95 (m, 2H, CH=CH₂), 4.81 (m, 1H, bridge CH), 2.31 (m, 2H, NCH₂CH₂), 1.94 (m, 2H, NCH₂CH₂). ¹³C NMR (125 MHz, C₆D₆): δ 169.8, 149.7, 149.2, 144.9, 142.6, 138.2, 128.7, 125.6, 125.2, 121.9, 120.6, 115.4, 66.1, 64.5, 33.8, 29.3. IR (Neat): 3075 (m), 2978 (m), 1655 (s), 1445 (s), 1329 (m), 1291 (w), 1214 (m), 1074 (w). HRMS (ESI) Calcd for C₁₅H₁₃NO [M + Na]: 248.1046. Found: 248.1055.

9-Pent-4-enyl-1,4-dihydro-1,4-epiazano-napthalene (A.30): Lithium aluminum hydride (920 mg, 24.2 mmol) was added to 1-(1,4-dihydro-1,4-epiazano-naphthalen-9-yl)-pent-4-en-1-one (1.82 g, 8.2 mmol) in dry ether (150 mL) at room temperature under an N₂ atmosphere. After 12 h, the reaction was cooled to 0 °C, and water (20 mL) was added to destroy excess reducing agent. The mixture was filtered over celite, then dried with MgSO₄ and concentrated in vacuo to a yellow oil, which was distilled under vacuum (0.04 mm Hg, 65 – 70 °C) to afford a clear, colourless oil. The material was further purified via column chromatography over alumina, eluting with 20 % ether in pentane to afford a clear, colorless oil (1.1 g, 5.2 mmol) in 64 % yield. ¹H NMR (500 MHz, C₆D₆): δ 7.06 (m, 2H, aryl CH), 6.85 (m, 2H, aryl CH), 6.80 – 6.20 (br, 2H, CH=CH), 5.75 (m, 1H, CH=CH₂), 4.96 (m, 2H, CH=CH₂), 4.28 (br, 2H, bridge CH), 2.60 – 2.10 (br, 2H, NCH₂CH₂), 2.06 – 1.90 (br, 2H, NCH₂CH₂), 1.49 (m, 2H, CH₂CH=CH₂). ¹³C NMR (125 MHz, C₆D₆): δ 143.8 (br), 139.4, 139.3, 126.7, 125.0, 115.0, 114.9, 70.9 (br), 65.9, 49.4 (br), 48.4. IR (Neat): 3072 (m), 2931 (s), 2837 (m), 1640 (m), 1452 (s), 1367 (w), 1297 (w), 1272 (s), 1108 (m). HRMS (ESI) Calcd for C₁₅H₁₇N [M + H]: 212.1434. Found: 212.1430.

2,4-Dimethyl-3-oxo-8-aza-bicyclo[3.2.1]oct-6-ene-8-carboxylic acid tert-butyl ester: (Used in the synthesis of A.37 – A.39.) An acetonitrile (50 mL) solution of 2,4-dibromopentanone (26 g, 107 mmol) was slowly added to a mixture of N-BOC-pyrrole, (8.9 mL, 53 mmol) sodium iodide, (96 g, 0.64 mol) and
powdered copper (22 g, 0.34 mol) in acetonitrile (2.0 L) with rapid stirring. The mixture was subsequently heated to 60 °C overnight. After cooling, acetonitrile was removed in vacuo, and the crude material dissolved into a CH₂Cl₂ and water. The mixture was extracted 6 times with CH₂Cl₂ (150 mL). All organic extracts were combined, with NH₄OH (2 x 50 mL), then with water (3 x 50 mL). The solution was dried over MgSO₄, filtered through alumina, and concentrated in vacuo to a yellow oil. The crude was purified by distillation under vacuum, (80 – 95 °C, 300 mTorr) to afford 7.2 g (29 mmol) of clear, slowly crystallizing oil in 54 % yield. ¹H NMR (300 MHz, C₆D₆, 20 °C): δ 5.73 (s, 2H, vinyl CH), 4.59 (br, bridge CH), 4.34 (br, bridge CH), 2.71 (br, CHMe), 2.50 (br, CHMe), 1.41 (s, 9H, C(CH₃)₃), 0.95 (m, 6H, CHCH₃). This material was judged to be solely the cis-isomer by ¹H, gCOSY, and HMQC NMR spectra, in comparison with previously reported data.¹⁸⁵ No further spectral data was obtained.

2,4-Dimethyl-3-hydroxy-8-aza-bicyclo[3.2.1]oct-6-ene-8-carboxylic acid tert-butyl ester: (Used in the preparation A.37 – A.39.) A CH₂Cl₂ solution of lithium di-iso-butylaluminumhydride (34 mL, 1.0 M) was slowly added to a solution of 2,4-dimethyl-3-oxo-8-aza-bicyclo[3.2.1]oct-6-ene-8-carboxylic acid tert-butyl ester (7.2 g, 29 mmol) in toluene (150 mL) at – 78 °C. After 2 h, then reaction was poured onto 10 % HCl(aq), then filtered through celite to remove aluminum salts. The biphasic mixture was extracted 3 times with ether (200 mL), dried over MgSO₄, and concentrated in vacuo to a grey oil. The crude material was purified by column chromatography over silica, using first 1.0 L of: (CH₂Cl₂:ether:pentane = 40:20:40), then 1.0 L g of (CH₂Cl₂:ether = 50:50). A brown oil was obtained, 6.2 g (24 mmol) in 85 % yield. ¹H NMR (500 MHz, C₆D₆, 20 °C): δ 5.79 (m, 2H, vinyl CH), 4.42 (s, 1H, bridge CH), 4.15 (s, 1H, bridge CH), 3.36 (m, 1H, CHOH), 2.21 (br m, 1H, CHMe), 2.03 (br m, 1H, CHMe), 1.47 (s, 9H, C(CH₃)₃), 1.02 (br, 1H, OH), 0.89 (d, 3H, J = 7.3 Hz, CHCH₃), 0.86 (d, 3H, J = 7.3 Hz, CHCH₃). No further spectral data obtained as this is a known compound.¹⁸⁵
2,4-Dimethyl-3-benzylxy-8-aza-bicyclo[3.2.1]oct-6-ene-8-carboxylic acid tert-butyl ester: (Used in the preparation of A.37 – A.39.) Potassium hydride (2.9 g, 73 mmol) was suspended in DMF (250 mL). A solution of 2,4-dimethyl-3-hydroxy-8-aza-bicyclo[3.2.1]oct-6-ene-8-carboxylic acid tert-butyl ester (6.15 g, 24 mmol) was cannula-transferred onto the DMF solution, and the resultant mixture stirred under N₂ for 1 h. Benzyl bromide (8.4 mL, 48 mmol) was via syringe to the red solution to turn the mixture pale yellow within 2 min; ther resultant mixture was stirred under N₂ over-night. Water and ether were added to quench the reaction. The mixture was extracted three times with ether (500 mL). All organic extracts were combined, washed with 10% NaOH(aq), then NH₄Cl(aq), dried (MgSO₄) and concentrated in vacuo to an orange oil. The crude material was purified by silica gel chromatography, eluting with ether/CH₂Cl₂/pentane (5/40/55) to obtain 6.2 g (18 mmol, 74% yield) of clear, yellow oil. ¹H NMR (500 MHz, C₆D₆, 20 °C): δ 7.23 – 7.10 (m, 5H, aryl CH), 5.99 (m, 2H, vinyl CH), 4.42 (br m, 1H, bridge CH), 4.16 (br m, 1H, bridge CH), 4.04 (m, 2H, CH₂Ph), 2.93 (t, 1H, J = 4.7 Hz, CHO-Bn), 2.25 (br m, 1H, CH-CH₂), 2.08 (br m, 1H, CH-CH₂), 1.47 (s, 9H, C(CH₃)₃), 0.79 (d, 3H, J = 7.1 Hz, CH₂CH₂), 0.77 (d, 3H, J = 7.1 Hz, CH₂CH₂). ¹³C NMR (125 MHz, C₆D₆, 20 °C): δ 152.6, 140.0, 135.0, 134.1, 127.7, 127.5, 81.3, 79.0, 62.8, 62.1, 39.8, 38.7, 29.9, 14.6, 14.4. IR (Neat): 3065 (w), 2973 (s), 1696 (s), 1454 (s), 1366 (s), 1333 (m), 1291 (s), 1179 (s), 1028 (m). HRMS (ESI) Calcd for C₂₁H₂₅NO₃ [M + Na]: 366.2040. Found: 366.2043.

3-Benzylxy-2,4-dimethyl-8-aza-bicyclo[3.2.1]oct-6-ene: (Used in the preparation of A.37 – A.39.) Trifluoroacetic acid (18 mL, 230 mmol) was added to a solution of 2,4-dimethyl-3-benzylxy-8-aza-bicyclo[3.2.1]oct-6-ene-8-carboxylic acid tert-butyl ester (4.0 g, 12 mmol) in CH₂Cl₂ (150 mL) at 0 °C. After 1 h, excess acid was neutralized by addition of NaHCO₃(aq) until pH ≈ 7. The resultant emulsion was filtered through celite, then extracted three times with CH₂Cl₂ (200 mL). The organic extracts were combined,
dried over MgSO₄ and concentrated in vacuo to 2.5 g of an orange oil, (9.7 mmol, 84 % yield) which slowly solidified. The crude material was judged sufficiently pure to carry forward without purification. ¹H NMR (500 MHz, C₆D₆, 20 °C): δ 7.20 – 7.00 (m, 5H, aryl CH), 5.61 (s, 2H, vinyl CH), 3.89 (s, 2H, CH), 3.56 (br s, OCH₂Ph), 2.90 (m, 1H, OCH), 2.52 (m, 2H, CHCH₃), 1.55 (s, NH), 0.56 (d, 6H, J = 7.0 Hz, CHCH₃). ¹³C NMR (125 MHz, C₆D₆, 20 °C): δ 139.3, 132.1, 128.0, 127.5, 79.4, 77.0, 62.1, 37.0, 30.4, 13.7. IR (Neat): 2964 (m), 1670 (s), 1625 (m), 1454 (m), 1261 (s), 1179 (s), 1129 (m), 1067 (m).

1-(3-Benzylloxy-2,4-dimethyl-8-aza-bicyclo[3.2.1]oct-6-en-8-yl)-prop-3-ene (A.37):

Potassium hydride (170 mg, 4.2 mmol) was added to a solution of 3-benzyloxy-2,4-dimethyl-8-aza-bicyclo[3.2.1]oct-6-ene (0.86 g, 3.5 mmol) in DMF (20 mL) at 0 °C to produce much gas evolution. Once all bubbling had ceased, a red solution was obtained. To this solution allyl bromide (0.36 mL, 4.2 mmol) was added, which quickly turned the solution to a yellow suspension. The mixture was stirred overnight, then subjected to a standard work-up. The mixture was poured onto NaHCO₃ (aq), extracted three times with CH₂Cl₂ (100 mL), dried (MgSO₄) and concentrated in vacuo. The crude material was purified via column chromatography on alumina to afford a pale yellow oil. ¹H NMR (500 MHz, C₆D₆, 20 °C): δ 7.32 – 7.00 (m, 5H, aryl CH), 6.08 (m, 1H, CH=CH₂), 5.88 (br m, 1H, vinyl CH), 5.06 (m, 2H, CH=CH₂), 4.11 (s, 2H, CH₂), 3.15 (s, 2H, CH), 3.05 (s, 1H, CHO), 3.02 (d, 2H, J = 6.4 Hz, CH₂), 2.41 (br m, 2H, CH₂), 1.55 (s, 2H, CH₂), 0.86 (br, 6H, CH₃).

**Representative Procedure 4.1:** CH₂Cl₂ solutions of vinyl acetic acid (0.2 mL, 2.3 mmol), then 3-benzyloxy-2,4-dimethyl-8-aza-bicyclo[3.2.1]oct-6-ene (0.50 g, 2.3 mmol) were sequentially added to a solution of dicyclohexylcarbodiimide (470 mg, 2.3 mmol) in CH₂Cl₂ at 0 °C to afford a milky white suspension. After 18 h, the white suspension was
filtered over celite to remove the insoluble urea, and the filtrated concentrated in vacuo to a yellow oil. The crude material was used without further purification.

1-(3-Benzylxy-2,4-dimethyl-8-aza-bicyclo[3.2.1]oct-6-en-8-yl)-but-3-en-1-one: (Used for the preparation of A.38.) Prepared via procedure 4.1, (2.4 g, 7.8 mmol) in quantitative yield. $^1$H NMR (500 MHz, $\text{C}_6\text{D}_6$, 20 °C): δ 7.32 (d, 2H, $J = 7.6$ Hz, aryl CH), 7.23 (m, 2H, aryl CH), 7.11 (t, 1H, $J = 7.6$ Hz, aryl CH), 6.03 (s, 2H, vinyl CH), 5.93 (m, 1H, CH=CH$_2$), 5.06 (m, 2H, CH=CH$_2$), 4.18 (s, 2H, CH$_2$), 3.10 (t, 1H, $J = 5.0$ Hz, CHO), 3.06 (d, 2H, $J = 2.1$ Hz, CH$_2$), 2.41 (t, 2H, $J = 7.3$ Hz, CH$_2$), 2.24 (m, 4H, CHCH$_3$ & CH$_2$), 0.92 (d, 6H, $J = 7.3$ Hz, CH$_3$). $^{13}$C NMR (125 MHz, $\text{C}_6\text{D}_6$, 20 °C): δ 139.8, 135.0, 133.2, 131.3, 127.5, 118.4, 117.6, 81.1, 77.0, 63.1, 60.8, 53.7, 41.3, 39.2, 14.4.

Representative Procedure 4.2: Lithium aluminum hydride (190 mg, 5.1 mmol) was added to 1-(3-benzylxy-2,4-dimethyl-8-aza-bicyclo[3.2.1]oct-6-en-8-yl)-but-3-en-1-one (0.8 g, 2.6 mmol) in dry ether (50 mL) at 0 °C under an N$_2$ atmosphere. After 1.5 h, the reaction was quenched by the addition of KOH$_{aq}$ (1 mL). The reaction was dried with MgSO$_4$ then filtered over celite and concentrated in vacuo to a yellow oil. The crude material was purified by column chromatography on alumina, eluting with 20 % ether in pentane, to afford a clear, colourless oil.

1-(3-Benzylxy-2,4-dimethyl-8-aza-bicyclo[3.2.1]oct-6-en-8-yl)-but-4-ene (A.38): Prepared via procedure 4.2 (0.25 g, 0.86 mmol) in 33 % yield. $^1$H NMR (500 MHz, $\text{C}_6\text{D}_6$, 20 °C): δ 7.32 (d, 2H, $J = 7.6$ Hz, aryl CH), 7.23 (t, 2H, $J = 7.6$ Hz, aryl CH), 7.11 (t, 1H, $J = 7.6$ Hz, aryl CH), 6.03 (s, 2H, vinyl CH), 5.93 (m, 1H, CH=CH$_2$), 5.06 (m, 2H, CH=CH$_2$), 4.18 (s, 2H, CH$_2$), 3.10 (t, 1H, $J = 5.0$ Hz, CHO), 3.06 (d, 2H, $J = 2.2$ Hz, CH$_2$), 2.41 (t, 2H, $J = 7.3$ Hz, CH$_2$), 2.24
(m, 4H, CH$_2$CH$_2$), 0.92 (d, 6H, J = 7.3 Hz, CH$_3$). $^{13}$C NMR (125 MHz, C$_6$D$_6$, 20 °C): δ 140.4, 138.2, 133.5, 127.6, 127.4, 115.4, 81.6, 76.8, 70.7, 54.2, 41.5, 34.6, 15.2. IR (Neat): 3065 (m), 2972 (s), 2930 (s), 1640 (m), 1453 (m), 1331 (m), 1178 (m), 1067 (s), 1028 (s). HRMS (ESI') Calcd for C$_{26}$H$_{27}$NO [M + H]: 298.2145. Found: 298.2153.

1-(3-Benzoyloxy-2,4-dimethyl-8-aza-bicyclo[3.2.1]oct-6-en-8-yl)-pent-4-en-1-one:

(Used for the preparation of A.39.) Prepared via procedure 4.1, (1.1 g, 3.3 mmol) in quantitative % yield. $^1$H NMR (500 MHz, C$_6$D$_6$, 20 °C): δ 7.23 (m, 3H, aryl CH), 7.10 (m, 2H, aryl CH), 6.00 (dd, 1H, J = 2.3 Hz, J = 6.3 Hz, vinyl CH), 5.90 (m, 1H, CH=CH$_2$), 5.90 (dd, 1H, J = 2.3 Hz, J = 6.3 Hz, vinyl CH), 5.09 (dd, 1H, J = 1.5 Hz, J = 17.1 Hz, CH=CH$_2$H$_b$), 4.99 (dd, 1H, J = 0.9 Hz, J = 10.1 Hz, CH=CH$_2$H$_a$H$_b$), 4.79 (s, 1H, bridge CH), 4.09 (d, 1H, J = 11.5 Hz, OCH$_2$H$_b$Ph), 4.03 (d, 1H, J = 11.5 Hz, OCH$_2$H$_b$H$_a$), 3.68 (s, 1H, bridge CH), 2.89 (t, 1H, J = 4.7 Hz, CHO), 2.57 (m, 2H, CH$_2$), 2.19 (m, 1H, CHMe), 2.14 (m, 2H, CH$_2$), 1.65 (m, 1H, CHMe), 0.82 (d, 3H, J = 7.0 Hz, CHCH$_3$), 0.69 (d, 3H, J = 7.0 Hz, CHCH$_3$). $^{13}$C NMR (125 MHz, C$_6$D$_6$, 20 °C): δ 168.9, 139.5, 136.5, 133.6, 132.8, 129.0, 127.9, 127.5, 116.3, 80.5, 77.0, 63.3, 61.9, 41.8, 39.3, 34.8, 28.7, 14.1. HRMS (ESI') Calcd for C$_{18}$H$_{21}$NO [M + H]: 244.1696. Found: 244.1695.

1-(3-Benzoyloxy-2,4-dimethyl-8-aza-bicyclo[3.2.1]oct-6-en-8-yl)-pent-4-ene (A.39):

Prepared via procedure 4.2 (300 mg, 0.99 mmol) in 30 % yield. $^1$H NMR (500 MHz, C$_6$D$_6$, 20 °C): δ 7.33 (d, 2H, J = 7.0 Hz, aryl CH), 7.22 (m, 2H, aryl CH), 7.11 (t, 1H, J = 7.3 Hz, aryl CH), 6.05 (s, 2H, vinyl CH), 5.84 (m, 1H, CH=CH$_2$), 5.04 (m, 2H, CH=CH$_2$), 4.18 (s, 2H, CH$_2$), 3.11 (t, 1H, J = 5.0 Hz, CHO), 3.07 (d, 2H, J = 2.75 Hz, CH$_2$), 2.33 (t, 2H, J = 3.7 Hz, CH$_2$), 2.24 (m, 2H, CHCH$_3$), 2.13 (m, 2H, CH$_2$), 1.56 (m, 2H, CH$_2$), 0.92 (d, 6H, J = 7.3 Hz, CH$_3$). $^{13}$C NMR (125 MHz, C$_6$D$_6$, 20 °C): δ 140.4, 139.7, 133.6, 128.8, 127.6, 127.5, 114.9, 81.6, 76.8, 70.7, 54.0, 41.6, 32.6, 29.2, 15.2. IR (Neat): 3065 (m), 2930 (s), 2872
(s), 1640 (m), 1453 (m), 1331 (m), 1177 (m), 1067 (s), 1028 (m). HRMS (ESI+) Calcd for C_{21}H_{29}NO [M + H]: 312.2322. Found: 312.2311.

4-Oxo-2-vinyl-3,4-dihydro-6H-pyridine-1-carboxylic acid benzyl ester: (Used in the synthesis of A.47 – A.49, A.53 and A.54.) Vinylmagnesium bromide (120 mL, 1.0 M in THF) was added dropwise to a solution of 4-methoxypyridine (10 mL, 99 mmol) in THF (100 mL) at –78 °C. Once the addition was complete, the mixture was warmed to –30 °C, and CBz-chloride (21 mL, 150 mmol) was added dropwise over 30 min. The reaction was slowly warmed to room temperature, with stirring under N$_2$ over 2 h. Ether (200 mL) and 10 % HCl$_{(aq)}$ (150 mL) were then added, and the resultant mixture was extracted with ether (3 × 200 mL). All organic extracts were combined, dried (Na$_2$SO$_4$) and concentrated in vacuo to afford a dark brown oil. The crude material was purified via column chromatography on silica gel, eluting with 30 % ethyl acetate in hexane, to afford 24 g (91 mmol) of a yellow oil, in 93 % yield. $^1$H NMR (300 MHz, CDCl$_3$): δ 7.82 (d, 1H, J = 8.1 Hz, CH=CH), 7.40 (s, 5H, aryl CH), 5.80 (m, 1H, CH=CH$_2$), 5.35 – 5.12 (m, 6H, CH=CH, CH=CH$_2$, OCH$_2$Ph & CH), 2.92 (dd, 1H, J = 6.9 Hz, J = 16.5 Hz, CH$_a$H$_b$), 2.56 (br d, 1H, J = 16.5 Hz, CH$_a$H$_b$). This spectrum matched that reported in the literature, therefore no further spectra were obtained.$^{186}$

4-Oxo-2,6-divinyl-pyridine-1-carboxylic acid benzyl ester: (Used in the synthesis of A.47 – A.49, A.53 and A.54.) MeLi (86 mL, 1.6 M in ether) was added drop-wise to a slurry of copper (I) cyanide (12 g, 140 mmol) in THF (150 mL) at –78 °C. After addition was complete, the slurry was warmed to 0 °C for 15 min, then re-cooled to –78 °C. Vinylmagnesium bromide (98 mL, 1.0 M in THF) was added drop-wise to the mixture. After addition was complete, the slurry was warmed to 0 °C for ten min, then re-cooled to –78 °C. A THF (200 mL) solution of 4-oxo-2-vinyl-3,4-dihydro-6H-pyridine-1-carboxylic acid benzyl ester (24 g, 91 mmol) was then added drop-wise to the mixture over 40 min. The resultant mixture was allowed to
slowly warm to room temperature overnight with stirring under N₂. The mixture was then poured onto a mixture of saturated NH₄Cl (aq) and concentrated NH₄OH (10:1), and stirred for 4 h. The mixture was extracted with ethyl acetate (3 x 200 mL), washed with water (2 x 100 mL) and brine (3 x 50 mL), then dried over MgSO₄ and concentrated in vacuo to 16 g (56 mmol, 62 % yield) of an orange oil. The crude material was judged sufficiently pure by ¹H NMR spectroscopy to use unpurified in the next step. ¹H NMR (500 MHz, C₆D₆): δ  7.25 (s, 5H, aryl CH), 5.84 (m, 2 H, CH=CH₂), 5.10 (m, 8H, CH=CH₂, CHCH=CH₂, OCH₂Ph), 2.59 (d, 4H, J = 5.5 Hz, CH₃). This spectrum matched that reported in the literature, therefore no further spectra were obtained.¹⁸⁶

3-Oxo-8-aza-bicyclo[3.2.1]oct-6-ene-8-carboxylic acid benzyl ester: (Used in the synthesis of A.47 – A.49, A.53 and A.54.) Ru-catalyst 2.1d (1.0 g, 1.6 mmol) and 4-oxo-2,6-divinyl-pyridine-1-carboxylic acid benzyl ester (9.1 g, 32 mmol) were stirred in an CH₂Cl₂ (150 mL) in an open flask at room temperature over 48 h. Solvent was removed under vacuum to afford a dark brown oil. The crude material was purified via column chromatography on silica gel, eluting with 30 % ethyl acetate in hexane to afford 3.6 g (14 mmol) of a pale yellow oil in 43 % yield. ¹H NMR (500 MHz, C₆D₆): δ  7.30 – 7.0 (m, 5H, aryl CH), 5.40 (d, 2H, J = 11.0 Hz, CH=CH), 5.08 (d, 2H, J = 16.5 Hz, OCH₂Ph), 4.59 (s, 1H, bridge CH), 4.27 (s, 1H, bridge CH), 2.57 (br d, 1H, J = 15 Hz, CH₃Hb), 2.25 (br d, 1H, J = 15 Hz, CH₃Hb), 2.00 (br d, 1H, J = 16.5 Hz, CH₃Hb), 1.91 (br d, 1H, J = 16.5 Hz, CH₃Hb). This spectrum matched that reported in the literature, therefore no further spectra were obtained.¹⁸⁶

3-Hydroxy-8-aza-bicyclo[3.2.1]oct-6-ene-8-carboxylic acid benzyl ester: (Used in the preparation of A.47 – A.49, A.53 and A.54.) A solution of L-selectride (13 mL, 1.0 M) in THF was added over 1 h to a solution of 3-oxo-8-aza-bicyclo[3.2.1]oct-6-ene-8-carboxylic acid benzyl ester (3.2 g, 13 mmol) in THF (125 mL) at – 78 °C. The reaction was slowly warmed to room temperature over 2 h with stirring
under N₂. Ethyl acetate (10 mL) and 10 % NaOH(aq) (10 mL) were added to the mixture; the mixture was then extracted with ethyl acetate (3 x 50 mL). All organic extracts were combined, washed with brine (50 mL), dried over MgSO₄, and concentrated in vacuo to a yellow oil. The crude material was purified via column chromatography on silica gel, eluting with 10 % hexane in ethyl acetate to afford 1.26 g (4.9 mmol, 39 % yield) as a clear, colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 7.40 – 7.29 (m, 5H, aryl CH), 6.42 (br d, 2H, J = 19.5 Hz, CH=CH), 5.18 (s, 2H, OCH₂Ph), 4.66 (br d, 2H, J = 17 Hz, bridge CH), 3.95 (m, 1H, CHOH), 2.32 (br d, 1H, J = 14 Hz, CH₃H₉), 2.20 – 2.16 (m, 3H, CH₂, OH), 1.81 (br d, 1H, J = 14 Hz, CH₃H₉). This spectrum matched that previously reported; therefore no further spectra were obtained.¹⁸²

3-tert-Butyldimethylsilyloxy-8-aza-bicyclo[3.2.1]oct-6-ene-8-carboxylic acid benzyl ester: (Used in the preparation of A.47 – A.49, A.53 and A.54.) A solution of TBS-chloride (1.5 g, 9.7 mmol), 3-hydroxy-8-aza-bicyclo[3.2.1]oct-6-ene-8-carboxylic acid benzyl ester (1.3 g, 4.9 mmol) and imidazole (0.66 g, 9.7 mmol) in DMF (12 mL) was stirred for 18 h at room temperature. The mixture was then diluted with ether (5 mL) and water (5 mL). The mixture was then extracted with ether (3 x 15 mL), washed with brine (2 x 10 mL), dried over MgSO₄, and concentrated in vacuo to a colorless oil. The crude material was purified by column chromatography over silica, eluting with 50 % ethyl acetate in hexane to afford 1.7 g (4.5 mmol, 91 % yield) of clear, colorless oil. ¹H NMR (500 MHz, CDCl₃): δ 7.38 (m, 5H, aryl CH), 6.13 (br d, 2H, J = 23 Hz, CH=CH), 5.17 (s, 2H, OCH₂Ph), 4.57 (d, 2H, J = 15 Hz, bridge CH), 4.00 (m, 1H, CHOTBS), 2.20 (br d, 1H, J = 14 Hz, CH₃H₉), 2.07 (m, 1H, CH₃H₉), 1.57 (m, 2H, CH₂), 0.87 (s, 9H, Si(CH₃)₃), -0.03 (s, 6H, Si(CH₃)₂). This spectrum matched that previously reported; therefore no further spectra were obtained.¹⁸²
3-tert-Butyldimethylsilyloxy-8-aza-bicyclo[3.2.1]oct-6-ene: (Used in the preparation of A.47 – A.49, A.53 and A.54.) Ammonia (~ 75 mL) was condensed over sodium (1.0 g, 45 mmol) in THF (50 mL) at - 78 °C to afford a deep-blue solution. A THF (50 mL) solution of 3-benzyloxy-8-aza-bicyclo[3.2.1]oct-6-ene-8-carboxylic acid benzyl ester (1.7 g, 4.5 mmol) and t-butanol (4.2 mL, 45 mmol) was cannula-transferred onto the sodium/ammonia solution. The resultant mixture was stirred under N₂, slowly warming to room temperature, overnight. Water and solid NH₄Cl was added to the mixture until pH ~ 10. The mixture was extracted with ether (3 × 75 mL), dried over MgSO₄, and concentrated in vacuo to 1.1 g (4.5 mmol, quantitative yield) as a colorless oil. The crude material was judged pure by the ¹H NMR spectrum. ¹H NMR (300 MHz, C₆D₆): δ 6.05 (s, 2H, CH=CH), 3.85 (m, 1H, CHOTBS), 3.54 (m, 2H, bridge CH), 2.06 (m, 2H, CH₂), 1.41 (m, 2H, CH₂), 0.89 (s, 9H, SiC(CH₃)₃), -0.14 (s, 6H, Si(CH₃)₂). ¹³C NMR (125 MHz, C₆D₆): δ 137.6, 66.2, 59.1, 37.4, 30.8, 26.4, 1.8.

1-(tert-Butyldimethylsilyloxy-8-aza-bicyclo[3.2.1]oct-6-en-8-yl)-prop-3-ene (A.47):

Potassium hydride (11 mg, 0.26 mmol) was added to a solution of 3-benzyloxy-8-aza-bicyclo[3.2.1]oct-6-ene (60 mg, 0.24 mmol) in DMF (5 mL) at 0 °C to produce much gas evolution. Once all bubbling had ceased, a red solution was obtained. To this solution allyl bromide (31 mg, 0.26 mmol) was added. ¹H NMR (500 MHz, C₆D₆): δ 6.03 (m, 1H, CH=CH₂), 5.88 (s, 2H, CH=CH), 5.17 (d, 1H, J = 16.8 Hz, CH=CH₂Hb), 5.07 (d, 1H, J = 10.1 Hz, CH=CH₂Ha), 3.91 (m, 1H, CHOTBS), 3.36 (m, 2H, bridge CH), 3.02 (d, 2H, J = 5.8 Hz, NCH₂), 2.16 (br, 2H, CH₂), 1.53 (d, 2H, J = 13.4 Hz, CH₂), 0.96 (s, 9H, SiC(CH₃)₃), -0.04 (s, 6H, Si(CH₃)₂). ¹³C NMR (125 MHz, C₆D₆): δ 133.0, 127.0, 100.5, 66.2, 64.7, 38.3, 30.8, 26.4, 15.9, 1.7.

Representative Procedure 4.3: 4-Pentenoyl chloride (51 µL, 0.46 mmol) was added to a CH₂Cl₂ solution (7 mL) of 3-tert-butyldimethylsilyloxy-8-aza-bicyclo[3.2.1]oct-6-ene (97
mg, 0.39 mmol), pyridine (43 μL, 0.46 mmol), and DMAP (5 mg, 0.02 mmol) at room temperature under N$_2$ to afford a milky white suspension. After 10 hours, 10 % HCl$_{(aq)}$ (1 mL) was added to the reaction. The mixture was extracted with CH$_2$Cl$_2$ (3 x 5 mL), dried over MgSO$_4$, and concentrated in vacuo to a yellow oil. The crude material was used without further purification. Lithium aluminum hydride (26 mg, 0.68 mmol) was added to a solution of the crude material (90 mg, 0.27 mmol) in dry ether (10 mL) at room temperature under an N$_2$ atmosphere. After 18 h, the reaction was quenched by the addition of NaOH$_{(aq)}$ (1 mL). The reaction was diluted with ether (10 mL), dried with MgSO$_4$ then filtered over celite and concentrated in vacuo to a yellow oil. The crude material was purified by column chromatography on alumina, eluting with 20 % ether in pentane, to afford a clear, colourless oil.

1-(3-tert-Butyldimethylsilyloxy-8-aza-bicyclo[3.2.1]oct-6-en-8-yl)-but-4-ene (A.48):

Prepared via procedure 4.3 (50 mg, 0.16 mmol) in 50 % yield. $^1$H NMR (500 MHz, C$_6$D$_6$): δ 5.92 (m, 3H, CH=CH & CH=CH$_2$), 5.09 (d, 1H, J = 17.7 Hz, C=CH$_{a}$H$_{b}$), 5.04 (d, 1H, J = 10.4 Hz, C=CH$_{a}$H$_{b}$), 3.90 (m, 1H, CHOTBS), 3.30 (s, 2H, bridge CH), 2.43 (t, 2H, J = 7.3 Hz, NCH$_2$), 2.25 (m, 2H, CH$_2$), 2.12 (m, 2H, CH$_2$), 1.54 (m, 2H, CH$_2$), 0.96 (s, 9H, Si(CH$_3$)$_3$), -0.02 (s, 6H, Si(CH$_3$)$_3$). $^{13}$C NMR (125 MHz, C$_6$D$_6$): δ 138.2, 133.3, 126.2, 115.5, 66.2, 65.1, 54.4, 38.5, 34.7, 30.8, 26.4, 18.4, 1.8.

1-(3-tert-Butyldimethylsilyloxy-8-aza-bicyclo[3.2.1]oct-6-en-8-yl)-pent-4-ene (A.49):

Prepared via procedure 4.3 (78 mg, 0.24 mmol) in 61 % yield. $^1$H NMR (500 MHz, C$_6$D$_6$): δ 5.94 (s, 2H, CH=CH), 5.85 (m, 1H, CH=CH$_2$), 5.08 (d, 1H, J = 17 Hz, C=CH$_{a}$H$_{b}$), 5.01 (d, 1H, J = 10 Hz, C=CH$_{a}$H$_{b}$), 3.90 (m, 1H, CHOTBS), 3.30 (s, 2H, bridge CH), 2.34 (t, 2H, J = 7.0
Hz, NCH$_2$, 2.11 (m, 2H, CH$_2$), 1.55 (m, 2H, CH$_2$), 0.98 (s, 9H, Si(CH$_3$)$_3$), -0.02 (s, 6H, Si(CH$_3$)$_2$). $^{13}$C NMR (125 MHz, C$_6$D$_6$): δ 139.7, 133.3, 114.9, 66.2, 65.1, 54.1, 38.5, 32.5, 30.8, 29.2, 26.4, 18.4, 1.7.

1-(3-tert-Butyldimethylsilyloxy-8-aza-bicyclo[3.2.1]oct-6-en-8-yl)-prop-3-methyl-3-ene (A.53): Potassium hydride (70 mg, 1.7 mmol) was added to a solution of 3-benzylaxyloxy-8-aza-bicyclo[3.2.1]oct-6-ene (400 mg, 1.6 mmol) in DMF (20 mL) at 0 °C to produce much gas evolution. Once all bubbling had ceased, a red solution was obtained. This solution was stirred a subsequent 4 h, to afford a green solution. Methallyl bromide (0.18 mL, 1.7 mmol) was added to this solution to produce a milky-white solution. The reaction was stirred overnight, then diluted with ether (5 mL) and water (5 mL). The mixture was extracted with ether (3 x 5 mL), washed with brine (5 mL), dried over MgSO$_4$ and concentrated in vacuo to a yellow oil. This material was purified by column chromatography over alumina, eluting with 5% ether in pentane, to afford 100 mg (0.3 mmol, 20% yield) of clear, colorless oil. $^1$H NMR (500 MHz, C$_6$D$_6$): δ 5.92 (s, 2H, CH=CH), 5.05 (s, 1H, C=CH$_2$H$_a$), 4.92 (s, 1H, C=CH$_2$H$_b$), 3.89 (m, 1H, CHOTBS), 3.33 (s, 2H, bridge CH), 2.94 (s, 2H, NCH$_2$), 2.09 (m, 2H, CH$_2$), 1.85 (s, 3H, CH$_3$), 1.53 (d, 2H, J = 13.5 Hz, CH$_2$), 0.97 (s, 9H, Si(CH$_3$)$_3$), -0.03 (s, 6H, Si(CH$_3$)$_2$). $^{13}$C NMR (125 MHz, C$_6$D$_6$): δ 145.2, 133.2, 112.2, 66.2, 64.7, 61.2, 38.5, 26.4, 21.5, 18.4, 1.8.

1-(3-tert-Butyldimethylsilyloxy-8-aza-bicyclo[3.2.1]oct-6-en-8-yl)-but-3-methyl-3-ene (A.54): Potassium hydride (73 mg, 1.8 mmol) was added to a solution of 3-benzylaxyloxy-8-aza-bicyclo[3.2.1]oct-6-ene (420 mg, 1.7 mmol) in DMF (30 mL) at 0 °C to produce much gas evolution. Once all bubbling had ceased, a red solution was obtained. This solution was stirred a subsequent 4 h, to afford a green solution. Prenyl bromide (0.21 mL, 1.8 mmol) was added to this solution to produce a milky-white solution. The reaction was stirred overnight, then
diluted with ether (5 mL) and water (5 mL). The mixture was extracted with ether (3 x 5 mL), washed with brine (5 mL), dried over MgSO$_4$ and concentrated *in vacuo* to a yellow oil. This material was purified by column chromatography over alumina, eluting with 5% ether in pentane, to afford 100 mg of clear, colorless oil. $^1$H NMR (500 MHz, C$_6$D$_6$): $\delta$ 5.94 (s, 2H, CH=CH), 5.56 (m, 1H, CH=C), 3.93 (m, 1H, CHOTBS), 3.41 (s, 2H, bridge CH), 3.07 (s, 2H, NCH$_2$), 2.16 (m, 2H, CH$_2$), 1.67 (s, 3H, CH$_3$), 1.60 (m, 2H, CH$_2$), 1.52 (s, 3H, CH$_3$), 0.96 (s, 9H, SiC(CH$_3$)$_3$), -0.04 (s, 6H, Si(CH$_3$)$_2$). $^{13}$C NMR (125 MHz, C$_6$D$_6$): $\delta$ 133.2, 124.8, 100.5, 74.8, 66.3, 63.3, 52.2, 38.6, 26.4, 18.4, 1.8.
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CURRICULUM VITAE

EDUCATION
Doctor of Philosophy, Massachusetts Institute of Technology May 2004

Organic Chemistry
Thesis: “New Chiral Molybdenum Metathesis Catalysts; Application to the
Enantioselective Preparation of Cyclic Amines.”
Advisor: Professor Richard R. Schrock
(Collaborative research with Professor Amir H. Hoveyda at Boston College)

Honours Bachelor of Science, University of Toronto June 1999
Chemistry & Mathematics, with High Distinction
Thesis: “Studies Toward an Enantioselective and Directed Cyclopropanation of α-Allenic
Alcohols”
Advisor: Professor Mark Lautens

RESEARCH EXPERIENCE
Massachusetts Institute of Technology September 1999 – Present

• Designed and synthesized new nitrogen-containing trienes for the study of
asymmetric ring-closing metathesis (ARCM) to afford chiral azacycles.
• Prepared and assessed new chiral dialkoxide ligands for discrete molybdenum-
  based catalysts for olefin metathesis.
• Constructed several variations of polymer-supported heterogeneous molybdenum
  alkylidenes; analyzed these products for activity toward olefin metathesis.

University of Toronto September 1998 – May 1999

• Investigated the utility of a chiral dioxaborolane auxiliary for enantioselective
cyclopropanation of α-allenic alcohols to prepare methylene-cyclopropanes.

Merck-Frosst Centre for Therapeutic Research May – September 1998

• Synthesized BK channel opener CGS 7181, an asymmetric N-urea; optimized
  reaction conditions and reproduced these on large scale.
• Sent isolated product for pharmacological testing.

PUBLICATIONS

Dolman, S. J.; Hultsch, K. C.; Pezet, F.; Teng, X; Hoveyda, A. H.; Schrock, R. R.
“Supported Chiral Mo-Based Complexes as Catalysts for Enantioselective Olefin

Dolman, S. J.; Schrock, R. R.; Hoveyda, A. H. “Enantioselective Synthesis of Cyclic
Secondary Amines through Mo-Catalyzed Asymmetric Ring-Closing Metathesis

Dolman, S. J.; Sattely, E. S.; Schrock, R. R.; Hoveyda, A. H. “Efficient catalytic
enantioselective synthesis of unsaturated amines. Preparation of small and medium ring


Belley, M.; Scheigetz, J.; Dube, P.; Dolman, S. “Synthesis of N-aminoindole ureas from ethyl 1-amino-6- (trifluoromethyl)-1H-indole-3-carboxylate.” *Synlett* **2001**, *222* – *225*.

**CONFERENCE PRESENTATIONS**


**HONOURS**

Best Poster Presentation Award, I.S.O.M. XV, Kyoto, Japan

Wyeth Scholar, Massachusetts Institute of Technology

Morse Travel Grant, Massachusetts Institute of Technology

Arbor Scholarship, Admission Scholarship, Univ. of Toronto

Professor R.K. Arnold Scholarship, Victoria College in Univ. of Toronto

L.V. Redman Scholarship in Math & Chemistry - III Year, Univ. of Toronto

N.S.E.R.C. Undergraduate Student Research Award, Merck-Frosst

William Ewart Staples Scholarship, Victoria College in Univ. of Toronto

Regents In-Course Scholarship, Victoria College in Univ. of Toronto

Charles Earl Auger Scholarship, Victoria College in Univ. of Toronto

Alexander Rutherford Scholarship, Ministry of Education, Alberta

Governor General’s Bronze Medal
ACKNOWLEDGEMENTS

To start, I have to thank Dick Schrock, for allowing an organic chemist into his organometallic chemistry lab. Even more important, however, was the freedom he gave me to focus on the organic aspect of my research project. I’ve had more freedom in my project than any of my peers; the opportunity to explore chemistry in my own way helped me to develop confidence in my abilities, my understanding, my intuition. I doubt I’ll ever have as much freedom again.

Amir Hoveyda has been like a co–advisor to me. Although ~ 95 % of the organic chemistry of this project was studied at Boston College, I was always welcomed by Amir and his students. I frequently visited BC to discuss synthetic problems and applications. Amir helped me to keep an organic chemist’s perspective, and kept me excited about my project just by his exuberance for organic chemistry.

Of course, the people you see day–to–day make the biggest differences. Part of what drew me to the Schrock group, was the warmth and friendliness of Jennifer Jamieson, Denyce Wicht and Sarah Aeilts. Within minutes, they made me feel like I belonged. George Greco introduced me to working in the glovebox, and somehow managed to tolerate a first–year student while putting the finishing touches to his thesis.

I started out at the same time as Jim Araujo, who was a total riot. Jim had the ability to make the most mundane task great fun. Unfortunately for all of us, he decided to leave after our second year, and no one ever could replace him. Post–docs Kai Hultzsch and Steve Miller were also very good friends. Not only were they both great sources of advanced chemistry lore, but each also had a great sense of balance. As Kai used to say, “Only do fun chemistry on the weekend.”

Over time, Parisa Mehrkhodavandi became one of my closest friends here. She’s the kind of person who has high standards for herself and all those around her. Her belief in my abilities gave me the confidence to accomplish as much as possible. If everyone had a friend like her, the whole world would be fixed. I was truly sad when she left for California, but I know that she’ll achieve great things.

When Nathan Smythe first started working in the same glovebox with me, I think we did nothing but fight. I don’t consider myself messy (still don’t) but he is fastidious. Furthermore, he wanted to re–plumb the entire setup. I’m a believer in the axiom “don’t fix it if it ain’t broke” and it scared me to fiddle around with that stuff. But in the end, I think I’m grateful because I’ve learned to no longer fear all things mechanical. More importantly, despite my tendency to download silly software for music–downloads, the man has kept my computer running.

Tatiana Pilyugina and Monica Duval only joined the group ~ 16 months ago, but both have become fast friends in that time. It feels like they’ve both been here since the beginning, and I wish they had been. Monica is always available to talk, whether it’s just to chat, discuss serious organic chemistry, or kvetch about some problem. With me, she probably had to listen to a lot more kvetching than ever before, but she always listened, and made me feel better. Tanya, despite her propensity to imitate a certain cat, kept my stress levels manageable, with healthy doses of coffee breaks, yoga classes, and thursday night TV.
Lara Pryor, Jen Adamchuk and Andrea Gabert (aka the polymer princesses) helped to keep me sane as well; in addition to being testosterone–based–music–free, their lab was always replete with various mid–afternoon noshes (swedish–berries, pretzels, popcorn) and girls ready for shopping–therapy.

So many other people have come and gone from the Schrock Lab over the years. I’ve shared many a happy Happy Hour with Klaus Ruhland, Frank Cochran, Yann Schrodi, Pet Bonitatebus, Pia Lopez, Adam Hock, Walter Weare, Zachary Tonzetich, Amrit Sinha, Fred Pezet and Vincent Ritleng. I’d like to thank everyone who’s helped me, in ways large and small, throughout my time here.

Many people in the Hoveyda Lab also deserve thanks, particularly Gabe Weatherhead, Jesper Jernelius, Alex Cortez and Elizabeth Sattely. Beth and I worked on closely related projects for a long time, and she helped me to solve many synthetic challenges. Beth also convinced me to go to Japan, for ISOM XV. I wouldn’t have gone alone, but with a travel companion, the trip didn’t seem so daunting. I had a great time, have memories and souvenirs that will last a lifetime, (including the squeaking–deer) and am already thinking about when I can go back. Traveling with Beth was great, she’s easy going about mishaps (getting lost non–stop) but always adventurous – got me to climb up and down the side of a mountain!

A great big THANK YOU to Matt Byrnes, who was brave enough to read the first draft of this entire thesis. Two big bottles of rum, comin’ your way. Caroline Woodrofe, Johann Chan and Kai Hultzsch read the second draft of certain chapters, and their help was enormous. I would also like to thank Professors Steve Buchwald and Greg Fu for helpful comments on my thesis, and an engaging defense.

Thank you Gretchen. This lab runs if and only if Gretchen Kappelman is here to run it. Après toi, le deluge. Without the people of the DCIF, Jeff Simpson, Mark Wall, David Bray and Li Li, none of this thesis would have been possible. Thank you to all of them for keeping the department running. Thank you to Susan Brighton, aka Grad–Student Mom, for always being there to listen.

It may sound silly, but at times the only thing that kept me at MIT was the Women’s Club Hockey team. Aspirations of representing Canada at the next Winter Olympics aside, the women on that team offered unconditional friendship. When nothing was going right in the lab, at least I could go blow off steam on the ice.

Finally, I have to thank my parents. For their support throughout all of my education. For driving an extra 25 minutes to send me to a school with AC classes, from grade 3. For letting me choose AP at a performing–arts high school over IB at a traditional school. For telling me, “McGill or U of T, you can’t go wrong” and “from here on in, it’s just an endurance test – hang in there”. For loving me even when I’m stressed out and at my worst. Thank you.